Options for Primary Prevention: Modifiable Lifestyle Factors
Prevention

- **Version 2012:**
  Dall / Diel

- **Version 2013:**
  Maass / Mundhenke

- **Version 2014:**
  Scharl / Stickeler
Risk Factors for Breast Cancer

Non-modifiable risk factors
- Older age
- Genetic risk factors
- Family cancer history
- Personal history of breast lesions
  - Non-proliferative lesions
  - Proliferative lesions w/o atypia
  - High risk lesions (ADH, LIN)
  - Breast cancer (DCIS, InvBC)
- Breast density
- Chest irradiation
- Lifetime number of menstrual cycles
  - Early menarche, late menopause, mat. pregnancy factors (e.g. preeclampsia (risk reduction), gestational diabetes and low phys. activity (risk increase))

Reproductive risk factors
- Lower number of births or no pregnancy
- Higher age at first full term delivery
Risk Factors for Breast Cancer

Modifiable risk factors

- Less breast feeding
- BMI <18.5 and > 25 and especially > 40 (obesity)
- Diabetes mellitus Type II
- Food content, vitamin D deficiency
- Steroid hormone therapy
  - Recent oral contraceptive use
  - Hormone therapy in postmenopausal women
- Alcohol intake
- Smoking
- Light exposure at night (night shifts)
- Less physical activity
- Toxic agents in fetal and early childhood development (DES, polyfluoroalkyls)
Recommendations

The Second Expert Report, Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective, features eight general and two special recommendations. The 10 recommendations are listed below. Together they comprise a blueprint that people can follow to help reduce their risk of developing cancer.

Click on each recommendation to find out more about it.

CHAPTER 12 of the Report features the recommendations in detail as does the Report summary.

BODY FATNESS
Be as lean as possible within the normal range of body weight

PHYSICAL ACTIVITY
Be physically active as part of everyday life

FOODS AND DRINKS THAT PROMOTE WEIGHT GAIN
Limit consumption of energy-dense foods
Avoid sugary drinks

PLANT FOODS
Eat mostly foods of plant origin

ANIMAL FOODS
Limit intake of red meat and avoid processed meat

ALCOHOLIC DRINKS
Limit alcoholic drinks

PRESERVATION, PROCESSING, PREPARATION
Limit consumption of salt
Avoid mouldy cereals (grains) or pulses (legumes)

DIETARY SUPPLEMENTS
Aim to meet nutritional needs through diet alone

BREASTFEEDING (Special Recommendation)
Mothers to breastfeed; children to be breastfed

CANCER SURVIVORS (Special Recommendation)
Follow the recommendations for cancer prevention

The policy implications of the recommendations are explored in the Policy Report.
Prevention by Changing Pregnancy Related Factors

- Any full term pregnancy
- Number of pregnancies
- First full term pregnancy before age of 30 years
- Breast feeding (protective if total breast feeding time exceeds 1.5–2 years)

Oxford / AGO LoE / GR

2b B
2b B
2b B
3a B
Parity and Breast Cancer Risk

Ma et al. Breast Cancer Research 2006, 8:R43
Prevention by Changing Lifestyle Factors: Body Mass Index / Diet

- **Maintaining normal weight**
  (BMI at 18.5 – 25 kg/m²)
  - Premenopausal
  - Postmenopausal

- **Prevention/Screening and treatment of diabetes mellitus Type II**
  (reduction of breast cancer incidence and mortality)

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<th>AGO</th>
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</table>
Prevention by Changing Lifestyle Factors: Diet

Dietary patterns
- Mediterranean prudent / healthy > Western unhealthy

Dietary components
- Fat reduced food
- Vitamins, minerals, tracer elements
- Vitamin D substitution for prevention
- Vegetables / fruits
- Phytoestrogens / Soya
- Fiber containing food

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<thead>
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</table>
Prevention by Modifying Lifestyle Risk Factors: Alcohol

- Reduction of alcohol intake reduces risk of breast cancer
  - Particularly for ER+/PgR+ tumors
  - Invasive lobular tumors

Oxford / AGO
LoE / GR
Prevention by Modifying Lifestyle Risk Factors: Physical Activity

- Physical exercise

(Metabolic equivalents to 3–5 hrs moderate pace walking per week)
Prevention by Modifying Lifestyle Risk Factors: Hormone Therapy in Postmenopausal Women

Avoiding hormonal therapy in postmenopausal women

- Avoiding estrogen / progestin combinations
  - 1b A +

- Avoiding estrogens only
  - 1b A +/-
  (no enhanced breast cancer risk with estrogen only therapy, maybe even risk reduction, but increased risk for endometrial cancer)
## Prevention Hormone (EGC) in der Post-MP

### Table: Treatment Effects and Additional Statements

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>MC-RR (95%CI)</th>
<th>Weitere Aussagen</th>
</tr>
</thead>
</table>
| **WHI**                       | ~ 27 000      | 1.3 (1.0-1.6)  | 1.3 (1.1-1.6) Koronare Events  
1.4 (1.1-1.9) Schlaganfälle  
2.1 (1.4-3.3) Lungenembolien  
2.1 (1.5-2.9) Thrombosen       |
| WHI: JAMA 2002                |               |                |                                                                                                                                                  |
| **HERS**                      | 1 2763        | 1.2 (0.95-1.5) | Med. Alter 67 J  
keine sekundäre Prävention  
Newkg. wie WHI + Cholzystektomien↑ |
| Hulley S: JAMA 2002           |               |                |                                                                                                                                                  |
| II 2763 RCT, med. 4.1 J      |               |                |                                                                                                                                                  |
| open-label, 2.7 J             |               |                |                                                                                                                                                  |
| **Million Women**             | 1.084 110     | 1.66 (1.6-1.8) | EPC > E  
Art der Anwendung egal  
Einnahmedauer > 5 Jahre  
Tibolon RR 1.45 (1.2-1.7)   |
| Beral V: Lancet 2003          |               |                |                                                                                                                                                  |
| ~ 50% HRT  
4.1 J. follow-up            |               |                |                                                                                                                                                  |
| **EPIC**                      | 1.153 747 person-years o | 1.4 (1.2-1.6) | E-Mono  
EPC > E                                                                                                                                          |
| Int J Cancer 2010             |               | 1.8 (1.4-2.2)  |                                                                                                                                                  |
| **Metaanalyse**              | 16 Studien    | 1.21-1.40      | Newkg. wie WHI +                                                                                                                                 |
| Nelson HD: JAMA 2002          |               |                |                                                                                                                                                  |

Chlebowski SABCS 2010
Prevention by Modifying Lifestyle Risk Factors: Oral contraception (OC)

- Overall, OC does not significantly increase risk of cancer

- Risk of breast cancer may be slightly increased, risk of ovarian, endometrial cancer is decreased

Oxford LoE
1a
1a(–)
OC and Breast Cancer Risk

Options for Primary Prevention: Modifiable Lifestyle Factors (2/15)

Further information:

Search:

Screened guidelines:
NCI (National Cancer Institute, 2013): http://www.cancer.gov/cancertopics/pdq/treatment/breast/healthprofessional
ASCO (American Association of Clinical Oncology, Practice Guidelines, 2013)
CMA (Canadian Medical Association, 2012): http://www.cmaj.ca/cgi/content/full/158/3/DC1
NCCN (National Comprehensive Cancer Network, 2013):

References:

General understanding of biological hypothesis upon life style factors and breast cancer risk:

Risk Factors for Breast Cancer (3/15)

Further information:

Individual risk factors can be classified into non-modifiable, modifiable and socially defined factors. Currently, there is good evidence that changes of some modifiable risk factors could decrease breast cancer risk substantially. That means that every woman could decrease her risk of breast cancer by healthy life style.

References:

Risk Factors for Breast Cancer Risk (4/15)

Further information:

Nearly all possible factors of environment, nutrition, modern lifestyle and profession have been investigated regarding possible influence on breast cancer risk. Obesity and severe underweight are significant risk factors for breast cancer. However most of these studies were small cohort or case control studies with a grade IIb to V at the scale of medical evidence. Therefore the conclusions were mostly controversial or inconclusive.(1) It is well known, how complicated it is to carry out well-designed and well-performed prospective randomized studies to investigate the effect of a single criteria (for instance fat reduced food) on breast cancer risk. Other factors, which could influence the individual risk, are genetic polymorphismens in metabolizing (e.g. alcohol, nicotin) or interactions between healthy and unhealthy effects of a single substance (e.g. phytoestrogens have different estrogenic effects and might include pesticides). Further questions of preventive intervention trails include:

- at which point in life time should intervention start or
- how long should intervention last,
- how long must the follow-up last and
- is the measured parameter (e.g. decreased vitamins level) the cause or the result of the disease.(2)

References:

4. B. Hyatt, Breast Cancer Risk and the Environment (SABCS 2011)
5. MF Forman, Environment and Breast Cancer (SABCS 2011)
Food, Nutrition, Physical Activity, and the Prevention of Cancer (5/15)

No further information

No references
Prevention by Changing Pregnancy Related Factors (6/15)

Further information:

It is well known that reproductive factors are correlated with the risk of breast cancer. A meta-analysis of 47 epidemiological studies investigated breastfeeding patterns and other aspects of childbearing. Women with breast cancer had, on average, fewer births (2.2 vs 2.6), ever (71% vs 79%) and shorter breastfed (9.8 vs 15.6 months) than did controls. The relative risk of breast cancer decreased by 4.3% (95% CI 2.9-5.8; p<0.0001) for every 12 months of breastfeeding in addition to a decrease of 7.0% (5.0-9.0; p<0.0001) for each birth. It is estimated that the cumulative incidence of breast cancer in developed countries would be halved (from 6.3 to 2.7% by age 70, if women had the average number of births and lifetime duration of breastfeeding that had been prevalent in developing countries until recently. The effect of parity on a woman's long-term risk of breast cancer is modified by age at first full-term pregnancy and by duration of breastfeeding. An assumed risk increase in ever having breast-fed girls could not be confirmed. (4)

References:


Parity and Breast Cancer Risk (7/15)

No further information

No references
Prevention by Changing Life Style Factors: Body Mass Index / Diet (8/15)

Further information:

Overweight (BMI 25-30 kg/m²) and obesity (Grade I 30 – 35, Grade II 35 – 40 Grade III ≥ 40) were found to be strong risk factor for postmenopausal breast cancer. In premenopausal pts. an inverse relationship was observed between BMI and breast cancer risk. In line with this relationship adult weight gain presented another risk factor for postmenopausal breast cancer. (1,8) In the EPIC-cohort study an a meta-analysis the relation of health (mediterranian) versus unhealthy (western) dietary patterns was examined. The breast cancer risk was significantly decreased in the highest compared to the lowest categories of mediterranian dietary patterns (OR 0.89; 95% CI: 0.82–0.99, p = 0.02), whereas there were no differences observed for western dietary patterns.(2-4) With exception of total fat intake, which might increase BMI and by that the breast cancer risk, there is no convincing data, that fruits/vegetables, micronutrition, tracer elements or vitamins intake reduced the breast cancer risk. (1,5-8) . Prevention of diabetes mellitus type II could reduce breast cancer incidence and – mortality (12).

References:


Prevention by Changing Life Style Factors: Diet (9/15)

No further information

No references
Further information:

Ethanol itself is not a carcinogen, but it is metabolized to potential carcinogenic compounds, for example, acetaldehyde. Alcohol induces oxidative stress in the liver so that other carcinogenic substances can be synthesized through enzyme induction, but cannot be metabolized. Alcohol increases the permeability of cell membranes thus facilitating the traffic of carcinogens into the cells. It also induces the proliferation of mammary epithelia in animal models and is resulting in higher serum concentrations of estradiol in premenopausal women. An established link to breast cancer would be of great interest since this noxious agent could be avoided easily.(1) A meta-analyses including 58,515 women with invasive breast cancer and 95,067 controls from 53 studies estimated the relative risks of breast cancer after stratifying by study, age, parity and, where appropriate, women's age when their first child was born and consumption of alcohol and tobacco. Compared with women who reported drinking no alcohol, the relative risk of breast cancer was 1.32 (1.19-1.45, P<0.00001) for an intake of 35-44 g per day alcohol, and 1.46 (1.33-1.61, P<0.00001) for >/=45 g per day alcohol. The relative risk of breast cancer increased by 7.1% (95% CI 5.5-8.7%; P<0.00001) for each additional 10 g per day intake of alcohol, i.e. for each extra unit or drink of alcohol consumed on a daily basis.(5) A further meta-analysis of 98 unique studies involving 75,728 and 60,653 cases in drinker versus non-drinker and dose-response analyses revealed an association with alcohol drinking by 22% (95% CI: 9-37%); each additional 10 g ethanol/day was associated with risk higher by 10% (95% CI: 5-15%). (4) Alcohol use may be more strongly associated with risk of hormone-sensitive breast cancers than hormone-insensitive subtypes, suggesting distinct etiologic pathways for these two breast cancer subtypes.(2,3) Alcohol consumption is consistently associated with increased breast density, which is associated with increase breast cancer risk. (6) Especially alcohol consumption before first pregnancy seems to be associated with increased risks of proliferative BBD and breast cancer. (6)

References:

Further information:

The preventive effect of physical exercise is explained by nonspecific immune stimulation and decreased estrogen levels during recovery and reduction of BMI. Most studies found that exercise, weight reduction, low-fat diet, and reduced alcohol intake were associated with a decreased risk of breast cancer. A review of 34 case-control and 28 cohort studies examined the different parameters of physical activity regarding the risk of breast cancer. Effect modification of this association by menopausal status, body mass index (BMI), racial group, family history of breast cancer, hormone receptor status, energy intake and parity were also considered.

Evidence for a risk reduction associated with increased physical activity was found in 47 (76%) of 62 studies with an average risk decrease of 25-30%. A dose-response effect existed in 28 of 33 studies. Stronger decreases in risk were observed for recreational activity, lifetime or later life activity, vigorous activity, among postmenopausal women, women with normal BMI, non-white racial groups, those with hormone receptor negative tumours, women without a family history of breast cancer and parous women. (2,3)

The metabolic equivalent of task (MET), or simply metabolic equivalent, is a physiological concept expressing the energy cost of physical activities as multiples of resting metabolic rate (RMR) and is defined as the ratio of metabolic rate (and therefore the rate of energy consumption) during a specific physical activity to a reference rate of metabolic rate at rest, set by convention to 3.5 ml O₂·kg⁻¹·min⁻¹ or equivalently 1 kcal·kg⁻¹·h⁻¹ or 4.184 kJ·kg⁻¹·h⁻¹. By convention 1 MET is considered as the resting metabolic rate obtained during quiet sitting. MET values of physical activities range from 0.9 (sleeping) to 18 (running at 17.5 km/h or a 5:31 mile pace). (http://en.wikipedia.org)

A meta-analysis of prospective studies regarding the association between physical activity and breast cancer risk confirmed the assumption, that physical activity could significantly reduce the risk of breast cancer. Overall, the combined relative risk (RR) with 95% CI of breast cancer was 0.88 (0.85-0.91) in 31 studies with 63,786 cases. In subgroup analysis by activity type, data from 27 studies including 37,568 cases for non-occupational activity (including recreational activity and household activity) and seven studies including 28,268 cases for occupational activity were used, and the RR (95% CI) of breast cancer was 0.87 (0.83-0.91) and 0.90 (0.83-0.97), respectively. The inverse association was consistent among all subgroups analyses. Stronger association was found for subjects with BMI <25 kg/m² [0.72 (0.65-0.81)], premenopausal women [0.77 (0.72-0.84)], and estrogen and progesterone receptor-negative breast cancer [0.80 (0.73-
Dose-response analysis suggested that the risk of breast cancer decreased by 2% (P < 0.00) for every 25 metabolic equivalent (MET)-h/week increment in non-occupational physical activity, 3% (P < 0.00) for every 10 MET-h/week (roughly equivalent to 4 h/week of walking in 2 miles/h or 1 h/week of running in 6 miles/h) increment in recreational activity, and 5% (P < 0.00) for every 2 h/week increment in moderate plus vigorous recreational activity, respectively. (4)

References:

Prevention by Modifying Life Style Risk Factors: Hormone Therapy in Postmenopausal Women (12/15)

Further information:

The use of (HRT) has been shown to be associated with increased risk of BC. For HRT, evidence from randomized controlled trials and observational studies has shown that women using post-menopausal hormone replacement therapy (HRT) are at an increased risk of BC (1,2,3) Moreover, the risk of BC associated with HRT is larger for users of combined HRT than for users of estrogen-only therapy, who may not be at increased risk at all. (1,4,5) In the Women's Health Initiative randomized, placebo-controlled trial, estrogen plus progestin was associated with greater breast cancer incidence, and the cancers were more commonly node-positive. Breast cancer mortality also appeared to be increased with combined use of estrogen plus progestin (1,4). In a Norwegian study current users had a risk twice as high as never-users. The use of combination therapy for more than five years tripled risk. Estradiol only use did not cause a statistically significant increase in risk (5).

According to a cohort study and metaanalysis the relative risks of invasive breast cancer in current users compared with never users of hormone therapy varied significantly according to tumour histology overall, the effects of hormone therapy on invasive ductal, lobular, and tubular cancer were generally greater for oestrogen-progestagen therapy than for oestrogen-only therapy, and were attenuated with increasing body-mass index (BMI) (3).

Studies from several countries show that the decline in the use of hormone therapy, following the publication of the WHI results, is followed by a decline in breast cancer incidence (5,6).

According to the results of the WHI randomized trials use of conjugated equine estrogens (CEE) alone (given only to women without uterus), younger women (aged 50-59 years) had more favorable results for all-cause mortality, myocardial infarction, and the global index. Absolute risks of adverse events (measured by the global index) per 10,000 women annually taking CEE plus MPA ranged from 12 excess cases for ages of 50-59 years to 38 for ages of 70-79 years; for women taking CEE alone, from 19 fewer cases for ages of 50-59 years to 51 excess cases for ages of 70-79 years. Quality-of-life outcomes had mixed results in both trials. Findings from the intervention and extended postintervention follow-up of the 2 WHI hormone therapy trials do not support use of this therapy for chronic disease prevention, although it is appropriate for symptom management in some women (7).
References:


<table>
<thead>
<tr>
<th>Menopausal Hormone Therapy Influence on Incidence and Related Mortality of Selected Cancer (Chlebowski et al SABCS 2010, abstr. S6-1)</th>
<th>E Alone</th>
<th>E+P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer Incidence</td>
<td>0.80 (0.62-1.04)</td>
<td>1.24 (1.01, 1.54)</td>
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<tr>
<td>Diagnosis</td>
<td>Death from</td>
<td>Incidence</td>
</tr>
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<td>-----------------</td>
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<tr>
<td>Colorectal Cancer</td>
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<td>1.12 (0.77, 1.63)</td>
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<td>NSCLC</td>
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<td>1.10 (0.74, 1.64)</td>
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</table>

Prevention - Hormone (EGC) in der Post-MP (13/15)

No further information

No references
Prevention by Modifying Life Style Risk Factors: Oral contraception (14/15)

Further information and references:

For the risk of use of oral contraceptives currently best comprehensive analysis can be obtained from:

Thus, we are citing the Conclusions of this paper:
“\[In a majority of studies there is no increase in the risk of breast cancer reported in OC users. When the RR was shown to be increased, this effect disappeared progressively after stopping OC use. Long duration of OC use at a young age before the FFTP seems to be the most important risk factor, as hormones act on a less differentiated tissue. The number of events attributable to OC use remains below 1% of the total breast cancers and 7% for premenopausal breast cancer if the RR of the Oxford meta-analysis is applied to calculate the attributable fraction of breast cancer in France (CGHFBC, 1996). The level of the increase in the RR is so low that it is not fully convincing and may have concerned the first generation of OC formulations. Although the modest and inconsistent associations may be attributable to variation in study design, it is also possible that they result from disease heterogeneity. Furthermore, significant involvement of screening or recall bias cannot be excluded (Marchbanks et al., 2002; Rosenberg et al., 2009; Shapiro, 2009). None of these studies has shown a role for the composition of OC on breast cancer risk. The possible, whereas currently unconfirmed, small increase in the risk of breast cancer in OC users with BRCA1/2 mutations is strongly counterbalanced by the benefits in terms of ovarian cancer protection.”

A recent systematic review concluded, that breast cancer incidence was slightly but significantly increased in OC users (OR, 1.08; CI, 1.00-1.17); results show a higher risk associated with more recent use of oral contraceptives. Risk of cervical cancer was increased with duration of oral contraceptive use in women with human papillomavirus infection. Colorectal cancer (OR, 0.86; CI, 0.79-0.95) and endometrial cancer incidences (OR, 0.57; CI, 0.43-0.77) were significantly reduced by oral contraceptive use. Compared with never use, ever use of oral contraceptives is significantly associated with decreases in colorectal and endometrial cancers and small increases in breast cancers (1).
A systematic review and meta-analysis on the association of oral contraceptives and risk of ovarian cancer and breast cancer among high-risk women (BRCA mutation carriers) suggest that associations between ever use of OCs and ovarian and breast cancer among women who are BRCA1 or BRCA2 mutation carriers are similar to those reported for the general population (2).


OC and Breast Cancer Risk (15/15)

No further information

No references
Breast Cancer Risk and Prevention
Breast Cancer Risk and Prevention

➤ **Versions 2003–2013:** Schmutzler with Albert / Blohmer / Fehm / Kiechle / Maass / Mundhenke / Thomssen

➤ **Version 2014:** Schmutzler / Rody
Principles in Prevention

• Women at increased risk for breast cancer are not considered *patients* but *healthy women* or *counselors*

• A comprehensive informed consent taking into consideration all potential side effects and risks is warranted prior to offering preventive measures

• Highest priority: „First, do no harm!“

*(Primum nil nocere)*
Who Should be Tested for BRCA1/2 Mutations?

Oxford LoE: 2b    GR: B    AGO: ++

Families with
at least three women with breast cancer independent of age or
at least two women with breast cancer, one < 51 yrs. or
at least one woman affected by breast and one by ovarian cancer or
at least one woman affected by breast and ovarian cancer or
at least two women affected by ovarian cancer or
at least one woman affected by bilateral breast cancer, first < 51 yrs. or
at least one woman affected by breast cancer < 36 yrs. or
at least one man affected by breast cancer and one additional relative
affected by breast or ovarian cancer* #

* in one side of the family

#Inclusion criteria of the German Consortium of Hereditary Breast and Ovarian Cancer (GCHBOC) based on a mutation detection rate ≥ 10% in ~17,000 families tested by 2013
Recruitment of the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC) up to 2013
### Suggested Use of a Screening Checklist *

**Checkliste zur Erfassung einer möglichen erblichen Belastung für Brust- und/oder Eierstockkrebs**

<table>
<thead>
<tr>
<th>Name der Patientin:</th>
<th>Geburtsdatum:</th>
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</table>

#### A. Patientin und deren Geschwister / Kinder

<table>
<thead>
<tr>
<th>Auftreten</th>
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<tr>
<td>eines Mamma-Karzinoms bei der Patientin vor dem 36. LJ</td>
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**Summe Patientin / Geschwister / Kinder**

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#### B. Mütterliche Linie

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<tr>
<td>eines Ovarial-/Tubenkarzinoms oder einer primären Peritonealkarzinose bei einer Angehörigen</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Summe mutterliche Linie**

<table>
<thead>
<tr>
<th></th>
<th>B</th>
</tr>
</thead>
</table>

#### C. Väterliche Linie

<table>
<thead>
<tr>
<th>Auftreten</th>
<th>Anzahl</th>
<th>Gewichtung</th>
<th>Ergebnis</th>
</tr>
</thead>
<tbody>
<tr>
<td>eines Mamma-Karzinoms bei einer Angehörigen vor dem 36. LJ</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines unilateralen Mamma-Karzinoms bei einer Angehörigen vor dem 51. LJ</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines bilateralen Mamma-Karzinoms bei einer Angehörigen, das erst vor dem 51. LJ</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines uni- oder bilateralen Mamma-Karzinoms bei einer Angehörigen nach dem 50. LJ</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines Mamma-Karzinoms bei einem angehörigen Mann</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines Ovarial-/Tubenkarzinoms oder einer primären Peritonealkarzinose bei einer Angehörigen</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Summe väterliche Linie**

<table>
<thead>
<tr>
<th></th>
<th>C</th>
</tr>
</thead>
</table>

#### D. Der höhere Wert aus B und C

<table>
<thead>
<tr>
<th></th>
<th>D</th>
</tr>
</thead>
</table>

#### E. Summe aus A und D = Risiko-Score

<table>
<thead>
<tr>
<th></th>
<th>A + D</th>
</tr>
</thead>
</table>

*online tool provided by the Ärztekammer Westfalen-Lippe based on the inclusion criteria of the GC-HBOC [www.aekwl.de/brustzentren-download](http://www.aekwl.de/brustzentren-download)
Variants of Unknown Significance (VUS): 5-30% of all BRCA1/2 Mutations Detected

Proposed Classification System for Sequence Variants Identified by Genetic Testing

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Probability of being pathogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Definitely pathogenic</td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>4</td>
<td>Likely pathogenic</td>
<td>0.95-0.99</td>
</tr>
<tr>
<td>3</td>
<td>Uncertain</td>
<td>0.05-0.949</td>
</tr>
<tr>
<td>2</td>
<td>Likely not pathogenic or of little clinical significance</td>
<td>0.001-0.049</td>
</tr>
<tr>
<td>1</td>
<td>Not pathogenic or of no clinical significance</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Testing Recommendations Associated With Each Class of Variant

<table>
<thead>
<tr>
<th>Class</th>
<th>Clinical testing</th>
<th>Surveillance recommendations if at-risk relative is positive</th>
<th>Research testing of family members</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Test at-risk relatives for variant</td>
<td>Full high-risk surveillance guidelines</td>
<td>Not indicated</td>
</tr>
<tr>
<td>4</td>
<td>Test at-risk relatives for variant*</td>
<td>Full high-risk surveillance guidelines</td>
<td>May be helpful to further classify variant</td>
</tr>
<tr>
<td>3</td>
<td>Do not use for predictive testing in at-risk relatives*</td>
<td>Based on family history (and other risk factors)</td>
<td>May be helpful to further classify variant</td>
</tr>
<tr>
<td>2</td>
<td>Do not use for predictive testing in at-risk relatives*</td>
<td>Treat as “no mutation detected” for this disorder</td>
<td>May be helpful to further classify variant</td>
</tr>
<tr>
<td>1</td>
<td>Do not use for predictive testing in at-risk relatives*</td>
<td>Treat as “no mutation detected” for this disorder</td>
<td>Not indicated</td>
</tr>
</tbody>
</table>

*Recommend continuing to test proband for any additional testing modalities available for the disorder in question; e.g., rearrangement testing.

(Plon et al., Human Mutation, 2008)
VUS: Problems and Questions

- Most VUS are **private** (>60%) or **extremely rare** (≤3, >80%)
- Additional analyses required, e.g. in vitro splicing assay, functional assay, segregation analysis, co-occurrence analysis, large case / control studies
- *in silico* prediction tools (PolyPhen2, SIFT) are not adequate for clinical decision making
- VUS classification and clinical decision making are not standardized
State of the Art
Unexplained Heritability: Oligogenic Traits and Genetic Heterogeneity

- high risk genes (OR >5.0)
  \(BRCA1/2\)
- moderately penetrant risk genes (OR 1.5 - 5.0)
  \(RAD51C, ATM, BRIP1, CDH1, CHEK2, NBN, PALB2, PTEN\ldots\)
- low risk variants / modifiers (OR/HR <1.5)
  \(FGFR2, TOX3, 2q35, 11q15, SLC4A7, 5p12, MAP3K1\ldots\)

Contribution of known genes to familial aggregation of breast cancer

Other genes familial risk factors
79 common SNPs
Non BRCA-associated Hereditary Cancer Syndromes with Increased Risk for Breast Cancer

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene alteration</th>
<th>Lifetime Risk BC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li Fraumeni</td>
<td>p53</td>
<td>~ 50 %&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cowden</td>
<td>PTEN</td>
<td>~ 25 %&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hereditary diffuse gastric cancer syndrome</td>
<td>CDH1</td>
<td>~40-50 % (lobular)&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Peutz-Jeghers Syndrome</td>
<td>STK11/ LKB1</td>
<td>~45-50 %&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ovary: ~20 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cervix: ~10 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uterus: ~10 %</td>
</tr>
<tr>
<td>Lynch</td>
<td>mismatch repair MLH1, MSH2, MSH6, PMS2</td>
<td>up to twofold increased risk compared to general population&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endometrial: ~25-60 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ovary: up to 25 %</td>
</tr>
</tbody>
</table>

Recommendation: genetic counselling: GCP
Germ-line mutations in breast and ovarian cancer pedigrees establish
RAD51C as a human cancer susceptibility gene

Nature Genetics April 18, 2010

Alfons Meindl¹, Heide Hellebrand¹, Constanze Wick², Verena Erven³, Barbara Wappenschmidt³, Dieter Niederacher⁴, Marcel Freund⁵, Peter Lichtner⁵, Linda Hartmann⁶, Heiner Schaal⁶, Juliane Ramser¹, Ellen Honisch⁴, Christian Kubisch⁷, Hans E. Wichmann⁸, Karin Kast⁹, Helmut Deißler¹⁰, Christoph Engel¹¹, Bertram Müller-Myhsok¹², Kornelia Neveling¹³, Marion Kiechle¹, Christopher G. Mathew¹⁴, Detlev Schindler¹³, Rita K. Schmutzler³, Helmut Hanenberg⁷,¹⁵

• 1,100 BRCA1/2 negative risk families:
  670 breast only, 430 breast and ovarian cancer
• 6 deleterious mutations in BC/OC families only (1.5%)
# Available, Non-validated Breast Cancer Gene Panels for Risk Prediction

<table>
<thead>
<tr>
<th>Gene Panel</th>
<th>Available for</th>
<th>Non-validated breast cancer gene panels for risk prediction</th>
</tr>
</thead>
<tbody>
<tr>
<td>BROCA 40 gene panel</td>
<td>cross-cancer</td>
<td><a href="http://www.ago-online.de">http://www.ago-online.de</a></td>
</tr>
<tr>
<td>AMBRY Genetics BreastNext (16 genes)</td>
<td><a href="http://www.ambrygen.com/tests/breastnext">http://www.ambrygen.com/tests/breastnext</a></td>
<td></td>
</tr>
<tr>
<td>CEGAT CAN02: Brust- und Ovarialkarzinom (30 genes)</td>
<td><a href="http://www.cegat.de/Tumorerkrankungen_171.html">http://www.cegat.de/Tumorerkrankungen_171.html</a></td>
<td></td>
</tr>
<tr>
<td>CENTOGENE BC/OC panel (16 genes)</td>
<td><a href="https://www.centogene.com/centogene">https://www.centogene.com/centogene</a></td>
<td></td>
</tr>
<tr>
<td>MYRIAD myRISK Panel (25 genes)</td>
<td><a href="http://www.ago-online.de">http://www.ago-online.de</a></td>
<td></td>
</tr>
</tbody>
</table>
## Low risk Variants from Genome Wide Association Studies (GWAS)

<table>
<thead>
<tr>
<th>Locus</th>
<th>SNP</th>
<th>Häufigkeit</th>
<th>TOTAL BCAC</th>
<th>Odds Ratio</th>
<th>P-trend</th>
<th>FRR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGFR2</td>
<td>rs2981582</td>
<td>38%</td>
<td>1.24</td>
<td>5x10⁻⁸⁷</td>
<td>1.6%</td>
<td></td>
</tr>
<tr>
<td>TOX3</td>
<td>rs3803662</td>
<td>25%</td>
<td>1.21</td>
<td>8x10⁻⁵²</td>
<td>1.1%</td>
<td></td>
</tr>
<tr>
<td>2q35</td>
<td>rs13387042</td>
<td>51%</td>
<td>1.12</td>
<td>3x10⁻³⁴</td>
<td>0.5%</td>
<td></td>
</tr>
<tr>
<td>11q15</td>
<td>rs614367</td>
<td>15%</td>
<td>1.20</td>
<td>5x10⁻¹⁶</td>
<td>0.5%</td>
<td></td>
</tr>
<tr>
<td>SLC4A7</td>
<td>rs4973768</td>
<td>46%</td>
<td>1.11</td>
<td>4x10⁻²³</td>
<td>0.4%</td>
<td></td>
</tr>
<tr>
<td>5p12</td>
<td>rs10941679</td>
<td>26%</td>
<td>1.12</td>
<td>4x10⁻²³</td>
<td>0.4%</td>
<td></td>
</tr>
<tr>
<td>MAP3K1</td>
<td>rs889312</td>
<td>28%</td>
<td>1.11</td>
<td>3x10⁻²⁰</td>
<td>0.3%</td>
<td></td>
</tr>
<tr>
<td>8q24</td>
<td>rs13281615</td>
<td>40%</td>
<td>1.10</td>
<td>8x10⁻¹⁵</td>
<td>0.3%</td>
<td></td>
</tr>
<tr>
<td>CASP8</td>
<td>rs1045485</td>
<td>13%</td>
<td>0.9</td>
<td>2x10⁻⁸</td>
<td>0.2%</td>
<td></td>
</tr>
<tr>
<td>ESR1</td>
<td>rs2046210</td>
<td>33%</td>
<td>1.09</td>
<td>2x10⁻¹⁵</td>
<td>0.2%</td>
<td></td>
</tr>
<tr>
<td>LSP1</td>
<td>rs3817198</td>
<td>30%</td>
<td>1.08</td>
<td>5x10⁻¹¹</td>
<td>0.2%</td>
<td></td>
</tr>
<tr>
<td>1p11.2</td>
<td>rs11249433</td>
<td>39%</td>
<td>1.10</td>
<td>7x10⁻¹⁰</td>
<td>0.2%</td>
<td></td>
</tr>
<tr>
<td>ZNF365</td>
<td>rs10995190</td>
<td>15%</td>
<td>0.88</td>
<td>4x10⁻¹⁵</td>
<td>0.2%</td>
<td></td>
</tr>
<tr>
<td>ZMIZ1</td>
<td>rs704010</td>
<td>39%</td>
<td>0.92</td>
<td>3x10⁻⁸</td>
<td>0.1%</td>
<td></td>
</tr>
<tr>
<td>CDKN2A/B</td>
<td>rs1011970</td>
<td>17%</td>
<td>1.08</td>
<td>7x10⁻⁸</td>
<td>0.09%</td>
<td></td>
</tr>
<tr>
<td>COX11</td>
<td>rs6504950</td>
<td>27%</td>
<td>0.95</td>
<td>10⁻⁸</td>
<td>0.07%</td>
<td></td>
</tr>
<tr>
<td>ANKRD16</td>
<td>rs2380205</td>
<td>43%</td>
<td>0.98</td>
<td>4x10⁻⁷</td>
<td>0.01%</td>
<td></td>
</tr>
<tr>
<td>RAD51L1</td>
<td>rs999737</td>
<td>24%</td>
<td>0.94</td>
<td>2x10⁻⁷</td>
<td>0.01%</td>
<td></td>
</tr>
</tbody>
</table>
Low Risk Variants as Modifiers

Retrospective

Gaudet et al., in coop with GC-HBOC 2013: Combined genotype distribution of 14 variants in 8,221 BRCA2 mutation carriers (FGFR2, TOX3, 12p11, 5q11, CDKN2A/B, LSP1, 8q24, ESR1, ZNF365, 3p24, 12q24, 5p12, 11q13)

- Couch et al. in coop with the GC-HBOC 2013: Combined genotype distribution of 10 variants in 11,705 BRCA1 mutation carriers (1q32, 10q25.3, 19p13, 6q25.1, 12p11, TOX3, 2q35, LSP1, RAD51L1, TERT)
- 5% of BRCA1 carriers at lowest risk (28–50%) compared to the 5% at highest risk (81–100%)

Prospective

Mavaddat et al., 2013: combined genotype distribution of 7 low-risk SNP in 909 BRCA2 carriers

BRCA2 carriers at the highest tertile of the score distribution were at significantly higher risk than women at the lowest tertile (HR = 4.1, 95%; CI = 1.2 to 14.5; P = .02)´

first ´proof of principle´

Associations are breast cancer subtype specific

Garcia-Closas et al., Clin Cancer Res, 2008
Genetically Defined Subtypes are Distinct Tumor Entities

Distinct genetic subtypes of breast cancer may show distinct clinical features. Prior to the offer of prophylactic measures the following questions should be addressed:

• Typical histopathological features?
• Sensitivity to current screening modalities?
• Better survival of early detected tumors?
• Natural disease course?
• Response to anti-tumor therapy?

Genotype-phenotype-correlations must be employed
Current Clinical Impact of Other Risk Genes

The remaining cancer susceptibility is most likely be transmitted by an oligo- or polygenic trait of moderate and low risk genes and alleles.

Moderate risk genes such as *RAD51C* exhibit very low mutation detection rates and may be associated with specific tumor subtypes.

Low risk variants confer only small risk elevations and also seem to be associated with specific tumor subtypes. Potential multiplicative effects that may be relevant for risk stratification and the provision of clinical prevention strategies remain to be elucidated.

Therefore genetic testing of moderate and low risk genes and variants should only be performed within large prospective cohort studies like the German Consortium for Hereditary Breast and Ovarian Cancer GC-HBOC.

Clinical genetic testing for *RAD51C; CHEK2*
and/or other moderate risk genes, e.g. gene panels

Clinical genetic testing for low risk variants

Referral to centres of the GC-HBOC
or cooperating centres

<table>
<thead>
<tr>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical genetic testing for <em>RAD51C; CHEK2</em></td>
<td>2b B -</td>
</tr>
<tr>
<td>Clinical genetic testing for low risk variants</td>
<td>3b D --</td>
</tr>
<tr>
<td>Referral to centres of the GC-HBOC</td>
<td>5 D ++</td>
</tr>
</tbody>
</table>
Requirements for the Introduction of New Diagnostic or Predictive Genetic Testing

- The risk collective is clearly defined by risk criteria
- The positive predictive value of risk criteria with respect to the identification of the genetic risk factor is known
- The cut-off values for genetic testing evolved through a transparent consensus process
- The genetic test is valid and reliable
- A spectrum bias is excluded or defined
- A clinical prevention strategy exists that leads to early detection or prevention and mortality reduction of the genetically defined subset of the disease
Non Directive Counseling for the Uptake of Preventive Measures

- According to the Genetic Diagnostic Law
- According to the Medical Devices Act, e.g. risk assessment requires professional training and expertise
- Communicate absolute risks within a manageable timeframe
- Communicate competing risks, e.g. risk of progressive disease in relation to the risk of a secondary primary in case women have already been affected by primary breast cancer
- Allow for appropriate time for consideration
Definition of Women at Moderate to High Risk

- Deleterious mutation in the BRCA1, BRCA2
- Heterozygous risk of $\geq 20\%$ or remaining lifetime risk of $\geq 30\%$ acc. to a validated standard risk prediction model
- Childhood cancer survivors after chest irradiation in adolescence (e.g. Hodgkin disease)

<table>
<thead>
<tr>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a A ++</td>
<td></td>
</tr>
<tr>
<td>2b B +</td>
<td></td>
</tr>
<tr>
<td>2a B ++</td>
<td></td>
</tr>
</tbody>
</table>
Surveillance Program for Women with Deleterious BRCA-mutations*

Multimodal intensive surveillance program

For the detection of early stage breast cancers

- Clinical breast exam >=25 years semi-annually
- Sonography >=25 years semi-annually
- Mammography >=40 years biannual
- Breast MRI >=25 years annual

For mortality reduction

5 D +

*Referral to centres of the GC-HBOC or cooperating centres is recommended
Modified Surveillance Program for BRCA-neg. Women at Moderate to High Risk or Survivors of Hodgkin Disease

Rationale:

- Increased risk of breast cancer after chest irradiation because of Hodgkin lymphoma in childhood (8-18 years)
- Increased risk of breast or ovarian cancer in women from BRCA1/2 negative families at risk that is, however, lower than in women from BRCA1/2 positive families
- Referral to centres of the GC-HBOC or cooperating centres for the evaluation of structured surveillance and follow-up
Surgical Prevention for Healthy BRCA1/2 Mutation Carriers

• Risk-reducing bilateral salpingo-oophorectomy (RR-BSO, PBSO) around 40 years of age reduces OvCa incidence and mortality.

• Risk-reducing bilateral mastectomy (RR-BM, PBM) reduces BrCa incidence and mortality.

RR-BSO is performed after completion of family planning.

RR-BM revealed a high incidence of premalignant lesions.

Oxford / AGO LoE / GR

2a B ++*

2a B +*

*Study participation recommended
Risk-reducing Interventions for BRCA1/2 Mutation Carriers Affected by Breast Cancer

- **Bilateral salpingo-oophorectomy (RR-BSO)**
  - Reduces OvCa incidence and mortality
  - Reduces BrCa mortality
  - Reduces overall mortality
  (contradictory results for reduction of cl BrCa incidence)

- **Bilateral mastectomy+ (RR-BM)**
  - Reduces cl BrCa incidence

- **Tamoxifen (reduces cl BrCa incidence)**

- **Indication for PBM should consider age at onset of first breast cancer and the affected gene**
  - Overall prognosis has to be considered

---

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Grade</th>
<th>Evidence</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral salpingo-oophorectomy (RR-BSO)</td>
<td>2b</td>
<td>B</td>
<td>+*</td>
</tr>
<tr>
<td>Bilateral mastectomy+ (RR-BM)</td>
<td>2b</td>
<td>B</td>
<td>+/-*</td>
</tr>
<tr>
<td>Tamoxifen (reduces cl BrCa incidence)</td>
<td>2b</td>
<td>B</td>
<td>+/-*</td>
</tr>
<tr>
<td>Indication for PBM should consider age at onset of first breast cancer and the affected gene</td>
<td>2a</td>
<td>B</td>
<td>++*</td>
</tr>
</tbody>
</table>

*Study participation recommended*
## Table 4. Risk-Reducing Salpingo-oophorectomy and All-Cause Mortality

<table>
<thead>
<tr>
<th>Risk-reducing salpingo-oophorectomy</th>
<th>All Eligible Women</th>
<th>No Prior Breast Cancer$^b$</th>
<th>Prior Breast Cancer$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n = 2462)</td>
<td>BRCA1 (n = 1587)</td>
<td>BRCA2 (n = 895)</td>
</tr>
<tr>
<td>Yes</td>
<td>993 (40.0)</td>
<td>706 (44.5)</td>
<td>287 (32.1)</td>
</tr>
<tr>
<td></td>
<td>Deaths</td>
<td>31 (3.1)</td>
<td>25 (3.5)</td>
</tr>
<tr>
<td>No</td>
<td>1469 (60.0)</td>
<td>881 (55.5)</td>
<td>608 (67.9)</td>
</tr>
<tr>
<td></td>
<td>Deaths</td>
<td>146 (6.8)</td>
<td>93 (10.6)</td>
</tr>
<tr>
<td>Age, mean (range), y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At time of risk-reducing oophorectomy</td>
<td>45.4 (20.5-79.0)</td>
<td>44.5 (20.5-79.0)</td>
<td>47.6 (30.4-72.9)</td>
</tr>
<tr>
<td>At start of follow-up for those without oophorectomy</td>
<td>39.8 (18.1-90.4)</td>
<td>38.5 (18.2-90.4)</td>
<td>41.6 (18.1-90.4)</td>
</tr>
<tr>
<td>Follow-up, mean (range), y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>To death</td>
<td>6.0 (0.5-23.5)</td>
<td>5.9 (0.5-22.3)</td>
<td>6.2 (0.5-23.5)</td>
</tr>
<tr>
<td>To censoring</td>
<td>5.0 (0.5-27.9)</td>
<td>5.0 (0.5-27.7)</td>
<td>4.9 (0.5-27.9)</td>
</tr>
<tr>
<td>All-cause mortality after risk-reducing salpingo-oophorectomy, HR (95% CI)$^d$</td>
<td>0.40 (0.26-0.61)</td>
<td>0.38 (0.24-0.62)</td>
<td>0.52 (0.22-1.23)</td>
</tr>
<tr>
<td>Age &lt;50 y</td>
<td>0.41 (0.25-0.67)</td>
<td>0.40 (0.24-0.68)</td>
<td>0.16 (0.02-1.30)</td>
</tr>
<tr>
<td>Age ≥50 y</td>
<td>0.37 (0.15-0.94)</td>
<td>0.22 (0.06-0.85)</td>
<td>0.47 (0.12-1.80)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.

$^a$Values are expressed as number (percentage) unless otherwise indicated. Participants were censored at last contact.

$^b$There were no breast cancer cases prior to risk-reducing salpingo-oophorectomy in those who did not undergo salpingo-oophorectomy prior to the start of follow-up.

$^c$Breast cancer allowed prior to risk-reducing salpingo-oophorectomy or start of follow-up.

$^d$Adjusted for age, year of birth, attained education, and stratified by center.
### Table 2 Cumulative risks (in %) and 95% confidence intervals (in parentheses) for contralateral breast cancer depending on age at first breast cancer observed in relatives of index patients.

<table>
<thead>
<tr>
<th>Age at first breast cancer</th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>BRCA negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 years after first breast cancer</td>
<td>14.1 (10.1-18.0)</td>
<td>2.9 (0.0-6.3)</td>
<td>4.8 (2.6-6.9)</td>
</tr>
<tr>
<td>10 years after first breast cancer</td>
<td>30.1 (24.0-36.2)</td>
<td>18.2 (7.9-28.5)</td>
<td>10.6 (6.8-14.4)</td>
</tr>
<tr>
<td>15 years after first breast cancer</td>
<td>40.8 (33.2-48.3)</td>
<td>20.9 (9.7-32.1)</td>
<td>15.3 (10.4-20.3)</td>
</tr>
<tr>
<td>25 years after first breast cancer</td>
<td>55.1 (45.4-64.9)</td>
<td>38.4 (18.5-58.2)</td>
<td>28.4 (20.5-36.3)</td>
</tr>
<tr>
<td>40-49 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 years after first breast cancer</td>
<td>9.2 (5.8-12.5)</td>
<td>6.9 (2.7-11.1)</td>
<td>4.2 (2.9-5.5)</td>
</tr>
<tr>
<td>10 years after first breast cancer</td>
<td>16.7 (11.7-21.7)</td>
<td>13.4 (7.0-19.8)</td>
<td>8.4 (6.3-10.5)</td>
</tr>
<tr>
<td>15 years after first breast cancer</td>
<td>23.2 (16.9-29.6)</td>
<td>22.0 (12.1-31.9)</td>
<td>10.7 (8.1-13.3)</td>
</tr>
<tr>
<td>25 years after first breast cancer</td>
<td>44.5 (33.2-55.7)</td>
<td>40.5 (22.4-58.6)</td>
<td>18.1 (13.9-22.3)</td>
</tr>
<tr>
<td>≥ 50 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 years after first breast cancer</td>
<td>7.1 (3.8-10.5)</td>
<td>3.5 (0.9-6.1)</td>
<td>3.6 (2.7-4.5)</td>
</tr>
<tr>
<td>10 years after first breast cancer</td>
<td>11.4 (6.5-16.3)</td>
<td>10.4 (4.9-16.0)</td>
<td>5.5 (4.3-6.7)</td>
</tr>
<tr>
<td>15 years after first breast cancer</td>
<td>18.7 (11.0-20.6)</td>
<td>15.5 (7.8-23.3)</td>
<td>8.1 (6.3-9.9)</td>
</tr>
<tr>
<td>25 years after first breast cancer</td>
<td>21.6 (12.3-30.8)</td>
<td>15.5 (7.8-23.3)</td>
<td>12.9 (9.9-17.0)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 years after first breast cancer</td>
<td>10.4 (8.3-12.5)</td>
<td>4.5 (2.5-6.5)</td>
<td>3.9 (3.2-4.6)</td>
</tr>
<tr>
<td>10 years after first breast cancer</td>
<td>20.4 (17.1-23.7)</td>
<td>13.2 (9.2-17.2)</td>
<td>7.1 (6.0-8.2)</td>
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</tr>
<tr>
<td>25 years after first breast cancer</td>
<td>44.1 (37.6-50.6)</td>
<td>33.5 (22.4-44.7)</td>
<td>17.2 (14.5-19.9)</td>
</tr>
</tbody>
</table>
### Therapy of BRCA1/2-associated Breast Cancer+

**Limited prospective cohort studies with short follow-up time**

- **Breast conserving therapy:**
  - Adequate local tumor control (10 years observation)  
    - Oxford / AGO LoE / GR: 2a B +

- **Systemic therapy according to sporadic breast cancer**  
  - Oxford / AGO LoE / GR: 3a B +

- **BRCA1 mutation status is predictive for chemotherapy response**  
  - Oxford / AGO LoE / GR: 3b B +

- **Platinum-based regimens**  
  - Oxford / AGO LoE / GR: 3 B +/-*

- **PARP inhibitor in breast cancer**  
  - Oxford / AGO LoE / GR: 2b D +/-*

  + Overall prognosis has to be considered

*Study participation recommended*
Cooperation of Certified Breast Centres (BC) with Specialized Centres of the GC-HBOC

Check list (inclusion criteria)

Counselling and testing

Communication, Exchange, Advice

BC

Spec. BC

Prophylactic surgery

Indication for prophylactic surgery
Medical Prevention for Women at Increased Risk

• Tamoxifen for women > 35 years
  Reduction of invasive BrCA, DCIS, and LN

• Raloxifene for postmenopausal women
  Reduction of invasive BrCa only

• AI for postmenopausal women

#Significant risk reduction was seen for anastrozole for ovarian and endometrial cancer, as well as skin, colorectal, hematologic, thyroid and urinary tract cancers

Chemopreventive regimes should only be offered after individual and comprehensive counseling. The net benefit strongly depends on risk status, age and pre-existing risk factors for side effects.

*Risk situation as defined in NSABP P1-trial (1.66% in 5 years)
Risk Reduction for Ipsi- and Contralateral Breast Cancer

Rationale: Women with breast cancer have an increased risk for a second primary

- Tamoxifen*
- Aromatase inhibitors*
- Suppression of ovarian function* + Tamoxifen

*Only proven for ER/PgR-positive primary sporadic BrCa

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a A +</td>
</tr>
<tr>
<td>1a A +</td>
</tr>
<tr>
<td>1b B +</td>
</tr>
</tbody>
</table>
Breast Cancer Risk and Prevention (2/29)

Further information:

Literature from PUBMED, ASCO- and SABCS-abstracts

No references
Principles in Prevention (3/29)

No further information

No references
Who Should be Tested for BRCA1/2 Mutations? (4/29)

No further information

References:

2. German Consortium for Hereditary Breast and Ovarian Cancer, personal communication of up-dated numbers. Molecular genetic testing is recommended for the above listed families in which the mutation probability exceeds 10%.
Recruitment of the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC) up to 2013 (5/29)

No further information

No references
Use of a Screening Checklist (6/29)

No further information

References:

www.aekwl.de/brustzentren-download
Variants of Unknown Significance (VUS): 5-30% of all BRCA1/2 Mutations Detected (7/29)

No further information

References:

Plon et al., Human Mutation, 2008
e.g. Guidugli et al. 2013
No further information

No references
State of the Art: Unexplained Heritability: Oligogenic Traits and Genetic Heterogeneity (9/29)

No further information

No references
Non BRCA-associated Hereditary Cancer Syndromes with Increased Risk for Breast Cancer (10/29)

No further information

References:

2. Tan et al., Lifetime cancer risks in individuals with germline PTEN mutations, Clin Cancer Res. 2012 Jan 15;18(2):400-7
Third Moderate to High Risk Gene Identified within the GC-HBOC (11/29)

No further information

References:


Available, non-validated Breast Cancer Gene Panels for Risk Prediction (12/29)

No further information

References:

Low Risk Variants from Genome Wide Association Studies (GWAS) (13/29)

No further information

References:

**Low Risk Variants as Modifier (14/29)**

*No further information*

Low Risk Variants as Modifiers (retrospective)

*References:*


Low Risk Variants as Modifiers (prospective)

*References:*

1. Mavaddat et al. 2013
Genetically Defined Subtypes are Distinct Tumor Entities (15/29)

No further information

References:

Current Clinical Impact of Other Risk Genes (16/29)

No further information

References:

Requirements for the Introduction of New Diagnostic or Predictive Genetic Testing (17/29)

No further information

References:

Non Directive Counseling for the Uptake of Preventive Measures (18/29)

No further information

No references
Definition of Women at Moderate to High Risk (19/29)

No further information

References:

**Surveillance Program for Women with deleterious BRCA-mutations (20/29)**

*Further information:*


These guidelines are in close agreement with the NICE-guidelines on Great Britain (McIntosh A et al.: Clinical Guidelines and evidence review for the classification and care of women at risk of familial breast cancer. London: national Collaborating Centre for Primary Care/University of Sheffield, 2004).

The surveillance program allows the detection of early stage breast carcinomas (MARIBS study group Lancet 2005, Kriege et al. NEJM 2004, Warner et al. JAMA 2004, Kuhl, Schmutzler et al. 2000 ). However, no data exist so far on long term follow-up and mortality reduction.


*References:*

**Modified Surveillance Program for BRCA-neg. Women at Moderate to High Risk or Survivors of Hodgkin Disease**

**No further information**

**References:**

5. Leach MO et al. Lancet 2005
**Surgical Prevention for Healthy BRCA1/2 Mutation Carriers (22/29)**

**Further information:**

Prophylactic bilateral salpingo-oophorectomy (PBSO) reduces the risk for ovarian cancer in BRCA1/2 mutation carriers to >95% and the risk for breast cancer to 50% (Kauff et al NEJM 2002, Rebbeck et al. NEJM 2002). Short term HRT does not negate the protective effect of PBSO on subsequent breast cancer risk (Rebbeck et al. 2005). The residual risk for peritoneal cancer after PBSO accumulates to 3.5% after 20 years of follow up (Casey et al. Gynecol Oncol 2005). Moreover, PBSO improves overall survival of mutation carriers (Domchek et al. The Lancet 2006). These studies support the current strategy of the German consortium to recommend PBSO in mutation carriers after completion of childbearing around the age of 40.

Prophylactic bilateral mastectomy (PBM) reduces the risk of breast cancer in BRCA1/2 mutation carriers by >95% (Meijers-Heijboer et al. NEJM 2001, Rebbeck et al. JCO 2004) and may be performed in these women after the age of 25. However, only few women opt for this intervention.

For women at high risk defined as having a heterozygote risk of >20% or a life time risk of >30% and in whom genetic analysis is not possible or not informative the beneficial effect of preventive surgery is not clear and requires an individualized strategy. Premalignant lesions of the breast develop especially over the age of 40 (Hoogerbrugge N et al. Eur J Cancer 2006). A recent cohort study proved a breast cancer specific, ovarian cancer specific and overall survival benefit for PBSO (Domchek et al. Lancet Oncology 2006).

The German Consortium for Hereditary Breast and Ovarian Cancer has developed guidelines for prophylactic surgery. Prophylactic surgery should be preceded by interdisciplinary counselling and, if possible, genetic testing within a familial breast cancer centre (addresses are deposited at www.deutsche-krebshilfe.de)
References:

2. Kauff et al NEJM 2002
3. Rebbeck et al. NEJM 2002
4. Domcheck et al. 2006
5. Meijers-Heijboer et al. 2001
6. Rebbeck et al. 2004
7. Hoogerbrugge et al. 2006
8. Domcheck et al. 2010
9. Sitzmann et al., JAMA Surg 2013
**Risk-reducing Interventions for BRCA1/2 Mutation Carriers Affected by Breast Cancer (23/29)**

*No further information*

**References:**

2. Pierce-LJ JCO 2006  
3. Graeser et al. JCO 2009  
4. Domcheck et al. 2006, 2010  
5. Rhiem et al. 2012

Rhiem K, Engel C, Graeser M, et al.. The risk of contralateral breast cancer in patients from BRCA1/2 negative high risk families as compared to patients from BRCA1 or BRCA2 positive families: a retrospective cohort study. Breast Cancer Res. 2012 Dec 7;14(6):R156.  
Risk-reducing Salpingo-oophorectomy and All-cause Mortality (24/29)

No further information

References:

Contralateral Cancer Risk in 6235 BRCA1/2 Positive and Negative Patients (retrospektive) (25/29)

No further information

No references
Therapy of BRCA1/2-associated Breast Cancer+ (26/29)

No further information

References:

2. Metcalfe et al. JCO 2004
3. Pierce L. et al. JCO 2006
4. Metcalfe et al. Gynecol Oncol 2005
5. Tassone et al. BJC 2003
9. Rottenberg et al. 2008
10. Ashworth et al. JCO 2008
11. Rottenberg et al. PNAS 2008
12. Fong et al. NEJM 2009
15. Tutt et al. Lancet 2010
16. Robson et al. BCR 2004
Cooperation of Certified Breast Centres (BC) with Specialized Centres of the GC-HBOC (27/29)

No further information

No references
Medical Prevention for Women at Increased Risk (28/29)

No further information

References:

1. NSABP-P1 (Tamoxifen): Fischer B et al JNCI 1998
2. Star (Raloxifen): Vogel VG et al. JAMA 2006
Risk Reduction for Ipsi- and Contralateral Breast Cancer (29/29)

No further information

No references
Early Detection and Diagnosis

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

Guidelines Breast
Version 2014.1
Early Detection and Diagnosis

Versions 2005–2013:

Albert / Blohmer / Fersis / Junkermann / Maass / Scharl / Schreer

Version 2014:

Schreer / Blohmer
# Early Detection Mammography

<table>
<thead>
<tr>
<th>Age</th>
<th>Interval</th>
<th>LOE /</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40</td>
<td>na</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>40–50</td>
<td>12–18</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>50–70*</td>
<td>24</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>&gt;70</td>
<td>24</td>
<td>4</td>
<td>C</td>
<td>+</td>
</tr>
</tbody>
</table>

* National Mammography-Screening-Program
## Breast Cancer Mortality Reduction

<table>
<thead>
<tr>
<th>Metaanalyses</th>
<th>RR 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Independent UK Panel, 2012</strong></td>
<td></td>
</tr>
<tr>
<td>13-year metaanalysis</td>
<td>0.80 (0.73–0.89)</td>
</tr>
<tr>
<td><strong>Cochrane Review, 2011</strong></td>
<td></td>
</tr>
<tr>
<td>Fixed-effect metaanalysis of 9 RCT-trials</td>
<td>0.81 (0.74–0.87)</td>
</tr>
<tr>
<td>As above, but excluding women &lt;50 years</td>
<td>0.77 (0.69–0.86)</td>
</tr>
<tr>
<td><strong>US Task Force, 2009</strong></td>
<td></td>
</tr>
<tr>
<td>Women 50–59 years</td>
<td>0.86 (0.75–0.99)</td>
</tr>
<tr>
<td>Women 60–69 years</td>
<td>0.68 (0.54–0.87)</td>
</tr>
<tr>
<td>Estimates weighted average</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>Canadian Task Force, 2011</strong></td>
<td></td>
</tr>
<tr>
<td>Women aged 50–69 years</td>
<td>0.79 (0.68–0.90)</td>
</tr>
<tr>
<td><strong>Duffy et al., 2012</strong></td>
<td></td>
</tr>
<tr>
<td>Review of all trials and age groups</td>
<td>0.79 (0.73–0.86)</td>
</tr>
</tbody>
</table>
Mammography-Screening
Women 40–49 Years

RR (invited women) 0.74 (95%CI 0.66-0.83)

40–44 J 0.83 (95%CI 0.67-1.00)
45–49 J 0.68 (95%CI 0.59-0.78)

Participants 0.71 (95%CI 0.62-0.80)

NNS 1252 (95%CI 958-1915)
(1 live saved / 10 years screening)

Hellquist BN et al.  Cancer 2011; 117(4) : 714-722
### Early Detection Sonography

<table>
<thead>
<tr>
<th>Screening-Breast Sonography</th>
<th>Oxford / AGO LOE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening-Breast Sonography</td>
<td>5 D - -</td>
</tr>
<tr>
<td>Automated 3D-Sonography</td>
<td>3b C - -</td>
</tr>
</tbody>
</table>

**As an adjunct:**

<table>
<thead>
<tr>
<th>Dense mammogram (ACR 3– 4)</th>
<th>2b B ++</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated risk</td>
<td>1b C ++</td>
</tr>
<tr>
<td>Mammographic lesion</td>
<td>2b B ++</td>
</tr>
<tr>
<td>Second-look US (MRI-only detected lesions)</td>
<td>2b C ++</td>
</tr>
</tbody>
</table>
Early Detection
Clinical Examination

As stand alone procedure

- Self-examination
- Clinical breast examination (CBE) by health professionals
- CBE because of mammo/sonographic lesion

CBE in combination with imaging

* May increase breast awareness
Assessment of Breast Symptoms or Lesions

- Clinical examination
  - 3b     B     ++
- Mammography
  - 1b     A     ++
    - Tomosynthesis
      - 3b     C     +/-
- Sonography
  - 2b     B     ++
    - Elastography (shear-wave)
      - 3b     C     +
    - Automated 3D-sonography
      - 3b     C     +/-
- MRI*
  - 2b     D     +/-
- Minimally invasive biopsy
  - 1c     A     ++

* If clinical examination, mammography and sonography do not allow a definite diagnosis

Oxford / AGO LOE / GR
Pretherapeutic Assessment of Lesion Extension and Staging

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Oxford / LOE / AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical examination</td>
<td>5 D ++</td>
</tr>
<tr>
<td>Mammography</td>
<td>2b B ++</td>
</tr>
<tr>
<td>Sonography</td>
<td>2b B ++</td>
</tr>
<tr>
<td>Axilla + FNP/CNB</td>
<td>2b B +</td>
</tr>
<tr>
<td>MRI *</td>
<td>1b B +/-</td>
</tr>
<tr>
<td>Minimally invasive biopsy**</td>
<td>1b A ++</td>
</tr>
</tbody>
</table>

* Weak reduction in reexcision rate in lobular- invasive cancer but sign. higher rate of initial mastectomy. Lobular invasive tumors, suspicion of multilocular disease, high-risk patients. MRI-guided vacuum biopsy mandatory in case of MRI-detected additional lesions.

** If clinical examination, mammography and sonography (e.g. plus MRI) do not allow assessment of lesion extension
MRI: Preoperative Staging?

False negative rate: 4–12%

False positive rate: up to 40%

No fewer positive margins

Odds ratio for mastectomy: 1.80

Delay in pretreatment evaluation: 22.4 days

MRI: Preoperative Staging

- 9 eligible studies (2 randomized trials; 7 comparative cohorts)
- 3112 patients with BC
- MRI versus no-MRI:
  - initial mastectomy 16.4% versus 8.1% [OR, 2.22 (P < 0.001); adjusted OR, 3.06 (P < 0.001)]
  - re-excision after initial breast conservation 11.6% versus 11.4% [OR, 1.02 (P = 0.87); adjusted OR, 0.95 (P = 0.71)]
  - overall mastectomy 25.5% versus 18.2% [OR, 1.54 (P < 0.001); adjusted OR, 1.51 (P < 0.001)]

MRI: Preoperative Staging in Lobular Invasive Breast Cancer

- 766 patients with invasive lobular cancer (ILC)
  - initial mastectomy: 31.1% versus 24.9% [OR, 1.36 (P = 0.056); adjusted OR, 2.12 (P = 0.008)]
  - re-excision after initial breast conservation 10.9% versus 18.0% [OR, 0.56 (P = 0.031); adjusted OR, 0.56 (P = 0.09)]
  - overall mastectomy 43.0% versus 40.2% [OR, 1.12 (P = 0.45); adjusted OR, 1.64 (P = 0.034)]

COMICE Trial (RCT)
MRI preop. vs. no preop. MRI

Results
816 patients were randomly assigned to MRI and 807 to no MRI. Addition of MRI to conventional triple assessment was not significantly associated with reduced reoperation rate, with 153 (19%) needing reoperation in the MRI group versus 156 (19%) in the no MRI group, (odds ratio 0.96, 95% CI 0.75–1.24; p=0.77).

Conclusion
• No significant reduction of reoperation rate
• More costs with low or no benefit

L Turnbull et al. Lancet 2010
### MONET Trial (RCT)
**Routine-Care vs. Preoperative MRI**

<table>
<thead>
<tr>
<th></th>
<th>Positive Margin</th>
<th>Addition Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine-Care</td>
<td>12%</td>
<td>28%</td>
</tr>
<tr>
<td>Preoperative MRI</td>
<td>34%</td>
<td>45%</td>
</tr>
</tbody>
</table>

„Breast MRI should not be used routinely for preoperative work-up of patients with non-palpable breast cancer.“

Peters NGGM et al. Eur J Cancer 2011
MRI Screening (High-risk) Benefit

- Early detection of cancer cases additionally to conventional imaging

- Improved patient prognosis? (Mortality reduction? Reduction of interval cancers?)
MRI Screening (High-risk) Problems

<table>
<thead>
<tr>
<th>MRI in addition to mammography</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment of benign lesions</td>
<td>3.43–4.86</td>
</tr>
<tr>
<td>Benign biopsies</td>
<td>1.22–9.50</td>
</tr>
<tr>
<td>Benign surgical biopsies (MARIBS)</td>
<td>2</td>
</tr>
<tr>
<td>False-negative MRI (MRISC)</td>
<td>22%</td>
</tr>
</tbody>
</table>
False-negative MRI in High-risk Women (MRISC)

- 97 malignant breast tumors
  - 19 /97 (20%) DCIS

- 21 /97 (22%) false-negative
  - 9 /21 (20%) DCIS

„…..Necessity of screening not only with MRI but also with mammography.“

Obdeijn IMA et al. 2010
# MRI and DCIS

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Cases</th>
<th>Overall accuracy (%)</th>
<th>Sens. (%)</th>
<th>Spec. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilles et al 1995</td>
<td>172</td>
<td>70</td>
<td>95</td>
<td>51</td>
</tr>
<tr>
<td>Westerhof et al 1998</td>
<td>63</td>
<td>56</td>
<td>45</td>
<td>72</td>
</tr>
<tr>
<td>Bazzocchi et al 2006</td>
<td>112</td>
<td>80</td>
<td>79</td>
<td>68</td>
</tr>
<tr>
<td>Kuhl et al 2007</td>
<td>75</td>
<td>-</td>
<td>88</td>
<td>-</td>
</tr>
<tr>
<td>Baur et al 2013</td>
<td>58</td>
<td>-</td>
<td>79,3</td>
<td>-</td>
</tr>
</tbody>
</table>

„Negative breast MRI findings should not be considered a sure marker of benignancy.“
Early Detection and Diagnosis (2/18)

Further information:

Screened data bases:
- Pubmed 2009 - 2013
- ASCO 2009 - 2013
- Cochrane 2009 - 2013
- Medline 2009 - 2013
- GIN 2009 - 2013

Guidelines
- S3 Brustkrebsfrüherkennung
- S3 Diagnostik, Therapie, Nachsorge

Screened: Metaanalysen / systematische Reviews / RCT / Beobachtungs- und Fallkontrollstudien

No references
**Early Detection – Mammography (3/18)**

*Further information:*

The aim of early detection and screening of breast cancer is to reduce the risk of dying from the disease. Detecting invasive breast cancer at an early stage (Stage I-IIA) offers the chance of survival with less treatment impairment and better quality of life. Professionals and women need to be informed about the benefits and harms of cancer screening tests before making medical decisions. This includes clear and understandable information in absolute terms about false positives, false negatives, overdiagnosis and overtreatment.

Since 2006 mammography screening is offered to women age 50-69 in Germany within a population-based organized quality assured programme in accordance with the European Guidelines for Quality Assurance in Mammography Screening.

Meta-analysis and reviews from randomised trials:
Conclusion of the meta-analysis of the Independent UK Panel on Breast Cancer Screening: “Considering the internal bias in the trials, which were done a long time ago, the relative risk reduction in breast cancer mortality from invitation to mammography screening is estimated to be 20%.”

The updated modelling of Forrest report (QUALYs after 7, 10 and 20 years) concludes “the introduction of breast cancer screening might have caused net harm for up to 10 years after start of screening”.

Data from observational studies and registries:
The EUROSCREEN Working Group has published their report about the impact of population-based screening with mammography on breast cancer in Europe. They conclude: 1. “the best “European” estimate of of breast cancer reduction is 25-31% for women invited for screening, and 28-38% for women actually screened. The estimate of overdiagnosis range from 1-10%. The chance for saving a woman’s life by population-based mammographic screening of appropriate quality is greater than that of over-diagnosis.
The population-based data from the United States (SEER-Cancer Statistics 1976 - 2008) showed an increase in number of early-stage breast cancer, a marginal reduction at advanced stage. The authors conclude “the imbalance suggests that there is substantial overdiagnosis, and that screening at best, only has a small effect on the rate of death from breast cancer”.

**References:**

Breast Cancer Mortality Reduction (4/18)

No further information

References:

**Mammography Screening Women 40–49 years (5/18)**

**Further information:**

On the basis of randomized controlled trials there is evidence of a 26% mortality reduction. The only one especially designed for this age group (“Age-Trial”) achieved a mortality reduction of 17% for those invited and 24% for those participating. These results were not yet statistically significant (95% CI, 0.66-1.04)), because the follow-up time is too short for this young age group. The data have been underlined by study results of several service screening studies. The most recent one (Hellquist and coauthors 2011) presented a 26% mortality reduction in those invited and 29% in those attending. The average follow-up time was 16 years.

To estimate overdiagnosis within the “Age-Trial” Markov-modelling was performed and yielded the following results (Gunsoy N, 2012): “The sensitivity of mammography for invasive and in-situ breast cancers was 90% (95% CI, 72-99) and 82% (43-99), respectively. The screen-detectable mean sojourn time of preclinical non-progressive and progressive in-situ cancers was 1.3 (0.4-3.4) and 0.11 (0.05-0.19) years, respectively, and 0.8 years (0.6-1.2) for preclinical invasive breast cancer. The proportion of screen-detected in-situ cancers that were non-progressive was 55% (25-77) for the first and 40% (22-60) for subsequent screens. In our main analysis, overdiagnosis was estimated as 0.7% of screen-detected cancers. A sensitivity analysis, covering a wide range of alternative scenarios, yielded a range of 0.5% to 2.9%.” The authors conclude: “The extent of overdiagnosis due to screening in women aged 40-49 was small. Results also suggest annual screening is most suitable for women aged 40-49 in the United Kingdom due to short cancer sojourn times.”

**References:**


4. FH01 Collaborative Teams Mammographic surveillance in women younger than 50 years who have a family history of breast cancer: tumour characteristics and projected effect on mortality in the prospective, single-arm, FH01 study. Lancet Oncol 2010;11:1127-1134


Early Detection Sonography (6/18)

Further information:

Results from the systematic review (Nothacker et al): The systematic search identified no randomized controlled trials or systematic reviews, six cohort studies of intermediate level of evidence (3b) were found. Only two of the studies included adequate follow-up of subjects with negative or benign findings. Supplemental breast ultrasound after negative mammographic screening permitted diagnosis of primarily invasive carcinomas in 0.32% of women in breast density type categories 2-4 of the American College of Radiology (ACR); mean tumor size for those identified was 9.9 mm, 90% with negative lymph node status. Most detected cancers occurred in mammographically dense breast ACR types 3 and 4. Biopsy rates were in the range 2.3%-4.7%, with PPV of 8.4-13.7% for those biopsied due to positive ultrasound, or about one third of the PPV of biopsies due to mammography. Supplemental breast ultrasound in the population of women with mammographically dense breast tissue (ACR 3 and 4) permits detection of small, otherwise occult, breast cancers. Potential adverse impacts for women in this intermediate risk group are associated with an increased biopsy rate.

The arguments against ultrasound use as a screening modality alone are reproducibility, high false-positive rate, low ppv for biopsy, inability to detect most DCIS cases, operator dependency and lack of quality assurance.

References:

**Early Detection Clinical Examination (7/18)**

*Further information:*

In a large well performed randomized study no difference in breast cancer mortality emerged after 11 years of follow-up. The only difference was that women in the self-examination arm had nearly twice as many biopsies for benign lesions than women in the control arm. Therefore based on current evidence breast self-examination cannot be recommended anymore. No randomized studies have been performed, where screening-examination by health professionals is compared to no screening. One Japanese case-control study suggests that examination by health professionals might reduce mortality from breast cancer. A randomized trial in Canada showed no difference in breast cancer mortality between a group of women offered clinical breast examination or mammography combined with clinical breast examination. Nevertheless in asymptomatic women participating in mammography screening programs there is the risk of interval cancer development. This is the reason why in the US mammography screening is recommended in close connection with clinical examination. Recent data (Haakinson and coauthors 2010) underscore this strategy.

*References:*

Assessment of Breast Symptoms or Lesions (8/18)

**Further information:**

If clinical examination, mammography and ultrasound are not conclusive, morphological diagnosis based on biopsy material is warranted. MRI has a high sensitivity but a low specificity to allow definitive diagnosis.

Minimally invasive biopsy allows definitive diagnosis in most cases at reduced expenditure. In case of suspicious microcalcifications extensively distributed in mammography several percutaneous biopsies should be performed before deciding upon mastectomy.

**References:**

Pretherapeutic Assessment of Lesion Extension (9/18)

Further information:

Sonography corresponds better than mammography with the pathological tumor size of the invasive component of breast tumours. Mammography delineates the in situ component better if microcalcifications are present. In these cases magnification mammography is warranted. MRI is the most sensitive method for invasive tumors, but lacks specificity. Thus MRI findings should be verified by percutaneous biopsy before definite treatment. The effect of MRI on the success of breast conserving therapy neither concerning short-time outcome parameter, i.e. reduction of re-excision rate nor longtime outcome parameter, i.e ipsilateral recurrence and overall survival have not been assessed in randomized studies. Therefore the overall contribution of MRI to successful breast conserving therapy cannot be assessed yet.

MRI for preoperative staging may be helpful in individual cases (high-risk women, multifocallity/ multicentricity demonstrated at conventional imaging and pathologically proven, invasive lobular cancer with inconclusive findings at conventional imaging).

In case of large areas of highly suspicious microcalcifications on mammography several percutaneous biopsies to define tumour size should be performed before deciding upon mastectomy.

References:

5. Houssami N, Hayes DF Review of preoperative magnetic resonance imaging (MRI) in breast cancer: Should MRI be performed on all women with newly diagnosed early stage breast cancer. CA Cancer J Clin 2009; 59:290-302
MRI Preoperative Staging? (10/18)

No further information

References:

MRI Preoperative Staging (11/18)

No further information

No references
MRI Preoperative Staging in Lobular Invasive Breast Cancer (12/18)

No further information

No references
COMICE Trial (RCT): MRI preop. vs. no preop. MRI (13/18)

No further information

References:

MONET Trial (RCT) (14/18)

No further information

References:

MRI Screening (High-risk) Benefit (15/18)

No further information

References:

MRI Screening (High-risk) Problems (16/18)

No further information

References:

False-negative MRI in High-risk Women (MRISC) (17/18)

No further information

References:

MRI and DCIS (18/18)

No further information

References:

Pathology
Pathology

- **Versions 2004–2013:** Costa / Fehm / Huober / Kreipe / Lück / Sinn / Thomssen

- **Version 2014:** Kreipe / Friedrichs
Handling and Reporting of Core Needle Biopsies

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<thead>
<tr>
<th>Oxford / LoE / GR</th>
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<tbody>
<tr>
<td>Routine workup in step sections (14G: 3 sections / 11G, 8G: 6–8 sections)</td>
<td>1b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Correlation with imaging (density, calcifications), use of B-Classification</td>
<td>5</td>
<td>D</td>
<td>- -</td>
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<tr>
<td>Frozen section diagnosis on core biopsies</td>
<td>3b</td>
<td>C</td>
<td>++</td>
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<tr>
<td>Routine evaluation of ER/PgR and HER2 status</td>
<td>5</td>
<td>D</td>
<td>+</td>
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<tr>
<td>Turn-around time &lt; 24 h (dignity)</td>
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<td>D</td>
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<tr>
<td>Optimal fixation time 6–48 h</td>
<td>5</td>
<td>D</td>
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<tr>
<td>Standard fixation and processing</td>
<td>5</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td>Participation in QA-programs</td>
<td>3</td>
<td>D</td>
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</tbody>
</table>
Fine Needle Aspiration Cytology*

- Nipple secretion
- Tumor
- Cyst
- Lymph node

* Ultrasound-guided core biopsy recommended

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<tr>
<th>Oxford / LoE / GR</th>
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<td>5 D +</td>
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<td>5 D -</td>
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<tr>
<td>5 D +/-</td>
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<td>5 D +/-</td>
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### Indications for Immediate Pathological Analysis Including Frozen Sections

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<tr>
<th>Oxford / AGO</th>
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<tbody>
<tr>
<td>Sentinal node biopsy for invasive cancer</td>
<td>5 D +</td>
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<tr>
<td><code>- if clinical consequence</code></td>
<td>5 D +/−</td>
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<tr>
<td><code>- if no clinical consequence from frozen section (e.g. cT1 or cT2 and cN0 and BET)</code></td>
<td></td>
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<tr>
<td>Closest margin of resection</td>
<td>5 D +</td>
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<tr>
<td><code>- if macroscopically &lt; 1 cm</code></td>
<td>5 D −</td>
</tr>
<tr>
<td><code>- if macroscopically &gt; 1 cm</code></td>
<td></td>
</tr>
<tr>
<td>Lesions ≥ 1 cm, without core biopsy</td>
<td>5 D +</td>
</tr>
<tr>
<td>Non-palpable lesions or lesions &lt; 1 cm</td>
<td>5 D −</td>
</tr>
<tr>
<td>Asservation of fresh tissue (tumor banking)</td>
<td>5 D +</td>
</tr>
</tbody>
</table>
General Recommendations for Specimen Handling

- Adherence to sampling protocols and guidelines for accurate evaluation of tumor size and margins
  
- Consideration of clinical imaging results (e.g. calcifications, multifocality) and topography
  
- Specimen radiography for non-palpable lesions and microcalcifications
  
- Minimum fixation time 6 h (max. 48 h) to minimize shrinking artifacts and allow determination of angioinvasion
  
- Tissue banking to be performed by or in cooperation with the pathologist
Workup of Breast-Conserving Specimens

- Slicing perpendicular to the longitudinal axis (or perpendicular to the nipple-peripheral axis in case of spherical specimens)
- Systematic sampling, at least 1 tissue block every 1 cm
- Inking of resection margins. Sampling of resection margins in all dimensions
- Documentation after slicing using specimen radiography, photodocumentation or diagram
Workup of Mastectomy Specimens

- Margins always to be sampled
  - skin close to tumor, at least 2 directions
  - deep margin
  - other margins, if close (< 1 cm)

- Attention to soft tissue margins in skin sparing mastectomy

- Routine sampling of uninvolved quadrants, skin above tumor, and retroareolar region

- More extensive sampling in prophylactic mastectomies (BRCA-1/2 pos. patients)
## Reporting of Invasive Carcinoma

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<tr>
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<th>3b C ++</th>
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<tr>
<td>Tumor type (WHO). Grade (UICC). Size (invasive and extensive in situ cancer). pT classification (UICC).</td>
<td>3b C ++</td>
</tr>
<tr>
<td>All margins, macroscopically, distance and topography. Histologic distance and topography of margins &lt; 1 cm. R-Classification according to TNM.</td>
<td>3b C ++</td>
</tr>
<tr>
<td>EIC (if present). Multifocality (if present). Lymphovascular invasion (present or not).</td>
<td>5 D ++</td>
</tr>
<tr>
<td>No. of axillary nodes removed. No. and size of lymph node metastases. Perinodal invasion. pN classification (UICC).</td>
<td>3b B ++</td>
</tr>
<tr>
<td>ER, PgR, HER2 status</td>
<td>3b C ++</td>
</tr>
<tr>
<td>Ki-67 (for re-assurance of grading)</td>
<td>3b B +</td>
</tr>
</tbody>
</table>
Evaluation after Neoadjuvant Chemotherapy

- Identification of tumor bed, otherwise ypTX
- Reporting of tumor size as total extent of tumor bed area involved by infiltrates of residual vital invasive carcinoma
- Reporting of tumor regression according to Miller-Payne (2003), Symmans (2007) or Sinn (1994), Sataloff or Chevallier (1993)
- pCR when absence of invasive and in situ Ca. and absence of vessel invasion or LN metastases
- Use of IHC to identify tumor residues
- Final reporting pTN before and after therapy

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</table>
Histologic Evaluation of Tumor Regression

- **NSABP B-18:** pCR / pPR / NR
- **Chevallier:** Grade of regression, 1–4
- **Sataloff:** Cellularity (Tu + Lnn), 1–4
- **Miller-Payne:** Cellularity, Score 0–5
- **Symmans:** 6 parameter (Tu + Lnn)
- **Sinn:** Grade of regression, Score 0–4
## Definition of pCR

<table>
<thead>
<tr>
<th>Author</th>
<th>Invasive Tumor</th>
<th>In-situ Tumor</th>
<th>Intra-vascular</th>
<th>Lymph-node Metas.</th>
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<tr>
<td>Chevallier</td>
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<td>1–4</td>
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<td>Sinn</td>
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<td>0-4</td>
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<td>Sataloff</td>
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<tr>
<td>Cellularity 1–4</td>
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<tr>
<td>Miller-Payne</td>
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<tr>
<td>Cellularity 1–5</td>
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<td>Symmans</td>
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<td>6 parameters</td>
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<td>NSABP B-18</td>
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<td>pCR / pPR / NR</td>
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<td>GBG / AGO-B</td>
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</table>
ER, PgR Testing

- Immunohistochemical detection on paraffin embedded (FFPE) tissue
- Reporting percentage of pos. tumor nuclei (pos. if ≥ 1%)
- Staining intensity of pos. tumor nuclei
- Quantitative RNA assessment (qt-pCR, array)
- Allred Score (0–8), Remmele Score (0–12)
- Re-evaluation on excision specimen if triple-negative on core biopsy
- Use of internal and external quality control schemes

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</table>
## ER/PgR Interpretation

<table>
<thead>
<tr>
<th>Bewertung</th>
<th>ASCO/CAP 2010</th>
<th>Remmele-Score</th>
<th>Allred-Score</th>
<th>St. Gallen Konsensus 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prozentalität</td>
<td>Farbeintensität (1-3) x Prozentalität (1-4) = max. 12</td>
<td>Farbeintensität (1-3) + Prozentalität (1-5) = max. 8</td>
<td>Prozentalität</td>
<td>Schwach positiv: &gt;0-49%</td>
</tr>
<tr>
<td>&gt; 0 bis &lt; 10% = 1</td>
<td>&gt; 0 bis 1% = 1</td>
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<tr>
<td>10 bis &lt; 50% = 2</td>
<td>&gt; 1% bis 10% = 2</td>
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<tr>
<td>50% bis 80% = 3</td>
<td>&gt; 10% bis 33% = Hoch positiv: = 50%</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 80% = 4</td>
<td>&gt; 33% bis 66% = 4</td>
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<tr>
<td>&gt; 66% bis 100% = 5</td>
<td>&gt; 66% bis 100% = 5</td>
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<tr>
<td>Positiv</td>
<td>Positiv =1% (Score)</td>
<td>Positiv = 3 (Score)</td>
<td>Positiv &gt; 0 (%)</td>
<td>mäßig gefärbt</td>
</tr>
<tr>
<td>Negativ</td>
<td>Negativ &lt;1% (Score)</td>
<td>Negativ = 2 (Score)</td>
<td>Negativ 0 (%)</td>
<td>Gefärbt</td>
</tr>
<tr>
<td>Diskrepante Positivitäts-Grenze im Vergleich zu ASCO/CAP</td>
<td>1% mindestens stark gefärbt</td>
<td>1% mindestens &gt;0%&lt;-1% stark gefärbt</td>
<td>mäßig gefärbt</td>
<td></td>
</tr>
<tr>
<td>Diskrepante Negativitäts-Grenze im Vergleich zu ASCO/CAP</td>
<td>49% schwach gefärbt, 1% schwach gefärbt; 9% mäßig gefärbt</td>
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</table>
HER2 Testing

- **Reporting of immunohistochemistry (IHC):**
  - HER2+ if strong complete circular membrane staining of >10% invasive cells (3+ staining pattern)
  - if > 10% circular but moderate/weak membrane staining or ≤10% strong staining (2+ staining pattern): ISH required (CISH, SISH, FISH)

- **Reporting of single-color In-Situ-Hybridisation (ISH):**
  - HER2+ if signal counts ≥6 in at least 20 cohesive cells, negative if signal counts < 4 signals/nucleus

- **Reporting of dual-color ISH:**
  - positive if signal ratio HER2:CEP17 ≥ 2.0 and/or HER2-signal ≥6

- **Equivocal results (2+ IHC, ≥4 - <6 HER2 signals ISH):** Retest using other method and/or tissue block

- **Validation of immunohistochemistry on core biopsies**

- **Use of internal and external quality control schemes**

- **Reporting by RNA-analysis (qtPCR, array-technology)**

<table>
<thead>
<tr>
<th>Oxford LoE / AGO</th>
<th>1a</th>
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<tbody>
<tr>
<td>Reporting of immunohistochemistry (IHC):</td>
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<tr>
<td>Reporting of single-color In-Situ-Hybridisation (ISH):</td>
<td>3a</td>
<td>C</td>
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<tr>
<td>Reporting of dual-color ISH:</td>
<td>3a</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>Equivocal results (2+ IHC, ≥4 - &lt;6 HER2 signals ISH): Retest using other method and/or tissue block</td>
<td>3a</td>
<td>C</td>
<td>++</td>
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<tr>
<td>Validation of immunohistochemistry on core biopsies</td>
<td>5</td>
<td>D</td>
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</tr>
<tr>
<td>Use of internal and external quality control schemes</td>
<td>5</td>
<td>D</td>
<td>++</td>
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<tr>
<td>Reporting by RNA-analysis (qtPCR, array-technology)</td>
<td>2b</td>
<td>B</td>
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</table>
HER2 Testing on Core Biopsies

False positive immunohistochemical labeling may occur in core biopsies. Therefore, methods of individual laboratories should be validated by comparison of core biopsies and resection specimens. Background staining should be evaluated by comparison with normal duct epithelium. Alternatively, all G1 and G2 cases with HER2 3+ in core biopsies may be analyzed by ISH or may be re-evaluated in the resection specimen.

False positivity is likely when HER+ was reported in G1 tumors of the following types: Infiltrating ductal or lobular carcinoma, ER and PgR positive, Tubular (at least 90% pure), Mucinous (at least 90% pure) Cribriform (at least 90% pure), Adenoid cystic carcinoma (90% pure)

In case of discrepancy between core biopsy and specimen, the HER2 overexpressing sample should be re-evaluated by a different method. If still discrepancy – anti-HER2-treatment if amplified in one of both samples.

Expected rate of HER2-overexpression: 15% HER2 positive
Intrinsic Breast Cancer Types
(Molecular and Immunohistochemical Definitions)

- Currently there is no generally accepted and proven translation of molecularly defined types (basal, luminal A/B-Typ, HER2) into immunohistochemical counterparts neither with regard to markers nor to thresholds.
- In terms of practical consequences re-labelling of clinically established and immunohistochemically defined subgroups might be useful (ER/PR+ for luminal, HER2+ for HER2-type, triple negative for basal type).
- The basal type shows an 80% overlap with the triple negative subgroup of ductal invasive breast cancer (ER <1% & PgR <1% & HER2 0/1+2+ (non-amplified, ratio <2)).
- None of the available markers (Ki-67, grading, recurrence score etc.) can reliably discriminate between luminal A and luminal B type.
- Although derived from RNA expression studies, RNA measurements are not suited for the definition of intrinsic types for purposes of therapy.
Triple-negative Breast Cancer (TNBC)

Oxford LoE: 5  GR: D  AGO: ++

- Definition: ER <1% & PgR <1% & HER2 0/1+2+ (not amplified, Ratio ≤ 2)

- Except: Salivary gland type tumors, myoepithelial Ca., adenoid-cystic Ca., apocrine Ca.

- Repeat IHC if equivocal result*

* Equivocal result: tubular, lobular, mucinous, cribriform breast ca., slowly proliferating IDC G2, possible sampling bias (core biopsy), negative for basal cytokeratins
Evaluation of Sentinel Node Biopsy

- Full workup using step sections of ≤ 500 µm on paraffin embedded tissue
  - Oxford / AGO: 5 D ++
- Cytokeratin immunohistochemistry
  - when suspicious, to detect micromet.
  - as a routine procedure
  - Oxford / AGO: 2b B ++
  - LoE / GR: 5 D +/-
- Frozen section (invasive Ca.)
  - if clinical consequence
  - if no clinical consequence from frozen section (e.g. cT1 or cT2 and cN0 and BET)
  - Oxford / AGO: 5 D +
  - LoE / GR: 5 D +/-
- Imprint cytology instead or in addition of frozen section
  - Oxford / AGO: 3b C +/-
- RT-PCR for epithelial genes
  - OSNA
  - Oxford / AGO: 4 D -
Mutation or Expression Analysis

Oxford LoE: 5    GR: D    AGO: - -

- TP53 (p53)
- PIK3CA (PI3K)
- PTEN
- Others

- Whole genome sequencing

- Currently, only for scientific use!
This chapter contains basic recommendations for routine procedures in pathology. It is not attempted to replace detailed protocols for the evaluation of operative specimens or for special studies. It is highly recommended to adhere to national quality assurance protocols concerning all aspects of working up and reporting of pathology specimens removed from women with breast cancer. Further information can be found in the following reports:

Update 1/2014 – Kreipe / Friedrichs


Screened guidelines:

- German S3-Guidline Early Detection of Breast Cancer
- German S3-Guidline Treatment of Breast Cancer (Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms)
- EUSOMA position paper: Diagnosis of breast disease
- Royal College of Pathologists & NHS Breast Screening Programme, Pathology Reporting of Breast Disease, January 2005
- European guidelines for quality assurance in breast cancer screening and diagnosis 4th Edition

References:

Handling and Reporting of Core Needle Biopsies (3/20)

Further information and references:

Statement: Routine workup in step sections

Routine workup of core needle biopsies is in step sections (14G: 3 sections / 11G, 8G: 6 – 8 sections). In general, ultrasound guided core biopsies (14G) are performed for mass lesions. It is recommended to cut only three routine sections to save tumor tissue for IHC and other studies. If in doubt, further sections should be cut. Vacuum cores (11G, 8G) are often used for non-palpable lesions and may include microcalcifications and/or B3 lesions. 6-8 step sections are required for adequate workup using H&E sections.


Statement: Correlation with imaging

The B-Classification is recommended to improve reproducibility and to standardize treatment and follow up. The use of the B-Classification requires knowledge about the imaging results and, optimally, discussion with the radiologist in a conference.


Statement: Frozen section diagnosis on core biopsies
Frozen tissue section of core biopsies is not recommended as a routine procedure and can be avoided by rapid tissue processing and reporting during daytime. Disadvantages of frozen section of core biopsies include: difficulties in interpretation, loss of relevant material, problems with immunohistochemistry.


**Statement: Routine evaluation of ER/PgR and HER-2 status**

It is safe and preferred to routinely perform immunohistochemistry or other special studies on core biopsies provided adequate tumor tissue was biopsied. Advantages are: better preservation of tumor tissue, planning of inclusion into clinical studies such as neoadjuvant chemotherapy, more accurate assessment of tumor grading and tumor typing. In case of triple-negative or triple-positive tumors, evaluation should be repeated on excision specimen because of possible sampling error (tumor heterogeneity).


**Statement: Turn-around time < 24h**

Turn-around time until reporting should be one working day or less.


**Statement: Cytology**
Core needle biopsy has replaced fine-needle aspiration cytology, not only because it is more sensitive and specific, but also because it enables differentiation between invasive and in situ carcinomas in most cases. The introduction of CB has led to a reduction in surgery on benign lesions.


Statement: Fixation Time

Incisional and excisional biopsy samples used for HER2 testing of either type should be fixed in 10% neutral buffered formalin for intervals ranging from at least 6 hours to no more than 48 hours. Fixation time alters protein antigen expression and also changes the requirements for enzymatic digestion that is part of the ISH protocol to detect gene amplification. Prolonged fixation, for example more than 48 hours, may result in false-negative results. Fixation times for needle biopsies have not been addressed.

Statement: Standard fixation and processing


Incisional and excisional biopsy samples used for HER2 testing of either type should be fixed in 10% neutral buffered formalin for intervals ranging from at least 6 hours to no more than 48 hours. Fixation time alters protein antigen expression and also changes the requirements for enzymatic digestion that is part of the ISH protocol to detect gene amplification. Prolonged fixation, for example more than 48 hours, may result in false-negative results. Fixation times for needle biopsies have not been addressed.

Statement: Participation in QA-programs
Systematic and effective use of diagnostic pathways is the basis for optimal treatment and the ability to substantially lower current breast cancer mortality rates and reduce the burden of this disease in the population. In order that benefits may be obtained, high-quality services are essential. These may be achieved through the underlying basic principles of training, specialisation, volume levels, multidisciplinary team working, the use of set targets and performance indicators and audit.

Quality assurance in surgical pathology is defined as a program for the systematic monitoring and evaluation of the various aspects of the laboratory service to ensure that standards of quality are being met. Quality improvement in surgical pathology is defined as a systematic attempt to improve specific quality measures in laboratory service.

Fine Needle Aspiration Cytology (4/20)

No further information

No references
Indications for Immediate Pathological Analysis Including Frozen Sections (5/20)

Further information and references:

Statement: Sentinel node biopsy for invasive cancer

Frozen section diagnosis of sentinel lymph nodes is used for detecting macrometastases (> 2mm), but inadequate to detect micrometastases or isolated tumor cells. Care must be taken not to lose too much tissue during frozen sectioning. Frozen sections should be restricted to cases with expected clinical consequences.


Statement: Closest margin of resection

Margins of resection can be evaluated on frozen section if the macroscopic margin is less than 1 cm or if the macroscopic evaluation is doubtful. However, sensitivity and specificity is only 86% and 83% because of possible sampling errors in frozen sections. With macroscopically wider margins, the probability to detect tumor in the margin on frozen section is considered to be too low and therefore frozen section is not recommended with a macroscopic margin of > 1 cm.

For intraoperative radiotherapy free status of margins has to be assessed during operation. This is best done by macroscopical work-up of the unfixed specimen by a pathologist with only exceptional frozen sections.

Statement: Lesions ≥ 1 cm, without core biopsy

The diagnosis of malignancy can be established on frozen section for lesions that measure at least 1 cm in greatest dimension or larger. Smaller lesions should not be examined on frozen section because too much tissue may be lost.


Statement: Non-palpable lesions or lesions < 1 cm

Non-palpable lesions (e.g. biopsies performed because of microcalcifications) cannot not be evaluated adequately on frozen sections

General Recommendations for Specimen Handling (6/20)

Further information:

Statement: Adherence to sampling protocols and guidelines for accurate evaluation of tumor size and margins

To achieve consistent and clinically meaningful results standard procedures must be followed for sampling and reporting of breast pathology specimens. It is recommended to follow the national guidelines. This is especially important for the evaluation of surgical margins and reproducible determination of tumor size, extent of DCIS, and many other criteria that should be reported.

Statement: Consideration of clinical imaging results

The specimen workup must consider imaging results and indications for a given therapy (e.g. mastectomy). When relevant clinical information is unknown, workup of the specimen should be postponed.

Statement: Specimen radiography for non-palpable lesions and microcalcifications

As a rule, non-palpable lesions also cannot be seen by the naked eye of the pathologist. In order to sample the specimen adequately, e.g. to embed all microcalcifications, a specimen radiograph should be provided for or performed by the pathologist, ideally after slicing the specimen.

Statement: Minimum fixation time 6-48 h to minimize shrinking artefacts and allow determination of angioinvasion

Many histological details are destroyed by too rapid processing of larger specimens. 24 h fixation time should be maintained before processing. Angioinvasion should be reported routinely (if unequivocal) and classified as blood vessel of lymphatic vessel invasion (if unequivocal). Distinguish peritumoral L1 from extensive L1 from L1 in skin. Report special situations (L1 in margins, skin, fascia, axillary fat). Not a prerequisite for diagnosis of inflammatory breast cancer.

Statement: Tissue banking to be performed by the pathologist

Tumor banking requires dissection of diagnostically relevant structures and therefore should be performed by the pathologist only.
References:

Workup of Breast-Conserving Specimens (7/20)

Further information:

Statement: Slicing perpendicular to the longitudinal axis

As a rule, breast-conserving specimens are to be sliced into 0.3 – 0.5 sections perpendicular to the longitudinal axis of the specimen. In this way, it is assured that the minimal distance of the tumor to the margins can be assessed accurately.

Statement: Systematic sampling, at least 1 tissue block every 1 cm

To rule out tumor deposits in areas not suspicious to the naked eye, at least 1 tissue block every 1 cm should be sampled.

Statement: Inking of resection margins. Sampling of resection margins in all dimensions

The topographic relationship of the tumor within the specimen is best documented by imaging of the sliced specimen (either by radiography, photodocumentation or a diagram)

Statement: Documentation after slicing using specimen radiography, photodocumentation or diagram

The total size of a tumour is measured macroscopically and verified by microscopy. In case of discrepant results the microscopic measurement is taken as tumour size. In case of a DCIS component extending > 0.5 cm outside the margin of invasion, the total metric extent of the tumor and the DCIS component should be reported in addition to the size of the invasive carcinoma.

References:


**Workup of Mastectomy Specimens (8/20)**

*Further information:*

Statement: Margins always to be sampled
- Skin close to tumor, at least 2 directions
- Deep margin
- Other margins, if close (< 1 cm)

Statement: Attention to soft tissue margins in skin sparing mastectomy

Statement: Routine sampling of uninvolved quadrants, skin above tumor, and retroareolar region

Statement: More extensive sampling in prophylactic mastectomies (BRCA-1 pos. patients)

These are minimal requirements for the workup of mastectomy specimens. The statements are designed to make sure that clinically relevant information (e.g. multifocality, margins) is not missed.

*References:*

**Reporting of Invasive Carcinoma (9/20)**

*Further information:*

Accurate pathological diagnoses and the provision of prognostically significant information are important to ensure that patients are managed appropriately and that the therapy is properly monitored and evaluated. A standard set of data from each patient, using the same terminology and diagnostic criteria is essential to achieve the latter objective. The opinions expressed here are based on the consensus view of the E.C. Working Group on Breast Screening Pathology [1] and take into account other consensus recommendations [2-8]. Special emphasis is put on the strict adherence and use of UICC and WHO classification systems and nomenclature [9, 10]. For grading of breast cancer, the Nottingham grading is recommended [11].

*References:*

8. NHSBSP guidelines for pathology reporting in breast disease


Evaluation after Neoadjuvant Chemotherapy (10/20)

Further information:

Statement: Identification of tumor bed, otherwise ypTX

After neoadjuvant chemotherapy, the tumor bed must be identified in the specimen, and examined for completeness, size, and regressive changes. Without complete resection of the tumor bed, there is a chance of residual tumor, even in case of complete regression. Without positive identification of the tumor bed, the tumor status must be considered unknown, and therefore classified as pTX.

Statement: Reporting of tumor size as total extent of invasive carcinoma

Chemotherapy results in a variable loss of tumor cellularity with interspersed fibrotic areas, leading to an apparent multifocality. Tumor size after neoadjuvant chemotherapy should report the whole area where vital tumor cells can be detected. Only when tumor foci that are macroscopically distinct, this should be reported as multiple tumor foci, and the size of the largest focus taken for the ypT category.

Statement: Reporting of tumor regression according to Miller-Payne (2003), Symmans (2007) or Sinn (1994)

Various schemes for assessing tumor regression have been reported. Currently there is no preference for a single scheme, because no comparative data have been published. Among the most frequently used systems are Miller-Payne (2003), Symmans (2007), and Sinn (1994)

Statement: pCR is absence of invasive Ca. and absence of Lymphangiosis ca. or LN metastases (without consideration of DCIS)

There is consensus to use the term “pathologic complete remission” pCR for absence of invasive carcinoma. Lymph node metastases or residual DCIS may be present.

Statement: Use of IHC to identify tumor rests

Immunohistochemistry may be used to identify residual invasive tumor cells (e.g. in case of invasive lobular carcinoma with subtotal tumor regression), but is not required as a routine measure for the assessment of pCR.
References:

1. Pinder S.E., Provenzano E., Earl H., Ellis I.O. Laboratory handling and histology reporting of breast specimens from patients who have received neoadjuvant chemotherapy. Histopathology 2007; 50(4):409-17
Histologic Evaluation of Tumor Regression (11/20)

No further information

No references
Definition of pCR (12/20)

No further information

No references
ER, PgR Testing (13 + 14/20)

Further information and references:

Statement: Immunohistochemical detection on paraffin embedded (FFPE) tissue


Statement: Reporting percentage and intensity of pos. tumor nuclei (pos. if ≥ 1%)

The percentage of cells with nuclear staining using either estimation or quantitation. Quantitation may be done either by image analysis or manually. Entire slide should be reviewed to assess the tumor-containing areas. With limited tumor cells and little tumor staining must have at least 100 cells counted. Report an average intensity of tumor cell nuclei recorded as strong, moderate, or weak. Quantitative image analysis is encouraged for samples with low percentages of nuclear staining or in cases with multiple observers in the same institution. It is also a valuable way to quantify intensity and assure day-to-day consistency of control tissue reactivity.


Statement: Allred Score (0 - 8)
Statement: Remmele Score (0 - 12)

A score may be provided if the scoring system is specified.

Statement: Re-evaluation on excision specimen if triple-negative on core biopsy

If an external or internal control does not produce the expected reaction, the result of patient testing must not be reported. Instead, the assay should be repeated with the standard reagents under the standard conditions until acceptable ER and/or PgR reactivity of control material is achieved. No patient material should be reported until controls react appropriately.

If the particular histologic type of breast cancer is unlikely to be ER negative (tubular, mucinous, or lobular morphology or Nottingham score of 1), the tumor should also be subjected to confirmatory testing, such as sending the same specimen to a reference laboratory for retesting or by repeating the assay on another block or on a separate breast cancer specimen.


Statement: Use of internal and external quality control schemes

Standardization of IHC reagents has been implemented by regulation of the FDA. Internally, most laboratories use control sections to validate their staining results. Supplementing these measures, standards should be compared between laboratories in interlaboratory trials. Such trials have focused on the quality of immunohistochemical stains or on standardized protocols for staining and specimen handling [1]. Quality control measures are mandatory in specialized breast units [2].


Other References:

**HER2-Testing (15 + 16/20)**

**Further information:**

It was shown that the immunohistochemical HER2-determination (if necessary with subsequent FISH) is safe if performed on core biopsy [1]. In the comparison of the results between the core biopsy and excision specimens the hormone receptor results were more reliable tumor, suggesting the fixation of the excision specimen may be detrimental [4].


*(abstracted from Ref. 4)*

- The HER2 assay should only be evaluated in invasive breast cancer or the invasive component of the breast cancer.
- Required fixation of breast tissue samples is 10% neutral buffered formalin. Optimal fixation times are 6 to 48 hours and should be documented in the pathology report.
- HER2 determination in core biopsies is possible provided that enough tumour tissue is represented. The reliability of results on core biopsies has been shown to be between 82-100% [4-6]. Core biopsies offer the advantage of optimal and standardized fixation and neoadjuvant therapy requires analysis to be done on core biopsies. Centres have to validate their methods by systematic comparison of HER2 assessment in core biopsies and resection specimens, then the congruence will be >95% [7].
- Assay procedures must be validated by the laboratory before offering the test clinically. The test should show 95% concordance with a validated reference assay.
- Assay procedures must be standardized. Any deviation from the standardized method must be recorded and justified by revalidation of the method. Personnel performing assays must have their competency assessed at regular intervals.
- Standardized control materials, either purchased products or products conforming to defined manufacturing standards (for example, cell lines of the European Collection of Cell Cultures or those produced by the National Institute of Standards and Technology [NIST]) or defined by the laboratory director, must be consistently used by each laboratory with each run of tests. Adequate control materials include cell lines or tumor blocks with well defined negative, equivocal, and positive expression and gene amplification assay results. Faux tissue blocks or xenografts with variable HER2 expression levels may also be used if the results expected are well characterized. If controls do not show usual results, the assay must be repeated rather than interpreted.
- Image analysis can be an effective tool for achieving consistent interpretation. However, a pathologist must confirm the image analysis result.
- Standardized interpretation criteria for all types of HER2 tests must be used, based on the interpretation criteria from recent clinical trials and international experience.
- Laboratory proficiency testing is required, e.g. by participating in interlaboratory trials (“Ringversuche”) of the Deutsche Gesellschaft für Pathologie, or UK NEQAS-ICC (UK National External Quality Assessment Scheme for Immunocytochemistry) or NordiQC.

References:

Ki-67-testing

Ki-67 is helpful in determining the grade of tumors. G1 tumors usually show a Ki-67 index below 15% and G3 tumors exhibit a labeling index ≥ 25%. In core biopsies Ki-67 is better suited to predict the final histological grade than mitotic counts. Whether a threshold of 14% is able to discriminate between the luminal A and B type awaits further research. Ki-67 determination has shown to be variable.

Intrinsic Breast Cancer Types (17/20)

No further information

No references
**Triple-negative breast cancer (18/20)**

*No further information*

*No references*
**Evaluation of Sentinel Node Biopsy (19/20)**

*Further information:*

**Statement: Evaluation of sentinel node biopsy:**

The aim of histological workup of sentinel nodes is to detect macrometastases (> 2 mm), and the histological techniques must be adequate to meet this aim. Therefore, it is recommended to work up sentinel lymph nodes using step sections of ≥ 500 µm in order to make certain not to miss a macrometastasis (Kühn 2005).

**Statement: Full workup using step sections of ≥ 500 µm on paraffin embedded tissue**

The additional use of immunohistochemistry (IHC) results in an increase of sensitivity to detect micrometastases and ITC. Because of the expense of routine IHC and the questionable benefit of detecting additional micrometastases, IHC is not recommended as a routine procedure.

The sensitivity of frozen sections on sentinel node biopsies to a large extent depends upon how extensive the workup of the paraffin section is, and therefore varies to a wide extent in the literature. If not performed adequately, frozen sections of sentinel nodes may lead to loss of tissue and diagnostic information.

**Statement: Imprint cytology instead or in addition of frozen section**

Imprint cytology has a similar sensitivity and specificity when compared with frozen section. However it requires special expertise and may be slower than frozen tissue section (Layfield, 2010, Limberis 2009).

**Statement: RT-PCR for epithelial genes**

RT-PCR for epithelial genes has been reported to have a similar sensitivity as frozen sections. Because of several disadvantages, the routine use of RT-PCR is discouraged. These disadvantages include:

- Not all breast cancers are positive for Ck19 and/or mammaglobin. Some of the most aggressive tumors, such as triple-negative breast cancers, are negative for for Ck19 and mammaglobin.
- The use of RT-PCR precludes the classification of lymph node metastases according to TNM (micro-/macrometastases, ITC).
- In an unknown proportion of cases, axillary lymph nodes may contain benign epithelial inclusions.

References:

Mutation or Expression Analysis (20/20)

No further information

No references
Prognostic and Predictive Factors
Prognostic and Predictive Factors

- **Version 2002:**
  Thomssen / Harbeck

- **Versionen 2003–2013:**
  Costa / Friedrichs / Gerber / Göhring / Harbeck / Loibl / Mundhenke / Nitz / Rody / Schaller / Schmidt / Schmutzler / Schneeweiss / Simon / Solomayer / Thomssen

- **Version 2014:**
  Liedtke / Harbeck
Definition

A **Prognostic Factor*** is any parameter available at the time of interest e.g. primary diagnosis that correlates with disease-free or overall survival, in the absence of any therapy and, as a result, is able to correlate with the natural history of the disease.

A **Predictive Factor** is any parameter associated with response to a given therapy.

*as mentioned in this context represent markers of BC recurrence*
“Low absolute risk implies low absolute benefit”

Threshold?
Karp et al SABCS 2012: cumulative leucemia/MDS after 10 yrs 0.5 %
Martin et al SABCS 2010: chronic heart failure (at ten years) in 3.5 % after TAC
Quality Criteria

- Biological hypothesis
- Simple and reliable determination method, quality assurance (QA) of the test
- Prospectively planned statistical evaluation (primary goal)
- Validation of clinical significance according to
  - „Oxford Level of Evidence (LoE_{Ox2001})“ criteria and „Grades of Recommendation (GR)“
  - „Grades of Recommendation (GR)“ as well as modified LoE criteria for the use in archived specimen (LoE_{2009}) and category of tumor marker study (CTS)
- Clinical relevance for treatment decisions

1 Simon et al, J Natl Cancer Inst 101: 1446-1452, 2009
2 Febbo et al, J Natl Compr Canc Netw 9 Suppl 5: S1-32, 2011
# Elements of Tumor Marker Studies that Constitute Levels of Evidence Determination

<table>
<thead>
<tr>
<th>Category Element</th>
<th>A Prospective</th>
<th>B Prospective using archived samples</th>
<th>C Prospective/observational</th>
<th>D Retrospective/observational</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical trial</strong></td>
<td>Prospective controlled trial (PCT) designed to address tumor marker</td>
<td>Prospective trial not designed to address tumor marker, but design accommodates tumor marker utility</td>
<td>Prospective observational registry, treatment and follow-up not dictated</td>
<td>No prospective aspect to study</td>
</tr>
<tr>
<td><strong>Patients and patient data</strong></td>
<td>Prospectively enrolled, treated, and followed in PCT</td>
<td>Prospectively enrolled, treated, and followed in clinical trial and, especially if a predictive utility is considered, a PRCT addressing the treatment of interest</td>
<td>Prospectively enrolled in registry, but treatment and follow-up standard of care</td>
<td>No prospective stipulation of treatment or follow-up; patient data collected by retrospective chart review</td>
</tr>
<tr>
<td><strong>Specimen collection, processing, and archival</strong></td>
<td>Specimens collected, processed, and assayed for specific marker in real time</td>
<td>Specimens collected, processed, and archived prospectively using generic SOPs. Assayed after trial completion</td>
<td>Specimens collected, processed, and archived prospectively using generic SOPs. Assayed after trial completion</td>
<td>Specimens collected, processed and archived with no prospective SOPs</td>
</tr>
<tr>
<td><strong>Statistical design and analysis</strong></td>
<td>Study powered to address tumor marker question</td>
<td>Study powered to address therapeutic question and underpowered to address tumor marker question</td>
<td>Study not prospectively powered at all. Retropective study design confounded by selection of specimens for study</td>
<td>Study not prospectively powered at all. Retropective study design confounded by selection of specimens for study</td>
</tr>
<tr>
<td><strong>Validation</strong></td>
<td>Result unlikely to be play of chance</td>
<td>Result more likely to be play of chance that A but less likely than C</td>
<td>Result very likely to be play of chance</td>
<td>Result very likely to be play of chance</td>
</tr>
</tbody>
</table>

### Revised Determination of Levels of Evidence using Elements of Tumor Marker Studies

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Category</th>
<th>Validation studies available</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>None required</td>
</tr>
<tr>
<td>I</td>
<td>B</td>
<td>One or more with consistent results</td>
</tr>
<tr>
<td>II</td>
<td>B</td>
<td>None or inconsistent results</td>
</tr>
<tr>
<td>II</td>
<td>C</td>
<td>2 or more with consistent results</td>
</tr>
<tr>
<td>III</td>
<td>C</td>
<td>None or 1 with consistent results or inconsistent results</td>
</tr>
<tr>
<td>IV–V</td>
<td>D</td>
<td>Not applicable because LOE IV and V studies will never be satisfactory for determination of medical utility</td>
</tr>
</tbody>
</table>

Requirements for a Marker-Based Test to Reach Level IB Evidence

1. Adequate amounts of archived specimen must be available from enough patients from a prospective trial ... for analyses to have adequate statistical power and for the patients included in the evaluation to be clearly representative of the patients in the trial.

2. The marker-based test should be analytically and preanalytically validated for use with archived specimens.

3. The plan for marker evaluation should be completely specified in writing before the performance of marker assays on archived specimens and should be focused on evaluation of a single completely defined marker-based test.

4. The results from archived specimens should be validated using specimens from one or more similar, but separate, studies.

McShane & Hayes, J Clin Oncol 30: 4223-4232, 2012
## Prognostic Factors I in Early Breast Cancer

<table>
<thead>
<tr>
<th>Factor</th>
<th>LoE\textsubscript{Ox2001}</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Nodal status</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>1a</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Histological tumor type (colloid, mucinous, tubular etc.)</td>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Grade (Elston&amp;Ellis)</td>
<td>2a</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Age</td>
<td>2a</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Peritumoral lymphatic vessel and vascular invasion (L1 V1)</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>pCR after NACT* in (HR+/G3, HER2+, TN)</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>BMI</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>

* NACT = Neoadjuvant Chemotherapy
Reproducibility

- ER/PR discordance central vs local ≈20% (ASCO/CAP JCO 2010)

- HER2 inaccurate testing suspected in approximately 20% (ASCO /CAP JCO 2007)

- Impact of routine pathologic review in N0 BC: 20% changes: grading 40%, LVI 26%, N 15%, margin 12% (JCO 2012)

- pN0 from MIRROR study: pN0 was upstaged in 22%, pN1mi: 11% upstaged, 15% downstaged in central pathology review (Ann Oncol 2012)

- Consistency: 107 cases examined by 23 pathologists in 4 rounds: Grading: Kappa 0.53; LVI Kappa 0.38 (ECWGBSP, 1999) (Virchows Arch 1999)
Critical Issues Regarding LoEs for Biomarkers

It needs to be emphasized that the levels of evidence obtained by Oxford-criteria and CTS-criteria cannot be directly compared.

The prospectively-planned retrospective validation of a biomarker (CTS level 1) may be biased by an insufficient number of clinical trial samples used for the biomarker analysis.

This sample collection may not represent the reported outcome of the clinical trial. An optimal percentage of sample needed from clinical trials needed for optimal biomarker validation has not yet been established *

# Prognostic Factors II in Early Breast Cancer

<table>
<thead>
<tr>
<th>Factor</th>
<th>LoE&lt;sub&gt;2001&lt;/sub&gt;</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER / PgR</td>
<td>2a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>HER2 (IHC, FISH)</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>ER / PgR / HER2 as surrogate markers for molecular subtypes</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>uPA / PAI (Femtelle® ELISA)&lt;sup&gt;§&lt;/sup&gt; in N0</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Proliferation markers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ki-67 before, during or after treatment</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Mitotic activity Index (MAI)</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
</tbody>
</table>

<sup>§</sup> Validated clinical data only available for this assay
## Commercially Available Molecular Tests

<table>
<thead>
<tr>
<th>Provider</th>
<th>70 gene signature (MammaPrint®) $</th>
<th>21 gene Recurrence score (Oncotype DX®) $</th>
<th>8 gene signature (Endopredict®) $</th>
<th>PAM 50 (Prosigna®) $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agendia</td>
<td>Fresh frozen (technical validation for FFPE available)</td>
<td>FFPE</td>
<td>FFPE</td>
<td>FFPE</td>
</tr>
<tr>
<td>Genomic Health</td>
<td>70-gene assay</td>
<td>21-gene recurrence score</td>
<td>11-gene assay</td>
<td>50-gene assay</td>
</tr>
<tr>
<td>Sividon</td>
<td>FFPE</td>
<td>FFPE</td>
<td>FFPE</td>
<td>FFPE</td>
</tr>
<tr>
<td>NanString</td>
<td>FFPE</td>
<td>FFPE</td>
<td>FFPE</td>
<td>FFPE</td>
</tr>
</tbody>
</table>

| Type of assay | 70-gene assay | 21-gene recurrence score | 11-gene assay | 50-gene assay |
| Type of tissue | Fresh frozen (technical validation for FFPE available) | FFPE | FFPE | FFPE |
| Technique     | Microarrays for RNA | qRT-PCR | q-RT-PCR | qRT-PCR |
| Central lab   | Yes | Yes | No | No |

| Indication and population studied | Prognostic N₀₋₁, <61 Jahre | Prognostic N₀₋₁ ER+ endocrine treated | Prognostic (pre-) postmenopausal N₀₋₁ ER+ HER2- endocrine treated | Prognostic postmenopausal N₀₋₁ ER+ HER2- endocrine treated |

| Clinical Validation | Yes | Yes | Yes | Yes |

| Registration | FDA clearance as “In Vitro Diagnostic Multivariate Index Assay (IVDMIA)” | Clinical Laboratory Improvement Amendments (CLIA) + College of American Pathologists (CAP)-accredited ref lab | CE-Mark | FDA 510(k) Clearance |

$ Validated clinical data only available for this assay
### Commercially Available Molecular Tests

<table>
<thead>
<tr>
<th></th>
<th>70 gene signature (MammaPrint®)</th>
<th>21 gene Recurrence score (Oncotype DX®)</th>
<th>8 gene signature (Endopredict®)</th>
<th>PAM 50 (Prosigna®)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prognosis after 5 yrs (late recurrences)</strong></td>
<td>not separately shown</td>
<td>No</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td><strong>Predictive impact (chemotherapy benefit)</strong></td>
<td>poorly validated</td>
<td>yes *</td>
<td>not shown</td>
<td>not shown</td>
</tr>
<tr>
<td><strong>Prospective-retrospective evidence (% of recruited patients)</strong></td>
<td>Multicenter validation</td>
<td>NSABP B-14 (14%)</td>
<td>ABCSG 6 (19%)</td>
<td>MA.12 (59%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSABP B-20 (28%)</td>
<td>ABCSG 8 (36%)</td>
<td>MA.5 (66%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ECOG 9127</td>
<td></td>
<td>ABCSG 8 (44%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SWOG 8814 (40%)</td>
<td></td>
<td>ATAC (16%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ATAC (30%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prospective evidence (pending)</strong></td>
<td>MINDACT (completed)</td>
<td>TAILORx (n0, completed)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RxPONDER (n1, ongoing)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Validated clinical data only available for this assay
* Trial performed before HER2 testing, HER2 positive patients may have been included
## Prognostic Factors III in Early Breast Cancer

<table>
<thead>
<tr>
<th>Faktor</th>
<th>LoE&lt;sub&gt;2009&lt;/sub&gt;</th>
<th>CTS</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disseminated tumor cells (DTC, in bone marrow)</td>
<td>I</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Circulating tumor cells (CTC, in blood, Cell Search&lt;sup&gt;®&lt;/sup&gt;) $</td>
<td>I</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Therapy decisions based on CTC phenotypes</td>
<td>III</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>21 gene recurrence score (Oncotype DX&lt;sup&gt;®&lt;/sup&gt;) $ (N0-1 ER+ HER2-, endocrine treated)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>I</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>N1</td>
<td>II</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>8 gene signature (EndoPredict&lt;sup&gt;®&lt;/sup&gt;) $ (postmenopausal, N0-1 ER+ HER2-, endocrine treated)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>I</td>
<td>B</td>
<td>+*</td>
</tr>
<tr>
<td>N1</td>
<td>II</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>70 gene signature (MammaPrint&lt;sup&gt;®&lt;/sup&gt;), N0-1</td>
<td>II</td>
<td>C</td>
<td>+/-</td>
</tr>
<tr>
<td>PAM 50 (Prosigna&lt;sup&gt;®&lt;/sup&gt;) $ (postmenopausal, N0-1 ER+ HER2-, endocrine treated)</td>
<td>II</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>IHC4 (central pathology, published algorithm) #</td>
<td>I</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>

* Should only be used in selected patients if all other criteria are inconclusive for therapeutic decision making

$ Validated clinical data only available for this assay

# Cuzick et al., J Clin Oncol 29: 4273-4278, 2011
## Neoadjuvant Systemic Chemotherapy

### Response Prediction I

<table>
<thead>
<tr>
<th>Factor</th>
<th>CTS</th>
<th>LoE\textsubscript{Ox2001}</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young age</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>cT1 / cT2 tumors o. N0 o. G3</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Negative ER and PgR status</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Triple negative breast cancer (TNBC)</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Positive HER2 status</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Non-lobular tumor type</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Early clinical response</td>
<td>B</td>
<td>1b</td>
<td>A</td>
<td>+</td>
</tr>
</tbody>
</table>
# Neoadjuvant Systemic Chemotherapy Response Prediction II

## Factor

<table>
<thead>
<tr>
<th>Factor</th>
<th>LoE&lt;sub&gt;2009&lt;/sub&gt;</th>
<th>CTS</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAM50 (Prosigna$)</td>
<td>III</td>
<td>C</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>70-Gensignatur (Mammaprint$)</td>
<td>III</td>
<td>C</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Ki-67</td>
<td>I</td>
<td>B</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Tumour infiltrating lymphocytes</td>
<td>II</td>
<td>B</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>PIK3CA mutation</td>
<td>II</td>
<td>B</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>

$ Validierte klinische Daten nur verfügbar für diesen Assay
Predictive Factors – Endocrine Therapy

<table>
<thead>
<tr>
<th>Factor</th>
<th>LoE_{Ox2001}</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER/PgR status</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>IHC staining intensity (ER/PgR)</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2D6 polymorphism</td>
<td>2b</td>
<td>D</td>
<td>-</td>
</tr>
<tr>
<td>Ovarian ablation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopausal status</td>
<td>1c</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Aromatase inhibitors vs. Tamoxifen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopausal status</td>
<td>1c</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>ER/PgR/HER2 as single markers</td>
<td>1c</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>Lobular subtype</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Ki-67 high (published cutoffs &gt; 11% and &gt;14 %)</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>BMI</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>
### Predictive Factors – HER2 Targeted Therapy / Adjuvant Chemotherapy

<table>
<thead>
<tr>
<th>Factor</th>
<th>LoE&lt;sub&gt;Ox2001&lt;/sub&gt; (§ LoE&lt;sub&gt;Ox2009&lt;/sub&gt;)</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HER2-Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Adjuvant Chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>uPA/PAI1 (Femtelle&lt;sup&gt;®&lt;/sup&gt;) ELISA $</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>21 gene recurrence score (Oncotype DX&lt;sup&gt;®&lt;/sup&gt;) $</td>
<td>l §</td>
<td>B $</td>
<td>+/-</td>
</tr>
</tbody>
</table>

$ Validated clinical data only available for this assay
# Prognostic factors – Metastatic breast cancer

<table>
<thead>
<tr>
<th>Factor</th>
<th>LoE&lt;sub&gt;2009&lt;/sub&gt;</th>
<th>CTS</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circulating tumor cells (CTC in blood, Cell Search®)</td>
<td>I</td>
<td>B&lt;sup&gt;a&lt;/sup&gt;</td>
<td>+</td>
</tr>
<tr>
<td>Prognosis</td>
<td>I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapy decision solely based on dynamics of CTC over time</td>
<td>I</td>
<td>A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>Therapy decisions based on CTC phenotypes</td>
<td>III</td>
<td>C</td>
<td>-*</td>
</tr>
</tbody>
</table>

* Study participation recommended
Prognostic and Predictive Factors (2/20)

Further information:


Guidelines screened:
- Canadian Medical Association (CMA, 2006: http://www.cmaj.ca/cgi/content/full/158/3/DC1)

References:


Reasons given for the particular evidence level:
Statement 1 (LoE 6): ref. 2 & 3 (retrospective RCT’s, <10% Power)
Definition (3/20)

No further information

No references
Low Absolute Risk Implies Low Absolute Benefit (4/20)

Further information:

Adjuvant chemotherapy reduces breast cancer mortality by one third. However, the benefit is closely related to the absolute risk of this individual patient. Especially in ER positive tumors one has to weigh the benefit against potentially chemotherapy-induced side effects like chronic heart failure and leucemia / MDS. Because of this, proper risk assessment is mandatory.

References:

Quality Criteria (5/20)

Further information:

Ranking of evidence is of pivotal importance for clinical decision-making. The Oxford Levels of Evidence (LoE\textsubscript{Ox2001}) and Grades of Recommendations (GR) were originally released in 2001 by the Centre of Evidence Based Medicine (www.cebm.net). These original Oxford LoE and Grades of Recommendation were modified in 2011. The authors simplified the Levels in several ways. For example, levels 1a-c were merged to level 1. The novel classification was also modified to represent the natural flow of a clinical encounter (diagnosis, prognosis, treatment, benefits, harms). These modified Oxford LoE also apply to prognostic factors. In this case, Level 1 can be reached with “systematic review of inception cohort studies”. Based on study quality and effect size, levels LoE can be graded up or down. Finally, the authors of the modified Oxford LoE state, that “levels be interpreted with a healthy dose of common sense and good judgment”. (1)

To improve the quality of research on biomarkers a guideline named REMARK (Reporting Recommendations of Tumor Marker Prognostic Studies) was defined. REMARK describes the informations which should be given when publishing a biomarker study such as study design, preplanned hypotheses, patient and specimen characteristics, assay methods, and statistical analysis methods. (2) Depending on the quality of a biomarker study, the Tumor Marker Utility Grading System was introduced assigning different levels of evidence to a certain marker. (3) To obtain the highest level of evidence, a marker had to be tested prospectively in a prospectively randomized clinical study. Recently a refined system for biomarker study design and evaluation that incorporates a revised level of evidence scale for tumor marker studies, including those using archived specimens, was introduced. (4) Although fully prospective randomized clinical trials to evaluate the medical utility of a prognostic or predictive biomarker are still considered the gold standard, such trials are costly, so more efficient indirect "prospective–retrospective" designs using archived specimens might reach level I evidence if validated with consistent results. This recommendation was recently elaborated on and finally resumed by the NCCN Task Force Report for evaluation of the clinical utility of tumor markers in oncology. (5,6)

In this chapter on prognostic and predictive factors the original Oxford LoE and the revised classification of Levels of Evidence using elements of tumor marker studies as proposed by Simon, Paik and Hayes, 2009 are used as applicable.
References:


Elements of Tumor Marker Studies that Constitute Levels of Evidence Determination (6/20)

*No further information*

**References:**


Revised Determination of Levels of Evidence Using Elements of Tumor Marker Studies (7/20)

No further information

References:


Requirements of a Marker-Based test to Reach Level IB Evidence (8/20)

*No further information*

References:


Prognostic Factors I in Early Breast Cancer (9/20)

No further information

References:

Canadian Medical Association (CMA, 2006: http://www.cmaj.ca/cgi/content/full/158/3/DC1)
Reproducibility (10/20)

Further information:

Conventional pathology and immunohistochemistry is for methodological reasons subject to high inter-observer variability/variable reproducibility. ASCO-CAP guidelines estimate discordance between central and local pathology in about one fifth of cases for ER and PgR and HER2 status. MIRROR trialists report upgrading of N0 status by central pathological review in a comparable amount. Thus the clinician should be aware of potential problems and pitfalls when decision for adjuvant treatment is taken together with the patient.

References:


Critical Issues regarding LoEs for Biomarkers (11/20)

No further information

No references
Prognostic Factors II in Early Breast Cancer (12/20)

No further information

References:

ER/PR

HER2

Ki-67


Post treatment ki 67:

SPF

uPA/PAI-1
Commercially Available Molecular Tests (13/20) and (14/20)

Further information:

Modern genomic platforms generate highly reproducible information about tumor biology, which has to be integrated during the next years to clinical routine. Since the additive clinical information is highly correlated to the validation sets the commercially available tests have been enumerated separately together with their retrospective-prospective evidence and future evidence projected for > 2015 from prospective randomized trials. ASCO-guidelines already integrated uPA/PAI1 and Oncotype DX®. German AGO members still feel that prospective evidence should be generated before general recommendation. According to the consensus (see Ärzteblatt Stellungnahme der AGO Kommission Mamma) use in selected cases is recommended.

References:

Endopredict


Mammaprint

OncoType


PAM50


Sestak I, Cuzick J, Dowsett M, Filipits M, Dubsky P, Cowens W, Ferree S, Schaper C, Fesl C, Gnant M. Prediction of late distant recurrence after 5 years of endocrine treatment: A combined analysis of 2485 patients from the ABCSG-8 and transATAC studies using the PAM50 risk of recurrence (ROR) score SABCS 2013 (S6-04)
Prognostic Factors III in Early Breast Cancer (15/20)

No further information

References:

Adjuvant!

CTC


DTC


Endopredict


IHC4


Mammaprint


Oncotype


Neoadjuvant Systemic Chemotherapy – Response Prediction I (16/20)

Further information:

This slide is based on the evidence mainly from analyses done by GEPRAR- trialists and remains widely unchanged. It helps to define those subgroups of patients who benefit from NACT in terms of downstaging/pCR. Correlations to survival parameter may differ according to individual parameters and are precised in the first slides. 
Ki 67 data from GEPARTRIO have been updated by Denkert et al. (SABCS 2012) and confirmed a strong correlation if cut-off values of ≤15 and > 35 are presumed to define low and high risk populations.
For the genomic signatures there are new data from the I-Spy trial confirming the predictive value of PAM50 and Mammaprint for pCR after neoadjuvant chemotherapy and – for the first time – correlation with 3 yr dfs.
The FDA Metaanalysis confirms preexisting data from neo ALLTO, Neosphere and GEPAR-trials demonstrating lower pCR rates in tumors coexpressing HR and HER2 compared to HER2+/HR-.

References:

TIL
**Neoadjuvant Systemic Chemotherapy – Response Prediction II (17/20)**

*Further information:*

This slide is based on the evidence mainly from analyses done by GEVAR- trialists and remains widely unchanged. It helps to define those subgroups of patients who benefit from NACT in terms of downstaging/pCR. Correlations to survival parameter may differ according to individual parameters and are precised in the first slides.

Ki 67 data from GEPARTRIO have been updated by Denkert et al. (SABCS 2012) and confirmed a strong correlation if cut-off values of ≤15 and > 35 are presumed to define low and high risk populations.

For the genomic signatures there are new data from the I-Spy trial confirming the predictive value of PAM50 and Mammaprint for pCR after neoadjuvant chemotherapy and – for the first time – correlation with 3 yr dfs.

The FDA Metaanalysis confirms preexisting data from neo ALLTO, Neosphere and GEPAR-trials demonstrating lower pCR rates in tumors coexpressing HR and HER2 compared to HER2+/HR-.

*References:*

TIL
Predictive Factors – Endocrine Therapy (18/20)

Further information:

EBCTCG analysis provides ample evidence that hormone receptor status is predictive for endocrine response, whereas little effect can be attributed to tumor size, nodal status, age and grading. According to the ASCO /CAP guidelines the panel recommended endocrine therapy in patients whose breast tumors show at least 1% ER positive cells. Same is true for PG receptor levels. HER2 overexpressing tumors present primarily with more aggressive biology. HER2 overexpression, quantitative ER and PR expression as single markers do not identify patients with better outcome after AI, when compared to TAM. (Dowsett M)

Cyp2D6 polymorphism detection is not recommended in daily routine as the metaanalysis done by Goertz is not conclusive. ABCSG12 trialists, who compared AI + Goserelin vs Tam in premenopausal women report a nearly 50% increase in the risk of disease recurrence (HR 1.49) and a three-fold risk of death for overweight patients (BMI > 25) receiving AI+ Gos in comparison to TAM. In postmenopausal women ATAC trialist report a nonsignificantly better relative benefit of AI vs Tam in thin women vs overweight women (BMI > 35).

A retrospective analysis from a representative subgroup of more than 2500 patients from BIG 1-98 demonstrated a strong correlation of AI superiority with invasive lobular histology and luminal B like tumors (ER+/PR+/Ki 67 >14, HER2-). The HR were 0.95 for ductal luminal A, 0.64 for ductal luminal B, 0.49 for lobular luminal a and 0.33 for lobular luminal B.

No references
Predictive Factors – HER2 Targeted Therapy / Adjuvant Chemotherapy (19/20)

Further information:

Her2 overexpression (ICH, FISH) is highly predictive for anti HER2 therapy. During SABCS 2012 Baselga presented biomarker analyses evaluating patients with higher benefit from addition of pertuzumab from the CLEOPATRA trial. Neither HER2 or HER3 (mRNA), nor EGFR (mRNA) were predictive.

The last EBCTCG metaanalysis involving over 100 000 chemotherapy patients from 123 randomized trials demonstrated proportional risk reduction little affected by age, nodal status, tumor diameter, HR status and grading. The evidence for HER2 overexpression is much less well evaluated. Most data are derived from trials evaluating chemotherapy + endocrine therapy versus endocrine therapy alone in HR+ patients (Viale IBCSG VIII + IX, Albain SWOG 8814 and Paik NSABP B-20). Uniformly the degree with chemotherapy interaction is non significant independently whether evaluated by central DAKO Hercept testing or her2 gene group as part of Oncotype DX.

The prospectively randomized chemo N0 trial demonstrated that high levels of upA/PAI-1 are associated to increased CMF chemotherapy benefit. In N0-1/HR+ patients the same has been demonstrated by retrospective analyses from the prospective trials NSABP – B20 and SWOG 8814 for CAF/Tam vs Tam alone. In N0 patients from B-20 the RR was 0.26, 0.61 and 1.31 for high risk, intermediate risk and low risk patients, with an net chemotherapy benefit of 28 % 10 year distant free survival benefit in the high risk group. In SWOG 8814 evaluating N+ patients the HRs for 5 yr overall survival were 0.56 in the high risk group, 0.84 in the intermediate and 1.18 in the low risk group resulting in a net 10 yrs dfs benefit of 12 % for the high risk group.

Data for Mammaprint (Knauer et al) refer to 541 patients from pooled study series from patients who received endocrine therapy +/- chemotherapy. In the high risk group the univariate HR was 0.21 (p < 0.01) compared to 0.58 (p= 0.6) in the low risk group. For other genomic signatures there are no data. PAM50 has been only evaluated in a neoadjuvant setting as surrogate parameter for pCR and Endopredict data refer to patients treated with endocrine therapy only.

Baseline Ki-67 is as Viale et al demonstrated from retrospective analyses of two IBCSG trials no independent predictor of chemotherapy outcome. Retrospective subgroup analyses of patients from large taxane trials (GEICAM, PACS 01, BCIRG 01,EC-Doc) demonstrate that luminal A like tumors identified by IHC are likely to have small benefit, but these third generation trials do not have endocrine only arms.

HER2 overexpression was highly predictive for anthracyline outcome, when compared to CMF. In a subgroup of the patients analysed by Gennari Di Leo published a metaanalysis comparing the impact of Her2 status and TOP2A (FISH). The HR for her2 amplification and non amplification were 0.89 and 0.71 respectively. Those for Topo normal versus Topo altered were 0.88 vs 0.64 respectively.

zurück
TOP2A coamplification, not HER2 amplification, is the clinically useful predictive marker of an incremental response to anthracycline-based chemotherapy.
Response to taxanes has been evaluated in different third generation trials comparing anthracycline based chemotherapy vs taxane/anthracycline based regimens. Identification of low proliferating tumors by central ki-67 evaluation was predictive for taxane outcome in EC-Doc, BCIRG 001 and PACS 001, but not in the GEICAM trial. Endopredict and Oncotype DX did not predict taxane response in the GEICAM trial and in NSABP B28 respectively.

*No references*
**Prognostic factors – Metastatic breast cancer (20/20)**

*No further information*

**References:**

**CTC**
Lesions of Uncertain Malignant Potential (B3)

(ADH, LIN, FEA, Papilloma, Radial Scar)
Lesions of Uncertain Malignant Potential (B3) (including “Precursor Lesions”)

- **Versions 2005–2013:** Albert / Audretsch / Brunnert / Fersis / Friedrich / Gerber / Kreipe / Nitz / Rody / Schreer / Sinn / Thomssen

- **Version 2014:** Sinn / Fersis
Pathology Reporting for Minimal Invasive Biopsies

B – Classification*

B1 = unsatisfactory / normal tissue only
B2 = benign lesion
B3 = lesion of uncertain malignant potential
B4 = suspicion of malignancy
B5 = malignant
   B5a = non-invasive
   B5b = invasive
   B5c = in-situ/invasion not assessable
   B5d = non epithelial, metastatic

* National Coordinating Group for Breast Screening Pathology (NHSBSP), E.C. Working Group on Breast Screening Pathology, S3-Leitlinien
B3-Lesions

- Lesions with risk of associated DCIS or invasive Ca:
  - Atypical ductal hyperplasia (ADH)
  - Lobular neoplasia (ALH, LCIS)
  - Flat epithelial atypia (FEA)

- Inhomogenous lesions with sampling risk:
  - Phyllodes tumor, cellular fibroadenoma
  - Papilloma, if incompletely removed
  - Radial scar, complex sclerosing lesion
Management after Minimally Invasive Biopsy

Interdisciplinary conference: Concordant findings in pathology and imaging?

→ yes: proceed according to histologic type 
   3a C ++

→ no: open biopsy 
   3a C ++
Atypical Ductal Hyperplasia (ADH)

- **Synonyms:** Atypical intraductal epithelial proliferation (AIDEP)
- **Definition:** Atypical intraductal proliferations with cytologic and structural features of well differentiated DCIS, such as rigid bridging or micropapillae, well demarcated cell borders and occupy less than two separate duct spaces. The extension of all involved lumina within one ductulo-lobular unit is less than 2 mm. Atypical ductal proliferations larger than 2 mm or in at least two ductules are classified as DCIS (low-grade).
- **Indicator/Precursor lesion:** Ipsi- and contralateral breast cancer risk: RR 3 - 5 x after 3 - 5 years.
- **Classification in ductal intraepithelial neoplasia grade 1 - 3 is not sufficiently validated.**
## Risk of Breast Cancer after Atypical Hyperplasie (ADH, ALH)

### Stratification of breast cancer risk*

<table>
<thead>
<tr>
<th>Feature</th>
<th>Value</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Foci</td>
<td>1, 2, ≥ 3</td>
<td>2.33, 5.26, 7.97</td>
</tr>
<tr>
<td>Microcalcifications</td>
<td>present, not present</td>
<td>3.21, 4.21</td>
</tr>
<tr>
<td>Type</td>
<td>ductal, lobular, both</td>
<td>3.83, 3.67, 7.10</td>
</tr>
<tr>
<td>Age</td>
<td>&lt; 45, 45 – 55, &gt; 55</td>
<td>6.76, 5.10, 2.67</td>
</tr>
</tbody>
</table>

Strategy after Diagnosis of ADH

ADH in core- / vacuum-assisted biopsy:

- Open excisional biopsy
- Open excisional biopsy may be omitted, with:
  a) A small lesion (≤ 2 TDLU* in vacuum biopsy) and
  b) Complete removal of imaging abnormality

ADH at margins in resection specimen:

- No further surgery, if incidental finding accompanying invasive or intraductal carcinoma

* Terminal ductal-lobular unit

Oxford / AGO
LoE / GR

3a  C  ++
5a  C  +
3a  C  ++
Lobular Intraepithelial Neoplasia (LIN)

- **Includes:** Atypical lobular hyperplasia, lobular carcinoma in situ, LCIS/CLIS
- LIN1 - 3 classification is not sufficiently validated prognostically
- Pleomorphic LIN and LIN with are classified as → B5a
- **Indicator/Precursor lesion:** Ipsilateral- and contralateral enhanced breast cancer risk: 7 x at 10 years
Variants of Lobular Neoplasia

Classical LIN

LIN with comedo type necrosis

Florid LIN

Pleomorphic LIN
LIN with High Risk

- Pleomorphic LCIS: high grade cellular atypia, frequent involvement of ductules, comedo-type necroses, microcalcifications
- Florid LCIS: Involvement of numerous lobuli with distension and near confluence, extension to ductules and neighbouring TDLU
- Type of LCIS with 21 cases of LCIS with microinvasion*:
  - classical LCIS: n=11
  - florid LCIS: n=4
  - pleomorphic LCIS: n=1
Strategy after Diagnosis of LIN

- **LIN in core- / vacuum-assisted biopsy:**
  - Open excisional biopsy, with pleomorphic LIN, florid LIN, or LIN with comedo type necrosis or when not concordant with imaging findings
  - **Oxford / AGO LoE / GR:** 2b C ++

- **LIN at margins of resection specimen (BCT):**
  - No further surgery
  - **Oxford / AGO LoE / GR:** 3a C ++
  - **Exceptions:**
    a) Pleomorphic LIN, florid LIN, or LIN with necrosis
    b) Imaging abnormality is not removed
  - Complete resection
  - **Oxford / AGO LoE / GR:** 5 D ++
Flat Epithelial Atypia (FEA)

- **Synonyms:** Columnar cell hyperplasia with atypia, columnar cell metaplasia with atypia, ductal intraepithelial neoplasia grade 1A (DIN 1A)

- **Differential diagnosis:**
  - ADH is discriminated by architectural features (micropapillary, cribriform) → B3
  - Clinging carcinoma is discriminated by high grade nuclear atypia (G2/G3) and classified as → B5a

- **Marker lesion:**
  FEA is frequently associated with calcifications and may be associated with intraductal carcinoma. Therefore, correlation with imaging is mandatory.
Strategy after Diagnosis of FEA

- **FEA in core biopsy/vacuum-assisted biopsy:**
  - Open excisional biopsy
  - Open excisional biopsy may be omitted, with:
    - a small lesion (≤ 2 TDLU* in vacuum biopsy) and complete removal of imaging abnormality  

- **FEA at margins in resection specimen:**
  - No further surgery, unless calcifications have not been completely removed

---

* Terminal ductal-lobular unit
Papilloma

- **Includes**: central papilloma, large duct papilloma, major duct papilloma, intraductal papilloma, atypical intraductal papilloma (B3)
- To be discriminated from papilloma with DCIS and from peripheral papillomas arising in the TDLU, size ≤ 2 mm, may be multiple
- To be discriminated from intraductal papillary carcinoma and encapsulated papillary carcinoma
- **Indicator lesion**: May be associated with in-situ or invasive cancer (10%, in case of atypical papilloma up to 20%), increased ipsilateral risk for cancer (4.6% to 13% in case of atypical papilloma)
Strategy after Diagnosis of Central Papilloma

- Papilloma in core- / vacuum-assisted biopsy:
  - Open excisional biopsy

- Papilloma at margins of resection specimen:
  - No study data available

Oxford / AGO
LoE / GR
3a  C  ++
Radially Sclerosing Lesion

- Benign pseudoinfiltrative lesion with central fibroelastic core and radical configuration.

- Includes:
  - radial scar
  - complex sclerosing lesion (> 1 cm)

- Additional risk factor in patients with benign epithelial hyperplasia (proliferating breast disease)

- Risk for upgrade in open biopsy after diagnosis of radial-sclerosing lesion in core biopsy: 8.3% (79/948)*

Strategy after Diagnosis of Radial Scar, Complex Sclerosing Lesion (CSL)

- **Radial scar / CSL in core biopsy/vacuum-assisted biopsy:**
  - Open excisional biopsy
  - Open excisional biopsy may be omitted, with a small lesion and complete removal of imaging abnormality

- **Radial scar / CSL at margins in resection specimen:**
  - No further surgery, unless calcifications have not been completely removed

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>3b</th>
<th>C</th>
<th>+</th>
</tr>
</thead>
<tbody>
<tr>
<td>LoE / GR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td></td>
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<td>+</td>
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<td>5a</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>++</td>
<td></td>
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</tr>
</tbody>
</table>
Follow-up Imaging for Women Age 50-69 Years with B3-Lesions

FEA, non-atypical Papilloma
➤ Screening mammography

LIN
➤ Mammography (12 months)

ADH
➤ Mammography (12 months)

➤ Women with LIN and ADH should be informed about their elevated risk of breast cancer

Oxford / AGO LoE / GR

FEA, non-atypical Papilloma
5  C  ++

LIN
3a  C  ++

ADH
3a  C  ++
Medical Prevention for Women at Increased Risk (including Women with LIN and ADH)

- Tamoxifen for women >35 years –
  Risk reduction of invasive BrCa and DCIS
  1a A +*

- Raloxifene for postmenopausal women -
  Risk reduction of invasive BrCa only
  1b A +*

- Aromatase inhibitors for postmenopausal women
  5 D +/−**

Medical prevention should only be offered after individual and comprehensive counseling; the net benefit strongly depends on risk status, age and pre-existing risk factors for side effects.

*Risk situation as defined in NSABP P1-trial (1,66% in 5 years)
** Study participation recommended
### Outcome of Medical Prevention (1)

#### NSABP-P1 Study, update 2005

<table>
<thead>
<tr>
<th></th>
<th>Placebo Rate / 1000 WE</th>
<th>Tamoxifen Rate / 1000 WE</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women</td>
<td>6.29</td>
<td>3.59</td>
<td>0.57</td>
<td>0.46-0.70</td>
</tr>
<tr>
<td>w/o LCIS</td>
<td>5.93</td>
<td>3.41</td>
<td>0.58</td>
<td>0.46-0.72</td>
</tr>
<tr>
<td>W LCIS</td>
<td>11.70</td>
<td>6.27</td>
<td>0.54</td>
<td>0.27-1.02</td>
</tr>
<tr>
<td>w/o AH</td>
<td>5.87</td>
<td>3.69</td>
<td>0.63</td>
<td>0.50-0.78</td>
</tr>
<tr>
<td>w AH</td>
<td>10.42</td>
<td>2.55</td>
<td>0.25</td>
<td>0.10-0.52</td>
</tr>
<tr>
<td>5 y risk &lt;2%</td>
<td>4.77</td>
<td>3.18</td>
<td>0.67</td>
<td>0.43-1.01</td>
</tr>
<tr>
<td>5 y risk &gt;5%</td>
<td>11.98</td>
<td>5.15</td>
<td>0.43</td>
<td>0.28-0.64</td>
</tr>
<tr>
<td>One 1° relatives</td>
<td>6.47</td>
<td>3.48</td>
<td>0.54</td>
<td>0.34-0.83</td>
</tr>
<tr>
<td>&gt;= three 1° relatives</td>
<td>11.24</td>
<td>5.48</td>
<td>0.49</td>
<td>0.16-1.34</td>
</tr>
<tr>
<td>Fractures</td>
<td>2.88</td>
<td>1.97</td>
<td>0.91</td>
<td>0.51-0.92</td>
</tr>
<tr>
<td>Endometrial Ca</td>
<td>0.68</td>
<td>2.24</td>
<td>3.28</td>
<td>1.87-6.03</td>
</tr>
</tbody>
</table>

#### NSABP-P2 Study, STAR trial 2006

<table>
<thead>
<tr>
<th></th>
<th>Tamoxifen Rate / 1000 WE</th>
<th>Raloxifen Rate / 1000 WE</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women</td>
<td>4.30</td>
<td>4.41</td>
<td>1.02</td>
<td>0.82-1.28</td>
</tr>
<tr>
<td>W/O LCIS</td>
<td>3.76</td>
<td>3.89</td>
<td>1.03</td>
<td>0.81-1.33</td>
</tr>
<tr>
<td>W LCIS</td>
<td>9.83</td>
<td>9.61</td>
<td>0.98</td>
<td>0.58-1.63</td>
</tr>
<tr>
<td>W/O AH</td>
<td>4.06</td>
<td>4.03</td>
<td>0.99</td>
<td>0.76-1.28</td>
</tr>
<tr>
<td>W AH</td>
<td>5.21</td>
<td>5.81</td>
<td>1.12</td>
<td>0.72-1.74</td>
</tr>
<tr>
<td>5 y risk &lt;3%</td>
<td>2.03</td>
<td>2.83</td>
<td>1.40</td>
<td>0.87-2.28</td>
</tr>
<tr>
<td>5 y risk &gt;5%</td>
<td>6.77</td>
<td>7.35</td>
<td>1.09</td>
<td>0.78-1.52</td>
</tr>
<tr>
<td>One 1° relatives</td>
<td>4.99</td>
<td>5.18</td>
<td>1.04</td>
<td>0.69-1.55</td>
</tr>
<tr>
<td>&gt;= two 1° relatives</td>
<td>5.16</td>
<td>5.00</td>
<td>0.97</td>
<td>0.60-1.56</td>
</tr>
<tr>
<td>Endometrial CA</td>
<td>2.00</td>
<td>1.25</td>
<td>0.62</td>
<td>0.35-1.08</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>3.71</td>
<td>2.61</td>
<td>0.70</td>
<td>0.54-0.91</td>
</tr>
<tr>
<td>Developing Cataracts</td>
<td>12.30</td>
<td>9.72</td>
<td>0.79</td>
<td>0.68-0.92</td>
</tr>
</tbody>
</table>

Should only be offered to women at high risk, e.g.
- with LIN
- with ADH
- with a strong family history

Should not be offered to women
- with a moderate risk over the age of 50
- with an increased risk for thromboembolic events
### Outcome of Medical Prevention (2)

Risks and benefits with long-term Tamoxifen use compared with placebo: results from the IBIS-I Trial, 96 months median follow-up  

<table>
<thead>
<tr>
<th>Event</th>
<th>RR</th>
<th>95% CI</th>
<th>AR per 1000*</th>
<th>NNT / NNH**</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC Incidence</td>
<td>0.73</td>
<td>0.58-0.91</td>
<td>15</td>
<td>68</td>
</tr>
<tr>
<td>Invasive BC</td>
<td>0.74</td>
<td>0.58-0.94</td>
<td>12</td>
<td>81</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>1.72</td>
<td>1.27-2.36</td>
<td>14</td>
<td>73</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>1.84</td>
<td>1.21-2.82</td>
<td>9</td>
<td>115</td>
</tr>
<tr>
<td>Headache</td>
<td>0.93</td>
<td>0.87-0.99</td>
<td>25</td>
<td>39</td>
</tr>
<tr>
<td>Gynecological / vasomotoric symptoms</td>
<td>1.08</td>
<td>1.06-1.10</td>
<td>64</td>
<td>16</td>
</tr>
<tr>
<td>Breast complains</td>
<td>0.77</td>
<td>0.70-0.84</td>
<td>58</td>
<td>17</td>
</tr>
</tbody>
</table>

**Risk communication:**

**AR**: absolute risk difference per 1000 women  
**NNT/NNH** number needed to treat or number needed to harm only shown for statistically significant events over the entire follow-up period

Data computed by guideline authors Visvanathan K et al. JCO 2009;27:3235-3258
Lesions of Uncertain Malignant Potential (B3) (2/22)

Further information:

Search:


Guidelines screened:

- Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Aktualisierung 2012
- NCCN Breast cancer V.1.2014
- NCCN Breast Cancer Risk Reduction I 2013
- NCCN Breast Cancer Screening and Diagnosis 2.2013
- NZ: HTA risk assessment 2007
- CMJA: no update
- NICE: no update
- SIGN: no update
- Cochrane: Decision aids for risk communication update 2009
- DARE: no relevant references. 2010
- ASCO 2012: done
- National Institute of health (NIH): done
- San Antonio Breast Cancer Conference (SABCC 2013): done
References

National and international guidelines

3. Leitlinienprogramm Onkologie der AWMF, Deutschen Krebgesellschaft e.V. und Deutschen Krebshilfe e.V. (Hrsg.). Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Langversion 3.0, Aktualisierung 2012 AWMF-Register-Nummer: 032 – 0450L
Pathology Reporting for Minimal Invasive Biopsies (3/22)

Further information:

The histologic B-classification of breast core biopsies as based on recommendations of the National Coordinating Group for Breast Screening Pathology (NHSBSP), and the European Commission Working Group on breast screening pathology.

References:

Further information:
Lesions of uncertain malignant potential include atypical ductal hyperplasia (ADH), lobular neoplasia (LN), flat epithelial atypia (FEA), atypical papillary proliferations, and lesions with sampling risk because of inhomogeneity, such as phyllodes tumor, cellular fibroadenoma, and radial scars. The lesions with atypical proliferations (ADH, ALH, LCIS, FEA) are regarded both as an indicator of increased risk, but also as precursor lesions, and are part of the low-grade pathway of breast cancers [1-4]. The accurate pathological identification and classification of lesions with atypical proliferations is important to assess the individual risk of the patient, and to decide if the lesion should be excised. The recognition of atypical epithelial proliferation is based on the distinction of hyperplastic from neoplastic lesions, that is on the identification of a clonal process. As a general rule, usual type epithelial hyperplasia is morphologically and phenotypically heterogeneous, while ADH, FEA, and LN are characterized by a homogeneity of cell type and marker expression. With all types of precursor lesions, careful attention must be paid to the pathologic-radiologic correlation for the guidance of the clinical management. B3 lesions are associated with a high rate of 6-16% discordance among first and second pathology compared to 0.5-1.3% discordance for B5 lesions [5].

References:


Management after Minimal Invasive Biopsy (5/22)

Further information:

What kind of treatment has to follow when a B3 diagnosis has been rendered should be individually determined in an interdisciplinary discussion of the imaging findings and the pathology results. Algorithm for quality assurance of minimal invasive guided biopsies.

After a review and quality assessment of 21 studies, diagnostic accuracy of VAB were evaluated. The summary estimates for VAB in diagnosis of breast carcinoma were as follows: sensitivity, 0.981 (95% confidence interval [CI], 0.972-0.987); specificity, 0.999 (95% CI, 0.997-0.999); positive likelihood ratio (PLR), 93.84 (95% CI, 41.55-211.95); negative likelihood ratio, 0.05 (95% CI, 0.03-0.09); diagnostic odds ratio, 1891.7 (95% CI, 683.8-5233.4); underestimate rate of ADH and DCIS were 20.9% (95% CI, 0.177-0.245) and 11.2% (95% CI, 0.098-0.128), respectively. VAB is a highly sensitive and specific biopsy method for evaluating mammographically detected breast in women.

References:

3. Bedei L, Falcini F, Sanna P: Atypical ductal hyperplasia of the breast: the controversial management of a


Atypical Ductal Hyperplasia (ADH) (6/22)

Further information:

The term atypical ductal hyperplasia (ADH) has been defined to describe small atypical ductal lesions with insufficient criteria for a definite diagnosis of DCIS. However, there is no general agreement on diagnostic criteria to distinguish ADH from low grade DCIS, and different definitions have been applied. Uncommon variants of ADH include atypical apocrine hyperplasia and atypical ductal proliferations developing within a pre-existing benign proliferative lesion such as sclerosing adenosis. Clonality is recognised by uniformity of morphology and phenotype, but also markers such as cytokeratin expression or hormone receptor expression can be used. Clinically, an excisional biopsy is recommended when ADH is identified in core-needle biopsy or in a vacuum-assisted biopsy specimen, but has no further consequences when found in a resection specimen, associated with benign lesions. The upgrade risk for ADH in a minimally invasive biopsy is estimated at 28% after open excision [1].

ADH and breast cancer are associated with postmenopausal hormone treatment. According to the data of the Breast Cancer Surveillance Consortium (USA) rates of ADH decreased from 5.5/10000 mammograms 1999 to 2.4/10000 mammograms in 2005.

References:

Risk of Breast Cancer after Atypical Hyperplasia (ADH, ALH) (7/22)

Further information:

Women have an enhanced breast cancer risk after ADH: one lesion RR 3.88 (95% CI 3.00-4.94), three lesions RR 10.35 (95% CI 6.13-16.4). Less than 45 years at diagnosis of ADH RR 6.78 (95% CI 3.24-12.4) [2].

References:

Strategy after Diagnosis of ADH (8/22)

Further information:

Significant histologic predictors of upgrade from ADH to carcinoma included number of terminal duct-lobular units (TDLU; >2) involved (P = .0306), presence of significant cytologic atypia suspicious for intermediate or high-grade carcinoma (P < .0001), and necrosis (P = .0006). Therefore, ADH lesions with significant cytologic atypia and/or necrosis are most likely to be associated with carcinoma and should be excised. ADH without these features, regardless of extent of involvement, and with complete removal of the targeted calcifications, is associated with a minimal risk (<3%) of carcinoma and may undergo mammographic follow-up only (Nguyen CV 2010, Allison KH 2010). Radiological calcification with suspicious or malignant characteristics and histological B3 with evidence of epithelial atypia has the highest positive predictive value (50%) (Rhaka et al. 2010). Even in the case of complete removal of microcalcifications there is a risk of 5% of underestimation of malignancy (Penco 2010). An open excisional is recommended with exception of very small lesions (≤ 2 TDLU) and minimal atypia and complete removed imaging abnormality.

ADH in core-/ vacuum-assisted biopsy (LoE 3a)
ADH at margins in resection specimen (LoE 3a)

References:

3. Penco S: Stereotactic vacuum-assisted breast biopsy is not a therapeutic procedure even when all mammographically found calcifications are removed: analysis of 4,086 procedures. AJR Am J Roentgenol. 2010


**Lobular Intraepithelial Neoplasia (LIN) (9/22)**

*Further information:*

Lobular neoplasia (LN) or lobular intraepithelial neoplasia (LIN) are the preferred terms for early neoplasia with lobular phenotype and include atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS). For a long time, LN was considered to be just as a risk indicator and not a precursor lesion for the subsequent development of carcinoma. More recently, because of pathological and molecular studies, it is now believed that lobular neoplasia indeed is a non-obligatory precursor of invasive carcinoma, and at the same time a risk lesion for ipsi- and contralateral disease. Several different morphologic variants of lobular neoplasia have been described to more precisely evaluate the individual risk. Specifically, florid LCIS and pleomorphic LCIS were shown to be behave more aggressively compared to classical lobular neoplasia. The distinction of pLCIS from classical LN relies on nuclear characteristics with pLCIS having larger, more pleomorphic nuclei with obvious nucleoli, and may show apocrine differentiation, necrosis and microcalcifications. After diagnosis of LIN on core needle, or on vacuum-assisted biopsy, the average upgrade rate is about 15%. The management of lobular neoplasia in excisional biopsies by the pathologist requires attention to the following points: 1) He should be aware of the risk of occult microinvasion and pay attention to the careful workup of the specimen. 2) In cases of pleomorphic LCIS attention must be paid to the margin status like in low-grade DCIS, to make sure that florid or pleomorphic LN has been completely excised. 3) The metric extent of LN should be determined approximately by the pathologist since extensive LN may be associated with a higher risk and to help correlate the findings with the radiologic findings. Lobular Intraepithelial Neoplasia (LIN; atypical lobular hyperplasia, lobular carcinoma in situ, LCIS/CLIS) provides an incidental finding and is not suited to explain any radiographic abnormality. LIN is categorized as B3 as long the criteria for pleomorphic LIN and LIN with necrosis or LIN with extensive involvement of lobules are not fulfilled which qualify for B5a. LIN is categorized as B3 as long the criteria for pleomorphic LIN and LIN with necrosis are not fulfilled which qualify for B5a.
References:


Statement: Indicator-/precursor lesion

**Variants of Lobular Neoplasia (10/22) and Lobular Neoplasia with High Risk (11/22)**

*Further information:*

Several different morphologic variants of lobular neoplasia have been described to more precisely evaluate the individual risk. Specifically, pleomorphic lobular carcinoma in situ (pLCIS) was shown to be behave more aggressively compared to classical lobular neoplasia [1]. The distinction of pLCIS from classical LN relies on nuclear characteristics with pLCIS having larger, more pleomorphic nuclei with obvious nucleoli, and may show apocrine differentiation, necrosis and microcalcifications. In this respect pLCIS mimics ductal carcinoma in situ (DCIS), but characteristically it is associated with classical LN and not with DCIS. Also, molecular profiling studies have shown that pLCIS is similar to classical LN, supporting its role as a special form of lobular neoplasia. As another approach for risk assessment, a classification of lobular neoplasia into three different grades of severity has been proposed, based on the extent of lobular cancerization [2]. The most severe grade (LIN 3) is called florid lobular carcinoma in situ nowadays [3]. It may be associated with microinvasion [4].

*References:*


Strategy after Diagnosis of LIN (12/22)

Further information:

In contrast to atypical ductal hyperplasia, it is less clear if a follow-up excisional biopsy is beneficial to the outcome of a patient with the finding of lobular neoplasia in the core biopsy, and therefore there is some disagreement if excision should be recommended as a rule or not. This is mainly due to the relative infrequency of lobular neoplasia as the most severe finding in core biopsies and the even lower number of excisional biopsies in this situation. Not surprisingly these small studies have led to widely discrepant results and conflicting interpretations of published data. An excisional biopsy was recommended in fully developed LCIS because of an upgrade rate of greater than of 25% [1] or 16% [2], but results were inconclusive with lesions of lesser extent, namely atypical lobular hyperplasia. The argument against a routine follow-up biopsy is that LN as the most significant pathology usually is an incidental finding in an otherwise benign core biopsy and if there is no other clinical or radiological detectable lesion, it is unlikely that an excisional biopsy could yield anything more significant [3]. This argument has to be taken seriously, and at least all cases with LCIS and a mass lesion should be followed up by a surgical biopsy. However, because of the reported upgrade rates in fully developed LCIS, the nature of these lesions as non-obligate precursors, and risk of missing a radiologically occult invasive cancer, an open biopsy in classical LCIS should be considered as an option also [2], especially if multiple lobules are involved [4-6].

References:

LIN in core- / vacuum-assisted biopsy (LoE 2b)

1. Shin SJ, Rosen PP. Excisional biopsy should be performed if lobular carcinoma in situ is seen on needle core biopsy. Arch Pathol Lab Med. 2002 May 31;126(6):697–701.


LIN accompanying intraductal or invasive carcinoma in patients with BCT (LoE 2a)

**Flat Epithelial Atypia (FEA) (13/22)**

**Further information:**

FEA represents one of the earliest morphologically recognizable neoplastic alterations of the breast. It is characterized by mildly to severely atypical cells simply replacing the single layer of native epithelial cells in a flat fashion without appreciable proliferation.

**Marker Lesion**

FEA is highly associated with microcalcification (77%). The mammographic features are amorphous and pleomorphpic microcalcification. In about one-third to one-quarter of cases of FEA seen at core biopsy, a more advanced lesion is found at excision: ADH, DCIS and tubulär carcinoma. A 2- to 3-fold increase in the occurrence of ADH in the presence of FEA versus in their absence (P < .005) was observed. A finding of FEA on benign breast biopsy may indicate the presence of ADH, a more worrisome lesion (Boulos FI). FEA might be associated with noninvasive cancer but not with invasive cancer.

**References:**

Statement: Marker Lesion (LoE 3b)

1. Kunju L: Significance of flat epithelial atypia on mammotome core needle biopsy: should it be excised? Hum Pathol 2006; 38:35-41
2. Noske A: Flat epithelial atypia is a common subtype of B3 breast lesions and associated with noninvasive cancer but not with invasive cancer in final excision histology. Hum Pathol 2009; Epub ahead of print.
**Strategy after Diagnosis of FEA (14/22)**

*Further information:*

If a FEA is detected in core biopsy further no further (open) biopsy is indicated if the underlying lesion/calcification is completely removed (Lee TJ, 2010). In cases of FEA combined with an ADH further surgery depends on the ADH lesion (Ingegnoli A, 2010).

Statement: FEA in core (LoE 3a)
Statement: FEA at margins in resection specimens (LoE 3b)

**References:**

**Papilloma (15/22)**

*Further information:*

Benign intraductal papillomas occur either as a central papilloma originating from the ducts in the subareolar region, or peripherally, and both locations can be either solitary or multiple. Both central and peripheral papillomas are characterized by fibrovascular cores with epithelial and myoepithelial cell layers. Central intraductal papillomas with a predominant or exclusive glandular differentiation are called ductal adenoma [1]. Intraductal papillomas and ductal adenomas may show regressive changes, such as sclerosis or infarction, also also epithelial or myoepithelial hyperplasia or squamous or apocrine metaplasia. These changes may cause diagnostic difficulties in core needle biopsy [2]. The term papillomatosis is not used in the WHO classification of the breast, because was historically used both for usual type ductal hyperplasia and for papillomas.

Atypical epithelial proliferations (ADH and DCIS) may occur in papillomas, and are usually of low grade. As with atypical intraductal proliferative lesions, the distinction of ADH and DCIS within a papilloma rests with quantitative criteria [1]. An intraductal papilloma with ADH is diagnosed when the atypical epithelial proliferation is < 3 mm, while larger atypical epithelial proliferations within a papilloma fulfill the criteria of an intraductal papilloma with low grade [3]. This definition replaces alternative terminologies that were focussed on the proportion of atypical cells (30% or 90%) within a papilloma. An intermediate or high grade DCIS within a papilloma can be diagnosed regardless of the extent of atypia.

*References:*

**Strategy after Diagnosis of Central Papilloma (16/22)**

*Further information:*

A policy of open excisional biopsy after the diagnosis of a central papilloma has been recommended by the European guidelines for quality assurance in breast cancer screening [1]. However, this recommendation is still controversial [1, 2]. The finding of an ADH or DCIS in a papilloma has similar therapeutic consequences, provided the surrounding transition system is free of DCIS. In both cases, complete excision of the lesion without subsequent radiotherapy [4] is sufficient. For this reason, the distinction between ADH and DCIS in a papilloma is rejected by some authors [4].

*References:*

Radially Sclerosing Lesion (17/22)

No further information

No references
Strategy after Diagnosis of Radial Scar, Complex Sclerosing Lesion (18/22)

No further information

No references
Follow-up Imaging for Women Age 50-69 Years with B3-Lesions (19/22)

Further information:

Women with ADH and LIN need to be informed about their elevated risk for breast cancer. Risk communication should provide women with information of risk reduction strategies (e.g. follow-up and medical intervention) providing comprehensive disclosure of risks and benefits in absolute terms, helping women to make an informed decision to her personal needs and values. Atypia patients who drank alcohol and had a first-degree relative with breast cancer have an increased risk of breast cancer compared to those without atypia [1].

References:


Medical Prevention for Women at Increased Risk (including Women with LIN and ADH) (20/22)

Further information:

Studies on medical prevention for women at increased risk include women with LIN and ADH.

References:

Outcome of Medical Prevention (1) (21/22)

No further information

References:

**Outcome of Medical Prevention (2) (22/22)**

*Further information:*

Risk communication should provide women with information of risk reduction strategies (e.g. follow-up and medical intervention) providing comprehensive disclosure of risks and benefits in absolut terms (numbers needed to treat and numbers needed to harm), helping women to make an informed decision to her personal needs and values.

*References:*

Ductal Carcinoma in Situ (DCIS)
Ductal Carcinoma in Situ
DCIS

- **Version 2002:** Gerber

- **Versions 2003–2013:** Audretsch / Brunnert / Costa / Fersis / Friedrich / Hanf / Junkermann / Lux / Maass / Möbus / Nitz / Oberhoff / Scharl / Souchon / Thomssen

- **Version 2014:** Thill / Solomayer
Pretherapeutic Assessment of Suspicious Lesions (BIRADS IV)

- **Mammography**
  - Magnification view of microcalcification
  - Increase of detection rate of G1/G2 DCIS by full-field digital mammography (versus screen-film)

- **Stereotactic core needle / vacuum biopsy (VAB)**
  - Specimen radiography
  - Marker (Clip) left at biopsy site for location if lesion is completely removed

- **Assessment of extension**
  - MRI
  - Clinical examination
  - FNA / ductal lavage
  - Interdisciplinary board presentation

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Procedure</th>
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<th>AGO</th>
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<tbody>
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<td>Mammography</td>
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<td>A</td>
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<tr>
<td>Magnification view of microcalcification</td>
<td>4</td>
<td>C</td>
<td>++</td>
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<tr>
<td>Increase of detection rate of G1/G2 DCIS by full-field digital mammography (versus screen-film)</td>
<td>2b</td>
<td>B</td>
<td>+</td>
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<tr>
<td>Stereotactic core needle / vacuum biopsy (VAB)</td>
<td>2b</td>
<td>B</td>
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<tr>
<td>Specimen radiography</td>
<td>2b</td>
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<td>++</td>
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<tr>
<td>Marker (Clip) left at biopsy site for location if lesion is completely removed</td>
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<td>D</td>
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<tr>
<td>Assessment of extension</td>
<td>3a</td>
<td>C</td>
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<td>MRI</td>
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<td>Interdisciplinary board presentation</td>
<td>5</td>
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### Surgical Treatment for Histologically Proven DCIS I

<table>
<thead>
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<th>Procedure</th>
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<td>Excisional biopsy (wire guided)</td>
<td>2b B ++</td>
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<tr>
<td>Bracketing wire localization in large lesions</td>
<td>5 D +</td>
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<tr>
<td>Specimen radiography</td>
<td>2b B ++</td>
</tr>
<tr>
<td>Intraoperative ultrasound (visible lesion)</td>
<td>3a C +/-</td>
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<tr>
<td>Immediate re-excision for close margins (specimen radiography)</td>
<td>1c B ++</td>
</tr>
<tr>
<td>Intraoperative frozen section</td>
<td>5 D - -</td>
</tr>
<tr>
<td>Interdisciplinary board presentation</td>
<td>2b C ++</td>
</tr>
</tbody>
</table>

Open biopsy in suspicious lesions (mammographical microcalcifications, suspicious US, MRI etc.) without preoperative needle biopsy should be avoided.
Surgical Treatment for Histologically Proven DCIS II

- Histologically clear margins (R0)
- Multifocal DCIS: BCT if feasible (incl. RT)
- Re-excision required for close margin ≤ 2 mm in paraffin section)
- Mastectomy*
  - Large lesions confirmed by multiple biopsies; no clear margins after re-excision
- SNE*
  - Mastectomy
    - In case of DCIS in the male breast
  - BCT: ≥ 5 cm or ≥ 2.5 cm + high nuclear grade/comedonecrosis
- ALND

* Patients who present with a palpable mass have a significantly higher potential for occult invasion (26%), multicentricity and local recurrence.
DCIS – Prognostic Factors for the Incidence of Local- / Locoregional Recurrence

- Resection margins
- Residual tumor-associated microcalcification
- Age
- Size
- Grading
- Comedo necrosis
- Architecture
- Method of diagnosis
- Focality
- (mod.) Van Nuys Prognostic Index
- Palpable DCIS
- Palpable + COX-2+, p16+, Ki-67+
- Palpable + ER-, HER2+, Ki-67+
- HER2/neu (positive vs. negative)
- ER/PgR (positive vs. negative)
- DCIS-Score
- DCIS with microinvasion – treatment in analogy to invasive breast cancer
- Intrinsic subtypes (luminal A, B, HER2+, triple negative)

<table>
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<th>Factor</th>
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<td>Resection margins</td>
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<tr>
<td>Residual tumor-associated microcalcification</td>
<td>2b C ++</td>
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<tr>
<td>Age</td>
<td>1a A ++</td>
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<tr>
<td>Size</td>
<td>1a A ++</td>
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<tr>
<td>Grading</td>
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<tr>
<td>Comedo necrosis</td>
<td>1a A ++</td>
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<tr>
<td>Architecture</td>
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<tr>
<td>Method of diagnosis</td>
<td>1a A ++</td>
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<tr>
<td>Focality</td>
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<tr>
<td>(mod.) Van Nuys Prognostic Index</td>
<td>2b C +/-</td>
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<tr>
<td>Palpable DCIS</td>
<td>2b C +/-</td>
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<tr>
<td>Palpable + COX-2+, p16+, Ki-67+</td>
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<td>Palpable + ER-, HER2+, Ki-67+</td>
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<tr>
<td>HER2/neu (positive vs. negative)</td>
<td>1a B +/-</td>
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<tr>
<td>ER/PgR (positive vs. negative)</td>
<td>1a B +/-</td>
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<td>DCIS-Score</td>
<td>2c C +/-</td>
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<tr>
<td>DCIS with microinvasion – treatment in analogy to invasive breast cancer</td>
<td>3b C ++</td>
</tr>
<tr>
<td>Intrinsic subtypes (luminal A, B, HER2+, triple negative)</td>
<td>2b C -</td>
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</table>
## DCIS Radiotherapy

### Radiotherapy after:
- Breast conserving surgery (BCS)
- Mastectomy

### Modality:
- Partial breast radiotherapy (PBI)
- Hypofractionated radiotherapy regimens
- Radiotherapy boost on the tumor bed
  - Women younger than 45-50 years

<table>
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<tr>
<th>Therapy Type</th>
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<tr>
<td>Partial breast radiotherapy (PBI)</td>
<td>3a D --</td>
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<td>Hypofractionated radiotherapy regimens</td>
<td>2b D -/+*</td>
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<tr>
<td>Radiotherapy boost on the tumor bed</td>
<td>2b D --</td>
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<tr>
<td>Women younger than 45-50 years</td>
<td>2b C +/-</td>
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Side effects and disadvantages of radiotherapy must be balanced against risk reduction. Omitting radiotherapy implies elevated risk for local recurrence without effect for overall survival even in the subset of “good risk” patients. There remains a lack of level-1 evidence supporting the omission of adjuvant radiotherapy in selected low-risk cases.

* Analysis in ongoing trials
Goodwin A, Parker S, Ghersi D, Wilcken N.

DCIS Postoperative Systemic Treatment

- Tamoxifen (only ER+)
  - AI if postmenopausal and contraindication against tamoxifen
- Other endocrine options
- Trastuzumab (only HER2+)

Oxford / AGO LoE / GR

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<th>1a</th>
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<tr>
<td>Tamoxifen</td>
<td>5</td>
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<tr>
<td>Other</td>
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<tr>
<td>Trastuzumab</td>
<td>5</td>
<td>D</td>
<td>--</td>
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</tbody>
</table>
Staley H, McCallum I, Bruce J.
Postoperative tamoxifen for ductal carcinoma in situ.
Local Recurrence of DCIS after Tumorectomy w/o Irradiation

- MRI (follow-up after history of LCIS)  
  Oxford / AGO LoE / GR  
  2b B +/-  

- Simple mastectomy  
  3a C ++  

- Secondary tumorectomy leads to recurrence rates about 30% (NSABP B17)  
  - Plus radiotherapy (in case of no previous RT)  
    3 C ++  

Prognosis for invasive recurrence seems to be better than in case of primary invasive breast cancer; ~ 50% of recurrences are invasive.
Key Points

- DCIS is a local disease and should primarily be treated with local approaches only
- Addition of Tamoxifen to radiotherapy reduces risk of local recurrence (LoE 1a)
- BCT offers an acceptable local control rate for many patients with DCIS (LoE 1a)
- After BCS, postoperative radiotherapy is recommended (LoE 1a)
- So far, no influence on survival by postoperative radiotherapy can be detected (LoE 1a)
- Young age is an independent risk factor for local recurrence (LoE 1a). Therefore, especially younger patients might benefit from a boost irradiation (LoE 2b)
- As margins are an important prognostic factor for local tumor control, R0-resection should be achieved (LoE 1b)
- So far, no patients’ subset has been identified that not benefit from radiotherapy after BCS in terms of improved local tumor control (LoE 1a)
- Hypofractionated radiotherapy might be as safe and effective as standard RT; wait for results of ongoing RCT.
**Ductal Carcinoma in Situ (DCIS) (2/12)**

*Further information:*

Scientific data source screened (for preparation of the current version):

Systematic review of published evidence for 2014-Version:

- **PUBMED** 2013
- **ASCO** 2013
- **SABCS** 2013

Screened guidelines:

*No references*
Pretherapeutic Assessment in Suspicious Lesions (BIRADS 4) (3/12)

Further information:

Regarding the pretherapeutic assessment of suspicious lesions (BIRADS IV) the stereotactic sore needle or the vacuum biopsy is recommended. If the lesion is completely removed by the biopsy, a marker clip should be left at the biopsy for the exact location of the lesion. Moreover, clinical examination should be performed. A further prospective observational study presented that the presence of DCIS significantly affects the accuracy of measuring the sizes of malignant breast tumors when using either B-mode sonography or real time elastography [Soliman et al., 2012]. The actual literature shows concordantly, that MRI is better than mammography for discriminating the exact size of DCIS especially for high grade lesions. On the other hand there is the risk of overestimating benign lesions with the consequence of consecutive interventions. DCIS is not a lethal disease and therefore the cost-risk relations have to be considered carefully. Because of this the AGO recommends +/-.

Regarding early cancer detection, full-field digital mammography has a higher detection rate of low- and intermediate-grade DCIS compared to screen-film mammography [Nederend et al., 2012].

References:


New 2011

D’Orsi C: (2010) “Imaging for the Diagnosis and Management of Ductal Carcinoma In Situ” J Natl Cancer Inst Monogr (41) 214 – 217


New 2013


New 2014

Stehouwer BL, Merckel LG, Verkooijen HM, Peters NH, Mann RM, Duvivier KM, Mali WP, Peeters PH, Veldhuis WB, van den Bosch MA. 3-T breast magnetic resonance imaging in patients with suspicious microcalcifications on


Rajitha Sunkara, Charu Taneja, Dorcas Chi, Gail Wolfe, Christine Segal, Allison Keel, Phoebe Olhava, Leslie A. Martin. Role of sentinel lymph node biopsy (SLNB) and preoperative MRI in the management of patients with pure high-grade ductal carcinoma in situ (DCIS). J Clin Oncol 31, 2013 (suppl 26; abstr 87)
Ahmed and Douek published a systematic review and a metaanalysis to evaluate the impact of intra-operative ultrasound (IOUS) in comparison to wire-guided localization (WGL) in non-palpable breast cancers and DCIS. Studies were considered eligible for inclusion in this systematic review if they (1) assessed the role of surgeon-performed IOUS for the treatment of non-palpable breast cancers and ductal carcinoma in situ (DCIS) and (2) specified surgical margin excision status. Those studies, which were randomized controlled trials (RCTs) or cohort studies with comparison WGL groups were included in the meta-analysis. For those studies included in the meta-analysis, pooled odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using fixed-effects analyses and random-effects analyses in case of statistically significant heterogeneity (p < 0.05).

Eighteen studies reported data on IOUS in 1,328 patients with non-palpable breast cancer and DCIS. Nine cohort studies with control WGL groups and one RCT were included in the meta-analysis. Successful localization rates varied between 95 and 100% in all studies and there was a statistically significant difference in the rates of involved surgical margins in favour of IOUS with pooled OR 0.52 (95% CI 0.38-0.71).

The authors concluded that compared with WGL, IOUS reduced involved surgical margin rates in non-palpable lesions as long as they are visible. For invisible DCIS and EIC IUOS can not be recommended.

References:


Kumar S, Sacchini V. The Surgical Management of Ductal Carcinoma In Situ. The Breast Journal 2010; 16: S 49-S52


New 2014

**Surgical Treatment for Histologically Proven DCIS II (5/12)**

**Further information:**

Dunne et. al. have evaluated the risk of recurrence in dependence of the tumorfree margins. They demonstrated that free margins of 5 mm and more have no significant advantages compared with free margins of at least 2 mm. The clinical recommendation has to be seen in the way that at DCIS tumorfree margins of 2 – 5 mm are enough, while for tumorfree margins of less than 2 mm a re-excision should be recommended.

Planning the surgery it should be recognized that patients who present a palpable mass in case of DCIS have a significantly higher potential for occult invasion (26%), multicentricity and local recurrence.

The indication for SLNE at DCIS should be discussed: there is no question that in case of mastectomy a SLNE should be performed, because a SLNE after mastectomy is not feasible and an axillary dissection had to be done. The recommendation for large DCIS (> 5cm) or DCIS ≥ 2.5 cm with high-grade and/or comedonecrosis is similar.

DCIS in male patients should be treated with mastectomy and SNE.

New data with small patient numbers show that intraoperative evaluation of margins by radiofrequence spectroscopy seems to be promising.

**References:**


New in 2011


Kumar S, Sacchini V. the Surgical Management of Ductal Carcinoma In Situ. The Breast Journal 2010; 16: S49 – S52


New 2013


New 2014


DCIS – Prognostic Factors for the Incidence of Local- /Locoregional Recurrence (6/12)

Further information:

With the help of the Van Nuys Prognostic Index – one of seven scores -, that is based on retrospective data analysis and that grading, tumor size, tumor free margins and age, id was tried to work out standard treatment recommendations. Nevertheless some studies demonstrated high recurrence rates in patients with low risk DCIS possibly based on heterogeneous morphology.

In the EORTC-Study 10853 with 863 patients age (< 40 years), method of diagnosis (mammography, palpable lesion), tumorfree margins (free/not free/ unclear), grading, architecture (clinging/crribiforme and clinging/solide, comedonecrosis) as well therapy (tumorectomy+-radiotherapy) are independent prognostic factors for local and locoregional recurrence in multivariate. The metaanalysis of Wang (2011) demonstrated, that comedonecrosis, focality, tumorfree margins, method of detection, grading and tumor size are independent predictors for local recurrences.

Regarding the age, the Italian Radiation Oncology Group performed a multi-institutional study of conservative treatment of DCIS [Vidalí et al., 2012]. The trial was characterized by a very long median follow-up (> 11 years). Age was a statistically significant prognostic factor (p=0.0009).

In the years 2010 und 2011 another two scores, that are based on morphological criterias and age, were published. At the moment there are no well evaluated prognostic factors in the area of molecular markers, molecular profiles, DNA methylating processes, a.s.o. Kerlikowske et al. have evaluated a molecular profile by Cox-2+ki67+p16+ and ER-HER2+Ki-67+ expression combined with palpability of the lesions, that was associated with a higher risk for invasive recurrences but not for non invasive recurrences. DCIS-Score from Solin could be helpfull tool in the future.

References:


New 2011

Pinder SE, C Duggan et al. A new pathological system for grading DCIS with improved prediction of local recurrence: results from the UKCCCR/ANZ DCIS trial. Br J Cancer 2010; 103: 94 – 100
Chan P, Lim S. Predictors of Invasive Breast Cancer in Ductal Carcinoma In Situ initially diagnosed by Core Biopsy. Asian J Surg 2010; 33: 76-82
Han JS, Molberg KH, Sarode V. Predictors of Invasion and Axillary Lymph Node Metastasis in Patients with a Core Biopsy Diagnosis of Ductal carcinoma In Situ: An Analysis of 255 Cases. The Breast Journal 2011; 17: 223-229

Silverstein MJ, Lagios MD. Choosing Treatment for Patients With Ductal Carcinoma In Situ: Fine Tuning the University of Southern california/Van Nuys Prognostic Index. J natl Cancer Inst Monogr 2010; 41: 193-196

New 2013


New 2014


Sarah Patricia Cate, Alyssa Gillego, Manjeet Chadha, John Rescigno, Paul R. Gliedman, Ilana Kats, Susan K. Boolbol. Does the Oncotype DCIS score impact treatment decisions? J Clin Oncol 31, 2013 (suppl 26; abstr 91)


**DCIS Radiotherapy (7/12)**

*Further information:*

A randomized controlled clinical trial comparing mastectomy alone with local excision by BCS consisting of removal of the DCIS to clear margins (regarding “clear margins” see also editorial by Morrow M, Katz SJ 2012) followed by radiation therapy has not been done. Nevertheless, the available data suggest that long-term survival is similar with both therapeutic approaches providing excellent outcomes.

After mastectomy for pure DCIS the rates of local or regional relapses are very low (<2%) independently of patient’s age (Ho A et al. Breast 2011). Thus, postmastectomy radiotherapy (PMRT) is not recommended. Even with positive or close mastectomy margins, the rates of chest wall recurrences were so low that PMRT is likely not warranted (Chadha M et al. Int J Surg Oncol 2012;2012:423520. doi: 10.1155/2012/423520. Epub 2012 Jun 13; Childs SK, Int J Radiat Oncol Biol Phys 2012 Sep 10. doi:pii: S0360-3016(12)03334-2. 10.1016/j.ijrobp.2012.07.2377. [Epub ahead of print]).

Because of the data of EORTC- and NSABP B-17 studies the radiotherapy of DCIS after BCS has to be seen as standard by reducing the local recurrence rate significantly (Julien JP Lancet 2000; 355: 528-533; Fisher B J Clin Oncol 1998; 16: 441-452; Solin LJ 2012). In small lesions of DCIS with tumor size smaller than 2 cm – 3 cm, tumorfree margins greater than >/= 10 mm and low or intermediate grading and VNPI </= 4 side effects and disadvantages of radiotherapy in relation to risk reduction of local recurrences should be discussed (Schwartz et al. Hum Path 2000).

The data of radiotherapy after BCS in newer studies have confirmed these results. The subgroup of patients who do not benefit from radiotherapy might be very small. A clear subgroup that does not benefit from radiotherapy cannot be defined at the moment (Shaitelman SF et al. 2012). Therefore the interdisciplinary tumor conference is of main importance (Bijker et.al. (EORTC) J.Clin Oncol, 2006).

With respect to retrospective studies nor small tumors nor larger tumor free margins nor a differentiation with histological criterias nor the Van Nuys PI allow to omit the radiotherapy.
Die EBCTCG (2010) has analysed the of 4 randomised studies concerning radiotherapy after BCS for DCIS and could demonstrate that an absolute reduced 10 years risk for recurrences of 15.2% for invasive recurrences with a higher reduction in elder patients independently from other prognostic factors. A prospective study of ECOG (ECOG 5194) without radiotherapy in patients with lesions < 2.5 cm + low-intermediate grade and high grade lesions < 1 cm (RR> 3mm) showed after a FU of 5 years 6.1% and 15.3% ipsilateral breast events. Possibly a huge part of recurrences in the low risk group will appear in later times so that the omission of radiotherapy after BCS has to be indicated carefully (Shaitelman SF et al. 2012). The partial breast irradiation for DCIS is experimental at that time; in small groups 5 year recurrence rates of 3.39% are described. Data published in Lancet Oncology 2011 with a FU of 12.7 months demonstrated a reduction of ipsilateral local recurrences after BCS and radiotherapy of 68% for invasive lesions and of 62% of non-invasive lesions (UK-trial). Wapnir et al. published in JNCI 2011 a cumulative 15-years breast cancer mortality after lumpectomy of 3.1%, after BCS and radiotherapy of 4.7% and after BCS and radiotherapy and Tamoxifen of 2.7%. There is no valid data for the use of AI (anastrozole, etc.).

Actual unanswered questions and study endpoints of actual randomized clinical trials regarding the impact of radiation therapy treatment of DCIS are:
1. RT beneficial even for patients with “good risk”-criteria (RT=G 9804; McCormick et al. 2012)?
2. Isoeffectiveness of different fractionation schedules (hypofractionation versus standard fractionation (TROG 07.01; Bonbis-Trial; ANZCTR.org; Azria et al. 2008; Wai et al. 2011; Riou et al. 2012)?
3. Additional benefit by boost irradiation of the tumor bed following BCS and WBI (TROG 07.01; Bonbis-Trial; ANZCTR.org; Azria et al. 2008; Wai et al. 2011; Riou et al. 2012)?
4. Non-inferiority and/or equieffectiveness of whole breast irradiation (WBI) with accelerated partial breast irradiation (APBI) (E5194-Studie, NSABP B-39-trial; National Cancer Institute website. NSABP B-39; Goyal et al. 2011; Jeruss et al. 2011; Park et al. 2011)?
5. Impact of trastuzumab given concurrently with irradiation for patients with HER2+ DCIS resected by lumpectomy (NSABP B-43-trial; Cobleigh MA et al. 2012)?
References:


Impact of pathological characteristics on local relapse after breast-conserving therapy: a subgroup analysis of the EORTC boost versus no boost trial.


New 2011

Kane RL, BA Virnig et al. (2010) : “The Impact Surgery, Radiation, and Systemic Treatment on Outcomes in Patients With Ductal Carcinoma In Situ” J Natl Cancer Inst Monogr (41) 130 – 133
EBCTCG Correa C et al. Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. J Natl Cancer Inst Monogr. 2010 (41); 162 – 77
Punglia RS, Burstein HJ, Weeks JC et al. Radiation Therapy for Ductal Carcinoma In Situ. Cancer 2011; (epub ahead)
New 2013


New 2014


Cochrane Analysis post-operative radiotherapy (8/12)

No further information

No references
**DCIS Postoperative Systemic Treatment (9/12)**

*Further information:*

The NSABP B24-Studie showed a risk reduction of ipsilateral non invasive recurrences of 18% (and contralateral of 78%) and of ipsilateral invasive recurrences of 44% (contralateral of 37%) at a median FU 74 months independently of ER-status (Fisher B Lancet 1999; 353: 1993-2000). This is confirmed by the data of the UK-trial from 2010. In San Antonio 2002 data had been presented that showed a significant reduction of all breast cancer events by 59% in ER-positive non invasive BC, while in ER-negative non invasive breast cancers the recurrence rate was reduced not significantly by 20% (Allred DC Breast Cancer Research and Treatment Vol 76 Suppl 1 Dec 2002: abstract 30). Wapnir et al. published in JNCI 2011 a cumulative 15-years breast cancer mortality after lumpectomy of 3.1%, after BCS and radiotherapy of 4.7% and after BCS and radiotherapy and Tamoxifen of 2.7%. There are no valid datas for the use of AI (anastrozole, etc.). Study participation is recommended.

**New 2013**

Regarding the use of tamoxifen after DCIS, a Cochrane meta-analysis was published in 2012 [Staley et al., 2012]. Two randomized controlled trials were included involving 3375 women. Tamoxifen after surgery for DCIS reduced recurrence of both ipsilateral (same side) DCIS (HR 0.75; 95% CI 0.61 to 0.92) and contralateral (opposite side) DCIS (RR 0.50; 95% CI 0.28 to 0.87). There was a trend towards decreased ipsilateral invasive cancer (HR 0.79; 95% CI 0.62 to 1.01) and reduced contralateral invasive cancer (RR 0.57; 95% CI 0.39 to 0.83). The number needed to treat in order for tamoxifen to have a protective effect against all breast events is 15. No reliable number needed to treat to harm could be calculated. Moreover, it was not clear how patient characteristics (e.g. menopausal status, age and tumour ERstatus) affect or predict response to tamoxifen. There was no evidence of a difference detected in all cause mortality (RR 1.11; 95% CI 0.89 to 1.39).
The impact of trastuzumab given concurrently with radiation therapy (RT) to RT alone for patients with HER2+ DCIS resected by lumpectomy is actually proven in a phase III clinical trial by the NSABP (NSAPB B-43; Cobleigh MA et al. 2012).

New in 2014
The NSABP B-43 trial is fully recruited. 5,645/5.861 had analyzable blocks; only 1,969 (34.9 %) were HER2 positive, lower than previously reported. A total of 1,428 patients have been accrued, 1,137 (79.6 %) of whom have follow-up information. The average follow-up time for the 1,137 patients is 23.3 months. No grade 4 or 5 toxicity has been observed. No trastuzumab-related safety signals have been observed. Other data from this trial will be awaited.

References:
Allred DC Breast Cancer Research and Treatment Vol 76 Suppl 1 Dec 2002: abstract 30

New 2011
New 2013


New 2014


Cochrane Analysis Tamoxifen after DCIS (10/12)

No further information

No references
Local Recurrence of DCIS after Tumorectomy w/o Irradiation (11/12)

Further information:

Surveillance of patients with DCIS should be performed similar to patients with invasive breast cancer. Regarding LCIS (LIN III) a retrospective review of 670 screening breast MR studies was performed between January 2003 and September 2008. 220 women with a history of LCIS were integrated [Sung et al., 2012]. The median follow-up of screening was 3 years (0.5-5 years). MR imaging was a useful adjunct modality for screening women with a history of LCIS at a high-risk of developing breast cancer, resulting in a 4.5% incremental cancer detection rate.

The treatment of choice of a locoregional recurrence after BCS and radiotherapy for DCIS is the salvage mastectomy especially on the basis that 50% of the recurrences are invasive and half of them were diagnosed in an unfavourable stage (Silverstein MJ J Clin Oncol 1998; 16:1367-1373). A second BCS is combined with a local recurrence rate of 30% (Fisher B et al. Cancer 1999; 86:429-438). At the moment there only is a low level of evidence for the mastectomy after local recurrence of a DCIS. There are no valid datas whether a second BCS is aequieffective with mastectomy and whether the prognosis of an invasive recurrence is better than the one of primary breast cancer.

References:


Key Points (12/12)

No further information

References:


New 2013


Recommended clinical Trial:

IBIS 2
Adjuvant Tamoxifen Compared With Anastrozole in Treating Postmenopausal Women With Ductal Carcinoma In Situ
http://www.gabg.de/studien/ibis2d.html

GEC-ESTRO APBI TRIAL

Interstitial Brachytherapy Alone Versus External Beam Radiation Therapy After Breast Conserving Surgery for Low-Risk Invasive Carcinoma and Low-Risk Ductal Carcinoma in Situ (DCIS) of the Female Breast
Breast Cancer Surgery
Oncological Aspects
Breast Cancer Surgery
Oncological Aspects

- **Versions 2002–2013:**
  Bauerfeind / Böhme / Blohmer / Costa /
  Fersis / Gerber / Hanf / Janni /
  Junkermann / Kaufmann / Kümmel / Nitz /
  Rezai / Simon / Solomayer / Thomssen /
  Untch

- **Version 2014:**
  Kühn / Kümmel
## Pretherapeutic Assessment

- **Palpation**
  - Oxford / AGO LoE / GR: 5 D ++

- **Mammography**
  - Oxford / AGO LoE / GR: 2b B ++

- **Ultrasound (breast & axilla)**
  - Oxford / AGO LoE / GR: 2b B ++

- **Minimalinvasive biopsy**
  - Oxford / AGO LoE / GR: 1c A +

- **MRI**
  - Oxford / AGO LoE / GR: 1c B +/-

* No reduction of re-excision rate.

The possibility of MRI guided biopsy is the precondition of breast MRI (e.g. dense breast tissue and invasive lobular cancer, suspicion of multifocal or multicentric disease)

** If clinical examination, mammography, ultrasound and in some cases MRI are not able to determine the extension of lesion
Perioperative Staging

- History and physical examination
  - High metastatic potential and/or symptoms:
    - Chest X-ray
    - Liver ultrasound
    - CT-scan
    - Bone-scan
    - FDG-PET or FDG-PET / CT
    - Whole body MRI

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and physical</td>
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</tr>
<tr>
<td>examination</td>
<td></td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>5 D +</td>
</tr>
<tr>
<td>Liver ultrasound</td>
<td>5 D +</td>
</tr>
<tr>
<td>CT-scan</td>
<td>5 D +</td>
</tr>
<tr>
<td>Bone-scan</td>
<td>5 D +</td>
</tr>
<tr>
<td>FDG-PET or FDG-PET / CT</td>
<td>4 C -</td>
</tr>
<tr>
<td>Whole body MRI</td>
<td>4 C -</td>
</tr>
</tbody>
</table>
Evidence of Surgical Procedure

- Survival rates after lumpectomy + XRT are equivalent to those after (modified) radical mastectomy
  - 1a A

- Survival rates after modified radical mastectomy are equivalent to those after radical mastectomy
  - 1b A

- Local recurrence rates after skin sparing mastectomy are equivalent to those after mastectomy
  - 2b B

- Conservation of the NAC (nipple areola complex) is an adequate surgical procedure in tumors of the periphery of the gland and after tumor-free section of retroareolar tissue
  - 4b C
Breast Conservation: Surgical Technical Aspects

- **Non-palpable lesion**
  - Wire guided localisation
  - Radionuclide guided localisation
  - Specimen radiography or ultrasound

- **Tumor-free margins required**

- **Immediate intraoperative re-excision for close margins (specimen radiography and/or intra-operative pathology)**

- **Re-excision required for involved margins (paraffin section)**

- **Therapeutic stereotactic excision alone**

- **Ultrasound guided surgery to prevent re-excision**

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<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
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<tbody>
<tr>
<td>2b B ++</td>
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<tr>
<td>2b B +/-</td>
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</tr>
<tr>
<td>2b B ++</td>
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<tr>
<td>2a A ++</td>
<td></td>
</tr>
<tr>
<td>1c B ++</td>
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<tr>
<td>3b C +</td>
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<tr>
<td>4 D - -</td>
<td></td>
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<tr>
<td>1a A +/-</td>
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</tr>
</tbody>
</table>
Breast Conservation Surgery (BCS)

- Multicentricity
- Positive microscopic margins after repeated excision
- Inflammatory breast cancer

Oxford / AGO
LoE / GR

2b   B   +/-
2b   B   - -
2b   B   - -

pCR after neoadjuvant chemotherapy   +/-
Axillary Lymph Node Dissection I

Axillary lymph node dissection (>=10 LN)
- To improve survival
- For staging
- For local control

Axillary lymph node dissection:
- DCIS
- cT1 /2 cN0 (without prior sentinel)
- SN + ( cT1/2 cN0; < 3 SN +, BCS + tangential radiation field, no subsequent axillary radiation, adequate systemic therapy)
- SN + (mic)
- SN (i+)
- SN + mastectomy

Axillary lymph node dissection indicated, but not feasible
- Radiation according to AMAROS-Trial

Oxford / AGO LoE / GR

3  D  -
3  A  ++
2a  A  +/-
2b  B  - -
1b  A  - -
1a  B  +/-
1b  A  -
2b  B  - -
1b  B  +
1ba  B  +/-
Surgical Treatment of Axillary Lymph Nodes pre and post NACT (Neoadjuvant Chemotherapy)

<table>
<thead>
<tr>
<th>SLNB pre or post NACT - cN0</th>
<th>Oxford / AGO LoE / GR</th>
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</thead>
<tbody>
<tr>
<td>SLNB pre NACT</td>
<td>2b</td>
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<tr>
<td>SLNB post NACT</td>
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</tr>
<tr>
<td>SLNB pre NACT</td>
<td>B</td>
</tr>
<tr>
<td>SLNB post NACT</td>
<td>+/-</td>
</tr>
</tbody>
</table>

### Surgical Procedure according to lymph node status

<table>
<thead>
<tr>
<th>cN-Status (prior Therapy)</th>
<th>pN-Status (prior Therapy)</th>
<th>cN-Status (after Therapy)</th>
<th>Surgical Procedure</th>
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<tbody>
<tr>
<td>cN0</td>
<td>pN0(sn)</td>
<td>-</td>
<td>nihil</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1a</td>
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<td>A</td>
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<td></td>
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<td></td>
<td>+</td>
</tr>
<tr>
<td>cN0</td>
<td>pN+(sn) according ACOSOG Z11* criteria</td>
<td>ycN0</td>
<td>ALND</td>
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<td>3</td>
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<td>B</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>+/-</td>
</tr>
<tr>
<td>cN0</td>
<td>pN+(sn) not according to ACOSOG* criteria</td>
<td>ycN0</td>
<td>ALND</td>
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<td></td>
<td>2b</td>
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<td>B</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>cN+</td>
<td>cN+ (CNB/FNA)</td>
<td>ycN0 (CNB/FNA)</td>
<td>SNB ALND</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
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<tr>
<td></td>
<td></td>
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<td>2b</td>
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<td>B</td>
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<td></td>
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<td></td>
<td>+/-</td>
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<td></td>
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<td>ycN+ (CNB/FNA)</td>
<td>ALND</td>
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<td>B</td>
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<td></td>
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<td>++</td>
</tr>
</tbody>
</table>

* T1/T2, BCT, 1-2 SLN pos, Breast radiation
<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically (cN0) / sonographically neg. axilla</td>
</tr>
<tr>
<td>T 1-2</td>
</tr>
<tr>
<td>T 3, 4a-c</td>
</tr>
<tr>
<td>Multifocal / multicentric lesions</td>
</tr>
<tr>
<td>DCIS</td>
</tr>
<tr>
<td>DCIS ≥ 5 cm or 2,5 cm + high grade (see DCIS) if mastectomy is required</td>
</tr>
<tr>
<td>Male breast cancer</td>
</tr>
<tr>
<td>In the elderly</td>
</tr>
<tr>
<td>Add. FNA/CNB of LN (clinical/sonogr. suspicious) in order to enable SNE</td>
</tr>
</tbody>
</table>
Sentinel Lymph Node Excision (SNE): Indications II

- During pregnancy and / or breast feeding (No blue dvy)
  
- After previous tumor excision
  
- Previous major breast surgery (e.g. reduction mammoplasty, mastectomy)
  
- Ipsilateral breast recurrence after prior BCS and prior SNE
  
- SN in the mammarian internal chain
  
- After axillary surgery
  
- Prophylactic bilateral / contralateral mastectomy
  
- Inflammatory breast cancer

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
<th>Level</th>
<th>Recommendation</th>
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</thead>
<tbody>
<tr>
<td>During pregnancy and / or breast feeding (No blue dvy)</td>
<td>3</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>After previous tumor excision</td>
<td>2b</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>Previous major breast surgery (e.g. reduction mammoplasty, mastectomy)</td>
<td>3b</td>
<td>C</td>
<td>+/-</td>
</tr>
<tr>
<td>Ipsilateral breast recurrence after prior BCS and prior SNE</td>
<td>4</td>
<td>D</td>
<td>+/-*</td>
</tr>
<tr>
<td>SN in the mammarian internal chain</td>
<td>2b</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>After axillary surgery</td>
<td>3b</td>
<td>B</td>
<td>+/-*</td>
</tr>
<tr>
<td>Prophylactic bilateral / contralateral mastectomy</td>
<td>3b</td>
<td>B</td>
<td>- -</td>
</tr>
<tr>
<td>Inflammatory breast cancer</td>
<td>3b</td>
<td>C</td>
<td>+/-</td>
</tr>
</tbody>
</table>

* Lymph node scintigraphy is necessary
Procedure after Neoadjuvant Therapy

- Marking of tumor
  - Oxford / AGO LoE / GR: 5 D ++
- Surgery
  - Oxford / AGO LoE / GR: 2b C ++
- Microscopically clear margins
  - Oxford / AGO LoE / GR: 5 D ++
- Tumor resection in the new margins
  - Oxford / AGO LoE / GR: 3b C +
Surgery and Irradiation after Neoadjuvant Therapy

Breast surgery:

After the nadir of the leucocyte count
(2 to 4 weeks after the last chemotherapy)

If irradiation after Mastectomy
is recommended

< 6 weeks after surgery

Indication based on the initial stage prior NT
(cN+, cT3/4a-d)
Breast conservation after clinical response possible:

- Multicentric lesion
- cT4a-c
- Inflammatory breast cancer (in case of pCR)

Mastectomy is recommended:

- If after re-excision no clear margins are achieved
- Extensive DCIS
- If irradiation is not feasible
### Adjuvant Therapy after Primary Surgery

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>Score</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start adjuvant systemic therapy and RT as soon as possible (a.s.a.p.) after surgery</td>
<td>1b</td>
<td>A ++</td>
</tr>
<tr>
<td>Start of adjuvant chemotherapy after surgery a.s.a.p., and prior to RT</td>
<td>1b</td>
<td>A ++</td>
</tr>
<tr>
<td>Without cytotoxic therapy:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start irradiation 6-8 weeks after surgery</td>
<td>2b</td>
<td>B ++</td>
</tr>
<tr>
<td>Start endocrine therapy after surgery and a.s.a.p.</td>
<td>5</td>
<td>D ++</td>
</tr>
<tr>
<td>Tamoxifen concurrent with radiotherapy</td>
<td>3b</td>
<td>C +</td>
</tr>
<tr>
<td>AI concurrent with radiotherapy</td>
<td>2a</td>
<td>B +/-</td>
</tr>
</tbody>
</table>
Further information and references: Kühn T., Kümmel S.

Update Januar 2014
Screened consensus conference:
Cochrane library:
Pretherapeutic Assessment (3/15)

Further information:

Preoperative breast diagnosis is required for planning breast surgery and avoiding surgery in benign conditions. Breast palpation, actual mammography and breast ultrasound are mandatory. Breast imaging diagnostic is avoidable in LABC (e.g., bleedings, ulceration). Malignancy and tumor size can best be evaluated by using both imaging procedures. Suspicious microcalcifications can be further characterized by magnification views. MRI staging causes more extensive breast surgery in an important proportion of women by identifying additional cancer, however there is a need to reduce FP MRI detection. Randomized trials are needed to determine the clinical value of detecting additional disease which changes surgical treatment in women with apparently localized breast cancer. MRI could be an option in patients with ambiguous mammographic and/or ultrasound findings to further characterize the lesions and in young women at high risk of breast cancer. Histological examination of every suspicious breast lesion should be carried out preoperatively by (image-directed) percutaneous needle biopsy to warrant one-session definitive surgery. The relationship between benign and malignant lesions should not exceed 1:2 after open biopsy. FDG PET is not recommended for axillary staging of patients with newly diagnosed breast cancer because of it fails to detect axillae with small and few nodal metastases.

References:

Statement: Palpation
GCP

Statement: All Methods:

Statement: Mammography / Ultrasound

**Statement MRI**

and meta-analysis of incremental cancer detection and impact on surgical management. JCO 2009; 27(33):5640-5649

17. Houssami N, Hayes DF Review of preoperative magnetic resonance imaging (MRI) in breast cancer: Should MRI be performed on all women with newly diagnosed early stage breast cancer. CA Cancer J Clin 2009; 59:290-302


Statement Minimal invasive biopsy


**Perioperative Staging (4/15)**

*Further information:*

A history and physical examination are good clinical practice and an obligation in every patient. Chest X-ray, liver ultrasound and bone scan have been used for initial staging of breast cancer. Patients with early, low risk breast cancer do not benefit from routine staging procedures. The routinously examination of serum liver enzymes, chest X-ray, liver ultrasound and bone scans in patients with high risk disease (clinically N1 and/or G3, cT3) could be helpful to avoid an overtreatment in cases with distant metastases. FDG-PET / PET-CT are valuable tools for detecting breast cancer recurrence and occult metastases, however a survival benefit due to early detection has not been proven yet. Moreover the technique is expensive and not everywhere available.

*References:*

Statement: history and physical examination  
GCP

Statement: high metastatic potential / symptoms
Evidence of Surgical Procedure (5/15)

Further information:

The standard surgical procedure for early breast cancer is breast conservation followed by radiation therapy. Ipsilateral breast tumor relapse rates should be lower than 10% after 10 years of follow-up. Randomised trials and clinical series of breast conservation report conflicting evidence relating to tumour size as a risk factor for local recurrence, although most studies report no association. There is little evidence to justify the use of tumour size alone as an exclusion criterion for breast-conservation therapy. Survival rates after modified radical mastectomy are equivalent to those after radical mastectomy. The skin sparing mastectomy with or without conservation of the nipple-areola complex and autologous reconstruction is a oncological safe treatment option in selected patients. Survival rates after modified radical mastectomy are equivalent to those after radical mastectomy according to Rotter-Halstedt.

References:

Statement: lumpectomy - mastectomy


Statement skin sparing mastectomy


**Statement: Nipple sparing mastectomy**


**Statement radical mastectomy vs. simple mastectomy**

Further information:

Excisional biopsy should be wire guided if the lesion is not palpable and specimen radiography should be performed. Radioguided occult lesion localisation' (ROLL) is a possible alternative to the commonly used 'wire-guided localisation' (WGL) of non-palpable breast lesions. Intratumoural injection of a radiotracer identifies both the primary tumour and the sentinel lymph nodes for intraoperative gamma probe guided dissection. The intraoperative radiography or ultrasound is in all cases of non-palpable lesions indicated (GCP). In breast conserving surgery the margins of the specimen have to be tumor free. There is no universal agreement on the width of the tumor free margin. Re-excision is required for a close margin < 1 mm in paraffin section. The re-excision is recommended in a period of < 4 weeks. Patients with involved margins, large tumour size and/or a DCIS component are more likely to have residual disease on re-excision. The rate of re-excision even in experienced and large breast centers is about 20% (up to 25% in case of DCIS).

References:

Statement: Wire guided ...  


Statement: Specimen radiography

Statement: specimen radiography ...
Statement: tumor free margins ...

Statement: ... re-excision ...
Statement: stereotactic excision alone ...


Breast Conservation Surgery (7/15)

Further information:

There are no randomized trials concerning BCS vs mastectomy in patients with multicentric breast cancer or inflammatory breast cancer. Multicentricity is defined as at least two separate lesions with a distance of > 4 cm. All indications for mastectomy in these patients are driven from the fact that local recurrence rate is significantly elevated in these patient groups. If there are no free margins after repeated excisions the option of mastectomy should discussed with the patient.

References:

Statement: all

Statement: positive microscopic ...

Statement: Inflammatory Carcinoma

1. Jennifer A. Low, Arlene W. Berman, Seth M. Steinberg: Long-Term Follow-Up for Locally Advanced and Inflammatory Breast Cancer Patients Treated With Multimodality Therapy. JCO 2004: 4067-4074


Axillary Lymph Node Dissection I (8/15)

Further information:

Axillary lymph node dissection improves clinical outcome only in patients with lymph node metastases. Axillary dissection is mainly a diagnostic procedure. Removal of tumor-free lymph nodes increases morbidity and has no prognostic impact. Available evidence suggests that quality assured sentinel lymph node biopsy (SLNB) is a reliable predictor of axillary lymph node status with high levels of sensitivity (90-95%), specificity (100%), negative predictive value (95%) and accuracy (97%).

In case of adequate multimodal treatment axillary dissection axillary dissection is not associated with improved overall survival.

References:

Statement: Axillary lymph node dissection
   Complete Axillary lymph node dissection after positive sentinel lymph node may be omitted in certain cases due to lack of benefit in pospectively randomized studies.

Statement AMAROS trial
Axillary dissection and radiotherapy are both associated with excellent regional control rates in clinically node-negative patients with a positive sentinel lymph node as has been shown in the AMAROS trial. Patients who recieved radiotherapy had significant less arm morbidity compared to patients who underwent axillary dissection. However some questions remain regarding this study such as the necessity of internal and supra-infra node irradiation. Due to many open questions the publication of the full paper of the AMAROS trial should be awaited before radiotherapy is used routinely to replace axillary surgery in patients, who require axillary dissection.
1. Rutgers E, Donker M Straver ME et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer patients: Final analysis of the EORTC AMAROS trial (10981/22023). J Clin Oncol 31,2013 (suppl;abstr LBA 1001)
Surgical Treatment of Axillary Lymph Nodes Pre and Post Nact (9/15)

Further information:

Statement surgical intervention in the axilla before or after Neoadjuvant Chemotherapy
Axillary surgery is a diagnostic procedure with the primary goal to provide prognostic information for the planning of treatment decisions. In the adjuvant setting the axillary status may tailor systemic (in luminal B) and regional treatment. The systemic treatment in patients, who undergo neoadjuvant therapy is (in general) predefined. In these patients the histopathologic response to chemotherapy (that includes response in the breast and the lymph nodes) is an important prognostic factor with a high potential to tailor future systemic and regional treatment decisions. Therefore it would be more reasonable to perform SLNB after NACT in order to provide this important prognostic factor.

SLNB after neoadjuvant chemotherapy is, however, associated with less favourable success rates (detection rate, false negative rate) compared to SLNB in primary surgery (as shown in the SENTINA trial). This relates especially to patients, who present initially with positive lymph nodes and convert to a negative axillary status under NACT. For patients with initially negative lymph nodes the success rates for SLNB after NACT appear more favourable although evidence from sufficiently powered prospective trials is lacking. Furthermore no data regarding oncologic endpoints (disease free survival, overall survival) are yet available for the SLN procedure after NACT.

In conclusion SLNB prior to NACT is a safe procedure, that can spare many patients with advanced tumors from axillary dissection. SLNB after NACT is an important future perspective, that should, however, be performed within clinical trials to provide the urgently awaited data on clinical outcome.

No references
Sentinel Lymph Node Excision: Indications I (10/15)

Further information:

Sentinel lymph node excision (SLN) has become a standard surgical procedure in patients with clinically and sonographically negative axilla (cN0). Sonographically critria for the definition of „negative lymph node“ has to be precised. Indication for SNE is not only focused on small tumours but nowadays possible and proven in many indications (cT3, Multicentricity). In large DCIS or if a mastectomy is requiered - SNE should be offered to the patient. Although male breast cancer patients presented with older age and larger tumors than female breast cancer patients - SLN procedure in clinically node-negative men is feasible and accurate. Preoperative ultrasound guided needle biopsy is accurate for initial staging of the axilla and should be used for women with invasive breast cancer and clinical suspect axillary lymph nodes, as has been shown in a recently published metaanalysis

References:

Statements


**Sentinel Lymph Node Excision: Indications I (11/15)**

*Further information:*

There are only few experiences reported about SNE during pregnancy. The radioactive dosage of the applied radiocolloid is estimated very low and therefore not harmful for the unborn. Nothing is known about altered lymph drainage during pregnancy. The Bundesamt für Strahlenschutz has stated in a letter to the author that no fetal harm will be expected after application of 11 MB at the day of surgery and that therefore is no indication for termination of pregnancy. By performing a SLN biopsy, a large proportion of patients with PABC may be spared the risk of a complete axillary lymph node dissection. Therefore the commission decided a + for the procedure during pregnancy. The management of internal mammary nodes (IMNs) in breast cancer is still controversial. RCT are in progress. Data from small series have shown that second SLNB after previous SLNB is technically feasible and likely effective in selected breast cancer patients. A SLNE is not recommended in patients with prior surgery and large disturbing the lymphatic vessels in the breast or axilla or between these regions. In Inflammatory BC the feasibilty of SNE is of limited data. Suspected clinical lymph node involvement should be clarified with FNA/CNB to avoid overtreatment in case of axillary lymph node dissection with negative involvement after clinicaly suspicious lymph nodes.

For patients, who undergo repeat SLNB after previous axillary surgery lymphoscintigraphy should be performed because a high rate of extraaxillary SLN has been described in this setting.

*References:*

Statement: pregnancy


Statement: mammarian internal

Statement: all others

Statement 10

Procedure after Neoadjuvant Therapy (12/15)

Further information:

Precise documentation of tumor location before – e.g. with intratumoral clip implantation -, during and at the end of primary systemic therapy (PST) is necessary. Surgery is an integral part of primary breast cancer treatment following PST. The aim of surgery is to completely remove invasive and non invasive breast cancer residues after PST and to obtain clear margins of at least 1 mm at pathology examination. No compromise should be made in surgical margins to obtain better cosmetic results. Under these circumstances excision within new tumor margins might be feasible according to current data.

References

Surgery and Irradiation after Neoadjuvant Therapy (13/15)

Further information:

It is unknown whether preoperative radiotherapy following primary systemic therapy (PST) achieved similar results as radiotherapy following PST and surgery. Preoperative radiotherapy might result in higher rates of breast conservation without compromising cosmetic result. However, preoperative external beam and brachytherapy are not established as modes of treatment in conjunction with PST and do not replace adequate surgery which should be performed after leucocyte nadir around 2 to 4 weeks following last cycle of chemotherapy. Adjuvant radiotherapy after PST should be administered according to the same recommendations made for those patients who do not receive PST. Even in patients with pathological complete response following PST whole breast irradiation is indicated after breast-conserving surgery. According to retrospective analyses the addition of radiation to PST and mastectomy reduces local regional recurrence and increases breast cancer specific survival for patients presenting with clinical T3 tumors or stage III and IV (ipsilateral supraclavicular nodal) disease and for patients with ≥ four positive axillary nodes regardless of their response to PST.

References:

Surgery after Neoadjuvant Therapy (14/15)

Further information:

Primary systemic therapy (PST) to achieve breast conserving surgery is not indicated in multicentric cancer, if extensive DCIS is present or if radiotherapy is not feasible.^{13}

References:

3. Osteen RT. Cancer 74, 366, 1994
Adjuvant Therapy after Primary Surgery (15/15)

No further information

References:

Concurrent use of endocrine therapy:

Timing of radiation and chemotherapy:


Oncoplastic and Reconstructive Surgery
Oncoplastic and Reconstructive Surgery

- **Versions 2002–2013:** Audretsch / Blohmer / Brunnert / Dall / Fersis / Hanf / Kümmel / Nitz / Rezai / Rody / Scharl / Thomssen

- **Version 2014:** Lux / Rezai
Definition of Oncoplastic Surgery

Oncoplastic surgery in its original form began as combining lumpectomy or quadrantectomy with local or regional tissue rearrangement so that the breast should be conserved and reshaped so as to avoid significant deformity.

Scott Spear MD, Washington DC 2009
Range of Options for Breast Reconstruction

- Implant
- Latissimus
- TRAM
- Microsurgery
  - DIEP
  - SIEA
  - SGAP

Sumner A. Slavin, M.D
Algorithm of Breast Reconstruction

1st choice:
Implant-Reconstruction

Implant alone not suitable – hostile environment

- TRAM-Flap
- Consider implant + additional acellular matrix and / or fat grafting

LADO + implant

if both not suitable

if not suitable

Microsurgery/free flaps
Postmastectomy Implant Reconstruction

- Use of silicone filled breast implants (no systemic health hazards documented, no influence on OS and detection of recurrence)
  - Oxford / AGO LoE / GR: 2a B +

- Implant reconstruction (IR)
  - IR without radiotherapy (RT)
    - Oxford / AGO LoE / GR: 2a B ++
  - IR following MX and RT
    - Oxford / AGO LoE / GR: 2b B +/-
  - IR prior to RT / following PBRT
    - No increase of complications by use of acellular dermal matrix (ADM)
      - Oxford / AGO LoE / GR: 3a C +/-
  - IR following Mx for local relapse after BCT
    - Oxford / AGO LoE / GR: 2a B +/-
  - Periop. antibiotic therapy (at least 48 h)
    - Oxford / AGO LoE / GR: 3b C +
# Radiotherapy after Implant Breast Reconstruction I

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient satisfaction</th>
<th>Failure Complications</th>
<th>Observation period</th>
<th>Pts. RT/CTR</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCarthy CM</td>
<td>Pre-or postop. radiation no significant risk factors</td>
<td>Independent risk factors: smoking, obesity, hypertension, age &gt;65 39% total complication rate</td>
<td>2003-2004 prospective</td>
<td>1170/1170</td>
</tr>
<tr>
<td>Berry T</td>
<td>70,1% successfull</td>
<td>Major complication rate 24,4% +RT 45,4%</td>
<td>-</td>
<td>Total 1037</td>
</tr>
<tr>
<td>Berry T</td>
<td></td>
<td>Risk factors for failure: surgeon, tumor size T3 or T4, smoking, pN+, Baker 3+4 32,5%</td>
<td>37 mths. 1998-2006</td>
<td>141</td>
</tr>
<tr>
<td>Whitfield GA</td>
<td>70 % free of CC after 6 years</td>
<td>CC p &lt; 0.001 (30 % vs. 0 %)</td>
<td>51 mths.</td>
<td>41/110</td>
</tr>
<tr>
<td>Christante D</td>
<td>not reported</td>
<td>7 % vs. 44 % p&lt;0.001</td>
<td>2000-2008</td>
<td>302</td>
</tr>
<tr>
<td>Cordeiro PG</td>
<td>n.s. acceptable</td>
<td>p=0.025 CC (68% vs. 40%)</td>
<td>1995-2001</td>
<td>81/606</td>
</tr>
<tr>
<td>McCarthey</td>
<td>80% satisfied no Baker IV</td>
<td>40% no difference 50% 1 Baker grade up 10% 2 Baker grades up</td>
<td>FU 23,5 mths. 1998-2002</td>
<td>71/410</td>
</tr>
<tr>
<td>Cordeiro PG</td>
<td>95% pts. satisfied</td>
<td>49,3% no CC</td>
<td>1992-2004 prospective</td>
<td>71/410</td>
</tr>
<tr>
<td>Behranwala</td>
<td>60% free of CC after 4 years</td>
<td>CC p&lt;0.001 (38,6% vs. 14,1%)</td>
<td>2-5 years</td>
<td>44/92br</td>
</tr>
<tr>
<td>Benediktsson K</td>
<td>Reop. n=16 free of CC after 5 years</td>
<td>CC p=0.01 (41,7% vs. 14,5%)</td>
<td>2-5 years</td>
<td>24/83</td>
</tr>
</tbody>
</table>
# Radiotherapy after Implant Breast Reconstruction II

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient satisfaction</th>
<th>Failure Complications</th>
<th>Observation period</th>
<th>Pts. RT/CTR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tran Tet al. 2011</td>
<td>no significant differences between irradiated and non-irradiated patients</td>
<td>more frequently lymphedema in radiated patients</td>
<td>2005-2010 retrospective</td>
<td>175 (25.7% with radiotherapy), 54.8% implant based reconstruction</td>
</tr>
<tr>
<td>Brooks S et al. 2012</td>
<td>70.1% successful expander/implant reconstruction</td>
<td>28.4% (&lt;50y.), 37% (&gt;50y.), 27.5 (BMI&lt;30), 49% (BMI&gt;30)</td>
<td>2000-2006 retrospective</td>
<td>560</td>
</tr>
<tr>
<td>Nava MB, Plast Reconstr Surg 2011</td>
<td>not reported</td>
<td>Implant + RT 6.4%, Expander + RT 40%</td>
<td>-</td>
<td>257 exp vs. implant rec</td>
</tr>
</tbody>
</table>
Radiotherapy after Implant Breast Reconstruction with use of ADM

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Level of Evidence/ Animal Model</th>
<th>RT and ADM Reconstructions (n)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Literature review</td>
<td>2007</td>
<td>III</td>
<td>TE/1 (5)</td>
<td>Irradiated ADM versus nonirradiated cohort demonstrated a 20% vs. 10.7% overall complication rate and 20% vs 0 expander loss rate at 10-mo follow-up.</td>
</tr>
<tr>
<td>Bindingnaswala et al.60</td>
<td>2007</td>
<td>III</td>
<td>TE/1 (10)</td>
<td>One (10%) irradiated expander was lost compared with none in the nonirradiated cohort; 85% expander fill volume at initial surgery.</td>
</tr>
<tr>
<td>Breuing and Colwell61</td>
<td>2008</td>
<td>III</td>
<td>TE/1 or A (11)</td>
<td>Radiation leads to 11-fold increase in complication rate of HADM patients with PMRT; highly select patients with prior BCT (n = 4) developed no complications.</td>
</tr>
<tr>
<td>Spear et al.81</td>
<td>2009</td>
<td>III</td>
<td>TE/1 (23)</td>
<td>Higher incidence of infection (8.7% vs. 3.9%), incisional dehiscence (13% vs 1.3%), and seroma (13% vs. 2.0%) in HADM irradiated versus nonirradiated breasts.</td>
</tr>
<tr>
<td>Nahabedian90</td>
<td>2010</td>
<td>III</td>
<td>TE/1 or A (54)</td>
<td>HADM reconstruction patients receiving PMRT developed a 29.6% capsular contracture rate compared with 0.7% in nonirradiated HADM patients at an overall follow-up of 16.1 mo.</td>
</tr>
<tr>
<td>Serny et al.85</td>
<td>2010</td>
<td>III</td>
<td>TE/1 (28)</td>
<td>For irradiated breasts, HADM use led to a significantly higher explantation rate compared with total muscle coverage (10.7% vs. 0, p = 0.02).</td>
</tr>
<tr>
<td>Israeli and Feingold80</td>
<td>2011</td>
<td>III</td>
<td>TE/1 (17)</td>
<td>Within HADM reconstructions, irradiated breasts had a significantly higher overall complication rate (50% vs. 3.5%, p = 0.0005) and expander loss rate (17.0% vs. 2.9%, p = 0.04) than nonirradiated breasts.</td>
</tr>
<tr>
<td>Rawlani et al.85</td>
<td>2011</td>
<td>III</td>
<td>TE/1 (26)</td>
<td>HADM patients receiving PMRT compared with no radiation had nonsignificantly higher overall complication, infection, flap necrosis, and implant exposure rates.</td>
</tr>
<tr>
<td>Salzberg et al.87</td>
<td>2011</td>
<td>III</td>
<td>I (21)</td>
<td>Irradiated breasts had a fourfold higher rate of complications for HADM breast reconstructions (14.9% vs. 3.9%).</td>
</tr>
<tr>
<td>Cotwell et al.90</td>
<td>2011</td>
<td>III</td>
<td>I (51)</td>
<td>Higher overall complication rate (25.2% vs. 13.9%, p = 0.005); prior BCT/RT had a significantly higher complication rate (24.2%) over PMRT (16.7%).</td>
</tr>
</tbody>
</table>

Animal studies
- Dublin et al.60 2000 36 rat hind limbs
- Ibnabreh et al.77 2000 36 rat hind limbs
- Komorowska-Tumek et al.60 2009 41 rat implant capsules

Muscle Fixation for Immediate Reconstruction after Mastectomy

- **Autologous tissue (e.g. LDF*)**
- **Acellular dermal matrix (ADM)**
  - No significant increase of long-term complication rate compared to implant without ADM
  - Less capsular contracture compared to two-stage expander/implant without ADM
- **Synthetic mesh**

* LDF = Latissimus dorsi flap

| Oxford / AGO LoE / GR | 3b C +# | 2b B +# | 2b C |
---|---|---|---|

* Participation in register studies recommended
Summary of Characteristics and Conclusions of Studies Comparing ADM and Non-ADM Breast Reconstruction

<table>
<thead>
<tr>
<th>Author, y</th>
<th>No. Patients</th>
<th>No. Breasts</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ADM</td>
<td>Non-ADM</td>
<td>ADM</td>
</tr>
<tr>
<td>Preminger et al, 2008¹⁴</td>
<td>45</td>
<td>45</td>
<td>—</td>
</tr>
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<td></td>
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<td></td>
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<tr>
<td>Nahabedian, 2009¹²</td>
<td>76</td>
<td>285</td>
<td>100</td>
</tr>
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<td></td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Lanier et al, 2010¹⁰</td>
<td>52</td>
<td>75</td>
<td>—</td>
</tr>
<tr>
<td>Chun et al, 2010⁹</td>
<td></td>
<td></td>
<td>269</td>
</tr>
<tr>
<td>Nguyen et al, 2010¹³</td>
<td>41</td>
<td>163</td>
<td>75</td>
</tr>
<tr>
<td>Liu et al, 2011¹¹</td>
<td>192</td>
<td>151</td>
<td>266</td>
</tr>
<tr>
<td>Present study</td>
<td>31</td>
<td>44</td>
<td>38</td>
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</tbody>
</table>

Lipofilling

- Lipofilling after implant-based reconstruction
- Lipofilling after breast-conserving therapy
- Autologous adipose-derived stem cells (ASCs)-enriched fat grafts

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Grade</th>
<th>Evidence</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipofilling after implant-based reconstruction</td>
<td>2a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Lipofilling after breast-conserving therapy</td>
<td>4</td>
<td>D</td>
<td>+/-</td>
</tr>
<tr>
<td>Autologous adipose-derived stem cells (ASCs)-enriched fat grafts</td>
<td>5</td>
<td>D</td>
<td>-</td>
</tr>
</tbody>
</table>
## Follow-up Results after Lipofilling

<table>
<thead>
<tr>
<th>Patients</th>
<th>Follow-up before lipofilling (months)</th>
<th>Local recurrence before n (%)</th>
<th>Follow-up after lipofilling, months (minimum–maximum)</th>
<th>Local recurrence after n (%)</th>
<th>Local recurrence after (incidence per 100 person-years)</th>
<th>Distant metastases (n)</th>
<th>Interval from lipofilling to recurrence (months)</th>
<th>Interval from lipofilling to metastasis (months)</th>
<th>Patients with free-disease survival at 5 years from surgery (%)</th>
<th>Patients with free-disease survival at 8 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rigotti et al. [20]</td>
<td>137</td>
<td>23</td>
<td>4 (2.92)</td>
<td>60</td>
<td>5 (3.6)</td>
<td>0.72</td>
<td>9</td>
<td>20 ± 12</td>
<td>21</td>
<td>95.6</td>
</tr>
<tr>
<td>Rietjens et al. [21]</td>
<td>155</td>
<td>35.2</td>
<td>–</td>
<td>18.3 (6–49)</td>
<td>1 (0.6)</td>
<td>0.43</td>
<td>0</td>
<td>2 weeks</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Petit et al. [23]</td>
<td>321</td>
<td>26</td>
<td>–</td>
<td>26 (1–128)</td>
<td>13 (4.0)</td>
<td>1.87</td>
<td>13</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Petit et al. [22]</td>
<td>513</td>
<td>39.7</td>
<td>0 (0)</td>
<td>19.2 (1–107)</td>
<td>– (2.4)</td>
<td>1.5</td>
<td>15</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Riggio E</td>
<td>60</td>
<td>56.5</td>
<td>1 (1.66)</td>
<td>92.2 (5–132)</td>
<td>2 (3.3)</td>
<td>0.43</td>
<td>4</td>
<td>47 ± 14.8</td>
<td>28.5</td>
<td>93.3</td>
</tr>
</tbody>
</table>

Postmastectomy Pedicled Flap Reconstruction

Reconstruction (BR) with autologous tissue

- TRAM, latissimus-dorsi-flap (both can be performed as a muscle-sparing technique)
- Delayed TRAM in risk patients
- Ipsilateral pedicled TRAM

Radiotherapy:

- BR following RT
- BR prior to RT (dependent on quality of blood supply)

Oxford / AGO LoE / GR

3b C +
3a B +
3b A +
4 C +
3b C +/-
Free Tissue Transfer

Free tissue transfer
- Free TRAM-flap
- DIEP-flap
- SIEA-flap
- SGAP- / IGAP-flap
- Free gracilis flap (TMG)
- Latissimus dorsi free flap

Advantage:
- Free TRAM and DIEP are potentially muscle-sparing procedures

Disadvantages:
- Time- and personnel-consuming microsurgical procedure
- Intensified postoperative monitoring
- Higher rate of reoperations
- Higher total failure rate
- Pre-reconstruction RT increases rate of vascular complications
- No higher patient satisfaction than with pedicled TRAM in multivariate analysis
Pedicled vs. Free Tissue Transfer

- Muscle-sparing techniques and accuracy of abdominal wall closure will lead to low rates of late donor site complications whatever method used.
- Autologous abdominal-based reconstructions have the highest satisfaction in all patient groups without any difference.
- Perforator flaps appear to have a higher risk for fat necrosis than free or pedicle TRAM.
- Donor site morbidity (e.g. impaired muscle function) has to be taken into consideration in all flap techniques.

Oxford / AGO
LoE / GR

3a A ++
Flap-Implant Combination

Flap-implant combination  TRAM, LDF* + implant

- IR following RT
- IR prior to RT

Advantages:

- TRAM: staged procedure preferable
- Improved implant coverage
- Suitable for radiated tissue

Disadvantage:

- Muscle contraction (LDF)

* LDF = Latissimus dorsi flap
Timing of Breast Reconstruction

- **Delayed BR**
  - No interference with adjuvant procedures (CHT, RT)
  - Disadvantage: loss of skin envelope

- **Immediate BR**
  - Preferential in combination with partial Mx (BCT)
  - Mandatory: SSM / NSM
  - Avoidance of a postmastectomy syndrome

- „Delayed-immediate“ BR

---

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>3b</th>
<th>B</th>
<th>++</th>
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</thead>
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in der DGGG e.V.
sowie
in der DKG e.V.
Guidelines Breast
Version 2014.1

www.ago-online.de
Skin/Nipple Sparing Mastectomy (SSM/NSM) and Reconstruction

- Skin sparing mastectomy (SSM/NSM)
  - Safe (same recurrence rate as MX)
  - Higher QoL for patients
  - NAC can be preserved under special conditions
    - Feasible after mastopexy / reduction mammoplasty

- Skin incisions ⇒ different options possible:
  - Periareolar („purse-string“) (higher risk of necrosis)
  - Reduction pattern: „inverted-T“ or vertical
  - Inferior lateral approach, inframammary fold
    - Lowest incidence of complications

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b B ++</td>
</tr>
<tr>
<td>2b B ++</td>
</tr>
<tr>
<td>2b B ++</td>
</tr>
<tr>
<td>4 C ++</td>
</tr>
</tbody>
</table>
## SSM / Nipple SM

<table>
<thead>
<tr>
<th>Author</th>
<th>Cases reported</th>
<th>Partial skin necrosis</th>
<th>Local recurrence</th>
<th>Time period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lanitis S et al. 2010</td>
<td>1104 SSM</td>
<td>--</td>
<td>6,2% SSM</td>
<td>1997–2009 Metaanalyse</td>
</tr>
<tr>
<td></td>
<td>2635 NSSM</td>
<td></td>
<td>4,2% NSSM n.s.</td>
<td></td>
</tr>
<tr>
<td>Jensen JA Ann Surg Oncol 2010</td>
<td>99</td>
<td>6 %</td>
<td>2,7 %</td>
<td>Median FU 60,2 mths</td>
</tr>
<tr>
<td>Yi M, Kronowitz SJ 2010 Cancer</td>
<td>799 SSM</td>
<td>-</td>
<td>n.s. (local+syst. 6.6%)</td>
<td>2000-2005</td>
</tr>
<tr>
<td></td>
<td>1011 CM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KIM HJ Ann Surg 2010</td>
<td>368 SSM</td>
<td>9.6% NAC</td>
<td>0.8% SSM</td>
<td>07.2001-12.2006</td>
</tr>
<tr>
<td></td>
<td>152 NSSM</td>
<td></td>
<td>2.0% NSSM (1.3%NAC)</td>
<td></td>
</tr>
<tr>
<td>Paepke S Ann Surg 2009</td>
<td>109 SSM (96 NSM)</td>
<td>1,0 % of nipple necrosis</td>
<td>no rec. in the nipple</td>
<td>2003-2006</td>
</tr>
<tr>
<td>Chen CM 2009 PRS</td>
<td>115 (62 benign)</td>
<td>Loss of NAC: 5.2% Occ.ca. 3.5% Necrosis</td>
<td>--</td>
<td>1998-2008</td>
</tr>
<tr>
<td>Garwood ER 2009 Ann Surg</td>
<td>170</td>
<td>Cohort 1: 16% Cohort 2: 11%</td>
<td>0,6%</td>
<td>2001-2007</td>
</tr>
<tr>
<td>Yano K et al. 2007 Breast Cancer</td>
<td>128</td>
<td>3,1%</td>
<td>2,3%</td>
<td>2001–2005</td>
</tr>
<tr>
<td>Petit JY et al. 2006 Breast Cancer Res Treat</td>
<td>106 NSM</td>
<td>4,7% Loss of NAC</td>
<td>0,9% Far from NAC</td>
<td>2002–2003</td>
</tr>
<tr>
<td>Gerber B et al. 2003 Ann Surg</td>
<td>112 (Incl.61 NSM)</td>
<td>0%</td>
<td>5,4%</td>
<td>1994–2000</td>
</tr>
</tbody>
</table>
Bilateral Risk Reducing Mastectomy in Healthy Women (RRBM)

- RRBM reduces breast cancer incidence
- RRBM in deleterious BRCA1/2 mutation
- RRBM in high risk (i.e. lifetime risk >=30% or heterozygote risk >=20%) but index case negative for BRCA1/2 mutations
- High risk and no BRCA counselling in specialized centre*
- Non-directive counselling prior to RRBM
- RRBM should be considered with other prophylactic surgical options incl. salpingoophorectomy (BSO)
- Further need for education of physicians regarding possibilities and advantages of RRBM

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>LoE</th>
<th>AGO</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>2a</td>
<td>A++</td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>B</td>
<td>++*</td>
</tr>
<tr>
<td>3a</td>
<td>C</td>
<td>+/-*</td>
</tr>
<tr>
<td>5</td>
<td>D</td>
<td>- -</td>
</tr>
</tbody>
</table>

*Counselling, risk prediction and follow-up in specialised centres recommended
Types of Risk Reducing Mastectomy in Healthy Women (RRBM)

Risk Reducing Mastectomy reduces breast cancer incidence; bc-spec mortality reduction likely

- Simple mastectomy
- RRBM by SSM
- RRBM by NSM (NAC sparing)
- Contralateral prophylactic MX

Oxford / AGO LoE / GR

2b B +
2b C +
2b C +
4 C +/-
# DIEP-Flap I

<table>
<thead>
<tr>
<th>Author</th>
<th>Cases reported</th>
<th>Complete loss of flap</th>
<th>Lipo-necrosis</th>
<th>Hernias in donor region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gill PS et al 2004 PRS</td>
<td>758</td>
<td>0,5%</td>
<td>15,4%</td>
<td>0,7%</td>
</tr>
<tr>
<td>Guerra et al 2004 Ann Plast Surg</td>
<td>280</td>
<td>0%</td>
<td>12,5%</td>
<td>2,1%</td>
</tr>
<tr>
<td>Nahabedian et al 2005 PRS</td>
<td>110</td>
<td>2,7%</td>
<td>6,4%</td>
<td>2,7%</td>
</tr>
<tr>
<td>Blondeel PN 1999 PRS</td>
<td>100</td>
<td>2%</td>
<td>13%</td>
<td>1%</td>
</tr>
<tr>
<td>De Greef C et al 2005 Ann Chir Plast Esthet</td>
<td>100</td>
<td>4%</td>
<td>7%</td>
<td>2%</td>
</tr>
<tr>
<td>Garvey PB et al 2006 PRS</td>
<td>96</td>
<td>0%</td>
<td>17,7%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9,4% bulges</td>
</tr>
</tbody>
</table>

- Xu H 2009 PRS 113 3,5 % 17,7% 0 % hernia 0,9 % bulges (med. FU only 12,3 months!)
- Wan DC 2010 PRS 275 1) fTRAM 2) MS fTRAM 3) DIEP 1+2)BMI<30: 0 % 1)BMI>30: 0 % 2)BMI>30: 2,8 % 3)BMI<30: 6,1 % 4)BMI>30:14,3%
## DIEP-Flap II

<table>
<thead>
<tr>
<th>Author</th>
<th>Cases reported</th>
<th>Complete loss of flap</th>
<th>Liponecrosis partial flap loss</th>
<th>Hernias/ Bulges in donor region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Munhoz AM et al 2007 Breast J (on DIEP and SSM)</td>
<td>30</td>
<td>3.7%</td>
<td>7.4%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Lindsey JT. 2007 PRS</td>
<td>140</td>
<td>6.4%</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Hofer SO et al. 2007 Ann Plast Surg</td>
<td>175</td>
<td>0.6%</td>
<td>8.6%</td>
<td>--</td>
</tr>
<tr>
<td>Peeters WJ 2009 PRS</td>
<td>202</td>
<td>n.a.</td>
<td>49% Clinical 14% US 35%</td>
<td>n.a.</td>
</tr>
<tr>
<td>Selber JC 2010 PRS</td>
<td>fTRAM 569 DIEP 97</td>
<td>0.2% 1.0% n.s.</td>
<td>4.1% 2.1% n.s.</td>
<td>1.9% n.s.</td>
</tr>
</tbody>
</table>
# DIEP-Flap III

<table>
<thead>
<tr>
<th>Author</th>
<th>Cases reported</th>
<th>Complete loss of flap</th>
<th>Liponecrosis partial flap loss</th>
<th>Hernias/ Bulges in donor region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garvey BP et al. PRS 2011</td>
<td>228</td>
<td>n.a.</td>
<td>8,3/3,3%</td>
<td>n.a.</td>
</tr>
<tr>
<td>Conroy K et al. PRAS 2011</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>3 epigastric hernia</td>
</tr>
<tr>
<td>Momoh AO et al. Ann PS 2011</td>
<td>217</td>
<td>n.a.</td>
<td>n.a.</td>
<td>2,3%/0%</td>
</tr>
<tr>
<td>Andree C. et al. Med Sci Monit 2012</td>
<td>1068</td>
<td>0,8%</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
</tbody>
</table>
## Pedicled / Free TRAM I

<table>
<thead>
<tr>
<th>Author</th>
<th>Reported cases</th>
<th>Complete loss of flap</th>
<th>Liponecrosis</th>
<th>Hernias in donor region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watterson PA, Bostwick J. 1995 PRS</td>
<td>556</td>
<td>0</td>
<td>10,6%</td>
<td>8,8%</td>
</tr>
<tr>
<td>Kroll SS (f-TRAM) 2000 PRS</td>
<td>279</td>
<td>0,4%(1,1%)</td>
<td>15,1%</td>
<td></td>
</tr>
<tr>
<td>Lacotte B, Lejour M 1994 Ann Chir Plast Esthet</td>
<td>156</td>
<td>0</td>
<td>10%</td>
<td>0</td>
</tr>
<tr>
<td>Clugston PA, Maxwell GP 2000 PRS</td>
<td>252</td>
<td>0</td>
<td>9,1%</td>
<td>5,8%</td>
</tr>
<tr>
<td>Petit JY, Rietjens M 1997 Ann Chir Plast Esthet</td>
<td>310</td>
<td>0</td>
<td>10,2%</td>
<td>7%</td>
</tr>
<tr>
<td>Rezai M IGCS 2010</td>
<td>234</td>
<td>0</td>
<td>10,2%</td>
<td>0,6%</td>
</tr>
<tr>
<td>Brunnert 2001 unpublished</td>
<td>776</td>
<td>0</td>
<td>8,4%</td>
<td>0,4%</td>
</tr>
<tr>
<td>Kim EK 2009 Ann Plast Surg</td>
<td>500</td>
<td>major fl. 0,2 %</td>
<td>14,2%</td>
<td>3% (bulges)</td>
</tr>
<tr>
<td>Chun YS 2010 PRS</td>
<td>105</td>
<td>biped,</td>
<td>11,4%</td>
<td>2,9%</td>
</tr>
</tbody>
</table>
# Pedicled / Free TRAM II

<table>
<thead>
<tr>
<th>Author</th>
<th>Reported cases</th>
<th>Complete loss of flap</th>
<th>Liponecrosis</th>
<th>Hernias in donor region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Momoh AO et al. Ann PS 2011</td>
<td>197</td>
<td>n.a.</td>
<td>n.a.</td>
<td>2.3%/0%</td>
</tr>
<tr>
<td>Garvey BP et al. PRS 2011</td>
<td>228</td>
<td>n.a.</td>
<td>11.3/2.8%</td>
<td>n.a.</td>
</tr>
</tbody>
</table>
## Radiotherapy after Autologous Reconstruction I

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient satisfaction</th>
<th>Failure complications</th>
<th>Observation period</th>
<th>Pts. RT/CTR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williams JK 1997 PRS</td>
<td>unchanged</td>
<td>nature of complications changes from fat necrosis to fibrosis</td>
<td>1981–1994</td>
<td>19/680</td>
</tr>
<tr>
<td>Soong IS 2004 Clin Oncol (Radiol)</td>
<td>cosmesis 85% good to excellent</td>
<td>no difference</td>
<td>1995–2001</td>
<td>25/--</td>
</tr>
<tr>
<td>Mehta VK 2004 Breast</td>
<td>no problems</td>
<td>10% skin desquam. 30% grade 2 erythema</td>
<td>1995–2000</td>
<td>22/--</td>
</tr>
<tr>
<td>Huang CJ 2006 PRS</td>
<td></td>
<td>fat fibrosis 8% n.s.</td>
<td>1997–2001</td>
<td>82/109</td>
</tr>
<tr>
<td>Kronowitz SJ 2009 PRS</td>
<td>Radiation Therapy and BR: A critical review of the literature</td>
<td></td>
<td>&gt;1985</td>
<td>49 articles reviewed</td>
</tr>
</tbody>
</table>
# Radiotherapy after Autologous Reconstruction II

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient satisfaction</th>
<th>Failure Complications</th>
<th>Observation period</th>
<th>Pts. RT/CTR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barry M, Breast Cancer Res Treat. 2011 Metaanalysis</td>
<td>not reported</td>
<td>OR = 0.21; 95% CI, 0.1-0.4 [autologous vs. implant-based]</td>
<td>-</td>
<td>1105 Implant vs. Autologous Recon.</td>
</tr>
</tbody>
</table>
Algorithm of Breast Reconstruction

Algorithm Breast Reconstruction*

- Prophylaxis – *pts at risk*
- Primary Invasive Breast Cancer
  - MX necessary or pt’s preference
- DCIS
  - Premalignant breast disease

- Physical status of pt. and donor sites
  - excellent - good
- Informed Consent
  - Patient – Physician – interaction
  - Publications

- Physical status and/or donor sites impaired
  - Local conditions fine
  - „High risk“

- Autologous Reconstruction
- Implant Reconstruction

Algorithm of Autologous Breast Reconstruction (1)

1st choice: Abdomen

Radiotherapy: yes or maybe

Delayed Reconstruction

Immediate-Delayed BR - (Permanent) Expander

Abdomen Not suitable

Radiotherapy Yes or maybe: Delayed Reconstruction if no Radiotherapy: Immediate Reconstruction

I/S-GAP-GRACILIS - Flap Autolog. Lado

Further Information

References
Algorithm of Autologous Breast Reconstruction (2)

1st choice: Abdomen
No Radiation

Small - Moderate Breast

- Single pTRAM (MS-2)
  or Autolog. Lado

Large Volume Breast >1000g

- Double MS-2 pTRAM
  or Free TRAM

Abdomen obese >5cm
"Apron" or "high risk"

- Delay
- CT-Angiography

- Bip TRAM (MS-2)
- fTRAM
- DIEP
Algorithm of Implant Breast Reconstruction

Premastectomy Sentinel Node Biopsy

Radiotherapy: yes or maybe

- SSM/NSM Expander/Implant
  - In case of CF: MPS-perm. Implant

No Radiotherapy

- Normal – moderate breast
  - If big skin island +/- NAC
    - SSM+perm. Exp. + Lado
  - SSM +/- NAC Perm. Exp. +/- Impl.

- Large vol. breast
  - Reduction pattern + perm. Exp./Implant
**Oncoplastic and Reconstructive Surgery (2/34)**

*Further information:*

Verwendete Literatur-Datenbanken:

Pubmed 2003 - 2013
Cochrane data base (z.B. Cochrane Breast Cancer Specialised Register)

Suchbegriffe: breast reconstruction; … AND random allocation, … AND cohort study


und Thomssen et al. SOPs für die Überarbeitung der AGO-Leitlinien zum Mammakarzinom 2006 2

Verwendete Guidelines zu Diagnostik und Therapie des Mammakarzinoms:
American Association of Clinical Oncology (ASCO) and Technology Assessments:
http://www.asco.org/portal/site/ASCO/menuitem. (Practice Guidelines),
Canadian Medical Association (CMA): http://www.cmaj.ca/cgi/content/full/158/3/DC1

Aesthetics must play a key role in the surgery of the breast in order to avoid deformities which could have a negative impact on a patient’s self esteem irrespective of age. With the help of oncoplastic surgery free margins due to wide
excisions of malignant tumors are possible without compromising the shape of the breast thus preserving physical integrity. As a result oncoplastic surgery plays an integral role in the primary surgical treatment of BC.
Definition of oncoplastic surgery (3/34)

No further information

References:

Scott Spear, Washington DC, 2009
Range of Options for Breast Reconstruction (4/34)

No further information

References:

Sumner A. Slavin, MD
Algorithm of Breast Reconstruction (5/34)

No further information

No references
**Postmastectomy Implant Reconstruction (6/34)**

*Further information and references:*

Link to no documented systemic health hazards and to IR following RT and prior RT and to advantage of implant reconstruction:

Silicone breast implants are safe and important building blocks in the variety of reconstructive techniques in breast reconstruction. The two-year results of the Michigan Breast Reconstruction Outcomes Study shows, that in regard to general satisfaction there is no statistical difference concerning implant or autogenous reconstruction. Only from an aesthetic viewpoint seems the breast reconstruction with living tissue superior. But the increasing use of Post-mastectomy-radiation-therapy (PMRT) endangers the aesthetic results of immediate (IBR) or delayed breast reconstruction with implants. On the other hand the survey of recent publications on immediate implant reconstruction demonstrates the feasibility of implant reconstruction, despite the fact, that certain complications as capsular contracture (CC) are more frequent after PMRT and IBR. On the other hand in the majority of cases CC is curable by a single operative procedure. Implant reconstruction in previously radiated patients proves to have a higher rate of perioperative complications after performing expander/implant breast reconstruction, but the absolute rate of complications remained low in the analysis of a prospectively maintained database of 1522 reconstructions in 1221 patients by Peter G. Cordeiro of the Memorial Sloan-Kettering Cancer Center. This is the reason for keeping expander/implant reconstruction after prior radiotherapy in their reconstructive armamentarium.

If the necessity of postsurgical radiotherapy is not known at the time of mastectomy and reconstruction there is the possibility of a delayed-immediate reconstruction. After SSM a traditional or permanent expander is implanted till the final decision about RT is made; after completion of RT or if not necessary at all immediately the planned standard reconstruction is performed.

In case of unilateral implant reconstruction alone a development of asymmetry over time has to be considered. The most predictable results in implant reconstruction can be achieved with the bilateral use of implants or the combination with a latissimus dorsi flap. Implants are generally placed in a dual plane position, i.e. a partial muscular coverage of the implant.
Only if there is a wide supple muscular pocket (lado+pectoralis m.) is a complete coverage advisable (tension-induced pain otherwise possible).

One hundred and seventy-eight immediate breast reconstructions performed at the Cambridge Breast Unit between 1.1.2001 and 31.12.2005 were identified. RT was delivered using a standard UK scheme of 40 Gray in 15 fractions over 3 weeks. The influence of hormones and chemotherapy as well as postoperative RT on time to development of severe CC after implant-based reconstruction was explored in univariate and multivariate analysis. One hundred and ten patients had implant-based reconstructions with a median follow-up of 51 months. In the RT group (41 patients), there were 8 patients with severe CC requiring revisional surgery, a crude rate of 19.5%, with actuarial rates of 0%, 5%, 5%, 21%, 30% and 30% at 1, 2, 3, 4, 5 and 6 years follow-up. In the unirradiated group, there were no cases of severe CC. This difference is highly significant (p<0.001). Hormones and chemotherapy were not significantly associated with severe CC (Whitfield et al.).

One hundred and thirty-six breast reconstructions were studied in 114 patients: 62 reconstructions were performed using submuscular implants alone and 74 had an implant-assisted latissimus dorsi myocutaneous flap using a McGhan 150 biodimensional permanent expander implant. Data were prospectively collected on capsule contracture, geometric measurements, photographic assessments and pain scores. The median follow-up was 4 (range, 2-5) years. The mean age of the 114 patients studied was 45 (range, 20-77) years. Forty-four reconstructed breasts received RT. Capsule formation was detected in 13/92 (14.1%) reconstructed breasts with no RT and in 17/44 (38.6%) reconstructed breasts with RT. On univariate analysis, RT was the only variable related to capsule formation (p<0.001). Significant differences in geometric measurements of symmetry were identified in patients with capsules compared with those without capsules. Photographic assessments were worse in the capsule group: mean photo score 8 (95% CI 8, 8.5) compared with the no capsule group 6.5 (95% CI 5, 7.5), p<0.001. Persistent pain two years or more after surgery was present in 8/30 patients with capsules and 1/106 with no capsule group, p<0.01. Capsule formation is three times more likely to occur after IBR in association with an RT field. However, as more than 60% of patients do not get capsules despite RT at four years, implant-assisted tissue expansion techniques using a biodimensional device is a viable breast reconstructive option in selected cases (Behranwala et al.).

Further data is based on a publication from 2012. Regarding that radiotherapy of reconstructed breasts is associated with major complications and poor cosmetic outcome Aristei et al. assessed complication rates, the link between risk factors
and prosthesis removal, as well as cosmetic outcomes [Aristei et al., 2012]. From 1997 to 2009, 101 consecutive patients received RT after breast reconstruction because of risk factors for relapse (92) or because relapse had occurred (9). At RT, 90 patients had temporary tissue expanders and 11 had permanent implants. Twelve patients underwent neo-adjuvant chemotherapy; all patients received adjuvant chemo- and/or hormone therapy. At a median follow-up of 50 months, late toxicities occurred in 28 patients: pain in 7, lymphedema in 6, G1 cutaneous toxicity in 5, and subcutaneous toxicity in 19 (2G1, 9G2, 7G3, 1G4), with more than one side effect in 12. In 8 patients the prosthesis ruptured (3), was displaced (3), was displaced and ruptured (1), or lost shape (1). Capsular contracture was classified in 89 patients as IA in 14, IB in 47, II in 10, III in 11, and IV in 7. Twelve prostheses (11.9%) were removed. The only significant factor for prosthesis removal was age (p = 0.007). Judgments of cosmetic results were available from 81 physicians and 84 patients. Outcome was excellent/good in 58/81 physician judgments and in 57/84 patient evaluations. Overall inter-rater agreement on outcome was good (κ-value 0.64; 95% CI: 0.48-0.79). The authors conclude that RT to reconstructed breasts was associated with low rates of late toxicity and prosthesis removal. Cosmetic outcomes were, on the whole, good to excellent.

References:


Link to no influence on DFS and detection of recurrence:

A matched retrospective cohort study was performed. Only patients with invasive breast cancer who had 2 years or more of follow-up and/or patients who had recurrence within 2 years of their primary cancer were included. In total, 618 patients who underwent mastectomy for invasive breast cancer from 1995 until 1999 were evaluated. Three hundred nine patients who had immediate, tissue expander/implant reconstruction were matched to 309 women who underwent mastectomy alone on the basis of age (+/-5 years) and breast cancer stage (I, II, or III). The incidence of locoregional recurrence following mastectomy was 6.8 percent in patients who had reconstruction and 8.1 percent in patients who had mastectomy alone (log rank p = 0.6015). Median time to detection of a locoregional recurrence was 2.3 years (range, 0.1 to 7.2 years) in the reconstructed cohort and 1.9 years (range, 0.1 to 8.8 years) in the nonreconstructed cohort (p = 0.733). Permanent implants were removed following infection in one patient and patient request in two. These results suggest that there is no difference in the incidence of locoregional recurrence in breast cancer patients who undergo immediate, tissue expander/implant reconstruction compared with those patients who do not have reconstruction. Prosthetic breast reconstruction does not appear to hinder detection of locoregional cancer recurrence. In the majority of patients, management of locoregional recurrence does not necessitate removal of a permanent prosthesis.

Between 1999 and 2004, 63 elderly patients underwent an immediate reconstruction after breast cancer treatment at the European Institute of Oncology. A conservative treatment, combined with breast repair by plastic surgical techniques, was performed in 14 patients. In the remaining 49 patients, a modified radical mastectomy was necessary in 30 breasts, a total mastectomy in 19, a subcutaneous mastectomy in one case and a radical mastectomy in one patient. Three nipple-sparing mastectomies, along with intra-operative radiotherapy, were performed in two patients. A definitive silicone implant was used in 41 breasts and a skin expander in eight cases. A latissimus dorsi flap was performed in two patients, a pedicled transverse rectus abdominis muscle (TRAM) flap in two cases and a local advancement fasciocutaneous flap in another two patients. In all patients, surgery was well tolerated despite patient age. No systemic and medically unfavourable events occurred in the immediate and late postoperative period. Infection occurred in four patients (6.34%) and partial necrosis of the mastectomy flaps in three cases (5.5% of the mastectomies). Capsular contracture grade III and IV was reported in four cases (8.89%). Total implant removal was rated 12.24%, due to infection (three prostheses), exposure (one expander) and capsular contracture grade IV (two implants). Implant-based technique of breast reconstruction should be made available to the elderly population.

References:

In this series of 77 reconstructed breasts, the overall complication rate was 26%, with surgical revision in 12% and reconstructive failure with implant removal in 8% of patients. The performance of an abdominal lift did not significantly influence the complication rate. The dual mesh-muscle technique rendered the use of bigger implants possible, with a significant difference between the resected weight (302+/−140g) and the implant size (346+/−93g) (P<0.05). This indicates that lower-pole restriction can be overcome and the original volume can be reconstituted or even augmented. In conclusion, the dual mesh-muscle technique is comparatively reliable and permits to overcome the limitations with definitive implant-based IBR after SSM without increasing the risk for postoperative complications even if abdominal skin is recruited to compensate for the skin removed with the mastectomy.

References:


A matched, retrospective cohort study was performed. Medical records of patients who underwent immediate TE/I reconstruction from 2004 to 2005 were reviewed. Two cohorts were identified: (1) underwent TE/I reconstruction with AlloDerm, and (2) underwent standard TE/I reconstruction. Individuals were matched 1:1 on the basis of: expander size (+/−100 mL), history of irradiation, and indication for mastectomy. Cohorts were compared for intraoperative volume injected (mL), rate of postoperative expansion (mL/ injection), number of expansions, and time to completion of expansion (days). Incidence of complications was evaluated. Pairwise comparisons were performed using the Wilcoxon sign rank test and McNemar test. Ninety immediate TE/I reconstructions were evaluated. Forty-five TE/I-AlloDerm reconstructions were matched to standard TE/I reconstructions. Intraoperatively, expanders in the AlloDerm and non-AlloDerm cohorts were filled to a mean volume of 223.8 and 201.1 mL (P = 0.180). Median number of expansions performed was 5 and 6 in the
AlloDerm and non-AlloDerm cohorts (P = 0.117). There was no difference in the mean rate of postoperative tissue expansion (AlloDerm: 97 mL/injection versus non-AlloDerm: 95 mL/injection [P = 0.907]), nor in the incidence of complications (P = 0.289). Minor complications occurred in 13.1% of AlloDerm cases (cellulitis [n = 3], seroma [n = 3], hematoma [n = 1]. Although this study does not address AlloDerm's efficacy in decreasing morbidity or improving esthetic outcomes in TE/I reconstruction, it indicates that AlloDerm does not increase the rate of tissue expansion after immediate TE placement. It does not, however, appear to increase the risk of postoperative complications.

Reference:

Link to higher complication rate for immediate implant reconstruction:

The authors reviewed all breast reconstructions after mastectomy for breast cancer performed under the supervision of a single surgeon over a 6-year period at a tertiary referral center. Reconstruction method and timing, patient characteristics, and complication rates were reviewed. Reconstruction was performed on 240 consecutive women (94 bilateral and 146 unilateral; 334 total reconstructions). Reconstruction timing was evenly split between immediate (n = 167) and delayed (n = 167). Autologous tissue (n = 192) was more common than tissue expander/implant reconstruction (n = 142), and the free deep inferior epigastric perforator was the most common free flap (n = 124). The authors found no difference in the complication incidence with autologous reconstruction, whether performed immediately or delayed. However, there was a significantly higher complication rate following immediate placement of a tissue expander when compared with delayed reconstruction (p = 0.008). Capsular contracture was a significantly more common late complication following immediate (40.4 percent) versus delayed (17.0 percent) reconstruction (p < 0.001; odds ratio, 5.2; 95 percent confidence interval, 2.3 to 11.6). Autologous reconstruction can be performed immediately or delayed, with optimal aesthetic outcome and low flap loss risk. However, the overall complication and capsular contracture incidence following immediate tissue
expander/implant reconstruction was much higher than when performed delayed. Thus, tissue expander placement at the time of mastectomy may not necessarily save the patient an extra operation and may compromise the final result.

Reference:


Patients who have undergone prior chest wall irradiation can present as challenging candidates for implant reconstruction because of troublesome rates of infectious complications. The issue of antibiotic prophylaxis remains controversial, and evidence-based postoperative strategies to reduce implant infections have not been well described in the literature. The purpose of this study was to determine the efficacy of extended trimethoprim/sulfamethoxazole therapy in preventing implant infections in the irradiated chest wall. A retrospective chart review of hospital and office records was performed on all patients undergoing implant reconstruction performed by a single surgeon (J.M.S.) from August of 2005 to March of 2008. Before 2007, the senior author used 5 to 7 days of cephalosporin prophylaxis. Subsequent to this period, the prophylactic regimen was amended to provide patients with previous chest wall irradiation prophylactic trimethoprim/sulfamethoxazole for 30 days after implant insertion. Fifty-one implant reconstructions, in the setting of prior ipsilateral chest wall irradiation, were performed. The mean follow-up time was 39 months. The infection rate for the routine cephalosporin group was 35 percent as compared with 8 percent for the extended trimethoprim/sulfamethoxazole group (p = 0.038). After multivariate analysis, extended trimethoprim/sulfamethoxazole remained the only significant factor that influenced the rate of infection (p = 0.05). The mean time to infection was 13 weeks for the routine cephalosporin group and 1.5 weeks for the extended trimethoprim/sulfamethoxazole group (p = 0.044). Extended trimethoprim/sulfamethoxazole therapy demonstrates preliminary evidence as an effective adjunctive measure for reducing the rate of implant infections in breast reconstruction. Clinical question/level of evidence: therapeutic, III.
The use of acellular dermal matrix (ADM) for implant-based breast reconstruction does not appear to increase or decrease the risk of complications, but it might provide psychological and aesthetic benefits [Clemens and Kronowitz, 2012]. The MEDLINE and EMBASE databases were reviewed for articles published between January of 2005 and February of 2012 on breast reconstruction using acellular dermal matrix in the setting of radiation therapy. The authors also reviewed their institutional experience of consecutive patients who met these criteria between January of 2008 and October of 2011. Thirteen articles were identified for review: three animal studies on acellular dermal matrix and 10 with level III evidence of its use in humans. The 10 clinical studies included 246 irradiated patients. The M. D. Anderson experience included 30 irradiated acellular dermal matrix patients for a total of 276 irradiated patients evaluated in this review. In general, the studies reviewed here suggest that although acellular dermal matrix increases the incidence of seroma formation and infection, it does not increase the overall complication rate. Use of acellular dermal matrix in implant-based breast reconstruction in the setting of radiation therapy did not predispose to higher infection or overall complication rates or prevent bioprosthetic mesh incorporation. However, the rate of mesh incorporation may be slowed. Its use allowed for increased intraoperative saline fill volumes, which improved aesthetic outcomes and allowed patients to awake from surgery with a formed breast. However, further multicenter or single-center randomized controlled trials that provide high-quality, level I evidence are warranted.

Reference:

Clemens MW, Kronowitz SJ. Acellular dermal matrix in irradiated tissue expander/implant-based breast reconstruction: evidence-based review.
**Radiotherapy after Implant Breast Reconstruction I (7/34)**

*Further information and references:*


Complications of implant-based breast reconstruction are rare but mastectomy flap necrosis and peri-implant infection are the most frequent and remain an important cause of early implant failure. This study aimed to compare the results of three different management strategies employed to deal with these complications at our institution. A consecutive series of 71 infected/exposed prostheses in 68 patients over a 20-year period were analysed. Management strategies included explantation and delayed reconstruction, implant salvage and explantation and immediate autologous reconstruction. Only 19 of 45 (42%), managed with implant removal, went on to delayed reconstruction. Methods of delayed reconstruction were distributed equally between implant-only, implant and autologous tissue and autologous-only reconstructions. The implant was successfully salvaged in nine cases, but reducing the implant size or introducing new tissue as a flap increased the success from 45% to 53%. Three patients with infected implant-only breast reconstruction underwent explantation and immediate conversion to autologous-only reconstructions. All the three interventions reviewed here have their place in the management of infected implant-based breast reconstructions. It is noteworthy that following implant removal, the likelihood of the patient proceeding to delayed reconstruction of any kind is similar to the likelihood of successful salvage (42% vs. 45%). This study population had high numbers of exposed implants in irradiated fields. Reducing implant size or introducing new tissue in the form of a flap increases the chances of successful implant salvage. In the presence of mild infection, removal of exposed/infected implants and immediate conversion to an autologous-only reconstruction can prove to be successful.
Radiotherapy after Implant Breast Reconstruction II (8/34)

Further information and references:


We sought to determine the differences in surgical outcomes associated with adjuvant radiation versus no radiation in patients undergoing concurrent breast oncologic and reconstructive operations. A retrospective review of patients who underwent combined oncologic and plastic surgeries for breast diseases from January 2005 to June 2010 was compared for demographic factors and outcomes by receipt of radiation therapy. During the study period, 175 patients were identified; 25.7 per cent received radiation therapy. Mean patient age was 51 years and median follow-up was 355 days. Overall, 80.2 per cent of patients underwent mastectomy; 19.8 per cent partial mastectomy; 42.1 per cent autologous tissue reconstruction; and 54.8 per cent implant-based reconstruction. There were no significant differences between radiated and nonradiated patients in rates of overall or oncoplastic-specific complications. Lymphedema was the only complication seen more frequently in the radiated arm (P = 0.03). In our series of carefully selected patients undergoing a variety of reconstructive techniques for repair of partial or total mastectomy defects, radiation was not associated with worse outcomes in patients undergoing immediate breast reconstruction. With careful collaboration among plastic surgeons, breast surgeons, and radiation oncologists, patients requiring breast surgery may safely be considered for reconstruction of partial or total mastectomy defects when adjuvant radiation is required.


Radiation therapy has been shown to increase complication rates of tissue expander/implant breast reconstructions. The purpose of this study was to evaluate patient characteristics to assess their impact on complications. A retrospective review
of patients who underwent mastectomy plus tissue expander/implant reconstruction from January 2000 to December 2006 was performed. The main outcome of interest was the development of postoperative complications. Analyses were performed to detect risk factors for complications. A total of 560 patients were included in the study. A total of 385 patients underwent unilateral and 174 underwent bilateral tissue expander/implant reconstructions, for a total of 733 reconstructions. A total complication rate of 31.8% and a major complication rate of 24.4% were calculated. The risk factors associated with a significantly increased incidence of complications were age greater than 50 years, body mass index (BMI) greater than 30, and radiation. Women younger than 50 years had a complication rate of 28.4%, whereas women older than 50 years had a complication rate of 37.0%. Women with a BMI less than 30 had a complication rate of 27.5%, whereas women with a BMI greater than 30 had a complication rate of 49%. The major complication rate in nonradiated and radiated patients was 21.2% and 45.4%, respectively. Despite higher complication rates, tissue expander/implant reconstructions were successful in 70.1% of radiated patients. Based on this study, the ideal radiated patient would have a BMI less than 30 and be younger than 50 years of age to maximize the likelihood of a successful tissue expander/implant reconstruction.


Complications of implant-based breast reconstruction are rare but mastectomy flap necrosis and peri-implant infection are the most frequent and remain an important cause of early implant failure. This study aimed to compare the results of three different management strategies employed to deal with these complications at our institution. A consecutive series of 71 infected/exposed prostheses in 68 patients over a 20-year period were analysed. Management strategies included explantation and delayed reconstruction, implant salvage and explantation and immediate autologous reconstruction. Only 19 of 45 (42%), managed with implant removal, went on to delayed reconstruction. Methods of delayed reconstruction were distributed equally between implant-only, implant and autologous tissue and autologous-only reconstructions. The implant was successfully salvaged in nine cases, but reducing the implant size or introducing new tissue as a flap increased the success from 45% to 53%. Three patients with infected implant-only breast reconstruction underwent explantation and immediate conversion to autologous-only reconstructions. All the three interventions reviewed here have their place in the management of infected implant-based breast reconstructions. It is noteworthy that following implant removal, the
likelihood of the patient proceeding to delayed reconstruction of any kind is similar to the likelihood of successful salvage (42% vs. 45%). This study population had high numbers of exposed implants in irradiated fields. Reducing implant size or introducing new tissue in the form of a flap increases the chances of successful implant salvage. In the presence of mild infection, removal of exposed/infected implants and immediate conversion to an autologous-only reconstruction can prove to be successful.
Radiotherapy after Implant Breast Reconstruction with use of ADM (9/34)

No further information

Reference:
Clemens MW, Kronowitz SJ. Acellular dermal matrix in irradiated tissue expander/implant-based breast reconstruction: evidence-based review.
Muscle Fixation for Immediate Reconstruction after Mastectomy (10/34)

Further information:

According to a national survey, greater than 50% of American Society of Plastic surgeons who predominantly perform implant-based breast reconstruction use ADM [Gurunluoglu et al., 2011]. There has been limited reported experience with the use of Strattice (LifeCell Corp., Branchburg, NJ), a porcine-derived acellular dermal matrix, in implant-based breast reconstruction. Salzberg et al. have evaluated their experience with this matrix [Salzberg et al., 2013]. Patients who underwent immediate single-stage or two-stage implant-based breast reconstruction with the assistance of Strattice were included in this study. Patient charts were reviewed for indications for mastectomy, adjunctive radiotherapy use, implant or expander volume, length of follow-up period, and type and incidence of complications during the follow-up period. Biopsies of ADM were taken for histological analyses. A total of 105 reconstructions were performed in 54 patients: 77% were prophylactic and 23% were oncologic. All, but 4, reconstructions were single stage. Mean implant volume of single-stage reconstructions were 444.1 (range: 150-700 cc) and mean expander volume after completion of expansion was 400 (range: 350-450). Mean follow-up period was 41.3 months (range: 35.5-48.4 months). Total complication rate was 8.6%. Complications occurred in 9 breasts: implant loss or explantation (3.8%), infection (3.8%), skin breakdown or necrosis (2.9%), seroma (1.9%), implant exposure (1.0%), and delayed skin healing (1.0%). Histological analyses of implanted ADM revealed a viable matrix with fibroblast infiltration and revascularization. The infection rate of 3.8% with Strattice is comparable to that reported in pooled analyses of human ADMs (5.3%-5.6%) and in pooled analyses of traditional submuscular reconstructions (4.7%). The absence of clinically significant capsular contracture is noteworthy and is in concordance with the low rate reported in other published series of Strattice (0%-4.5%) as well as human ADMs (0%-4.3%). In conclusion, over a mean 3.5-year follow-up period, low complication rates and good outcomes were observed with the use of Strattice that are comparable to those reported with human acellular dermal matrices.
A further study was performed by Hanna and colleagues [Hanna et al., 2013]. The authors compared tissue expansion properties, complication rates, and patient satisfaction for both operative techniques at the same institution. A retrospective review was completed on 75 patients and 100 tissue expander/implant-based breast reconstructions at a single academic institution from 2007 to 2010. Of these cases, 31 patients were reconstructed with ADM and 44 with a submuscular coverage technique. The submuscular group had a higher rate of minor complications (29.5% vs. 19.4%), whereas the ADM group had a higher rate of major complications (22.6% vs. 9%); however, this difference did not reach statistical significance. Total complications including seroma, hematoma, infection, skin necrosis, and explantation did not significantly differ between groups (n = 13 for ADM vs. 17 for submuscular, P = 0.814). Consistent with prior reports, ADM-based reconstructions were associated with significantly increased intraoperative fill volumes and lower total number of sessions to achieve final volume. Submuscular reconstructions required a significantly higher tissue expander fill volume. Eight patients in the submuscular group required surgical revision of the breast and inframammary fold, compared with 4 in the ADM group; however, this difference was not significant. Patient satisfaction was equivalent between the 2 groups; however, it was higher in patients with bilateral reconstruction and lower among those who had received adjuvant radiation therapy. Satisfaction with nipple reconstruction was inversely proportional to time elapsed from the procedure to survey conduction. This is the first study to perform a head-to-head comparison on the basis of patient satisfaction, the results of which may be useful in preoperative planning and counseling.

Regarding the rate of capsular contracture with ADM a number of published studies addressed this subject [Basu and Jeffers, 2012]. There is animal model and human histopathologic evidence showing that acellular dermal matrices slow or thwart the likely pathogenesis of capsular contracture. However, further long-term studies are needed to see if indeed these observations continue over time. A review of clinical studies show that the majority of clinical evidence lies in the direct-to-implant and two-stage tissue expander arena in reconstructive breast implant surgery [Basu and Jeffers, 2012]. Only two articles specifically address capsular contracture rates of acellular dermal matrices in revisionary aesthetic breast surgery. Most of the evidence is in the form of case series and retrospective, noncomparative review, underpowered, and of limited follow-up. Only one prospective review was found, and only one true comparative study between an acellular dermal matrix and nonmatrix cohort were found [Vardanian et al., 2011]. The comparative study did show that matrix use was associated with less capsular contracture (odds ratio, 0.18; 95 percent confidence interval, 0.08 to 0.43), providing the highest level of evidence to date (Level III). In addition, although the level of evidence remains III or lower
and the studies are limited by duration of follow-up or by small sample size (low power), the authors did find that all the clinical studies revealed capsular contracture rates ranging between 0 percent and 4 percent. Also, of the 15 clinical articles, only four involved a dermal matrix other than AlloDerm. The rates of capsular contracture in these four articles are similar to AlloDerm rates. However, only one study compared two different acellular dermal matrix products. While the evidence for capsular contracture is suggestive, especially in postmastectomy breast reconstruction, the level of evidence should improve through better controlled studies with higher power, longer follow-up, and attention to the use of acellular dermal matrix and capsular contracture rates in revisionary breast surgery.

There is no difference in post-operative pain with or without ADM. A multicenter, blinded, randomized controlled study was designed to evaluate the effectiveness of acellular dermal matrix in the setting of tissue expander/implant reconstruction [McCarthy et al., 2012]. The primary objective of the study was to determine whether the use of matrix would decrease patient-reported postoperative pain. The randomized controlled trial was conducted at two U.S. centers from 2008 to 2011. Immediately following mastectomy, all patients were randomized to one of two treatment arms: (1) acellular dermal matrix-assisted, tissue expander/implant reconstruction; and (2) submuscular tissue expander/implant placement. All patients were blinded to their treatment arm. There were no differences seen in immediate postoperative pain (p = 0.19) or pain during the expansion phase (p = 0.65) between treatment arms. There was similarly no difference in postoperative narcotic use (p = 0.38). The rate of postoperative expansion did not differ between groups (p = 0.83). The results suggest that the use of acellular dermal matrix in the setting of tissue expander/implant reconstruction neither reduces postoperative pain nor accelerates the rate of postoperative expansion.

Moreover, the use of acellular dermal matrix in the context of a one-stage technique seems to be cost-effective compared to the two-stage use of expander followed by implant [Johnson et al., 2013]. Johnson et al. performed a cost analysis (using UK 2011/12 NHS tariffs as a proxy for cost) comparing immediate breast reconstruction using the new one-stage technique of acellular dermal matrix (Strattice) with implant versus the standard alternative techniques of tissue expander (TE)/implant as a two-stage procedure and latissimus dorsi (LD) flap reconstruction. Clinical report data were collected for operative time, length of stay, outpatient procedures, and number of elective and emergency admissions in
our first consecutive 24 patients undergoing one-stage Strattice reconstruction. Total cost to the NHS based on tariff, assuming top-up payments to cover Strattice acquisition costs, was assessed and compared to the two historical control groups matched on key variables. Eleven patients having unilateral Strattice reconstruction were compared to 10 having TE/implant reconstruction and 10 having LD flap and implant reconstruction. Thirteen patients having bilateral Strattice reconstruction were compared to 12 having bilateral TE/implant reconstruction.

For unilateral cases, our results suggest that funding Strattice is less costly (£3685 versus £4985) than tissue expansion and delayed exchange for permanent implant, and considerably less costly than LD reconstruction (£3685 versus £6321). Patient benefit appears to be at least as good, and if it were shown to be greater in a health economic study, immediate reconstruction with Strattice would be described as “dominating” unilateral tissue expansion. For bilateral cases, the use of Strattice in the index operation (and in any subsequent unplanned surgery) is more expensive (£6771 versus £5478) than reconstruction with tissue expansion. This reflects an anomaly in the current reimbursement system in England, in which reimbursement of bilateral mastectomy is the same as unilateral mastectomy, although average hospital costs are self-evidently higher in bilateral than in unilateral mastectomy patients.

The cost analysis shows a financial advantage of using acellular dermal matrix (Strattice) in unilateral breast reconstruction versus alternative procedures.

Regarding the use of synthetic meshes several retrospective studies are available. These can be used in the following patients:

- Patients undergoing IBBR after SSM or NSM with well preserved skin soft tissue proportions,
- Patients with primary or secondary prophylactic subcutaneous mastectomy,
- Patients undergoing nipple areola complex sparing subcutaneous mastectomy and well preserved skin soft tissue proportions,
- Patients with tuberous breasts, Poland syndrome or other congenital deformities.

Dieterich et al. have performed a retrospective analysis of 42 patients undergoing immediate or delayed implant based breast reconstruction (IBBR) using a titanium-coated polypropylene mesh (TCPM) over a 26-month period [Dieterich et al., 2012]. The aim of this study was to discuss indications, limitations and complications of TCPM in IBBR. Primary endpoints were incidence of infection and expander/implant with mesh removal due to infected fluid collection or
extrusion. In two patients, mild hematoma, seroma or infection occurred. Skin necrosis or capsular contraction was observed in one patient. Mesh explantation was needed in 3 cases. These events were higher among the first cases and in patients with postoperative skin infection (p = 0.003). In conclusion, TCPM seems to be a helpful tool for implant stabilization in terms of lateral stabilization and fixation of the musculus pectoralis major in selected patients with adequate soft tissue cover. In comparison to ADM, TCPM is cheaper and initial results are promising. In patients with poor soft tissue cover ADM should be used.

Further follow-up data are necessary - the participation in register studies is recommended.

The scarless latissimus dorsi flap is an effective method for providing durable homogenous device coverage in the thinner patient (body mass index <24). With the advent of acellular dermal matrices, device coverage has been made simpler, but this comes at a cost. Coverage is thin, the matrix is not initially vascularized, and products are expensive. For these reasons, use of the scarless latissimus dorsi flap is an excellent alternative, particularly in the patient with a low body mass index.

References:


Summery of outcomes of studies comparing ADM and Non-ADM BR (11/34)

No further information

Reference:

Summary of Characteristics and Conclusions of Studies Comparing ADM and Non-ADM Breast Reconstruction

No further information

Reference:

Lipofilling (13/34)

Further information:

Link to fat modelling after implant-based reconstruction:

The use of lipomodelling by autologous fat transfer is increasing regarding the offer of an additional tool to refine breast reconstructive surgery. Several publications about the use after implant-based reconstruction are available. Bonomi et al. reported their findings regarding large-volume fat transfer in patients who have undergone autologous breast reconstruction with the latissimus dorsi (LD) flap and/or implant-based reconstruction with subsequent lipomodelling for symmetrisation [Bonomi et al., 2013]. They retrospectively collected data on all patients who have undergone lipomodelling from October 2008 to October 2011. Fat was harvested using a low-negative pressure syringe method and centrifuged at 3000 r.p.m. for 3 min. The purified fat was injected in 1 mL increments into multilayered microtunnels, starting from deeper layers and moving to superficial layers in the subcutaneous tissue. Patient satisfaction was assessed using validated Picker questions in a face-to-face consultation during follow-up visits, and the results were documented in the case notes. Thirty-one patients underwent lipomodelling following autologous breast reconstruction using the LD flap and implant-based reconstruction. Three patients in the study group had bilateral lipomodelling, and one patient required 3 lipomodelling sessions. Seven patients required 2 sessions, and 21 patients required a single session to achieve bilateral symmetry. The mean volume of fat that was harvested was 396 mL, and the mean injected volume of fat was 247 mL. Four patients (1 breast cancer recurrence, 2 patients with fat necrosis and 1 patient with oil cysts) developed postoperative complications. Twenty-nine patients (93%) were satisfied with the postoperative cosmetic outcome. The authors conclude that large volumes of fat can be injected for sculpture optimization and for reshaping reconstructed breasts with improved softness and a natural feel.

The combination of fasciotomies and fat grafting seems to be an innovative concept in reconstructive surgery to improve the shape of the breast.

The management of breast deformities can be very difficult in the presence of breast shape retraction. Percutaneous fasciotomies, which release fibrous strings, can be a very useful tool for shape improvement in the recipient site for a fat
graft. Ho Quoc et al. have evaluated the efficacy of fasciotomies in association with fat grafting in breast surgery [Ho Quoc et al., 2013]. A retrospective chart review was conducted for 1000 patients treated with concurrent fasciotomies and fat grafting between January 2006 and December 2011. The recipient site was prepared with fasciotomies, and fat was harvested from other parts of the body using a low-pressure 10-mL syringe lipoaspiration system. Fat was centrifuged and injected into the breast for reconstruction or chest deformities. The postoperative appearance of the breast scars was scored by both the surgeon and the patient. Each complication was recorded, including instances of hematoma, infection, tissue wounds, scar healing, and fat necrosis. In this series of patients, for whom the primary indications for the procedure were sequelae of breast-conserving surgery after cancer, latissimus dorsi flap breast reconstruction, breast implant reconstruction, tuberous breast, Poland syndrome, and funnel chest, we recorded the following complications: 0.8% local infections (8/1000), 0.1% delayed wound healing that required medical care (1/1000), and 3% fat necrosis (31/1000). Fasciotomy scarring was considered minor by the patient in 98.5% of cases and by the surgeon in 99% of cases at 1 year postoperatively. The authors conclude that fat grafting is a safe and reliable technique that improves the aesthetic outcomes of breast surgery. Percutaneous fasciotomies provide excellent aesthetic results and an improvement in breast shape with no scarring.

Link to long-term safety:

There are reported concerns that the injection of fat may be involved in tumourigenesis, by stimulating angiogenesis and cell growth and thus dormant cancer cells [Lohsiriwat et al., 2011; Pearl et al., 2011; Fraser et al., 2011]. Current grafting techniques separate the destructed detritus and oil as well as blood and supernatant fluid. The final result is a cellular graft, which is an unpurified pool of various cells including adipocytes, preadipocytes, resident tissue cells and stromal stem cells, which include mesenchymal stem cells [Kumboeck et al., 2013]. The number of stem cells varies individually and dependent on the technique for liposuction, processing and grafting. Adipose derived stem cells are meanwhile well characterized, but little is known on how the transplanted or differentiated cells will react on a long-term or in cell-cell interaction with highly reproductive tissue or residual tumor cells. Moreover, human adipose tissue for lipografting is also a source of endothelial progenitor cells, which do not only exhibit MSC properties but were demonstrated to promote breast cancer progression and metastases in murine models.
By this, the oncologic risk should be evaluated by the impact on overall survival, disease-free survival, and local events, in comparison with the general population of breast cancer patients; and also by interferences on follow-up, which could increase the number of unnecessary biopsies, anxiety, and delay in the diagnosis of a true recurrences or new breast cancers [Vallejo et al., 2013].

Lipofilling has already been performed for breast reconstruction in over 2,000 patients in published trials from Europe and the United States. In addition, two systematic reviews have been published. In clinical series, until now, there has been no report of increasing risk of local events or metastasis in the follow-up of invasive breast cancer patients. Delay et al. reported data on 734 lipomodelling procedures for breast cancer reconstruction who were followed up for 10 years and noted that 96% remained free of recurrence and 98% remained free of distant metastases 5 years after the procedure [Delay et al., 2009]. Rigotti et al. reported data from lipomodelling in 137 patients and found 9 local recurrences and 9 distant recurrences (11.7%) [Rigotti et al., 2010]. At the 5-year follow-up, 95.6% of the patients were free from local relapse and 97.7% were free from distant metastases. The multicenter study by Petit and colleagues reported data on 646 procedures in 513 patients with an overall oncological event rate of 5.6%, with a loco regional event rate of 2.4% [Petit et al., 2011]. Bonomi et al. reported one recurrence (3.7%), which occurred four years after the original cancer surgery and two years after the lipomodelling procedure [Bonomi et al., 2013]. Petit and colleagues, in a matched-cohort study, found a 1.5 percent rate of local events in a population of 513 breast cancer patients who underwent lipofilling [Petit et al., 2013]. This rate was similar to that of the general population. However, particularly concerning was the higher local event rate (six times higher) in the subgroup of intraepithelial neoplasia patients compared with the control group. Lipofilling increased the risk of local events in women younger than 50 years, women with high-grade neoplasia, women with a Ki-67 proliferation index greater than 14, and women who had undergone quadrantectomy. Considering important limitations of this study (e.g., being a retrospective series, with different types of cancer treatments included, a relatively small number of patients analyzed, and follow-up limited to a median of 5 years after primary surgery), this subgroup analysis is considered only as exploratory by the authors, and no definitive conclusion could be drawn from this until now.

In patients with breast conserving surgery the risk of recurrence in the ipsilateral breast is up to 10% over 10 years and rises up to 16% over 20 years postoperatively. However the peak is within the first 5 years with almost 9% of relapse. In these recurrent cases ipsilateral, but different localization occurs in up to 31% and tumor progression to invasiveness was observed to be as high as 77%. The goal of breast conserving therapy is a good aesthetic result without complete resection
of all breast tissue, which can be achieved safely in many cases. So fat grafting might only be necessary for scar correction or to achieve improved symmetry. Therefore a longer period can be tolerated between breast surgery and correction through fat grafting. Based on the oncological outcome studies Krumboeck et al. would recommend an interval of at least 5 years before fat grafting after breast conserving therapy. Treatment should strictly be limited to the scar and subcutaneous tissue [Krumboeck et al., 2013].

Regarding patients with BRCA1/2-mutation these patients have an increased risk for developing breast cancer also on the contralateral site, Krumboeck et al. discourage from fat grafting in this population, even after complete tumor resection.

**Link to technique:**

Resorption rates ranging of fat grafts from 25% to 80% have been reported – 30% in normal postoperative tissue and 50% in tissue after local radiotherapy. Regarding the type of autologous fat grafting different techniques are available – e.g. fat grafts enriched with autologous adipose-derived stem cells (ASCs) or non-enriched fat grafts. Kolle et al. have published the results of a triple-blind, placebo-controlled trial to compare the survival of fat grafts enriched with autologous adipose-derived stem cells (ASCs) versus non-enriched fat grafts [Kolle et al., 2013]. Healthy participants underwent two liposuctions taken 14 days apart: one for ASC isolation and ex-vivo expansion, and another for the preparation of fat grafts. Two purified fat grafts (30 mL each) taken from the second liposuction were prepared for each participant. One graft was enriched with ASCs (20 \( \times \) 10⁶ cells per mL fat), and another graft without ASC enrichment served as a control. The fat grafts were injected subcutaneously as a bolus to the posterior part of the right and left upper arm according to the randomization sequence. The volumes of injected fat grafts were measured by MRI immediately after injection and after 121 days before surgical removal. The primary goal was to compare the residual graft volumes of ASC-enriched grafts with those of control grafts. 13 participants were enrolled, three of whom were excluded. Compared with the control grafts, the ASC enriched fat grafts had significantly higher residual volumes: 23·00 (95% CI 20·57–25·43) cm³ versus 4·66 (3·16–6·16) cm³ for the controls, corresponding to 80·9% (76·6–85·2) versus 16·3% (11·1–21·4) of the initial volumes, respectively (p<0·0001). The difference between the groups was 18·34 (95% CI 15·70–20·98) cm³, equivalent to 64·6% (57·1–72·1; p<0·0001). No serious adverse events were noted. By this, the procedure of ASC-enriched fat grafting had excellent feasibility and safety. Although the results present that the fat resorption rates are less ASC-enriched fat grafts cannot be recommended for breast cancer patients due to missing results for long-term safety.
References:


Follow-up results after lipofilling (14/34)

No further information

Reference:

Postmastectomy Pedicled Flap Reconstruction (15/34)

Further information and references:

Link to TRAM and DIEP:

When choosing autologous or heterologous reconstructive techniques, advantages or disadvantages have to be taken into consideration. The final choice has to be appropriate to the problem and the safest applicable technique should be chosen. Risk management has an important impact on complications and the aesthetic result.

As for the controversy between TRAM and DIEP-flap advocates the main argument in favour of the DIEP-flap is donor site morbidity. But the hernia rate of 2.1% in 280 published bilateral DIEP-flaps does not substantiate a better donor site morbidity. Brunnert series of 330 double pedicled TRAM flaps: 0.4% hernia rate. In addition, pedicled flaps can be performed in a muscle sparing technique as well.

Glyn Jones takes in his article: The pedicled TRAM flap in breast reconstruction.Clin Plastic Surg. 2007(34); 83-104 the following conclusion: Pedicled TRAM flap breast reconstruction remains the first choice for autologous reconstruction. And concerning the abdominal wall: over time, pedicled and free TRAM flap patients develop similar functional outcomes with little impact on the activities of daily living. Abdominal bulge and hernia rates appear to be independent of the type of flap harvested and may relate to the care with which repair has been undertaken as well as the quality of the fascia to be repaired. The exact mechanism for these observed differences has yet to be explained satisfactorily.

References:


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Chevray PM, BR with SIEA flap: a prospective comparison with TRAM and DIEP flaps. PRS 2004, 114:5


Williams JK, Carlson GW, Bostwick J III. et al., The effects of radiation after TRAM flap breast reconstruction. PRS 1997, 100:1153

Link to delay-Surgery:

To reduce the complication rate of pTRAM especially in high risk patients, a surgical delay has been suggested: the preoperative location and evaluation of perforating vessels and the variations of the DSEA a preoperative multidetector computed tomography angiography (MDCTA) is useful after performing a delay.

Reference:


Link to prophylaxis of deep vein thrombosis:

A multicenter retrospective review of consecutive TRAM flap cases identified 679 patients, 392 in the heparin-treated group and 287 in the control group. The post hoc sample sizes were adequate to detect a 5 percent difference in hematoma rate with 89 percent power at an alpha level of 5 percent (p < 0.05). Outcome measures of reoperative hematoma, deep
vein thrombosis, and pulmonary embolism were recorded. Reoperative hematoma occurred in 0.5 percent of patients in the heparin-treated group and 1.0 percent of patients in the control group; this difference was not statistically significant (p = 0.66). Thromboembolic events were detected at a low rate (0.8 percent in the heparin-treated group versus 1.4 percent in the untreated group; p = 0.46). The use of heparin for venous thrombotic prophylaxis did not increase the risk of reoperative hematoma after breast reconstruction with abdominal tissue. The authors propose a risk assessment that balances a statistical hematoma rate of 0.5 to 5 percent (clinically observed rate, 0.5 percent) with use of heparin prophylaxis against a rare (clinically observed rate, 1.4 percent) but morbid occurrence of thromboembolic complications when chemoprophylaxis is omitted.

Reference:


Links

Link to quilting sutures and drains in lat. dorsi reconstruction:

Latissimus dorsi (LD) flap breast reconstruction is associated with a high incidence of donor site seromas, despite the use of surgical drains. The aim of this study was to evaluate the use of donor site quilting sutures, as well as drains, on the incidence, volume and frequency of seroma aspiration. The trial randomized 108 women undergoing LD breast reconstruction to quilting procedures (54) or control group (52) for intention-to-treat analysis; two were excluded. Outcome measures were the incidence and volume of postoperative seroma. Secondary outcome measures included postoperative back pain, analgesic consumption, shoulder movement and duration of hospital stay. Quilting significantly reduced the overall incidence of seroma from 46 of 48 (96 per cent) to 43 of 52 (83 per cent) (P = 0.036), including the 38 women who had extended LD flap (with or without implants). There were further significant reductions in seroma volume (P = 0.004), frequency of aspiration (P = 0.001) and overall seroma volumes, including surgical drainage and symptomatic seromas (P = 0.013). Subset analyses for LD-implant (60 women) and extended LD (with or without implant) showed similar significance. Quilting did not affect back pain or compromise shoulder mobility. Quilting significantly reduced
overall seroma volumes after LD breast reconstruction including extended LD, and is recommended in combination with surgical drains.

Reference:


Link to pain management:

In this prospective, randomized, double-blind trial (Heller et al.), a dual-catheter continuous infusion pump system was placed in the muscle-sparing TRAM flap donor-site area in all patients. Bupivacaine (0.375%; continuous infusion pump group) or isotonic saline (control group) was infused at 4 ml/hour. All patients also had a patient-controlled anesthesia system delivering intravenous narcotics on demand. Pain scores, patient satisfaction, narcotic use, milestones of surgical recovery, and side effects of narcotics were compared between the two groups. Forty-eight patients were included in the study (23 continuous infusion pump patients and 25 control patients). The continuous infusion patients used less mean patient-controlled anesthesia narcotic during the first 2 postoperative days (78.0 mg versus 42.7 mg; p = 0.019) and transitioned earlier to oral narcotics than did control patients. Patients' overall pain satisfaction scores were significantly better in the continuous infusion group than in the control group. There were no significant differences between groups with regard to overall abdominal pain intensity scores, total narcotic use, length of hospitalization, incidence of narcotic side effects, or milestones of surgical recovery. The continuous infusion pump system appears to be a safe and effective method for postoperative donor-site pain management in TRAM flap breast reconstruction patients and should be considered for postoperative donor-site pain management. However, continuous infusion pump local anesthetic delivery to the muscle-sparing TRAM flap donor site did not eliminate narcotic use for pain control.
Reference:


Link to prevention of seroma:

To systematically analyze the effectiveness of quilting of latissimus dorsi (LD) flap donor site in the prevention of seroma and related morbidities. All published studies comparing the effectiveness of quilting versus no-quilting of LD flap donor site in the prevention of seroma and related morbidities in patients undergoing breast reconstruction were analysed systemically. Five comparative studies on quilting versus no-quilting encompassing 440 patients were suitable for statistical analysis. There was no heterogeneity among trials. Therefore, in the fixed-effects model, quilting was effective in terms of reducing the incidence of donor-site seroma formation, reducing the average volume of the seroma, and reducing the total volume of drained seroma. In addition, quilting did not increase the risk of postoperative complications. Combined quilting and fibrin glue was also effective in reducing the average volume of the seroma and total drained volume of the seroma. Combination of quilting and glue did not influence the incidence of seroma formation at LD flap donor site and overall operative complications. Quilting of the LD flap donor site is helpful in reducing the incidence of seroma formation, reducing seroma volume, and reducing total drained seroma volume. Combined quilting and fibrin glue further enhances its effectiveness. Quilting with or without fibrin glue may be considered an option in patients undergoing LD flap breast reconstruction to control seroma-related morbidity. However, a major multicenter randomized controlled trial is required to achieve stronger and reliable evidence before recommending it as a routine procedure.

Reference:

**Free Tissue Transfer(16/34)**

*Further information and references:*

**Link to TRAM and DIEP:**

When choosing autologeous or heterologeous reconstructive techniques, advantages or disadvantages have to be taken into consideration. The final choice has to be appropriate to the problem and the safest applicable technique should be chosen. Risk management has an important impact on complications and the aesthetic result.

As for the controversy between TRAM and DIEP-flap advocates the main argument in favour of the DIEP-flap is donor site morbidity. But the hernia rate of 2.1% in 280 published bilateral DIEP-flaps does not substantiate a better donor site morbidity. Brunnert series of 330 double pedicled TRAM flaps: 0.4% hernia rate. In addition, pedicled flaps can be performed in a muscle sparing technique as well.

Glyn Jones takes in his article: The pedicled TRAM flap in breast reconstruction. Clin Plastic Surg. 2007(34); 83-104 the following conclusion: Pedicled TRAM flap breast reconstruction remains the first choice for autologous reconstruction. And concerning the abdominal wall: over time, pedicled and free TRAM flap patients develop similar functional outcomes with little impact on the activities of daily living. Abdominal bulge and hernia rates appear to be independent of the type of flap harvested and may relate to the care with which repair has been undertaken as well as the quality of the fascia to be repaired. The exact mechanism for these observed differences has yet to be explained satisfactorily.

**Reference:**


Kroll S, Fat necrosis in Free TRAM and DIEP flaps. PRS 2000, 106:576;
Chevray PM, BR with SIEA flap: a prospective comparison with TRAM and DIEP flaps. PRS 2004, 114:5;
Williams JK, Carlson GW, Bostwick J III. et al., The effects of radiation after TRAM flap breast reconstruction. PRS 1997, 100:1153
Giordano et al. Latissimus dorsi free flap harvesting may affect the shoulder joint in long runs. Scan J Surg 2011; 100: 202-207
Garvey PB, Salavati S, Feng L, Butler CE. Perfusion-related complications are similar for DIEP and muscle-sparing free TRAM flaps harvested on medial or lateral deep inferior epigastric Artery branch perforators for breast reconstruction. Plast Reconstr Surg. 2011 Dec;128(6):581e-9e.

Anatomical studies suggest that the deep inferior epigastric artery (DIEA) medial branch perfuses more tissue across the midline than the lateral branch. The authors hypothesized that unilateral deep inferior epigastric perforator (DIEP) and muscle-sparing free transverse rectus abdominis musculocutaneous (TRAM) flaps based on medial branch perforators would have fewer perfusion-related complications. The authors evaluated consecutive DIEP or muscle-sparing TRAM free flaps definitively harvested from a single DIEA branch. Flaps were grouped by tissue volume (hemiflaps, cross-midline flaps, or total flaps). Primary outcome measures were fat necrosis and partial flap necrosis. Logistic regression was used to evaluate the association between patient and reconstruction characteristics and outcomes. There were 228 patients, with
120 medial (52.6 percent) and 108 lateral (47.4 percent) branch flaps. Mean follow-up was 33.2 months. Cross-midline flaps (79.8 percent) were the most common design. Medial and lateral branch flaps had similar rates of fat necrosis (8.3 percent and 13.0 percent, respectively; p = 0.26) and partial flap necrosis (3.3 percent and 2.8 percent, respectively; p = 1.0). There was no difference in the incidence of fat necrosis between DIEP and muscle-sparing free TRAM flaps (10.2 percent and 11.3 percent, respectively; p = 0.81) or in partial necrosis (3.2 percent and 2.8 percent, respectively; p = 1.0). Medial and lateral branch flap perfusion-related complications were also similar among the flap volume classifications.

The authors suggest that surgeons base their decisions regarding DIEA branch harvest on the clinical assessment of perforator perfusion quality rather than relying on the theoretical benefit of medial branch perforator harvest. Clinical question/level of evidence: Therapeutic, III.


Donor site hernias are a rare but well recognised complication of deep inferior epigastric perforator (DIEP) flap breast reconstruction but there are no reported cases of epigastric hernias after such surgery. We report three patients who developed symptomatic epigastric hernias within 2-8 months after discharge from follow-up. Patients who were referred to the Breast Plastic Surgery Clinic with symptomatic epigastric hernias following DIEP flap breast reconstruction were retrospectively reviewed. The three patients were aged between 50 and 70 years. Their mean BMI was 29 and none were smokers or diabetic. The incidences of other predisposing factors were: previous abdominal surgery (1/3), heavy lifting (2/3) and multiparity (2/3). They were successfully treated laparoscopically (2) or by open technique (1) confirming the CT scan findings. The aetiology of epigastric hernias is obscure in general. The association with DIEP flap harvest may be purely coincidental. However, it appears that abdominal flap harvest predisposed these patients to epigastric hernias. One or more of the following factors may have caused either weakness of the anterior abdominal wall or increased intraabdominal pressure: This series of 3 symptomatic epigastric hernias following DIEP flap breast reconstruction is interesting as it documents donor site morbidity at a site distant from the exact site of flap harvest; this subject merits further detailed investigation.

The purpose of this study was to evaluate complications and patient satisfaction after pedicled transverse rectus abdominis myocutaneous (TRAM) and deep inferior epigastric perforator (DIEP) flap reconstruction at a single institution. There were 346 patients identified from 1999 to 2006 who underwent 197 pedicled TRAM and 217 DIEP flap reconstructions. Flap complication rates were similar between groups, whereas pedicled TRAM reconstructions had higher rates of abdominal bulge (9.5% vs. 2.3%, P = 0.0071) and hernias (3.9% vs. 0%, P = 0.0052). DIEP flap patients had significantly higher general satisfaction (81.7% vs. 70.2%, P = 0.0395), whereas aesthetic satisfaction was similar between groups. Furthermore, DIEP flap patients, particularly those undergoing bilateral reconstructions, were more likely to choose the same type of reconstruction compared with pedicled TRAM patients (92.5% vs. 80.7%, P = 0.0113). Understanding the differences in complications and satisfaction will help physicians and patients make informed decisions about abdominal-based autologous breast reconstruction.

Tamoxifen may increase the risk of microvascular flap complications. Surgeons should consider temporarily stopping the drug 28 days before microsurgical breast reconstruction.

Pedicled vs. Free Tissue Transfer (17/34)

*Further information and references:*

Link to TRAM and DIEP:

When choosing autologeous or heterologeous reconstructive techniques, advantages or disadvantages have to be taken into consideration. The final choice has to be appropriate to the problem and the safest applicable technique should be chosen. Risk management has an important impact on complications and the aesthetic result. As for the controversy between TRAM and DIEP-flap advocates the main argument in favour of the DIEP-flap is donor site morbidity. But the hernia rate of 2.1% in 280 published bilateral DIEP-flaps does not substantiate a better donor site morbidity. Brunnert series of 330 double pedicled TRAM flaps: 0.4% hernia rate. In addition, pedicled flaps can be performed in a muscle sparing technique as well.

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Giordano et al. Latissimus dorsi free flap harvesting may affect the shoulder joint in long runs. Scan J Surg 2011; 100: 202-207


**Background:** the latissimus dorsi (Ld) muscle or myocutaneous flap is one of the most commonly used flaps and is believed to result in minimal donor-side morbidity. the impact on shoulder function from Ld removal is important due to the common nature of this procedure. previous studies have been performed after relatively short follow-up time and mostly after breast reconstruction. the purpose of this study was to objectively evaluate shoulder function years after latissimus dorsi muscle free flap operation. **Methods:** between 1998 and 2004, eight patients who underwent Ld-free flap for low-er limb (7) or head and neck (1) soft tissue reconstruction were enrolled in this study. scar, shoulder pain, function, mobility, stability and strength were evaluated and measured by using the patient scar assessment Questionnaire (psaQ), the scar evaluation scale (ses) score, the american shoulder and elbow surgeons (ases) form, goniometer and
isokinetic tests. Measurements of the operated sides were compared to the non-operated sides. Results: Mean age was 54 ± 21 years and mean follow-up was 92.5 ± 36 months after surgery. Mean psaQ was 73 (65%), mean ses score was 2 ± 1. When comparing the operated sides to the unoperated sides, ases score was significantly lower in the operated side (76 versus 93, p = 0.008); the range of motion in active and passive endorotation, active extrarotation and active forward elevation were significantly reduced after surgery. Operated side revealed a significant joint instability (3.6 versus 1.2, p = 0.007) using the ases form. Isokinetic tests revealed that only intra-rotation strength was significantly reduced (35.74 newton-metre versus 42.7 newton-metre, p = 0.03) in the operated side. Conclusion: Ld harvesting can affect the function of the shoulder joint in the long run. Reduced mobility, instability and weakness could be obtained with objective measurements. However, the results should be interpreted with caution because of the small sample size, internal controls and retrospective nature of this study. Key words: Latissimus dorsi flap; donor site; morbidity; shoulder function; joint; free flap


Latissimus dorsi flap harvesting may affect the shoulder joint in the long run. Giordano1, M. Kääriäinen2, J. alavaikko2, T. Kaistila2, H. Kuokkanen21 Department of Surgery, Vaasa Central Hospital, Vaasa, Finland2 Department of Plastic Surgery, Tampere University Hospital, Tampere, Finland

Abstract

Background: The latissimus dorsi (Ld) muscle or myocutaneous flap is one of the most commonly used flaps and is believed to result in minimal donor-side morbidity. The impact on shoulder function from Ld removal is important due to the common nature of this procedure. Previous studies have been performed after relatively short follow-up time and mostly after breast reconstruction. The purpose of this study was to objectively evaluate shoulder function years after latissimus dorsi muscle free flap operation.

Methods: Between 1998 and 2004, eight patients who underwent Ld-free flap for lower limb (7) or head and neck (1) soft tissue reconstruction were enrolled in this study. Scar, shoulder pain, function, mobility, stability and strength were evaluated and measured by using the patient scar assessment Questionnaire (psaQ), the scar evaluation scale (ses) score, the American Shoulder and Elbow Surgeons (ases) form, goniometer and isokinetic tests. Measurements of the operated sides were compared to the non-operated sides. Results: Mean age was 54 ± 21 years and mean follow-up was 92.5 ± 36 months after surgery. Mean psaQ was 73 (65%), mean ses score was 2 ± 1. When comparing the operated sides to the unoperated sides, ases score was significantly lower in the operated side (76 versus 93, p = 0.008); the range of motion in active and passive endorotation, active extrarotation and active forward elevation were significantly reduced after surgery. Operated side revealed a significant joint instability (3.6 versus 1.2, p = 0.007) using the ases form. Isokinetic tests revealed that only intra-rotation strength was significantly reduced (35.74 newton-
metre versus 42.7 newton-metre, p = 0.03) in the operated side. **Conclusion:** Ld harvesting can affect the function of the shoulder joint in the long run. Reduced mobility, instability, and weakness could be obtained with objective measurements. However, the results should be interpreted with caution because of the small sample size, internal controls, and retrospective nature of this study.

**Key words:** Latissimus dorsi flap; donor site; morbidity; shoulder function; joint; free flap.


It is controversial whether surgical denervation of the thoracodorsal nerve should be performed in breast reconstruction with a myocutaneous latissimus dorsi flap. Denervation may prevent discomforting symptoms caused by muscle contraction, but the flap may also lose significant volume. The authors prospectively evaluated the influence of latissimus dorsi flap innervation on the latissimus dorsi muscle structure in delayed breast reconstruction. Between 2007 and 2008, 28 breast reconstructions were performed and divided randomly into the denervation group (surgical denervation by excision of 1 cm of thoracodorsal nerve, n = 14) and the intact group (thoracodorsal nerve saved intact, n = 14). Muscle biopsy specimens were taken during the operation and 6 months after reconstruction. Histologic (hematoxylin and eosin), immunohistochemical (human developmental, neonatal, slow, and fast myosin heavy chains), and morphometric analyses were performed. Magnetic resonance imaging of the breasts was performed 1 and 12 months after surgery. There was a significant decrease in type I and type II myofiber diameters from 0 to 6 months in both groups. Denervation caused more significant atrophy than disuse alone. However, there was no significant difference in flap thickness between groups that can be explained by more pronounced fatty tissue infiltration in the denervation group. The authors' data suggest that the volume and consistency of the flap remain more or less the same, regardless of whether the thoracodorsal nerve is cut or not. Thus, in their practice, the authors do not cut the nerve to save surgical time. Clinical question/level of evidence: Therapeutic, II.

The purpose of this study was to evaluate complications and patient satisfaction after pedicled transverse rectus abdominis myocutaneous (TRAM) and deep inferior epigastric perforator (DIEP) flap reconstruction at a single institution. There were 346 patients identified from 1999 to 2006 who underwent 197 pedicled TRAM and 217 DIEP flap reconstructions. Flap complication rates were similar between groups, whereas pedicled TRAM reconstructions had higher rates of abdominal bulge (9.5% vs. 2.3%, \( P = 0.0071 \)) and hernias (3.9% vs. 0%, \( P = 0.0052 \)). DIEP flap patients had significantly higher general satisfaction (81.7% vs. 70.2%, \( P = 0.0395 \)), whereas aesthetic satisfaction was similar between groups. Furthermore, DIEP flap patients, particularly those undergoing bilateral reconstructions, were more likely to choose the same type of reconstruction compared with pedicled TRAM patients (92.5% vs. 80.7%, \( P = 0.0113 \)). Understanding the differences in complications and satisfaction will help physicians and patients make informed decisions about abdominal-based autologous breast reconstruction.
**Flap-Implant Combination (18/34)**

*Further information and references:*

**Link to muscle contraction:**

Between January 2002 and April 2006, 71 consecutive patients underwent delayed unilateral breast reconstructions with LD flap and sub-pectoral implant after mastectomy. All patients reporting discomforting signs and symptoms from muscle contraction in the reconstructed breast were included in this prospective study. Thirteen patients (18.3%) were selected and treated with BTX-A percutaneous local injections. Signs and symptoms were evaluated, after 4, 8 and 12 months, by the patients and by a panel of three physicians not involved in the study, using a five-point scale. During the study period all patients reported a decrease or disappearance of the signs and symptoms. After 12 months, 11 patients received three BTX-A infiltrations, demonstrating considerable improvements compared to the pre-treatment status. Wilcoxon matched pairs rank sum test showed a statistical difference between pre-treatment and post-treatment scores after 14 days (P<0.01) and 12 months (P<0.001). Our experience shows that muscular contraction deformities after breast reconstruction with a LD flap plus implant are not uncommon complications. The use of BTX-A infiltrations is an effective, not surgical, low cost and low risk procedure to treat these complications. It is an easy procedure to be performed on an outpatient basis with a temporary effect but safely repeatable and reproducible; it avoids hospitalisation or further surgical procedures and demonstrates tolerable latency with satisfactory outcomes.

**References:**

Timing of Breast Reconstruction (19/34)

Further information and references:

See slide 3.


To compare the postoperative complications after immediate breast reconstruction (IBR) versus mastectomy alone and to examine the impact on the delivery of chemotherapy.
In this prospective series, there were 391 consecutive women who underwent mastectomy (243 mastectomy alone and 148 mastectomy and IBR). The outcome measures were complications (within 3 months after surgery) and time to adjuvant chemotherapy.
Compared to the IBR group, patients in the mastectomy alone group were significantly older (P < 0.0001), smokers (P = 0.007) and less likely to have had previous radiation or lumpectomy (P < 0.0001). Overall, the complication rate was significantly greater in the IBR group than mastectomy alone (27.0% vs. 15.6%, P = 0.009). Univariate analyses revealed that mastectomy with IBR [odds ratio (OR) = 2, 95% confidence interval (CI) 1.21-2.30]; bilateral procedure (OR = 1.84, 95% CI 1.07-3.16); previous radiotherapy (OR = 2.4, 95% CI 1.29-4.47); and previous lumpectomy (OR = 1.84, 95% CI 1.11-3.03) were significant predictors of increased complications. With multivariable analysis, none of these variables were significantly associated with increased complications. 106 patients received adjuvant chemotherapy; median time from mastectomy to chemotherapy was 6.8 (0.71-15) weeks in the mastectomy alone group (n = 96) compared to 8.5 (6.3-11) weeks in the IBR group (n = 10) (P = 0.01).
Although the incidence of overall and major postoperative complications was higher after IBR than mastectomy alone, there were no significant relationships in the multivariable analysis. IBR was associated with a modest increase in time to chemotherapy that was statistically but not clinically significant.
A further retrospective study has investigated the association between IBR, complications and adjuvant chemotherapy delivery [Chang et al., 2013]. A retrospective analysis of patients in an academic breast service, who underwent mastectomy, with or without reconstruction, and received adjuvant chemotherapy was performed. Comparisons were made between 107 patients who received IBR and 113 who received mastectomy alone. Those receiving IBR were on average younger, with lower body mass index (BMI) and better prognoses. Overall complication rates were comparable (mastectomy alone: 45.1% versus IBR: 35.5%, p = 0.2). There was more return to surgery in the IBR group with 11.5% of tissue expanders requiring removal, whilst more seromas occurred in the mastectomy group. There was no significant difference in the median time to chemotherapy. In conclusion, the authors found no evidence that IBR compromised the delivery of adjuvant chemotherapy, although there was a significant incidence of implant infection. The finding that 10% of implants required removal was higher than expected. Most previous series have reported implant removal rates between 2 and 8% due to infection, extrusion and pain. Rey et al. [2005] reported a 2.9% implant removal rate in the group which received conventional adjuvant chemotherapy and 13% late removal rate after high dose adjuvant chemotherapy.

References:


Breast cancer is the most prevalent cancer in women and has a lifetime incidence of one in nine in the UK. Curative treatment requires surgery, and may involve adjuvant and neo-adjuvant therapy. In many women, post-mastectomy breast reconstruction is essential to restore body image and improve quality of life. Timing of reconstruction may be immediately at the time of mastectomy or delayed until after surgery. Outcomes such as psychosocial morbidity, aesthetics and complications rates may differ between the two approaches.

To assess the effects of immediate versus delayed reconstruction following surgery for breast cancer.

We searched the Cochrane Breast Cancer Group (CBCG) Specialised Register on 22 July 2010, MEDLINE from July 2008 to 26 August 2010, EMBASE from 2008 to 26 August 2010 and the WHO International Clinical Trials Registry Platform (ICTRP) on 26 August 2010.

Randomised controlled trials (RCTs) comparing immediate breast reconstruction versus delayed or no reconstruction in women in any age group and stage of breast cancer. We considered any recognised methods of reconstruction to one or both breasts undertaken at the same time as mastectomy or at any time following mastectomy.

Two review authors independently screened papers, extracted trial details and assessed the risk of bias in the one eligible study. We included only one RCT that involved that involved 64 women. We judged this study as being at a high risk of bias. Post-operative morbidity and mortality were not addressed, and secondary outcomes of patient cosmetic evaluations and psychosocial well-being post-reconstruction were inadequately reported. Based on limited data there was some, albeit unreliable, evidence that immediate reconstruction compared with delayed or no reconstruction, reduced psychiatric morbidity reported three months post-operatively. The current level of evidence for the effectiveness of immediate versus delayed reconstruction following surgery for breast cancer was based on a single RCT with methodological flaws and a high risk of bias, which does not allow confident decision-making about choice between these surgical options. Until high quality evidence is available, clinicians may wish to consider the recommendations of relevant guidelines and protocols. Although the limitations and ethical constraints of conducting RCTs in this field are recognised, adequately powered controlled trials with a focus on clinical and psychological outcomes are still required. Given the paucity of RCTs in this subject, in future versions of this review we will look at study designs other than RCTs specifically good quality cohort and case-control studies.

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Previous published studies evaluating the outcomes of immediate free flap breast reconstruction following NC and timing of adjuvant treatment have reported conflicting results. Albino et al. [Albino et al., 2010] compared outcomes in patients who underwent NC prior to immediate breast reconstruction, including 47 patients and 29 controls who had undergone free flap breast reconstruction. The study found that NC was significantly associated with complications, with a nearly a fivefold increase in total complications measured. Azzawi et al. [Azzwai et al., 2010] compared outcomes in patients including 28 immediate free flap breast reconstructions following NC with 36 comparator reconstructions. Overall complications were not significantly different between all patients who had received NC and those who had not, but the study included pedicled flaps, pedicled flaps with implants, and implant only reconstructions. The rate of minor complications in the group receiving NC was almost twice that of the control group although this was not significantly different. No delay in adjuvant therapy was found. Mehrara et al. [Mehara et al., 2010] reported outcomes in a study of 1195 free flap breast reconstructions in 952 patients, 694 of which were immediate reconstructions. Seventy patients had NC, defined as chemotherapy administered less than or equal to 6 weeks before reconstruction, and NC was an independent predictor of complications, associated with wound-healing problems at the donor site and fat necrosis.

The following prospective trial has been reported by Schaverien and Munnoch [2013]: A prospective study of immediate free flap breast reconstructions comparing patients who received NC with those who did not was conducted in a single specialist regional unit. Eighty-seven patients (95 flaps) were included in the study, 30 of which (35 flaps) received NC followed by free flap breast reconstruction. Twenty patients in the NC group had one or more complications compared with 37 patients in the control group (p = 0.87). Nine patients in the NC group had more than one complication compared with 11 patients in the control group, although this difference was not significant (p = 0.26). Both obesity (p = 0.016) and current cigarette smoking (p = 0.014) were significantly associated with the occurrence of any complication in patients who had received NC. Adjuvant radiotherapy was delayed in 3 patients in the NC group, and adjuvant chemotherapy was delayed in 3 control patients (p = 1). The mean preoperative haemoglobin was significantly lower in the NC group than in the control group (p = 0.00037), although there was no significant difference in blood transfusion requirements.
The authors conclude that patients undergoing immediate autologous breast reconstruction following NC have a similar complication and reoperation rate to patients not receiving NC. Preoperative blood haemoglobin level was found to be significantly lower following NC and postoperative blood transfusion triggers should take this into account.

References:


Skin/Nipple Sparing Mastectomy (SSM/NSM) and Reconstruction (20/34)

Further information and references:

Link to safety and preservation of NAC (nipple areola complex):

SSM is considered a safe alternative to MRM especially if a BR is incorporated. SSM is widely practised in major centers which manage large numbers of breast cancer but anxiety still exists over the safety of SSM both from oncological and aesthetic points of view. Agrawal et al. have reviewed the literature to date in SSM and summarized and discussed the current evidence [Agrawal et al., 2013]. Studies were identified by an online search of the English language literature in the PubMed database till April 2012 followed by an extensive review of bibliographies from relevant articles. There is abundance of evidence with regards to the safety of SSM both oncologically and aesthetically especially in immediate breast reconstruction. The use of SSM technique broadens the repertoire of oncoplastic techniques and at the same time facilitates such techniques by preserving patient's native skin and anatomical landmarks. SSM is a safe technique providing better cosmetic outcome without compromising oncological safety as per the current evidence. However, prospective data collection of its application in various newer types of reconstructions, and continuing long-term follow-up of current data series would be prudent to evaluate long-term outcomes.

Preservation of a skin envelope and, in an increasing number, the NAC does not put the patient at risk. Latter is possible in a more peripheral location of the tumor and is validated by intraoperative frozen section. All of the glandular tissue has to be removed. This may cause healing problems due to reduced blood supply as a result of heavy smoking or preoperative RT.

From March 2002 to November 2006, 579 cases (in 570 patients) of NSM (nipple sparing mastectomy) were performed for carcinoma. The median follow up time was 19 months (Range: 1-60). The subcutaneous mastectomy was performed through an incision removing a portion of the skin overlying the tumour. An extemporaneous histological examination was performed on the retroareolar glandular tissue. If the histology was positive the patient was not considered eligible. Then an intraoperative radiotherapy with electrons (ELIOT) of 16 Gy in one shot was delivered on the NAC area. An immediate
breast reconstruction was done using implants in most cases and in several cases a musculocutaneous flaps, usually in large breast. The number of local recurrences was recorded and the correlation between their occurrence and the clinical and histological criteria were analysed using the Gray test statistical method in a competing framework. In 516 cases the negative retroareolar frozen section biopsy was confirmed by the final histology, while in 63 cases, the final histology showed foci of carcinoma. Seven out of these 63 cases underwent a secondary NAC removal. In the 56 cases which preserved areolas the authors did not observe any local recurrence after 19 months follow up. The probability of retro areola positive histology increases with the tumour size. and was not related to the nodal status. The rate of local relapses was 0.9% per year. They didn't find any significant difference in the local relapse rate according to different patient's and tumour's features. Most relapses were located close to the tumour bed but never in the NAC area. This study confirms that the local recurrence rate in the NSM completed with local radiotherapy on the NAC is not higher than the usual rate observed in the literature and the preservation of the NAC does not increase the risk. The absence of local recurrence in the region where a portion of glandular tissue has been purposely preserved is a good argument in favour of ELIOT (Petit et al.).

Gerber et al. (2003) selected retrospectively 286 patients with a breast cancer observed preoperatively 2 cm distant from the NAC. From 246 patients follow-up data could be observed. Intraoperative a frozen section of the retroareolar region was performed. The result of the frozen section was the resection of the NAC in 61 patients despite an originally planned SSM. An IBR using latissimus dorsi flap with an implant or TRAM was performed in these cases. 51 patients got a modified mastectomy. After a median follow-up of 59 months the patients with a SSM had a local recurrence rate of 5.4% and the patients with a MME of 8.2%. Only one patient of the SSM group suffered from a retromammary recurrence. Crowe et al. (2004) planned in 44 patients in 54 breasts to performe a SSM. In 6 of these patients a MME had to be performed as a result of the intraoperative frozen section. The remaining 48 patients with a SSM had a good postoperative result with well perfused NAC. In 3 patients they observed partial necroses. Vaughan et al. identified 206 patients who underwent 210 skin-sparing mastectomies with immediate reconstruction from 1998 to 2006 in our database. Eleven patients had local recurrences (5.3%). Nine developed in the quadrant of the corresponding primary tumor. There were no significant differences between patients who recurred and those who did not with respect to tumor size/stage, margin status, estrogen receptor/progesterone receptor/Her2neu status, lymph node metastases, or radiation therapy (P > .05). Patients with grade 3 invasive tumors or high-grade ductal carcinoma in situ were more likely to recur than patients with grade 1 or 2 invasive tumors or low- or intermediate-grade ductal carcinoma in
situ (P = .0035). Those patients who recurred had a significantly decreased overall survival compared to patients who did not recur (P = .0006). Skin-sparing mastectomy and immediate reconstruction has a low local recurrence rate. Recurrences occur most commonly in the same quadrant as the primary tumor and treatment approaches include surgery, chemotherapy, and radiation therapy. Local recurrence portends a poorer overall survival.

Two-hundred and sixteen patients, mean age of 52.8 (29-81) years with primary unilateral breast cancer, not suitable for partial mastectomy because of large (>3cm) or multifocal carcinoma, underwent NSM, a single procedure lasting about 1h 30min, between December 1988 and September 1994 (Benediktsson et al.) . Lymph node metastases were found in 40.3% of the patients, and 47 patients received radiotherapy (RT) postoperatively. All patients were monitored for at least 11.6 years or as long as they lived. Median follow-up was 13 years. The end-points were locoregional recurrence (LRR) or distant metastases (DM) as first events, disease-free survival (DFS) and overall survival (OS). Specificity at frozen section from sub-areolar tissues was 98.5%. LRR occurred in 52 patients and DM in 44 patients. DFS was 51.3% and OS was 76.4%. The frequency of LRR was 8.5% among irradiated and 28.4% among non-irradiated patients (p=0.025). These results compare well with results after conventional mastectomy in other trials. All patients were monitored for at least 6 years after the occurrence of LRR, finding 5 years freedom from further LRR or DM of 60% and OS of 82%. NSM is an oncologically safe procedure and could be offered to most patients with breast cancer unsuitable for sector resection only. RT effectively lowers the frequency of LRR. The occurrence of LRR after this operation does not significantly affect OS.

References:


Bleicher RJ et al., SSM. Speciality bias and worldwide lack of consensus. Cancer 2003, 98:11;


Link to higher quality of life:

Between 2004 and 2006, 310 women with NAC preservation and 143 patients with successive NAC reconstruction were mailed the questionnaire at follow-up 1 year after definitive complete breast reconstruction surgery. 256 questionnaires was available. The results showed significant differences in favour of the NAC sparing group regarding body image (difficulty in looking at themselves naked and being seen naked by their partners after surgery, P = 0.001 and P = 0.003, respectively); regarding satisfaction with the appearance of the nipple (P < .0001) and with the sensitivity of the nipple (P = 0.001); regarding the feeling of mutilation (P = 0.003). NAC sparing in mastectomy has a positive impact on patient satisfaction, body image and psychological adjustment (Didier et al.).
The periareolar incision provides good access to the breast tissue. On the other hand will the incision in the inframammary fold provide more undisturbed blood supply to the NAC and less damage to the tissue of the areola. SSM has to be combined with a reconstructive method to preserve shape and volume and prevent shrinkage postoperatively. Die Nekroserate ist am geringsten, wenn ein radiärer Schnitt durch den MAK geführt wird und wenn mit autologem Gewebe rekonstruiert wurde. Zu diesem Ergebnis kommt eine prospektive outcome-Studie (Wijayanayagam et al.), in der an einem universitären Zentrum 64 hautsparende Mastektomien an 43 Frauen durchgeführt wurden. Darunter waren prophylaktische Mastektomien (n=29), invasive Karzinome (n=24) und präinvasive Karzinome (n=11). Es wurde präoperativ ein MRT durchgeführt und es wurden die Patientinnen ausgewählt mit einem Mamakarzinom, das weiter als 2 cm vom MAK entfernt war. Das Retroareolärgewebe wurde pathologisch besonders aufgearbeitet (Serienschnitte). Die Schnittführungen waren periareolar, inframammär, wie bei Reduktion/Mastopexie, Inzisionen (Kreuzform) durch den MAK und radiäre Schnittführungen. Es wurde immer eine Sofortrekonstruktion mit autologem und heterologem Gewebe (Implantate, Expander) durchgeführt. Ein okkultes DCIS wurde in 3% der Patientinnen histologisch beschrieben. Komplikationen waren Implantatverlust, Hautnekrosen, Infektionen. Kein Rezidiv.

Blechman et al. have reviewed 55 consecutive NSMs performed through a lateral IMF incision with immediate implant-based reconstruction, with or without tissue expansion, between June 2008 and June 2011 [Blechman et al., 2012]. Mean patient age was 46 years, and mean follow-up time was 12 months. Twelve mastectomies (22%) were therapeutic, and the remaining 43 (78%) were prophylactic. Mastectomy flap necrosis, requiring operative debridement, occurred in two breasts (4%), both in the same patient. One of these breasts required a salvage latissimus dorsi myocutaneous flap to complete the reconstruction. Three nipples (6%) required office debridement for partial necrosis and operative reconstruction later. No patient had complete nipple necrosis. No statistically significant differences existed between therapeutic and prophylactic mastectomies for developing partial skin and/or nipple necrosis (p = 0.35). Three episodes (5%) of cellulitis occurred, which responded to antibiotics without the need for explantation. The authors conclude that excellent results can be achieved with immediate implant-based reconstruction of NSM through a lateral IMF incision. NAC survival is reliable, and complication rates are low.
Moreover, SSM with preservation of the NAC is also feasible after mastopexy or reduction mammoplasty. Vaughn et al. reviewed the outcomes of TSSM in 11 patients who underwent 21 TSSM procedures at our institution between 2008 and 2011 [Vaughn et al. 2013]. All patients had undergone previous breast surgery including reduction mammoplasty (7 breasts), mastopexy (4 breasts), augmentation (3 breasts), and combined mastopexy-augmentation (7 breasts). Incisions from previous breast surgery included circumareolar (11 cases) and Wise pattern (10 cases) incisions. All patients underwent TSSM through an inframammary incision followed by immediate tissue expander reconstruction and subsequent implant exchange. Patient demographics, previous breast surgery details, tumor and treatment characteristics, and postoperative complications were reviewed. Mean patient age was 43 years (range, 35-53 years) and mean body mass index was 24 kg/m² (range, 19-32 kg/m²). Mean follow-up was 10.2 months (range, 3-20 months).

Indications for TSSM included prophylactic risk reduction in 10 cases, in situ cancer in 2 cases, and invasive cancer in 9 cases. Mean time from previous breast surgery to mastectomy was 6.9 years (range, 6 months - 26 years). Major complications requiring operative reintervention included 1 (4.8%) case of cellulitis requiring expander removal and 2 (9.5%) cases of wound breakdown requiring operative closure. There were no complications involving the NAC.

The authors conclude that total skin-sparing mastectomy with immediate reconstruction can safely be performed in patients who have undergone previous breast surgery involving circumareolar incisions. The preferred technique in this group of patients is to perform TSSM through an inframammary incision with 2-stage expander-implant reconstruction to minimize NAC ischemia and subsequent complications.

References:


SSM / Nipple SM (21/34)

No further information

No references
The prophylactic mastectomy is a preventive option for patients with a high risk of BC-development. Volume replacement and preservation of a natural breast shape are a substantial part of the therapeutical and surgical strategy. The choice of technique has to be made individually as usual. Alternative systemic options and advanced imaging for screening purposes (MRI) must be discussed with the patient.

Link to reduction of incidence of bc in high risk patients:

Cochrane analyses published 2004: The primary objective was to determine whether prophylactic mastectomy reduces death from any cause in women who have never had breast cancer and in women who have a history of breast cancer in one breast. The secondary objective was to examine the effect of prophylactic mastectomy on other endpoints including breast cancer incidence, breast cancer mortality, disease-free survival, physical morbidity, and psychosocial outcomes. Electronic searches were performed in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Cancerlit, and the Science Citation Index. Inclusion criteria were studies in English of any design type including randomized or nonrandomized controlled trials, cohort studies, case-control studies, and case series with at least ten participants. Participants included women at risk for breast cancer in at least one breast. Interventions included all types of mastectomy performed for the purpose of preventing breast cancer, including subcutaneous mastectomy, total or simple mastectomy, modified radical mastectomy, and radical mastectomy. Information on patients, interventions, methods, and results were extracted by at least two independent reviewers. Methodological quality was assessed based on how well each study minimized potential selection bias, performance bias, detection bias, and attrition bias. Data for each study were summarized descriptively; quantitative meta-analysis was not feasible due to heterogeneity of study designs and insufficient reporting. Data were analyzed separately for bilateral prophylactic mastectomy (BPM) and contralateral...
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(usually due to problems with reconstruction); however, these data need to be updated to reflect changes in surgical procedures and reconstruction. Regarding psychosocial outcomes, women generally reported satisfaction with their decisions to have PM but reported satisfaction less consistently for cosmetic outcomes, with diminished satisfaction often due to surgical complications. Therefore, physical morbidity and post-operative surgical complications were areas that should be considered when deciding about PM. With regard to emotional well-being, most women recovered well postoperatively, reporting reduced cancer worry and showing reduced psychological morbidity from their baseline measures; exceptions also have been noted. Of the psychosocial outcomes measured, body image and feelings of femininity were the most adversely affected.

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Between August 1995 and October 2006 100 consecutive women with a hereditary increased risk of breast cancer underwent prophylactic mastectomy (PM) at Malmö University Hospital. Fifty of the 100 women had no previous breast cancer. Fifty were BRCA1 or BRCA2 mutation carriers. All breast specimens have been examined histopathologically according to a prospective protocol. Follow-up data was collected from medical records and data in the Regional Cancer Registry. In the PM specimens abnormal lesions were found in 18 women (three with invasive cancers, eight in situ cancers and seven atypical hyperplasia). In previously healthy women lesions were more frequent after the age of 40 than among younger women (p=0.03). BRCA mutation carriers were more likely to present with ADH (atypical ductal hyperplasia)/ALH (atypical lobular hyperplasia) compared to the non-carriers/untested cases (p=0.01). After a median follow-up of 52 months (range 1-136 months) none of the women have developed breast cancer in the area of the prophylactically removed breast. Prevalent atypical or malignant lesions are relatively a common finding in PM specimens in asymptomatic women with hereditary increased risk of breast cancer. Such findings were significantly more common above age 40 in women without previous breast cancer. The risk of newly formed breast cancer after PM is small. From 358 high-risk women (including 236 BRCA1/2 carriers) undergoing PM between 1994 and 2004 (Heemskerk-Gerritsen et al.), relevant data on the occurrence of BC in relation to PM, complications in relation to breast reconstruction
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References:


Link to patients´s satisfaction and counseling:

The aim of this retrospective study was to find areas for future surgical improvements to optimize patient satisfaction with the aesthetic result after bilateral prophylactic mastectomy and immediate breast reconstruction with implants. Nipple-areola complexes were reconstructed. Twenty-four consecutive and standardized operated women were included. The
follow-up time was an average of 5.4 (range: 2.4-10.2) years. The outcome in terms of breast symmetry, size, and firmness were measured with objective and subjective methods, and results were compared to those from a control group of 24 women. Patient satisfaction was evaluated with a questionnaire. Main findings were that the overall aesthetic result was regarded as good in both objective and subjective evaluations and that breast symmetry in patients was as common as in the control group, but reconstructed breasts were firmer. Twenty of 24 patients thought that the aesthetic result exceeded their expectations, and 22/24 would recommend this kind of breast reconstruction to another woman. In contrast with the predictions of plastic surgeons, patients were most dissatisfied with the nipple-areola reconstruction. The overall aesthetic result after bilateral prophylactic mastectomy and immediate breast reconstruction with implants was good and symmetrical. Patient satisfaction with nipple-areola reconstruction was only moderate. The results emphasize the importance of a preoperative discussion with the patient regarding whether to keep or reconstruct the nipple-areola complex while planning a prophylactic mastectomy.

Sixty-one women underwent prophylactic mastectomy and immediate breast reconstruction in Malmö, Sweden (Isern et al.), between 1995 and 2003. Forty women underwent bilateral prophylactic mastectomy and immediate reconstruction. Ten of these had a previous breast cancer diagnosis. Twenty-one women underwent contralateral prophylactic mastectomy and immediate reconstruction after a previous breast cancer. Fifty-four of the women (89%) were evaluated clinically for aesthetic results and complications. Patient satisfaction and quality of life were evaluated with one study-specific and two standardised health-related questionnaires administered at time of clinical follow-up. Median follow-up time was 42 months (range 7-99 months). The position of the reconstructed breasts was judged as satisfactory in 77% of breasts. Symmetry in relation to the midline was adequate in 89% of breasts. A capsular contracture grade III according to Baker and indentation tonometry was observed in 1% of breasts (1/104). The complication rate was 18% (7% early and 11% late). Secondary corrections were carried out in 11% of breasts. The study-specific questionnaire revealed a high degree of satisfaction. No woman regretted the procedure, and all women would have chosen the same type of surgery again. An age-stratified comparison of Swedish women using the Short Form 36 Health Survey Questionnaire (SF-36) questionnaire was carried out for this study. The study population scores were high, suggesting that prophylactic mastectomy and immediate reconstruction on both physical and psychological issues in this retrospective study had no negative effect. Also, the Hospital Anxiety and Depression Scale (HAD) questionnaire did not suggest any increased anxiety or depression among the patients. Prophylactic mastectomy and immediate breast reconstruction in women at risk of hereditary breast
cancer may be carried out with a satisfactory aesthetic outcome and an acceptable rate of complications comparable to those in other studies, and does not in itself seem to be associated with a decreased quality of life.

The authors (Bresser et al.) conducted a retrospective study using a short self-report questionnaire administered to 114 genetically predisposed women who underwent prophylactic mastectomy and breast reconstruction mainly by subpectoraly implanted silicone prostheses performed at one institution. The median follow-up time between prophylactic mastectomy/breast reconstruction and completion of the questionnaire was 3 years. Sixty percent of all participants were satisfied with the result of prophylactic mastectomy/breast reconstruction. Satisfaction was significantly and negatively correlated with perceived lack of information, experienced complications, ongoing complaints, whether or not the reconstructed breasts feel "like your own," and not choosing this type of breast reconstruction again. Adverse effects in the patient's sexual relationship were strongly correlated with perceived lack of information, discrepant expectations, ongoing complaints and limitations, whether or not the reconstructed breasts feel "like your own," altered feelings of femininity, partner's negative perception on femininity and sexuality, and not choosing this type of breast reconstruction again.

CONCLUSIONS: A majority of women would choose the procedure again, but adverse effects and untoward changes in the perception of the sexual relationship need to be addressed in the counselling of women at high risk, to optimize an informed choice and enable adequate adjustment postoperatively.

Although prophylactic mastectomy (PM) has proven to be the most effective method to reduce the risk of breast cancer in high-risk women, there is a need for further education of physicians regarding the possibilities and advantages of PM. Knowledge about breast/ovarian cancer genetics is likely to be associated with being more positive about PM, because the high risks of cancer as well as the limitations of breast cancer screening are most likely better understood by knowledgeable practitioners [Den Heijer et al., 2013]. It has been shown that the uptake of PM varies significantly across countries, with Dutch and United Kingdom (UK) studies reporting remarkably high uptakes (33–50%). One study among newly diagnosed breast cancer patients demonstrated that physician’s recommendation influenced women’s decision for PM. Julian-Reynier [2000] reported that only 18.7% of physicians involved in breast cancer management found PM an acceptable procedure in women with a BRCA1/2 mutation.

Den Heijer et al. presented the attitudes towards PM among physicians in France, Germany, the Netherlands and the United Kingdom (UK) [Den Heijer et al., 2013]. An international sample of 1196 general practitioners (GPs) and 927
breast surgeons (BS) were surveyed using a mailed questionnaire. Only 30% of the French and 27% of the German GPs were of opinion that PM should be an option for an unaffected female BRCA1/2 mutation carrier, as compared to 85% and 92% of the GPs in the Netherlands and UK, respectively. Similarly, 78% of the French and 66% of the German BS reported a positive attitude towards PM, as compared to 100% and 97% of the BS in the Netherlands and UK, respectively. In the whole sample of GPs, a positive attitude towards PM was associated with country of residence, being female, and having more knowledge of breast/ovarian cancer genetics, while among BS there was a positive association with country of residence and having more knowledge of breast/ovarian cancer genetics as well, and, in addition, with a higher number of newly diagnosed breast cancer patients last year. These results demonstrated the international variations in the attitude towards PM among physicians.

References:


Types of Risk Reducing Mastectomy in healthy women (RRBM) (23/34)

**Further information and references:**


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**Link to reduction of incidence of bc in high risk patients:**

Cochrane analyses published 2004: The primary objective was to determine whether prophylactic mastectomy reduces death from any cause in women who have never had breast cancer and in women who have a history of breast cancer in one breast. The secondary objective was to examine the effect of prophylactic mastectomy on other endpoints including breast cancer incidence, breast cancer mortality, disease-free survival, physical morbidity, and psychosocial outcomes. Electronic searches were performed in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Cancerlit, and the Science Citation Index. Inclusion criteria were studies in English of any design type including randomized or nonrandomized controlled trials, cohort studies, case-control studies, and case series with at least ten participants. Participants included women at risk for breast cancer in at least one breast. Interventions included all types of mastectomy performed for the purpose of preventing breast cancer, including subcutaneous mastectomy, total or simple mastectomy, modified radical mastectomy, and radical mastectomy. Information on patients, interventions, methods, and results were extracted by at least two independent reviewers. Methodological quality was assessed based on how well each study minimized potential selection bias, performance bias, detection bias, and attrition bias. Data for each study were summarized descriptively; quantitative meta-analysis was not feasible due to heterogeneity of study designs and insufficient reporting. Data were analyzed separately for bilateral prophylactic mastectomy (BPM) and contralateral
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CONCLUSIONS: A majority of women would choose the procedure again, but adverse effects and untoward changes in the perception of the sexual relationship need to be addressed in the counselling of women at high risk, to optimize an informed choice and enable adequate adjustment postoperatively.

Concerning the contralateral prophylactic mastectomy (CPM) in women with breast cancer, the satisfaction of patients can be high with this kind of procedure. Soran et al. have evaluated decision making and factors influencing women’s long-term satisfaction with CPM [Soran et al., 2013]. Descriptive analysis was used to analyze the results of the designed questionnaire approved by an Institutional Review Board. The authors searched their institutional cancer registry for patients diagnosed with breast cancer between 2000 and 2010. The studied time frame was of significance as this study was the first to measure response rate in questions examining patient satisfaction for >1 year after undergoing CPM. The questionnaire was mailed to all consented participants to examine factors contributing to the choice of CPM and postoperative satisfaction. Of the 206 women included in the study, 147 were aged up to 50 years. Majority of women who underwent CPM in this cohort was with a bachelor’s degree or higher, married or partnered women, and women earning >$60,000/y. Almost all women were “happy with overall surgery” and would recommend CPM to other patients. Psychological factors, such as fear of recurrence, were more commonly associated with the decision for CPM in patients with invasive carcinoma. Opinions of partners, relatives, friends, and physicians further contributed to the decision to
undergo surgery. The availability of reconstruction was also an influential factor in the overall decision. The authors conclude the majority of our study participants experienced long-term satisfaction with the surgical procedure of CPM.

Link to Breast sensibility after bilateral risk-reducing mastectomy (RRM) and immediate breast reconstruction (IBR):

Gahm J et al. (2013) reported on breast sensibility after bilateral risk-reducing mastectomy and immediate breast reconstruction (IBR) from a small prospective study of 46 patients. The primary aim of this study was to prospectively compare breast sensibility before and after RRM in a consecutive series of women. The study also investigated whether the nipples were less numb if the nipple areola complexes (NACs) were spared compared with regrafted nipple tips. Forty-six women who selected bilateral RRM with immediate reconstruction using implants at the Karolinska University Hospital, Solna, Stockholm, Sweden, were included in the study. The median patient age at the time of surgery was 39 years (range 26-58). All patients were evaluated preoperatively and at least 2 years postoperatively (median 29 months). Tactile, thermal and nociceptive cutaneous sensibilities were studied with quantitative techniques. The patients at the postoperative evaluation completed a questionnaire about subjective feelings in both breasts. The results showed that breast sensibility is significantly impaired after RRM. Additionally, the ability to experience sexual sensations in the breast is often lost. An NAC-sparing surgery did not result in better nipple sensibility.

Link to Timing of reconstruction - immediate versus delayed reconstruction:

Nelson JA et al. (2013) reported in a retrospective cohort study of all free autologous breast reconstruction patients between 2005 and 2009, focussing on ethnicity, cancer stage, unilateral or bilateral reconstructions, initial management, distance from the institution, and average income. Delayed reconstructions were compared to immediate reconstructions. All delayed reconstructions were surveyed to examine treatment and reconstruction decisions and satisfaction. Of 709 patients, 169 (24%) underwent delayed treatment. Delayed reconstruction patients had higher cancer stages (p < 0.001), higher rates of pre-reconstruction radiation therapy (64% vs. 20%, p < 0.0001) and higher rates of unilateral reconstruction (64% vs. 48%, p < 0.001). Seventy delayed patients responded to the survey (41%), with 75% having had initial mastectomy at an outside health system. Only 51% discussed immediate reconstruction prior to electing delayed treatment and 41% had no discussion regarding advantages or disadvantages to reconstructive options. Approximately
30% noted no choice in their reconstructive timing. Forty five percent would elect immediate reconstruction if given the option. The authors draw the conclusion from this study that women may not be receiving all available information prior to undergoing mastectomy for initial breast cancer treatment. As a significant portion of women electing delayed reconstruction would elect immediate reconstruction.

References:


Jessica Gahm, Per Hansson, Yvonne Brandberg, Marie Wickman; Breast sensibility after bilateral riskreducing mastectomy and immediate breast reconstruction: A prospective study; Journal of Plastic, Reconstructive & Aesthetic Surgery (2013) 66, 1521e1527

**DIEP-Flap I (24/34)**

*Further information and references:*

A further method to preserve muscular strength of the abdominal wall is the SIEA flap based on the superficial inferior epigastric artery. This free flap can be performed only when the size of the SIEA is 1.5 mm in diameter or wider. This method has a rather high rate of postoperative vascular revisional surgery.

Further information:
A further method to preserve muscular strength of the abdominal wall is the SIEA flap based on the superficial inferior epigastric artery. This free flap can be performed only when the size of the SIEA is 1.5 mm in diameter or wider. This method has a rather high rate of postoperative vascular revisional surgery.

References:


Results of Bonde CT et al. Abdominal strength after breast reconstruction using a free abdominal flap. J Plast Reconstr Aesthet Surg. 2007;60(5):519-523 are accordingly except for eccentric muscle strength pt. with a DIEP had a small ,but sign. advantage over pts with MS-2 TRAM.

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Pedicled/ Free TRAM I (27/34)

No further information

References:


Spear SL et al. Effect of obesity on flap and donor-site complications in pedicled TRAM flap breast reconstruction. Plast Reconstr Surg. 2007 Mar;119(3):988-95: Obese patients (BMI ≥ 30) have in contrast to normal weight or overweight pts. (BMI up to 29) a significantly higher risk for developing overall and multiple flap complications.

Pedicled/ Free TRAM II (28/34)

No further information

References:


Spear SL et al. Effect of obesity on flap and donor-site complications in pedicled TRAM flap breast reconstruction. Plast Reconstr Surg. 2007 Mar;119(3):988-95: Obese patients (BMI ≥ 30) have in contrast to normal weight or overweight pts. (BMI up to 29) a significantly higher risk for developing overall and multiple flap complications.

Further information:

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References:

Further information:

A further method to preserve muscular strength of the abdominal wall is the SIEA flap based on the superficial inferior epigastric artery. This free flap can be performed only when the size of the SIEA is 1.5 mm in diameter or wider. This method has a rather high rate of postoperative vascular revisional surgery.

References:

Algorithm of Breast Reconstruction (31/34)

No further information

No references
Algorithm of Autologous Breast Reconstruction (1) (32/34)

No further information

No references
Algorithm of Autologous Breast Reconstruction (2) (33/34)

No further information

No references
Algorithm of Implant Breast Reconstruction (34/34)

Further information

Link to pre-mastectomy sentinel node biopsy:

The pre-mastectomy sentinel lymph node biopsy (PM-SLNB) is a technique that provides knowledge regarding nodal status prior to mastectomy. Because radiation exposure is associated with poor outcomes in breast reconstruction and reconstructed breasts can interfere with the planning and delivery of radiation therapy (RT), information regarding nodal status has important implications for patients who desire immediate breast reconstruction. This study explores the safety and utility of PM-SLNB as part of the treatment strategy for breast cancer patients desiring immediate reconstruction. Teven et al. [2013] reviewed the charts of adult patients (≥18 years old) who underwent PM-SLNB from January 2004 to January 2011. PM-SLNB was offered to patients with stage I or IIa, clinically and/or radiographically node-negative breast cancer who desired immediate breast reconstruction following mastectomy. PM-SLNB was also offered to patients with ductal carcinoma in situ if features concerning for invasive carcinoma were present. Ninety-one patients underwent PM-SLNB of 94 axillae. PM-SLNB was positive in 25.5% of breasts (n = 24). Nineteen node-positive patients (79.2%) have undergone or planning to undergo delayed reconstruction at our institution. Seventeen of these 19 node-positive patients (89.5%) have received adjuvant RT. Two patients (10.5%) elected against RT despite our recommendation for it. No biopsy-positive patient underwent immediate reconstruction or suffered a radiation-induced complication with their breast reconstruction. There were two minor complications associated with PM-SLNB, both in node-negative patients. This study demonstrates the utility of PM-SLNB in providing information regarding nodal status, and therefore the need for adjuvant RT, prior to mastectomy. This knowledge can be used to appropriately counsel patients regarding optimal timing of breast reconstruction.
References

Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients
Adjuvant Endocrine Therapy

Versions 2002–2013:

Bauerfeind / Dall / Diel / Fersis / Friedrichs / Gerber / Göring / Harbeck / Huober / Jackisch / Lisboa / Maass / Möbus / Müller / Oberhoff / Schaller / Scharl / Schneeweiss / Schütz / Solomeyer / Stickeler / Thomssen / Untch / von Minckwitz

Version 2014:
Jackisch / Lück
Assessment of Steroid Hormone Receptor Status

Endocrine responsiveness:
Immunohistochemistry (ER and / or PgR)

0% pos. cells: endocrine non-responsive
≥ 1 pos. cells: endocrine responsive

Status unknown: endocrine responsive
Adjuvant Endocrine Therapy
Assessment of Menopausal Status

Assessment of menopausal status

- Menstruation history
- FSH, E2

Assessment of ovarian reserve

- Anti-Müllerian Factor
- Antral follicle count
Adjuvant Endocrine Therapy in Premenopausal Patients

Standard therapy in endocrine responsive tumors:

- Endocrine therapy 1a A ++
- Chemo-endocrine therapy (dependent on individual risk and level of ER/PgR expression) 1a A ++

Oxford / AGO LoE / GR

Guidelines Breast Version 2014.1

www.ago-online.de
Adjuvant Endocrine Therapy in Postmenopausal Patients

- **Endocrine responsive & doubtful:**
  - Endocrine therapy
    - 1a A ++

- **Endocrine therapy sequentially after CT**
  - 2b C ++

- **Non-responsive:**
  - No endocrine therapy
    - 1a A ++
General Principles in Adjuvant Endocrine Therapy
AGO ++

- Treatment duration might be considered up to 10 years, up to 10 years based on the individual risk of relapse (e.g., N+ status at presentation)
  - Premenopausal: after 5 yrs. of Tam; EAT: 5 yrs. of TAM
  - Postmenopausal: after 5 yrs. of Tam: EAT 5 yrs. Tam or AI

- Duration, choice & sequence of AI or Tam mainly rely on menopausal status and side effects

- Switch to another endocrine treatment (Tam or AI) is better than to stop

- AI as first treatment preferably in patients at high risk (lobular cancers)

- So far no evidence for AI > 5 yrs
## Duration of Adjuvant Endocrine Treatment in Premenopausal Patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Duration</th>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen*</td>
<td>5 yrs. (vs. shorter)</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Tamoxifen*</td>
<td>10 yrs. (vs. 5 yrs)</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>GnRH-analogues**</td>
<td>2–5 yrs.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Induction of amenorrhea after CT by GnRH-analogues</td>
<td></td>
<td>2b</td>
<td>D</td>
</tr>
</tbody>
</table>

* Treat as long as tolerable and premenopausal  

**The prognosis of the disease after GnRHa (≥ 2 years) treatment is independent of ovarian function (restored / non restored)
Adjuvant (Chemo-)endocrine Therapy in Premenopausal Patients

- **High or intermediate risk**
  - Chemo → Tam
  - Chemo → Tam + GnRHa
  - < 40 yrs.

- **Low or intermediate risk**
  - Tam alone
  - Tam + GnRHa
  - GnRHa alone

(only if relevant contraindications for Tam)
Adjuvant Endocrine Therapy with Aromatase-Inhibitors in Premenopausal Patients

- **GnRHa + Al**
  - If severe contraindications against Tam
- **Al alone**
- **Al after GnRHa (induced amenorrhea)**
- **Upfront Al in patients with chemotherapy-induced amenorrhea (CIA, TIA)**
- **EAT in perimenopausal pts. with validated postmenopausal status after 5 yrs. of Tam**
Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving Adjuvant Chemotherapy (CT)

CT + GnRHa
(GnRHa application > 2 weeks prior to chemotherapy)

- HR-
- HR+

Impairment of CT – effect cannot be excluded!

Fertility preservation counselling*

Fertility preservation with assisted reproduction therapy

Oxford / AGO LoE / GR

1b B -

1b B -

4 C +

4 C +
Contraceptive Options for Premenopausal Women after Diagnosis of Breast Cancer

- Barrier methods
- Sterilization (tubal ligation / vasectomy)
- Non-hormonal intrauterine devices (IUDs)
- Levonorgestrel-releasing IUDs
  - Removal in newly diagnosed patients
- Timing methods
- Injectable progestin-only contraceptives
- Progestin-only oral contraceptives
- Combined oral contraceptives

No trial included women after diagnosis of breast cancer, non-estrogen containing devices do not increase the risk to develop primary breast cancer
Adjuvant Tamoxifen / Aromatase Inhibitors (AI) Treatment in Postmenopausal Patients

- Al for 5 yrs.
  - Preference in lobular inv. cancers
- Sequential therapy for 5 yrs.
  - Tam followed by AI
  - AI* followed by Tam
    Preference in N+
- Tamoxifen 20 mg/d for 5-10 yrs.

*Currently data available for letrozole, only
Endocrine Therapy after Tamoxifen in postmenopausal patients

After 5 yrs. tamoxifen (EAT)

- Al up to 3 to 5 yrs.
  - Node-positive disease
  - Long tamoxifen-free interval

Consider EAT with Al for pts. who changed to postmenopausal status during 5 yrs. Tam

- Continuation of Tam up to total 10 yrs.

Oxford / AGO LoE / GR

1b A ++
2b B ++
2b B +
1a A ++
# Ovarian Function Preservation – Comparison of Randomized Trials

<table>
<thead>
<tr>
<th></th>
<th>ZORO</th>
<th>PROMISE</th>
<th>Munster et al. - US</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient number</strong></td>
<td>60 (60 HR-)</td>
<td>281 (50 HR-)</td>
<td>49 (13 HR-) of 124</td>
</tr>
<tr>
<td><strong>Age median</strong></td>
<td>38 years</td>
<td>39 years</td>
<td>39 years</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>goserelin</td>
<td>triptorelin</td>
<td>triptorelin</td>
</tr>
<tr>
<td><strong>Start of treatment</strong></td>
<td>&gt;2 weeks prior to cht</td>
<td>&gt;1 week prior to cht</td>
<td>&gt; 1 week prior to cht</td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>menstruation at month 6 after chemotherapy</td>
<td>rate of early menopause at month 12 after chemotherapy</td>
<td>menstruation rate within 2 years after cht</td>
</tr>
<tr>
<td><strong>Primary objective</strong></td>
<td>to detect 30% absolute increase of menstruation rate</td>
<td>to detect at least 20% absolute reduction in early menopause</td>
<td>to detect 20% difference in amenorrhea rate - from 10% to 30%</td>
</tr>
<tr>
<td><strong>Multivariable analysis</strong></td>
<td>age as only independent predictive factor</td>
<td>treatment as only independent predictive factor</td>
<td>n.d.</td>
</tr>
<tr>
<td><strong>Resumption of menses at month 12 in HR- cohort</strong></td>
<td>83% with LHRH vs. 80% w/o</td>
<td>93% with LHRHa vs. 74% w/o</td>
<td>74% with LHRH vs. 68% w/o</td>
</tr>
<tr>
<td><strong>Median time to restoration of menstruation (months)</strong></td>
<td>6.1 with LHRHa vs. 6.8 w/o; p=0.30</td>
<td>not reached with LHRH vs. 6.7 w/o; p=0.07</td>
<td>5.8 with LHRH vs. 5.0 w/o; p=0.58</td>
</tr>
<tr>
<td><strong>Cyclophosphamide dose</strong></td>
<td>4600 vs. 4700mg</td>
<td>4080 vs. 4008 mg</td>
<td>n.r.</td>
</tr>
</tbody>
</table>
Use of Luteinising-Hormone-Releasing Hormone Agonists as Adjuvant Treatment in Premenopausal Patients with Hormone-Receptor-Positive Breast Cancer: A Metaanalysis of Individual Patient Data from Randomised Adjuvant Trials

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>RRR*</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemo ± LHRH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≤ 40 years</td>
<td>714</td>
<td>-24.7</td>
<td>(-39.5 to 6.2),</td>
<td>0.01</td>
</tr>
<tr>
<td>Age &gt; 40 years</td>
<td>1662</td>
<td>- 5.1</td>
<td>(-20.1 to 12.7),</td>
<td>0.55</td>
</tr>
</tbody>
</table>

| **Chemo + Tam ± LHRH**     |     |      |                   |       |
| Age ≤ 40 years             | 81  | -31.2| (-67.5 to 46.0), | 0.33  |
| Age > 40 years             | 284 |  5.3 | (-33.3 to 66.3), | 0.82  |

**(Chemo ± Tam) ± LHRH** (combination of previous comparisons: chemo ± LHRH and chemo + Tam ± LHRH!)

| Age ≤ 40 years             | 795 | -25.2| (-39.4 to -7.7), | 0.01  |
| Age > 40 years             | 284 | - 3.9| (-18.1 to 12.9), | 0.63  |

* relative risk reduction

Cuzick J et al., Lancet 2007; 369:1711-23
Chemo + Castration + Tam vs. Castration + Tam

174 patients premenopausal median age 45 node-positive, endocrine-responsive

Randomisation

4xAC → OFS + Tam

OFS + Tam

10y f-up

DFS hazard ratio = 1.02 (0.57-1.83); P = 0.94
OS hazard ratio = 0.97 (0.44-2.16); P = 0.94

- Trial was closed prematurely due to low accrual rate.
- No evidence that AC chemotherapy provides additional disease control for premenopausal patients with lower-risk node-positive endocrine-responsive breast cancer who receive adequate adjuvant endocrine therapy.

# GnRHa: RCTs

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>39</td>
<td>39</td>
<td>25</td>
</tr>
<tr>
<td><strong>Pts.-charact.</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>pT</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>N+</strong></td>
<td>-</td>
<td>-</td>
<td>50 %</td>
</tr>
<tr>
<td><strong>Horm. rec. pos.</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Age (med., years)</strong></td>
<td>30</td>
<td>29</td>
<td>39</td>
</tr>
<tr>
<td><strong>Med. F/U [mths]</strong></td>
<td>8</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td><strong>GnRH-a appl.</strong></td>
<td>during Chemo</td>
<td>during Chemo</td>
<td>during Chemo</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td>6x FA\textsubscript{500C} d1q6-8w</td>
<td>6x FAC, AC-T, TAC</td>
<td>6x FEC, AC-T, TAC</td>
</tr>
<tr>
<td><strong>Regular menstr.</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1 year - end of F/U</td>
<td>90%</td>
<td>33%</td>
<td>83%</td>
</tr>
<tr>
<td><strong>Pregn. / Births</strong></td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
</tbody>
</table>
## GnRHa: Observation Studies

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>100</td>
<td>24</td>
<td>29</td>
<td>60</td>
</tr>
<tr>
<td><strong>Pts.-charact.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT</td>
<td>2–3</td>
<td>1–2</td>
<td>1–3</td>
<td>-</td>
</tr>
<tr>
<td>N+</td>
<td>58%</td>
<td>50%</td>
<td>55%</td>
<td>-</td>
</tr>
<tr>
<td>Horm. rec. pos.</td>
<td>52%</td>
<td>-</td>
<td>86%</td>
<td>72%</td>
</tr>
<tr>
<td>Age (med., years)</td>
<td>43</td>
<td>35</td>
<td>38</td>
<td>34</td>
</tr>
<tr>
<td>Med. F/U [mths]</td>
<td>75</td>
<td>34</td>
<td>72</td>
<td>43</td>
</tr>
<tr>
<td><strong>GnRH-a application</strong></td>
<td>during Chemo up to 1 year</td>
<td>during Chemo</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td>FAC, CMF, E₁₂₀-CMF, Taxane, high-dose Chemo</td>
<td>AC, AC-T, FAC, AT-CMF</td>
<td>FEC, AC-T</td>
<td>FEC, FEC-T, AC, EC-T</td>
</tr>
<tr>
<td>Regular menstr.</td>
<td>100% (&lt;40 y.)</td>
<td>96%</td>
<td>94% (&lt;40y)</td>
<td>86%</td>
</tr>
<tr>
<td>≤1 year after Chemo</td>
<td>56% (&gt;40 y.)</td>
<td>-</td>
<td>42% (&gt;40y)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Pregnancies/ Births</strong></td>
<td>3% / 2%</td>
<td>21% / 8%</td>
<td>-</td>
<td>20% / 16%</td>
</tr>
</tbody>
</table>
# Trials with Aromatase Inhibitors

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIG 1-98</td>
<td>6 years</td>
</tr>
<tr>
<td>TAMOXIFEN</td>
<td></td>
</tr>
<tr>
<td>ANASTROZOLE</td>
<td>5 years</td>
</tr>
<tr>
<td>LETROZOLE</td>
<td>5 years</td>
</tr>
<tr>
<td>EXEMESTANE</td>
<td></td>
</tr>
<tr>
<td>Plazebo</td>
<td></td>
</tr>
<tr>
<td>ATAC</td>
<td>5 years</td>
</tr>
<tr>
<td>IES</td>
<td>2–3 years</td>
</tr>
<tr>
<td>ARNO</td>
<td>2 years</td>
</tr>
<tr>
<td>ABCSG-8</td>
<td>3 years</td>
</tr>
<tr>
<td>ITA</td>
<td>2–3 years</td>
</tr>
<tr>
<td>ABCSG-8</td>
<td>3 years</td>
</tr>
<tr>
<td>TEAM</td>
<td>2 years</td>
</tr>
<tr>
<td>MA.17</td>
<td>3 years</td>
</tr>
<tr>
<td>NSABP B-33</td>
<td>3 years</td>
</tr>
<tr>
<td>ABCSG 6a*</td>
<td>5 years*</td>
</tr>
</tbody>
</table>

*half of pts + amino-gluthetimide for 2 years
Aromatase Inhibitors in Adjuvant Therapy

Overview over Published Trials: Upfront and Extended Therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Source</th>
<th>Al</th>
<th>Indication</th>
<th>Pts</th>
<th>F/U mo</th>
<th>DFS/BCFS/TTR/TTDR/CBC</th>
<th>OS</th>
<th>Side Effects</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATAC</td>
<td>ATAC Trialists’ Group 2010</td>
<td>A</td>
<td>upfront vs T</td>
<td>6241</td>
<td>120</td>
<td>HR + patients: DFS HR 0.86, p=0.003 TTR -0.79, p=0.0002 TTDR 0.85, p=0.02</td>
<td>HR 0.87 p=0.4</td>
<td>SAE T&gt;A</td>
<td>only anastrozole vs tamoxifen, combination arm stopped after first analysis; ER+PR=ER+PR+ (Cuzick 2010) QoL→ (Cella 2006)</td>
</tr>
<tr>
<td>BIG 1-98</td>
<td>BIG 1-98 Collaborative Group 2011</td>
<td>L</td>
<td>upfront vs T</td>
<td>4922</td>
<td>97</td>
<td>DFS = 0.86 P = 0.007</td>
<td>P = 0.048</td>
<td>SAE T=L gyn AE T&gt;L TE T&gt;L CE L&gt;T SE L&gt;T</td>
<td>L&gt;T in particular in case of N+</td>
</tr>
<tr>
<td>NCIC CTG MA.27</td>
<td>Goss 2010</td>
<td>E</td>
<td>upfront vs A</td>
<td>7576</td>
<td>49</td>
<td>EFS HR 1.02 DDFS HR 0.95</td>
<td>ns</td>
<td>Osteoporosis A&gt;E El. liver enzymes E&gt;A Hyperlypidaemia A&gt;E</td>
<td>Randomization for Celecoxib cancelled</td>
</tr>
</tbody>
</table>

Extended Adjuvant Therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Source</th>
<th>Al</th>
<th>Indication</th>
<th>Pts</th>
<th>F/U mo</th>
<th>DFS/BCFS/TTR/TTDR/CBC</th>
<th>OS</th>
<th>Side Effects</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA 17</td>
<td>Goss 2005</td>
<td>L</td>
<td>extended after 5y T vs P</td>
<td>5170</td>
<td>30</td>
<td>DFS HR 0.58, p&lt;0.01 TTDR HR 0.60, p&lt;0.01 CBC HR 0.63, p=0.13</td>
<td>HR 0.61 in N+, p=0.04</td>
<td>CE L=P</td>
<td>QoL↓ (Whelan 2005) Lipids → (Wasan 2005)</td>
</tr>
<tr>
<td>ABSCG6a</td>
<td>Jakesz 2007</td>
<td>A</td>
<td>extended after 5y T vs Nil</td>
<td>856</td>
<td>62</td>
<td>DFS HR 0.642 p=0.031</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSABP-B33</td>
<td>Mamounas 2008</td>
<td>E</td>
<td>Extended after 5y T Vs P</td>
<td>1598</td>
<td>30</td>
<td>DFS HR 0.68 p=0.07 RFS HR 0.44 p= 0.004</td>
<td>ns</td>
<td>SE E=P after 6 Mo</td>
<td>Grad 3 AE E&gt;P 9%vs3%, p=0.03 Profit from E particular in N+</td>
</tr>
</tbody>
</table>

A anastrozole; gyn AE, gynecological adverse event; BCFS, breast cancer-free survival; CBC, contralateral breast cancer; CE, cardiac events; CVE, cardiovascular events; Cx, chemotherapy; DFS, disease-free survival; RFS relapse-free survival; E, exemestane; ER, estrogen receptor; HR, hazard ratio; L, letrozole; OS, overall survival; P, placebo; PR, progesterone receptor; Qol, quality of life; Rx, radiotherapy; SAE, serious adverse event; SE, skeletal event; T, tamoxifen; TE, thromboembolism; TTR, time-to-recurrence; TTDR, time-to-distant-recurrence; VE, vascular event; (?) according to retrospective analysis. * only HR positive population
### Aromatase Inhibitors in Adjuvant Therapy

**Overview over Published Trials: Switching/Sequential trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Source</th>
<th>Al</th>
<th>Indication</th>
<th>Pts</th>
<th>F/U mo</th>
<th>DFS/BCFS/TTR/TTDR/CBC</th>
<th>OS</th>
<th>Side Effects</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>IES</td>
<td>Bliss JM</td>
<td>E</td>
<td>switch after 2-3y T vs T</td>
<td>4599</td>
<td>91</td>
<td>DFS HR 0.76, ITT p&lt;0.01 DFS HR 0.75, ER+/u BCFS HR 0.76, ITT, s BCFS HR 0.75, ER+/u TTDR HR 0.83, ITT, s TTDR HR 0.82 ER+/u, s</td>
<td>HR, 0.86; 95% CI, 0.75 to 0.99; P = .04)</td>
<td>gyn AE T&gt;A TE T&gt;E SE E&gt;T diarrhea E&gt;T</td>
<td>Random after 2-3y T, only pts. relapse-free after 2-3 y T were included</td>
</tr>
<tr>
<td>ITA</td>
<td>Boccardo 2006</td>
<td>A</td>
<td>switch after 2-3y T vs T</td>
<td>448</td>
<td>64</td>
<td>EFS HR 0.57, p&lt;0.01 RFS HR 0.56, p=0.01</td>
<td>ns</td>
<td>SAE T&gt;A</td>
<td>Random after 2-3y T, only pts. relapse-free after 2-3 y T were included</td>
</tr>
<tr>
<td>ABCSG-08</td>
<td>Jakesz 2005</td>
<td>A</td>
<td>switch after 2y T vs T</td>
<td>3224</td>
<td>28</td>
<td>DFS HR 0.59, p&lt;0.01 TTR HR 0.60, p&lt;0.01 TTDR HR 0.61, p&lt;0.01</td>
<td>ns</td>
<td>TE T&gt;A SE A&gt;T</td>
<td></td>
</tr>
<tr>
<td>ABCSG-08</td>
<td>Jakesz 2005</td>
<td>A</td>
<td>switch after 2y T vs T</td>
<td>2529</td>
<td>31</td>
<td>DFS HR 0.61, p=0.01 TTDR HR 0.68, p=0.11 CCB HR 0.45, p=0.07</td>
<td>ns</td>
<td>TE T&gt;A SE A&gt;T</td>
<td>Analysis of switch data only, random upfront</td>
</tr>
<tr>
<td>ARNO 95</td>
<td>Kaufmann 2007</td>
<td>A</td>
<td>switch after 2y T vs T</td>
<td>979</td>
<td>30</td>
<td>DFS HR 0.66, p=0.049</td>
<td>HR 0.53, p=0.045</td>
<td>SAE T&gt;A 30.8 vs 22.7 %</td>
<td>No chemotherapy, random after 2 y T; only pts relapse-free after 2 y T were included</td>
</tr>
<tr>
<td>BIG 1-98</td>
<td>Regan et al 2011</td>
<td>L</td>
<td>switch after 2y T vs. Let switch after 2y L vs. Let.</td>
<td>1548</td>
<td>97</td>
<td>disease-free survival; 87.5%, 87.7%, 85.9% ns</td>
<td>89.9%, 88.7%, 88.1% ns</td>
<td>SE L&gt;T VE L = T</td>
<td>Comparison of switch L/T or T/L vs. L</td>
</tr>
<tr>
<td>TEAM</td>
<td>Van de Velde 2011</td>
<td>E</td>
<td>TEAM: E alone vs Tam switch after 2 – 3 y to E</td>
<td>4868</td>
<td>60</td>
<td>hazard ratio 0.97, 95% CI 0.88-1.08; p=0.60</td>
<td>n.a.</td>
<td>DVT; endometrial &gt; switch Musculoskeletale problems hyperlipidaemia &gt; E mono</td>
<td></td>
</tr>
<tr>
<td>N-SAS BC03</td>
<td>Aus Japan 2010</td>
<td>A</td>
<td>Tam 5 y vs Tam A switch after 1 – 4 y Tam</td>
<td>706</td>
<td>42</td>
<td>DFS: 0.69 P = 0.14 RFS 0.54 P = 0.06</td>
<td>n.a.</td>
<td>dito</td>
<td></td>
</tr>
</tbody>
</table>

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A, anastrozole; gyn AE, gynecological adverse event; BCFS, breast cancer-free survival; CBC, contralateral breast cancer; CE, cardiac events; Cx, chemotherapy; DFS, disease-free survival; E, exemestane; ER, estrogen receptor; HR, hazard ratio; ITT, intent to treat; L, letrozole; OS, overall survival; P, placebo; PR, progesterone receptor; Qol, quality of life; Rx, radiotherapy; s, significant; serious adverse event; SE, skeletal event; T, tamoxifen; TE, thromboembolism; TTR, time-to-recurrence; TTDR, time-to-distant-recurrence; u, unknown; VE, vascular event; (?) according to retrospective analysis.
Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients (2/22)

No further information

No references
Assessment of Steroid Hormone Receptor Status (3/22)

Further information and references:

Endocrine responsiveness can be predicted by analysis of hormone receptor status and is positively correlated to the degree of receptor expression in tumor tissue (1, 2, 3). The assessment should be performed in a well-established, skilled laboratory. Immunohistochemical assays appear to be superior in predicting response to adjuvant endocrine therapy compared to standard ligand-binding assays (3). Since the risk-benefit ratio of endocrine therapy is excellent and the majority of tumors is endocrine responsive, endocrine therapy is suggested if receptor status is unknown and no tumor tissue is available for testing.

Statement 1 (LoE 1a: ref. 1&2 (consistent prospective RCT and metaanalysis)
Further information:

The menstruation history is reliable only in women < 45 years of age. A more precise evaluation, especially in perimenopausal patients is possible with the measurement of FSH and E2 levels in peripheral blood. Hormonal replacement should be stopped at least 6 weeks before measurement. In perimenopausal women undergoing treatment for breast cancer, it can be difficult to determine true menopausal status because adjuvant chemotherapy, tamoxifen, and gonadotropin-releasing hormone analogues can induce transient (or permanent) ovarian suppression [1, 2]. Low AMH (antimüllerian hormone) levels seem to be indicative for reduced ovarian reserve and chemotherapy-related amenorrhea (CRA) in chemotherapy-treated breast cancer patients [3, 4, 5, 6]. Antral follicle count, defined as the sum of follicle diameters of all follicles of 10mm in both ovaries. [7]

References:

amenorrhea among premenopausal women with early stage breast cancer. Cancer Invest. 2008 Apr-May;26(3):286-95


Adjuvant Endocrine Therapy in Premenopausal Patients (5/22)

Further information:

The EBCTCG performed a meta-analysis of randomized trials evaluating the effect of systemic hormone and cytotoxic treatment of early breast cancer. Results after 15-year follow-up were published in 2005: Adjuvant polychemotherapy in women younger than 50 years resulted in a 10% absolute gain in 15-year survival (HR 42% vs. 32%). The absolute improvement in survival was twice as great at 15 years as it was at 5 years (10% vs. 4.7%). The reduction in risk of recurrence was similar in the presence or absence of tamoxifen (1). The benefit of tamoxifen was restricted to women with ER-positive or ER-unknown breast cancer. The 15-year absolute improvements in relapse and mortality associated with 5 years tamoxifen were 12% and 9%, respectively (1). 5 years of use reduced the annual breast cancer death rate by 31%, largely irrespective of age (<50 years, 50 to 69 years, ≥70 years), and of the use of chemotherapy (1). The benefit from 5 years of tamoxifen in women younger than 50 years was similar to that obtained by older women. The proportional reductions in both recurrence and mortality were irrespective of nodal status, but the absolute improvement in survival was greater in nodal postive disease (1). Similar results were found in the International Breast Cancer Study Group-1393 trial (2). 5 years of tamoxifen after adjuvant chemotherapy resulted in improvement of DFS (hazard ratio [HR] for tamoxifen v no tamoxifen 0.59; 95% CI, 0.46 to 0.75; P .0001). However, this was seen in the ER-positive cohort only. Tamoxifen had a detrimental effect on patients with ER-absent tumors compared with no tamoxifen in an unplanned exploratory analysis (HR 2.10; 95% CI, 1.03 to 4.29; P .04). Patients with ER-positive tumors who achieved chemotherapy-induced amenorrhea had a significantly improved outcome (HR for amenorrhea v no amenorrhea 0.61; 95% CI, 0.44 to 0.86; P .004).

The benefit from chemotherapy is dependent on the risk for relapse and metastasis and might be low even in a lower risk node positive endocrine responsive situation (3)
References:


Statement 1 (LoE 1a: ref. 1 (consistent prospective RCT and metaanalysis))
Statement 2 (LoE 1a: ref. 1&2 (consistent prospective RCT and metaanalysis))
Statement 3 (LoE 1b; ref. 3 prospective RCT with narrow confidence interval)
Adjuvant Endocrine Therapy in Postmenopausal Patients (6/22)

Further information:

Endocrine therapy is one important systemic therapy option in primary breast cancer. The last Oxford Overview Analysis estimates an at least 31% relative reduction of mortality by adjuvant endocrine therapy (EBCTCG 2005). Endocrine therapy is only effective in steroid hormone receptor positive tumors, but not in steroid hormone receptor negative tumors (EBCTCG 2005, Hutchins 1999).

These data result in the following therapy recommendations: Patients with receptor negative tumors (ER− and PgR−) should not receive endocrine therapy (neither tamoxifen nor aromatase inhibitors in postmenopausal patients; also not ovarian ablation in premenopausal patients). An overall survival benefit by prevention of contralateral breast cancer has not been shown (Hutchins 1999). Patients with receptor positive tumors (either ER+ or PgR+) should receive endocrine therapy. An exception to this principle may only be discussed in individual patients with a very low relapse risk (e.g. node negative low-risk according to St. Gallen 2005). If chemo-endocrine therapy is indicated, tamoxifen should be given sequentially after adjuvant chemotherapy. Tamoxifen given concomitantly with adjuvant chemotherapy seems to be less effective regarding DFS and OS than tamoxifen given sequentially. Thus, simultaneous endocrine therapy may decrease chemotherapy effectiveness. However, clinical data for this statement are only available for tamoxifen, but not for other endocrine therapies (Albain 2002). The indication for chemo-endocrine therapy should depend on the individual relapse risk: In patients with receptor-positive tumors and increased risk for relapse (e.g. node positive tumors; node negative tumors with G3, elevated tumor levels of uPA/PAI-1 or very young patients), additional adjuvant chemotherapy does improve patient outcome (EBCTCG 1998, Fisher 2001, Jänicke JNCI 2001).
References:


Further information:

More and more evidence is arising that hormone-receptor positive tumors have to be treated as long as possible, potentially life-long with endocrine therapy. As current trials report only on a maximum duration of 10 years, the commission is currently restricting its recommendation to this duration. However, it is likely that a patient starting endocrine treatment today will be informed in 10 years time that even longer treatment is of benefit as current trial are underway comparing 10 vs 15 years of treatment.

Given the small absolute differences observed for various approaches to give tamoxifen and/or aromatase-inhibitors, the commission felt that it is more important to motivate patients to comply at full dose the whole treatment period than to stick on one of these approaches. So to switch to another endocrine treatment is better than to stop or to loose compliance of the patient.

As tumors with high early relapse risk (e.g. node-positive disease) or as recently been shown in lobular invasive cancers, aromatase-inhibitors have shown their largest benefit compared to tamoxifen and should therefore be considered as first treatment approach.

References:


References of AI trials: see slide 21 and 22.
**Duration of Adjuvant Endocrine Treatment in Premenopausal Patients (8/22)**

*Further information:*

The EBCTCG meta-analysis as well as several large randomised trials addressed the optimal duration of tamoxifen use. According to the EBCTCG meta-analysis 5 years of tamoxifen are significantly advantageous over 1 to 2 years concerning the risk of recurrence (proportionate reduction 15.2%; \( P < .001 \)) and mortality (proportionate reduction 7.9%; \( P = .01 \)) after 15 years of follow-up [1]. The NSABP-B14 study [2] and the Scottish adjuvant tamoxifen trial [3] compared 5 years to 10 years of adjuvant tamoxifen for women with early-stage ER-positive node-negative and node positive breast cancer and did not find any advantage for a longer than 5 year duration of use, on the contrary, there was a trend toward a worse outcome associated with a longer duration of treatment. An ECOG trial [4] randomized patients after 5 years of tamoxifen to continuation versus cessation of treatment. Continued tamoxifen was associated with a longer time to relapse but with no difference in OS. Recently first results of the ATLAS-trial showed a slight, but significant reduction in the risk for relapse without a significant improvement of the risk for death with 10 compared to 5 years of tamoxifen use [4]. Therefore 5 years of adjuvant tamoxifen are recommended.

In most studies GnRH was given for 2-3 years. It has not been evaluated whether a longer duration is of advantage. Chemotherapy induced amenorrhoea (CIA) seems to be a good prognostic factor. A meta-analysis about the influence of CIA on the prognosis could prove a significant advantage of survival for amenorrhoeic patients in 15 of 23 included studies [5]. Newer data with modern type chemotherapy suggest similar outcome [6, 7]. So far there is no data to show that re-start of menses is a predictive factor to give GnRH [8, 9]. This is a question to be answered by ongoing studies.

**References:**


Adjuvant (Chemo-)endocrine Therapy in Premenopausal Patients (9/22)

Further information:

Tamoxifen is the endocrine standard treatment in hormone sensitive premenopausal breast cancer [1-3, 6, 7, 9]. Tamoxifen only can be considered in special cases (low or intermediate risk) or if the patient does not consent or tolerate additional chemotherapy or GnRH therapy.

Best data for endocrine therapy with tamoxifen is given by the meta-analysis from the early breast cancer trialists’ collaborative group [1]. Results after 15-year follow-up were published in 2005: Adjuvant polychemotherapy in women younger than 50 years resulted in a 10% absolute gain in 15-year survival (HR 42% vs. 32%). The absolute improvement in survival was twice as great at 15 years as it was at 5 years (10% vs. 4.7%). The reduction in risk of recurrence was similar in the presence or absence of tamoxifen. The benefit of tamoxifen was restricted to women with ER-positive or ER-unknown breast cancer. The 15-year absolute improvements in relapse and mortality associated with 5 years tamoxifen were 12% and 9%, respectively (1). 5 years of use reduced the annual breast cancer death rate by 31%, largely irrespective of age (<50 years, 50 to 69 years, ≥70 years), and of the use of chemotherapy. The benefit from 5 years of tamoxifen in women younger than 50 years was similar to that obtained by older women. The proportional reductions in both recurrence and mortality were irrespective of nodal status, but the absolute improvement in survival was greater in nodal positive disease. Similar results were found in the International Breast Cancer Study Group-1393 trial [2]. 5 years of tamoxifen after adjuvant chemotherapy resulted in improvement of DFS (hazard ratio [HR] for tamoxifen vs. no tamoxifen 0.59; 95% CI, 0.46 to 0.75; *P* .0001). However, this effect was seen in the ER-positive cohort only. Tamoxifen had a detrimental effect on patients with ER-absent tumors compared with no tamoxifen in an unplanned exploratory analysis (HR 2.10; 95% CI, 1.03 to 4.29; *P* .04). Patients with ER-positive tumors who achieved chemotherapy-induced amenorrhea had a significantly improved outcome (HR for amenorrhea vs. no amenorrhea 0.61; 95% CI, 0.44 to 0.86; *P* .004). The benefit from chemotherapy is dependent on the risk for relapse and metastasis and might be low even in a lower risk node positive endocrine responsive situation [3].
As a consequence of these data, all (international) consensus statements recommended single agent tamoxifen as the current standard adjuvant endocrine therapy for premenopausal women with endocrine responsive tumors (often preceded by chemotherapy).

Although there are more and more data available concerning GnRH-analogues (GnRHa) the role of GnRHa remains under active investigation (see studies). If GnRH are recommended, they should be combined with tamoxifen. GnHR +/- Tamoxifen can be considered for certain subgroups (<40 years, premenopausal E2 levels after chemotherapy). “Very“ young women with hormone sensitive tumors have a significantly worse prognosis than patients with hormone insensitive tumors (25 % vs. 47 % 10-year-disease free survival HR=1.49, p=.014), particularly those who did not achieve amenorrhea compared with those who experienced some cessation of menses (23% ± 6% vs. 38 ± 3%; HR=1.67; 95% CI=1.19-2.34; p=.003) in various trials of the timing and duration of adjuvant therapy containing CMF [4]. The explanation for this effect is that younger women do not develop ovarian suppression following chemotherapy. A meta-analysis about the influence of CIA on the prognosis could prove a significant advantage of survival for amenorrheic patients in 15 of 23 included studies [5].

A recent meta-analyses [6] of 14 randomized trials that involved over 13 000 patients assessing the effect of GnRHa + Tamoxifen + Chemotherapy concluded in concordance with an older meta-analyses [7]:

(A) GnRHa monotherapy: results suggest that adjuvant GnRHa monotherapy is similar to older chemotherapy protocols (eg. CMF) in terms of recurrence-free and overall survival in ER+ patients. There are insufficient data to compare GnRHa monotherapy to tamoxifen alone, but available results suggest that these treatments are comparable in terms of recurrence-free survival.

(B) GnRHa + anti-oestrogen therapy: there are insufficient data to compare the combination of an GnRHa plus tamoxifen to tamoxifen alone. Results suggest that the GnRHa plus tamoxifen combination may be superior to an GnRHa alone or to chemotherapy alone, but the chemotherapy protocols tested are outdated. The data comparing GnRHa plus aromatase inhibitors to GnRHa plus tamoxifen are currently inconclusive.

(C) GnRHa + chemotherapy: there are insufficient data to compare the GnRHa + chemotherapy combination to an GnRHa alone, although results from a single study suggest comparable efficacy in ER+ patients. There is a trend
towards improved recurrence-free and overall survival in patients who received an GnRHa plus chemotherapy combination in comparison to chemotherapy alone.

(D) chemotherapy + tamoxifen + GnRHa: there are only 365 patients in this metaanalysis that were randomized to chemotherapy + tamoxifen with or without GnRHa, 81 of them were \( \leq 40 \) years of age at diagnosis. These limited data do not provide reliable support for the use of GnRH analogues in this situation.

In cases of relevant contraindications against tamoxifen GnRHa alone is an option with nearly the same effectivness than Tamoxifen alone (ZIPP-trial) [8]. Two years of goserelin treatment was as effective as 2 years of tamoxifen treatment 15 years after starting therapy. In women who did not take tamoxifen, there was a large benefit of goserelin treatment on survival and recurrence, and in women who did take tamoxifen, there was a marginal potential benefit on these outcomes when goserelin was added.

Statement 1 (LoE 1a: ref. 1 (consistent prospective RCT and metaanalysis)
Statement 2 (LoE 1a: ref. 1&2 (consistent prospective RCT and metaanalysis)
Statement 3 (LoE 1b; ref. 3 prospective RCT with narrow confidence interval)

References:

Adjuvant Endocrine Therapy with Aromatase-Inhibitors in Premenopausal Patients (10/22)

Further information:

First analyses of a prospective randomized study comparing Zoladex + Tamoxifen versus Zoladex + Anastrazole for 3 years showed a non-significant disadvantage for AI regarding DFS and OS. Side effects were different and were composed of typical effects of TAM and AI: arthralgia, bone pain, and fever were significantly more frequent in the Anastrazole group, whereas uterine polyps and thrombosis were significantly more frequent with TAM [1]. Therefore GnRH+Anastrazole should not be considered as an alternative to Tam alone or GnRH + TAM. In patients with contraindications against TAM consider GnRH alone. Smaller phase II studies with letrozole and exemestane in this indication support these results [6].

AI alone in premenopausal patients even in pts. with chemotherapy induced amenorrhea and postmenopausal hormone levels may be induce resumption of ovarian function [2,3,5]. Therefore AI’s alone are not indicated in premenopausal women. Premenopausal women who started with TAM and became postmenopausal during treatment and were switched to Letrozole revealed a significant greater benefit regarding DFS (HR 0.25; 95% CI: 0.12-0.51) compared to primary postmenopausal pts (HR 0.69; 95% CI: 0.52-0.91). However the OAS was comparable. Otherwise premenopausal pts. With letrozole reported significant more side effects and lower quality of life [3].

References:

4. Goss PE et al: Outcomes of women who were premenopausal at diagnosis of early stage breast cancer. Cancer Res 69(Suppl.1);2009:487s(#13)
Further information:

Chemotherapy carries a risk of permanent ovarian failure [1, 2]. Ovarian protection is therefore discussed in patients who want to preserve fertility.

Four observational studies reported an ovarian protective effect of GnRH-a. All concluded, that GnRH-a prevent ovarian function. Chemotherapy ranged from CMF, anthracycline-based until high-dose chemotherapy regimens. Especially in patients younger than 40 years nearly 90% of all pts reported resumption of ovarian function. In pts. older than 40 years reappearance of ovary function was reported in only 50, although the received an ovarian protection. It is also seen that the real number of pregnancies and moreover living births were very low [3-6].

Only one of three RCT investigating the ovarian protection by GnRH-a during chemotherapy revealed a preventive effect of GnRH-a. In a unicentric study from Egypt 78 patients ages 18 to 40 years were randomized to FAC-chemotherapy with or without Goserelin [7]. They reported a resumed menstruation rate of 89.6% in the Goserelin arm and 33.3% in the observation arm (p<0.001). The reported ovulating rate amounted to 69.2% respectively 25.6% and was also significant different with P<0.001. Astonishing were the doses (5-Fluorouracil 500mg/m2, Doxorubicin 500 mg/m2, Cyclophosphamide 500 mg/m2) and schedules (day 1 and repeated every 6-8 weeks) of chemotherapy application. In this study node positive patients were also included, in which taxanes are indicated. The german ZORO-study [8] included adequate and modern chemotherapy regimens including taxanes in 60 pts. with hormone insensitive tumors. The menstruation rate in the Goserelin and observation arm after 6 months amounted to 70.0 respectively 58.6% (p=0.4219). After two years of follow up all evaluable patients of both arms reported resumpted ovarian function. In the third randomized trial from Florida [9] with 49 patients and Triptorelin the menstruation resumed at 6, 12 and 18 months of chemotherapy in the respective groups (Triptorelin vs. control) as follow: 44% vs. 60%, 83% vs. 79% and 88% vs. 84%. The study by Munster et al. Has not finished recruitment. Only 49 out of 124 planned pts were randomised. However, the results are in concordance with the ZORO study. Supporting the fact that the observed effect of LHRH is at its best small. [9]
Fertility preservation counselling is suggested in all patients who want to preserve their fertility.

References:

Fertility Preservation


Contraceptive Options for Premenopausal Women after Diagnosis of Breast Cancer (12/22)

No further information

References:

**Adjuvant Tamoxifen / Aromatase Inhibitors (AI) Treatment in Postmenopausal Patients (13/22)**

*Further information:*

Tamoxifen 20mg/d given for 5 yrs improves DFS and survival in hormone receptor-positive primary breast cancer (EBCTCG 2005) compared to placebo and 10 years improves DFS over 5 years (ATLAS). Aromatase inhibitors have shown improvements for DFS and metastases-free survival. Additionally improved survival has also been shown in the MA.17 study for extended adjuvant therapy with letrozole for node positive patients (Goss 2004) and in the ARNO and IES (ER+/unknown) studies for the switching strategy to an AI. After 2-3 years of tamoxifen switching to an AI resulted in superior survival compared to continuing tamoxifen (Coombes et al 2006, Kaufmann et al. 2006). Also a small meta-analysis (Jonat 2005) including 3 studies (ARNO, ABCSG8 and ITA) showed superior survival for the AI arms. Also in receptor-positive patients with tamoxifen contraindications or intolerance (e.g. venous thrombosis, endometrium carcinoma, etc.), adjuvant aromatase inhibitor therapy is recommended. Combination therapy of tamoxifen with aromatase inhibitors is not more effective than tamoxifen therapy alone (Baum 2002) and should therefore not be administered.

*References:*


References of AI trials: see slide 22 and 23.
Endocrine Therapy after Tamoxifen in postmenopausal patients (14/22)

Further information:

As extended adjuvant therapy after 5 years of tamoxifen therapy letrozole (vs. placebo) and anastrozole (vs. nil) are superior to no additional endocrine therapy with regard to DFS (Davies, 2012, Goss 2005, Jakesz 2005). In node-positive patients, extended adjuvant therapy with letrozole therapy resulted in a significant OS advantage (Goss 2005). The ATLAS study recently showed also a benefit for patients continuing tamoxifen for another 5 years after pretreatment with tamoxifen. The CI of the HR is overlapping with the one of extended adjuvant letrozol treatment, so that both options are considered feasible. Letrozole could be started up to 30 months after cessation of tamoxifen (Goss 2005). An intent to treat analysis of the NSABP-B33 study showed a trend towards better DFS and a significant better RFS in favour of extended adjuvant therapy with exemestane compared to placebo (Due to the results of the MA.17 study recruitment in the B33 study was stopped and unblinded October 2003. At this time 1598 of 3000 planned patients were enrolled.

References:

**Ovarian Function Preservation – Comparison of Randomized Trials (15/22)**

**Further information and references:**

This overview compares the different randomised trials comparing fertility preservation with GnRHasalogue without GnRHasalogue.


Gonadotropin-releasing hormone analogue for premenopausal women with breast cancer.

The study by Munster et al. Has not finished recruitment. Only 49 out of 124 planned pts were randomised. However, the results are in concordance with the ZORO study. Supporting the fact that the observed effect of LHRH is at its best small.
Use of Luteinising-Hormone-Releasing Hormone Agonists as Adjuvant Treatment in Premenopausal Patients with Hormone-Receptor-Positive Breast Cancer: A Metaanalysis of Individual Patient Data from Randomised Adjuvant Trials (16/22)

No further information

No references
Chemo + Castration + Tam vs. Castration + Tam (17/22)

*No further information*

*No references*
**GnRHa: RCTs (18/22)**

**Further information:**

Only one of three RCT investigating the ovarian protection by GnRHa during chemotherapy revealed a preventive effect of GnRHa. In a unicentric study from Egypt 78 patients ages 18 to 40 years were randomized to FAC-chemotherapy with or without Goserelin [1]. They reported a resumed menstruation rate of 89.6% in the Goserelin arm and 33.3% in the observation arm (p<0.001). The reported ovulating rate amounted to 69.2% respectively 25.6% and was also significant different with P<0.001. Astonishing were the doses (5-Fluorouracil 500mg/m2, Doxorubicin 500 mg/m2, Cyclophosphamide 500 mg/m2) and schedules (day 1 and repeated every 6-8 weeks) of chemotherapy application. In this study node positive patients were also included, in which taxanes are indicated. The german ZORO-study [2] included adequate and modern chemotherapy regimens including taxanes in 60 pts. with hormone insensitive tumors. The menstruation rate in the Goserelin and observation arm after 6 months amounted to 70.0 respectively 58.6% (p=0.4219). After two years of follow up all evaluable patients of both arms reported resumpted ovarian function. In the third randomized trial from Florida [3] with 49 patients and Triptorelin the menstruation resumed at 6, 12 and 18 months of chemotherapy in the respective groups (Triptorelin vs. control) as follow: 44% vs. 60%, 83% vs. 79% and 88% vs. 84%.

**References:**

2. Gerber B et al: ZORO: A prospective randomized multicenter study to prevent chemotherapy induced ovarian failure with the GnRH-Agonist Goserelin in young hormone insensitive breast cancer patients receiving anthracycline containing (neo-)adjuvant chemotherapy. J Clin Oncol 27 (Nr. 15 S); 2009:#526
GnRHa: Observation Studies (19/22)

Further information:

Four observational studies reported an ovarian protective effect of GnRHa. All concluded, that GnRH-a prevent ovarian function. Chemotherapy ranged from CMF, anthracycline-based until high-dose chemotherapy regimens. Especially in patients younger than 40 years nearly 90% of all pts reported resumption of ovarian function. In pts. older than 40 years reappearence of ovary function was reported in only 50, although the reviewed an ovarian protection. It is also seen that the real number of pregnancies and moreover living births were very low [1-5].

References:

Trials with Aromatase Inhibitors (20/22)

Further information:

There are differences between the trials investigating aromatase inhibitors in the adjuvant setting in terms of time of randomization and duration of therapy. In IES, ARNO and ITA (a small trial), patients who remained disease-free after 2-3 years of tamoxifen entered the trial and were randomized to stay on tamoxifen or switch to an AI (exemestane or anastrozole). So this is a selected population that excludes patients with early recurrence = higher-risk disease, and selects patients with endocrine-responsive disease. In ABCSG8, ATAC and BIG, patients were randomized upfront to tamoxifen for 5 years or to treatment with tamoxifen/AI (or an AI for 5 years in BIG/ATAC). In MA.17, NSABP-B33 and ABCSG 6a the duration of therapy exceeded the 5 years and was between 8 and 10 years. There are also other differences in patient populations among these trials. It’s important to bear the patient population in mind when looking at the results.

No references
Aromatase Inhibitors in Adjuvant Therapy (21/22)

No further information

References:

6. Duffy S. Gynecological adverse events including hysterectomy with anastrozole tamoxifen: Data from the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial. J Clin Oncol 2005;23(Suppl.):58S, Abs 723.
Aromatase Inhibitors in Adjuvant Therapy. Overview over Published Trials: Switching/Sequential trials (22/22)

No further information

References:

4. Coombes RC et al. First mature survival analysis of the Intergroup exemestane study (IES).A randomized trial in disease free postmenopausal patients with early breast cancer randomized to continue tamoxifen or switch to exemestane following an initial 2-3 years of adjuvant tamoxifen. PROC Asco 2006, LB abstract 527
8. Kaufmann M et al. Survival benefit of switching to anastrozole after 2 years treatment with tamoxifen versus continued tamoxifen therapy: the ARNO 95 study. PROC Asco 2006, abstract: 547

zurück
Adjuvant Cytotoxic and Targeted Therapy
Adjuvant Cytotoxic and Targeted Therapy

- **Version 2002:** Möbus / Nitz

- **Versionen 2003–2013:** Harbeck / Jackisch / Janni / Loibl / von Minckwitz / Möbus / Müller / Nitz / Schneeweiss / Simon / Solomeyer / Stickeler / Thomssen

- **Version 2014:** Untch / von Minckwitz
Subtype-specific General systemic Strategies

HR+/HER2- and “low risk”:
- Endocrine therapy without chemotherapy

HR+/HER2- and “high risk”
- Conventionally dosed AT-based chemotherapy
- Dose dense & escalated in case of high tumor burden
- Followed by endocrine therapy

HER2+
- Trastuzumab plus
  - Sequential A/T-based regimen with concurrent T + H
  - Anthracycline-free, carboplatin-cont. regimen
  - Dose dense & escalated in case of high tumor burden

TNBC
- Conventionally dosed AT-based chemotherapy
- Dose dense & escalated

In case of indication for chemotherapy, consider neoadjuvant approach
Adjuvant Chemotherapy without Concurrent Trastuzumab: Overview

- Anthracyclines (instead of CMF) 1a A ++
- Taxanes 1a A ++
- Dose-dense (node-positive disease) 1a A ++
- CMF (instead of no therapy) 1a A ++
- EC - T (instead of FEC – T) 1b A ++
Non-Anthracycline Containing Regimens without Trastuzumab

Equivalent OS efficacy to ≥ 4 x A / EC:
- 4-6 x Pac q3w
- 6 x CMF

Superior OS efficacy to 4 x AC:
- 4 x DC

Oxford / AGO LoE / GR

1b B +/-
1a A +/-
1b B +
Taxanes
Optimal Combinations and Dosages

Regimen

- EC → P_w  E_{90}C q3w x 4 → P_{80} qw1 x 12
- DAC  D_{75}A_{50}C q3w x 6
- AC → P_w  A_{60}C q3w x 4 → P_{80} qw1 x 12
- AC → D  A_{60}C q3w x 4 → D_{100} qw3 x 4
- EC → D  E_{90}C q3w x 4 → D_{100} qw3 x 4

Oxford / AGO LoE / GR

1b^a  B  ++
1b  A  ++
1b  A  ++
1b  A  ++
1b^a  B  ++
## Recommended Taxane-Based Regimens – Standard Dose

### Combination Treatment
- DAC (BCIRG 001, instead of FAC)
- DC (US Oncol., instead of AC)
- AD (E2179, instead of AC)

### Sequential Treatment (Equal Duration)
- EC → Pw (GIM, instead of FEC → Pw)
- FEC → D (PACS 01, instead of FEC)
- AC → Pw (E1199, instead of AC → P3w)
- FE$_{60}$C → D (TACT, instead of FE$_{60}$C)
- AP → CMF (ECTO, instead of A → CMF)

### Sequential Treatment (Unequal Duration)
- AC → P (NSABP B-28, instead of AC)
- FEC → P (GEICAM 9906, instead of FEC)
- AC → D (BCIRG 005, instead of DAC)
- EC → D (WSG/AGO, instead of FE$_{100}$C)
- EC → D (ADEBAR, instead of FE$_{120}$C)
- A → D → CMF > AD → CMF (BIG 2-98, instead of A ± C → CMF)
- E → D → CMF (TAXIT 216, instead of E → CMF)

### In studies with adequately dosed anthracyclines, benefit from adding taxanes seems to be small. In the sequence AC-Taxane, there is no evidence of superiority of either taxane. Next to substance-specific side-effects, weekly administration was in general less toxic (LoE 2b, B). In Germany, often EC (90/600) is used instead of AC.
## Adjuvant Chemotherapy (Other Drugs)

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>1a B +/-</th>
<th>2b B +/-</th>
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<tbody>
<tr>
<td>Capecitabine containing regimen</td>
<td>✔</td>
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<tr>
<td>(in case of HER2 neg., ER/PgR neg., TPN)</td>
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<tr>
<td>E-Cis-F</td>
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<tr>
<td>Gemcitabine containing regimen</td>
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</table>

- **Capecitabine containing regimen**
  - ✔
  - (in case of HER2 neg., ER/PgR neg., TPN)
- **E-Cis-F**
  - ✔
- **Gemcitabine containing regimen**
  - ✔
Adjuvant Chemotherapy
(Dose-dense and / or Dose-escalated)

Dose-dense regimen (N +)

- dd ACP / AC-P q2w (instead of q3w)
  (CALGB 9741)
- AC / ddP q1w x 12 (instead of P q3w)
- *EC / ddP q1w x 12 (instead of P q3w)
- EC/ddP q2w (instead of q3w)
- AC/ddP q1w (instead of q2w)
- ddEC q2w/ddP q1w (instead of EC q3w)
- ddE_{120}C_{830} q2w x 6 => P q3w x 4
- ddAC→Pq2w = 6x TAC

Dose-dense and dose-escalated regimen
(N ≥ 4+)

- dd E-P-C q2w (instead of EC-P q3w) (AGO)

* Extrapolated from doxorubicin trials
Adjuvant Treatment with Trastuzumab I

- Node-positive disease
  - Node-negative disease
    (whenever chemotherapy is considered as adequate)
      - > 10 mm
        - Strength: 1a, Grade: A, Level of Evidence: ++
      - > 5–10 mm
        - Strength: 2b, Grade: B, Level of Evidence: +
      - ≤ 5 mm
        - Strength: 2b, Grade: B, Level of Evidence: +/-
Adjuvant Treatment with Trastuzumab II

Start of treatment
- Simultaneously with taxanes
- Sequentially up to 3 months after chemotherapy

Duration
- For 1 year
- For 2 years
- For 0.5 years

Dosage
- 2 (4*) mg/kg every week
- 6 (8*) mg/kg every 3 weeks

*Loading dose
Adjuvant Trastuzumab
Cardiac Monitoring for CHF

Oxford LoE: 5  GR: D  AGO: ++

Before start of trastuzumab
- History, physical examination (edema, hepatomegaly)
- Echocardiography (alternative to MUGA)

During trastuzumab
Regular assessment of
- Heart rate increase > 15% above individual base level
- Body weight increase ≥ 2 kg/week

3 monthly assessment of LVEF
### Adjuvant Treatment with Trastuzumab: Schedules

#### Simultaneously

- With paclitaxel / docetaxel after AC / EC
- With P q1w 12 x without A in pT (< 3 cm), pN0
- With docetaxel and carboplatin

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<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
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<td>1b</td>
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- With anthracyclines
- With taxanes dose-dense

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<th>Oxford / AGO LoE / GR</th>
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<td>2b&lt;sup&gt;b&lt;/sup&gt;</td>
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#### Radiotherapy concurrent with Trastuzumab

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<th>Oxford / AGO LoE / GR</th>
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* Study participation recommended
Adjuvant Therapy with Other Targeted Agents

- **Lapatinib**
  - (delayed adjuvant treatment)

- **Pertuzumab**

- **Bevacizumab**

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<thead>
<tr>
<th>Treatment</th>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
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<tbody>
<tr>
<td>Lapatinib</td>
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<tr>
<td>Pertuzumab</td>
<td>1b</td>
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<tr>
<td>Bevacizumab</td>
<td>1b&lt;sup&gt;a&lt;/sup&gt;</td>
<td>B</td>
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</table>

<sup>a</sup> LOE 1b evidence and level B recommendation only valid in cases of ER-negative or HER2-positive disease.
Further information:

Screened data bases:

Screened guidelines:

- NCI: http://www.cancer.gov/cancertopics/pdq/treatment/breast/HealthProfessional/page7#Section_519

References:


**Subtype-specific General Systemic Strategies (3/14)**

*Further information:*

In patients with HR+/HER2- and “low risk” the treatment of choice is endocrine therapy without chemotherapy
In patients with HR+/HER2- and “high risk” the recommended treatment is conventionally dosed AT-based chemotherapy or dose dense & escalated regimens in case of high tumor burden followed by endocrine therapy

In patients with HER2+ disease Trastuzumab is recommended for one year plus
- Sequential A/T-based regimen with concurrent T + H
- Or an anthracycline-free, carboplatin-containing regimen
- Or dose dense & escalated in case of high tumor burden
- In patients with TNBC the treatment contains conventionally dosed AT-based chemotherapy
- Or dose dense & escalated chemotherapy

In case of an indication for chemotherapy, the neoadjuvant approach should be considered

*No references*
Adjuvant Chemotherapy without Concurrent Trastuzumab: Overview (4/14)

Further information:

CMF should be given at a dosage of C 600 mg/m2 d1+8 q4w i.v., alternatively the classical oral application can be chosen with C 100 mg/m2 d1-14 p.o. q4w. The three-weekly administration implies an underdosing, because a dose of CMF less than 85% of the conventional dosage leads to a reduction of the efficacy (Bonadonna 1995). Similar conclusions can be drawn from the data of a study in the metastatic setting (Engelmann 1991) and in an older metaanalysis (Hryniuk 1986). Therefore, CMF at a dosage of 600/40/600 mg/m2 q3w is regarded as not adequate.

If the indication for adjuvant chemotherapy is given after evaluation of risk, potential benefits and side effects, an anthracycline-based combination chemotherapy is regarded as minimum standard treatment. As shown in a meta-analysis, there is a reduction of the relapse rate (ratio 0.89, p=0.0001) and mortality (ratio 0.84, p<0.001) compared with adjuvant CMF-therapy after 15 years (EBCTCG, Lancet 2005).

In general, by adding a taxane in most studies disease-free survival and overall survival can further be improved. The corresponding relative reduction of risk is rather dependent from tumor biology than from nodal status and extent of disease. (Hayes, Albain). In trials adding four separate cycles of a taxane to a fixed anthracycline-based control regimen, breast cancer mortality was reduced (RR 0.86, p=0.0005; EBCTCG Lancet 2012).

The EBCTCG meta-analysis demonstrates a continuous benefit for the taxanes from year 1 to 10 in contrast to the much shorter lasting effect of the anthracyclines (EBCTCG, Lancet 2012).

In the major studies that evaluated the role of adjuvant trastuzumab in patients with HER2-overexpression, a benefit of trastuzumab was shown also with taxane containing regimens. This current evidence is discussed in the context of trastuzumab treatment (see slide 10-13).

Dose-dense (q2w) adjuvant chemotherapeutic schedules improve the relapse-free and overall survival compared to conventional adjuvant treatment options (Bonilla 2010, Moebus 2010, Citron 2003). Dose-dense and dose-intensive chemotherapeutic options improve the relapse-free and overall survival compared to conventional chemotherapy independent of the hormone receptor status if at least four lymph nodes are involved (Moebus 2010).
Anthracyclines followed by Taxane sequences have traditionally included 5 Fluorouracil in the first part of the sequence. A large randomised phase 3 study presented as an abstract at the Aan Antonio Meeting 2013 has shown that 5 FU does not have to be an integral part of the anthracycline combination (EC→T equal to FEC→ T).

Interaction between molecular breast cancer types and choice of chemotherapy.
Recent retrospective subgroup analyses of major prospective trials suggest differential efficacy of CMF, anthracycline combinations and taxanes containing regimen in triple-negative tumors, HER2-overexpressing tumors and luminal A and B tumors.

- Patients with luminal A tumors might not benefit from adjuvant chemotherapy.
- Patients with luminal B tumors should benefit from adjuvant chemotherapy, it is unclear whether addition of anthracyclines is necessary.
- Patients with HER2-type tumors will benefit from therapies that contain both, anthracyclines and taxanes.
- Patients with triple-negative tumors also seem to benefit from both, anthracyclines and taxanes. However, also CMF and platinum-containing regimen may be effective.

Caveats:
Molecular typing is based on molecular genetic testing. Immunohistochemical results correlate in only 70% of the tumors. There is no clear data, how luminal A and B can be distinguished by immunohistochemistry. Probably the most practical approach is the measurement of Ki-67 with a sensitivity and specificity of Ki-67 of about 80%.

Other markers e.g. uPA/PAI-1 or RANKL are also discussed as suitable discriminators of luminal A and B type cancers. In addition, prospective validation of the interaction between choice of chemotherapy and molecular typing is lacking.
References:


EBCTCG 2005

EBCTCG 2012


Statement 5 FU

Epirubicin and cyclophosphamide (EC) followed by paclitaxel (T) versus fluorouracil, epirubicin and cyclophosphamide (FEC) followed by T, all given every 3 weeks or 2 weeks, in node-positive early breast cancer (BC) patients (pts). Final results of the Gruppo Italiano Mammella (GIM)-2 randomized phase III study  Cognetti F, Bruzzi P, De Placido S, De Laurentiis M, Boni C, Aitini E, Durando A, Turletti A, Valle E, Garrone O, Puglisi F, Montemurro F, Barni S, Di Blasio B, Gamucci T, Colantuoni G, Olneo N, Tondini C, Parisi AM, Bighin C, Pastorino S, Lambertini M, Del Mastro L. I.F.O. Istituto Regina Elena e Istituto San Gallicano - Mostacciano, Roma, Italy; IRCCS AOU San Martino-IST, Genova, Italy; Università degli Studi di Napoli Federico II, Napoli, Italy; Istituto Nazionale Tumori - IRCCS Fondazione Pascale, Napoli, Italy; Arcispedale S. Maria Nuova-IRCCS, Reggio Emilia, Italy; Ospedale di Mantova, Mantova, Italy; Città della Salute e della Scienza - ASO OIRM S Anna, Torino, Italy; Ospedale Evangelico Valdese - ASLTO1, Torino, Italy; Ospedale Businco, Cagliari, Italy; Oncologia ASO S. Croce e Carle, Cuneo, Italy; Azienda Ospedaliero Universitaria - Santa Maria della Misericordia, Udine, Italy; IRCCS Candiolo, Candiolo (Torino), Italy; Azienda Ospedaliera Treviglio, Treviglio (Bergamo), Italy; Azienda Ospedaliero-Universitaria di Parma, Parma, Italy; Unità Operativa Complessa di Oncologia della ASL di Frosinone, Frosinone, Italy; A.O.R.N. “S.G. Moscati”, Avellino, Italy; UOC Oncologia Medica Ospedale Civile, Sassari, Italy; Ospedale Papa Giovanni XXIII, Bergamo, Italy; Ospedale S. Camillo-Forlanini, Roma, Italy. San Antonio Breast Cancer Symposium 2013. S5-06.
Statement KI 67
Prognostic Value of a Combined Estrogen Receptor, Progesterone Receptor, Ki-67, and Human Epidermal Growth Factor Receptor 2 Immunohistochemical Score and Comparison With the Genomic Health Recurrence Score in Early Breast Cancer

Non-Anthracycline Containing Regimens without Trastuzumab (5/14)

Further information:

The efficacy of CMF has been shown in numerous single studies with a long term follow up of meanwhile up to 20 years and has been proven in metaanalysis (Bonadonna 1995, EBCTCG 2005). Therefore, six cycles of CMF can be given in patients with contraindications for anthracycline-containing regimens. If considering all risks (cardiac toxicity, secondary leucemia), an anthracycline-containing regimen seems to be contraindicated, an anthracycline-free combination can be chosen (Jones 2006, Jones 2009). However, the comparator arm in the US Oncology trial was merely 4xAC. Ongoing clinical trials are currently evaluating the role non-anthracycline regimens in comparison to triplet combinations or anthracycline-taxane sequences. The CALGB B 40101 phase III study showed in a 2x2 factorial design for patients with 0 to 3 positive lymph nodes no benefit for extended treatment with 6 x AC or T over 4 x AC or T, respectively (Shulman et al, 2012).

References:

References for statement “CMF”

References for statement “Equivalent OS efficacy to \( \geq 4 \times A / EC \)”
Phase III trial comparing two dose levels of epirubicin combined with cyclophosphamide with cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer.


Further information
Four cycles of anthracycline with cyclophosphamide at threeweekly intervals (4 x AC or EC) followed by 12 cycles of weekly Paclitaxel is superior to threeweekly Paclitaxel in node negative and node positive patients.
Six cycles of Docetaxel Anthracycline and Cyclophosphamide (TAC) at threeweekly intervals is superior to six cycles of FAC at threeweekly intervals. TAC has to be given with bone marrow stimulating growth factors and prophylactic antimiotics to avoid febrile neutropenia
Four cycles of anthracycline cyclophosphamide (AC or EC) at threeweekly intervals, followed by four cycles of Docetaxel 100, given at threeweekly intervals without growth factor support is equally effective to six cycles of TAC.
**References:**


**Taxanes: Optimal Combination and Dosage (6/14)**

**Further information:**

In patients with node-positive disease, taxane-containing regimens improve the relapse-free survival (Mamounas 2005, Martin 2005, Bianco 2006) and overall survival (Henderson 2003, Martin 2005, Roche 2006, Bria 2006, Ferguson 2007, De Laurentiis 2008) compared to taxane-free protocols. Docetaxel in a sequential schedule at standard dose seems to reveal superior benefit compared to docetaxel in combination with the anthracycline in reduced dosage (Crown 2006). No consistent superiority was demonstrated in most prospective studies with taxane-containing schedules versus taxane-free regimen in node-negative patients (Gianni 2005, Goldstein 2005, Jones 2006) except for one trial.

In the sequence AC followed by a taxane, both taxanes are equally effective; however, the weekly administration of paclitaxel offers a better DFS and OS compared to the three-weekly regimen with acceptable toxicity (Sparano 2008). Some of the large prospective trials like the Sparano trial and others have included about 30 % patients with high risk, node negative disease.

**References:**

See references to 5/14
**Recommended Taxane-Based Regimens – Standard Dose (7/14)**

*Further information:*

In patients with node-positive disease, taxane-containing schedules improve the relapse-free survival (Mamounas 2005, Martin 2005, Bianco 2006) and overall survival (Henderson 2003, Martin 2005, Roche 2006, Bria 2006, Ferguson 2007, De Laurentiis 2008) compared to taxane-free protocols. Docetaxel in a sequential schedule at standard dose seems to reveal superior benefit compared to docetaxel in combination with the anthracycline in reduced dosage (Crown 2006). No superiority was demonstrated in most prospective studies with taxane-containing schedules versus taxane-free regimen in nodal-negative patients (Gianni 2005, Goldstein 2005, Jones 2006) except for one trial not published as full paper (Martin 2008), see also comment in slide 3. The EBCTCG Meta-analysis based on 100,000 women in 123 randomised trials confirmed the superiority of the addition of taxanes to a fixed anthracycline-based regimen (RR 0.86, p= 0.0005). The proportional risk reductions were minimally affected by age, nodal status, tumor size or differentiation, (Lancet 2012).

Taxanes can be used as combinations

- TAC instead of FAC (BCIRG 001 study)
- DC instead of AC (US Oncology study)
- or AD instead of AC (E 2179 study)

Or as sequential treatment of equal duration like

- EC → P weekly instead of FEC → P weekly (GIM trial, Cognetti 2013)
- FEC → Docetaxel instead of 6 X FEC (PACS 01 study)
- AC → P weekly instead of P threeweekly (E 1199 study, Sparano)
- FEC → Docetaxel instead of FEC (TACT study)
- FEC → Docetaxel instead of E → CMF (TACT study)
- AP → CMF instead of A → CMF (ECTO study)

Phase III Trial Evaluating the Addition of Paclitaxel to Doxorubicin Followed by Cyclophosphamide, Methotrexate, and Fluorouracil, As Adjuvant or Primary Systemic Therapy: European Cooperative Trial in Operable Breast Cancer. Luca Gianni, Jose´ Baselga, Wolfgang Eiermann, Vincente Guillem Porta, Vladimir Semiglazov, An`a Lluch, Milvia Zambetti,
Or sequential treatment of unequal duration
AC\rightarrow P instead of AC (NSABP B 28)

FEC \rightarrow P instead of FEC (GEICAM 9906 study)  Martin et al., J Natl Cancer Inst. 2008; 100(11):805-814) 
AC \rightarrow D instead of TAC (BCIRG 005 study) see above: Eiermann et al
EC \rightarrow D instead of FEC (WSG/AGO study)
EC \rightarrow D instead of FEC (ADEBAR study),
A(D) \rightarrow D\rightarrow CMF instead of A(C) \rightarrow CMF (BIG 2-98 study) 
E \rightarrow D\rightarrow CMF instead of E \rightarrow CMF (TAXIT study)

In the sequence AC followed by a taxane, both taxanes are equally effective; however, the weekly administration of paclitaxel offers a better DFS and OS with acceptable toxicities compared to the three-weekly regimen inpatients with node positive and high risk node negative disease (Sparano 2008).

A current meta-analysis of phase III trials for 8728 patients receiving sequential or concurrent anthracyclines and taxanes revealed significant differences in favor of the sequential regimens in regards to DFS (RR: 0.90, p=0.01) as well as OS (RR: 0.88; p = 0.02), respectively (Shao et al. 2012).

References (see also references to 5/14 and 6/14):
Sequential versus concurrent anthracyclines and taxanes as adjuvant chemotherapy of early breast cancer: a meta-analysis of phase III randomized control trials.
Shao N, Wang S, Yao C, Xu X, Thang Y, Zhang Y, Lin Y, 
Further information:

Capecitabine, gemcitabine and platin have been investigated in adjuvant trials. So far none of these drugs can be recommended to be included into anthracycline/taxane based regimen. One phase III trial investigated capecitabine and docetaxel followed by FEC versus weekly paclitaxel followed by FEC. After 50 months of follow-up no differences in regards to relapse free survival were seen (Kelly et al. 2012) Besides these first findings, numerous trials are still ongoing and the final results need to be awaited for the coming years. High risk populations or TNBC might benefit from the addition of Capecitabine. However, those data are not sound enough to base recommendations on it. However, a first meta-analysis of 4107 patients in two trials (USO and FinXX) reported a significant improvement by the addition of capecitabine to anthracycline and taxane based adjuvant therapy in regards to DFS (HR = 0.83, p = 0.027), OS (HR = 0.71, p = 0.008) and distant recurrence (HR = 0.79, p = 0.008) respectively. The subgroup analyses revealed a special benefit for triple negative, hormone receptor negative and Her2/neu negative patients (Jiang et al. 2012).

References:

Gemcitabine in adjuvant trials


C. J. Poole, L. Hiller, H. C. Howard, J. A. Dunn, P. Canney, A. M. Wardley, M. J. Kennedy, R. E. Coleman, R. C. Leonard, H. M. Earl, tAnGo trial collaborators. tAnGo: A randomized phase III trial of gemcitabine (gem) in paclitaxel containing,epirubicin/cyclophosphamide-based, adjuvant chemotherapy (CT) for women with early-stage breast cancer
Capecitabine in Adjuvant Trials

<table>
<thead>
<tr>
<th>Adj trials</th>
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<td>CDX3→CycECX3</td>
<td>DX3→CycEFX3</td>
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<td>5-year OS</td>
<td>92.6 vs. 89.7; p=0.08</td>
</tr>
<tr>
<td>US Oncology</td>
<td>2,611</td>
<td>ACycX4→CDX4</td>
<td>ACycX4→DX4</td>
<td>5-year DFS</td>
<td>89% vs 87%; p=0.125</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5-year OS</td>
<td>94% vs 92%; p=0.011</td>
</tr>
<tr>
<td>TACT2</td>
<td>4,400</td>
<td>EX4→CX4</td>
<td>EX4→CMFX4</td>
<td>5-year DFS</td>
<td>Follow-up</td>
</tr>
<tr>
<td>GEICAM</td>
<td>1,382</td>
<td>EDX4→CX4</td>
<td>ECycX4→DX4</td>
<td>5-year DFS</td>
<td>Follow-up</td>
</tr>
<tr>
<td>GAIN</td>
<td>3,028</td>
<td>ECycX4→CPX4</td>
<td>EX3→PX3→CycX3</td>
<td>EFS</td>
<td>Follow-up</td>
</tr>
<tr>
<td>MINDACT</td>
<td>6,600</td>
<td>ACX6</td>
<td>AnthracyclineX6</td>
<td>5-year DFS</td>
<td>recruiting</td>
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<tr>
<td>CIBOMA</td>
<td>876</td>
<td>ACyc/FECyc/AD→CX8</td>
<td>ACyc/FECyc/AD</td>
<td>5-year DFS</td>
<td>Follow-up</td>
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<tr>
<td>JBCRG04</td>
<td>900</td>
<td>CX8 ± endoc.therapy</td>
<td>Observation ± endocr. th.</td>
<td>DFS</td>
<td>Follow-up</td>
</tr>
<tr>
<td>ICE</td>
<td>1,500</td>
<td>Ibandronate + CX6</td>
<td>Ibandronate</td>
<td>EFS</td>
<td>Follow-up</td>
</tr>
<tr>
<td>CALGB-49907</td>
<td>633</td>
<td>CX6</td>
<td>ACycX4/CycMFX6</td>
<td>RFS</td>
<td>follow-up</td>
</tr>
<tr>
<td>Shao et al.</td>
<td>455</td>
<td>CycECX6</td>
<td>CycEFX6</td>
<td>Safety</td>
<td></td>
</tr>
</tbody>
</table>
So far, none of the trials could demonstrate an additional benefit of adding capcitabine to an anthracycline/taxane based therapy. However, most of the trials used lower doses of either the taxane or capcitabine in order to cope with the toxicity. In the neoadjuvant setting the addition of capcitabine did not improve the pCR rate in the Geparquattro trial but in the ABCSG 24 trial and the metanalysis of several German neoadjuvant trials. The reason for the positive results of the latter one is the correction for the necessary dose reduction of docetaxel.

D=docetaxel; Cyc=cyclophosphamide; E=epirubicin; F=5-FU; A=doxorubicin; P=paclitaxel; bev=bevacizumab; G=gemcitabine; M=methotrexate; DFS=disease-free survival; EFS=event-free survival

References Reviews and Metaanalyses:

Review of Capecitabine for the Treatment of Triple-Negative Early Breast Cancer.
Steger GG, Barrios C, O'Shaughnessy J, Martin M, Gnant M. SABCS PD01-3
www.abstracts2view.com/sabcs10/view

First efficacy results of capecitabine with anthracycline-and taxane-based adjuvant therapy in high-risk early breast cancer: a meta-analysis.
Adjuvant Chemotherapy (Dose-dense and/or Dose-escalated) (9/14)

Further information:

Dose-dense regimens are defined as chemotherapy schedules in which the intervals between the cycles can be shortened to a minimum (in general from three weeks to two weeks) due to the administration of granulocyte-colony stimulating substances. The principle of dose-dense schedules has been discussed for a long time (especially Skipper 1964, Goldie 1979, Frei 1980, Bonadonna 1981, Hryniuk 1986, Norton 1988). The CALGB 9741 study demonstrated for the first time in a clinical setting that administration of a dose-dense regime can achieve a relevant benefit in patients with node-positive breast cancer. Because of the short follow up period, these data cannot be considered as a basis for general recommendations (Citron 2003). As compared with standard therapy, weekly paclitaxel after standard AC chemotherapy is also associated with improved survival (Sparano 2008). Dose-dense and intensive chemotherapy schedules improve the relapse-free and overall survival compared to conventional adjuvant chemotherapy treatment plans independent of the hormone receptor status in patients with $\geq 4$ lymph nodes (Moebus 2006).

In a large three arm randomised 3 trial, dose dense AC followed by Paclitaxel at twoweekly intervals was equivalent to standard threeweekly TAC (NSABP B 38 study).


The question of efficacy and side effects of weekly Paclitaxel (Sparano like) versus twoweekly Paclitaxel (dose dense like) has been answered by a large multicentre two by two factorial trial, S 0221, with more then 1.600 patients per arm, showing no difference in DFS and OS between 12 weekly Paclitaxel 80 cycles (without growth factor support) and six twoweekly (dose dense) Paclitaxel 175 cycles with growth factor support (Comparison of two schedules of Paclitaxel for adjuvant therapy of breast cancer. G. T. Budd, W. E. Barlow, H. C. F. Moore, T. J. Hobday, J. A. Stewart, C. Isaacs, M.

The comparision of dose dense anthracycline (4x EC) followed by Paclitaxel (4x) both q2w and standard EC followed by Paclitaxel was one important gap to be closed in the scientific debate between dose dense, dose intensified twoweekly application and standard application.

The GIM study randomised more than 2.000 node positive patients (60% 1-3 nodes, 40% more then 4 nodes). Dose dense EC at twoweekly intervals followed by weekly Paclitaxel was superior to threeweekly EC followed by threeweekly Paclitaxel. Most interesting, the Forrest plot showed all subgoups having a significant benefit, including those with more than 4 and more than 10 nodes (Cognetti, GIM 2 study, SABCS 2013)

High-dose chemotherapy regimens followed by autologous stem cell transplantation should only be used in the context of well-designed clinical trials (Berry 2007).

For details and references of studies see also following slide and references.

References:


A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. Goldie JH, Coldman AJ. Cancer Treat Rep. 1979 Nov-Dec;63(11-12):1727-33


Statement: dd ACP / AC-P q2w (instead of q3w)


Statement: AC / ddP q1w x 12 (instead of p q3w)

Weekly paclitaxel in the adjuvant treatment of breast cancer.

Statement: ddE - P - C q2w (instead of EC - P q3w)
Ten year follow-up analysis of intense dose-dense adjuvant epirubicin (E), paclitaxel (T) and cyclophosphamide (C) (iddETC) confirms superior DFS and OS benefit in comparison to conventional dosed chemotherapy in high-risk breast cancer patients with \( \geq 4 \) positive lymph nodes. Volker J Moebus, A Schneeweiss, A du Bois, H.-J. Lueck, H Eustermann, W Kuhn, C Kurbacher, U Nitz, R Kreienberg, C Jackisch, J Huober, C Thomssen and M Untch. San Antonio Breast Cancer Symposium 2012, Abstract S3-4


Statement: ddE120C830 q2w x 6 \( \Rightarrow \) P q3w x 4E
TACT2
The UK TACT2 Trial: Comparison of Standard vs Accelerated Epirubicin in Patients Requiring Chemotherapy for Early Breast Cancer (EBC) (CRUK/05/019).
Statement: High-dose regimen (N ≥ 10+)

No further information

References Dose Density: Overview over Published Phase III Trials with N > 1000

<table>
<thead>
<tr>
<th>Trial</th>
<th>Source</th>
<th>Ind</th>
<th>Treatment</th>
<th>N</th>
<th>F/U</th>
<th>DFS/EFS</th>
<th>OS</th>
<th>Remarks</th>
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</thead>
<tbody>
<tr>
<td>CALGB 9741</td>
<td>Citron 2003</td>
<td>N+</td>
<td>4xA_{60} → 4xP_{175} → 4xC vs 4xA_{60}C → 4xP_{175} q2w vs q3w</td>
<td>2005</td>
<td>36</td>
<td>q2 vs q3w HR 0.74, p=0.010 vs con HR 0.93, p=0.58</td>
<td>q2 vs q2w HR 0.69, p=0.013 seq vs con HR 0.89, p=0.48</td>
<td>ER+ vs ER- HR 0.18, p&lt;0.01; retrospective analysis</td>
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<tr>
<td>CALGB 9741</td>
<td>Hudis 2005</td>
<td>N+</td>
<td>4xA_{60} → 4xP_{175} → 4xC vs 4xA_{60}C → 4xP_{175} q2w vs q3w</td>
<td>1938</td>
<td>36</td>
<td>q2 vs q2w ER+ ns vs con HR 0.93, p=0.014</td>
<td>q2 vs q2w ER+ ns vs con HR 0.93, p=0.039</td>
<td></td>
</tr>
<tr>
<td>AGO</td>
<td>Moebus 2006</td>
<td>N≥4+</td>
<td>3xE_{150} → 3xP_{225} → 3xC_{2500} q2w vs 4xE_{60}C_{600} → 4xP_{175} q3w</td>
<td>1284</td>
<td>62</td>
<td>HR 0.72, p&lt;0.01</td>
<td>HR 0.76, p=0.029</td>
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<tr>
<td>GONO-MIG</td>
<td>Venturini 2005</td>
<td>N+/N-</td>
<td>6xFE_{60}C q3w vs 6 xFE_{60}C q2w</td>
<td>1214</td>
<td>125</td>
<td>EFS HR 0.88, p=0.31</td>
<td>HR 0.87, p=0.35</td>
<td></td>
</tr>
<tr>
<td>E1199</td>
<td>Sparano 2007</td>
<td>N+/N-</td>
<td>4xA_{60}C → 4xP_{175} q3w vs 4xA_{60}C → 12xP_{80} qw vs 4xA_{60}C → 4xD_{100} q3w</td>
<td>4950</td>
<td>64</td>
<td>P3 vs P1 HR 1.27, p=0.006 vs D3 HR 1.23, p=0.02 vs D1 HR 1.09, ns</td>
<td>P3 vs P1 HR 1.32, p=0.01 vs D3 HR 1.13, p=ns vs D1 HR 1.02, ns</td>
<td></td>
</tr>
<tr>
<td>NCIC CTG MA21</td>
<td>Burnell 2006</td>
<td>N+/N-</td>
<td>vs 4xA_{60}C → 12xD_{35} qw</td>
<td>6xCE_{120}F vs 6xE_{120}C q2w → 4xP q3w vs 4xA_{60}C q3w → 4xP q3w</td>
<td>2104</td>
<td>30</td>
<td>AC-P vs CEF HR 1.49, p=0.005 AC-P vs ddEC-P HR 1.68, p=0.006 ddEC-P vs CEF HR 0.89, ns</td>
<td>ND</td>
</tr>
</tbody>
</table>

A, doxorubicin; C, cyclophosphamide; con, concurrent; D, Docetaxel; DFS, disease-free survival; E, epirubicin; EFS, event-free survival; ER, estrogen receptor; F/U, follow-up; HR, hazard ratio; ns, not significant; OS, overall survival; P, paclitaxel; q2w, two weekly; q3w, three weekly; seq, sequential; vs, versus.

**Metaanalysis:**

**Adjuvant Treatment with Trastuzumab I (10/14)**

*Further information:*

All studies demonstrating a benefit for adjuvant trastuzumab therapy included node-negative and node-positive patients and subgroup analysis showed a benefit for both groups of patients. Therefore, trastuzumab-containing regimens should be also used in node-negative patients with risk factors. References for use of trastuzumab and further information see also slide “Adjuvant Treatment with Trastuzumab (2)”. Limited data suggests that also patients with HER2-positive tumors smaller than 1cm have a substantially increased risk of recurrence compared to patients with non-amplified tumors. Since benefit from trastuzumab in the adjuvant studies was also observed independent of tumor size, the use of trastuzumab also needs to be considered in small tumors. Therefore, in patients with tumors > 5 mm and risk factors in addition to HER2 overexpression/gene amplification who are also candidates for adjuvant chemotherapy, the use of Trastuzumab can be considered.

*References:*

Statements: “node-positive” and “node-negative”
See following slides

Reference for “Disease with additional risk factors and tumors <1 cm”

Further information

In three trials (Romond 2005, Piccart-Gebhart 2005, Smith 2007, Slamon 2006) trastuzumab has been administered for one year. 2-year treatment was not superior to one year in the HERA-trial despite a transient advantage in DFS for the 2-year arm in the hormone receptor negative cohort (Goldhirsch 2012). The PHARE-trial failed to show that 6 months of trastuzumab is non inferior to 12 months. Subgroup analysis suggested that sequential modality for ER negative tumors impacted the overall results while results in other groups seemed compatible with non-inferiority hypothesis (Pivot 2012). In a much smaller randomized study (FinHer; 232 patients) trastuzumab given simultaneously to chemotherapy for only nine weeks reduced hazard ratios for relapse (0.46, p=0.0078) and distant metastases (0.43, p=0.0078), respectively (Joensuu 2006).

As a sequential therapy in the HERA trial (Piccart-Gebhart 2005, Smith 2007), patients received different regimens containing anthracyclines with or without taxanes and trastuzumab after completion of chemotherapy. All other studies applied taxanes simultaneously with trastuzumab. The fully published study (Romond 2005) combined analysis of the two US trials and used paclitaxel either weekly or three-weekly in combination with trastuzumab after four cycles of AC.

Based on the published registration trials, both options (sequential and concurrent use of trastuzumab) are possible. Yet, recent evidence (Sequential Versus Concurrent Trastuzumab in Adjuvant Chemotherapy for Breast Cancer. Edith A. Perez, Vera J. Suman, Nancy E. Davidson, Julie R. Gralow, Peter A. Kaufman, Daniel W. Visscher, Beiyun Chen, James N. Ingle, Shaker R. Dakhil, JoAnne Zujewski, Alvaro Moreno-Aspitia, Thomas M. Pisansky, and Robert B. Jenkins.J Clin Oncol 29:4491-4497. 2011) suggests a substantial numerical advantage of concurrent use of trastuzumab with a taxane vs. sequential administration even though the p-value is not significant after correction for multiple testing as stated in the study protocol. Thus, concurrent use is preferable.

An additional study used an anthracycline-free regimen of docetaxel and carboplatin with similar efficacy as AC followed by docetaxel and trastuzumab (Slamon 2011).

All studies included node-negative patients and subgroup analysis showed also a benefit for these patients. Therefore, taxane-based regimens can be considered also in node-negative patients.
**References:**

Reference for statement “Start of treatment up to 3 months after chemotherapy“: Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer.


**HERA TRIAL:**

PHARE Trial Results of Subset Analysis Comparing 6 to 12 Months of Trastuzumab in Adjuvant Early Breast Cancer

References for statement “Start of treatment simultaneously with taxanes or platin/docetaxel“

Trastuzumab in the adjuvant treatment of HER2-positive early breast cancer patients: a meta-analysis of published randomized controlled trials.


http://www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=47&abstractID=35229


The question of anthracycline free chemotherapy with trastuzumab is still under debate

Choosing the Best Trastuzumab-Based Adjuvant Chemotherapy Regimen: Should We Abandon Anthracyclines? Harold J. Burstein, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA Martine J. Piccart-Gebhart, Institut Jules Bordet, Brussels, Belgium. Edith A. Perez, Mayo Clinic, Jacksonville, FL. Gabriel N. Hortobagyi, MD Anderson Cancer Center, Houston, TX. Norman Wolmark, Allegheny General Hospital, National Surgical Adjuvant Breast and Bowel Project, Pittsburgh, PA. Kathy S. Albain, Loyola University Chicago Stritch School of Medicine, Maywood, IL. Larry Norton, Memorial Sloan-Kettering Cancer Center, New York, NY. Eric P. Winer, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA. Clifford A. Hudis, Memorial Sloan-Kettering Cancer Center, New York, NY Journal of Clinical Oncology, Vol 30, No 18 (June 20), 2012: pp 2179-2182

The magnitude of benefit from Trastuzumab was present in all patient subgroups.

Especially for patients with node negative Her 2 positive disease with tumors less than 3 cm, a first study showed an excellent outcome after 12 weekly Paclitaxel 80 without anthracyclines, with Trastuzumab followed by Trastuzumab (SABCS 2013)

A phase II study of adjuvant paclitaxel (T) and trastuzumab (H) (APT trial) for node-negative, HER2-positive breast cancer (BC). Tolaney SM, Barry WT, Dang CT, Yardley DA, Moy B, Marcom PK, Albain KS, Rugo HS, Ellis M, Shapira I, Wolff AC, Carey LA, Overmoyer BA, Partridge AH, Guo H, Hudis CA, Krop IE, Burstein HJ, Winer EP. Dana- Farber Cancer Institute, Boston, MA; Memorial Sloan Kettering Cancer Center, New York, NY; Sarah Cannon Research Institute, Nashville, TN; Massachusetts General Hospital, Boston, MA; Duke University, Durham, NC; Loyola University, Maywood, IL; University of California, San Francisco, CA; Washington University, St. Louis, MO; Long Island Jewish Medical Center, New Hyde Park, NY; Johns Hopkins University, Baltimore, MD; University of North Carolina, Chapel Hill, NC. SABCS 2013. S1-04

References for statements for “duration” and “dosage” see above
Adjuvant Trastuzumab Cardiac Monitoring for CHF (12/14)

Further information:

All clinical trials examining the adjuvant use of trastuzumab included monitoring of cardiac function by either echocardiography or MUGA scans. An increase in cardiotoxicity in patients receiving trastuzumab in addition to chemotherapy was reported. The NSABP B-31 5-year update identified four risk factors for heart failure in trastuzumab-treated patients:

- Age (50–59 years, 5.1%; ³60 years, 5.4%)
- Use of hypertensive medications (6.8%)
- Baseline LVEF values of 50%–54% (12.9%)
- Post-anthracycline chemotherapy LVEF values of 50%–54% (12.6%)

References:

Statement: Cardiac safety


Adjuvant Treatment with Trastuzumab: Schedules (13/14)

No further information

References:

Adjuvant Therapy with Other Targeted Agents (14/14)

Further information:

The BEATRICE-trial demonstrated no statistically significant improvement in invasive DFS with the addition of 1 year’s bevacizumab to adjuvant chemotherapy for triple negative breast cancer (HR = 0.87 (95% CI: 0.72 – 1.07; p=0.1810) (Cameron 2012).

The BETH trial demonstrated no advantage of the addition of Bevacizumab to Platinum, Docetaxel and Trastuzumab in a large multicentre study with more than 3.000 patients, first presented at SABCS 2013.

References:


Neoadjuvant (Primary) Systemic Therapy
Neoadjuvant Systemic Therapy

- **Version 2002:**
  Costa

- **Versions 2003–2013:**
  Blohmer / Dall / Fersis / Göhring / Harbeck / Heinrich / Huober / Jackisch / Kaufmann / Lux / von Minckwitz / Müller / Nitz / Schneeweiss / Schütz / Solomayer / Untch

- **Version 2014:**
  Bauerfeind / Loibl
Subtype-specific General Systemic Strategies

- **HR+/HER2- and “low risk”:**
  - Endocrine therapy without chemotherapy

- **HR+/HER2- and “high risk”**
  - Conventionally dosed AT-based chemotherapy
  - Dose dense & escalated in case of high tumor burden
  - Followed by endocrine therapy

- **HER2+**
  - Trastuzumab plus
    - Sequential A/T-based regimen with concurrent T + H
    - Anthracycline-free, carboplatin-cont. regimen
    - Dose dense & escalated in case of high tumor burden

- **TNBC**
  - Conventionally dosed AT-based chemotherapy
  - Dose dense & escalated

- In case of indication for chemotherapy, consider neoadjuvant approach
Neoadjuvant Systemic Chemotherapy Clinical Benefit

- Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy
- Pathological complete response is associated with improved survival in particular subgroups
- Can achieve operability in primary inoperable tumors
- Improved options for breast conserving surgery
- Allows individualization of therapy according to mid-course treatment effect

Oxford / AGO LoE / GR

- Survival: 1a A
- Pathological complete response: 1b A
- Operability: 1b A ++
- Improved options: 1b A ++
- Individualization: 1b B +*

* Study participation recommended
Neoadjuvant Systemic Chemotherapy Indications

- Inflammatory breast cancer
  - Oxford / AGO LoE / GR: 2b B ++
- Inoperable breast cancer
  - Oxford / AGO LoE / GR: 1c A ++
- Large operable breast cancer primarily requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation
  - Oxford / AGO LoE / GR: 1b B +
- If similar postoperative adjuvant chemotherapy is indicated
  - Oxford / AGO LoE / GR: 1b A +
- TNBC
- HER2 positive
  - Oxford / AGO LoE / GR: 1b B +
# Neoadjuvant Systemic Chemotherapy Response Prediction I

<table>
<thead>
<tr>
<th>Factor</th>
<th>CTS</th>
<th>LoE\textsubscript{Ox2001}</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young age</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>cT1 / cT2 tumors o. N0 o. G3</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Negative ER and PgR status</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Triple negative breast cancer (TNBC)</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Positive HER2 status</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Non-lobular tumor type</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Early clinical response</td>
<td>B</td>
<td>1b</td>
<td>A</td>
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## Neoadjuvant Systemic Chemotherapy Response Prediction II

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<th>GR</th>
<th>AGO</th>
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<td>PAM50/Mammaprint</td>
<td>III</td>
<td>C</td>
<td>B</td>
<td>+/-</td>
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<tr>
<td>Ki-67</td>
<td>I</td>
<td>B</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Tumour infiltrating Lymphocytes</td>
<td>II</td>
<td>B</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>PIK3CA mutation</td>
<td>II</td>
<td>B</td>
<td>B</td>
<td>+</td>
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Neoadjuvant Systemic Chemotherapy
Recommended Regimens and Schedules

- Standard regimens used in the adjuvant setting with a duration of at least 18 weeks
  
- AC or EC → D q3w or P q1w
  
- DAC
  
- AP → CMF
  
- Taxane followed by anthracycline sequence
  
- Dose-dense regimen (e.g. E-P-CMF, E-P-C)
  
- Capecitabine in combination with anthracycline and taxane
  
- Platinum in TNBC independent of BRCA-mutation

Oxford / AGO LoE / GR

1a A ++
2b A ++
2b B ++
1b A +
2b B +
1b B +*
1b B +/-
2b B +*

*Study participation recommended
### Possible Carboplatin Containing Regimen in the Neoadjuvant Setting

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Regimen</th>
<th>pCR rate ypT0/is, ypN0</th>
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<tbody>
<tr>
<td><strong>Positive studies</strong></td>
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<td></td>
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</tr>
<tr>
<td>Sikov et al. (SABCS 2013)</td>
<td>CALGB 40603</td>
<td>Paclitaxel 80mg/m² weekly x 12+Carboplatin AUC 6q3w x4 – dd AC (q2w)</td>
<td>49% 60% (+Bev)</td>
</tr>
<tr>
<td>von Minckwitz et al. (ASCO 2013)</td>
<td>Phase II</td>
<td>NPLD20mg/m²+ Paclitaxel 80mg/m² +Carboplatin AUC 1.5mg/m² weekly x18</td>
<td>53% (+Bev)</td>
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<tr>
<td><strong>Negative study</strong></td>
<td></td>
<td></td>
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<tr>
<td>Alba et al. BCRT 2013</td>
<td>Phase II basal like</td>
<td>EC (90/600mg/m²)q3w x4 – Docetaxel 75mg/m²+ Carboplatin AUC 6 q3w x 4</td>
<td>30%</td>
</tr>
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</table>
Neoadjuvant Systemic Chemotherapy
Recommended Methods of Monitoring of Response

- Breast ultrasound
- Palpation
- Mammography
- MRI
- PET(-CT)
- Clip tumour region

<table>
<thead>
<tr>
<th>Method</th>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast ultrasound</td>
<td>2b</td>
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</tr>
<tr>
<td>Palpation</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Mammography</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>MRI</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>PET(-CT)</td>
<td>1b</td>
<td>D</td>
</tr>
<tr>
<td>Clip tumour region</td>
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<td>D</td>
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# Neoadjuvant Targeted Therapy in HER2 Positive Tumors

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<tr>
<th>Therapy Description</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab in combination with chemotherapy</td>
<td>1b A ++</td>
</tr>
<tr>
<td>Lapatinib in combination with chemotherapy</td>
<td>1b B -</td>
</tr>
<tr>
<td>Lapatinib + Trastuzumab in combination with chemotherapy</td>
<td>2b B +/-</td>
</tr>
<tr>
<td>Pertuzumab + Trastuzumab in combination with chemotherapy</td>
<td>2b B +*</td>
</tr>
<tr>
<td>Two anti-HER2 agents without chemotherapy</td>
<td>2b B +/-</td>
</tr>
</tbody>
</table>

* Study participation recommended
Neoadjuvant Targeted Therapy in HER2 Negative Tumors

Chemotherapy in combination with Bevacizumab

- In hormone receptor positive BC
- In TNBC

Oxford / AGO LoE / GR

2b B +/- 1b B +/-
Neoadjuvant Systemic Therapy Procedures in Case of Early Response

In case of early response following 6 to 12 weeks of neoadjuvant chemotherapy:

- Complete all chemotherapy before surgery i.e. ≥ 18 weeks of treatment
- In case of response after 2 cycles of DAC in HR positive breast cancer consider 8 instead of 6 cycles of DAC

Oxford / AGO LoE / GR

1b A ++

2b C +
Neoadjuvant Systemic Therapy
Procedures in Case of No Early Response

<table>
<thead>
<tr>
<th>In case of no change:</th>
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<tbody>
<tr>
<td>Completion of NST, followed by surgery</td>
<td>2b C ++</td>
</tr>
<tr>
<td>Continuation of NST with non cross-resistant regimen</td>
<td></td>
</tr>
<tr>
<td>AC or EC x 4 → D x 4 or Pw x 12</td>
<td>2b B +</td>
</tr>
<tr>
<td>DAC x 2 → NX x 4</td>
<td>1b B +</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>In case of progressive disease:</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop of NST and immediate surgery or radiotherapy</td>
<td>4 D ++*</td>
</tr>
<tr>
<td>Additional adjuvant chemotherapy with non cross-resistant regimen</td>
<td>4 D +/-*</td>
</tr>
</tbody>
</table>

* Study participation recommended
Local/Regional Procedure after Neoadjuvant Therapy

- Mark previous tumor region 5 D ++
- Surgery 2b C ++
- Microscopically clear margins 5 D ++
- Tumor resection in the new margins 3b C +
- Sentinel node biopsy (see chapter “Surgery”)
## Surgical Procedure of the Axilla Before or After NACT

### SLNB before or after NACT in cN0

<table>
<thead>
<tr>
<th>SLNB before NACT</th>
<th>SLNB after NACT</th>
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</thead>
<tbody>
<tr>
<td>SLNB before NACT</td>
<td></td>
<td>2b 3 B + +/-</td>
</tr>
<tr>
<td>SLNB after NACT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Further surgical procedures depending on SLNB

<table>
<thead>
<tr>
<th>cN-Status (before NST)</th>
<th>pN-Status (before NST)</th>
<th>cN-Status (after NST)</th>
<th>Surgical procedure</th>
<th>Oxford / AGO LoE / GR</th>
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<tr>
<td>cN0</td>
<td>pN0(sn)</td>
<td>-</td>
<td>nihil</td>
<td>1a A +</td>
</tr>
<tr>
<td>cN0</td>
<td>pN+(sn) analogue ACOZOG</td>
<td>ycN0</td>
<td>ALND</td>
<td>3 B +/-</td>
</tr>
<tr>
<td>cN0</td>
<td>pN+(sn) not analogue ACOZOG</td>
<td>ycN0</td>
<td>ALND</td>
<td>2b B +</td>
</tr>
<tr>
<td>cN+</td>
<td>cN+ (CNB/FNA)</td>
<td>ycN0</td>
<td>SNB ALND</td>
<td>3 2b B +/- +</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ycN+ (CNB/FNA)</td>
<td>2b B ++</td>
</tr>
</tbody>
</table>
Neoadjuvant Systemic Therapy
Indications for Mastectomy

- Positive margins after repeated excisions
  - 3b C ++
- Radiotherapy not feasible
  - 5 D ++
- In case of clinical complete response
  - Inflammatory breast cancer
    - 2b C +
    - In case of pCR
      - +/-
  - Multicentric lesions
    - 3 C +/-
  - cT4a-c breast cancer
    - 2b B +/-

Oxford / AGO LoE / GR
Neoadjuvant Systemic Therapy
Timing of Surgery and Radiotherapy

- **Surgery**
  - After the nadir of the leucocyte count
    (2 to 4 weeks after last course of chemotherapy)

- **Radiotherapy after surgery**
  2–3 weeks after surgery BCS

**Oxford / AGO LoE / GR**

4 C ++

2b B ++
## Adjuvant Systemic Therapy after Neoadjuvant Systemic Treatment

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade</th>
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<tbody>
<tr>
<td>Endocrine treatment in endocrine responsive disease</td>
<td>1a A ++</td>
<td></td>
</tr>
<tr>
<td>Complete trastuzumab treatment for 1 year in HER2-positive disease</td>
<td>2b B ++</td>
<td></td>
</tr>
<tr>
<td>In case of insufficient response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Further chemotherapy</td>
<td>3 C -</td>
<td></td>
</tr>
<tr>
<td>Experimental therapies in clinical trials</td>
<td>5 D +</td>
<td></td>
</tr>
</tbody>
</table>
Neoadjuvant Endocrine Therapy

Postmenopausal patients with endocrine-responsive breast cancers who are inoperable and can/will not receive chemotherapy

Optimizes the option for breast conserving therapy in postmenopausal patients with endocrine-responsive tumors

Aromatase inhibitors (for > 3 months)

Premenopausal patients with endocrine-responsive breast cancers who are inoperable and can/will not receive chemotherapy

Tamoxifen

Aromatase inhibitors+ LHRH

Concurrent chemo-endocrine therapy

Prognostic factors during/after NST: quantitative ER-expression, level of Ki-67, N status, T status

Optimal duration of neoadjuvant endocrine therapy is unknown

No long term results for neoadjuvant endocrine therapy (vs. adjuvant endocrine therapy)
Neoadjuvant (Primary) Systemic Therapy (2/20 and 3/20)

Further information:

Systematic review of published evidence:
PUBMED 1999-2012
ASCO 1999-2012
SABCS 1999-2012
ECCO/ESMO 1999-2012

Systematic review of national and international guidelines: St. Gallen, NIH, ASCO, German guidelines

References:

Selected review articles:
Neoadjuvant Systemic Chemotherapy - Clinical Benefit (4/20)

Further information:

Survival rates are similar after primary systemic (preoperative, neoadjuvant) therapy (NST) and adjuvant therapy.\(^1\)\(^-\)\(^4\) Pathological complete response (pCR) is associated with improved survival.\(^4\)\(^-\)\(^8\) In retrospective analyses of the German patient cohorts, this treatment effect is confined to specific subgroups in particular to patients with triple negative, HER2+ (non-luminal) and luminal B (HER2 negative) breast cancer.\(^8\)\(^,\)\(^9\) Achievement of pCR according to the most strict definition of no invasive and no non-invasive tumor residues in the breast and axilla (ypT0 ypN0) predicts the most favorable overall survival.\(^7\)\(^,\)\(^8\)

Advantages of NST are

1. improved operability of primary inoperable tumors,\(^10\)
2. higher rate of breast conserving surgery,\(^10\)
3. selection of individualized therapy by early identification of treatment failures,\(^8\)
4. evaluation of short-term surrogate markers (clinical, pathologic, molecular) to predict long-term outcome,\(^8\) and
5. rapid evaluation of new drugs or treatment modalities.\(^11\)

Disadvantage of NST is

1. In one metaanalysis from 2005 an increased rate of loco-regional recurrences was suggested. However, this metaanalysis included trials where surgery was withheld in numerous patients.\(^12\)
References:

Neoadjuvant Systemic Chemotherapy Indications (5/20)

Further information:

Neoadjuvant systemic therapy (NST) is indicated in inoperable and inflammatory breast cancer, but also in operable breast cancer with tumor diameters of at least 2 centimeters.\(^1-3\) NST is a valid treatment option, if mastectomy seems necessary, but patient wishes breast conservation,\(^3,4\) and for all patient who would need adjuvant chemotherapy after adequate evaluation of radiological, histological and clinical prognostic factors.\(^5\) Patients may choose to receive systemic therapy before surgery to take advantage of the response assessment of the primary tumor as tumor response to NST is a surrogate for the effect of chemotherapy on micrometastases.\(^6\) Furthermore, a demonstrable response to NST may have a positive effect on patients compliance. NST may also be an option for patients who wish to delay surgery, eg. in the second or third trimester of pregnancy.\(^7\)

It is especially indicated in TNBC and HER2+ breast cancer, because pCR correlates very well with the outcome in these subtypes.\(^8,9\)

References:

2. Buzdar AU. Cancer 110, 2394, 2007
Neoadjuvant Systemic Chemotherapy Response Prediction I (6/20)

Further information:

According to a metaanalysis including 3332 patients treated in 7 German neoadjuvant trials clinico-pathological factors predicting pCR following NST are younger age, smaller tumor size, non-lobular histology, higher grade, negative hormone receptor (HR) status, triple negative and HER2 positive status.\(^1,2\) Considering subgroups higher probability of pCR was associated with longer treatment in HR positive tumors, higher anthracycline doses in HR negative tumors, short-term higher-dose taxane- and anthracycline-based treatment in triple negative tumors, trastuzumab-containing treatment in HER2 positive tumors and the addition of capecitabine in all subtypes.\(^1\)

References:

**Neoadjuvant Systemic chemotherapy - Response Predictiong II (7/20)**

*Further information:*

Further predictive parameters are the presence of tumor-associated lymphocytes, and other proliferation marker like Ki-67 and topoisomerase IIα. 1-4 The assessment of Ki-67 before therapy has prognostic and predictive impact. 5,6 Although results of several gene expression profiling studies are promising, at the moment, none of these signatures has been proven to be of sufficient discriminatory power to be used in clinical setting. 7

It has been shown that TNBC subclassified by the Vanderbilt/Lehman signature into 7 subtypes has predictive information. 8 It was previously shown that the androgen receptor positive TNBC have a lower rate of achieving a pCR. 9 The luminal AR subtype is one of the 7 classified by Lehmann. In HER2 positive breast cancer, the absolute amount of ER seems to play a role in predicting response to neoadjuvant therapy. 10 The PIK3CA mutated HER2+ tumours achieve a significantly lower pCR rate than the wild-type tumours. 11-13 Especially in patients receivin a dual anit-HER2 treatment.

*References:*

3 Denkert C, et al. SABCS 2013  
4 Loi S, et al. SABCS 2013  

Loibl S, Breast Cancer Res Treat, 2010


Gianni L, et al. SABCS 2011

Baselga J, ECC13, 2013

Loibl S, SABCS 2013
Neoadjuvant Systemic Chemotherapy Recommended Regimens and Schedules (8/20 and 9/20)

Further information:

Outside clinical trials the same regimens should be used for NST as in the adjuvant setting ie. anthracyclines and taxanes concurrently or sequentially for at least 6 cycles (18 weeks) or 6 months, respectively.¹ Trastuzumab should be provided to all patients with HER2 overexpressing breast cancer and no cardiac comorbidity.²,³ Recommended regimens are those used in the superior treatment arms of large randomized trials (NSABP B-27,⁴ GeparDuo,⁵ GeparTrio,⁶,⁷ ECTO⁸).

A short dose-dense chemotherapy regimen with epirubicin and paclitaxel increased pCR rate and survival as compared to four cycles of standard dose epirubicin plus paclitaxel.⁹ A sufficiently long NST with dose intensified epirubicin and paclitaxel followed by CMF, however, increased only pCR rate but not DFS as compared to standard treatment.¹⁰,¹¹ Nevertheless analogue to the adjuvant setting, the use of a standard dose intensified regimen as neoadjuvant treatment should be considered if the patients would most probably receive this regimen in the adjuvant setting. Several regimen from the adjuvant setting and the neoadjuvant setting can be used.

Several studies have examined the use of capecitabine in the neoadjuvant setting with conflicting results.¹²-¹⁴ One metaanalysis of the German neoadjuvant trials point to the fact that capecitabine might play a role in NST but further prospective trials are needed.¹⁵

Platinum salts, have recently been shown in large prospectively randomized trials (the German GeparSixto study and the American CALGB 40603 study¹⁶,¹⁷) to increase pCR rates when given as part of the neoadjuvant chemotherapy, supporting the previous data from mainly small, non-randomized trials¹⁸-²¹. The study from Alba et al. combining Carboplatin with docetaxel (75mg/m²) compared to docetaxel 100mg/m² could not demonstrate superiority for the carboplatin arm. However, it has not been shown that this is specific platinum effect and not merely the effect of an alkylating agent.

References:

Neoadjuvant Systemic Chemotherapy Recommended Methods of Monitoring of Response (10/20)

Further information:

Monitoring during treatment must include breast examination before each cycle. The frequency and nature of imaging assessment during chemotherapy is controversial. Minimal requirements for the surgeon include clinical examination, mammogram, ultrasound, and in selected cases MRI. The response measured by breast ultrasound after 2 cycles of NST is a good predictor of later pCR. Various studies describe a good prediction of pCR if the breast MRI shows a good response in size of the tumor and reduction in volume and in contrast agent dynamic. However, the accuracy of MRI is not adequate to obviate either the need for staging by sentinel node biopsy or the need for complete axillary dissection in women determined to be node positive prior to NST. FDG-PET does not provide an accurate assessment of residual tumour after primary chemotherapy of breast cancer and is therefore not recommended outside clinical trials.

References:

Neoadjuvant Targeted Therapy in HER2 Positive Tumors (11/20)

Further information:

Several studies have examined the use of trastuzumab in combination with chemotherapy for patients with HER2 positive breast cancer in the neoadjuvant setting.\(^1\)\(-\)\(^6\) The results of randomized trials demonstrated that, compared to chemotherapy alone, neoadjuvant trastuzumab plus chemotherapy significantly increased pathologic complete response rate.\(^1\)\(-\)\(^5\) Improvements in disease-free, event-free and overall survival were also reported.\(^1\)\(-\)\(^5\) The achievement of pCR with chemotherapy and trastuzumab was associated with improved disease-free survival, distant disease-free survival and overall survival.\(^2,3,6\)-\(^9\)

The use of lapatinib instead of trastuzumab can not be recommended, although efficacy can be seen in HER2 positive tumors.\(^10,11\)

The combination of chemotherapy with trastuzumab and lapatinib or pertuzumab can significantly increase the pathologic complete response rate, but should preferably be used in clinical studies in the neoadjuvant setting until further results are available, although the combination of trastuzumab and pertuzumab has been licensed by the FDA for neoadjuvant therapy.\(^11\)\(-\)\(^14\) Chemotherapy-free regimens combining 2 anti-HER2 agents were also active.\(^15,16\)

Subcutaneous trastuzumab, has a pharmacokinetic profile and efficacy non-inferior to standard intravenous administration, and therefore offers a valid treatment alternative.\(^17\)

References:

**Neoadjuvant Targeted Therapy in HER2 Negative Tumors (12/20)**

*Further information:*

Three large randomized phase III studies showed a higher pCR rate after combination of chemotherapy and bevacizumab than with chemotherapy alone in patients with HER2 negative breast cancer in the neoadjuvant setting. In the German GeparQuinto trial, while no effect of bevacizumab was seen in hormone receptor (HR) positive patients,\(^1\) bevacizumab significantly increased the pCR rate in the triple negative subgroup.\(^1,2\) In the NSABP B40 trial, however, the effect of bevacizumab was seen predominantly in HR positive breast cancer.\(^3\) This controversial results cannot be explained for now. The CALGB study is the 3\(^{rd}\) trial showing an increased pCR by adding bevacizumab to chemotherapy.\(^4\) Long term data need to be awaited before the recommendation for neoadjuvant bevacizumab can be granted.

*References:*

Neoadjuvant Systemic Therapy Procedures in Case of Early Response (13/20)

Further information:

Early response following 2 to 4 cycles (6 to 12 weeks) of an anthracycline-containing NST as assessed by clinical examination or ultrasound is associated with higher pCR rates at surgery.\textsuperscript{1-3} In case of early response NST should be completed as planned.\textsuperscript{4} In patients responding to 2 cycles of TAC, however, continuation of treatment with additional 6 instead of 4 cycles of TAC significantly improved disease-free and overall survival. In a retrospective, unplanned subgroup analysis this benefit was confined to patients with hormone receptor positive breast cancer.\textsuperscript{5}

References:

Neoadjuvant Systemic Therapy Procedures in Case of No Early Response (14/20)

Further information:

In case of no change following 2 two 4 cycles (6 to 12 weeks) of an anthracycline-containing NST as assessed by clinical examination or ultrasound alternative strategies should be discussed. Completion of NST as planned is associated with a clinical response in around 50% of patients. The pCR rate, however, is only 2-6%. Following 4 cycles of an anthracycline-containing regimen the switch to taxanes is recommended. Survival in an unselected group of patients, however, is not improved. The addition of everolimus to paclitaxel is not justified. In case of no response following 2 cycles of TAC, however, the switch to 4 cycles of vinorelbine plus capecitabine (NX) instead of continuation with 4 cycles of TAC significantly improved disease-free and overall survival. In a retrospective subgroup analysis this benefit was confined to patients with hormone receptor positive breast cancer. In case of progressive disease immediate surgery or primary radiotherapy is recommended. Patients who have extensive residual cancer after a full course anthracycline and taxane containing NST remain at high risk for relapse, in particular patients with grade 3 and hormone receptor negative breast cancer. Those patients should be referred to participation in postneoadjuvant clinical trials.

References

Neoadjuvant Systemic Therapy - Surgical Procedures (15/20 and 16/20)

Further information:

Precise documentation of tumor location before, during and at the end of NST is necessary. Surgery is an integral part of primary breast cancer treatment following NST. The aim of surgery is to completely remove invasive and non invasive breast cancer residues after NST and to obtain clear margins at pathology examination. No compromise should be made in surgical margins to obtain better cosmetic results. Under these circumstances excision within new tumor margins might be feasible according to current data. Thus far, studies evaluating sentinel node biopsy after NST have been inconsistent with regard to feasibility and efficacy. Therefore, it is not recommended outside of clinical trials, see also chapter surgery.¹⁴

References:

**Neoadjuvant Systemic Therapy - Indications for Mastectomy (17/20)**

**Further information:**

Breast conserving surgery (BCS) should not be considered if negative margins are not achievable even after repetitive excisions, in case of widespread DCIS or microcalcifications, in case of inflammatory breast cancer or if adjuvant radiotherapy is not feasible.\(^{1-3}\) In cases with cT4a-c tumors or multicentric lesions (lesions in different quadrant) BCS is also not recommended.\(^{1-5}\) However, if a clinical complete response is achieved following NST, BCS should be evaluated within controlled clinical trials.

**References:**

Neoadjuvant Systemic - Therapy Timing of Surgery and Radiotherapy (18/20)

Further information:

It is unknown whether preoperative radiotherapy following NST achieved similar results as radiotherapy following NST and surgery. Preoperative radiotherapy might result in higher rates of breast conservation without compromising cosmetic result. However, preoperative external beam and brachytherapy are not established as modes of treatment in conjunction with NST and do not replace adequate surgery which should be performed after leucocyte nadir around 2 to 4 weeks following last cycle of chemotherapy. Adjuvant radiotherapy after NST should be administered according to the same recommendations made for those patients who do not receive NST. Even in patients with pCR following NST whole breast irradiation is indicated after breast-conserving surgery. If surgery can be omitted after pCR has still be to confirmed.

References:

**Adjuvant Systemic Therapy after Neoadjuvant Systemic Treatment (19/20)**

**Further information:**

Postneoadjuvant therapy is indicated in patients at high risk of relapse after neoadjuvant therapy. The NATAN study using a bisphosphonate in unselected women with residual cancer was not successful. Currently several trials have started investigating palbociclib in patients at very high risk after neoadjuvant therapy with luminal type breast cancer. The Katherine study investigates the use of T-DM1 instead of trastuzumab after PST.

**References**

1. Mittendorf et al. J CLin Oncol 2011
2. von Minckwitz et al. Cancer Res 2013, SABCS abstract
Neoadjuvant Endocrine Therapy (20/20)

Further information:

NST with aromatase inhibitor represents an option for postmenopausal patients with highly endocrine responsive breast cancer, which can improve breast conservation rate.\(^1\) However, chemotherapy is still widely used in this setting despite small studies showing little advantage over an endocrine approach.\(^3\) The lack of a practice standard reflects the absence of a phase III trial definitively comparing neoadjuvant endocrine therapy with neoadjuvant chemotherapy. Neoadjuvant endocrine therapy might be reasonable for postmenopausal patients with hormone receptor positive breast cancer who are inoperable and for whom it is desirable to avoid certain chemotherapy related adverse events. According to prospective data from randomized trials and systemic review, aromatase inhibitors are more active and better tolerated than tamoxifen.\(^1\)\(^2\)\(^5\) All 3 third generation aromatase inhibitors have similar activity.\(^6\) Current data support a duration of at least 3 months, but do not support the use of concurrent preoperative chemotherapy.\(^5\)\(^7\) The achievement of pCR is not a suitable surrogate endpoint for survival in luminal A type and HER2+ luminal B type breast cancer.\(^8\) Patients with pathologically node-negative T1 or T2 disease with a fully suppressed Ki67 level and persistent estrogen receptor expression after completion of NST have a very low risk of relapse.\(^9\) A small study in premenopausal women comparing ARI plus GnRH with Tam + GnRH demonstrate a superiority for the ARI.\(^10\)

References:

10. XX Lancet Oncol 2011 (Japanese group)
Adjuvant Radiotherapy
Adjuvant Radiotherapy (RT)

➢ Versions 2002 – 2013:
  Souchon / Blohmer / Friedrichs / Göhring /
  / Janni / Möbus / Seegenschmiedt

➢ Version 2014:
  Souchon / Blohmer
Preliminary Note

- The recommendations of the AGO differ in a few statements from those of the Societies of the Radiooncologists (DEGRO and ARO).
- AGO and Radiooncologic Societies are working on a common statement.
Postmastectomy Radiotherapy (PMRT)* to the Chest Wall

- > 3 tumor infiltrated lymph nodes (Lnn.)
- 1–3 tumor infiltrated lymph nodes (Lnn.) (depending on patient‘s age)
- T3 / T4
  - pT3 pN0 R0 (and no additional risk factors)
  - If R0 is impossible to reach (for invasive tumor)
- After neoadjuvant chemotherapy (NACT) based on the initial stage prior to NACT (cN+, cT3/4a-d)
  - In young pts with high risk features
  - Omission of radiotherapy in case of ypT0 ypN0 after NACT
- Additional RT of supra-/infraclav. region in >3+Lnn
- Additional RT of regional lymphatics (i.e. parasternal Lnn.) in high risk/pN0 or pN1-3

* Indications for PMRT and regional RT are independent of adjuvant systemic treatment

<table>
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<tr>
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<th>1a</th>
<th>A</th>
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<td>&gt; 3 tumor infiltrated lymph nodes (Lnn.)</td>
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<td>+</td>
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<tr>
<td>1–3 tumor infiltrated lymph nodes (Lnn.) (depending on patient’s age)</td>
<td>1a</td>
<td>A</td>
<td>++</td>
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<tr>
<td>T3 / T4</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>pT3 pN0 R0 (and no additional risk factors)</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>If R0 is impossible to reach (for invasive tumor)</td>
<td>1a</td>
<td>A</td>
<td>+</td>
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<tr>
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<td>A</td>
<td>+</td>
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<tr>
<td>In young pts with high risk features</td>
<td>2b</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>Omission of radiotherapy in case of ypT0 ypN0 after NACT</td>
<td>3b</td>
<td>C</td>
<td>+/-</td>
</tr>
<tr>
<td>Additional RT of supra-/infraclav. region in &gt;3+Lnn</td>
<td>1a</td>
<td>A</td>
<td>++</td>
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<tr>
<td>Additional RT of regional lymphatics (i.e. parasternal Lnn.) in high risk/pN0 or pN1-3</td>
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<td>B</td>
<td>+/-</td>
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<tr>
<td>* Indications for PMRT and regional RT are independent of adjuvant systemic treatment</td>
<td>1a</td>
<td>A</td>
<td>++</td>
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RT of the Breast after Breast Conserving Surgery (BCS) in Invasive Carcinoma

- Whole breast irradiation (WBI)
  - Standard fractionation
  - Hypofractionation for WBI (+/- sequential boost)
- Boost-irradiation (improves local control)
  - Absolute benefit depending on patient’s age
  - Dose-effect relationship independent of pts.’ age
- Boost-irradiation in node-negative tumors, endocrine responsive, complete resection
- Intraoperative irradiation (IORT/IOERT)
  - As boost-irradiation followed by WBI
  - As sole radiotherapy modality
    - IORT using 50 kV (pT1, N0, G1-2, non-lobular cancer, age >50 y, R0, no extensive DCIS, IORT during first surgery, HR+)
    - IOERT
- Brachytherapy as sole radiotherapy modality
  - Interstitial brachytherapy
  - Intracavity balloon technique

<table>
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<th>LoE / GR</th>
<th>Level of Evidence</th>
<th>Grade</th>
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<tr>
<td>Standard fractionation</td>
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<td>Boost-irradiation (improves local control)</td>
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<tr>
<td>Absolute benefit depending on patient’s age</td>
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<td></td>
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<tr>
<td>Dose-effect relationship independent of pts.’ age</td>
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<td></td>
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<tr>
<td>Intraoperative irradiation (IORT/IOERT)</td>
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<tr>
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<tr>
<td>IORT using 50 kV (pT1, N0, G1-2, non-lobular cancer, age &gt;50 y, R0, no extensive DCIS, IORT during first surgery, HR+)</td>
<td>1b B +*</td>
<td></td>
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</tr>
<tr>
<td>IOERT</td>
<td>1b B -*</td>
<td></td>
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<tr>
<td>Brachytherapy as sole radiotherapy modality</td>
<td>1b B +/-*</td>
<td></td>
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<tr>
<td>Interstitial brachytherapy</td>
<td>1b B +/-*</td>
<td></td>
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<tr>
<td>Intracavity balloon technique</td>
<td>1b C -*</td>
<td></td>
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</tbody>
</table>

° GR is dissent from the updated DEGRO practical guidelines 2013/14

* Study participation recommended
Boost RT after BCS in Invasive Carcinoma

- Improved local tumor control
  - All ages: LRR reduction (7–12%)
  - < 40 years: LRR reduction (10–29%)
  - High grade invasive ductal cancer

- Additional boost RT does not impact survival (10-years data)

- No worsened adverse effects in hypofractionated WBI if boost is given sequentially after WBI

- Hypofractionated WBI + sequential boost
- Hypofractionated WBI + simultaneously integrated boost
- Normofractionated WBI + simultaneously integrated boost
- Intraoperative boost + hypofractionated WBI

---

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Procedure</th>
<th>LoE</th>
<th>Grade</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boost RT after BCS</td>
<td>1b</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Boost RT after BCS</td>
<td>1b</td>
<td>A</td>
<td>+</td>
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<tr>
<td>Boost RT after BCS</td>
<td>1b</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Boost RT after BCS</td>
<td>2b</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Hypofractionated WBI + sequential boost</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Hypofractionated WBI + simultaneously integrated boost</td>
<td>2b</td>
<td>C</td>
<td>+/- *</td>
</tr>
<tr>
<td>Normofractionated WBI + simultaneously integrated boost</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Intraoperative boost + hypofractionated WBI</td>
<td>5</td>
<td>D</td>
<td>-*</td>
</tr>
</tbody>
</table>

* Study participation recommended
Radiotherapy of the Axilla

- Tumor residuals after axillary dissection
  - Oxford / AGO LoE / GR: 2b B ++

- Sentinel node negative
  - Oxford / AGO LoE / GR: 1 B --

- Axillary dissection not indicated
  - (e.g. SLN positive, see surgical chapter)
  - Oxford / AGO LoE / GR: 2a B -

- Extracapsular tumor spread (ECS)
  - Oxford / AGO LoE / GR: 2b B --

- Axillary micrometastases or isolated cells found in regional lymph nodes
  - Oxford / AGO LoE / GR: 3b B --

- Instead of axillary lymph node dissection if SNB is positive°
  - Oxford / AGO LoE / GR: 1 B +/-

° AMAROS trial
Radiotherapy (RT) of Other Locoregional Lymph Node Areas

Supra-/infraclavicular lymphatics irradiation:
- Level III involved
- In case of irradiation of axilla
- pN1a
- pN2a
- (p)N3a-c
- After NACT/NAT (if pretreatment nodal status was clinically positive)*

Axillary irradiation:
- Following axillary clearing of level I + II
- SNB -
- In case of contraindication or patients withdrawal of sufficient axillary clearing

Internal mammaria lymph node irradiation
The respective contribution of RNI by site (SCN vs. IMN) on improved outcome cannot be distinguished

<table>
<thead>
<tr>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
<th>Level III involved</th>
<th>pN1a</th>
<th>pN2a</th>
<th>(p)N3a-c</th>
<th>After NACT/NAT (if pretreatment nodal status was clinically positive)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 B +</td>
<td>3b B +</td>
<td>1 A +/-</td>
<td>1 A ++</td>
<td>1 A ++</td>
<td>3 C +/-</td>
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</tbody>
</table>

*consider risk / benefit relationship of RT

ªAMAROS trial
Radiotherapy of Other Locoregional Lymph Node Areas

- **Internal mammary lymph node irradiation***:
  - N2b, N3b
  - ≥pN1b (involvement of internal mammary lymph node detected by SNB)
  - pN1c–pN3
  - medial / central tumor, pN0 +/- risk factors

*RT of internal mammary lymphatics may provide benefits (OS, DMFS, LRR) in recently published RCTs and a meta-analysis*
## Concomitant Use of Systemic Therapy with Radiotherapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
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<tbody>
<tr>
<td>Trastuzumab concurrent with radiotherapy</td>
<td>2b B +</td>
</tr>
<tr>
<td>Tamoxifen concurrent with radiotherapy</td>
<td>3b C +</td>
</tr>
<tr>
<td>AI (Letrozol) concurrent with radiotherapy</td>
<td>2a B +/-</td>
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</table>
Radiotherapy in the Elderly Patient

Omission of radiotherapy in low risk* patient if adjuvant endocrine treatment (Tam, 5-yrs) takes place

Increase in local recurrence, no influence on OS, decrease in toxicity

* ≥ 70 year of age, pT1, pN0, HR positive, G1-2, HER2-negative, negative resection margin width >1 mm
Adjuvant Radiotherapy (2/11)

Further information and references:

Update January 2014 – Souchon, Blohmer


MAIN TOPICS:

New in 2013:

I. New or updated guidelines 2013 / recommendations mostly regarding evidence based medicine criteria 2013

Alberta Health Services (AHS), Canada, published March 1, 2013: Adjuvant Radiotherapy for Invasive Breast Cancer


National Cancer Institute USA, updated 11/19/2013

Scottish Intercollegiate Guidelines Network (SIGN), updated September 1, 2013: Treatment of primary breast cancer (SIGN CPG 134)

Ia. Unchanged guidelines 2013 / recommendations 2013


Unchanged guidelines (regarding radiooncological issues): In 2013 no update and/or changed guideline recommendations, respectively, regarding RT in primary treatment of breast cancer:

American Society of Clinical Oncology (ASCO); National Health and Medical Research Council (NHMRC Australia)


II New overviews / (updated) metaanalyses / systematic reviews:

New in 2013:


IIa: New overview / metaanalysis / systematic reviews regarding DCIS in 2013:
Updated Meta-analysis:

OBJECTIVES:
To summarise the data from RCTs testing the addition of RT to BCS for treatment of DCIS to determine the balance between the benefits and harms.

SEARCH METHODS:
We searched the Cochrane Breast Cancer Group Specialised Register (2 June 2011), Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2008, Issue 1), MEDLINE (2 June 2011), EMBASE (2 June 2011) and the World Health Organization's International Clinical Trials Registry Platform (WHO ICTRP; 2 June 2011). Reference lists of articles and handsearching of ASCO (2007), ESMO (2002 to 2007), and St Gallen (2005 to 2007) conferences were performed.

SELECTION CRITERIA:
RCTs of breast conserving surgery with and without radiotherapy in women at first diagnosis of pure ductal carcinoma in situ (no invasive disease present).

MAIN RESULTS:
Four RCTs involving 3925 women were identified and included in this review. All were high quality with minimal risk of bias. Three trials compared the addition of RT to BCS. One trial was a two by two factorial design comparing the use of RT and tamoxifen, each separately or together, in which participants were randomised in at least one arm. Analysis confirmed a statistically significant benefit from the addition of radiotherapy on all ipsilateral breast events (hazards ratio (HR) 0.49; 95% CI 0.41 to 0.58, \( P < 0.00001 \)), ipsilateral invasive recurrence (HR 0.50; 95% CI 0.32 to 0.76, \( p=0.001 \)) and ipsilateral DCIS recurrence (HR 0.61; 95% CI 0.39 to 0.95, \( P = 0.03 \)). All the subgroups analysed benefited from addition of radiotherapy. No significant long-term toxicity from radiotherapy was found. No information about short-term toxicity from radiotherapy or quality of life data were reported.

**AUTHORS' CONCLUSIONS:**

This review confirms the benefit of adding radiotherapy to breast conserving surgery for the treatment of all women diagnosed with DCIS. No long-term toxicity from use of radiotherapy was identified.

*Further references regarding DCIS published in 2013:*


CONCLUSIONS: Accelerated partial-breast irradiation using MammoSite seems to provide a safe and cosmetically acceptable outcome; however, the 9.8% IBTR rate with median follow-up of 5.3 years is concerning. Prospective randomized trials are necessary before routine use of APBI for DCIS can be recommended.


CONCLUSION:

At 15 years, almost one in three nonirradiated women developed an LR after LE for DCIS. RT reduced this risk by a factor of 2. Although women who developed an invasive recurrence had worse survival, the long-term prognosis was good and independent of the given treatment.

BACKGROUND:
The impact of close margins in patients with ductal carcinoma-in situ (DCIS) treated with mastectomy is unclear; however, this finding may lead to a recommendation for postmastectomy radiotherapy (PMRT). We sought to determine the incidence and consequences of close margins in patients with DCIS treated with mastectomy.

RESULTS:
Overall, 94 patients (11.7%) had close margins (positive, n = 5; negative but \( \leq 1 \) mm, n = 54; 1.1-2.9 mm, n = 35). Independent risk factors for close margins included multicentricity, pathologic lesion size \( \geq 1.5 \) cm, and necrosis, but not age, use of skin-sparing mastectomy, or immediate reconstruction (p > 0.05). Seven patients received PMRT, and none had a locoregional recurrence (LRR). Among the remaining 803 patients, the 10-year LRR rate was 1% (5.0% for margins \( \leq 1 \) mm, 3.6% for margins 1.1-2.9 mm, and 0.7% for margins \( \geq 3 \) mm [p < 0.001]). The 10-year rate of contralateral breast cancer was 6.4%. On multivariate analysis, close margins was the only independent predictor of LRR (p = 0.005).

CONCLUSIONS:
Close margins occur in a minority of patients undergoing mastectomy for DCIS and is the only independent risk factor for LRR. As the LRR rate in patients with close margins is low and less than the rate of contralateral breast cancer, PMRT is not warranted except for patients with multiple close/positive margins that cannot be surgically excised.


Three meta-analyses and 17 randomised controlled trials have been published in invasive disease and one meta-analysis and four randomised controlled trials for DCIS. Overall, adjuvant radiotherapy provides a 15.7% decrease in local recurrence and 3.8% decrease in 15-year risk of breast cancer death. The key clinico-pathological factors, which enable stratification into high, intermediate or low risk groups include age, oestrogen receptor positivity, use of tamoxifen and extent of surgery. Absolute reductions in 15-year risk of breast cancer death in these three prediction categories are 7.8%, 1.1%, and 0.1% respectively. Adjuvant radiotherapy provides a 60% risk reduction in local recurrence in DCIS with no impact on distal metastases or overall survival. Size, pathological subtype and margins are major risk factors for local recurrence in DCIS.


Conclusions The DCIS Score quantifies IBE risk and invasive IBE risk, complements traditional clinical and pathologic factors, and provides a new clinical tool to improve selecting individualized treatment for women with DCIS who meet the ECOG E5194 criteria.


Special aspect: PMRT in patients with DCIS if R0 is impossible to reach


IIB) invasive breast cancer

1. The impact of age on outcome in early-stage breast cancer

New in 2013:


BACKGROUND:

Randomized clinical trials (RCT) have demonstrated equivalent survival for breast-conserving therapy with radiation (BCT) and mastectomy for early-stage breast cancer. A large, population-based series of women who underwent BCT or mastectomy was studied to observe whether outcomes...
of RCT were achieved in the general population, and whether survival differed by surgery type when stratified by age and hormone receptor (HR) status.

METHODS:
Information was obtained regarding all women diagnosed in the state of California with stage I or II breast cancer between 1990 and 2004, who were treated with either BCT or mastectomy and followed for vital status through December 2009. Cox proportional hazards modeling was used to compare overall survival (OS) and disease-specific survival (DSS) between BCT and mastectomy groups. Analyses were stratified by age group (< 50 years and ≥ 50 years) and tumor HR status.

RESULTS:
A total of 112,154 women fulfilled eligibility criteria. Women undergoing BCT had improved OS and DSS compared with women with mastectomy (adjusted hazard ratio for OS entire cohort = 0.81, 95% confidence interval [CI] = 0.80-0.83). The DSS benefit with BCT compared with mastectomy was greater among women age ≥ 50 with HR-positive disease (hazard ratio = 0.86, 95% CI = 0.82-0.91) than among women age < 50 with HR-negative disease (hazard ratio = 0.88, 95% CI = 0.79-0.98); however, this trend was seen among all subgroups analyzed.

CONCLUSIONS:
Among patients with early stage breast cancer, BCT was associated with improved DSS. These data provide confidence that BCT remains an effective alternative to mastectomy for early stage disease regardless of age or HR status.


RESULTS:
We included 5 randomized clinical trials comprising 3,190 patients. Overall, 39% of the patients were ≥70 years old, and most had hormone receptor-positive T1 tumors without nodal involvement. All patients received adjuvant systemic therapy. Patients who received radiotherapy had a
lower relative risk of locoregional recurrence (pooled odds ratio [OR] 0.36; 95% confidence interval [CI] 0.25-0.50). The 5-year absolute risk was 2.2% (95% CI 1.6-3.1) among patients who received radiotherapy, versus 6.5% (95% CI 5.3-7.9) among patients who did not. The absolute risk difference was 4.3% (95% CI 2.9-5.7), corresponding with a number needed to treat of 24. No differences were observed for distant recurrence or overall survival.

**CONCLUSIONS:**

Although patients who received radiotherapy had a lower relative risk of locoregional recurrence, the absolute risk was low, and overall survival was not affected. We propose that the debate should not only focus on the relative risk but also on the absolute benefit of radiotherapy and the number needed to treat. Both treatment options may be reasonable in clinical practice.

1a. Prognostic factors after BCS

New in 2013:


1b. Postmastectomy-RT (PMRT): Prognostic factors/application/receipt after postmastectomy RT

New in 2013:


**METHODS:**
Between 1995 and 2006, a total of 1,331 patients with T1-T2 tumors and 1 to 3 positive ALN underwent mastectomy. We excluded T3/T4 tumors and neoadjuvant chemotherapy; we analyzed 1,087 patients (924 without PMRT, 163 with PMRT). Chi square testing compared clinicopathologic features between groups. The Kaplan-Meier method and Cox regression analysis examined the association between PMRT and LRR, RFS, and OS. **CONCLUSIONS:**

By using clinicopathologic features, clinicians delivered PMRT to a select group of patients with T1-T2 tumors and 1 to 3 positive ALN, resulting in similarly low rates of 5-year LRR. Among patients not receiving PMRT, age ≤50 years and LVI were associated with increased LRR rates and warrant PMRT consideration.


**CONCLUSIONS:**

Our pooled analysis revealed that PMRT significantly reduces the risk of LRR in patients with T1-T2 tumors with 1-3 positive nodes, and the magnitude of the LRR risk reduction is slightly greater for larger tumors. Our results suggest that PMRT should be considered for patients with T1-T2 tumors with 1-3 positive nodes to decrease the relatively high risk of LRR.

Chen X, Yu X, Chen J, Yang Z, Shao Z, et al. Radiotherapy can improve the disease-free survival rate in triple-negative breast cancer patients with T1-T2 disease and one to three positive lymph nodes after mastectomy. Oncologist 2013;18:141-147


Further references:


2. Radiation therapy of regional lymphatics

New in 2013:


Due to the heterogeneity of lymph node examination and the conflicting results existing for the same classification of lymph node ratio (LNR), it is necessary to conduct a meta-analysis to evaluate the prognostic effects of different LNRs on breast cancer. PubMed, EMBASE, and ISI Web of Knowledge were searched to find all published cohort studies that evaluated the prognostic value of different LNRs on breast cancer. The outcomes were overall survival (OS), disease-free survival (DFS), breast cause-special survival (BCCS), mortality, locoregional recurrence (LRR), and distant metastasis. Data was analyzed using comprehensive meta-analysis software version 2.0, and 23 studies were included. The available evidence showed that LNR was a prognostic predictor for breast cancer, especially for clinically node-positive breast cancer, but the available evidence could not judge which cutoff point is the most reliable. Meanwhile, the cutoff values 0.2 and 0.65 could be suitable to predict breast cancer OS, DFS, BCCS, and mortality.


Abstract

Sentinel node biopsy (SN) in breast cancer treatment was introduced in the mid-1990s in order to be able to stage patients before decision of definitive surgery. Since then, both the pathological examinations of the SN and the systemic adjuvant treatment have improved and cause new challenges in the correct decision making regarding whether or not to radically treat the axilla in case of a positive SN. In SN positive patients, current St. Gallen guidelines support no completion ALND (axillary lymph node dissection) in clinically node-negative patients with 1-2 macrometastatic sentinel nodes operated with breast conservation and receiving tangential field adjuvant radiotherapy (RT). ALND is being questioned due to increased morbidity compared with SN biopsy alone, and to limited long term benefit on disease free survival in selected patients. An alternative to ALND is treating the axilla with nodal RT although this treatment is mostly used as adjuvant treatment after ALND in high risk patients. Few studies have investigated the benefit of nodal RT compared to ALND, and no consensus has yet been reached. Clinical decision making regarding treating the axilla should be based on relevant data, and in this review studies aiming at deciding whether or not and how the axilla should be treated in SN positive patients will be discussed. Furthermore treatment choice will be discussed, since besides ALND, both breast irradiation and nodal irradiation might cure residual disease after SN. Also the issue of improved systemic adjuvant treatment will be discussed in relation to eventually no regional axillary treatment.


3. Radiation therapy – late normal tissue complications and long-term cosmesis; IMRT vs. standard RT using wedged tangential fields: Boost RT

New in 2013:

Meta-analysis:


Further references in 2013:


There are few randomized controlled trial data to confirm that improved homogeneity with simple intensity-modulated radiotherapy (IMRT) decreases late breast tissue toxicity. The Cambridge Breast IMRT trial investigated this hypothesis, and the 5-year results are reported.

CONCLUSION:

Improved dose homogeneity with simple IMRT translates into superior overall cosmesis and reduces the risk of skin telangiectasia. These results are practice changing and should encourage centers still using two-dimensional RT to implement simple breast IMRT.

See also comment on this issue: Kavanagh BD, Rabinovitch R, Mohideen N. Improved cosmesis in early breast cancer using conformal radiotherapy. J Clin Oncol 2013;31:4483-4485


The dose-volume effect of radiation therapy on breast tissue is poorly understood. We estimate NTCP parameters for breast fibrosis after external beam radiotherapy.
MATERIALS AND METHODS:
We pooled individual patient data of 5856 patients from 2 trials including whole breast irradiation followed with or without a boost. A two-compartment dose volume histogram model was used with boost volume as the first compartment and the remaining breast volume as second compartment. Results from START-pilot trial (n=1410) were used to test the predicted models.

CONCLUSIONS:
This large multi-centre pooled study suggests that the effect of volume parameter is small and the maximum RT dose is the most important parameter to influence breast fibrosis. A small value of volume parameter 'n' does not fit with the hypothesis that breast tissue is a parallel organ. However, this may reflect limitations in our current scoring system of fibrosis.


The meta-analysis suggests that XRCC1 R399Q polymorphism was significantly associated with increased risk of normal tissue injury after radiotherapy in breast cancer patients, and XRCC1 R399Q polymorphism is a genetic marker of normal tissue injury after radiotherapy in breast cancer patients.

4. Cardiac toxicity in breast cancer patients treated with radiation therapy (PMRT or following BCS)

New in 2013:


5. Sequencing RT and chemotherapy

Fowble B. Local-regional management issues for the radiation oncologist in the neoadjuvant chemotherapy setting. SABCS 2013, abstr.


Radiation therapy should follow chemotherapy when chemotherapy indicated


2012:


6. Radiation therapy after breast-conserving surgery

6.1 New LoE for special topics which might impact daily clinical practice: Hypofractionating, APBI including IORT

New in 2013:

Classification system for identifying women at risk for altered partial breast irradiation recommendations after breast magnetic resonance imaging


6.2. Hypofractionating

**Hypofractionated radiotherapy:** Should hypofractionating be the new standard for radiation therapy following BCS?

New in 2013:


See also comment: Haffty BG, Buchholz TA: Hypofractionated breast radiation: preferred standard of care? Lancet Oncol 2013;14:1032-33

6.3. Short course RT with simultaneous integrated boost (SIB)-RT

New in 2013:


6.4. Indications, limitations and cautions regarding APBI including IORT

New in 2013:


6.5. Technical aspects / new techniques regarding delivery of RT, in particular delivery APBI / IMRT, and toxicity regarding simultaneous integrated boost radiotherapy (SIB)

New in 2013:


There are few randomized controlled trial data to confirm that improved homogeneity with simple intensity-modulated radiotherapy (IMRT) decreases late breast tissue toxicity. The Cambridge Breast IMRT trial investigated this hypothesis, and the 5-year results are reported.

CONCLUSION:

Improved dose homogeneity with simple IMRT translates into superior overall cosmesis and reduces the risk of skin telangiectasia. These results are practice changing and should encourage centers still using two-dimensional RT to implement simple breast IMRT.

See also comment on this issue: Kavanagh BD, Rabinovitch R, Mohideen N. Improved cosmesis in early breast cancer using conformal radiotherapy. J Clin Oncol 2013;31:4483-4485


Further references:


7. Long-term cosmesis WBI +/- boost

New in 2013:


8. APBI by use of IORT / interstitial brachytherapy / external beam irradiation administered as sole radiation therapy modality immediately after breast conserving surgery

New in 2013:


9. Boost-RT to the tumor (region) prior versus after BCS:

New in 2013:


10. Randomized clinical trials in breast cancer regarding radiooncological issues


NORA-Survey: “International survey of nodal radiotherapy in the era of personalized surgery of the axilla for early breast cancer” (Belkacemi et al.)


Williams LJ, Kunkler IH, King CC. A randomised controlled trial of post-operative radiotherapy following breast-conserving surgery in a minimum-risk population. Quality of life at 5 years in the PRIME trial. Health Technol Assess 2011:i-xi, 1-57

10.1. Randomized clinical trials in breast cancer regarding APBI:


Phase III randomized clinical trials with 3D-EBCRT (external beam conformal radiotherapy) as experimental arm:


IRMA (Innovazioni nella Radioterapia della Mammella). Launched 2006

GEC-ESTRO-trial

IMPORT-LOW (Intensity Modulated and Partial Organ RadioTherapy)-trial launched in 2006 as an extension to the START trials.


10.2. Ongoing RCT, recruitment ended, further, interims or (more) mature results awaited in 2014

MRC/EORTC (BIG 2-04) SUPREMO Trial: Elucidating the role of chest wall irradiation in 'intermediate-risk' breast cancer: the MRC/EORTC SUPREMO trial.

Kunkler IH, Canney P, van Tienhoven G, Russell NS; MRC/EORTC (BIG 2-04) SUPREMO Trial Management Group.


10.3. Ongoing Phase III RCT of hypofractionated WBI comparing sequential tumor bed boost to concurrent boost (still accruing pts.)

Freedman et al. Radiother Oncol 2013;106:15-20

RTOG 1005

IMPORT HIGH (Intensity Modulation and Partial Organ Radiation Therapy)

IMRT MC2

10.4. Radiotherapy in patients with pathologic response (e.g. ypT0 ypN0) after preoperative chemotherapy and mastectomy or BCS:

NCT01279304: Maastricht Radiation Oncology — register trial: Radiotherapy After Primary Chemotherapy for Breast Cancer (RAPCHEM) trial (NCT01279304).

10.5. Preoperative radiotherapy in patients with progression during or incomplete neoadjuvant chemotherapy:

NCT01618357: Sidney Kimmel Comprehensive Cancer Center: Pre-Operative Radiation With Incomplete Neo-Adjuvant Chemotherapy for Breast Cancer
10.6. DCIS: trials

NSABP B-43: A phase III clinical trial to compare trastuzumab (T) given concurrently with radiation therapy (RT) to RT alone for women with HER2+ DCIS resected by lumpectomy (Lx). Cobleigh MA, Anderson SJ, Julian TB, et al. SABCS 2012; OT1-2-01

RTOG 9804 –DCIS:

McCormick B, Moughan J, Hudis C, Kuerer H et al. Low-risk breast ductal carcinoma in situ (DCIS): results from the Radiation Therapy Oncology Group 9804 Phase 3 Trial. Int J Radiat Oncol Biol Phys 2012;84(5) Suppl., S5, abstract 11: In this “good risk” subset of DCIS, the LF rate was decreased significantly with the addition of RT. Longer follow-up is planned, as late failures continue to occur.

11. Adjuvant Radiotherapy – actual topics and areas of incertainty

Questions – areas of controversies - ongoing clinical trials - what we (still) need to know

• Subgroups suitable for quitclaim any RT for DCIS or invasive carcinoma?
  • DCIS/invasive cancer: no subgroup even with pure DCIS and low-risk criteria that does not benefit from RT in terms of decreased local recurrence: ongoing trials, confirming data in 2013; no significant long-term toxicity from RT; Boost-RT: benefit of additional boost radiotherapy for invasive breast cancer has been demonstrated in RCT with most benefit in younger patients. The role of boost radiotherapy in patients with pure DCIS is now being investigated in ongoing RCT and might be substantial for young patients.
  • Pure DCIS: newest data from RCT confirm the benefit of adding radiotherapy to breast conserving surgery for the treatment of all women diagnosed with DCIS. No long-term toxicity from use of radiotherapy was identified. However, the impact of RT is limited to local control by decreasing recurrence rate. Up to 15 year of follow-up, RCT which evaluated the role of additional RT failed to demonstrate overall survival benefit. Ongoing trials; role of molecular/genetic biomarkers has to be defined
  • DCIS: impact of RT by the fact that recent data not showing survival benefit?: ongoing trials; role of molecular/genetic biomarkers

• Subgroups suitable for (accelerated) partial breast irradiation / IORT after BCS?
  • Comparative effectiveness of WBI vs. PBI or APBI? For which subgroup equal effectiveness is considered?: ongoing trials
  • Used as definitive radiotherapy without external WBI? Limited to interstitial PBI (GEC-ESTRO)? Still an open question

• Fraction size: hypofractionation (hf) vs standard fractionation (nf) regimens?
• Comparative effectiveness of fractionation regimens? Hf equivalent and also accepted to be a “new” standard? For which subgroup?: still a matter of debate and controversies regarding selection criteria identifying patients as well as subgroups of patients, for whom it might be more or equally effective and safe compared with normofractionated schedules. Ongoing trials!

RT fraction size, esp. (accelerated) hypofractionation: UK START-Trials demonstrated no inferiority to WBI after 10-year follow-up (10 yrs f/u 2013).

However, some scientific boards consider hyperfractionated RT to be equivalent to normofractionated RT recommending hf-RT as optional alternative in some guidelines. Even more, hypofractionation is considered to be “the new standard” in some countries. If hypofractionated RT is the chosen schedule, single fraction dose of 2.66 Gy up to a total dose of 39-42 Gy in 15 or 16 fractions is recommended in international guidelines. See also critical remarks regarding hypofractionation in the updated DEGRO Practice Guidelines 2013 (references see: I. in front of this slice!)

• Hypofractionation even, when boost RT is indicated? Majority of patients in RCTs (e.g. START-trials) received sequential boost-RT after hf-RT!

  • Post-mastectomy irradiation (PMRT) of the thoracic wall:

    • Risk factors? Who are at risk for developing relapse, particularly the “intermediate risk” subgroup (RR: 10-20%; T1-2 and N+(1-3), G3, vascular invasion, lobular subtype; >T2 N0; pT3, N0; N+(1-3), etc) ? New data from RCTs confirm benefits from RT for “intermediate risk” pts.

    • survival benefit even for pT1-2 pN+(0-3) after mastectomy (LoE 2b); documented for patients after BCS (LoE 1a):

Postmastectomy radiotherapy (PMRT) in „intermediate risk“-patients - further informations:

Effects of adjuvant RT on cardiovascular mortality differ according to primary tumor location in node-negative patients

Effects of adjuvant radiotherapy on mortality differ according to primary tumor location in node-positive patients:

Lymphonodal micrometastasis or isolated tumor cells are associated with poorer survival compared to pN0 disease: new data show: LRR appears similar for women with pN0(i+) compared to their pN0-counterparts (but keep in mind: limitation of small available sample size of pN0(i+)-patients).

pN0(i+) vs pN0 pts. outcome: Outcome (OS, LRR) of pN0(i+) pts. appears similar to matched pN0 counterparts.

  • In patients with positive SNB but no axilla dissection? New data from RCTs: pN0-patients with central/medial tumor benefit from PMRT

  • Positive margins but no further surgery? No new data from RCTs
After pathological (complete?) response to preoperative chemotherapy (NACT)? ongoing prospective register study: RAPCHEM


- **Boost RT to the tumor bed following BCS?**
  - No subgroup that does not benefit from boost RT in terms of decreased local recurrence. Boost-RT for young pts with DCIS ?: ongoing trials; up to now, no mature data of RCTs yet available
  - Simultaneously integrated boost RT (SIB): ongoing RCT; no mature data from RCTs; see statement of the DEGRO/ÖGRO Expert Panel 2013
  - Should SIB replace sequential PBI boost in the context of WBI?: ongoing RCTs; no mature data from RCTs

- **Which locoregional lymphatics have to be irradiated?**
  - Post surgery: which nodal areas? Axilla, periclavicular, mammaria interna lymphatics? New data from RCTs and one new meta-analysis show some benefits for distinguished subgroups of patients
  - Post PST, even, if primary tumor is responsive to primary systemic treatment: no mature data from RCT; ongoing trials: NCT01279304: RAPCHEM

- **Impact of advanced technologies?**
  - External beam conformal RT techniques: 3D-CRT, IMRT, Tomotherapy, VMAT, Protons, IGRT, SIB
  - Contouring guidelines for RT: RTOG Breast Cancer Atlas; national guidelines+contouring atlas by the Danish Breast Cancer Cooperative Group 2013

  *Contouring guidelines for RT: RTOG Breast Cancer Atlas; national guidelines+contouring atlas by the Danish Breast Cancer Cooperative Group:*


  - **New techniques used for APBI approaches:**

External beam conformal radiation therapy techniques:
a) 3 dimensional conformal radiation therapy (3D-CRT)

The most widely used 3D-CRT approach uses multiple (three to five) tangentially static positioned non-coplanar beams with static photons, and/or electrons fields. The tumor bed is defined by the computed tomography visualized seroma cavity, postoperative changes, and surgical clips, when available. The clinical target volume (CTV) is defined as the tumor bed with a 1.5 cm margin limited by 0.5 cm from the skin and chest wall. The planning tumor volume (PTV) is defined as the CTV with a 1.0 cm uniform three-dimensional expansions. This expansion accounts for potential breathing and setup errors and hence this approach might deliver higher doses to normal breast tissue than IMRT–APBI. This technique was adopted for use as one of the allowed treatment modalities for patients randomized to APBI in the National Surgical Adjuvant Breast and Bowel Project B-39/Radiation Therapy Oncology group (NSABP/RTOG) 0413 phase III trial. The prescription dose used for NSABP/RTOG protocol is 3.85 Gy twice daily (separated by at least 6 h) to a total dose of 38.5 Gy delivered within 1 week [Njeh et al. 2012].

b) Intensity modulated radiation therapy (IMRT):

Intensity modulated radiation therapy (IMRT) is a form of external beam radiation therapy (EBRT) that uses complex structure-based planning techniques and variable intensity beam fluencies to optimize dose delivery.

The major value of IMRT for breast radiotherapy is reduction of dose inhomogeneity within the target volume. A secondary advantage is the reduction of high dose irradiation to some normal tissues and organ at risk (OAR) such as the heart and ipsilateral lung. These have been supported by several studies comparing IMRT with standard 3D tangential field radiation therapy for breast cancer. However, the multiple beams in IMRT could results in a substantial volume of normal tissue receiving a low or moderate radiation dose (i.e. increase in integral dose) [Njeh et al. 2012].

c) Tomotherapy:

Helical tomotherapy (“slice therapy”) combines helical intensity modulated (IM) delivery with an integrated image guided (IG) system using machine specifically designed for IMRT delivery. In tomotherapy the patient moves through the bore of the gantry simultaneously with gantry rotation. Radiation is delivered by a narrow 6 MV beam rotating around the patient analogous to computed tomography. Online imaging is achieved by using megavoltage computed tomography (MVCT) scans acquired with the linear accelerator. Because of the integration of IMRT and image guided radiation therapy (IGRT), tomotherapy has potential for breast treatment and especially APBI [Njeh et al. 2012].

d) Volumetric modulated arc therapy (VMAT) or intensity-modulated arc therapy (IMAT):

Volumetric modulated arc therapy (VMAT) also known as, intensity-modulated arc therapy (IMAT), delivers highly conformal dose distributions by combining gantry rotation and dynamic multileaf collimation. Instead of delivering intensity-modulated beams with fixed gantry angles, VMAT delivers optimized dose distributions by rotating the radiation beam around the patient. During delivery, the field shape, which is formed by a multileaf collimator (MLC), changes continuously as determined by the treatment plan. Intensity distributions at all angles around the patient are achieved with multiple overlapping arcs, with each arc having a different set of field apertures. The weight or the total monitor units (MUs) delivered in each arc, are typically different. VMAT uses intensity-modulated fan beams rotating around the patient, delivering the treatment slice
by slice. As with tomotherapy, VMAT combines intensity modulation and rotational delivery. Recently several VMAT delivery techniques have been developed for clinical applications, including RapidArc (Varian, CA) and VMAT (Elekta AB, Stockholm, Sweden).

Compared to a conventional 3D-CRT technique VMAT is considered to be to be more efficient, rendering equivalent or better dose conformity, delivers lower doses to the ipsilateral lung and breast [Njeh et al. 2012].

Mandatory: Improvement of risk stratification of patients in order to select individualized optimal radiooncological treatment for each individual

12. Prognostic outcome of local/regional recurrence in breast cancer pts. treated by BCS + RT as their first site of failure:

Shenouda M, Sadek BT, Abi Raad RF, Goldberg SI, et al. Prognostic outcomes of local-regional recurrence in breast cancer patients treated by breast-conservation treatment. Int J Radiat Oncol Biol Phys 2012;84(5) Suppl., S36, abstract 89: With a long follow-up, patients who develop LRR as first event have a 56% 10-year overall survival. The interval between diagnosis and breast failure, multiple LRR, type of recurrence and surgical treatment were significantly prognostic factors for the overall survival.


13. Excess mortality for long-term survivors of breast cancer:

New in 2013/2014:


BACKGROUND:

Coinciding with the relatively good and improving prognosis for patients with stage I-III breast cancer, late recurrences, new primary tumours and late side-effects of treatment may occur. We gained insight into prognosis for long-term breast cancer survivors.

PATIENTS AND METHODS:

Data on all 205 827 females aged 15-89 diagnosed with stage I-III breast cancer during 1989-2008 were derived from the Netherlands Cancer Registry. Conditional 5-year relative survival was calculated for every subsequent year from diagnosis up to 15 years.

RESULTS:
For stage I, conditional 5-year relative survival remained ~95% up to 15 years after diagnosis (a stable 5-year excess mortality rate of 5%). For stage II, excess mortality remained 10% for those aged 15-44 or 45-59 and 15% for those aged 60-74. For stage III, excess mortality decreased from 35% at diagnosis to 10% at 15 years for those aged 15-44 or 45-59, and from ~40% to 30% for those aged ≥60.

CONCLUSIONS:

Patients with stage I or II breast cancer had a (very) good long-term prognosis, albeit exhibiting a small but significant excess mortality at least up to 15 years after diagnosis. Improvements albeit from a lower level were mainly seen for patients who had been diagnosed with stage III disease. Caregivers can use this information to better inform (especially disease-free) cancer survivors about their actual prognosis.

14. Secondary neoplasia following adjuvant radiotherapy for breast cancer:

New in 2013:


Allgemeine Aspekte adjuvanter RT:


PURPOSE:

Population-based studies suggest underuse of radiation therapy, especially after mastectomy. Because radiation oncology is a referral-based specialty, knowledge and attitudes of upstream providers, specifically surgeons, may influence patients' decisions regarding radiation, including whether it is even considered. Therefore, we sought to evaluate surgeons' knowledge of pertinent risk information, their patterns of referral, and the correlates of surgeon knowledge and referral in specific breast cancer scenarios.

METHODS AND MATERIALS:

We surveyed a national sample of 750 surgeons, with a 67% response rate. We analyzed responses from those who had seen at least 1 breast cancer patient in the past year (n=403), using logistic regression models to identify correlates of knowledge and appropriate referral.

RESULTS:
Overall, 87% of respondents were general surgeons, and 64% saw >10 breast cancer patients in the previous year. In a scenario involving a 45-year-old undergoing lumpectomy, only 45% correctly estimated the risk of locoregional recurrence without radiation therapy, but 97% would refer to radiation oncology. In a patient with 2 of 20 nodes involved after mastectomy, 30% would neither refer to radiation oncology nor provide accurate information to make radiation decisions. In a patient with 4 of 20 nodes involved after mastectomy, 9% would not refer to radiation oncology. Fewer than half knew that the Oxford meta-analysis revealed a survival benefit from radiation therapy after lumpectomy (45%) or mastectomy (32%). Only 16% passed a 7-item knowledge test; female and more-experienced surgeons were more likely to pass. Factors significantly associated with appropriate referral to radiation oncology included breast cancer volume, tumor board participation, and knowledge.

CONCLUSIONS:

Many surgeons have inadequate knowledge regarding the role of radiation in breast cancer management, especially after mastectomy. Targeted educational interventions may improve the quality of care.

Do radiation therapy is needed even in small invasive breast cancers and DCIS following BCS?


Who should not undergo breast conservation? In all patients where radiotherapy cannot be given.


Abstract

Optimal local control is one of the three main aims of breast cancer treatment (next to optimal regional control and reducing the risk of distant relapses by adequate systemic treatments). To this end, many women desire breast conservation provided local control is comparable to that of ablative procedures, the cosmetic outcome is good and side effects of treatment are limited. To achieve this delicate balance the following should be part of the information to the patient with an operable breast cancer: Patients should have an open discussion with there care providers to enable a shared decision: this will lead to less anxiety and stress with the best satisfaction and recovery. The possibility of breast conservation should always be explored. Even with equal local control and survival outlook, quite a minority (about 20%) of patients opt for ablative procedures (with or without breast reconstruction). Higher risk of local relapse (i.e. persistent cancer growth in the breast) is associated with higher risk of distant disease and subsequent risk of dying of breast cancer. Rough estimates indicate that for every four local relapses one patient may die from breast cancer due to persistent disease. This estimate may vary substantially with the type of cancers (see dr. Morrow), age at diagnosis, application and duration of systemic treatments. To limit the negative effect on overall survival through local relapses, it is generally accepted that for early breast cancer local relapse rates should be within the limit of 1% per year, or within 10% at 10 years. Current population based overviews and hospital based studies show that the risk of local relapse after breast conservations are very well below this limit, being around 2-3% at 5 years. There is no absolute risk threshold of local relapse incidence above which breast conservation is absolutely contra indicated: this will remain an individual
decision. Oncoplastic procedures should widely be available to adjust to the width of the local excision and to improve cosmetic outcome. In larger cancers, the option of neo-adjuvant chemotherapy must be considered: about one-third of "mastectomy candidates" can be conversed to an oncologically safe breast conservation. The most important independent risk factors for a breast relapse are: more than focally incomplete margins (roughly 2 times increased risk), young age (<35 years, 2 times increased risk) no radiotherapy (2-4 times increased risk). These risk factors again may also be influenced by the biological type of breast cancer. Combination of risk factors should be added: e.g. young women (<35 years) who had breast conservation for DCIS without radiotherapy may face 15 years breast relapse rate of over 40%. In aggregate, in the following clinical situations the increased risk of breast relapse should be extensively discussed with the patient and breast conservation should be executed with caution: Very young women (<35 years) Extensive DCIS (heralded by extensive microcalcifications) mounting up to one quarter of the breast, particularly in women under 40 years of age. More than focally incomplete resection of an invasive or in situ cancer. Radiotherapy cannot be given. The following factors should, as it stands, not be considered as a contra indication for breast conservation: multi-focal breast cancer, multi-centric breast cancer, the location of the cancer in the breast (including retro areola location), vascular invasion and lobular histology. All with the provision that by the breast conserving surgery complete margins a good cosmetic outcome should be achieved.

For further informations on radiooncological issues:


Treatment of breast cancer ideally requires a multidisciplinary approach. For most patients with invasive breast cancer, the recommended treatment is surgical resection of the primary tumor with assessment of axillary lymph nodes; adjuvant systemic treatment with chemotherapy, endocrine and/or targeted therapy, or combination of all, and adjuvant radiation therapy.

The equivalence of breast conserving therapy (BCT) to mastectomy in the treatment of women with early-stage breast cancer has been demonstrated in several phase III trials with over 25 years of follow-up. Despite the undisputed efficacy of this treatment approach, recent investigations have explored methods to either reduce the overall time, inconvenience or toxicity of its application. These approaches have included (1) accelerating the dose delivery scheme, (2) reducing the treatment target to less than whole breast, or (3) identifying subgroups of women in which adjuvant radiation therapy (RT) following lumpectomy can be safely omitted Accelerated partial breast irradiation (APBI) has been investigated as a possible option that incorporates both a decrease in the overall treatment time and a reduction in the amount of normal tissue irradiated.

Radiation kills cells largely through the generation of free radicals, which deposit large amounts of energy that cause single- and double-strand breaks in the cell's DNA. The aim and clinical goal of radiation treatment is to eradicate tumor cells selectively, without injuring normal tissue in irradiated fields. In general, tumors are less able to repair DNA damage than are normal tissues and more frequently are in radiosensitive cell-cycle phases, such as mitosis.
Division of the radiation dose into a number of treatment fractions, i.e. fractionated radiation therapy, provides two important biologic advantages: it allows DNA repair to take place within the normal tissues and allows proliferating tumor cells to redistribute through the cell cycle and move into the more radiosensitive phase.

Indications for postmastectomy radiotherapy (PMRT) and regional radiotherapy are independent from the amount of surgery and the administration of adjuvant systemic treatments (LoE 1a).

Radiation therapy continues to provide a significant benefit, both statistically and clinically: Radiation therapy has been shown to minimize the risk of local recurrence after mastectomy and lumpectomy in a breast conserving treatment concept (in-field recurrences) by 70% (LoE 1a), respectively. Regarding to data of the last meta-analysis of the EBCTCG, for every 4 locoregional recurrences prevented at 5 years, 1 life at 15 years will be saved (LoE 1a). Postmastectomy radiotherapy (PMRT) and regional RT is a standard from tumour stage pT3 and/or pN2a on (LoE 1a). There are increasing data available to advise RT also for patients from pN1a stage on (LoE 1a). The target volumes are under discussion, but quite some arguments exist for comprehensive locoregional RT. There exists, after proper surgery, no indication for irradiation of the axilla (LoE 2a).

Medial tumor location is associated with poorer prognosis. However, the survival outcome of local-regional treatments seems to be not affected by tumor location, arguing that tumor location is not a sufficient indication to modify local-regional treatments in node-negative patients. Local-regional treatment should be based on tumor characteristics and not tumor location. Use of radiation therapy (RT) decreased the 15-year risk of dying from breast cancer from 31% to 26% for patients with negative lymph nodes and from 55% to 48% for patients with positive lymph nodes (LoE 1a).

Rates of local tumour relapse after breast conservation treatment in women with early breast cancer are falling. Explanations for this decline are advances in breast cancer management and aging of the breast cancer population. Breast surgery has become more standardised following publication of practice guidelines and is mostly carried out by specialist surgeons. Systemic therapies (endocrine therapy and chemotherapy) are now more effective and are recommended to a higher proportion of patients than ever before. Significant technical advances in radiotherapy have also been achieved as well as radiotherapy techniques have also improved: CT-based treatment planning, electronic portal imaging devices etc. have improved accuracy and reproducibility of patient set-up, definition and localisation of clinical target volume as well as boost volume, homogeneity of dose distribution and precision of set-up verification. However, due to the lack of data from prospective trials or cohort studies, it is impossible to quantify or judge their impact on local tumor control. Nevertheless, the contributions of each factor are difficult to quantify precisely, but all are likely to be relevant.

Further information (II):

Now, the evidence is strong for survival benefits for both postmastectomy radiation therapy and irradiation after breast conserving surgery. Data from recently published metaanalyses demonstrate conclusively the impact of radiation therapy on local tumor control. Now these data are emerging that even local as well as locoregional relapse has an adverse impact not only for quality of life but also for survival, and substantially affect 15-year
overall mortality. Avoidance of a local recurrence in the remaining breast after BCS as well as avoidance of a locoregional relapse (eg. the thoracic wall or regional lymph nodes) after mastectomy are of comparable relevance to 15-year breast cancer mortality.

New analyses from the SEER and the UZ Brussel data bases provide new evidence for a survival benefit even for the subgroup of pT1-2 pN+ (0-3) breast cancer patients which is in the same range compared with the subgroup of patients with 4 or more pN+: The 15-year OS in the subgroup with ME and ≤3 pN+ nodes was 57.0% and 46.6% (p = 0.0004) with RT (UZ Brussel) and without RT (SEER), respectively. For BCS and ≤3 pN+, the same significant difference in OS at 15 years was seen: 63.8% after RT (UZ Brussel) and 60.4% without RT (SEER; p = 0.0029) (Voordeckers M et al. Strahlenther Onkol 2009; 185:656-662).

Even more, newest meta-analyses published in 2013 confirm previous results of an update of the EBCTCG Meta-analysis, as presented by S. Darby in December 2009 at the 32nd SABCS, substantially underlining the role of radiation therapy for both locoregional control as well as survival in different subgroups of patients:


Preliminary Note (3/11)

No further information

No references
Postmastectomy Radiotherapy (PMRT) to the Chest Wall (4/11)

Further information and references:

Empfehlungen zur Indikationsstellung zur Postmastektomie-Radiotherapie der Thoraxwand:

New in 2013:

Meta-analyses:


Updated recommendations regarding indication for PMRT of the chest wall even in “intermediate risk” patients:

Alberta Health Services (AHS), Canada, published March 1, 2013: Adjuvant Radiotherapy for Invasive Breast Cancer


National Cancer Institute USA, updated 11/19/2013

Scottish Intercollegiate Guidelines Network (SIGN), updated September 1, 2013: Treatment of primary breast cancer (SIGN CPG 134)

**Recommendations for additional RT of regional lymphatics for patients with 1-3 positive lymph nodes (intermediate risk) in updated guidelines:**

Alberta Health Services (AHS), Canada, published March 1, 2013: Adjuvant Radiotherapy for Invasive Breast Cancer: “with RNI”


Cardoso F, Loibl S, Pagani O, et al.; European Society of Breast Cancer Specialists. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. Eur J Cancer 2012;48:3355-77: “Young patients should be informed the high local recurrence risk if radiation therapy is avoided….Internal mammary chain irradiation should be discussed on the basis of clinical, histopathological and radiological findings in the multidisciplinary team (LoE expert opinion)”

Scottish Intercollegiate Guidelines Network (SIGN), updated September 1, 2013: Treatment of primary breast cancer (SIGN CPG 134): strongly recommendation for participation in ongoing clinical trials (SUPREMO). – RT of supraclavicular fossa: “No RCTs were identified to guide the use of supraclavicular fossa radiotherapy after axillary clearance in patients with positive lymph node involvement….Participation in clinical trials should be encouraged”.


Further references:

National Institute for Health and Clinical Excellence UK– (NICE UK) Guidelines:


In node positive patients, the benefit in terms of absolute overall survival is observed in all sub-groups of the meta-analysis. Thus, RT indication is not a subject of debate.

Conversely, the debate is important in sub-groups of N− patients. The rationale for indicating PMRT in N− patients is generally based on the presence of local recurrence risk factors. In the Danish trials, the independent factors influencing survival were: large tumour size, high number of involved nodes +/- extracapsular extent, nodal relapse (supra- or sub-clavicular), less than 2 years interval before the first relapse.

Regarding the updated guidelines for clinical practice from the French expert review board (Belkacemi et al. 2010), the recommendations in N− patients were based on the existence of one or more risk factors for local recurrence such as age (less than 40 years), tumour size (≥pT3), grade III, multifocality, lymphovascular and/or muscular and/or cutaneous invasion. This is in accordance with the updated Guideline recommendations of the expert group of the German Society of Radiation Oncology (DEGRO) (Wenz et al. 2014, in press) and is not particularly specified in other recently updated guidelines (NCCN 2011; NZGG 2009; Belgian KCE 2013) indicating RT in cases of tumor size >5 cm and close margins (<1 mm) (NCCN 2013).

For the particular cases of T3N0, there is a lack of information and conflicting data. For example, in the USA the majority of practising radiation oncologists recommends PMRT for these tumours. In the study from Taghian et al. (2006) the 10-year recurrence rates were different according to systemic therapy administration (7%) or not (16%). The authors concluded that, in the context of systemic therapy, isolated recurrence rates as first events is lower then 6%. This rate is low enough that the benefit from routine PMRT might not outweigh its potential adverse effects. Controversely as for intermediate risk patients (with 1–3 nodes positive), in whom it has to be demonstrated PMRT provide statistically significant benefit, the lack of randomized trials in T3N0, cannot allow a systematic omission of PMRT.

Further information:

Meta-analyses and randomised clinical controlled trials (RCTs) of locoregional postmastectomy radiation therapy (PMRT) have consistently demonstrated that PMRT reduces the risk of locoregional failure to the chest wall and regional lymphatic drainage sites, including the ipsilateral axillary, supraclavicular and infraclavicular and internal mammary nodes by approximately two-thirds (level I evidence).

In patients with large tumors (pT3 or pT4), R1-/R2-status of tumor resection and four or more involved lymph nodes (pN2), local and locoregional failure (LRF) as first event of disease recurrence remains a clinically significant problem. Regarding these factors, the beneficial worth of PMRT is sufficiently documented and based on high levels of evidence (level 1 evidence) (Jagsi and Pierce 2009). Even patients with an initial T3 or T4 tumor who are treated with primary systemic chemotherapy (i.e. preoperative or neoadjuvant chemotherapy) and subsequently achieve a pCR, still have a high rate of local-regional recurrences and profit from postmastectomy irradiation.
There is little known about the impact of other parameters, e.g. age, influence of EIC and other histopathological factors as well as combination effects. Although PMRT is currently recommended for patients with four or more LN+, there is increasing evidence PMRT may also improve survival rate, which seems to be in the same range for patients with one to three positive lymph nodes or for patients with four or more positive lymph nodes. However, the updated results of the meta-analysis 2006 of the EBCTCG are still unpublished.

For the subgroup of patients with high risk criteria for local recurrence or systemic progression (eg. axillary lymph node-positive premenopausal patients) treated by mastectomy and adjuvant chemotherapy (CMF), PMRT statistically significant reduces isolated locoregional recurrence, distant recurrence, cancer specific deaths, and overall mortality based on the long-term results encompassing a 20-year follow-up. For these patients breast cancer survival is improved with locoregional radiation therapy (Ragaz et al. 2005).

Randomized trials consistantly provide evidence for improved outcomes with postmastectomy radiotherapy (PMRT) in high-risk patients (LoE 1a), e.g. node-positive patients with locally advanced breast cancer. The largest absolute reduction in 5-year local relapse probability after radiotherapy was seen for the poor prognosis group. Consequently, PMRT to chest wall and supra-/infraclavicular area should be „strongly considered“ according to the actual guidelines of NCCN (NCCN 2011). In particular, young age continues to evolve as a potentially important risk factor in patients with high-risk features after mastectomy (Garg 2008) (LoE 3b). In contrast to older patients, young patients experience an abnormally high risk of death caused by breast cancer. Among elderly patients, the risk of death from breast cancer does not decrease with increasing age. These facts are important in the discussion of options for adjuvant treatment in patients with breast cancer and in individualising decision whether or not adjuvant treatment should be delivered. Translation of local recurrence reduction into breast cancer mortality reduction after postmastectomy radiotherapy to high-risk breast cancer patients seems to be heterogeneous, with the largest translation occurring within the good prognosis group (Kyndi 2009).

Although nodal status is the major determinant of risk of locoregional relapse (LRR), other factors also contribute, and these assume a greater significance for those with node-negative breast cancer. The role of postmastectomy radiotherapy (PMRT) for lymph node-negative locally advanced breast carcinoma (T3N0M0) after modified radical mastectomy (MRM) with regard to improvement in survival remains an area of controversy. It has been suggested that patients with T3N0 breast cancer represent a favorable subgroup for which PMRT renders little benefit. A retrospective, population-based analysis demonstrated no increase in CSS with PMRT for women with T3N0 breast cancer, lending further support to the hypothesis that T3N0 disease postmastectomy represents a favorable subset of locally advanced breast cancer. The increased OS associated with PMRT in the absence of improved CSS likely reflects patient selection in a nonrandomized dataset. This suggestion is strongly supported in another analysis confirming the use of PMRT for T3N0M0 breast carcinoma after MRM.

PMRT is also highly beneficial in reducing the risk of local recurrence in patients with invasive lobular breast cancer. Local control is excellent for patients with invasive lobular breast cancer who undergo postmastectomy radiotherapy and significantly better than for patients not receiving radiotherapy (LoE 2c) (Poortman et al. 2013, Diepenmaat 2009).
For patients with *stage II breast cancer with one to three positive lymph nodes*, controversy existed about whether radiation therapy as a component of treatment provides a survival benefit. Retrospectively analyzed cohort studies confirm that radiation use was independently associated with improved survival for patients with stage II breast cancer with one to three positive lymph nodes. Because multivariate analyses of retrospective data cannot account for all potential biases, these data required confirmation in randomized clinical trials. In 2013 published data from clinical studies as well as one meta-analysis provided benefits for this subgroup of patients, if PMRT is applied in combination with regional node irradiation (RNI).

In the recent update of the results of the French trial (Hennequin et al. 2013), no difference was observed in terms of control of loco-regional disease or survival between patients that have had IMC RT or not, for inner and central tumours. However, the defenders of systematic RT to the IMC in case of central or internal localisation, in addition to anatomic arguments, suggest that optimising local control by a complete IMC irradiation sterilises the nodal areas to avoid any risk of diffusion from the areas where occult tumour involvement is frequently located. Moreover, the risk of recurrence is probably multiparametric. For Huang et al. (2008) a high risk of IMN metastasis is observed in patients: with ≥4N+, with medial tumour and N+, with T3 tumour and younger than 35 years, with T2 tumour and N+ and patients with T2 and medial tumour (French Guidelines 2010).

**Detailed new references:**

**PMRT in triple negative T1-2 N1-patients:**

Chen X, Yu X, Chen J, Yang Z, Shao Z et al. Radiotherapy can improve the disease-free survival rate in triple-negative breast cancer patients with t1-t2 disease and one to three positive lymph nodes after mastectomy. Oncologist 2013;18:141-147

**PMRT in T1-2 N0-patients:**


**PMRT in T3-N0-patients after primary systemic treatment:**


**PMRT after primary systemic treatment:**

*Radiotherapy in patients with pathologic response (e.g. ypT0 ypN0) after preoperative chemotherapy and mastectomy*

New in 2013/2014:


Further references:


**Additional aspect:**

*Sequencing breast reconstruction and PMRT:*

New systematic review in 2013:

Further reference:

Overviews 2013/2014

Which patients gain a survival benefit?

Post-mastectomy radiotherapy (PMRT) has shown an absolute overall survival benefit of about 10% in pre- or post-menopausal node positive (N+) patients. Thus, the indications for PMRT are clearly established for the T3–T4 patients and for those presenting with nodal involvement (level 1, grade A) (Belkacemy et al. 2010).


Impact of mastectomy resection margins

• If R0 is impossible to reach


• PMRT to chest wall for node-negative breast cancer


Irradiation of the internal mammary and medial supraclavicular lymph nodes in stage I to III breast cancer: 10 years results of the EORTC Radiation Oncology and Breast Cancer Groups phase III trial 22922/10925. Eur J Cancer 2013;49 (Suppl 3): S1 abstract BA2


PMRT in lobular breast cancer


PMRT in locally advances breast cancer


PMRT in pN1a (depending on patients' age)

PMRT or – alternatively at minimum – a consultation by a radiation oncologist for discuss PMRT in order to assess individually benefit/risk ratio are also recommended in the updated guidelines of AHS (2013), German Guidelines ((2012), NCCN USA (2013), NICE CG80 (2009), Belgian KCE (2013), NZGG (2009), French Guidelines (2012), SIGN (2013):

References published in 2013 regarding influence of patient’s age:


Further references:


PMRT in T4

PMRT is also strongly recommended in the updated guidelines of NCCN USA (2013), NICE CG80 (2009), Belgian KCE (2010/2012), NZGG (2009), French Guidelines (2012), German Guideline (2012)


PMRT in patients with invasive cancer if R0 is impossible to reach

PMRT is also strongly recommended in the updated guidelines of NCCN USA (2013), NICE CG80 (2009), Belgian KCE (2013), NZGG (2009), French Guidelines (2012), German Guideline (2012) and the Guideline of the Netherlands:


Special aspect: PMRT in patients with DCIS if R0 is impossible to reach

New in 2013:


Close margins occur in a minority of patients undergoing mastectomy for DCIS and is the only independent risk factor for LRR. As the LRR rate in patients with close margins is low and less than the rate of contralateral breast cancer, PMRT is not warranted except for patients with multiple close/positive margins that cannot be surgically excised.

PMRT after primary systemic treatment (PST) based on the initial stage prior to PST (cN+, cT3/4a-d)

Identical recommendation regarding this statement by the updated international guidelines (see references on top)

PMRT in young pts with high risk features

Identical recommendation regarding this statement by the updated international guidelines (see references on top)


PMRT with additional RT of supra-/infraclavicular region in >3 Lnn.

Identical recommendation regarding this statement by the updated international guidelines (see references on top)


Further references


Indications for PMRT are independent of adjuvant systemic treatment

Identical recommendation regarding this statement by the updated international guidelines (see references on top)


New in 2013:


In a retrospective trial including 151 patients with mastectomy presenting ypN0 status after NAC, 105 received PMRT and 46 did not. There were no differences regarding 5-year DFS, LRR and OS, respectively. The authors concluded that PMRT might not be necessary for ypN0 patients after NAC. Nevertheless, prospective randomized studies are warranted to assess, whether PMRT might be safely omitted for a subgroup of patients after NAC and mastectomy resulting in ypN0.

This issue is now addressed in the Maastricht Radiation Oncology – register trial: Radiotherapy After Primary Chemotherapy for Breast Cancer (RAPCHEM) trial (NCT01279304).
Further information and references:


New
Whole breast irradiation (WBI) 1a A ++

Updated guideline recommendation in favor of RT following BCS:

Alberta Health Services (AHS), Canada, published March 1, 2013: Adjuvant Radiotherapy for Invasive Breast Cancer

Hypofractionation for WBI: 1a B ++*

Hypofractionated (hf) radiotherapy is safe and effective at 10-year follow-up. A lower total radiation dose given in fewer slightly larger fractions and delivered over a shorter period of time was as safe and effective as the standard five-weeks schedule of radiotherapy. Of note: Most patients included in the hypofractionation RCT received a sequential boost to the tumor bed following WBI!
Nevertheless, the issue of fractionation of RT of the whole breast is still a subject of discussion in international societies of radiation oncology (ASTRO, NICE, ESTRO, DEGRO, French expert review board). Regarding hypofractionated WBI, new data from RCT are convincing and gave reason to state that hypofractionated radiation therapy should be the new standard in selected patients. Therefore, hypofractionated radiation therapy schemes are considered in updated guidelines.

It is important to keep in mind that the impact of HF on late cardiac toxicity is not yet evaluated beyond ten years [Whelan et al. 2010; Haviland et al. 2013]; as the latency for clinical manifestation of cardiovascular effects is 15 years or longer, HF might turn out to be critical in cases of relevant dose exposure to the heart, especially in women with a longer life expectancy.

Updated (guideline) recommendations in favor of hypofractionation as alternative fractionation regime for RT following BCS:


National Cancer Institute USA, updated 11/19/2013

Scottish Intercollegiate Guidelines Network (SIGN), updated September 1, 2013: Treatment of primary breast cancer (SIGN CPG 134): “shorter fractionation schedules should be considered”.


Boost-irradiation (improves local control) 1a A +

Updated guideline recommendation in favor of boost to tumor bed following WBI BCS:


National Cancer Institute USA, updated 11/19/2013
Scottish Intercollegiate Guidelines Network (SIGN), updated September 1, 2013: Treatment of primary breast cancer (SIGN CPG 134): “recommended in all patients aged 50 years or under 50 year at diagnosis and should be considered in patients over 50 years, especially those with high grade cancer”

Sedlmayer F, Sautter-Bihl ML, Budach W, et al.; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). DEGRO practical guidelines: radiotherapy of breast cancer I : Radiotherapy following breast conserving therapy for invasive breast cancer. Strahlenther Onkol 2013;189:825-833: „A boost in addition to WBI reduces local recurrence in all age groups and should therefore be offered to patients who appear biologically and mentally fit enough to experience the benefit of improved local control”

“For the remaining patients especially when they are >60 years with small, node - negative, hormone receptor-positive tumors, omission of a boost may be considered”.

“Regarding SIB techniques within normofractionated WBI, single tumor bed doses of 2.1 Gy for low-risk tumors up to 2.25 Gy for constellations with higher risk of local recurrence seem to be within the acceptable range.”

Boost-RT to the tumor (region) prior versus after BCS:


Short course RT with simultaneous integrated boost-RT: 2a C +/-

New in 2013:


2012:


**APBI / IORT as sole radiotherapeutic modality in comparison to WBI:**

New in 2013:


*IORT administered as sole radiation therapy modality immediately after breast conserving surgery*


IORT administered as anticipated boost radiation therapy during breast conserving surgery followed by whole breast irradiation

Bartelink H, Bourgier C, Elkhuizen P. Has partial breast irradiation by IORT or brachytherapy been prematurely introduced into the clinic? Radiother Oncol 2012;104:139-42.

2012:


Bartelink H, Bourgier C, Elkhuizen P. Has partial breast irradiation by IORT or brachytherapy been prematurely introduced into the clinic? Radiother Oncol 2012;104:139-42


**Technical aspects / new techniques regarding delivery of RT, in particular delivery APBI / IMRT, and toxicity regarding simultaneous integrated boost radiotherapy (SIB)**

New in 2013:


RT-field size / planned target volume in SN+, cN0 breast cancer without axillary dissection


Long-term cosmesis WBI +/- boost

Immink JM, Putter H, Bartelink H, Cardoso JS, Cardoso MJ, van der Hulst-Vijgen MH, Noordijk EM, Poortmans PM, Rodenhuis CC, Struikmans H. Long-term cosmetic changes after breast-conserving treatment of patients with stage I-II breast cancer and included in the EORTC 'boost versus no boost' trial. Ann Oncol 2012;23:2591-8: A boost dose worsens the change in breast appearance in the first 3 years. Moreover, the development of fibrosis associated with whole-breast irradiation, as estimated with the relative asymmetry features, is an ongoing process until (at least) 9 years after irradiation.

Long-term cosmesis WBI +/- boost

The impact of age on outcome in early-stage breast cancer


Boost-RT and hypofractionation on outcome in DCIS

Areas of incertaint, but, however, with improving data in favour radiation therapy:

- Survival benefit in stage II patients with one to three positive lymph nodes
- Impact of radiotherapy of the locoregional lymphatics in pN1a (1-3 positive nodes)
- Best approach after a microscopically incomplete tumor resection in a breast conserving strategy
- Properly definition of patient subgroups, with a low risk for a local relapse after complete surgical tumor removal or after radiotherapy by use of lower dose and smaller volume concepts
- Shortening RT course by use of hypofractionation concepts

Further references


Mannino M, Yarnold JR. Local relapse rates are falling after breast conserving surgery and systemic therapy for early breast cancer: can radiotherapy ever be safely withheld? Radiother Oncol 2009;90:14-22. Review.


Special aspects

Systematic review

Effect of resection margin status on local relapse after BCS and RT in DCIS:


Combined effects of systemic therapy and RT on local relapse rates

Mannino M, Yarnold JR. Local relapse rates are falling after breast conserving surgery and systemic therapy for early breast cancer: can radiotherapy ever be safely withheld? Radiother Oncol 2009;90:14-22.

Intraoperative RT as antecipated boost radiotherapy


Further references:

Whole breast irradiation (WBI) 1a A ++

RT in addition to breast conserving surgery is strongly recommended in the updated guidelines of NCCN USA (2012), NICE CG80 (2009), Belgian KCE (2011), NZGG (2009), French expert review board (2012), German Expert Group (28012), The Netherlands (2012):


Mannino M, Yarnold JR. Local relapse rates are falling after breast conserving surgery and systemic therapy for early breast cancer: Can radiotherapy ever be safely withheld? Radiother Oncol 2009;90:14-22


Truong PT, Jones SO, Kader HA, Wai ES, Speers CH, Alexander AS, Olivotto IA. Patients with T1 to T2 breast cancer with one to three positive nodes have higher local and regional recurrence risks compared with node-negative patients after breast-conserving surgery and whole-breast radiotherapy. Int J Radiat Oncol Biol Phys 2009;73:357-64


Hypofractionation schedules for WBI: 1a A ++*

See: New data of RCT published in 2012 listed above!

The authors of the Cochrane Collaboration Breast Cancer Group have also reviewed (2010) the data of the RCT dealing with hypofractionated schemes altering their conclusion of the last review from 2008 substantially stating „Two new studies have been published since the last version of the review, altering our conclusions. “We have evidence from four low to medium quality randomised trials that using unconventional fractionation regimens (greater than 2 Gy per fraction) does not affect local recurrence, is associated with decreased acute toxicity and does not seem to affect breast appearance or late toxicity for selected women treated with breast conserving therapy. These are mostly women with node negative tumours smaller than 3 cm and negative pathological margins“. Nevertheless, caution is still warranted because long-term follow up (>5 years) is available for only a small proportion of the patients randomised. Longer follow up is required for a more complete assessment of the effect of altered fractionation.


Limitations and cautions regarding hypofractionated radiation therapy in addition to breast conserving surgery:

Due to relatively short median follow up reported from RCT, there is a lack of randomized data regarding long term outcome and adverse late effects, respectively.

Further new references: Hypofractionation should be the new ‘standard’ for radiation therapy after breast conserving surgery:


Harnett A. Fewer fractions of adjuvant external beam radiotherapy for early breast cancer are safe and effective and can now be the standard of care. Why the UK’s NICE accepts fewer fractions as the standard of care for adjuvant radiotherapy in early breast cancer. Breast 2010;19:159-62


Rodger A. Should fewer fractions be the new standard for postoperative radiotherapy in patients with early breast cancer? Breast 2010;19:157-8


Additional references:


Partial breast irradiation (PBI) - No long term follow up! Only as part of prospective trials!

New:

ASTRO Consensus Panel Guideline:

GEC-ESTRO-Recommendations:

Limitations and first results regarding suitability of the ASTRO APBI guidelines:


Further references:


Kirova YM, Botti M, Campana F, Dendale R, Zervoudis S, Kyrias G, Bollet MA, Fourquet A. Delayed reaction after adjuvant whole breast radiotherapy at the dose of 42.9 Gy in 13 fractions over 5 weeks: the need for rapid post irradiation clinical assessment and who are the patients at risk? J BUON 2009;14:729-30.


Further references:


Swanson TA, Vicini FA. Overview of accelerated partial breast irradiation. Curr Oncol Rep 2008;10:54-60 (review)


Boost-irradiation (improves local control)

Following whole breast irradiation boost RT of the tumor bed is recommended in the updated guidelines of NCCN USA (2012), NICE CG80 (2009), Belgian KCE (2010), NZGG (2009), French Guidelines (2012):

In the updated guidelines of NCCN USA (20121), NICE CG80 (2009), Belgian KCE (2012), NZGG (2009), French expert review board (2012) as well as in guidelines of other expert groups delivery of a boost of 10–16 Gy to the tumour bed following whole breast irradiation is recommended based on the results of three RCT showing the importance of an increase in the dose to the tumour bed in order to improve local control (LoE 1A). Updated data from the EORTC trial have confirmed this advantage for patients of all ranges of ages, including those over 60 years of age. For older patients (>70 years) the decision to deliver the boost should be discussed taking in consideration individual factors, i.e. the tumour size, extent of
surgical margins and a possible presence of a large extensive in situ component as well as grade. The surgical clips marking the original tumour bed should indicate the borders of the excision particularly in the case of oncoplastic remodelling procedures.

References:

Further references:


Absolute benefit depending on patient’s age


Dose-effect relationship independent of pts.‘ age


Poortmans PM, Collette L, Bartelink H, Struikmans H, Van den Bogaert WF, Fourquet A, Jager JJ, Hoogenaad W, Müller RP, Dubois JB, Bolla M, Van Der Hulst M, Wárlám-Rodenhuis CC, Pierart M, Horiot JC; EORTC Radiation Oncology and Breast Cancer Groups. The addition of a boost


Boost-irradiation in node-negative tumors, endocrine responsive, complete resection

Updated NCCN guideline recommends boost to the tumor bed in patients being at higher risk for local failure (age <50, positive axillary nodes, lymphovascular invasion, or close margins) (NCCN 2012). French guideline supports individual discussion and decision making keeping in mind individual factors for elderly patients (Belkacemi et al. 2010). For patients received hyperfractionated WBI boost RT should be conventional fractionated, i.e. 1.8-2.0 Gy per fraction.


Boost RT after BCS in Invasive Carcinoma (6/11)

Further information and references:

Boost-Radiotherapie der Tumorregion nach nach brusterhaltender operativer Therapie:

Boost-irradiation (improves local tumor control) 1a A +

Updated guideline recommendation in favor of boost to tumor bed following WBI after BCS:


National Cancer Institute USA, updated 11/19/2013

Scottish Intercollegiate Guidelines Network (SIGN), updated September 1, 2013: Treatment of primary breast cancer (SIGN CPG 134): “recommended in all patients aged 50 years or under 50 year at diagnosis and should be considered in patients over 50 years, especially those with high grade cancer”

Sedlmayer F, Sautter-Bihl ML, Budach W, et al.; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). DEGRO practical guidelines: radiotherapy of breast cancer I : Radiotherapy following breast conserving therapy for invasive breast cancer. Strahlenther Onkol 2013;189:825-833: „A boost in addition to WBI reduces local recurrence in all age groups and should therefore be offered to patients who appear biologically and mentally fit enough to experience the benefit of improved local control”
“For the remaining patients especially when they are >60 years with small, node-negative, hormone receptor-positive tumors, omission of a boost may be considered.”

“Regarding SIB techniques within normofractionated WBI, single tumor bed doses of 2.1 Gy for low-risk tumors up to 2.25 Gy for constellations with higher risk of local recurrence seem to be within the acceptable range.”

Hypofractionation and sequential boost:

No increased toxicity has been observed in START A and START B-trials.


*Whole breast radiation with simultaneous integrated boost-RT*


*IOERT as anticipated boost prior WBI:*


Improved local tumor control:

Absolute benefit depending on patient’s age

In the updated guidelines of NCCN USA (2013), NICE CG80 (2009), Belgian KCE (2012), NZGG (2009), French expert review board (2012) delivery of a boost of 10–16 Gy to the tumour bed following whole breast irradiation is recommended based on the results of three RCT showing the importance of an increase in the dose to the tumour bed in order to improve local control (LoE 1A). Updated data from the EORTC trial have confirmed this advantage for patients of all ranges of ages, including those over 60 years of age. For older patients (>70 years) the decision to deliver the boost should be discussed taking in consideration individual factors, i.e. the tumour size, extent of surgical margins and a possible presence of a large extensive in situ component as well as grade. The surgical clips marking the original tumour bed should indicate the borders of the excision particularly in the case of oncoplastic remodelling procedures.
Intraoperative RT as anticipated boost radiotherapy


*Long-term cosmesis WBI +/- boost*

Imminck JM, Putter H, Bartelink H, et al. Long-term cosmetic changes after breast-conserving treatment of patients with stage I-II breast cancer and included in the EORTC 'boost versus no boost' trial. Ann Oncol 2012;23:2591-8: A boost dose worsens the change in breast appearance in the first 3 years. Moreover, the development of fibrosis associated with whole-breast irradiation, as estimated with the relative asymmetry features, is an ongoing process until (at least) 9 years after irradiation.

Dose-effect relationship independent of pts.’ age


*Further information*

Regarding local tumor control in breast-conserving treatment, radiation therapy is required (LOE 1a). There exists a dose–effect relationship, which is independent of patients’ age (LOE 1b).

Additional boost-RT is able to reduce the local recurrence rate significantly in every age group with most benefit for young patients. With a median follow up of 10 years, boost RT could not be demonstrated to have an impact on survival rate (LOE 1b).

Actual published 10-year results of the randomised EORTC Trial 22881-10882 'boost versus no boost' confirmed:
Increase of the dose with 16 Gy after whole breast irradiation (WBI) delivered as boost radiotherapy confined to the tumor bed, is associated with an improved local control for patients after a complete lumpectomy only. Up till now, with 10 years median follow-up, no impact on survival was observed (LOE 1b).

There was no statistically significant difference in local control or survival between the high boost dose of 26 Gy and the low boost dose of 10 Gy in patients with microscopically incomplete excision of early breast cancer.

**Further References:**

Statement: Improved local tumor control


Statement: All ages: LRR reduction (12 ≥ 7%)


Statement: <40 years: LRR reduction (29 ≥ 10%)


Statement: high grade invasive ductal cancer


Statement: Additional boost RT does not impact survival


Radiotherapy of the Axilla (7/11)

Further information and references:

Indikationsstellung zur Radiotherapie der Axilla

Neu 2013:

Radiation therapy of regional lymphatics


Abstract

Due to the heterogeneity of lymph node examination and the conflicting results existing for the same classification of lymph node ratio (LNR), it is necessary to conduct a meta-analysis to evaluate the prognostic effects of different LNRs on breast cancer. PubMed, EMBASE, and ISI Web of Knowledge were searched to find all published cohort studies that evaluated the prognostic value of different LNRs on breast cancer. The outcomes were overall survival (OS), disease-free survival (DFS), breast cause-special survival (BCCS), mortality, locoregional recurrence (LRR), and distant metastasis. Data was analyzed using comprehensive meta-analysis software version 2.0, and 23 studies were included. The available evidence showed that LNR was a prognostic predictor for breast cancer, especially for clinically node-positive breast cancer, but the available evidence could not judge which cutoff point is the most reliable. Meanwhile, the cutoff values 0.2 and 0.65 could be suitable to predict breast cancer OS, DFS, BCCS, and mortality.


Abstract

Sentinel node biopsy (SN) in breast cancer treatment was introduced in the mid-1990s in order to be able to stage patients before decision of definitive surgery. Since then, both the pathological examinations of the SN and the systemic adjuvant treatment have improved and cause new challenges in the correct decision making regarding whether or not to radically treat the axilla in case of a positive SN. In SN positive patients, current St. Gallen guidelines support no completion ALND (axillary lymph node dissection) in clinically node-negative patients with 1-2 macrometastatic sentinel nodes operated with breast conservation and receiving tangential field adjuvant radiotherapy (RT). ALND is being questioned due to increased morbidity compared with SN biopsy alone, and to limited long term benefit on disease free survival in selected patients. An alternative to ALND is treating the axilla with nodal RT although this treatment is mostly used as adjuvant treatment after ALND in high risk patients. Few studies have investigated the benefit of nodal RT compared to ALND, and no consensus has yet been reached. Clinical decision making regarding treating the axilla should be based on relevant data, and in this review studies aiming at deciding whether or not and how the axilla should be treated in SN positive patients will be discussed. Furthermore treatment choice will be discussed, since besides ALND, both breast irradiation and nodal irradiation might cure residual disease after SN. Also the issue of improved systemic adjuvant treatment will be discussed in relation to eventually no regional axillary treatment.


Further references

**Radiation therapy of axillary nodes**

Vestjens JH, de Boer M, van Diest PJ, et al. Prognostic impact of isolated tumor cells in breast cancer axillary nodes: single tumor cell(s) versus tumor cell cluster(s) and microanatomic location. Breast Cancer Res Treat 2012;131:645-51. Outcome of pNmic vs pN0 breast cancer patients: Lymphonodal micrometastasis or isolated tumor cells are associated with poorer survival compared to pN0 disease –

**RT-field size/planned target volume in SN+, cN0 breast cancer without axillary dissection**


**Prognostic factors after BCS in young patients**


**Radiotherapy (RT) of Other Locoregional Lymph Node Areas (8/11)**

*Further information and references:*

Indikationsstellung zur Radiotherapie weiterer lokoregionaler Lymphabflussregionen

Neu 2013:

**Metaanalysen:**

Budach W, Kammers K, Boelke E, Matuschek C. Adjuvant radiotherapy of regional lymph nodes in breast cancer – meta-analysis of randomized trials. Radiat Oncol 2013; 8:267: additional regional lymph nodes irradiation of medial supraclavicular and internal mammary for patients with positive axillary sentinel nodes provide statistically significant benefits regarding disease-free survival, distant metastases-free survival and overall survival, respectively


**Recommendations in updated guidelines:**

Alberta Health Services (AHS), Canada, published March 1, 2013: Adjuvant Radiotherapy for Invasive Breast Cancer: “with RNI”


Cardoso F, Loibl S, Pagani O, et al.; European Society of Breast Cancer Specialists. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. Eur J Cancer 2012;48:3355-77: “Young patients should be informed the high local recurrence risk if radiation therapy is avoided….Internal mammary chain irradiation should be discussed on the basis of clinical, histopathological and radiological findings in the multidisciplinary team (LoE expert opinion)”

Scottish Intercollegiate Guidelines Network (SIGN), updated September 1, 2013: Treatment of primary breast cancer (SIGN CPG 134): strongly recommendation for participation in ongoing clinical trials (SUPREMO). – RT of supraclavicular fossa: “No RCTs were identified to guide the use of supraclavicular fossa radiotherapy after axillary clearance in patients with positive lymph node involvement….Participation in clinical trials should be encouraged”.


Further references:


Abstract

Sentinel node biopsy (SN) in breast cancer treatment was introduced in the mid-1990s in order to be able to stage patients before decision of definitive surgery. Since then, both the pathological examinations of the SN and the systemic adjuvant treatment have improved and cause new challenges in the correct decision making regarding whether or not to radically treat the axilla in case of a positive SN. In SN positive patients, current St. Gallen guidelines support no completion ALND (axillary lymph node dissection) in clinically node-negative patients with 1-2 macrometastatic sentinel nodes operated with breast conservation and receiving tangential field adjuvant radiotherapy (RT). ALND is being questioned due to increased morbidity compared with SN biopsy alone, and to limited long term benefit on disease free survival in selected patients. An alternative to ALND is treating the axilla with nodal RT although this treatment is mostly used as adjuvant treatment after ALND in high risk patients. Few studies have investigated the benefit of nodal RT compared to ALND, and no consensus has yet been reached. Clinical decision making regarding treating the axilla should be based on relevant data, and in this review studies aiming at deciding whether or not and how the axilla should be treated in SN positive patients will be discussed. Furthermore treatment choice will be discussed, since besides ALND, both breast irradiation and nodal irradiation might cure residual disease after SN. Also the issue of improved systemic adjuvant treatment will be discussed in relation to eventually no regional axillary treatment.


Guidelines 2012 / recommendations 2012 for irradiation of the locoregional lymphatics


For patients with breast cancer ipsilateral lymph edema of the arm, restriction of shoulder motion as well as brachial plexopathy are relevant functional treatment sequelae correlated with treatment modality which also have a strong negative influence on the quality of life. Specific morbidity of surgical (e.g., extent of the axillary dissection, length of the scar) and radiotherapeutic (radiation following surgery, radiation without previous surgery) treatment as well as individual host factors may influence functional outcome. Axillary dissection provides sufficient information on nodal status being clinically a major prognostic factor. Nonetheless, axillary node dissection is responsible for functional sequelae which might be enhanced by additional postoperative irradiation of the axilla (with or without additional irradiation of ipsilateral supraclavicular lymph nodes). Local treatment sequelae are mainly an arm edema, swelling of the arm caused by lymphostasis, functional reduction of ipsilateral shoulder joint responsible for consecutive impairment in shoulder movement as well as other motoric and neurological deficits. With the sentinel lymph node biopsy (SNB) this aspect of reducing the adverse postsurgical treatment effects in the shoulder-arm-area is already taken into account from operative side. Regarding percutaneous irradiation there exist also differentiated indicators for postoperative radiation therapy for the treatment of the regional lymphatics. The recommendations about the irradiation of the regional lymph nodes are internationally still mixed since, up to now, the validation of the radiotherapeutic effects in retrospective studies are as yet inadequate and current international prospective studies including large numbers of patients are not yet completed.

Current studies prospectively examined whether the sentinel node biopsy is as effective as the axillary lymph node dissection. Concordance rates between 97-100% and a rate of false negative SNB reports of 0-<10% have been specified so far. The alternative of an axilla-irradiation as well as the irradiation of the additional regional lymphatics has as yet been validated, but the results are still pending. At present international studies regarding this subject are being carried out. In detail these are the SUPREMO-phase III-trial/EORTC-trial; EORTC-Protocol 22922-10925; EORTC-Protocol 22023-10981(AMAROS)-trial, NSABP-B32-trial (negative SN- and axillary node status respectively). A negative SNB status means that no further operative therapy is necessary and that there is no need for adjuvant radiation therapy of the regional lymph nodes; a positive SNB however justifies further adjuvant therapy-measures (Kuehn et al. 2004). The meaning of micrometastases detected in the SNB is unclear (Leidenius et al. 2005). Without any further axillary dissection in case of a positive SNB status the irradiation of the axilla offers a therapeutic alternative. Whether it is an equivalent alternative to surgery and whether there exists an equivalence of both therapy modalities has not been sufficiently clarified yet and should be examined in randomized interdisciplinary studies. Retrospectively the irradiation of the axilla achieves a local control which is just as good as the sole axillary dissection, nonetheless, with reduced functional treatment sequelae regarding axilla, shoulder and arm (Louis-Sylvestre et al. 2004).
The irradiation of the axilla is currently recommended for patients presenting extended lymph node involvement (>3 affected lymph nodes; pN2a) and with contraindication or omission of a sufficient operative exploration of the armpit. However, the extracapsular nodal tumor extension of axillary node metastases is prognostically judged controversially as well as the indication derived from with regard to a need for axillary node irradiation (Gruber et al. 2008; Stranzl et al. 2004). However, the indication for radiotherapy has to be considered individually and should include further factors, e.g. the extent of the axillary lymph node dissection and the number of affected nodes. An irradiation of the regional undissected lymph nodes therefore appears to be appropriate in case of locally advanced breast cancer, extended involvement of the axillary nodes, especially with additional extracapsular tumor extension, with inadequate surgical removal of axillary lymph nodes, contraindication or the refusal of an axillary dissection. However, there is growing evidence that the benefit of irradiation of regional undissected lymph nodes for selected patients with one to three positive axillary lymph nodes (pN1a) is as equal as has been demonstrated for those with four or more involved lymph nodes (pN2a) (Marks et al. 2008; Russel et al. 2009).

Radiation use was independently associated with improved survival for patients with Stage II breast cancer with one to three positive lymph nodes (Buchholz 2009, 2011; Darby 2009; Jagsi and Pierce 2009). Because multivariate analyses of retrospective data cannot account for all potential biases, these data require confirmation in randomized clinical trials (LoE Ib) (Buchholz 2008).

Patients with 1-3N+ and young age, Grade III, or ER-negative disease have high LRR risks approximating 15% to 20% despite BCS, whole-breast RT and systemic therapy. These patients may benefit with more comprehensive RT volume encompassing the regional nodes (Darby 2009; Jagsi and Pierce 2009; Truong et al. 2009).

In the pTNM classification system of UICC 2002, which has been refined in 2010, nodal status of breast cancer is based on the number of involved lymph nodes and does not account for the total number of lymph nodes removed. Numerous studies suggest that lymph nodal ratios (LNR; ie, ratio of positive over excised lymph nodes) may have greater prognostic value than absolute numbers of involved nodes. This has been supported by a systematic review and in multiple reports from both prospective and retrospectively collected data sets, respectively. The prognostic value of the LNR was compared with pN staging and its optimal cutoff points were determined by the International Nodal Ratio Working Group (Truong et al. 2008; Vinh-Hung et al. 2009; Woodward et al. 2006). In summary, LNR have been shown to be significant predictors of outcome, including locoregional recurrence and overall survival. LNR predicts survival after breast cancer more accurately than pN classification and should be considered as an alternative to pN staging. Consequently, this might be of influence for accurate indications for radiation therapy of regional lymphatics more precisely.

Extracapsular tumor spread (ECS) has been identified as a possible risk factor for breast cancer recurrence, but controversy exists regarding its role in decision making for regional radiotherapy. The International Breast Cancer Study Group has evaluated extracapsular tumor spread as a predictor of local, axillary, and supraclavicular recurrence in node-positive, premenopausal patients with breast cancer. In the International Breast Cancer Study Group Trial IV 1.475 eligible pre- and perimenopausal women with node-positive breast cancer were accrued. The authors concluded, that the results of this trial indicate that the decision for additional regional radiotherapy should not be based solely on the presence of ECS Gruber et al. 2008).
Radiotherapy (RT) of Other Locoregional Lymph Node Areas (9/11)

Further information and references:

Indikationsstellung zur Radiotherapie der regionalen Lymphabflussregionen
Neu 2013:

Metaanalysen:
Budach W, Kammers K, Boelke E, Matuschek C. Adjuvant radiotherapy of regional lymph nodes in breast cancer – meta-analysis of randomized trials. Radiat Oncol 2013; 8:267: additional regional lymph nodes irradiation of medial supraclavicular and internal mammary for patients with positive axillary sentinel nodes provide statistically significant benefits regarding disease-free survival, distant metastases-free survival and overall survival, respectively.


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Further references:


Due to the heterogeneity of lymph node examination and the conflicting results existing for the same classification of lymph node ratio (LNR), it is necessary to conduct a meta-analysis to evaluate the prognostic effects of different LNRs on breast cancer. PubMed, EMBASE, and ISI Web of Knowledge were searched to find all published cohort studies that evaluated the prognostic value of different LNRs on breast cancer. The outcomes were overall survival (OS), disease-free survival (DFS), breast cause-special survival (BCCS), mortality, locoregional recurrence (LRR), and distant metastasis. Data was analyzed using comprehensive meta-analysis software version 2.0, and 23 studies were included. The available evidence showed that LNR was a prognostic predictor for breast cancer, especially for clinically node-positive breast cancer, but the available evidence could not judge which cutoff point is the most reliable. Meanwhile, the cutoff values 0.2 and 0.65 could be suitable to predict breast cancer OS, DFS, BCCS, and mortality.

Guidelines 2012 / recommendations 28012 for irradiation of the locoregional lymphatics


Important prospective data recently suggested that internal mammary chain radiotherapy would not be necessary, even in cases of internal or central tumor locations, or in patients with positive axillary lymph nodes. Although these data warrant confirmation by two other prospective trials, there is evidence that the indications for internal mammary chain radiotherapy should be careful and that high quality techniques should be used for decreasing the dose delivered to the heart. This review of literature presents the state of art on the radiotherapy of internal mammary chain, with special focus on the indications, techniques, and potential toxicity.


Further information:

The management of internal mammary nodes (IMN) in breast cancer is controversial. Surgical series from the 1950s showed that one third of breast cancer patients had IMN involvement, with a higher risk in patients with medial tumors and/or positive axillary nodes. IMN metastasis, a major independent prognostic factor in breast cancer patients, has similar prognostic importance as axillary nodal involvement.

After three randomized trials showed no survival benefit from extended mastectomy compared with radical or modified radical mastectomy, IMN dissection was largely abandoned. Recently, lymphoscintigraphy studies have renewed interest in IMN evaluation. Approximately one fifth of internal mammary sentinel nodes are pathologic, although most centers do not perform IMN biopsies or sampling of IM sentinel nodes (IMSN) because of concerns about morbidity and lack of established survival benefit.
It has been demonstrated, evaluation of IMSN improves nodal staging in breast cancer (Heuts et al. 2009). Patients with IM hotspots on lymphoscintigraphy have a substantial risk (22%) of metastatic involvement of the IM chain. In addition, true IM node-negative patients can be spared the morbidity associated with adjuvant radiotherapy.

Two large randomized trials (French Group-trial (n = 1.334 pts.; Romestaing et al. 2009), European Organization for Research and Treatment of Cancer [EORTC]-Trial 22922/10925 (n = 4.004 pts.)) are currently evaluating the possible benefit of irradiation of the internal mammary lymphatics. Thus, the role of irradiation of the internal mammary lymphatics will be revealed after 2010 by results of several prospective trials, for example the EORTC phase III randomized trial 22922/10925 or a trial of a French Group. Before mature results from current randomized trials assessing the benefit of IMN irradiation become available, lymphoscintigraphy may be used to help guide decisions regarding systemic and local-regional treatment (Heuts et al. 2009).

The updated recommendations of the NCCN 2010 state, that if internal mammary lymph nodes are clinically or pathologically positive, radiation therapy should be given to the internal mammary nodes. CT treatment planning should be utilized in all cases, where radiation therapy is delivered to the internal mammary lymph node field (NCCN 2010).

However, even in patients with visualized primary IMN drainage, the potential benefit of treatment should be balanced against the risk of added morbidity (Romestaing et al. 2009; NCCN 2010).
Concomitant Use of Systemic Therapy with Radiotherapy (10/11)

Further information and references:

Kombination von systemischen antineoplastischen Therapien mit der Radiotherapie:

Sequenz RT und endokrine systemische Therapie


RT concurrent to aromatase inhibitors


RT concurrent to tamoxifen


2010-2012:


Belkacemi and J. Gligorov, Concurrent trastuzumab — internal mammary irradiation for HER2 positive breast cancer: “It hurts to be on the cutting edge”. Radiother Oncol 2010;94:119-20 (Letter to the editor).

Fernando IN, Bowden SJ, Buckley L, et al., on behalf of the SECRAB Steering Committee. SECRAB: The optimal SEquencing of adjuvant CHEmotherapy (CT) and RAdiotherapy (RT) in early Breast cancer (EBC), results of a UK multicentre prospective randomised trial. SABCS 2010;[S4-4], no full paper version available.


Sequenz RT und Trastuzumab:

Further information:

The human epidermal growth factor receptor-2 (HER2) is overexpressed and/or amplified in up to 25% of breast cancer patients, and this feature is associated with an aggressive phenotype, high recurrence rate and reduced survival. Trastuzumab combined with chemotherapy has been recently shown to improve outcome in HER2-positive breast cancer. However, many questions related to trastuzumab use in the adjuvant setting including concurrent radiotherapy still have to be answered.

Evaluation of possible toxic effects of concurrent radiation therapy and administration of trastuzumab in the adjuvant setting is under investigation. So far, acute toxicity analyses and data from clinical observation studies of breast cancer patients treated with trastuzumab and concurrent radiotherapy with irradiation of internal mammary chain with, in most cases, anthracycline-based chemotherapy revealed no significant increase in the rate of abnormal LVEF (Halyard et al. 2009). There was no excess acute cardiotoxicity observed with the combination of left-sided IMC.
irradiation and concurrent trastuzumab (Halyard et al. 2009; Shaffer et al. 2009). Even more, skin toxicity was acceptable in routine (Kirova et al. 2009).

More patients and a longer follow-up are needed to ascertain that this regimen with concurrent radiotherapy and trastuzumab is safe and feasible without compromising therapeutic benefit. However, cardiac volume sparing and patient selections for IMC irradiation are highly recommended. Longer follow-up is warranted to evaluate late toxic effects.

References:


Bollet MA, Kirova YM, Granger B, et al. Preliminary result of a mono-institutional, prospective study of skin and cardiac toxicities in breast cancer patients treated by concurrent adjuvant trastuzumab and radiotherapy involving in most cases the internal mammary chain. SABCS 2008, abstract # 5132


1.503 irradiated patients with early-stage resected human epidermal growth factor receptor 2 (HER-2)-positive breast cancer were enrolled in the NCCTG Phase III Trial N9831, who were randomly assigned to doxorubicin and cyclophosphamide, followed by weekly paclitaxel, trastuzumab and sequential radiotherapy. An analysis was performed, to assess whether trastuzumab with radiotherapy increases adverse events after breast-conserving surgery or mastectomy. In this trial the radiotherapy was performed either as postlumpectomy breast or (optional) postmastectomy chest wall irradiation. However, concurrent radiotherapy of internal mammary nodes was prohibited. At a median follow-up of 3.7 years (range, 0 to 6.5 years), radiotherapy with trastuzumab did not increase relative frequency of cardiac events regardless of treatment side. Thus, concurrent adjuvant radiotherapy and trastuzumab for early-stage breast cancer was not associated with increased acute adverse events. Further follow-up is required to assess late adverse event (Halyard et al. 2009).


Conclusions: There was no excess acute cardiotoxicity observed with the combination of left-sided IMC irradiation and concurrent trastuzumab. In the Scottish and Institut Curie experiences, the concomitant administration of trastuzumab with RT of the IMC does not seem to be deleterious to the heart in the short- or middle-term (Kirova et al. 2009; Shaffer et al. 2009). However, regarding the short term of follow-up in these published studies and the uncertainties concerning the use of LVEF to predict late cardiac toxicity, it should be recommended to strongly limit the dose to the heart structures when RT of the IMC is delivered.

Aromatase Inhibitors und simultane RT


BACKGROUND: Letrozole radiosensitises breast cancer cells in vitro. In clinical settings, no data exist for the combination of letrozole and radiotherapy. We assessed concurrent and sequential radiotherapy and letrozole in the adjuvant setting.

METHODS: This phase 2 randomised trial was undertaken in two centres in France and one in Switzerland between Jan 12, 2005, and Feb 21, 2007. 150 postmenopausal women with early-stage breast cancer were randomly assigned after conserving surgery to either concurrent radiotherapy and letrozole (n=75) or sequential radiotherapy and letrozole (n=75). Randomisation was open label with a minimisation technique, stratified by investigational centres, chemotherapy (yes vs no), radiation boost (yes vs no), and value of radiation-induced lymphocyte apoptosis (< or = 16% vs >16%). Whole breast was irradiated to a total dose of 50 Gy in 25 fractions over 5 weeks. In the case of supraclavicular and internal mammary node irradiation, the dose was 44-50 Gy. Letrozole was administered orally once daily at a dose of 2.5 mg for 5 years (beginning 3 weeks pre-radiotherapy in the concomitant group, and 3 weeks post-radiotherapy in the sequential group). The primary endpoint was the occurrence of acute (during and within the first 12 weeks after radiotherapy) and late (within 2 years) radiation-induced grade 2 or worse toxic effects of the skin. Analyses were by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00208273.

FINDINGS: All patients were analysed apart from one in the concurrent group who withdrew consent before any treatment. During radiotherapy and within the first 12 weeks after radiotherapy, 31 patients in the concurrent group and 31 in the sequential group had any grade 2 or worse skin-related toxicity. The most common skin-related adverse event was dermatitis: four patients in the concurrent group and six in the sequential group had grade 3 acute skin dermatitis during radiotherapy. At a median follow-up of 26 months (range 3-40), two patients in each group had grade 2 or worse late effects (both radiation-induced subcutaneous fibrosis).
INTERPRETATION: Letrozole can be safely delivered shortly after surgery and concomitantly with radiotherapy. Long-term follow-up is needed to investigate cardiac side-effects and cancer-specific outcomes.

Further references:
Radiotherapy in the Elderly Patient (11/11)

No further information

No references
Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

Therapy Side Effects
Therapy Side Effects

- **Versions 2004–2013:**
  Albert / Bischoff / Costa / Friedrich / Friedrichs / Gerber / Göhring / Jackisch/ Lisboa / Müller / Nitz / Schmidt / Souchon / Stickeler / Untch

- **Version 2014:**
  Huober / Brunnert
Toxicity Assessment

Acute Toxicity
According to WHO¹ or NCI-CTC²

<table>
<thead>
<tr>
<th>Grade</th>
<th>Information required</th>
</tr>
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<tbody>
<tr>
<td>0 none</td>
<td>organs involved</td>
</tr>
<tr>
<td>1 mild</td>
<td>type of toxicity</td>
</tr>
<tr>
<td>2 moderate</td>
<td>time interval after treatment</td>
</tr>
<tr>
<td>3 severe</td>
<td>effect on general health status</td>
</tr>
<tr>
<td>4 life threatening</td>
<td>treatment required</td>
</tr>
<tr>
<td></td>
<td>recovery achieved</td>
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</table>

Long-Term Toxicity
No general assessment scale

¹ WHO Handbook for reporting results of cancer treatment, N0 48 (1979) (WHO offset Publications, Geneva)
## Cytotoxic Anti-Cancer Drugs – Acute Toxicity I

<table>
<thead>
<tr>
<th>Drug</th>
<th>Haematol. Toxicity</th>
<th>Nausea/Vomit</th>
<th>Alopecia</th>
<th>Mucositis/Stomatitis</th>
<th>Cardiac Toxicity</th>
<th>Renal Toxicity</th>
<th>Hepatic Toxicity</th>
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# Cytotoxic Anti-Cancer Drugs – Acute Toxicity II

<table>
<thead>
<tr>
<th>Drug</th>
<th>Allergic Reaction</th>
<th>Bladder Toxicity</th>
<th>Neuro-pathy</th>
<th>Skin Toxicity</th>
<th>Diarrhea</th>
<th>Hand-Foot-S.</th>
<th>Other</th>
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<td>++</td>
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</tbody>
</table>
Long-Term Toxicity Cardiotoxicity

- Equivalent cardiotoxicity of doxorubicin and epirubicin at recommended dose levels (450–500 and 900–1000 mg/m² cum. dose, resp.)
  - Oxford / AGO LoE / GR 2b B

- Liposome encapsulated anthracyclines (doxorubicin) induce less cardiotoxicity
  - Oxford / AGO LoE / GR 1b B

- Anthracycline- or trastuzumab-associated cardiotoxicity may occur earlier/more frequently:
  - Elderly patients
  - Obesity
  - Hypertension
  - Hypercholesterolemia
  - Pre-existing cardiac diseases (incl. borderline LVEF)
  - Diabetes mellitus
  - Monitoring of cardiac function before / during / after treatment: Echocardiography (LVEF or SF in %)
    - Oxford / AGO LoE / GR 3b C +
# Feasibility of Treatment Combinations Considering Toxicities

## Regarding cardiac toxicity

- **Trastuzumab simultaneous to radiotherapy**
- **Trastuzumab simultaneous to epirubicin**
- **Trastuzumab simultaneous to doxorubicin**
- **Anthracycline simultaneous to radiotherapy**

<table>
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<th>LoE / GR</th>
<th>Feasibility</th>
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</tr>
<tr>
<td>2b</td>
<td>B</td>
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<tr>
<td>2b</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>2c</td>
<td>C</td>
<td>-</td>
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## Regarding lung and breast fibrosis

- **Tamoxifen simultaneous to radiotherapy**
- **Chemotherapy simultaneous to radiotherapy**

<table>
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<tr>
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<th>LoE / GR</th>
<th>Feasibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>C</td>
<td>+/-</td>
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<tr>
<td>1b</td>
<td>B</td>
<td>-</td>
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Side Effects of Trastuzumab/Pertuzumab
Algorithm in Case of Cardiac Toxicity

LVEF drop from baseline

- LVEF ≥50%
  - LVEF drop ≤20% points
    - CONTINUE treatment
  - LVEF drop >20% points
    - CONTINUE treatment and repeat LVEF in 3 weeks
- LVEF <50%
  - LVEF drop <10% points
    - CONTINUE treatment and repeat LVEF in 3 weeks
  - LVEF drop ≥10% points
    - HOLD treatment and repeat LVEF in 3 weeks

- Not confirmed (LVEF drop ≤20% points or LVEF ≥50%)
  - CONTINUE treatment
  - LVEF drop CONFIRMED (LVEF drop >20% points and LVEF ≥50%)
    - CONTINUE treatment
  - LVEF drop CONFIRMED (LVEF drop <10% points and LVEF <50%)
    - CONTINUE treatment and repeat LVEF in 3 weeks
- LVEF drop CONFIRMED (LVEF drop ≥10% points and LVEF <50%)
  - STOP treatment
- Not confirmed (LVEF drop <10% points or LVEF ≥50%)
  - RESUME treatment
Secondary Malignancies I

- With regard to solid tumours, chemotherapy induced secondary malignancies are rare events
- Alkylating agents increase the risk of leukaemia dose-dependently to a total of 0.2–0.4 % within 10 - 15 years
- Anthracycline-containing regimens increase the risk of MDS and leukaemia to 0.2–1.7 % within 8 to 10 years
- Radiotherapy increases the risk of leukaemia by 0.2–0.4% in patients treated with anthracycline-containing chemotherapy
- Tamoxifen approximately doubles the risk for developing endometrial cancer

Oxford LoE

2a
2a
2a
2b
2b
Secondary Malignancies II (after Radiotherapy)

- The risk of developing secondary cancers is low if modern radiation techniques are applied and should not deter the use of radiotherapy when indicated 2b

- Radiotherapy may moderately enhance the risk of ipsilateral lung cancer and angiosarcoma appearing 5–10 years after treatment 1a
  - Enhanced risk especially among ever smokers 2b

Oxford LoE
Chemotherapy Related Amenorrhea (CRA)

- CRA may be permanent or temporary
- Depends on CTX regimen used
- CRA is an (imperfect) surrogate for menopause and fertility
- Adjuvant endocrine therapy induces reversible amenorrhea, but delays conception to a less fertile period
- Risk of CRA increases with age / treatment duration
- Ovarian reserve of women who remain premenopausal after CTX is reduced
- CRA is associated with improved outcome (DFS/OS)

Synonyma: Chemotherapy / Treatment induced Amenorrhea (TIA, CIA)
Fatigue frequently present in breast cancer patients (30–60%).

Exclusion of somatic reasons (anemia, tumor burden, co-morbidity, medication) for fatigue.

Psycho-social interventions specifically addressing fatigue are efficient in reducing fatigue.

Physical exercise with ambiguous effects regarding fatigue.

Methylphenidate might improve fatigue.
Sleep disturbances are a common problem of breast cancer patients during and after therapy (20–70%) 2a B

Behavioral therapies demonstrated efficacy in the treatment of insomnia and improved the quality of life 1b A ++
Depression is an often reported adverse event in breast cancer patients (20–30%)  

Psychological interventions are effective to improve mood, but not survival in distressed and depressed patients  

Antidepressents have shown to improve depression in breast cancer patients  

Regular exercise participation can prevent depression among breast cancer survivors
**(Therapy Associated)**

**Cognitive Impairment**

- Therapy-related cognitive deficits (chemobrain frequently described (16–75%))
  - Oxford / AGO LoE / GR: 2a B

- Cognitive-behavioral therapy is beneficial for cognitive function
  - Oxford / AGO LoE / GR: 2b B

- Methylphenidate might improve cognitive function in patients with cancer
  - Oxford / AGO LoE / GR: 3a C
### Side-effects and Toxicity of Endocrine Agents

<table>
<thead>
<tr>
<th></th>
<th>Visual Disturbances</th>
<th>Osteoporosis</th>
<th>Cerebro-Vascular Events *</th>
<th>Fracture</th>
<th>Cardiac risk</th>
<th>Cognitive functions</th>
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<tr>
<td>AI 3rd Gen*</td>
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<tr>
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<table>
<thead>
<tr>
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<th>Dysfunctional Bleeding*</th>
<th>Endometrial Changes</th>
<th>Deep Venous Thrombosis</th>
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</table>
Side-Effects and Toxicity of Bone Modifying Agents (BMA) Bisphosphonates (BP) and Denosumab (DB)

- Renal function deterioration due to IV-amino-BP 1b
- Osteonecrosis of the jaw (ONJ) mostly under IV-BP and DB therapy (appr. 2%) 1b
- Acute phase reaction (IV Amino-BPs, DB) 10–30% 1b
- Gastrointestinal side effects (oral BPs) 2–10% 2b

In adjuvant bisphosphonate therapy, major side effects were observed rarely (except APR)
Recommendations for Precautions to Prevent Osteonecrosis of the Jaw (ONJ)

Oxford LoE: 4  GR: C  AGO: +

- During bisphosphonate treatment, avoid any elective dental procedures, which involve jaw bone manipulations – if interventions are inevitable, prophylactic antibiotics are recommended (LoE 2b)

- Optimize dental status before start of bisphosphonate treatment, if feasible (LoE 2b)

- Inform patients about ONJ risk and educate about early symptom reporting

- In case of high risk for ONJ, use oral bisphosphonate

In adjuvant bisphosphonate therapy, ONJ was rare
# Frequent Side Effects of Bone Modifying Agents (BMA)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Acute Phase React.</th>
<th>Renal Phase Tox.</th>
<th>Upper GI-SE</th>
<th>Diarrhea</th>
<th>ONJ</th>
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<td>Denusomab 120 mg sc q4w</td>
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<td>+</td>
<td>+</td>
<td>Hypocalcemia</td>
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</table>

- Acute Phase: Immediate side effects that occur shortly after administration.
- Renal Phase Tox.: Side effects related to the kidneys.
- Upper GI-SE: Side effects related to the upper gastrointestinal system.
- Diarrhea: Side effects related to the digestive system.
- ONJ: Osteonecrosis of the Jaw.
### Key-Toxicities – Small Molecules / Antibodies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Toxicities</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab</td>
<td>Cardiotoxicity in the adjuvant setting (0,8–4,0%)</td>
<td>1b A</td>
</tr>
<tr>
<td></td>
<td>Troponin I might identify patients who are at risk for cardiotoxicity</td>
<td>2b B</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>Skin rash, diarrhea, mucositis</td>
<td>2b B</td>
</tr>
<tr>
<td>T-DM1</td>
<td>Thrombocytopenia, hepatotoxicity, pyrexia, headache, pneumonitis</td>
<td>2b B</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Diarrhea, skin rash, fatigue</td>
<td>1b A</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Hypertonus, proteinuria, bleeding, left ventricular dysfunction</td>
<td>1a A</td>
</tr>
<tr>
<td>Everolimus</td>
<td>Pneumonitis, stomatitis, hyperglycemia, infections, skin rash,</td>
<td>2b B</td>
</tr>
</tbody>
</table>

**Key**

- **Toxicities** – Small Molecules / Antibodies
- **Oxford / AGO LoE / GR**
Therapy Side Effects (2/20)

Further information:


Screened guidelines:

No references
Toxicity Assessment (3/20)

Further information:

Acute toxicity and in most cases 100 day mortality rates are well documented in the majority of phase III trials. Toxicities are graded according to WHO or NCI standards. This implies that toxicities concerning liver, kidney heart or skin are well documented and graded. Other toxicities like fatigue, depression, menopausal symptoms or impairment of cognitive function are systematically underreported by these tools. Most trials end five or ten years after the last patient in, such that late and very late effects are rarely documented.

Acute Toxicity according to WHO1 or NCI-CTC2:

References:

2. NCI, Bethesda, USA. Common Terminology Criteria for Adverse Events v4.0 (CTCAE; published 2010); http://evs.nci.nih.gov/ftp1/CTCAE/About.html
Cytotoxic Anti-Cancer Drugs – Acute Toxicity I (4/20)

No further information

References:


Kaufmann PA, Awada A, Twelves C et al. Phase 3 open label randomized multicenter study Eribulin Mesylate versus Capecitabine in patients with locally advanced or metastatic breast cancer previously treated with anthracyclirns and taxanes SABCS 2012, abstract S6-6
No further information

References:
see slide 4
**Long-Term Toxicity Cardiotoxicity I (6/20)**

Further information:

Anthracycline (A) based standard chemotherapy regimens as used in the adjuvant therapy of breast cancer are associated with a relatively low acute toxicity and treatment related mortality rates < 1%. In terms of long-term toxicity cardiotoxicity and secondary acute leukemia/MDS are clinically relevant.

Cardiotoxicity:

Early cardiotoxicity of anthracyclines has been well established in clinical trials. Limited data are available on long-term cardiac safety of A based regimens. As patients with breast cancer are getting older and as survival rates improve long term cardiotoxicity is of growing interest.

**AC:** Among patients treated with four cycles of AC on NSABP B31 17% of patients developed asymptomatic cardiac disease defined as the decline in left ventricular ejection fraction of more than 10% to an ejection fraction of less than 55%. Similar data were presented recently by Perez et al. in N9831 trial. In 2992 patients completed AC 5% had LVEF decrease disallowing trastuzumab (decrease below normal: 2.4%, decrease > 15%: 2.6%).

**FAC:** The Southwest Oncology Group evaluated long term cardiotoxicity from patients randomized to protocol S8897. In this trial patients were randomized to CAF or to CMF. A was given on day 1 and 8. 180 patients from an potential sample of 1176 patients entered. There was no significant difference in the proportion of women with an LVEF less than 50% at 5 to 8 years (CAF vs. CMF: 8% vs. 5%, p=0.68) or at 10 to 13 years (CAF vs. CMF: 3% vs. 0%, p=0.16). However in an exploratory analysis the mean LVEF in the doxorubicin group was statistically significantly lower in the 5 to 8 year sample (p=0.01), but not in the 10 to 13 year sample.

**French FEC:** The FASG reports ten year follow-up data in patients receiving either FE50C or FE100C from FASG 05. Delayed (> 1 month after the end of chemotherapy) symptomatic cardiotoxicity was reported in 1.5% of patients from the FE50C arm and in 1.1% of patients from the FE100C arm. In summary early and delayed cardiotoxicity was reported in 4.3% and in 4.8% of patients.

The second analysis from the FASG trials compared E+ and E- (antihormontherapy or nil) regimens in 3577 breast cancer patients. E+ therapy was associated with 1.36% decrease in LVEF after 7 years vs. only 0.21% in controls (p=0.004). In these analysis age > 65 years old and body mass index > 27 were significant predictors of cardiac toxicity.
A containing regimens outside clinical trials in the elderly

There are 2 important studies from the SEER database in older women. The first one by Doyler et al. analyzed data from 31478 patients, 5575 of them received A-based chemotherapy (18%). This study highlights bias of all studies, investigating cardiac affects of A-chemotherapy, because these patients are per se younger, with less comorbidities and a higher risk of recurrence. The hazard ratios for cardiomyopathy, cardiac failure, and heart disease for patients > 65 years treated with doxorubicin compared with patients who received no chemotherapy were 2.48 (95% CI, 2.10 to 2.93), 1.38 (95% CI, 1.25 to 1.52), and 1.35 (95% CI, 1.26 to 1.44), respectively. The relative risk remained elevated 5 years after diagnosis. Preexisting heart disease was beside of afro-american race the most important risk factor for cardiac failure after A-exposure.

Pinder et al reported data from a total of 43,338 women from the SEER’S database. Similarly as in the previous study anthracycline–treated women were younger, with less comorbidity and had more advanced diseases than women who received non anthracycline based regimens. The adjusted hazard ratio was 1.26 for women aged 66 to 70 treated with a compared other chemotherapy. In this age group at five years of follow-up the observed absolute differences were of 1 % and 4.6 % respectively in rates of chronic heart failure between anthracycline based chemotherapy and other adjuvant chemotherapy or no chemotherapy. After ten years the increased risk of chronic heart failure was amplified rather than attenuated, with absolute differences of 5.9 % and 9.7 % when comparing anthracycline treated patients to the other or no adjuvant chemotherapy groups. For women aged 71 to 80 adjuvant chemotherapy was not associated with chronic heart failure.

Taxanes and cardiac safety

Data on cardiac safety in anthracycline-taxane sequential trials are in favour of taxane-based combinations, in which lower doses of anthracyclines are used. E.g. the PACS 01 trial reported significantly lower incidence of cardiac toxicity in the 3xFEC-3xDoc arm than in the 6xFEC arm (0.4% vs. 1.3%, p=0.027). These data have been confirmed in the Cochrane analysis, where trials in which total doses of anthracyline was reduced by substitution of taxane, had subsequently less cardiac events, than standard A-based regimens (OR=0.37 (95%CI: 0.14-0.95)). There are only limited data on cardiac safety of A-free regimens in adjuvant setting in breast cancer. Jones et al. reported 5 cardiac events in 510 patients treated by 4 cycles of AC and only 1 in 506 patients in the 4xTC arm in the US Oncology study.
In the BCIRG 006 study there were also significantly less patients with >10% decrease of LVEF value in the Taxotere/Carboplatin/Herceptin (TCH) arm than in AC-TH arm (8% vs. 17.3%), although the negative synergistic cardiac effect of Herceptin should be considered separately of anthracycline cardiac side effects.

Trastuzumab and cardiac safety
Most studies have excluded elderly patients (> 60 or 65 years) or patients with other risk factors (cardiovascular diseases, obesity, hypertension) from studies including trastuzumab. In clinical practice, 32% of HER2+ EBC patients treated with trastuzumab are 'over-60'. These patients have an increased cardiovascular risk profile and develop trastuzumab related cardiotoxicity commonly. Also with regard to other risk factors there is an increased risk of trastuzumab related cardiotoxicity during treatment, which is reversible after cessation of trastuzumab.

References:

Statements
“Equivalent cardiotoxicity of doxorubicin and epirubicin at recommended dose levels (450–500 and 900–1000 mg/m² cum. dose, resp.)”
“Liposome encapsulated anthracyclines (doxorubicin) induce less cardiotoxicity”

“Anthracycline- or trastuzumab-associated cardiotoxicity may occur earlier/more frequently…”


“Trastuzumab-related cardiotoxicity in the elderly: a role for cardiovascular risk factors.”

“Monitoring of cardiac function before / during / after treatment: Echocardiography (LVEF or SF in %)”

Further references:


Feasibility of Treatment Combinations Considering Toxicities (7/20)

Further information:

The frequency of adverse events for patients with HER-2 positive early breast cancer was examined in a randomized study with a median follow-up time of 3.7 years. 1503 patients were irradiated. Radiotherapy (RT) was administered either without or with concurrent trastuzumab (H). At a median follow-up of 3.7 years (range, 0 to 6.5 years), RT with H did not increase relative frequency of cardiac events (CEs) regardless of treatment side. The cumulative incidence of CEs with AC-T-H was 2.7% with or without RT. With AC-TH-H, the cumulative incidence was 1.7% vs 5.9% with or without RT, respectively. Thus, concurrent adjuvant RT and H for early-stage BC was not associated with increased acute AEs (Halyard al, 2009). Reported data regarding the influence of tamoxifen given simultaneously to radiotherapy are diverging. Simultaneously given tamoxifen to radiotherapy might increase the risk of Grade 1 lung fibrosis (p = 0.01) and might increase the risk of late lung sequelae (OR = 2.442, 95% CI 1.120-5.326, p = 0.025). However other reports did not confirm such an connection. Therefore the results of the ongoing CONSeT-trials has to be awaited.

References:

Statements
“Trastuzumab simultaneous to radiotherapy”
“Trastuzumab simultaneous to epirubicin”


“Trastuzumab simultaneous to doxorubicin”

“Anthracycline simultaneous to radiotherapy”

“Tamoxifen simultaneous to radiotherapy”


Further references:
Valakh V, Trombetta MG, Werts ED, Labban G, Khalid MK, Kaminsky A, Parda D.
**Side Effects of Trastuzumab and Pertuzumab: Algorithm in Case of Cardiac Toxicity (8/20)**

**Further information:**

Cardiotoxicity has been reported to occur with trastuzumab when administered alone and in combination with antineoplastic agents, particularly anthracyclines. The risk of cardiotoxicity with trastuzumab has been reported to be 4% with monotherapy and 27% when administered in combination with an anthracycline and cyclophosphamide. However, severe and life-threatening damages are rare and the majority of reported cardiac effects are mild to moderate, nonspecific, and medically manageable. Signs and symptoms are similar to those observed in patients who develop anthracycline-induced cardiomyopathy and include tachycardia, palpitations, and exertional dyspnea, which may ultimately progress to congestive heart failure (Keefe, 2002). Trastuzumab-associated toxicity usually responds to standard treatment or the discontinuation of trastuzumab, and there is no evidence that the toxicity is dose related. Left ventricular ejection fraction (LVEF) should be measured at baseline and at regular intervals. An algorithm based on LVEF changes is presented to aid in the question whether continuation of trastuzumab is safe and feasible or whether discontinuation is warranted.

There are also data for trastuzumab and pertuzumab from phase 2 trials and randomized phase 3 trials, in neither trial cardiotoxicity was increased through the addition of pertuzumab to trastuzumab both in the absence or presence of taxane containing chemotherapy. In the Cleopatra trial 808 pts with metastatic breast cancer were randomized to docetaxel and trastuzumab and placebo or to docetaxel and trastuzumab and pertuzumab. LVEF dysfunction (any grade) was more frequently seen in the placebo group than in the pertuzumab group (8,3% vs 4,4%). LVEF dysfunction of grade 3 or higher was reported in 2,8% and 1,2% of the patients in the placebo and pertuzumab arms respectively.

**References:**


Secondary Malignancies I (9/20)

Further information:

Approximately one in every 20 breast cancer patients developed a second non-breast primary tumour within 10 years following a breast cancer diagnosis (10 years cumulative incidence rate 5.4%; 95%CI 5.1 to 5.7). Compared with the general female Dutch population, these breast cancer patients had a 22% increased relative risk in second non-breast primary cancers and an absolute excess risk of 13 cases per 10,000 women-years (13.6 (95%CI 9.7 to 17.6). The occurrence of a second non-breast cancer was associated with a decrease in overall survival (HR 3.98, 95%CI 3.77 to 4.20).

Standard incidence ratios were elevated for cancers of esophagus, stomach, colon, rectum, lung, uterus, ovary, kidney, bladder, soft tissue sarcomas, melanoma, non Hodgkin’s lymphoma, acute myeloid leukemia.

Patients younger than 50 years, radiotherapy was associated with increased lung cancer risk (HR 2.31; 95%CI 1.15 to 4.60) and chemotherapy with decreased risk for all secondary non-breast cancers.

Patients 50 years and older, radiotherapy was associated with increased risk of soft tissue sarcoma (HR 3.43, 95%CI 1.46 to 8.04), chemotherapy with increased risk of melanoma, uterine cancer, acute myeloid leukemia and hormonal therapy with uterine cancer (HR 1.78, 95%CI 1.40 to 2.27).

Risk of secondary acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS)

Women with a prior breast cancer were ~2.6 times more likely to develop AML than the total female Australian population, with highest age-specific relative risk for AML in the 30- to 49-age group.

Mitoxoantrone-based chemotherapy was associated with a higher leukemic risk than with anthrazyclines (RR 16.8, 95%CI 7.1 to 34.2 than RR 2.7, 95%CI 1.7 to 4.5). Epirubicin and doxorubicin had a similar risk.

For women > 65 years receiving polychemotherapy (CAF, ACP) the risk to develop grade 4 hematologic toxicity, to have discontinued treatment for toxicity or to die of acute myeloid leucemia/MDS was significantly elevated.

Granulocyte colony-stimulating factor (G-CSF) increased the risk of developing AML/MDS.
Details to chemotherapy regimes:

French FEC
The French Adjuvant Study Group reviewed their 16-year experience with their FEC regimen of 5-Fluorouracil, epirubicin (50, 75, 100 mg/m2) and cyclophosphamide i.v. q3w. Cumulative epirubicin doses mostly were below 600 mg/m2. As for leukemia, data of 3653 women are available, which were followed for a median of 104 months. About two-third of the patient population received epirubicin-based adjuvant chemotherapy while slightly lower than one-third received CMF-like regimens. The incidence of secondary leukemia was very low: 0.3 % for those patients treated with adjuvant epirubicin and <0.1 % for those treated with other adjuvant therapies (CMF-like, antihormonal therapy).

Canadian FEC
The National Cancer Institute of Canada Clinical Trials Group analysed the risk of secondary acute leukemia (sAL) following adjuvant therapy with regimens containing epirubicin. The analysis were performed to assess the conditional probability of sAL in 1545 women having received adjuvant (n = 1477) or neoadjuvant (n = 68) chemotherapy in four National Cancer Institute of Canada Clinical Trials Group trials from 1990 to 1999. The leukemia risks associated with epirubicin-containing regimens (CEF or EC) and other regimens as doxorubicin and cyclophosphamide (AC or CMF) were registered. A total of 10 cases of sAL were observed (eight acute myelogeneous leukemia, two acute lymphoblastic leukemia): Seven among women treated with CEF, two who had received AC, and one following CMF. Using competing risk statistics, the conditional probability of sAL was 1.7 % (95 % confidence interval [CI], 0.5 to 3.6) among 539 women treated with CEF chemotherapy at a follow-up of 8 years, 0.4 % (95 % CI, 0 % to 1.3 %) among the 678 who received CMF, and 1.3 % (95 % CI, 0 % to 4.7 %) among the 231 treated with AC. Of note, Canadian CEF comprises epirubicin doses of 120 mg/m2. The conditional probability for breast cancer death at 8 years for the whole group treated with epirubicin-containing regimens in all four trials was approximately 34.9%. The group concluded that CEF chemotherapy for breast cancer carries a small increased risk of sAL compared with CMF which has to be taken into account when discussing treatment options with patients who are at a lower risk of breast cancer death, e. g. node negative patients. The rates of acute leukemia had not changed since the original report when updated 10-years results have been reported in 2005.
US – AC

Purpose: We reviewed data from all adjuvant NSABP breast cancer trials that tested regimens containing both doxorubicin (A) and cyclophosphamide (C) to characterize the incidence of subsequent acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS).

Materials and Methods: Six complete NSABP trials have investigated AC regimens (B-15, B-16, B-18, B-22, B-23, and B-25). Six distinct AC regimens have been tested and are distinguished by differences in cyclophosphamide intensity, cumulative dose and by the presence or absence of mandated prophylactic support with growth factor and ciprofloxacin. In all regimens, A was given at 60 mg/m2 q 21 days x 4. C was given as follows: 600 mg/m2 q 21 days x 4 ("standard AC"); 1200 mg2 q 21 days x 2; 1200 mg/m2 q 21 days x 4; 2400 mg/m2 q 21 days x 2; and 2400 mg/m2 q 21 days x 4. Occurrence of AML/MDS was summarized by incidence per 1,000 patient-years at risk and by cumulative incidence. Rates were compared across regimens, by age, and by treatment with or without breast radiotherapy.

Results: The incidence of AML/MDS was sharply elevated in the more intense regimens. In patients receiving two or four cycles of C at 2400 mg/m2 with granulocyte colony-stimulating factor (G-CSF) support, cumulative incidence of AML/MDS at 5 years was 1.01% (95% confidence interval [CI], 0.63% to 1.62%), compared with 0.21% (95% CI, 0.11% to 0.41%) for patients treated with standard AC. Patients who received breast radiotherapy experienced more secondary AML/MDS than those who did not (RR = 2.38, \( P = .006 \)), and the data indicated that G-CSF may also be independently correlated with increased risk.

AML/MDS in older patients

In summary Conclusion for FEC and :AC secondary AML/MDS rates correlate with regimens employing intensified doses of cyclophosphamide requiring, G-CSF support and to a smaller extent which were characterized by increased rates of subsequent AML/MDS, although the incidence of AML/MDS was small relative to that of breast cancer relapse. Breast radiotherapy appeared to be associated with an increased risk of AML/MDS, but data are inconsistent (see slide 10/20).

References for statements 1-4:


**Reference for Statement Tamoxifen and endometrial cancer**

Secondary Malignancies II (10/20)

Further information:

Radiotherapy increased the risk of sarcoma and lung cancer. Results of a Dutch population-based study, patients younger than 50 years, radiotherapy was associated with an increased lung cancer risk (HR 2.31, 95%CI 1.15 to 4.60) and patients older than 50 years were more likely to develop soft tissue sarcoma (HR 3.43, 95%CI 1.46 to 8.04).\(^1\)

According to the cohort data of the SEER registries 1973 to 2000 risk for second cancers was dose dependend. Radiotherapy treatment assuming standard protocol with 50Gy tumour dose and beem energy 6 MV photons. The RR were 1.45 (95%CI 1.33 to 1.58) for high dose second cancer sites (1 +Gy, lung, oesophagus, pleuro, bone and soft tissue sarcoma) with no evidence of elevated risk for sites receiving medium (05.-0,9 Gy) or low doses (< 0,5 Gy). Overall risks were generally lower for patients treated in recent years (1993 +). But the pattern of risks observed were consistend with the general literature on radiation carcinogenesis, risks were higher for sites that should have received higher doses and also higher for young age at exposure.\(^6\^-\^8\)

The risk of lung cancer was elevated for ever-smokers who receive PMRT (HR18.9, 95%CI 7.9-45.4) according the results of the nested breast cancer cohort study population of the Connecticut Tumor Registry.\(^5\)

Data are inconsistent for an elevated risk of AML/MDS after radiation exposure.\(^6\^-\^8\)

References:


Chemotherapy Related Amenorrhea (CRA) (11/20)

Further information:

Synonyma: Chemotherapy / Treatment induced Amenorrhea (TIA, CIA)
Preservation of ovarian function is an important issue in the population of breast cancer patients especially in the patient younger than 40. Up to now neither data for ovarian protection with e.g. GnRH analogues nor cryopreservation of ovarian tissue are convincing. The treatment compromising most oftenly fertility is chemotherapy.\(^1\) After modern taxan-anthracyclin containing chemotherapy the risk of CRA is markedly lower compared to older chemotherapy regimens. Especially in younger patients the restitution of menses after 2 years is greater than 90 \%.\(^2\)

However one third of the patients probably will be infertile after chemotherapy. The effects are more pronounced the older the patient and the longer the chemotherapy.

Data from the NSABBP B-30 trial (sequential versus concurrent ACT, doxorubicin-docetaxel in women with operable, node-positive, early stage breast cancer) amenorrhoe in premenopausal women was associated with improved dissease-free and overall survival regardless of treatment, in particular when the tumor was ER-positive.\(^3,4\) The dose of drug delivered was not a key factor explaining the differences.\(^4\)

References:


Fatigue is a common side effect during and after antineoplastic therapy. Especially in breast cancer incidence of moderate to severe fatigue ranges between 30 and as high as 60% (Lawrence 2004, Blaney 2012). This symptom is typically under-reported and under-treated and might adversely affect quality of life (Bower, 2008). Studies of long-term breast cancer survivors suggest that approximately one quarter to one third experience persistent fatigue for up to 10 years after cancer diagnosis (Bower et al, 2006).

Several factors are thought to contribute to cancer-related fatigue, including direct effects of cancer, adverse effects of cancer treatment, psychosocial factors, comorbid physical symptoms, and comorbid medical conditions. Anemia might contribute to a subset of cancer patients presenting with fatigue (Cella et al, 2004). Recent studies suggest an inflammatory basis for persistent fatigue in breast cancer survivors like increased NF-κB and decreased glucocorticoid signaling in breast cancer survivors with persistent fatigue (Bower et al, 2010).

Behavioral and psychological interventions (Stanton et al, 2005) as well as physical exercise (McNeely et al, 2006, Bower et al, 2011) have demonstrated efficacy in reducing fatigue among breast cancer patients and survivors. It was shown in a meta-analysis by the Cochrane Collaboration that psychosocial interventions specifically addressing fatigue proved efficient (Goedendorp et al, 2009) and the same authors reported a randomized controlled trial showing that cognitive behavioural therapy was effective in reducing cancer-related fatigue. Contrary to what was expected, physical activity did not mediate the effect of cognitive behavioural therapy on fatigue in this study (Goedendorp et al, 2010).

Another Cochrane Collaboration meta-analysis for physical exercise and fatigue only found statistically non-significant improvements for participants in the exercise intervention groups compared to control (non-exercising) groups. These authors concluded that improvements in fatigue were ambiguous and that strategies for behaviour change should underpin these interventions (Markes et al, 2006). In terms of pharmacological treatments for fatigue in a palliative setting, a study using methylphenidate (Ritalin™) in 112 cancer patients showed that this medication was not significantly superior to placebo after 1 week of treatment (Bruerat al, 2006). However, a significant effect of methylphenidate against cancer-related fatigue was confirmed in a meta-analysis performed by the Cochrane Collaboration (Peuckmann-Post et al, 2010). However the effectiveness of glucocorticoids, which are used broadly in daily praxis, has not yet been evaluated.
References:

Fatigue is frequently present...


Psycho-social interventions...

Physical exercise.....


Methylphenidate...


**Further information:**

Sleep disturbances are a common problem of breast cancer patients during and after therapy (20-70%) leading to disruption in women's quality of life and general ability to function (Bower, 2008; Savard et al, 2001; Ancoli-Israel et al, 2006). In a recently published study examining 823 cancer patients treated with chemotherapy, it was shown that 43% of the patients met the criteria for insomnia syndrome. Insomnia was approximately three times higher than the proportions reported in the general population. 60% of the patient sample reported that their insomnia symptoms remained unchanged from cycle 1 to cycle 2. Those with insomnia complaints had significantly more depression and fatigue than good sleepers (Palesh et al, 2010). Comorbidity, evening fatigue, and depressive symptoms predicted baseline levels of subjective sleep disturbance, and depressive symptoms predicted the trajectory of subjective sleep disturbance (Dhruva et al 2012).

Empirical studies of benzodiazepines and benzodiazepine receptor antagonists indicate that they are effective in improving various aspects of sleep, although no trials have evaluated the efficacy of these medications in cancer populations. Behavioral therapies have demonstrated efficacy in the treatment of insomnia, including insomnia secondary to medical conditions, supporting their use among breast cancer patients (Berger et al, 2009). Comparative studies have shown that behavioral therapies are at least as effective and longer lasting than pharmacotherapy in treating insomnia (McChargue DE et al 2012; Berger et al. 2009). Indeed, a randomized controlled trial of behavioural therapy for women with insomnia caused or exacerbated by breast cancer found significant improvement in subjective sleep complaints, as well as improvements in mood and quality of life (Savard et al, 2005).

**References:**

Sleep disturbances are a common problem....


Behavioral therapies have demonstrated efficacy.....


Further information:

Depression is an often reported adverse event in breast cancer patients. The majority of studies find that 20-30% of breast cancer patients experience elevated depressive episodes (Bower, 2008), even though the occurrence of a major depressive disorder might be lower. Psychological distress and depressive symptoms are typically highest in the first 6 months after cancer diagnosis and then decline over time. Depression negatively affects quality of life and there is also evidence of increased morbidity and, possibly, mortality in depressed cancer patients (Gallo et al, 2007). The occurrence of depression in breast cancer patients is more strongly influenced by psychosocial and physical factors, rather than severity of the disease or treatment regimen (Bardwell et al, 2006). Depressed mood is correlated with fatigue and sleep disturbance in the context of breast cancer. In terms of treatment psychological interventions seem to be most effective distressed patients even though these interventions do not prolong survival. Regular exercise participation and tea consumption were shown in a population-based cohort study from Shanghai to play an important role in the prevention of depression among breast cancer survivors (Chen et al, 2010). Antidepressants have also shown to improve depression, in particular paroxetine has been shown to be effective in reducing depressive symptoms in breast cancer patients, even among those who were not depressed at study entry.

References:

Statements 1-4


Reports of cognitive deficits, often referred to as chemobrain, among breast cancer patients during and after chemotherapy have been reported in 16 to 75% (Bower et al. 2008; Vardy et al. 2007; Stewart et al. 2006). Neuroimaging findings provide compelling evidence that chemotherapy has a negative effect on cognition in a subset of women and that these effects may persist for years after successful treatment (Silverman et al., 2007). A study on young premenopausal patients was able to clearly correlate chemotherapy-induced changes in cerebral white matter with impaired cognitive functioning (Deprez et al., 2011). Among breast cancer survivors who remain disease-free for more than a decade, the previous cancer treatment may further augment cognitive dysfunction associated with age-related brain changes. In patients after treatment completion there is improvement in cognitive function over time, although a subset of patients continued to show deficits for up to 10 years after treatment (Fan et al., 2005). Interestingly, subjective cognitive complaints are typically not correlated with objective cognitive performance in breast cancer patients but are correlated with subjective reports of fatigue and depressed mood. In a current study examining 120 breast cancer patients treated with CMF, neuropsychological tests did not reveal any differences in cognitive function between breast cancer patients after chemotherapy and healthy controls (Debess et al., 2010). Patients rated their own cognitive functions as improved after 6 months. These results again do not support that adjuvant chemotherapy is associated with cognitive side effects in breast cancer patients. Considering adjuvant endocrine treatment, tamoxifen use was associated with statistically significant lower functioning in verbal memory and executive functioning, whereas exemestane use was not associated with statistically significant lower cognitive functioning in postmenopausal patients with breast cancer (Schilder et al., 2010).

The biologic base for these changes is unclear. However, are there several candidate mechanisms for chemotherapy-induced cognitive changes, including direct neurotoxic effects, DNA damage and telomere length, inflammation and cytokine dysregulation, and estrogen or testosterone reduction, as well as genetic polymorphisms (Ahles et al., 2007).

Cognitive behavioral therapy might lead to significant improvements in self-reported cognitive function, quality of life, and standard neuropsychological test performance after treatment and at the 2-month and 6-month follow-ups (Ferguson et al., 2007). Other potential treatment approaches include methylphenidate, which has been used to improve cognitive
function in patients with advanced cancer. E:\Dokumente und Einstellungen\ute\Locale Einstellungen\Temp\Literatur Nebenwirkungen\Bower, behavioral symptoms in breast cancer survivors 2008.htm - R130#R130
E:\Dokumente und Einstellungen\ute\Locale Einstellungen\Temp\Literatur Nebenwirkungen\Bower, behavioral symptoms in breast cancer survivors 2008.htm - R110#R110

References:

Therapy-related cognitive deficits (chemobrain)…….


Cognitive-behavioral therapy...


Methylphenidate might improve cognitive function....


**Side-effects and Toxicity of Endocrine Agents I (16/20)**

**Further information:**

In a metaanalysis on 19,818 pts. treated with 3rd generation aromatase inhibitors the risk of developing cardiovascular adverse events was slightly higher in comparison to tamoxifen with an RR of 1.34 translating into a minimal risk of 0.5%. (Cuppone F et al 2008)

In an actual systematic review and metaanalysis of 30,023 patients in 7 trials comparing aromatase inhibitors with tamoxifen, the increased risk for developing cardiovascular disease (OR=1.26) for aromatase inhibitors was confirmed, as well as the occurrence of bone fractures (OR=1.47), while the OR for endometrial carcinoma (OR=0.34) and venous thrombosis (OR=0.55) was significantly lower in comparison to tamoxifen (Amir et al, 2011).

**References:**


Side-Effects and Toxicity – of Bone Modifying Agents (BMA, Bisphosphonates, Denosumab) (17/20)

Further information:

A recently published randomized study compared denosumab, a fully human monoclonal antibody against receptor activator of nuclear factor κ B (RANK) ligand, with zoledronic acid in delaying or preventing skeletal-related events (SREs) in patients with breast cancer with bone metastases. In terms of toxicity rates of adverse events (AEs) and serious AEs were similar between groups. An excess of renal AEs and acute-phase reactions occurred with zoledronic acid; hypocalcemia occurred more frequently with denosumab. Osteonecrosis of the jaw occurred infrequently (2.0%, denosumab; 1.4%, zoledronic acid; P = .39) (Stopeck et al, 2010). In a pooled analysis of three randomized phase III trials of denosumab versus zoledronic acid in patients treated for metastatic cancer this occurrence rate for denosumab was confirmed with 1.67% (RR = 1.61) (Van den Wyngaert et al, 2011). Although there amounting data, that bisphosphonates might have anticancer benefits for older postmenopausal women, the routine use of bisphosphonates as adjuvant treatment for patients with early breast cancer is not recommended (Paterson et al 2012; Wong et al 2012).

References:


Acute phase rea
Gastrointestinal side effects...

Recommendations for Precautions to Prevent ONJ (18/20)

Further information:

The reported incidence of osteonecrosis of the jaw (ONJ) ranges from 0.94% to 18.6%. A study with 1,621 patients who received 29,006 intravenous doses of BP, given monthly reported an crude ONJ incidence of 8.5%, 3.1%, and 4.9% in patients with multiple myeloma, breast cancer, and prostate cancer, respectively. Patients with breast cancer demonstrated a reduced risk for ONJ development, which turned out to be non-significant after adjustment for other variables. Multivariate analysis demonstrated that use of dentures (aOR = 2.02; 95% CI, 1.03 to 3.96), history of dental extraction (aOR = 32.97; 95% CI, 18.02 to 60.31), having ever received zoledronate (aOR = 28.09; 95% CI, 5.74 to 137.43), and each zoledronate dose (aOR = 2.02; 95% CI, 1.15 to 3.56) were associated with increased risk for ONJ development. Smoking, periodontitis, and root canal treatment did not increase risk for ONJ in patients receiving BP. In conclusion, validated dental extractions and use of dentures are risk factors for ONJ development. Ibandronate and pamidronate at the dosages and frequency used in this study seem to exhibit a safer drug profile concerning ONJ complication; however, randomized controlled trials are needed to validate these results. Before initiation of a bisphosphonate, patients should have a comprehensive dental examination.

References:


Frequent Side Effects of Bisphosphonate Treatment (19/20)

Further information:

Side-Effects and Toxicity – Bisphosphonates

References:

Go to slide 17-18/20!
Further information:

In the HERA trial, the incidence of discontinuation of trastuzumab because of cardiac disorders was low (5.1%). At a median follow-up of 3.6 years, the incidence of cardiac end points remained low, though it was higher in the trastuzumab group than in the observation group (severe CHF, 0.8% v 0.0%; confirmed significant LVEF decreases, 3.6% v 0.6%). In the trastuzumab group, 59 of 73 patients with a cardiac end point reached acute recovery; of these 59 patients, 52 were considered by the cardiac advisory board (CAB) to have a favorable outcome from the cardiac end point. The incidence of cardiac end points remains low even after longer-term follow-up and the majority of cardiac events resolved (Procter et al, 2010).

In the NSABP B-31- and NCCTG 9831-trial trastuzumab-treated patients had a 2.0% incidence of symptomatic heart failure events compared with 0.45% in the chemotherapy-alone arm. Complete or partial recovery was observed in 86.1% of trastuzumab-treated patients with symptomatic heart failure events after cessation of trastuzumab. Independent predictors for cardiac events were age older than 50 years, a low ejection fraction at the start of paclitaxel treatment, and trastuzumab treatment. The majority of these patients recover with appropriate treatment (Russell et al, 2010).

The usefulness of troponin I in the identification of patients at risk for trastuzumab induced cardiotoxicity (TIC) and in the prediction of LVEF recovery was investigated in 251 women treated with trastuzumab. TNI was measured before and after each trastuzumab cycle. TIC occurred more frequent in patients with troponin elevation (TNI+; 62% v 5%; P < .001). Thus, Troponin increase identifies trastuzumab-treated patients who are at risk for cardiotoxicity and are unlikely to recover from cardiac dysfunction despite HF therapy.

In the Phase III trial of Capecitabine with or without the oral tyrosinkinase-inhibitor lapatinib which led to the approval of lapatinib in advanced HER-2 positive breast cancer, asymptomatic cardiac events were identified in four women in the combination-therapy group and in one woman in the monotherapy group. All of these events in the combination-therapy group were considered to be related to treatment, and all women had an LVEF value that was at or above the lower limit of the normal range on subsequent assessment.
The most common adverse events were diarrhea, the hand–foot syndrome, nausea, vomiting, fatigue, and rash that was distinct from the hand–foot syndrome. Most adverse events were grade 1, 2, or 3. Grade 4 diarrhea occurred in two women in the combination-therapy group (1%). One case each of grade 4 fatigue, headache, and dizziness was reported in the monotherapy group. Diarrhea, dyspepsia, and rash occurred more often in the group of women who received combination therapy.

A systematic review and meta-analysis of five randomized phase III clinical trials that used bevacizumab alone or in combination with chemotherapy in metastatic breast cancer showed a statistically significant bevacizumab associated increased risk for proteinuria (OR=27.68), hypertension (OR=12.76), left ventricular dysfunction (OR=2.25) and hemorrhagic events (OR=4.07), while no increased incidence was found for gastrointestinal perforation, vascular or fatal events and febrile neutropenia, respectively.

References

Cardiotoxicity....


**Troponin I...**


**Bevacizumab ....**


**Lapatinib**


**Pertuzumab**


**T-DM1**
Supportive Care
Supportive Care

- **Version 2002:**
  Diel

- **Versions 2003–2013:**

- **Version 2014:**
  Schmidt / Möbus
Guideline Spectrum

Specific national and international guidelines deal with various aspects of evidence-based supportive therapy of cancer patients.

We try to quote these guidelines wherever appropriate, but underline that the listings of relevant guidelines do not claim to be complete. The listing is clearly biased towards German and English language.

Special emphasis is put on aspects concerning breast cancer patients.

In the German environment, special interest is earnt by the publications of the „Arbeitsgem. Supportive Maßnahmen in der Onkologie, Rehabilitation und Sozialmedizin der DKG: http://www.onkosupport.de“

In preparation: multidisciplinary guidelines of the AWMF:

„Supportive Therapie bei onkologischen Patientinnen - interdisziplinäre Querschnittsleitlinie“, announced 1.7.2012, planned release: 30.6.2015

„Palliativmedizin“, announced 03.12.2010, planned release 31.03.2014
Erythropoiesis-stimulating agents (ESAs)

- Indicated in asymptomatic anaemia
  - In dose-dense / dose-escalated CT (iddETC)

- Indicated in symptomatic anaemia
  - In the adjuvant setting
  - In the neoadjuvant/metastatic setting

- Treatment and secondary prophylaxis of chemotherapy induced anemia (CIA)
- Improvement of outcome (DFS, OS)
- Treatment start at Hb-levels approaching < 10 g/dL
- Target Hb 11–12 g/dL
- Thromboembolic events are increased with ESAs

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Practical Use of ESAs

- Epoetin α and Darbepoetin are equieffective

**Dose:**

- Epoetin α: 150 IU/kg 3 x weekly s.c. or 40,000 IU 1 x/week s.c.
- Epoetin α: 80,000 IU q2w s.c. or 120,000 IU q3w s.c.
- Darbepoetin: 2.25 µg/kg s.c. weekly
- Darbepoetin: 500 µg s.c. q3w

**Hb measurements weekly**

- Dose reduction at Hb-increase > 1g/dl within 2 weeks
- Dose increase at Hb-increase < 1g/dl within 4-6 weeks

- In case of FID give IV iron supplementation
- p.o. iron supplementation
- STOP ESA-treatment in case of missing increases of Hb-levels after 9 weeks

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Relevant Guidelines


## Prophylaxis of Infections

NB Rarely Applicable to Patients with Solid Tumors (e.g. BC)

ASCO Practice Guideline „Antimicrobial Prophylaxis...“ 2013

<table>
<thead>
<tr>
<th>Oxford / LoE / GR</th>
<th>LoE</th>
<th>GR</th>
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<tbody>
<tr>
<td>Avoidance of highly infection-risking behaviour or situations</td>
<td>5</td>
<td>D</td>
</tr>
<tr>
<td>Prophylactic treatment in low risk patients</td>
<td>1a</td>
<td>B</td>
</tr>
<tr>
<td>Prophylactic treatment in high risk* patients (e.g. according to NCCN Guidelines) with</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Anti-fungal agents (triazole)</td>
<td>1a</td>
<td>B</td>
</tr>
<tr>
<td>Virostatics in solid tumors</td>
<td>5</td>
<td>D</td>
</tr>
<tr>
<td>Granulocyte colony-stimulating factors</td>
<td>1a</td>
<td>A</td>
</tr>
</tbody>
</table>

* High risk definition: estimated duration of neutropenia < 100/µl > 7d
Mucositis


- **Desinfecting / antiphlogistic measures:**
  Mouth rinsing with infusions of camomile or salvia, extracts of camomile, etheric oils, polyvidon-iodine, hexetidine. Local therapy with crystal violet solution 0.5% or tinctura myrrhei, H. mometasonfuroate + propylene glycol

- **Mucosa protecting measures (during / after application of chemotherapy):**
  Sucking ice cubes (especially from pineapple juice) during 5-fluorouracile- or HD-melphalane. Calcium folinate (Leucovorin-Mundgel®) every 4–6 hrs for HD-methotrexate: do not start earlier than 24 hours after end of MTX-Infusion (otherwise potential loss of efficacy of MTX!). Dexpanthenole (Panthenol®-Solution. 5%) mouth rinsing.

- **Local antimycotic treatment:**
  Amphotericine B, nystatine, fluconazole

- **Local antiviral treatment**
  Aminoquinuride / tetracaine-HCI, Aciclovir®

- **Local anaesthesia:**
  Benzocaine PO
Granulocyte Colony-stimulating Factors

- **Primary prophylaxis for expected febrile neutropenia (FNP)**
  - If expected risk for FNP 10–20%:
    - In case of individual risk factors
  - If expected risk for FNP >20% (e.g. DAC, dose-dense CT)

- **Secondary prophylaxis during chemotherapy**
  (previous FNP or neutropenia grade IV > 7 days)

- **Therapeutic usage for FNP**

- **Start related to chemotherapy and duration**
  - Pegfilgrastim day 2
  - Lipegfilgrastim day 2
  - Filgrastim/Lenograstim from day 2–3 until ANC > 2–3 x 10^9

**Oxford / LoE / AGO LoE / GR**

- 1b B +/-
- 3b C +
- 1a A ++
- 1b B ++
- 1a A +/-
- 1b A ++
- 1b B +
- 1b A ++


### Management of Febrile Neutropenia


**Definition**

oral temperature of >38.5°C or two consecutive readings of >38°C for 2 h in a patient with an ANC of <500 cells/mm³ or expected to fall to <500 cells/mm³

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<td>Clinical examination</td>
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<tr>
<td>Daily evaluation</td>
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<td>D</td>
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<td>Hospitalization of high risk patients</td>
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<tr>
<td>Homecare in low risk patients</td>
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<td>A</td>
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<tr>
<td>Differential blood count</td>
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<td>D</td>
</tr>
<tr>
<td>Blood cultures</td>
<td>5</td>
<td>D</td>
</tr>
<tr>
<td>Imaging of lungs</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Immediate initial empiric antibiotic therapy</td>
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<td>A</td>
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<tr>
<td>Empiric antifungal therapy 4–7d</td>
<td></td>
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<tr>
<td>in case of failure of antibiotic therapy</td>
<td>1b</td>
<td>A</td>
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<tr>
<td>G-CSF for treatment (not prophylactic)</td>
<td>2b</td>
<td>B</td>
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</table>
Recommendations need to be regularly updated according to the changes in microbial sensitivity and resistance towards antiinfective treatments.

Arbeitsgemeinschaft Infektionen in der Hämatologie und Onkologie (AGIHO) der Deutschen Gesellschaft für Hämatologie und Onkologie e.V. (DGHÖ) regularly issues such recommendations in German.
Dexrazoxane

http://www.onkosupport.de/e974/e2538/e3782/e3494/ASORS_AV_Paravasate-Guidelines_04-2010.pdf

- Treatment of anthracycline extravasation
- In combination with anthracyclines for cardiac protection
- In cardiac risk patients
  - Dexrazoxane
  - Consider alternative regimens (anthracycline-free, liposomal)

Oxford / AGO
LoE / GR

2b B +
1a B +/-
1b B +
5 D ++
Paravasation
Dexrazoxane

Day 1: 1000 mg/m² (max. 2000 mg), IV 1–2 hrs
Day 2: 1000 mg/m² (max. 2000 mg), IV 1–2 hrs
Day 3: 500 mg/m² (max. 1000 mg), IV 1–2 hrs

Otherwise or if treatment with dexrazoxane is not indicated, following measures are recommended

1. Local cooling: ice packs for 15 min every 6 hrs, for at least 3 days, alternatively: 24 h continuous ice cooling

2. Local application (with swab) of dimethylsulfoxid 99% (DMSO) every 3-4 hours for at least 3 days (better 14 days), allow it to dry on air. The interval may be extended to 6 hours from day 4 onward.
Antiemetic Therapy

http://www.mascc.org/antiemetic-guidelines

- After assessment of emetic potential of chemotherapy protocol
- Neurokinin-1-receptor-antagonists
- Dexamethasone
- 5-HT₃-antagonists
- Metoclopramide

Oxford / AGO LoE / GR
5  D  ++
1b  A  ++
1a  A  ++
1b  A  ++
3b  C  +
MASCC/ESMO Antiemetic Guideline 2011

Multinational Association of Supportive Care in Cancer

Organisation und Vorstand:
Richard J. Gralla, MD
Fausto Roila, MD
Maurizio Tonato, MD
Jørn Herrstedt, MD
# Supportive Therapy

## Antiemetics

<table>
<thead>
<tr>
<th>Wirkstoffgruppe</th>
<th>Substanz</th>
<th>Dosierung</th>
<th>Nebenwirkungen</th>
<th>Potenzial</th>
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<tr>
<td><strong>Serotoninantagonisten</strong></td>
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<tr>
<td></td>
<td>Ondansetron</td>
<td>8 mg i.v., 2 x 4-8 mg p.o.</td>
<td>Kopfschmerzen, Diarrhoe, Flushsymptomatik</td>
<td>sehr hoch</td>
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<tr>
<td></td>
<td>Tropisetron</td>
<td>5 mg i.v., 5 mg p.o.</td>
<td>Transaminasenanstieg</td>
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<td></td>
<td>Granisetron</td>
<td>1-3 mg i.v.</td>
<td>Darmatonie in hoher Dosierung</td>
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<tr>
<td></td>
<td>Palonosetron</td>
<td>0, 25 mg i.v.</td>
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<tr>
<td><strong>NK 1-Antagonisten</strong></td>
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<td>sehr hoch</td>
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<tr>
<td></td>
<td>Aprepitant</td>
<td>125 mg d1, 80 mg d 2-3 p.o.</td>
<td>Cytochrom-P-450-Aktivierung mit Dosisreduktion von Dexamethason (2 x 8 mg). Keine Kombination mit Astemizol, Terfenadin, Cisaprid</td>
<td>hoch</td>
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<tr>
<td></td>
<td>Fosaprepitant</td>
<td>150 mg d1 i.v.</td>
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<tr>
<td><strong>Dopaminantagonisten/substituierte Benzamide</strong></td>
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<td></td>
<td>Metoclopramid</td>
<td>bis zu 120 mg/24h als Dauerinfusion od. als Tropfen</td>
<td>Dyskinesien (Antidot:Biperiden) Angstreaktion, Depressionen, Diarrhoe</td>
<td>hoch</td>
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<td></td>
<td>Alizaprid</td>
<td>bis zu 300 mg i.v. oder p.o./24 h ( 6 Amp. od. 6 Tbl.)</td>
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<td><strong>Phenothiazine/Butyrophenone</strong></td>
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<td></td>
<td>Haloperidol</td>
<td>1-3 mg 4 x/d</td>
<td>Sedation, Senkung der Krampschwelle, transiente Leberwerterhöhung</td>
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<td><strong>Corticosteroide</strong></td>
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<td>mäßig</td>
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<td></td>
<td>Dexamethason</td>
<td>8-20 mg i.v. 1-3 x/d</td>
<td>Blutzuckerentgleisung, psychotische Reaktionen, Flush, Blutdruckanstieg</td>
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<td></td>
<td>Prednisolon</td>
<td>100-250 mg i.v. 1-3 x/d</td>
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<td><strong>Benzodiazepine</strong></td>
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<td></td>
<td>Diazepam</td>
<td>bis zu 20 mg/d</td>
<td>Sedation, Atemdepression</td>
<td>gering</td>
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<td>Lorazepam</td>
<td>0,5-1,0 mg/d</td>
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<td><strong>Antihistaminika</strong></td>
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<td>gering</td>
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<td></td>
<td>Dimenhydrinat</td>
<td>bis zu 3 x 50 mg/d</td>
<td>Sedation, Mundtrockenheit</td>
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Analgesia
(See Specific Guidelines for Analgesia www.dgss.org)

- **Non-opioids; WHO Step 1**
  Diclofenac resinate, ibuprofene and / or metamizole, paracetamole

- **Mild opioids; WHO Step 2**
  Tramadol (preferentially „retard“-formulations)
  or tilidine / naloxone (also as „retard“-formulations)

- **Strong opioids; WHO Step 3**
  Morphine, buprenorphine (sublingual or transdermal), fentanyl (transdermal), hydromorphone, oxycodone, as back-up levomethadone. The dose of opioids should be titrated step by step according to the analgetic effect.

- **Additional drugs – „adjuvants“**
  Gabapentine, pregabaline, carbamazepine, amitriptyline, bisphosphonats
Diarrhea

- **Adsorbent agents**
  - Carbo medicinalis; caoline / pectine, Al-Mg-silicate hydrate

- **Analgetics, opioids**
  - Loperamide; codeine, morphine IV, tinctura opii, butylscopolamine

- **Colitis pseudomembranosa**
  - Metronidazols or (if not effective) vancomycine
Constipation

Important Side Effect of Opioid Treatment

- **Swelling agents**
  - Psyllium, flaxseed (shredded)

- **Osmotic laxatives**
  - Macrogol > Lactulose (Cochrane review LoE 1a, AGO+)
  - Oral radio-opaque material: ultima ratio e.g. sodium amidotrizoate
  - Sorbite

- **Motility stimulating laxatives**
  - Sennae, Ricinus, Bisacodyl, sodium-picosulfate

- **Emollients** (Internal lubricants e.g. paraffin)
  - MethylNaltrexone (in opioid-related constipation)
Palliative Care

- “...expert consensus that combined standard oncology care and palliative care should be considered early in the course of illness for any patient with metastatic cancer and/or high symptom burden.”

- “Palliative care should be initiated by the primary oncology team and augmented by collaboration with an interdisciplinary team of palliative care experts.”

- “Expert palliative care, including effective control of pain and other symptoms, should be a priority.”

1 Smith et al, J Clin Oncol 30 880-887, 2012
3 Cardoso et al, Breast 21:242-252, 2012
Supportive Care (2/22)

No further information

No references
**Guideline spectrum (3/22)**

*Further information:*

Specific national and international guidelines deal with various aspects of evidence-based supportive therapy of cancer patients. We try to quote these guidelines wherever appropriate, but underline that the listings of relevant guidelines do not claim to be complete. The listing is clearly biased towards German and English language. Special emphasis is put on aspects concerning breast cancer patients. In the German environment, special interest is earnt by the publications of Arbeitsgem. Supportive Maßnahmen in der Onkologie, Rehabilitation und Sozialmedizin der DKG: http://www.onkosupport.de


*No references*
Further information:

Prior to 2007, the erythropoiesis-stimulating agents (ESAs) epoetin alfa and darbepoetin alfa were indicated for use in chemotherapy-induced anemia to achieve target hemoglobin (Hb) levels of approximately 12 grams per deciliter (gm per dL), and treatment was to be withheld if Hb exceeded 13 gm per dL. In March 2007, the FDA changed the labeling of the ESAs to add boxed warnings, updated in November 2007, to include the following key points: (a) ESAs should be used only to treat anemia that occurs in patients with cancer while they are undergoing chemotherapy; (b) treatment with ESAs should be stopped when chemotherapy ends; and (c) dosing ESAs to an Hb target of 12 gm per dL or greater has resulted in more rapid cancer progression or shortened overall survival in patients with breast, head and neck, lymphoid, cervical, and non-small cell lung malignancies. In January 2008, the FDA specified that the increased risk of more rapid tumor growth or shortened survival was associated with ESAs when "administered in an attempt to achieve a Hb level of 12 gm per dL or greater, although many patients did not reach that level." A new black-box warning regarding this association was added to the labels of the ESAs in March 2008, and the FDA mandated further label changes on July 30, 2008, that ESA therapy should not be initiated in patients receiving chemotherapy at Hb levels of 10 gm per dL or higher.

OBJECTIVE: To (a) assess the prevalence and predictors of ESA administrations at Hb levels above 12 gm per dL among patients with a diagnosis of solid or hematologic cancer or myelodysplastic syndrome who began their first regimen of conventional myelosuppressive chemotherapy between 2002 and 2006, and (b) describe patterns of ESA treatment subsequent to the first ESA administration at Hb above 12 gm per dL.

In 2012 a Cochrane review was published by Tonia et al., extracting data from a total of 91 trials with 20,102 participants to perform a systematic review, concluding that ESAs reduce the need for red blood cell transfusions but increase the risk for thromboembolic events and deaths. There is suggestive evidence that ESAs may improve QoL. Whether and how ESAs affects tumour control remains uncertain. The increased risk of death and thromboembolic events should be balanced against the potential benefits of ESA treatment taking into account each patient’s clinical circumstances and preferences. More data are needed for the effect of these drugs on quality of life and tumour progression. Further research is needed to clarify cellular and molecular mechanisms and pathways of the effects of ESAs on thrombogenesis and their potential effects on tumour growth.
References:


Further references:

Statement: An increased mortality and tumor progression by the use of ESF can not be safely ruled out

levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study, J Clin Oncol. 2005 Sep 1;23(25):5960-72

Relevant Guidelines:

American society of clinical oncology/american society of hematology clinical practice guideline update on the use of epoetin and darbepoeitin in adult patients with cancer.
Rizzo JD, Brouwers M, Hurley P, Seidenfeld J, Somerfield MR, Temin S.


Practical Use of ESAs (5/22)

Further information:

For practical use refer to relevant practice guidelines. The increased risk of death and thromboembolic events should be balanced against the potential benefits of ESA treatment taking into account each patient’s clinical circumstances and preferences.

References:

Relevant guidelines (6/22)

No further information

References:

Prophylaxis of Infection (7/22)

Further information:

According to relevant guidelines, antibiotic prophylaxis of asymptomatic patients under chemotherapy should be restricted to high risk cases: one selective criterion could be expected duration of neutropenia of greater than 10 days (NCCN). (ASCO absolute neutrophil count < 100/µl > 7days) N.B.: Standard chemotherapy protocols such as used in breast cancer patients do not regularly justify antibiotic prophylaxis.

The use of oral prophylactic antibiotics in patients with neutropenia is controversial and not recommended by the Australian Consensus Guidelines 2011 Steering Committee because of a lack of evidence showing a reduction in mortality and concerns that such practice promotes antimicrobial resistance. Recent evidence has demonstrated non-significant but consistent, improvement in all-cause mortality when fluoroquinolones (FQs) are used as primary prophylaxis. However, the consensus was that this evidence was not strong enough to recommend prophylaxis.

Engels EA, Lau J, Barza M. Efficacy of quinolone prophylaxis in neutropenic cancer patients: a meta-analysis. J Clin Oncol 1998;16:1179-1187: In a meta-analysis that evaluated 18 trials (N=1408) in which fluoroquinolones were compared to either placebo or TMP/SMX, fluoroquinolone prophylaxis significantly reduced the incidence of Gram-negative infections by about 80% compared with those without prophylaxis (relative risk=0.21; 95% CI, 0.12-0.37), leading to an overall reduction in total infections.

Latest update: in the latest ASCO Guidelines on Antimicrobial Prophylaxis and Outpatient Management… (2013) the use of antimicrobial prophylaxis is only recommended for patients expected to have 100 neutrophils/µL for 7 days, unless other factors increase risks for complications or mortality to similar levels. The authors clearly state, that chemotherapy for solid tumors rarely leads to the mentioned conditions. An oral fluoroquinolone is preferred for antibacterial prophylaxis and an oral triazole for antifungal prophylaxis. The guideline encourages the use of myeloid growth factor prophylaxis to render antimicrobial prophylaxis unnecessary.
Interventions such as footwear exchange, protected environments, respiratory or surgical masks, neutropenic diet, or nutritional supplements are not recommended because evidence is lacking of clinical benefits to patients from their use.

References:


Relevant Guidelines
Antimicrobial Prophylaxis and Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy: American Society of Clinical Oncology Clinical Practice Guideline
Christopher R. Flowers, Jerome Seidenfeld, Eric J. Bow, Clare Karten, Charise Gleason, Douglas K. Hawley, Nicole M. Kuderer, Amelia A. Langston, Kieren A. Marr, Kenneth V.I. Rolston, and Scott D. Ramsey
Published Ahead of Print on January 14, 2013 as 10.1200/JCO.2012.45.8661
Relevant guidelines (8/22)

No further information

References

**Mukositis (9/22)**

**Further information:**


Die Pathogenese der Mukositis ist nicht vollständig geklärt. Diagnostik, Therapie und Prophylaxe werden bisher nicht standardisiert durchgeführt und sind hauptsächlich auf die Symptomkontrolle ausgerichtet.“

**References:**

**Relevant Guidelines**

Granulocyte Colony-stimulating Factors (10/22)

Further information:

The ability to deliver the planned dose and intensity of chemotherapy (the amount of drug administered/unit of time) is important for tumor control and survival. In clinical practice, neutropenic events are the main limiting factors towards achieving this aim. Furthermore, severe neutropenia accompanied by fever, so called „febrile neutropenia (FN)“, is the most serious manifestation of neutropenia usually requiring hospitalization and intravenous antibiotics. Without stringent management FN is associated with significant morbidity and mortality. The primary use of recombinant granulocyte colony-stimulating factors has reduced the incidence of febrile neutropenia during dose-dense adjuvant/neoadjuvant chemotherapy programs for breast cancer.

In 2012, a Cochrane review sought to assess the effect of prophylactic colony-stimulating factors (CSFs) in reducing the incidence and duration of FN, and all-cause and infection-related mortality during chemotherapy in patients with breast cancer.

The authors concluded that „In patients with breast cancer receiving chemotherapy, CSFs have shown evidence of benefit in the prevention of FN. There is evidence, though less reliable, of a decrease of all-cause mortality during chemotherapy and a reduced need for hospital care. No reliable evidence was found for a reduction of infection-related mortality, a higher dose intensity of chemotherapy with CSFs or diminished rates of severe neutropenia and infections. The majority of adverse events reported from CSF use were bone pain and injection-site reactions but no conclusions could be drawn regarding late-term side effects. “

In a comparative effectiveness study, pegfilgrastim prophylaxis was associated with a reduced risk of neutropenia-related or all-cause hospitalization relative to filgrastim prophylaxis.

A recent study demonstrated in high risk breast cancer that 6 mg lipegfilgrastim, a novel glyco-pegylated granulocyte-colony stimulating factor, was as effective as pegfilgrastim in reducing neutropenia in patients with breast cancer receiving myelosuppressive chemotherapy.
References:

Relevant Guidelines:

ASCO:  
*Thomas J. Smith (Chair), James Khatcheressian, Gary H. Lyman, Howard Ozer, James O. Armitage, Lodovico Balducci, Charles L. Bennett, Scott B. Cantor, Jeffrey Crawford, Scott J. Cross, George Demetri, Christopher E. Desch, Philip A. Pizzo, Charles A. Schiffer, Lee Schwartzberg, Mark R. Somerfield, George Somlo, James C. Wade, James L. Wade, Rodger J. Winn, Antoinette J. Wozniak, and Antonio C. Wolff*  

NCCN:  
NCCN Guidelines Version 1.2012 Panel Members Myeloid Growth Factors


Stimulation der Granuloapoese mit G-CSF
Relevant guidelines (11/22)

No further information

References:

Management of Febrile Neutropenia (12/22)

Further information:

The most important treatment aspect is to initiate calculated antibiotic treatment as soon as possible, but no later than 2 hours after onset of fever, according to updated guidelines.

A Cochrane review sought to evaluate the safety and effectiveness of adding colony stimulating factors (CSF) to antibiotic therapy when treating febrile neutropenia caused by cancer chemotherapy. The authors looked for all randomized controlled trials (RCTs) that compare CSF plus antibiotics versus antibiotics alone for the treatment of established febrile neutropenia in adults and children. After inclusion of 13 studies the authors concluded, that „the use of CSF in patients with febrile neutropenia due to cancer chemotherapy does not affect overall mortality, but reduces the amount of time spent in hospital and the neutrophil recovery period. It was not clear whether CSF has an effect on infection-related mortality.“

References:


Relevant Guidelines:

ASCO:
*Thomas J. Smith (Chair), James Khatcheressian, Gary H. Lyman, Howard Ozer, James O. Armitage, Lodovico Balducci, Charles L. Bennett, Scott B. Cantor, Jeffrey Crawford, Scott J. Cross, George Demetri, Christopher E. Desch, Philip A. Pizzo, Charles A. Schiffer, Lee Schwartzberg, Mark R. Somerfield, George Somlo, James C. Wade, James L. Wade, Rodger J. Winn, Antoinette J. Wozniak, and Antonio C. Wolff*

NCCN:
NCCN Guidelines Version 1.2012 Panel Members Myeloid Growth Factors


Arbeitsgemeinschaft Infektionen in der Hämatologie und Onkologie (AGIHO) der Deutschen Gesellschaft für Hämatologie und Onkologie e.V. (DGHO) [www.dgho-infektionen.de](http://www.dgho-infektionen.de) (H. Link et al: erstellt 04/07)
**Calculated Antibiotic Therapy in FN (13/22)**

*Further information:*

*The most important treatment aspect is to initiate calculated antibiotic treatment as soon as possible, but no later than 2 hours after onset of fever, according to updated guidelines.* Recommendations need to be regularly updated according to the changes in microbial sensitivity and resistance towards antiinfective treatments.

*References:*

*Relevant practice guidelines:*

Arbeitsgemeinschaft Infektionen in der Hämatologie und Onkologie (AGIHO) der Deutschen Gesellschaft für Hämatologie und Onkologie e.V. (DGHO) [www.dgho-infektionen.de](http://www.dgho-infektionen.de) (H. Link et al: erstellt 04/07)
**Dexrazoxane (14/22)**

*Further information:*

Anthracyclines are among the most active chemotherapeutic agents in cancer treatment. Although infrequent, cumulative dose-dependent cardiotoxicity is nevertheless a significant side effect of this therapy resulting in reduced cardiac reserve or even frank cardiac failure. Although used in several types of malignancy, anthracyclines are most commonly used in breast cancer treatment. Importantly, recent advances have also seen the increasing use of another cardiotoxic agent, the monoclonal antibody trastuzumab, both in the metastatic as well as in the adjuvant breast cancer setting. A great number of studies review and discusses the relationship of cardiotoxicity and anthracycline use, particularly in the breast cancer setting, and explores available treatment options for the anthracycline-treated patients based on evidence from recent Phase III trials.

Dexrazoxane is not recommended for routine use in breast cancer (BC) in adjuvant setting, or metastatic setting with initial doxorubicin-based chemotherapy. Consider use with metastatic BC and other malignancies, for patients who have received more than 300 mg/m(2) doxorubicin who may benefit from continued doxorubicin-containing therapy. Cardiac monitoring should continue in patients receiving doxorubicin.

A Cochrane review investigated Cardioprotective interventions for cancer patients receiving anthracyclines and concluded: “…The nine included studies of dexrazoxane enrolled 1403 patients. The meta-analysis of dexrazoxane showed a statistically significant benefit in favour of dexrazoxane for the occurrence of heart failure (Relative Risk (RR) 0.29, 95% CI 0.20 to 0.41). No evidence was found for a difference in response rate or survival between the dexrazoxane and control group. Only for one adverse effect (abnormal white blood cell count at nadir) a difference in favour of the control group was identified.”

**References:**


**Paravasation Dexrazoxane (15/22)**

*Further information:*

Although indicated and approved for cardioprotection, dexrazoxane has been suggested as being helpful in the case of anthracyclin paravasation. The agent is administered systemically.

*References:*

*Relevant practice guideline*

Zytostatika-induzierte Paravasate - Empfehlungen zu Diagnose, Prophylaxe und Therapie [ PDF-Datei ]
Arbeitsversion der ASORS Paravasate-Guidelines (Stand April 2010)
Maike de Wit, Petra Ortner, Hans-Peter Lipp, Jalid Sehouli, Michael Untch, Markus Ruhnke, Regine Mayer-Steinacker, Carsten Bokemeyer, Karin Jordan
download: http://www.onkosupport.de/e974/e2538/e3782/e3494/ASORS_AV_Paravasate-Guidelines_04-2010.pdf

Witte J, de Wit M.
Prävention, Diagnostik und Therapie der zytostatikaassozierten Paravasation - Was tun wenn’s brennt?
Im Focus Onkologie 2010;6:50-55.
Antiemetic Therapy (16/22)

Further information:

Nausea and vomiting are two of the most severe problems for patients treated with chemotherapy. Until the late 1970s, nausea and vomiting induced by chemotherapy was an almost neglected research area. With the introduction of cisplatin, the cytotoxin with the highest emetic potential, research was stimulated and has now resulted in the development of two new classes of antiemetics, the serotonin and neurokinin antagonists. A large number of trials have fine-tuned antiemetic therapy and made evidence-based recommendations possible for the majority of patients receiving chemotherapy. A systematic Review summarizes recommendations from the evidence-based guidelines developed by the Multinational Association of Supportive Care in Cancer (MASCC).

The combination of ondansetron, dexamethasone and aprepitant is able to protect 66–78% of patients from emesis and 48–49% from nausea during the first cycle of cisplatin-based chemotherapy. In a subsequent trial, single-dose intravenous fosaprepitant (150 mg) given with ondansetron and dexamethasone was noninferior to standard 3-day oral apreptiant in preventing CINV during OP and DP.

In women receiving cyclophosphamide/anthracycline-based chemotherapy for breast cancer, the corresponding figures are 76% and 33%. In patients with breast cancer treated with anthracycline plus cyclophosphamide chemotherapy and receiving the same antiemetic prophylaxis for acute emesis, dexamethasone was not superior to apreptiant but instead had similar efficacy and toxicity in preventing delayed emesis.

New antiemetics have been highly successful in the prophylaxis of emesis, but are less effective in the prevention of nausea. There is, therefore, a particular interest in initiating trials to investigate agents with potential anti-nausea effect, such as olanzapine. Guidelines such as the MASCC antiemetic guidelines are only useful if they are continuously updated and implemented in the daily clinic. To encourage implementation, the MASCC guidelines have been translated into several languages, are updated every 6 months (as new data arise), and are always accessible on the MASCC website.

References:

www.mascc.org
Keith B.: Systematic review of the clinical effect of glyocorticoids on nonhematologic malignancy. BMC Cancer (2008);8:84
Schmoll HJ et al. (2006) Comparison of an aprepitant regimen with a multiple-day ondansetron regimen, both with dexamethasone, for antiemetic efficacy in high-dose cisplatin treatment. Ann Oncol 17: 4112–4119
Massa E, Astara G, Madeddu C, Dessi M, Lepori S, Mantovani G. Palonosetron plus dexamethasone effectively prevents acute and delayed chemotherapy-induced nausea and vomiting following highly or moderately emetogenic chemotherapy in pre-treated patients who have failed to respond to a previous antiemetic treatment: Comparison between elderly and non-elderly patient response. Crit Rev Oncol Hematol. 2008 Aug 23. [Epub ahead of print]


Relevant Guidelines

http://www.mascc.org/antiemetic-guidelines

Antiemetische Prophylaxe gemäß MASCC- und ASCO-Guidelines

[ PDF-Datei (auf www.krebsgesellschaft.de) ]
Kurzgefasste interdisziplinäre Leitlinie 2008 der Deutschen Krebsgesellschaft, die unter der Verantwortung der ASO bzw. ASORS erstellt wurde.

Supportive Therapie: Antiemetic Guideline MASCC (17/22)

No further information

No references
Supportive Therapie: Antiemetics (18/22)

No further information

No references
Analgesia (19/22)

No further information

References:

Relevant guidelines

Deutsche Gesellschaft zum Studium des Schmerzes, www.dgss.org

Schmerztherapie bei Tumorerkrankungen http://www.krebsgesellschaft.de/download/l1_n_02.pdf
Diarrhea (20/22)

No further information

References:

Relevant Guidelines


**Constipation (21/22)**

*Further information:*

Constipation is not infrequently encountered during chemotherapy. Particularly around the time in autumn and winter, when indoor heating begins and air humidity is consequentially reduced. Sufficient fluid uptake should be encountered by treating health care providers. Opioid therapy usually results in constipation and regular digestion should always be aimed at.

A Cochrane meta-analysis investigated differential efficacy of different agents, the authors concluded, that „The findings of our work indicate that Polyethylene glycol is better than lactulose in outcomes of stool frequency per week, form of stool, relief of abdominal pain and the need for additional products. On subgroup analysis, this is seen in both adults and children, except for relief of abdominal pain. Polyethylene Glycol should be used in preference to Lactulose in the treatment of Chronic Constipation.“

More recently, the use of parenteral methylnaltrexone for the management of constipation in palliative care patients was evaluated. Subcutaneous methylnaltrexone; an opioid-receptor antagonist, is now licensed for the treatment of opioid-induced constipation in palliative care when response to usual laxative therapy is insufficient. The authors concluded, that „Here it found that subcutaneous methylnaltrexone is effective in inducing laxation in palliative care patients with opioid-induced constipation and where conventional laxatives have failed. However, the safety of this product is not fully evaluated. Large, rigorous, independent trials are needed.“

*References:*


Candy B, Jones L, Goodman ML, Drake R, Tookman A. Laxatives or methylnaltrexone for the management of constipation in palliative care patients. Cochrane Database of Systematic Reviews 2011, Issue 1.
Growing evidence and increasing awareness in international recommendations underlines the relevance of combined standard oncology care and palliative care. This should be considered early in the course of illness for any patient with metastatic cancer and/or high symptom burden. It is evident that the access to palliative care, including effective control of pain and other symptoms, is important in the treatment of metastatic breast cancer patients.

References:

Smith et al, J Clin Oncol 30 880-887, 2012
Breast Cancer: Specific Situations
Breast Cancer:
Specific Situations

- **Versions 2005-2013:**
  Dall / Fersis / Friedrich / Gerber / Göhring / Harbeck / Huober / Janni / Loibl / Lück / Lux / Maass / Mundhenke / Oberhoff / Rody / Scharl

- **Version 2014:**
  Fehm / Schneeweiss
Breast Cancer: Specific Situations

- Young patients
- Pregnancy-associated BC
- Elderly patients
- Male patients
- Inflammatory BC
- Occult Primary [Carcinoma of unknown primary (CUP)]
- Paget’s disease
- Malignant Phyllodes Tumor
- Sarcomas
# Breast Cancer in Young Women ≤ 35 Years

- **Aggressive biological behavior**
  - Oxford / AGO LoE / GR: 2a B

- **Benefit from chemotherapy**
  - Oxford / AGO LoE / GR: 1b A ++

- **Benefit from endocrine therapy**
  - Oxford / AGO LoE / GR: 1b A ++

- **Benefit from HER2 targeted therapy**
  - Oxford / AGO LoE / GR: 2b B ++

- **Benefit from CT induced temporary amenorrhoea**
  - Oxford / AGO LoE / GR: 2b B +/-*
  - GnRH as ovary protection 2 weeks prior CT
    - Oxford / AGO LoE / GR: 1a A - *

- **Surgery like ≥ 35 y (in particular BCT)**
  - Oxford / AGO LoE / GR: 2b B +

- **Stage II–III benefit from PMRT**
  - Oxford / AGO LoE / GR: 2b C +

- **Genetic and fertility counseling**
  - Oxford / AGO LoE / GR: 2b B ++

* Study participation recommended
Breast Cancer During Pregnancy* or Breast Feeding

- Breast imaging & biopsy like in non-pregnant
- Staging: ultrasound, chest X-ray if indicated
- Surgery like in non-pregnant patients
- Sentinel node excision (technetium only)

**SNE during 1st trimester**

- Sensitivity and specificity not established (during lactation); breast feeding should be avoided for 24 hrs
- Blue dye (has not been tested in pregnant animals or humans)

* Participation in register study recommended
Breast Cancer During Pregnancy*

- Radiation therapy during pregnancy
- (Neo-)adjuvant chemotherapy only after first trimester (indication as in non-pregnant)
  - AC, FAC (FEC)
  - Taxanes
  - MTX (e.g. CMF)
- Endocrine treatment
- HER2-neu targeted treatment
- Bisphosphonates

Oxford / AGO
LoE / GR

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford</th>
<th>LoE</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Radiation therapy during pregnancy</td>
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<td>C</td>
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<tr>
<td>(Neo-)adjuvant chemotherapy only after first trimester</td>
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<td>AC, FAC (FEC)</td>
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<td>Taxanes</td>
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<td>MTX (e.g. CMF)</td>
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<td>Endocrine treatment</td>
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<td>HER2-neu targeted treatment</td>
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<td>Bisphosphonates</td>
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* Participation in register study recommended
Breast Cancer During Pregnancy*

- Delivery should be postponed until sufficient fetal maturation (avoid iatrogenic prematurity) 2b C ++
- Termination of pregnancy does not improve maternal outcome 3b C
- Delivery mode like in healthy women, avoid delivery ≤3 weeks from prior chemotherapy 4 C ++
- If further systemic therapy is needed after delivery, breast feeding may be contra-indicated depending on drug toxicities 5 D ++

* Participation in register study recommended
Pregnancy Associated Breast Cancer*: Outcome

BC during pregnancy / lactation
   ➢ Adequate treatment is essential

Pregnancy and lactation after BC
   ➢ Outcome not compromised

* Participation in register study recommended

Oxford
LoE

3a
Geriatric Assessment

- No specific algorithm is available
- Ability to tolerate treatment varies greatly („functional reserve“)
- Comprehensive geriatric assessment (CGA) describes a multidisciplinary evaluation of independent predictors of morbidity and mortality for older individuals
  - Physical, mental, and psycho-social health
  - Basic activities of daily living (dressing, bathing, meal preparation, medication management, etc.)
  - Living arrangements, social network, access to support services
- Assessment tools:
  - Charlson Comorbidity Index (widely used; good predictor over a 10-year period)
  - 12 prognostic indicators to estimate 4-year mortality risk
  - Short screening tests (more qualitative evaluation)
  - IADL (IADL = The Lawton Instrumental Activities of Daily Living Scale with 8 domains of function, that are measured), G8
Treatment for Fit Elderly Patients
(Life Expectancy > 5 yrs. and Acceptable Comorbidities)

- Geriatric assessment
- Treatment according to standard
  - Surgery similar to „younger“ age
  - Endocrine treatment (endocrine resp.)
- Chemotherapy
  - < 70 years
  - > 70 years (especially N+, ER/PgR-)
- Radiotherapy
- Omit Radiotherapy after BCT in low risk with endocrine treatment**
- Trastuzumab

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<tr>
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<th>LoE / GR</th>
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<tr>
<td></td>
<td>2b B ++</td>
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<td></td>
<td>2a C ++</td>
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<td>1a A ++</td>
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<tr>
<td>&lt; 70 years</td>
<td>1a A +</td>
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<tr>
<td>&gt; 70 years</td>
<td>2a C +*</td>
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<tr>
<td>(&lt;especially N+, ER/PgR-)</td>
<td>1a A +</td>
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<tr>
<td>(especially N+, ER/PgR-)</td>
<td>1b(a) B +</td>
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<tr>
<td>Trastuzumab</td>
<td>2b C +</td>
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*Study participation recommended

**Population > 70 y, hormone receptor positive and if endocrine therapy is planned (CAVE: increased risk local recurrence)
Treatment for Frail Patients
(Life Expectancy <5 yrs, Substantial Comorbidities)

- Reduced standard treatment
  - Options extrapolated from trials in elderly:
    - No breast surgery
      (consider endocrine options)
      - Grade B, Level II, Strength ++
    - No axillary clearing (≥ 60 y, cN0, Rec pos)
      - Grade B, Level II, Strength +
    - No radiotherapy (≥ 65 y, pT1, pN0, Rec pos)
      - Grade B, Level I, Strength ++
    - Hypofractionated radiotherapy
      - Grade C, Level II, Strength +
    - No chemotherapy >70 years and negative risk-benefit analysis
      - Grade C, Level II, Strength +
Male Breast Cancer: Diagnostic Work-Up and Loco-Regional Therapy

- Diagnostic work-up as in women
  - Mammography
  - Ultrasound
- Standard-surgery: Mastectomy
  - BCT my be an option (tumor breast relation)
  - Sentinel-node excision (SNE)
- Radiotherapy as in women (consider tumor breast relation!)
- Genetic counselling if one additional relative affected (breast/ovarian cancer)
- Screening for 2nd malignancies according to guidelines

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<th>Oxford / AGO</th>
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*Participation in register study recommended
## Male Breast Cancer: Systemic Therapy

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>Level of Evidence (LoE)</th>
<th>Grade (GR)</th>
<th>Recommendation</th>
</tr>
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<tbody>
<tr>
<td><strong>Adjuvant chemotherapy as in women</strong></td>
<td>2a B</td>
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<tr>
<td><strong>HER2 targeted therapy</strong></td>
<td>5 D</td>
<td>+*</td>
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<tr>
<td><strong>Endocrine therapy</strong></td>
<td>4 D</td>
<td>++</td>
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<tr>
<td>- Tamoxifen</td>
<td>2b B</td>
<td>++</td>
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<tr>
<td>- Aromatase inhibitors (adjuvant)</td>
<td>2b B</td>
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<tr>
<td>- Aromatase inhibitors (metastatic BC)</td>
<td>4 C</td>
<td>+/-</td>
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<tr>
<td>- GnRHa and Al (metastatic BC)</td>
<td>4 C</td>
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<tr>
<td>- Fulvestrant (metastatic BC)</td>
<td>4 C</td>
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<tr>
<td><strong>Palliative chemotherapy as in women</strong></td>
<td>4 C</td>
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* Participation in register study recommended
Primary Inflammatory Breast Cancer (IBC, cT4d)

- In case of invasive BC and clinical signs of inflammation (e.g. ≥ 1/3 of the breast affected) determine stage cT4d
- Staging
  - Skin punch biopsy (at least 2; detection rate < 75%)
- Preoperative chemotherapy
  - Regimens as in non-inflammatory BC
  - Anthracycline and taxane-based
  - In HER2+ disease addition of trastuzumab
- Mastectomy after chemotherapy
  - Breast conserving therapy in case of pCR
  - Sentinel excision only
- Radiotherapy
- Postoperative systemic therapy as in non-inflammatory BC

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<thead>
<tr>
<th>Oxford / AGO LOE / GR</th>
<th>2c</th>
<th>B</th>
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<tbody>
<tr>
<td>Skin punch biopsy</td>
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<tr>
<td>Preoperative chemotherapy</td>
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<td>Radiotherapy</td>
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<tr>
<td>Postoperative therapy</td>
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Axillary Metastasis in Carcinoma of Unknown Primary (CUP)

- Mammography / Breast ultrasound
- Breast MRI
- Staging (CT thorax / abdomen, thyroid sonography, ENT investigation)
- PET / PET-CT
- Gene expression profiling (e.g. CupPrint™)
- ER, PgR, HER2
- Axillary dissection
- Systemic treatment according N+ tumor
- Mastectomy if breast MRI is negative
- Breast irradiation if breast MRI is negative
- Irradiation of regional lymph nodes according to breast cancer guidelines

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Oxford / AGO LOE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammography / Breast ultrasound</td>
<td>3 B ++</td>
</tr>
<tr>
<td>Breast MRI</td>
<td>3 B ++</td>
</tr>
<tr>
<td>Staging (CT thorax / abdomen, thyroid sonography, ENT investigation)</td>
<td>3 B ++</td>
</tr>
<tr>
<td>PET / PET-CT</td>
<td>3b B +/-</td>
</tr>
<tr>
<td>Gene expression profiling (e.g. CupPrint™)</td>
<td>2c B +/-</td>
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<tr>
<td>ER, PgR, HER2</td>
<td>5 D ++</td>
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<tr>
<td>Axillary dissection</td>
<td>3a C ++</td>
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<tr>
<td>Systemic treatment according N+ tumor</td>
<td>3a C ++</td>
</tr>
<tr>
<td>Mastectomy if breast MRI is negative</td>
<td>3a C -</td>
</tr>
<tr>
<td>Breast irradiation if breast MRI is negative</td>
<td>3b C +/-</td>
</tr>
<tr>
<td>Irradiation of regional lymph nodes according to breast cancer guidelines</td>
<td>3b B +</td>
</tr>
</tbody>
</table>
Paget’s Disease of the Breast

- Histological verification
- Mammography, sonography
  - MR of the breast if other imaging negative
- Surgery must include NAC (R0)
  - Wide excision (like DCIS) + radiotherapy
  - Sentinel-node excision (SNE)
- Paget’s disease with underlying disease (e.g. invasive breast cancer, DCIS)
  - Therapy according to standard of the underlying disease
- Isolated Paget’s disease of the NAC (<5%):
  - Surgical resection only, no adjuvant radiotherapy

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<th>Oxford / AGO</th>
<th>LOE / GR</th>
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Malignant Phyllodes Tumor

- Complete (wide) local excision or MRM
- SNE / Axillary dissection in cN0
- Staging
- Systemic adjuvant therapy (chemo, endocrine)
- Adjuvant radiotherapy
  - if $T \geq 2$ cm (BCT) or $T \geq 10$ cm (mastectomy)
- Treatment of local recurrence
  - R0 resection
  - Radiotherapy, chemotherapy after R1 resection
- Distant metastases (very rare)
  - Treatment like soft tissue sarcomas

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<tr>
<th>Treatment</th>
<th>Oxford / AGO LOE / GR</th>
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<tr>
<td>Complete (wide) local excision or MRM</td>
<td>2b B ++</td>
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<td>SNE / Axillary dissection in cN0</td>
<td>4 C --</td>
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<td>Staging</td>
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<td>Systemic adjuvant therapy (chemo, endocrine)</td>
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<td>Adjuvant radiotherapy</td>
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<td>R0 resection</td>
<td>4 C ++</td>
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<tr>
<td>Radiotherapy, chemotherapy after R1 resection</td>
<td>4 C +/-</td>
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<tr>
<td>Treatment like soft tissue sarcomas</td>
<td>4 C ++</td>
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</tbody>
</table>
Sarcoma / Angiosarcoma of the Breast
(Note: very aggressive!)

### Treatment of Primary Disease:
- Mammography, Sonography to determine extent of disease
- Preoperative MRI to determine extent of disease
- Diagnosis by core biopsy
- Diagnosis by FNB
- Staging
- Prognostic factors: size, grade, margins
- Surgery with wide clear margins
  - Breast-conserving therapy if feasible
- Axillary dissection if cN0
- Adjuvant chemotherapy, radiotherapy
  - Adjuvant chemotherapy (anthracycline-based), radiotherapy in case of high risk (grade II-III, size > 5 cm, R1)

### Treatment of Local Recurrence:
- R0 resection
- Radiotherapy, chemotherapy after R1 resection

### Distant Metastases / Unresectable Tumors:
- Treatment like soft tissue sarcomas
- Paclitaxel weekly / liposomal doxorubicin (in angiosarcoma)
- Antiangiogenic treatment
- Trabectedin (after anthracycline/ ifosfamide failure in leiomyosarcoma)
Breast Cancer: Specific Situations (2/18)

Further information:

Update January 2014 – Fehm/Schneeweiss
Update January 2013 – Fersis/Friedrich
Update January 2012 – Lux/Lück
Update Februar 2011 – Janni/Huober
Update Januar 2010 – Mundhenke/Rody

Screened for: Clinical Trials, Meta-Analysis, Practice Guideline, Randomized Controlled Trial, Reviews

Screened guidelines:

This chapter of rare diseases cannot deliver references for every statements separately but is providing them where possible.

No references
Breast cancer: Specific situations (3/18)

No further information

No references
Breast Cancer in Young Women ≤ 35 years (4/18)

Further information:

Breast cancer in young women is rare and probably a specific entity of high risk for recurrence. Therefore chemotherapy is almost always indicated. Radiotherapy seems to deliver additional benefit. Treatment with tamoxifen of up to ten years is beneficial.
It could be demonstrated that therapy induced amenorrhea might be of some benefit in premenopausal women but if this is especially true for pts<35 years has not been proven.

Counselling for fertility protection should be offered and the patient needs to be informed about the possibility of compromised ovarian function due to adjuvant chemo- or endocrine therapy. In Germany the FERTIPROTECT Project is a platform to gain information how and where to get information.

References:

Prognosis in young women:

3. Gonzalez-Angulo AM et al., Women age < or = 35 years with primary breast carcinoma: Disease features at presentation. Cancer 2005;103: 2466-2472


Chemotherapy in young women:
1. Aebi S. Special issues related to the adjuvant therapy in very young women. Breast 2005, 14: 594-599 (Review)

Endocrine therapy in young women:
2. C. Davies et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013;381,805–816

Benefit from trastuzumab:


Benefit from temporary amenorrhoea after adjuvant chemotherapy (chemotherapy induced or GnRHa-related)

Surgery in young women (Surgery like $\geq 35$y - in particular BCT):


Genetic and fertility counselling:


Breast Cancer During Pregnancy or Breast Feeding (5/18)

Further information:


Study link:
http://germanbreastgroup.de/studien/adjuvant/brustkrebs-in-der-schwangerschaft.html

The individual breast cancer risk is strongly influenced by endocrine factors. Early menarche, late menopause, low number of children, short nursing periods, and increasing age at first birth are significant risk factors. The life style of the industrialized western world is thus causing an increase in breast cancer incidence.

Moreover, breast cancer incidence is also increasing with age. Pregnant breast cancer patients have an average age of about 32-38 years. Given the increasing average age of pregnant women, the co-incidence of a breast cancer diagnosis with the patient also being pregnant or nursing is becoming more frequent. This fact urgently needs to be acknowledged and accepted by physicians since the diagnosis of breast cancer is frequently being delayed in pregnancy. The average time interval between first symptoms and a definite diagnosis is about 5-15 months. Thus, the diagnosis is typically made at a later stage than outside of pregnancy. This delayed diagnosis is most likely one of the main reasons for the fact that overall survival of pregnant breast cancer patients is worse than that of non-pregnant breast cancer patients even though their stage-adapted prognosis is similar. As a consequence, we not only recommend that pregnant or nursing women need to examine their breast on a regular basis but also that clinical examination of breasts and loco-regional lymph nodes should be part of routine medical care during pregnancy and nursing period.

Another reason for the delayed diagnosis next to “simply not thinking about it” is the reluctancy to order appropriate imaging and diagnostic test during pregnancy. Pregnancy or nursing period are no reason for delaying appropriate diagnostic work-up of a suspicious lesion. The same imaging techniques as in non-pregnant women are available. Breast ultrasound will not harm the fetus. Moreover, mammography can also be used if needed, since the danger of too much radiation for the fetus can be overcome by appropriate protective measures. MRI does not have the danger of radiation but
experiences with pregnant breast tissue is limited and interpretation may be difficult. Moreover, the position in the MRI may not be acceptable for most pregnant women. Thus, there is no reason to replace an indicated mammography by an MRI in pregnant patients. Physiological changes in pregnant or nursing breasts cause an increased false-positive rate in imaging procedures. Thus, in pregnant or nursing women, every suspicious palpable tumor definitely needs to be submitted to a histological diagnosis. As in non-pregnant patients, this can be done by minimal invasive techniques such as core or vacuum biopsies under local anesthesia. An open biopsy is only indicated in situations where minimal invasive procedures may not allow a definite diagnosis. In addition, pregnant women as well as their physicians may be more reluctant towards an open biopsy than towards a minimal invasive procedure, thus increasing again the danger of a delay in diagnosis. It is important to make the pathologist aware of the concurrent pregnancy or nursing period in order to avoid pregnancy-associated diagnostic histological changes to cause any diagnostic difficulties or even false-positive findings.

After diagnosis, therapy recommendations follow treatment outside of pregnancy with a few modifications: Therapeutic radiation of the breast is contraindicated during pregnancy so that a mastectomy would theoretically be the surgical method of choice. However, since adjuvant chemotherapy may be indicated in most cases anyway, the beginning of a radiation therapy may automatically be delayed by a few months thus allowing the pregnancy to reach (almost) full term by the end of chemotherapy. Thus, after delivery, radiation therapy is of course possible and thus breast conserving therapy is a valid option in breast cancer during pregnancy.

In general, chemotherapy can only be applied after the 12th week of pregnancy, i.e. after organogenesis. After the first trimester, chemotherapy does not cause an increased rate of malformations. Yet, there is an increased risk for growth retardation, premature labour, premature delivery, and intrauterine fetal death. Little is known about gonade development of and about the risk for malignancy in the children who were subjected to chemotherapy while still in utero. Indication for chemotherapy follows the guidelines for non-pregnant patients. Yet, one has to consider the individual teratogenic potential of the different chemotherapeutics and plan the delivery date accordingly. Among the most frequently used chemotherapeutics in breast cancer, antimetabolites such as methotrexate (or 5-fluorouracil) should not be used due to their teratogenic potential. For anthracyclines, there is no evidence for major complications. FEC, EC and Epi weekly are safe combinations. Undertreatment should be avoided. There is growing evidence that the use of taxanes is safe. So far, no major complications have been reported. The same is probably true for vinorelbine. Which is possible cytotoxic agent in pregnant metastatic breast cancer patients. Dose-dense chemotherapy does not appear to increase the risk of fetal or
maternal complications, but is not recommended at the moment. In conclusion, pregnancy is not a reason for withholding an indicated chemotherapy – the timing however, should take the delivery date into account. Treatment with trastuzumab in HER2-positive tumours in pregnant women cannot be recommended. Results of studies of bisphosphonates in pregnant animals have shown maternal toxicity, fetal underdevelopment, embryo lethality, hypocalcaemia and skeletal retardation, so that bisphosphonates are contraindicated in pregnancy. The delivery should not be planned for the immediate three weeks following a chemotherapy cycle, since maternal side effects (e.g. fatigue, hematotoxicity) may increase the maternal risk for delivery-associated complications. Moreover, the placental excretion function disappears after delivery and the newborn may not be able to metabolize potential chemotherapy remainders. Prognosis is not improved by cessation of nursing. However, nursing should be stopped before surgery on order to reduce volume of the breast and its blood flow. Moreover, nursing is not recommended during chemotherapy due to excretion of many chemotherapeutics into the milk. There is neither evidence of direct damage to the fetus due to breast cancer nor of metastases into the fetus. Yet, rare placental metastases have been described. Termination of pregnancy does not improve the prognosis of the breast cancer and thus is not considered a therapeutic option. Yet, depending on gestational age, termination may be considered if therapy options for the mother are severely compromised by the pregnancy. Diagnosis of a malignancy during pregnancy causes extreme burden and conflicts for the pregnant women and their families touching on emotional, religious, social and ethical aspects next to medical issues. Most pregnant cancer patients want to “live long enough to see their child grow up”. Thus, decisions about continuing the pregnancy and about treatment should not only consider medical arguments but also take psychological as well as emotional needs of the pregnant patient into account.

References:

Statement: Breast imaging & biopsy like in non-pregnant:

Statement: Staging: ultrasound, chest X-ray if indicated:

Statement: Surgery like in non-pregnant patients:

Statement: „Sentinel node biopsy“ during pregnancy:
Reviews:

1. Sophie E. McGrath Chemotherapy for breast cancer in pregnancy: evidence and guidance for oncologists
Breast Cancer During Pregnancy (6/18)

No further information

References:

Statement: Radiotherapy during pregnancy:

Statement: (Neo-)adjuvant chemotherapy only after first trimester (indication as in non-pregnant):

Statement: AC, FAC, (FEC):
Statement: MTX (e.g. CMF):

Statement: Taxanes:

Statement: Endocrine treatment:

Statement Trastuzumab during pregnancy:

Statement Bisphosphonate during pregnancy:
Breast cancer during pregnancy (7/18)

Further information:

These statements are derived from common sense and literature cannot fully be assigned.

References:
In general:

Statements: Delivery should be postponed until sufficient fetal maturation since termination of pregnancy does not improve maternal outcome:

Statements: Delivery mode like in non-pregnant; Avoid delivery ≤3 weeks from prior chemotherapy:

Statements: If further systemic therapy is needed after delivery, breast feeding may be contraindicated depending on drug toxicities:
6. Williams Obstetrics lecture book
Further information:

The outcome of pregnant breast cancer patients do not seem to be inferior to those being non pregnant. Data investigating this topic are inconsistent incorporating pregnant patients and PABC. A recent study however demonstrated a poorer survival for PABC. Most investigations did not report on the applied therapy which might be a confounding factor.

Pregnancy after breast cancer is safe and does not compromise the outcome. A healthy mother effect might be the reason, however, larger case series including also patients with advanced disease prosposed additional effects.

References:

Statement: Breast cancer during pregnancy / lactation: Outcome not compromised, if treated adaequately:


**Statement:** Pregnancy and lactation after breast cancer: Outcome not compromised:

9. Gelber S et al. Effect of pregnancy on overall survival after diagnosis of early stage breast cancer. JCO 2001; 19:1671-5: IBCSG-participants - matched pair analysis: 94 patients pregnant after treatment (RR 0.44 – 0.96; p=0.04).


**Review articles:**


Geriatric Assessment (9/18)

Further information:

There is no accepted definition of the “older patient” but criteria exist for the assessment of biological age. The distinction between fit patients, vulnerable patients and frail patients has been established. Geriatric evaluation is an optimal tool for individually assessing the feasibility of treatment.

References:

**Treatment for Fit Elderly Patients (10/18)**

*Further information:*

Chemotherapy is feasible in fit elderly pts. The first randomized prospective trial in >600 pts. Demonstrated a survival benefit for patients treated with AC or CMF compared to those treated with Capecitabine alone. In an unplanned subset analysis, patients with hormone receptor negative disease derived the highest benefit from the combination therapy. Another German trial (ICE II) is investigating a combination of capecitabine with nab-paclitaxel compared to EC/CMF. In a retrospective analysis of four german randomized (neo)adjuvant trials taxanes seem feasible. Sequence therapies should be preferred; paclitaxel weekly seems to be the preferred taxane regimen in terms of toxicity for elderly pts. The study by Jones et al. evaluating TC as anthracycline free regimen showed especially good results in pts. older than 65 years.

In respect to older patients, current data increasingly suggest that the operation of the axilla could be avoided in cases of small tumours and a clinically negative axilla. Martelli et al. presented the update of a study including 671 patients ≥ 70 years (172 with axillary dissection and 499 patients without an operation of the axilla) at a median follow up time interval of 15 years. There was no significant difference in mortality within this group in the case of pT1 cN0 disease (10.7% versus 10.7%, p=0.836).

*References:*

*Statement: Treatment according to standard:*


Statement: Surgery similar to „younger“ age:


Statement: Endocrine treatment (endocrine resp.):
22. C. Davies et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013;381, 805–816

Statement: Chemotherapy in pts. < 70 years:
25. Fargeot P: Disease-free survival advantage of weekly epirubicin plus tamoxifen versus tamoxifen alone as adjuvant treatment of operable, node-positive, elderly breast cancer patients: 6-year follow-up results of the French adjuvant study group 08 trial. J Clin Oncol. 2004 Dec 1;22(23):4622-30

Statement: Chemotherapy in pts. > 70 years:

Statement: Radiotherapy:
Recently the long term results of a randomized phase 3 trial investigating the role of radiotherapy in elderly patients with breast conserving was reported. Patients 70 years or older with a clinically negative axilla, T1 tumors, breast conserving surgery, and hormone receptor positive tumor were randomized to Tamoxifen and radiation or to tamoxifen alone. Half of the pts were older than 75 years and around 60 % had no axillary surgery. Distant disease free survival and overall
survival at 10 years were without significant difference between the groups. Local relapse was rare however higher in the no radiation arm (Breast: 2% vs 9%; Axilla: 0 % vs 3%).

In a selected low risk population (T1, N0,) in elderly patients (< 70 years) with ER positive disease radiotherapy may be omitted when endocrine treatment with tamoxifen is planned.

28. Sautter M.L et al When are breast cancer patients old enough for the quitclaim of local control Strahlenther Onkol 2012 :1-5
39. Kunkler IH et al. The PRIME II trial: Wide local excision and adjuvant hormonal therapy ± postoperative whole breast irradiation in women ≥ 65 years with early breast cancer managed by breast conservation SABCS 2013[S2-01]

Statement: Trastuzumab:
41. Tan-Chiu E: Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol. 2005 Nov 1;23(31):7811-9
Treatment for Frail Patients (Life Expectancy < 5 Years, Substantial Comorbidities (11/18))

Further information:

Frailty is a factor that is crucial in modern times for assessing older patients who are fit to undergo more invasive/aggressive management. The presence of multiple co-morbidities also affects outcome of surgery and/or adjuvant treatment for older breast cancer patients and can increase the risk of death from causes other than breast cancer. There thus may circumstances where non-operative therapies or even no treatment may be considered preferable due to these patients’ factors and evaluations.

References:

1. Walzer DE Measuring the value of radiotherapy in older women with breast cancer J Clin Oncol 2012 30 (23) 2809-2811
2. Audisio RA et al When reporting on older patients with cancer, frailty information is needed Ann Surg Oncol 2011; 18: 4-5
3. Smith BD et al Improvement in breast cancer outcomes over time: are older missing out? J Clin Oncol 2011 29 (35) 4647-4653
4. Hughes KS et al Lumpectomy plus tamoxifen with or without irradiation in women age 70 or older with early breast cancer 2010 J Clin Oncol 28:69s (suppl 15, abstr 507).

Statement: Reduced standard treatment:

Statement: No breast surgery (consider endocrine options):


Statement: No axillary clearing (≥ 60 y, cN0, Rec pos):


Statement: No radiotherapy (≥ 70 y, pT1, pN0, Rec pos):

15. Kunkler IH et al. The PRIME II trial: Wide local excision and adjuvant hormonal therapy ± postoperative whole breast irradiation in women ≥ 65 years with early breast cancer managed by breast conservation SABCS 2013[S2-01]

Statement: Hypofractionated radiotherapy:

Statement: No chemotherapy > 70 years and negative risk benefit analysis:
Male Breast Cancer: Diagnostic Work-up and Loco-regional Therapy (12/18)

Further information:

General:
The median age of male breast cancer is around 10 years later than in female. Survival seems to be not inferior to that of women with breast cancer. Male breast cancer patients developed secondary malignancies in more than 20% of the patients. In general the level of evidence is low and most recommendations are linked to those of postmenopausal women.

Diagnostic:
In men 80-90% of maligne breast tumors are not detected by mammography or they are covered by a gynecomastia. Ultrasound seems more effective

Surgery:
Wide excision in male breast cancer will almost always include resection of the nipple due to the small amount of breast tissue, and there is some evidence that this is not the most effective method of local control. To establish axillary status in clinically node-negative cases evidence is building up of the accuracy and low morbidity associated with sentinel-node biopsy in women. The technique has also been used in men with similarly encouraging results and sentinel node biopsy will probably become standard practice in the future for node-negative male breast cancer.

Genetic counselling:
Approximately 3-5% of female breast cancers are thought to result from autosomal dominant inheritance, particularly BRCA1 and BRCA2 mutations. The equivalent figure for men is estimated to be between 4% and 40%. Cases of male breast cancer are much more common in BRCA2 than BRCA1 families. In a southern Californian population, there were no BRCA1 mutations in 54 patients with male breast cancer, whereas there was a BRCA2 mutation in two (4%) patients. In 94 patients in the UK there were no germline BRCA1 mutations, but five (6%) patients had BRCA2 mutations with 20% reporting a first-degree relative with breast cancer. In neither study was there a correlation between the location of the mutations with in the BRCA2 gene and risk of breast cancer.

Radiotherapy: Adjuvant radiotherapy has been delivered proportionally more frequently to men with breast cancer than to women, because the disease was more advanced locally in men and thought to be more aggressive. There is no evidence, however, that stage by stage the indications for radiotherapy should be different in men than in women. However,
retrospective studies that investigated the effects of radiotherapy in male breast cancer have not clearly shown a survival benefit.

References:

General:

Statement: Diagnostic work up as in women

Statement: Mammography:

Statement: Ultrasound:

Statement: Standard-surgery: Mastectomy –men:

Statement: Sentinel-node excision (SNE):

Statement: Radiotherapy as in women (consider tumor breast relation!):

Statement: Genetic counselling if 1 additional relative affected (breast/ovarian cancer):

Statement: Screening for 2nd malignancies according guidelines:

Statement: Systemic therapy:

Review articles:
**Male Breast Cancer: Systemic Therapy (13/18)**

*Further information:*

Adjuvant chemotherapy: LoE: 4; References 1-4 (retrospective analysis, case series)
Adjuvant CMF chemotherapy was associated with an improvement in disease-free and overall survival. Only 50% of the patients (N=24) actually received the planned 12 cycles of CMF due to side effects.

Adjuvant endocrine therapy: LoE: 4; References 1-6 (retrospective analysis, case series)
Male cancers are mostly endocrine responsive: 91% of male BC are ER positive and 96% PR positive. It is proved that adjuvant tamoxifen in men improves 5-year disease-free survival and OS. Tamoxifen is well tolerated with the most common side effects being: Loss of libido (29%), weight gain (25%), heat flushes (21%), mood changes (21%), and depression (17%). The use of aromatase inhibitors has to be regarded as an experimental therapy at present. Due to the different physiological prerequisites for estrogen production in men and women, the effect of lowering serum estrogen levels in men has not yet been scientifically validated. Comparing adjuvant therapy with tamoxifen to aromatase inhibitors for 257 male breast cancer patients the overall survival was significantly better after treatment with tamoxifen.

Palliative endocrine therapy: LoE: 4; References 1-4 (retrospective analysis, case series)
In the metastatic setting there are data on achievement of stable disease being the maximum response to AI. Case reports do exist for anastrozol, letrozol and also fulvestrant.

Because of the low evidence level for the treatment of male breast cancer we believe that new studies should not exclude male patients. International registries should be participated in.

*References:*

*Statement: Adjuvant Chemotherapy:*


Statement Trastuzumab:

Statement endocrine therapy:

Statement palliative chemotherapy:
Inflammatory Breast Cancer (cT4d) (14/18)

Further information:

There is little information on inflammatory breast cancer (IBC) alone. Most retrospective analysis focus on T4 carcinomas without separating T4d cancer. Primary IBC is probably a distinct biological entity compared to non IBC. Prospective randomised studies for the diagnosis and treatment of patients suffering from inflammatory breast cancer are still missing. The matter of current updates is aiming on the definition, including the confirmation of an invasive carcinoma as well as clinical signs of the skin affection ≥ 1/3 of the breast involved (previous definition > 2/3 of the breast) [Dawood et al., 2011]. Biopsies of the skin should be acquired for diagnostic reasons [AGO 2c/B/+], with a detection rate of < 75%.

Because of that a multidisciplinary approach consisting of preoperative chemotherapy, mastectomy and postoperative radiotherapy and adjuvant treatment is necessary. In the NOAH trial patients with locally advanced HER2 positive breast cancer were randomized to chemotherapy and trastuzumab preoperatively followed by adjuvant trastuzumab after surgery or to preoperative chemotherapy alone. 27% of the patients had inflammatory disease. pCR rates were significantly higher with the combination of trastuzumab and chemotherapy. In addition trastuzumab significantly improved event-free survival both in the whole study group and in pts with inflammatory breast cancer.

The use of Trastuzumab as neoadjuvant treatment option for inflammatory breast cancer [AGO 2b/B/++] is further supported by the current data of the NOAH-study [Semiglazov et al., 2011].

References:

Statement: Staging:


**Statement: Preoperative chemotherapy:**

**Statement: Regimens as in non-inflammatory BC:**

**Statement: in HER2 positive disease addition of trastuzumab:**
**Statement: Mastectomy after chemotherapy:**


**Statement: Sentinel lymph node**


**Statement: Radiotherapy:**


Statement: Postoperative systemic therapy as in non-inflammatory BC

Reviews:
Axillary Metastasis in Carcinoma of Unknown Primary (CUP) (15/18)

Further information:

Magnetic resonance imaging of the breast enables identification of an occult breast primary tumor in < or = 75% of women who present with adenocarcinoma in the axillary lymph nodes and can influence surgical management. Positron emission tomography scan also can be used in the diagnosis of CUPs, but its value is controversial. (Varadhachary GR: Cancer. 2004 May 1;100(9):1776-85) MRI is also reliable in finding a breast cancer in women with axillary nodal metastases and unknown primary tumour. (Lalonde L: Can Assoc Radiol J. 2005 Dec;56(5):301-8) All patients should have a standard evaluation including CT thorax / abdomen, thyroid ultrasound, ENT investigation, urinanalysis, fecal occult blood test. Jerusalem G: Ann Oncol 17 (Suppl 10) 2006:168-176) The appropriate treatment of the breast after an axillary presentation of CUP continues to be a controversial issue. Khandelwal AH: Am J Surg. 2005 Oct;190(4):609-13) Probably these patients need to be treated as typical stage II patients. (Matsuoka, K: Breast Cancer. 2003;10(4):330-4 / Pavlidis N: Eur J Cancer. 2003 Sep;39(14):1990-2005) The management of axillary node metastases in women with adenocarcinoma should be the same as the management of patients with lymph node metastases in breast cancer. If mammary MRI is negative, surgical treatment is not recommended and an axillary node excision should be performed. (Buqat R:Bull Cancer. 2002 Oct;89(10):869-75).

The radiation therapy of the ipsilateral breast could be considered if axillary metastases are detected in patients suffering from carcinoma of unknown primary (CUP) with inconspicuous MRI of the breast [AGO 3b/C/+/-]. 48 patients with negative MRI results were included into a non-randomised study, herein 73% were treated with radiation and 27% were observed. The median follow-up after 68 months showed a recurrence free survival in 84% versus 34% (p<0.001) [Barton et al., 2011].

A systematic review of 24 retrospective studies enrolling 689 patients with axillary metastases of unknown origin showed that axillary CUP is associated with similar presentation, biology and outcome to node positive overt breast cancer and should be treated accordingly.
References:


Statement: Mammography / Breast ultrasound/ Breast MRI:

1. Lalonde L: Can Assoc Radiol J. 2005 Dec;56(5):301-8

Statement: Staging:


Statement: PET

5. Varadhachary GR: Cancer. 2004 May 1;100(9):1776-85

Statement: Gene expression profiling:

2. Gauri et al., JCO, 26:4442-8, 2008;
3. Horlings et al., JCO, 26: 4435-4441, 2008
Statement: ER, PR, HER2

Statement: Axillary dissection:

Statement: Systemic treatment according N+ tumor:

Statement: Mastectomy without (in-)breast tumor:
LoE: 4; References 1-4 (retrospective analysis, case reports)
Statement: Breast irradiation if breast MRI is negative:

Paget’s Disease of the Breast (16/18)

Further information:

Pagest’s disease is a rare disease, therefore separate literature is scarce.

References:

Statement: MR of the breast if other imaging negative


Statement: Wide excision (like DCIS) + radiotherapy:


Statement: Sentinel-node excision (SNE):

Statement: Paget’s disease with underlying disease (e.g. invasive breast cancer, DCIS): therapy according to standard of the underlying disease:


Statement: Isolated Paget’s disease of the NAC (<5%): surgical resection only, no adjuvant radiotherapy
Phyllodes tumors (PTs) of the breast are biphasic neoplasms composed of epithelium and a spindle-cell stroma. Currently, PTs are classified as benign, borderline, or malignant based on histopathologic features. The presence of pain (P = 0.03), tumor size > 5 cm (P = 0.005), postmenopausal status (P < 0.04), heavy cellular pleomorphism (P = 0.007), high mitotic activity (P = 0.002), tumoral grade (P = 0.006) and metastasis (P < 0.00001) were prognostic factors of poor survival. (Roa JC: Pathol Int. 2006 Jun;56(6):309 / Chaney AW: Cancer. 2000 Oct 1;89(7):1502-11).


References:

Statement: Complete (wide) local excision or MRM (LoE: 2c):
References 1-4 (retrospective analysis, case reports)
1. Macdonald OK: Cancer. 2006 Nov 1;107(9):2127-33

Statement: SNE / Axillary dissection in cN0 (LoE: 4):
References 1-3 (retrospective analysis, case reports)
2. Chen WH: J Surg Oncol. 2005 Sep 1;91(3):185-94

Statement: Staging:

Statement: Systemic adjuvant therapy/ Chemotherapy (LoE: 4):
References 1 (cohort studies, case reports)
**Endocrine therapy (LoE: 5):**


**Statement: Adjuvant radiotherapy: Radiotherapy after R0 (LoE: 4):**

References 1-3 (retrospective analysis, cohort studies)

2. Chen WH: J Surg Oncol. 2005 Sep 1;91(3):185-94

**Statement: Adjuvant radiotherapy, if \( T \geq 2 \text{cm (BCT)} \) or \( T \geq 10 \text{cm (mastectomy)} \):**


**Statement: Treatment of local recurrence => R0 Resection: LoE: 4; References (retrospective analysis , case reports):**

1. Soumarova R: Arch Gynecol Obstet. 2004 May;269(4):278-81

**Statement: Radiotherapy, chemotherapy after R1 resection**

**Statement: Distant metastases (very rare) => Treatment like soft tissue sarcomas**

**Sarcoma / Angiosarcoma of the Breast (18/18)**

**Further information:**

The management of angiosarcomas at different sites were recently summarized in review. Radical surgery with complete RO resection is the primary treatment of choice. Because of the high risk of local recurrence radiotherapy should be considered. In view of the risk of metastatic disease there is a rationale for adjuvant chemotherapy. However up to now there is no convincing evidence to support the use of adjuvant chemotherapy. Active agents in metastatic angiosarcoma are anthracylines, taxanes and ifosfamide. In phase 2 trials antiangiogenic drugs showed promising activity.

**Reference:**


*Primary angiosarcoma* (AS) predominantly occurs in premenopausal women with a mean age of 39 years and must be distinguished from secondary (radiotherapy-associated) angiosarcoma which occurs in older patients. Angiosarcoma differs from other soft tissue sarcomas of the breast in terms of its aggressive behavior with a tendency to local recurrence and distant metastasis. At time of diagnosis 37.5% of breast AS had evidence of distant metastasis. Cases of primary AS arising in pregnancy have been described and tend to be of higher histological grade and is reported to have an especially poor prognosis. However, despite the association with young age of onset and pregnancy, there is no evidence that breast AS is hormone dependent.

Breast AS present as a large, ill defined mass and has an average tumor diameter of 4 – 5.5 cm. The imaging features of AS are non-specific in mammography and up to 33% are undetectable. On ultrasound examination, there is a heterogenous echogenicity with hyperechoic areas without acoustic shadowing. The most useful imaging technique to determine the extent of AS is breast MRI that shows hypervascular, heterogenous masses that are hypointense on T1-weighted images and hyperintense on T2-weighted images. Histologic grading is important for the assessment of prognosis with the 5-year recurrence free survival of 76% for low grade AS and 15% for high grade AS but reported survival data differ widely. The role of adjuvant radiotherapy and
Chemotherapy is controversial. In a recent study, 29 of 69 patients received adjuvant combination chemotherapy with antracycline-ifosfamide or gencitabine-taxane. Four had complete response and 10 a partial response (48% overall response rate), but there was no difference in DFS or OS between patients who received no adjuvant treatment. In an older series, 20% of low, 40% of intermediate and 71% of high-grade lesions recurred following chemotherapy. In contrast 27%, 40% and 100% of low, intermediate and high-grade lesions recurred in patients who did not receive adjuvant chemotherapy. Therefore, the role of adjuvant chemotherapy for AS of the breast remains unclear.

Secondary angiosarcoma (AS) occurs following radiotherapy after breast conserving therapy or after chest wall irradiation after mastectomy. Therefore the term radiotherapy-associated angiosarcoma may also be used. Another, much rarer occurrence of post-treatment angiosarcoma is in the upper limb following longstanding lymphoedema after mastectomy, with or without radiotherapy. This has also been called Steward-Treves syndrome and is not radiotherapy-associated and therefore not considered here.

The risk of radiotherapy-associated angiosarcoma is maximal 5-10 years postradiation. Current data show that not the type of operation in the case of sarcomas of the breast, particularly the angiosarcoma, a serious disease that could appear 10-15 years after radiation therapy, but factors such as size, grading and especially the adequate safety margins are important diagnostic factors. Thus, breast conserving surgeries could be performed with larger safety margins, if feasible and after given consent of the associated risk [AGO 4/C/++] (Al-Benna et al. 2010; Voutsadakis et al., 2011). It should be diagnosed through punch biopsy not via fine-needle biopsy. Postoperatively an anthracycline-based chemotherapy in combination with radiotherapy could be considered particularly in high-risk situations [AGO 4/C/+/-] (Barrow et al., 1999). If metastases have already occurred, paclitaxel as well as liposomal doxorubicin should be applied especially in patients with angiosarcoma. In case of unsuccessful treatment with anthracyline and ifosfamid, trabectedin could be used in patients suffering from leiomyosarcoma [AGO 2b/B/+] (Schöffski et al., 2011).

References:

Breast Cancer Follow-Up
Breast Cancer
Follow-Up

- **Versions 2002–2013:**
  Bauerfeind / Bischoff / Blohmer / Böhme / Costa / Diel / Gerber / Hanf / Heinrich / Janni / Kaufmann / Kümmel / Lux / Möbus / Mundhenke / Oberhoff / Scharl / Thomssen

- **Version 2014:**
  Solomayer / Thomssen
Breast Cancer Follow-Up

Objectives

- Improve quality of life
- Improve physical performance
- Reduce therapy related side effects (after surgery, systemic therapy and radiation therapy)
Breast Cancer Follow-Up

Objectives

- **Re-evaluation** of current adjuvant therapy
  - incl. monitoring of compliance with endocrine therapies

- **Pro-active improvement of compliance:**
  - Patient information about efficacy data of 5-10 year endocrine therapy
  - Early therapy of side effects (sports, NSAIDs, vitamin D/Calcium)
Breast Cancer Follow-Up
Objectives

Early detection of curable events
- In-breast recurrence
- Loco-regional recurrence

Early detection of metastases
- Early detection of symptomatic metastases
- Early detection of asymptomatic metastases

Oxford / AGO
LoE / GR

1a B ++
1a B ++
3b C +
1a A -
Breast Cancer Follow-Up Objectives

- Psycho-social aspects of support and counseling
  - Pregnancy, contraception, sexuality, quality of life, menopausal symptoms, fear for recurrence

- Second opinion on primary therapy

- General counseling (genetics, HRT)
Breast Cancer Follow-Up Objectives

Intervention with regard to co-morbidities and life-style risks in order to reduce negative effects on disease course

- **Treatment of type II-diabetes**
  (>25% undetected DM in postmenopausal BC patients)
  ++

- **Weight intervention**
  (if BMI <18.5 and >40)
  2a B +

- **Smoking**
  (bc related mortality 2 x and BC unrelated mortality 4 x elevated)
  2b B ++

- **Moderate sport intervention when physical activity was reduced**
  (rel. reduction of mortality up to 25%)
  1b A ++
Follow-up Objectives Reported by Patients

- Examination of the breast
- Reassurance
- Guidance of patients, answering questions
- Evaluation of treatment and treatment of side effects
- Psychosocial support

Oxford LoE 4 C
### Follow-up Goals Reported by Health Professionals and Patients

<table>
<thead>
<tr>
<th>Health professionals</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Often mentioned</strong></td>
<td></td>
</tr>
<tr>
<td>Early detection of recurrences and second tumors</td>
<td>Examination of the breast</td>
</tr>
<tr>
<td>Psychosocial support</td>
<td>Reassurance</td>
</tr>
<tr>
<td>Guidance, information and referral</td>
<td>Guidance of patients, answering questions</td>
</tr>
<tr>
<td><strong>Occasionally mentioned</strong></td>
<td></td>
</tr>
<tr>
<td>Evaluation of treatment and treatment side effects</td>
<td>Evaluation of treatment and treatment side effects</td>
</tr>
<tr>
<td>Early detection of metastases</td>
<td>Psychosocial support</td>
</tr>
<tr>
<td>Clinical trials, building own database</td>
<td></td>
</tr>
</tbody>
</table>

From: **Kwast AB et al. Eur J Cancer Care (Engl). 2013 Nov;22(6):754-64.**
## Routine Follow-Up Examinations in Asymptomatic Patients

### Tests:

- **History (specific symptoms)**
  - Oxford / AGO LoE / GR: 1a A ++

- **Physical examination**
  - Oxford / AGO LoE / GR: 1a B ++

- **Breast self-examination**
  - Oxford / AGO LoE / GR: 5 D +

- **Mammography**
  - Oxford / AGO LoE / GR: 1a A ++

- **Sonography of the breast**
  - Oxford / AGO LoE / GR: 2a B ++

- **Routine MRI of the breast**
  - Oxford / AGO LoE / GR: 3b B +/-

- **MRI of the breast in case of inconclusive conventional imaging**
  - Oxford / AGO LoE / GR: 3b B +

- **Pelvic examination**
  - Oxford / AGO LoE / GR: 5 D ++
## Routine Follow-Up Examinations in Asymptomatic Patients

<table>
<thead>
<tr>
<th>Examination</th>
<th>LoE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine biochemistry (incl. tumor markers)</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Ultrasound of the liver</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Bone scan</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>CT of chest, abdomen and pelvis</td>
<td>2a</td>
<td>D</td>
</tr>
<tr>
<td>Detection of isolated / circulating tumor cells</td>
<td>2a</td>
<td>D</td>
</tr>
<tr>
<td>PET</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Whole body MRI</td>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>
Local recurrence & in-breast recurrence:

- Incidence 7–20% (depending on time of F/U)
- Breast self-examination
- Physical examination, mammography & US
- Magnetic resonance imaging (MRI)

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Event</th>
<th>Oxford</th>
<th>AGO LoE</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrence &amp; in-breast recurrence</td>
<td>5</td>
<td>D</td>
<td>+</td>
</tr>
<tr>
<td>Breast self-examination</td>
<td></td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Physical examination, mammography &amp; US</td>
<td>1a</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Magnetic resonance imaging (MRI)</td>
<td>3b</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Early Detection of Potentially Curable Events

Contralateral breast cancer:

- Rel. risk: 2.5–5
- Incidence: 0.5–1.0 % / year
- Breast self-examination
- Physical examination, mammography & US
- Routine breast MRI

Oxford / AGO LoE / GR

5 D +

1a A ++

5 D -
Unrelated site carcinoma:

- Colon RR 3.0; endometrium RR 1.6; ovary RR ca. 1.5

- Screening for secondary malignancies according to current guidelines ++

- Pelvic examination and PAP smear 5 D ++

- Routine endometrial ultrasound / biopsy 1b B -
Follow-Up Care for Breast Cancer (incl. LCIS/DCIS)

Recommendations for asymptomatic pts.
(modified ASCO guidelines 2012, NCCN 2.2011 and S3 national German guideline 2012)

<table>
<thead>
<tr>
<th>Clinical follow-up</th>
<th>Follow-Up*</th>
<th>Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years after primary therapy</td>
<td>1 2 3 4 5</td>
<td>&gt; 6</td>
</tr>
<tr>
<td>History, physical examination, counseling</td>
<td>inv.: every 3 months</td>
<td>inv.: every 6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>inv.: every 12 months</td>
</tr>
<tr>
<td></td>
<td>LCIS / DCIS: every 6-12 months</td>
<td>LCIS/DCIS: every 12 months</td>
</tr>
<tr>
<td>Self-examination</td>
<td></td>
<td>monthly</td>
</tr>
<tr>
<td>Imaging modalities and biochemistry</td>
<td>indicated only by complaints, clinical findings or suspicion of recurrence</td>
<td></td>
</tr>
<tr>
<td>Mammo- and sonography</td>
<td>inv.: BCT**</td>
<td>ipsilat.: every 6-12 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>contralat.: every 12 months</td>
</tr>
<tr>
<td></td>
<td>inv.: Mastectomy</td>
<td>on both sides: every 12 months</td>
</tr>
<tr>
<td></td>
<td>LCIS / DCIS</td>
<td>contralateral every 12 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>every 12 months</td>
</tr>
</tbody>
</table>

* Continued follow-up visits if still on adjuvant treatment
** First mammography 6-12 months after completion of breast-conserving radiotherapy
Breast Cancer Follow-up Duration. Breast Nurses.

- Duration of follow-up
  - until 5 yrs
  - until 10 yrs

- Surveillance by specialized breast nurses

Oxford / AGO
LoE / GR

- 1c A ++
- 1c A +
- 2b B +/-*

*Studies recommended
Luminal-like, HER2-positive and Triple-negative Breast Cancer Patients

- Intrinsic typing of breast cancer leads to subgroups with different course of disease. Thus, postoperative surveillance should be adapted to specific time-dependent hazards of recurrence.

- ER-positive patients have stable risk over many years requiring long term surveillance.

- However, patients with HER2-positive disease and TNBC have more risk in the early phase of follow-up and should therefore receive more intense surveillance in the first years of follow-up.

Ribelles et al. BCR 2013
Breast Cancer Follow-Up (2/17)

Further information:

Update 08. Januar 2009 – Janni / Gerber
Update Januar 2011 – Lux/Scharl: minor changes and additions
Update Januar 2012 – Kümme/Bauerfeind: some changes and additions
Update Januar 2013 – Möbus Mundhenke: some changes and additions
Update Januar 2014 – Solomayer, Thomssen: some changes and additions


Screened guidelines:
- Strategies for subtypes—dealing with the diversity of breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011
- CMA: http://www.cmaj.ca/cgi/content/full/158/3/DC1
- Cochrane Collaboration: http://www.cochrane.org/reviews/en/topics/52_reviews.html

No references
Breast Cancer Follow-Up Objectives (3/17)

Further information:

There are indications, that physical activity (as for example walking, yoga, …) and weight reduction during follow-up is able to improve quality of life, improve physical performance, reduce Fatigue, and optimize Outcome. Therefore during follow-up patients should be encouraged to and be supported in measures to achieve these goals.

References:

Statement: Obesity, physical activity and quality of life

Statement: Obesity and breast cancer prognosis
**Breast Cancer Follow-Up Objectives (4/17)**

*Further information:*

Based on the variety of adjuvant treatment options and emerging new evidence within short time, patients’ current and ongoing adjuvant therapy should be re-evaluated repeatedly in order to assure state of the art treatment. With increasing complexity and time length of primary adjuvant treatment, the surveillance and counselling during the follow-up period becomes increasingly important. However, the benefit of this ongoing counselling has to be substantiated yet. During follow-up compliance with endocrine therapies should be monitored. Predictors for discontinuation of treatment are young age and old age, BCT (vs mastectomy), more than 2 comorbidities, higher co-payment required, smaller blister pack, and prescription by general practitioner. Predictors for good compliance are marriage, adjuvant chemotherapy, adjuvant radiotherapy. Intensified surveillance has proved to decrease the lead time until the detection of distant metastases in comparison to conventional surveillance, but has not shown to improve overall survival. In the context of novel treatment modalities for distant disease, however, this objective should be re-examined.

*References:*

**Statement: Re-evaluation of current adjuvant therapy**
1. Expert opinion Organkommission

**Statement: Monitoring of compliance**
1. Hershman DL et al., SABCS, 2010
3. Neven P, Markopoulos C, Tanner MME et al.: The Impact of Educational Materials on Compliance and Persistence with Adjuvant Aromatase Inhibitors: 2 Year Follow-Up and Final Results from the CARIATIDE Study. SABCS 2011 [P5-16-02].
Statement: Early Detection of Distant Disease


Breast Cancer Follow-Up Objectives (5/17)

Further information:

The main objective of following patients after the primary treatment of breast cancer is the detection of potentially curable events, particularly the detection of local recurrences and contralateral breast cancer. With increasing complexity and time length of primary adjuvant treatment, the surveillance and counselling during the follow-up period becomes increasingly important. The psycho-social aspects of support and counselling will gain relevance as more patients survive breast cancer and will encounter long-term treatment.

References:

Statement: Early Detection

Statement: Psycho-social aspects


Breast Cancer Follow-Up Objectives (6/17)

Further information:

The main objective of following patients after the primary treatment of breast cancer is the detection of potentially curable events, particularly the detection of local recurrences and contralateral breast cancer. With increasing complexity and time length of primary adjuvant treatment, the surveillance and counselling during the follow-up period becomes increasingly important. The psycho-social aspects of support and counselling will gain relevance as more patients survive breast cancer and will encounter long-term treatment.

References:

Statement: Early Detection

Statement: Psycho-social aspects

Further information:

Intervention in order to treat co-morbidities and to counsel for life-style risks is recommended aimed at reducing unfavourable effects on the course of the breast cancer disease.

Treatment of type II-diabetes
./.

Weight intervention

Smoking
./.

Moderate sport intervention when physical activity was reduced
Follow-up objectives reported by patients (8/17)

Further information:

Expectations of follow-up and objectives are differently reported by health professionals and patients.

Reference:

Follow-up Goals Reported by Health Professionals and Patients (9/17)

No further information

Reference:

**Routine Follow-Up Examinations in Asymptomatic Patients (10/17)**

*Further information:*

Routine follow-up examinations in asymptomatic patients should comprise history (for specific symptoms), physical examination, mammography, sonography of the breast, MRI of the breast in case of inconclusive conventional imaging and pelvic examination. Breast self-examination is encouraged by expert especially for self awareness, but no survival benefit has been scientifically substantiated so far. Additional examination (compare following slide) are explicitly discouraged for the time being.

*References:

**Statement: History (specific symptoms)**


**Statement: Physical examination**


**Statement: Breast self-examination**

Expert Opinion
Statement: Mammography

Statement: Sonography of the breast

Statement: MRI of the breast in case of inconclusive conventional imaging

Statement: Pelvic examination
Expert Opinion
Routine Follow-Up Examinations in Asymptomatic Patients (11/17)

Further information:
Performing additional tests for recurrence and/or distant metastases screening after primary treatment of breast cancer has shown to reduce disease free survival but does not influence overall survival. Based on current evidence, the AGO discourages additional follow-up examinations in asymptomatic patients, but encourages the performance of future studies on the relevance of additional tests in the context of modern imaging and treatment modalities.

References:

Statement: Magnetic resonance imaging (MRI) of the breast

Statement: Routine biochemistry (incl. tumor markers)

Statement: Ultrasound of the liver

Statement: Bone scan

Statement: Chest X-ray

Statement: CT of chest, abdomen and pelvis

**Statement: Detection of isolated/circulating tumor cells**


**Statement: PET**


**Statement: Whole body MRI**

Early Detection of Potentially Curable Events (12/17)

Further information:

Locoregional recurrences include chest wall recurrences, in-breast-recurrences and other locoregional recurrences (tumor spread in the internal mammary, supraclavicular, infraclavicular, ipsilateral axillary nodes or in the non-breast skin of the ipsilateral chest wall). All other sites of tumor recurrence are classified as distant metastases (DM). The early detection of locoregional recurrences represent a potentially curable situation. A total of 30-40% of potentially treatable relapses are detected by patient self-examination. In studies published before 2000, 15% of such relapse is mammographically detected with 46% detected by routine clinical examination. In those published after 2000, 40% are mammographically detected with 15% detected on routine clinical examination. Mammography detected primaries are more likely to be noninvasive, low tumor stage and node negative. MRI could be useful in patients with unclear mammography and/or ultrasound findings.

References:

Statement incidence:

Statement breast self examination:

Statement physical examination, mammography & US:
**Early Detection of Potentially Curable Events (13/17)**

**Further information:**

Breast cancer patients have an increased risk for contralateral breast cancer (CBC). Young patients with BC treated with tangential breast irradiation experience increased risk of CBC. Adjuvant chemotherapy seems to reduce the risk of CBC during the first 5 years after treatment only. Contalateral breast cancer is diagnosed with more favorable prognostic factors when physical examination and mammography is used during follow-up of breast cancer. Mammography detected primaries are more likely to be noninvasive, low tumor stage and node negative. Annual mammography, routine physical examination and patient self-examination are recommended surveillance to detect IBTR while it can be cured by salvage surgery. MRI should be used to distinguish recurrent tumor from benign post-therapeutic changes in the treated breast.

**References:**

**Statement risk and incidence:**

**Statement breast self examination:**
**Statement physical examination, mammography & US:**

Further information:

There is a significantly increased risk of several kinds of second malignancy in women treated for BC, compared with the general population. These may be due to a co-incidence (ovary), similar mechanisms in carcinogenesis (endometrium), treatment side effects (endometrium), genetic or unknown associations (colon). Patients with breast cancer should be screened for secondary malignancies according to current guidelines. Pelvic examination and PAP smear a recommended every 6 months. The impact of imaging diagnostics is questionable, even in high risk patients. Routine transvaginal sonography or hysteroscopy with biopsy increase the number of interventions in benign changes without proven effects of early detection of malignant disease.

References:

Statement: Risk:


Statement: Screening for secondary malignancies according to current guidelines

Statement: Pelvic examination and PAP smear

1. Rieck GC, Lim K, Rogers MT: Screening for familial ovarian cancer--management and outcome of women with moderate to high risk of developing ovarian cancer. Int J Gynecol Cancer. 2006 Jan-Feb;16 Suppl 1:86-91


Statement: Endometrial ultrasound / biopsy


Follow-Up Care for Breast Cancer (incl. LCIS/DCIS) (15/17)

Further information:

Following these guidelines improves:
- diagnosis of contralateral breast cancer, IBTRs, chest wall recurrences while curable
- improves the detection of treatment related complications and distant disease and
- avoids unnecessary, expensive and potentially harmful tests.

There is no evidence to suggest that clinical examination confers a survival disadvantage compared with other methods of detection. A third of patients may wish to maintain a regular review. There is no clear evidence to recommend a follow-up three monthly. Some guidelines recommended 3 to 6 monthly. It has been shown that after 2 years following the diagnosis of breast cancer there is no evidence to support the view that regular clinical review improves psychological morbidity or quality of life. Patients do not appear to be compromised in terms of early detection of recurrence. Point of need access can be provided by suitably trained specialist nurses and provides a fast, responsive management system at a time when patients really need it. Follow-up of women with LCIS or DCIS includes interval history and physical examinations every 6 to 12 months for five years and then annually, as well as yearly diagnostic mammography. In Patients undergoing breast-conserving therapy, the first follow-up mammogram should be performed 6-12 months after the completion of breast conserving radiation therapy.

This table summarizes a consensus by the AGO.

References:


Breast Cancer Follow-up Duration. Breast Nurses (16/17)

Further information:

The accumulating evidence of the potential benefit that may be achieved by prolonged endocrine therapy, suggests longer surveillance of these patients. Especially in patients with ER-positive disease, recurrence frequently occur after year 5.

The goals of follow-up as perceived and reported by the patients comprises:

- Examination of the breast
- Reassurance
- Guidance of patients, answering questions
- Evaluation of treatment and treatment of side effects
- Psychosocial support.

These goals may be similarly or better achieved by specialized breast nurses. International trials have shown equivalence between physician’s and nurses’ surveillance. Clinical trials should test this also with regard to the German health care situation.

References:

**Luminal-like, HER2-positives and triple-negative breast cancer patients (17/17)**

**Further information:**

Intrinsic typing of breast cancer leads to subgroups with different course of disease. Thus, postoperative surveillance should be adapted to specific time-dependent hazards of recurrence. ER-positive patients have stable risk over many years requiring long term surveillance. However, patients with HER2-positive disease and TNBC have more risk in the early phase of follow-up and should therefore be receive more intense surveillance in the first years of follow-up.

**References:**

Loco-regional Recurrence
Loco-regional Recurrence

- **Version 2002:**
  Brunnert / Simon

- **Versions 2003–2013:**
  Audretsch / Bauerfeind / Costa / Dall / Fehm / Fersis / Friedrich / Gerber / Göhring / Hanf / Lisboa / Mundhenke / Rezai / Solomayer / Souchon / Thomssen

- **Version 2014:**
  Dall / Maass
## Loco-regional Recurrence

### Incidence and Prognosis

<table>
<thead>
<tr>
<th>Localization</th>
<th>Frequency (%)</th>
<th>5-y. Overall Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral recurrence$^1$</td>
<td>10 (2–20)</td>
<td>65 (45–79)</td>
</tr>
<tr>
<td>(post BCT + irradiation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest wall$^1$</td>
<td>4 (2–20)</td>
<td>50 (24–78)</td>
</tr>
<tr>
<td>(post mastectomy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>As above plus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>supraclavicular fossa$^2$</td>
<td>34%</td>
<td>49% (3-y. OS)</td>
</tr>
<tr>
<td>Axilla:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After ALND$^1$</td>
<td>1 (0.1–8)</td>
<td>55 (31–77)</td>
</tr>
<tr>
<td>After SNB$^4$</td>
<td>1</td>
<td>93%</td>
</tr>
<tr>
<td>Multiple localizations$^2$</td>
<td>16 (8–19)</td>
<td>21 (18–23)</td>
</tr>
</tbody>
</table>

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$^2$ Reddy JP. Int J Radiat Oncol Biol Phys 80(5):1453-7, 201;  
Loco-regional Recurrence Staging

Examinations before treatment:

- Tissue Biopsy
- Reassessment of ER, PR, HER2
- Complete re-staging

Oxford LoE / AGO LoE / GR

<table>
<thead>
<tr>
<th>Examination</th>
<th>LoE</th>
<th>D</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue Biopsy</td>
<td>5</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td>Reassessment of ER, PR, HER2</td>
<td>5</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td>Complete re-staging</td>
<td>5</td>
<td>D</td>
<td>++</td>
</tr>
</tbody>
</table>
Increased risk for loco-regional recurrence

- Young age
- Positive microscopic margins
- Number of involved lymph nodes
- Omitting adjuvant radiotherapy (if indicated)
- Extensive intraductal component
- Vessel invasion
- Triple negative and HER2 / HR- vs. HR+
- Grading (G3 vs. G1)
- Elevated proliferation markers: partic. Ki67
- pT (> 2 vs. ≤ 2cm)
  * node negative
- pN (N1 vs. N0)
- Inflammatory breast cancer
- Medial tumor localisation (vs. central/lateral)
Metaanalysis: TNBC and Local Recurrence

Wang et al., Surg Oncol 2013 (Epub)

n = 15312 BC-patients, 22 studies, Hazard-ratios

<table>
<thead>
<tr>
<th></th>
<th>BCT</th>
<th>vs.</th>
<th>ME</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILRR</td>
<td>0.75 (0.65-0.87)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>0.68 (0.60-0.76)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>TNBC-subtype</th>
<th>vs.</th>
<th>other subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILRR</td>
<td>1.88 (1.58-2.22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>2.12 (1.72-2.62)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>TNBC-subtype</th>
<th>vs.</th>
<th>HER2-subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILRR</td>
<td>0.69 (0.53-0.91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>n.s.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ILRR: ipsilateral locoregional recurrence
DM: distant metastasis
TNBC: triple negative breast cancer
BCT: breast conserving therapy
ME: mastectomy
Risk Factors for Locoregional Recurrences after ME


IBCSG-study, 13 randomized trials, n= 8106 patients

Risk factors for 10 yr. cumulative incidence …:

...>15% chest wall: age <40; ≥4 pos. nodes, 0-7 uninvolved nodes

...>10% supraclavicular: ≥4 pos. nodes

...>5% axillary failure: age <40; unknown tumor size, 0-7 uninvolved nodes

After BCT:
HR-positive tumors show a lower risk for LRR than...
triple negative tumors (RR 0.38) and....
HER2-expressing tumors (RR 0.34)

After ME:
HR-positive tumors show a lower risk for LRR than...
HER2-expressing tumors (RR 0.69) and...
triple negative tumors (RR 0.61)

Result:
HR-positive tumors exhibit the lowest rate of local recurrence.
Loco-regional Recurrence

Prognostic / Predictive factors

Parameters in local recurrence to define risk for re-recurrence

➢ Tumor size 2a B
➢ Multifocality 2a B
➢ Localisation 2b B

Parameters in local recurrence to define risk for distant metastasis/survival

➢ Early (<2-3 yrs.) vs. late recurrence 2b B
➢ LVSI/Grade/ERneg/close margin (if ≥ 2 factors pos.) 3b B

Predictive factors for treatment considerations

➢ HER2 2b B ++
➢ ER and PgR 2b B ++
Clinicopathological Factors of the Recurrent Tumor to Predict Outcome in Patients with Ipsilateral Breast Tumor Recurrence


n=6020 pat., retrospective cohort-study
pT1/2, N0 tumors, breast conserving treatment
269 ipsilateral breast tumor recurrences (IBTR)

Multivariate analysis:
TTR <48 months
LVSI (of the LRR)
ER negative LR-tumor
high grade
close margins of recurrent tumor

=> if ≥2 factors positive => worse OS
Ipsilateral Recurrence after BCT Surgery

- Mastectomy (aim: R0)
- Re-BCS with tumor-free margins
  ± flap reconstruction
  - Disadvantage for overall survival cannot be excluded
  - Impaired cosmetic result cannot be ruled out
  - Impaired local tumor control cannot be fully excluded
- Axillary intervention after prior AxDiss if cN0
- SNE after prior SNE if cN0*
- Palliative surgery in M1-situation
  (e.g. pain, ulceration, psychosocial)

* If no sentinel lymph node could be identified, axillary dissection is not recommended
Chest-Wall Recurrence after Mastectomy / Axillary Recurrence Surgery

- **Curative situation:** R0-resection
  - Oxford AGO LoE / GR: 2b A ++

- **Palliative situation:** Resection of deep parts of the chest wall
  - Oxford AGO LoE / GR: 5 D +/−

- **Palliative surgery in M1-situation** (e.g. pain, ulceration, psychosocial)
  - Oxford AGO LoE / GR: 5 D +
Loco-regional Recurrence after R0-Resection
Systemic Treatment

According to pathohistological re-evaluation
of the recurrent tumor (ER, PgR, HER2)

- Endocrine therapy in endocrine responsive tumors
- Chemotherapy (consider neoadjuvant)
- In case of HER2 positive disease
  Chemotherapy + HER2 targeted therapy

Oxford AGO
LoE / GR

Endocrine therapy in endocrine responsive tumors: 2b B ++
Chemotherapy (consider neoadjuvant): 2b B +
In case of HER2 positive disease
Chemotherapy + HER2 targeted therapy: 5 D +
Cytotoxic Treatment in Pts with Local Recurrent Breast Cancer

➢ CALOR Trial – Overall Survival

Kein Unterschied bei ER-/ER+
Unabhängiger prognostischer Marker!

Aebi et al. SABCS 2012
Locoregional Recurrence in Case R0
Resection not Likely - Systemic Treatment

According to pathohistological re-evaluation
of the recurrent tumor (ER, PgR, HER2)

- Endocrine therapy in endocrine responsive tumors 2b B ++
- Chemotherapy (pre- or postoperatively) 2b B ++
- HER2-targeted therapy in HER2-overexpressing tumors(+ chemotherapy) 1b A ++
Ipsilateral Recurrence after BCT Radiotherapy

After Re-BCS

- Whole breast irradiation
  (in case adjuvant radiotherapy was not performed)
- Re-breast irradiation
  (Partial breast radiation, brachytherapy, external beam RT)

After mastectomy

- Radiation of chest wall +/- regional lymph nodes
  (14% involved supraclavicular metastases)
- Radiation dose escalation (+10%)

Oxford AGO LoE / GR

After Re-BCS

- Whole breast irradiation
  (in case adjuvant radiotherapy was not performed)
- Re-breast irradiation
  (Partial breast radiation, brachytherapy, external beam RT)

After mastectomy

- Radiation of chest wall +/- regional lymph nodes
  (14% involved supraclavicular metastases)
- Radiation dose escalation (+10%)

3b  C  ++
3b  C  +/-
2b  B  +/-
3b  C  -
## Chest-Wall Recurrence after Mastectomy

- If no prior postmastectomy radiotherapy
  - Curative situation: irradiation of the chest wall +/- regional lymph nodes  
    - Re-irradiation (chest wall + hyperthermia)

## Axillary recurrence

Irradiation of axilla after R0-surgery
- No prior adjuvant irradiation of the axilla
- Adjuvant irradiation of the axilla

---

### Oxford AGO

<table>
<thead>
<tr>
<th>LoE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>3b</td>
<td>C</td>
</tr>
<tr>
<td>5</td>
<td>D</td>
</tr>
</tbody>
</table>
Loco-Regional Recurrence Treatment Options in Non Curative Cases

- **Topical chemotherapy (miltefosine)**
  - Oxford / AGO LoE / GR: 3b C +

- **Concomitant radio-chemotherapy**
  - Oxford / AGO LoE / GR: 3b C +

- **Hyperthermia (in centers listed on DKG website)**
  - In combination with radiotherapy: 1b B +
  - In combination with chemotherapy: 4 C +/-

- **Intra-arterial chemotherapy**
  - Oxford / AGO LoE / GR: 4 C +/-

- **Photodynamic therapy**
  - Oxford / AGO LoE / GR: 4 C +/-

- **Electrochemotherapy**
  - Oxford / AGO LoE / GR: 3b C +/-
**Loco-regional Recurrence (2/18)**

*Further information:*


*Guidelines:*


*No references*
Loco-regional Recurrence Incidence and Prognosis (3/18)

Further information:

About 10 (2-20 %) of patients who undergo breast-conservation surgery and radiation therapy will subsequently develop ipsilateral breast tumor recurrence. Chest wall recurrences after mastectomy and isolated axillary recurrences are relatively rare events. Although the local outcome following salvage therapy is quite good, the risk of distant metastases for patients with local recurrence is three to five times greater than for those without recurrence. The reason for this association has been controversially discussed, but it now appears that local recurrence is both a marker of the underlying biological aggressiveness of the tumor and a possible source for further tumor dissemination. The slide denotes 5 year overall survival rates of 65 %, 50 %, 55 % and 21 % after recurrences in ipsilateral breast, chest wall, axilla or multiple localisations, respectively. The patients with loco-regional recurrence survived almost significantly better than those with distant recurrence. The disease-free time-to-recurrence correlated positively with the time of survival after a recurrence. Isolated recurrences in the ipsilateral supraclavicular fossa fare as well as isolated chest wall recurrences, whereas locoregional recurrences of any site fare worse if the supraclavicular fossa is additionally affected: the 3-year overall survival has been determined with only 49%. Axillary recurrence after sentinel lymph node biopsy is a rare event and occurs in approx. 1% of patients with initially negative sentinel lymph node biopsy. The survival rate is higher than 90 % in these patients.

References:

Loco-regional Recurrence Staging (4/18)

Further information:

The 5-year overall survival of patients with isolated loco-regional recurrence amounted to 50%. There are no data about the frequency of distant metastases detected by modern staging examinations at time of recurrence. Moreover there are no studies confirming a implication of the re-staging findings in systemic treatment or improvement of overall survival of asymptomatic patients with resectable loco-regional recurrence. Nevertheless to avoid „over- or undertreatment“ and to prevent complications the AGO recommends a re-staging in all patients with resectable recurrences.

References:

Loco-regional Recurrence Risk Factors at Primary Diagnosis (5/18)

Further information:

Risk factors for IBTR include tumor size, nodal status, estrogen receptor status, molecular subtype, young age, positive microscopic margins, extensive intraductal component, higher grading, vessel invasion multifocality, an extensive intraductal component, and lymphatic vessel invasion. Multivariate analysis stratified by treatment showed that age was an independent prognostic factor for local control. Systemic treatment and radiation therapy significantly reduced local recurrence.

References:

Statement: Increased risk for loco-regional recurrence


Statement: Young age


Statement: Positive microscopic margins

Statement: Extensive intraductal component

Statement: Vessel invasion

Statement: ER and PR negative/ basal like or triple negative tumors /Her 2 positive tumors

Statement: Grading (G3 vs. G1)


Statement: pT (> 2 vs. ≤ 2cm)


Statement: pT (> 2 vs. ≤ 2cm) and Grading (G3 vs. G1) in node negative
Statement: pN (N1 vs. N0)
7. Truong PT, Jones SO, Kader HA, Wai ES, Speers CH, Alexander AS, Olivotto IA. Patients with t1 to t2 breast cancer with one to three positive nodes have higher local and regional recurrence risks compared with node-negative patients after breast-conserving surgery and whole-breast radiotherapy. Int J Radiat Oncol Biol Phys 73(2):357-64, 2009

Statement: number of involved lymph nodes

Statement: Medial tumor localisation (vs. central/lateral)

Statement: elevate proliferation marker, esp. Ki67

Statement: Inflammatory breast cancer

Statement: Nomograms
Metaanalysis: TNBC and Local Recurrence (6/18)

No further information

No references
Risk Factors for Locoregional Recurrence after ME (7/18)

No further information

No references
Metaanalysis: 7174 BCT and 5418 ME (8/18)

No further information

No references
**Loco-regional Recurrence Prognostic/Predictive factors (9/18)**

*No further information*

**References:**

Parameters in local recurrence to define risk for re-recurrence

**Statement: Tumour size**


**Statement: Multifocality**


**Statement: Localisation**


**Statement: Early vs. Late recurrence**


**LVSI/Grade/ERneg/close margins**


**Predictive factors for treatment considerations**

**Statement: HER-2**


**Statement: ER and PR**

Clinicopathological Factors of the Recurrent Tumor to Predict Outcome in Patients with Ipsilateral Breast Tumor Recurrence (10/18)

No further information

No references
**Ipsilateral Recurrence after BCT - Surgery (11/18)**

**Further information:**

Mastectomy is the current standard of care for ipsilateral recurrence of breast carcinoma. Some retrospective analyzes showed that second conservative treatments for local relapse were feasible and gave results comparable to standard mastectomy. A repeat BCT demands tumor free margins and an interstitial brachytherapy. However, the indication for second lumpectomy is restricted for suited patients (small-size, low-risk). As data from prospective randomized clinical trials are missing, an impaired regional tumor control (without disadvantages for overall survival) cannot be ruled out completely. In patients with distant metastases a local surgery is indicated in pain, endangered ulceration and in some cases for psychological reasons. Reoperative SLNB after previous axillary surgery is technically feasible after breast conserving therapy. In case no sentinel lymph node can be identified, axillary dissection is not recommended.

**References:**

**Statement: Mastectomy (aim: R0)**


**Statement: Re-BCS with tumor-free margins ± flap reconstruction**


Statement: disadvantage for overall survival cannot be excluded, poor cosmetic result, impaired local tumor control


Statement: Axillary intervention (SNE/AxDiss) after prior SNE and BCS if cN0


Statement: Palliative surgery in M1-situation

Further information:

Because chest wall recurrences are not infrequently a marker of concurrent or future metastatic disease, local management with curative intent is advocated only after thorough re-staging.

References:

Statement: Curative situation: R0-resection

Statement: Palliative situation: Resection of deep parts of the chest wall

Statement: Palliative surgery in M1-situation (e.g. pain, ulceration, psychosocial)
**Locoregional Recurrence after R0-Resection - Systemic Treatment (13/18)**

*Further information:*

Systemic therapy after resected local recurrence (readjuvant) is associated with improved disease-free and overall survival. Endocrine treatment in hormone sensitive tumors improves disease free survival. The impact on overall survival has not been proven.

*References:*

Statement: Endocrine therapy in endocrine responsive disease


Statement: Chemotherapy


Statement: Trastuzumab-based therapy in HER-2 overexpressing tumors
So far, extrapolations from adjuvant Her2-directed studies and from studies in metastatic breast cancer


Cytotoxic Treatment in pts with Local Recurrent Breast Cancer (14/18)

No further information

No references
Locoregional Recurrence in case R0-resection not likely - Systemic Treatment (15/18)

No further information

References:

Statement: Endocrine therapy in endocrine responsive disease

Statement: Chemotherapy (pre- or postoperatively)

Statement: Trastuzumab based therapy in HER-2 overexpressing tumors
So far, extrapolations from adjuvant Her2-directed studies and from studies in metastatic breast cancer.
Ipsilateral recurrence after BCT - Radiotherapy (16/18)

Further information:

Repeat irradiation breast for recurrent breast cancer is feasible. If no prior radiotherapy has performed after BCS, whole breast radiation should be performed. In patients with no prior radiotherapy after mastectomy irradiation of chest wall and regional lymph nodes is recommended.

References:

Statement: Whole breast radiation

Statement: Re-irradiation (breast)


Statement: Curative situation: irradiation of the chest wall +/- regional lymph nodes

Chest-wall recurrence / Axillary recurrence - radiotherapy (17/18)

No further information

References:

Statement: If no prior postmastectomy radiotherapy

Statement: Re-irradiation (chest wall + hyperthermia)

Statement Axillary recurrence
**Loco-Regional Recurrence - Treatment Options in Non-Curative Cases (18/18)**

**Further information:**

The combination of chemotherapy and hyperthermia (HT) is a promising approach in the treatment of malignant tumors. Local hyperthermia combined with radiotherapy may be effective in the treatment of locally recurrent breast cancer, especially for previously irradiated cases, where only a reduced total irradiation dose is applicable. Care should be taken, to select experienced providers that treat accordingly to recognised guidelines. While the combination of hyperthermia and radiotherapy has been used for several decades and shown its efficacy in prospective randomized trials, the combination of chemotherapy and hyperthermia (HT) has much less intensively been studied in breast cancer. Few recent papers report on trimodal therapeutic attempts: chemotherapy, radiotherapy plus hyperthermia, the additional benefit of chemotherapy is not quite clear.

**References:**

Statement: Topical chemotherapy (miltefosine)

Statement: Concomitant radio-chemotherapy
Statement: Hyperthermia + radiotherapy +/- chemotherapy

Statement: Intraarterial chemotherapy

Statement: Photodynamic therapy

Statement: Electrochemotherapy
Endocrine and “Targeted” Therapy in Metastatic Breast Cancer
Endocrine Therapy of Metastatic Breast Cancer

- **Version 2002:**
  Gerber / Friedrichs

- **Versions 2003–2013:**
  Albert / Bischoff / Dall / Fersis / Friedrich / Gerber / Huober / Janni / Jonat / Kaufmann / Loibl / Lück / von Minckwitz / Müller / Nitz / Schneeweß / Stickeler

- **Version 2014:**
  Mundhenke / Schütz
Endocrine Therapy in Metastatic Breast Cancer

Indication

Oxford LoE: 1a  GR: A  AGO: ++

Endocrine therapy represents the first choice for metastatic breast cancer with positive (unknown) hormone receptor status.

- Exception: acute life threatening disease
- Cave: HR might change during the course of the disease. Histology of recurrent site should be obtained, whenever possible
## Comparison ER/PgR and HER2 Metastasis vs. Primary Tumor

<table>
<thead>
<tr>
<th>Publication</th>
<th>Number of patients</th>
<th>ER %</th>
<th>PgR%</th>
<th>HER2%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospektiv</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thompson</td>
<td>137</td>
<td>10</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>Amir</td>
<td>94</td>
<td>14</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>Retrospektiv</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lindström</td>
<td>459</td>
<td>33</td>
<td>40</td>
<td>14</td>
</tr>
<tr>
<td>Niikura</td>
<td>182</td>
<td>-</td>
<td>-</td>
<td>24</td>
</tr>
</tbody>
</table>

Changes from primary tumor to metastatic disease
Endocrine Therapy in Premenopausal Patients with HER2 Negative Metastatic Breast Cancer

- GnRHa + tamoxifen (vs. OFS or Tam) 1a A ++
- Ovarian function suppression (OFS) 2b B +
- Tamoxifen 2b B +
- GnRHa + AI (first or second line) 2b B +
- GnRHa + Fulvestrant 4 C +/-
- Aromatase inhibitors without OFS 3 D - -
Endocrine Therapy in Postmenopausal Patients with HER2 Negative Metastatic Breast Cancer

Treatment options for postmenopausal patients pretreated with adjuvant tamoxifen or without adjuvant endocrine therapy

<table>
<thead>
<tr>
<th>Treatment Options</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aromatase inhibitors (3rd gen) (&gt; non-Al*)</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Tamoxifen (vs. no therapy)</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Fulvestrant 500 mg</td>
<td>1b B ++</td>
</tr>
<tr>
<td>Fulvestrant 250 mg (= Al)</td>
<td>2b B +</td>
</tr>
<tr>
<td>MPA/MA (&lt; Al)</td>
<td>1a A +/-</td>
</tr>
<tr>
<td>Fulvestrant 250 mg + Anastrozol (vs. Ana)</td>
<td>1b B +/-</td>
</tr>
</tbody>
</table>

*There is no evidence for superiority of a single aromatase inhibitor. As everolimus + exemestane are indicated after Al treatment, a non-steroidal Al should be preferred in first line.
Endocrine Therapy in Postmenopausal HER2 Negative Metastatic Breast Cancer Patients after Adjuvant Tamoxifen or no Prior Endocrine Treatment

<table>
<thead>
<tr>
<th>Treatment sequence</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st line</strong>:</td>
<td></td>
</tr>
<tr>
<td>aromatase inhibitors (3rd gen)*</td>
<td>1a A ++</td>
</tr>
<tr>
<td>fulvestrant 250 mg + anastrozole</td>
<td>2b C +/-</td>
</tr>
<tr>
<td><strong>2nd line</strong>:</td>
<td></td>
</tr>
<tr>
<td>fulvestrant</td>
<td>1b B</td>
</tr>
<tr>
<td>fulvestrant 500 mg</td>
<td>1b B ++</td>
</tr>
<tr>
<td>fulvestrant 250 mg</td>
<td>2b B +/-</td>
</tr>
<tr>
<td>exemestane + everolimus</td>
<td>1b A ++</td>
</tr>
<tr>
<td>tamoxifen</td>
<td>3b C +</td>
</tr>
<tr>
<td>aromatase inhibitor**</td>
<td>2b B +</td>
</tr>
<tr>
<td>tamoxifen + everolimus</td>
<td>2b B +</td>
</tr>
<tr>
<td><strong>Further Lines</strong>:</td>
<td></td>
</tr>
<tr>
<td>MPA/MA</td>
<td>4 D +/-</td>
</tr>
<tr>
<td>estradiol 6 mg daily</td>
<td>3b C +/-</td>
</tr>
<tr>
<td>repeat prior treatments</td>
<td>5 D +/-</td>
</tr>
</tbody>
</table>

* To date, there is no evidence for superiority of a single aromatase inhibitor.

** steroidal or non-steroidal depending on previous AI
Therapy Algorithm After Adjuvant Tamoxifen

Non-steroidal AI 3rd generation

- Exemestane + everolimus
  - Fulvestrant 500mg
    - Tamoxifen
  - Fulvestrant 500mg
- Fulvestrant 500mg
- Exemestane + everolimus
  - Tamoxifen
# Endocrine Therapy in Postmenopausal HER2 Negative Metastatic Breast Cancer Patients after Adjuvant AI

## Treatment sequence

<table>
<thead>
<tr>
<th></th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; line:</td>
<td></td>
</tr>
<tr>
<td>- tamoxifen</td>
<td>2b B ++</td>
</tr>
<tr>
<td>- fulvestrant 500 mg</td>
<td>1b B ++</td>
</tr>
<tr>
<td>- exemestane + everolimus* (relapse within 12 mths)</td>
<td>1b A ++</td>
</tr>
<tr>
<td>- steroidal after non-steroidal AI</td>
<td>2b B +</td>
</tr>
<tr>
<td>- non-steroidal after steroidal AI</td>
<td>2b B +</td>
</tr>
<tr>
<td>- tamoxifen + everolimus</td>
<td>2b B +</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line:</td>
<td></td>
</tr>
<tr>
<td>- fulvestrant 500 mg</td>
<td>1b B ++</td>
</tr>
<tr>
<td>- exemestane + everolimus*</td>
<td>1b A ++</td>
</tr>
<tr>
<td>- tamoxifen (if previously not given)</td>
<td>5 D +</td>
</tr>
<tr>
<td>- tamoxifen + everolimus</td>
<td>2b B +</td>
</tr>
<tr>
<td>Further lines:</td>
<td></td>
</tr>
<tr>
<td>- MPA/MA</td>
<td>4 C +/-</td>
</tr>
<tr>
<td>- repeat prior treatments</td>
<td>5 D +/-</td>
</tr>
</tbody>
</table>

*After pretreatment with at least a non-steroidal AI in the metastatic and/or adjuvant setting

**Trial participation
Therapy Algorithm After Adjuvant AI

Short treatment free interval ≤12 months

- Exemestane + everolimus
- Fulvestrant 500 mg
- Tamoxifen

Long treatment free interval >12 months

- Fulvestrant 500 mg
- Tamoxifen
- Exemestane + everolimus
  - Tamoxifen
  - Fulvestrant 500 mg
Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

HER2 Positive and HR-Positive Metastatic Breast Cancer
Endocrine Therapy in Postmenopausal HER2 Positive Metastatic Breast Cancer Patients

- Anastrozole and trastuzumab $\text{LoE}^1\text{b} B +/-$
- Letrozole and trastuzumab $\text{LoE}^2\text{b} B +/-$
- Letrozole and lapatinib $\text{LoE}^1\text{b} B +/-$
- Fulvestrant and lapatinib $\text{LoE}^1\text{b}^a B -$

Poor efficacy of endocrine therapy alone. Consider chemotherapy + anti-HER2-therapy!
## Combination of Endocrine Treatment with Anti-HER2-Treatment

<table>
<thead>
<tr>
<th>Treatment (no. of pats)</th>
<th>PFS (mo)</th>
<th>Response (CBR)</th>
<th>OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab + anastrozole vs. anastrozole</td>
<td>4.8 vs. 2.4</td>
<td>42.7% vs. 27.9%</td>
<td>28.5 vs. 23.9 mo; n.s.</td>
</tr>
<tr>
<td>(n=207)</td>
<td>(5.6 vs. 3.8 with central confirmed receptor status)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trastuzumab + letrozole vs. letrozole</td>
<td>14 vs. 3.3</td>
<td>27% vs. 13%</td>
<td>n.r.</td>
</tr>
<tr>
<td>(n=57)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lapatinib + letrozole vs. letrozole</td>
<td>8.2 vs. 3.0</td>
<td>48% v 29%</td>
<td>33.3 vs. 32.3 mo</td>
</tr>
<tr>
<td>(n=219/1286)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lapatinib + fulvestrant vs. fulvestrant</td>
<td>5.2 vs. 4.0 (all)</td>
<td></td>
<td>22.3 vs. 21.9 (all)</td>
</tr>
<tr>
<td>(n=267/324)</td>
<td>5.9 vs. 2.8 (HER2+)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Concomitant or Sequential Endocrine-Cytostatic Treatment

- **Concomitant endocrine-cytotoxic treatment**
  - Increases response rates without prolongation of progression free interval or overall survival
  - Increases toxicity

- **Maintenance endocrine therapy after chemotherapy induced response**
  - Increases progression free interval

Oxford / AGO
LoE / GR

1b A --

3 C ++
Endocrine Therapy of Metastatic Breast Cancer (2/14)

Further information:

Search:
Medline, PubMed Central 12/2012-01/2013

References


**Endocrine Therapy in Metastatic Breast Cancer – Indication (3/14)**

*Further information:*

**Endocrine therapy as the first choice in hormone receptor positive breast cancer**

Endocrine therapy remains the most important approach to the treatment of hormone-sensitive non-life-threatening metastatic breast cancer. This systemic therapy has the advantage of combining efficacy, minimal toxicity, and good quality of life. Endocrine therapy use in clinical practice is based on a positive estrogen receptor (ER) and/or progesterone receptor status of the primary tumour or, if at all possible, of an easily accessible metastasis. This type of therapy is usually the first choice when the risk of rapid disease progression is low, i.e. if there is no life-threatening disease. The selection of the most appropriate endocrine therapy takes into account the receptor status of the metastasis, menopausal status of the patient, the type of adjuvant endocrine therapy received, and past medical history of thrombolic disease.

A Cochrane Data Base Meta-Analysis was performed in 2003 whether chemotherapy alone versus endocrine therapy alone for metastatic breast cancer is more favorable.

The primary analysis of overall effect using hazard ratios derived from published survival curves involved six trials (692 women). There was no significant difference seen (HR=0.94, 95%CI 0.79-1.12, p=0.5). A test for heterogeneity was p=0.1. A pooled estimate of reported response rates in eight trials involving 817 women shows a significant advantage for chemotherapy over endocrine therapy with RR=1.25 (1.01-1.54, p=0.04). However the two largest trials showed trends in opposite directions, and a test for heterogeneity was p=0.0018.

There was little information available on toxicity and quality of life. Six of the seven fully published trials commented on increased toxicity with chemotherapy, mentioning nausea, vomiting and alopecia. Three of the seven mentioned aspects of quality of life, with differing results. Only one trial formally measured quality of life, concluding that it was better with chemotherapy.

The Reviewers concluded that in women with metastatic breast cancer and where hormone receptors are present, a policy of treating first with endocrine therapy rather than chemotherapy is recommended except in the presence of rapidly progressive disease (Cochrane 2011).
**Response to endocrine treatment (De Laurentiis M, et al. 2005):**

<table>
<thead>
<tr>
<th>ER</th>
<th>PR</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>negative</td>
<td>&lt; 10%</td>
</tr>
<tr>
<td>Positive</td>
<td>negative</td>
<td>20 – 30%</td>
</tr>
<tr>
<td>Negative</td>
<td>positive</td>
<td>30 – 50%</td>
</tr>
<tr>
<td>Positive</td>
<td>positive</td>
<td>50 – 75%</td>
</tr>
</tbody>
</table>

**References**


Further information:

Changes in receptor profiles

Changes in receptor profiles are an important issue, since the molecular phenotype of the primary tumor is often used for treatment decisions in the metastatic setting.

Several retrospective studies have evaluated this biological phenomenon.

There is evidence for a prognostic impact of receptor profile changes in metastatic breast cancer: In a retrospective analysis, patients with tumors that changed from ER positive primary to negative metastasis experienced a significantly shorter median survival than patients with unchanged receptor profiles, while changes in PR status were not associated with a change in survival. Therefore, optimal metastatic treatment cannot be determined solely on primary ER and PR analyses (Lower et al. 2005).

A published retrospective study (Broom et al. 2009) evaluated data from 100 patients for whom tissue from primary and metastatic sites was available. Estrogen receptor (ER), progesterone receptor (PR) and Her-2/neu status in the primary and metastasis were compared. The discordance rate for ER was 17.7% (2-sided p=0.0039) with 9.7% of tumors changing from ER-positive to ER-negative and 8.0% changing from ER-negative to ER-positive. The discordance rate for PR was 37.3% (2-sided p<0.0001), with all of these tumors changing from PR-positive to PR-negative. No significant discordance for Her-2/neu was found. This study suggested that significant discordance exists for hormone receptor status between primary and metastatic breast cancer samples. Loss of PR was particularly frequent.

Further evidence was shown by a retrospective analysis of 97 consecutive relapsed patients (Nishimura et al. 2011). Changes in the positive/negative evaluation were seen at the rate of 10.3% and 25.8% for ER and PgR. Ki-67 index increased significantly from a mean of 29.1% at primary tumor to 36.6% at relapse. The rates of change in HER2 and p53 positivity were 14.4% and 12.4%. The change of subtypes were seen in 25%, however the lowest rate of change was seen
in the triplenegative cases. A multivariat analysis revealed that the status of distant metastasis and PgR level at relapse, and Ki-67 levels at primary tumor were all significant factors.

One prospective study, BRITS (Breast Recurrence In Tissue Study), investigated 137 matched primary and recurrent breast cancer tissue samples. The recurrent biopsy was excisional tissue in 100 (73%) and core biopsy in 37 (27%). Central laboratory analysis of the original primary was ER positive in 109 (79.6%), PR positive in 85 (62.0%) and HER2 positive in 14 (10.2%); the recurrent disease was ER positive in 101 (73.7%), PR positive in 75 (54.7%) and HER2 positive in 16 (11.7%). A switch in receptor status, in either direction, was identified for ER in 14 patients (10.2%; p=0.983 Wilcoxon sign rank test), PR in 34 (24.8%; p=0.003 Wilcoxon sign rank test) and HER2 in 4 (2.9%; p=0.074 Wilcoxon sign rank test). There was no difference between locoregional or distant recurrence in the proportion who switched. In the judgement of the investigators the switch led to a change in the subsequent treatment in 24 patients (17.5%). This study demonstrated that the management of locally recurrent or metastatic breast cancer should include tissue sampling, since switches of ER, PR or HER2 status in the breast cancer recurrence may change the planned treatment for one in six patients (Thompson 2010).

However if treatment guided by the new ER, PR or HER2 status of the metastasis is superior when findings are different to the primary tumor has not been investigated so far.

References:


Endocrine Therapy in Premenopausal Patients with HER2 Negative Metastatic Breast Cancer (5/14)

Further information and references:

GnRHa + tamoxifen
The combination of GnRH + tamoxifen represents the first choice as endocrine first line therapy of hormone receptor positive premenopausal breast cancer.

Due to the results of one randomized trial and a metaanalysis of additional 4 trials in a three-arm, randomized, prospective trial a total of 161 premenopausal patients with advanced breast cancer were randomly assigned to treatment with buserelin, tamoxifen, or both. The median follow-up was 7.3 years. Combined treatment with buserelin and tamoxifen was superior to treatment with buserelin or tamoxifen alone by objective response rate (48%, 34%, and 28% respectively; P = .11 [chi(2) test]), median progression-free survival (9.7 months, 6.3 months, and 5.6 months; P = .03), and overall survival (3.7 years, 2.5 years, and 2.9 years; P = .01). Actuarial 5-year survival percentages were 34.2%, 14.9%, and 18.4%, respectively. No differences in antitumor effects were observed between single-agent treatment groups (Klijn et al. 2000). For patients with solitary bone metastasis a prospective multicenter study on 318 patients revealed even a survival benefit besides a significant improvement of progression free survival (Jonat et al 1995).

The metaanalysis (Klijn et al. 2001) confirmed the above findings in four clinical trials randomizing a total of 506 premenopausal women with advanced breast cancer to LHRH agonist alone or to the combined treatment of LHRH agonist plus tamoxifen. With a median follow-up of 6.8 years, there was a significant survival benefit (P = .02; hazards ratio [HR] = 0.78) and progression-free survival benefit (P = .0003; HR = 0.70) in favor of the combined treatment. The overall response rate was significantly higher on combined endocrine treatment (P = .03; odds ratio = 0.67).
**References:**


**Ovarian function suppression, tamoxifen**

A further option in the treatment of metastasized premenopausal hormone receptor positive breast cancer is ovarian ablation. Oophorectomy and GnRHa have been demonstrated to be equally efficacious in the metastatic setting. Taylor et al. evaluated these two methods for premenopausal patients with ER-positive, PR-positive, and unknown hormone status metastatic breast cancer. 136 patients were randomly assigned to either bilateral oophorectomy (n = 67) or goserelin (n = 69). The overall response rate was 31% for those in the goserelin group versus 27% in the oophorectomy group. The complete response (CR) rate for the two arms was 14 and 10%, respectively. The response rates between the two arms were not statistically significant.
An additional randomized, nonblinded trial compared oophorectomy and radiation ablation for metastatic breast cancer, 97 patients were treated with oophorectomy, and 61 had ovarian ablation by radiation. In the oophorectomy arm, 30% had a response (CR + partial response), and 18% had stable disease. In the radiation arm, 21% had a response (CR + partial response), and 15% had stable disease. These differences were not statistically significant (Lees et al. 1980).

Tamoxifen is well established as an alternative to ovarian suppression as first-line treatment for hormone receptor-positive breast cancer in the metastatic setting, especially in case of contraindications against a combination therapy with GnRHa (Oborne 1998). Several studies were reported over the last decade (Ingle et al. 1986, Buchanan et al. 1986, Sawka et al. 1997).

A meta-analysis of randomized trials comparing tamoxifen to ovarian ablation carried out either by surgery or irradiation as first-line hormonal therapy for pre-menopausal women with metastatic breast cancer enrolled 220 patients in four trials. There was no difference in overall response rate between tamoxifen and oophorectomy across the four trials (p = 0.94, Mantel-Haenszel test). The odds reduction for progression was 14% +/- 12% and for mortality 6% +/- 13% in favour of tamoxifen, which was not statistically significant (p = 0.32 and 0.72, respectively). Although the design of all four studies included a cross-over to the other therapy, only 54/111 patients receiving ovarian ablation and 34/109 patients receiving tamoxifen as primary therapy actually crossed over to the other arm at the time of disease progression. The efficacy of tamoxifen appears to be similar to that of ovarian ablation by surgery or irradiation as first-line therapy for premenopausal, ER positive metastatic breast cancer (Crump et al. 1997).

References


GnRH-A + AI

Even if the evidence is rather limited, aromatase inhibitors can be an option in the treatment of metastatic premenopausal breast cancer.

Based on a Phase II trial (Forward et al. BR J Cancer 2004) the combination of GNRHa plus aromatase inhibitors is a second line option after GNRHa + tamoxifen treatment failure.

A total of 16 premenopausal women with metastatic breast cancer (N=13) or locally advanced primary breast cancer (N=3) were treated with a combination of a gonadotropin-releasing hormone agonist goserelin, and a selective aromatase inhibitor anastrozole. All had previously been treated with goserelin and tamoxifen. In all, 12 patients (75%) achieved objective response or durable stable disease at 6 months, with a median duration of remission of 17+ months (range 6-47 months). Four patients still have clinical benefit. Introduction of goserelin and tamoxifen resulted in an 89% reduction in
mean oestradiol levels (pretreatment vs 6 months=224 vs 24 pmol l(-1)) (P<0.0001). Substitution of tamoxifen by anastrozole on progression resulted in a further 76% fall (to 6 pmol l(-1) at 3 months) (P<0.0001) (Forward et al. 2004).

Additionally there is evidence for GnRHa+ aromatase inhibitors as first line treatment in premenopausal patients. Besides a case study of 3 patients (El-Saghir et al. 2006), a small randomized trail compared GnRHa + anastrozol vs. GnRHa+ tamoxifen in 119 peri/premenopausal women with hormone dependent metastatic breast cancer (Milla-Santos et al.2002). In comparison to GnRHa+tamoxifen the study combination showed higher response rates (80% vs. 53%, P=0.023), improved clinical benefit rates (P=0.05) as well as prolonged overall survival (18.9 vs. 14.3 months).

A phase II trial (Carlson RW et al JCO 2010) with a cohort of 32 patients with metatastic disease were treated with GnRHa+anastrozol: One participant (3.1%) experienced a complete response, 11 (34.4%) experienced partial response, and 11 (34.4%) experienced stable disease for 6 months or longer for a clinical benefit rate of 71.9%. Median time to progression was 8.3 months (range, 2.1 to 63+) and median survival was not been reached (range, 11.1 to 63+).

References:


Further information:

In women with advanced (metastatic) breast cancer, aromatase inhibitors including those in current clinical use show a survival benefit when compared to other endocrine therapy. 3rd Generation aromatase agents should be the first endocrine treatment choice in patients with distant metastases of hormone responsive breast cancer and no adjuvant aromatase inhibitor treatment. This is demonstrated in numerous clinical trials and confirmed in a meta-analysis updated in 2009 (see references).

The clinical benefit of tamoxifen for treatment of metastatic breast cancer is shown in numerous trials and tamoxifen remains a mayor treatment option in the metastatic setting despite the superiority of aromatase inhibitors for first line treatment.

Fulvestrant in the dose of 250mg every four weeks is not superior to aromatase inhibitors or tamoxifen as first line or second line treatment of MBC. In the recently approved dose of 500mg four weeks it is superior to aromatase inhibitors as second line treatment of MBC.

MPA/MA are options as sequential therapies after other endocrine therapies have been used. However, they seem to be inferior to AI.

Trials comparing aromatase inhibitors for their efficacy have not delivered conclusive results, although one study stated that response with anastrozole was higher compared with letrozole. However, this was not the primary end point of this trial (see references “comparison of different AI”)

References:

„Aromatase inhibitors (3rd gen) (> non-AI*)“


4. Thuerlimann, B, Robertson, JFR, Nabholtz, JM, Buzdar, A, Bonneterre, J, Efficacy of tamoxifen following anastrozole (‘Arimidex’) compared with anastrozole following tamoxifen as first-line treatment for advanced breast cancer in postmenopausal women European Journal of Cancer 2003 39

5. Bonneterre, J, Buzdar, A, Nabholtz, JA, Robertson, JFR, Thuerlimann, B, von Euler, M, Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma Cancer 2001 92


"Fulvestrant is equivalent to AI (or tamoxifen) in the first line endocrine treatment of metastatic breast cancer."


2. Howell, A, Robertson, JFR, Quaresma Albano, J, Ascgermannova, A, Mauriac, L, Kleeberg, UR, Fulvestrant, formerly ICI 182, 780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment Journal of Clinical Oncology 2002 20

3. Mauriac, L, Pippen, JE, Quaresma Albano, J, Gertler, SZ, Osborne, CK, Fulvestrant (Faslodex) versus anastrozole for the second-line treatment of advanced breast cancer in subgroups of postmenopausal women with visceral and non-visceral metastases: combined results from two multicentre trials European Journal of Cancer 2003 39

4. Osborne, CK, Pippen, J, Jones, SE, Parker, LM, Ellis, M, Come, S, Double-blind, randomized trial comparing the efficacy and tolerability of the fulvestrant versus anastrozole in postmenopausal women with advanced breast
cancer progressing on prior endocrine therapy: results of a North American Trial Journal of Clinical Oncology
2002 20


“MPA/MA inferior to AI”


5. Goss, PE, Winer, EP, Tannock, IF, Schwarz, LH, Randomized phase III trial comparing the new potent and selective third generation aromatase inhibitor vorozole with megestrol acetate in postmenopausal advanced breast cancer patients Journal of Clinical Oncology 1999 17


**Fulvestrant + Anastrozole**


Comparison of different AI


**Endocrine Therapy in Postmenopausal HER2 Negative Metastatic Breast Cancer Patients after Adjuvant Tamoxifen or no prior Endocrine Treatment (7/14)**

*Further information and references:*

**AI (3rd gen), bevacizumab**

Additional aspects not discussed on the previous slide:
- Evidence suggests that switching therapy from non-steroidal to a steroidal AI is as effective as fulvestrant in its approved dose of 250mg/q4 weeks (study “EFFECT”). It seems likely that also the switch from steroidal to non steroidal AI is effective and is therefore a therapeutic option.

*References:*


**Fulvestrant 500 mg > AI**

The “FIRST” trial using the higher dose of 500mg/q4w stated first-line fulvestrant HD was at least as effective as anastrozole for CBR (the primary end point) and ORR, but was associated with significantly longer TTP (a secondary end point) in patients pre-treated with endocrine treatment. A follow up analysis showed an even stronger superiority with a median TTP of 23.4 months for fulvestrant HD and 13.1 months for anastrozole (p=0.01).

**References:**


**Fulvestrant 500 mg > 250 mg**

In addition to the approved dose of 250 mg by intramuscular injection, highdose (HD) regimen of fulvestrant (500 mg once a month plus 500 mg on day 14 of month 1) is associated with a significantly longer progression-free survival (PFS) and can be recommended for patients who had progressed on prior endocrine therapy (Effect Trial, Confirm Trial, Finder I and II Trial).
REFERENCES:


Estradiol

In women with advanced breast cancer and acquired resistance to aromatase inhibitors, a daily dose of 6 mg of estradiol provided a similar clinical benefit rate of 28% as 30 mg, with fewer serious adverse events.

References:

Therapy Algorithm After Adjuvant Tamoxifen (8/14)

No further information

No references
Further information:

For patients with progression or relapse after the adjuvant use of an AI Fulvestrant plays an important role for second line treatment.

In the Bolero-2 study a phase 3, randomized trial, everolimus (10mg/die) and exemestane versus exemestane and placebo (randomly assigned in a 2:1 ratio) was compared in 724 patients with hormone-receptor-positive advanced breast cancer who had recurrence or progression while receiving previous therapy with a nonsteroidal aromatase inhibitor in the adjuvant setting or to treat advanced disease (or both). The primary end point was progression-free survival. Secondary end points included survival, response rate, and safety. A preplanned interim analysis was performed by an independent data and safety monitoring committee after 359 progression-free survival events were observed. The median age was 62 years, 56% had visceral involvement. Previous therapy included letrozole or anastrozole (100%), tamoxifen (48%), fulvestrant (16%) and prior chemotherapy for metastatic disease (25%). The number of previous therapies was at least 3 regimens in 54% of the patients. Overall response (0.4 vs 9.5%, p<0.0001) and clinical benefit rate (18 vs 33.4%, p<0.0001) was significantly higher in the combination group versus exemestane alone. Further at interim analysis median PFS was significantly increased with the combination of exemestane and everolimus both by local (2.8 vs 6.9 months, HR 0.43, 59% CI 0.35-0.54, p<0.001) and central assessment (4.1 vs 10.6 months, HR 0.36, 95%CI, 0.27-0.47, p<0.001). The most common grade 3/4 adverse events were stomatitis (8 vs 1%), anemia (4 vs <1%), dyspnea (4 vs 1%), and pneumonitis (3 vs 0%) and more frequently seen with the combination of exemestane and everolimus. The potential of everolimus to benefit patient survival is not yet known.

In a small randomized phase 2 study 111 patients with hormone receptor positive metastatic disease and prior aromatase inhibitor therapy were randomized to tamoxifen (n=57) or tamoxifen and everolimus (n=54; 10mg/die). The clinical benefit rate (42.1 vs 61.1%, p=0.045) time to progression (4.5 vs 8.6 months, HR 0.53, 95% CI 0.35-0.81, p=0.0026 exploratory log rank) and overall survival (HR 0.32 95% CI 0.15-0.68, p=0.0019) were significantly superior in the combination treatment compared to tamoxifen alone.
References:


Therapy Algorithm After Adjuvant AI (10/14)

No further information

No references
Endocrine Therapy in Postmenopausal HER2 Positive Metastatic Breast Cancer Patients (12/14)

Further information:

Several lines of evidence support the hypothesis that HER2-positive breast cancer is associated with endocrine resistance. The addition of trastuzumab or lapatinib to aromatase inhibitor treatment is able to enhance the efficacy over endocrine treatment alone. However, given the relative short progression free interval in the phase III trials compared to those observed in trials with chemotherapy, we recommend to consider chemotherapy in HER2-positive patients.

One phase III trial comparing fulvestrant + placebo vs. Fulvestrant + lapatinib could not demonstrate an improved PFS or OS in 324 patients pretreated with an AI.
For further information on trials combining endocrine treatment with anti-HER2 therapy, see following slide.

References:


Combination of Endocrine Treatment with Anti-HER2-Treatment (13/14)

No further information

References:


Concomitant or Sequential Endocrine-Cytostatic Treatment (14/14)

Further information:

Concomitant endocrine cytostatic therapy can not be recommended because it induces an increase in toxicity and does not induce a prolongation of disease free interval or overall survival despite the increase of response rates. Thus, endocrine – cytostatic therapy should be performed as sequential treatment modality.

Endocrine mainenance therapy after chemotherapy induced response might be considered, even if the evidence is quite small and not homogeneous, since only relatively little side effects are observed with this sequential treatment option.

References:


Chemotherapy With or Without Targeted Drugs* in Metastatic Breast Cancer

*Substances are only discussed if there is at least published evidence on one phase III / IIb study available
Chemotherapy ± Targeted Drugs in Metastatic Breast Cancer

- **Version 2002:**
  von Minckwitz / Schaller / Untch

- **Versions 2003–2013:**
  Bischoff / Dall / Fersis / Friedrichs / Harbeck / Jackisch / Janni / Möbus / Rody / Scharl / Schmutzler / Schneeweiss / Schütz / Stickeler / Thomssen

- **Version 2014:**
  Bischoff / Janni
Disease-Free and Overall Survival in Metastatic Breast Cancer

General observation, not specific for cytotoxic chemotherapy

- An increase in survival over time in MBC has been shown in retrospective analyses 2a

- A survival benefit has been shown in recent single prospective randomized studies of combination chemotherapy 1b

- Multiple lines of sequential therapy are beneficial (at least same efficacy, less toxicity) 1b

- In some combinations of chemotherapy with targeted drugs, a relevant survival benefit has been observed 1b
## Treatment of Metastatic Breast Cancer

### Predictive Factors

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Factor</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endocrine therapy</strong></td>
<td>ER / PR (primary tumor, metastasis)</td>
<td>1a A ++</td>
</tr>
<tr>
<td></td>
<td>previous response</td>
<td>2b B ++</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td>previous response</td>
<td>1b A ++</td>
</tr>
<tr>
<td><strong>Anti-HER2-drugs</strong></td>
<td>HER2 (primary tumor, better metastasis)</td>
<td>1a A ++</td>
</tr>
<tr>
<td><strong>Bone modifying drugs</strong></td>
<td>bone metastasis</td>
<td>1a A ++</td>
</tr>
<tr>
<td><strong>Any therapy</strong></td>
<td>CTC monitoring</td>
<td>1b A +*</td>
</tr>
</tbody>
</table>

(Other potentially biological factors see chapter „Predictive factors“)

*within clinical trials*
Cytotoxic Therapy

Goals

Mono-Chemotherapy:
- Favourable therapeutic index
- Indicated in case of
  - Slow, not life-threatening progression
  - Insensitive to or progression during endocrine therapy

Poly-Chemotherapy:
- Unfavourable therapeutic index
- Indicated to achieve rapid remission in the case of
  - Extensive symptoms
  - Imminent life-threatening metastases
- Survival benefit in comparison to sequential single-agent therapies with the same compounds not proven

Therapeutic index evaluates overall efficacy, toxicity and impact on quality of life
Cytotoxic and Targeted Therapy

- Evaluate compliance before and during therapy (especially in elderly patients, with reduced PS, or significant co-morbidities)
- Assess subjective and objective toxicities, symptoms and PS repeatedly
- Use dosages according to published protocols
- Assess tumor burden at baseline and approx. every 2 months, i.e. every 2-4 cycles. Assessment of a target lesion might be sufficient. In slow growing disease, longer intervals are acceptable.

LoE: 1c  GR: A  AGO: ++
Cytotoxic Therapy

Duration

As long as therapeutic index remains positive

- Treatment until best response
  - Oxford / AGO LoE GR
  - 2b B +
- Treatment until progression
  - Oxford / AGO LoE GR
  - 2b B +
- Change to alternative regimen before progression
  - Oxford / AGO LoE GR
  - 2b B -
- Stop therapy in case of
  - Progression
    - Oxford / AGO LoE GR
    - 1c A ++
  - Non-manageable toxicity
    - Oxford / AGO LoE GR
    - 1c A ++
Chemotherapy for MBC – General Considerations: Drug Selection

The choice of cytotoxic drugs to be used depends on:

- ER / PR, HER2; combination with biologicals
- Previous treatments (and their toxicities)
- Aggressiveness of disease and localization of metastases
- Biologic age
- Co-morbidities (including organ dysfunctions)
- Patients preference and expectations
MBC HER2 negative
Cytotoxic 1st-Line Therapy*

Monotherapy:
- Doxorubicin, epirubicin, mitoxantrone (A), Peg. liposomal doxorubicin (A_{lip})
- Docetaxel (q3w), paclitaxel (q1w) (T)
- Vinorelbine
- Capecitabine
- Nab-paclitaxel
- Ixabepilone

Polychemotherapy:
- A + T
- Paclitaxel + capecitabine
- Docetaxel + capecitabine after adj. A
- T + gemcitabine after adj. A
- (F) + A + C or A_{lip} + C
- CMF(1+8)
- BMF (bendamustine)
- Ixabepilone + capecitabine

Oxford / AGO LoE / GR

Monotherapy:
- Doxorubicin, epirubicin, mitoxantrone (A), Peg. liposomal doxorubicin (A_{lip})
  - 1b A ++
- Docetaxel (q3w), paclitaxel (q1w) (T)
  - 1b A ++
- Vinorelbine
  - 3b B +
- Capecitabine
  - 2b B +
- Nab-paclitaxel
  - 2b B +
- Ixabepilone
  - 1B B -

Polychemotherapy:
- A + T
  - 1b A ++
- Paclitaxel + capecitabine
  - 2b^a B +
- Docetaxel + capecitabine after adj. A
  - 1b A +
- T + gemcitabine after adj. A
  - 2b B ++
- (F) + A + C or A_{lip} + C
  - 1b B ++
- CMF(1+8)
  - 2b B +/-
- BMF (bendamustine)
  - 1b B +/-
- Ixabepilone + capecitabine
  - 1b B +/-

*In ER pos. disease only if endocrine therapy is not or not anymore indicated
MBC HER2 negative: Cytotoxic Therapy after Anthracycline Treatment*

- Docetaxel q3w  
- Paclitaxel q1w  
- Capecitabine  
- Nab-paclitaxel  
- Peg-liposomal doxorubicin  
- Vinorelbine  
- Docetaxel + Peg-liposomal Doxo  
- Etoposid / cisplatinum

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
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<tbody>
<tr>
<td>Docetaxel</td>
<td>1a</td>
<td>A</td>
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<tr>
<td>Paclitaxel</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>2b</td>
<td>B</td>
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<tr>
<td>Nab-paclitaxel</td>
<td>2b</td>
<td>B</td>
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<tr>
<td>Peg-liposomal doxorubicin</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Docetaxel + Peg-liposomal Doxo</td>
<td>1b</td>
<td>B</td>
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<tr>
<td>Etoposid / cisplatinum</td>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>

*independent whether anthracyclines were used in adjuvant or 1st line metastatic situation
MBC HER2 negative: Cytotoxic Therapy After Taxane and Anthracycline Treatment

- Experimental therapies within studies
- Capecitabine
- Eribulin
- Vinorelbine
- (Peg)-liposomal Doxorubicin
- Gemcitabine + Cisplatin / Carboplatin
- Gemcitabine + Capecitabine
- Gemcitabine + Vinorelbine*
- Ixabepilone + Capecitabine*

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Oxford / AGO LoE / GR</th>
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<tbody>
<tr>
<td>Experimental therapies within studies</td>
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<tr>
<td>Capecitabine</td>
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<tr>
<td>Eribulin</td>
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<tr>
<td>Vinorelbine</td>
<td>2b B ++</td>
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<tr>
<td>(Peg)-liposomal Doxorubicin</td>
<td>2b B +</td>
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<tr>
<td>Gemcitabine + Cisplatin / Carboplatin</td>
<td>2b B +/-</td>
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<td>Gemcitabine + Capecitabine</td>
<td>2b B +/-</td>
</tr>
<tr>
<td>Gemcitabine + Vinorelbine*</td>
<td>1b B -</td>
</tr>
<tr>
<td>Ixabepilone + Capecitabine*</td>
<td>1b B -</td>
</tr>
</tbody>
</table>

*Cave neutropenia / therapeutic index!
Triple Negative Metastatic Breast Cancer (TNBC: ER-, PR-, HER2-)

- Cytotoxic therapy as for ER pos. HER2 neg. patients ++
- Experimental therapies within studies ++
- Platinum-based regimen 4 C +/-
- Bevacizumab added to cytotoxic therapy 2b B +

Oxford / AGO LoE / GR
Targeted Agents Registered in Other Indications – Potentially Effective in HER2 negative BC

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>1b B -</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>1b B -</td>
</tr>
<tr>
<td>Ramucirumab added to cytotoxic therapy</td>
<td>1b* B --*</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>1b B --*</td>
</tr>
</tbody>
</table>

* Study participation recommended
Bevacizumab Treatment in HER2-neg. Metastatic Breast Cancer

1\textsuperscript{st} line in combination with:
- Paclitaxel (q1w)
- Capecitabine
- Anthracyclines
- Nab-Pac
- Docetaxel (q3w)

2\textsuperscript{nd} line in combination with:
- Taxanes
- Capecitabine
- Gemcitabine or vinorelbine

*Study participation recommended
### First Line Therapy of HER2 Overexpressing Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel + trastuzumab + pertuzumab</td>
<td>1b A ++</td>
</tr>
<tr>
<td>Paclitaxel + trastuzumab + pertuzumab</td>
<td>5 D +</td>
</tr>
<tr>
<td>T-DM 1 (relapse within 6 months after taxane and trastuzumab-pretreatment)</td>
<td>2b B +</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt;-Line chemotherapy* + trastuzumab</td>
<td>1b B +</td>
</tr>
<tr>
<td>Trastuzumab mono</td>
<td>2b B +/-</td>
</tr>
<tr>
<td>Taxanes + lapatinib</td>
<td>1b&lt;sup&gt;a&lt;/sup&gt; B +/-</td>
</tr>
<tr>
<td>Trastuzumab + aromatase inhibitors (if ER+)</td>
<td>2b B +/-**</td>
</tr>
<tr>
<td>Lapatinib + aromatase inhibitors (if ER+)</td>
<td>2b B +/-**</td>
</tr>
</tbody>
</table>

*Taxanes; vinorelbine; paclitaxel/carboplatin; capecitabine/docetaxel

**see Chapter Endocrine +/- targeted
# Second Line Therapy of HER2 Overexpressing Metastatic Breast Cancer (If Pretreatment with Trastuzumab)

<table>
<thead>
<tr>
<th>Treatment Options</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-DM 1</td>
<td>1b A ++</td>
</tr>
<tr>
<td>Capecitabine + lapatinib</td>
<td>1b B +</td>
</tr>
<tr>
<td>Trastuzumab + lapatinib (HR neg. disease)</td>
<td>2b B +</td>
</tr>
<tr>
<td>TBP: 2\textsuperscript{nd}-line chemotherapy + trastuzumab</td>
<td>2b D +</td>
</tr>
<tr>
<td>Taxane + trastuzumab + pertuzumab</td>
<td>5 D +</td>
</tr>
<tr>
<td>Any other 2\textsuperscript{nd}-line chemotherapy* + trastuzumab + pertuzumab</td>
<td>5 D +/-</td>
</tr>
<tr>
<td>Trastuzumab + aromatase inhibitors (if ER+)</td>
<td>3b B +</td>
</tr>
<tr>
<td>Lapatinib + aromatase inhibitors (if ER+)</td>
<td>3b B +</td>
</tr>
</tbody>
</table>

*e.g. vinorelbine; taxane/carboplatin; capecitabine/docetaxel (toxicity!)*
Further Lines of Therapy of HER2-Positive Metastatic Breast Cancer

Pretreatment with Trastuzumab

- T-DM 1
- Capecitabine + lapatinib
- Trastuzumab + lapatinib (HR neg. disease)
- Chemotherapy* + trastuzumab + („treatment beyond progression“)
  - Trastuzumab + pertuzumab
  - Vinorelbine + trastuzumab + everolimus

There is no data for patients pretreated with trastuzumab and pertuzumab

- Experimental anti-HER2-regimen

For patients pretreated with trastuzumab and pertuzumab, treatment according to the recommendations above. There is no data for treatment beyond progression for pertuzumab.
Trastuzumab in HER2-positive Metastatic Breast Cancer

- **As Monotherapy**
  - After cytotoxic pretreatment
  - As 1<sup>st</sup> line therapy

- **As combination therapy**
  - With taxanes (1<sup>st</sup> line)
  - With paclitaxel / carboplatin
  - Vinorelbine (first line)
  - Capecitabine / docetaxel
  - Other cytotoxic agents
  - In combination with aromatase inhibitors

- **As treatment beyond progression**
  - With capecitabine
  - With lapatinib for heavily pre-treated pts.

**Duration and dosing of treatment:**
- Start of treatment as early as possible
- Treatment until progression of disease
- Weekly or 3weekly

<table>
<thead>
<tr>
<th>Oxford / AGO</th>
<th>LoE</th>
<th>GR</th>
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</thead>
<tbody>
<tr>
<td>1b A ++</td>
<td>2b B +</td>
<td></td>
</tr>
</tbody>
</table>
Lapatinib in HER2-positive Metastatic Breast Cancer

In combination with

- Paclitaxel in 1\textsuperscript{st} line
- Capecitabine in ≥ 2\textsuperscript{nd} line
- AI in ER positive disease
- Trastuzumab for heavily pre-treated pts

- In patients with brain metastases (radioresistance) in combination with capecitabine
Palliative High Dose Chemotherapy

- High dose-therapy
  (No treatment outside studies)

- Dose dense therapy
  (No treatment outside studies)

Oxford / AGO LoE / GR

1a A - -

1a A - -
Chemotherapy With or Without Targeted Drugs* in Metastatic Breast Cancer (2/20)

Further information and references:

Update 2013 based on versions 2012.1 E (fusion of Chapter 21, Cytotoxic Therapy in Metastatic Breast Cancer, and Chapter 25, Targeted Agents).

Screened Sources:
Pubmed 1.12012 - 15.1.2013
S3-Leitlinie
Lorenz, W., Ollenschläger, G., et al. Das Leitlinein-Manual von AWMF und ÄZQ. ZaeFQ 2001, 95; Suppl. 1, 1-84

2013:
International Guidelines
Further information and references:

As shown in recent single prospective randomized studies survival can be significantly prolonged even in metastatic disease. If outcome in clinical trials over various time periods is compared, survival of patients with metastatic breast cancer has become longer and longer (Gennari et al. Cancer 2005) These observations strongly support the use of cytotoxic therapy in this stage of disease.
It also could be demonstrated that also in metastatic breast cancer it might be worth to keep the relative dose intensity as high as possible. (Loibl et al. ASCO 2009)


Die Bisphosphonate stellen für die ossären Metastasen als häufigste Organmanifestation eines MBC dar. Die Therapie sollte bei apparativem Nachweis lytischer Knochendestruktionen mit lokalisierten Knochenschmerzen begonnen werden. Eine lebensverlängernde Wirkung von Bisphosphonaten wurde in der metastasierten Situation nicht nachgewiesen. (Hilner et al. 2003 JCO)
Cytotoxic Therapy Goals (5/20)

Further information and references:

Monotherapy has a better therapeutic index than polychemotherapy. Monochemotherapy is indicated if progression is slow and not life threatening or if endocrine therapy becomes ineffective. Polychemotherapy has a less favorable therapeutic index and is indicated if a fast remission should be achieved.

With two exceptions (O'Shaugnessy et al, 2003, Albain, 2004) polychemotherapy could not show an advantage over sequential monotherapy with anthracyclines, taxanes, capecitabine, vinorelbin in a prospective randomised study in the last more than 10 years. Life quality tends to be worse under polychemotherapy compared to monochemotherapy.

An example for the similar survival of patients with combination versus monotherapy with the same cytotoxic drugs is a phase 2 study: AP vs A → P vs P → A. (Sledge et al, 2003).

A recent metanalysis found a modest advantage for combination chemotherapy regimens compared with single agents with a hazard ratio (HR) for overall survival of 0.88 (95% CI=0.83-0.94, P<0.0001). Combination regimens are favourably associated with time to progression (overall HR of 0.78 (95% CI=0.73-0.83, P<0.00001) and tumour response rates (OR 1.28, CI=1.15-1.42, P<0.00001)

(S Carrick et al, The Cochrane Database of Systematic Reviews 2005)

2013

Combination vs single agent

Belfiglio M, Fanizza C, Tinari N, Ficorella C, Iacobelli S, Natoli C; Consorzio Interuniversitario Nazionale per la Bio-Oncologia (CINBO). Meta-analysis of phase III trials of docetaxel alone or in combination with chemotherapy in

Docetaxel alone or in combination

Metaanalysis; MBC

Combination chemotherapy regimens with docetaxel show a statistically significant advantage for TTP, but not for OS and ORR in MBC.


Single trials:

Combination not superior compared to single agent regimen.

Pallis AG, Boukovinas I, Ardavanis A, Varthalitis I, Malamos N, Georgoulias V, Mavroudis D.


Tailored therapy in MBC

Toxicity-adjusted treatment with ET and TEX showed similar efficacy in terms of PFS, OS, and OR. In this trial with limited power, the addition of capecitabine to epirubicin and paclitaxel as first-line treatment did not translate into clinically relevant improvement of the outcome.


Cytotoxic and Targeted Therapy (6/20)

Further information:

Before chemotherapy, patients' compliance should be evaluated. The chemotherapy effect is less if patients' health condition is affected, if metastases progress and depends on previous therapies. Under therapy, objective and subjective toxicity evaluation should be performed. The dosage should be according to published protocols. A lead parameter (metastases, tumor marker, symptoms) should be assessed before therapy and two monthly to evaluate therapeutic effects.

References:

2013

International Guidelines
Cytotoxic Therapy Duration (7/20)

Further information:

Chemotherapy should be given as long as the therapeutic index is positive, e.g. until progress or toxicity. Intermittent therapy is superior to cytostatic maintenance therapy. Although progression-free survival is longer, toxicity is higher and survival is not prolonged. Chemotherapy should be stopped if disease progresses or intolerable side effects occur.

No references
**Chemotherapy for MBC – General Considerations: Drug Selection (8/20)**

*Further information:*

The selection of the drugs and drug combinations should take into account patients expectations, general health conditions, aggressiveness of the disease, localisation of metastases and previous therapies.

*References:*

2013
Quality of life: Paclitaxel/gemcitabine vs paclitaxel-mono. Combination tends to be better
Moinpour CM, Donaldson GW, Liepa AM, Melemed AS, O'Shaughnessy J, Albain KS.
Evaluating health-related quality-of-life therapeutic effectiveness in a clinical trial with extensive nonignorable missing
data and heterogeneous response: results from a phase III randomized trial of gemcitabine plus paclitaxel versus paclitaxel

Limitations of palliative chemotherapy
Ribeiro JT, Macedo LT, Curigliano G, Fumagalli L, Locatelli M, Dalton M, Quintela A, Carvalheira JB, Manunta S,
Mazzarella L, Brollo J, Goldhirsch A. Cytotoxic drugs for patients with breast cancer in the era of targeted treatment: back

Metaanalyses
HRQOL is one of the key indicators of treatment benefit in advanced breast cancer, but contemporary systemic therapies
in this setting do not appear to affect HRQOL differentially.
Adamowicz K, Jassem J, Katz A, Saad ED. Assessment of quality of life in advanced breast cancer. An overview of
MBC HER2 negative Cytotoxic 1st-Line Therapy* (9/20)

Further information and references:

The most effective drugs in breast cancer are anthracyclines (including liposomal anthracyclines), taxanes and vinorelbine and capecitabine. Therefore these drugs should be used in first line monotherapy.
Metanalysis of 4256 pts. In 12 trials showed single agent A was better than single agent T in terms of PFS, marg. better in terms of RR, no differences in terms of OS. T-based combinations were significantly better than A-based comb. in terms of RR, PFS, but not better in terms of OS (Piccart SABCS 2005).
Liposomal doxorubicin is equally effective to doxorubicin but has less cardio and myelotoxicity but more skin toxicity (O’Brien et al, 2004).
Polychemotherapy with anthracyclines and taxanes induce high remission rates but are more toxic then anthracycline or taxane free combinations.
After anthracycline treatment two studies could show a survival benefit with gemcitabine paclitaxel or with Docetaxel/Capecitabine (O’Shaughnessy et al, 2002 and Albain, 2004).
Retrospective date show that patients who respond to first line therapy with a complete response have a survival benefit compared to patients without CR (Greenberg et al, 1996).
Doxorubicin/docetaxel vs. Doxorubicin/paclitaxel as first line treatment in metastatic breast cancer (ERASME3-study) did not show any significant differences in terms of efficacy and overall QoL. Cassier et al., Breast Cancer Research and Treatment (electronic publication 2007).

2013
Individual trials
1. Taxanes +/- Bevacizumab
2. NabPaclitaxel vs Ixabepilone vs paclitaxel
Rugo HS, Barry WT, Moreno-Aspitia A, Lyss AP, Cirrincione C, Mayer EL, Naughton M, Layman RM, Carey LA, Somer RA, Perez EA, Hudis C, Winer EP (2012) CALGB 40502/NCCTG N063H: Randomized phase III trial of weekly paclitaxel (P) compared to weekly nanoparticle albumin bound nab-paclitaxel (NP) or ixabepilone (Ix) with or without bevacizumab (B) as first-line therapy for locally recurrent or metastatic breast cancer (MBC). J Clin Oncol 30, 2012 (suppl; abstr CRA1002)

Nab-Paclitaxel
1st line MBC, rand Phase II (n=302)
Treatment with nab-paclitaxel 150 mg/m(2) qw 3/4 resulted in a median overall survival (OS) of 33.8 months compared with 22.2, 27.7, and 26.6 months for nab-paclitaxel 100 mg/m(2) qw 3/4, nab-paclitaxel 300 mg/m(2) q3w, and docetaxel, respectively (overall P = .047).
A trend toward a longer OS was noted in the 150 mg/m(2)nab-paclitaxel arm versus docetaxel arm (hazard ratio, 0.688). Grade 3 or 4 fatigue, neutropenia, and febrile neutropenia were less frequent in all nab-paclitaxel arms compared with docetaxel.


Ixabepilone + capecitabine vs capecitabine alone in 1st line MBC
Results: In 293 patients, ixabepilone plus capecitabine, as compared to capecitabine alone, increased PFS (median: 5.6 months vs. 2.8 months; hazard ratio, 0.58; p < 0.0001), ORR (46% vs. 24%) and OS (median: 15.1 months vs. 12.5 months; hazard ratio, 0.84; p = 0.208). Major toxicities of this regimen included neuropathy, neutropenia and hand-foot syndrome, but were manageable.

Metaanalyses
Docetaxel alone or in combination
Metaanalysis; MBC
Combination chemotherapy regimens with docetaxel show a statistically significant advantage for TTP, but not for OS and ORR in MBC.


**MBC HER2 negative: Cytotoxic Therapy after Anthracycline Treatment***(10/20)*

*Further information and references:*

Suggested after anthracyclines (in alphabetical order): Capecitabine, Docetaxel, study-integrated experimental therapies, Gemcitabine, Pegliposomes Doxorubicin, Paclitaxel and Vinorelbine.

As monotherapy after anthracyclin-pretreatment only Docetaxel improved OAS as compared to a standard treatment arm in a prospective randomized trial in metastatic breast cancer (*Nabholtz et al, 1999*).

A Cochrane-metaanalysis of taxane treatment in metastatic breast cancer (*Ghersi et al, 2003*) shows a significant survival advantage as compared to non-taxane-based therapies. There was no significant difference in QoL or treatment related deaths. Final analysis of further end points was difficult due to significant heterogeneity of the single studies.

Indirect and direct comparisons of docetaxel and paclitaxel show a trend towards higher efficacy of docetaxel (*Ghersi et al, 2003; Ravdin et al, 2003*). Due to different toxicity profiles of each substance individual indication is needed.

Docetaxel in Combination with Pegliposomal Doxorubicin was superior to docetaxel alone in a randomised phase III trial by Sparano et al. It is one of the largest trials in this setting with 751 pts and demonstrated a clear PFS advantage from 9.8 vs 7 months without improving the OS. QoL was not different. Hand foot syndrome and mucositis were more common with the combination.

2013
Nab-Paclitaxel
MBC HER2 negative: Cytotoxic Therapy After Taxane and Anthracycline Treatment (11/20)

Further information and references:

Nab Paclitaxel (100-150mg/m² d1,8,15,q28) has been tested in different populations. Not all pts received an anthracycline and a taxane. It seems that a weekly dosing is superior to a 3 weekly dosing in terms of efficacy and side effects. Suggested after anthracycline and taxane treatment (alphabetical order): capecitabine, study-integrated experimental therapies, pegliposomal doxorubicin and vinorelbin. Studies with more than 100 patients showed overall remissions of 9% and 20% using vinorelbine and pegylated liposomal doxorubicin vs. capecitabine, respectively and a median survival of 9 months and 13 months. Ixabepilone/Capecitabine vs. Capecitabine after anthracycline and taxane treatment in metastatic breast cancer is a phase III randomised trial showing a significant improvement in PFS for the combination with a higher toxicity especially in neurotoxicity. Ixabepilone is not licensed in Germany; Thomas et al., JCO 25:5210-7 (2007) Gemcitabine/vinorelbine vs. vinorelbine after anthracycline/taxane treatment in metastatic breast cancer; Martin et al., Lancet Oncol 8:219-25 (2007) -38 pts treated with Gemcitabine/Cisplatin after anthracycline and taxane pretreatment as (neo)adjuvant, or 1st line met therapy demonstrated a TTP of 5.2 months CI 3.6-6.8 and an OS of 19.5 months CI 11.2-27.8 months. Kim JH; Cancer Res Treat 2008; 40: 101-105

Scarpace SL.
New microtubule-targeting agents.

Review

The development of new microtubule-targeting agents helps to address the need for additional effective regimens for patients progressing after standard treatment with anthracycline- and taxane-containing regimens.

Triple Negative Metastatic Breast Cancer (TNBC: ER-, PR-, HER2-) (12/20)

No further information

References:

Triple negative patients
J Clin Oncol 26: 2008 (May 20 suppl; abstr 1051)
Author(s):
B. Sirohi, M. Arnedos, S. Popat, S. Ashley, A. Nerurkar, G. Walsh, S. Johnston, I. E. Smith
Citation:
Author(s):
J. W. Chia, P. Ang, H. See, Z. Wong, L. Soh, Y. Yap, N. Wong

2013
Met-TNBC Phase II (n=40; RR 35%, med OS 12 m, med TTP 6 m; 27% neutropenia °3/4)
Targeted Agents Registered in Other Indications – Potentially Effective in HER2 negative BC (13/20)

No further information

No references
**Bevacizumab Treatment in HER2-neg. Metastatic Breast Cancer (14/20)**

*Further information and references:*


**2013**

**Individual trials**

1. Taxanes +/- Bevacizumab
2. NabPaclitaxel vs Ixabepilone vs paclitaxel

paclitaxel (P) compared to weekly nanoparticle albumin bound nab-paclitaxel (NP) or ixabepilone (Ix) with or without bevacizumab (B) as first-line therapy for locally recurrent or metastatic breast cancer (MBC). J Clin Oncol 30, 2012 (suppl; abstr CRA1002)

Review and opinion

Side effects
Metaanalysis:
**First Line Therapy of HER2 Overexpressing Metastatic Breast Cancer (15/20)**

*Further information and references:*

2013

**Docetaxel + trastuzumab + pertuzumab (LoE 1bA AGO++)**

Baselga et al., December 7, NEJM 2011

Side effects Pertuzumab

Skin rash

Pertuzumab is associated with a significant risk of rash, and the incidence varies among different tumor types. Prevention, early recognition, and appropriate treatment of this rash may lead to improvement in patient quality of life, adherence to therapy, and possibly optimize clinical outcomes.


**Paclitaxel + trastuzumab + pertuzumab (LoE 5D AGO+-)**

1st-Line chemotherapy* + trastuzumab (LoE 1bB AGO+)

(*taxanes; vinorelbine; paclitaxel/carboplatin; capecitabine/docetaxel)


Valero V., Forbes J., Pegramet M. D. et al.: Multicenter Phase III Randomized Trial Comparing Docetaxel and Trastuzumab With Docetaxel, Carboplatin, and Trastuzumab As First-Line Chemotherapy for Patients With HER2-Gene-
Amplified Metastatic Breast Cancer (BCIRG 007 Study): Two Highly Active Therapeutic Regimens. DOI: 10.1200/JCO.2010.28.6450


Trastuzumab mono (LoE 2bB AGO+/-)


Taxanes+ lapatinib (LoE 1bA AGO+/-)


Gelman KA, Boyle F, Kaufman B, Hunstman D et al. (2012) Open-Label phase III randomized controlled trial comparing taxane-based chemotherapy (Tax) with lapatinib (L) or trastuzumab (T) as first-line therapy for women with HER2+ metastatic breast cancer: Interim analysis (IA) of NCIC CTG MA.31/GSK EGF 108919. J Clin Oncol 30 (suppl, abstr LBA671), 2012 ember 7, NEJM 2011

Trastuzumab + aromatase inhibitors (if ER+) (LoE 2bB AGO+/-)

Lapatinib + aromatase inhibitors (if ER+) (LoE 2bB AGO+-)
Second Line Therapy of HER2 Overexpressing Metastatic Breast Cancer (If Pretreatment with Trastuzumab) (16/20)

Further information and references:

Baselga et al., December 7, NEJM 2011

2013
Capecitabine + lapatinib (LoE 1b B AGO+)
When compared against capecitabine alone, the addition of lapatinib has a cost-effectiveness ratio exceeding the threshold normally used by NICE.

Trastuzumab + lapatinib (if CT not possible) (LoE 3b B AGO+)

Trastuzumab plus lapatinib vs lapatinib
Met-HER2posBC phase iii (2nd and further lines; n=291, HR-PFS =0.74, p=0.011; HR OS =0.74, p=0.026)

TBP: 2nd-Line chemotherapy + trastuzumab (Treatment beyond progression) (LoE 2b D AGO +)

Review
“Emerging evidence from randomized controlled trials supports the potential clinical utility of continuing trastuzumab-based therapy beyond progression and supports the National Comprehensive Cancer Network recommendation to consider this treatment approach. Future treatment of HER2-positive MBC may involve trastuzumab being used in successive regimens in combination with other targeted therapies.”

Taxane + trastuzumab + pertuzumab (LoE 5 D AGO +)
Any other 2nd-Line chemotherapy* + trastuzumab + pertuzumab (LoE 5 D AGO +/−)
Trastuzumab mono (DATEN?) (LoE 2b B AGO +/−)

2nd line:

1st line:
Trastuzumab + aromatase inhibitors (if ER+)(LoE 3b B AGO +)

Lapatinib + aromatase inhibitors (if ER+)(LoE 3b B AGO +)
Further Lines of Therapy of HER2 Overexpressing Metastatic Breast Cancer (17/20)

Further information and references:

2013

TBP: 2nd-line chemotherapy + trastuzumab + pertuzumab („treatment beyond progression“; with taxanes, vinorelbine, paclitaxel/carboplatin, or capecitabine/docetaxel) (LoE 5 D AGO +/-)
Baselga, J. et al. (2010) Phase II trial of Pertuzumab and Trastuzumab in patients with human epidermal growth factor receptor 2 – positive metastatic breast cancer that prograded during prior Trastuzumab therapy. JCO 28, 1138-1144

Review
“Emerging evidence from randomized controlled trials supports the potential clinical utility of continuing trastuzumab-based therapy beyond progression and supports the National Comprehensive Cancer Network recommendation to consider this treatment approach. Future treatment of HER2-positive MBC may involve trastuzumab being used in successive regimens in combination with other targeted therapies.”

Capecitabine + lapatinib (LoE 2b B AGO +)

Trastuzumab + lapatinib (if CT not possible) (LoE 3bB AGO +)
Blackwell KL, Burstein HJ, Sledge GW, Stein S, Ellis C, Casey M, Baselga J, O'Shaughnessy J; Updated Survival Analysis of a Randomized Study of Lapatinib Alone or in Combination with Trastuzumab in Women with HER2-Positive Metastatic Breast Cancer Progressing on Trastuzumab Therapy. JCO 2010, 28: 1124-1130

Experimental anti-HER2-regimen (including trastuzumab-Emtansine, T-DM1) (LoE 5D AGO +)
EMILIA
Blackwell K. et al. (2012) Primary Results From EMILIA, a Phase 3 Study of Trastuzumab Emtansine (T-DM1) vs Capecitabine and Lapatinib in HER2-Positive Locally Advanced or Metastatic Breast Cancer Previously Treated With Trastuzumab and a Taxane. ASCO 2012
Baselga et al., Dec
Trastuzumab in HER2-positive Metastatic Breast Cancer (18/20)

Further information and references:

Registered in HER-2 positive disease (Dosage / Duration):

Dosage:
Duration of treatment:

2013
Trastuzumab treatment beyond progression
Review
“Emerging evidence from randomized controlled trials supports the potential clinical utility of continuing trastuzumab-based therapy beyond progression and supports the National Comprehensive Cancer Network recommendation to consider this treatment approach. Future treatment of HER2-positive MBC may involve trastuzumab being used in successive regimens in combination with other targeted therapies.”
Lapatinib in HER2-positive Metastatic Breast Cancer (19/20)

Further information and references:

Anthracycline and Taxane and Trastuzumab pre-treatment


Blackwell KL, Burstein HJ, Sledge GW, Stein S, Ellis C, Casey M, Baselga J, O'Shaughnessy J; Updated Survival Analysis of a Randomized Study of Lapatinib Alone or in Combination with Trastuzumab in Women with HER2-Positive Metastatic Breast Cancer Progressing on Trastuzumab Therapy. JCO 2010, 28: 1124-1130

Trastuzumab naive patients: first line therapy
Brain metastases (radioresistance)
Palliative High Dose Chemotherapy (20/20)

Further information and references:

A recent Cochrane systematic review on six randomised controlled trials and 850 patients found an increase in treatment-related deaths among the high dose group compared to the control (conventional dose) group (RR 4.07 (95% CI 1.39, 11.88)). There was no statistically significant difference in overall survival between the high dose and control groups at one year, three years or five years. At one and five years of follow up, there was a statistically significant difference in event-free survival, favouring the high dose group (one year: RR 1.76 (95% CI 1.40, 2.21); five years: RR 2.84 (95% CI 1.07, 7.50). Toxicity was more severe in the high dose group. Only one of the trials has followed up all women for five years and further data are awaited. Although there is statistically significant evidence that high dose chemotherapy and autograft improves event free survival compared to conventional chemotherapy, the authors of this report conclude that high dose chemotherapy with bone marrow or stem cell transplantation should not be given to women with metastatic breast cancer outside of clinical trials.
This conclusion remains valid, if more recent published trials are also taken into consideration.

Vredenburgh JJ et al., Bone Marrow Transplantation, 37:985-7 (2006)
Biron P et al., Bone Marrow Transplantation, Epub 11/2007

Tailored therapy in MBC
Toxicity-adjusted treatment with ET and TEX showed similar efficacy in terms of PFS, OS, and OR. In this trial with limited power, the addition of capecitabine to epirubicin and paclitaxel as first-line treatment did not translate into clinically relevant improvement of the outcome.
Osteoooncology and Bone Health
Osteoanecology and Bone Health

- **Versions 2002-2013:**
  Bischoff / Böhme / Brunnert / Dall / Diel / Fehm / Fersis / Friedrich / Friedrichs / Huober / Jackisch / Janni / Lux / Maas / Oberhoff / Schaller / Scharl / Schütz / Seegenschmiedt / Solomayer / Souchon

- **Version 2014:**
  Diel / Nitz
Bisphosphonates in Breast Cancer

- Hypercalcemia
- Reduction of skeletal events (complications)
- Reduction of bone pain
- Treatment beyond progression of bone met‘s
- In combination with neoadjuvant chemotherapy
- Prevention of bone metastases/ survival advantage
  - Adjuvant in postmenopausal patients
  - Advanced breast cancer
- Prevention of breast cancer with oral BPs (in women receiving BP for low BMD)

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>1a A ++</th>
<th>1a A ++</th>
<th>1a A ++</th>
<th>5 D ++</th>
<th>2b C +/-</th>
<th>1a A +</th>
<th>2b C +/-</th>
<th>3b C +/-</th>
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## Denosumab in Breast Cancer

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Level of Evidence</th>
<th>Grade</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Reduction of hypercalcemia</td>
<td>2a A ++</td>
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<td></td>
</tr>
<tr>
<td>Reduction of skeletal complications</td>
<td>1a A ++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction of bone pain</td>
<td>1b B ++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increasing bone pain-free survival</td>
<td>1b A ++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment beyond progression</td>
<td>5 D +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression under bisphosphonates</td>
<td>4 C +/-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Bone Modifying Agents for the Therapy of Bone Metastases

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose and Schedule</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clodronate</td>
<td>PO</td>
<td>1600 mg daily</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Clodronate</td>
<td>IV</td>
<td>1500 mg q3w / q4w</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>IV</td>
<td>90 mg q3w / q4w</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>IV</td>
<td>6 mg q3w / q4w</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>PO</td>
<td>50 mg daily</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>IV</td>
<td>4 mg q4w</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Denosumab</td>
<td>s.c.</td>
<td>120 mg q4w</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Other doses or schedules,</td>
<td></td>
<td>derived from</td>
<td>5 D - -</td>
</tr>
<tr>
<td>e.g. derived from studies</td>
<td></td>
<td>of adjuvant therapy or therapy of osteoporosis</td>
<td></td>
</tr>
</tbody>
</table>
Skeletal Metastasis
Treatment with Radionuclids

- Tumor progression after standard treatment of multiple / disseminated metastases and intolerable bone pain
  (prerequisite: hot spots in the bone scintigraphy)
  - $^{186}$Rhenium-hydroxyethylidene-diphosphonat (e.g. $^{186}$Re-HEDP)
  - $^{153}$Samarium
  - $^{89}$Strontium (e.g. Sr$^{89}$)
  - $^{223}$Radium

Cave: Myelosuppression with risks of pancytopenia has to balance potential benefits.
Metastatic Bone Disease of the Spine

Indications for surgery

Oxford LoE: 2b
GR: C
AGO: ++

- Spinal cord compression
  - With progressive neurological symptoms
  - With pathological fractures
- Instability of the spine
- Lesions in pre-irradiated parts of the spine
Bone Metastases
Acute Spinal Cord Compression / Paraplegia

- Decompression surgery, reduction of tumor volume, stabilisation surgery (< 24 h) and irradiation of the spine (RT) 2b C ++
- Irradiation of the spine (< 24 h) +/- steroids 3b C ++
- Immediate start of treatment 1c D ++

Clinical trials have included patients with different tumor entities!
Surgery for Bone Metastases

Spine and limbs

Oxford LoE: 3b  GR: C  AGO: +

- Marrow splints
- Osteosynthesis
- Bone replacement by PMMA or titanspacer
- Tumor-Endoprothesis
- Vertebroplasty / Kyphoplasty
- Kypho-IORT (only in studies)*
- Resection of involved bone in oligometastatic disease
  (sternum, ribs, vertebrectomy and replacement with spondylodesis)

*Study participation recommended
Bone metastases

- With fracture risk
- With functional impairment
- With bone pain
  - Single RT = fractionated RT
- With neuropathic bone pain
- Asymptomatic isolated bone metastases

Only few studies included breast cancer patients!
Metastatic Bone Disease
Recurrent Bone Pain

Recurrent bone pain in pre-irradiated parts of the skeleton:

- Single RT (1 x 8 Gy)  
  - Oxford / AGO LoE / GR
  - Metastatic Bone Disease
  - Recurrent Bone Pain
  - 3b C ++

- Fractionated RT (6 x 4 Gy)  
  - 3b C +

- Radionuclid therapy  
  - 3b C +
Side-Effects and Toxicity – Bisphosphonates (BP) and Denosumab (Db)

- Renal function deterioration due to IV-aminobisphosphonates 1b
- Osteonecrosis of the jaw (ONJ) mostly under IV-BP and denosumab therapy (1.8% / 1.8%) 1b
  - Association with anti-angiogenetic therapies 3b
- Severe hypocalcemia (Dmab>BPs) 1b
- Acute phase reaction (IV Amino-BPs, Db) 10-30% 1b
  - Gastrointestinal side effects (oral BPs) 2-10% 1b

In adjuvant bisphosphonate therapy, major side effects were rarely observed (except APR).
Recommendations for Precautions to Prevent ONJ*

Oxford LoE: 4  GR: C  AGO: +

- During bisphosphonate or denosumab treatment, avoid any elective dental procedures, which involve jaw bone manipulations – if interventions are inevitable, prophylactic antibiotics are recommended (LoE 2b)

- Optimize dental status before start of bisphosphonate or denosumab treatment, if feasible (LoE 2b)

- Inform patients about ONJ risk and educate about early symptom reporting

- In case of high risk for ONJ, use oral bisphosphonate

In adjuvant bisphosphonate therapy, ONJ was rare

*Osteonecrosis of the jaw
### Adjuvant Bisphosphonates for Reduction of Bone Metastases and Survival Advantage

<table>
<thead>
<tr>
<th>Bisphosphonates</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clodronate (oral)</strong></td>
<td></td>
</tr>
<tr>
<td>Postmenopausal patients</td>
<td>1a A +</td>
</tr>
<tr>
<td>Premenopausal patients</td>
<td>1a B +/-</td>
</tr>
<tr>
<td><strong>Aminobisphosphonates (iv or oral)</strong></td>
<td></td>
</tr>
<tr>
<td>Postmenopausal patients</td>
<td>1a A +</td>
</tr>
<tr>
<td>Premenopausal patients</td>
<td>1a B +/-</td>
</tr>
</tbody>
</table>
Adjuvant Bisphosphonates for Reduction of Bone Metastases and Survival Advantage

- Chlebowski RT, Col N. Bisphosphonates and breast cancer, incidence and recurrence. Breast Disease 2011;33:83-101
Dosage of Adjuvant Bisphosphonates for Improvement of Survival

- **Non-Aminobisphosphonates:**
  - Clodronate PO 1600mg/d (Bonefos/ Clodronic acid)
  - Clodronate PO 1040mg/d (Ostac)
- **Aminobisphosphonates:**
  - Zoledronate IV 4mg/6m (Zometa/ Zoledronic acid)
  - Ibandronate PO 50mg/d (Bondronat/ Ibandronic acid)
  - Pamidronate PO (orally not available in most countries)
  - Risedronate PO 35mg/w (Actonel/ Risedronic acid)
  - Alendronate PO 70mg/w (Fosamax/ Alendronic acid)

Aminobisphosphonates include:
Zoledronic acid (65%), Oral ibandronate (24%), Oral pamidronate (8%), Oral resildronate (2%), Oral alendronate (1%) (data from EBCTCG-metaanalysis)
Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis

- **Bisphosphonates**
  - **Therapy**
  - **Prevention**

- **Denosumab**
  - **Therapy**
  - **Prevention**

- **HRT (independent from ER-status of BC)**

- **Regular BMD-measurement recommended**
  (Intervals depending from previous T-values)

---

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b B ++</td>
</tr>
<tr>
<td>1b A +</td>
</tr>
<tr>
<td>1b B ++</td>
</tr>
<tr>
<td>1b A +</td>
</tr>
<tr>
<td>5 D -</td>
</tr>
<tr>
<td>2b B +</td>
</tr>
</tbody>
</table>
Further recommendations (based on DVO-guidelines for treatment, diagnosis and prevention of osteoporosis)*

- Physical activity
- Avoiding immobilisation
- Calcium (1000–1500 mg/d. Nutrit./Suppl.)**
- Vitamine D suppl. (800–2000 U/d)
- Reduction of smoking
- Avoiding BMI < 20 mg/m²
- Drugs approved for the treatment of osteoporosis in adults (see next slide)

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>4</th>
<th>C</th>
<th>++</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
<td>C</td>
<td>++</td>
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<tr>
<td></td>
<td>4</td>
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<td>++</td>
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<td></td>
<td>4</td>
<td>C</td>
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<tr>
<td></td>
<td>4</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>3b</td>
<td>C</td>
<td>++</td>
</tr>
</tbody>
</table>


New DVO-guidelines will be presented soon in 2014

**if intestinal uptake is reduced (in combination with Vit D only)
# Medical Treatment of Osteoporosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate 70 mg po/w*</td>
<td>1b B ++</td>
</tr>
<tr>
<td>Denosumab 60 mg sc/6m*</td>
<td>1b B ++</td>
</tr>
<tr>
<td>Ibandronate 150 mg po/m*</td>
<td>1b B ++</td>
</tr>
<tr>
<td>Ibandronate 3 mg iv/3m</td>
<td>1b B +</td>
</tr>
<tr>
<td>Parathyroid hormone (1-84) 100 µg sc/d</td>
<td>1b B +</td>
</tr>
<tr>
<td>Raloxifene 60 mg po/d</td>
<td>1b B +</td>
</tr>
<tr>
<td>Risedronate 35 mg po/w*</td>
<td>1b B ++</td>
</tr>
<tr>
<td>Strontium ranelate 2 g po/d</td>
<td>1b B +</td>
</tr>
<tr>
<td>Teriparatide (1-34) 20 µg sc/d</td>
<td>1b B +</td>
</tr>
<tr>
<td>Zoledronate 5 mg iv/12 m*</td>
<td>1b B ++</td>
</tr>
</tbody>
</table>

* Drugs tested in clinical studies with breast cancer patients and tumor therapy-induced osteoporosis
IV.3 ggf. weitere Abklärung und Therapie sekundärer Ursachen bei klinischen und/oder laborchemischen Hinweisen auf sekundäre Ursachen einer hohen Frakturgefährdung, ggf. in Absprache mit dem Fachspezialist (B-D)

IV.4 ggf. medikamentöse Therapie entsprechend der folgenden Tabelle, wenn keine Änderung des Risikos durch IV.1. oder IV.3 zu erwarten ist

<table>
<thead>
<tr>
<th>ohne WK-Fraktur bei Lebensalter (Jahre)</th>
<th>-2.0 bis -2.5</th>
<th>-2.5 bis -3.0</th>
<th>-3.0 bis -3.5</th>
<th>-3.5 bis -4.0</th>
<th>&lt; -4.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frau 50-60</td>
<td>Nein</td>
<td>Nein</td>
<td>Nein</td>
<td>Nein</td>
<td>Ja</td>
</tr>
<tr>
<td>Mann 60-70</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frau 60-65</td>
<td>Nein</td>
<td>Nein</td>
<td>Nein</td>
<td>Nein</td>
<td>Ja</td>
</tr>
<tr>
<td>Mann 70-75</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frau 65-70</td>
<td>Nein</td>
<td>Nein</td>
<td>Nein</td>
<td>Ja</td>
<td>Ja</td>
</tr>
<tr>
<td>Mann 75-80</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frau 70-75</td>
<td>Nein</td>
<td>Ja</td>
<td>Ja</td>
<td>Ja</td>
<td>Ja</td>
</tr>
<tr>
<td>Mann 80-85</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frau &gt;75</td>
<td>Ja</td>
<td>Ja</td>
<td>Ja</td>
<td>Ja</td>
<td>Ja</td>
</tr>
<tr>
<td>Mann &gt;85</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

mit WK-Fraktur

Ja - Rasche Therapie wichtig, da hohes akutes Folgerisiko für WK-Frakuren!

1. Bei Vorliegen eines oder mehrerer der folgenden Risikofaktoren wird eine max. um einen T-Wert höher liegende Therapieschwelle empfohlen (d.h. Therapie z.B. ab einem T-Wert von max. -2.5 statt -3.5):
   A. periphere Fraktur, B. Schenkelhalsfraktur eines Elternteils, C. Nikotinkonsum, D. multiple Stürze, E. Immobilität

2. In Abhängigkeit von der klinischen Gesamtsituation ist eine um max. einen T-Wert niedriger liegende Therapieschwelle möglich (d.h. Therapie z.B. ab einem T-Wert von max. -3.5 statt -2.5)

Präparate (Reservemedikation siehe Kurz- und Langfassung)
**Therapieempfehlung für Personen ohne spezifische Risiken und/oder Frakturen**

Schwellenwerte der T-Werte der Knochendichte für eine medikamentöse Therapie in Abhängigkeit vom Geschlecht und dem Lebensalter für Personen ohne prävalente Frakturen oder andere spezifische Frakturrisiken

**Lebensalter in Jahren** | **T-Wert**
---|---
Frau | Mann | T-Wert

<table>
<thead>
<tr>
<th>Lebensalter</th>
<th>T-Wert</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>&lt;60</td>
</tr>
<tr>
<td>50–60</td>
<td>60–70</td>
</tr>
<tr>
<td>60–65</td>
<td>70–75</td>
</tr>
<tr>
<td>65–70</td>
<td>75–80</td>
</tr>
<tr>
<td>70–75</td>
<td>80–85</td>
</tr>
<tr>
<td>&gt;75</td>
<td>&gt;85</td>
</tr>
</tbody>
</table>

Neue DVO-Leitlinie erscheint voraussichtlich 2014
Therapieempfehlung für Personen mit spezifische Risiken und/oder Frakturen

Risikofaktoren, die die Therapieschwelle mitbestimmen (auszugsweise*)

1. Allgemeine Risiken
   periphere Fraktur nach dem 50. Lebensjahr B
   multiple Stürze B
   Immobilität B
   fortgesetzter Nikotinkonsum B
   Abnahme der DXA-Knochendichte am Gesamtfemur um 5% und mehr in 2 Jahren B
   Hypogonadimus B

2. Krankheiten
   Diabetes mellitus Typ 1 B
   rheumatoide Arthritis D

3. Medikamente
   Antiandrogene/ Antiöstrogene Therapie B
   Aromatasehemmer-Therapie D
   orale Glukokortikoide < 7,5 mg für mehr als 3 Monate B

Neue DVO-Leitlinie erscheint vermutlich 2014
Osteoncology and Bone Health (2/22)

No further information

No references
**Bisphosphonates in Breast Cancer (3/22)**

*No further information*

**References:**

Chlebowski RT, Col N. Bisphosphonates and breast cancer, incidence and recurrence. Breast Disease 2011;33:83-101


No further information

No references
Bone Modifying Agents for the Therapy of Bone Metastases (5/22)

No further information

No references
**Skeletal Metastasis Treatment with Radionuclids (6/22)**

*Further information:*

Bei multilokaler Schmerzsymptomatik aufgrund einer kleinherdigen disseminierten ossären Metastasierung stellt die Therapie mit osteotropen Radionukliden eine zusätzliche Option im multimodalen analgetischen Therapiekonzept dar. Sie kann angewendet werden, wenn durch eine zuvor erforderliche diagnostische Skelettszintigraphie mit $^{99m}$Technetium (Tc) eine ausreichend hohe Affinität in befallenen Knochenabschnitten dokumentiert ist, keine pathologische Fraktur vorliegt und die Hämatopoese nicht (z.B. durch eine Karzinose oder myelotoxische Chemotherapie) eingeschränkt ist. Der Effekt der Radionuklidtherapie ist dabei weniger von der Histologie, sondern vor allem vom pathologisch gesteigerten Knochenstoffwechsel abhängig. Verwendet werden heutzutage vor allem die Radiopharmaka $^{153}$Samarium (Sm-EDTMP), $^{89}$Strontium (Sr-Chlorid) und $^{186}$Rhenium (Re-HEDP). Sie unterscheiden sich in ihrer Reichweite, physikalischen Halbwertzeit und Energiedosisleistung, die maßgeblich sind für deren therapieassozierte Nebenwirkungen. Die Ansprechraten liegen zwischen 70 und 90 % mit kompletter Schmerzfreiheit bei 20-30%. Die Anzahl der in Studien zur Schmerzbeeinflussung ossärer Metastasen von Mammakarzinomen mit Radionukliden untersuchten Patientinnen ist jedoch relativ klein. Der maximale analgetische Effekt wird nach etwa 10 Tagen erreicht und hält – abhängig vom eingesetzten Radiopharmakon – im Mittel 5 bis 8 Wochen an.

Vorteile gegenüber der lokalen perkutanen Radiotherapie bestehen in der Möglichkeit von Wiederholungsbehandlungen und der Beeinflussung bereits anreichernder, aber noch nicht symptomatischer Metastasen. Einschränkungen der Radionuklidtherapie sind begründet in deren z.T. ausgeprägter, jedoch zumeist reversiblen Myelosuppression bei 20-60% der Patientinnen und die Beschränkung der Therapie auf kleinherdige Knochenmetastasen aufgrund der begrenzten Reichweite der hierbei emittierten β-Strahlung. Sie ist nicht geeignet bei größeren Knochenmetastasen oder begleitenden Weichteiltumoren.
References:

Übersicht:

89Strontium (89Sr-Chlorid)

186Rhenium (186Re-HEDP)
153Samarium (153Sm-EDTMP)
Kolesnikov-Gauthier H et al., J Nucl Med 2000; 41: 1689-1694
Limouris GS et al., Anticancer Res 1997; 17: 1767-1772
de Klerk JM et al., J Nucl Med 1996 37: 244-249
Palmedo H et al., Nuklearmedizin 1996 35: 63-67
Metastatic Bone Disease of the Spine (7/22)

Further information:

Bei Wirbelsäuleninstabilität, ossärer Kompression und/oder Paraplegie stellt die operative Intervention mit anschließender Radiotherapie das mit hoher Evidenz belegte geeignetste Vorgehen dar. Bei subklinischer Rückenmarkkompression, d.h. bei nicht paraplegischen und ambulant zu behandelnden Patientinnen ohne Anhalt für Instabilität, ist die Radiotherapie als Therapie der Wahl gut validiert. In dieser Situation kann auf eine begleitende Kortisontherapie verzichtet werden. Wenn bei ossären Wirbelsäulenmetastasen mit konsekutiver Spinalkanalbeteiligung Kortikoide eingesetzt werden, ist der Nutzen nur für eine hochdosierte Dexamethason-Medikation (96 mg/d) gut belegt.

References:

Bone Metastases Acute Spinal Cord Compression / Paraplegia (8/22)

Further information:

Metastatic spinal cord compression (MSCC) as well as bone metastases should be managed in an interdisciplinary approach mostly as combined modality treatment according to the specific clinical situation. Best results are achieved by close interdisciplinary cooperation minimizing the interval between diagnosis and onset of treatment. Most important criteria for prognosis and choice of treatment (mostly combined multimodal therapy) are neurological status at diagnosis of MSCC, time course of duration and progression of the neurological symptoms. RT is effective and regarded as treatment of choice for MSCC with or without motor deficits and / or bone metastases, which do not need immediate surgical intervention. It may be used either postoperatively or as primary treatment in case of inoperability. An optimal dose-fractionation schedule or optimal standard dose for treatment of bone metastases has not been established. With regard to different therapeutic goals, different dose concepts and fractionation schedules, single versus multifraction palliative RT (1 x 8, 5 x 4, 10 x 3, 15 x 2.5, 20 x 2 Gy), should be adapted individually.

The role of radiotherapy is well established in the case of MSCC without neurological deficits. Additionally, primary radiotherapy is indicated in the case of beginning paraplegia with complete response to steroids and lack of necessity to operate. Radiotherapy is the method of choice in inoperable cases due to low rate of side effects, short hospitalisation / outpatient procedure and – a key factor – the radiosensitivity of breast cancer. These advantages are also relevant in patients with a dismal overall prognosis, short life expectancy and severe co-morbidity, especially because radiotherapy is equivalent to simple laminectomy with respect to the functional outcome. Local radiotherapy is indicated postoperatively to achieve local tumour control and should be initiated as soon as possible (LoE IIa, grade of recommendation A).

3D conformal radiotherapy or intensity modulated radiotherapy (IMRT) allows concave shaping of isodose distributions with at least partial sparing of critical structures adjacent to the target volume.(14, 25, 65). Thus, the maximal and mean doses to the spinal cord can be kept below 20% and 50% respectively of the dose given to the vertebral body.
In case of in-field recurrence of MSCC, re-irradiation can be performed in selected cases, again considering individual factors and therapeutic aims (LoE III). In these situations all technical efforts should be used to limit the dose to the spinal cord.

References:

New

Further references


Bei beginnender Querschnittsymptomatik infolge metastatischer Rückenmarkkompression ist eine operative Entlastung (z.B. Laminektomie) so früh als möglich anzustreben, um notfallmäßig durch die operativ-mechanische Dekompression eine spinale Entlastung zu erreichen. Die operative Entlastung sollte innerhalb kürzester Zeit (Stunden!) erfolgen, was ggf. auch für die Radiotherapie gilt: Notfallbehandlung innerhalb von 24 Stunden! In allen operierten Fällen ist eine lokale Nachbestrahlung erforderlich, um eine lokale Tumor- und Metastasenkontrolle zu erreichen. Das Ausmaß der Rückbildung von spinalen Symptomen ist maßgeblich vom Zeitintervall zwischen dem Einsetzen der Symptome und dem Beginn der Radiotherapie sowie vom prätherapeutisch bestehendem Mobilitätsgrad der Patientin abhängig.


Surgery for Bone Metastases (9/22)

Further information:


References:

**Metastatic Bone Disease: Radiotherapy (10/22)**

*Further information:*

Bone metastases in breast cancer have a high clinical relevance and are commonly seen by the radiation oncologist. Different therapeutic goals (pain relief, local tumour control, prevention or improvement of motor deficits, stabilization of the spine or other bones) require complex approaches considering individual factors (i.e. life expectancy, tumour progression at other sites). Best results are achieved by close interdisciplinary cooperation minimizing the interval between diagnosis and onset of treatment. Most important criteria for prognosis and choice of treatment (mostly combined multimodal therapy) are neurological status at diagnosis of MSCC, time course of duration and progression of the neurological symptoms. RT is effective and regarded as treatment of choice for MSCC with or without motor deficits and/or bone metastases, which do not need immediate surgical intervention. It may be used either postoperatively or as primary treatment in case of inoperability. An optimal dose-fractionation schedule or optimal standard dose for treatment of bone metastases has not been established. With regard to different therapeutic goals, different dose concepts and fractionation schedules, single versus multifraction palliative RT (1 x 8, 5 x 4, 10 x 3, 15 x 2.5, 20 x 2 Gy), should be adapted individually.

The principles of therapy and the guidelines for palliative radiotherapy of bone metastases in patients with breast cancer might be summarized regarding different therapeutic goals:

**Therapeutic goal: pain reduction:** Single dose RT 1 x 8 Gy (cave: >8 Gy to the myelon may cause paresis) (LoE III)

**Therapeutic goal: stabilisation, good prognosis:** Fractionated regimen preferable e.g. 10-12 x 3 Gy (LoE IIb)

**Oligometastases:** Full dose fractionated regimen recommended, e.g., 20-25 x 2 Gy to 40-50 Gy (LoE IIb, III)
References:

New:
Metastatic Bone Disease Recurrent Bone Pain (11/22)

Further information:

Indication and dosage of an optional re-irradiation depend on the previously applied dose, the initial response, the interval to the preceding radiation therapy, and the dose per fraction to critical organs. A re-irradiation of metastases in the extremities or the peripheral parts of the trunk is usually possible. In most cases one may again apply full doses, e.g. 10 x 3 Gy or 20 x 2 Gy, favouring the use of small single doses.

Prior to re-irradiation of the base of skull, the vertebral column and the pelvic bones overall radiation tolerance of the critical organs like brain stem, spinal cord, bowel and bladder has to be considered. Following a typical first course of 10 x 3 Gy without hot spots in the brain stem or the spinal cord, a partial recovery after about 6 months may be assumed.

Therefore, a second course of radiotherapy can be performed in urgent cases with an increased but acceptable risk by applying doses of up to 15 x 2 Gy, provided that tolerance doses of the critical organs are respected.

References:


Side-Effects and Toxicity – Bisphosphonates (BP) and Denosumab (Db) (12/22)

No further information

No references
Recommendations for Precautions to Prevent ONJ* (13/22)

No further information

No references
Adjuvant Bisphosphonates for Reduction of Bone Metastases and Survival Advantage (14/22)

No further information

No references
Adjuvant Bisphosphonates for Reduction of Bone Metastases and Survival Advantage (15/22)

No further information

No references
Dosage of Adjuvant Bisphosphonates for Improvement of Survival (16/22)

No further information

No references
Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis (17/22)

No further information

No references
Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis (18/22)

No further information

No references
Medical Treatment of Osteoporosis (19/22)

No further information

No references
No further information

No references
Therapieempfehlungen für Personen ohne spezifische Risiken und/oder Frakturen (21/22)

*No further information*

*No references*
Therapieempfehlungen für Personen mit spezifischen Risiken und/oder Frakturen (22/22)

No further information

No references
Specific Sites of Metastases
Specific Sites Of Metastases
Local Approaches to Metastatic Disease

- **Version 2002:**
  Dall / Fersis / Friedrich

- **Versions 2003–2013:**
  Bauerfeind / Bischoff / Böhme / Brunnert / Diel / Friedrich / Friedrichs / Gerber / Hanf / Janni / Lück / Maass / Oberhoff / Rezai / Schaller / Seegenschmiedt / Solomayer / Souchon

- **Version 2014:**
  Fehm / Gerber
Specific Sites of Metastases

- Liver and lung metastases
- Malignant pleural and pericardial effusions
- Ascites
- Bone marrow involvement
- Soft tissue metastases
- Any other organs

Consider also chapter „CNS Metastases“ and „Locoregional Recurrence (Loco-Regional Recurrence Treatment Options in Non Curative Cases)“
General Aspects of Metastases Surgery or Ablation

- Histological / cytological verification
- Systemic treatment preferred
- Consider surgery only in case of good response to palliative treatment
- Metastases surgery is an option in good condition pts. with late occurrence oligometastases
- Surgical treatment in the case of pain, exulceration, persistance after systemic treatment, bowel obstruction
- Systemic treatment after surgery

Oxford / AGO LoE / GR

<p>| | | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>3</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>2a</td>
<td>B</td>
<td>++*</td>
</tr>
<tr>
<td>2b</td>
<td>C</td>
<td>+</td>
</tr>
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<td>D</td>
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<td>5</td>
<td>D</td>
<td>+/-</td>
</tr>
<tr>
<td>5</td>
<td>D</td>
<td>++</td>
</tr>
</tbody>
</table>

* See chapters with systemic treatment recommendations
Breast Surgery in Primary Metastatic Disease

- Local treatment (R0) of primary tumor
- Axillary surgery for cN1
- Sentinel in cN0

<table>
<thead>
<tr>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>
Liver Metastasis
Local Therapy

- **Resection of liver metastasis (R0)**
  - Individual cases (liver function) with resectable metastases
  - HR positive; chemotherapy sensible
  - LOE: 3b, GRADE: C, +/-

- **Regional chemotherapy**
  - LOE: 3b, GRADE: C, +/-

- **Regional radiotherapy**
  - (SIRT, radiochemoembolization, other modalities)
  - LOE: 4, GRADE: C, +/-

- **Thermoablation**
  - (RFA, LITT, cryotherapy)
  - LOE: 3b, GRADE: C, +/-
Pulmonary Metastases
Local Therapy

- VATS or conventional resection 3b C +/-
- Thermoablation (CT-guided RFA, LITT) 3b C +/-
Malignant Pleural Effusions (MPE)

Incidence:
- ~10% of all breast cancer patients
- ~50% of pat. with advanced breast cancer
- ~30% of all MPE are caused by breast cancer

Clinical presentation:
- Extensive MPE are mostly due to malignancy
- The majority of MPE are symptomatic
- Survival is related to the presence of additional metastases, age and extent of involving the pleural surface

Diagnostic procedures:
- Clinical examination
- Imaging techniques (chest X-Ray, US, CT-Scan)
- Proven malignant effusion (cytology, histology by thoracoscopy)
### Malignant Pleural Effusion (MPE)

**Local Therapy**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>VATS and Talcum-pleurodesis*</td>
<td>1b B ++</td>
</tr>
<tr>
<td>Chemical pleurodesis</td>
<td></td>
</tr>
<tr>
<td>Talcum slurry</td>
<td>1a B +</td>
</tr>
<tr>
<td>Bleomycin, Doxycycline, Mitoxantrone</td>
<td>2b C +/-</td>
</tr>
<tr>
<td>Povidone iodide</td>
<td>3b C +/-</td>
</tr>
<tr>
<td>Contineous pleural drainage</td>
<td>2a B +</td>
</tr>
<tr>
<td>Systemic treatment after pleurodesis</td>
<td>3b C +/-</td>
</tr>
<tr>
<td>Local antibody therapy (i.e. Catumaxomab)</td>
<td>3b C -</td>
</tr>
<tr>
<td>Repeated pleural drainage</td>
<td>5 D -</td>
</tr>
</tbody>
</table>

* Adequate pain-relief  
VATS: video-assisted thoracoscopic surgery
Malignant Ascites
Local Therapy

Treatment according to:

- Symptoms
- Clinical manifestations
- Anticipated response to systemic therapy

Ascites:

- Puncture, drainage
- Local chemotherapy
- Systemic therapy
- Local antibody therapy (i.e. Catumaxomab)

Oxford / AGO
LoE / GR

- | | | |
  - | 4 | D | ++ |
  - | 3b | D | +/- |
  - | 3b | D | ++ |
  - | 3b | D | +/- |
Symptomatic pericardial effusion:

- Drainage, fenestration 3b B ++
- VATS (video-assisted thorac. surgery) 4 D +
- US-guided puncture + instillation of mitoxantron, cisplatin 4 D +/-
Bone Marrow Involvement Associated with Pancytopenia

Weekly chemotherapy with*:

Epirubicin, Doxorubicin, Paclitaxel, Capecitabine

HER2 pos.: add anti-HER2 treatment

* Consider pre-treatment
Radiotherapy (if no immediate surgery is indicated or even after surgery):

- Paresis, spinal cord compression
  
- Plexus infiltration

- Soft tissue metastasis
Specific Sites of Metastases (2/13)

Further information:


Screened guidelines:
NCI (National Cancer Institute , 2013): http://www.cancer.gov
CMA (Canadian Medical Association , 2013): http://www.cmaj.ca

No references
Specific Sites Of Metastases (3/13)

Further information:

Specific sites of metastases are liver, lung, pleura, pericard, ascites, bone marrow, soft tissue (muscle, subcutaneous fatty tissue, fascia etc.). Breast cancer metastases in the orbita, adrenals, ovaries, uterus, stomach, colon, gall bladder a.s.o. are very seldom seen clinically. So there are only case reports or series. In such cases treatment options must discussed individual.

No references
General Aspects of Metastases Surgery or Ablation (4/13)

Further information:

The systemic treatment of metastatic disease is standard. In general surgery of distant metastases of breast cancer should be considered in patients with a good health condition, oligometastases and a long distance between primary treatment and the occurrence of metastases.(1-5). Good response to palliative treatment may also indicate patients who will benefit from breast surgery. Reported improved overall survival might be the result of patients selection. Before surgery is done metastases should be confirmed as such one by histology. By that a secondary malignancy can be excluded. A re-evaluation of receptor- and HER2-status in metastases is mandatory, because a receptor-shift occurs in nearly 20 % with an impact on systemic treatment. Other indications for surgical intervention are symptoms like pain, exulceration or persistance after systemic treatment. Because no data from prospective studies are available, clinicians must weigh retrospective experiences and clinical judgment in deciding whether to offer surgery or techniques for tumor disturbance to these patients. An ongoing trial, E2108 (http://clinicaltrials.gov/show/NCT01242800) has been designed to assess the effect of breast surgery in metastatic patients responding to first-line systemic therapy

References:

17. Soran A et al. Early follow up of a randomized trial evaluating resection of the primary breast tumor in women presenting with de novo stage IV breast cancer; Turkish study (protocol MF07-01) SABCS [S2-03], 2013
Breast Surgery in Metastatic Disease (5/13)

Further information:

The management of primary stage IV (metachronous or primary metastatic) breast cancer focuses on systemic therapy for distant sites. The impact of local treatment extent on overall survival is still under discussion. However retrospective data on more than 30,000 women from North America and Europe have now been published, showing a robust association between surgery or radiotherapy for the primary tumor and prolonged survival. Many questions remain, most importantly, whether this observed association reflects a selection of women with good prognosis for primary site therapy; others relate to the fraction of women in published studies who were diagnosed with metastatic disease postoperatively, whether specific subsets of metastases and biological subtypes would derive greater benefit, and the appropriate timing and extent of local therapy. Depending on the extent of metastatic disease, a local excision of primary tumor or mastectomy with sufficient health margins is recommended. An axillary surgery is only indicated for bulky disease. The impact of local radiotherapy on survival is unknown. It should be mentioned, that there are reports, which could not found an advantage regarding overall survival for local surgery in this situation.

References:

9. Soran A et al. Early follow up of a randomized trial evaluating resection of the primary breast tumor in women presenting with de novo stage IV breast cancer; Turkish study (protocol MF07-01) SABCS [S2-03], 2013
Liver Metastasis - Local Therapy (6/13)

Further information:

Resection of liver metastases should only be performed if histological verification was done, if R0-resection is feasible and no extrahepatic metastases were present. Other procedures like regional radiotherapy as well as thermoablation are indicated in individual cases. The efficacy of the last ones is primarily determined by preablation tumor size and location in relation to the hilum. There are no data to legitimate a regional chemotherapy of liver alone. Mostly a survival benefit for surgery or other ablation techniques have been reported. However this could be the result of patients selection. Diagnostic laparoscopy in combination with intraoperative ultrasound should be planned in future experience.

References:

Resection of liver metastases:

**Systemic Reviews:**

**Regional chemotherapy: (TACE= transarterial chemoembolization)**

**SIRT (selective internal radiation therapy):**
**RFA (Radiofrequency ablation):**

**LITT (Laser-induced Thermotherapy):**

**Cyrotherapy:**

**Target Therapy**
Pulmonary Metastases Local Therapy (7/13)

Further information:

For proven pulmonary metastases, the level of evidence for a curative approach is low, but some patients might benefit from a metastasectomy followed by an appropriate systemic treatment. In accordance with treatment of liver metastases resection of lung metastases should only be performed if R0-resection is feasible and if histological verification was done. Other procedures like thermoablation are indicated in individual cases.

References:

Resection

**Thermoablation:**

**Radio Frequency Ablation:**
Further information:

Metastatic breast cancer is the second-ranking cause of malignant pleural effusion (MPE), resulting in dyspnoea and reduced subjective well-being. About 10% of all patients develop this clinical complication, in almost 50% of these cases malignant pleural effusion is the first sign of metastatic disease. Median time from primary diagnosis of the cancer to the appearance of pleural effusion is 42 months. (1) It should be treated in symptomatic cases exclusively. Tumor type, extent of involving the pleural surfaces, age and extra-pleural metastases influences the success of a pleurodesis, regardless of the sclerosing agent used. Malignant effusions due to mesothelioma and lung cancer are particularly prone to a failed procedure. (2)

References:

Malignant Pleural Effusion - Local Therapy (9/13)

Further information:

Thoracoscopy with Talcum pleurodesis is the treatment option of choice for malignant pleural effusion. The main procedure for chemical pleurodesis is talcum slurry. Bleomycin, Doxycycline and Mitoxantrone are individual options. Povidone-iodine can be considered as a good alternative to TTP to ensure effective pleurodesis for patients with malignant pleural effusion due to MBC. The drug is available, cost effective and safe, can be given through a thoracostomy tube and can be repeated if necessary. (2) There is no aproval for povidone iodide in Germany.

The CALGB trial 9334 showed that bedside talcum pleurodesis was equivalent to thorascopic pleurodesis. Two randomized studies could show that indwelling pleural catheter or tunneled catheter (versus thorascopic pleurodesis) for palliation of malignant pleural effusion is a therapeutic and quality of life sustaining alternative. Retrospectively study confirmed a higher efficacy of pleurodesis followed by systemic treatment may be superior to that of systemic treatment alone with respect to local control of pleural effusions (8.5 versus 4.1 months) in breast cancer patients. Indwelling pleural catheters are indicated in individual cases. Catumaxomab is not recommended because of its side effects.

References:

VATS and talcum-pleurodesis


Indwelling catheter/pleural drain

Antibody therapy:
Further information:

Malignant ascites are the cancer-associated accumulation of fluids in the peritoneal cavity. The cancers most commonly associated to ascites are ovarian (37%), pancreato-biliary (21%), gastric (18%), oesophageal (4%), colorectal (4%), and breast (3%). After histological confirmation and re-evaluation of receptors the most effective treatment consist in adequate systemic treatment. Management of malignant ascites takes place in the context of palliative care and aims at improving the quality of life of these patients. Patients with symptomatic ascites should undergo drainage. Local antibody therapy with catumaxomab remains an option in individual cases. It has to be payed attention to the side effects.

References:

Malignant Pericardial Effusion - Local Therapy (11/13)

Further information:

Malignant pericardial effusion and cardiac tamponade remains a rarity, which are known complications of many advanced malignancies such as breast cancer, lung cancer, lymphomas and leukemias. In general overall survival is low, due to other metastatic localizations. The standard treatment of malignant effusion and cardiac tamponade has not yet been defined. Physicians should consider the status and the prognosis of each case.
In symptomatic patients drainage and fenestration are the treatment options of choice. VATS is an alternative treatment option. In individual cases US-guided puncture with instillation of mitoxantrone is possible.

References:

**Bone Marrow Involvement Associated with Pancytopenia (12/13)**

**Further information:**

The choice between supportive care or specific anticancer treatment for poor performance status (PS) breast cancer patients with multimetastatic disease and pancytopenia due to bone marrow involvement (BMI) often remains a clinical dilemma. If hormonal treatment options have been exhausted, concomitant weekly low-dose chemotherapy (anthracycline, paclitaxel or capecitabine) and either bisphosphonates or RANK-Ligands antibodies are indicated. Low-dose chemotherapy with epirubicin or paclitaxel as well as treatment with anti-HER2-therapy is the therapy of choice for patients with bone marrow involvement and pancytopenia. Otherwise it has been reported that even in patients with severe BMI-associated cytopenia, aggressive combination treatment regimens were effective, since most patients show improved marrow function after chemotherapy and long-lasting survival is possible.

**References:**

**Soft Tissue Metastasis - Local Radiotherapy (13/13)**

**Further information:**

Local radiotherapy is the most important treatment for patients with paresis or spinal cord compression, who cannot be operated or have failed to systemic treatment. Even after surgery a concomitant radiotherapy and a systemic treatment is indicated. Plexus infiltration and other inoperable soft tissue metastasis should be treated by radiotherapy.

**References:**

CNS Metastases in Breast Cancer
CNS Metastases in Breast Cancer

- **Versions 2003–2013:**
  Bischoff / Diel / Friedrich / Gerber / Lück / Maass / Nitz / Jackisch / Jonat / Junkermann / Rody / Schütz

- **Version 2014:**
  Maass / Müller
Breast cancer is the 2nd most common cause of CNS metastases

At autopsy:
- Parenchymal CNS metastases: ~30–40%
- Leptomeningeal CNS metastases: ~ 5–16%

Increasing incidence (10 % ⇒ 40 %)

Increasing incidence due to
- More effective treatment of extracerebral sites with improved prognosis
- Increasing use of MRI in diagnostic evaluation

Lack of knowledge about treatment of brain metastases from breast cancer since most studies are not breast cancer specific. Therefore, participation in registry study Germany recommended.
CNS Metastases in Breast Cancer (BC) 
Risk Factors

- **Primary Tumor:**
  - Negative estrogen receptor status (Basal-like cell type / triple negative)
  - High Grading, High Ki-67 index
  - HER2 and/or EGFR (HER1) overexpression
  - Prior trastuzumab therapy in patients with metastatic BC

Brain metastases are more likely to be estrogen receptor negative and overexpress HER2 and/or EGFR

There is no evidence for BM-screening in asymptomatic BC-patients
Graded Prognostic Assessment (GPA) Worksheet to Estimate Survival from Brain Metastases (BM) by Diagnosis

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>Score</th>
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<tbody>
<tr>
<td>KPS</td>
<td></td>
<td></td>
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<td>50</td>
<td>60</td>
<td>70-80</td>
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<td></td>
<td></td>
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<td>Basal</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>n/a</td>
<td>LumA</td>
<td>HER2</td>
<td>LumB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>&gt; 60</td>
<td>&lt; 60</td>
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<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Sum total</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Median survival by GPA:
GPA 0-1.0 = 3.4 months
GPA 1.5-2.0 = 7.7 months
GPA 2.5-3.0 = 15.1 months
GPA 3.5-4.0 = 25.3 months

Subtype: Basal: triple negative; LumA: ER/PR positive, HER2 negative; LumB: triple positive; HER2: ER/PR negative, HER2 positive. ECM, extracranial metastases; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; KPS, Karnofsky performance score; LumA, luminal A; LumB, luminal B; PR, progesterone receptor.

### Independent Prognostic Factors in BM

Multivariate analyses of significant factors associated with survival after WBRT

- OS in 1, 2 and 3 years was 33.4 %, 16.7%, and 8.8 %
- Median survival time by Recursive partitioning analysis (RPA) class in months: Class I: 11.7, class II: 6.2 and class III: 3.0

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>P</th>
<th>HR</th>
<th>(95%-confidence interval)</th>
</tr>
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<tbody>
<tr>
<td>SURGICAL RES</td>
<td>&lt;0.0001</td>
<td>4.34</td>
<td>2.5</td>
</tr>
<tr>
<td>SINGLE METASTASES</td>
<td>0.14</td>
<td>1.08</td>
<td>0.97</td>
</tr>
<tr>
<td>KPS &gt;= 70</td>
<td>0.55</td>
<td>1.31</td>
<td>0.55</td>
</tr>
<tr>
<td>BRAIN MET SCORE (BS-BM)</td>
<td>0.58</td>
<td>0.63</td>
<td>0.12</td>
</tr>
<tr>
<td>RPA</td>
<td>&lt;0.0001</td>
<td>1.64</td>
<td>1.32</td>
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<tr>
<td>CONTR PRIM TU</td>
<td>0.66</td>
<td>0.92</td>
<td>0.63</td>
</tr>
<tr>
<td>NO EXCRANIAL MET</td>
<td>&lt;0.0001</td>
<td>2.38</td>
<td>1.63</td>
</tr>
</tbody>
</table>

Viani GA et al. BMC Cancer 2007, 7:53
### Brain Metastases (1–3 lesions)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Level</th>
<th>Evidence</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBRT + SRS boost or neurosurgery (vs. WBRT)</td>
<td>2a</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Improved local control rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRS (lesions &lt; ~ 3 cm) or neurosurgery +/- WBRT*</td>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>WBRT**</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Stereotactic fractionated RT (SFRT)</td>
<td>3b</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>

* In individual cases additional WBRT may be omitted. Additional WBRT provides improved local control rate and symptom control but not survival benefit in all patient cohorts. Combined treatment is recommended especially in patients with single brain metastases and good performance status.

** In patients with poor prognosis and / or performance status

* SRS = stereotactic radiosurgery
* WBRT = whole brain radiotherapy
Possible Factors for Decision Making
Neurosurgery versus Stereotactic Radiosurgery

Factors in favor of neurosurgery:

- Histological verification e.g. after a long recurrence-free interval
- Need for immediate decompression, life-threatening symptoms
- Tumor size > ~ 3cm not allowing stereotactic radiosurgery
- Surgically favorable location

Factors in favor of primary radiotherapy:

- No need for rapid decompression
- No need for histological verification
- Tumor location poorly amenable to surgery
Adjuvant Whole-brain Radiotherapy Versus Observation After Radiosurgery or Surgical Resection of One to Three Cerebral Metastases: Results of the EORTC 22952-26001 Study

2-year relapse rate after whole-brain radiotherapy (WBRT) versus observation

<table>
<thead>
<tr>
<th></th>
<th>after surgical resection (n=160)</th>
<th>after radiosurgery (n=199)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WBRT</td>
<td>observation</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>27%</td>
<td>59%</td>
</tr>
<tr>
<td></td>
<td>(p&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>New lesions</td>
<td>23%</td>
<td>42%</td>
</tr>
<tr>
<td></td>
<td>(p=0.008)</td>
<td></td>
</tr>
</tbody>
</table>

- Only 12% of the patients had brain metastases from breast cancer.
- Overall survival was similar in the WBRT and observation arms (median, 10.9 vs. 10.7 months, respectively; P = .89).
- Intracranial progression caused death in 44% patients in the OBS arm and in 28% patients in the WBRT arm.

Kocher M. J Clin Oncol 2011, 29:134-141
Multiple Brain Metastases

- WBRT (add corticosteroids*)
  - Prolonged RT (≥ 1 week)
- Radiochemotherapy
- Chemotherapy alone
- Corticosteroids alone

In case of radioresistance / recurrence:
- Chemotherapy alone
- Lapatinib +/- Capecitabine (HER2 pos. disease)
- Re-radiation (if feasible)

*Symptom adjusted therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBRT</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Prolonged RT</td>
<td>3b B ++</td>
</tr>
<tr>
<td>Radiochemotherapy</td>
<td>3b C +/-</td>
</tr>
<tr>
<td>Chemotherapy alone</td>
<td>3a D +/-</td>
</tr>
<tr>
<td>Corticosteroids alone</td>
<td>3a B +/-</td>
</tr>
<tr>
<td>Chemotherapy alone</td>
<td>3a D +/-</td>
</tr>
<tr>
<td>Lapatinib +/- Capecitabine</td>
<td>2b B +</td>
</tr>
<tr>
<td>Re-radiation (if feasible)</td>
<td>3a D +/-</td>
</tr>
</tbody>
</table>
Possible Treatment Approach for Brain Metastases (BM) in Breast Cancer

1-3 brain metastases (BM)

- Good performance and prognosis (KPS>70)
  - Surgery / SRS + WBRT*

- Impaired performance and prognosis (KPS<70)
  - WBRT or SRS

Multiple BM
  - WBRT

* In individual cases additional WBRT may be omitted. Additional WBRT after surgery/SRS provides improved local control rate and symptom control but not survival benefit in all patient cohorts.

More aggressive approach in patients with good performance status, single metastases and good prognosis recommended.

SRS = stereotactic radiosurgery
WBRT = whole brain radiotherapy
## Systemic and Symptomatic Therapy of Brain Metastases

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue anti-HER2-treatment in case of extracranial remission (HER2 positive)</td>
<td>2c C +</td>
</tr>
<tr>
<td>Lapatinib + Capecitabine as initial treatment (HER2 positive)</td>
<td>1b B +/-</td>
</tr>
<tr>
<td>Chemotherapy alone as primary treatment</td>
<td>3 D -</td>
</tr>
<tr>
<td>Routine prophylactic use of anticonvulsants</td>
<td>3 C -</td>
</tr>
<tr>
<td>Glucocorticoids (only when symptoms and / or mass effect)</td>
<td>3 C ++</td>
</tr>
</tbody>
</table>
LANDSCAPE: An FNCLCC Phase II Study with Lapatinib (L) and Capetitabine (C) in Patients with Brain Metastases (BM) from HER2-positive (+) Metastatic Breast Cancer (MBC) before Whole-brain Radiotherapy (WBRT)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nr. of eligible patients</td>
<td>N=45</td>
</tr>
<tr>
<td>CNS- ORR</td>
<td>67%</td>
</tr>
<tr>
<td>Median TTP</td>
<td>5.5 Mo.</td>
</tr>
<tr>
<td>Median time to WBRT</td>
<td>8.3 Mo.</td>
</tr>
</tbody>
</table>

Bachelot T, Lancet Oncology 2013, 14:64-71
Leptomeningeal Carcinomatosis
Local Therapy

Intrathecal or ventricular therapy

- MTX 10–15 mg 2–3x/ week (+/- folinic acid rescue) 2b B ++
- Liposomal cytarabine 50 mg, q 2w 3b C ++
- Thiothepa 3b C +
- Steroids 4 D +/-
- Trastuzumab 4 C +/-

Radiotherapy

- Focal (bulky disease) 4 D +
- WBRT 4 D +
- Neuroaxis (disseminated spinal lesions ) 4 D +/-

Due to bad prognosis consider best supportive care, especially in patients with poor performance status
CNS Metastases in Breast Cancer (2/14)

No further information

No references
CNS Metastases in Breast Cancer – Incidence (3/14)

Further information:

Breast cancer represents the second most frequent etiology of brain metastasis (BM). It is estimated that 10-30 % of patients with metastatic breast cancer are diagnosed with BM. The incidence of breast cancer BM is increasing probably due to detection of subclinical disease with improved imaging techniques and increased use of imaging. Also, as systemic therapies to treat extracranial disease improve, many patients survive longer, and the frequency of CNS involvement therefore seems to be increasing.

BM are a major cause of morbidity and mortality and also impairment of quality of life. Therefore, despite major therapeutic advances in the management of patients with breast cancer, CNS metastases remain an highly relevant problem, particularly in patients with metastatic HER2-positive and triple-negative breast cancer.

Patients with CNS metastases diagnosed in Germany can be registered retrospectively and prospectively in a collaborative registry study: For further information see: http://www.germanbreastgroup.de/

References:


Kehrli P. Epidemiology of brain metastases. Neurochirurgie 1999;45:357-63


Lin NU, ClausE, Sohl J et al. Sites of distant recurrence and clinical outcomes in patients with metastatic triple-negative breast cancer Cancer 2008; 113:2638-2645


Lai R, Dang CT, Malkin MG et al. The risk of central nervous system metastases after trastuzumab therapy in patients with breast carcinoma Cancer 2004; 101:810-816

Further information

HER2-positive and triple negative patients are at increased risk for the development of CNS metastases. Nevertheless, no evidence for screening exists. Better systemic control (especially in HER2-positive patients) is supposed to improve survival, thereby leading to an “unmasking” of cerebral metastases. This is attributed to insufficient control of cerebral tumor spread by current treatment strategies as well as to a higher CNS-tropism of HER2-positive and triple-negative tumor cells (see references).

References risk factors:


References Brain metastases (BM) are more likely to be estrogen receptor negative, and overexpress HER2 or EGFR.


References: There is no evidence for BM-screening in asymptomatic BC-patients

Graded Prognostic Assessment (GPA) worksheet to estimate survival from brain metastases (BM) by diagnosis (5/14)

Further information:

Several prognostic scores were described for risk estimation of patients with BM. One of them, the diagnosis-specific Graded Prognostic Assessment (GPA) was published to improve prognosis estimation for patients with BM. This score was validated in breast cancer patients as Breast-GPA and confirmed by analyzing a larger cohort and tumor subtypes. The Breast-GPA documents wide variation in prognosis and shows separation between subgroups of patients with breast cancer and brain metastases. This tool could aid clinical decision making and stratification in clinical trials. The published analyses describe an effect of tumor subtype on survival and show the Breast-GPA offers significantly more predictive power than the tumor subtype alone.

References for Breast-GPA:


Further References: Prognostic Factors for Survival:


**Independent Prognostic Factors in BM (6/14)**

**Further information:**

**Abstract**

BACKGROUND: Brain metastases (BM) are the most common form of intracranial cancer. The incidence of BM seems to have increased over the past decade. Recursive partitioning analysis (RPA) of data from three Radiation Therapy Oncology Group (RTOG) trials (1200 patients) has allowed three prognostic groups to be identified. More recently a simplified stratification system that uses the evaluation of three main prognostics factors for radiosurgery in BM was developed. METHODS: To analyze the overall survival rate (OS), prognostic factors affecting outcomes and to estimate the potential improvement in OS for patients with BM from breast cancer, stratified by RPA class and brain metastases score (BS-BM). From January 1996 to December 2004, 174 medical records of patients with diagnosis of BM from breast cancer, who received WBRT were analyzed. The surgery followed by WBRT was used in 15.5% of patients and 84.5% of others patients were submitted at WBRT alone; 108 patients (62.1%) received the fractionation schedule of 30 Gy in 10 fractions. Solitary BM was present in 37.9% of patients. The prognostic factors evaluated for OS were: age, Karnofsky Performance Status (KPS), number of lesions, localization of lesions, neurosurgery, chemotherapy, absence extracranial disease, RPA class, BS-BM and radiation doses and fractionation. RESULTS: The OS in 1, 2 and 3 years was 33.4%, 16.7%, and 8.8%, respectively. The RPA class analysis showed strong relation with OS (p < 0.0001). The median survival time by RPA class in months was: class I 11.7, class II 6.2 and class III 3.0. The significant prognostic factors associated with better OS were: higher KPS (p < 0.0001), neurosurgery (P < 0.0001), single metastases (p = 0.003), BS-BM (p < 0.0001), control primary tumor (p = 0.002) and absence of extracranial metastases (p = 0.001). In multivariate analysis, the factors associated positively with OS were: neurosurgery (p < 0.0001), absence of extracranial metastases (p <0.0001) and RPA class I (p < 0.0001). CONCLUSION: Our data suggests that patients with BM from breast cancer classified as RPA class I may be effectively treated with local resection followed by WBRT, mainly in those patients with single BM, higher KPS and cranial extra disease controlled. RPA class was shown to be the most reliable indicators of survival.
Reference:

Brain Metastases (1-3 lesions) (7/14)

Further information:

The optimal strategy for treatment of single brain metastases (BM) is unclear. As options, surgery or stereotactic radiotherapy are available. The therapy of BM remains controversial regarding use and timing of surgical resection, application of whole-brain radiotherapy (WBRT), stereotactic radiotherapy and systemic drugs in patients with breast cancer. Despite numerous trials, the interpretation of these has resulted in differing treatment perspectives. In general, for patients with limited systemic disease and/or good treatment options more aggressive treatment is recommended, especially in patients with single brain metastases where most guidelines recommend combined treatment of stereotactic radiosurgery or neurosurgery and WBRT. In most cohorts, groups were divided between patients with 1-3 (sometimes 1-4) versus more metastatic sites. Radiosurgery boost with WBRT may improve local disease control in selected participants as compared to WBRT alone, although survival remains unchanged for participants with multiple brain metastases. The updated review from Tsao et al. includes a total of three randomized controlled trials examining the use of radiosurgery alone versus WBRT and radiosurgery. The addition of WBRT to radiosurgery improves local and distant brain control but there is no difference in overall survival in this analysis. Patients treated with radiosurgery alone were found to have better neurocognitive outcomes in one trial as compared to patients treated with additional WBRT and radiosurgery.

Factors in favor of primary surgery are:
Histological verification after a long recurrence-free interval, need for immediate decompression in case of rapidly developing symptoms, life-threatening symptoms, tumor size > 3.5 cm and surgically favorable location

Factors in favor of primary radiotherapy are:
RPA class II; no need for rapid decompression; short recurrence-free interval; no need for histological verification due to unambiguous medical history (e.g., additional metastatic spread); tumor location poorly amenable to surgery.
WBRT following surgery or stereotactic radiotherapy improves outcome of patients concerning symptom free survival. However, an overall survival advantage was not demonstrated for an overall patient cohorts and has to be outweighed against side effects of WBRT. For patients with good performance status and control of extra cranial disease, WBRT should be offered since some studies indicate an survival advantage.

References:


Possible Factors for Decision-Making Neurosurgery versus Stereotactic Radiosurgery (8/14)

Further information:

See text for slide 7

Factors in favor of primary surgery are:
Histological verification after a long recurrence-free interval, need for immediate decompression in case of rapidly developing symptoms, life-threatening symptoms, tumor size > 3.5 cm and surgically favorable location

Factors in favor of primary radiotherapy are:
RPA class II; no need for rapid decompression; short recurrence-free interval; no need for histological verification due to unambiguous medical history (e.g., additional metastatic spread); tumor location poorly amenable to surgery.

No references
Adjuvant Whole-brain Radiotherapy Versus Observation After Radiosurgery or Surgical Resection of One to Three Cerebral Metastases: Results of the EORTC 22952-26001 Study (9/14)

Further information:
As most studies, this trial was not limited to breast cancer patients.

Abstract
PURPOSE: This European Organisation for Research and Treatment of Cancer phase III trial assesses whether adjuvant whole-brain radiotherapy (WBRT) increases the duration of functional independence after surgery or radiosurgery of brain metastases. PATIENTS AND METHODS: Patients with one to three brain metastases of solid tumors (small-cell lung cancer excluded) with stable systemic disease or asymptomatic primary tumors and WHO performance status (PS) of 0 to 2 were treated with complete surgery or radiosurgery and randomly assigned to adjuvant WBRT (30 Gy in 10 fractions) or observation (OBS). The primary end point was time to WHO PS deterioration to more than 2. RESULTS: Of 359 patients, 199 underwent radiosurgery, and 160 underwent surgery. In the radiosurgery group, 100 patients were allocated to OBS, and 99 were allocated to WBRT. After surgery, 79 patients were allocated to OBS, and 81 were allocated to adjuvant WBRT. The median time to WHO PS more than 2 was 10.0 months (95% CI, 8.1 to 11.7 months) after OBS and 9.5 months (95% CI, 7.8 to 11.9 months) after WBRT (P = .71). Overall survival was similar in the WBRT and OBS arms (median, 10.9 v 10.7 months, respectively; P = .89). WBRT reduced the 2-year relapse rate both at initial sites (surgery: 59% to 27%, P < .001; radiosurgery: 31% to 19%, P = .040) and at new sites (surgery: 42% to 23%, P = .008; radiosurgery: 48% to 33%, P = .023). Salvage therapies were used more frequently after OBS than after WBRT. Intracranial progression caused death in 78 (44%) of 179 patients in the OBS arm and in 50 (28%) of 180 patients in the WBRT arm. CONCLUSION: After radiosurgery or surgery of a limited number of brain metastases, adjuvant WBRT reduces intracranial relapses and neurologic deaths but fails to improve the duration of functional independence and overall survival.
Reference:

Multiple Brain Metastases (10/14)

Further information:

The treatment of choice for multiple BM is whole brain radiotherapy. Compared to single or limited BM, the role additional stereotactic radiotherapy is less clear. Remission rates and duration of response were comparable between subgroups treated with regimens of 50 Gy/4 w, 40 Gy/3 w, 40 Gy/4 w, 30 Gy/2 w, 30 Gy/3 w, 20 Gy/1 w. More hypofractionated regimens like 1 × 10 Gy or 2 × 6 Gy rapidly alleviate symptoms. However, the duration of this effect is short; therefore, these regimens are not recommended. The addition of chemotherapy has not been proven to improve control of brain metastases in trials with breast cancer patients. One trial examined the use of capecitabine and lapatinib instead of radiotherapy as first treatment and demonstrated some efficacy for this treatment. However, this approach was not compared to initial radiotherapy, see slide 11. Also, some efficacy of lapatinib alone or in combination with capecitabine was observed in patients with BM progression after radiotherapy.

References:


Re-Radiation:

Radiochemotherapy

Further information

The management of patients with single or multiple BM depends on estimated prognosis and the aims of treatment as survival, local treated lesion control, neurocognitive preservation. As stated, the management of patients with BM from breast cancer was examined only in a few trials and most analyses are retrospective and include patients with BM of several tumor entities.

A possible treatment algorithm could be as illustrated in slide 13:
Patients with single BM and good prognosis and performance status (e.g. expected survival 3 months or more and Karnowski status > 70%): For a BM larger than 3 to 4 cm and amenable to safe surgical resection, whole brain radiotherapy (WBRT) and surgery should be considered. For single metastasis less than 3 to 4 cm, WBRT and radiosurgery or WBRT and surgery should be considered. For single brain metastasis (less than 3 to 4 cm) that are not resectable or incompletely resected, WBRT and radiosurgery, or radiosurgery alone should be considered. The addition of WBRT to radiosurgery or surgery offers no certain survival benefit in overall patient cohorts. For nonresectable single brain metastasis (larger than 3 to 4 cm), WBRT should be considered (level 3).

Multiple brain metastases and good prognosis (expected survival 3 months or more): For selected patients with multiple brain metastases (all less than 3 to 4 cm), WBRT and radiosurgery, otherwise WBRT alone should be considered. Safe resection of a brain metastasis or metastases causing significant mass effect and postoperative WBRT may also be considered. Patients with poor prognosis (expected survival less than 3 months): Patients with either single or multiple brain metastases with poor prognosis should be considered for palliative care with or without WBRT.
References:


NCCN guidelines on CNS Cancers and Metastases


Role of surgery
Systemic and Symptomatic Therapy of Brain Metastases (12/14)

Further information:

In patients without progression of extracranial metastatic disease, local therapy of BM should be performed and systemic therapy continued. Especially for anti-HER2-therapies, there is a relevant body of (retrospective) evidence for continuation of therapy despite the diagnosis of BM. This might be due to the fact that in manifest BM the permeability of the Blood Brain Barrier is decreased.

For patients with asymptomatic BM, systemic treatment should be chosen according to optimal treatment of extracranial disease.

For adults with brain metastases who have not experienced a seizure due to their metastatic brain disease, routine prophylactic use of anticonvulsants is not recommended.

For asymptomatic BM patients without mass effect no steroid treatment is recommended. Corticosteroids are recommended to provide temporary relief of symptoms related to increased intracranial pressure and edema secondary to in patients with mild symptoms related to mass effect. It is recommended for patients who are symptomatic from BM that a starting dose of 4-8 mg/day of dexamethasone is used. If patients exhibit severe symptoms with increased intracranial pressure, it is recommended that higher doses such as 16 mg/day or more can be used. If corticosteroids are given, dexamethasone is the best drug choice given the available evidence. Corticosteroids should be tapered slowly over a 2 week time period, or longer in symptomatic patients, based upon an individualized treatment regimen considering the long-term sequelae of corticosteroid therapy.
References:


**Anticonvulsants**

**Steroids**
LANDSCAPE: An FNCLCC Phase II Study with Lapatinib (L) and Capecitabine (C) in Patients with Brain Metastases (BM) from HER2-positive (+) Metastatic Breast Cancer (MBC) before Whole-brain Radiotherapy (WBR) (13/14)

Further information:

Abstract
BACKGROUND: Brain metastases occur in 30-50% of patients with metastatic HER2-positive breast cancer. In the case of diffuse brain metastases, treatment is based on whole brain radiotherapy (WBRT). Few systemic options are available. We aimed to investigate the combination of lapatinib plus capecitabine for the treatment of previously untreated brain metastases from HER2-positive breast cancer.

METHODS: In this single-arm phase 2, open-label, multicentre study, eligible patients had HER2-positive metastatic breast cancer with brain metastases not previously treated with WBRT, capecitabine, or lapatinib. Treatment was given in 21 day cycles: patients received lapatinib (1250 mg, orally) every day and capecitabine (2000 mg/m(2), orally) from day 1 to day 14. The primary endpoint was the proportion of patients with an objective CNS response, defined as a 50% or greater volumetric reduction of CNS lesions in the absence of increased steroid use, progressive neurological symptoms, and progressive extra-CNS disease. All responses had to be confirmed 4 weeks after initial response. Efficacy analyses included all patients who received the study drugs and were assessable for efficacy criteria. This trial is registered with ClinicalTrials.gov, number NCT00967031.

FINDINGS: Between April 15, 2009, to Aug 2, 2010, we enrolled 45 patients, 44 (98%) of whom were assessable for efficacy, with a median follow-up of 21·2 months (range 2·2-27·6). 29 patients had an objective CNS response (65·9%, 95% CI 50·1-79·5); all were partial responses. Of all 45 treated patients, 22 (49%) had grade 3 or grade 4 treatment-related adverse events, of which the most common were diarrhoea in nine (20%) patients and hand-foot syndrome in nine (20%) patients. 14 (31%) patients had at least one severe adverse event; treatment was discontinued because of toxicity in four patients. No toxic deaths occurred.
INTERPRETATION: The combination of lapatinib and capecitabine is active as first-line treatment of brain metastases from HER2-positive breast cancer. A phase 3 trial is warranted.

References:

**Leptomeningeal Carcinomatosis Local Therapy (14/14)**

**Further information:**

Leptomeningeal Carcinomatosis occurs in approximately 5%-10% of all patients with metastatic breast cancer, and aggressive supportive measures are a important component of comprehensive care. Although the prognosis for those diagnosed with Leptomeningeal Carcinomatosis is poor, treatment and supportive care may allow stabilization of neurologic symptoms and afford protection from further neurologic deterioration, allowing patients to maximize their function and independence.

However, due to bad prognosis best supportive care should be considered as treatment option, especially in patients with poor performance status.

**References:**


**Trastuzumab intrathecal**


**MTX high dose**

Complementary Therapy

Survivorship
Complementary Therapy – Hormonal Treatment and Alternatives in Breast Cancer Survivors – Survivorship

- **Version 2002–2013:**
  Bauerfeind / Blohmer / Gerber / Göhring / Hanf / Janni / Kümmel / von Minckwitz / Oberhoff / Scharl / Schmidt / Schütz / Thomssen

- **Version 2014:**
  Albert / Hanf / Fersis / Friedrich
„Alternative“ Therapies

<table>
<thead>
<tr>
<th>CAM</th>
<th>Unconventional methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complementary + alternative medicine</td>
<td>CAM</td>
</tr>
</tbody>
</table>

**Complementary**  
In addition to scientifically based medicine

**Alternative**  
Instead of scientifically based medicine

**UCT**  
Unconventional Thx

**Unconventional**  
Unproven outsider methods
Complementary Therapy
Pre- and Postoperative

Preoperative:

- Hypnosis (reduces anxiety, pain, fatigue, nausea)  
  1b B +/-

Postoperative:

- Acupuncture (pain relief)  
  2b B +/-
- Acupuncture (nausea, vomiting)  
  2b B +
- Early postop. exercise reduces upper-limb dysfunction (beware: increased wound drainage)  
  1a A +
- Prophylactic lymph drainage  
  1b B -
Complementary Treatment Impact on Toxicity I

While on anti-cancer treatment: beware of drug interactions

- Mistletoe (Viscum album) in order to reduce side effects of therapy (influence on efficacy of antitumorotherapy unknown)
  - Oxford / AGO LoE / GR 1a B +/-

- Thymic peptides (lowered the risk of severe infections)
  (influence on efficacy of antitumorotherapy unknown)
  - Oxford / AGO LoE / GR 2a B +/-

- Ginseng (in order to reduce cancer rel. fatigue)
  HR-
  HR+
  - Oxford / AGO LoE / GR 3b C +/-

- Ginger (consider interaction with antitumor drugs)
  - Oxford / AGO LoE / GR 1b C +/-
## Complementary Treatment Impact on Toxicity II

<table>
<thead>
<tr>
<th>Complementary Treatment</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antioxidant supplements</td>
<td>1b B -</td>
</tr>
<tr>
<td>High dose vitamine C</td>
<td>1b C -</td>
</tr>
<tr>
<td>Vitamine E</td>
<td>2b D -</td>
</tr>
<tr>
<td>Selenium for alleviating side effects of therapy</td>
<td>1b B -</td>
</tr>
<tr>
<td>Co-Enzyme Q 10 (fatigue, QoL)</td>
<td>1b B -</td>
</tr>
<tr>
<td>Proteolytic enzymes in order to reduce chemotherapy-induced toxicity</td>
<td>3b B -</td>
</tr>
<tr>
<td>Chinese herbal medicine improves wound healing after mastectomy</td>
<td>1b B -<em>inf</em></td>
</tr>
<tr>
<td>Oxygen and ozone therapy</td>
<td>5 D - -</td>
</tr>
</tbody>
</table>

*inf: i.v.-infusion (in Germany not approved)
Additional Complementary Therapy
Side Effects Related to Cancer Treatments
e.g. Chemotherapy

- Chinese medicinal herbs to treat the side effects of chemotherapy in breast cancer patients
  - May offer some benefit to breast cancer patients in terms of bone marrow improvement and quality of life

- Homoeopathic medicines for adverse effects of cancer treatments

- Topical calendula (>= 20% Calendula amount) for prophylaxis of acute dermatitis during radiotherapy

- Traumeel S mouthwash to treat chemotherapy-induced stomatitis

- Topical Silymarin for prophylaxis of acute dermatitis during radiotherapy

- Acupuncture in order to improve on
  - Chemotherapy-induced >=nausea and vomiting
  - Aromatase-inhibitor treatment induced arthralgia
  - Cognitive dysfunction
  - Fatigue
  - Pain
  - Leucopenia

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Oxford LoE / AGO LoE / Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chinese medicinal Herbs</td>
<td>1b B -</td>
</tr>
<tr>
<td>Homoeopathic Medicines</td>
<td>1b B +/-</td>
</tr>
<tr>
<td>Topical Calendula</td>
<td>3a B +/-</td>
</tr>
<tr>
<td>Acupuncture</td>
<td>1a B +</td>
</tr>
<tr>
<td>Aromatase-Inhibitor</td>
<td>2b C +</td>
</tr>
<tr>
<td>Cognitive Dysfunction</td>
<td>5 D +/-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1a B +/-</td>
</tr>
<tr>
<td>Pain</td>
<td>1a B +/-</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>2b B -</td>
</tr>
</tbody>
</table>
Complementary Treatment
Mind-Body Medicine I

MBSR (Mindfulness-Based Stress Reduction) Programme improves quality of life, coping strategies, attentiveness, lowers stress and depressive syndromes)

Physical exercise / sport
min. 150 min. moderate endurance training per week in combination with work out exercises (2x per week) improve quality of life, cardio-respirat. fitness, physical performance and fatigue
Complementary Treatment
Mind-Body Medicine II

Yoga
Improves sleep, quality of life, stress, anxiety, depression
Improves fatigue

Qi Gong
May improve quality of life, fatigue, mood

Tai Chi
Improves quality of life, physical performance

Hypnosis (in combination with cognitive training)
Improves fatigue and muscle weakness under radiation therapy

Oxford / AGO LoE / GR

Yoga
1b A +

Qi Gong
2a B +/-

Tai Chi
2b D +/-

Hypnosis
2a B +/-
Modifiable Lifestyle Factors
Prevention of Recurrence I

- **Physical exercise**
  (Equivalents to 3–5 hrs moderate walking per week improves DFS and OS, cardio-respiratory fitness, physical functioning)

- **Smoking**

- **Alcohol consumption** (>6 g/die)
### Modifiable Lifestyle Factors

**Nutrition after Breast Cancer Diagnosis**

**Prevention of Recurrence II**

<table>
<thead>
<tr>
<th>Adherence to normal BMI/weight loss if overweight</th>
<th>(improves prognosis – DFS/OS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low fat diet</td>
<td>(improves prognosis – DFS – esp. post-menopausal, ER neg.; ≤20% fat calories, only with dietary counseling!)</td>
</tr>
<tr>
<td>Flaxseed/increased fibre intake</td>
<td></td>
</tr>
<tr>
<td>Adherence to general nutrition guidelines (e.g. DGE, WCRF)</td>
<td></td>
</tr>
<tr>
<td>Dietary extremes</td>
<td>(are associated with less favourable outcomes)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oxford /AGO LoE / GR</th>
<th>2b B ++</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low fat diet</td>
<td>1b(-) B +</td>
</tr>
<tr>
<td>Flaxseed/increased fibre intake</td>
<td>2a B +/-</td>
</tr>
<tr>
<td>Adherence to general nutrition guidelines (e.g. DGE, WCRF)</td>
<td>2a B +</td>
</tr>
<tr>
<td>Dietary extremes</td>
<td>1b B - -</td>
</tr>
</tbody>
</table>
### Complementary Treatment

#### Prevention of Recurrence III

**Dietary Supplements – Herbal Therapies**

<table>
<thead>
<tr>
<th>Compl./alternative methods instead of systemic treatment:</th>
<th>Oxford LoE</th>
<th>AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>While on anti-cancer treatment: beware of drug interactions;</td>
<td>2b B +/-</td>
<td>-</td>
</tr>
<tr>
<td>Antioxidants</td>
<td>2b B</td>
<td>+/-</td>
</tr>
<tr>
<td>Orthomolecular substances</td>
<td>5 D</td>
<td>-</td>
</tr>
<tr>
<td>(Selenium, Zinc...)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamines (in pts. on a balanced diet)</td>
<td>2b B</td>
<td>-</td>
</tr>
<tr>
<td>Proteolytic enzymes</td>
<td>3b B</td>
<td>-</td>
</tr>
<tr>
<td>(Papain, Trypsin, Chymotrypsin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soy (phytoestrogens)</td>
<td>2b B</td>
<td>+/-</td>
</tr>
<tr>
<td>In receptor-positive tumors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black Cohosh (Cimicifuga racemosa)</td>
<td>2b C</td>
<td>+/-</td>
</tr>
<tr>
<td>Mistletoe (Viscum album)</td>
<td>1b C</td>
<td>-</td>
</tr>
<tr>
<td>Thymic peptides (impact on OS)</td>
<td>2a B</td>
<td>-</td>
</tr>
<tr>
<td>Oxygen- and ozone therapy</td>
<td>5 D</td>
<td>-</td>
</tr>
<tr>
<td>Antioxidant supplements (after completion of radiotherapy)</td>
<td>2b B</td>
<td>+/-</td>
</tr>
<tr>
<td>Laetrile</td>
<td>1c D</td>
<td>--</td>
</tr>
<tr>
<td>Cancer bush (Sutherlandia frutescens), Devil's claw</td>
<td>5 D</td>
<td>-</td>
</tr>
<tr>
<td>(Harpagophytm procumbens), Rooibos tea (Aspalathus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>linearis), Bambara groundnut (Vignea subterranean)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

While on anti-cancer treatment: beware of drug interactions;

Compl./alternative methods instead of systemic treatment:
Alternatives to Reduce Menopausal Symptoms after BC I

General approaches:

- Physical exercise

- Mind Body-medicine (yoga, hypnosis, education, counselling)

- Acupuncture
  (take note: no acupuncture in tumor bearing region, possibility of cell seeding)

Oxford / AGO LoE / GR

2b D +

1b B +

1a A +
“Herbal” Approaches to Reduce Menopausal Symptoms

While anti-cancer treatment: Beware of drug interactions!

- Soy-derived phytoestrogens – isoflavonoids (might stimulate BC especially in endocrine responsive disease)
- Flaxseed-supplementation (40 g/d) (in HR+ ≤ 10 g/d)
- Black Cohosh for hot flushes (effectiveness could not be clearly shown)
- St. John’s Wort in combination-therapy (pharmacokinetic interference with endocrine therapy, cytotoxic drugs and tyrosinkinase inhibitors)
- Kava-Kava (Piper methysticum)
- Red Clover leaf (Trifolium pratense)
- Dong Quai root (Angelica sinensis)
- Ginseng root (Panax ginseng or P. quinquefolius)
- Bromelain + Papain + Selen + Lektin (vs. AI induced joint symptoms)

Oxford / AGO LoE / GR

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<th>Procedure</th>
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Complementary Treatment
Cancer Pain Reduction

Acupuncture for cancer pain in adults
Transcutaneous electric nerve stimulation (TENS) for cancer pain in adults

Cave: No delay in diagnostic process

Oxford / AGO
LoE / GR

2b D +/-
## Immunodiagnostic Tests and Immunotherapy

### Immunodiagnostic tests:

- **Analysis of:**
  - Immunological parameters in peripheral blood

### Local immunotherapy

- Imiquimod topically for skin metastases

### Systemic immunotherapy - including items below – only within clinical trials:

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Complementary Therapy– Survivorship (2/16)

Further information:

Screened Data Sources:
Pubmed 2003 -01/2014

ASCO 2003 – 2013
Cochrane library summary Jan. 2014:

There are 149 results out of 7646 records for: "Complementary & alternative medicine and cancer” in Record Title in Cochrane Database of Systematic Reviews"

External advice:

The commission wants to thank the following external advisors for their contribution:

2010: Advice on nutritional facts by Prof. Dr. G. Stangl, Martin-Luther-University Halle Wittenberg, Germany
2011+ 2013: Prof. Dr. G. Dobos and team,
Alfred Krupp von Bohlen und Halbach-Stiftungsprofessur für Naturheilkunde an der Universität Duisburg-Essen,
Klinik für Innere Medizin V, Naturheilkunde und Integrative Medizin

No references
The term “alternative therapies” has to be more precisely defined. The above scheme divides the subject into two main aspects:

- UCT refers to unconventional therapies with unproven methods; they frequently include outsider methods with possible considerable inherent risks.
- CAM includes both alternative therapies, which are used instead of conventional, scientifically based medicine, and complementary methods, which are used in addition to conventional methods. While conventional clinicians tend to more readily approve of the complementary approach than one of the other options, complementary approaches, if administered simultaneously with conventional therapies, always carry the risk that the treatments unexpectedly interfere with each other to produce untoward effects, i.e., drug interactions with partially incalculable outcomes.

*No references*
Complementary Pre- and Postoperative Therapy (4/16)

Further information and references:

Statement on preoperative hypnosis
Briefly hypnotizing patients before they underwent breast cancer surgery reduced the amount of anesthesia administered during the operation, the level of postoperative pain, and the cost of the procedure according to an RCT with 200 patients. The patients, who were scheduled to undergo excisional breast biopsy (72%) or lumpectomy (28%), were randomly assigned to a 15-minute presurgical hypnosis session (n = 105) conducted by a psychologist or to a nondirective empathic listener (attention control) (n = 95). Patients in the hypnosis group required less propofol (means = 64.0 versus 96.6) and lidocaine (means = 24.2 versus 31.1 mL) than patients in the control group. Patients in the hypnosis group also reported less intense postoperative pain (means = 22.4 versus 47.8 mm VAS), less unpleasantness of pain (means = 21.2 versus 39.1 mm VAS), less nausea (means = 6.6 versus 25.5 mm VAS), less fatigue (29.5 vs. 54.2 mm VAS), less discomfort (23.0 vs. 43.2 mm VAS), and less emotional upset (8.7 vs. 33.5 mm VAS). No statistically significant differences were seen in the use of fentanyl, midazolam, or recovery room analgesics.


In another RCT ninety patients who were awaiting excisional breast biopsy were randomly assigned to undergo either a 15-minute presurgical hypnosis session (n = 49) or a 15-minute presurgical attention control session (n = 41). Results of this trial indicated that hypnosis prior to surgery helps control presurgical distress in women awaiting diagnostic breast cancer surgery.

A meta-analysis across surgical settings demonstrated large effects (d=1.2) on emotional distress. Surgical patients in hypnosis groups had better outcomes than 89% of patients in control groups. Further beneficial effects were found on pain, pain medication, nausea, fatigue, and treatment time.


A recent review on hypnosis for cancer care conclude that the use of hypnosis for side effects of cancer surgery is strong and consistent. Clinical and cost-effectiveness has been demonstrated.


Acupuncture and Postoperative Pain


Acupuncture and Postoperative Nausea and Vomiting


Statement on postoperative exercise

A recently published Cochrane analysis of the effects of postoperative exercise included 24 studies involving 2132 participants. The methodological quality of 10 of the 24 studies was considered adequate. Ten studies examined the effect of early versus delayed implementation of post-operative exercising. Early exercising was more effective than delayed exercising in the short term recovery of shoulder flexion ROM (abbr.: „range of movement“) (Weighted Mean Difference (WMD): 10.6 degrees; 95% Confidence Interval (CI): 4.51 to 16.6); however, early exercising also resulted in a statistically significant increase in wound drainage volume (Standardized Mean Difference (SMD) 0.31; 95% CI: 0.13 to 0.49) and duration (WMD: 1.15 days; 95% CI: 0.65 to 1.65). Fourteen studies compared the effect of structured exercising with that of the usual care. Of these, six were post-operative trials, three were carried out during adjuvant treatment, and five following cancer treatment. Structured exercise programs in the post-operative period significantly improved shoulder flexion ROM in the short run (WMD: 12.92 degrees; 95% CI: 0.69 to 25.16). Physical therapy yielded additional benefit for post-intervention shoulder function (SMD: 0.77; 95% CI: 0.33 to 1.21) and at the 6-month follow-up (SMD: 0.75; 95% CI: 0.32 to 1.19).

There was no evidence of increased risk of lymphedema from exercise at any time. The authors concluded that exercise results in a significant and clinically meaningful improvement in postoperative ROM of the shoulder in women with breast cancer. In the early post-operative period, exercising may be beneficial, although it may increase the volume and duration of wound drainage. Trials that closely monitor both exercise prescription factors (e.g., intensity) and persistent upper-limb dysfunction are needed.
A literature review of 4 RCT’s indicates that weight training exercises do not appear to increase lymphedema risk under structured conditions. All four of the studies reviewed report results of either a decrease in the development of lymphedema or no increased risk of development of lymphedema when early exercise regimens are incorporated into postoperative care.


**Statement on prophylactic lymph drainage**

Manual lymph drainage applied after axillary lymph node dissection for breast cancer is not effective in the short-term prevention of lymphedema of the arm.

Complementary Treatment. Treatment phase. Impact on Toxicity I-II (5-6/16)

Further information and references:

**Mistletoe**
The evidence from RCTs to support the view that the application of mistletoe extracts has impact on survival or leads to an improved ability to fight cancer or to withstand anticancer treatments is weak. The 5-years-data from a randomized trial with Viscum album additional to chemotherapy with CAF did not influence frequency of relapse or metastasis.

- Tröger W, Zdrale Z, Stankovic N, Matijasevic M: Five-year follow-up of patients with early stage breast cancer after a randomized study comparing additional treatment with viscum album (L.) extract to chemotherapy alone. Breast Cancer 2012, 6:173-80

Nevertheless, there is some evidence that mistletoe extracts may offer benefits on measures of QOL during chemotherapy for breast cancer, but these results need replication. Overall, more high quality, independent clinical research is needed to truly assess the safety and effectiveness of mistletoe extracts. Patients receiving mistletoe therapy should be encouraged to take part in future trials.


Thirteen prospective and controlled studies which met the inclusion/exclusion criteria reported positive effects in favor of the Iscador application. A random-effect meta-analysis estimated the overall treatment effect at standardized mean difference = 0.56 (CI: 0.41 to 0.71, P < .0001). However, the methodological quality of the studies was poor. Conclusions. The analyzed studies give some evidence that Iscador treatment might have beneficial short-time effects on QoL-associated dimensions and psychosomatic self-regulation.

Further references:


**Thymus**

In the recent Systematic Review Thymic peptides for treatment of cancer patients in addition to chemotherapy or radiotherapy, or both purified thymus extracts (pTE) and synthetic thymic peptides (sTP) were thought to enhance the immune system of cancer patients in order to fight the growth of tumour cells and to resist infections due to immunosuppression induced by the disease and antineoplastic therapy.

The authors identified 26 trials (2736 patients). Twenty trials investigated pTE (thymostimulin or thymosin fraction 5) and six trials investigated sTP (thymopentin or thymosin α1). Twenty-one trials reported results for OS, six for DFS, 14 for TR, nine for AE and 10 for safety of pTE and sTP. Addition of pTE conferred no benefit on OS (RR 1.00, 95% CI 0.79 to 1.25); DFS (RR 0.97, 95% CI 0.82 to 1.16); or TR (RR 1.07, 95% CI 0.92 to 1.25). Heterogeneity was moderate to high for all these outcomes. For thymosin α1 the pooled RR for OS was 1.21 (95% CI 0.94 to 1.56, P = 0.14), with low heterogeneity; and 3.37 (95% CI 0.66 to 17.30, P = 0.15) for DFS, with moderate heterogeneity. The pTE reduced the risk of severe infectious complications (RR 0.54, 95% CI 0.38 to 0.78, P = 0.0008; I² = 0%). The RR for severe neutropenia in patients treated with thymostimulin was 0.55 (95% CI 0.25 to 1.23, P = 0.15). Tolerability of pTE and sTP was good.

Most of the trials had at least a moderate risk of bias.

Overall, the authors found neither evidence that the addition of pTE to antineoplastic treatment reduced the risk of death or disease progression nor that it improved the rate of tumour responses to antineoplastic treatment. For thymosin α1, there was a trend for a reduced risk of dying and of improved DFS. There was preliminary evidence that pTE lowered the risk of severe infectious complications in patients undergoing chemotherapy or radiotherapy.

Further References:


Ginseng

The pilot study of Barton et al. investigated whether American ginseng (Panax quinquefolius) helps alleviate cancer-related fatigue. In addition, they evaluated its toxicity. Eligible adults with cancer were randomized in a double-blind manner to receive American ginseng in doses of 750, 1,000, or 2,000 mg/day or placebo, divided into two daily doses for 8 weeks. Outcome measures included the Brief Fatigue Inventory, vitality subscale of the medical outcome scale Short Form-36 (SF-36), and the Global Impression of Benefit Scale at 4 and 8 weeks.

Two hundred ninety patients took part in this trial. Nonsignificant trends for all outcomes were seen in favor of the 1,000- and 2,000-mg/day doses of American ginseng. Area-under-the-curve analysis of activity interference from the Brief Fatigue Inventory was 460-467 in the placebo group and 750 mg/day group versus 480-551 in the 1,000- and 2,000-mg/day arms, respectively. Change from baseline in the vitality subscale of the SF-36 was 7.3-7.8 in the placebo and the 750-mg/day arm versus 10.5-14.6 in the 1,000- and 2,000-mg/day arms. Over twice as many patients on ginseng as on placebo perceived a benefit and were satisfied with treatment. There were no significant differences in any measured toxicities between any of the arms. Since American ginseng appears to be somewhat active and its toxicity is tolerable at 1,000-2,000 mg/day doses, further trials to evaluate its efficacy in alleviating cancer-related fatigue are warranted.

Since ginseng contains phytoestrogens. its use is discouraged for women with hormone-receptor-positive breast cancer. Depending on its dose, in vitro ginseng inhibits cytochrome P enzymes (e.g. CYP 3A4). Interactions are possible and need to be considered.

Ginger
In this double blind, multicenter trial, 744 cancer patients were randomly assigned to four arms: 1) placebo, 2) 0.5 g ginger, 3) 1.0 g ginger, or 4) 1.5 g ginger. Nausea occurrence and severity were assessed at a baseline cycle and the two following cycles during which patients were taking their assigned study medication. All patients received a 5-HT3 receptor antagonist antiemetic on Day 1 of all cycles. Patients took three capsules of ginger (250 mg) or placebo twice daily for 6 days starting 3 days before the first day of chemotherapy. A total of 576 patients were included in final analysis Mixed model analyses demonstrated that all doses of ginger significantly reduced acute nausea severity compared to placebo on Day 1 of chemotherapy (p=0.003). Ginger supplementation at a daily dose of 0.5 g–1.0 g significantly aids in reduction of the severity of acute chemotherapy-induced nausea in adult cancer patients.

Preclinical studies have shown that ginger is effective as an anti-emetic agent and that it possesses 5HT3 antagonistic activity, which is responsible for reducing chemotherapy induced nausea. The clinical data are insufficient to draw firm conclusions.


In this pilot, randomized, open-label clinical trial, 100 women (mean age = 51.83 ± 9.18 years) with advanced breast cancer who were initially assigned to standard chemotherapy protocol with docetaxel, epirubicin, and cyclophosphamide
(the TEC regimen) were randomized to receive ginger (1.5 g/d in 3 divided doses every 8 hours) plus standard antiemetic regimen (granisetron plus dexamethasone; the ginger group) or standard antiemetic regimen alone (control group). The duration of treatment with ginger was specified to 4 days from the initiation of chemotherapy. Addition of ginger (1.5 g/d) to standard antiemetic therapy (granisetron plus dexamethasone) in patients with advanced breast cancer effectively reduces the prevalence of nausea 6 to 24 hours postchemotherapy. However, there is no other additional advantage for ginger in reducing prevalence or severity of acute or delayed CINV.


Antioxidant supplements
Greenlee et al. (2009) concluded that current evidence on the administration of antioxidant supplements during breast cancer treatment does not suffice to provide clinicians and patients with guidelines for their use. Because of possible interactions between chemotherapy and the antioxidants selenium, coenzyme Q10, and vitamin E, these antioxidants are rated (−).


Vitamin C
In their review, Ohno et al. (2009) mention case reports and clinical trials in which intravenous high-dose vitamin C prolonged survival in patients with advanced cancer. However none of the trials was randomized or placebo controlled. Two randomized clinical trials with orally administered vitamin C conducted by the Mayo Clinic did not show any benefit. Because it may interact with chemotherapy, high-dose vitamin C therapy is rated (−).


Selenium
This is an updated version of the original Cochrane review published in Issue 3, 2006. Selenium supplements are frequently used by cancer patients. Selenium is an essential trace element and is involved in antioxidant protection and the redox-regulation in humans. Several adverse effects of radiotherapy and chemotherapy in cancer patients as well as cellular processes that maintain chronic lymphoedema have been linked to oxidative cell processes in the human body. Selenium has been claimed to alleviate side effects of conventional cancer therapy and recently been investigated as a remedy against chemotherapy and radiotherapy-associated side effects and secondary lymphoedema. There is insufficient evidence at present that selenium supplementation alleviates the side effects of tumour specific chemotherapy or radiotherapy treatments or that it improves the after-effects of surgery, or improves quality-of-life in cancer patients or reduces secondary lymphoedema. To date, research findings do not provide a basis for any recommendation in favour or against selenium supplementation in cancer patients. Potential hazards of supplementing a trace mineral should be kept in mind. Since the last version of this review, the one new additional study has not provided information to change the conclusions of the original review.


Further references:

Coenzyme Q10
Eligible women with newly diagnosed breast cancer and planned adjuvant chemotherapy were randomized to oral supplements of 300 mg CoQ10 or placebo, each combined with 300 IU vitamin E, divided into 3 daily doses. Treatment
was continued for 24 weeks. Blood tests, QOL measures, and levels of plasma CoQ10 and vitamin E were obtained at baseline and at 8, 16, and 24 weeks.

Supplementation with conventional doses of CoQ10 led to sustained increases in plasma CoQ10 levels but did not result in improved self-reported fatigue or QOL after 24 weeks of treatment.


Further references:

Proteolytic enzymes and toxicity of chemotherapy:

Wobe Mugos(®), a mixture consisting of an extract of the calf thymus gland and enzymes (the proteases trypsin and papain) from plant and animal sources, is commonly used in complementary medicine. Data from non-randomized studies have indicated that it has multiple favorable effects, and in particular that it reduces the side effects of radiotherapy and chemotherapy in oncology patients. Patients with invasive breast cancer receiving adjuvant or palliative chemotherapy between 2005 and 2006 and who were scheduled for at least two further cycles of that specific chemotherapy were included in this pilot study of Petru et al. (2). During the preceding cycle these patients had experienced a specific toxicity of at least grade 2 according to the NCI common toxicity criteria, indicating that it was relevant to the patient. To determine whether Wobe Mugos(®) reduces the side effects in individual patients, it was coadministered during two further chemotherapy cycles, and this specific toxicity, e.g. grade 2 emesis, was again evaluated. The majority of the 57 consecutive patients received palliative chemotherapy. The enzyme therapy, orally administered as two uncracked coated tablets three times daily on all days of a chemotherapy cycle except the day of chemotherapy administration, was well
tolerated. Positive and neutral effects on toxicity parameters were observed in 11 and 42 patients, respectively, and a negative influence was observed in 4 women. Petru et al. (2) observed only a marginal influence of Wobe Mugos(®) in patients with breast cancer who had experienced at least a grade 2 toxicity in the preceding cycle and who received two further identical cycles of this chemotherapy in conjunction with the enzyme preparation. There are no randomized studies.


**Bromelain**


**Chinese herbal medicine and wound healing**

Skin flap ischemia and necrosis are common complications of mastectomy. Chen et al. (4) from the Sichuan University in China evaluated the influence of anisodamine and Salvia miltiorrhiza on the complications of wound healing after mastectomy for breast cancer. Ninety patients undergoing mastectomy for breast carcinoma were divided into three groups. Demographic characteristics did not differ among the groups. Group 1 received routine wound care, group 2 received intravenous Salvia miltiorrhiza after surgery for 3 days, and group 3 similarly received intravenous anisodamine. Skin flaps were observed on postoperative days 4 and 8; areas of wound ischemia and necrosis were graded and adverse events recorded. Four days after surgery the rate of ischemia and necrosis in groups 2 and 3 was significantly less than that in control group 1 (median wound score 6·80 versus 23·38, P = 0·002, and 3·76 versus 23·38, P < 0·001, respectively). This improvement in groups 2 and 3 continued to postoperative day 8 (both P < 0·001), but wound scores at this stage were better in group 3 than in group 2 (1·82 versus 6·92 respectively; P = 0·022). The volume of wound drainage was lower in group 3 than in group 1 (P = 0·004). The incidence of adverse effects was highest in group 3, and two patients in this group discontinued treatment. No significant complications were noted in group 2. Anisodamine and S. miltiorrhiza were both effective in reducing skin flap ischemia and necrosis after mastectomy, although anisodamine was associated with a higher rate of adverse effects. In Germany these drugs have not been tested and are not approved for patient administration!
**Additional Complementary Therapy - Side effect Related to Cancer Treatments (7/16)**

*Further information and references:*

**Chinese medicinal herbs**

Zhang et al. reviewed the effectiveness and safety of Chinese medicinal herbs in alleviating chemotherapy-induced short term side effects in breast cancer patients. The authors identified seven randomised controlled trials involving 542 breast cancer patients undergoing or having recently undergone chemotherapy. All studies were conducted and published in China. Authors did not pool the results because few studies were identified and no more than two used the same intervention. All were of low quality and used CMH plus chemotherapy compared with chemotherapy alone.

This review provides limited evidence about the effectiveness and safety of Chinese medicinal herbs in alleviating chemotherapy induced short term side effects. Chinese medicinal herbs, when used together with chemotherapy, may offer some benefit to breast cancer patients in terms of bone marrow improvement and quality of life, but the evidence is too limited to make any confident conclusions. Well designed clinical trials are required before any conclusions can be drawn about the effectiveness and safety of CHM in the management of breast cancer patients.


**Homeopathic medicines for adverse effects of cancer treatments**

The review evaluates the effectiveness and safety of homeopathic medicines used to prevent or treat adverse effects of cancer treatments.
This review found preliminary data in support of the efficacy of topical calendula for prophylaxis of acute dermatitis during radiotherapy and Traumeel S mouthwash in the treatment of chemotherapy-induced stomatitis. These trials need replicating. There is no convincing evidence for the efficacy of homeopathic medicines for other adverse effects of cancer treatments. Further research is required.


**Topical use of Silymarin**

A total of 101 patients were evaluated after breast-conserving surgery followed by RT with 50.4 Gy plus boost 9–16 Gy. Of these, 51 patients were treated with the silymarin-based cream. In addition, 50 patients were documented receiving a panthenol-containing cream interventionally, if local skin lesions occurred. The median time to toxicity was prolonged significantly with silymarin-based cream (45 vs. 29 days (SOC), p < 0.0001). Only 9.8% of patients using silymarin-based cream showed grade 2 toxicity in week 5 of RT in comparison to 52% with SOC. At the end of RT, 23.5% of patients in the silymarin-based study group developed no skin reactions vs. 2% with SOC, while grade 3 toxicity occurred only in 2% in the silymarin-based arm compared to 28% (SOC). Silymarin-based cream Leviaderm® may be a promising and effective treatment for the prevention of acute skin lesions caused by RT of breast cancer patients. To confirm the results of this nonrandomized, observational trial, this component should be tested in larger multicenter studies in this setting.


**Acupuncture**

Chemotherapy-induced Nausea and Vomiting

Cognitive dysfunction

Fatigue
Three hundred two outpatients with breast cancer participated. 75 patients were randomly assigned to usual care and 227 patients to acupuncture plus usual care (random assignment of 1:3 respectively) with minimization controlling for baseline general fatigue and maintenance treatment. Treatment was delivered by acupuncturists once a week for 6 weeks through needling three pairs of acupoints (Ma 36, MP 6, Di 4). The usual care group received a booklet with information about fatigue and its management. Primary outcome was general fatigue at 6 weeks, measured with the Multidimensional Fatigue Inventory (MFI). Other measurements included the Hospital Anxiety and Depression Scale, Functional Assessment of Cancer Therapy–General quality-of-life scale, and expectation of acupuncture effect.
Two hundred forty-six of 302 patients randomly assigned provided complete data at 6 weeks. The difference in the mean General Fatigue score, between those who received the intervention and those who did not, was -3.11 (95% CI, -3.97 to -
The intervention also improved all other fatigue aspects measured by MFI, including Physical Fatigue and Mental Fatigue (acupuncture effect, -2.36 and -1.94, respectively; both at P < .001), anxiety and depression (acupuncture effect, -1.83 and -2.13, respectively; both at P < .001), and quality of life (Physical Well-Being effect, 3.30; Functional Well-Being effect, 3.57; both at P < .001; Emotional Well-Being effect, 1.93; P = .001; and Social Functioning Well-Being effect, 1.05; P < .05).


Further references:

Pain

Leucopenia
Acupuncture therapy has not been shown to prevent leucopenia. Since leucopenia may increase the risk of infection through acupuncture, patients with leucopenia should not be encouraged to undergo acupuncture treatment.

**ALC to prevent chemotherapy induced peripheral neuropathy**
Chemotherapy-induced peripheral neuropathy (CIPN) is common and leads to suboptimal treatment. Acetyl-L-carnitine (ALC) is a natural compound involved in neuronal protection. A total of 409 patients were evaluable (208 received ALC; 201, placebo). In a multivariate linear regression, week-12 scores were 0.9 points lower (more CIPN) with ALC than placebo (95% CI, -2.2 to 0.4; P = .17), whereas week-24 scores were 1.8 points lower with ALC (95% CI, -3.2 to -0.4; P = .01). Patients receiving ALC were more likely to have a > 5-point decrease in FACT-NTX scores (38% v 28%; P = .05), and FACT-TOI scores were 3.5 points lower with ALC (P = .03). Grade 3 to 4 neurotoxicity was more frequent in the ALC arm (eight v one). No differences between arms were observed for FACIT-Fatigue or other toxicities. Serum carnitine level increased with ALC but remained stable with placebo.

Conclusion: There was no evidence that ALC affected CIPN at 12 weeks; however, ALC significantly increased CIPN by 24 weeks. This is the first study to our knowledge showing that a nutritional supplement increased CIPN. Patients should be discouraged from using supplements without proven efficacy.

**Complementary Therapies - Mind-Body-Medicine I-II (8/16 and 9/16)**

*Further information and references:*

**Mind-Body Medicine (MBM)**
In the absence of an adequate equivalent that does not have other connotations, the term mind/body medicine (MBM), denoting a concept of methods and therapeutic programs developed and scientifically evaluated in the United States and integrated into European medicine, has been entered every day. Speech ist Rede, language ist Sprache - NB: hat der Term das geschaffen??) in the German language. The National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes for Health (NIH) defines MBM as “Practices that focus on the interactions among the brain, mind, body and behavior with the intent to use the mind to affect physical functioning and promote health.”


Its main goal is the activation and promotion of the patient’s ability for self-regulation and thereby his or her power of self-healing in the sense of salutogenesis.

A general overview of mind/body therapies in cancer survivorship


**MBSR**
Mindfulness based stress-reduction (MBSR) is an 8-week program, covering 24 contact-hours and 45 minutes daily home practice. The program aims at developing participants’ coping resources and developing participants’ mindful awareness. Thus the program consists of guided meditations, guided body scan (a specific awareness exercise) and through meditation, yoga and psychoeducation concerning stress and stress-reactions, while meditation and bodyscan is practiced at home by the use of specific audio-CDs guiding the patient.
In 2011 three systematic reviews on MBSR have been published. All of them found evidence of improved psycho-social factors which are often associated with cancer diagnosis and treatment e.g. stress, depression, reduced mood and quality of life. The review of Matchim et al. (2011) which included only women with breast cancer alone and some in heterogeneous cancer populations where breast cancer was the most common diagnosis found a large effect of MBSR on psychological symptoms, mainly stress and anxiety, but a meta-analysis was not performed.


In 2012 two systematic reviews and meta-analyses in patients with breast cancer showed positive effects on the mental health of breast cancer patients. The metaanalysis of Cramer et al. (2012), that included only RCT’s, reported small effects on depression and moderate effects on anxiety. Zainal et al. (2012) included both RCT’S and uncontrolled trials and reported moderate to large effects on stress, depression and anxiety.


A recent rct of 336 women who had been operated on for breast cancer (stage I-III) found clinically meaningful, statistically significant effects of an 6 week MBSR Program in comparison to usual care on depression and anxiety after 12 months’ follow-up and medium-to-large effect sizes. Another publication of the same RCT reported that MBSR had a statistically significant effect on sleep quality just after the intervention but no long-term effect.


A randomized controlled trial of 82 breast cancer patients found that MBSR promotes a more rapid recovery of functional T cells capable of being activated by a mitogen with the Th1 phenotype, whereas substantial recovery of B and NK cells after completion of cancer treatment appears to occur independent of stress-reducing interventions.


Another RCT of MBSR (n= 68) reported improved the symptoms and quality of life of breast cancer patients across a variety of cancer symptoms and quality-of-life measures.


A recent RCT of good methodological quality carried out in 229 women after surgery, chemotherapy, and radiotherapy for breast cancer, found significant improvements in mood, breast- and endocrine-related quality of life, and well-being in the MBSR group compared with standard care. These results persisted at three months.

Physical exercise

Physical training has been shown to be an efficacious adjuvant to breast cancer therapy. Physical exercise appears to be safe during and after cancer treatments and results in improvements in physical functioning, quality of life, and cancer-related fatigue.

Breast cancer patients can generally be advised to avoid physical inactivity and to return to normal physical activities as soon as possible after surgery. Patients should be physically active and should exercise throughout the whole period of medical treatment. The intensity of exercise depends on the phase of medical treatment, the individual’s general condition, and the patient’s possibilities. Generally patients should begin exercising slowly to avoid excessive strain.

The American College of Sports Medicine (ACSM) published a comprehensive review of exercise intervention studies in breast cancer populations as part of a recent roundtable discussion of exercise in cancer survivors. The review included data from 54 rct’s of exercise in breast cancer patients: 22 in the adjuvant setting and 32 in the posttreatment setting. The authors found consistent evidence that exercise could be performed safely in both the adjuvant and posttreatment settings. Exercise led to significant improvements in aerobic fitness and strength in both settings and led to increased flexibility and physical functioning in the posttreatment setting. A moderate level of evidence also suggested that exercise led to improvements in quality of life, anxiety, depression, fatigue, body image, body size, and body composition in breast cancer survivors, although findings were not always consistent. Furthermore, the ACSM guidelines cite that exercise may be associated with a reduced risk of developing a recurrence or secondary cancer.


This narrative literature review indicates that regular participation in physical activity after breast cancer diagnosis may mitigate common side effects of breast cancer adjuvant therapy, including fatigue, depression, impaired quality of life, decreased muscular strength, decreased aerobic capacity, and weight gain.

A randomized trial of exercise showed that starting a supervised exercise regimen that is tailored to an individual's strength following breast cancer surgery appears safe and may lead to improvements in physical functioning.


A systematic review identified 7 studies addressing resistance exercise (6 rct’s), seven studies on aerobic and resistance exercise (3 rct’s), and five studies on other exercise modalities (4 rct’s). Studies concluded that slowly progressive exercise of varying modalities is not associated with the development or exacerbation of breast cancer-related lymphedema and can be safely pursued with proper supervision. Combined aerobic and resistance exercise appear safe, but confirmation requires larger and more rigorous studies. It was concluded that it is safe for breast cancer survivors to exercise throughout the trajectory of their cancer experience, including during treatment.


A small study examining the effect of a home-based exercise program on lymphedema and QOL in postmastectomy patients showed that an individualized home-based exercise program led to improvement in affected upper-limb volume and circumference and QOL of postmastectomy lymphedema patients.

A recent trial randomizing sedentary breast cancer survivors between telephone-based exercise intervention or usual care as control group reported that patients randomized to a telephone-based physical activity intervention had increased physical activity and experienced significant improvements in fitness and physical functioning.


According the guidelines of the American Cancer Society and the American College of Sports Medicine (Schmitz, 2010, see above) adults aged 18 to 64 years should engage in at least 150 minutes per week of moderate intensity or 75 minutes per week of vigorous intensity aerobic physical activity, or an equivalent combination of moderate and vigorous intensity aerobic physical activity. Some activity is better than none and exceeding the guidelines is likely to provide additional health benefits. Activity should be done in episodes of at least 10 minutes per session and preferably spread throughout the week. Furthermore, adults should do muscle-strengthening activities involving all major muscle groups at least 2 days per week. Adults aged older than 65 years should also follow these recommendations if possible, but if chronic conditions limit activity, older adults should be as physically active as their abilities allow and avoid long periods of physical inactivity.


Exercising is contraindicated with fever or body temperature > 38°C, diarrhea, vomiting, pain, acute infection (during antibiotic treatment), non-medicated hypertension, acute bleeding, bone or bone marrow metastases with a high likelihood of fracture, severe thrombocytopenia (under 20/ nl), circulatory problems, confusion, hemoglobin < 8 g/dl, reduced consciousness, cardio- or nephrotoxicity. chemotherapy (earliest physical activities after 1 day), or chemotherapy + Herceptin (earliest physical activities after 1 day).
Further References:


Statement on quality of life:
This systematic review of 9 randomized controlled trials with an average quality only presents components of exercise programmes that are effective for QoL. From this review, it is evident that aerobic exercise has a favourable effect on the QoL for patients with, and survivors of, breast cancer. Clinicians Results are optimal when performed thrice a week, at a moderate intensity (50–70% of HRmax) for greater than 30 minutes for at least 8 weeks, under supervision. This result would be regardless of the stage of breast cancer and the medical management the participants may be undergoing.


A meta-analysis on 56 RCT’s provides a comprehensive summary of studies exploring the effectiveness of a range of behavioral techniques and physical exercise interventions, during and after treatment, on long-term sequelae such as fatigue, depression, anxiety, body-image, stress and HRQoL in breast cancer patients and survivors. Statistically significant, but modest, results were found for the effect of behavioral techniques on fatigue and stress, with stronger
effects found of depression and anxiety. No significant effects were observed for body-image or HRQoL. For physical exercise interventions (17 studies), statistically significant and moderate effects were observed for fatigue, depression, body-image and HRQoL. The effect on anxiety was in the expected direction, but was not statistically significant. Only one study assessed the effect of physical exercise on stress, and thus a summary effect size could not be calculated. The results indicate that behavioral techniques and physical exercise improve psychosocial functioning and HRQoL in breast cancer patients and survivors.


A Cochrane review of 40 (RCTs) and controlled clinical trials (CCTs) with 3694 participants indicates that exercise may have beneficial effects on HRQoL and certain HRQoL domains including cancer-specific concerns (e.g. breast cancer), body image/self-esteem, emotional well-being, sexuality, sleep disturbance, social functioning, anxiety, fatigue, and pain at varying follow-up periods. Cancer diagnoses in study participants included breast, colorectal, head and neck, lymphoma, and other. Thirty trials were conducted among participants who had completed active treatment for their primary or recurrent cancer and 10 trials included participants both during and post cancer treatment. Mode of the exercise intervention included strength training, resistance training, walking, cycling, yoga, Qigong, or Tai Chi. The positive results must be interpreted cautiously due to the heterogeneity of exercise programs tested and measures used to assess HRQoL and HRQoL domains, and the risk of bias in many trials.


The goal of this systematic review was to examine the effect of exercise on the quality of life (QOL) of women with breast cancer. Nine relevant randomized controlled trials were found, four of moderate methodological quality and five of high methodological quality. Evidence was strong that exercise positively influences QOL in women with breast cancer. Thus, exercise may be an effective means of improving QOL in women with this disease. Further research is needed to determine optimal types and parameters of appropriate exercises.

A review of 14 RCTs (n=717) indicated that exercise is an effective intervention to improve quality of life, cardiorespiratory fitness, and physical functioning and to decrease fatigue in breast cancer patients and survivors.

• McNeely ML, Campbell KL, Rowe BH et al. (2006): Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. CMAJ, 175 (1) 34-41.

This meta-analysis of 10 studies (N = 588) indicates that aerobic exercise significantly improved cardiopulmonary function as assessed by absolute VO2 peak (standardized mean difference [SMD] 0.916, p < 0.001), relative VO2 peak (SMD 0.424, p < 0.05), and 12-minute walk test (SMD 0.502, p < 0.001). Similarly, aerobic exercise significantly improved body composition as assessed by percentage body fat (SMD -0.890, p < 0.001), but body weight and lean body mass did not change significantly. Aerobic exercise during or after cancer adjuvant therapy seems to be an effective means of improving cardiopulmonary function and decreasing the percentage of body fat in women with breast cancer.


**Statement on fatigue**

This meta-analysis with twenty-eight studies (n = 2083 participants, n = 1172 with breast cancer) showed that exercise benefited individuals with cancer-related fatigue during and after cancer therapy. Further research is required to determine the optimal type, intensity, and timing of an exercise intervention.

This meta-analysis evaluated the effects of various exercise parameters on cancer-related fatigue (CRF) during cancer treatment. Eighteen RCTs (12 in breast cancer, 4 in prostate cancer, and 2 in other cancer patients) met all the inclusion criteria. During breast cancer treatment, home-based exercise led to a small, non-significant reduction in fatigue (standardized mean difference 0.10, 95% confidence interval -0.25 to 0.45), whereas supervised aerobic exercise showed a medium, significant reduction in CRF (standardized mean difference 0.30, 95% confidence interval 0.09 to 0.51) as compared with no exercise.


**Yoga**

Mind-body interventions like yoga receive increasing attention for breast cancer survivors.

A systematic review that included 13 RCTs with a total of 760 patients found strong evidence for anxiety, stress, depression, and health-related quality of life. Effects on fatigue were inconclusive.


A meta-analysis on 6 RCTs with a total of 382 patients that compared yoga to no interventions reported small effects on health-related quality of life (Hedge’s g=0.27) but no effects on anxiety, depression, distress, sleep, and fatigue.

A more comprehensive meta-analysis on 12 RCTs and 742 patients found small to moderate effects of yoga on global health-related quality of life, functional, social, and spiritual well-being. These effects were, however, not clearly distinguishable from bias. Large effects that were present in studies with low risk of bias were found for anxiety (g=1.51), depression (g=1.59), perceived stress (g=1.14), and psychological distress (g=0.86). Subgroup analyses revealed evidence of efficacy only for yoga during active cancer treatment (chemotherapy or radiotherapy) but not in cancer survivors after completion of active treatment.


Finally, a meta-analysis that included 6 RCTs (including 1 RCT that was not included in the above meta-analysis of Zhang et al., 2012) with a total of 362 patients found small effects on fatigue (g=0.33).


Bhargav et al. review some mechanisms by which Yoga can positively influence cancer stem cells susceptibility to conventional cancer treatment.

Qigong
The first systematic review on qigong in cancer treatment found no large RCTs. Four RCTs and 5 non-randomized trials were included. No large CRTs were found. The review found inconclusive results with some RCTs suggesting effects on overall health, and white blood cell counts. Effects on tumour progression, survival rates, and health-related quality of life were inconclusive.


A more recent systematic review on qigong in supportive cancer care included 8 RCTs and 15 non-randomized trials mainly on samples with mixed types of cancer. Five of the included RCTs suggested favorable effects of qigong exercise on symptoms, inflammation, quality of life, and mood disturbance. The other 3 RCTs showed no effect. All but 1 non-randomized trials found favorable effects of qigong.


An RCT (n=162) found improvements in QOL, fatigue, mood, and inflammation markers after qigong. The intervention was compared with TAU (treatment as usual).

A small study in 9 patients with histologically confirmed breast cancer awaiting surgery failed to confirm any effect on clinical changes in tumor measurements from pre- to post- qigong treatment. There was also no suggestion of change in QOL. However, this study was on external qigong, i.e. on a therapist-provided form of mental healing that is not comparable to internal qigong, i.e. patient-practiced aerobic exercise.

Tai Chi
A 2010 systematic review on Tai Chi for breast cancer patients included 3 RCTs and 4 non-randomized controlled trials. RCTs showed no effects on quality of life, psychological, and physical outcomes. The review included a meta-analysis of 2 RCTs that failed to show effects on quality of life (Hedge’s g=0.45; 95% Confidence Interval -0.25; 1.14). Three of the non-randomized trials found effects on quality of life, mood, self-efficacy, shoulder and upper limb function.


A more recent systematic review included 4 RCTs and found limited evidence for improved physical functioning, mental health, muscle strength, quality of life, and self-esteem.


Hypnosis
In a RCT, 42 women undergoing breast cancer radiotherapy, a combination of hypnosis and cognitive therapy was compared to standard medical care. In the control group, fatigue increased linearly over the course of the radiotherapy while there was no increase in the hypnosis group. Effect size was large on the FACIT-F (d=0.82).


A second RCT investigated the effects of this intervention on affect and lower rates of negative affect and higher rates of positive affect in the hypnosis group than in the control group. At week 5, patients in the hypnosis group had 66% lower negative affect scores and 43% greater positive affect scores than the control group.

A recent review concluded that the results of hypnosis for cancer patients undergoing are heterogeneous. The authors suggested that suggestions in the hypnosis should focus specifically on breast cancer radiotherapy and that hypnosis should be combined with cognitive therapy. (sorry das verstehe ich nicht)

Further information and references:

Data on the impact of nutrition on the risk of recurrence (secondary prevention) are rare. Therefore clinical advice during remission is often based on the extrapolation of primary prevention data. In 2007, the World Cancer Research Fund/American Institute of Cancer Research published its second expert-report. A recent prospective investigation of pre-diagnosis body mass index (BMI) and mortality among 14,948 breast cancer patients in the After Breast Cancer Pooling Project. Showed that women who were underweight and morbidly obese before breast cancer diagnosis were at the greatest risk of all-cause mortality. Morbidly obese women were also at increased risk of death from breast cancer (Kwan et al, 2011). Interestingly, a recent retrospective evaluation of treatment adherence according to body weight demonstrated that patients with increasing BMI had a higher motivation and perseverance to the recommended treatment (Schmidt et al, 2011).

However, published data of the prospective Women’s Healthy Eating and Living (WHEL) study demonstrated that diet had a beneficial effect only when combined with physical activity (Pierce et al. 2007). Nutritional advice as an adjuvant treatment can be based on recently published data from a prospective trial: the women’s intervention nutrition study (WINS). In this trial Chlebowsky et al. (2006) found significantly improved disease-free survival (DFS) for patients with ER-neg. tumors if less than 21% of the daily calorie intake was derived from fat. This dietary modification can only be achieved with the help of continual professional dietary counselling. The WHEL data did not confirm the beneficial effect of a low-fat diet in general.

Goodwin presented data indicating that adherence to a normal BMI improves disease outcome (SABCS 2009). However, being underweight seems to increase the risk of recurrence, and since up to 30% of breast cancer patients are in danger becoming cachectic, malnutrition screening seems necessary. ESPEN (The European Society for Clinical Nutrition and Metabolism) recommends the “Malnutrition Universal Screening Tool” (MUST) for adults according to Kondrup J. et al. (Clinical Nutrition 2003;22: 415-421 ww.bapen.org.uk/must_tool.html).

Dietary extremes, especially fasting excesses, are dangerous and are associated with poor survival when BMI drops pathologically low.—
Concerning cardiovascular risk factors, a recent non-randomized controlled study in breast cancer survivors comparing high fat, low carbohydrate versus low fat, high carbohydrate found a lack of evidence of a negative effect of dietary pattern on biomarkers associated with cardiovascular risk (Thompson et al, 2012)


Recently, more and more attention is being paid to diet quality, inflammation, and biomarkers of inflammation in breast cancer survivors (lower levels of chronic inflammation like low C-reactive protein at baseline have been associated with improved survival after breast cancer (Pierce et al, 2009)). Studies evaluating the effect of a low fat versus a low carbohydrate weight loss dietary intervention on biomarkers of long term survival in breast cancer patients like the 'CHOICE' protocol are underway, measuring inflammatory biomarkers like C-reactive protein among others (Sedlacek et al, 2011). Ongoing research.


There is growing evidence that the impact of dietary factors on risk of BC differs according to the particular molecular subtypes of cancer. E.g. overweight had no prognostic impact among women with early stage triple receptor-negative BC. Supervising are the findings in the research area of nutrigenomics.
Body mass Index is an established risk factor for developing breast cancer, for its recurrence, and for early death. Obese patients have a 50 to 75% higher probability of recurrence and a 36 to 50% higher risk of dying from breast cancer. A recent observational study, however, showed that obesity plays an important role in mortality among white but not black patients with breast cancer (Lu et al, 2011).

A recent prospective investigation of pre-diagnosis body mass index (BMI) and mortality among 14,948 breast cancer patients in the After Breast Cancer Pooling Project showed that women who were underweight and morbidly obese before breast cancer diagnosis were at the greatest risk of all-cause mortality. Morbidly obese women were also at increased risk of death from breast cancer (Kwan et al, 2011). Interestingly, a recent retrospective evaluation of treatment adherence according to body weight demonstrated that patients with increasing BMI had a higher motivation and perseverance to the recommended treatment (Schmidt et al, 2011). Cave: Female patients often connote weight loss positively. Note the difference between intentional vs. unexplained (maybe as consequence of disease).


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Further references:


• Kroenke CH, Chen WY, Rosner B et al. (2005): Weight, weight gain, and survival after breast cancer diagnosis. J Clin Oncol 23:1370–1378. – weight gain unfavourable

• Chlebowski RT, Aiello E, McTiernan A et al. (2002): Weight loss in breast cancer patient management. J Clin Oncol 20:1128–1143. – suggest beneficial effects on overall survival extrapolated from prognostic impact of weight and by beneficial effects to other conditions


**Statement on low fat diet**

Besides the amount of fat, fat quality (type of fat intake) seems to count, but few in vivo data so far. Lower intake of saturated fat and trans fat (in post-diagnoses diet) could be associated with improved survival after BC diagnosis.


**Statement on lignans/ flaxseed**

Dietary lignans make up one class of phytoestrogens and have been identified as potentially protective against breast cancer via estrogen-dependent and independent anticarcinogenic activity. Flaxseed is a major source of lignans. Lignans are metabolized by the gut microflora into enterolignans, enterolactone is the main metabolite. A recent observational study (Buck et al, 2011) found in 1,140 postmenopausal breast cancer patients that high serum enterolactone levels were associated with an improved survival. These findings were supported by a recent meta-analysis indicating a significant inverse association between serum enterolactone and postmenopausal breast cancer risk, which was stronger for ER-PR- than for ER+PR+ tumors but not differential by further expression of HER2 (Zaineddin et al, 2011). Furthermore, a recent epidemiologic study showed that higher prediagnostic plasma levels of enterolactone were related to lower mortality among breast cancer patients (Olsen et al, 2011). Accordingly, a meta-analysis showed an overall reduction of postmenopausal breast cancer risk in women with the highest vs. lowest plant lignan consumption (Buck et al 2010). However, two epidemiologic studies concerning the association of the reported dietary intake of lignans and breast cancer prognosis gave inconsistent results (McCann et al, 2009; Fink et al, 2007). These differences might be explained by the fact that a serum biomarker, which provides an index of intake, metabolism, and absorption of phytoestrogens and is not prone to recall bias and misclassification, might be a more appropriate measure. Concerning the occurrence of hot flushes, a recent randomized phase III trial failed to demonstrate a significant reduction of hot flushes for postmenopausal patients taking additional 410 g of lignans as compared to placebo (Pruthi et al, 2012). Besides, seeds in general are a source of dietary fiber, which itself may play a protective role as a recent meta-analysis suggests. More specifically relevant for the prevention of recurrences are data from the HEAL-study: Dietary fiber was associated with a nonsignificant inverse association with breast cancer events and total mortality.


The American Journal of Clinical Nutrition published „an in-depth analysis of combined evidence from cohort studies of US and Chinese women“. Overall 9514 breast cancer patients were randomized between 1991 and 2006. A significant relative risk reduction was shown: (HR: 0.75; 95% CI: 0.61, 0.92). („Slightly stronger among women with ER-negative breast cancers…“). Similar results were demonstrated by the German study (Zaineddin et al. s.o.) a significantly decreased risk for breast cancer coinciding with increased intake of soy beans, sun flower seeds and cabbage seeds independent of the patients estrogen receptor status (but statistically not significant for Lignane).

A general recommendation regarding physto-estrogen rich or enriched food cannot be made at this time while in some studies indicate, that oral intake of soy beans decreases the effectiveness of Tamoxifen on decreasing the risk for breast cancer and while the possibility is being discussed that Daidzein (the other physto-estrogen in soy beans next to Genistein) might enhance cell proliferation.
Moreover Nechuta et al. point out, that: „Limitation of this study should be considered. First, ..., a higher intake of isoflavones was associated with lifestyle-related factors, including regular exercise and higher consumption of cruciferous vegetables (...) and lower BMI and nonsmoking status (...). ... Further studies ... are needed.”
In conclusion: continued observation is advised. There are increasing evidence that oral intake of soy beans may translate into a health benefit for ’survivors’. In this context other mechanisms of action of Phyto-estrogens are being discussed such as enhancing apoptosis and suppressing angiogenesis.


**Statement on adherence to general nutrition guidelines**
Because of rare data about the risk of recurrence (secondary prevention), clinical advice during remission is often based on the extrapolation of primary prevention data. In 2007 the World Cancer Research Fund published its second report. In summer 2012 for the first time ever the American Cancer Society published ‘Nutrition and Physical Activity Guidelines for Cancer Survivors’. Nutritional advice as an adjuvant treatment can be based on data from a prospective trial: the women’s intervention nutrition study (WINS). In this trial Chlebowsky et al. (2006) found significantly improved disease-free survival (DFS) for patients with ER-neg. tumors if less than 21% of the daily calorie intake was derived from fat. This dietary modification can only be achieved with the help of continual professional dietary counselling. The WHEL data did not confirm the beneficial effect of a low-fat diet in general. Published data of the prospective Women’s Healthy Eating and Living (WHEL) study demonstrated that diet had a (big) beneficial effect only when combined with physical activity (Pierce et al. 2007).

The primary prevention EPIC study did not show that dietary fruits and vegetables protected against breast cancer, and no data are available regarding the prevention of recurrence of BC. Nevertheless, EPIC shows an inverse association between the risk of BC overall and in postmenopausal women and adherence to Mediterranean diet, more pronounced in receptor-negative tumors (Buckland et al 2012, Masala et al 2012). And some studies suggest a lower risk of ER-tumors, which are harder to treat (e.g. Fung et al).
Finally, a recent study by Beasley et al (2011) suggests that lower intake of saturated and trans fat in the post-diagnosis diet is associated with improved survival after breast cancer diagnosis.

- Sofi et al. (2008): Adherence to Mediterranean diet and health status: meta-analysis. BMJ Sep 11; 337:a1344. (12 studies with a total of 1,574,299 subjects)


*Post-diagnosis dietary factors and survival after invasive breast cancer.*


*Statement on dietary extremes (are associated with less favorable outcomes)*

Dietary extremes, especially fasting excesses, are dangerous and are associated with poor survival when BMI drops pathologically low.


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Physical training has been shown to be an efficacious adjuvant to breast cancer therapy. Physical exercise appears to be safe during and after cancer treatments and results in improvements in DFS and OS, physical functioning, quality of life, and cancer-related fatigue.

Breast cancer patients can generally be advised to avoid physical inactivity and to return to normal physical activities as soon as possible after surgery. Patients should be physically active and should exercise throughout the whole period of medical treatment. The intensity of exercise depends on the phase of medical treatment, the individual’s general condition, and the patient’s possibilities. Generally patients should begin exercising slowly to avoid excessive strain.

The American College of Sports Medicine (ACSM) published a comprehensive review of exercise intervention studies in breast cancer populations as part of a recent roundtable discussion of exercise in cancer survivors. The review included data from 54 RCT’s of exercise in breast cancer patients: 22 in the adjuvant setting and 32 in the posttreatment setting. The authors found consistent evidence that exercise could be performed safely in both the adjuvant and posttreatment settings. Exercise led to significant improvements in aerobic fitness and strength in both settings and led to increased flexibility and physical functioning in the posttreatment setting. A moderate level of evidence also suggested that exercise led to improvements in quality of life, anxiety, depression, fatigue, body image, body size, and body composition in breast cancer survivors, although findings were not always consistent. Furthermore, the ACSM guidelines cite that exercise may be associated with a reduced risk of developing a recurrence or secondary cancer.


Additionally, there is increasing evidence of an inverse relationship between exercise and markers of systemic inflammation like C-reactive protein.


Another potential link between exercise and survival of breast cancer patients was described in a study suggesting that increasing physical activity after a breast cancer diagnosis may affect epigenetic regulation of tumor suppressor genes like L3MBTL1, which have favorable impact on survival outcomes of breast cancer patients.


According the guidelines of the American Cancer Society and the American College of Sports Medicine (Schmitz, 2010, see above) adults aged 18 to 64 years should engage in at least 150 minutes per week of moderate intensity or 75 minutes per week of vigorous intensity aerobic physical activity, or an equivalent combination of moderate and vigorous intensity aerobic physical activity. Some activity is better than none and exceeding the guidelines is likely to provide additional health benefits. Activity should be done in episodes of at least 10 minutes per session and preferably spread throughout the week. Furthermore, adults should do muscle-strengthening activities involving all major muscle groups at least 2 days per week. Adults aged older than 65 years should also follow these recommendations if possible, but if chronic conditions limit activity, older adults should be as physically active as their abilities allow and avoid long periods of physical inactivity.


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of fracture, severe thrombocytopenia (under 20/ nl), circulatory problems, confusion, hemoglobin < 8 g/dl, reduced consciousness, cardio- or nephrotoxicity. chemotherapy (earliest physical activities after 1 day), or chemotherapy + Herceptin (earliest physical activities after 1 day).

References:


Statement on improvements in DFS and OS
Published data have shown that physical activity (PA) reduces the risk of breast cancer. However, data on the role of PA in breast cancer outcome have been inconsistent. The lack of a meta-analysis concerning this issue prompted the current report. A comprehensive search of the literature identified eight studies, two of which could be excluded. The remaining six studies (12,108 patients with breast cancer) were included in this meta-analysis. Pre-diagnosis PA reduced all causes of mortality by 18% but had no effect on breast cancer deaths. Post-diagnosis PA reduced breast cancer deaths by 34% (HR = 0.66, 95% CI, 0.57-0.77, P < 0.00001), all causes of mortality by 41% (HR = 0.59, 95% CI, 0.53-0.65, P < 0.00001), and
disease recurrence by 24% (HR = 0.76, 95% CI, 0.66-0.87, P = 0.00001). Breast cancer mortality was reduced by pre-diagnosis PA in women with body mass index (BMI) < 25 kg/m2, while post-diagnosis PA reduced that risk among those with BMI >/= 25 kg/m2. On the other hand, post-diagnosis PA reduced all causes of mortality regardless of the BMI. The analysis showed that post-diagnosis PA reduced breast cancer deaths (HR = 0.50, 95% CI, 0.34-0.74, P = 0.0005) and all causes of mortality (HR = 0.36, 95% CI, 0.12-1.03, P = 0.06) among patients with estrogen-receptor (ER)-positive tumors, but not in women with ER-negative disease. The current meta-analysis provides evidence for an inverse relationship between PA and mortality in patients with breast cancer and supports the notion that breast cancer survivors should engage in appropriate PA (Ibrahim et al, 2010).

In addition, the After Breast Cancer Pooling Project (n = 13,302) reported that at least 10 MET-hours/week of PA was associated a 25% reduction in breast cancer mortality (n = 971 events, HR = 0.75, 95% CI 0.65-0.85) compared with women who did not meet the PA Guidelines (<10 MET-hours/week) (Beasley et al, 2012).


Statement on smoking
The association of smoking with outcomes following breast cancer prognosis is not well understood.

In the LACE cohort study, 2265 women diagnosed with breast cancer were followed for a median of twelve years. Compared with never smokers, women who were current smokers had a two-fold higher rate of dying from breast cancer (HR=2.01, 95% CI 1.27–3.18) and an approximately four-fold higher rate of dying from competing (non-breast cancer) causes (HR=3.84, 95% CI 2.50–5.89).

Among seven studies that met the inclusion criteria in the systematic review, four studies reported significantly increased risk of breast cancer death with current smoking. Little evidence was found of an association between former smoking and breast cancer mortality (HR=1.24, 95% CI 0.94–1.64).


Further references:


• Hamajima N, Hirose K, Tajima K et al.: Alcohol, tobacco and breast cancer--collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. Br J Cancer. 2002 Nov 18;87(11):1234-45.


Statement on alcohol
The association between alcohol intake and recurrence may depend on menopausal status at breast cancer diagnosis. In the international “After Breast Cancer Pooling Project” an investigation was conducted of postdiagnosis alcohol consumption among 9,329 women with a mean follow-up of 10.3 years. 58% of the women were considered drinkers (≥0.36g/d, median 5.3g/d). Overall, compared with nondrinking, regular alcohol intake (≥6.0g/d) was not associated with risk of recurrence. However, risk varied significantly by menopausal status. Postmenopausal women who regularly consumed alcohol (≥6.0g/d) had increased risk of recurrence (HR, 1.19; 95% CI, 1.01-1.40). Alcohol was not associated with mortality.

Accordingly, alcohol intake was not associated with survival among 3146 women diagnosed with invasive breast cancer in the Swedish Mammography Cohort. Women who consumed 10 g per day (corresponding to approximately 0.75 to 1 drink) or more of alcohol had an adjusted HR (95% CI) of breast cancer-specific death of 1.36 (0.82–2.26; p(trend)=0.47) compared with non-drinkers. Thus indicating that alcohol intake up to approximately one small drink per day does not negatively impact breast cancer-specific survival (Harris et al, 2012). This contrasts earlier findings from the LACE study showing that drinking ≥ 6 g/d of alcohol compared with no drinking was associated with an increased risk of breast cancer recurrence (HR, 1.35; 95% CI, 1.00 to 1.83) and death due to breast cancer (HR, 1.51; 95% CI, 1.00 to 2.29) (Kwan et al, 2010). Interestingly, both of these studies found an inverse relationship between alcohol intake and non-breast cancer death suggesting cardioprotective effects of alcohol on non-breast cancer death.


In addition to being a risk factor for breast cancer, a high pre-diagnostic alcohol intake also seems to have an effect on the course of the disease. Holm et al. (2013) found a modest but significant association between pre-diagnostic alcohol consumption and breast cancer recurrence with a median follow-up of six years after date of diagnosis in a prospective cohort of 29,875 women. Results for breast cancer specific mortality were also suggestive of a higher risk but were not statistically significant.


Further references:

• Kwan M et al (2009): Alcohol Consumption and Breast Cancer Prognosis and Survival in the Lace Study: a Prospective Cohort Study of Breast Cancer Survivors
• Reding et al.: Effect of Prediagnostic Alcohol Consumption on Survival after Breast Cancer in Young women. Cancer Epidemiol Biomarkers Prev. 2008; 17: 1988-1996. These results suggest that women who consume alcohol before a diagnosis of breast cancer have improved survival, which does not appear to be attributable to differences in stage, screening, or treatment.
Further information and references:

To make it quite clear: the biggest threat from unconventional therapies including CAM is from the danger of omitting evidence based therapy, in specific systemic therapy. This could be clearly demonstrated by Saquib et al (2012). The purpose of their study was to assess whether CAM use affected breast cancer prognosis in those who did not receive systemic therapy. They used a secondary data analysis of baseline/survey data from the Women's Healthy Eating and Living (WHEL) study including 2562 breast cancer survivors. Mean follow-up approached 7.3 years. Those women who did not receive any systemic treatment had a higher risk for time to additional breast cancer events (HR=1.9, 95% CI: 1.32, 2.73) and for all-cause mortality (HR=1.7, 95% CI: 1.06, 2.73) compared to those who had received systemic treatment. Among 177 women who did not receive systemic treatment, CAM use was not significantly related to additional breast cancer events. The use of dietary supplements or CAM therapies did not change this risk. This indicates that complementary and alternative therapies did not alter the outcome of breast cancer and should not be used in place of standard treatment.


CAM (long-term breast cancer survivors who use CAM may have poorer emotional functioning and more medical problems than non-users)

In contrast to popular belief there’s virtually no usable data on the safety and efficacy of most CAM-modalities, let alone unconventional therapies. Fortunately some CAM approaches are now being reviewed using evidence-based rationales. However, most studies are still in the protocol stage. Lin T, Ding Z, Li N, et al: Seleno-cyclodextrin sensitises human breast cancer cells to TRAIL-induced apoptosis through DR5 induction and NF-κB suppression. Eur J Cancer. 2011 Aug;47(12):1890-907.
Many other modalities listed on this slide belong to the group of unproven methods with the potential of causing side effects and drug interaction and are therefore rejected by the guideline panel (AGO -). Mistletoe and black cohosh extracts have been “uprated“ from AGO – to AGO +/- because safety data suggest that adverse outcomes are not necessarily to be feared. Soy-derived isoflavonoids are potent phytoestrogens with complete estrogenic interaction with estrogen receptors and complicated dose-response relationships in vitro. Since they could potentially stimulate ER-responsive tumor cells under unpredictable circumstances, there is a long lasting discussion whether they can be safely consumed as medical adjuvants. Guha et al showed in a cohort of 1954 breast cancer patients with diagnoses from 1997 through 2000 an inverse association between postdiagnosis soy isoflavone intake and breast cancer recurrence. However, the inverse association was not observed among women not taking tamoxifen. Contrasting these findings, a large, population-based cohort study of 5042 female breast cancer survivors in China demonstrated that soy food consumption was significantly associated with decreased risk of death and recurrence. This association was evident among women with either estrogen receptor-positive or -negative breast cancer and was present in both users and nonusers of tamoxifen (Shu et al, 2009). Occasional consumption of soy - derived foodstuff, e.g., tofu or soy milk, as part of a vegetable-based diet is probably harmless.


**Vitamins / Antioxidants**

A population-based prospective cohort study of 4,877 women in Shanghai aged 20 to 75 years diagnosed with invasive breast cancer demonstrated that vitamin use shortly after breast cancer diagnosis was associated with reduced mortality and recurrence risk, adjusted for multiple lifestyle factors, sociodemographics, and known clinical prognostic factors. Women who used antioxidants (vitamin E, vitamin C, multivitamins) had 18% reduced mortality risk (HR = 0.82, 95% CI: 0.65-1.02) and 22% reduced recurrence risk (HR = 0.78, 95% CI: 0.63-0.95). The inverse association was found regardless of whether vitamin use was concurrent or nonconcurrent with chemotherapy, but was present only among patients who did
not receive radiotherapy. This does not support the current recommendation that breast cancer patients should avoid use of vitamin supplements (Nechuta et al, 2010). Greenlee and co-workers reported that frequent use of vitamin C and vitamin E in the period after breast cancer diagnosis was associated with a decreased likelihood of recurrence, whereas frequent use of combination carotenoids was associated with increased mortality. The effects of antioxidant supplement use after diagnosis likely differ by type of antioxidant.


Laetrile treatment for cancer

Milazzo S, Ernst E, Lejeune S, Boehm K, Horneber M.: Laetrile is the name for a semi-synthetic compound which is chemically related to amygdalin, a cyanogenic glycoside from the kernels of apricots and various other species of the genus Prunus. Laetrile and amygdalin are promoted under various names for the treatment of cancer although there is no evidence for its efficacy. Due to possible cyanide poisoning, laetrile can be dangerous.

The claims that laetrile or amygdalin have beneficial effects for cancer patients are not currently supported by sound clinical data. There is a considerable risk of serious adverse effects from cyanide poisoning after laetrile or amygdalin, especially after oral ingestion. The risk–benefit balance of laetrile or amygdalin as a treatment for cancer is therefore unambiguously negative.

Alternatives to reduce Menopausal Symptoms after BC I (13/16)

Further information and references:

Menopausal symptoms are bothersome for breast cancer survivors and affect quality of life. Since hormonal replacement therapy should be avoided in ER positive breast cancer patients alternatives are important. Antidepressants may help with hot flashes. Acupuncture and hypnosis can also be used but the evidence is conflicting. For urogenital problems vaginal moisturizers or topical estrogens can be used (Loibl et al, 2011).

General approaches

This A wait-list controlled RCT (n=422) evaluates the effect of cognitive behavioral therapy (CBT), physical exercise (PE), and of these two interventions combined (CBT/PE) on menopausal symptoms (primary outcome), body image, sexual functioning, psychological well-being, and health-related quality of life (secondary outcomes) in patients with breast cancer experiencing treatment induced menopause. Compared with the control group, the intervention groups had a significant decrease in levels of endocrine symptoms (P =.001; effect size, 0.31-0.52) and urinary symptoms (P =.002; effect size, 0.29-0.33), and they showed an improvement in physical functioning (P =.002; effect size, 0.37-0.46). The groups that included CBT also showed a significant decrease in the perceived burden of hot flashes and night sweats (P =.001; effect size, 0.39-0.56) and an increase in sexual activity (P=.027; effect size, 0.65). Most of these effects were observed at both the 12-week and 6-month follow-ups.

Conclusion: CBT and PE can have salutary effects on endocrine symptoms and, to a lesser degree, on sexuality and physical functioning of patients with breast cancer experiencing treatment-induced menopause. PE seems to affect primarily the frequency with which endocrine symptoms are experienced, as assessed by the FACT-ES, but not the frequency of hot flashes and night sweats specifically. CBT, in contrast, seems to not only affect symptom frequency, but also the perceived burden of hot flashes and night sweats. These results tend to support the hypothesis that cognitive and emotional factors can modify the experience of menopausal symptoms, whereas stress reduction techniques and physical exercise may have a more direct effect on menopausal symptoms via the thermoregulatory system and an improvement in overall physical condition.

Physical Training

Mind-Body-Medicine (Relaxation training, Yoga, Hypnosis)

A unique relaxation training consisting of deep breathing, imagination, and PME and subsequent independent practicing at home with an audiotape for 20 minutes daily one month long significantly decreased the frequency and intensity of hot flashes in n=76 women compared with n=74 women with no intervention.
Yoga (n=17), 8 monthly 120-minute units, compared with waitinglist (n=20). Result: Significant improvement in hot flashes score, joint pain, fatigue, sleep, mood, and relaxation. These results remain significant after 3 months follow-up.


RCT (n=51): 5 weekly hypnosis sessions (ca. 50 min.) and instructions on self-hypnosis compared with waiting list. Results: hot flash scores (frequency x average severity) decreased 68% compared with control group. In addition significant improvement in anxiety, depression, and sleep.


**Vaginal Lubricants**


**Acupuncture**

In their review Lee et al. assessed the effectiveness of acupuncture as a treatment option for hot flashes in patients with breast cancer. They searched the literature using 14 databases from their inceptions to August 2008, without language restrictions. They included randomized clinical trials (RCTs) comparing real with sham acupuncture or another active treatment or no treatment. Methodological quality of the trials was assessed using the modified Jadad score. Three RCTs compared the effects of manual acupuncture with sham acupuncture. One RCT showed that acupuncture reduced hot flash frequency, while the other two RCTs did not. The meta-analysis showed significant effects of acupuncture compared with sham acupuncture (n = 189, weight mean difference, 3.09, 95% confidence intervals -0.04 to 6.23, P = 0.05) but marked heterogeneity was observed in this model (chi (2) = 8.32, P = 0.02, I (2) = 76%). One RCT compared the effects of
electroacupuncture (EA) with hormone replacement therapy. Hormone therapy was more effective than EA. Another RCT compared acupuncture with venlafaxine and reported no significant intergroup difference. A further RCT compared acupuncture with applied relaxation and failed to show a significant intergroup difference. Lee et al. concluded that acupuncture is not an effective treatment for hot flashes in patients with breast cancer. Further research is required to determine whether acupuncture is suitable for treating hot flashes in patients with breast cancer.


In contrast to this, in a recent trial 94 women were randomized into three study arms: 31 had acupuncture, 29 had sham acupuncture and 34 had no treatment. In the acupuncture group, 16 patients (52%) experienced a significant effect on hot flashes compared with seven patients (24%) in the sham group (p < 0.05). The effect came after the second acupuncture session and lasted for at least 12 weeks after last treatment. A statistically significant positive effect was seen on sleep in the acupuncture group compared with the sham-acupuncture and no-treatment groups. The effect was not correlated with increased levels of plasma estradiol. No side effects of acupuncture were registered.

In this study acupuncture significantly relieves hot flashes and sleep disturbances and is a good and safe treatment in women treated for breast cancer. The project is registered at Clinical Trials.gov (no: NCT00425776).


In another trial with breast cancer survivors, acupuncture was compared with venlafaxine. It was demonstrated that acupuncture appears to be equivalent to drug therapy in these patients. It is a safe, effective and durable treatment for vasomotor symptoms secondary to long-term antiestrogen hormone use in patients with breast cancer (Walker et al, 2010).


However, in the trial of Deng et al. acupuncture and sham-acupuncture both reduced hot flash symptoms. After the cross-over, the initial sham-acupuncture group further improved after receiving true acupuncture treatment.

In the trial of Nedstrand et al. acupuncture and relaxation therapy were equally successful in reducing hot flashes. Acupuncture was also as effective as venlafaxin in reducing the symptoms.


Finally, a word of caution: acupuncture should be used by knowledgeable practitioners applying general medically sensed caution. A case report by Tseng et al (2011) sheds light of the potential risks: acupuncture in TCM with needles placed into a cutaneous tumor manifestation resulted in disseminated skin metastases. Notwithstanding the beneficial effects referenced above, even measures like acupuncture have their specific risks and should not be applied uncritically.


Further references:


**Herbal Approaches to Reduce Menopausal Symptoms - (14/16)**

*Further information and references:*

Roberts reviewed and summarised current evidence on the efficacy and safety of herbal medicinal products for the relief of hot flushes in women with previous breast cancer. The majority of studies, regarding the efficacy of herbal treatments for hot flushes, have not been conducted in women with breast cancer and many are of short duration. Increased pharmacovigilance practices for herbal medicines are required with initiatives to stimulate reporting of suspected adverse reactions.


More recently, Ma et al (2011) review a diverse array of estrogenic botanical supplement (EBS) to find out whether the use influences breast cancer survivors' health-related outcomes. The findings were also very diverse and indicated that several specific types of EBS might have important influences on a woman's various aspects of quality of life, but further verification is necessary. Red clover users were less likely to report weight gain, night sweats, and difficulty concentrating (all OR approximately 0.4 and all 95% CIs exclude 1). This is the reason, why we change the AGO recommendation from -- to -.  


**Phytoestrogens**

Soy-derived isoflavonoids are potent phytoestrogens, which can interact with estrogen receptors, and their dose-response relationships with estrogen receptors in vitro are complicated. Since they have the potential to stimulate ER-responsive tumor cells under unpredictable circumstances, they should not be consumed as medical adjuvants. For the same reason the use of red clover, ginseng and dong quai as medical adjuvants should be discouraged. However, the occasional consumption of soy-derived foodstuffs, e.g., tofu or soy milk, as part of a vegetable-based diet is probably harmless.


Flaxseed
Concerning the occurrence of hot flushes, a recent randomized phase III trial failed to demonstrate a significant reduction of hot flushes for postmenopausal patients taking additional 410 g of lignans as compared to placebo (Pruthi et al, 2012). Flower et al very recently performed a systematic review of the current literature and concluded that current evidence suggests that flax may be associated with decreased risk of breast cancer. Flax demonstrates antiproliferative effects in breast tissue of women at risk of breast cancer and may protect against primary breast cancer. Mortality risk may also be reduced among those living with breast cancer.


**Black cohosh (Cimicifuga racemosa)**

= (Phyto-SERM = selective estrogen receptor modulator)


St John's Wort


**Red clover**


**Dong Quai**


In a case-control study conducted in Korea, ginseng intakers had a decreased risk [odds ratio = 0.50, 95% confidence interval (CI) = 0.44-0.58] for cancer compared with nonintakers. However, breast cancer, there was no association with ginseng intake.


Bromelain+Papain+Selen+Lektin bei AI-induzierten Gelenkbeschwerden


A clinical investigation (representing evidence-based medicine level III) of Uhlenbruck et al. (3) was performed to evaluate the benefit of complementary medicine in breast cancer patients undergoing adjuvant hormone therapy (HT). The patients (n=129) were treated according to international guidelines. All patients suffered from arthralgia and mucosal dryness induced by the adjuvant HT. To reduce these side effects, the patients were administered a combination of sodium selenite, proteolytic plant enzymes (bromelaine and papain), and Lens culinaris lectin as a complementary treatment. On the basis of case report formulas (CRFs), the patients’ self assessments of defined side-effects of HT (arthralgia and mucosal dryness) were documented before as well as 4 and 8 weeks after complementary treatment. Results were validated by scoring from 1 (no side-effects/optimal tolerability) to 6 (extreme side-effects/extremely bad tolerability). The severity of side effects of HT was reduced by the complementary treatment with sodium selenite, plant enzymes (bromelaine and papain) and Lens culinaris lectin. The mean score of symptoms declined from 4.2 (before treatment) to 3.2 (after 4 weeks of treatment) to 2.7 (after 8 weeks of treatment) for arthralgia and from 3.2 (before treatment) to 2.9 (after 4 weeks of treatment) to 2.6 (after 8 weeks of treatment) for mucosal dryness, the primary aims of this investigation. The reduction of
side effects of HT was statistically significant (p<0.001 after 4 weeks and p<0.0001 after 8 weeks). This investigation demonstrated the benefits of indication-based complementary treatment in breast cancer patients, e.g., reduction of the side effects of adjuvant HT. A randomized controlled trial is planned to integrate the complementary treatment of sodium selenite combined with proteolytic enzymes.
Complementary Treatment: Cancer Pain reduction (15/16)

Further information and references:

A total of 15 RCTs met the inclusion criteria of this systematic review. All of the included RCTs were associated with a high risk of bias. The majority of acupuncture treatments or combination therapies with analgesics exhibited favourable effects compared with conventional treatments in individual studies. However, a meta-analysis suggested that acupuncture did not generate a better effect than drug therapy (n0886; risk ratio (RR), 1.12; 95% CI 0.98 to 1.28; P00.09). The comparison between acupuncture plus drug therapy and drug therapy alone demonstrated a significant difference in favour of the combination therapy (n0437; RR, 1.36; 95% CI 1.13 to 1.64; P00.003). The results of this systematic review provide no strong evidence for the effectiveness of acupuncture in the management of cancer pain.


Forty percent of individuals with early or intermediate stage cancer and 90% with advanced cancer have moderate to severe pain and up to 70% of patients with cancer pain do not receive adequate pain relief. It has been claimed that acupuncture has a role in management of cancer pain and guidelines exist for treatment of cancer pain with acupuncture. Three RCTs (204 participants) were included in this review.

There is insufficient evidence to judge whether acupuncture is effective in treating cancer pain in adults.


More recently a similar result was extracted from a systematic literature review by Garcia et al (2013). The authors concluded that acupuncture is an appropriate adjunctive treatment for chemotherapy-induced nausea/vomiting. For other symptoms (including pain), efficacy remains undetermined.
Transcutaneous electric nerve stimulation (TENS) for cancer pain in adults

Cancer-related pain is complex and multi-dimensional but the mainstay of cancer pain management has predominately used a biomedical approach. There is a need for non-pharmacological and innovative approaches. Transcutaneous Electric Nerve Stimulation (TENS) may have a role for a significant number of patients but the effectiveness of TENS is currently unknown.

The aim of this systematic review was to determine the effectiveness of TENS for cancer-related pain in adults. Only two RCTs met the eligibility criteria (64 participants). These studies were heterogenous with respect to study population, sample size, study design, methodological quality, mode of TENS, treatment duration, method of administration and outcome measures used. In one RCT, there were no significant differences between TENS and placebo in women with chronic pain secondary to breast cancer treatment. In the other RCT, there were no significant differences between acupuncture-type TENS and sham in palliative care patients; this study was underpowered.

The results of this systematic review are inconclusive due to a lack of suitable RCTs. Large multi-centre RCTs are required to assess the value of TENS in the management of cancer-related pain in adults.

Further references:

**Immunodiagnostic Tests and Immunotherapy (16/16)**

*Further information:*

Recently, the recognition that chronic inflammation in the tumor microenvironment promotes tumor growth and survival during different stages of breast cancer development has led to the development of novel immunotherapies. Several immunotherapeutic strategies have been studied both preclinically and clinically and already have been shown to enhance the efficacy of conventional treatment modalities. Therefore, therapies targeting the immune system may represent a promising next-generation approach for the treatment of breast cancers.

A prospective case series was published by Adams et al (2012) to evaluate the local tumor response rate of breast cancer skin metastases treated with topical imiquimod, applied 5 d/wk for 8 weeks. Ten patients were enrolled. Two patients achieved a partial response. Responders showed histologic tumor regression with evidence of an immune-mediated response, showed by changes in the tumor lymphocytic infiltrate and locally produced cytokines.

**Dendritic cell intradermal vaccination**

In a recent paper from China (Qi et al, 2012) Dendritic cell (DC) vaccines were generated from CD14+ precursors pulsed with autologous tumor lysates. DCs were matured with defined factors that induced surface marker and cytokine production. Individuals were immunized intradermally four times. Overall survival and disease progression rates were compared with those of contemporaneous patients who were not administered DC vaccines. There was no difference in overall survival between the patients with and without DC vaccine. The 3-year progression-free survival was significantly prolonged: 76.9% versus 31.0% (with vs. without DC vaccine, p < 0.05). The authors concluded that their findings strongly suggest that tumor lysate-pulsed DCs provide a standardized and widely applicable source of breast cancer antigens that are very effective in evoking anti-breast cancer immune responses.
Recently, quite a number of preliminary clinical trials have been evaluated and published reporting on immunotherapeutic interventions yielding promising early results. In this context, Montero et al (2012) reported on the addition of NOV-002 (a formulation of disodium glutathione disulfide) to chemotherapy, which has been shown to increase anti-tumor efficacy in animal models and some early phase oncology trials. Concurrent NOV-002 resulted in 38% pCR rate for AC → T chemotherapy higher than previously reported e.g. in the B27 or the Geparduo trials.

This and other early indications of efficacy do not at all allow general recommendation, however they show, that further evaluation in the context of randomised trials should be actively supported.

References: