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Prognostic and Predictive Factors

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Prognostic and Predictive Factors

- **Versions 2002–2015:**
  Costa / Fersis / Friedrichs / Gerber / Göhring / Harbeck /Janni / Liedtke / Loibl / Mundhenke / Nitz / Rody / Schaller / Schmidt / Schmutzler / Schneeweiss / Simon / Solomayer / Thomssen

- **Version 2016:**
  Witzel / Nitz

Definition

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

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

***As mentioned in this context represent markers of BC recurrence**

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“Low absolute risk implies low absolute benefit”

Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Lancet 379: 432-444, 2012

Quality Criteria

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

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Further Information

References

[1]Simon et al, J Natl Cancer Inst 101: 1446-1452, 2009
[2]Febbo et al, J Natl Compr Canc Netw 9 Suppl 5: S1-32, 2011
[3]McShane, Hayes, J Clin Oncol 30: 4223 – 4232, 2012

Elements of Tumor Marker Studies that Constitute Levels of Evidence Determination

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

Simon, Paik, Hayes, J Natl Cancer Inst 101: 1446-1452, 2009

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

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

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Further Information

References

Simon, Paik, Hayes, J Natl Cancer Inst 101: 1446-1452, 2009

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

- **1. Adequate amounts of archived specimen must be available from enough patients from a prospective trial … for analyses to have adequate statistical power and for the patients included in the evaluation to be clearly representative of the patients in the trial.**
- **2. The marker-based test should be analytically and preanalytically validated for use with archived specimens.**
- **3. The plan for marker evaluation should be completely specified in writing before the performance of marker assays on archived specimens and should be focused on evaluation of a single completely defined marker-based test.**
- **4. The results from archived specimens should be validated using specimens from one or more similar, but separate, studies.**

McShane & Hayes, J Clin Oncol 30: 4223-4232, 2012

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Prognostic Factors I in Early Breast Cancer

Factor	LoE_{Ox2001}	GR	AGO
➢ Tumor size	1a	A	++
➢ Nodal status	1a	A	++
➢ Distant metastases	1a	B	++
➢ Histological tumor type (colloid, mucinous, tubular etc.)	2b	B	++
➢ Grade (Elston & Ellis)	2a	B	++
➢ Age	2a	B	++
➢ Peritumoral lymphatic vessel and vascular invasion (L1 V1)	2b	B	+
➢ pCR after NACT* in (HR+/G3, HER2+, TN)	1a	A	++
➢ Obesity (BMI >30 kg/m²)	1b	B	+

* NACT = Neoadjuvant Chemotherapy

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Further Information

References

Reproducibility

- **ER/PR: concordance central vs local is high (97%; Plan B, SABCS 2014)**
- **Grading: concordance central vs local is 68 % (PlanB, JCO 2016)**
- **HER2: frequency of false-positive test results 6 % (ASCO /CAP JCO 2013)**
- **Impact of routine pathologic review in N0 BC: 20% changes : grading 40%, LVI 26%, N 15%, margin 12% (JCO 2012)**
- **pN0 from MIRROR study: pN0 was upstaged in 22%, in central pathology review (Ann Oncol 2012)**
- **Inter- and intraobserver variability in measurement of ki-67 is high (J Nat. Cancer Institute 2011)**

Critical Issues Regarding LoEs for Biomarkers

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

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

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

*** Simon, Paik, Hayes, J Natl Cancer Inst 101: 1446-1452, 2009**

Prognostic Factors II in Early Breast Cancer

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Factor	LoE_{Ox2001}	GR	AGO
➢ ER / PgR	2a	B	+
➢ HER2 (IHC, FISH)	2b	B	+
➢ ER / PgR / HER2/ Ki-67 as surrogate markers for molecular subtypes	2b	B	+
➢ uPA / PAI (Femtelle® ELISA)§ in N0	1a	A	+
➢ Proliferation markers			
➢ Ki-67 before, during or after treatment	2b	B	+

§ Validated clinical data only available for this assay

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Further Information

References

Commercially Available Molecular Tests

	70 gene signature (MammaPrint®) $	21 gene Recurrence score (Oncotype DX®) $	8 gene signature (Endopredict®) $	PAM 50 (Prosigna®) $
Provider	Agendia	Genomic Health	Sividon	NanoString
Type of assay	70-gene assay	21-gene recurrence score	11-gene assay	50-gene assay
Type of tissue	fresh frozen (technical validation for FFPE available)	FFPE	FFPE	FFPE
Technique	Microarrays for RNA	qRT-PCR	q-RT-PCR	Direct hybridization
Central lab	yes	yes	no	no
Indication and population studied	prognostic N-/+, <61 Jahre	prognostic N-/+, ER+ endocrine treated	prognostic (pre-) postmenopausal N-/+, ER+ HER2- endocrine treated	prognostic postmenopausal N-/+, ER+ HER2- endocrine treated
Clinical Validation	yes	yes	yes	yes
Registration	FDA clearance as “In Vitro Diagnostic Multivariate Index Assay (IVDMIA)"	Clinical Laboratory Improvement Amendments (CLIA) + College of American Pathologists (CAP)-accredited ref lab	CE-Mark	CE-Mark FDA 510(k) Clearance

$ Validated clinical data only available for this assay

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Commercially Available Molecular Tests

	70 gene signature (MammaPrint®) $	21 gene Recurrence score (Oncotype DX®) $	8 gene signature (Endopredict®) $	PAM 50 (Prosigna®) $
Prognosis after 5 yrs (late recurrences)	not separately shown	no	yes	yes
Predictive impact (chemotherapy benefit)	poorly validated	yes *	not shown	not shown
Prospective-retrospective evidence (% of recruited patients)	Multicenter validation	NSABP B-14 **(14%)** NSABP B-20 **(28%)** ECOG 9127 SWOG 8814 **(40%)** ATAC **(30%)**	ABCSG 6 **(19%)** ABCSG 8 **(36%)** GEICAM-9906 **(45%)** ATAC **(10%)**	MA.12 **(59%)** MA.5 **(66%)** ABCSG 8 **(44%)** ATAC **(16%)**
Prospective evidence (pending)	MINDACT (completed)	$TAILOR_X$ (N0, low-risk, RS<11) PlanB (N0, high-risk/N+)	-	-

$ Validated clinical data only available for this assay
*** Trial performed bevore HER2 testing, HER2 positive patients may have been included**

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Prognostic Factors III in Early Breast Cancer

Faktor	LoE_{2009}	CTS	AGO
➢ Disseminated tumor cells (DTC, in bone marrow)	I	B	+/-
➢ Circulating tumor cells (CTC, in blood, Cell Search®) $	I	A	+/-
➢ Therapy decisions based on CTC phenotypes	III	C	-
➢ Multigene assays			
➢ (Oncotype DX®) (N0-/+, HR+ HER2-, 5 Jahre)	I	A	+*
➢ (EndoPredict®, Prosigna®) (N-/+, HR+ HER2-)	I	B	+*
➢ 70 gene signature (MammaPrint®), N0-1	II	C	+*
➢ IHC4 (central pathology, published algorithm) #	I	B	+/-

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Further Information

References

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

$ Validated clinical data only available for this assay

Cuzick et al., J Clin Oncol 29: 4273-4278, 2011

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Neoadjuvant Systemic Chemotherapy Response Prediction I

Factor	CTS	LoE_{Ox2001}	GR	AGO
➢ Young age	B	1a	A	+
➢ cT1 / cT2 tumors o. N0 o. G3	B	1a	A	++
➢ Negative ER and PgR status	B	1a	A	++
➢ Triple negative breast cancer (TNBC)	B	1a	A	++
➢ Positive HER2 status	B	1a	A	++
➢ Non-lobular tumor type	B	1a	A	+
➢ Early clinical response	B	1b	A	+

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Neoadjuvant Systemic Chemotherapy Response Prediction II

Factor	LoE_{2009}	CTS	GR	AGO
➢ Multigene signature	III	C	B	+/-
➢ (Mammaprint, Endopredict Oncotyp Dx,PAM50 Prosigna[$])				
➢ Ki-67	I	B	A	+
➢ Tumor infiltrating lymphocytes*	I	B	B	+
➢ *PIK3CA* mutation	II	B	B	+/-

[$] **validated clinical data only available for this assay**

**defined as dense lymphocytic infiltration of inner peritumoral stroma outside of the invasion front (lymphocytes make up >50% of stroma area)*

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Further Information

References

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Predictive Factors – Endocrine Therapy

Factor	LoE_{Ox2001}	GR	AGO
➢ **Endocrine therapy**			
➢ **ER/PgR status**	1a	A	++
➢ **IHC staining intensity (ER/PgR)**	1a	A	+
➢ **Tamoxifen**			
➢ **CYP2D6 polymorphism**	2b	D	-
➢ **Ovarian ablation**			
➢ **Menopausal status**	1c	A	++
➢ **Aromatase inhibitors vs. Tamoxifen**			
➢ **Menopausal status**	1c	A	++
➢ **ER/PgR/HER2 as single markers**	1c	A	-
➢ **Lobular subtype**	2b	B	+
➢ **Ki-67 high (published cutoffs > 11 % and >14 %)**	2b	B	+/-
➢ **Obesity (BMI >30 kg/m²)**	2b	B	+/-

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Further Information

References

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Predictive Factors – HER2 Targeted Therapy / Adjuvant Chemotherapy

Factor	LoE_{Ox2001} (§ LoE_{Ox2009})	GR (§ CTS)	AGO
➢ **Anti-HER2-Therapy**			
➢ **HER2**	1a	A	++
➢ **Adjuvant Chemotherapy**			
➢ **uPA/PAI1 (Femtelle®) ELISA $^{$}$**	1a	A	+
➢ **21 gene recurrence score (Oncotype DX®) $^{$}$**	I §	B §	+/-

$^{$}$ **Validated clinical data only available for this assay**

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Further Information

References

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Prognostic Factors – Metastatic Breast Cancer

Factor	LoE_{2009}	CTS	AGO
➢ Circulating tumor cells (CTC in blood, Cell Search®)			
➢ Prognosis at baseline	I	A	+
➢ Early response assessment (3w)	I	B	+
➢ Therapy decision solely based on dynamics of CTC numbers over time or CTC phenotype	I	A	-*

* Study participation recommended

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Further Information

References

Prognostic and Predictive Factors (2/20)

Further information:

Data bases screened: Pubmed 2008 - 2015, ASCO 2003 – 20015, SABCS 2003 – 2015, Cochrane data base (n.d.)

Guidelines screened:
A. Goldhirsch et al. : Personalizing the treatment of women with early breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013 Ann Oncol(2013) 1-18
Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2009: Goldhirsch A et al. Ann Oncol. 2008;20:1319-39.
- Canadian Medical Association (CMA, 2006: http://www.cmaj.ca/cgi/content/full/158/3/DC1)
- NCCN 2008: http://www.medscape.com/files/editorial/articles/548868/breast.pdf
- ASCO 2007: Harris L et al. American Society of Clinical Oncology 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer. J Clin Oncol. 2007 Nov 25 (33): 5287-5312

References:

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2. Graeff, H., Wilmanns, W., Jänicke, F., Sauer, H., Classen, S. (1997) Prognostische und therapierelevante Faktoren beim Mammakarzinom – Ergebnisse einer Konsensuskonferenz. In: Excerpta Oncologica. Prognostische und therapierelevante Faktoren beim Mammakarzinom. Ergebnisse einer Konsensuskonferenz. Classen S, Graeff H, Jänicke F, Sauer H, Wilmanns W (Hrsg.), Novartis Pharma Verlag, Nürnberg, S. 135 - 158.

Definition (3/20)

No further information

No references

Low Absolute Risk Implies Low Absolute Benefit (4/20)

Further information:

Adjuvant chemotherapy reduces breast cancer mortality by one third. However, the benefit is closely related to the absolute risk of this individual patient.
Especially in low risk tumors one has to weigh the benefit against potentially chemotherapy-induced side effects like chronic heart failure and leucemia / MDS/ other secondary cancers. Because of this, proper risk assessment is mandatory.
Adjuvant chemotherapy reduces breast cancer mortality by one third. Because of this, proper risk assessment is mandatory.
In the MINDACT trial for example a group of international experts consented not to propose adjuvant chemotherapy in patients with an estimated distant metastasis free survival of 92% after five years.

References:

1. Peto, R., Davies, C., Godwin, J., Gray, R., Pan, H.C., Clarke, M., Cutter, D., Darby, S., McGale, P., Taylor, C., Wang, Y.C., Bergh, J., Di Leo, A., Albain, K., Swain, S. & Piccart, M. et al. 2012. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet 379, 432–444. doi:10.1016/S0140-6736(11)61625-5.
2. Nielsen T, Jensen B, et al High risk premenopausal luminal A breast cancer patients derive no benefit from adjuvant chemotherapy: results from DBCG77B, SABCS 2015S1-08

Quality Criteria (5/20)

Further information:

Ranking of evidence is of pivotal importance for clinical decision-making. The Oxford Levels of Evidence (LoE_{Ox2001}) and Grades of Recommendations (GR) were originally released in 2001by the Centre of Evidence Based Medicine (www.cebm.net).
These original Oxford LoE and Grades of Recommendation were modified in 2011. The authors simplified the Levels in several ways. For example, levels 1a-c were merged to level 1. The novel classification was also modified to represent the natural flow of a clinical encounter (diagnosis,prognosis, treatment, benefits, harms). These modified Oxford LoE also apply to prognostic factors. In this case, Level 1 can be reached with “systematic review of inception cohort studies”. Based on study quality and effect size, levels LoE can be graded up or down. Finally, the authors of the modified Oxford LoE state, that “levels be interpreted with a healthy dose of common sense and good judgment”.(1)
To improve the quality of research on biomarkers a guideline named REMARK (Reporting Recommendations of Tumor Marker Prognostic Studies) was defined. REMARK describes the informations which should be given when publishing a biomarker study such as study design, preplanned hypotheses, patient and specimen characteristics, assay methods, and statistical analysis methods. (2) Depending on the quality of a biomarker study, the Tumor Marker Utility Grading System was introduced assigning different levels of evidence to a certain marker. (3) To obtain the highest level of evidence, a marker had to be tested prospectively in a prospectively randomized clinical study. Recently a refined system for biomarker study design and evaluation that incorporates a revised level of evidence scale for tumor marker studies, including those using archived specimens, was introduced. (4) Although fully prospective randomized clinical trials to evaluate the medical utility of a prognostic or predictive biomarker are still considered the gold standard, such trials are costly, so more efficient indirect "prospective–retrospective" designs using archived specimens might reach level I evidence if validated with consistent results. This recommendation was recently elaborated on and finally resumed by the NCCN Task Force Report for evaluation of the clinical utility of tumor markers in oncology. (5,6)

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

References:

1. Febbo PG, Ladanyi M, Aldape KD, Marzo AM de, Hammond ME et al. (2011) NCCN Task Force report: Evaluating the clinical utility of tumor markers in oncology. J Natl Compr Canc Netw 9 Suppl 5: S1-32; quiz S33.
2. Hayes DF, Bast RC, Desch CE, Fritsche H, Kemeny NE et al. (1996) Tumor marker utility grading system: a framework to evaluate clinical utility of tumor markers. J. Natl. Cancer Inst. 88 (20): 1456–1466.
3. Jeremy Howick, Iain Chalmers, Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, and Hazel Thornton. Explanation of the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence (Background Document). Oxford Centre for Evidence-Based Medicine.
4. McShane LM, Altman DG, Sauerbrei W, Taube SE, Gion M et al. (2005) Reporting recommendations for tumor marker prognostic studies. J. Clin. Oncol. 23 (36): 9067–9072. Available: doi:10.1200/JCO.2004.01.0454.
5. McShane LM, Hayes DF (2012) Publication of tumor marker research results: the necessity for complete and transparent reporting. J. Clin. Oncol. 30 (34): 4223–4232. Available: doi:10.1200/JCO.2012.42.6858.
6. Simon RM, Paik S, Hayes DF (2009) Use of archived specimens in evaluation of prognostic and predictive biomarkers. J. Natl. Cancer Inst. 101 (21): 1446–1452. Available: doi:10.1093/jnci/djp335.

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

No further information

References:

1. *McShane LM, Hayes DF*. Publication of tumor marker research results: the necessity for complete and transparent reporting. J. Clin. Oncol. 2012; 30(34): 4223 – 4232
2. Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. J. Natl. Cancer Inst. 2009; 101(21): 1446 – 1452

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

No further information

References:

1. *McShane LM, Hayes DF*. Publication of tumor marker research results: the necessity for complete and transparent reporting. J. Clin. Oncol. 2012; 30(34): 4223 – 4232
2. Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. J. Natl. Cancer Inst. 2009; 101(21): 1446 – 1452

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

No further information

References:

1. *McShane LM, Hayes DF*. Publication of tumor marker research results: the necessity for complete and transparent reporting. J. Clin. Oncol. 2012; 30(34): 4223 – 4232
2. Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. J. Natl. Cancer Inst. 2009; 101(21): 1446 – 1452

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

No further information

References:

1. ASCO 2007: Harris L et al. American Society of Clinical Oncology 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer. J Clin Oncol. 2007 Nov 25 (33): 5287-5312
2. Canadian Medical Association (CMA, 2006: http://www.cmaj.ca/cgi/content/full/158/3/DC1)
3. Febbo PG, Ladanyi M, Aldape KD, Marzo AM de, Hammond ME et al. (2011) NCCN Task Force report: Evaluating the clinical utility of tumor markers in oncology. J Natl Compr Canc Netw 9 Suppl 5: S1-32; quiz S33.
4. Goldhirsch et al. : Personalizing the treatment of women with early breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013 Ann Oncol(2013) 1-18
5. Goldhirsch, A., Wood, W.C., Coates, A.S., Gelber, R.D., Thürlimann, B. & Senn, H.-J. 2011. Strategies for subtypes--dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann. Oncol. 22, 1736–1747
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7. Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2009: Goldhirsch A et al. Ann Oncol. 2008;20:1319-39.

Statement: Obesity

1. D. S. M. Chan et al. Body mass index and survival in women with breast cancer—systematic literature review and meta-analysis of 82 follow-up studies Ann Oncol. Oct 2014; 25(10): 1901–1914. Published online Apr 27, 2014. doi: 10.1093/annonc/mdu042 PMCID: PMC4176449.

2. Xia X, Chen W, Li J, Chen X, Rui R, Liu C, Sun Y, Liu L, Gong J, Yuan P. Body mass index and risk of breast cancer: a nonlinear dose-response meta-analysis of prospective studies. Sci Rep. 2014 Dec 15;4:7480. doi: 10.1038/srep07480.

Reproducibility (10/20)

Further information:

Conventional pathology and immunohistochemistry is for methodological reasons subject to high inter-observer variability/variable reproducibility. However, comparison of large series in recently conducted trials show high concordance for HR status in central and local pathology, whereas discordances for Ki-67 and grading are clinically meaningful. HER2 discordances in German trials are observed in up to 10% of cases. In the ASCO-CAP guidelines Her2 discordances are reported in up to 6% of cases. In the landmark trials a small number of patients tested HER2negative by IHC derive some benefit from trastuzumab.
For grading a concordance in about 68 % of cases in German trials was seen. MIRROR trialists report upgrading of N0 status by central pathological review in an comparable amount. A high inter- and intraobserver variability in measurement of the proliferation marker ki-67 has been described. Preanalytical and analytical assessment is not standardized. Thus the clinician should be aware of potential problems and pitfalls when decision for adjuvant treatment is taken together with the patient.

References:

1. Dowsett M, Nielsen TO, A'Hern R, Bartlett J, Coombes RC, Cuzick J, Ellis M, Henry NL, Hugh JC, Lively T, McShane L, Paik S, Penault-Llorca F, Prudkin L, Regan M, Salter J, Sotiriou C, Smith IE, Viale G, Zujewski JA, Hayes DF: Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in Breast Cancer working group. *J Natl Cancer Inst* 2011, **103**(22):1656-1664.
2. Hammond, M.E.H., Hayes, D.F., Dowsett, M., Allred, D.C., Hagerty, K.L., Badve, S., Fitzgibbons, P.L., Francis, G., Goldstein, N.S., Hayes, M., Hicks, D.G., Lester, S., Love, R., Mangu, P.B., McShane, L. & Miller, K. et al. 2010. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for

immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J. Clin. Oncol. 28, 2784–2795. doi:10.1200/JCO.2009.25.6529.

3. Sloane, J.P., Amendoeira, I., Apostolikas, N., Bellocq, J.P., Bianchi, S., Boecker, W., Bussolati, G., Coleman, D., Connolly, C.E., Eusebi, V., Miguel, C. de, Dervan, P., Drijkoningen, R., Elston, C.W., Faverly, D. & Gad, A. et al. 1999. Consistency achieved by 23 European pathologists from 12 countries in diagnosing breast disease and reporting prognostic features of carcinomas. European Commission Working Group on Breast Screening Pathology. Virchows Arch. 434, 3–10.
4. Vestjens, J.H.M.J., Pepels, M.J., Boer, M. de, Borm, G.F., van Deurzen, C.H.M., van Diest, P.J., van Dijck, J.A.A.M., Adang, E.M.M., Nortier, J.W.R., Rutgers, E.J.T., Seynaeve, C., Menke-Pluymers, M.B.E., Bult, P. & Tjan-Heijnen, V.C.G. 2012. Relevant impact of central pathology review on nodal classification in individual breast cancer patients. Ann. Oncol. 23, 2561–2566. doi:10.1093/annonc/mds072.
5. Kennecke, H.F., Speers, C.H., Ennis, C.A., Gelmon, K., Olivotto, I.A. & Hayes, M. 2012. Impact of routine pathology review on treatment for node-negative breast cancer. J. Clin. Oncol. 30, 2227–2231. doi:10.1200/JCO.2011.38.9247.
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Critical Issues regarding LoEs for Biomarkers (11/20)

No further information

No references

Prognostic Factors II in Early Breast Cancer (12/20)

Further information:

St Gallen Consensus accepted a cut-off for KI-67 of 20%.
Semiquantitative IHC expression of PR (</> 20%) adds prognostic value with the current IHC based luminal A definition (for cut-off Ki-67 14 %)

References:

ER/PR

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Commercially Available Molecular Tests (13/20) and (14/20)

Further information:

Modern genomic platforms generate highly reproducible information about tumor biology, which has to be integrated during the next years into clinical routine. Since the additive clinical information is highly correlated to the validation sets the commercially available tests have been enumerated separately together with their retrospective-prospective evidence. ASCO- guidelines already integrated uPA/PAI1 and Oncotype DX®.
There is new retrospective evidence from the prospective ATAC trial involving 928 patients from the ATAC trial (> 9000 patients) conducted in postmenopausal women (Trans ATAC). In this cohort EP and EP clin were highly prognostic for distant recurrence in endocrine treated patients with ER+/HER2- disease. EPclin provided more prognostic information than RS, particularly after 5 years follow-up and in node positive patients.
In the GEICAM 9906 trial 555 tumors from 1246 patients randomized to receive two different chemotherapy regimens (FEC with or without paclitaxel) between 1999 and 2002 could be analyzed with Endopredict. There were no survival differences for patients with low or high EP Score or EPClin Score with regard to the chemotherapy arms, but the authors state that no event (recurrence) could be observed in the group of patients with low EpClin Score.
In 2015, the first evidence from prospective randomized trials was available for the low-risk group in the TAILOR-X trial (Oncotype Dx) and for the low-/intermediate and high-risk group in the PlanB trial. In the Tailor-X trial a 5 year distant free relapse rate of 99.3% was reported in patients with a low risk situation defined as recurrence score (RS) between 0 and 10. Results refer to 1226 node-negative patients, who received no chemotherapy.
In Plan B according to the inclusion criteria only node negative high risk and node positive candidates for chemotherapy were eligible. 348 (15.3%) patients with RS 0-11 were classified as low risk and did not receive any chemotherapy. 3 year disease-free survival (DFS) in this group was 98%. In the chemotherapy group 3 year DFS was 98% for the RS 12-25 group and 92% for the patients with RS> 25. Results from other prospective trials are pending.

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Prognostic Factors III in Early Breast Cancer (15/20)

No further information

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

Further information:

This slide is based on the evidence mainly from analyses done by GEPAR- trialists and remains widely unchanged. It helps to define those subgroups of patients who benefit from NACT in terms of downstaging/pCR. Correlations to survival parameter may differ according to individual parameters and are precised in the first slides.
Ki 67 data from GEPARTRIO have been updated by Denkert et al. (Ann Oncol 2013) and confirmed a strong correlation if cut-off values of ≤15 and > 35 are presumed to define low and high risk populations.
For the genomic signatures there are new data from the I-Spy trial confirming the predictive value of PAM50 and Mammaprint for pCR after neoadjuvant chemotherapy and – for the first time – correlation with 3 yr dfs.
The FDA Metaanalysis confirms preexisting data from neo ALLTO, Neosphere and GEPAR-trials demonstrating lower pCR rates in tumors coexpressing HR and HER2 compared to HER2+/HR-.

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

No further information:

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Predictive Factors – Endocrine Therapy (18/20)

Further information:

EBCTCG analysis provides sample evidence that hormone receptor status is predictive for endocrine response, whereas little effect can be attributed to tumor size, nodal status, age and grading. According to the ASCO /CAP guidelines the panel recommended endocrine therapy in patients whose breast tumors show at least 1% ER positive cells. Same is true for PG receptor levels.HER2 overexpressing tumors present primarily with more aggressive biology. HER2 overexpression, quantitative ER and PR expression as single markers do not identify patients with better outcome after AI, when compared to TAM. (Dowsett M)
Cyp2D6 polymorphism detection is not recommended in daily routine as the metaanalysis done by Goertz is not conclusive.
ABCSG12 trialists, who compared AI + Goserelin vs Tam in premenopausal women report a nearly 50% increase in the risk of disease recurrence (HR 1.49) and a three-fold risk of death for overweight patients (BMI > 25) receiving AI+ Gos in comparison to TAM. In postmenopausal women ATAC trialist report a nonsignificantly better relative benefit of AI vs Tam in thin women vs overweight women (BMI > 35).
A retrospective analysis from a representative subgroup of more than 2500 patients from BIG 1-98 demonstrated a strong correlation of AI superiority with invasive lobular histology and luminal B like tumors (ER+/PR+/Ki 67 >14, HER2-). The HR were 0.95 for ductal luminal A, 0.64 for ductal luminal B, 0.49 for lobular luminal A and 0.33 for lobular luminal B.

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Predictive Factors – HER2 Targeted Therapy / Adjuvant Chemotherapy (19/20)

Further information:

HER2 overexpression (IHC, ISH) is highly predictive for anti HER2 therapy. During SABCS 2012 Baselga presented biomarker analyses evaluating patients with higher benefit from addition of pertuzumab from the CLEOPATRA trial. Neither HER2 or HER3 (mRNA), nor EGFR (mRNA) were predictive.
The last EBCTCG metaanalysis involving over 100 000 chemotherapy patients from 123 randomized trials demonstrated proportional risk reduction little affected by age, nodal status, tumor diameter , HR status and grading. The evidence for HER2 overexpression is much less well evaluated. Most data are derived from trials evaluating chemotherapy + endocrine therapy versus endocrine therapy alone in HR+ patients (Viale IBCSG VIII + IX, Albain SWOG 8814 and Paik NSABP B-20). Uniformely the degree with chemotherapy interaction is non significant independently whether evaluated by central DAKO Hercept testing or her2 gene group as part of Oncotype DX.
The prospecitvely randomized chemo N0 trial demonstrated that high levels of upA/PAI-1 are associated to increased CMF chemotherapy benefit. In N0-1/HR+ patients the the same has been demonstrated by retrospective analyses from the prospective trials NSABP – B20 and SWOG 8814 for CAF /Tam vs Tam alone. In N0 patients from B-20 the RR was 0.26, 0.61 and 1.31 for high risk, intermediate risk and low risk patients, with an net chemotherapy benefit of 28 % 10 year distant free survival benefit in the high risk group. In SWOG 8814 evaluating N+ patients the HRs for 5 yr overall survival were 0.56 in the high risk group, 0.84 in the intermediate and 1.18 in the low risk group resulting in a net 10 yrs dfs benefit of 12 % for the high risk group.
Data for Mammaprint (Knauer et al) refer to 541 patients from pooled study series from patiens who received endocrine therapy +/- chemotherapy. In the high risk group the univariate HR was 0.21 ($p < 0.01$) compared to 0. 58 ($p= 0.6$) in the low risk group. For other genomic signatures there are no data. PAM50 has been only evaluated in a neoadjuvant setting as surrogate parameter for pCR and Endopredict data refer to patients treated with endocrine therapy only.

Baseline Ki-67 is as Viale et al demonstrated from retrospective analyses of two IBCSG trials no independent predictor of chemotherapy outcome. Retrospective subgroup analyses of patients from large taxane trials (GEICAM, PACS 01, BCIRG 01,EC-Doc) demonstrate that luminal A like tumors identified by IHC are likely to have small benefit, but these third generation trials do not have endocrine only arms.
HER2 overexpression was highly predictive for anthracyline outcome when compared to CMF. In a subgroup of the patients analysed by Gennari Di Leo published a metaanalysis comparing the impact of Her2 status and TOP2A (FISH). The HR for her2 amplification and non amplification were 0.89 and 0.71 respectively. Those for Topo normal versus Topo altered were 0.88 vs 0.64 respectively. TOP2A coamplification, not HER2 amplification, is the clinically useful predictive marker of an incremental response to anthracycline-based chemotherapy.
Response to taxanes has been evaluated in different third generation trials comparing anthracycline based chemotherapy vs taxane/anthracycline based regimens. Identification of low proliferating tumors by central ki-67 evaluation was predictive for taxane outcome in EC-Doc, BCIRG 001 and PACS 001, but not in the GEICAM trial. Endopredict and Oncotype DX did not predict taxane response in the GEICAM trial and in NSABP B28 respectively.

No references

Prognostic factors – Metastatic breast cancer (20/20)

Further information

The prognostic value of circulating tumor cells (CTC) in primary and metastatic breast cancer is subject of several publications. CTC detection helps to identify patients with increased risk for relapse. A number of trials showed that CTC can be used for treatment monitoring or direct treatment target. Nevertheless the role of CTC in breast cancer is still currently limited and further development in techniques will be pivotal in enhancing the broad applicability of CTCs and advancing the field of personalized breast cancer therapy.

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CTC

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