Untersuchungen zur Therapieentscheidung bei Brustkrebs

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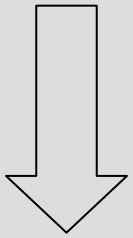
Morphologie und Stadieneinteilung

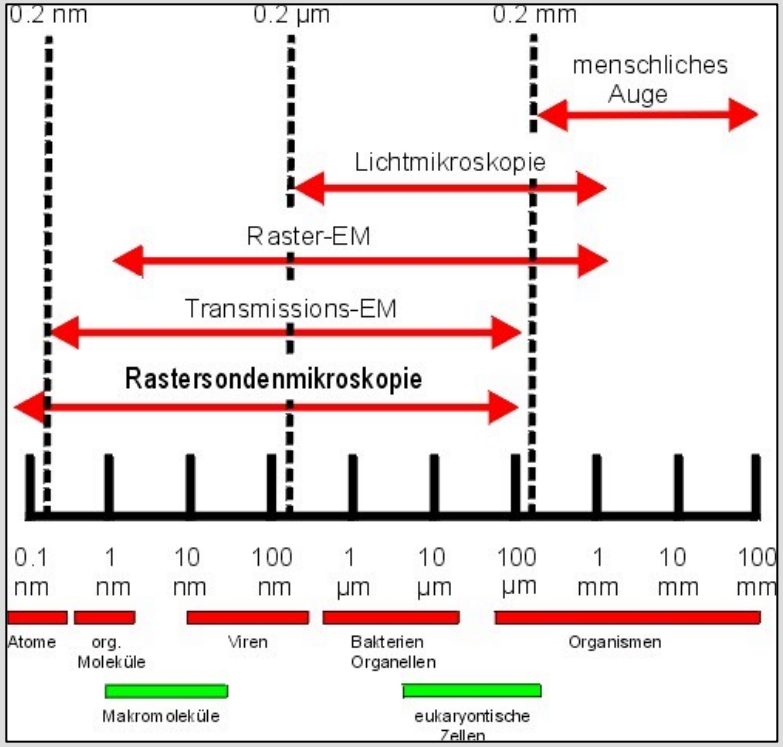
Molekulare Biomarker

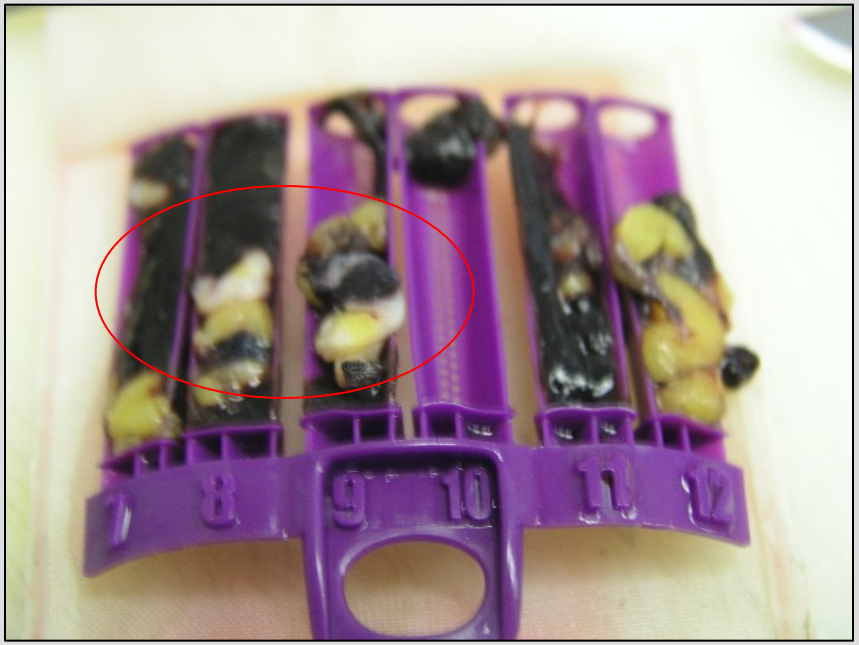
Proteasen



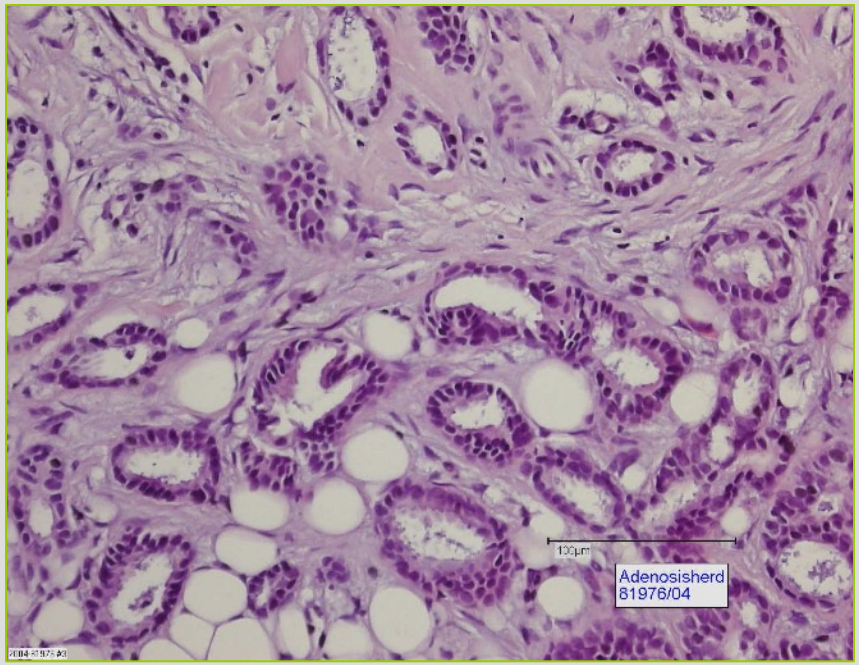
Therapieentscheidung

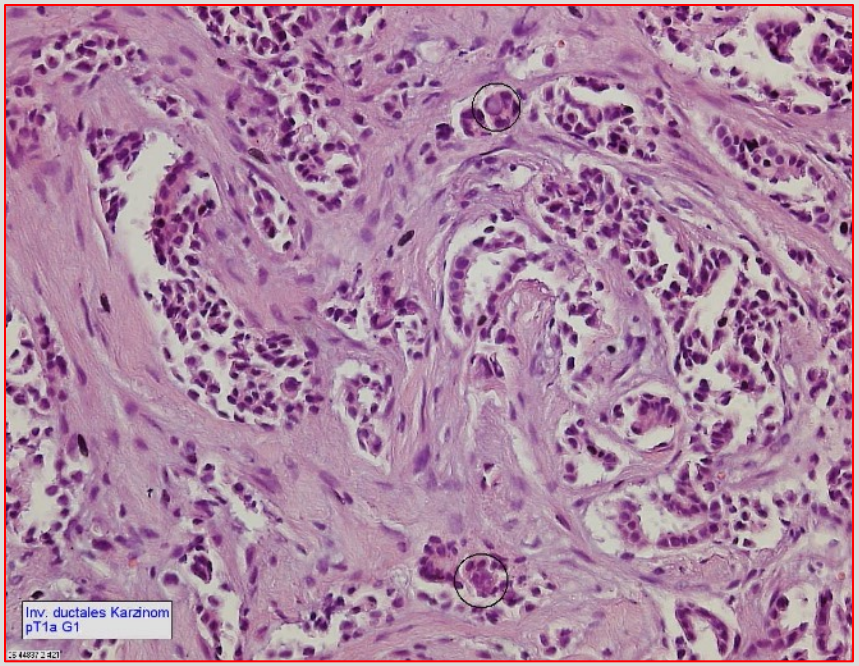
Morphologie





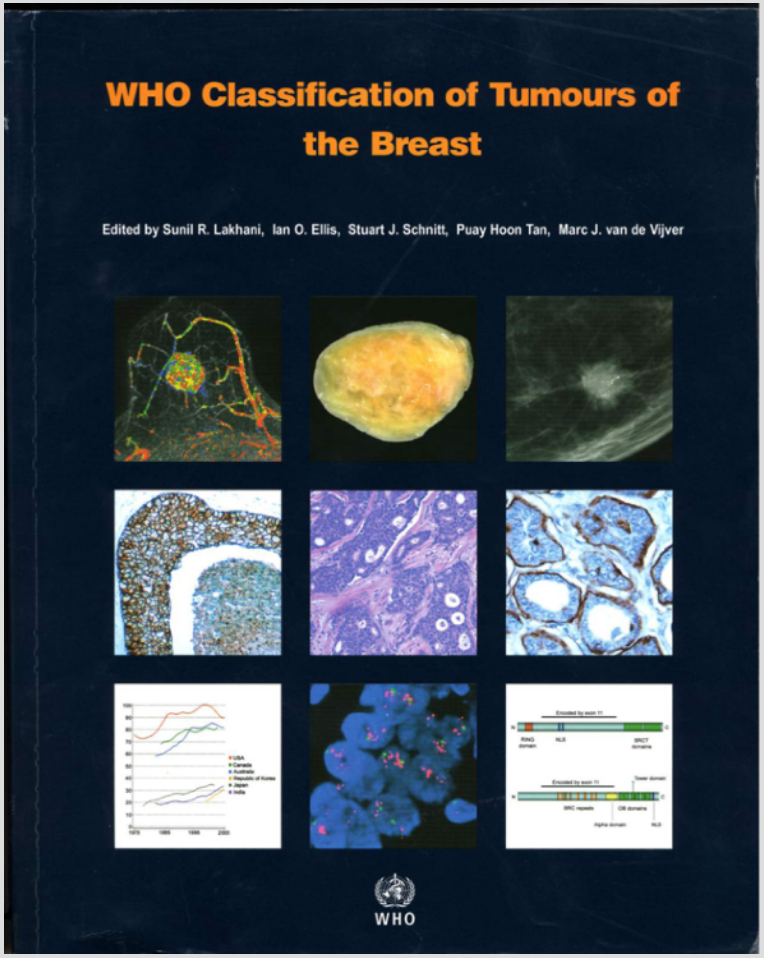
Histologie





WHO

Die neue Serie der Weltgesundheitsorganisation (WHO) standardisiert die **Klassifikation von Tumoren** nach deren histologischen Typ.



4. Edition, 2012

WHO - Klassifikation

WHO classification of tumours of the breast

EPITHELIAL TUMOURS

Microinvasive carcinoma

Invasive breast carcinoma

Invasive carcinoma of no special type (NST)	8500/3
Pleomorphic carcinoma	8022/3
Carcinoma with osteoclast-like stromal giant cells	8035/3
Carcinoma with choriocarcinomatous features	
Carcinoma with melanotic features	
Invasive lobular carcinoma	8520/3
Classic lobular carcinoma	
Solid lobular carcinoma	
Alveolar lobular carcinoma	
Pleomorphic lobular carcinoma	
Tubulolobular carcinoma	
Mixed lobular carcinoma	
Tubular carcinoma	8211/3
Cribriform carcinoma	8201/3
Mucinous carcinoma	8480/3
Carcinoma with medullary features	
Medullary carcinoma	8510/3
Atypical medullary carcinoma	8513/3
Invasive carcinoma NST with medullary features	8500/3
Carcinoma with apocrine differentiation	
Carcinoma with signet-ring-cell differentiation	
Invasive micropapillary carcinoma	8507/3*
Metaplastic carcinoma of no special type	8575/3
Low-grade adenosquamous carcinoma	8570/3
Fibromatosis-like metaplastic carcinoma	8572/3
Squamous cell carcinoma	8070/3
Spindle cell carcinoma	8032/3
Metaplastic carcinoma with mesenchymal differentiation	
Chondroid differentiation	8571/3
Osseous differentiation	8571/3
Other types of mesenchymal differentiation	8575/3
Mixed metaplastic carcinoma	8575/3
Myoepithelial carcinoma	8982/3
Rare types	
Carcinoma with neuroendocrine features	
Neuroendocrine tumour, well-differentiated	8246/3
Neuroendocrine carcinoma, poorly differentiated (small cell carcinoma)	8041/3
Carcinoma with neuroendocrine differentiation	8574/3
Secretory carcinoma	8502/3
Invasive papillary carcinoma	8503/3
Acinic cell carcinoma	8550/3
Mucoepidermoid carcinoma	8430/3
Polymorphous carcinoma	8525/3
Oncocytic carcinoma	8290/3
Lipid-rich carcinoma	8314/3
Glycogen-rich clear cell carcinoma	8315/3
Sebaceous carcinoma	8410/3
Salivary gland/skin adnexal type tumours	
Cylindroma	8200/0
Clear cell hidradenoma	8402/0*

Epithelial–myoepithelial tumours

Pleomorphic adenoma	8940/0
Adenomyoepithelioma	8983/0
Adenomyoepithelioma with carcinoma	8983/3*
Adenoid cystic carcinoma	8200/3

Precursor lesions

Ductal carcinoma in situ	8500/2
Lobular neoplasia	
Lobular carcinoma in situ	
Classic lobular carcinoma in situ	8520/2
Pleomorphic lobular carcinoma in situ	8519/2*
Atypical lobular hyperplasia	

Intraductal proliferative lesions

Usual ductal hyperplasia
Columnar cell lesions including flat epithelial atypia
Atypical ductal hyperplasia

Papillary lesions

Intraductal papilloma	8503/0
Intraductal papilloma with atypical hyperplasia	8503/0
Intraductal papilloma with ductal carcinoma in situ	8503/2*
Intraductal papilloma with lobular carcinoma in situ	8520/2
Intraductal papillary carcinoma	8503/2
Encapsulated papillary carcinoma	8504/2
Encapsulated papillary carcinoma with invasion	8504/3
Solid papillary carcinoma	
In situ	8509/2
Invasive	8509/3

Benign epithelial proliferations

Sclerosing adenosis
Apocrine adenosis
Microglandular adenosis

Radial scar/complex sclerosing lesion	
Adenomas	
Tubular adenoma	8211/0
Lactating adenoma	8204/0
Apocrine adenoma	8401/0
Ductal adenoma	8503/0

MESENCHYMAL TUMOURS

Nodular fasciitis	8828/0*
Myofibroblastoma	8825/0
Desmoid-type fibromatosis	8821/1
Inflammatory myofibroblastic tumour	8825/1
Benign vascular lesions	
Haemangioma	9120/0
Angiomatosis	
Atypical vascular lesions	
Pseudoangiomatous stromal hyperplasia	
Granular cell tumour	9580/0
Benign peripheral nerve-sheath tumours	
Neurofibroma	9540/0
Schwannoma	9560/0
Lipoma	8850/0
Angiolipoma	8861/0
Liposarcoma	8850/3
Angiosarcoma	9120/3
Rhabdomyosarcoma	8900/3
Osteosarcoma	9180/3
Leiomyoma	8890/0
Leiomyosarcoma	8890/3

FIBROEPITHELIAL TUMOURS

Fibroadenoma	9010/0
Phyllodes tumour	9020/1
Benign	9020/0
Borderline	9020/1
Malignant	9020/3
Periductal stromal tumour, low grade	9020/3
Hamartoma	

TUMOURS OF THE NIPPLE

Nipple adenoma	8506/0
Syringomatous tumour	8407/0
Paget disease of the nipple	8540/3

MALIGNANT LYMPHOMA

Diffuse large B-cell lymphoma	9680/3
Burkitt lymphoma	9687/3
T-cell lymphoma	
Anaplastic large cell lymphoma, ALK-negative	9702/3
Extranodal marginal-zone B-cell lymphoma of MALT type	9699/3
Follicular lymphoma	9690/3

METASTATIC TUMOURS

TUMOURS OF THE MALE BREAST

Gynaecomastia	
Carcinoma	
Invasive carcinoma	8500/3
In situ carcinoma	8500/2

CLINICAL PATTERNS

Inflammatory carcinoma	8530/3
Bilateral breast carcinoma	

[a] The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) [463B]. Behaviour is coded /0 for benign tumours, /1 for unspecified, borderline or uncertain behaviour, /2 for carcinoma in situ and grade III intraepithelial neoplasia, and /3 for malignant tumours; [b] The classification is modified from the previous WHO histological classification of tumours [1413] taking into account changes in our understanding of these lesions. In the case of neuroendocrine neoplasms, the classification has been simplified to be of more practical utility in morphological classification; * These new codes were approved by the IARC/WHO Committee for ICD-O.

Tumor - Grading

Die histologische Graduierung invasiver Brustkarzinome wird routinemäßig angewandt nach der Bloom & Richardson - Methode und modifiziert nach **Elston & Ellis**.

Feature	Score
Tubule and gland formation	
Majority of tumour (> 75%)	1
Moderate degree (10–75%)	2
Little or none (< 10%)	3
Nuclear pleomorphism	
Small, regular uniform cells	1
Moderate increase in size and variability	2
Marked variation	3
Mitotic counts	
Dependent on microscope field area	1–3 (see Table 1.04)
Final grading	
Add scores for gland formation, nuclear pleomorphism and mitotic count:	
Grade 1	Total score, 3–5
Grade 2	Total score, 6 or 7
Grade 3	Total score, 8 or 9

WHO, 2012

Guidelines Breast
Version 2012.1D

Prognosefaktoren I – Primäres Mammakarzinom

Faktor	Oxford / AGO LoE	GR	
Tumorgröße	1a	A	++
Lymphknotenstatus	1a	A	++
Vorliegen von Fernmetastasen	1a	B	++
Histologischer Typ (kolloid, muzinös, tubulär etc.)	2b	B	++
Grading (Tumordifferenzierung) (Elston-Ellis)	2a	B	++
Alter	2a	B	++
Einbruch in Lymph- und/oder Blutgefäße	2b	B	+

International Union Against Cancer

Das TNM-System zur Klassifikation maligner Tumoren wurde 1943-1952 entwickelt und dient der klinischen **Stadieneinteilung** sowie Ihrer statischen Erfassung.

TNM

TNM classification of tumours of the breast

T – Primary tumour

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular carcinoma in situ
Tis (Paget)	Paget disease of the nipple not associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma.

Note: Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted.

T1	Tumour 2 cm or less in greatest dimension
T1mi	Microinvasion 0.1 cm or less in greatest dimension*

Note: *Microinvasion is the extension of cancer cells beyond the basement membrane into the adjacent tissues with no focus more than 0.1 cm in greatest dimension. When there are multiple foci of microinvasion, the size of only the largest focus is used to classify the microinvasion. (Do not use the sum of all individual foci.) The presence of multiple foci of microinvasion should be noted, as it is with multiple larger invasive carcinomas.

T1a	More than 0.1 cm but not more than 0.5 cm in greatest dimension
T1b	More than 0.5 cm but not more than 1 cm in greatest dimension
T1c	More than 1 cm but not more than 2 cm in greatest dimension
T2	Tumour more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumour more than 5 cm in greatest dimension
T4	Tumour of any size with direct extension to chest wall and/or to skin (ulceration or skin nodules)

Note: Invasion of the dermis alone does not qualify as T4. Chest wall includes ribs, intercostal muscles, and serratus anterior muscle but not pectoral muscle.

T4a	Extension to chest wall (does not include pectoralis muscle invasion only)
T4b	Ulceration, ipsilateral satellite skin nodules, or skin oedema (including peau d'orange)
T4c	Both 4a and 4b, above
T4d	Inflammatory carcinoma

Note: Inflammatory carcinoma of the breast is characterized by diffuse, brawny induration of the skin with an erysipeloid edge, usually with no underlying mass. If the skin biopsy is negative and there is no localized measurable primary cancer, the T category is pTX when pathologically staging a clinical inflammatory carcinoma (T4d). Dimpling of the skin, nipple retraction, or other skin changes, except those in T4b and T4d, may occur in T1, T2, or T3 without affecting the classification.

N – Regional lymph nodes

NX	Regional lymph nodes cannot be assessed (e.g. previously removed)
N0	No regional lymph-node metastasis
N1	Metastasis in movable ipsilateral level I, II axillary lymph node(s)
N2	Metastasis in ipsilateral level I, II axillary lymph node(s) that are clinically fixed or matted; or in clinically detected* ipsilateral internal mammary lymph node(s) in the absence of clinically evident axillary lymph-node metastasis
N2a	Metastasis in axillary lymph node(s) fixed to one another (matted) or to other structures
N2b	Metastasis only in clinically detected* internal mammary lymph node(s) and in the absence of clinically detected axillary lymph-node metastasis
N3	Metastasis in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph-node involvement; or in clinically detected* ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph-node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastasis in infraclavicular lymph node(s)
N3b	Metastasis in internal mammary and axillary lymph nodes
N3c	Metastasis in supraclavicular lymph node(s)

Note: * "Clinically detected" is defined as detected by clinical examination or by imaging studies (excluding lymphoscintigraphy) and having characteristics highly suspicious for malignancy or a presumed pathological macrometastasis based on fine-needle aspiration biopsy with cytological examination. Confirmation of clinically detected metastatic disease by fine-needle aspiration without excision biopsy is designated with an (f) suffix, e.g., cN3a(f).

Excisional biopsy of a lymph node or biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, e.g., cN1. Pathological classification (pN) is used for excision or sentinel lymph node biopsy only in conjunction with a pathological T assignment.

M – Distant metastasis

M0	No distant metastasis
M1	Distant metastasis

pN – Regional lymph nodes

The pathological classification requires the resection and examination of at least the low axillary lymph nodes (level I). Such a resection will ordinarily include six or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

pNX	Regional lymph nodes cannot be assessed e.g. previously removed, or not removed for study)
pN0	No regional lymph-node metastasis*

Note: *Isolated cells not more th… H & E stains or … posed to inclu… cross-section. … tive node count … the total numbe…

pN1	Mic… lym… met… not … pN1
pN1	…
pN1	…
pN1	…
pN2	Met… pN2 … at least one that is larger than 2 mm
pN2b	Metastasis in clinically detected* internal mammary lymph node(s), in the absence of axillary lymph-node metastasis
pN3	Metastasis as described below:
pN3a	Metastasis in 10 or more axillary lymph nodes (at least one larger than 2 mm) or metastasis in infraclavicular lymph nodes
pN3b	Metastasis in clinically detected* internal ipsilateral mammary lymph node(s) in the presence of positive axillary lymph node(s); or metastasis in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic or macroscopic metastasis detected by sentinel lymph-node biopsy but not clinically detected
pN3c	Metastasis in ipsilateral supraclavicular lymph …

Stage grouping

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T0, T1	N1mi	M0
Stage IIA	T0, T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0, T1, T2	N2	M0
	T3	N1, N2	M0
Stage IIIB	T4	N0, N1,N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

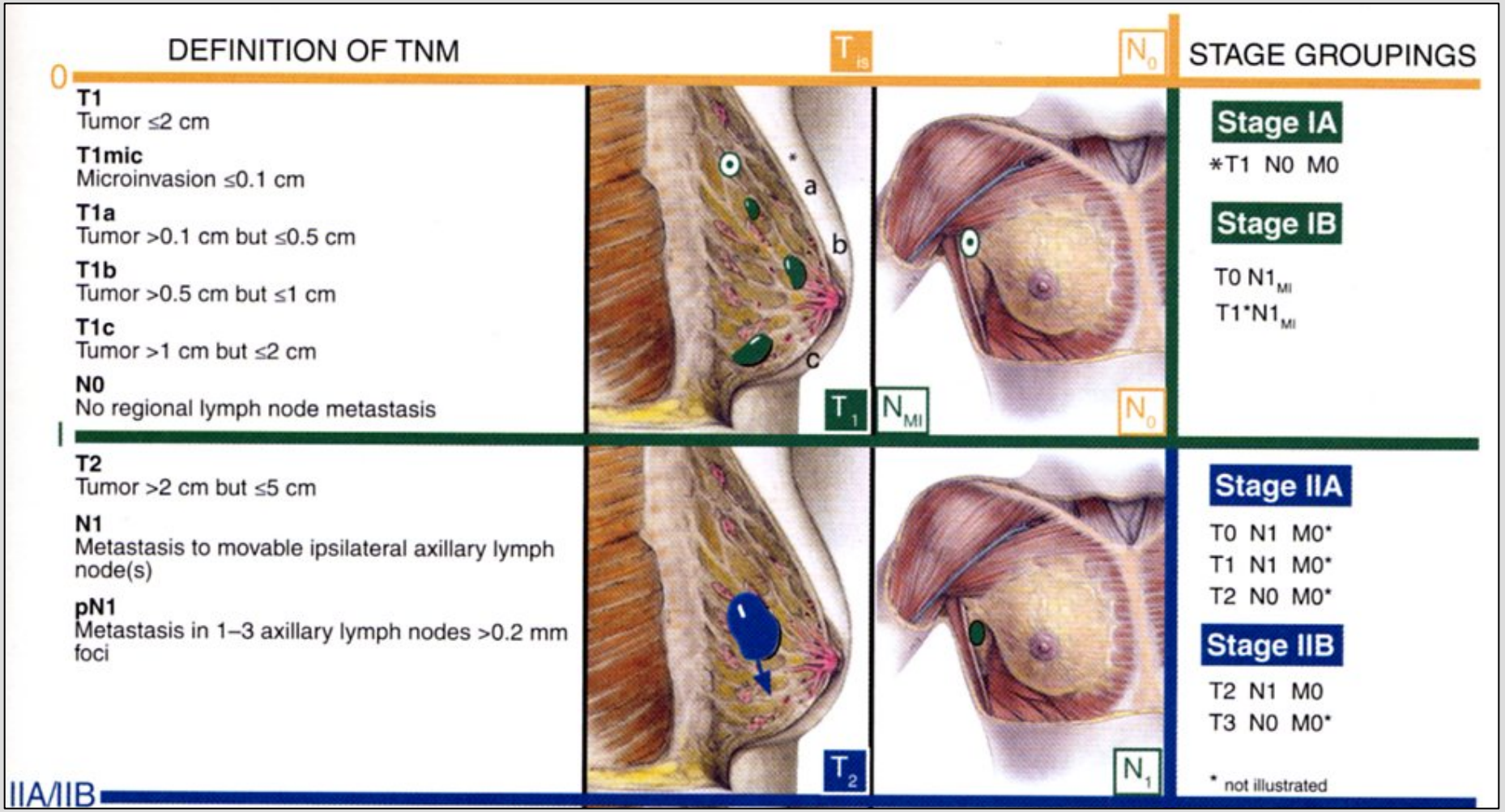
A help-desk for specific questions about the TNM classification is available at http://www.uicc.org.

References

1. American Joint Committee on Cancer (AJCC) Cancer Staging Manual 7th ed. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti III H. eds. New York: Springer. 2009

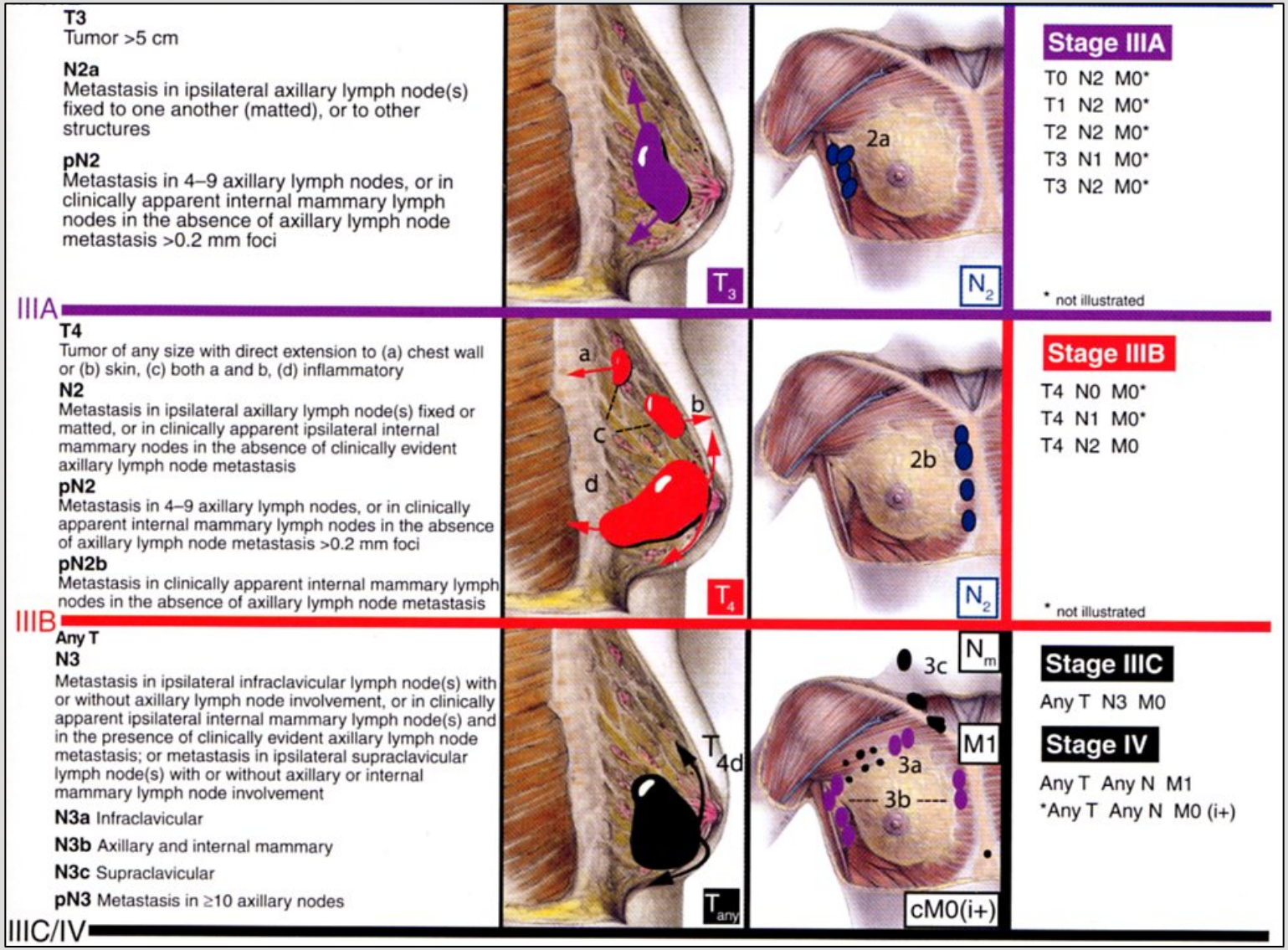
2. International Union against Cancer (UICC): TNM classification of malignant tumors 7th ed. Sobin LH, Gospodarowicz MK, Wittekind Ch. eds. Wiley-Blackwell. Oxford. 2009

Tumorstadium I-II



TNM Staging Atlas, second edition 2012

Tumorstadium III-IV



TNM Staging Atlas, second edition 2012

Operative Therapieentscheidung

Indikation für BET

Günstige Relation von Tumorgröße und Brustvolumen

Keine ausgedehnte Hautinfiltration des Tumors

Keine ausgedehnte Infiltration in den Pectoralismuskel

BET-Wunsch der Patientin

Indikation für Ablatio

Multizentrische Karzinome

Inflammatorisches Karzinom (cutane Lymphangiosis carcinomatosa)

T4 – Karzinome

Ausgedehnte in situ – Tumorkomponente

Tumorentfernung auch mit Nachresektion nicht im Gesunden möglich

Operative Therapieentscheidung

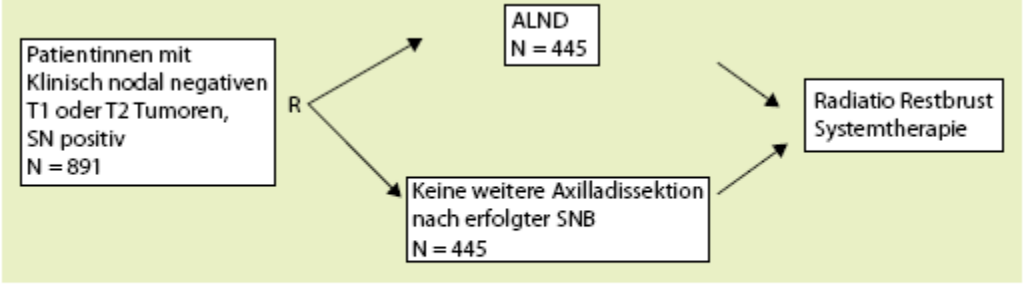


Abb. 1 ▲ Studiendesign der Z0011-Studie (*ALND* axilläre Lymphknotendissektion, *SNB* „Sentinel-Node-Biopsie", *SN* Sentinel-Lymphknoten)

Fazit der ACOSOG Z0011 – Studie

- Kein Vorteil der lokalen und regionalen Rezidivrate
- Kein signifikanter Unterschied des Gesamtüberlebens

Giuliano et al, Ann.Surg. 2010

Guidelines Breast
Version 2012.1D

Prognosefaktoren II – Primäres Mammakarzinom

Faktor	Oxford / AGO LoE / GR		
➢ Östrogen- (ER), Progesteron-Rezeptor (PgR)	2a	B	++
➢ uPA / PAI-1 (ELISA)	1a	A	+
➢ Triple-negativer Tumortyp	2b	B	+
➢ HER2 (IHC, FISH)	2b	B	+/-
➢ Tumorzell-Nachweis im Knochenmark	1a	B	+/-
➢ Zirkulierende Tumorzellen	2b	B	+/-
➢ Marker der Zellteilungsaktivität	2b	B	+/-
➢ Ki-67	1b	B	+
➢ Thymidin-Färbe Index	1b	B	+/-
➢ S-phase Fraktion	2b	B	+/-
➢ Ploidie	2b	B	+/-
➢ Aktuell verfügbare Gen-/Protein-Tests	2b(-)	D	-*#
➢ Computergestützte Entscheidungshilfen (adjuvantonline.com)	2b(-)	D	+
➢ Lebensstil (z.B. regelmäßiger Alkoholkonsum ≥ 6 g/d)	2b[a]	B	+
➢ BMI >25 kg/m²	2b[a]	B	+

*Studienteilnahme empfohlen

#abgesehen der spezifisch erwähnten Indikationen in diesen Empfehlungen

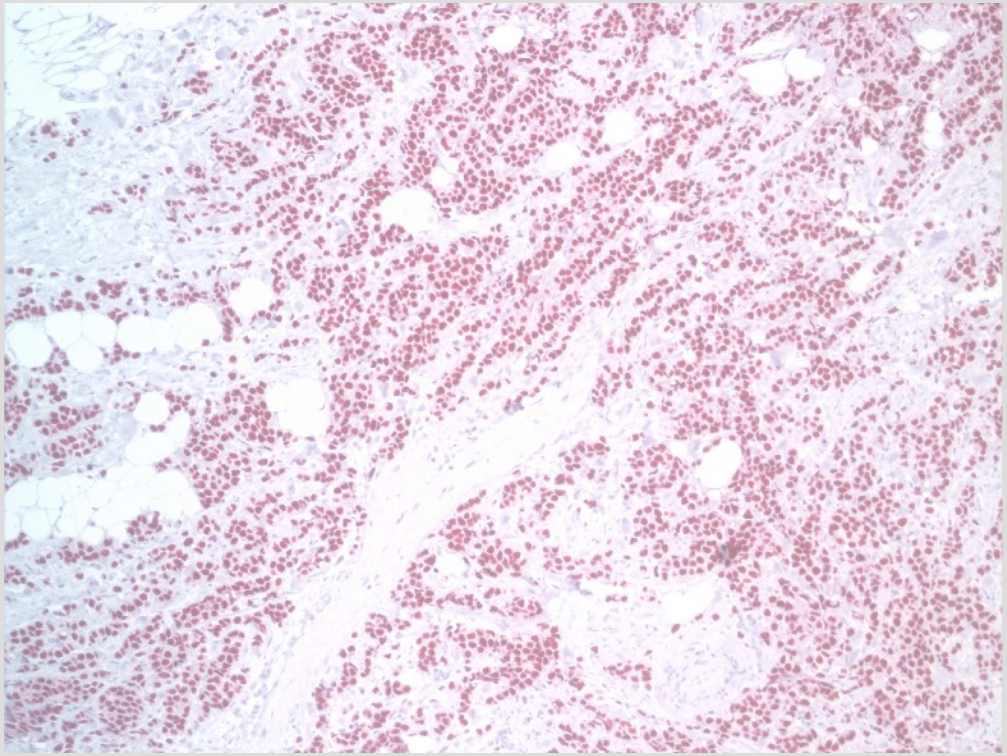
Molekulare Biomarker

In den histopathologischen Routineuntersuchungen werden 3 relevante molekulare Biomarker als **immunhistochemische Reaktionen** eingesetzt:

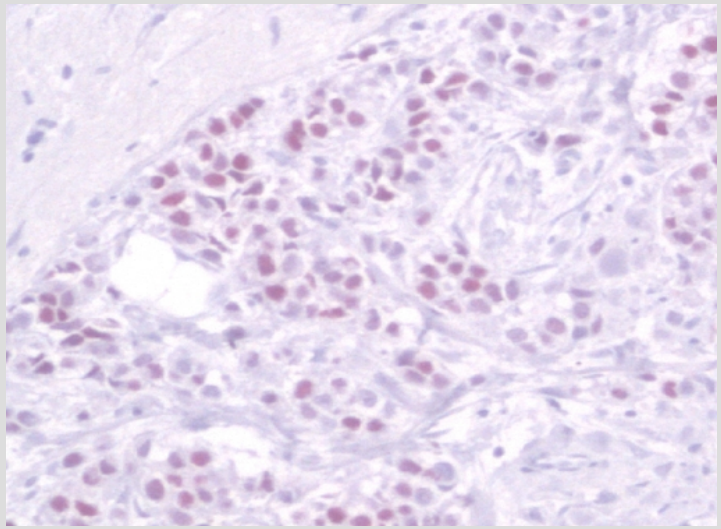
Oestrogenrezeptor (ER),
Progesteronrezeptor (PR) und
Her-2/neu.

Ggf. wird eine **in situ – Hybridisierung** für die Bestimmung einer Her-2/neu – Gen Amplifikation durchgeführt.

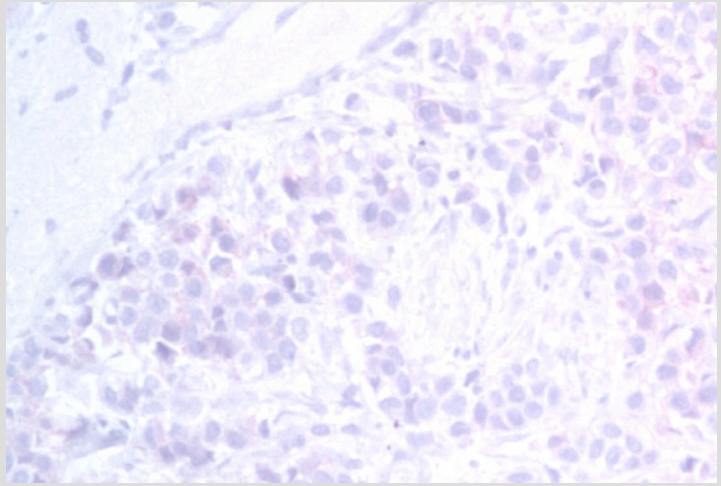
Molekulare Biomarker (IHC)



Oestrogen

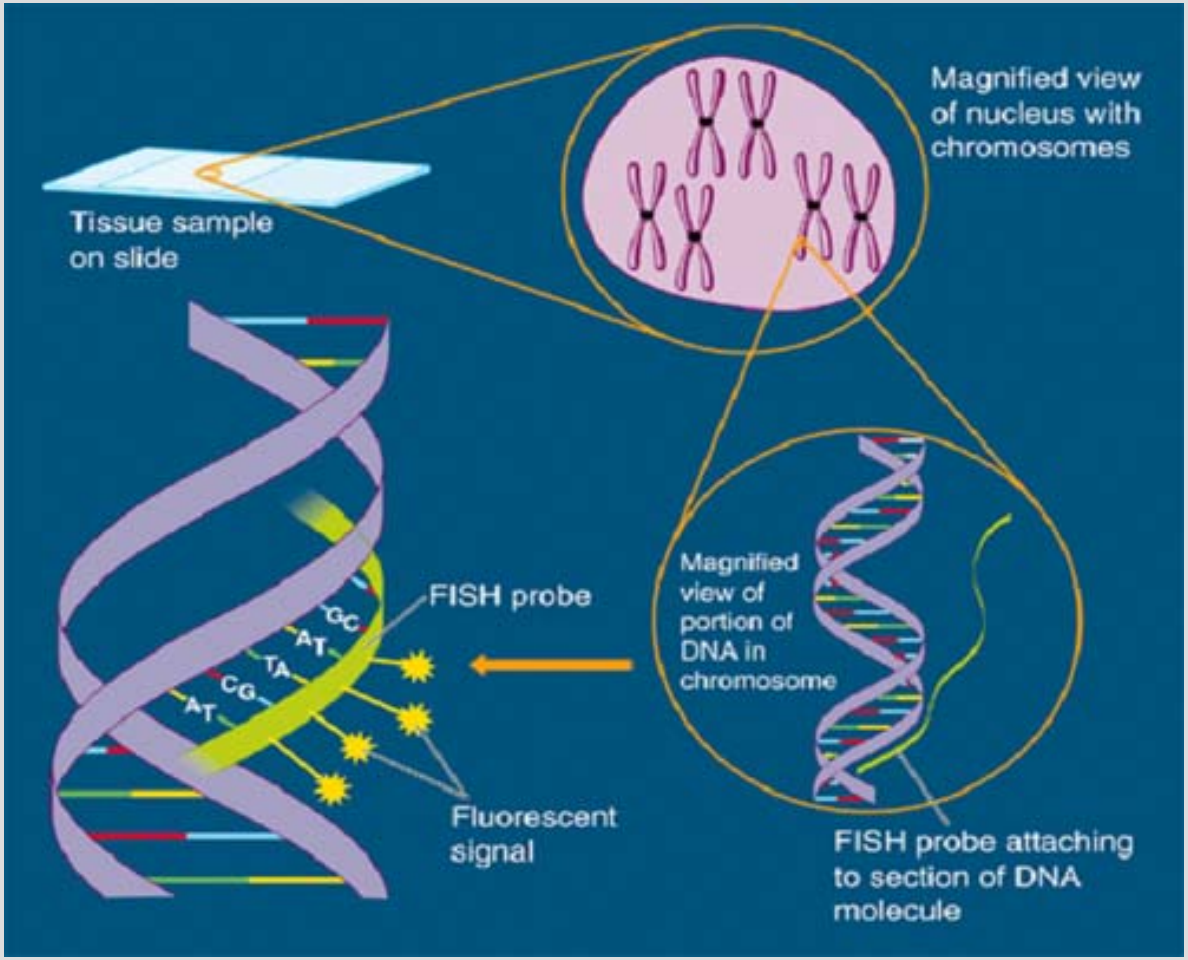


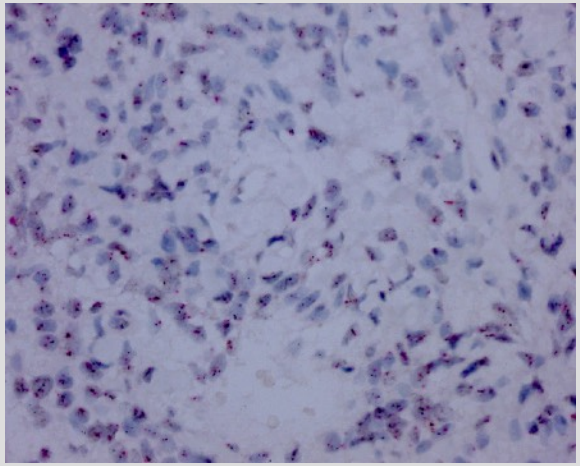
Progesteron



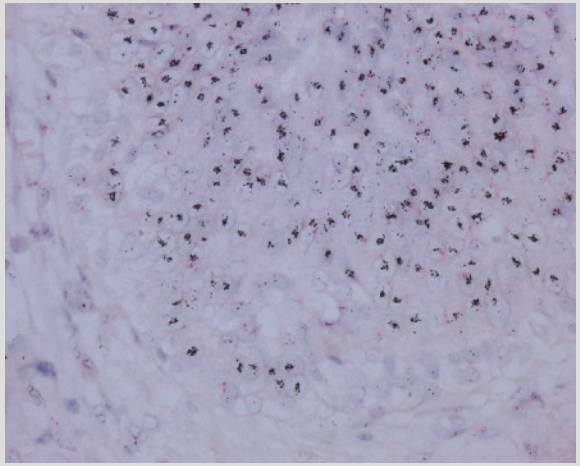
Her-2/neu

Molekulare Biomarker (ISH)



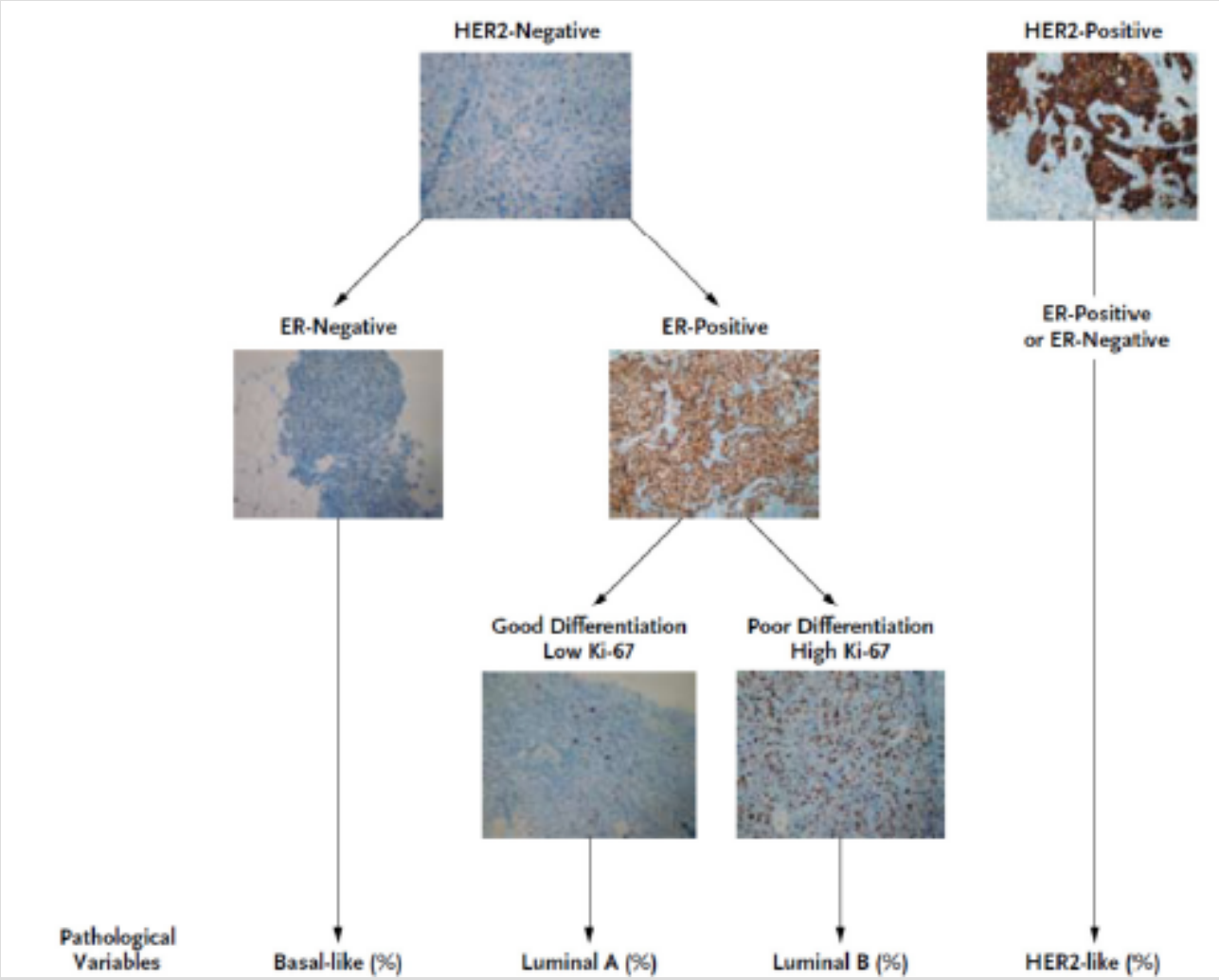


Her-2/neu – Gen nicht amplifiziert



Her-2/neu - Gen amplifiziert

Molekulare Subtypen



N Engl J Med, 2009; 360:790-800

Guidelines Breast
Version 2012.1D

Molecular Tests

	Mammaprint	Oncotype DX	Theros	MapQuant Dx	Endopredict	PAM 50
Provider	Agendia	Genomic Health	Biotheranostics	Ipsogen	Sividon	ARUP
Type of assay	70-gene assay	21-gene recurrence score	2-gene ratio HOXB13 IL7R	Genomic grade	11-gene assay	50-gene
Type of tissue	Fresh frozen	FFPE	FFPE	Fresh frozen	FFPE	FFPE
Technique	DNA microarrays	qRT-PCR	qRT-PCR	DNA microarray	q-RT-PCR	qRT-PCR
Central lab	yes	yes	yes	yes	no	yes
Indication	Prognostic <61stage I-II; N0	Prognostic ER +; tam;	Prognostic ER+ good repsonse to ET	Prognstic G2 low and high risk esp. ER+	Prognostic ER+	Prognostic Subtype classifieer;
LoE	III	II	III	III	II	III
AGO	+/-	+/-	-	-	+/-	-

Oncotype DX® Recurrence Score
berechnet aus 21 verschiedenen Genen

16 KREBS ASSOZIIERTE GENE

Estrogen	Proliferation	HER2	Invasion	Others
ER PR Bcl2 SCUBE2	Ki-67 STK15 Survivin Cyclin B1 MYBL2	GRB7 HER2	Stromelysin 3 Cathepsin L2	CD68 GSTM1 BAG1

5 REFERENZGENE

Beta-actin | GAPDH | RPLPO | GUS | TFRC

Paik et al. *N Engl J Med.* 2004;351:2817-2826.

Genomic Health | oncotype DX Breast Cancer Assay

Genomic Health, Inc.
301 Penobscot Drive
Redwood City, CA 94063 USA
Toll Free Tel 866-ONCOTYPE (866-662-6897)
Worldwide Tel +1 650-569-2080
www.oncotypeDX.com

PATIENT REPORT

Patient/ID: Vester, Petra
Sex: Female
Date of Birth: 05-Jul-1960

Requisition: R0COA8O
Specimen Received: 11-Jan-2013
Date Reported: 22-Jan-2013

QUANTITATIVE SINGLE GENE REPORT

The Oncotype DX assay uses RT-PCR to determine the RNA expression of the genes below. These results may differ from ER, PR, or HER2 results reported using other methods or reported by other laboratories.[1]

The ER, PR, and HER2 Scores are also included in the calculation of the Recurrence Score.

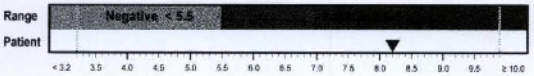
ER Score = 10.1 **Positive**

The ER Score positive/negative cut-off of 6.5 units was validated from a study of 761 samples using the 1D5 antibody (immunohistochemistry) and 607 samples using the SP1 antibody (immunohistochemistry). The standard deviation for the ER Score is less than 0.5 units.[2]

Clinical Experience:

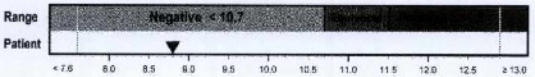
For ER positive breast cancer, the magnitude of tamoxifen benefit increases as the ER Score increases from 6.5 to ≥12.5.[3]
Please note: The Average Rate of Distant Recurrence reported on Page 1 based on the Recurrence Score was determined in patients who received 5 years of tamoxifen treatment and takes into account the magnitude of tamoxifen benefit indicated by the ER Score.

PR Score = 8.2 **Positive**



The PR Score positive/negative cut-off of 5.5 units was validated from a study of 761 samples using the PR636 antibody (immunohistochemistry) and another study of 607 samples using the PR636 antibody (immunohistochemistry). The standard deviation for the PR Score is less than 0.5 units.[2]

HER2 Score = 8.8 **Negative**



The HER2 positive cut-off of ≥ 11.5 units, equivocal range from 10.7 to 11.4 units, and negative cut-off of < 10.7 units were validated from concordance studies of 755 samples using the HercepTest™ assay (immunohistochemistry) and another study of 568 samples using the PathVysion® assay (FISH). The standard deviation for the HER2 score is less than 0.5 units.[4]

References:

1. ER Score based on quantitative ESR1 expression (estrogen receptor); PR Score based on quantitative PGR expression (progesterone receptor); HER2 Score based on quantitative ERBB2 expression.
2. *ASCO Breast Cancer Symposium 2007* Abstracts #87 by S.S. Badve et al., and #88 by F.L. Baehner et al.
3. *ASCO Annual Meeting 2005* Abstract #510 by S. Paik et al.
4. *ASCO Breast Cancer Symposium 2008* Abstracts #13 by F.L. Baehner et al., and #41 by F.L. Baehner et al.

Laboratory Director: Patrick Joseph, MD

CLIA Number 05D1018272

This test was developed and its performance characteristics determined by Genomic Health, Inc. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. These results are adjunctive to the ordering physician's workup.

Online Ordering and Reports Available — Please contact Customer Service at customerservice@genomichealth.com

GHI004 Rev021

Genomic Health | oncotype DX Breast Cancer Assay

Genomic Health, Inc.
301 Penobscot Drive
Redwood City, CA 94063 USA
Toll Free Tel 866-ONCOTYPE (866-662-6897)
Worldwide Tel +1 650-569-2080
www.oncotypeDX.com

PATIENT REPORT

Patient/ID: Vester, Petra
Sex: Female
Date of Birth: 05-Jul-1960
Medical Record/Patient #:
Date of Surgery: 21-Dec-2012
Specimen Type/ID: Breast/53185/12 I6

Requisition: R0COA8O
Specimen Received: 11-Jan-2013
Date Reported: 22-Jan-2013
Client: Henriettenstift - Frauenklinik
Ordering Physician: Dr. Kristina Luebbe
Submitting Pathologist: Dr. Herbert Radner
Additional Recipient: Dr. Sebastian Raeth

BREAST CANCER ASSAY DESCRIPTION

Oncotype DX Breast Cancer Assay uses RT-PCR to determine the expression of a panel of 21 genes in tumor tissue. The Recurrence Score® is calculated from the gene expression results. The Recurrence Score range is from 0-100.

RESULTS

Breast Cancer Recurrence Score = 15

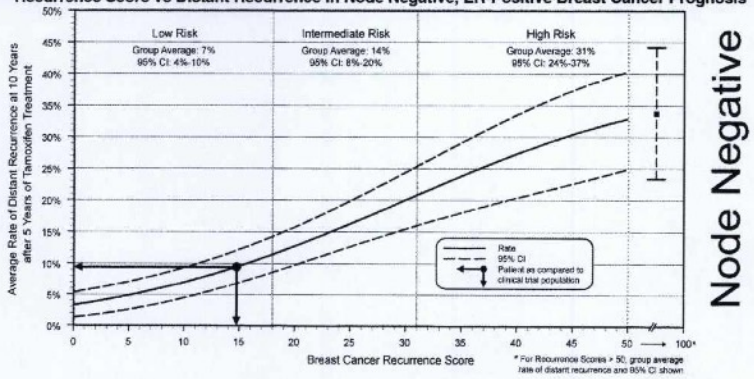
The findings summarized in the Clinical Experience sections of this report are applicable to the patient populations defined in each section. It is unknown whether the findings apply to patients outside these criteria.

CLINICAL EXPERIENCE: PROGNOSIS FOR NODE NEGATIVE, ER-POSITIVE PATIENTS

The Clinical Validation study included female patients with Stage I or II, Node Negative, ER-Positive breast cancer treated with 5 years of tamoxifen. Those patients who had a Recurrence Score of 15 had an Average Rate of Distant Recurrence of **9% (95% CI: 7%-12%)**

The following results are from a clinical validation study of 668 patients from the NSABP B-14 study. *N Engl J Med* 2004; 351: 2817-26.

Recurrence Score vs Distant Recurrence in Node Negative, ER-Positive Breast Cancer Prognosis



Laboratory Director: Patrick Joseph, MD

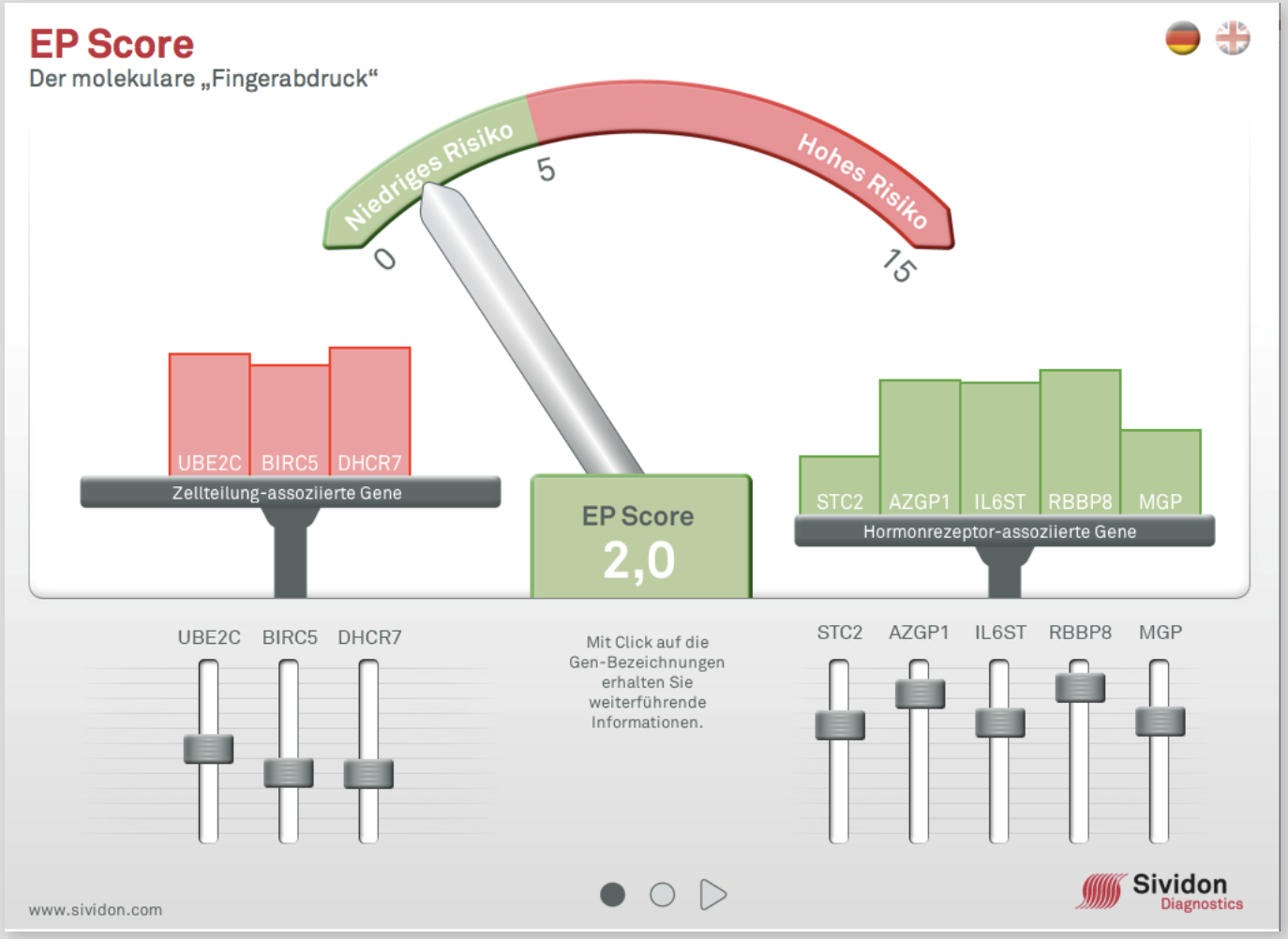
CLIA Number 05D1018272

This test was developed and its performance characteristics determined by Genomic Health, Inc. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. These results are adjunctive to the ordering physician's workup.

Online Ordering and Reports Available — Please contact Customer Service at customerservice@genomichealth.com

GHI004 Rev021

EndoPredict® - EP-Score als molekularer Fingerabdruck



EndoPredict Report

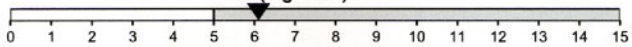
2012-12-17 14:36

Patient ID: 47867-12 Histo-No: H47867/12 Sample: A

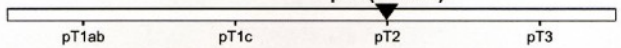
Remarks:

Tumor Properties

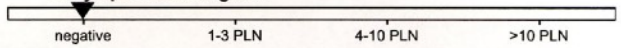
EP Score: **6.1 (high risk)**



Tumor size: **pT2 (>2-5cm)**

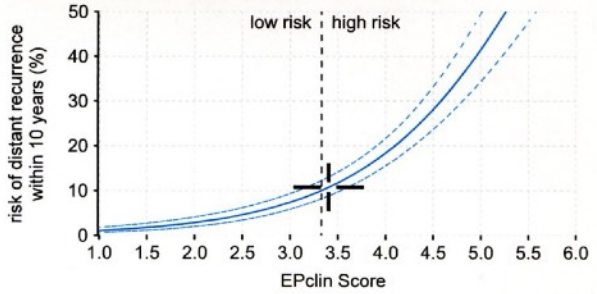


Nodal status: **all lymph nodes negative**



Risk Assessment by EPclin

EPclin combines the EP Score, tumor size, and the number of positive lymph nodes into a score with a superior predictive power.



Test Result

EPclin Score:	EPclin 10y risk:	EPclin Class:
3.4	**11%**	**high risk**

Pathologists Approval

Controls were run as required and test result is valid.

authorized signature

based on: *Filipits et al: A new molecular predictor of distant recurrence in ER-positive, HER2-negative breast cancer adds independent information to conventional clinical risk factors. Clinical Cancer Research, 2011*

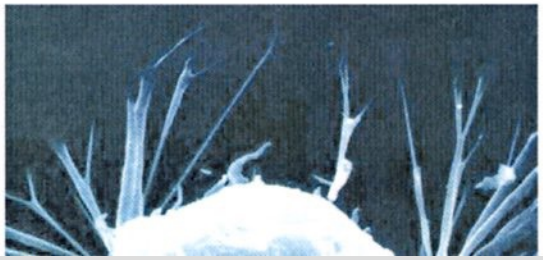
Molekulare Diagnostik

MAMMAKARZINOM-THERAPIE

Der routinemäßige Einsatz von Gentests ist derzeit nicht sinnvoll

Der Markt für Genexpressionsanalysen, die das Ansprechen auf bestimmte Chemotherapien vorhersagen, ist hart umkämpft. Die Kommission Mamma der Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) gibt eine Einordnung.

Eine effektive anthrazyklin- und taxanhaltige Chemotherapie senkt die brustkrebsassoziierte Zehnjahressterblichkeit um etwa ein Drittel – unabhängig von Alter, TN-Stadium und Hormonrezeptorexpression. Der absolute Gewinn für die einzelne Patientin hängt jedoch entscheidend von ihrem



weiterer tumorbiologischer Faktoren durchzuführen.

Von diesen Faktoren hat derzeit die Bestimmung der tumorassoziierten Proteolysefaktoren Urokinase-Plasminogen-Aktivator (uPA)/ Plasminogen-Aktivator-Inhibitor-1 (PAI-1) (2), die bei N0-Patientinnen (HR+/−) evaluiert wurden, den

Ärzteblatt, Okt. 2012

Proteasen

Randomized Adjuvant Chemotherapy Trial in High-Risk, Lymph Node-Negative Breast Cancer Patients Identified by Urokinase-Type Plasminogen Activator and Plasminogen Activator Inhibitor Type 1

Fritz Jänicke, Anita Prechtl, Christoph Thomssen, Nadia Harbeck, Christoph Meisner, Michael Untch, C. G. J. Fred Sweep, Hans-Konrad Selbmann, Henner Graeff, Manfred Schmitt

For the German Chemo N_0 Study Group

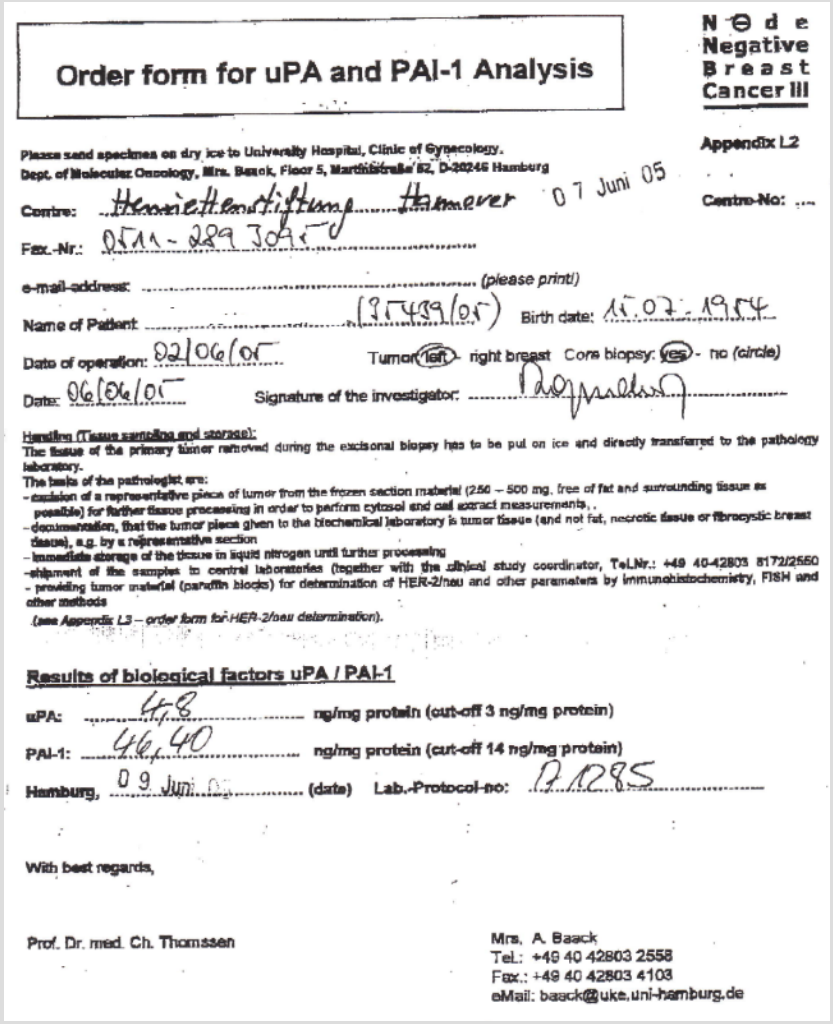
Background: **Most patients with lymph node-negative breast cancer are cured by locoregional treatment; however, about 30% relapse. Because traditional histomorphologic and clinical factors fail to identify the high-risk patients who may benefit from adjuvant chemotherapy, other prognostic factors are needed. In a unicenter study, we have found that levels of urokinase-type plasminogen activator (uPA) and plasminogen activator inhibitor type 1 (PAI-1) in the pri-**

tify the high-risk patients (who will need adjuvant chemotherapy) and the low-risk patients (who can be spared adjuvant chemotherapy) by traditional histomorphologic and clinical characteristics, such as tumor size, histologic grade, age, steroid hormone receptor status, or menopausal status *(3)*. If these characteristics were used to select therapies for patients, as recommended by the 1998 and 2001 St. Gallen consensus statements [*(4);* 7th International Consensus Conference on Adjuvant Therapy of Primary Breast Cancer, St. Gallen, Switzerland, Feb-

(2001)

Mithilfe der Invasionsfaktoren uPA/PAI-1 kann das Rezidivrisiko für Patientinnen mit Nodal-negativem Mammakarzinom besser abgeschätzt werden.

Proteasen



Order form for uPA and PAI-1 Analysis

N⊖de Negative Breast Cancer III

Appendix L2

Please send specimen on dry ice to University Hospital, Clinic of Gynecology.
Dept. of Molecular Oncology, Mrs. Baack, Floor 5, Martinistraße 52, D-20246 Hamburg

Centre: Henriettenstiftung Hannover 07 Juni 05 Centre-No: ...

Fax.-Nr.: 0511 - 289 3095

e-mail-address: ..... (please print!)

Name of Patient: (37459/05) Birth date: 15.07.1954

Date of operation: 02/06/05 Tumor (left) - right breast Core biopsy: (yes) - no (circle)

Date: 06/06/05 Signature of the investigator: .....

Handling (Tissue sampling and storage):
The tissue of the primary tumor removed during the excisional biopsy has to be put on ice and directly transferred to the pathology laboratory.
The tasks of the pathologist are:
- excision of a representative piece of tumor from the frozen section material (250 – 500 mg, free of fat and surrounding tissue as possible) for further tissue processing in order to perform cytosol and cell extract measurements,.
- documentation, that the tumor piece given to the biochemical laboratory is tumor tissue (and not fat, necrotic tissue or fibrocystic breast tissue), e.g. by a representative section
- immediate storage of the tissue in liquid nitrogen until further processing
- shipment of the samples to central laboratories (together with the clinical study coordinator, Tel.Nr.: +49 40-42803 8172/2550
- providing tumor material (paraffin blocks) for determination of HER-2/neu and other parameters by immunohistochemistry, FISH and other methods

(see Appendix L3 – order form for HER-2/neu determination).

Results of biological factors uPA / PAI-1

uPA: 4.8 ng/mg protein (cut-off 3 ng/mg protein)

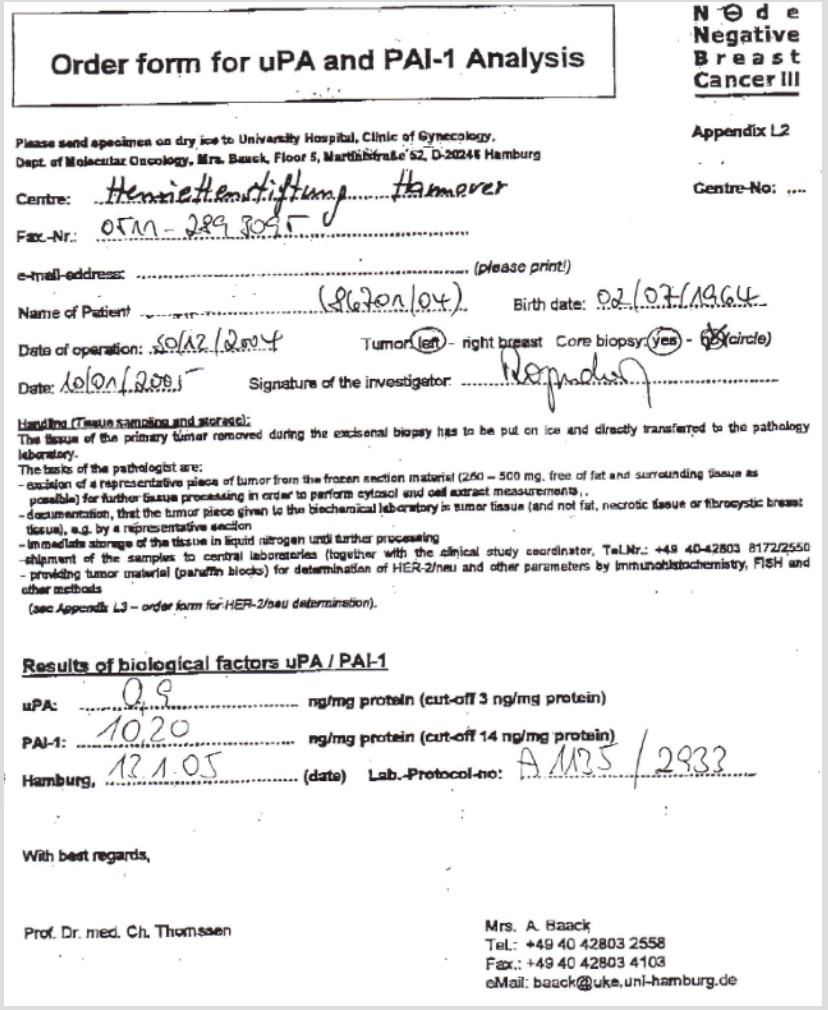
PAI-1: 46,40 ng/mg protein (cut-off 14 ng/mg protein)

Hamburg, 09 Juni 05 (date) Lab.-Protocol-no: A 1285

With best regards,

Prof. Dr. med. Ch. Thomssen

Mrs. A. Baack
Tel.: +49 40 42803 2558
Fax.: +49 40 42803 4103
eMail: baack@uke.uni-hamburg.de



Order form for uPA and PAI-1 Analysis

N⊖de Negative Breast Cancer III

Appendix L2

Please send specimen on dry ice to University Hospital, Clinic of Gynecology.
Dept. of Molecular Oncology, Mrs. Baack, Floor 5, Martinistraße 52, D-20246 Hamburg

Centre: Henriettenstiftung Hannover Centre-No: ...

Fax.-Nr.: 0511 - 289 3095

e-mail-address: ..... (please print!)

Name of Patient: (86201/04) Birth date: 02/07/1964

Date of operation: 20/12/2004 Tumor (left) - right breast Core biopsy: (yes) - no (circle)

Date: 20/01/2005 Signature of the investigator: .....

Handling (Tissue sampling and storage):
The tissue of the primary tumor removed during the excisional biopsy has to be put on ice and directly transferred to the pathology laboratory.
The tasks of the pathologist are:
- excision of a representative piece of tumor from the frozen section material (250 – 500 mg, free of fat and surrounding tissue as possible) for further tissue processing in order to perform cytosol and cell extract measurements,.
- documentation, that the tumor piece given to the biochemical laboratory is tumor tissue (and not fat, necrotic tissue or fibrocystic breast tissue), e.g. by a representative section
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- providing tumor material (paraffin blocks) for determination of HER-2/neu and other parameters by immunohistochemistry, FISH and other methods

(see Appendix L3 – order form for HER-2/neu determination).

Results of biological factors uPA / PAI-1

uPA: 0.9 ng/mg protein (cut-off 3 ng/mg protein)

PAI-1: 10,20 ng/mg protein (cut-off 14 ng/mg protein)

Hamburg, 12.1.05 (date) Lab.-Protocol-no: A 1125 / 2933

With best regards,

Prof. Dr. med. Ch. Thomssen

Mrs. A. Baack
Tel.: +49 40 42803 2558
Fax.: +49 40 42803 4103
eMail: baack@uke.uni-hamburg.de

Systemische Therapieentscheidung

pT2 N0 M0 G2

Stadium IIA

HR pos.
Her-2/neu neg.
Ki-67 < 15%

⇩

endokrine Therapie
Chemotherapie ?

⇩

Oncotype Dx oder
Endopredict
uPA/ PAI-1

HR pos./ neg.
Her-2/neu pos.
Ki-67 < 15%

⇩

Chemotherapie
Herceptin

Systemische Therapieentscheidung

pT1c N1a M0 G2

Stadium IIA

HR pos.
Her-2/neu neg.
Ki-67 < 15%

⇩

endokrine Therapie
Chemotherapie ?

⇩

Oncotype Dx oder
Endopredict

HR pos./ neg.
Her-2/neu pos.
Ki-67 < 15%

⇩

Chemotherapie
Herceptin

Systemische Therapieentscheidung

pT1a N0 M0 G3

Stadium IA

HR neg.
Her-2/neu neg.
Ki-67 >30%

⇩

Chemotherapie

HR pos./ neg.
Her-2/neu pos.
Ki-67 >30%

⇩

Chemotherapie
Herceptin ?

Vielen Dank

Institut für Pathologie Hannover - Zentrum
Berliner Allee 48 in 30175 Hannover
info@hannover-pathologie.de