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>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>1a A ++</th>
<th>1a A +</th>
<th>1a A ++</th>
<th>2b B +/-</th>
<th>2b C ++</th>
<th>3b C +/-</th>
<th>1a A ++</th>
<th>2a B +/-</th>
<th>1a A ++</th>
</tr>
</thead>
</table>

* PMRT: Postmastectomy Radiotherapy

**LoE:** Level of Evidence
**GR:** Grade of Recommendation
**NACT:** Neoadjuvant Chemotherapy
**PMRT:** Postmastectomy Radiotherapy

---

[Oxford / AGO LoE / GR Table]
RT of the Breast after Breast Conserving Surgery (BCS) in Invasive Carcinoma

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>Whole breast irradiation (WBI)</th>
<th>Boost-irradiation (improves local control)</th>
<th>Intraoperative irradiation (IORT/IOERT)</th>
<th>Brachytherapy as sole radiotherapy modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a A ++</td>
<td>Standard fractionation</td>
<td>Absolute benefit depending on patient’s age</td>
<td>As boost-irradiation followed by WBI</td>
<td>Interstitial brachytherapy</td>
</tr>
<tr>
<td>1a A +°</td>
<td>Hypofractionation for WBI (+/- sequential boost)</td>
<td>Dose-effect relationship independent of pts.’ age</td>
<td></td>
<td>Intracavity balloon technique</td>
</tr>
<tr>
<td>1a A ++°</td>
<td>Boost-irradiation in node-negative tumors, endocrine responsive, complete resection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a A +</td>
<td></td>
<td>3a C +/-</td>
<td>2a B +</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Whole breast irradiation (WBI)</td>
<td>Boost-irradiation in node-negative tumors, endocrine responsive, complete resection</td>
<td>Intraoperative irradiation (IORT/IOERT)</td>
<td>Brachytherapy as sole radiotherapy modality</td>
</tr>
<tr>
<td></td>
<td>Standard fractionation</td>
<td>Absolute benefit depending on patient’s age</td>
<td>As boost-irradiation followed by WBI</td>
<td>Interstitial brachytherapy</td>
</tr>
<tr>
<td></td>
<td>Hypofractionation for WBI (+/- sequential boost)</td>
<td>Dose-effect relationship independent of pts.’ age</td>
<td></td>
<td>Intracavity balloon technique</td>
</tr>
<tr>
<td></td>
<td>Boost-irradiation (improves local control)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3a C +/-</td>
<td>2a B +</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Whole breast irradiation (WBI)</td>
<td>Boost-irradiation in node-negative tumors, endocrine responsive, complete resection</td>
<td>Intraoperative irradiation (IORT/IOERT)</td>
<td>Brachytherapy as sole radiotherapy modality</td>
</tr>
<tr>
<td></td>
<td>Standard fractionation</td>
<td>Absolute benefit depending on patient’s age</td>
<td>As boost-irradiation followed by WBI</td>
<td>Interstitial brachytherapy</td>
</tr>
<tr>
<td></td>
<td>Hypofractionation for WBI (+/- sequential boost)</td>
<td>Dose-effect relationship independent of pts.’ age</td>
<td></td>
<td>Intracavity balloon technique</td>
</tr>
<tr>
<td></td>
<td>Boost-irradiation (improves local control)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3a C +/-</td>
<td>2a B +</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Whole breast irradiation (WBI)</td>
<td>Boost-irradiation in node-negative tumors, endocrine responsive, complete resection</td>
<td>Intraoperative irradiation (IORT/IOERT)</td>
<td>Brachytherapy as sole radiotherapy modality</td>
</tr>
<tr>
<td></td>
<td>Standard fractionation</td>
<td>Absolute benefit depending on patient’s age</td>
<td>As boost-irradiation followed by WBI</td>
<td>Interstitial brachytherapy</td>
</tr>
<tr>
<td></td>
<td>Hypofractionation for WBI (+/- sequential boost)</td>
<td>Dose-effect relationship independent of pts.’ age</td>
<td></td>
<td>Intracavity balloon technique</td>
</tr>
<tr>
<td></td>
<td>Boost-irradiation (improves local control)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3a C +/-</td>
<td>2a B +</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Whole breast irradiation (WBI)</td>
<td>Boost-irradiation in node-negative tumors, endocrine responsive, complete resection</td>
<td>Intraoperative irradiation (IORT/IOERT)</td>
<td>Brachytherapy as sole radiotherapy modality</td>
</tr>
<tr>
<td></td>
<td>Standard fractionation</td>
<td>Absolute benefit depending on patient’s age</td>
<td>As boost-irradiation followed by WBI</td>
<td>Interstitial brachytherapy</td>
</tr>
<tr>
<td></td>
<td>Hypofractionation for WBI (+/- sequential boost)</td>
<td>Dose-effect relationship independent of pts.’ age</td>
<td></td>
<td>Intracavity balloon technique</td>
</tr>
<tr>
<td></td>
<td>Boost-irradiation (improves local control)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3a C +/-</td>
<td>2a B +</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Whole breast irradiation (WBI)</td>
<td>Boost-irradiation in node-negative tumors, endocrine responsive, complete resection</td>
<td>Intraoperative irradiation (IORT/IOERT)</td>
<td>Brachytherapy as sole radiotherapy modality</td>
</tr>
<tr>
<td></td>
<td>Standard fractionation</td>
<td>Absolute benefit depending on patient’s age</td>
<td>As boost-irradiation followed by WBI</td>
<td>Interstitial brachytherapy</td>
</tr>
<tr>
<td></td>
<td>Hypofractionation for WBI (+/- sequential boost)</td>
<td>Dose-effect relationship independent of pts.’ age</td>
<td></td>
<td>Intracavity balloon technique</td>
</tr>
<tr>
<td></td>
<td>Boost-irradiation (improves local control)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3a C +/-</td>
<td>2a B +</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Whole breast irradiation (WBI)</td>
<td>Boost-irradiation in node-negative tumors, endocrine responsive, complete resection</td>
<td>Intraoperative irradiation (IORT/IOERT)</td>
<td>Brachytherapy as sole radiotherapy modality</td>
</tr>
<tr>
<td></td>
<td>Standard fractionation</td>
<td>Absolute benefit depending on patient’s age</td>
<td>As boost-irradiation followed by WBI</td>
<td>Interstitial brachytherapy</td>
</tr>
<tr>
<td></td>
<td>Hypofractionation for WBI (+/- sequential boost)</td>
<td>Dose-effect relationship independent of pts.’ age</td>
<td></td>
<td>Intracavity balloon technique</td>
</tr>
<tr>
<td></td>
<td>Boost-irradiation (improves local control)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3a C +/-</td>
<td>2a B +</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Whole breast irradiation (WBI)</td>
<td>Boost-irradiation in node-negative tumors, endocrine responsive, complete resection</td>
<td>Intraoperative irradiation (IORT/IOERT)</td>
<td>Brachytherapy as sole radiotherapy modality</td>
</tr>
<tr>
<td></td>
<td>Standard fractionation</td>
<td>Absolute benefit depending on patient’s age</td>
<td>As boost-irradiation followed by WBI</td>
<td>Interstitial brachytherapy</td>
</tr>
<tr>
<td></td>
<td>Hypofractionation for WBI (+/- sequential boost)</td>
<td>Dose-effect relationship independent of pts.’ age</td>
<td></td>
<td>Intracavity balloon technique</td>
</tr>
<tr>
<td></td>
<td>Boost-irradiation (improves local control)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3a C +/-</td>
<td>2a B +</td>
<td></td>
</tr>
</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**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Grade</th>
<th>Evidence</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<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

*consider risk / benefit relationship of RT  

Oxford / AGO  
LoE / GR

<table>
<thead>
<tr>
<th>Level</th>
<th>LoE</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level III involved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In case of irradiation of axilla</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pN1a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pN2a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(p)N3a-c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After NACT/NAT (if pretreatment nodal status was clinically positive)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*consider risk / benefit relationship of RT  

\(^a\)AMAROS trial
Radiotherapy of Other Locoregional Lymph Node Areas

- **Internal mammary lymph node irradiation**: 1 B +/-
  - 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

- **Trastuzumab** concurrent with radiotherapy
  - Oxford / AGO LoE / GR: 2b B +
- **Tamoxifen** concurrent with radiotherapy
  - Oxford / AGO LoE / GR: 3b C +
- **AI (Letrozol)** concurrent with radiotherapy
  - Oxford / AGO LoE / GR: 2a B +/-
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

Oxford / AGO
LoE / GR

1b A +
**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 ≤1 mm, n = 54; 1.1-2.9 mm, n = 35). Independent risk factors for close margins included multicentricity, pathologic lesion size ≥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 ≤1 mm, 3.6% for margins 1.1-2.9 mm, and 0.7% for margins ≥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 uncertainty

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 \(\geq60\).

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 < or = 3 pN+ nodes was 57.0% and 46.6% (p = 0.0004) with RT (UZ Brussel) and without RT (SEER), respectively. For BCS and < or = 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) (Voordeckeres 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
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 consistently 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


**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 to 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 uncertainty, 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 anticipated 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:


Absrbct 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, Hoogenaard 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.


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*

Immink 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”
D/2013/10.273/38: “should be discussed on a case by case basis in the multidiscipline team meeting (expert opinion)”
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


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
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 6 weeks of 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:
No further information

No references