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Prognostische und prädiktive Faktoren

Prognostische und prädiktive Faktoren

- **Version 2002:**
  Thomssen / Harbeck

- **Versionen 2003–2012:**
  Costa / Friedrichs / Gerber / Göhring / Harbeck / Loibl / Mundhenke / Rody / Schaller / Schmutzler / Schneeweiss / Simon / Solomayer / Thomssen

- **Version 2013:**
  Nitz / Schmidt

Definition

Ein *prognostischer Faktor ist ein Parameter, der zu einem interessierenden Zeitpunkt z.B. bei Erstdiagnose vorliegt und, sofern keine weitere Therapie erfolgt, mit dem krankheitsfreien oder dem Gesamtüberleben d.h. mit dem natürlichen Krankheitsverlauf korreliert.**

Ein *prädiktiver Faktor* ist ein Parameter, der das Ansprechen auf eine bestimmte Therapie definiert.

***Im Sinne dieser Leitlinie gemeint sind Faktoren, die mit Krankheitsrezidiv assoziiert sind.**

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“Low absolute risk implies low absolute benefit”

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

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

Qualitätskriterien

- **Biologisches Modell**
- **Einfache und zuverlässige Bestimmung, Qualitätssicherung des Tests**
- **Prospektive Planung der statistischen Auswertung (primäres Zielkriterium)**
- **Validierung der klinischen Bedeutung nach „Oxford Level of Evidence (LoE_{Ox2001})“-Kriterien und „Grades of Recommendation (GR)“ sowie nach modifizierten LOE Kriterien am archivierten Gewebe (LoE_{2009}) und Kategorie der Tumormarkerstudie (CTS) [1-3]**
- **Klinische Relevanz für Therapieentscheidung**

[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

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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Prognosefaktoren I – Primäres Mammakarzinom

Faktor	LoE_{2009}	CTS	LoE_{Ox2001}	GR	AGO
➢Tumorgröße	II	B	1a	A	++
➢Lymphknotenstatus	I	B	1a	A	++
➢Vorliegen von Fernmetastasen	II	B	1a	B	++
➢Histologischer Typ (kolloid, muzinös, tubulär etc.)	II	B	2b	B	++
➢Grading (Elston&Ellis)	II	B	2a	B	++
➢Alter	II	B	2a	B	++
➢Einbruch in Lymph- und/oder Blutgefäße	II	B	2b	B	+
➢pCR nach NACT* bei (HR+/G3, HER2+, TN)	I	B	1a	A	++
➢BMI	II	B	1b	B	+

* NACT = Neoadjuvante Chemotherapie

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Reproducibility

- **ER/PR discordance central vs local ≈20% (ASCO/CAP JCO 2010)**
- **HER2 inaccurate testing supected in approximately 20 % (ASCO /CAP JCO 2007)**
- **Impact of routine pathologic review in N0 BC: 20% changes : grading 40%, LVI 26%, N 15%, margin 12% (JCO 2012)**
- **pN0 from MIRROR study: pN0 was upstaged in 22%, pN1mi: 11% upstaged, 15% downstaged in central pathology review (Ann Oncol 2012)**
- **Consistency: 107 cases examined by 23 pathologists in 4 rounds: Grading: Kappa 0,53; LVI Kappa 0,38 (ECWGBSP, 1999) (Virchows Arch 1999)**

Prognosefaktoren II – Primäres Mammakarzinom

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Faktor	LoE_{2009}	CTS	LoE_{Ox2001}	GR	AGO
➢ ER / PgR	II	B	2a	B	+
➢ HER2 (IHC, FISH)	II	B	2b	B	+
➢ ER/PgR/HER2 als Surrogat für molekulare Subtypen	I	B	2b	B	+
➢ uPA / PAI-1 (ELISA) bei N0	I	A	1a	A	+
➢ Proliferationsmarker					
➢ Ki-67 vor oder während oder nach Therapie	II	B	2b	B	+
➢ Mitotic activity Index (MAI)	I	A	1a	A	+

Commercially Available Molecular Tests

	Mammaprint®	Oncotype DX®	Endopredict®	PAM 50
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	FFPE	FFPE	FFPE
Technique	DNA microarrays	qRT-PCR	q-RT-PCR	qRT-PCR
Central lab	yes	yes	no	yes
Indication and population studied	Prognostic N_{0-1}	Prognostic N_{0-1} ER+	Prognostic postmenopausal N_{0-1} ER+ HER2-	Prognostic Subtype classifier N_{0-1}
Analytical validation	no	yes	yes	no
Clinical Validation	yes	yes	yes	yes
Clinical Utility	no	yes	yes	No
Prospective-retrospective evidence		NSABP B-14 NSABP B-20 ECOG 9127 SWOG 8814 ATAC	ABCSG 6 ABCSG 8	MA.12 MA.5
Prospective evidence (pending)	MINDACT	$TAILOR_X$ RxPONDER		

Prognosefaktoren III – Primäres Mammakarzinom

Faktor	LoE_{2009}	CTS	LoE_{Ox2001}	GR	AGO
➢Tumorzell-Nachweis im Knochenmark	I	B	1a	B	+/-
➢Zirkulierende Tumorzellen	I	B	1b	B	+/-
➢Validierte Genexpressionstests bei HR+ (Oncotype DX®, EndoPredict®)	I	B	2b	B	+/-
➢Mammaprint® bei N0-1	II	C	2b	B	+/-
➢Computergestützte Entscheidungshilfen (Adjuvant!®)	II	C	2b	B	+/-
➢Mammostrat	I	B	2b	B	+/-
➢PAM50	II	B	2b	B	+/-
➢IHC4	I	B	2b	B	+/-

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Neoadjuvante systemische Chemotherapie
Prädiktion des Ansprechens

Faktor	LoE_{2009}	CTS	LoE_{Ox2001}	GR	AGO
➢Alter < 35 Jahre	I	B	1a	A	++
➢cT1 / cT2 Tumoren o. N0 o. G3	I	B	1a	A	++
➢Negativer ER und PgR Status	I	B	1a	A	++
➢Triple negative breast cancer (TNBC)	I	B	1a	A	++
➢Positiver HER2-Status	I	B	1a	A	++
➢Nicht-lobulärer Tumortyp	I	B	1a	A	+/-
➢PAM50/Mammaprint	III	C	2b	B	+/-
➢Ki-67	I	B	1a	A	+
➢Peritumorale Lymphozyteninfiltration	II	B	2b	B	+
➢Frühes sonogr. Ansprechen	I	B	1b	A	+
➢ER/PR Status bei HER2 positiv (CHT+ T/L/P)	I	B	1b	A	+

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Prädiktive Faktoren – Endokrine Therapie

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Faktor	LoE_{2009}	CTS	LoE_{Ox2001}	GR	AGO
➢ Endokrine Therapie					
➢ ER/PgR Status	I	B	1a	A	++
➢ IHC Anfärbeintensität (ER/PgR)	I	B	1a	A	+
➢ Tamoxifen					
➢ CYP2D6 Polymorphismus	II	B	2b	D	-
➢ Ovarsuppression					
➢ Menopausenstatus	I	B	1c	A	++
➢ Aromataseinhibitoren vs. Tamoxifen					
➢ Menopausenstatus	I	B	1c	A	++
➢ ER/PgR/HER2 als Einzelmarker	I	B	1c	A	-
➢ Lobulärer Tumortyp	II	B	2b	B	+/-
➢ Ki-67 > 14 %	II	B	2b	B	+/-
➢ BMI	II	B	2b	B	+/-

Prädiktive Faktoren – HER2 gezielte Therapie / Adjuvante Chemotherapie

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Faktor	LoE_{2009}	CTS	LoE_{Ox2001}	GR	AGO
➢ **Anti-HER2 Therapie**					
➢ **HER2**	I	B	1a	A	++
➢ **Adjuvante Chemotherapie**					
➢ **uPA/PAI-1**	I	B	1a	A	+
➢ **Oncotype DX®**	I	B	2b	B	+/-