Pathologie der MAMMA – II.

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Frühlingsemester
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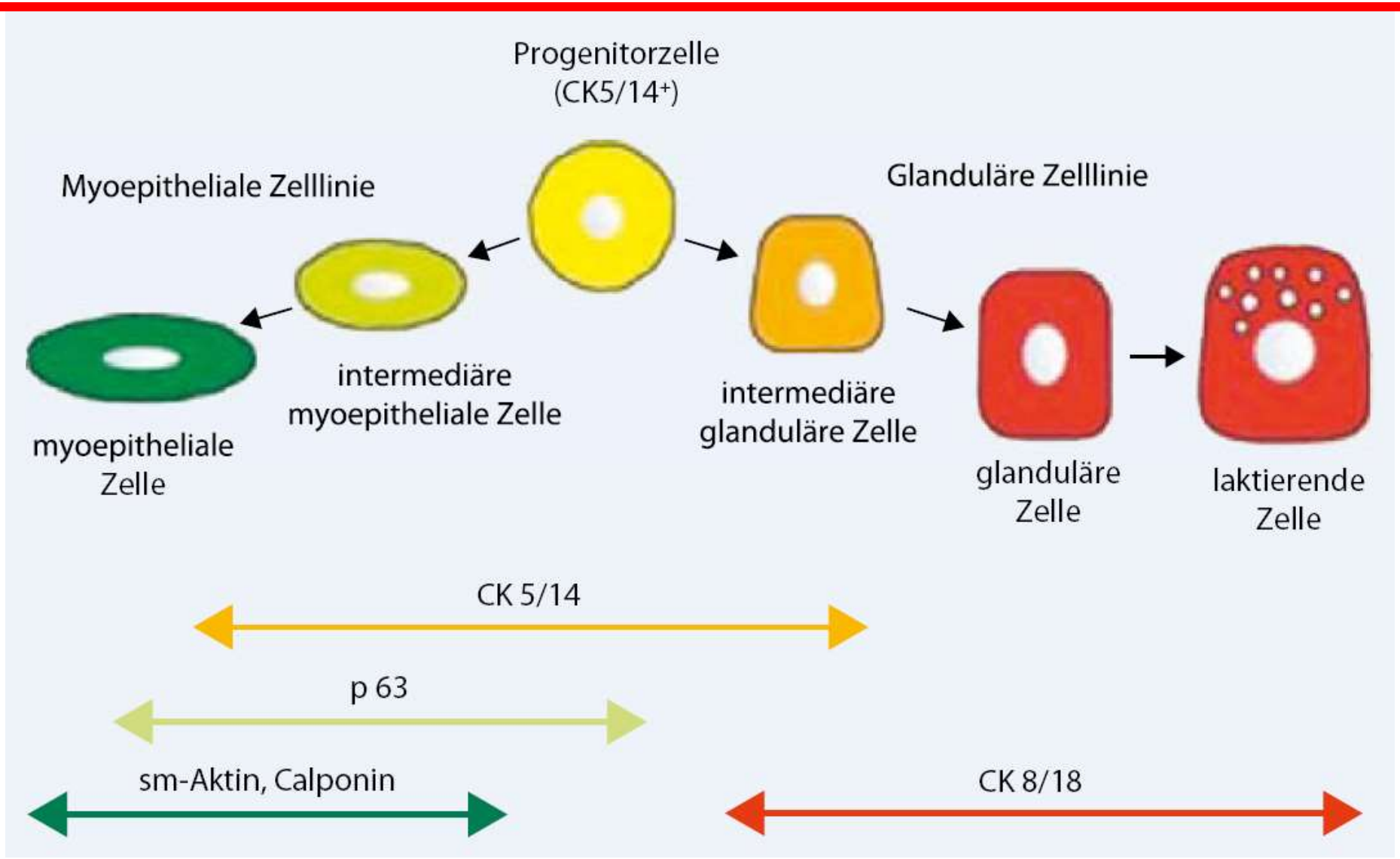

Pathologe 2009;30:6-12, Böcker W et al

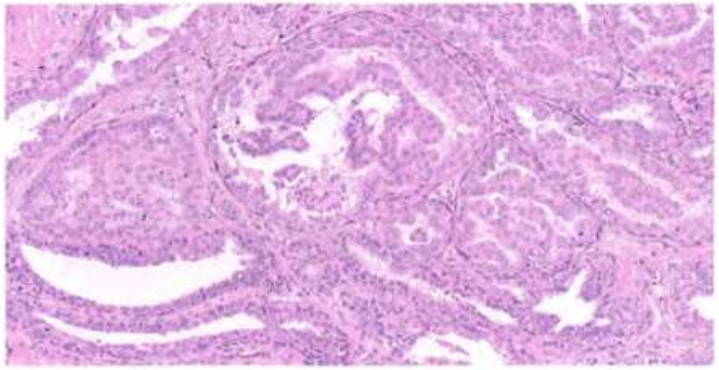

Abb 3a: Duktale Hyperplasie (im Bereich eines peripheren Papilloms)

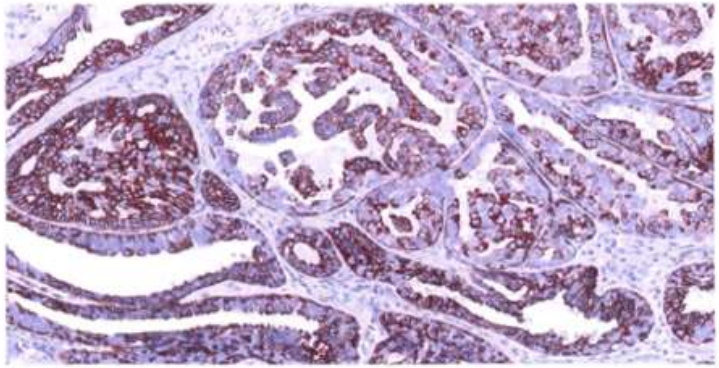

Abb 3b: Duktale Hyperplasie: Typische mosaikartige Verteilung der CK14 positiven luminalen (Progenitor-) Zellen

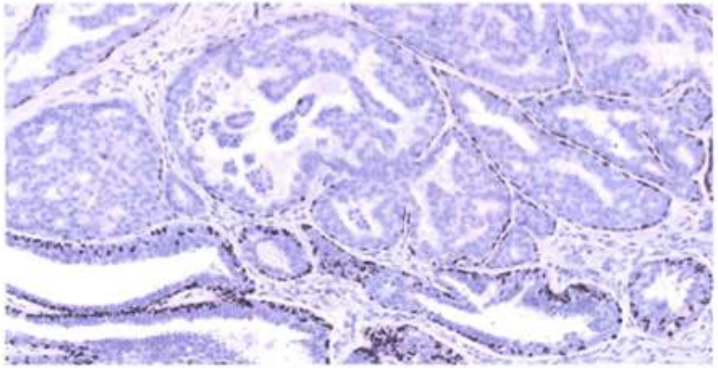

Abb 3c: Duktale Hyperplasie: p63 positive Myothelien nur als Gangbegrenzung. Myoepithelien sind nicht an der intraduktalen Proliferation beteiligt.

	Papillom	Papilläres DCIS	Gekapseltes papilläres Karzinom	Solid papilläres Karzinom
Architektur	meist plumpe, teils fibrosierte Papillen	verzweigte, schlanke Papillen	verzweigte, schlanke Papillen	solide Epithelproliferation mit zarten Papillen
Deckepithel	heterogene Zellproliferation, nicht atypisch, oft mit Metaplasie und Hyperplasie	monotone gleichförmige Proliferation, gering atypisch, keine Metaplasie	monotone gleichförmige Proliferation, gering atypisch, keine Metaplasie	monotone gleichförmige Proliferation, gering atypisch, neuroendokrine oder muzinöse Differenzierung
Orientierung der Kernachsen der Epithelien	zufällig	senkrecht auf Papillen	oft senkrecht of Papillen	oft strömende Verbände, parallel zu Papillen
Myoepithelschicht der Papillen	erhalten, gelegentlich hyperplastisch	fehlt weitgehend	fehlt völlig	fehlt völlig
Myoepithelschicht der Kapsel	erhalten	weitgehend erhalten	weitgehend fehlend	weitgehend fehlend
Epithel in angrenzenden Gängen	oft hyperplastisch	oft DCIS	gelegentlich DCIS	gelegentlich DCIS

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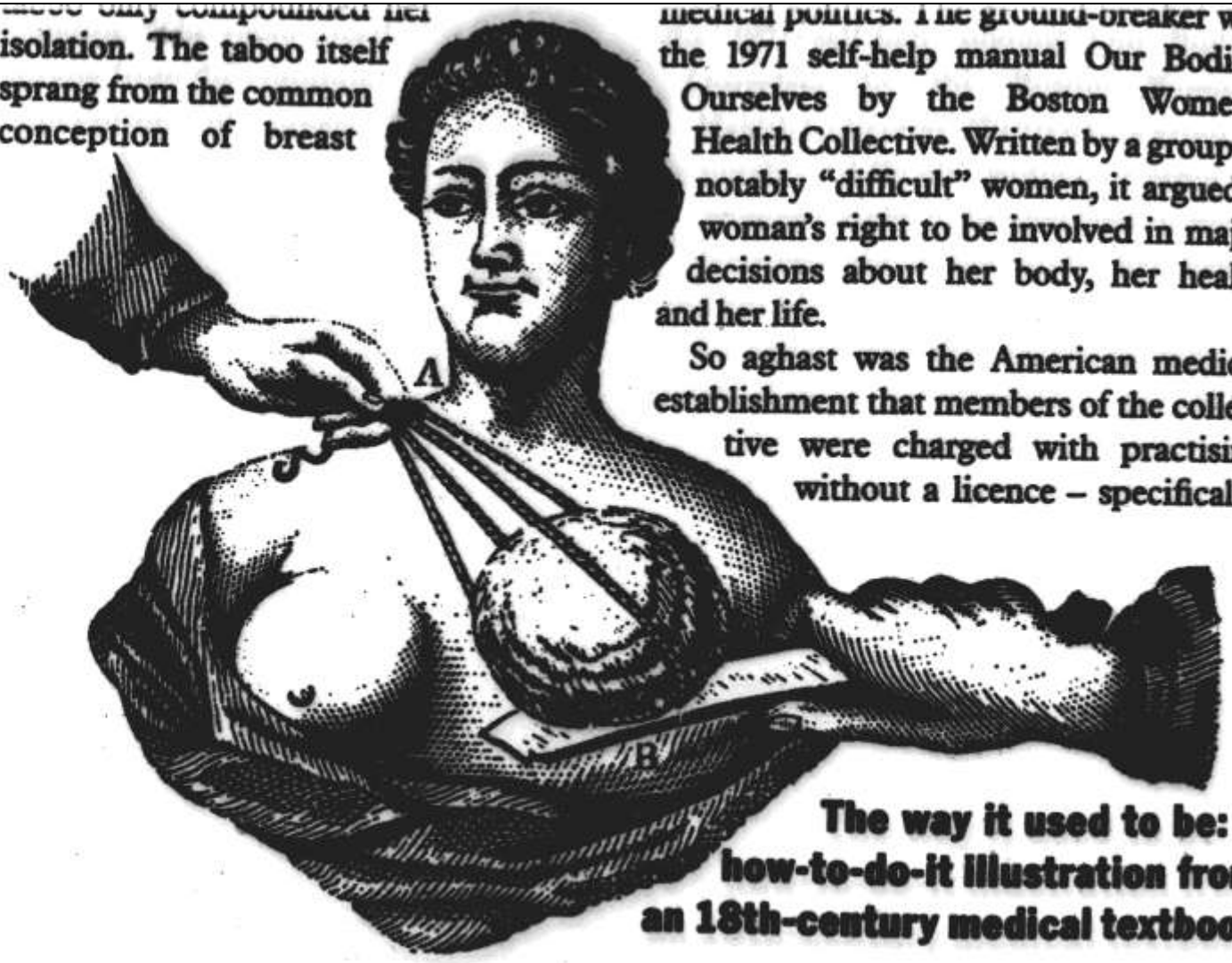
isolation. The taboo itself sprang from the common conception of breast



The way it used to be: a how-to-do-it illustration from an 18th-century medical textbook

medical politics. The ground-breaker was the 1971 self-help manual Our Bodies, Ourselves by the Boston Women's Health Collective. Written by a group of notably "difficult" women, it argued a woman's right to be involved in major decisions about her body, her health and her life.

So aghast was the American medical establishment that members of the collective were charged with practising without a licence – specifically,

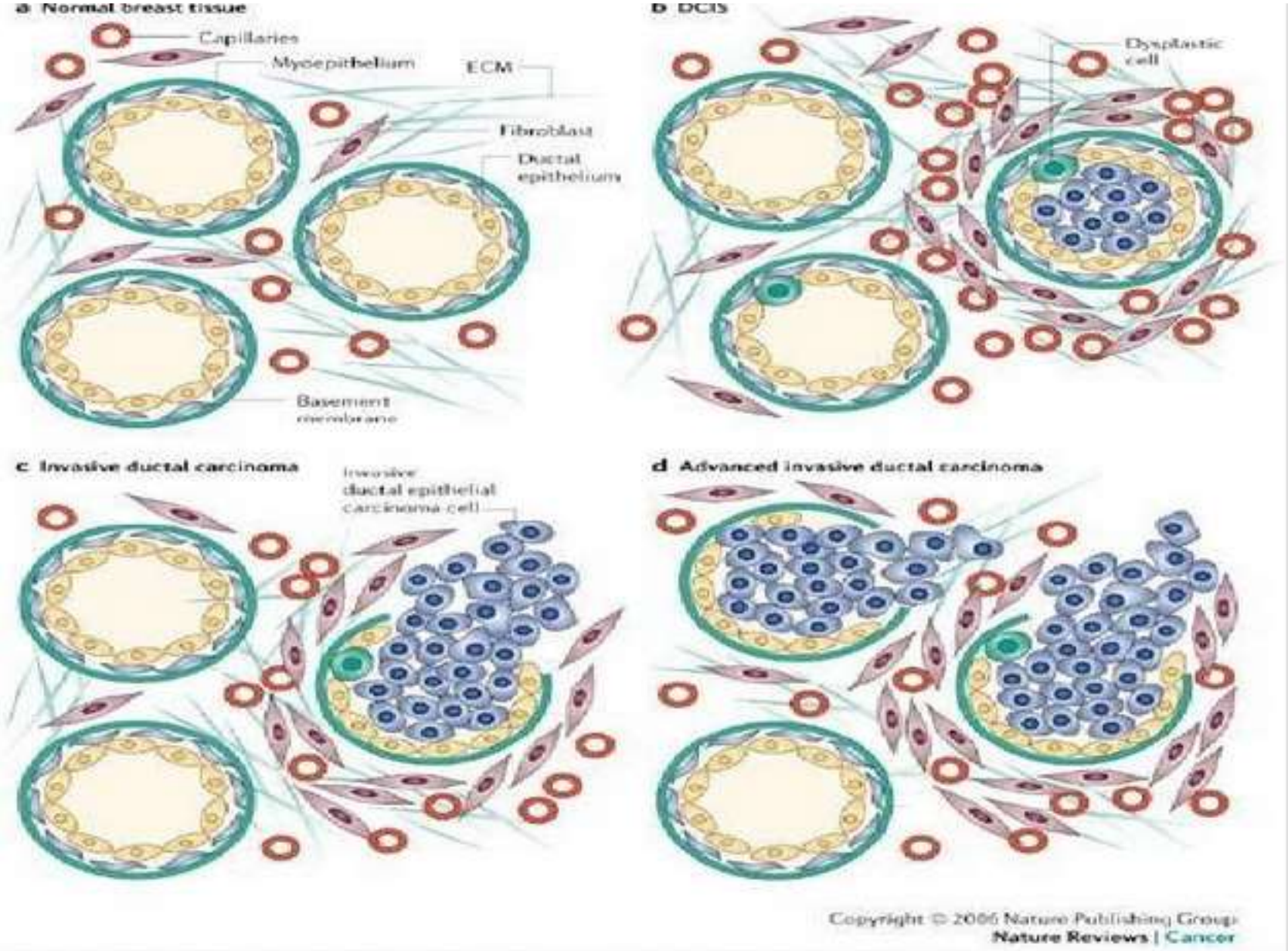
BÖSARTIGE TUMOREN

- selten mesenchymale: z.B. Hämangiosarkom
- häufigste bösartige Mammatumoren sind tumoren der Brustdrüse

MAMMAKARZINOM !!!!

steht an erster Stelle in den malignen Tumoren der FRAU !!!

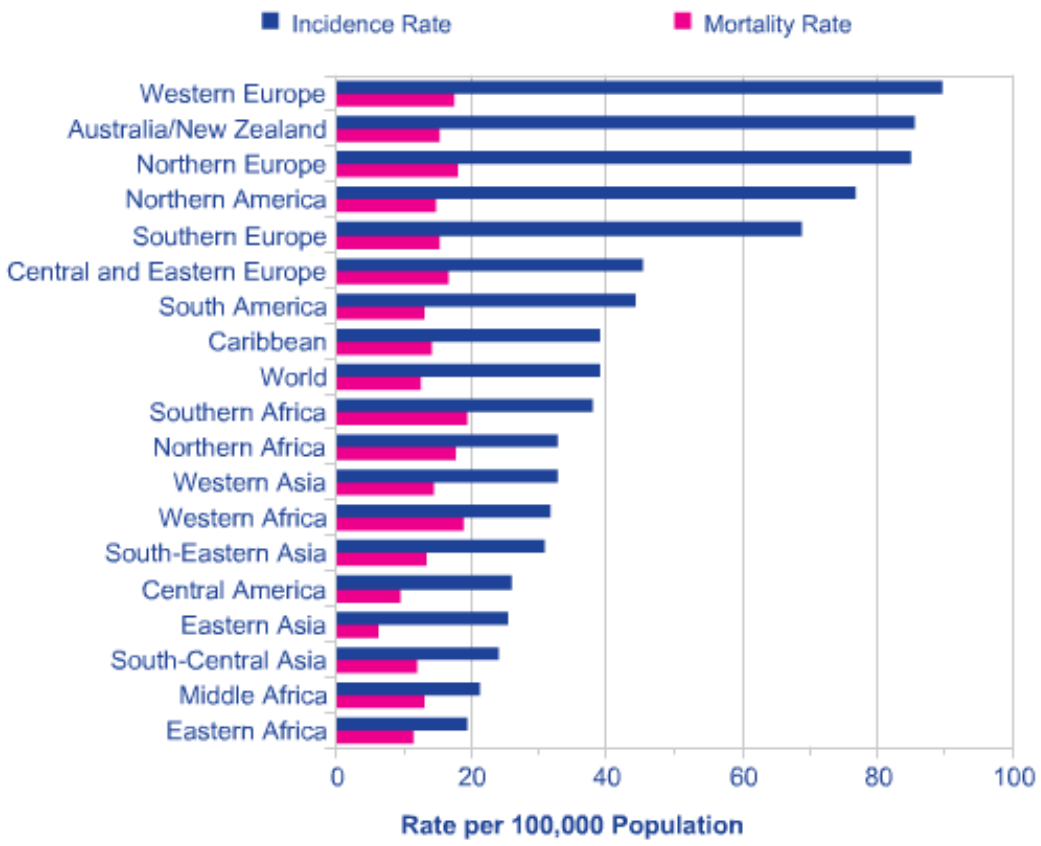
- es gibt auch der Brustkrebs des Mannes: Carcinoma virile mit einer schlechteren Prognose



Nature Reviews | Cancer

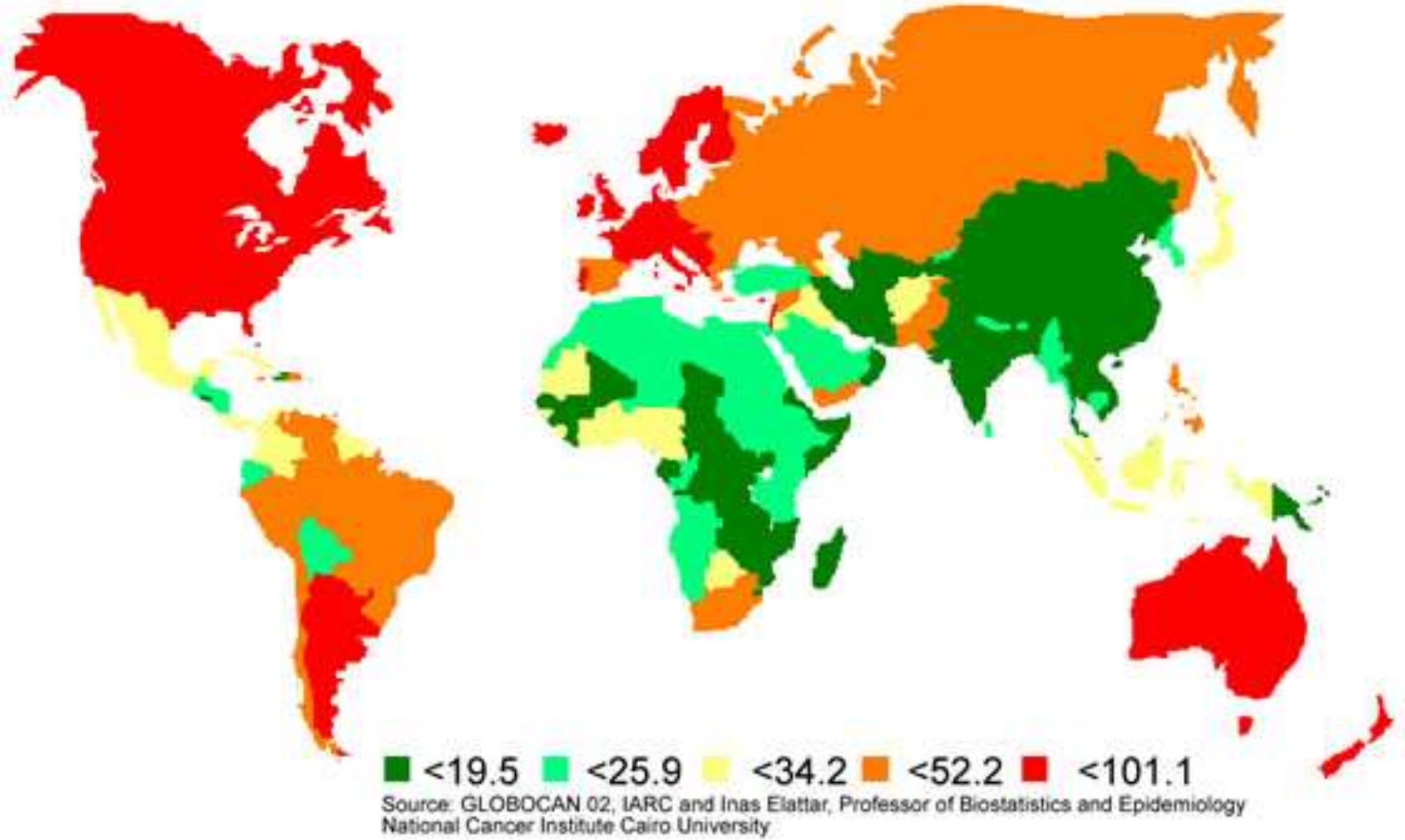
Inzidenz des Brustkrebs

Figure 1.2: Breast Cancer (C50), World Age-Standardised Incidence and Mortality Rates, World Regions, 2008 Estimates



info.cancerresearchuk.org

Breast Cancer Age-Standardized Incidence Rate Per 100,000



Source: GLOBOCAN 02, IARC and Inas Elattar, Professor of Biostatistics and Epidemiology
National Cancer Institute Cairo University

BRUSTKREBS

Alter: 30-90 Jahre

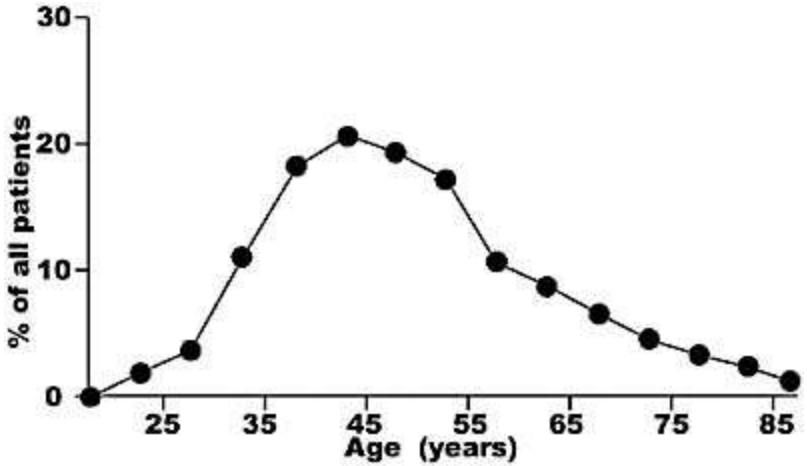
USA: (1989) 142.000 neue Falle und 43.000 Todesfalle

In 1999: 200.000 neue Falle !!!

Heute: 1 aus 8 Frauen ist betroffen

In 2007: 41 000 Todesfalle in der USA

Perzent aller Todesfallen der Frauen zurückführbar zu Brustkrebs



www.mindfully.org/Health/Breast-Cancer-ABCsfig05_02.jpg

BMJ 2000;321:624-628

K McPherson, C M Steel, J M Dixon

„ With **1 million new cases in the world each year**, breast cancer is the **commonest malignancy in women** and comprises **18% of all female cancers.** In the United Kingdom, the disease is the single commonest cause of death among women aged 40-50, accounting for about a fifth of all deaths in this age group. There are more than 14 000 deaths each year, and the incidence is increasing particularly among women aged 50-64, probably because of breast screening in this age group. "

BÖSARTIGE TUMOREN

RISIKOFAKTOREN - 1.

- **Östrogene (frühe Menarche, späte Menopause, exogene Östrogenzufuhr (nicht die nicht östrogenbetonte "Pille")**
- **Adipositas, fettreiche Ernährung (ungesättigte Fettsäure)**
- **heterozyklische aromatische Amine (Hamburger, Barbecue - Grill ?)**

BÖSARTIGE TUMOREN

RISIKOFAKTOREN -2.

- **Kinderlosigkeit**
- **besonders frühe oder späte erste Schwangerschaft**
- **höheres Lebensalter (70 % der Patientinnen sind über 50 Lebensjahr)**
- **Ethnische Faktoren - das unterschiedliche Risiko der Rassen scheint eher ernährungsbedingt zu sein**

BÖSARTIGE TUMOREN

LOKALIZATION

- **Hälfte der Mammakarzinomen ist in dem oberen äusseren Quadranten lokalisiert!!!**

Histologischer Abgang

- **maligne Tumoren der Milchgänge:**
  duktales Karzinom

- **maligne Tumoren der Drüsenläppchen:**
  lobuläres Karzinom

BÖSARTIGE TUMOREN

nach Tumor-Stroma-Verhältnis:

- **carcinoma solidum simplex**
  ausgewogenes Verhältnis
- **szirrhöses Karzinom**
  Stromaüberschuss

INVASIVITÄT

- ***IN SITU -***
- **INVASIVES KARZINOM**

HISTOLOGISCHE LOKALIZATION

85 % DUKTALES **15 % LOBULÄRES**

RISIKO FAKTOREN

Brustkrebs der Mutter oder Schwester

(↑wenn premenopausal oder bilateral)

Keine Graviditat oder spater als 35 Jahre

Frühe Menarche (vor Alter 12)

Spates Menopausa (nach Alter 50)

Fibrocystische Krankheit mit Papillomatose oder atypische Epitheliose

Endometriales Karzinom

Karzinom der kontralateralen Brust

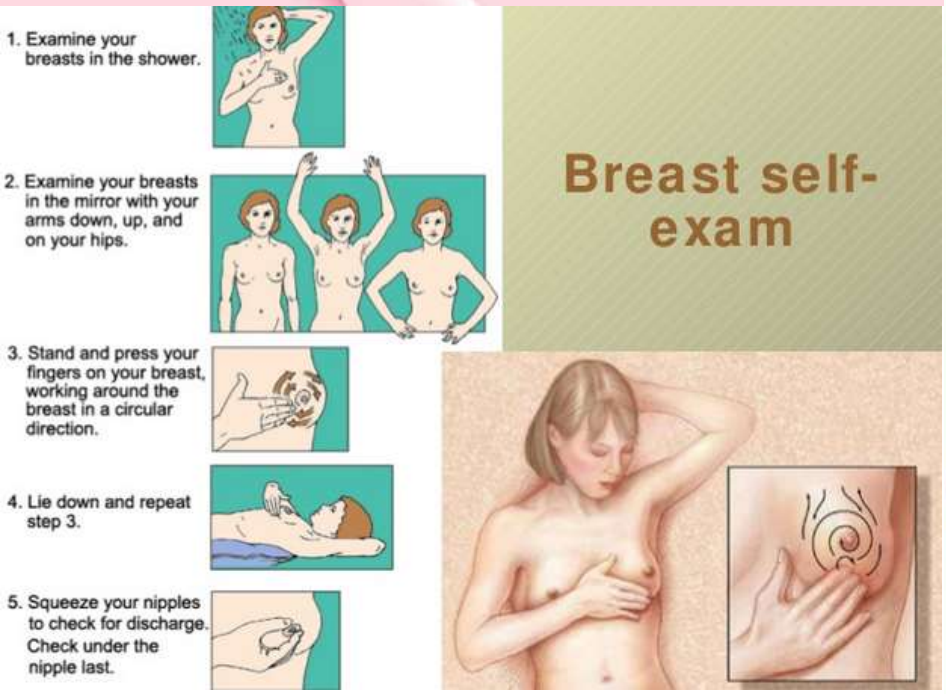
Weisse (Kaukazische) Rasse

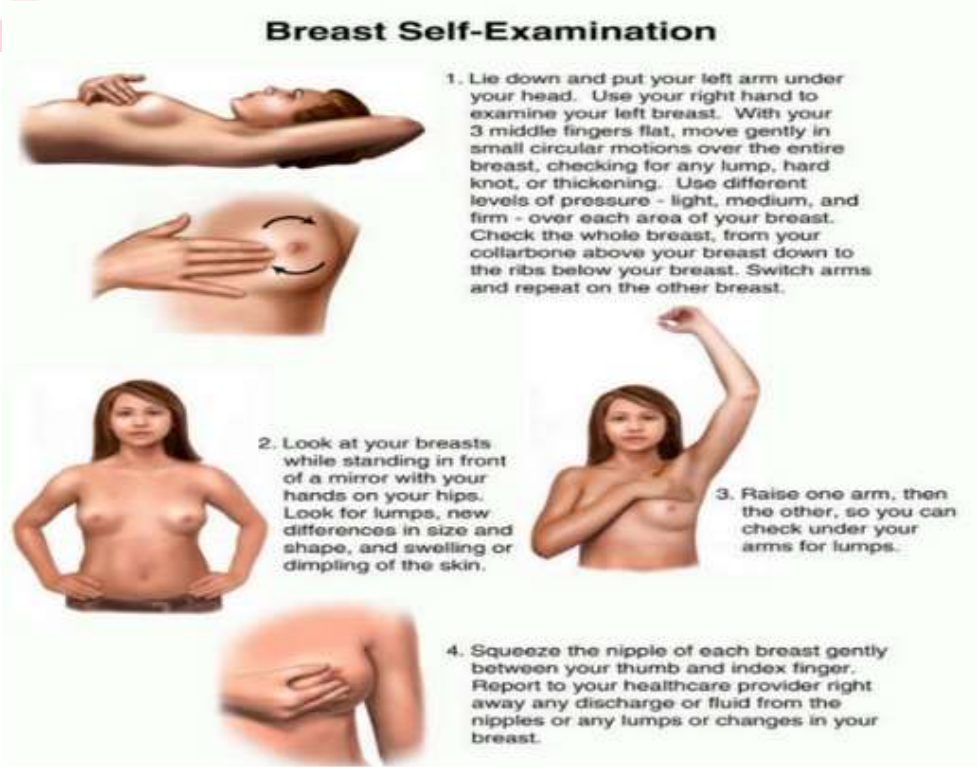
Hormon Substitution Therapie

Alkoholismus

When to do BSE

- Menstruating women- 5 to 7 days after the beginning of their period
- Menopausal women - same date each month
- Pregnant women – same date each month
- Takes about 10 minutes
- Perform BSE at least once a month
- Examine all breast tissue





Sichere und wahrscheinliche risikofaktoren des Brustkrebs

Factor	Relative risk	High risk group
Age	>10	Elderly
Geographical location	5	Developed country
Age at menarche	3	Menarche before age 11
Age at menopause	2	Menopause after age 54
Age at first full pregnancy	3	First child in early 40s
Family history	2	Breast cancer in first degree relative when young
Previous benign disease	4-5	Atypical hyperplasia
Cancer in other breast	>4	
Socioeconomic group	2	Groups I and II
Diet	1.5	High intake of saturated fat
Body weight:		
Premenopausal	0.7	Body mass index >35
Postmenopausal	2	Body mass index >35
Alcohol consumption	1.3	Excessive intake
Exposure to ionising radiation	3	Abnormal exposure in young females after age 10
Taking exogenous hormones:		
Oral contraceptives	1.24	Current use
Hormone replacement therapy	1.35	Use for 10 years
Diethylstilbestrol	2	Use during pregnancy

Die **nicht-proliferative Lasionen** (nicht assoziiert mit Wachstum des Brustgewebes) **scheinen das Brustkrebs-Risiko nicht beeinflussen. (Wenn Überhaupt,** es passiert in ganz geringer Anzahl)

Die sind di folgende:

Fibrose
Zysten
Milde Hyperplasie
Adenose (nicht-skelosierende)
einfaches Fibroadenom
phyllodes Tumor (gutartig)
Einzelnes Papillom
fattige Nekrose
Mastitis
Duktus Ektasie
gutartige Tumoren (Lipom, Hamartom, Hemangiom, Neurofibrom)

kein RISIKO

Die **proliferative Lasionen ohne Atypie** (die mit exzessivem Wachstum der duktularen oder lobularen Zellen des Brustgewebes einheergehen) scheinen das Risiko der Frauen für Brustkrebs leichtmassig zu erhöhen **(1 bis 2-mal des normales Risiko**). Dies sind die folgende:

Gewöhliche duktale Hyperplasie (ohne Atypie)
komplex Fibroadenoma
Sklerosierende Adenose
mehrere Papillome oder Papillomatose
Radial Scar (Narbe)

minimales Risiko Anstieg

Die **proliferative Lasionen mit Atypie** (die einem exzessiven Wachstum der duktalen und lobularen Zellen des Brustgewebes einhergehen und die Zellen scheinen nicht mehr normal zu sein) haben **stronger Effekt an Brustkrebs-Risiko, erhöhen das Risiko 4 bis 5 mal höher als** normal. Die sind die folgende:

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atypische duktal Hyperplasie (ADH)
atypische lobulare Hyperplasie (ALH)

deutlicher Risiko-Anstieg

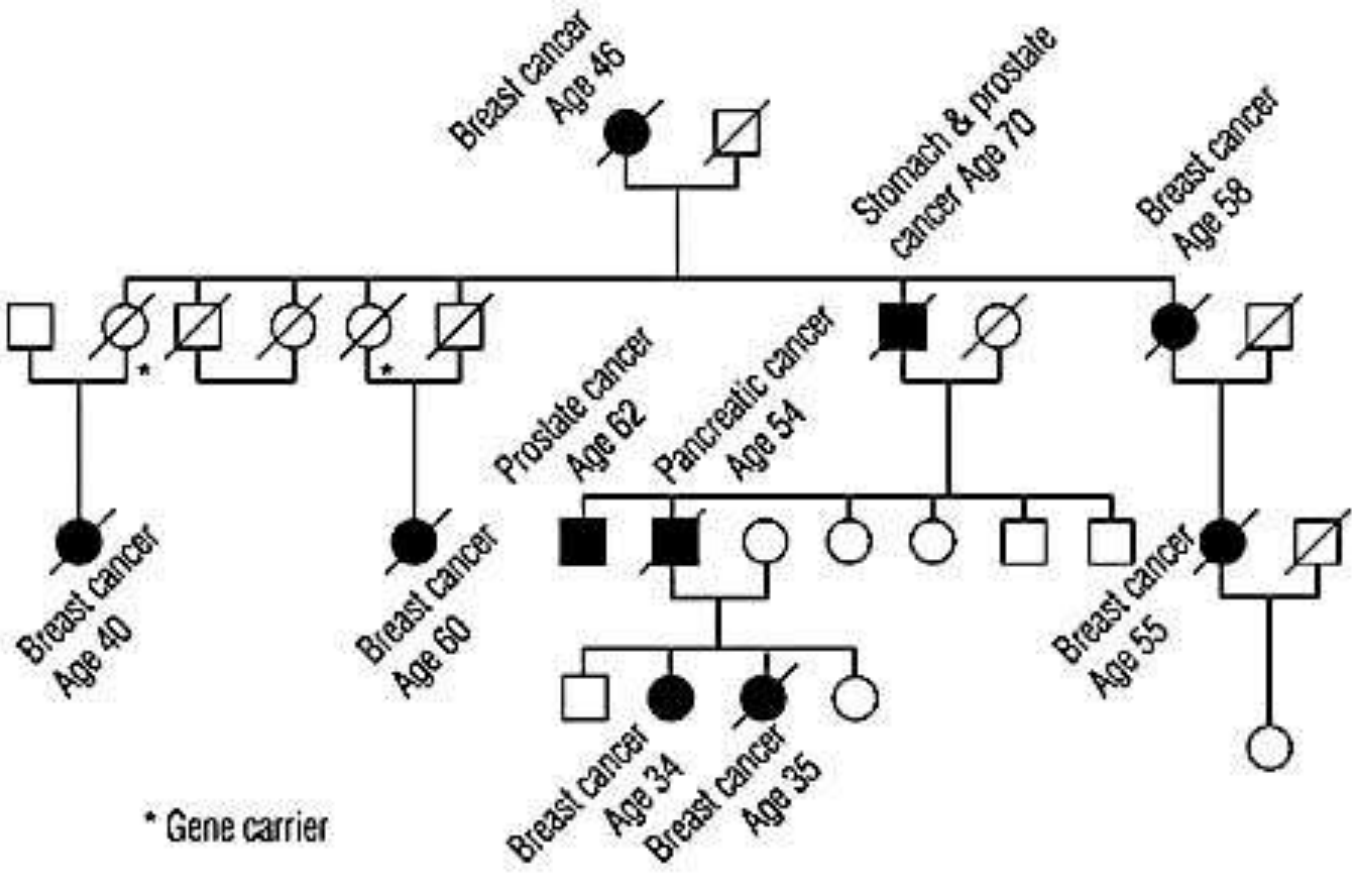
Family history and relative risk of BC

No close relative with breast cancer	1.0
One close relative with BC	1.5-2.0
Two close relatives with BC	5.0
Close relative with bilateral postmenopausal BC	10
Close relative with bilateral premenopausal BC	20

Familiarer Brustkrebs

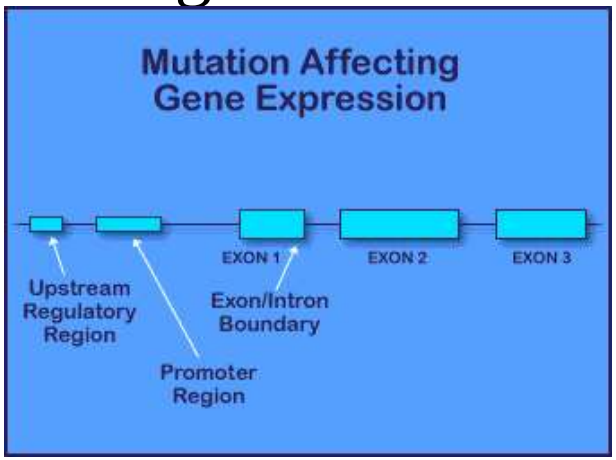
- **Cowden Syndrom** **PTEN**
  - 10q
  - dominant Vererbung
- **Breast/ovarium Krebs Syndrom** **BRCA1**
  - 17q
  - dominant Vererbung
- **Brustkrebs** **BRCA2**
  - 13q
  - dominant Vererbung
- **Li-Fraumeni Syndrom** **TP53**
  - 17p13
  - dominant Vererbung

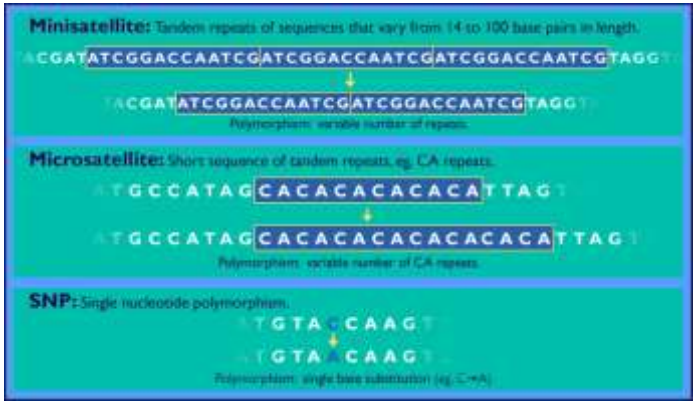
Familirer Brustkrebs



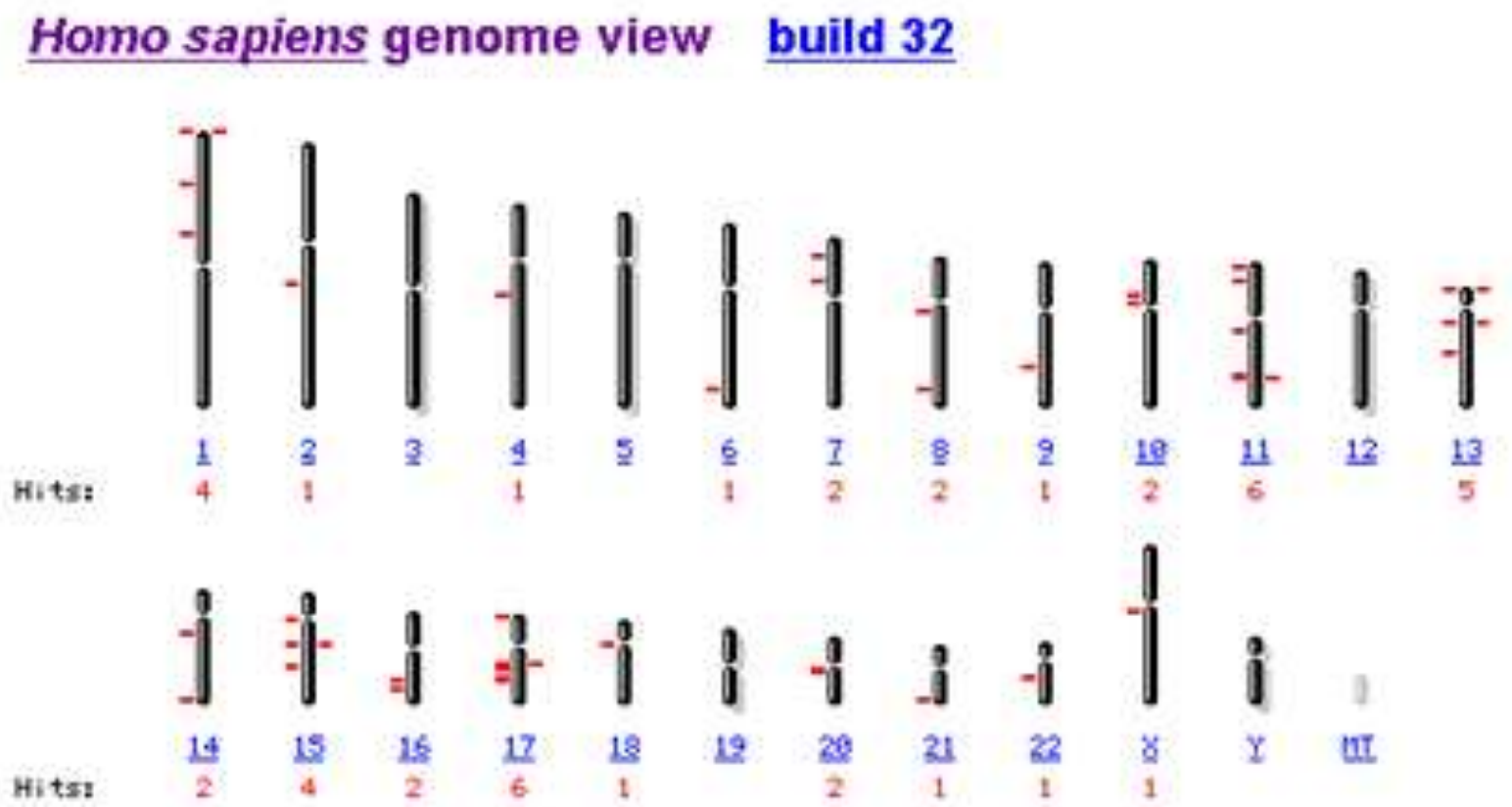
Genetik des Brustkrebs

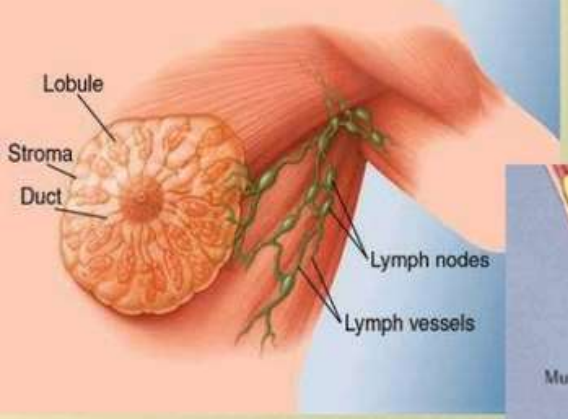
- Genetische Verenderungen: viele Gene sind verdachtig eine Rolle in der Brust Karziogenes zu spielen
- Mechanismen
  - Loss of heterozygosity(LOH)
  - Mikrosatellit Instabilitat
  - Mutationnen
  - Translokationen
  - Epigenetische Veranderungen

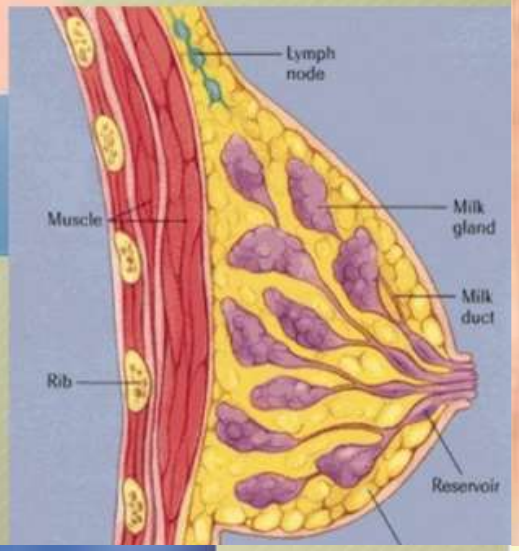


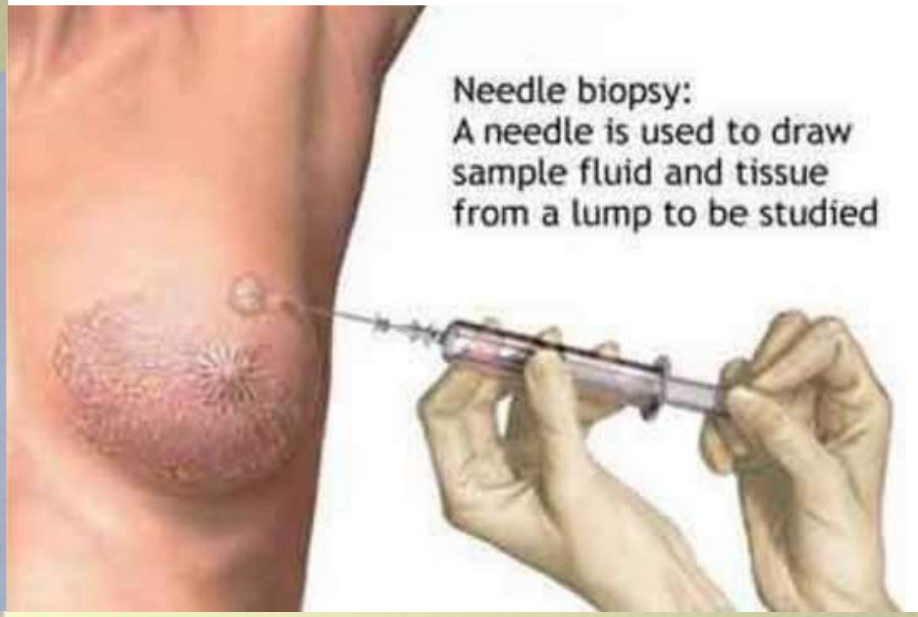


Betroffene Chromosomen in Brustkrebs





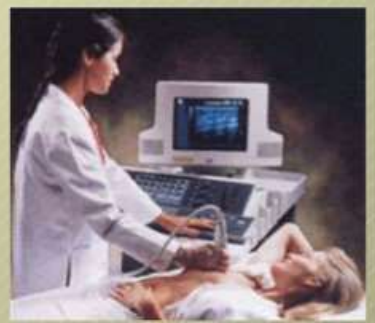




Mammogram

CAD Mammogram

Digital mammography



Breast Ultrasound

Clinical breast exam

- Mammogram - to check breast tissue

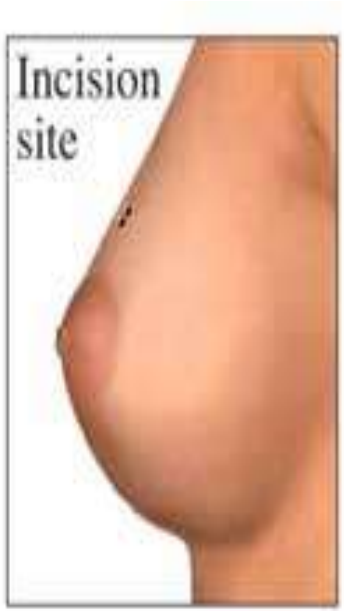
Other tests

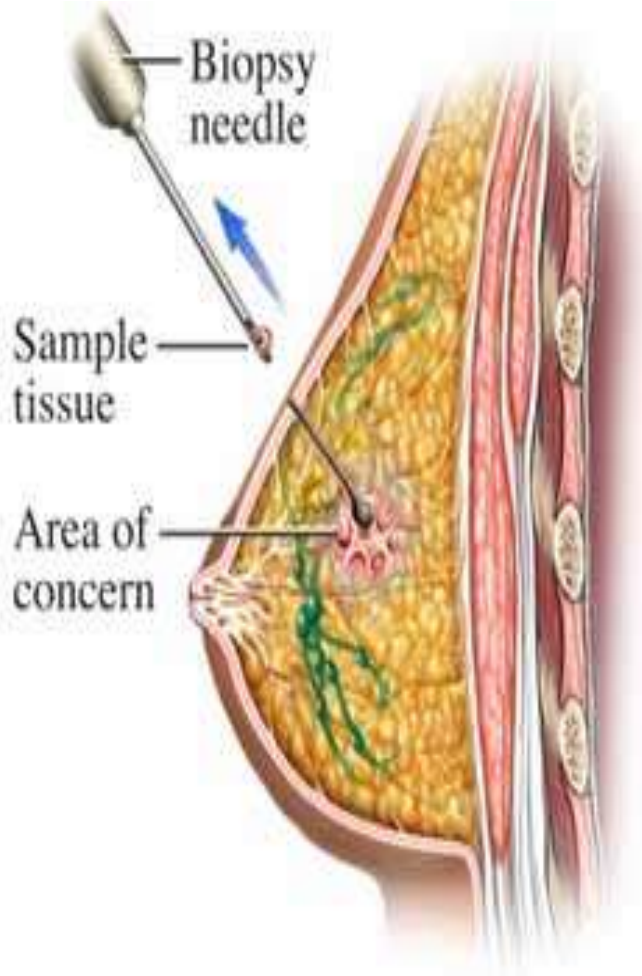
- Computer-aided detection (CAD)
- Digital mammography
- Magnetic resonance imaging (MRI)
- Breast ultrasound (ultrasonography)

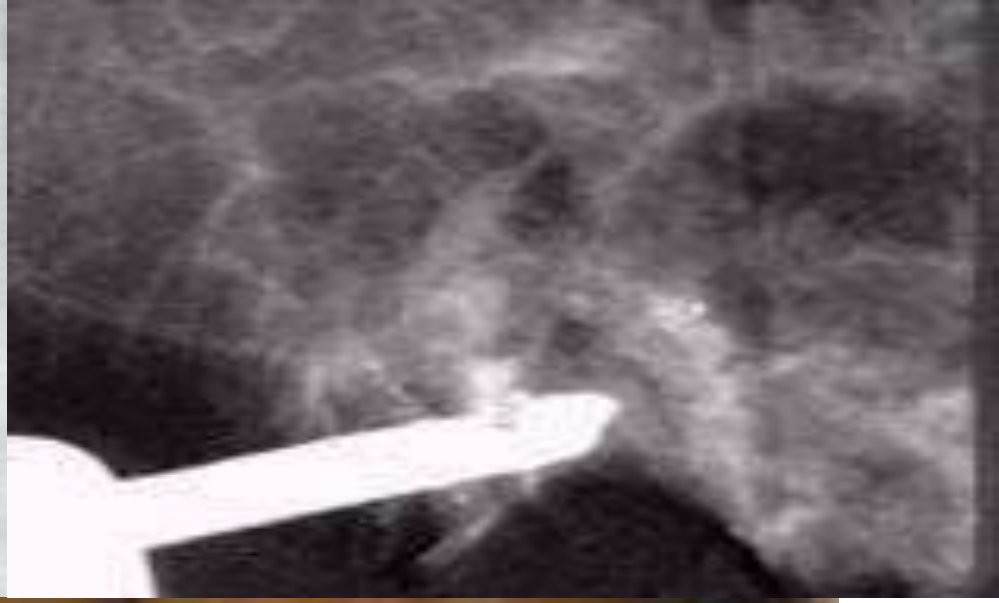
Experimental procedures

- Ductal lavage
- Molecular breast imaging (MBI)

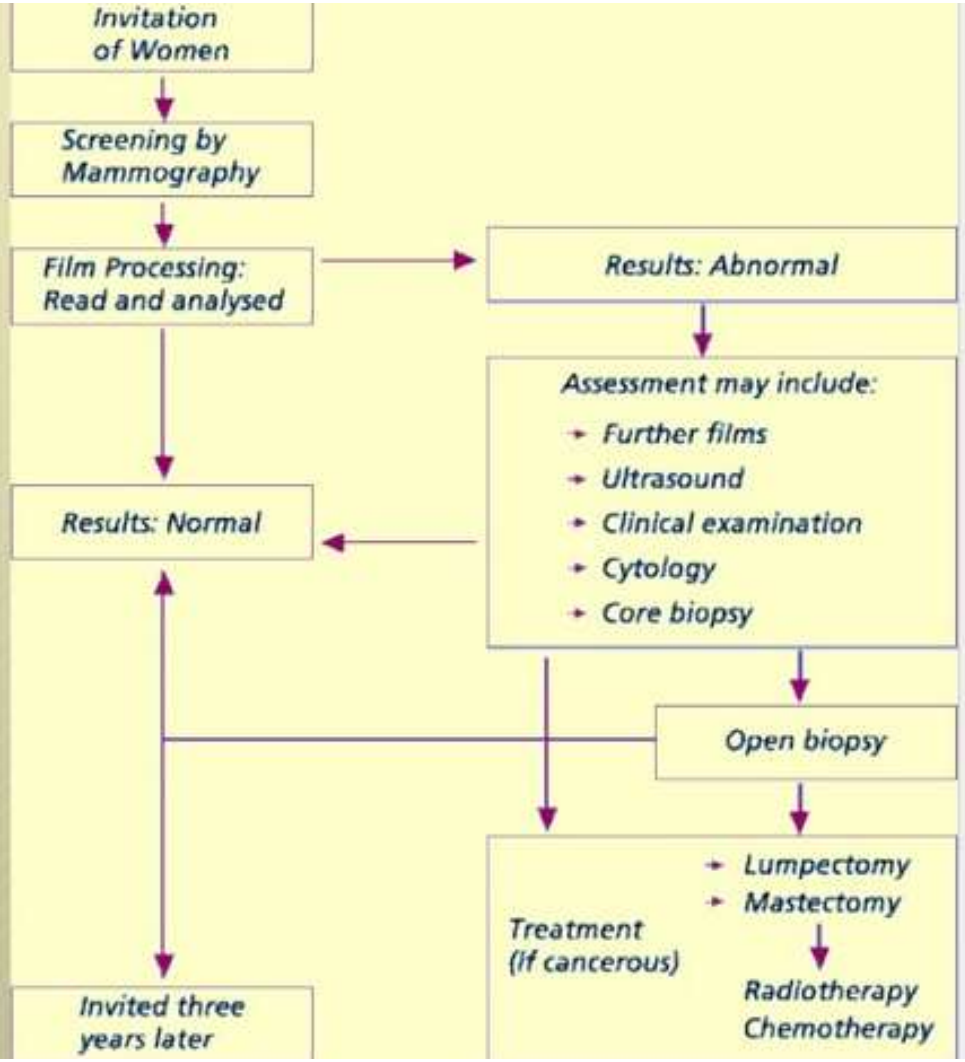
Früherkennung

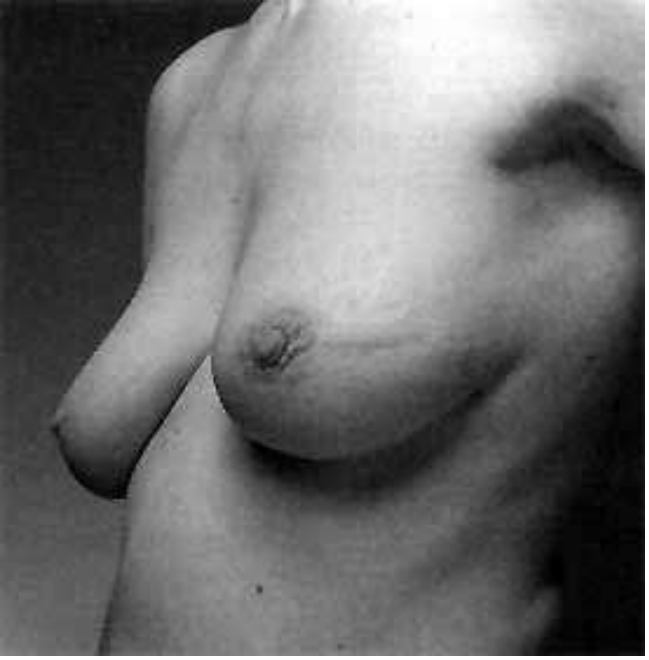


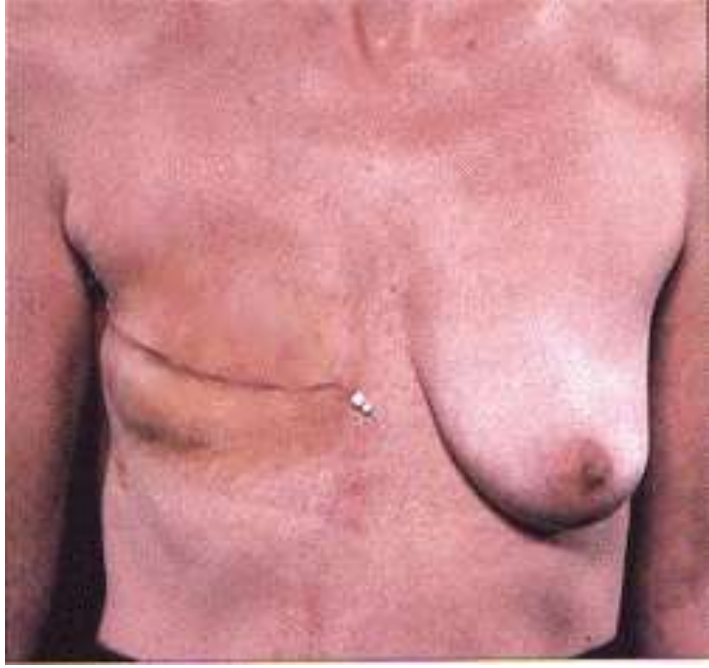


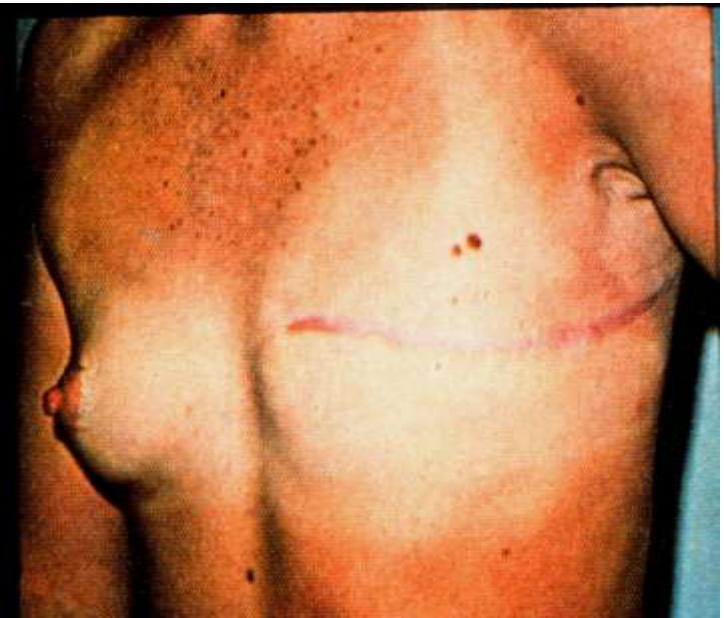


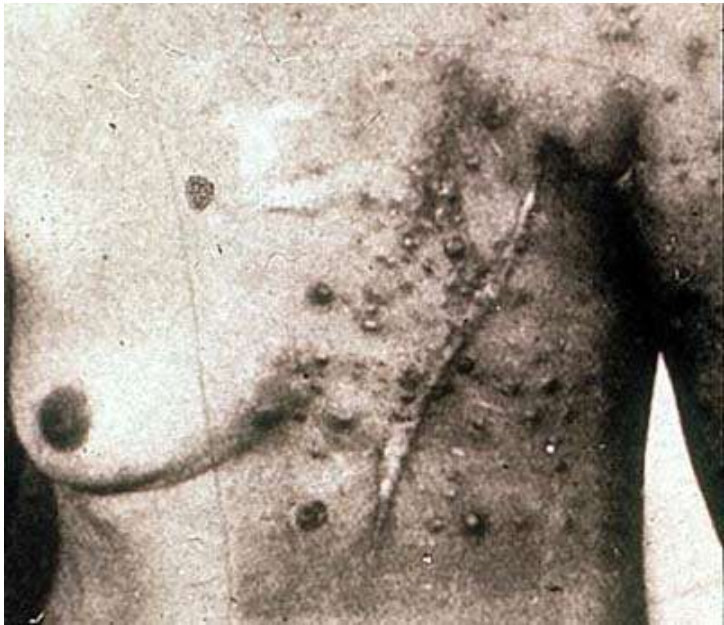
Screening


Invitation of Women
Screening by Mammography
Film Processing: Read and analysed
Results: Abnormal
Assessment may include:
Further films
Ultrasound
Clinical examination
Cytology
Core biopsy
Results: Normal
Open biopsy
Lumpectomy
Mastectomy
Treatment (if cancerous)
Radiotherapy
Chemotherapy
Invited three years later









Brust Karzinom

In situ

DUKTALES, DCIS, DIN

- *Klassifikation No1*

  nukleares Grade 1,2,3
- *Klassifikation No2*

  Van Nuys 1,2,3
- *Klassifikation No3*

  Komedo, cribriform,
  solid, micropapillar, usw.

LOBULAR, LCIS, LIN

Invasiv

Invasives duktales
NOS/NST

Spezial Type
tubular
mucinös
medullar
papillar
micropapillar
sekretorisch....uzw.

Invasives lobulares
klassisches
solides
alveolares
pleiomorphes

gemischte Karzinome

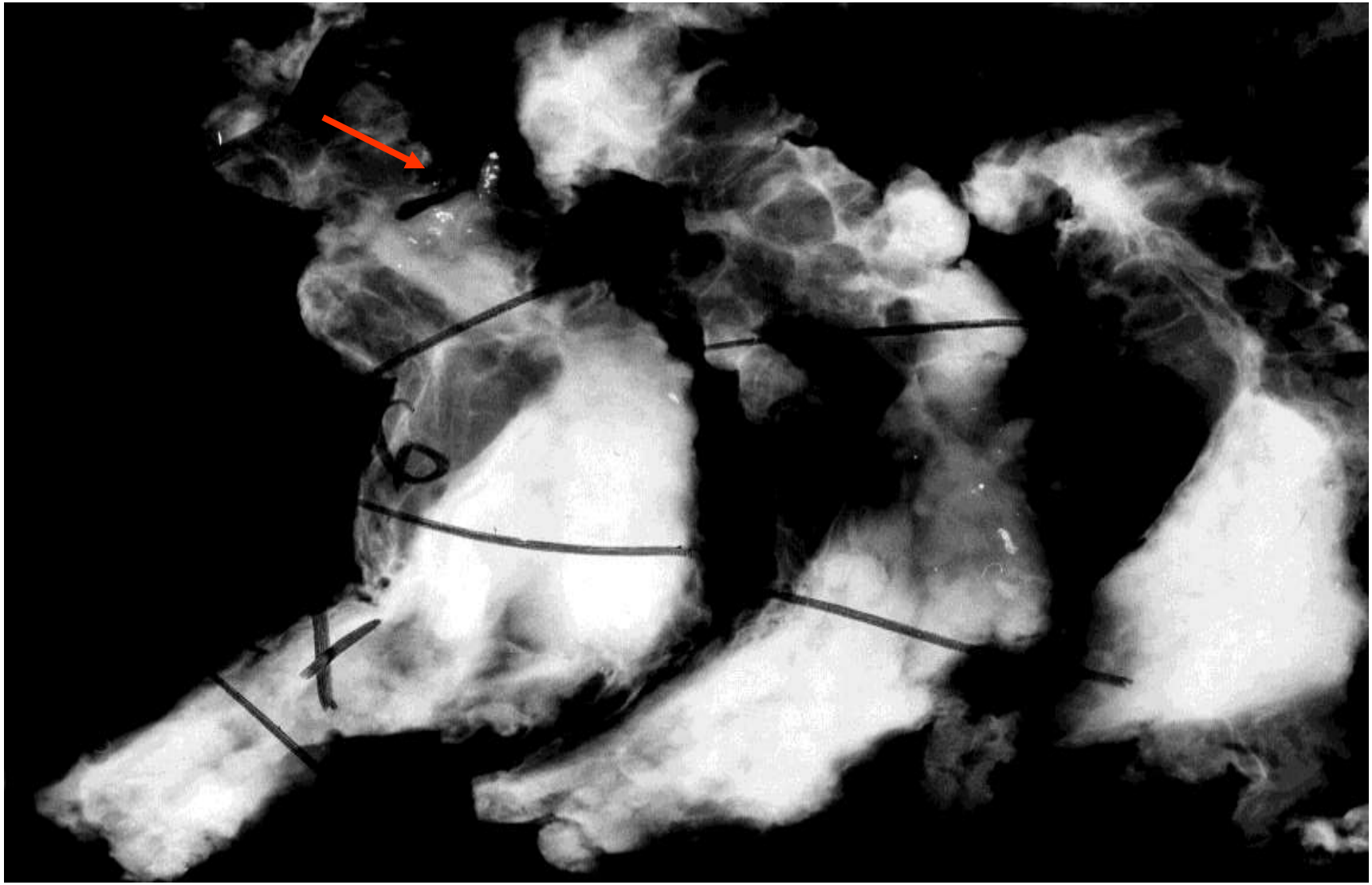
BÖSARTIGE TUMOREN

- **Mikroverkalkungen !!!**
  - DD: Mastopathie

SONDERFORM:
Inflammatorisches Mammakarzinom

- **lymphangiosis carcinomatosa**
- **lymphogene Ausbreitung in Mamillenbereich**
- **DD: Mastitis**

Bei nicht puerperalen Mastitis muss ein Mammakarzinom ausgeschlossen werden !!!



Präparat – Spezimen-mammografische Aufnahme Mikrokalzifikation

BÖSARTIGE TUMOREN - in situ

- **Duktales Carcinoma in situ DCIS !!!**

Minimal invasives DCIS: Invasion weniger als 1 mm!

Intraduktales Karzinom !!

Es wächst innerhalb der Milchganglumina, solider, papilläres oder drüsenähnliches Wachstum

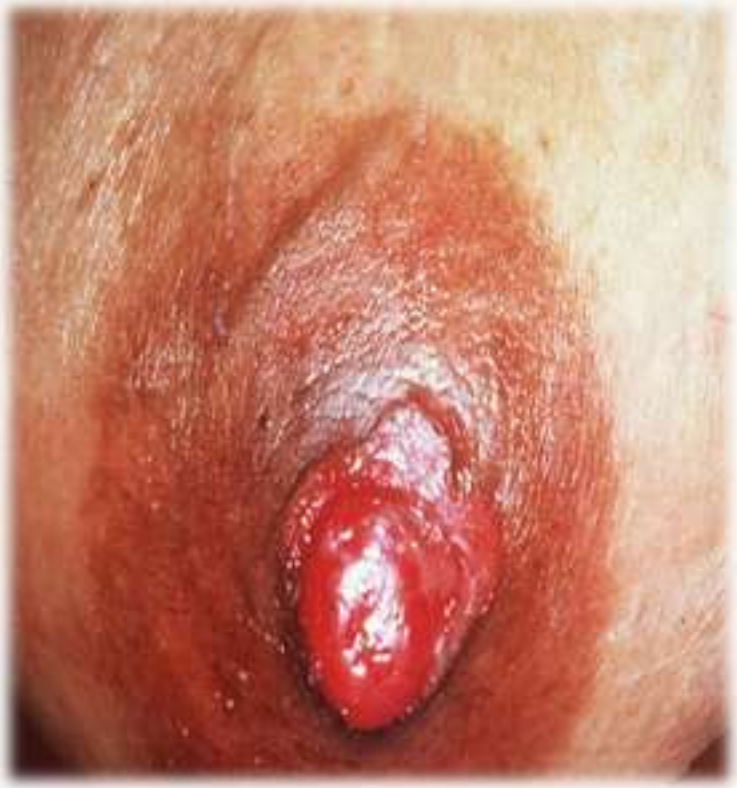
- **Mit zentraler Nekrose:**

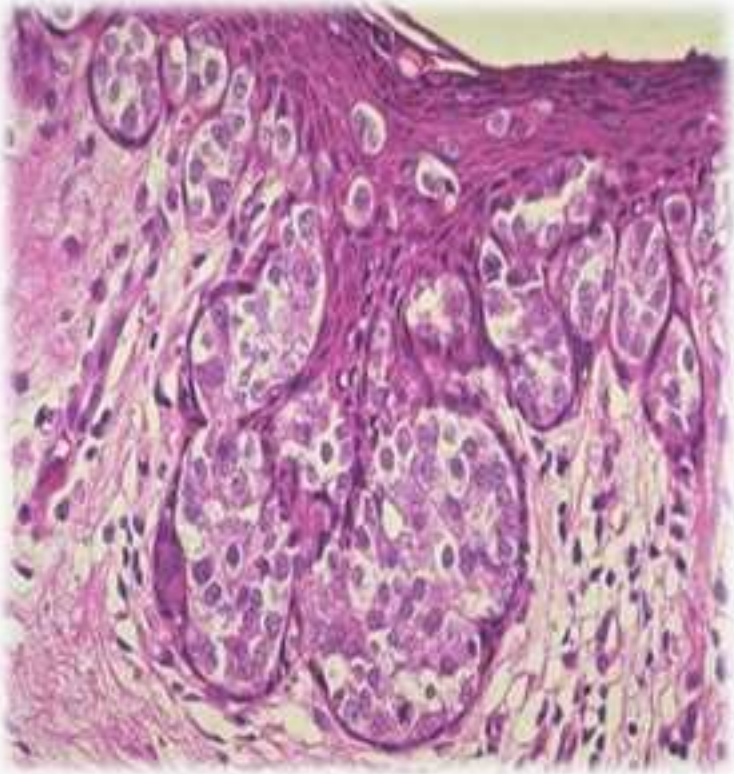
KOMEDOKARZINOM

Karzinomen die die Haut infiltrieren und haben eine ekzemartige chronische Erscheinung

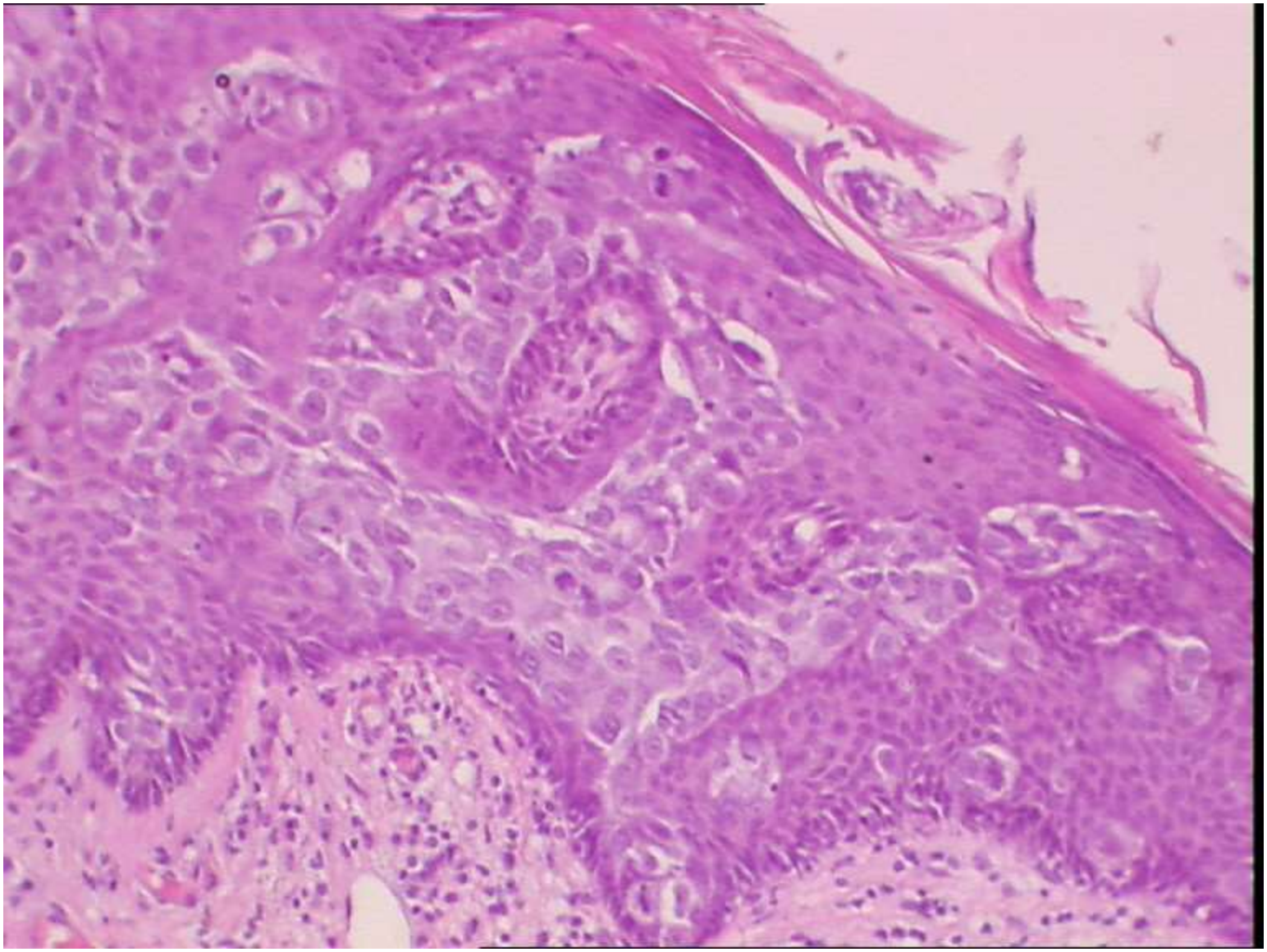
- **PAGET-KARZINOM**

PAGET'S DISEASE OF NIPPLE





Paget Karzinom



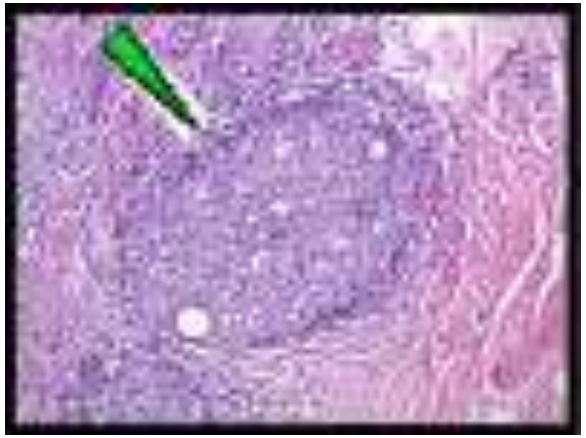
BÖSARTIGE TUMOREN

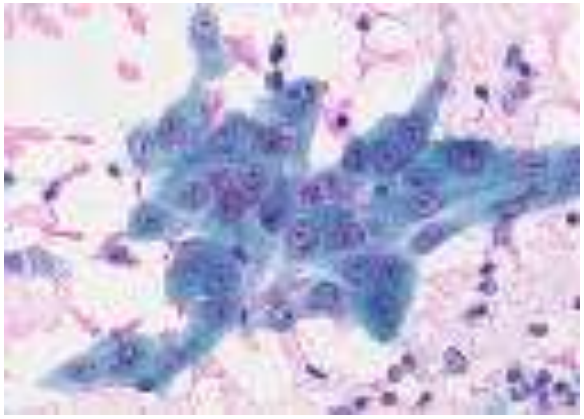
- **Lobuläres Carcinoma in situ LCIS !!!**
  Lobuläre Neoplasie !!

Solide Wucherungen mit Atypie, die Zellen füllen die Azini eines oder mehreren Läppchen aus

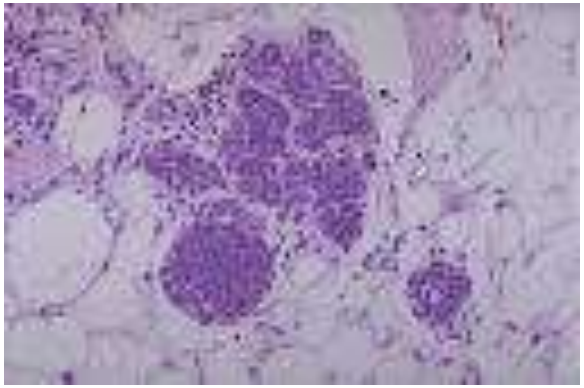
Es kann multizentrisch sein !! In ~ 30 % der Fällen kontralateraler Befall !! In ~ 20 Jahren gehen etwa 30 % der LCIS in invasives lobuläres Karzinom über.

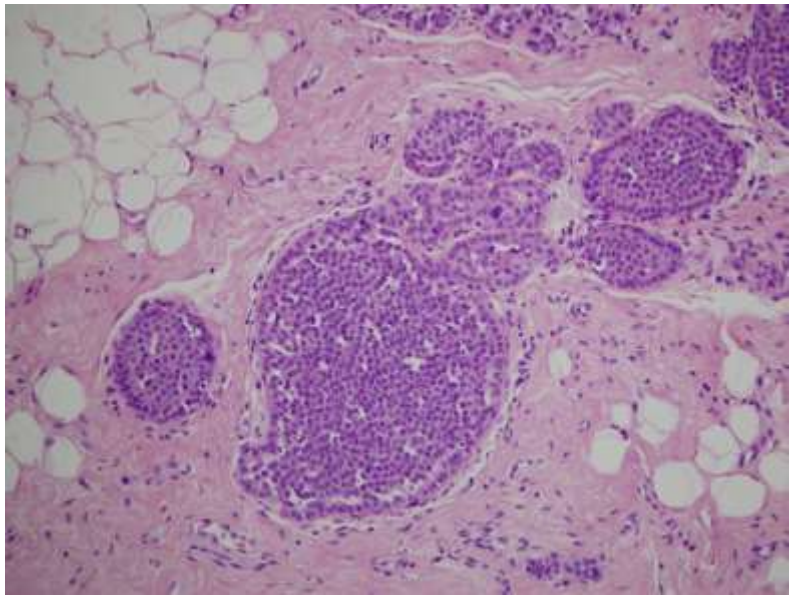
DCIS





LCIS

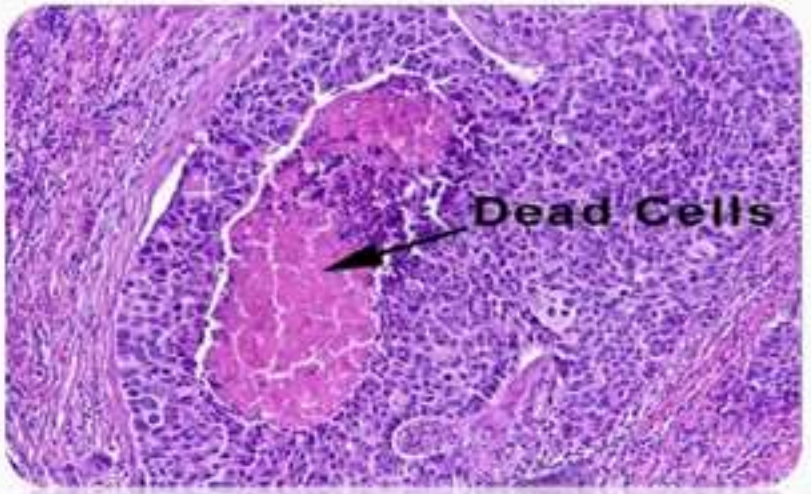


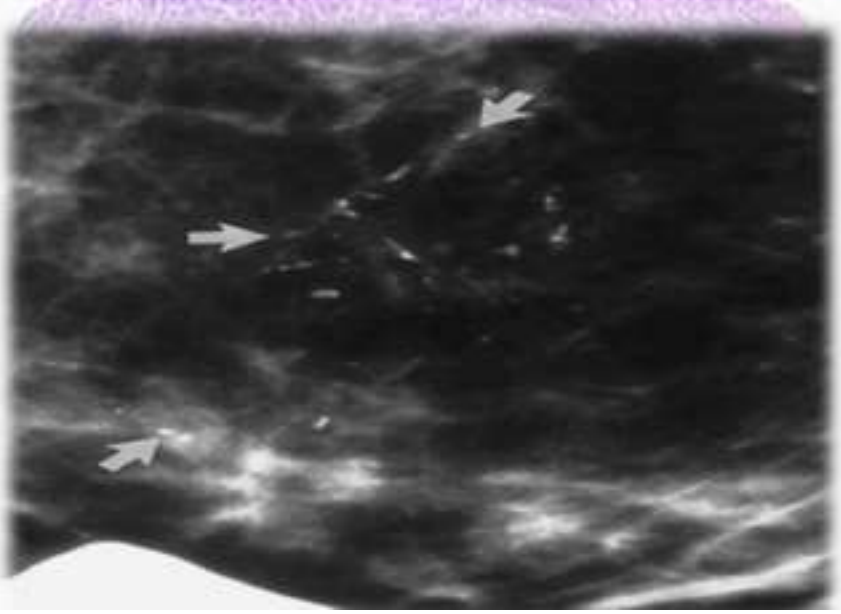


DCIS – 5 Architectural subtypes

Comedocarcinoma

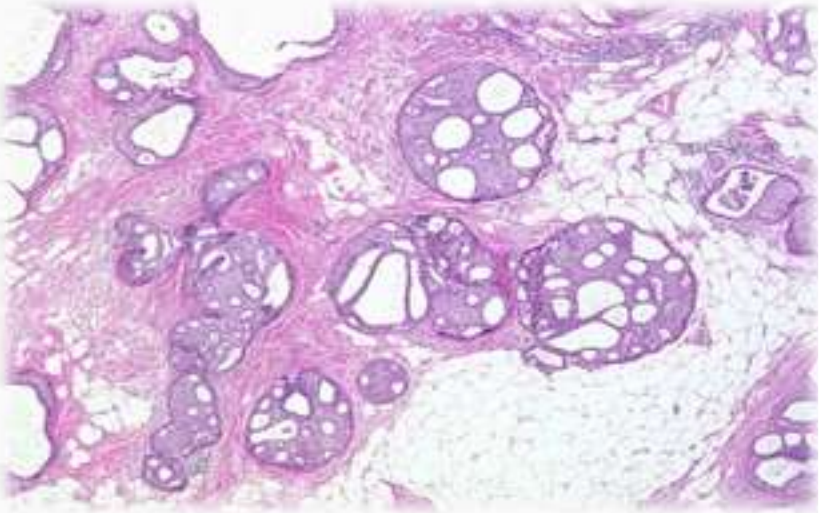
- Solid sheets of pleomorphic cells with high grade hyperchromatic nuclei.
- Areas of central necrosis +nt.
- Necrotic cell membranes – calcify →clusters/linear & branching microcalcifications on mammography.
- Periductal concentric fibrosis & chronic inflammation.
- Extensive lesions – palpable as vague nodularity.





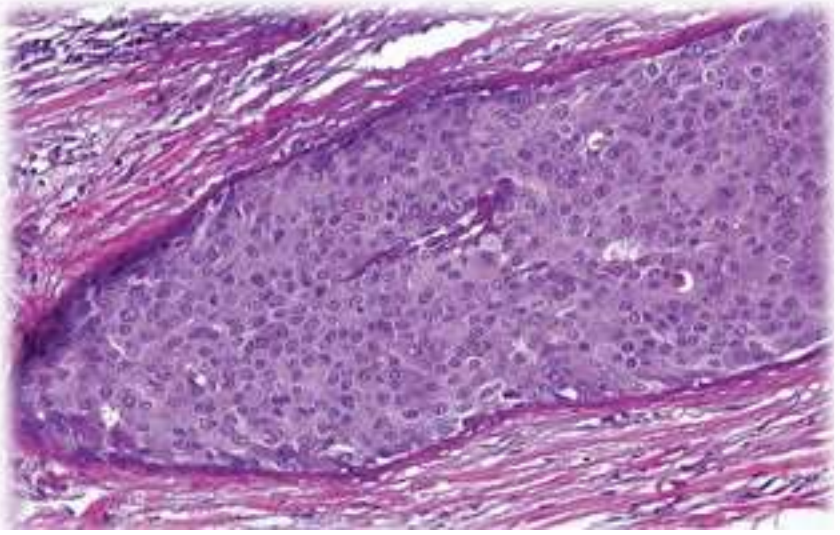
Noncomedo DCIS

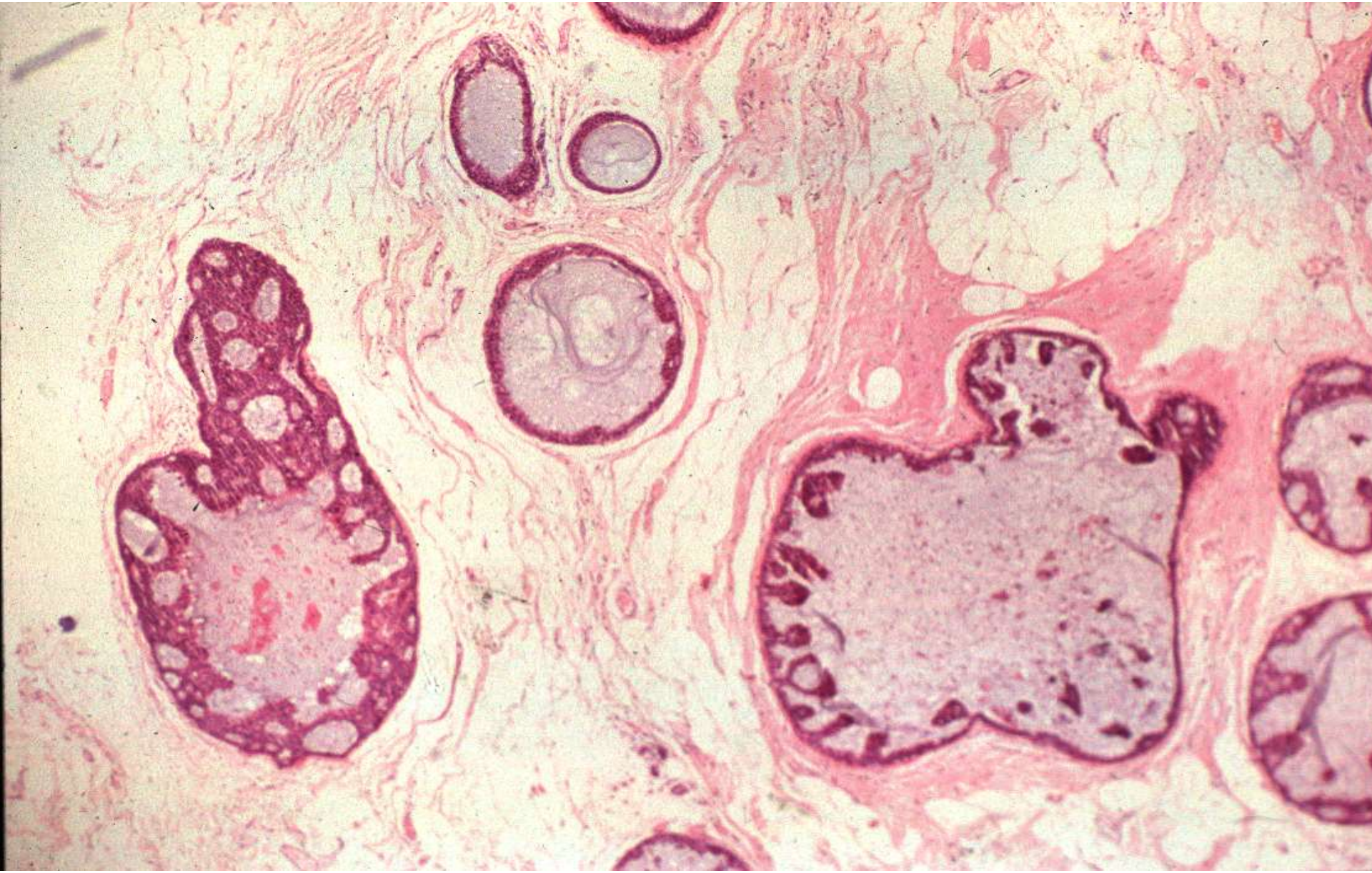
- Monomorphic cell population – nuclear grades → low to high.
- ***CRIBRIFORM DCIS***
  - Intra-epithelial spaces – evenly distributed, regular in shape.



  - *COOKIE CUTTER – LIKE*

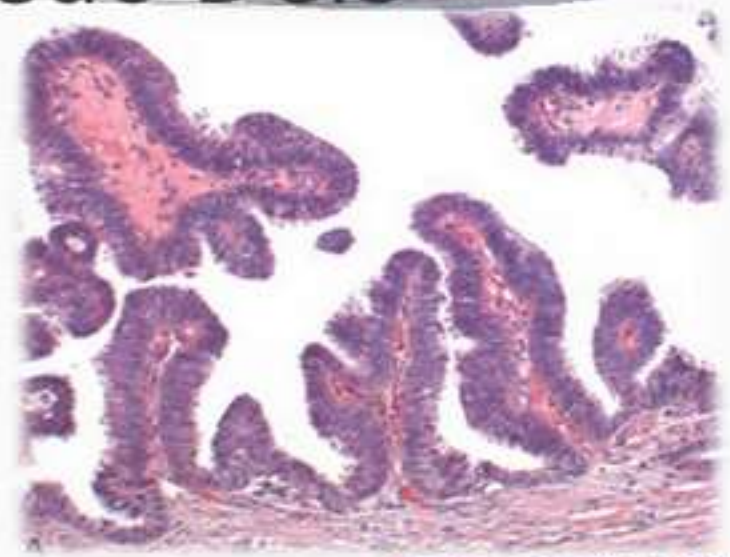
- ***SOLID DCIS***
  - Completely fills the involved spaces.



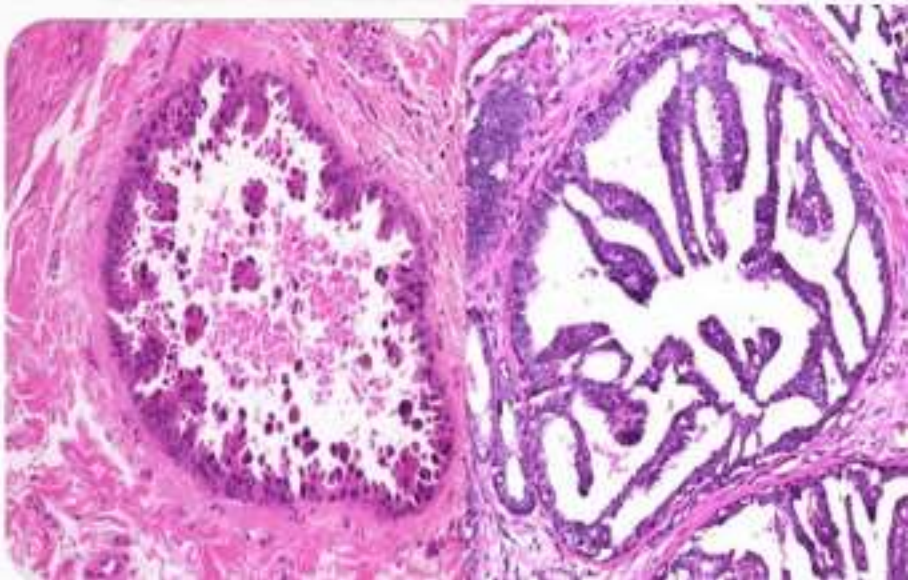


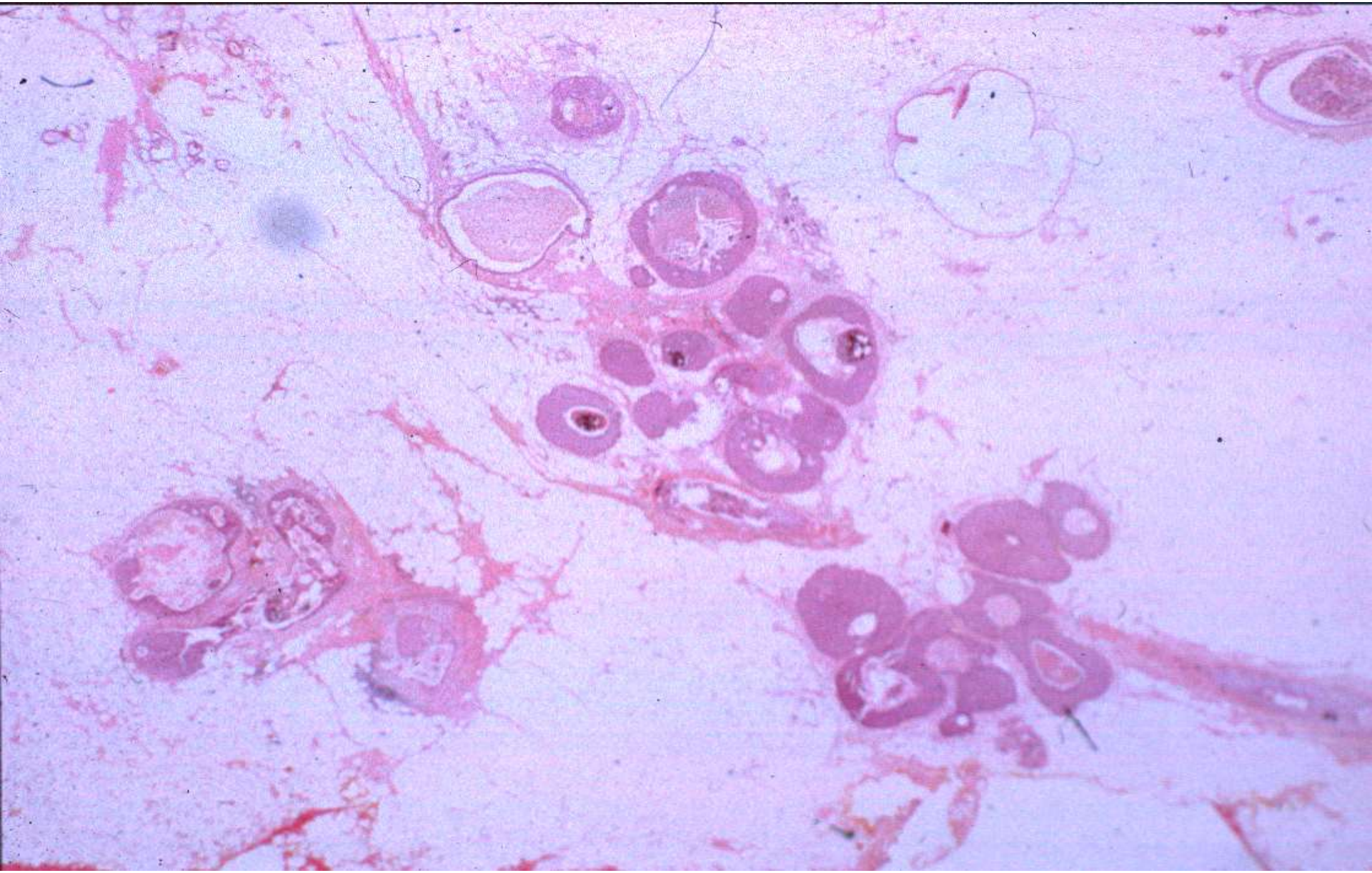
Noncomedo DCIS

- ***PAPILLARY DCIS***
  - Grows into spaces along fibrovascular cores → lack myoepithelial cell layer.

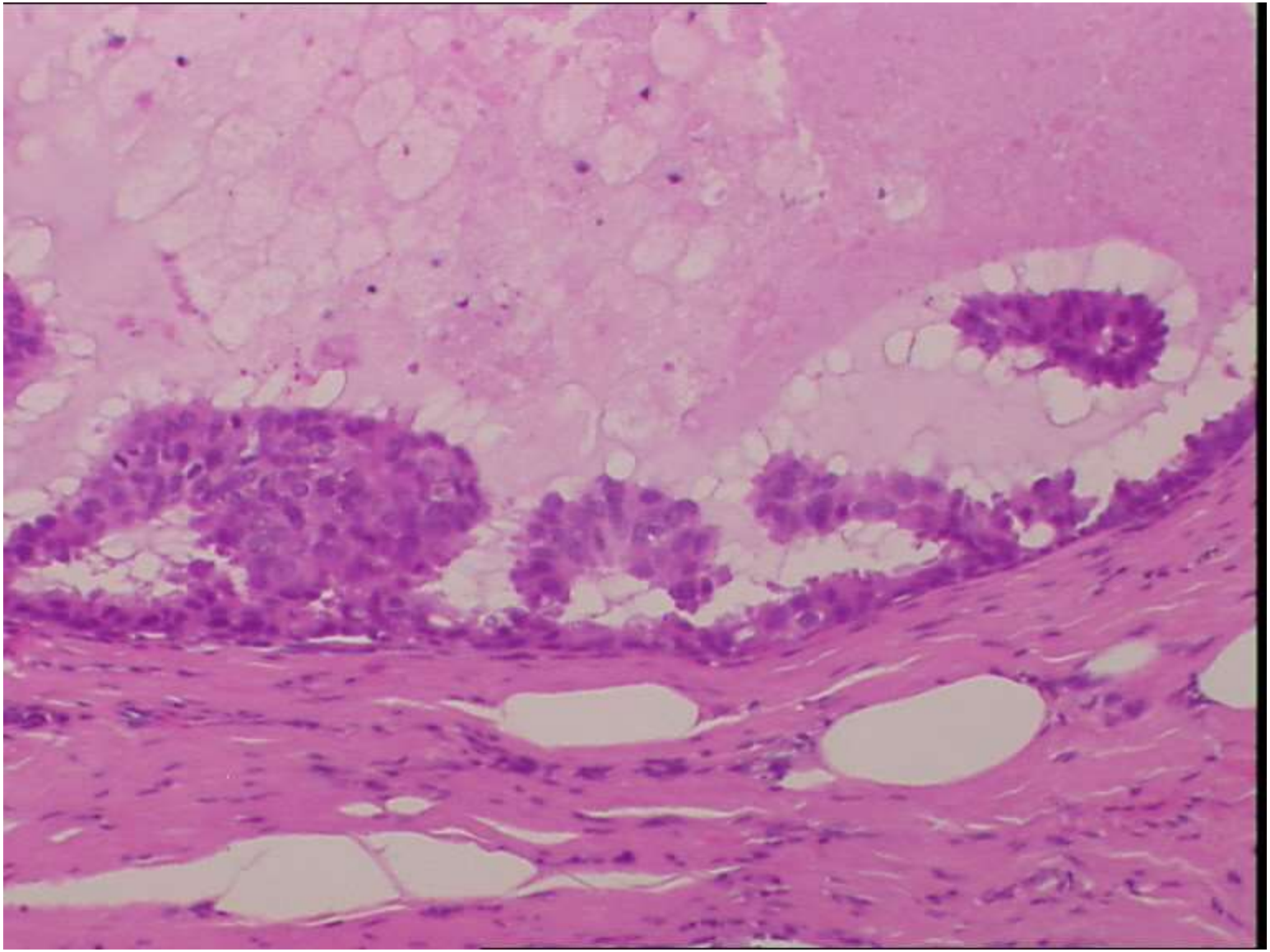


- ***MICROPAPILLARY DCIS***
  - Bulbous protrusions without a fibrovascular core arranged in complex intraductal patterns.
  - Calcifications – assoc.with necrosis/form on intraluminal secretions.

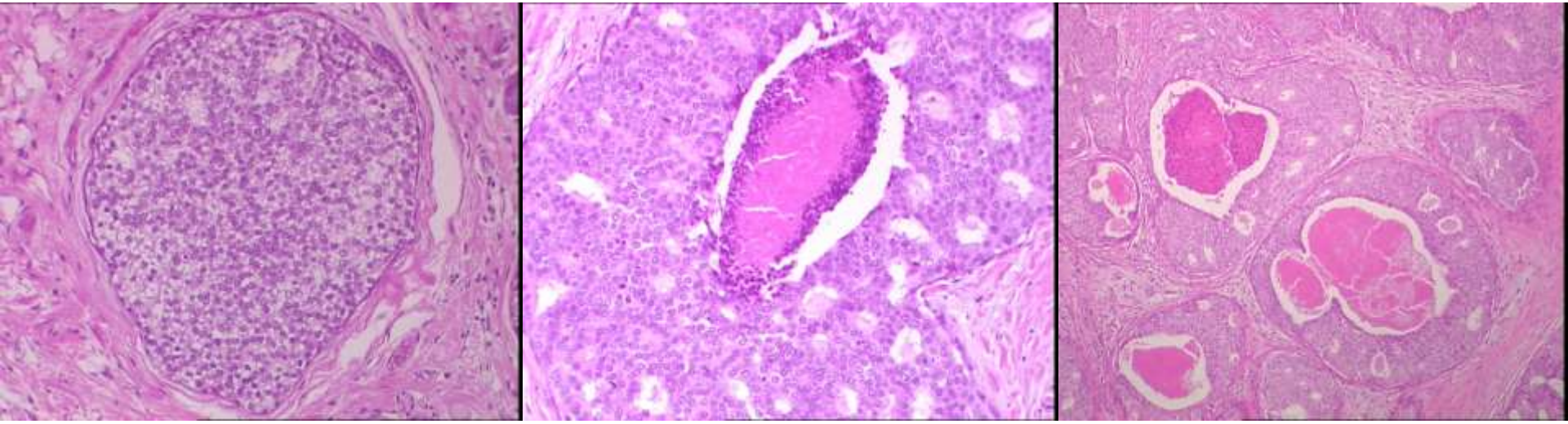




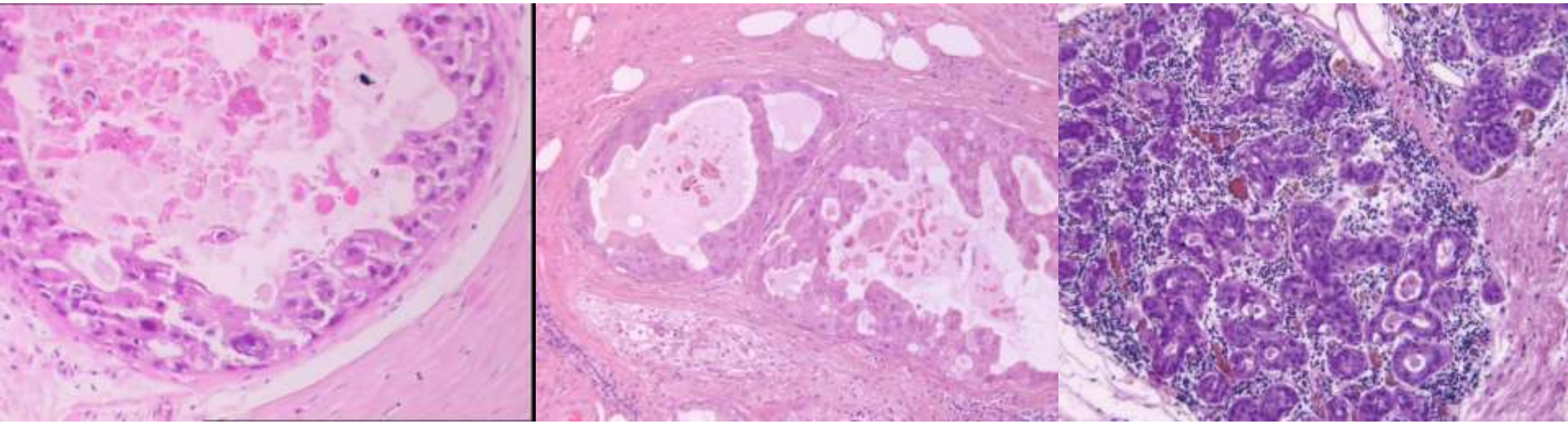
Mikropapilläres DCIS



DCIS is eine heterogene Gruppe



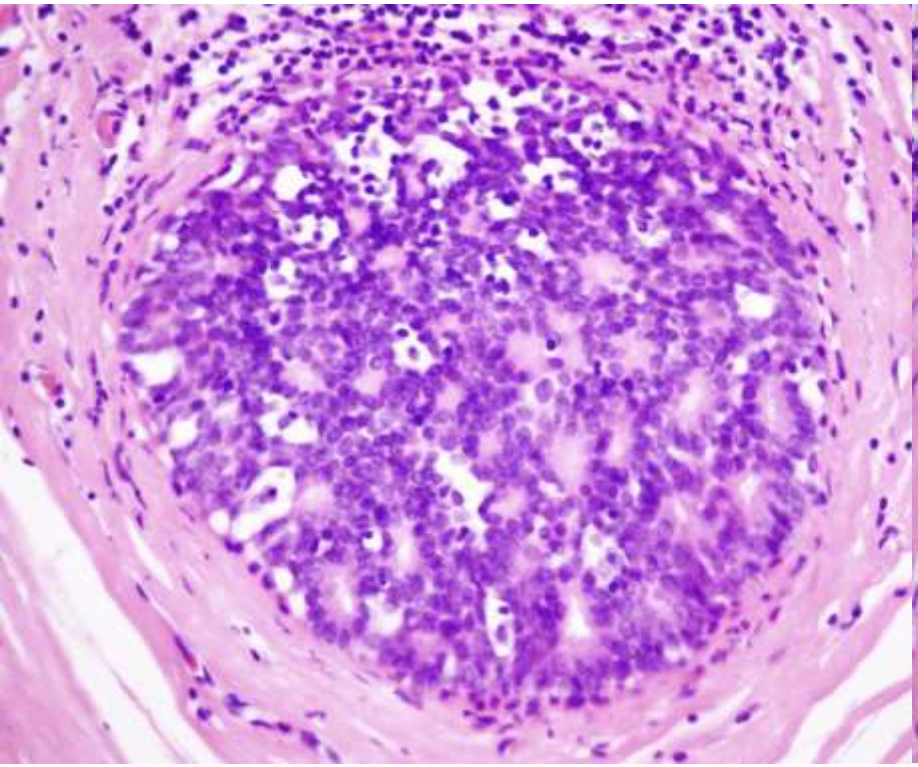
'DCIS is a small but critical part of the breast cancer puzzle' M.Silverstein



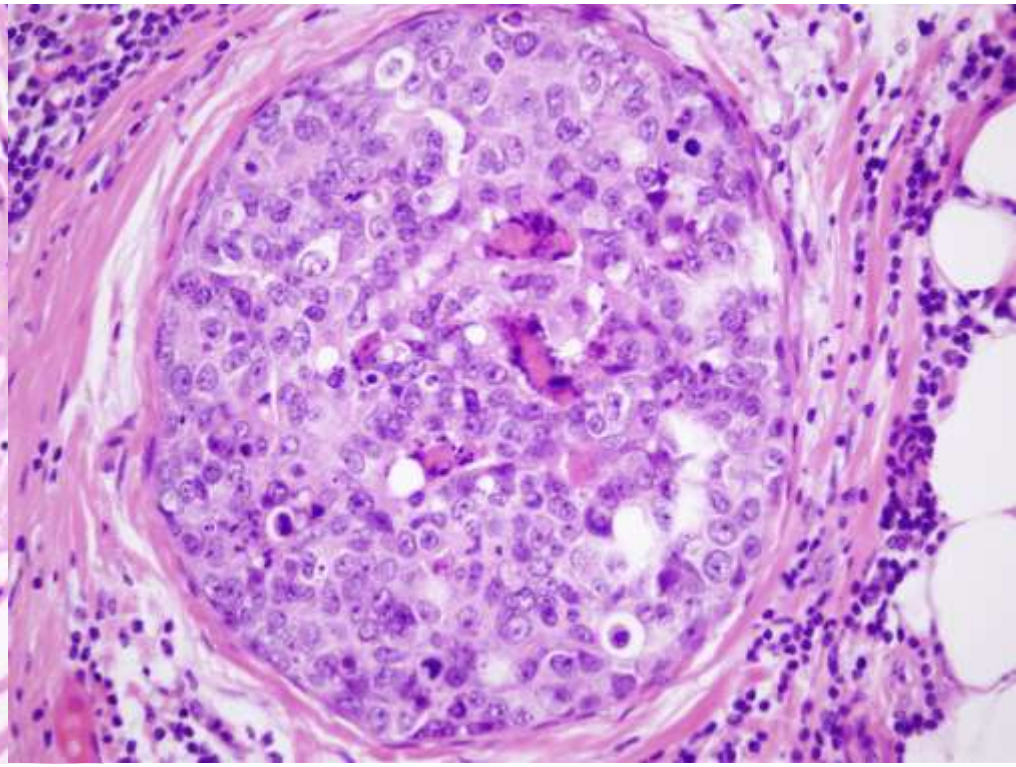
DCIS ist kein obligates Prekursor des invasiven Brustkarzinoms

Farabegoli et al J Pathol 196:280-286, 2002

Nuklear Grade: niedrig (low), intermediar, hoch (high)

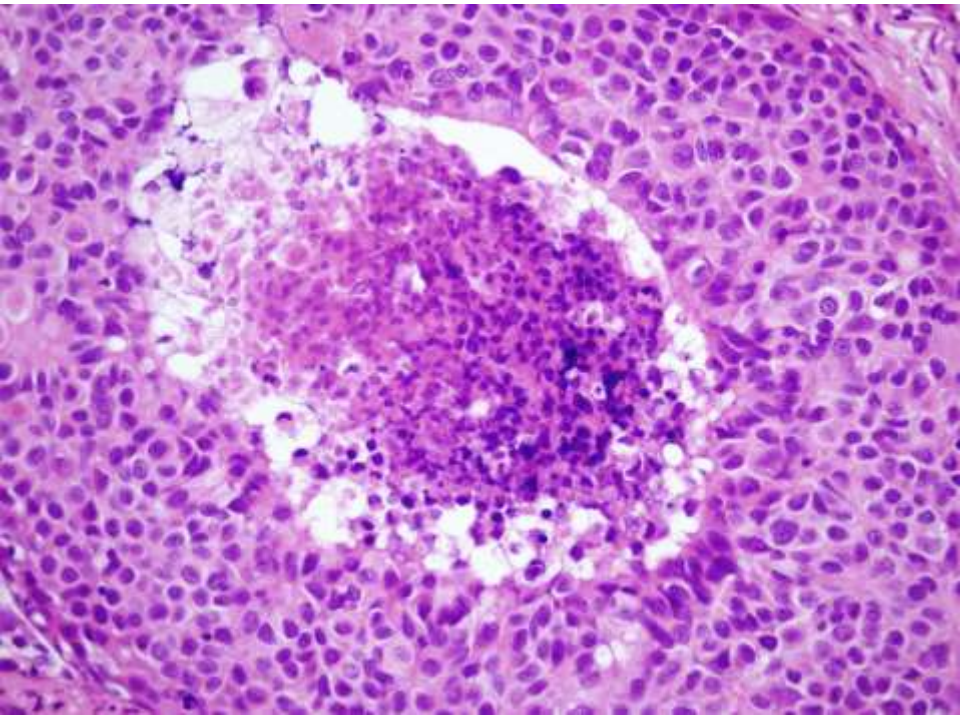


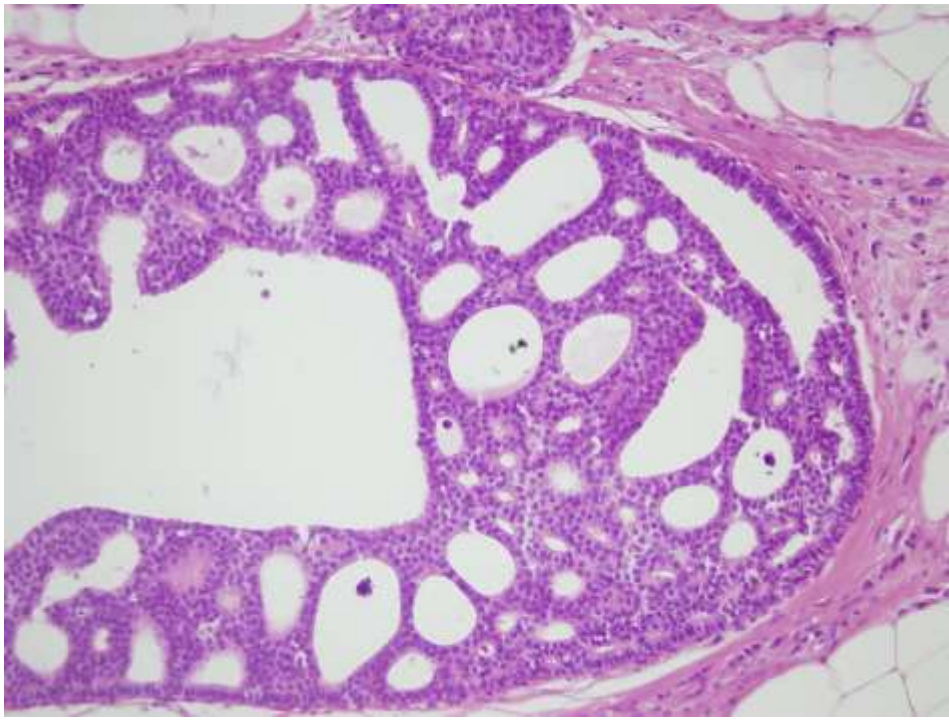
Niedrige nukleares Grade



Hoches nukleares Grade

Comedo Nekrose: ja oder nein



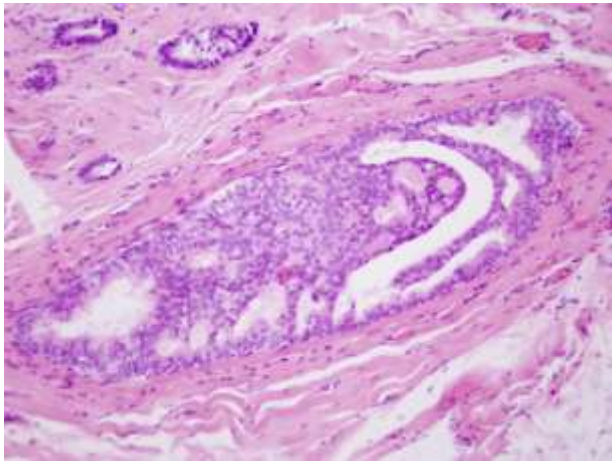


DCIS Grade - Roland Holland

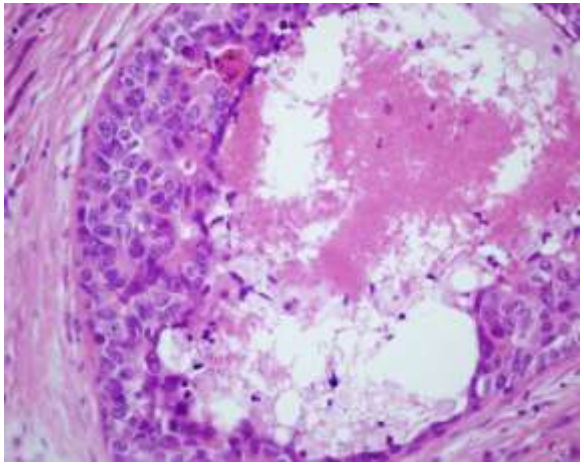
	Nuclei	Mitoses	Necrosis	Polarisation
HIGH GRADE	pleomorphic, irregular, large nucleoli, coarse chromatin	often seen	central, comedo, amorph calcif +	absent
INTERMEDIATE G.	mild-moderate pleomorphism, nucleoli evident fine to coarse chromatin	occasional	variable, calcif. lamin. or amorph	moderate
LOW GRADE	monomorphic, regular, fine fine chromatin	rare	absent/rare laminated calcif.	marked

DCIS Grade - Van Nuys

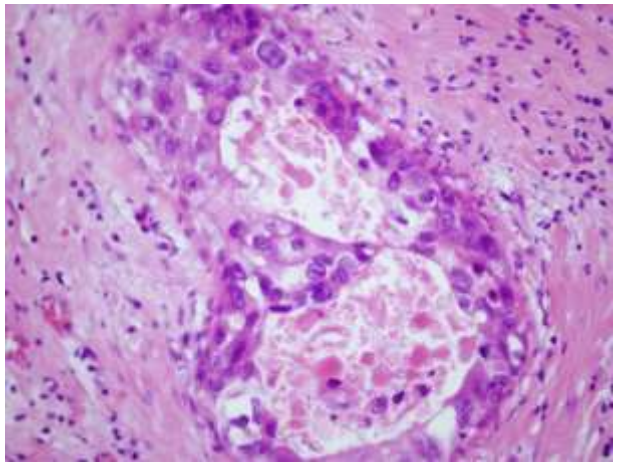
- Nicht-high Grade Kerne, keine Nekrose
- Nicht-high Grade Kerne, Nekrose ist anwesend
- High grade Kerne, Nekrose ja/nein



VN1



VN2



VN3

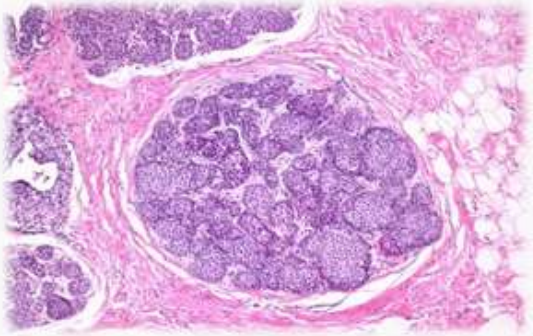
Van Nuys Prognostisches Index

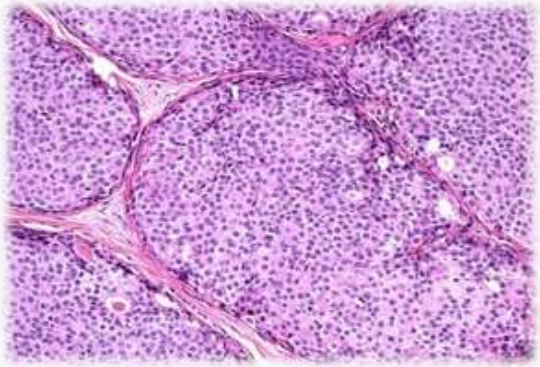
VN grade	1	2	3
Grösse	16mm	16-40mm	>40mm
Abstand (Distance)	>10mm	1-10mm	<1mm
Alter	>60	40-60	<40
SCORE	**1**	**2**	**3**

Minimum Score: 4 Maximum Score 12
Korreliert mit der Prognose und hilft die passende Terapie auszuwahlen

LOBULAR CARCINOMA IN SITU - MORPHOLOGY

- Dyscohesive round cells with oval or round nuclei and small nucleoli. Absence of atypia, pleomorphism, mitoti activity, necrosis.
- Involved acini – recognizable as lobules.
- Mucin-positive signet-ring cells.
- ER and PR +ve.

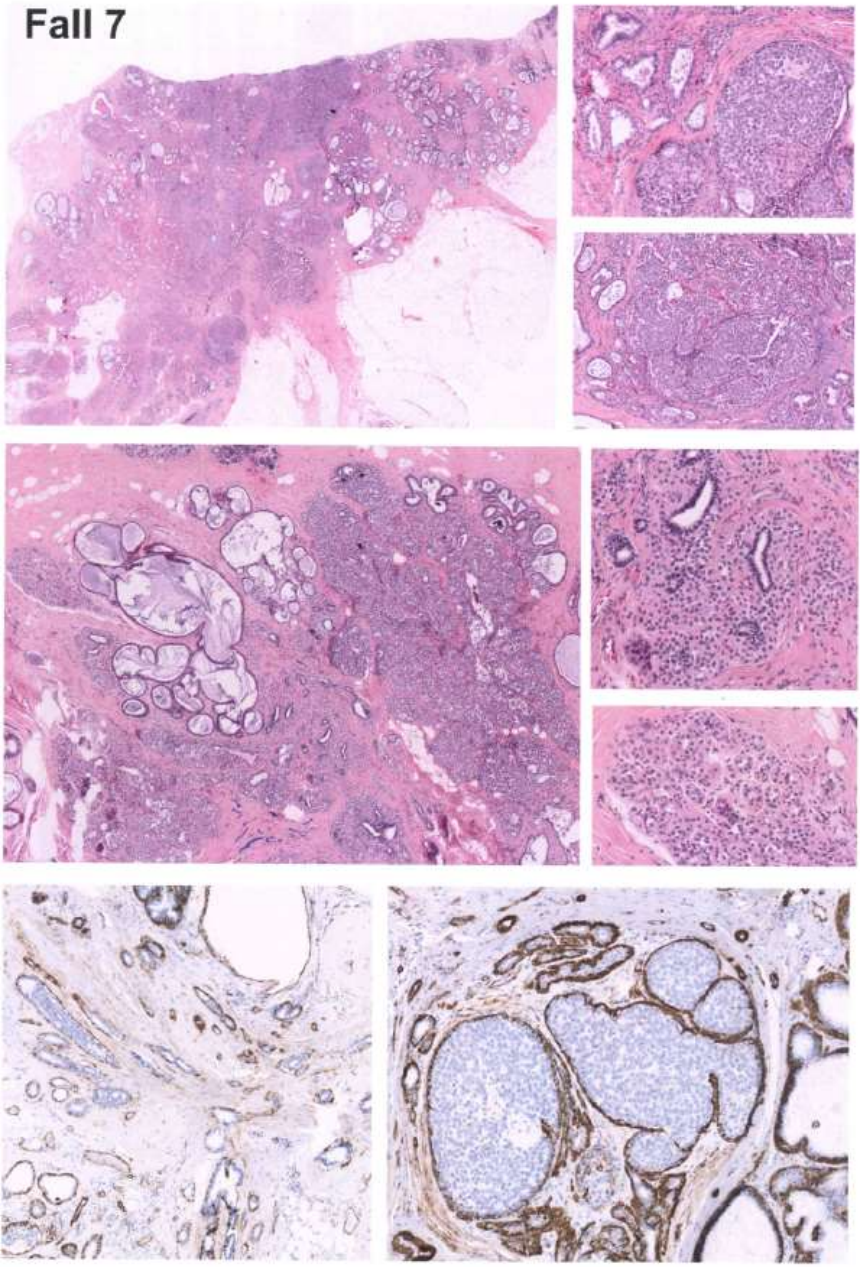




LOBULAR CARCINOMA IN SITU

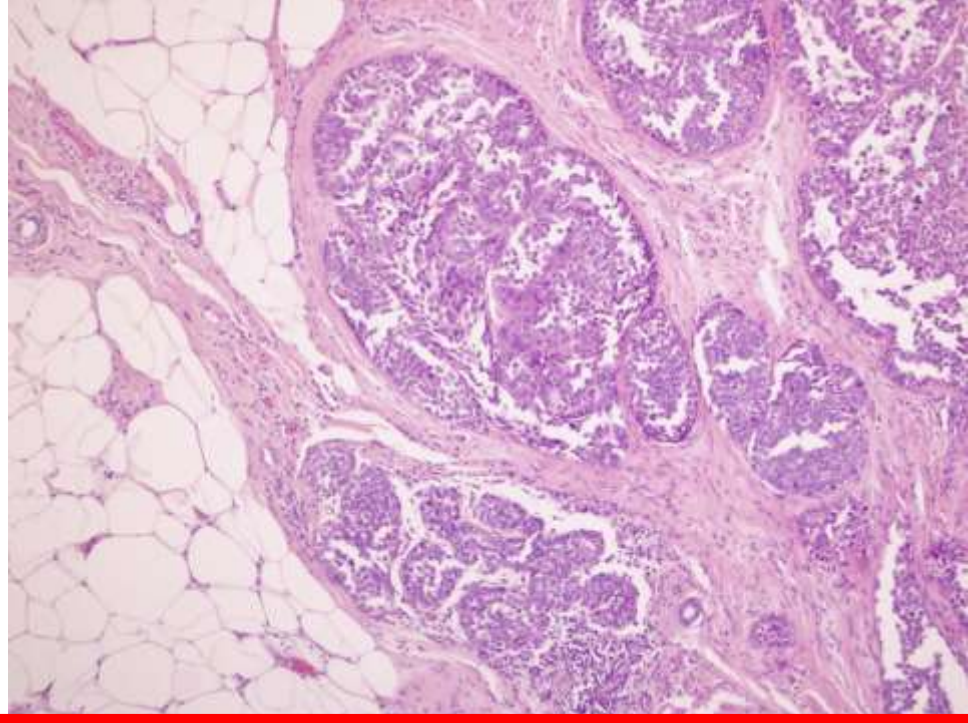
- Invasive carcinoma → 1% per year.
- Both breasts - increased risk. Risk - slightly higher in the ipsilateral breast.
- Invasive carcinomas - lobular type.
- **Treatment:**

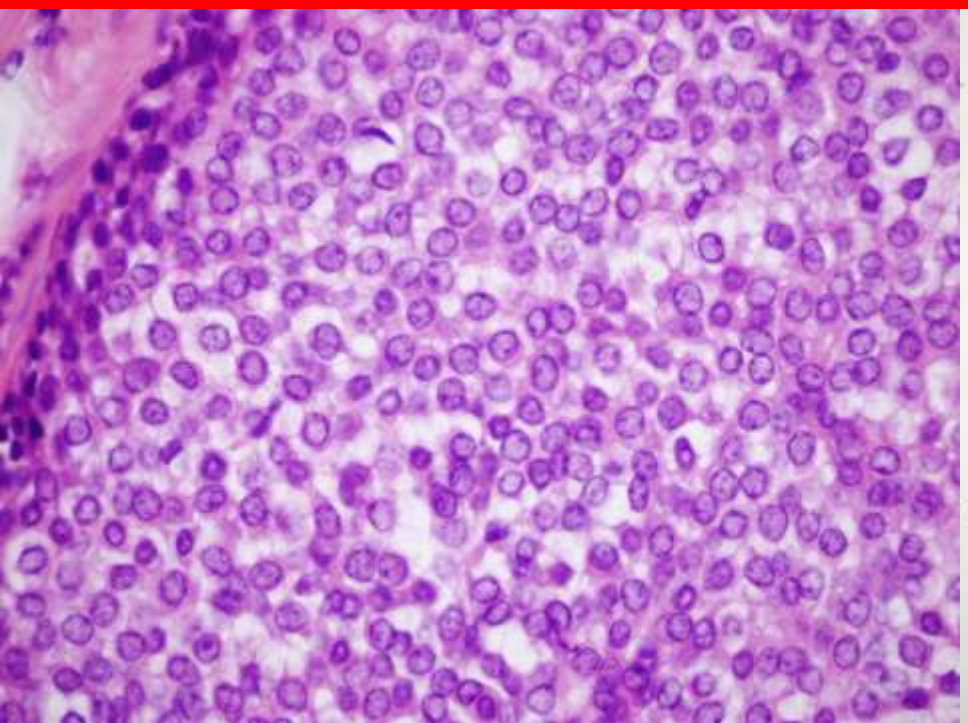
10. Bilateral prophylactic mastectomy.
11. Tamoxifen.
12. Close clinical follow-up.
13. Mammographic screening.

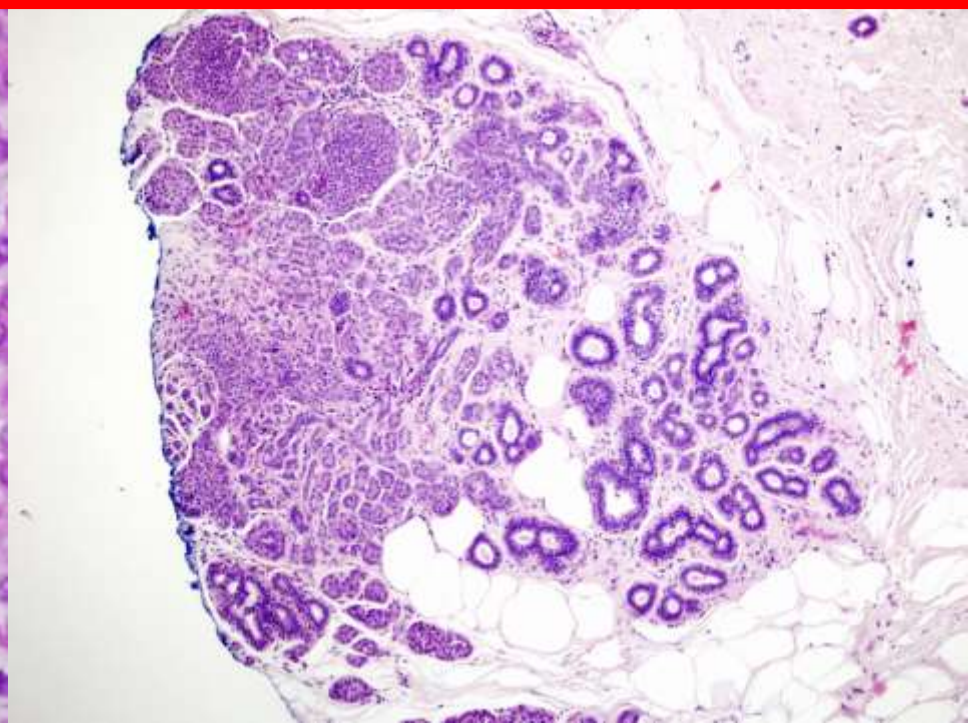


Lobulares Carcinoma *in situ* in einer komplexen sklerosierten Lasion

In situ lobulares Karzinom
WHO: lobulare intraepitheliale Neoplasie
LN1 - 3. LN3=LCIS

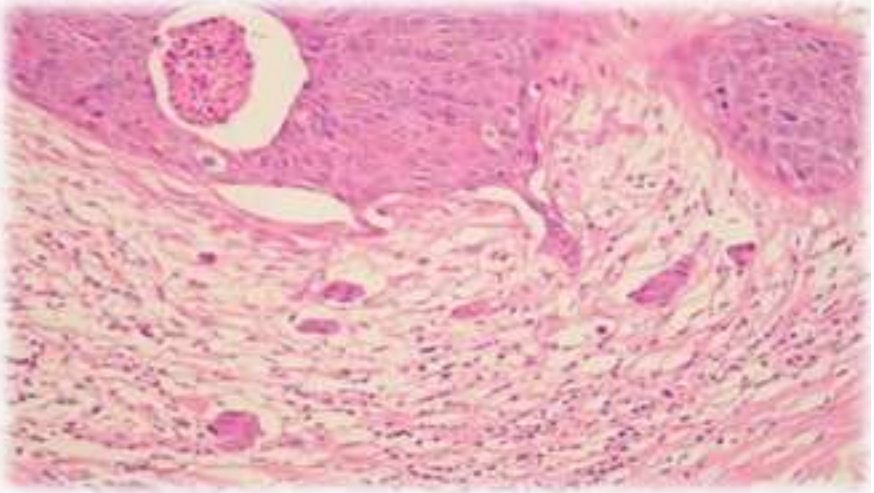


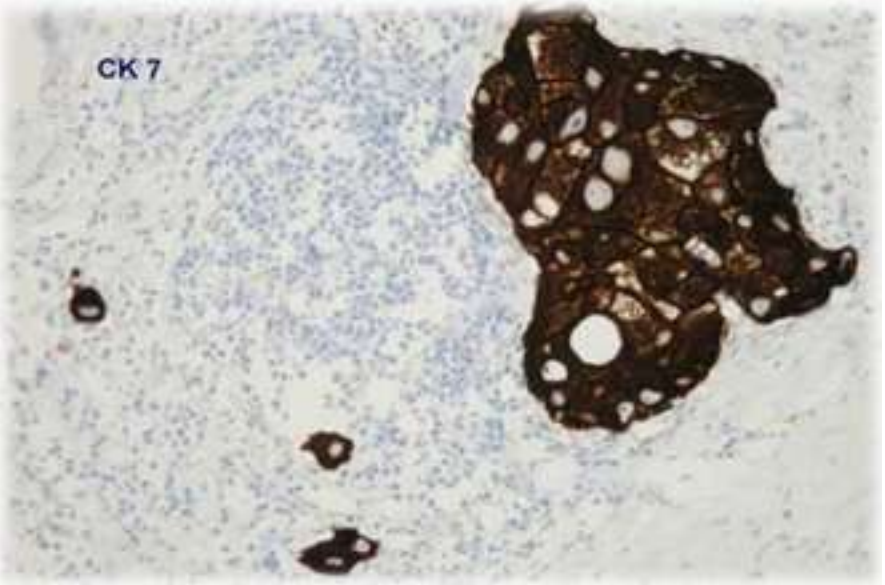


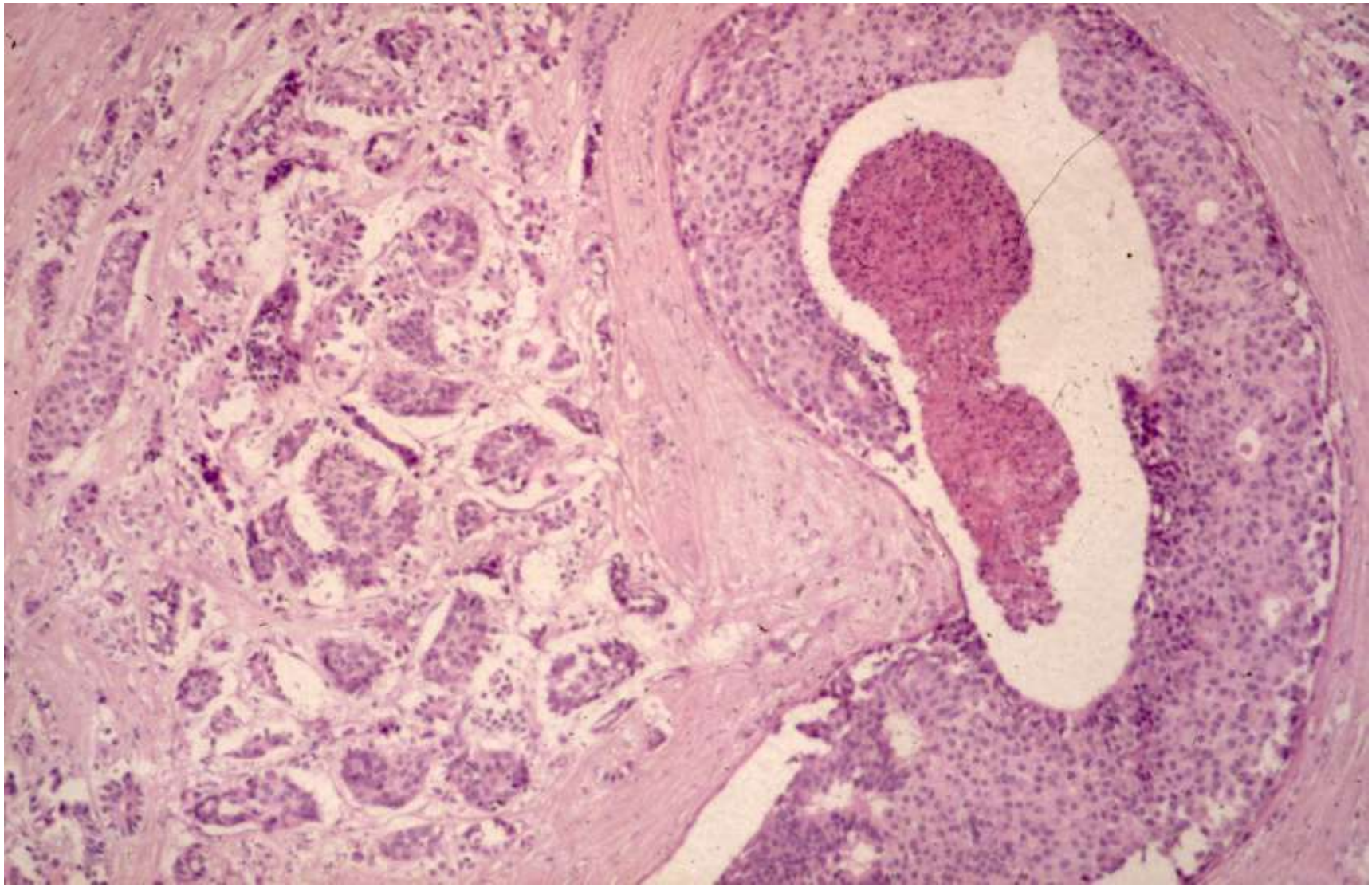


DCIS WITH MICROINVASION

- Area of invasion through BM → stroma - > 0.1 cm.
- Assoc. with comedocarcinoma.
- Few microinvasion foci → prognosis similar to DCIS.







Mikroinvasives DCIS

MANNLICHE BRUST

GYNECOMASTIE

Pubertat

Leberzirrhose

Hormon produzierende testikulare Tumoren

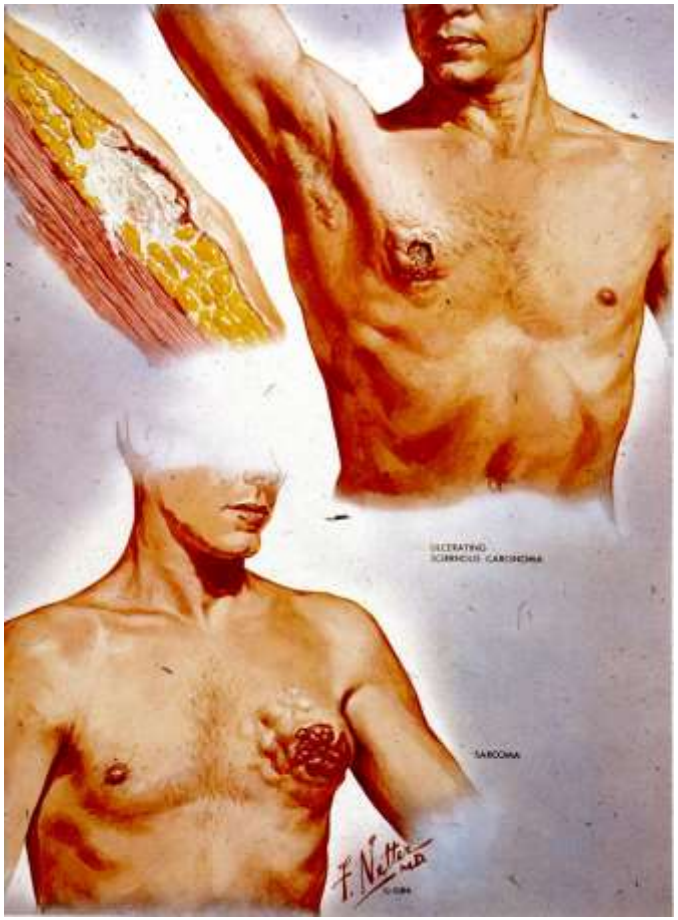
Lungenkarzinom: paraneoplastisch

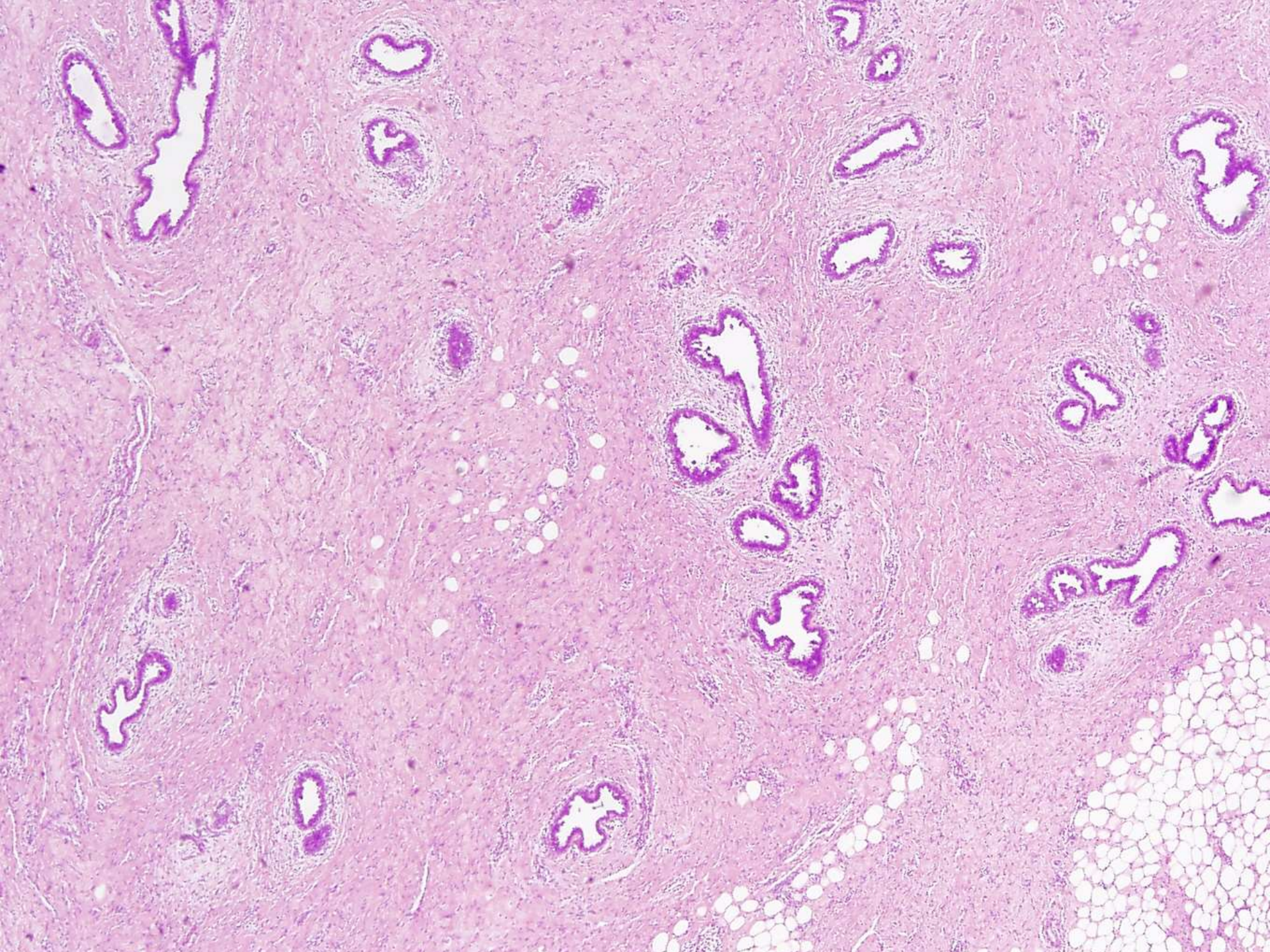
Prostata Karzinom nach der Therapie

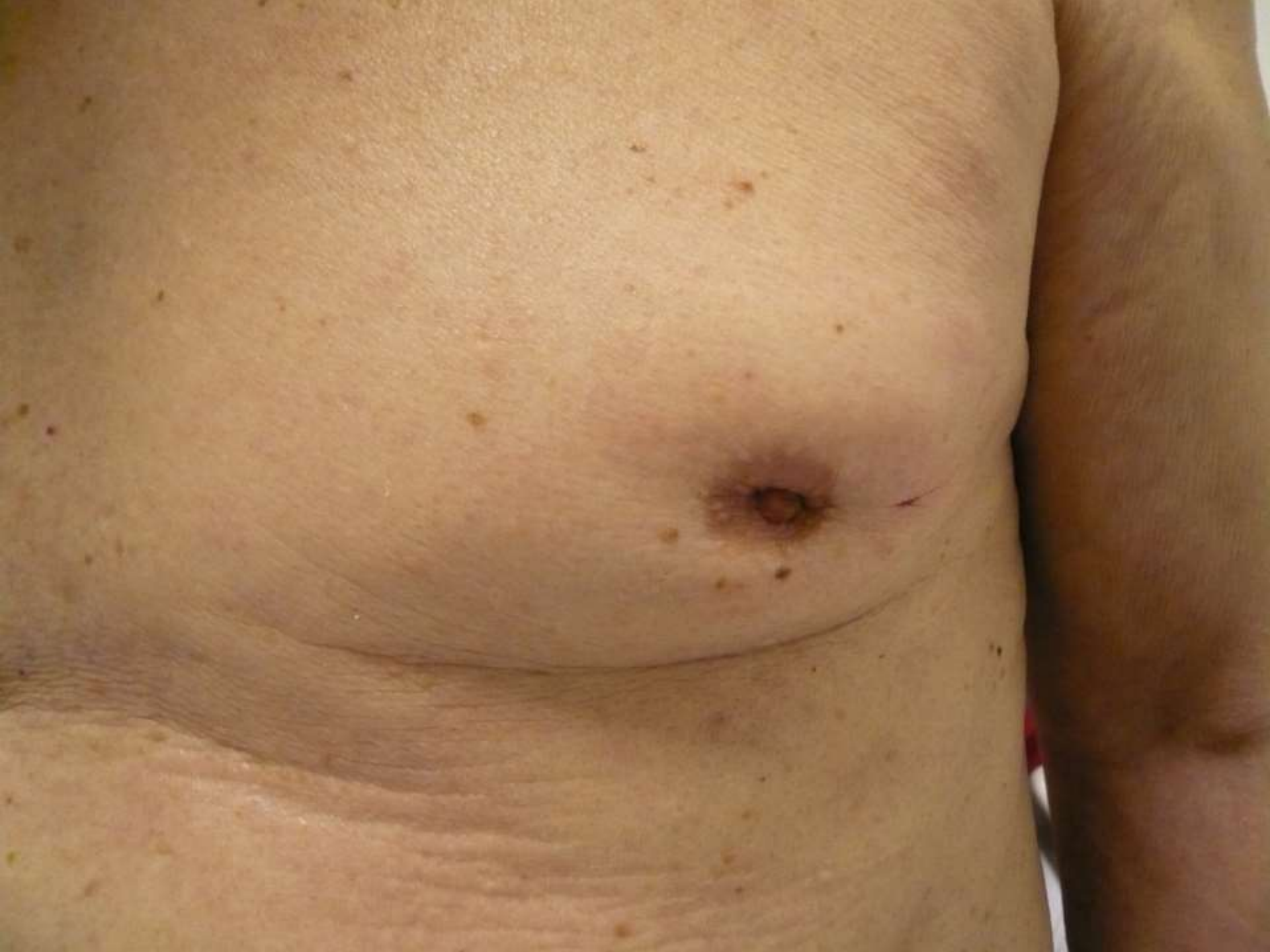
Idiopathisch

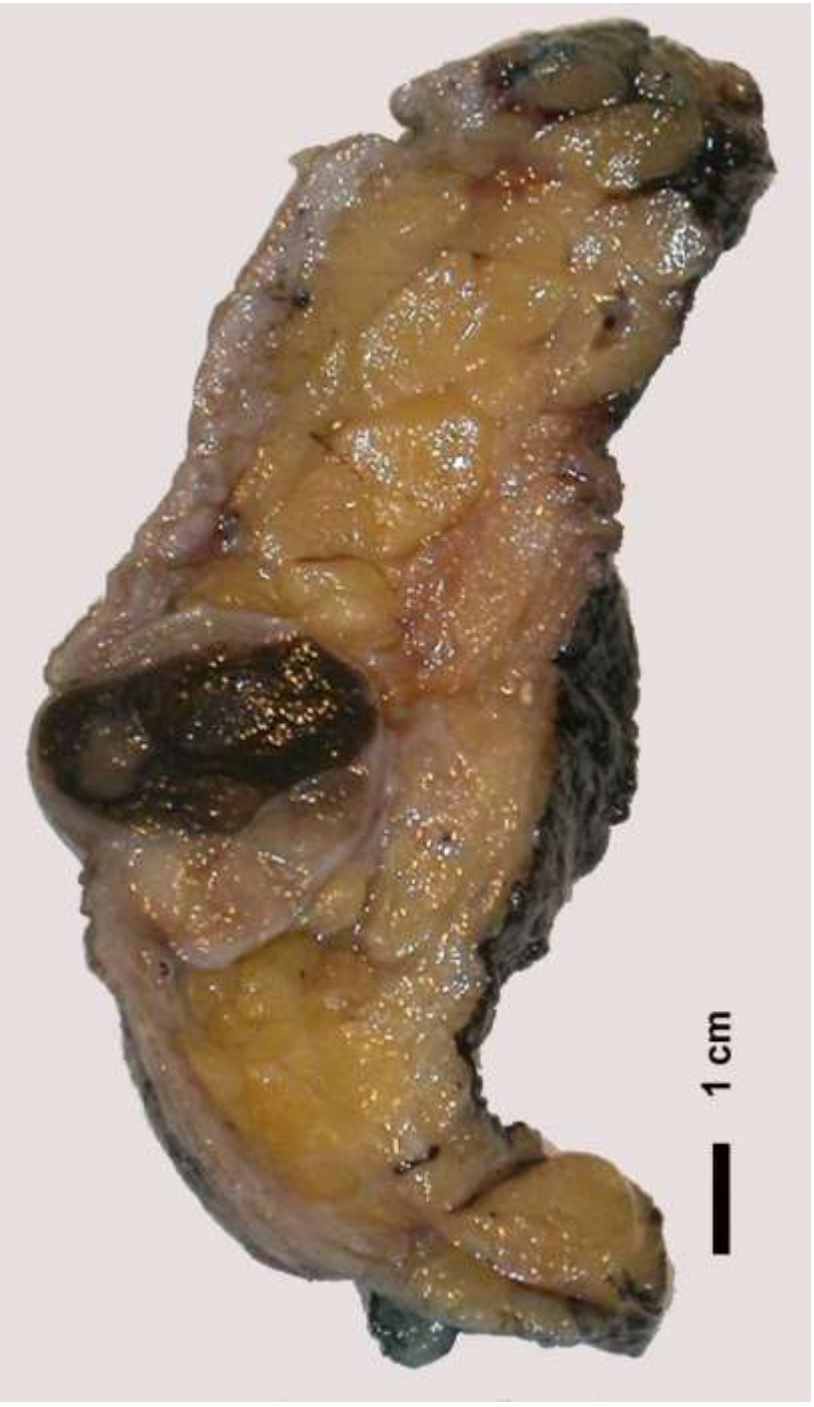
MANNLICHER BRUSTKREBS

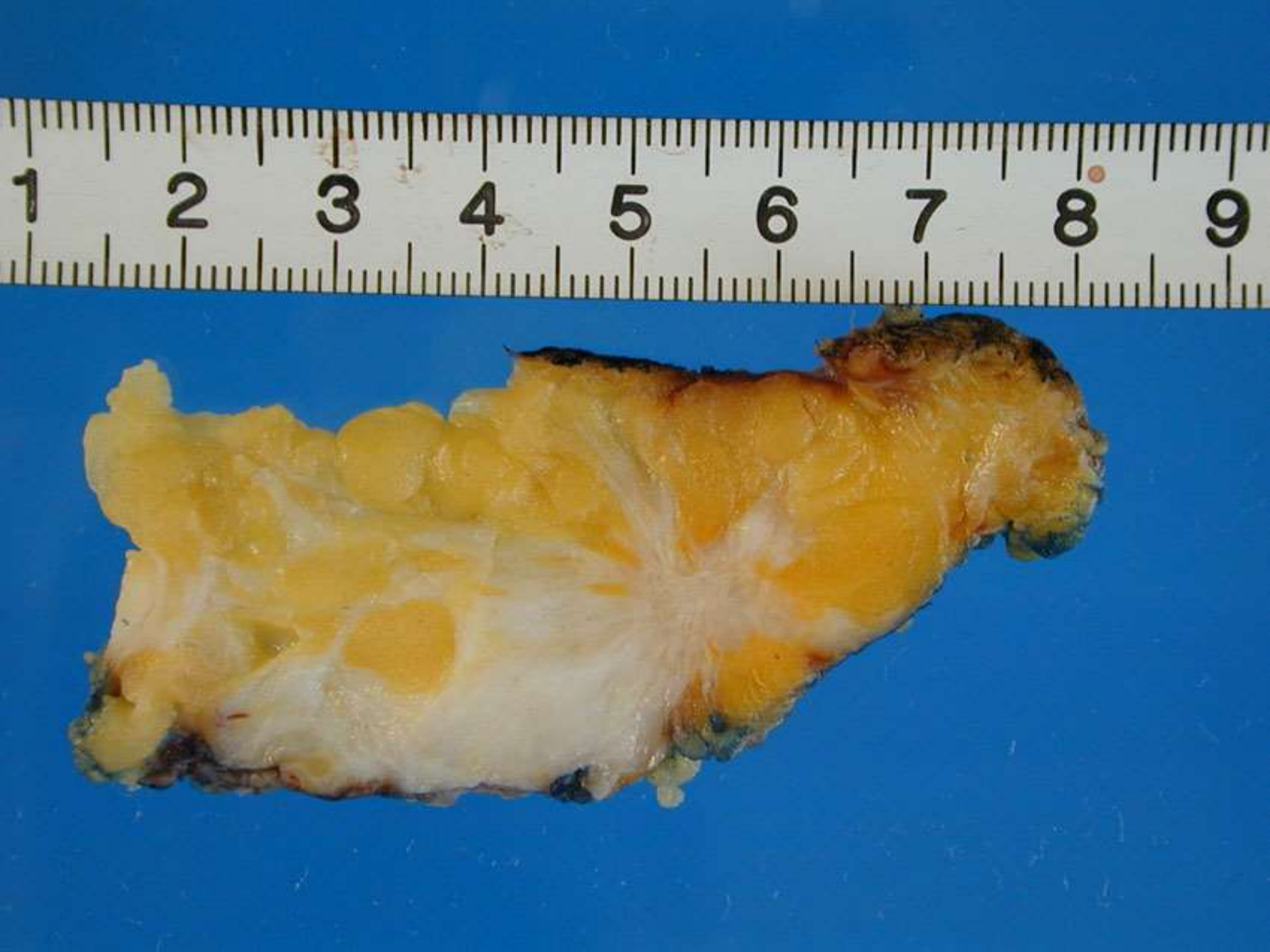
sekten, Prognose ist ungünstig








1 cm


1 2 3 4 5 6 7 8 9

Tab. 1: Die aktuelle WHO-Klassifikation der invasiven Mammakarzinome (Lakhani et al., 2012)

Histologischer Typ	ICD-O Code
• Invasives Karzinom, kein spezieller Typ (NST)	8500/3
• Pleomorphes Karzinom	8022/3
• Karzinom mit osteoklastenartigen Riesenzellen	8035/3
• Karzinom mit chorionkarzinomartigen Merkmalen	
• Karzinom mit melanotischen Merkmalen	
• Invasives lobuläres Karzinom	8520/3
• Klassisches lobuläres Karzinom	
• Solides lobuläres Karzinom	
• Alveoläres lobuläres Karzinom	
• Pleomorphes lobuläres Karzinom	
• Tubulolobuläres Karzinom	
• Gemischtes lobuläres Karzinom	
• Tubuläres Karzinom	8211/3
• Kribriformes Karzinom	8201/3
• Muzinöses Karzinom	8480/3
• Karzinom mit medullären Eigenschaften	
• Medulläres Karzinom	8510/3
• Atypisches medulläres Karzinom	8513/3
• Invasives Karzinom NST mit medullären Eigenschaften	8500/3
• Karzinom mit apokriner Differenzierung	#
• Karzinom mit siegelringzelliger Differenzierung	#
• Invasives mikropapilläres Karzinom	8507/3*
• Metaplastisches Karzinom, kein spezieller Typ	8575/3
• Low-grade adenosquamöses Karzinom	8570/3
• Fibromatose-ähnliches metaplastisches Karzinom	8572/3
• Plattenepithelkarzinom	8070/3
• Spindelzellkarzinom	8032/3
• Metaplastisches Karzinom mit mesenchymaler Differenzierung	
• Chondroide Differenzierung	8571/3
• Ossäre Differenzierung	8571/3
• Andere mesenchymale Differenzierung	8575/3
• Gemischtes metaplastisches Karzinom	8575/3
• Myoepitheliales Karzinom	8982/3
Seltene Typen:	
• Karzinome mit neuroendokrinen Eigenschaften:	
• Neuroendokriner Tumor, gut differenziert	8246/3
• Neuroendokrines Karzinom, schlecht differenziert (kleinzelliges Karzinom)	8041/3
• Karzinom mit neuroendokriner Differenzierung	8574/3
• Sekretorisches Karzinom	8502/3
• Invasives papilläres Karzinom	8503/3
• Azinuszell-Karzinom	8550/3
• Mukoepidermoides Karzinom	8430/3
• Polymorphes Karzinom	8525/3
• Onkozytäres Karzinom	8290/3
• Lipidreiches Karzinom	8314/3
• Glykogenreiches klarzelliges Karzinom	8315/3
• Sebazeöses Karzinom (Talgdrüsenkarzinom)	8410/3
• Adenoid-zystisches Karzinom	8200/3
• Adenomyoepitheliom mit Karzinom	8983/3*
• Gekapseltes papilläres Karzinom mit Invasion	8504/3
• Solides papilläres Karzinom, invasiv	8509/3

ICD-O= International Classification of Diseases for Oncology

ICD-O-Codierung erfolgt entsprechend des primären invasiven Typs

*neuer ICD-O Code (genehmigt von dem IARC/WHO-Kommitte für ICD-O)

Tab. 2: Die wichtigsten Änderungen in der 4. Auflage der WHO-Klassifikation (Lakhani et al., 2012)

3. Auflage WHO (Tavassoli and Devilee, 2003)	4. Auflage WHO (Lakhani et al., 2012)	Art der Änderung
Invasives duktales Karzinom NOS (not otherwise specified, nicht näher bezeichnet)	**Invasives Karzinom NST (no special type, kein spezieller Typ)**	Terminologie
Medulläres Karzinom Invasives duktales Karzinom mit medullären Eigenschaften	**Karzinom mit medullären Eigenschaften**	Zusammenfassung der Karzinome mit medullären Eigenschaften in einer Kategorie.
Apokrines Karzinom	**Karzinom mit apokriner Differenzierung**	Keine eigenständige Entität mehr. Klassifikation entsprechend des primären invasiven Typs
Siegelringzellkarzinom	**Karzinom mit siegelringzelliger Differenzierung**	Keine eigenständige Entität mehr. Klassifikation entsprechend des primären invasiven Typs
- Atypischer Karzinoidtumor - Solides neuroendokrines Karzinom - Kleinzelliges Karzinom - Großzelliges neuroendokrines Karzinom	**- Neuroendokriner Tumor, gut differenziert** **- Karzinom mit neuroendokriner Differenzierung** **- Neuroendokrines Karzinom, schlecht differenziert (kleinzelliges Karzinom)**	Klassifikation in Analogie zu Karzinomen in anderen Organsystemen.
Rein epitheliale metaplastische Karzinome - Plattenepithelkarzinom - Adenokarzinom mit Spindelzell-Metaplasie - Adenosquamöses Karzinom - Mukoepidermoides Karzinom Gemischtes epithelial-/mesenchymales metaplastisches Karzinom	**Metaplastisches Karzinom** **- Low-grade adenosquamöses Karzinom** **- Fibromatose-ähnliches metaplastisches Karzinom** **- Plattenepithelkarzinom** **- Spindelzellkarzinom** **- Metaplastisches Karzinom mit mesenchymaler Differenzierung** • **Chondroide Differenzierung** • **Ossäre Differenzierung** • **Andere mesenchymale Differenzierung** **Myoepitheliales Karzinom**	Deskriptives Klassifikationssystems. Herausnahme des mukoepidermoiden Karzinoms. Aufnahme des myoepithelialen Karzinoms.

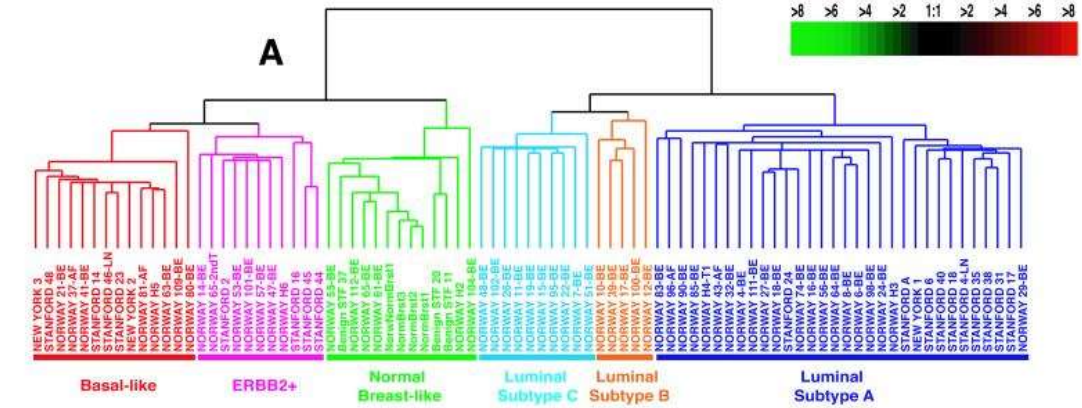
BÖSARTIGE TUMOREN

- **Invasives duktales Karzinom (IDK)**

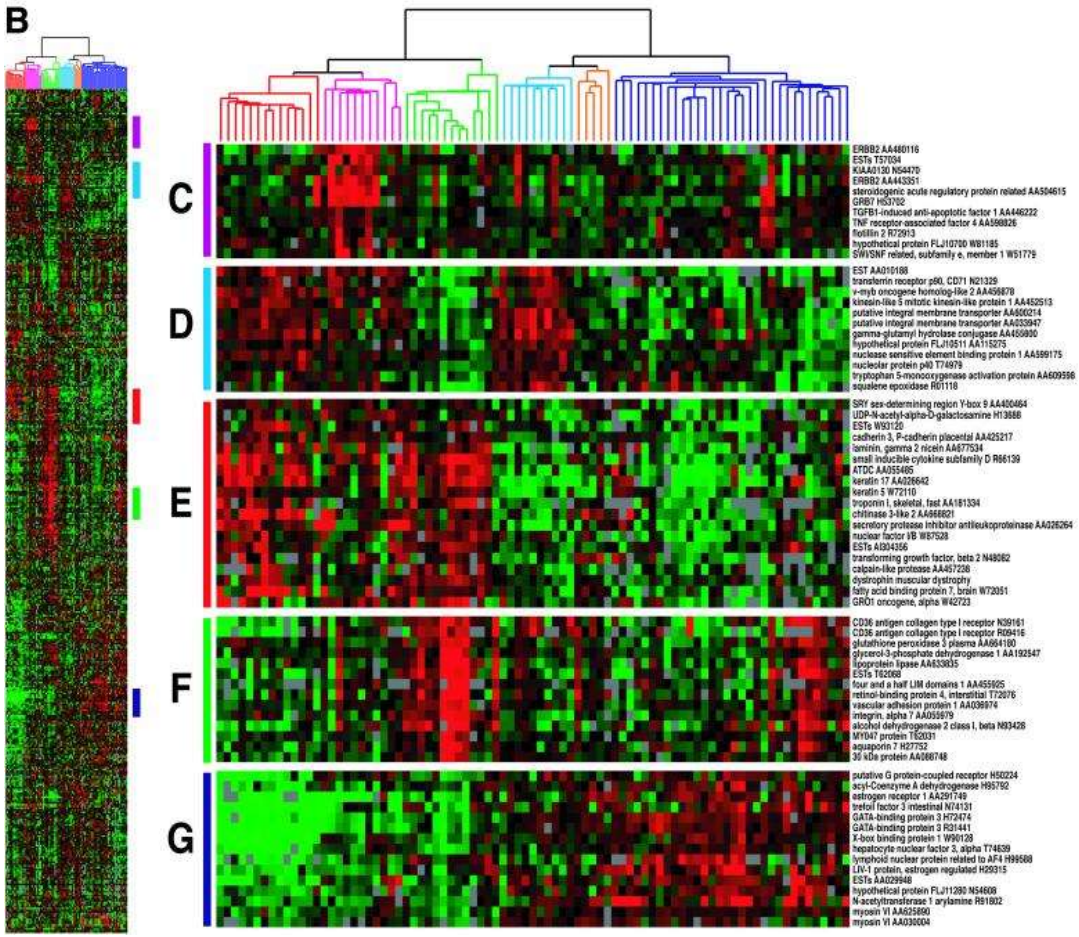
Es ist mit einem Anteil vont etwa 85 % die häufigste Variante
krallenförmige Fortsätze
solide, szirrhös, adenomatös

- **Invasives lobuläres Karzinom (ILK)**

mit einem Anteil von ~ 10 %
~ 10-30 % der Fällen sind bilateral !!!
Einzellzellreihen, “ Indianer auf dem Kriegspfad” oder “Gänsemarsch”



Neue Klassifikation



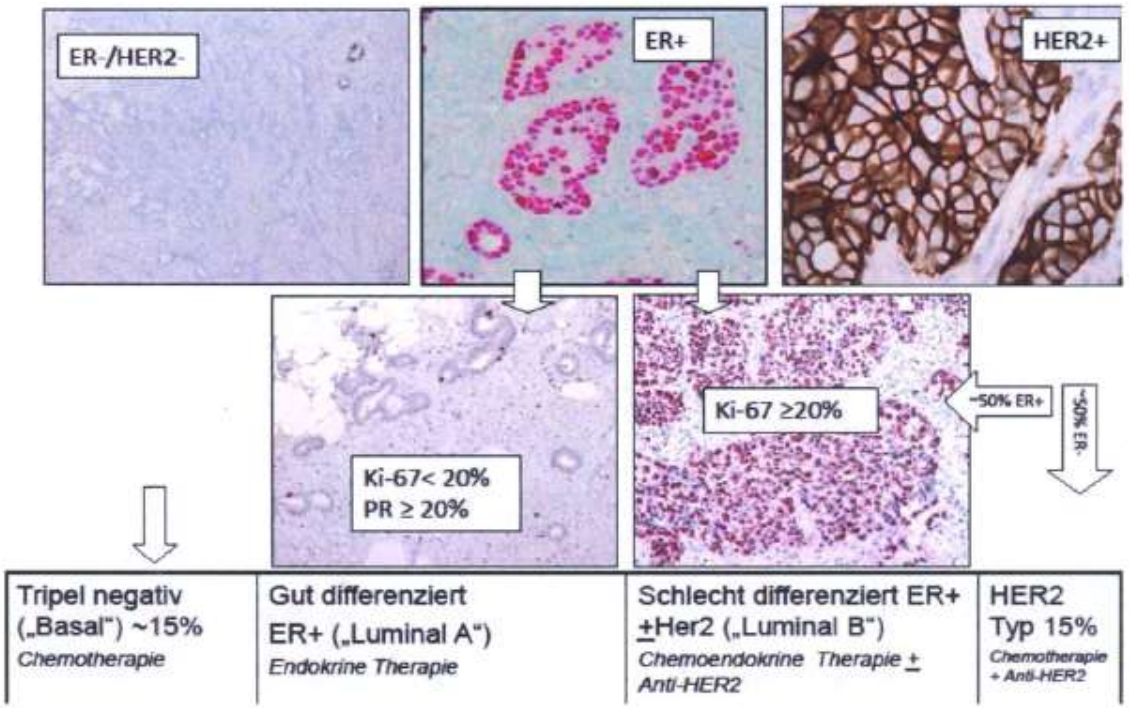
Luminal A
Luminal B
Basal-like
Her2
Normal-ahnlich

Neue Klassifikation

- Basiert an GENETISCHEN Fingerprint
- Östrogen Rezeptor positiv
  - Luminal Typ A
  - Luminal Typ B
- Östrogen Rezeptor negativ
  - Normal Brust-like
  - Her 2 positiv
  - „Triple negativ”

Perou et al 2000, van’t Veer 2002

Intrinsische Typen des Mammakarzinoms



Tab. 1: Übersicht der immunhistochemisch bestimmten Phänotypen des Mammakarzinoms [60]

Luminal A	Luminal B HER2 negativ	Luminal B HER2 positiv	HER2 Typ	Tripel negativer Typ
ER positiv	ER positiv	ER positiv	ER negativ	ER negativ
PR positiv (≥20%)	PR positiv/negativ	PR positiv/negativ	PR negativ	PR negativ
HER2 negativ	HER2 negativ	HER2 positiv	HER2 positiv	HER2 negativ
Ki-67 <20%	Ki-67 ≥20%			
G1, G2	G2, G3	G2, G3	G2, G3	G1, G2, G3

IAP, Bonn, 2014

Tab. 2 Klassifikation der Hormonrezeptorexpression

Klassifikation	ASCO/CAP 2010	Remmele-Score	Allred-Score	St Gallen Konsensus 2009
Bewertung	Prozentualität	Färbeintensität (1-3)x Prozentualität (1-4) = max. 12	Färbeintensität (1-3)+ Prozentualität (1-5)= max. 8	Prozentualität
		> 0 bis < 10% = 1	> 0 bis 1% = 1	Schwach positiv: >0-49%
		10 bis < 50% = 2	> 1% bis 10% = 2	
		50% bis 80% = 3	> 10% bis 33% = 3	Hoch positiv: ≥ 50%
		> 80% = 4	> 33% bis 66% = 4	
			> 66% bis 100% = 5	
Positiv	Positiv ≥1%	Positiv ≥ 3 (Score)	Positiv ≥ 3 (Score) 1% mäßig gefärbt	Positiv > 0 (%)
Negativ	Negativ <1%	Negativ ≤ 2 (Score)	Negativ ≤ 2 (Score)	Negativ 0 (%)
Diskrepante Positivitäts-Grenze im Vergleich zu ASCO/CAP		1% mindestens stark gefärbt	1% mindestens mäßig gefärbt	>0%-<1%
Diskrepante Negativitäts-Grenze im Vergleich zu ASCO/CAP		49% schwach gefärbt; 9% mäßig gefärbt	1% schwach gefärbt	>0%-<1%

Tabelle 3: Bewertung der HER2 Analyse

Positiver HER-2-Status	Grenzwertiger HER-2-Status	Negativer HER-2-Status
• immunhistochemisch 3+ (gleichmäßige, starke, die gesamte Zellzirkumferenz erfassende Membranfärbung von > 10 % der invasiven Tumorzellen) • und/oder durchschnittliche HER-2-Gen-Kopienzahl ≥ 6 pro Zellkern in mindestens 20 zusammenhängenden invasiven Tumorzellen • und/oder ISH/CISH-Ratio positiv: HER-2/Chromosom-17-Quotient ≥ 2 in mindestens 20 zusammenhängenden invasiven Tumorzellen	• immunhistochemischer Score 2+ (schwache bis mäßige oder ungleichmäßige die gesamte Zellzirkumferenz erfassende[1)] Membranfärbung von >10 % der invasiven Tumorzellen oder starke komplette Membranreaktion in ≤ 10 % der invasiven Tumorzellen • oder durchschnittliche HER-2-Kopienzahl ≥4 bis <6 pro Zellkern • Bei grenzwertigem Testergebnis sind weitere diagnostische Maßnahmen zur Festlegung des HER-2-Status erforderlich, was durch eine zusätzliche IHC, ISH und/oder Analyse einer anderen Gewebeprobe bewirkt werden kann.	• immunhistochemischer Score 0 und 1+ (keine Membranreaktion oder schwache, nicht die gesamte Zellzirkumferenz erfassende Membranfärbung von >10% der Tumorzellen)[1)] • oder durchschnittliche HER-2-Gen-Kopienzahl < 4 pro Zellkern. • oder ISH-Ratio HER-2/Chromosom-17-Quotient <2 bei <4 HER2 Signalen

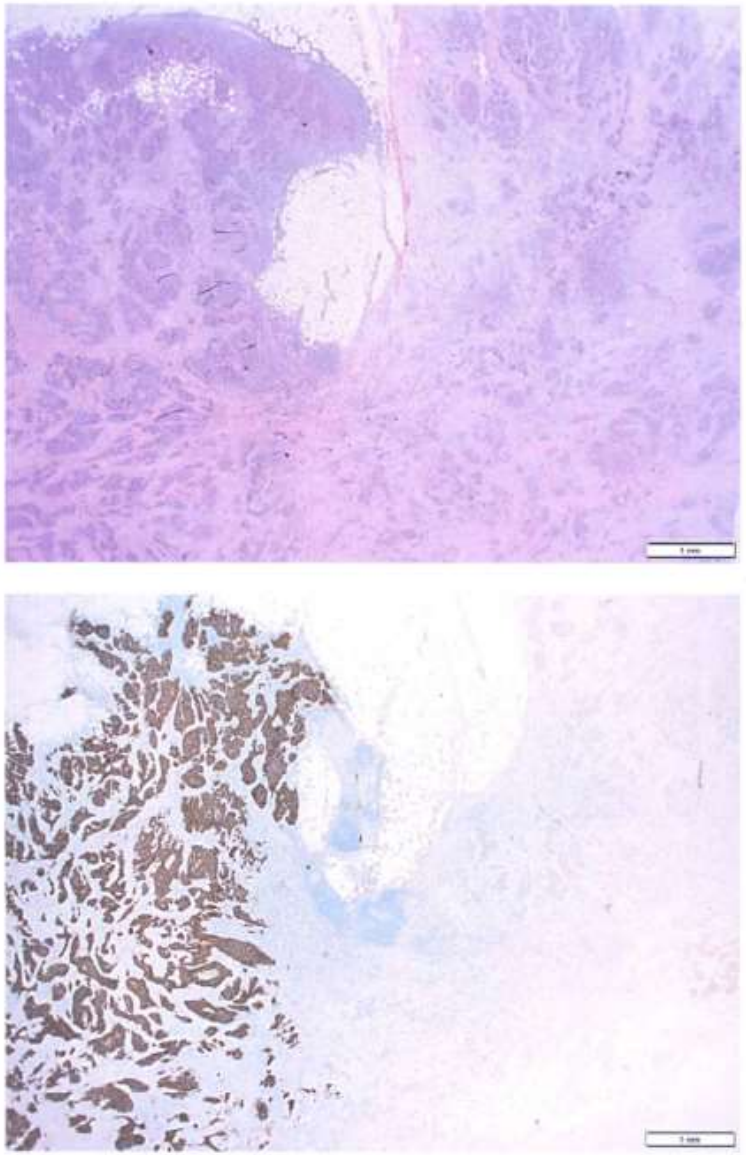
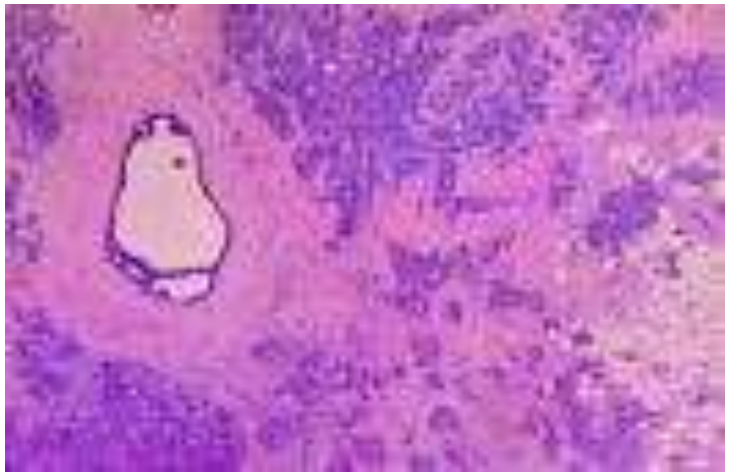


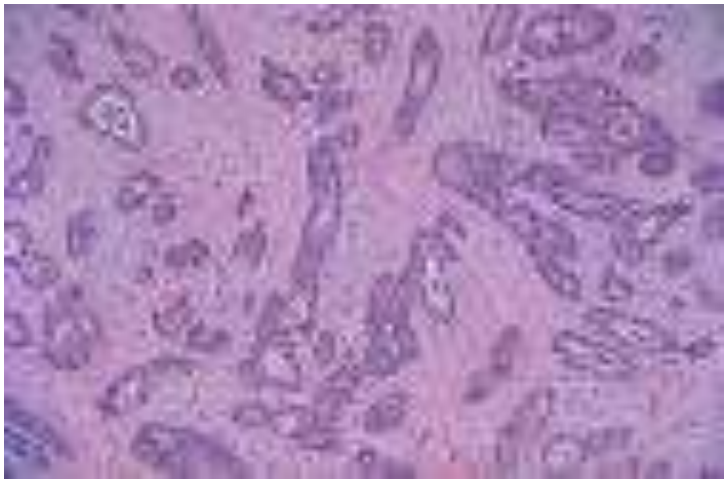
Abbildung 2a: Ein Kollissionstumor aus zwei unterschiedlich differenzierten Mammakarzinomen, der linksseitige mit HER2 Überexpression. Die Patientin entwickelte eine Lebermetastase unter Trastuzumab Therapie, die von dem rechsseitigen HER2 negativen Tumor stammte

Die neue Klassifikation

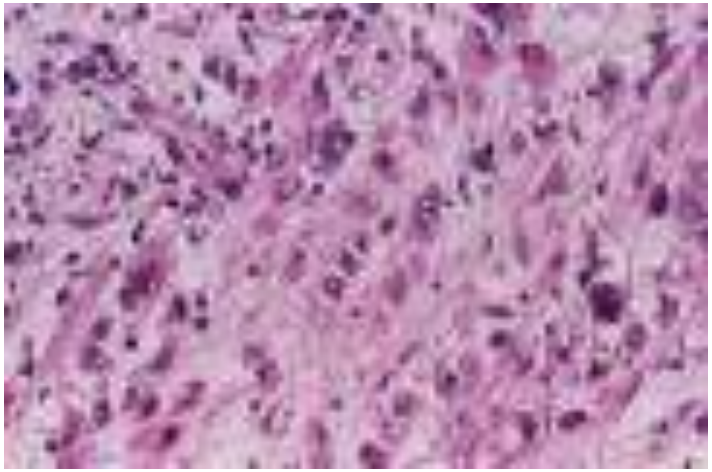
- Es ist mit der Verwendung einer 70 Gene cDNA Microarray bewiesen
- Korreliert eindeutig mit der Prognose
- Erklart die Kontroverse mit der heutigen Staging Systeme gesehen
- Es kann neue Ziele für Therapie identifizieren

Invasives duktales Karzinom (IDK)

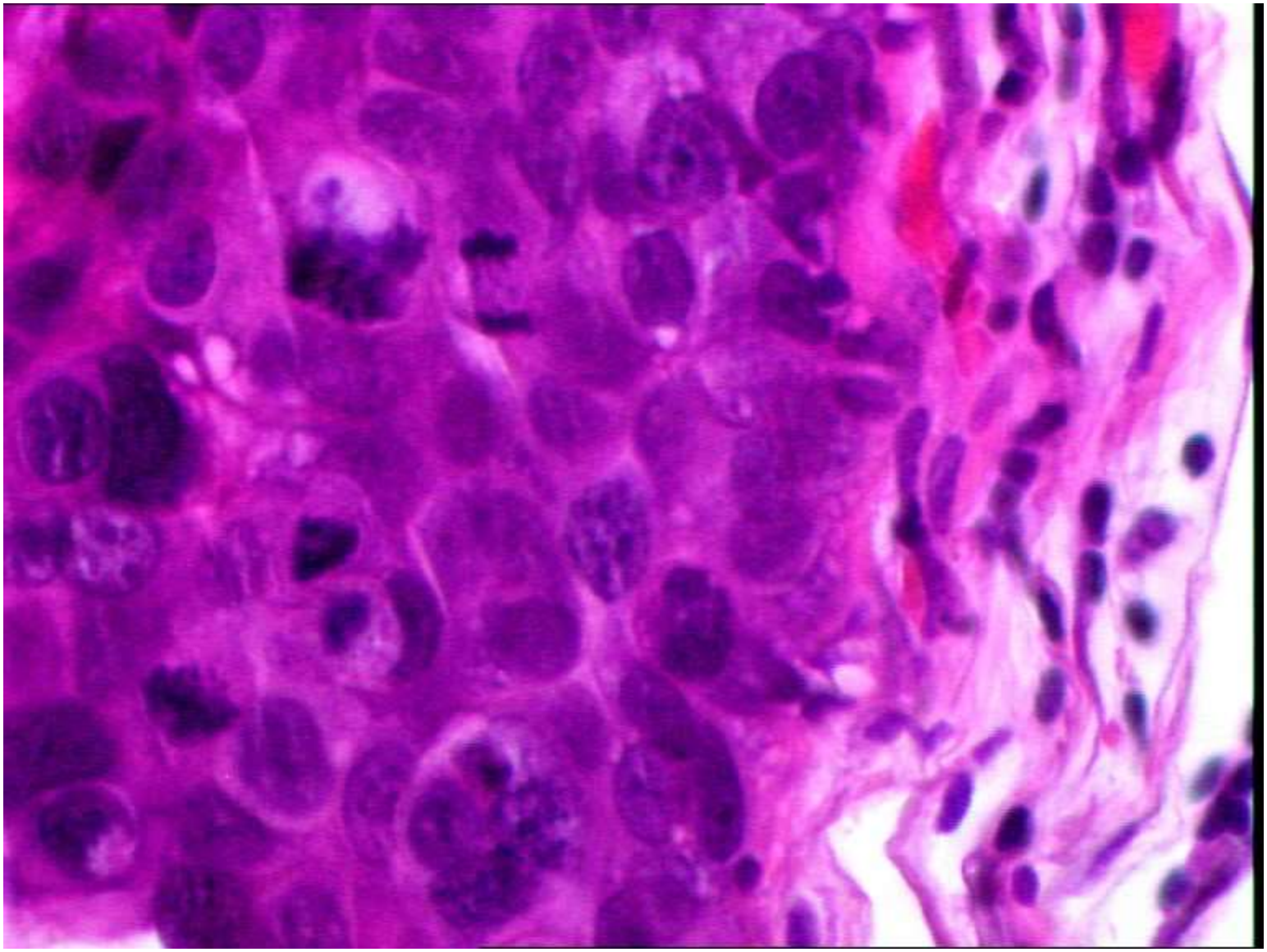




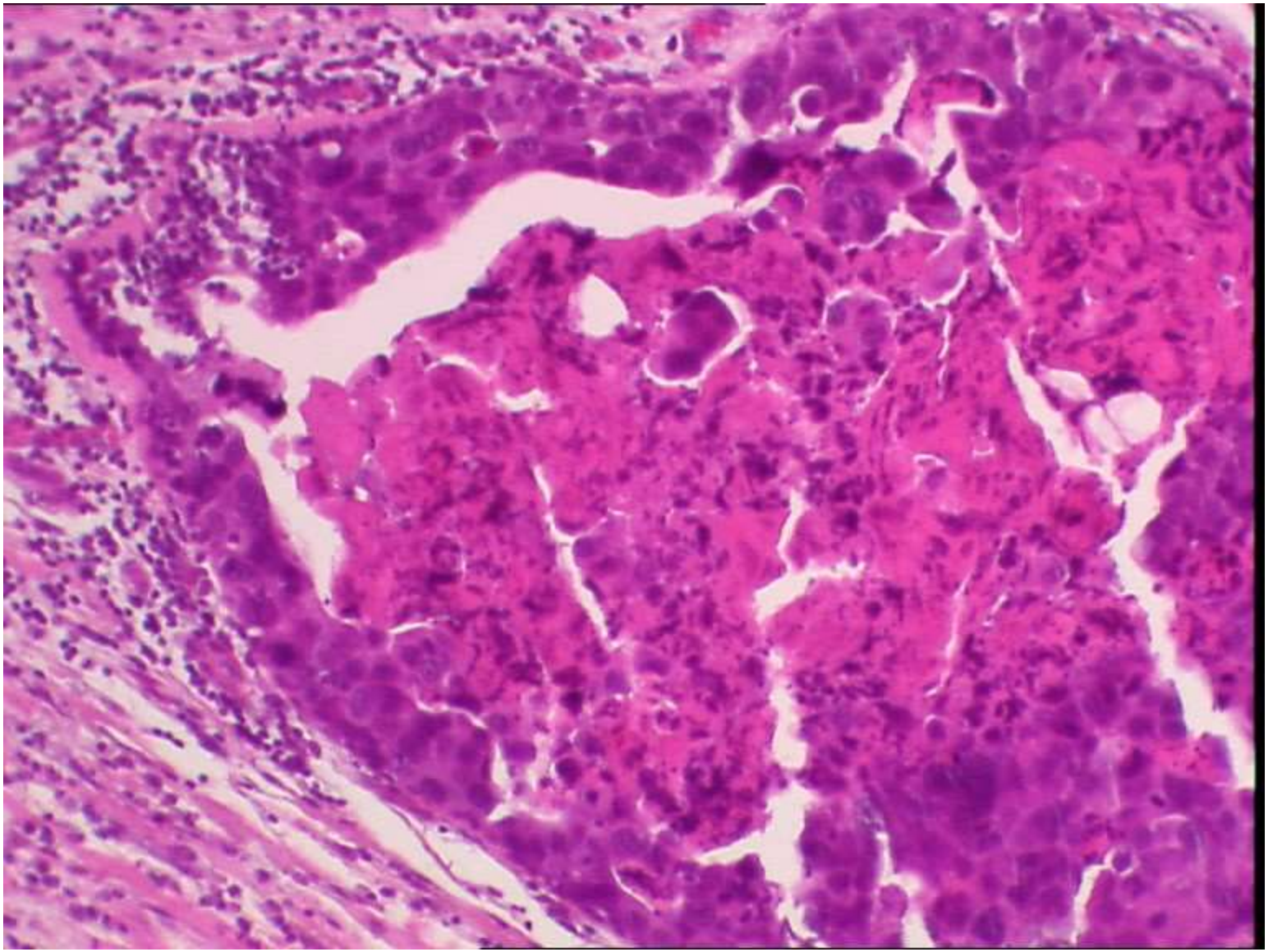
Invasives lobuläres Karzinom (ILK)



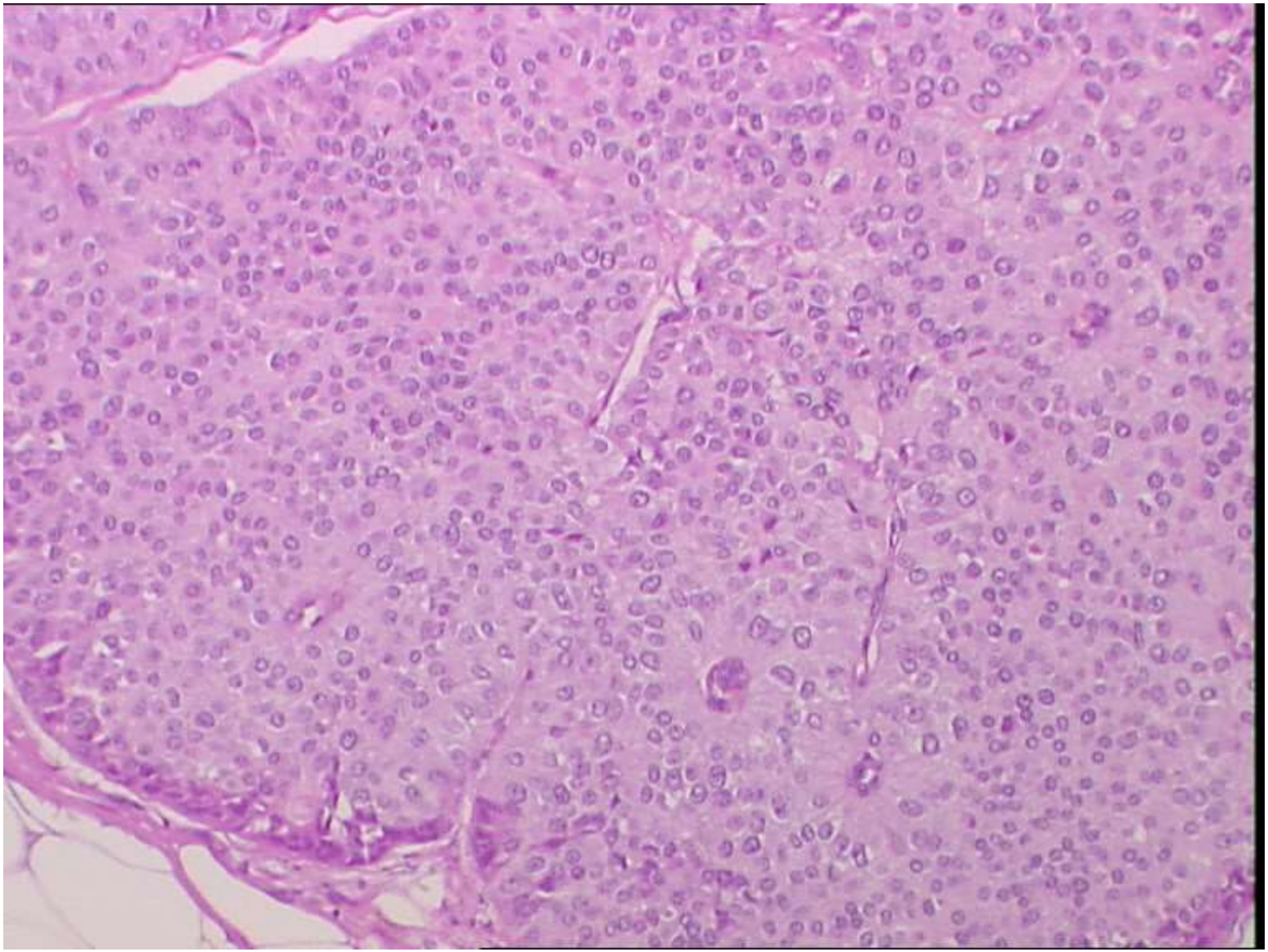
Invasives duktales Karzinom (IDK)

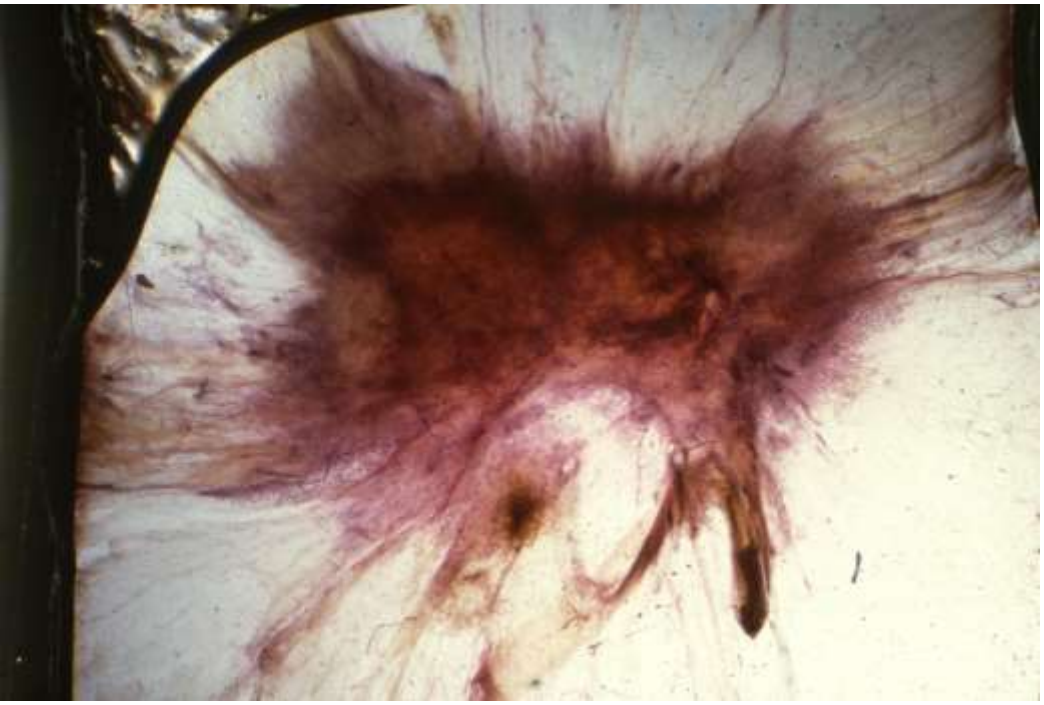


Invasives duktales Karzinom (IDK)



Invasives duktales Karzinom (IDK)





Invasives

Invasives duktales

NOS/NST

Spezielle Typen

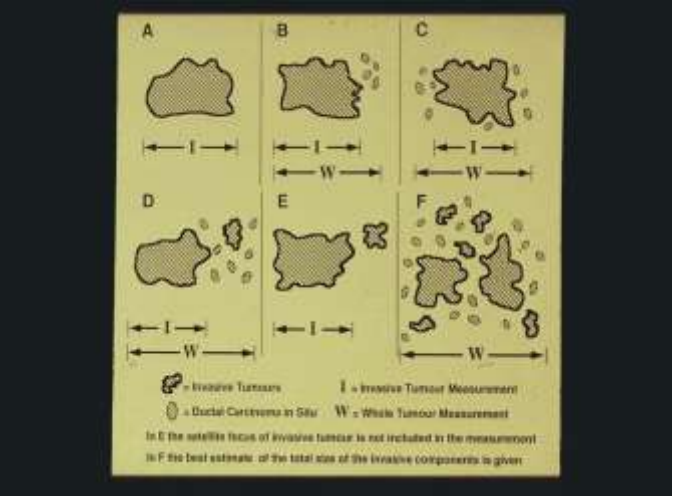
- tubular
- mucinös
- medullar
- papillar
- micropapillar
- secretorisch.…uzw.

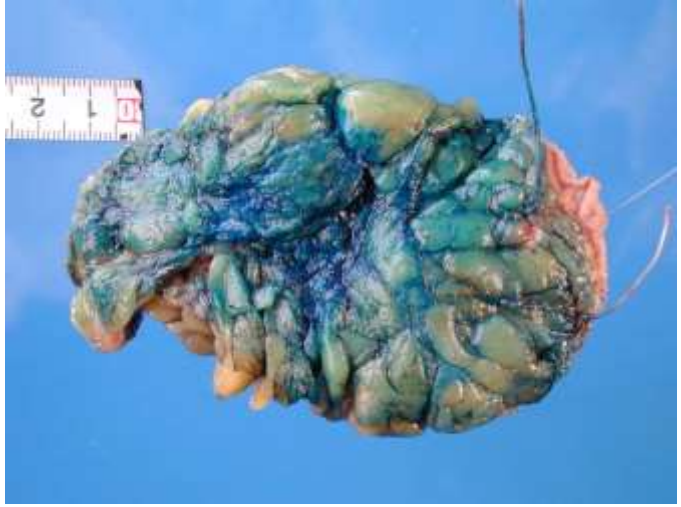
.

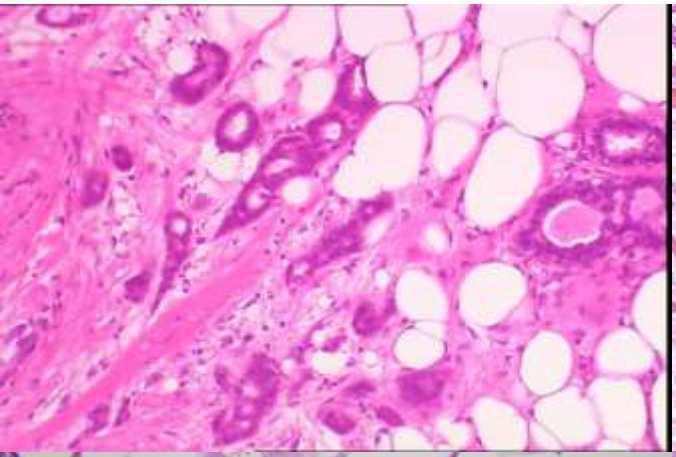
Invasives lobulares

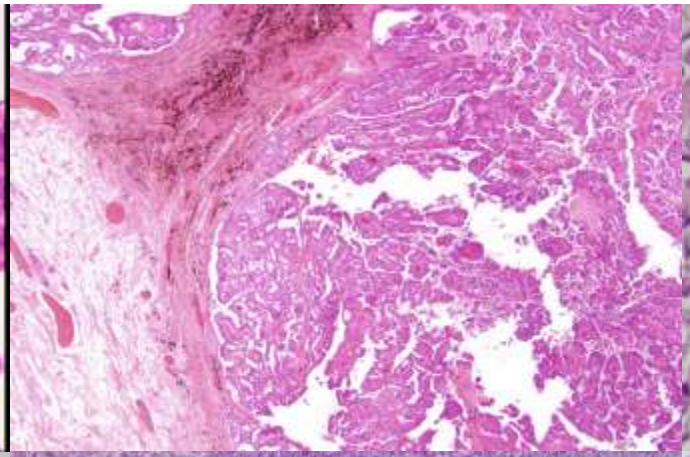
- classisches
- solides
- alveolares
- pleiomorphes

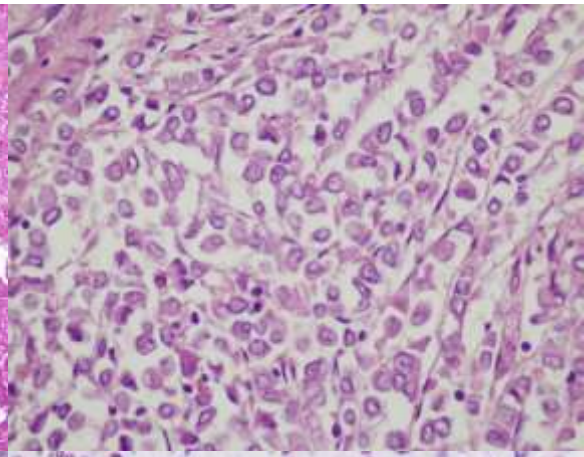
Gemischte Karzinome

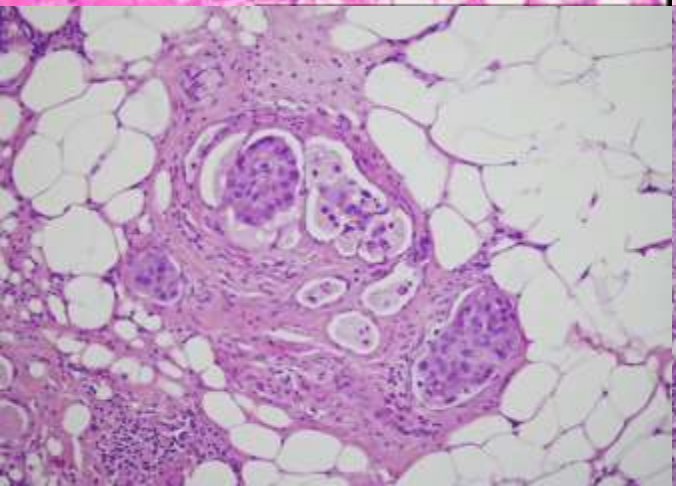

A
B
C
D
E
F
I
W
= Invasive Tumours
= Ductal Carcinoma in Situ
I = Invasive Tumour Measurement
W = Whole Tumour Measurement
In E the satellite focus of invasive tumour is not included in the measurement
In F the best estimate of the total size of the invasive components is given

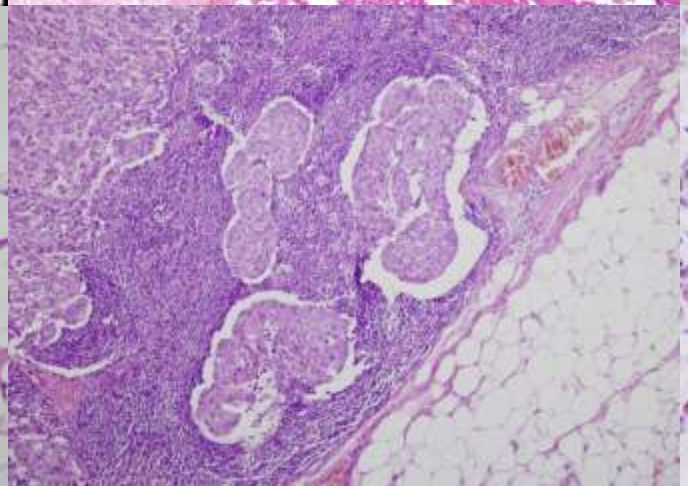


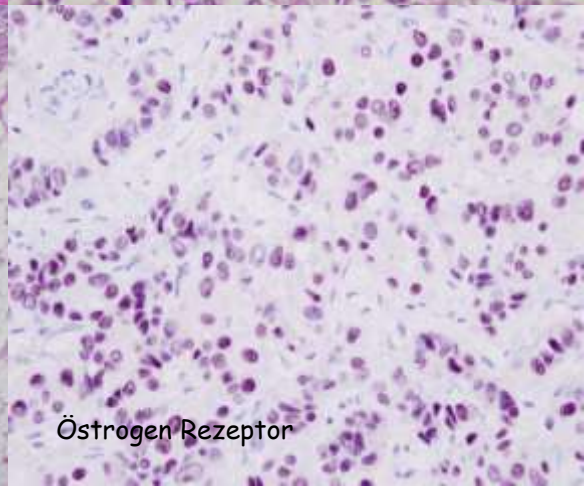


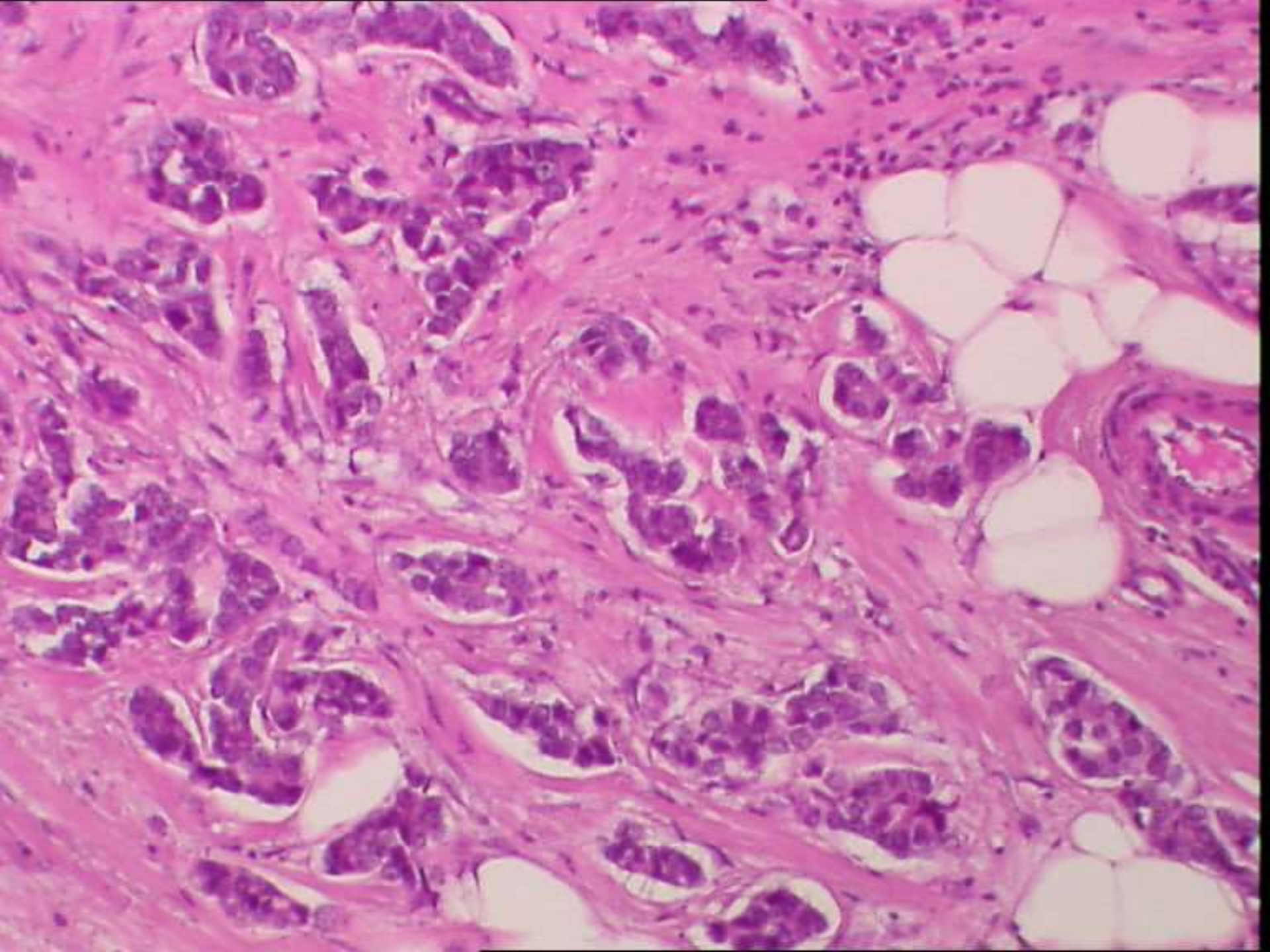


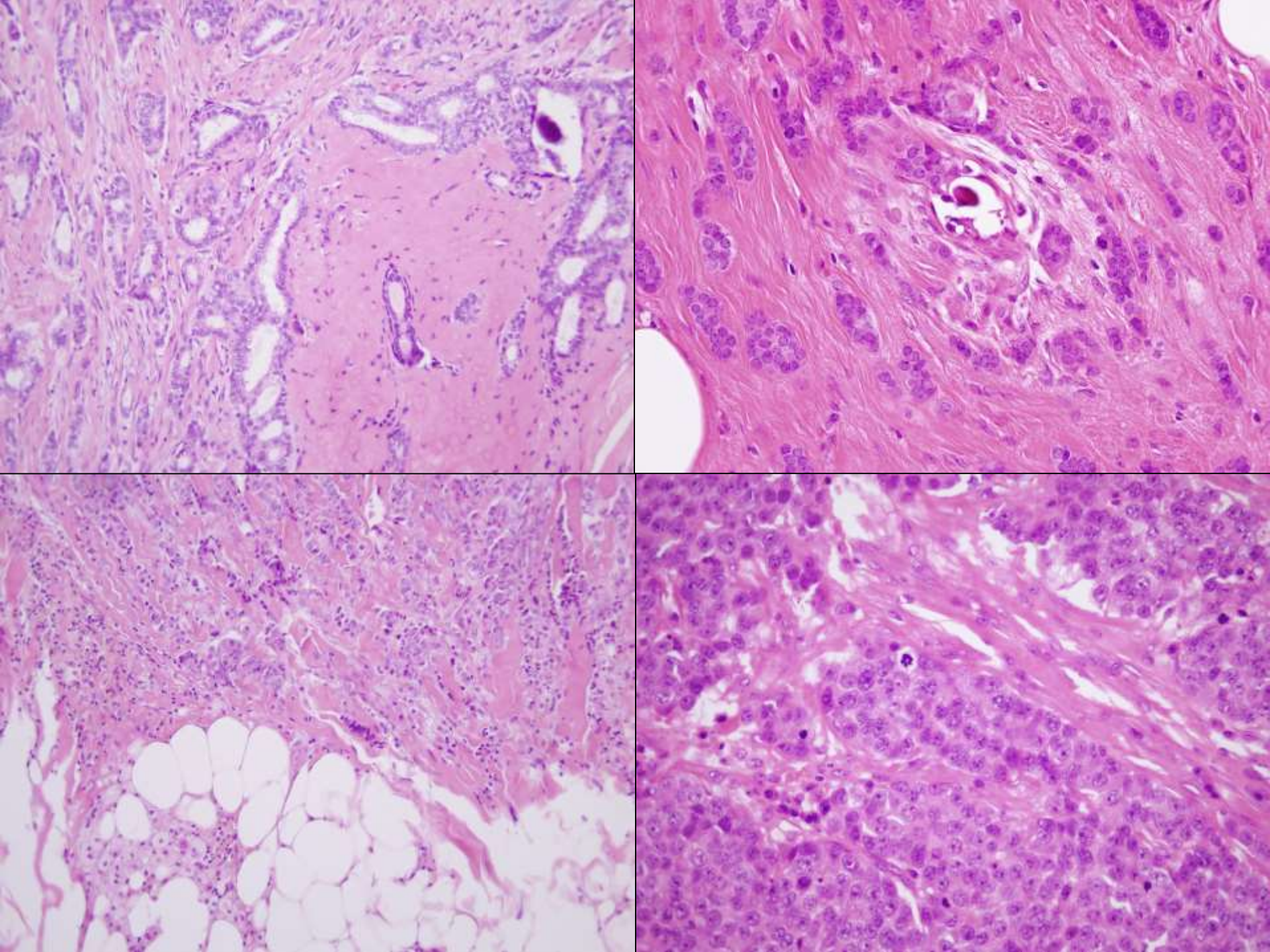






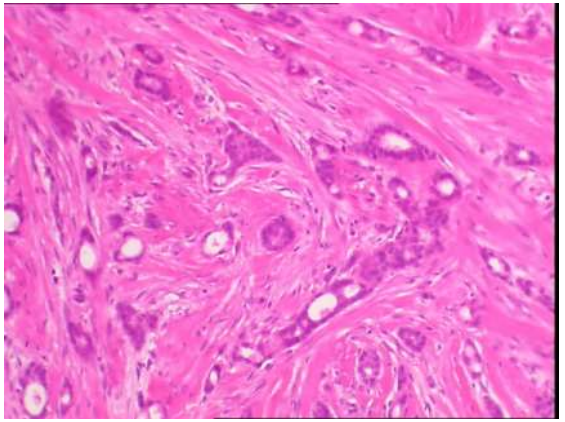

Östrogen Rezeptor

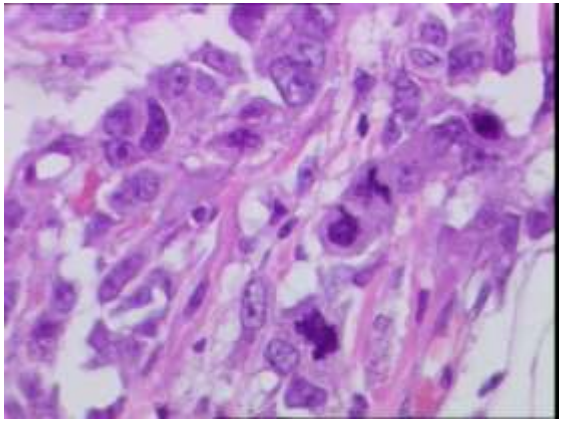




Tumor Grade: invasive Tumoren

- **Nottingham Grade (Elston-Ellis)**
  - Tubulus Formation
    - 0-10% 10-70% >70%
  - Polymorphismus
    - gering massig schwergradig
  - Mitotisches Index
    - 10 HMF





So-genannte „GENOMISCHES GRADE”

- Characteristische „Unterschift ” der Grad 1 und Grade 3 Tumoren
- Anscheinend, histologisch Grad 2 Tumoren könnten klar in zwei GENETISCH verschiedene Gruppe unterteilt: eine ist mit Histologie Grad 1 identisch, dei andere ist mit der Histologie Grad 3. identisch

Andere histologische Typen der invasiven Mammakarzinoms

BÖSARTIGE TUMOREN

Karzinomtypen mit günstigerer Prognose !!!

- **Muzinöses Karzinom (Gallertkarzinom)**

Muzin im Intra oder Extrazellulärraum

Siegelringzellen

- **Papilläres Karzinom - häufig**

submamillär

- **Adenoid-zystisches Karzinom**

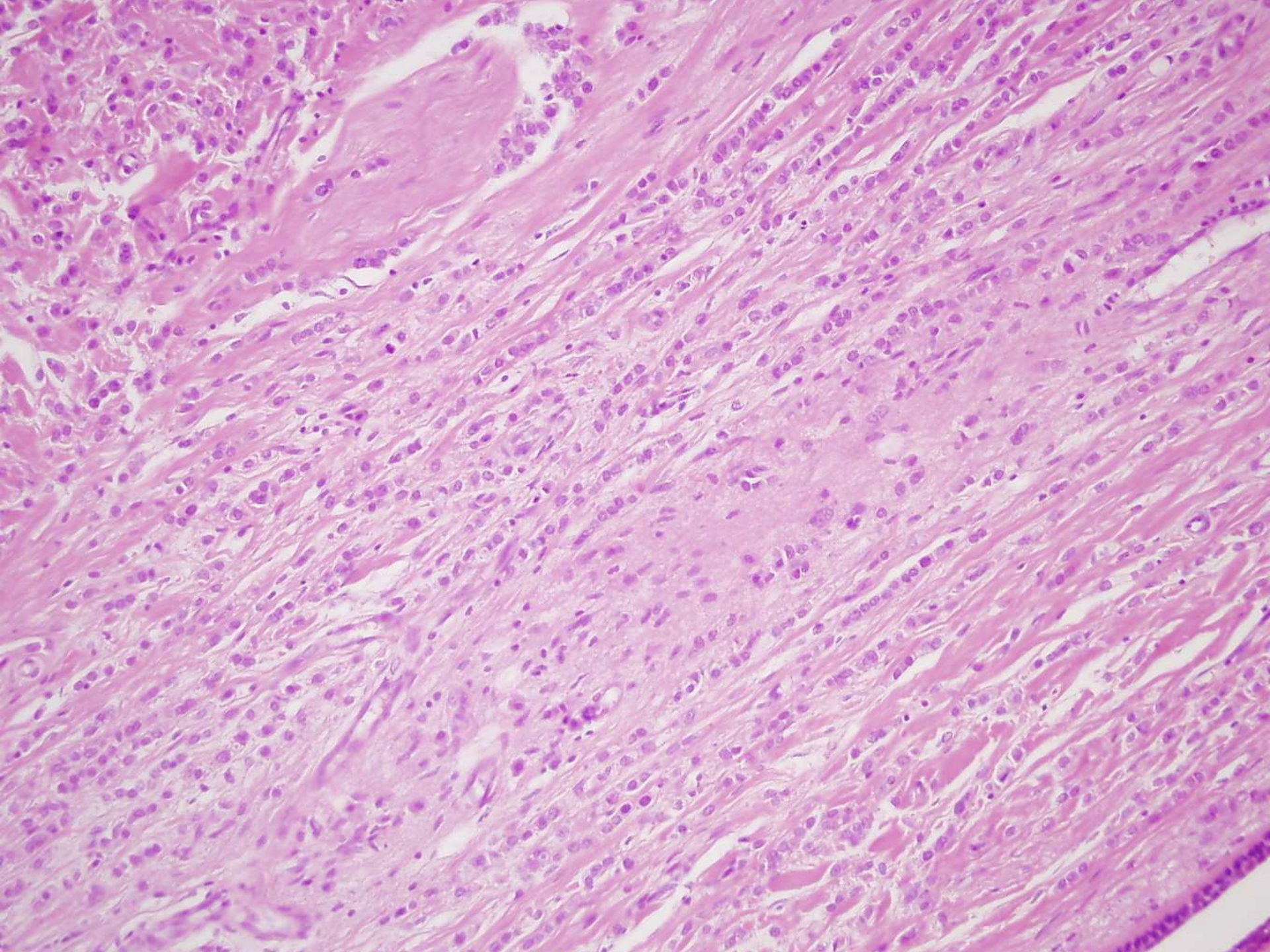
PAS positive Zellen

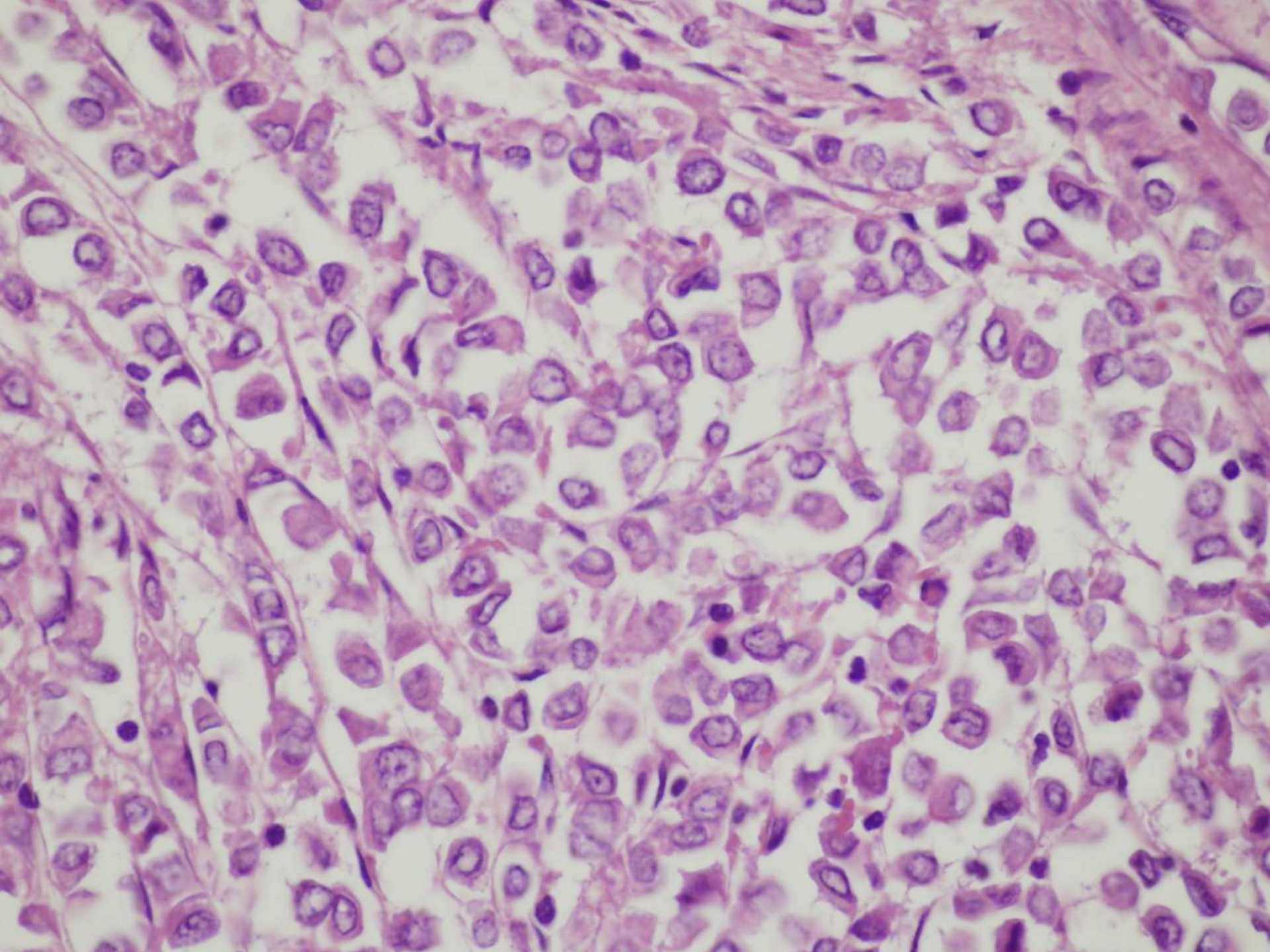
- **Medulläres Karzinom - markig,**

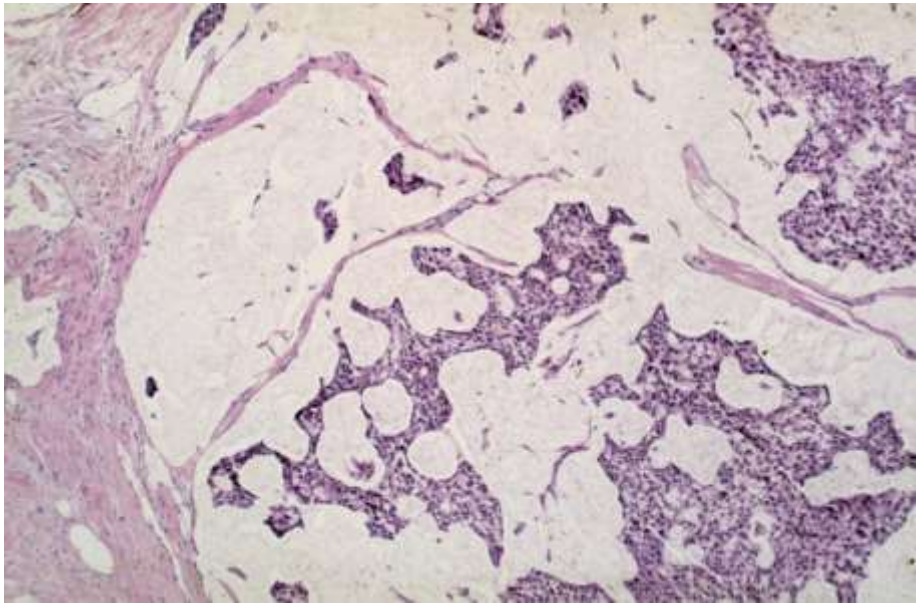
synzytiale Zellgruppen, Lymphozyteninfiltration

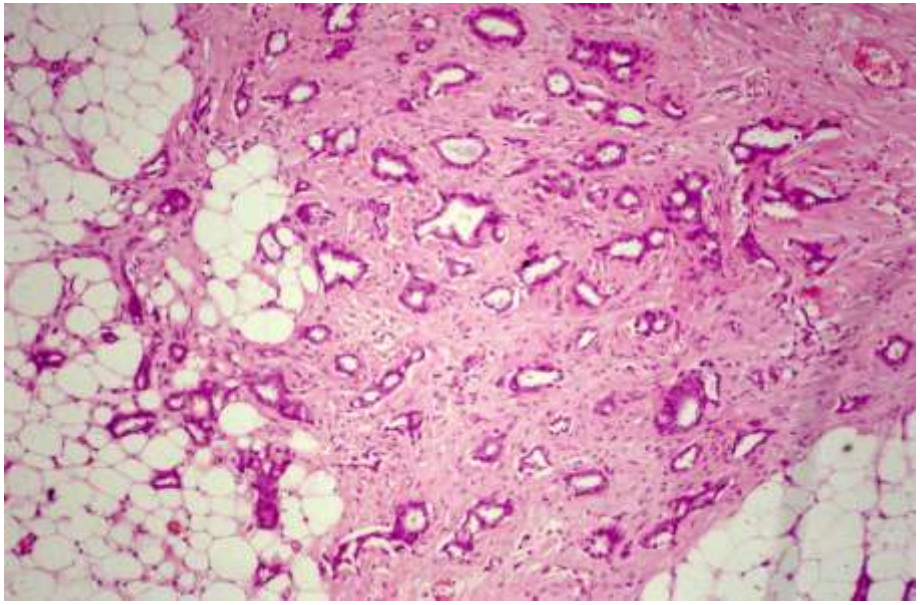
- **Tubuläres Karzinom, in dichten**

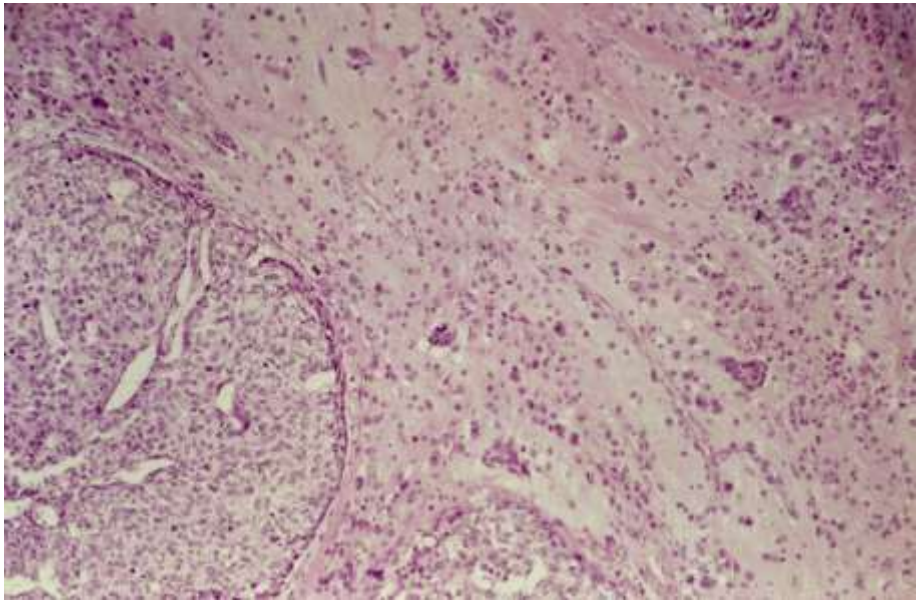
Bindegewebe einreihige Epithelproliferation

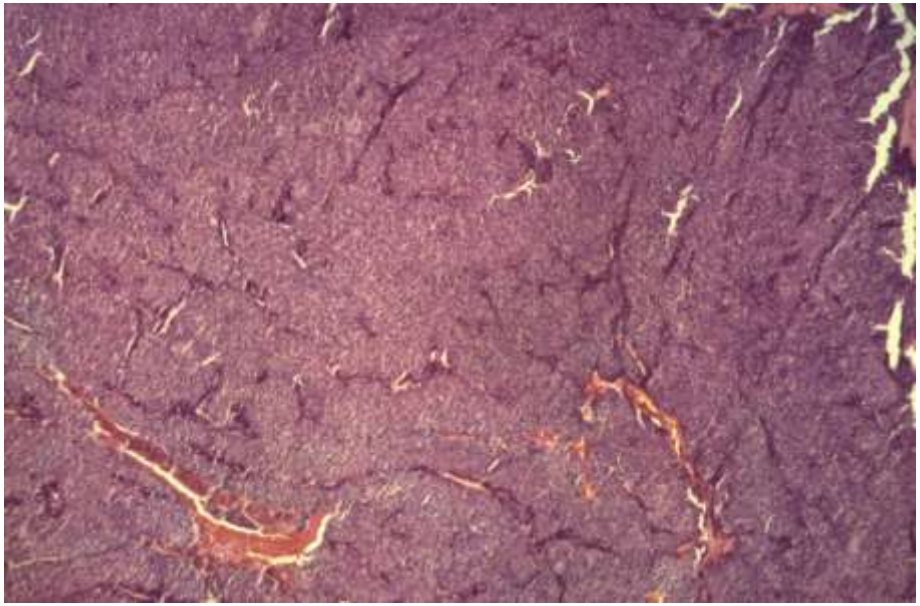


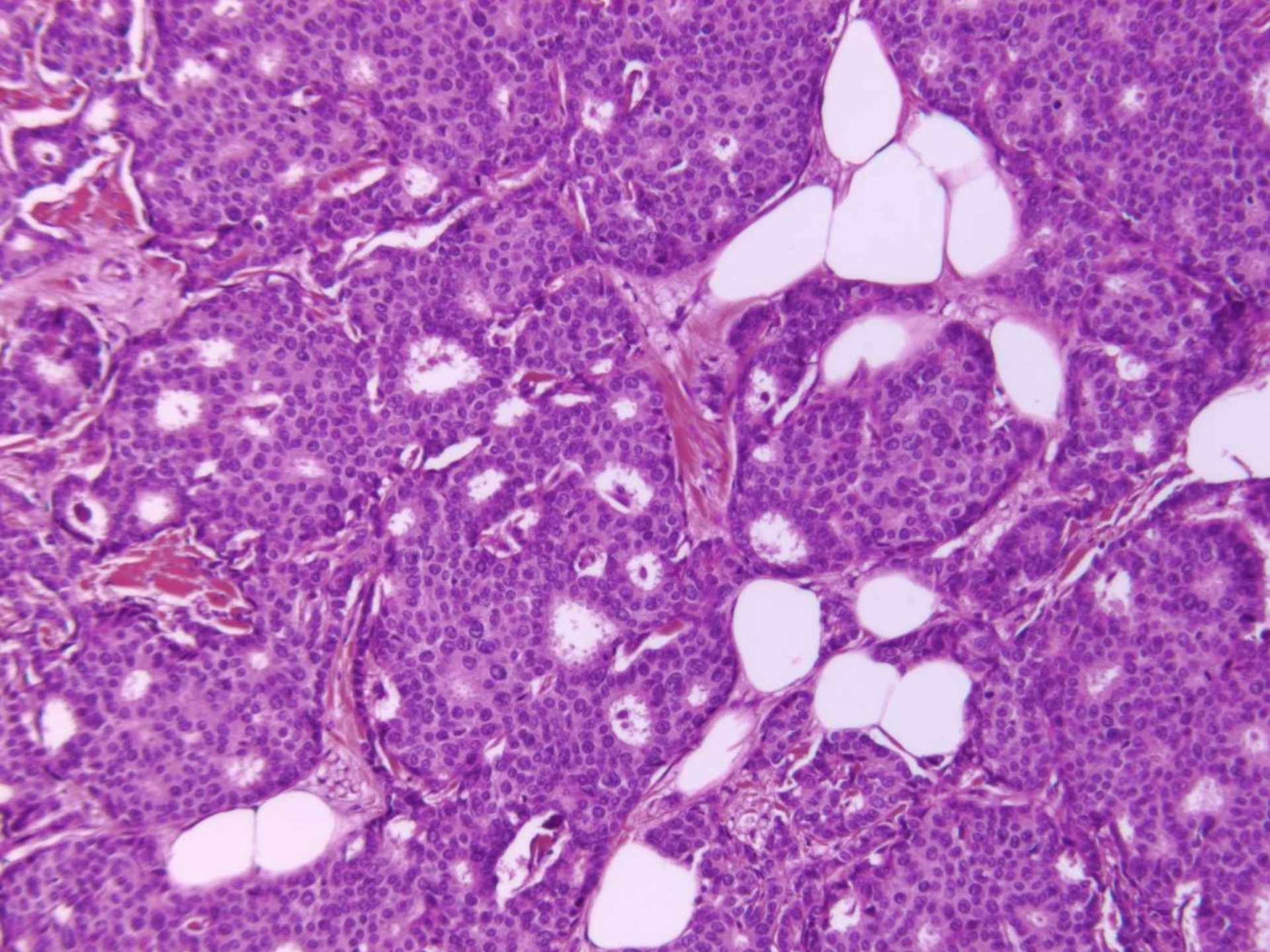


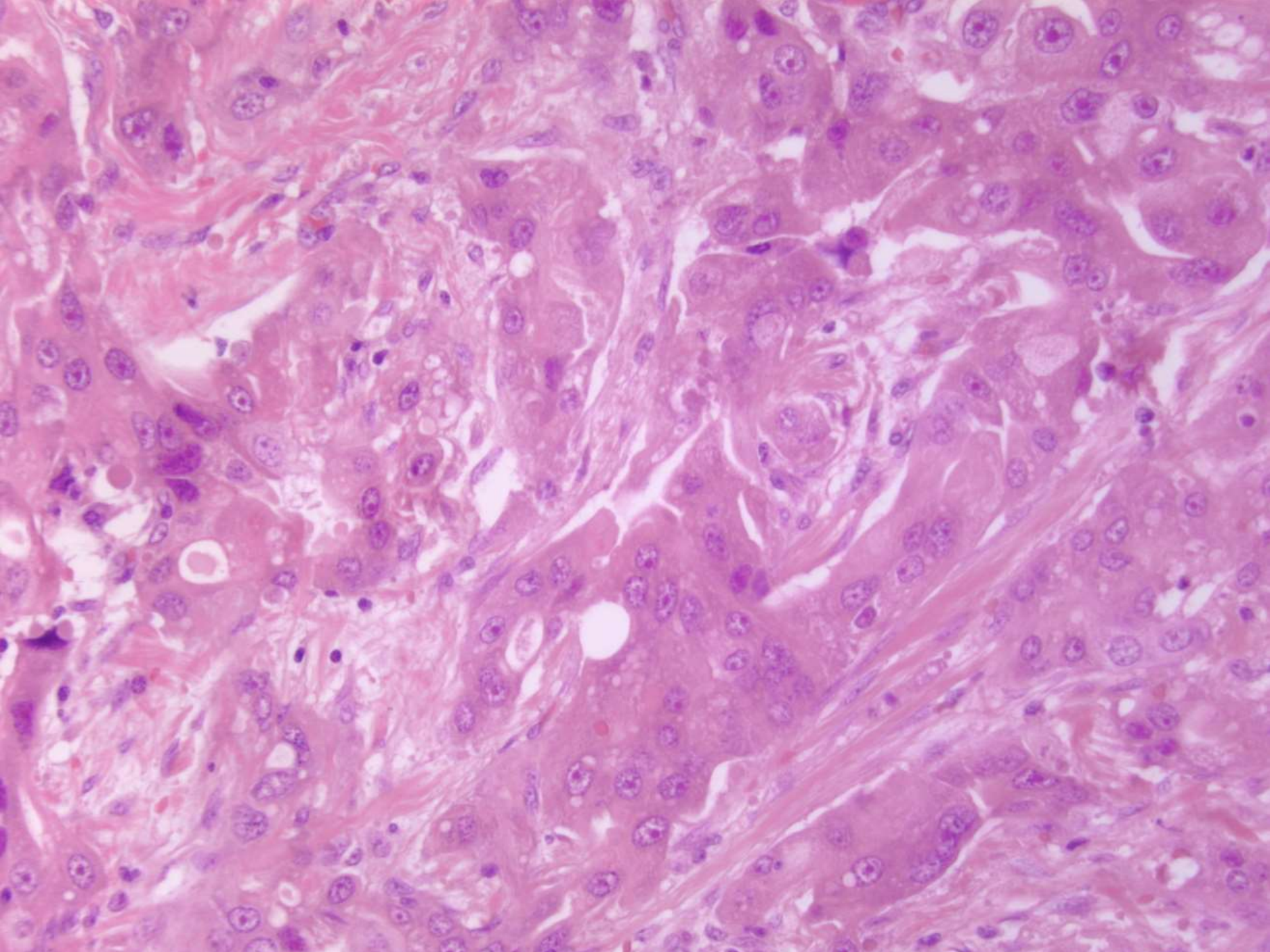




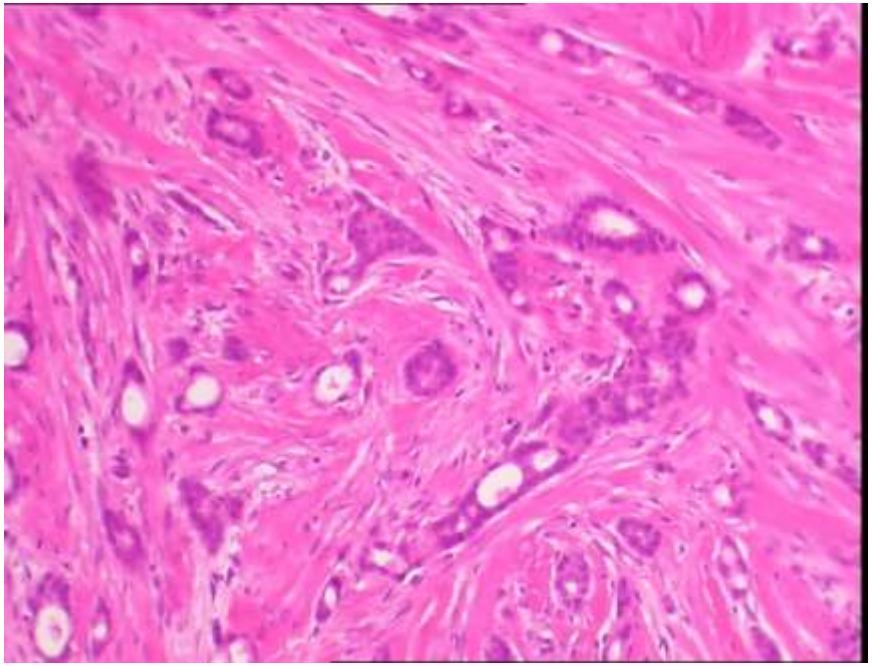


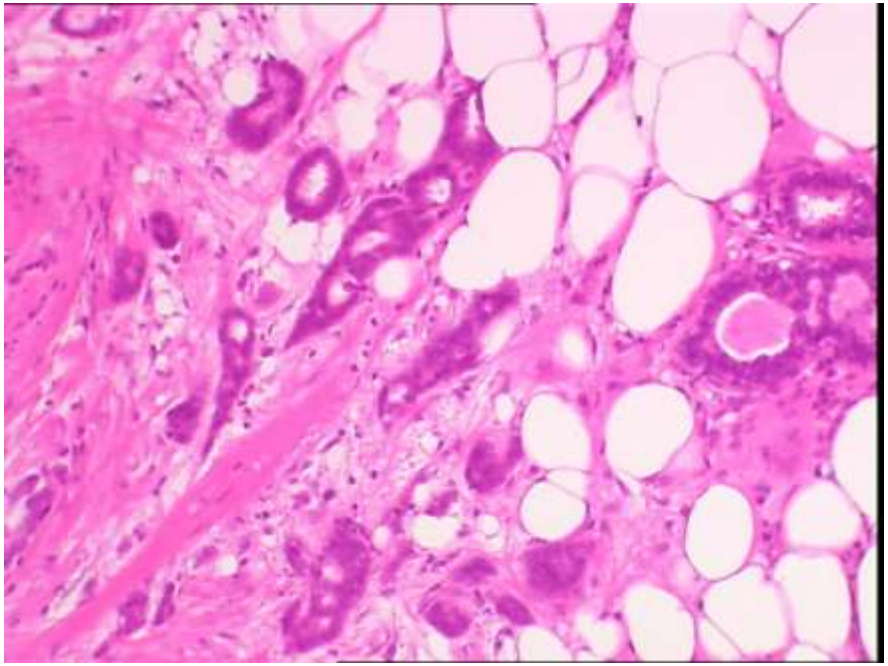




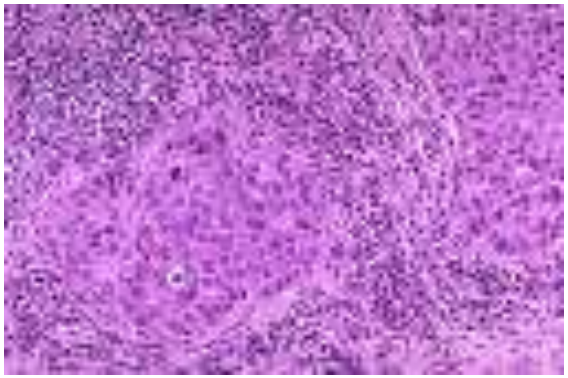


Tubuläres Karzinom

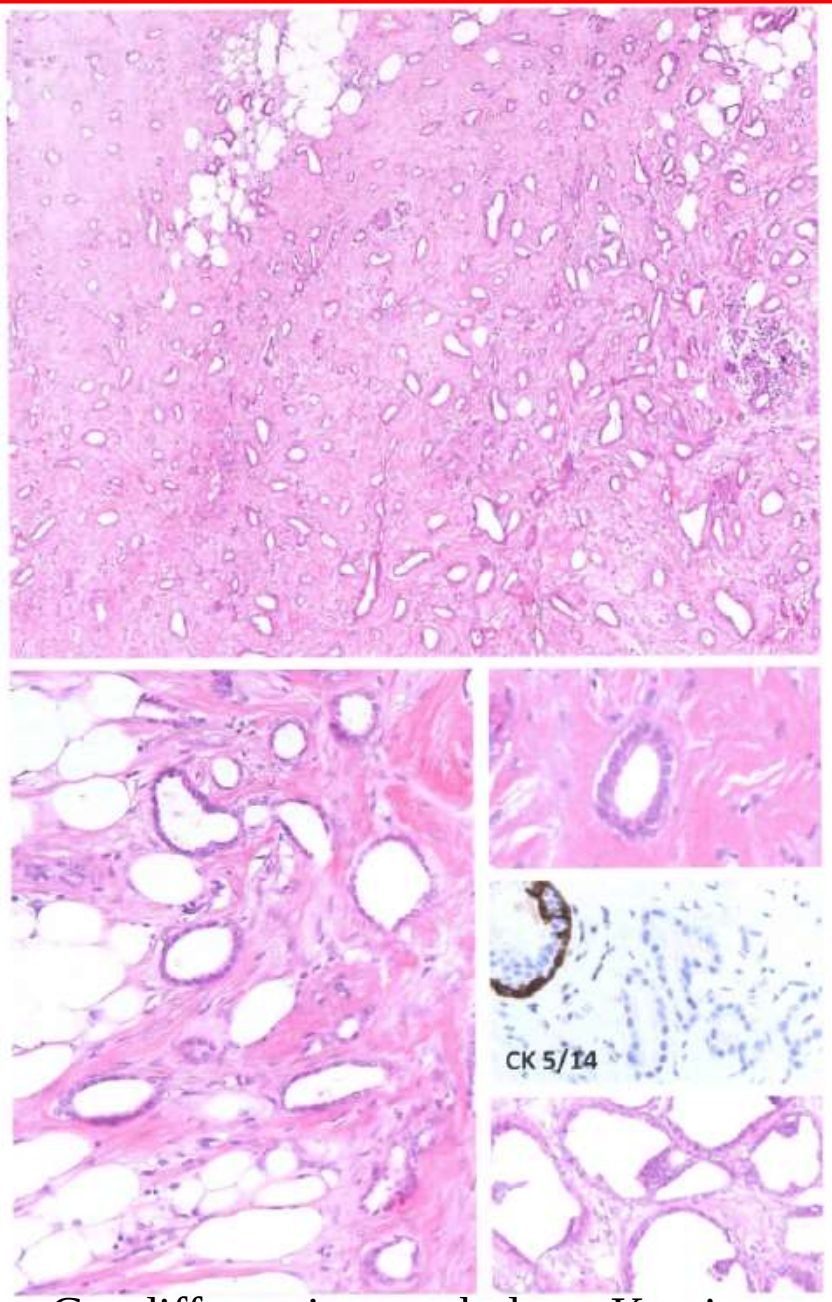




Medulläres Karzinom

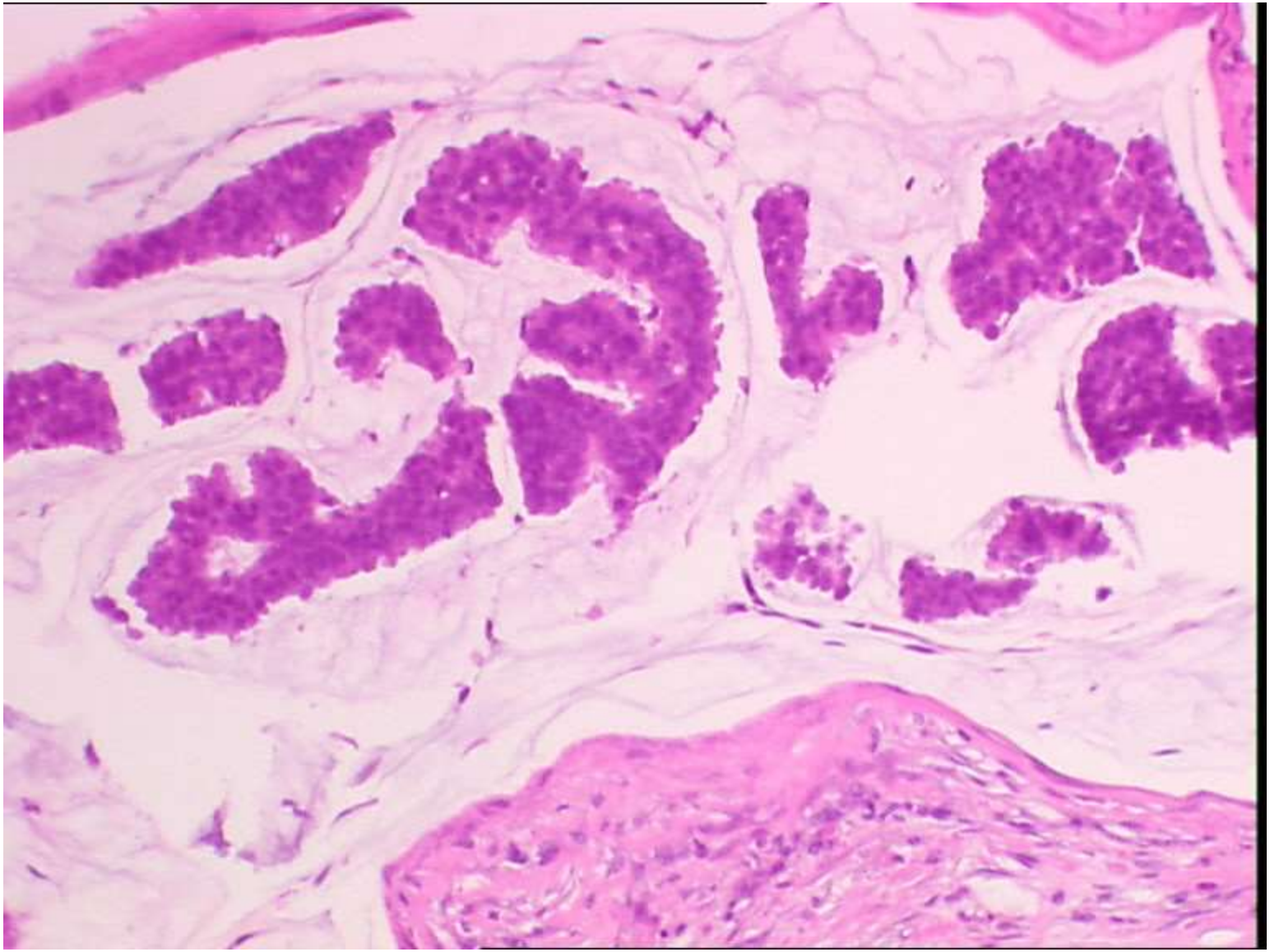


Tubuläres Karzinom



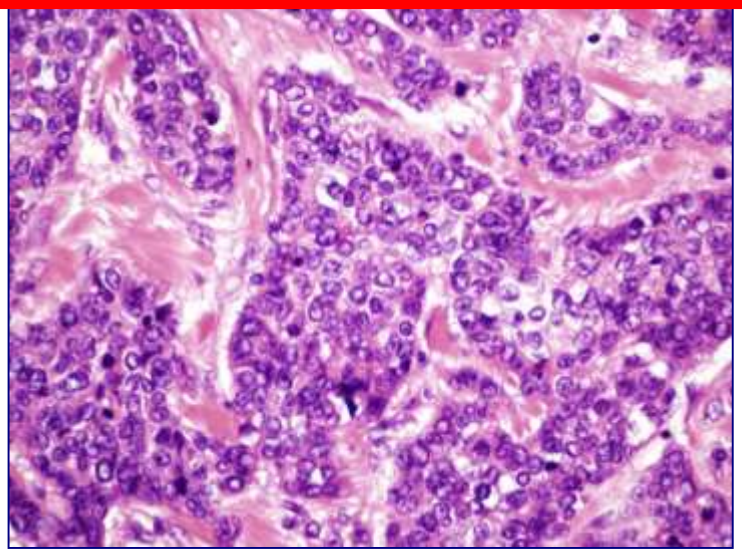
Gut differenziertes tubulares Karzinom

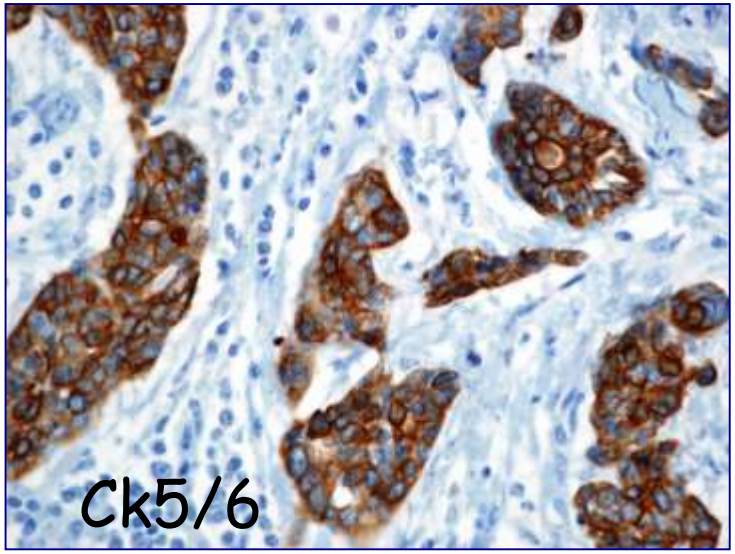
Muzinöses Karzinom

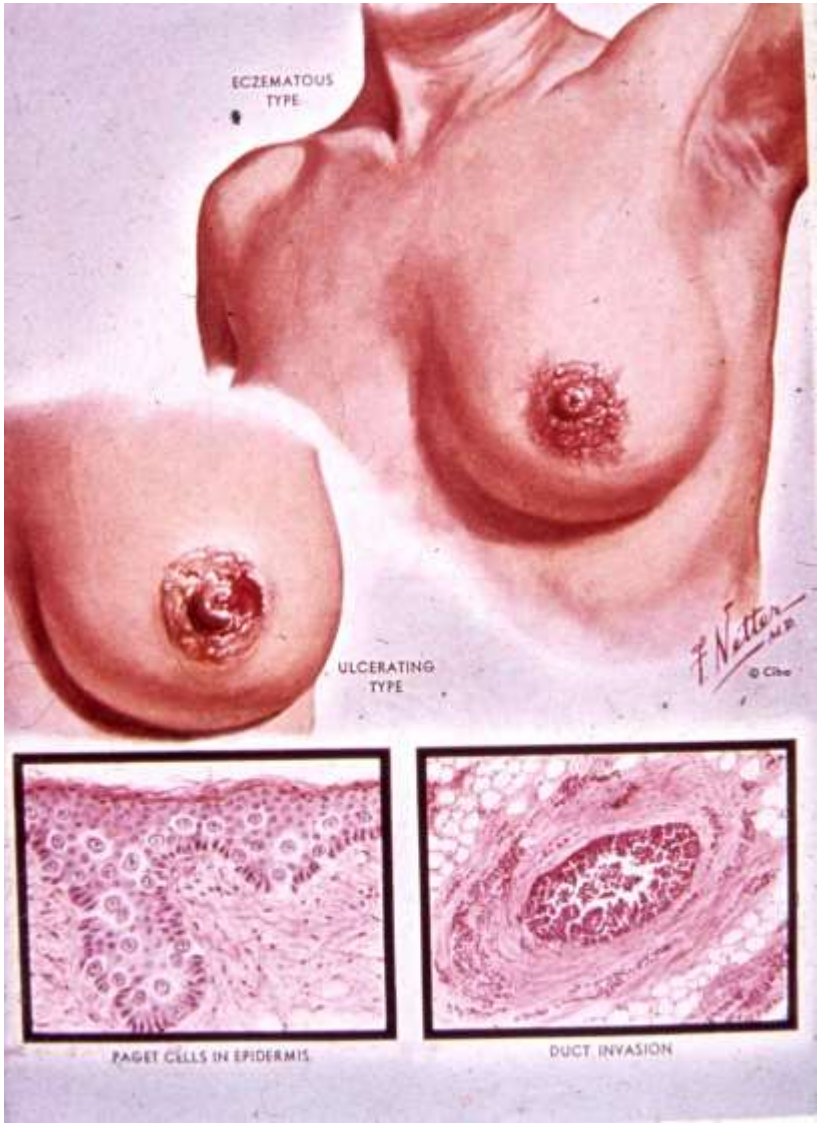


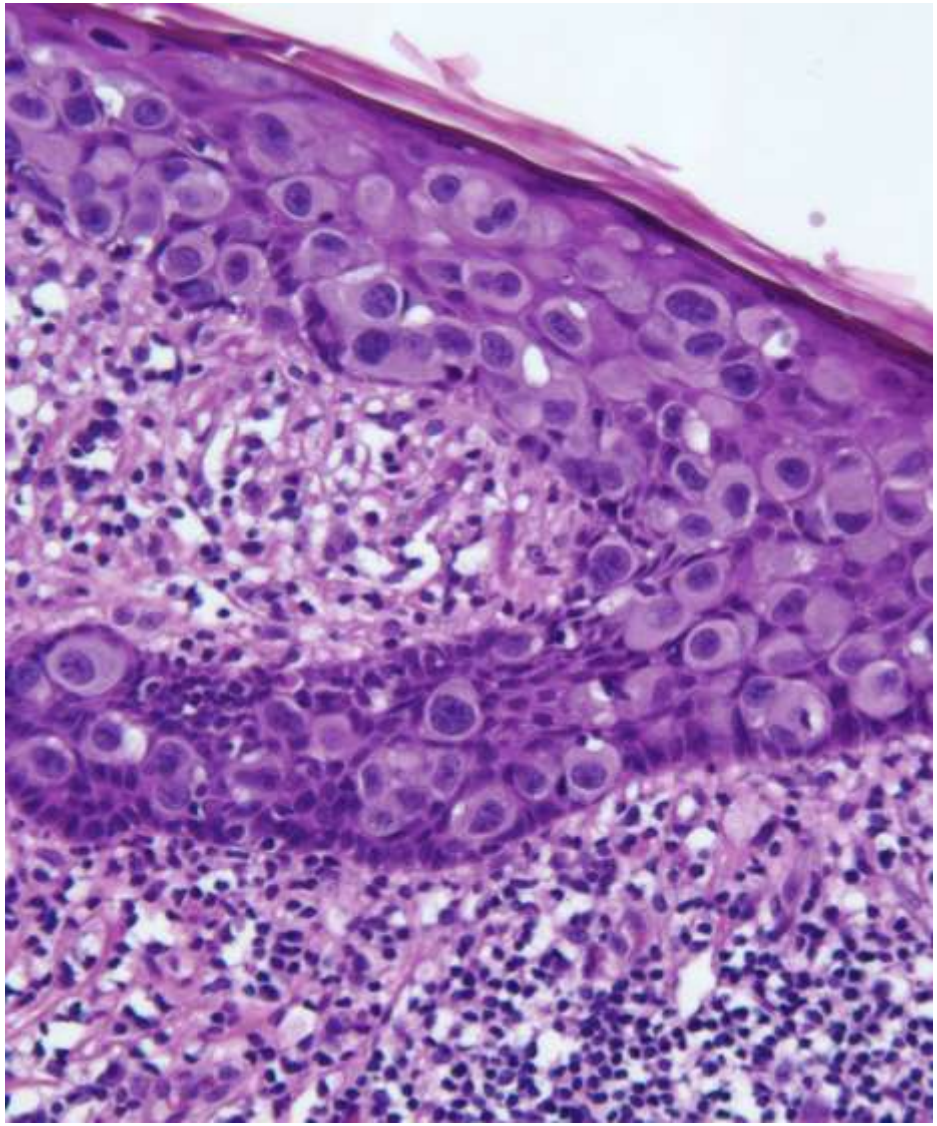
Beispiel für Identifizierung molekularen Subtypen in alltaglicher Routine: „Basal-like" Karzinoms

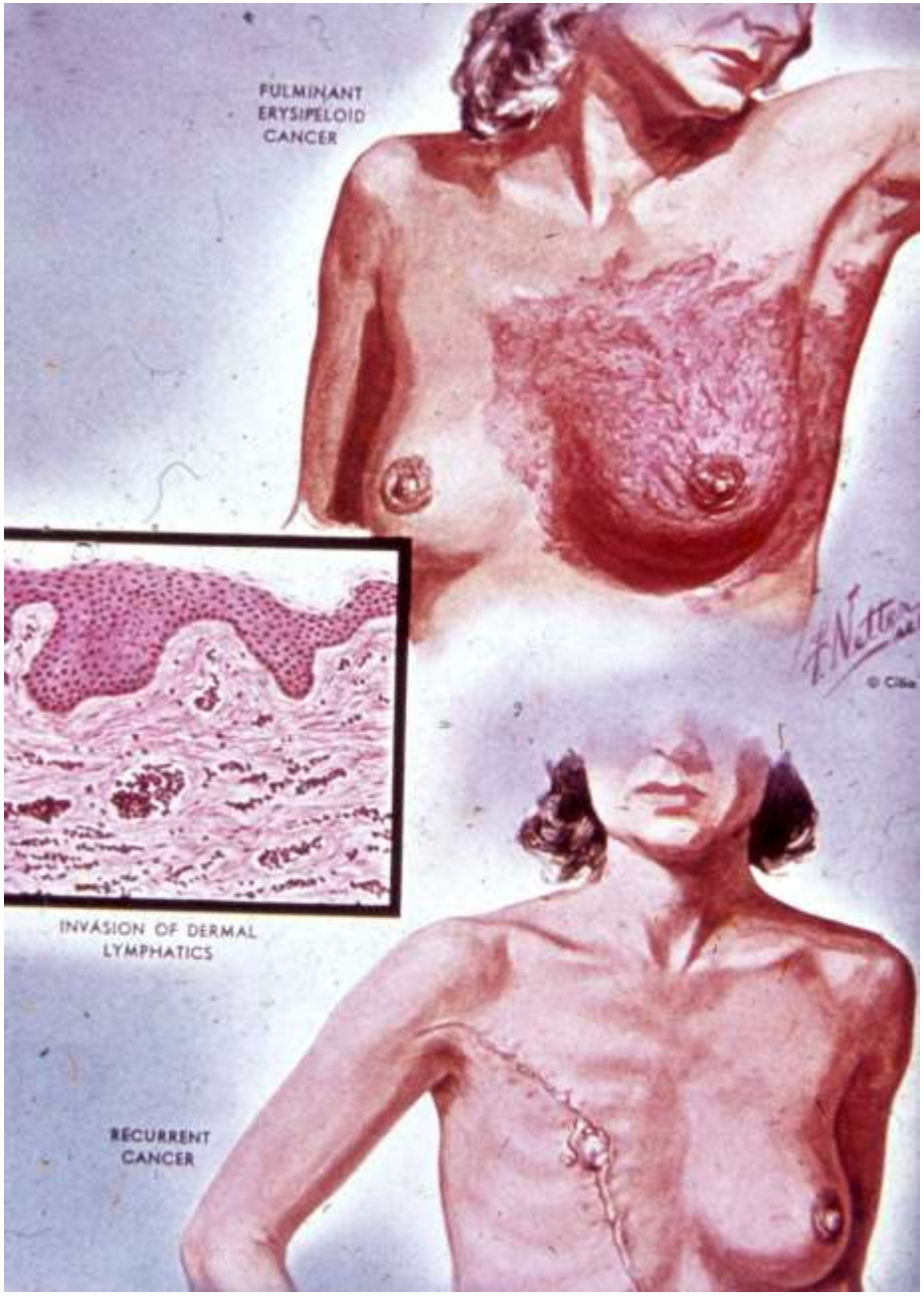
- Grade 3
- ÖR negativ
- Her2 negativ
- zu Zeit wir können diese mit der folgenden identifizieren
  - Cytokeratin 5/6, cytokeratin 14, cytokeratin 17 Immunohistochemie
- Die Mehrheit ist EGFR positiv
- Schlechte Prognose






ECZEMATOUS TYPE
ULCERATING TYPE
F. Netter M.D.
© Ciba
PAGET CELLS IN EPIDERMIS
DUCT INVASION




FULMINANT
ERYSIPELOID
CANCER
INVASION OF DERMAL
LYMPHATICS
RECURRENT
CANCER

BÖSARTIGE TUMOREN

STAGING – TNM

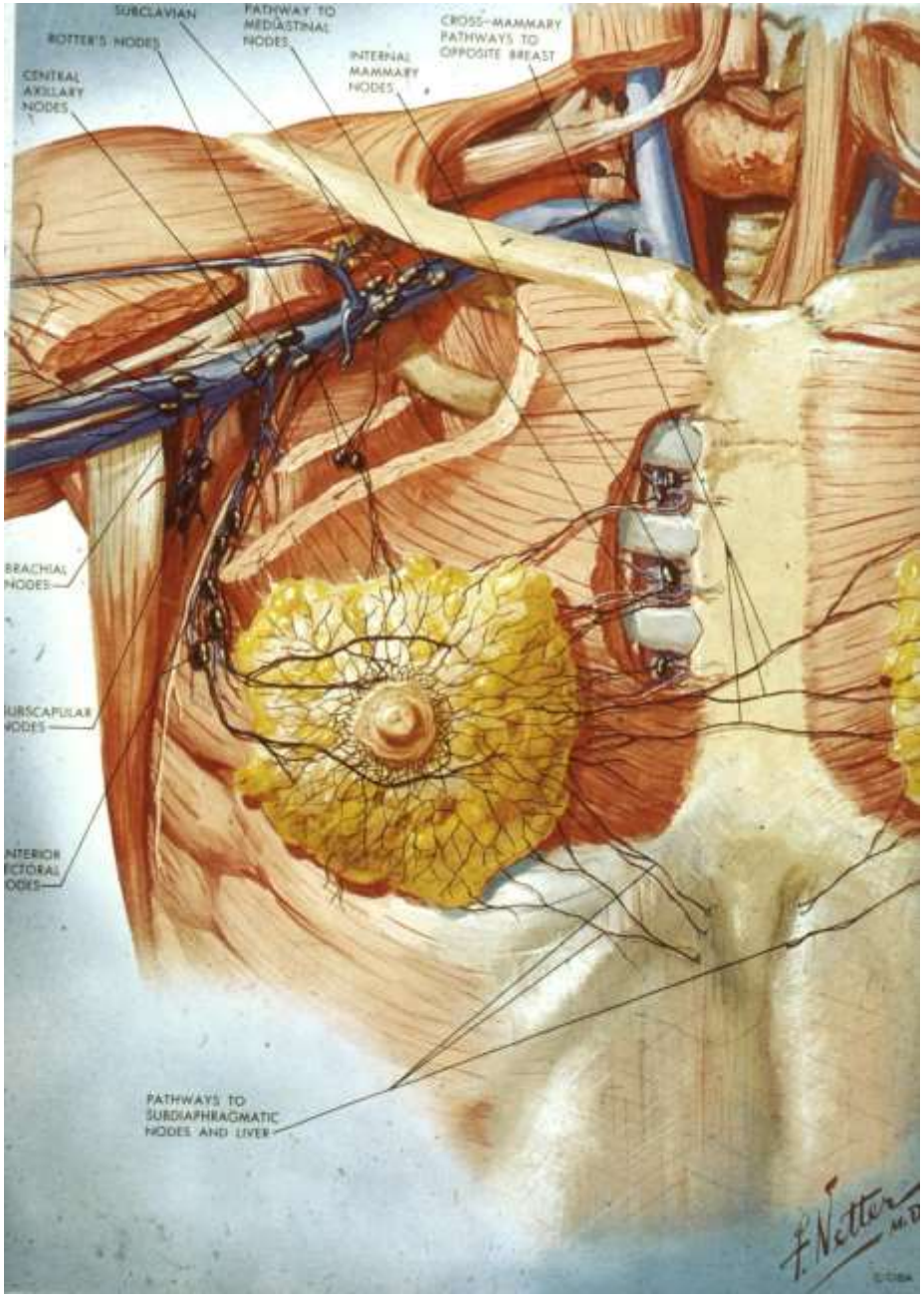
- **Tis - DCIS, LCIS**
- **T1 < 2 cm**
- **T2 2-5 cm**
- **T3 > 5 cm**
- **jeder Tumor mit Ausdehnung auf Brustwand oder Haut, ausser M. pectoralis**

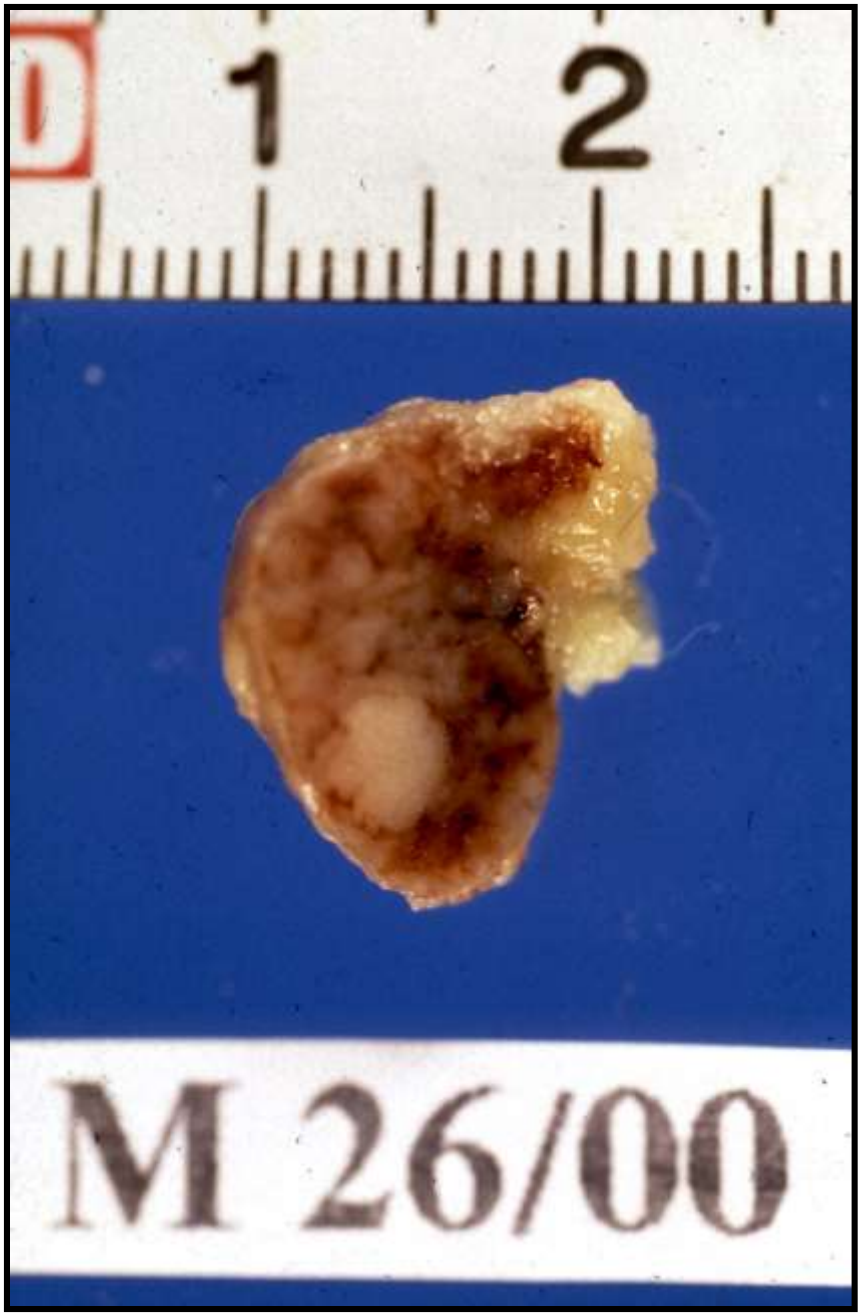
Nothingam Prognostic Index: NPI
Van Nyss System, Tavassoli Klassifikation

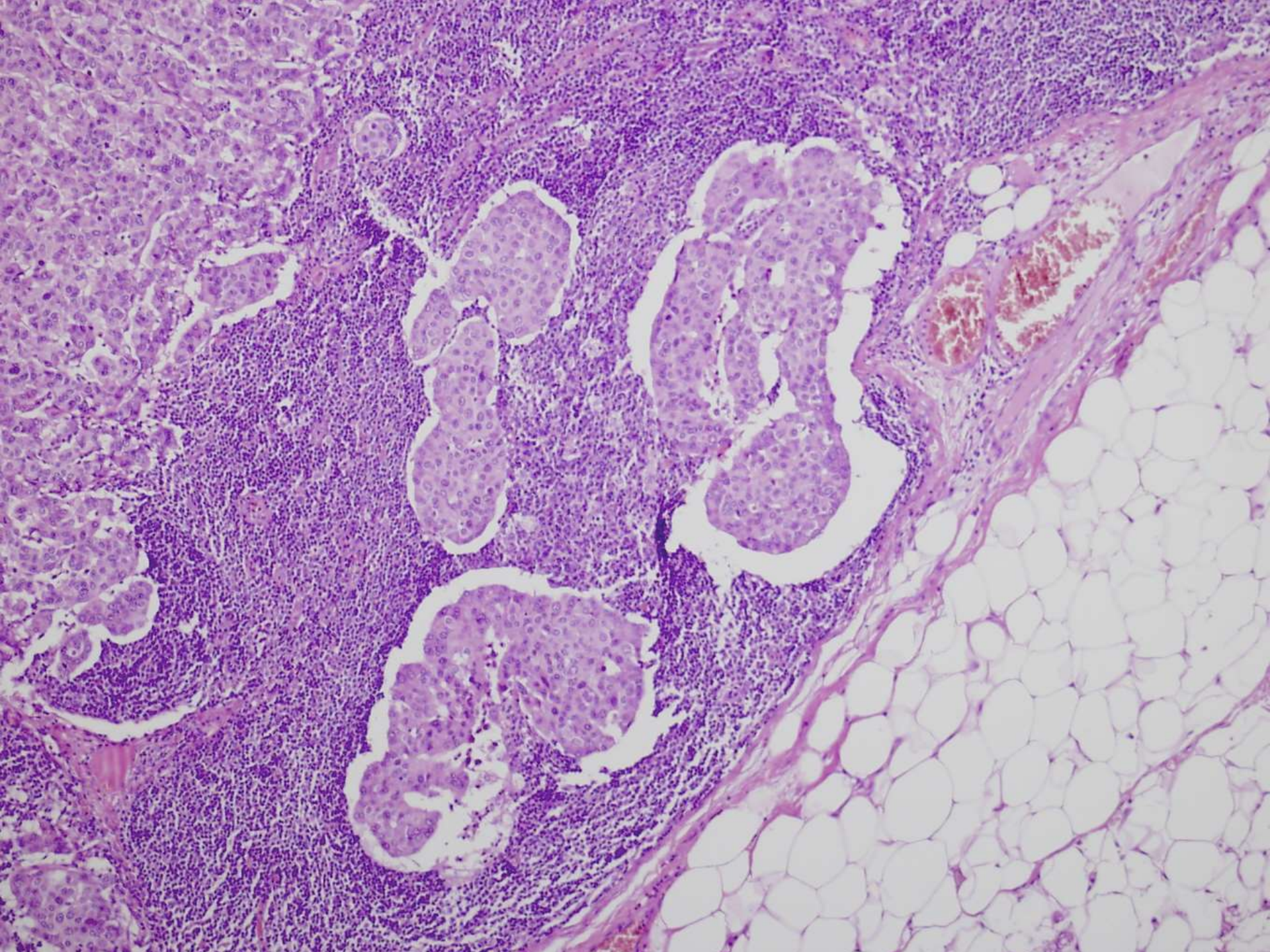
BÖSARTIGE TUMOREN

pT Kategorien

- Tis In situ duktales oder lobulares Karzinom
- T1mic Mikroinvasives (<1mm) Karzinom
- T1a >1-5mm invasives Karzinom
- T1b >5-10mm invasives Karzinom
- T1c >10-20mm invasives Karzinom
- T2 >20-50mm invasives Karzinom
- T3 >50mm invasives Karzinom
- T4 Invasion der Haut, Thorax-Wand oder Mastitis carcinomatosa


SUBCLAVIAN
ROTTER'S NODES
PATHWAY TO MEDIASTINAL NODES
INTERNAL MAMMARY NODES
CROSS-MAMMARY PATHWAYS TO OPPOSITE BREAST
CENTRAL AXILLARY NODES
BRACHIAL NODES
SUBSCAPULAR NODES
INTERIOR PECTORAL NODES
PATHWAYS TO SUBDIAPHRAGMATIC NODES AND LIVER
F. Netter M.D.


1
2
M 26/00



Sentinel (Wache) Lymknoten

- Axilla >> mammaria interna LK > intramammale LK (>> infraklavikulare LK >>> supraklavikulare LK)
- sorgfaltige Untersuchung
  - Intraoperative „imprint" Zytologie und Gefrierschnitten
  - „Step sectioning" +/- CK Immunohistochemie
- ODER: schnelle molekulare Methode (OSNA=One Step Nucleic acid Amplification)
- Zwifelhafte Meinungen über weitere Management der Axilla wenn Mikrometastasen oder isolierte Tumorzellen sind anwesend

pN Kategorien in der TNM Atlas

- pNx
- pN0 (i+)
- pN1mi
- pN1a 1-3 *ax*, *mam* neg
- pN2a 4-9 *ax*, *mam* neg
- pN3a ≥10 *ax*, *mam* neg
  oder *infraclav met*

- pN1b *Ax neg*, micr *mam*+
- pN1c *1-3 Ax*, micr *mam*+
- pN2b *Ax neg*, *clin mam*+
- pN3b *1-3 Ax*, *clin mam*+
  or 4 -9 Ax, *micr/clin mam*+
  or ≥10 Ax, *micr/clin mam*+
- pN3c supraclav +

Axillary Dissection vs No Axillary Dissection in Women With Invasive Breast Cancer and Sentinel Node Metastasis

A Randomized Clinical Trial

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Peter W. Blumencranz, MD
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Sukamal Saha, MD
Linda M. McCall, MS
Monica Morrow, MD

Context Sentinel lymph node dissection (SLND) accurately identifies nodal metastasis of early breast cancer, but it is not clear whether further nodal dissection affects survival.

Objective To determine the effects of complete axillary lymph node dissection (ALND) on survival of patients with sentinel lymph node (SLN) metastasis of breast cancer.

Design, Setting, and Patients The American College of Surgeons Oncology Group Z0011 trial, a phase 3 noninferiority trial conducted at 115 sites and enrolling patients from May 1999 to December 2004. Patients were women with clinical T1-T2 invasive breast cancer, no palpable adenopathy, and 1 to 2 SLNs containing metastases identified by frozen section, touch preparation, or hematoxylin-eosin staining on permanent section. Targeted enrollment was 1900 women with final analysis after 500 deaths, but the trial closed early because mortality rate was lower than expected.

Interventions All patients underwent lumpectomy and tangential whole-breast irradiation. Those with SLN metastases identified by SLND were randomized to undergo ALND or no further axillary treatment. Those randomized to ALND underwent dissection of 10 or more nodes. Systemic therapy was at the discretion of the treating physician.

Main Outcome Measures Overall survival was the primary end point, with a noninferiority margin of a 1-sided hazard ratio of less than 1.3 indicating that SLND alone is noninferior to ALND. Disease-free survival was a secondary end point.

Results Clinical and tumor characteristics were similar between 445 patients randomized to ALND and 446 randomized to SLND alone. However, the median number of nodes removed was 17 with ALND and 2 with SLND alone. At a median follow-up of 6.3 years (last follow-up, March 4, 2010), 5-year overall survival was 91.8% (95% confidence interval [CI], 89.1%-94.5%) with ALND and 92.5% (95% CI, 90.0%-95.1%) with SLND alone; 5-year disease-free survival was 82.2% (95% CI, 78.3%-86.3%) with ALND and 83.9% (95% CI, 80.2%-87.9%) with SLND alone. The hazard ratio for treatment-related overall survival was 0.79 (90% CI, 0.56-1.11) without adjustment and 0.87 (90% CI, 0.62-1.23) after adjusting for age and adjuvant therapy.

Conclusion Among patients with limited SLN metastatic breast cancer treated with breast conservation and systemic therapy, the use of SLND alone compared with ALND did not result in inferior survival.

Trial Registration clinicaltrials.gov Identifier: NCT00003855

JAMA. 2011;305(6):569-575 www.jama.com

AXILLARY LYMPH NODE DISSECTION (ALND) has been part of breast cancer surgery since the description of the radical mastectomy.[1] ALND reliably identifies nodal metastases and maintains regional control,[2,3] but the contribution of local therapy to breast cancer survival is controversial.[4,5] The Early Breast Cancer Trialists' Collaborative Group synthesized findings from 78 randomized controlled trials, concluding that local control of breast cancer was associated with improved disease-specific survival.[6]

ALND, as a means for achieving local disease control, carries an indisputable and often unacceptable risk of complications such as seroma, infection, and lymphedema.[7-9] Sentinel lymph node dissection (SLND) was therefore developed to accurately stage tumor-draining axillary nodes with less morbidity than ALND.[10] SLND alone is the accepted management for patients whose

For editorial comment see p 606.

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Corresponding Author: Armando E. Giuliano, MD, John Wayne Cancer Institute at Saint John's Health Center, 2200 Santa Monica Blvd, Santa Monica, CA 90404 (giulianoa@jwci.org).

# of Axillary Lymph Node Breast Cancer

…IDAGE, AND THAT CER-…ast cancer. Forty years …or this disease was the …, an aggressive opera-…aly the breast but also …y lymph nodes. Better …y revealed that aggres-…dequate. As treatment …nsive surgery, axillary …ained part of the treat-…. Axillary lymph node …ator that systemic dis- …for chemotherapy. …enefitted greatly from …nized controlled trials. …ss surgery was better, …less surgical interven-…cations. In the first ma-…rvant Breast and Bowel …began in 1971, 1765 …domized into 5 treat-…mph nodes were ran- …mastectomy or a total …aly without the under- …g with regional radia- …ncer without palpable …ized into 1 of 3 study …with ALND, total mas- …tment, or mastectomy …recurrences were ob- …of occult nodal metas- …p. Despite an axillary …tial mastectomy group, …groups after 25 years …ith clinically palpable …vival than those with- …Local treatment of oc- …had no effect on over-

Recognition of the waning utility of ANLD led to the development of sentinel lymph node dissection (SLND). This technique involves injecting dye into the primary tumor and selectively resecting lymph nodes that take up the dye and thus indicate that they are the nodes draining the tumor mass. SLND has supplanted ALND for staging the axilla in early breast cancer, because less aggressive axillary surgery results in less arm stiffness, pain, paresthesia, and risk of lymphedema. A recently published single-institution study[2] with 10-year follow-up randomized 516 patients with breast cancer to undergo both SLND and ALND or SLND alone with ALND only if the sentinel lymph nodes (SLNs) contained cancer; that study showed better arm mobility and less pain in the SLND-alone group. At a median follow-up of 102 months, the regional failure rate in the SLND-alone group was 0.77%. There was no significant difference in disease-free survival between the groups, suggesting that ALND is not beneficial.

Retrospective analyses add indirect evidence regarding the lack of utility of ALND. These studies are not definitive because, as with all retrospective evaluations, it is difficult to control for selection bias and treatment bias. In general, these analyses show low axillary recurrence rates in women with minimal axillary disease and with positive SLNs who did not have completion ALND.[3,4] These patients tended to be older; had small, low-grade tumors with micrometastatic (<2 mm) nodal disease; and underwent breast conservation surgery. Predictors of non-SLN metastasis include tumor size, size of SLN metastatic deposit, number of SLNs involved, tumor lymphovascular invasion, and extranodal extension. In an effort to identify patients who might benefit from ALND, nomograms using these characteristics have been developed to predict who should undergo ALND.[5] Despite increasing evidence disfavoring ALND, it remains part of widely recognized guidelines for breast cancer care.[6] However, the apparent lack of utility of ALND has influenced clinicians treating breast cancer because the performance of ALND following SLND has declined.[7,8]

In this issue of *JAMA*, Giuliano and colleagues from the American College of Surgeons Oncology Group[9] report results of the Z0011 randomized trial comparing SLND alone with ALND in women with breast cancer and SLN metas-

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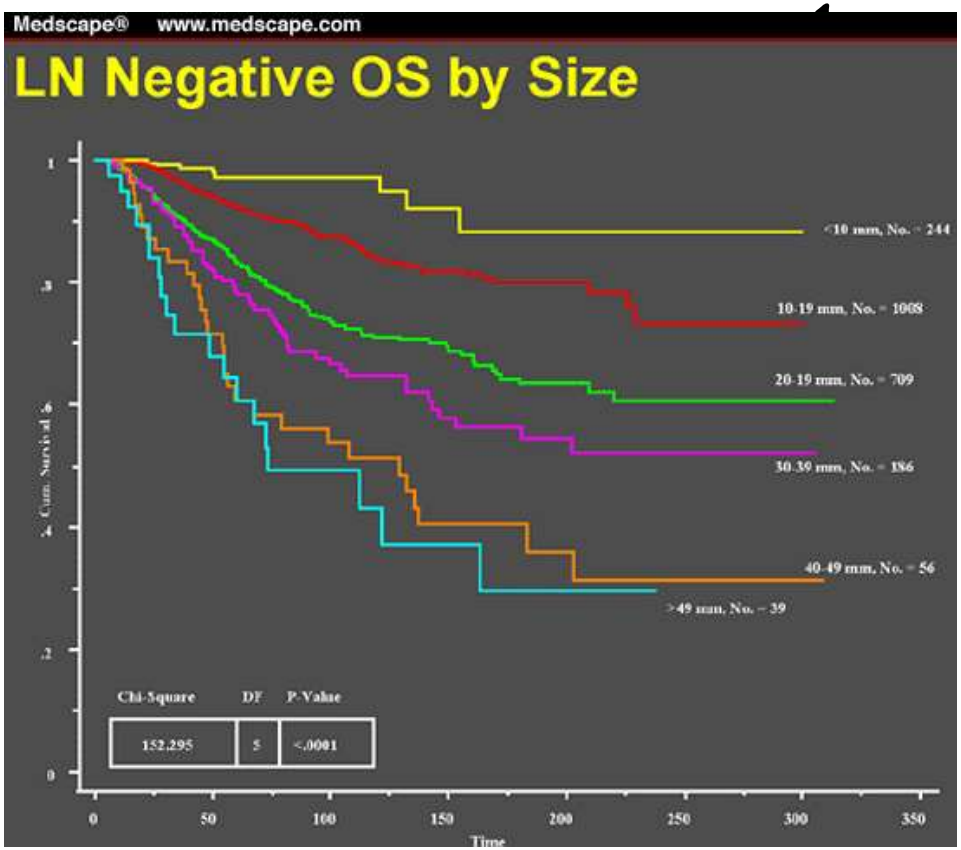
Wichtige prognostische Faktoren

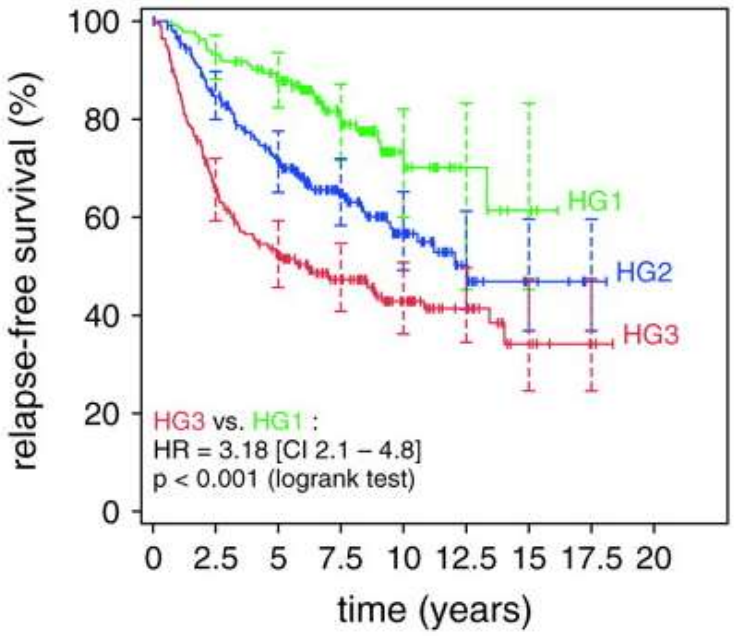
- Tumor Grösse
- Tumor Grad
- Lymphknoten
- Vaskulare Invasion
- Tumor Typ
- Alter
- Resektionsrande

POSTOPERATIVE BEHANDLUNG IST AUF GRUND DIESER FAKTOREN



Tumor grade

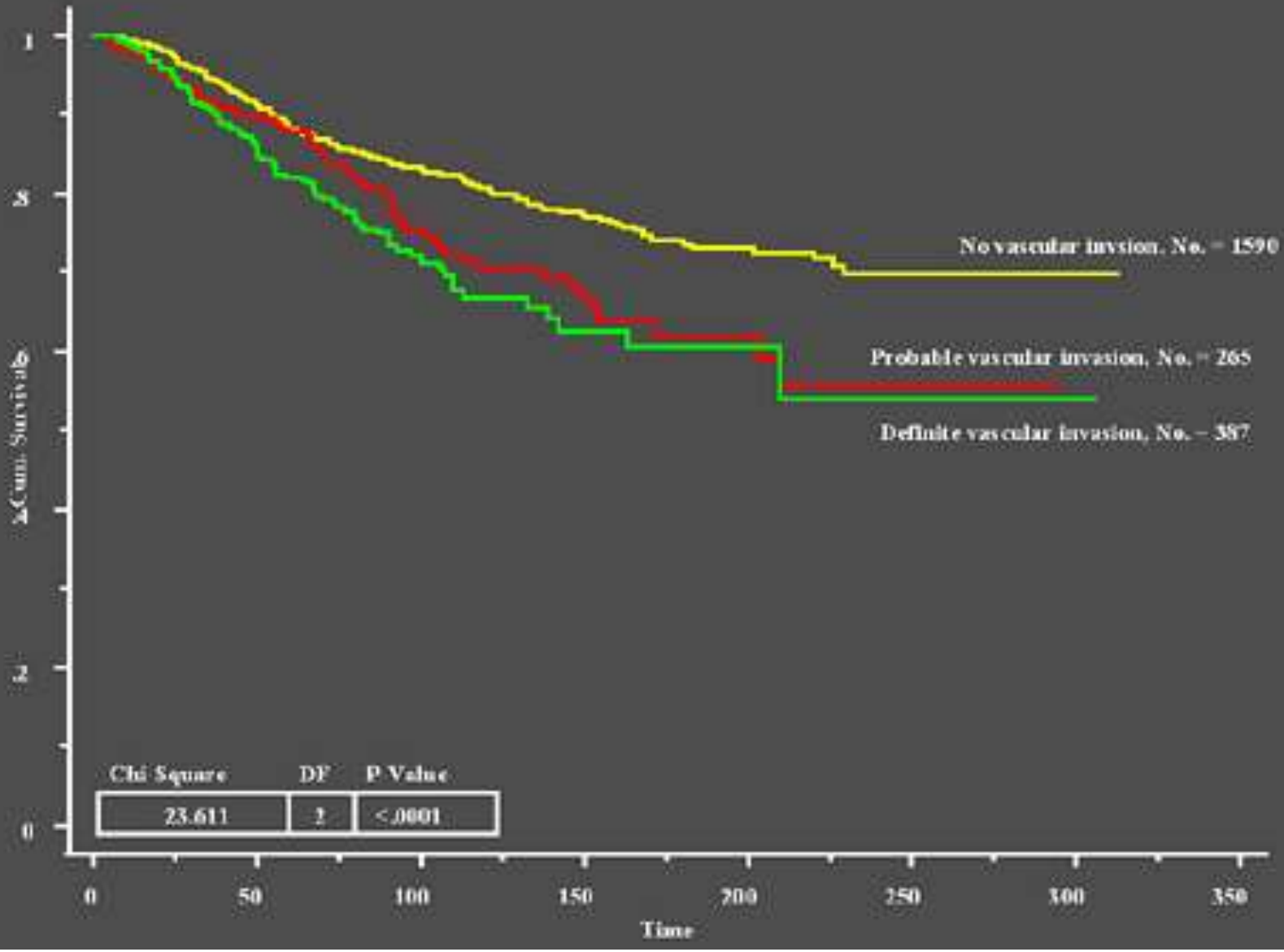
2



1: A. Langerød et al. Breast Cancer Research 2007, **9**:R30do

2: Sotiriou C et al. JNCI Journal of the National Cancer Institute 2006 98(4):262-272

LN Negative OS by Vascular Invasion



Nottingham Prognostischer Index

0,2x Tumorgrösse (cm) + Grad + LK Status

unter 2,4 : hervorragend

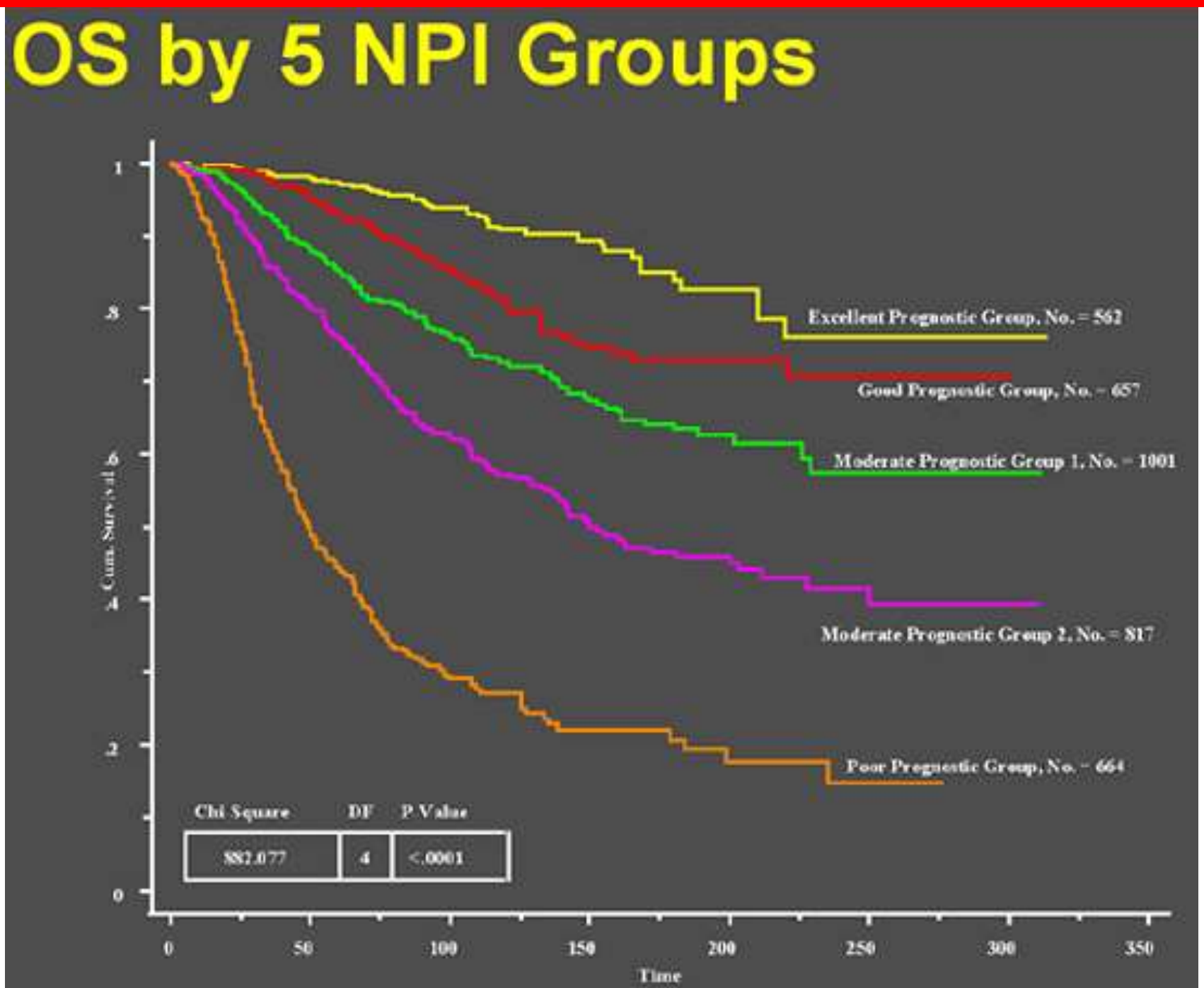
2,41-3,4: gut

3,41-4,4: mittelmassig gut

4,41-5,4: mittelmassig schlech

über 5,41 : schlecht

OS by 5 NPI Groups



Additionelle prognostische Faktoren
die verplichtend zu melden sind

- Molekulare Markers in Routine
- Sind Prognose oder Behandlung bestimmend
  - Sind einfach in alltaglicher Praxis nachzuweisen

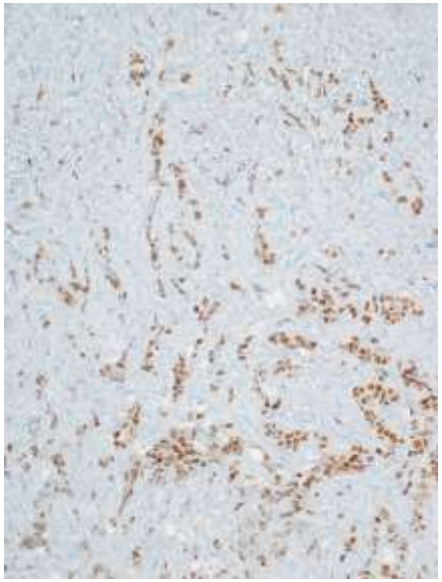
BEEINFLUSST DIE ART DER POSTOPERATIVEN BEHANDLUNG:

PERSONALISIERTE BEHANDLUNG

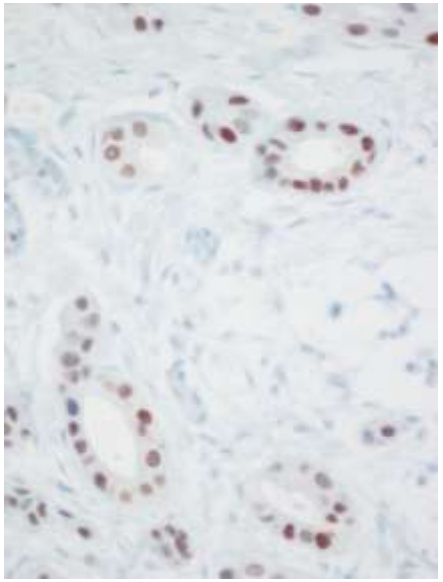
Östrogen- und Progesteron Rezeptoren
Her2 Rezeptor
Proliferationsindex (Ki-67 – mib-1)

Prediktive und prognostische Faktoren

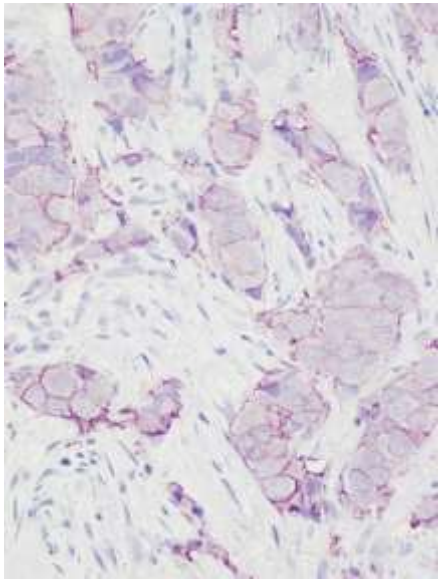
- Östrogen Rezeptor
- Progesteron Rezeptor
- Her2 (IH und ISH wenn nötig)
- Proliferation Index (Ki67- mib-1)



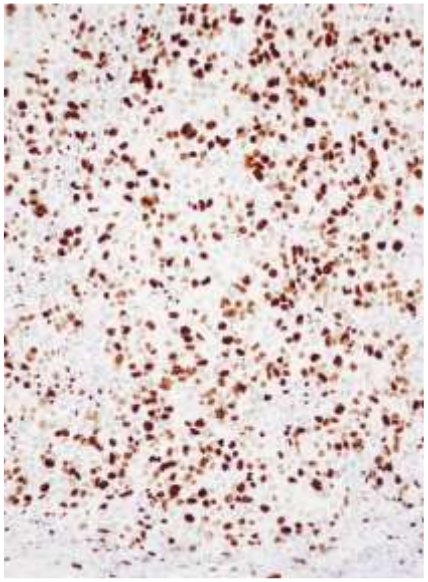
ÖR



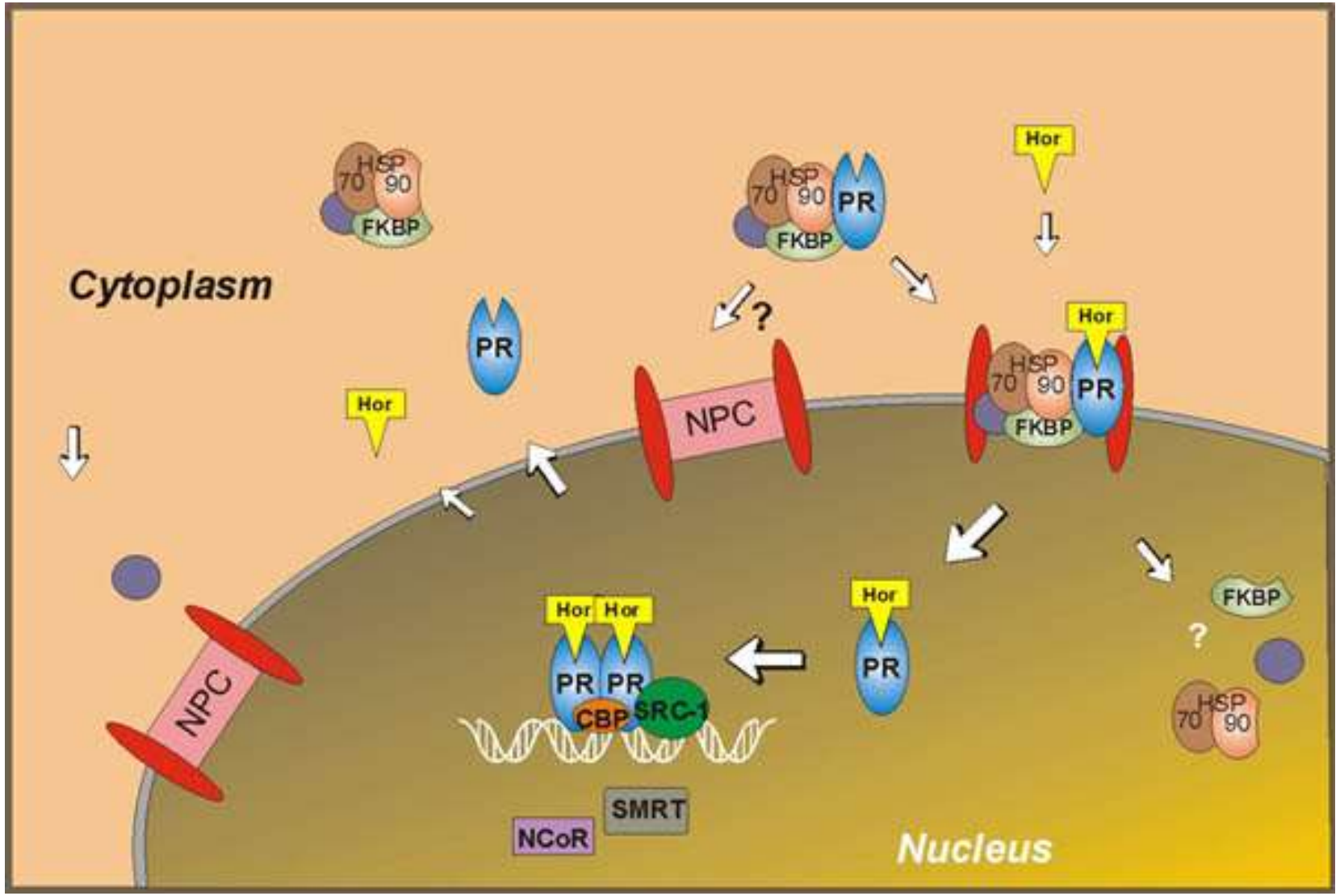
PR



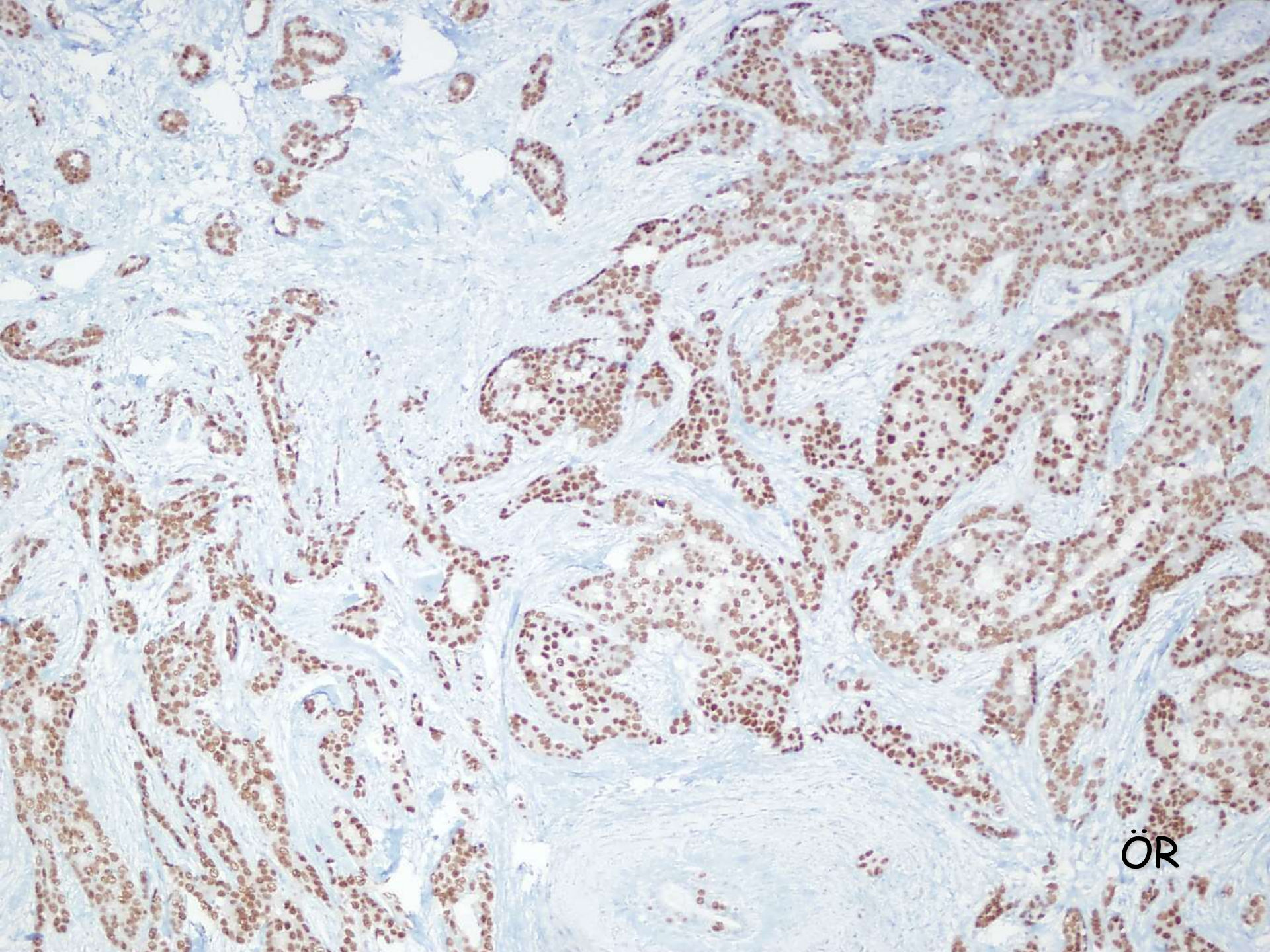
HER2



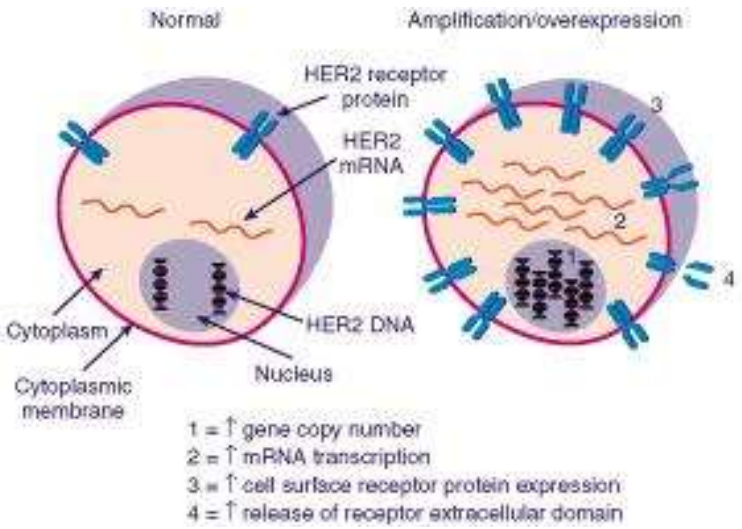
Ki67

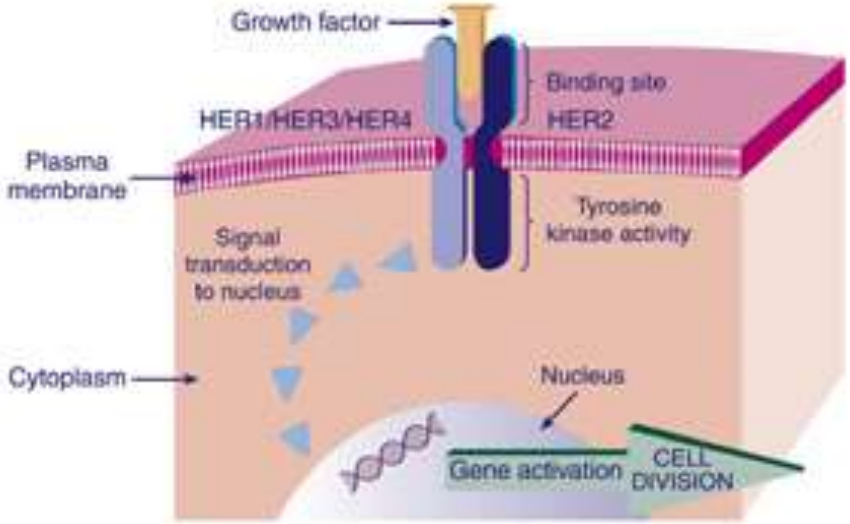


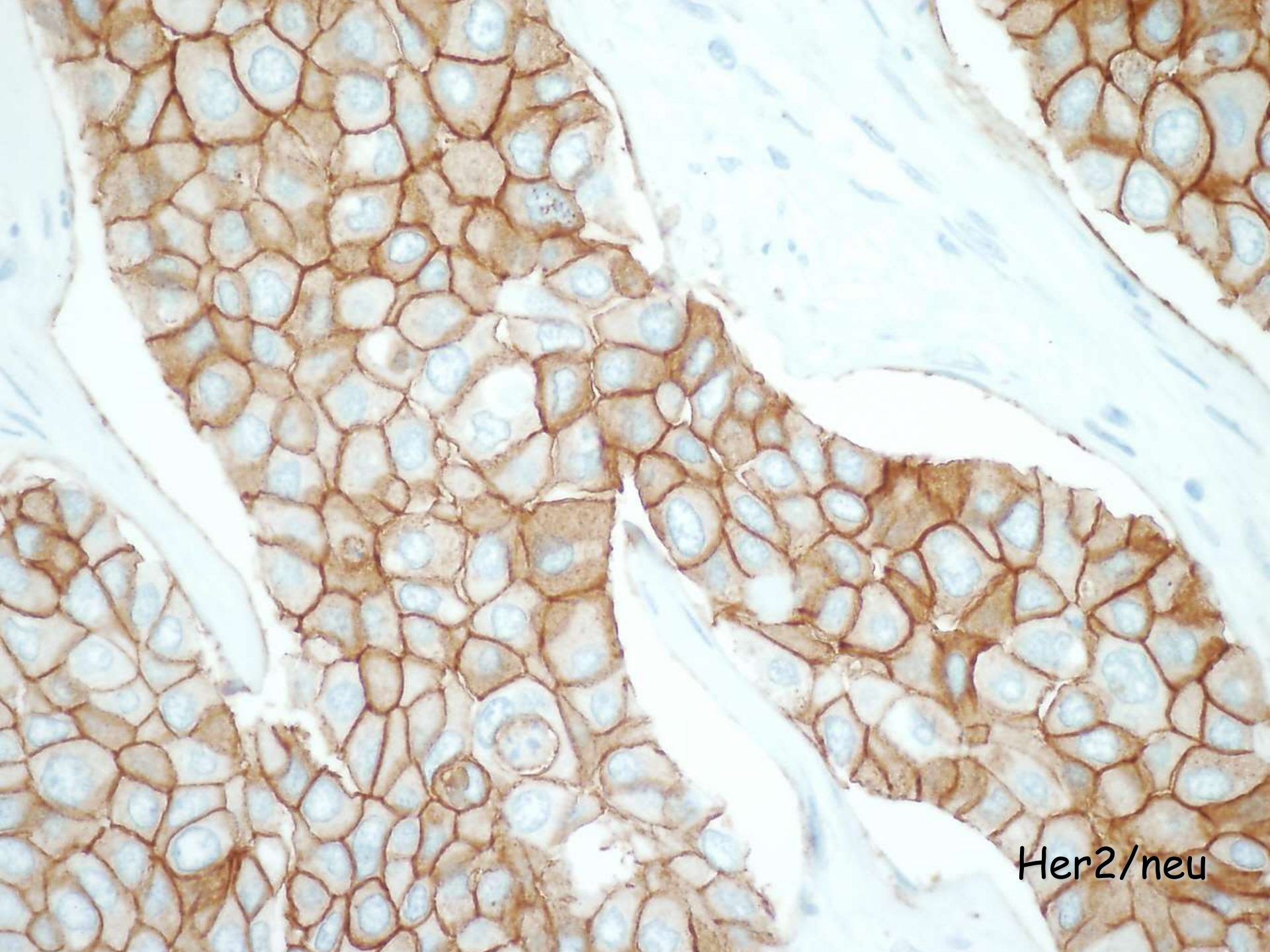
ÖSTROGEN UND PROGESTERON REZEPTOREN


ÖR

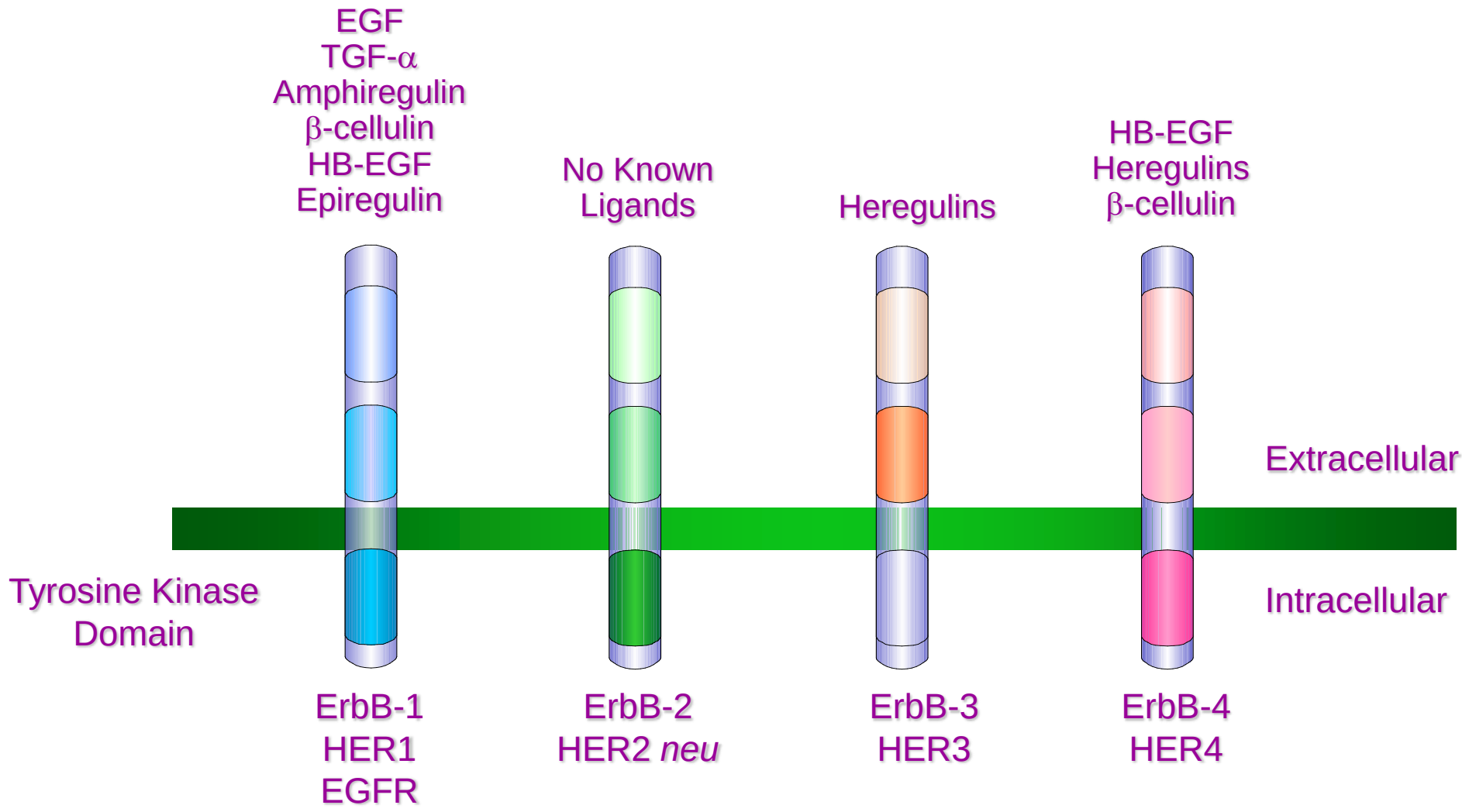
Her2/neu Amplifikation - Rezeptor Protein Überexpression



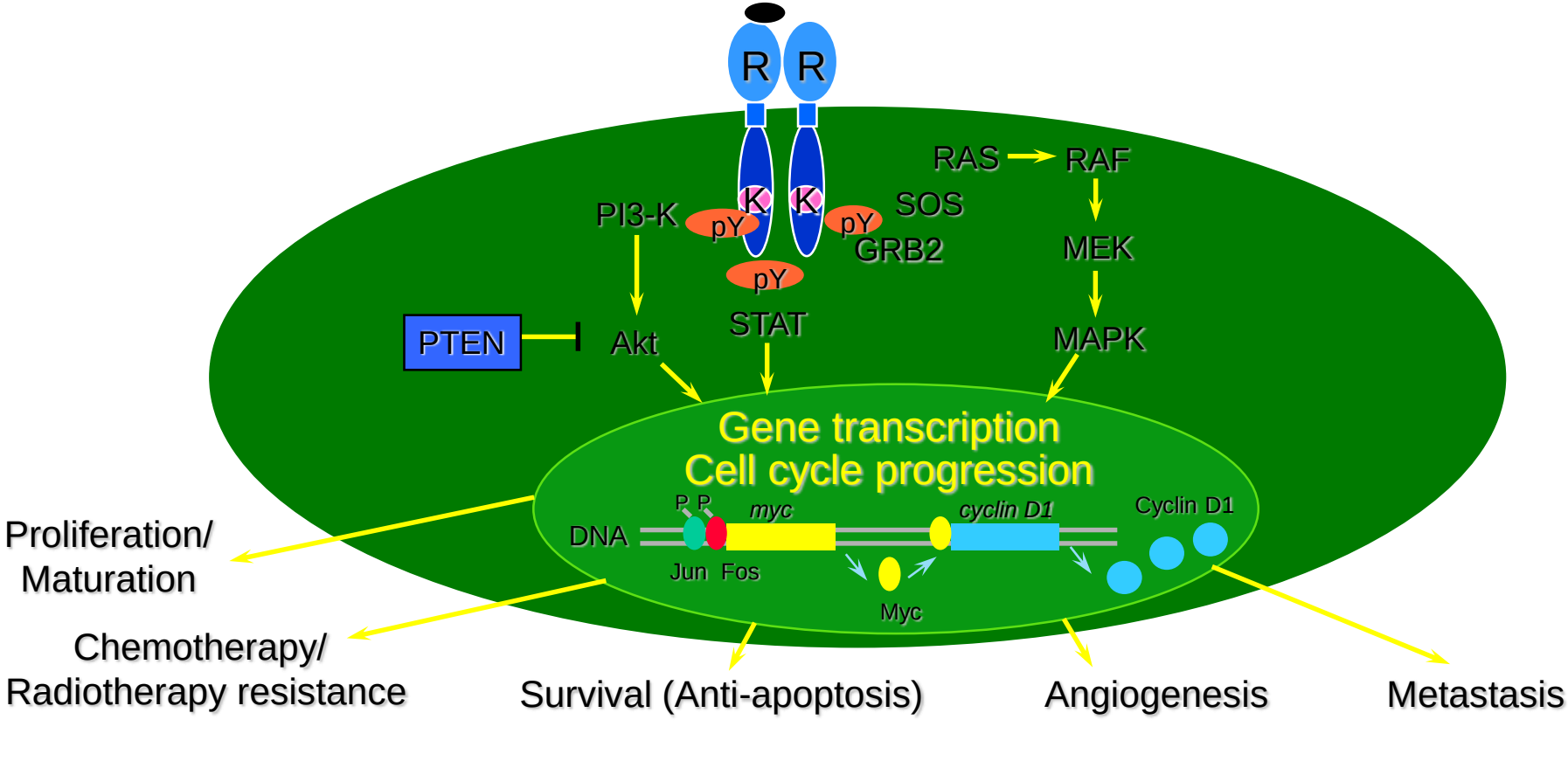



Her2/neu

Die ErbB Familie und Liganden



Aktiviertes EGFR-TK Induziert malignes Phenotyp [1-6]



Adapted with permission from Baselga J. *Signal*. 2000;1:12-21. 1. Raymond E et al. *Drugs*. 2000;60(suppl 1):15-23. 2. Woodburn JR. *Pharmacol Ther*. 1999;82:241-250. 3. Wells A. *Int J Biochem Cell Biol*. 1999;31:637-643. 4. Hanahan D, Weinberg RA. *Cell*. 2000;100:5
5. Balaban N et al. *Biochim Biophys Acta*. 1996;1314:147-156. 6. Akimoto T et al. *Clin Cancer Res*. 1999;5:2884-2890.

EGFR Expression in menschlischen Tumoren

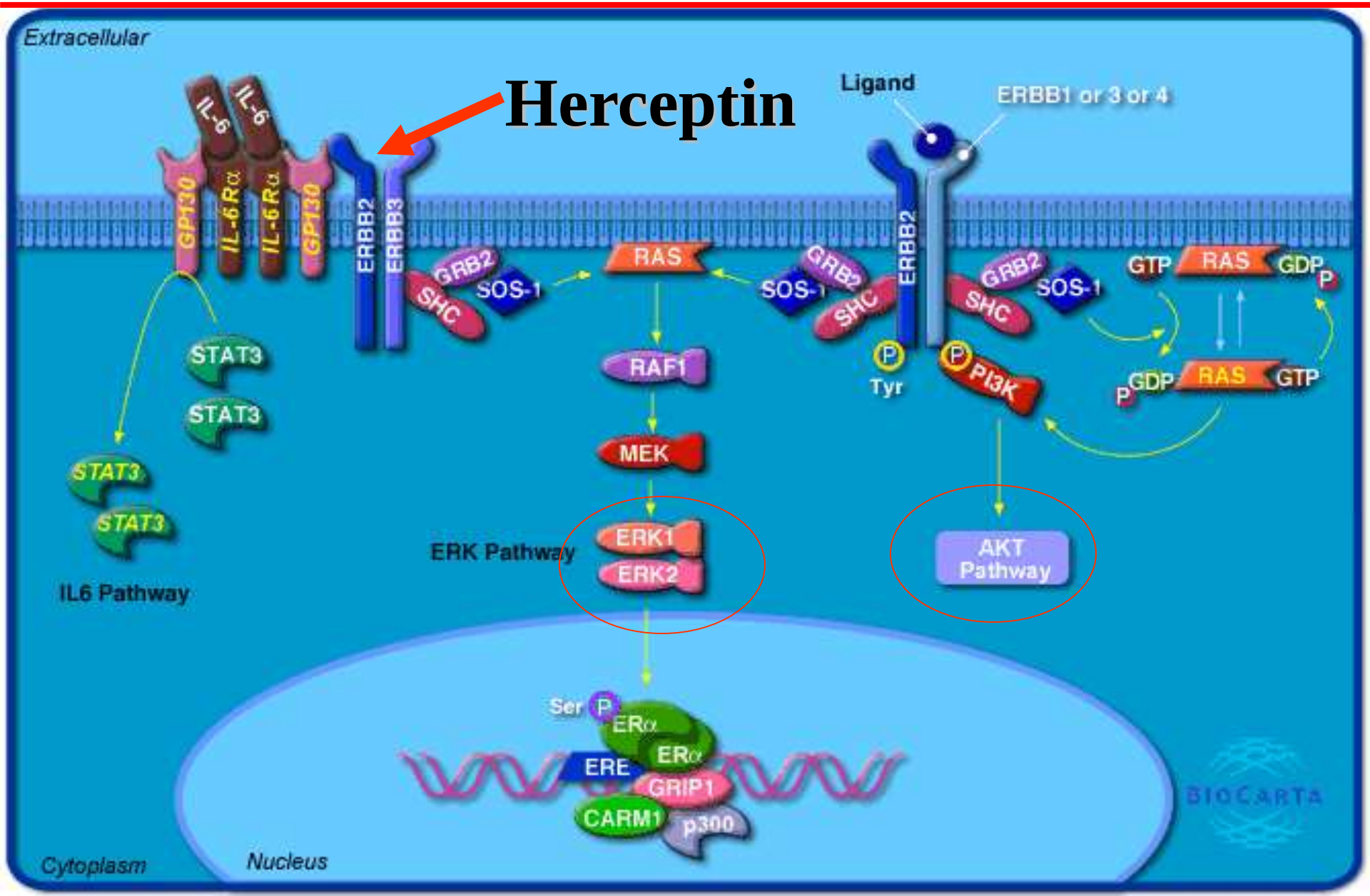
Colon	25-77%
Head and Neck	95-100%
Pancreatic	30-89%
NSCLC	40-80%
Renal cell carcinoma	50-90%
Breast	**14-91% (45%)**
Ovarian	35-70%
Glioma	40-63%
Bladder	31-48%

Prognostische Bedeutung der EGFR Expression

Tumor Type	Prognosis	Survival	Risk of Metastases	Reference
NSCLC	Poor	OS		Volm (1998) Veale (1993) Ohsaki (2000)
Breast	Poor	OS		Nicholson (2001) Perez (2001)
Colorectal	Poor	OS		Nicholson (2001) Mayer (1993) Hemming (1992)
Head and neck	Poor	DFS OS	—	Grandis (1998) Maurizi (1996)

DFS = disease-free survival; OS = overall survival.

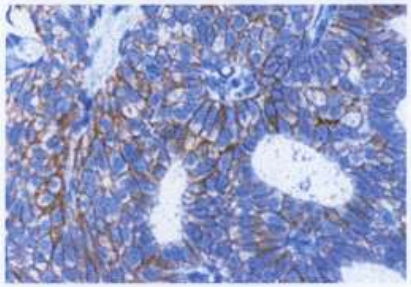
EGFR2/HER2 signal transduction (physiologic cond.)



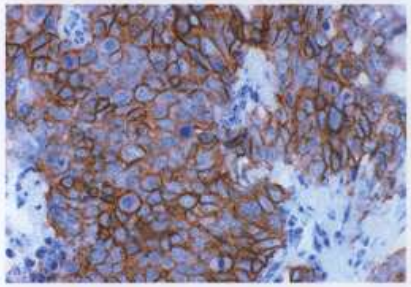
Guidelines for Scoring **HercepTest™**

DAKO

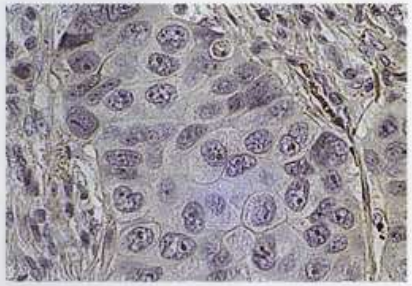
Score to report	HER2 protein overexpression assessment	Staining pattern
0	Negative	No staining is observed, or membrane staining in less than 10% of the tumour cells.
1+	Negative	A faint/barely perceptible membrane staining is detected in more than 10% of the tumour cells. The cells are only stained in part of the membrane.
2+	Positive	A weak to moderate complete membrane staining is observed in more than 10% of the tumour cells.
3+	Positive	A strong complete membrane staining is observed in more than 10% of the tumour cells.



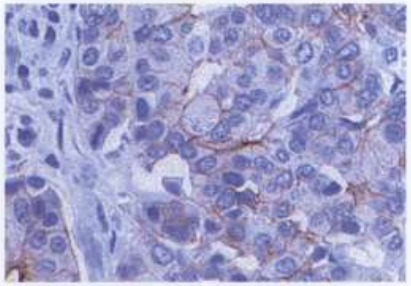
Score: 2+



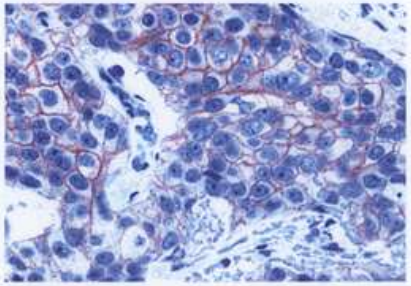
Score: 3+



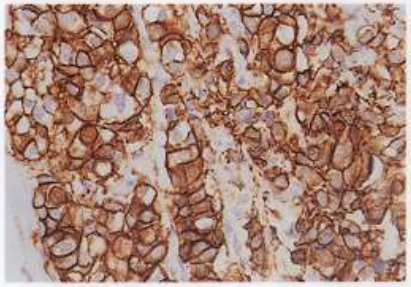
Score: 0



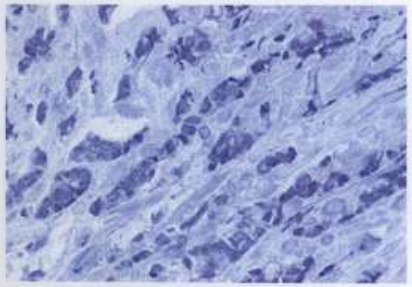
Score: 1+



Score: 2+



Score: 3+



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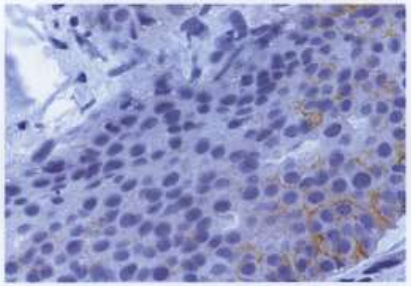
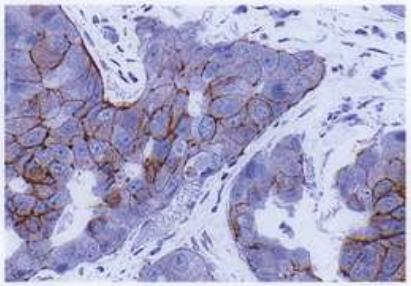
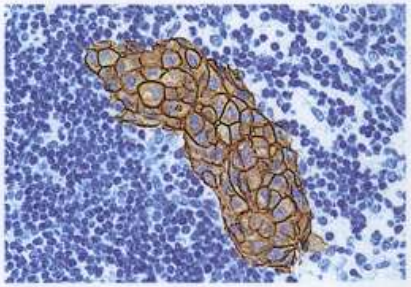


Score: 1+

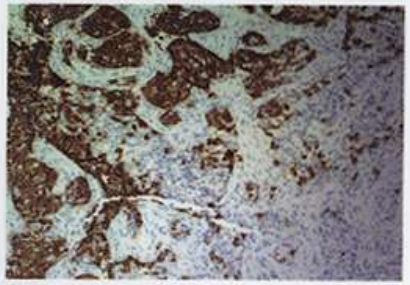


Score: 2+

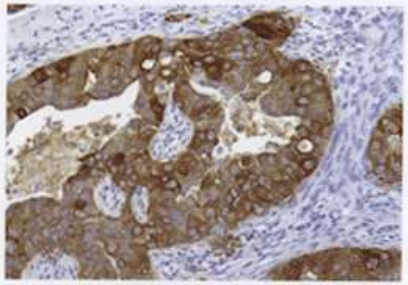


Score: 3+

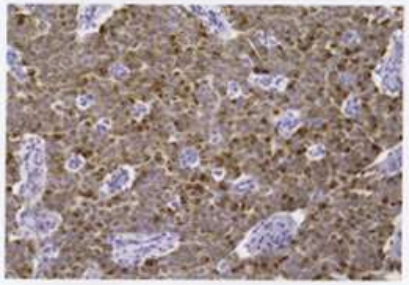
HercepTest™ Rare Staining Patterns and Artifacts



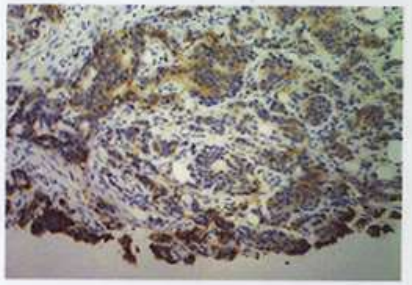
Example of heterogenous staining. Score: 3+



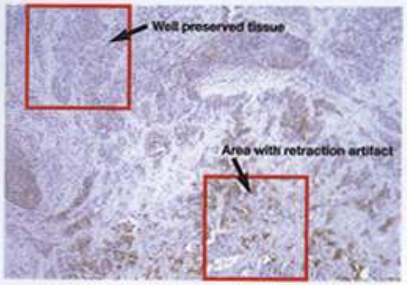
Example of cytoplasmic staining. Score: 0



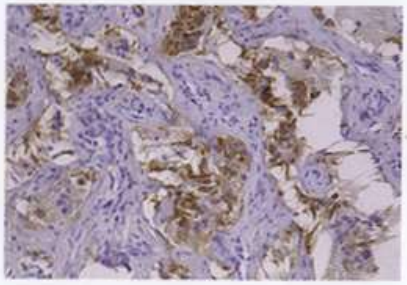
Example of dot artifact. Score: 0



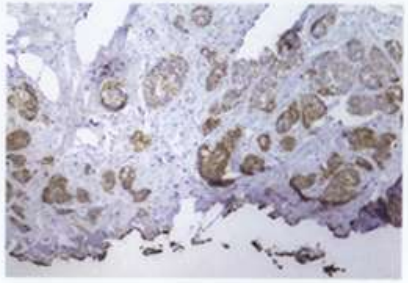
Example of edge artifact. Score: 1+



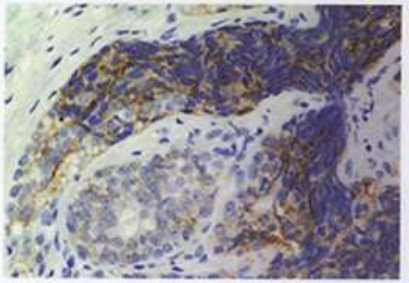
Example of retraction artifact. Score: 1+



Example of retraction artifact. Score: 1+



Example of thermal artifact. Score: 1+



Example of crushing artifact. Score: 1+

DAKO

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Photos by James Thompson, MD, PhD, Director of Pathology, Biopharmaceutical Services, Impath Laboratories, Frolian Espinoza, MD, Molecular Tissue Pathology, Quest Diagnostics/Nichols Institute and DAKO.

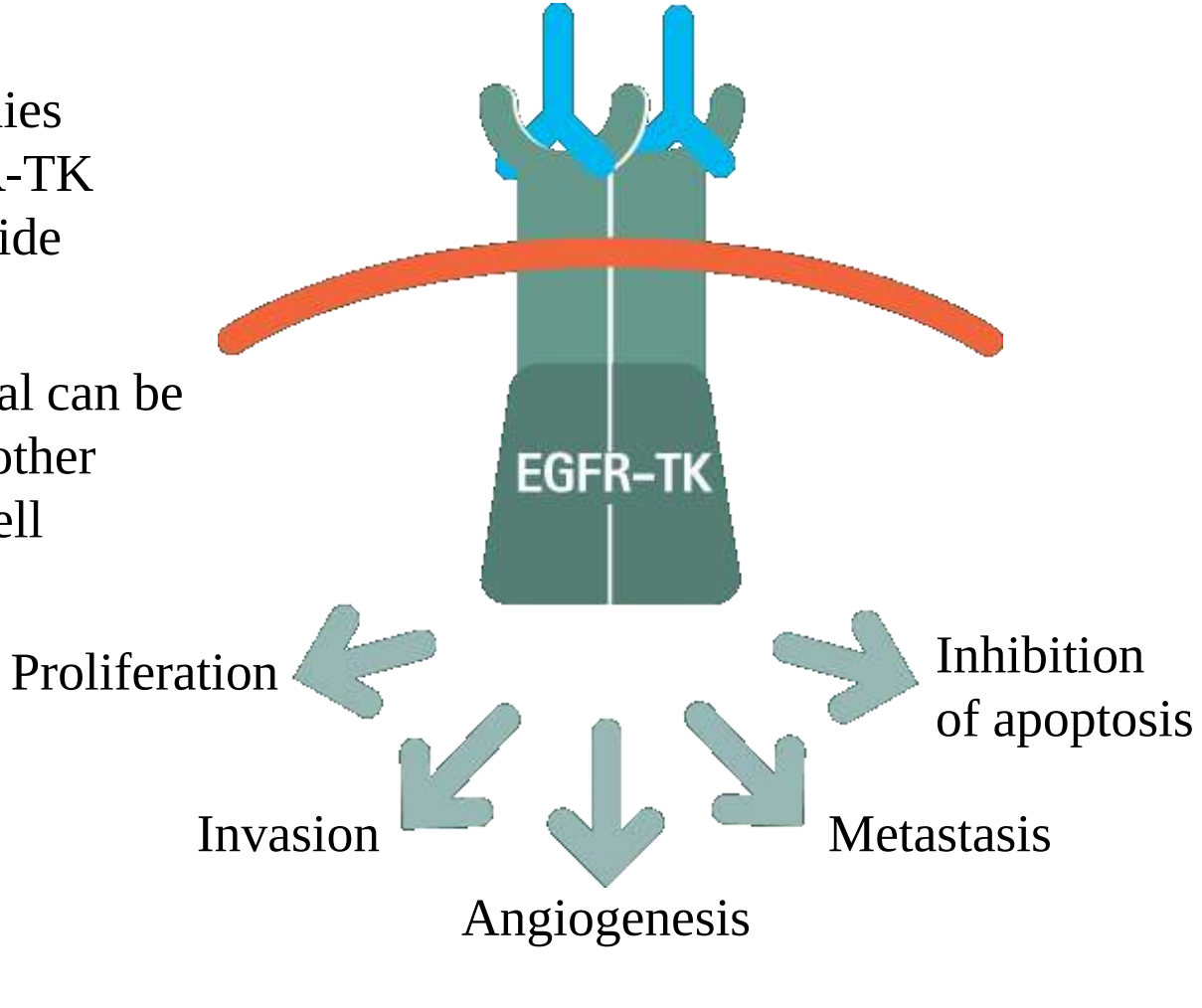
Vielfaltige Aktivation-Mechanismus für EGFR-TK[1-4]

1. Overexpression of EGFR protein
2. Increased ligand expression/autocrine loop
3. Heterodimerization
4. Lateral signal propagation, cross talk (G-protein coupled receptors, cytokine receptors, cell stress)
5. Mutant EGFR – constitutive activation
6. Decreased phosphatase
7. Altered downstream signal function

1. Raymond E et al. *Drugs*. 2000;60(suppl 1):15-23. 2. Velu TJ. *Mol Cell Endocrinol*. 1990;70:205-216. 3. Wells A. *Int J Biochem Cell Biol*. 1999;31:637-643. 4. Moghal N et al. *Curr Opin Cell Biol*. 1999;11:190-196.

Blockierung der EGFR-TK Signal [1-3]

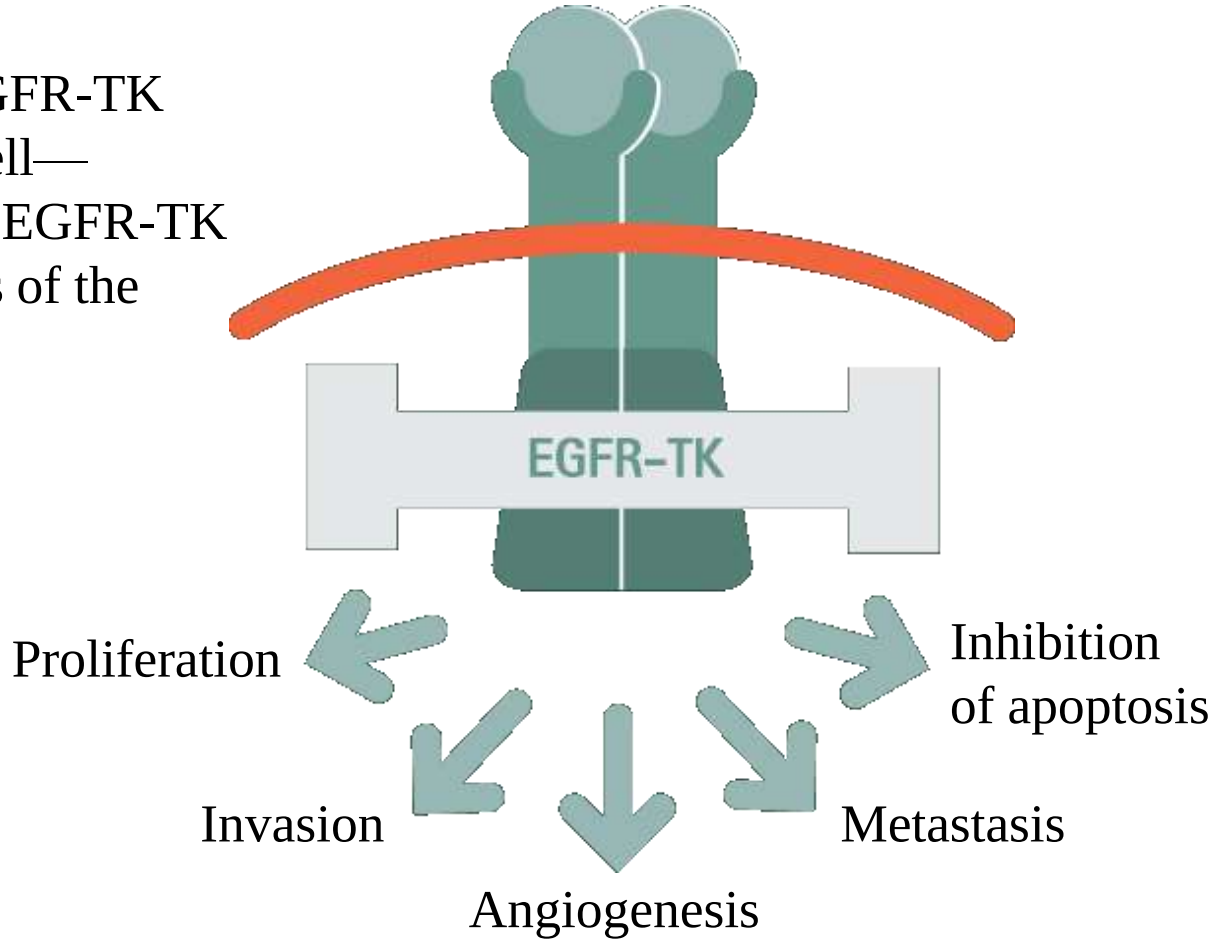
- Monoclonal antibodies can block the EGFR-TK signal from the outside
- The EGFR-TK signal can be turned on by many other triggers inside the cell



1. Huang S-M, Harari PM. *Invest New Drugs*. 1999;17:259-269. 2. Baselga J. *J Clin Oncol*. 2000;18(suppl):54s-59s.
3. Wells A. *Int J Biochem Cell Biol*. 1999;31:637-643.

Blockierung der EGFR-TK Signal [1-3]

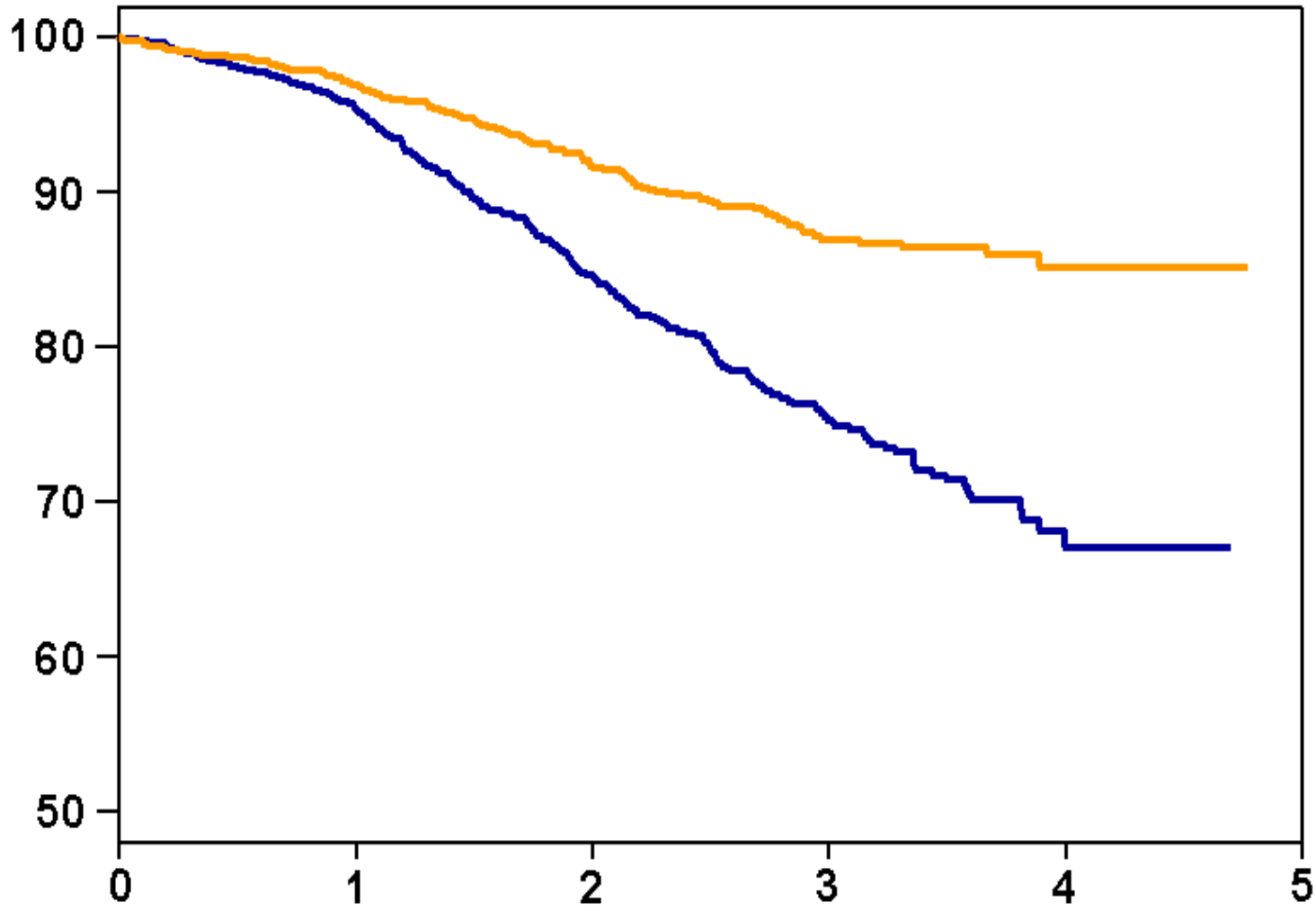
- Inhibition of the EGFR-TK itself—inside the cell—completely inhibits EGFR-TK signaling regardless of the triggering event



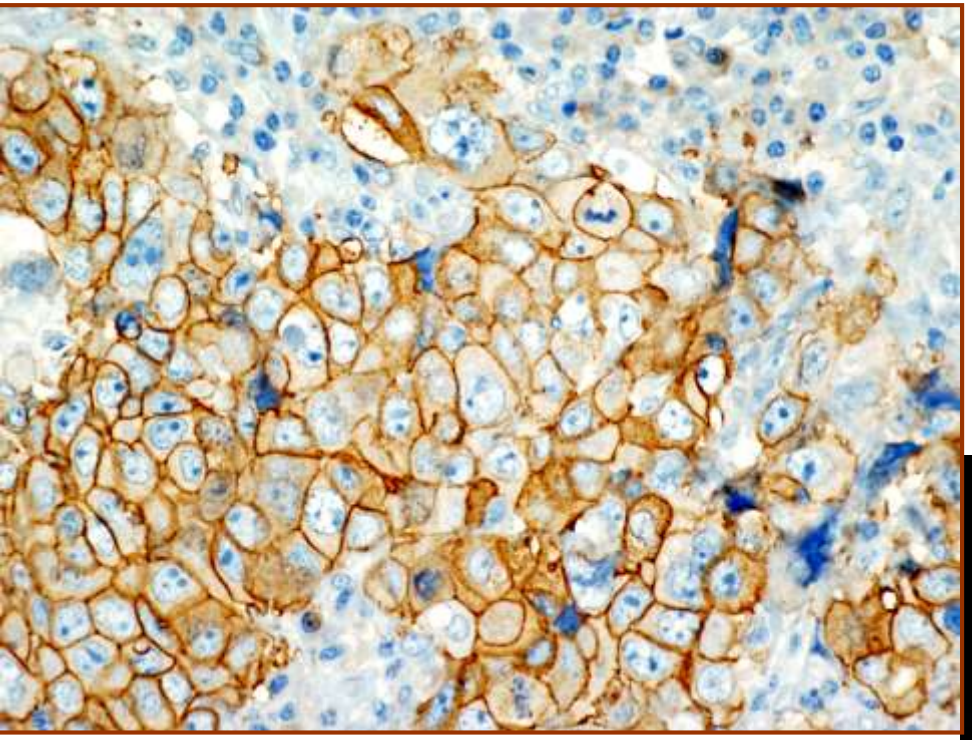
1. Leserer M et al. *IUBMB Life*. 2000;49:405-409. 2. Raymond E et al. *Drugs*. 2000;60(suppl 1):15-23.
3. Prenzel N et al. *Endocr Relat Cancer*. 2001;8:11-31.

Krankheits-Frei Überleben

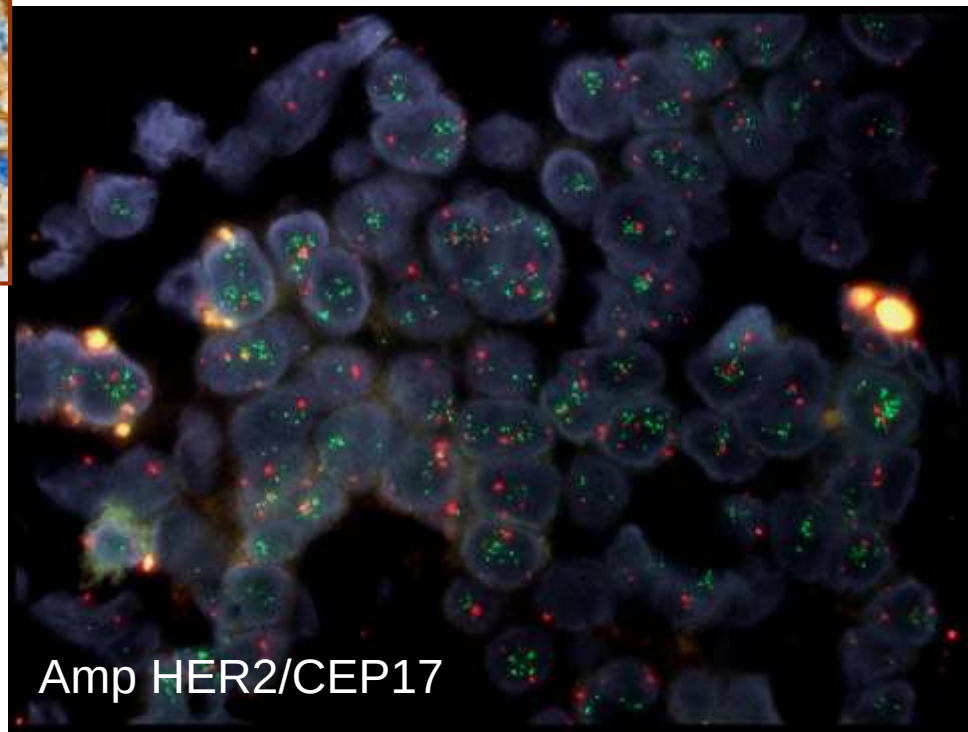
Romond H et al. Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer NEJM 2005; 353:1673-1684



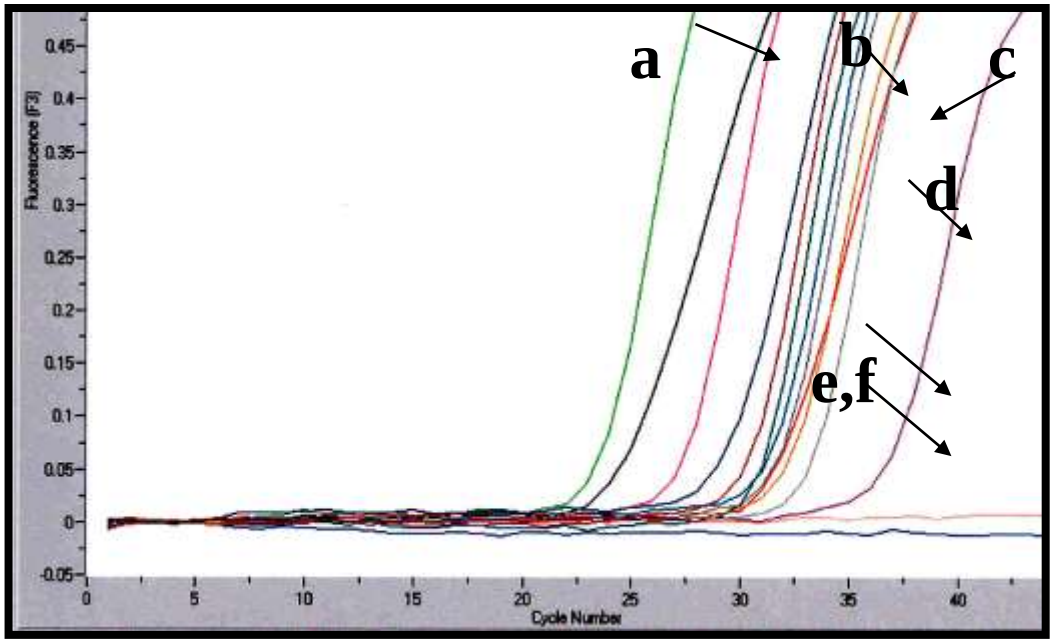
HER2 expression in breast cancer



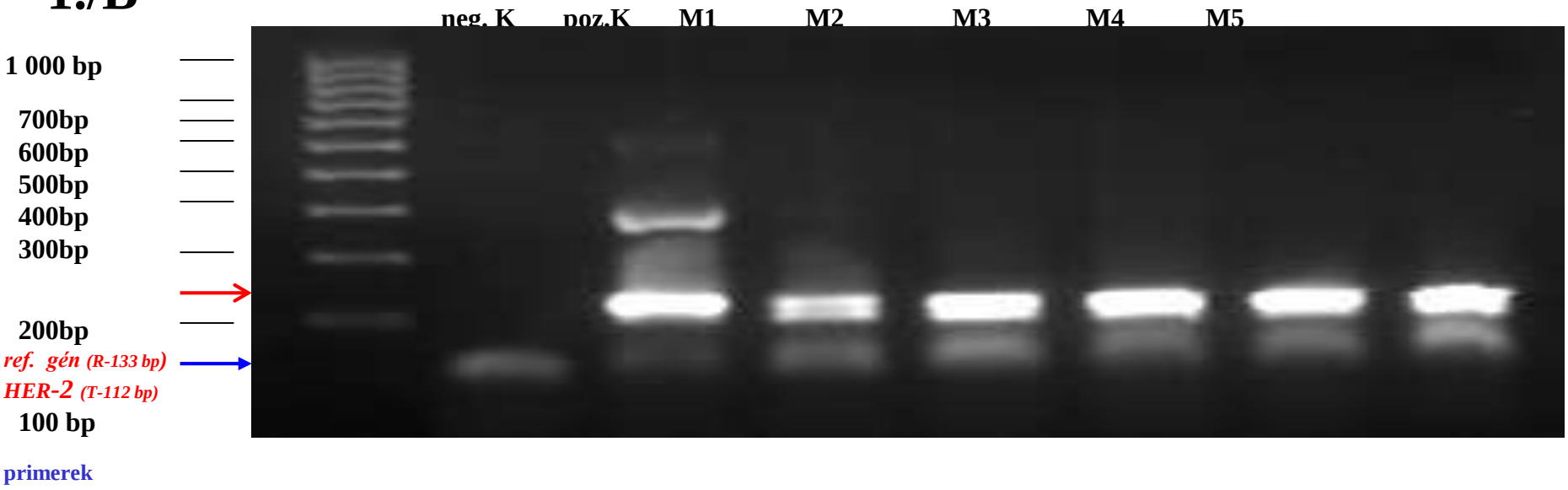
3+ CB11



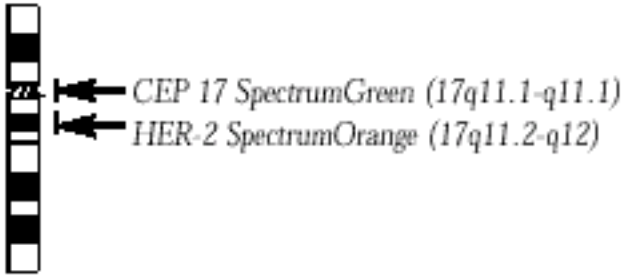
1/A

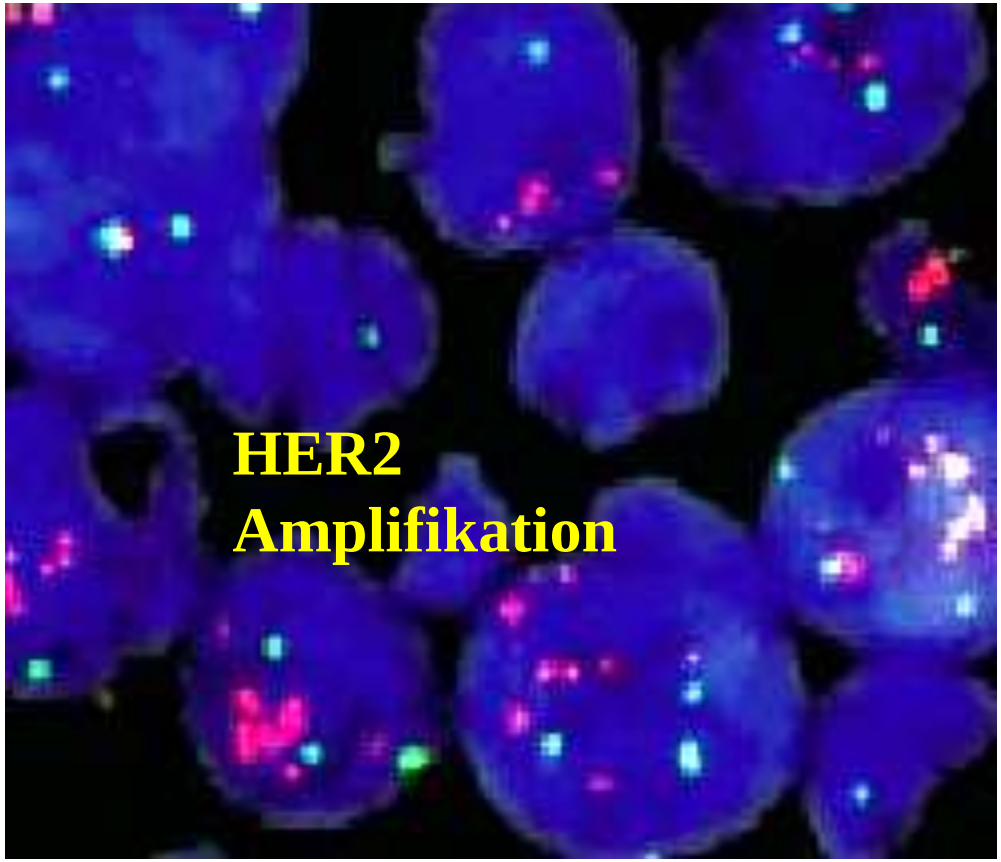

a
b
c
d
e,f
Fluorescence (F3)
Cycle Number
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
-0.05
0
5
10
15
20
25
30
35
40

1./B

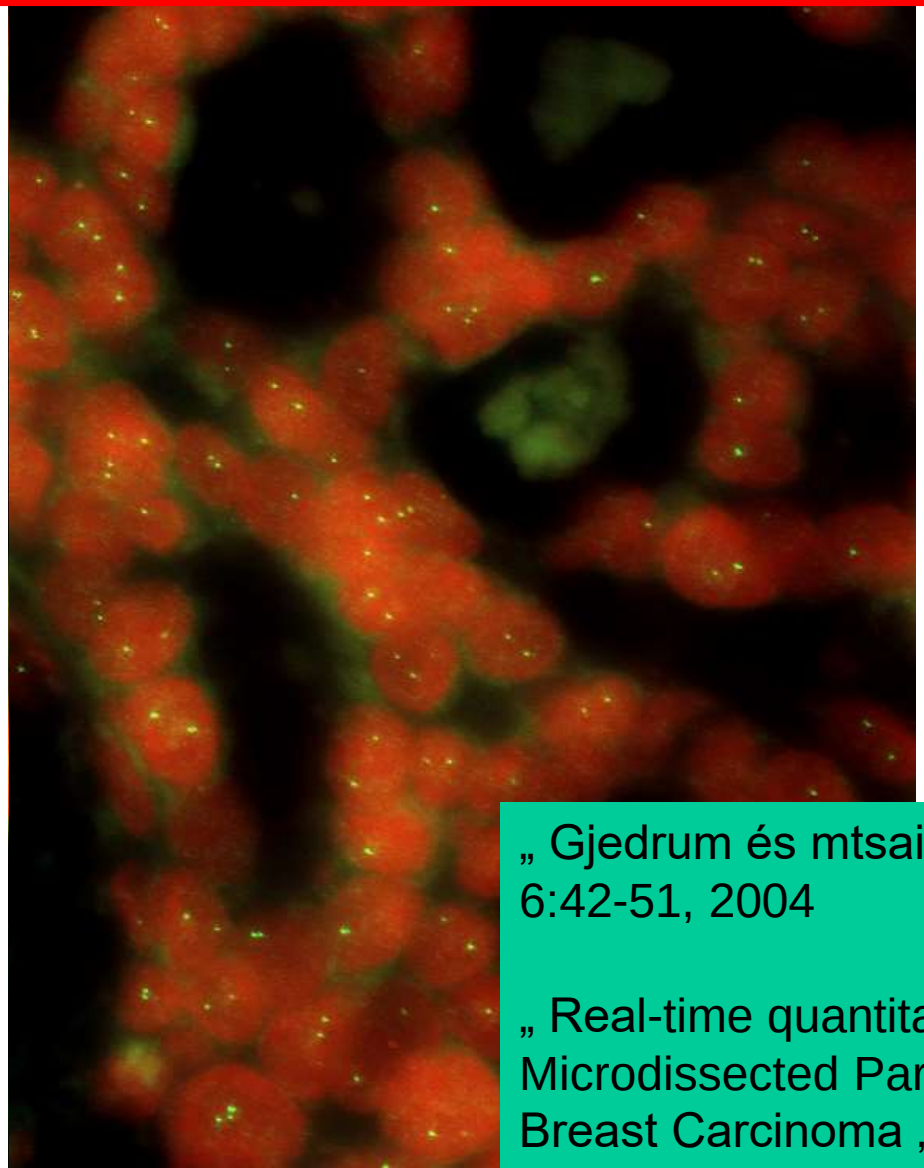

neg. K
poz.K
M1
M2
M3
M4
M5
1 000 bp
700bp
600bp
500bp
400bp
300bp
200bp
ref. gén (R-133 bp)
HER-2 (T-112 bp)
100 bp
primerek

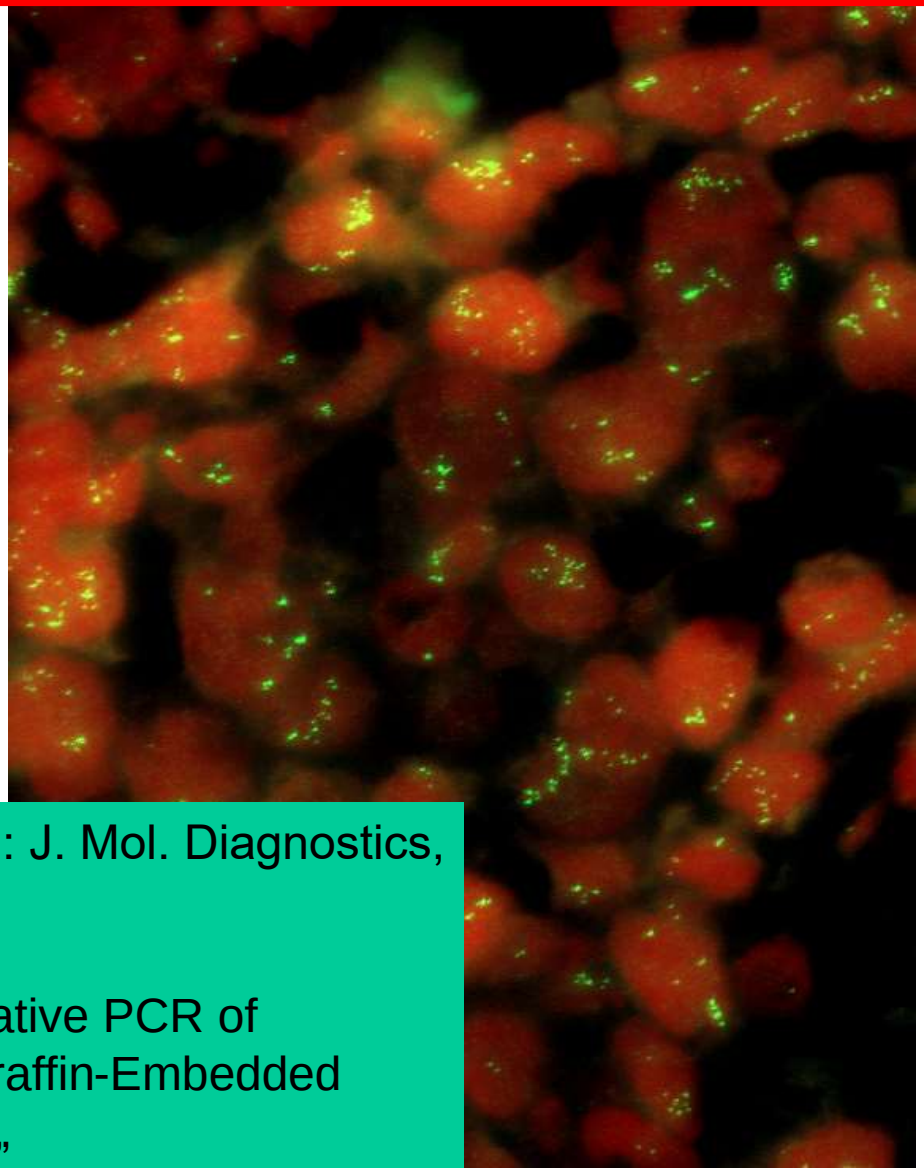
MOLEKULAR PATHOLOGIE
HER-2 - Mammakarzinom





Importance of pretreatment – heat treatment (HER2 FISH)



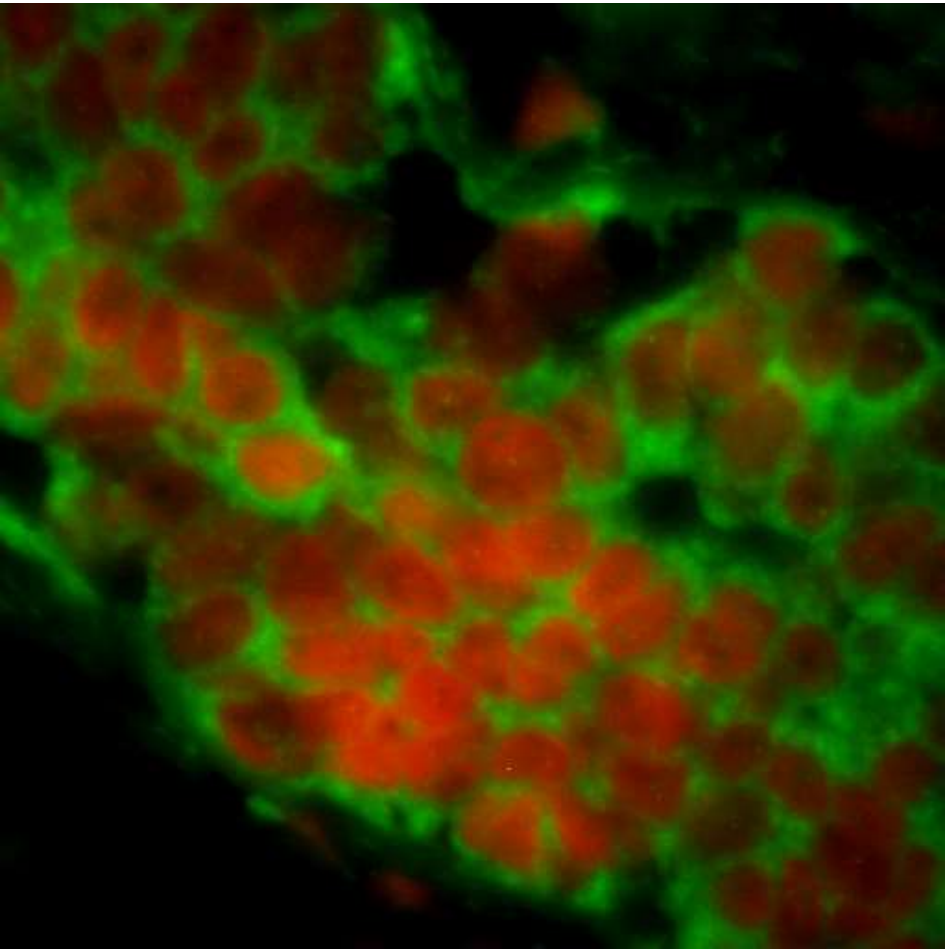


„ Gjedrum és mtsai: J. Mol. Diagnostics, 6:42-51, 2004

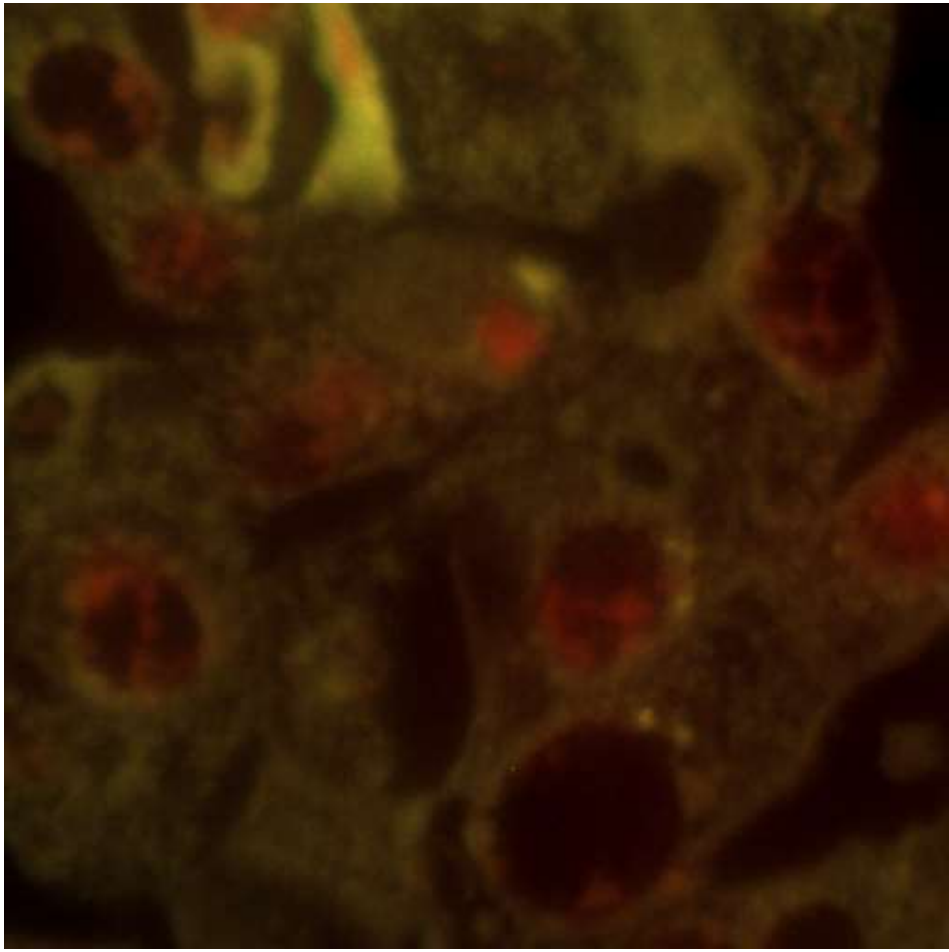
„ Real-time quantitative PCR of Microdissected Paraffin-Embedded Breast Carcinoma „

Importance of pretreatment – enzymatic digestion (HER2 FISH)

Underdigested



Overdigested



Kontroversen in der biologischen Verhalten der Brustkrebs

- Tis (in situ) Tumoren sind heterogen – sie verhalten sich vershieden, einige sind agressiv
- T1N0: Frühstaidum Karzinom
- ABER, 30% der T1N0 Tumoren zeigen Rezidiv oder sind disseminiert innerhalb von 5 Jahren

…gleichzeitig

- einige histologische Typen des Brustkarzinoms zeigen hervorragende Prognose: muzinöses und tubulares Karzinom.

- Medullares Karzinom: das Verhalten entspricht nicht unbedingt der Differentiation.

Prognose Aussichten bei dem genetischen Profil

- ES GEBEN ZWEI DEUTLICH VERSHIEDENE GRUPPEN
- (Data AUFGRUND 151 Pazienten <53 Jahre, pN0, 10 Jahre follow up)
  - **Gute Prognose (40%)**
  - **Schlechte Prognose (60%)**
- DIE WAHRSCHEINLICHKEIT DER METASTASE IST VORGESAGT
  - 4x mehr genauer als pN Stadium
  - 3x mehr genauer als Tumorgrösse
  - 1,5x mehr genauer als Tumor Grad

BÖSARTIGE TUMOREN

GRADING

- **Mitoserate, Zellpolymorphie, Drüsenbildung**

Lymphogene Metastasierung: Anzahl der betroffenen Lymphknoten korreliert mit der Prognose

- **Axillare Lympknote, kontralaterale Mamma, Mediastinum, Pleura**

lymphangiosis carcinomatosa

Hämatogene Metastasierung:

- **Knochen, Lungen, Leber, Nebennieren, Haut, Hirn**

BÖSARTIGE TUMOREN

KREBSVORSORGEUNTERSUCHUNGEN:

- **Inspektion • Palpation (ab 20 Lj. 1x Monat)**
- **Mammographie (ab 35 Lj.) • Sonographie**
- **DopplerSonographie**

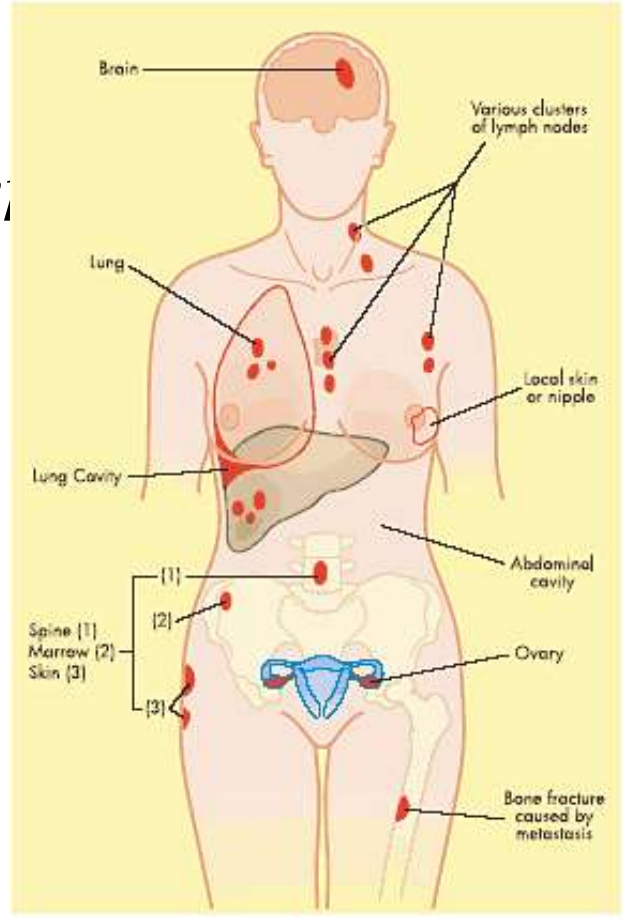
Jeder Tumor ist abklärungsbedürftig !

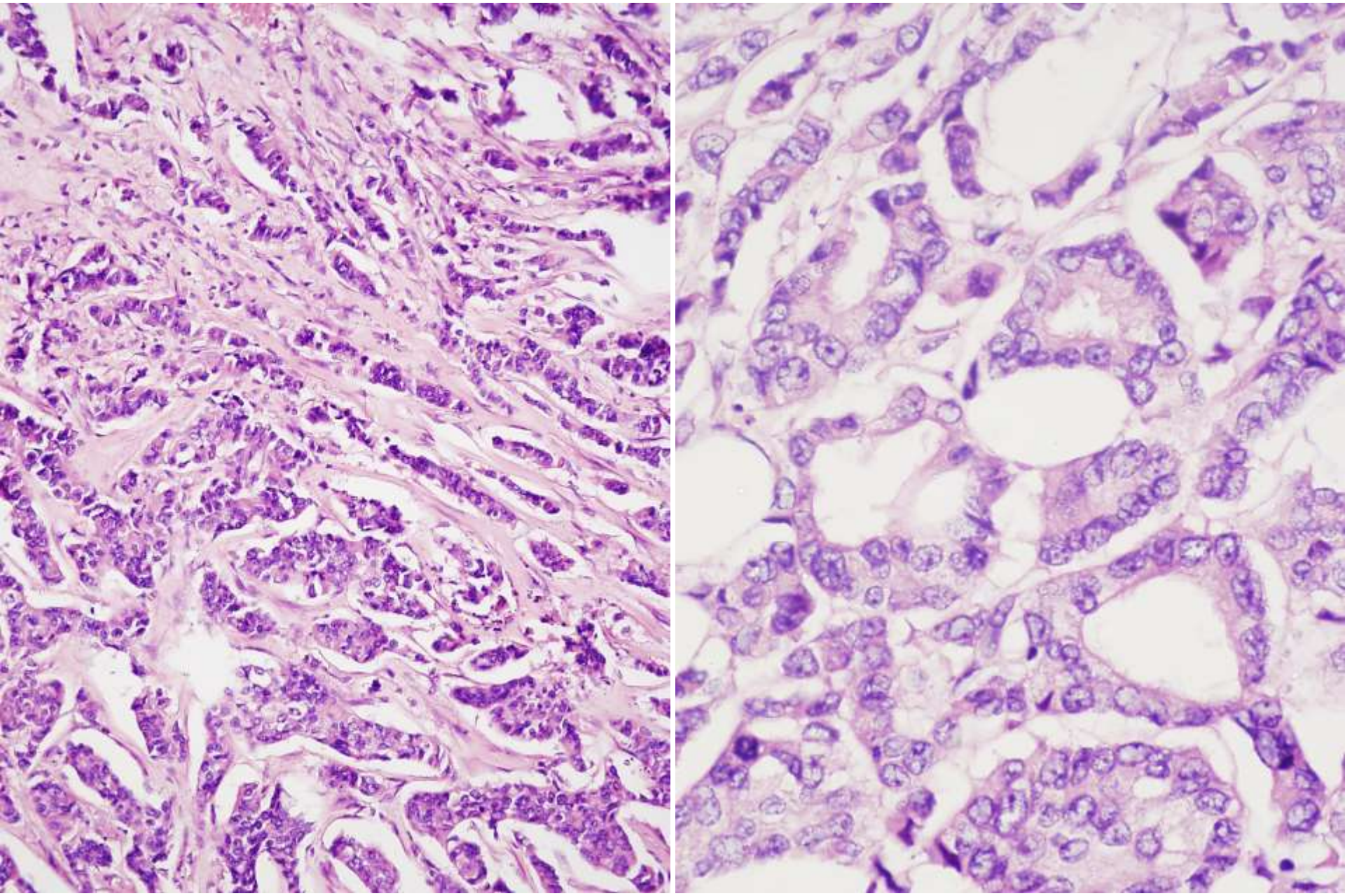
Feinnadelpunktion, Core Biopsie,
Tumorexstirpation möglich mit Brusterhaltende Operationen, Nachbestrahlung
mit Fernmetastasen: adjuvante Chemo oder Hormontherapie
Bei multifokale oder retromamillare Ausbreitung: Ablatio mammae

METASTASEN:

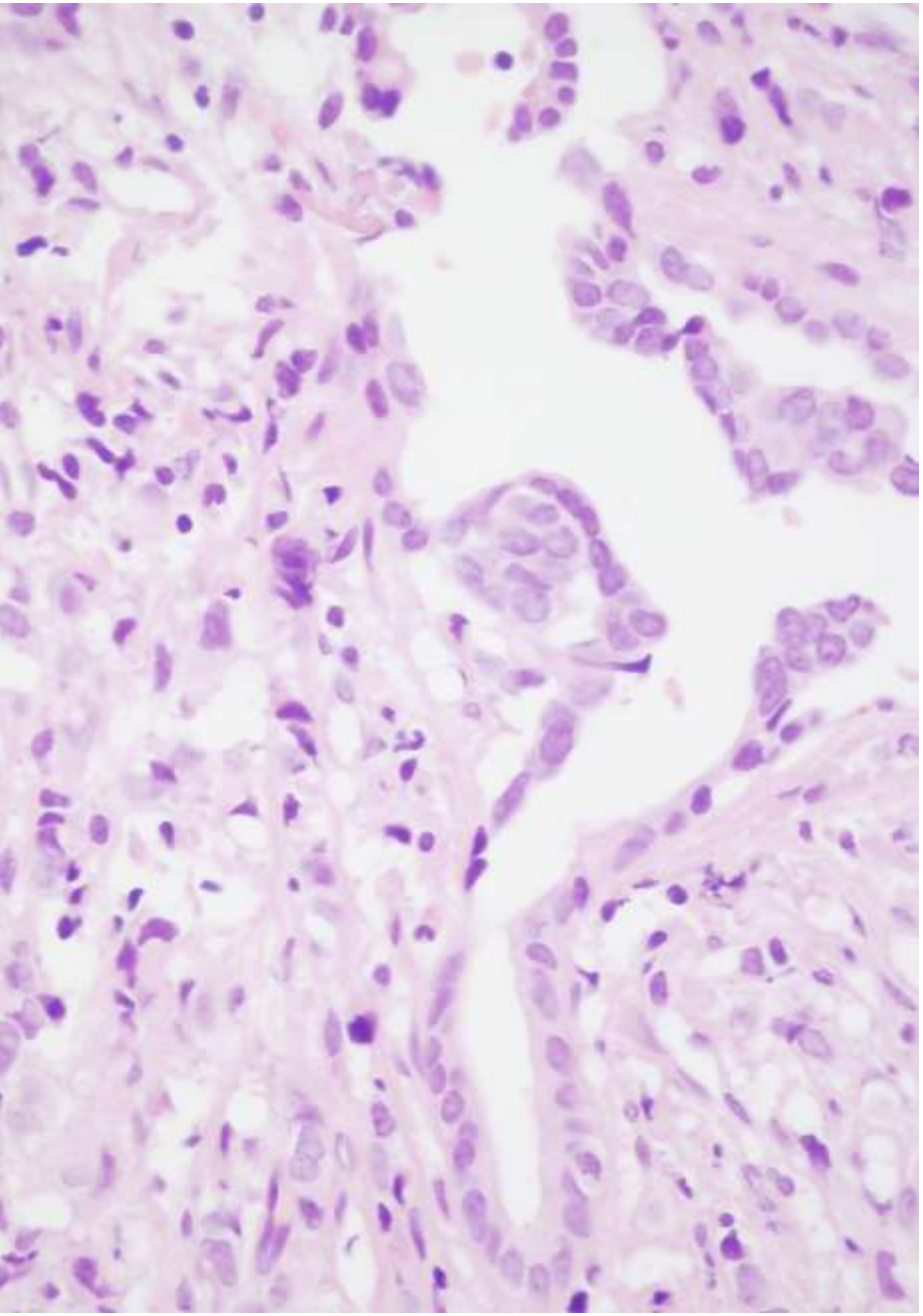
Lunge und Pleura, Knochen, Leber, Gehirn

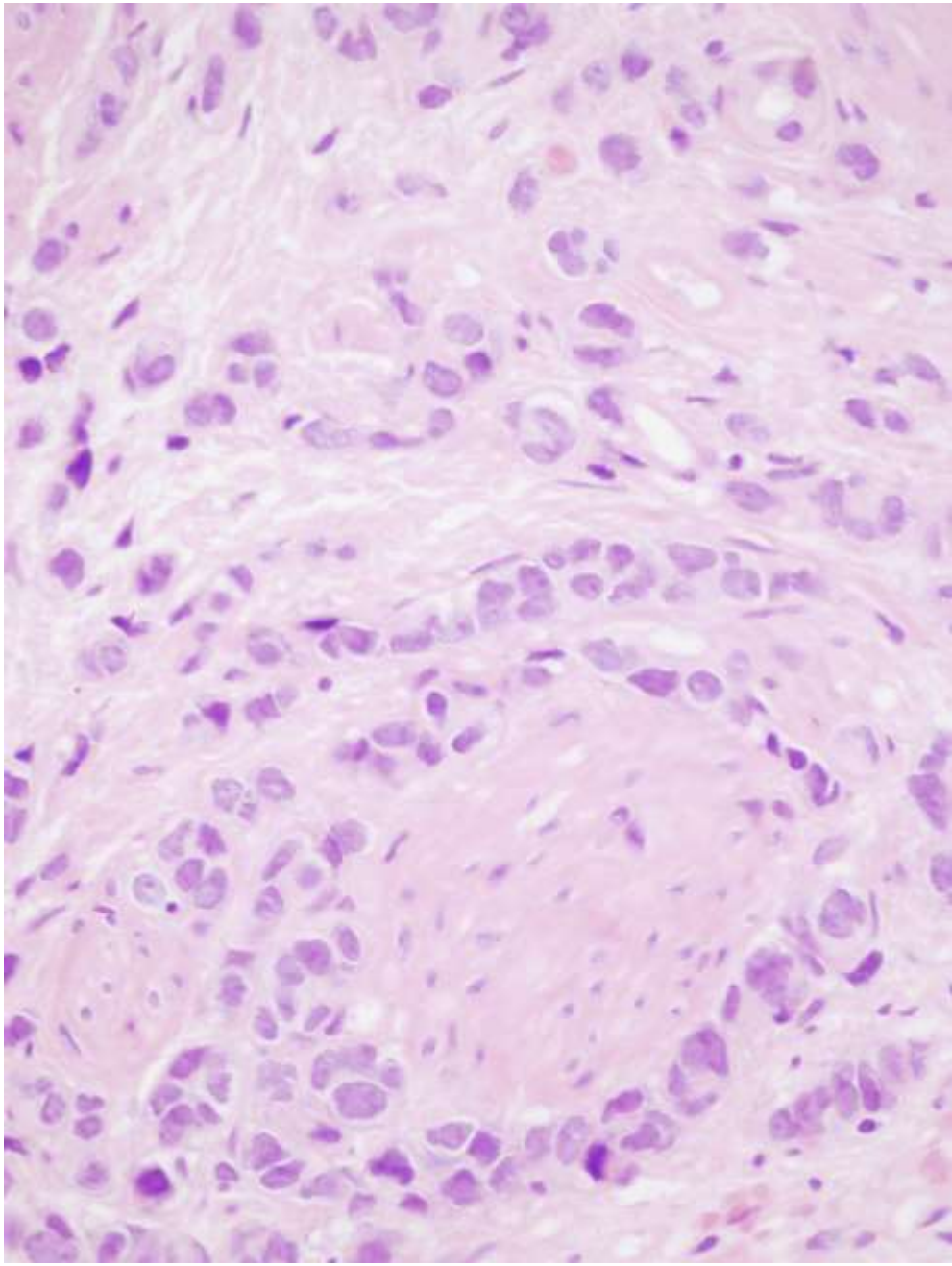
aber es kann *überall vorkomme*



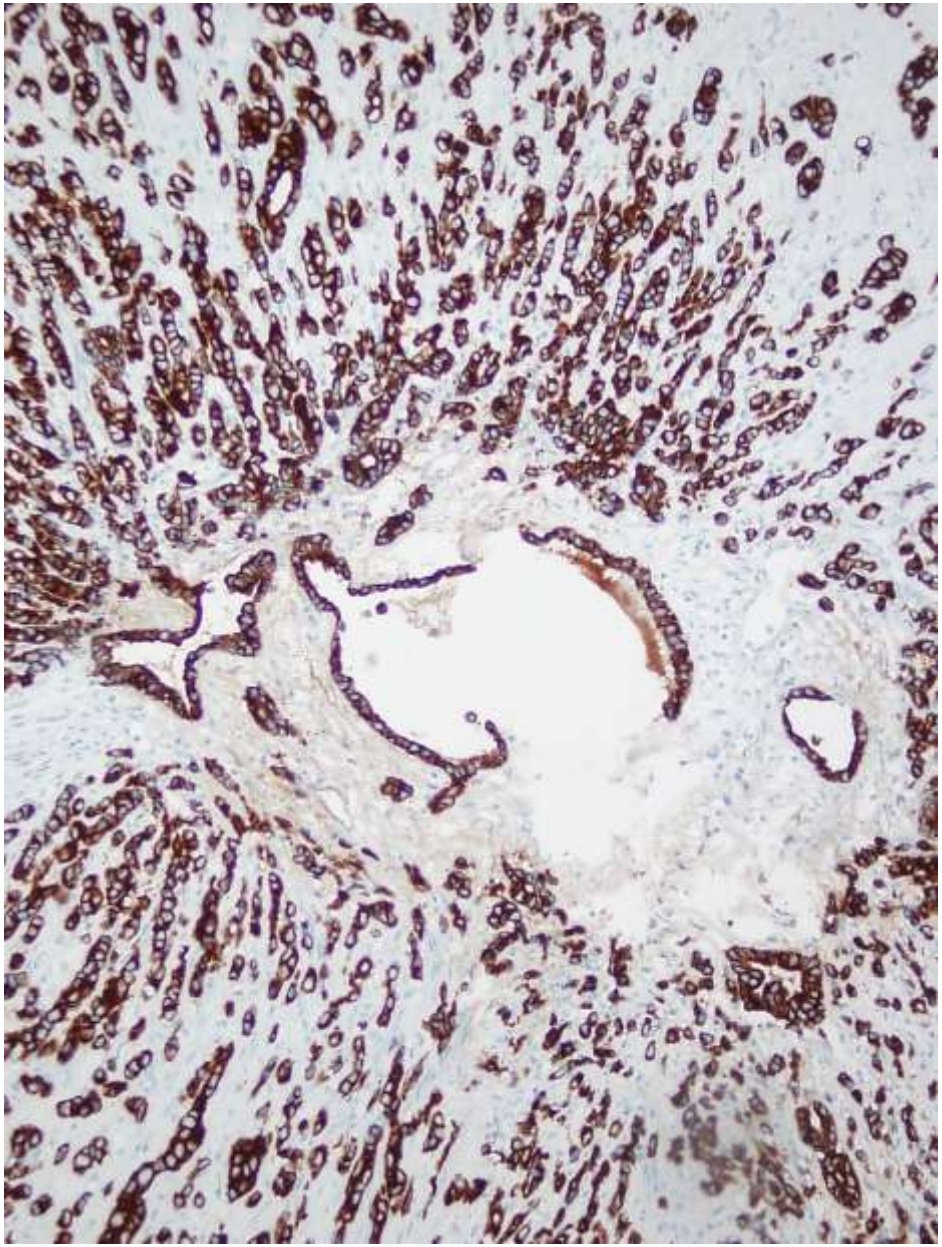


Brustkarzinom 1994

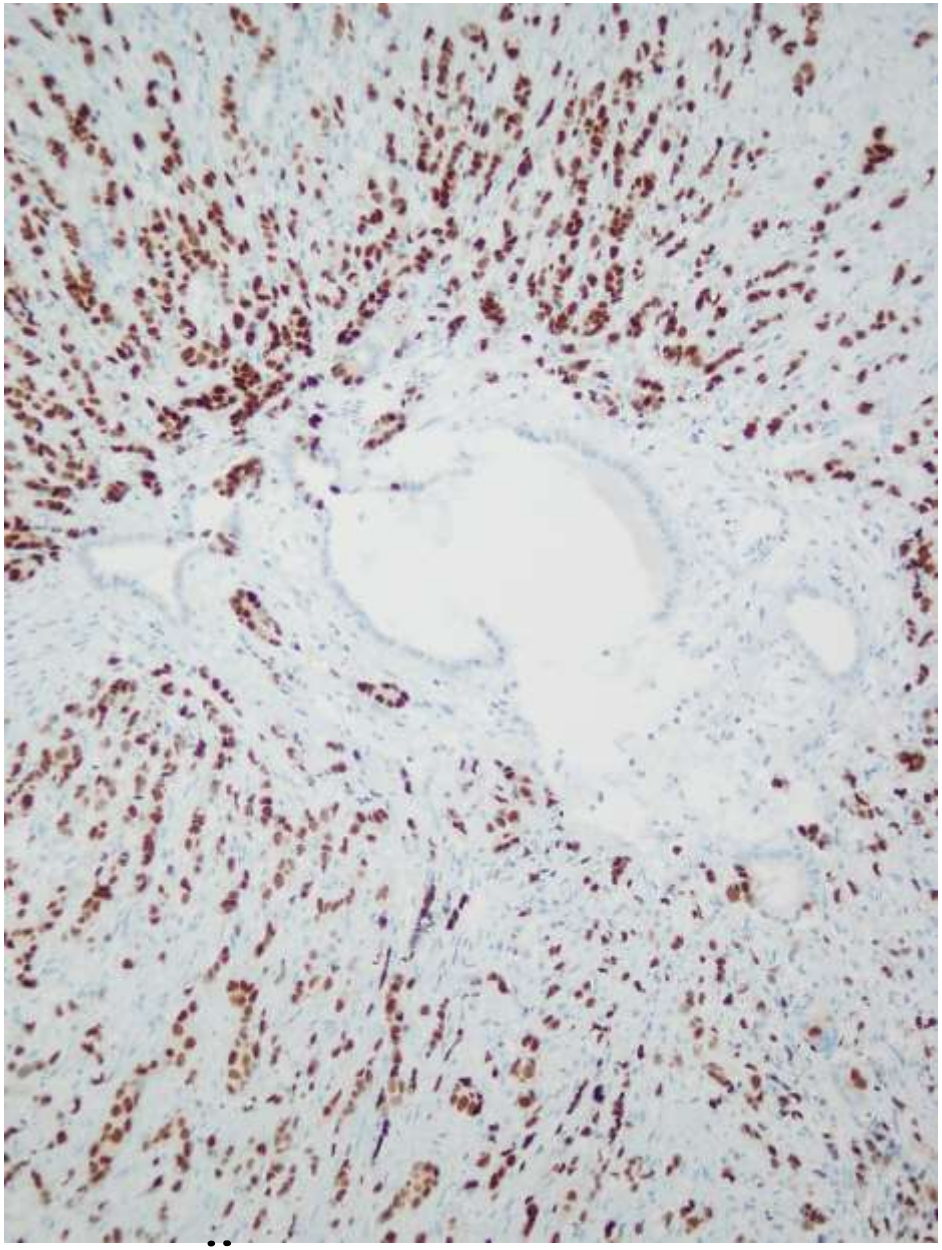




Ductus cysticus Resektions-spezimen 2004

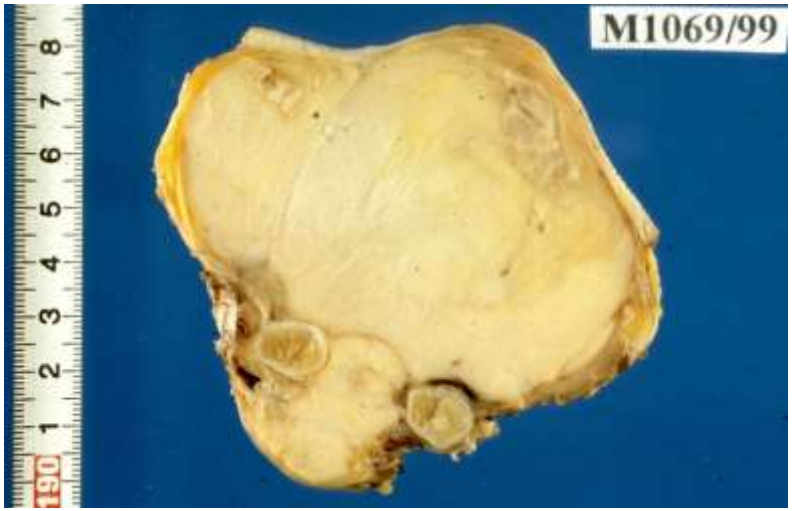


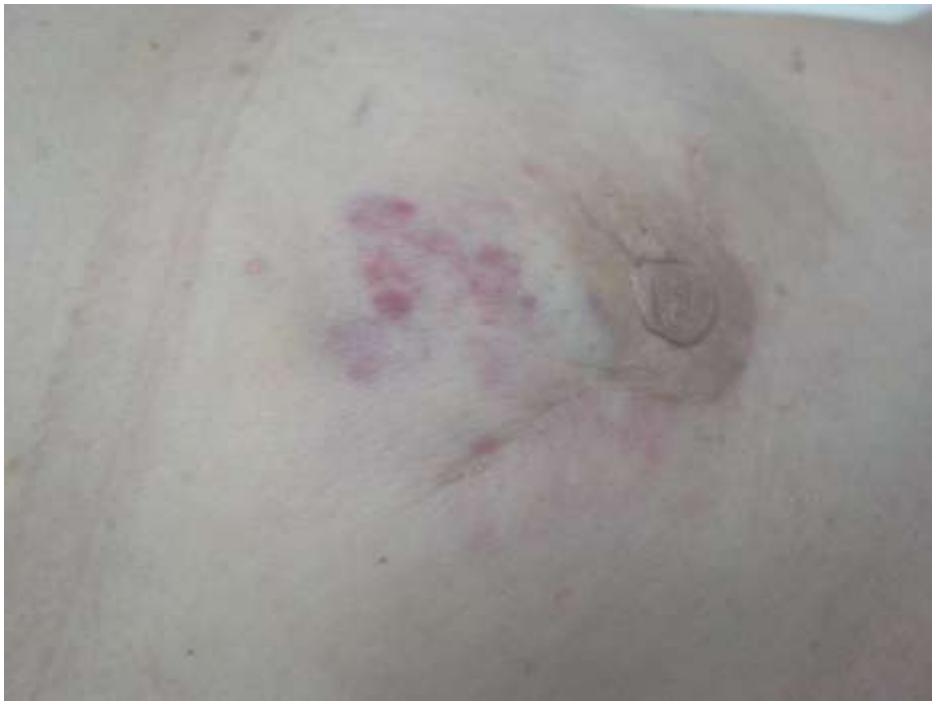
CK 7

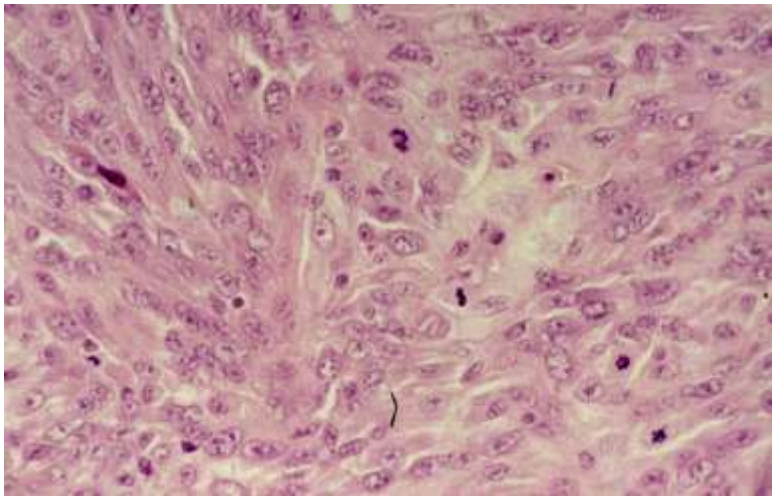


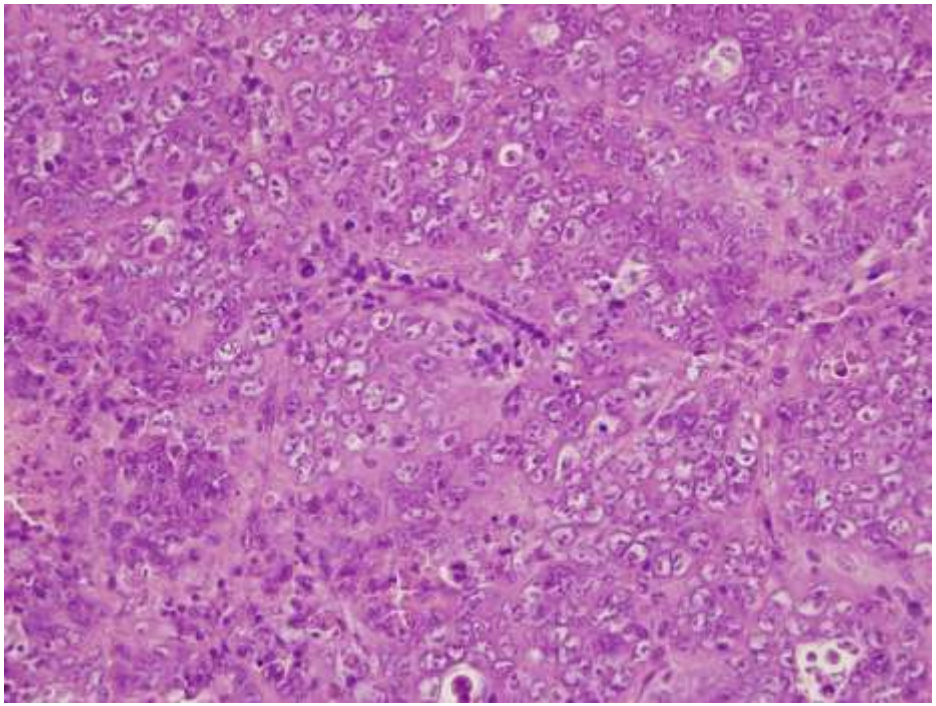
Östrogen Rezeptor

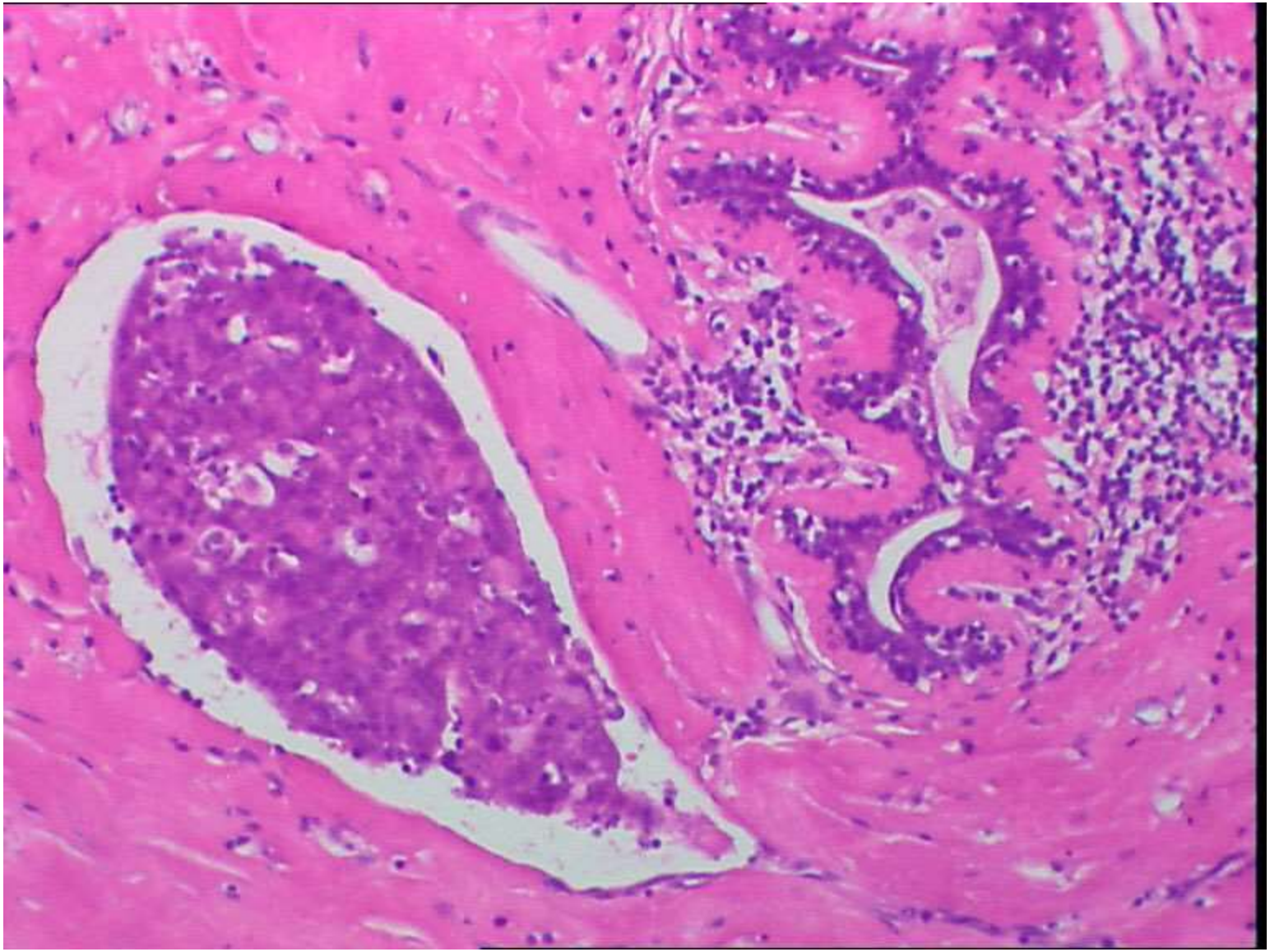
NICHT-epitheliale maligne Tumoren

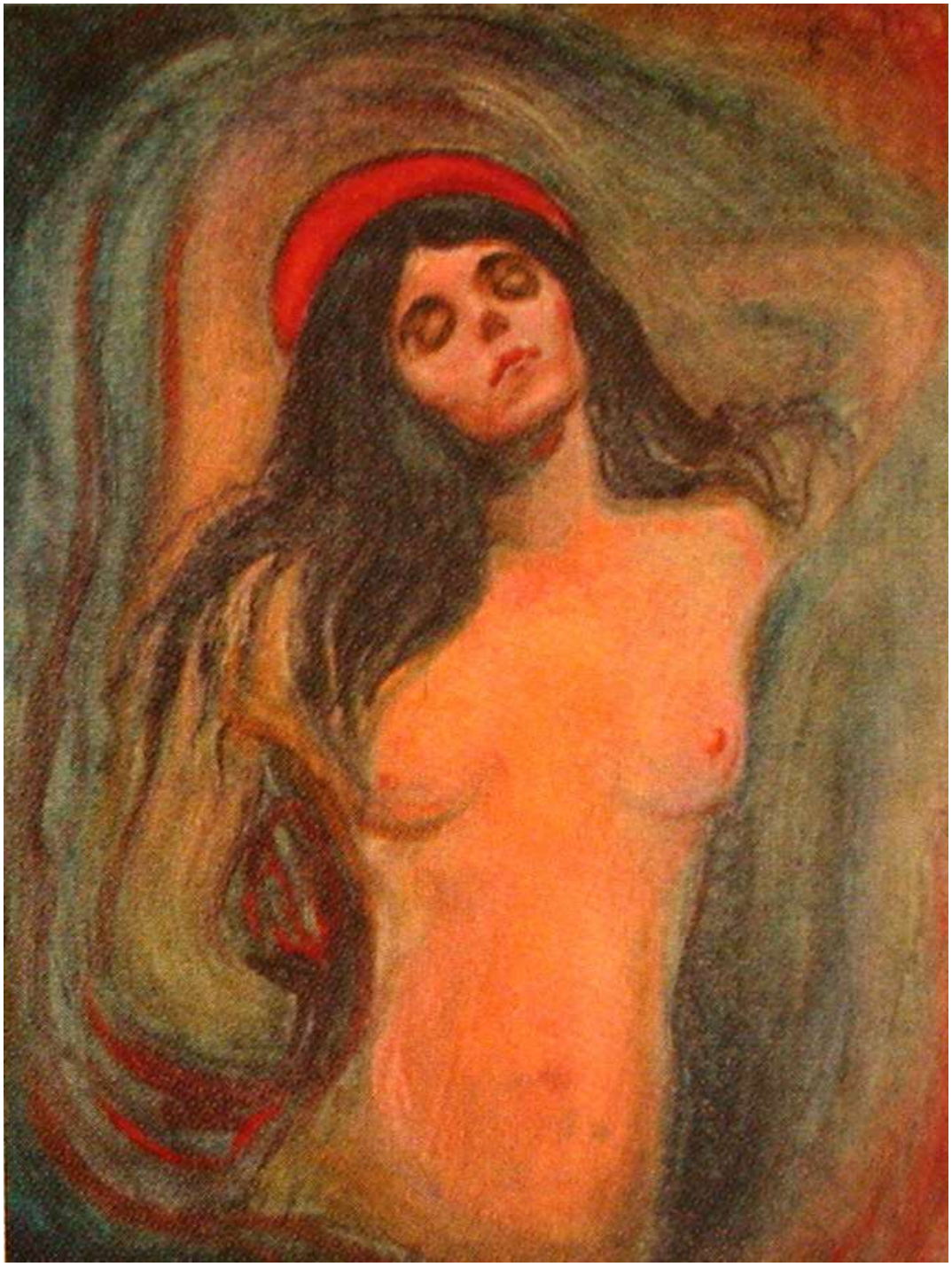












Vielen Dank für

Ihre Aufmerksamkeit !