Allgemeine Tumorlehre V.

Tumorprogression, Metastasenbildung

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2020

250 Jahre EXZELLENZ in medizinischer Lehre, Forschung & Innovation und Krankenversorgung

Was ist Karzinogenese ?

Entstehungsweg der Tumoren
Entartung einer normalen Zelle zu bösartigem Phenotyp.

NEOPLASIE

Krebs ist eine GENETISCHE Krankheit !!

Die Wirkung eines kranken Gen oder eine Kooperation mehreren Gene !

ONKOGENE (z. B. EGFR Familie, ras Familie)
und
TUMORSUPRESSORGENE

Gestörte Regulation der Zellproliferation und Zelltodes

- Protoonkogene – Onkogene
- Suppressor Gene, Tumorsuppressor Gene
- Wachstum Faktoren/Citokine, Rezeptoren
- Regulation des Zellzyklus
- Dysregulation der Zellälterung
- Dysregulation der Apoptose

Tumorsuppressorgene

- Funktion: Hemmung der Zellproliferation
  - Signal Transduktion, Regulation der Proliferation, Genom Stabilitat, Korrektion der Replikationsfehler oder Mutationen, Indultion der Apoptose
- Konsequenz: Verlust der Funktion
  - Recessive (Ausnahme p53)
  - Retinoblastom Genfamilie (RB)- Zell Zyklus Regelung, Apoptose, génhiba javítás: Deletion, Punktmutation

    Folge: das Fehlen der Proteine
  - TP53 – p53
  - NF-1, -2 (Neurofibromatose I)
  - WT-1 (Wilms tumor)
  - DCC (Kolon cc)
  - BRCA1, 2 (Brust cc)
  - PTEN (Prostata cc)

Published in final edited form as:
Science. 2013 March 29; 339(6127): 1546–1558. doi:10.1126/science.1235122.

Cancer Genome Landscapes

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Abstract

Over the past decade, comprehensive sequencing efforts have revealed the genomic landscapes of common forms of human cancer. For most cancer types, this landscape consists of a small number of "mountains" (genes altered in a high percentage of tumors) and a much larger number of "hills" (genes altered infrequently). To date, these studies have revealed ~140 genes that, when altered by intragenic mutations, can promote or "drive" tumorigenesis. A typical tumor contains two to eight of these "driver gene" mutations; the remaining mutations are passengers that confer no selective growth advantage. Driver genes can be classified into 12 signaling pathways that regulate three core cellular processes: cell fate, cell survival, and genome maintenance. A better understanding of these pathways is one of the most pressing needs in basic cancer research. Even now, however, our knowledge of cancer genomes is sufficient to guide the development of more effective approaches for reducing cancer morbidity and mortality.

Glossary

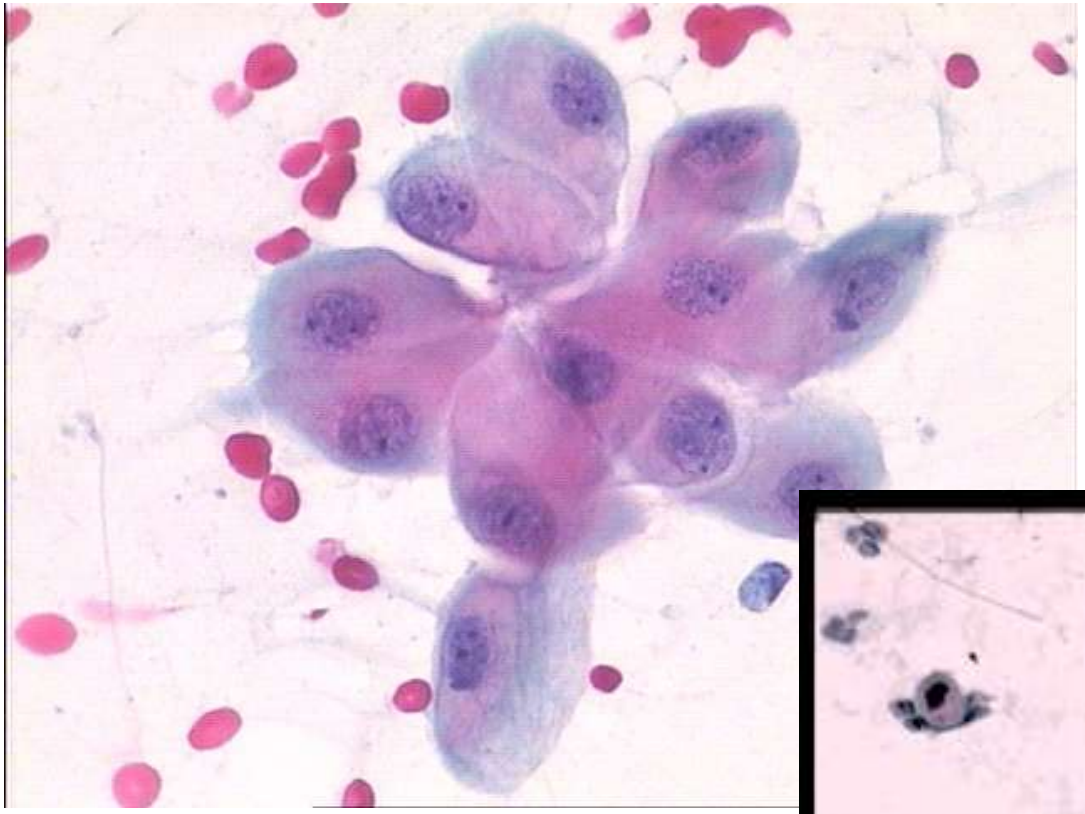
Adenoma	A benign tumor composed of epithelial cells.
Alternative lengthening of telomeres (ALT)	A process of maintaining telomeres independent of telomerase, the enzyme normally responsible for telomere replication.
Amplification	A genetic alteration producing a large number of copies of a small segment (less than a few megabases) of the genome.
Angiogenesis	the process of forming vascular conduits, including veins, arteries, and lymphatics.

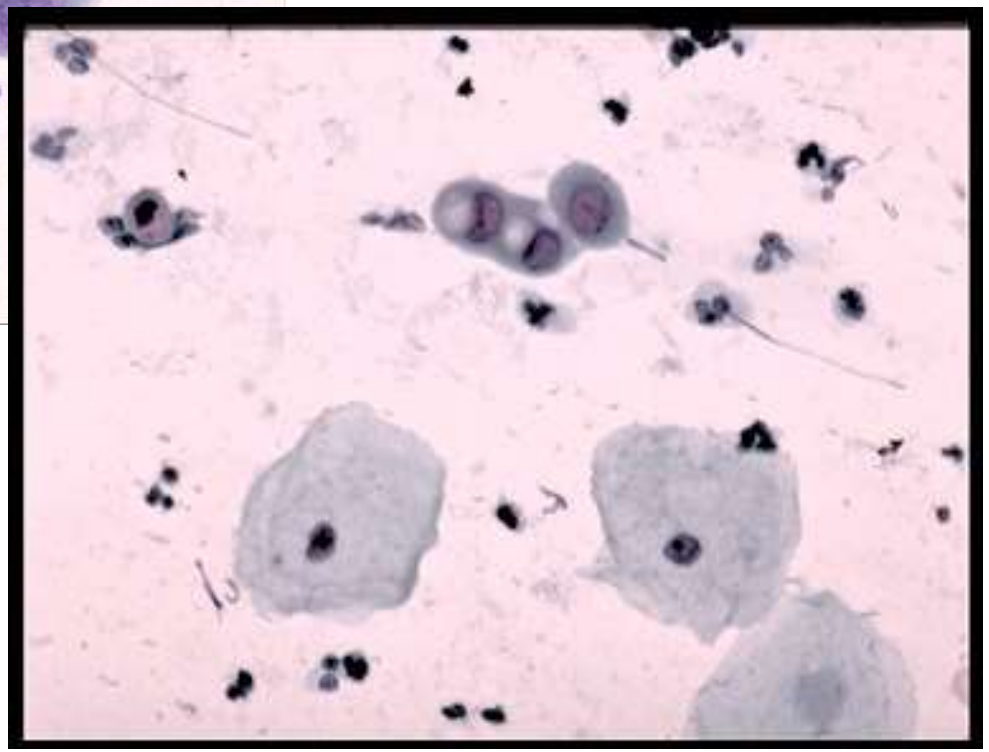
Benign tumor	An abnormal proliferation of cells driven by at least one mutation in an oncogene or tumor suppressor gene. These cells are not invasive (i.e., they cannot penetrate the basement membrane lining them), which distinguishes them from malignant cells.
Carcinoma	A type of malignant tumor composed of epithelial cells.
Clonal mutation	A mutation that exists in the vast majority of the neoplastic cells within a tumor.
Driver gene mutation (driver)	A mutation that directly or indirectly confers a selective growth advantage to the cell in which it occurs.
Driver gene	A gene that contains driver gene mutations (Mut-Driver gene) or is expressed aberrantly in a fashion that confers a selective growth advantage (Epi-Driver gene).
Epi-driver gene	A gene that is expressed aberrantly in cancers in a fashion that confers a selective growth advantage.
Epigenetic	Changes in gene expression or cellular phenotype caused by mechanisms other than changes in the DNA sequence.
Exome	The collection of exons in the human genome. Exome sequencing generally refers to the collection of exons that encode proteins.
Gatekeeper	A gene that, when mutated, initiates tumorigenesis. Examples include *RB*, mutations of which initiate retinoblastomas, and *VHL*, whose mutations initiate renal cell carcinomas.

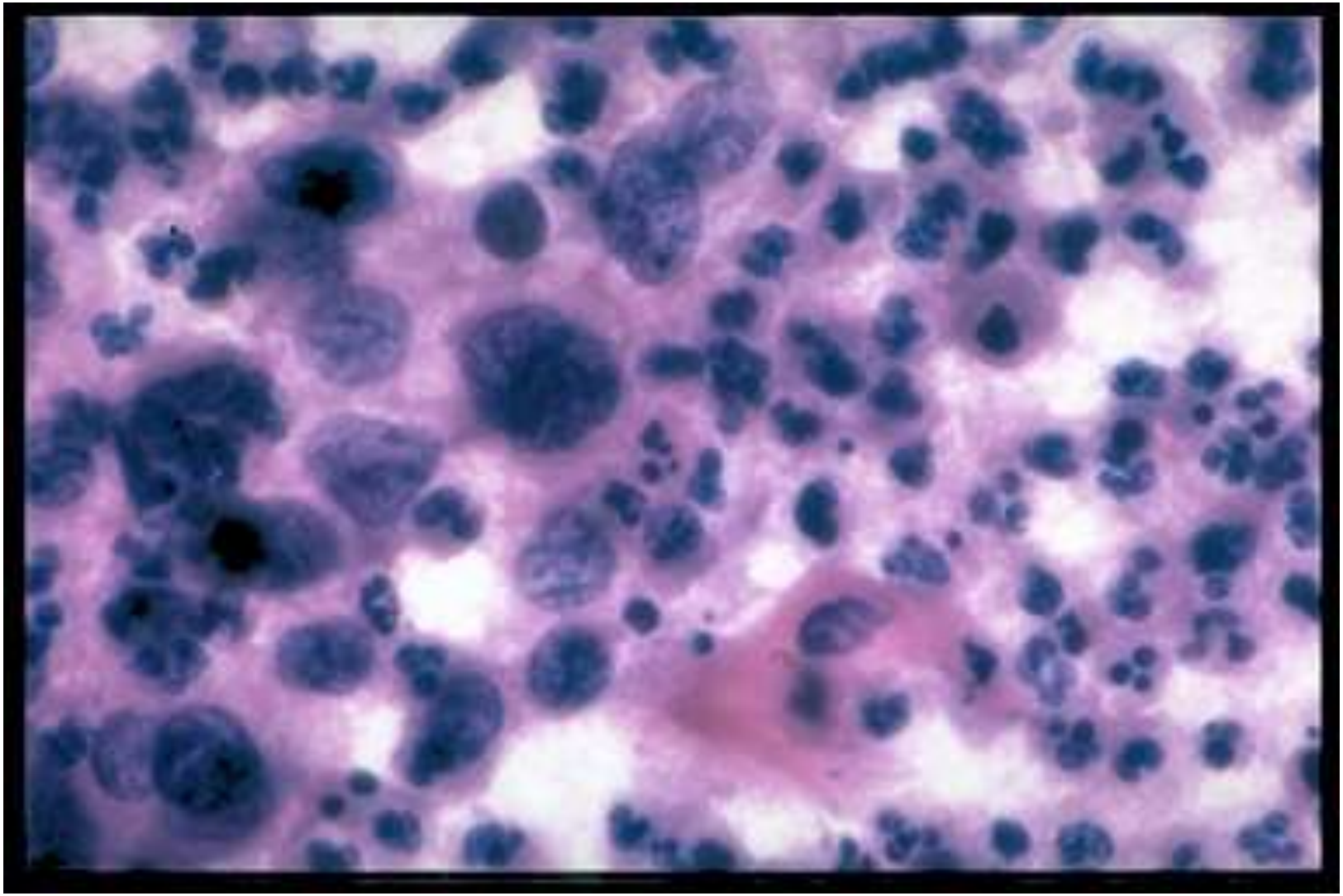
Germline genome	An individual's genome, as inherited from their parents.
Germline variants	Variations in sequences observed in different individuals. Two randomly chosen individuals differ by ~20,000 genetic variations distributed throughout the exome.
Human leukocyte antigen (HLA)	A protein encoded by genes that determine an individual's capacity to respond to specific antigens or reject transplants from other individuals.
Homozygous deletion	Deletion of both copies of a gene segment (the one inherited from the mother, as well as that inherited from the father).
Indel	A mutation due to small insertion or deletion of one or a few nucleotides.
Karyotype	Display of the chromosomes of a cell on a microscopic slide, used to evaluate changes in chromosome number as well as structural alterations of chromosomes.
Kinase	A protein that catalyzes the addition of phosphate groups to other molecules, such as proteins or lipids. These proteins are essential to nearly all signal transduction pathways.

Liquid tumors	Tumors composed of hematopoietic (blood) cells, such as leukemias. Though lymphomas generally form solid masses in lymph nodes, they are often classified as liquid tumors because of their derivation from hematopoietic cells and ability to travel through lymphatics.
Malignant tumor	An abnormal proliferation of cells driven by mutations in oncogenes or tumor suppressor genes that has already invaded their surrounding stroma. It is impossible to distinguish an isolated benign tumor cell from an isolated malignant tumor cell. This distinction can be made only through examination of tissue architecture.
Metastatic tumor	A malignant tumor that has migrated away from its primary site, such as to draining lymph nodes or another organ.
Methylation	Covalent addition of a methyl group to a protein, DNA, or other molecule.
Missense mutation	A single-nucleotide substitution (e.g., C to T) that results in an amino acid substitution (e.g., histidine to arginine).
Mut-driver gene	A gene that contains driver gene mutations.
Nonsense mutation	A single-nucleotide substitution (e.g., C to T) that results in the production of a stop codon.
Nonsynonymous mutation	A mutation that alters the encoded amino acid sequence of a protein. These include missense, nonsense, splice site, translation start, translation stop, and indel mutations.
Oncogene	A gene that, when activated by mutation, increases the selective growth advantage of the cell in which it resides.

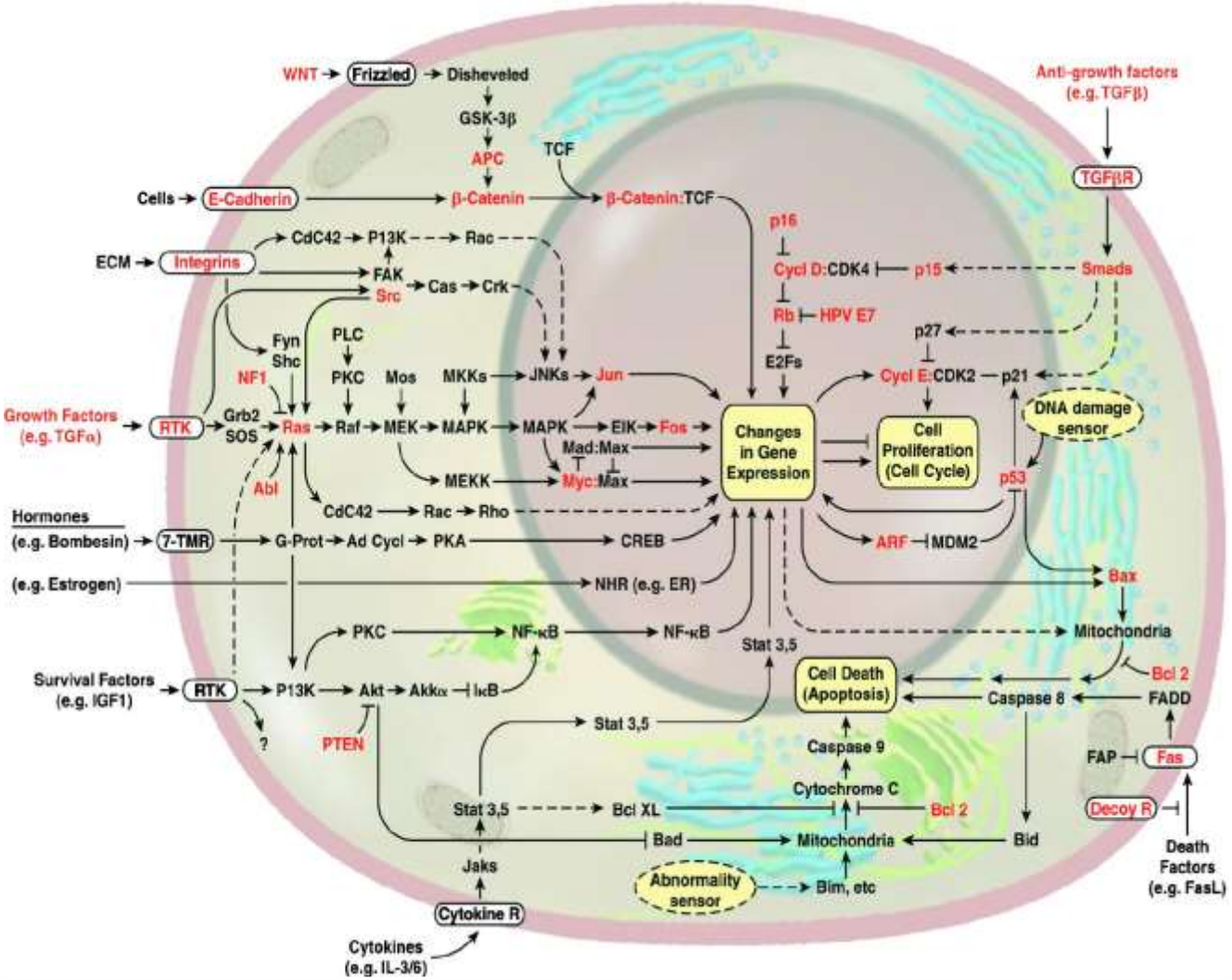
Passenger mutation (passenger)	A mutation that has no direct or indirect effect on the selective growth advantage of the cell in which it occurred.
Primary tumor	The original tumor at the site where tumor growth was initiated. This can be defined for solid tumors, but not for liquid tumors.
Promoter	A region within or near the gene that helps regulate its expression.
Rearrangement	A mutation that juxtaposes nucleotides that are normally separated, such as those on two different chromosomes.
Selective growth advantage (s)	The difference between birth and death in a cell population. In normal adult cells in the absence of injury, $s = 0.000000$.
Self-renewing tissues	Tissues whose cells normally repopulate themselves, such as those lining the gastrointestinal or urogenital tracts, as well as blood cells.
Single-base substitution (SBS)	A single-nucleotide substitution (e.g., C to T) relative to a reference sequence or, in the case of somatic mutations, relative to the germline genome of the person with a tumor.
Solid tumors	Tumors that form discrete masses, such as carcinomas or sarcomas.
Somatic mutations	Mutations that occur in any non–germ cell of the body after conception, such as those that initiate tumorigenesis.
Splice sites	Small regions of genes that are juxtaposed to the exons and direct exon splicing.
Stem cell	An immortal cell that can repopulate a particular cell type.
Subclonal mutation	A mutation that exists in only a subset of the neoplastic cells within a tumor.
Translocation	A specific type of rearrangement where regions from two nonhomologous chromosomes are joined.
Tumor suppressor gene	A gene that, when inactivated by mutation, increases the selective growth advantage of the cell in which it resides.
Untranslated regions	Regions within the exons at the 5′ and 3′ ends of the gene that do not encode amino acids.







Krebs: molekuläre Signaltransduktionswege



erworbene preneoplastische Veranderungen Prekanzerosen

- Endometriale Hyperplasie- Karzinom (Hormon abh.)
- Zervikale Dysplasie, CIN I.,II.,III. – Krebs (HPV Infektion)
- Zigarett Rauchen -Bronchiale Metaplasie, Dysplasie – Lungenkrebs
- Chronische Hepatitis/Zirrhose – hepatozelluläres Karzinom (HBV, HCV, Alkohol, Aflatoxin, anaboliche Steroiden usw.)
- Atrophische Gastritis – Krebs (H.pylori)
- Solare Keratose – Hautkrebs(UV)
- Leukoplakie – Mundhöhlenkrebs
- Ulzerative Colitis – Kolonkrebs

Karzinogenese

Initiation

- Promotion - von initiierten onkogeneen Potenz der Zelle zur vollstandigen Entartung

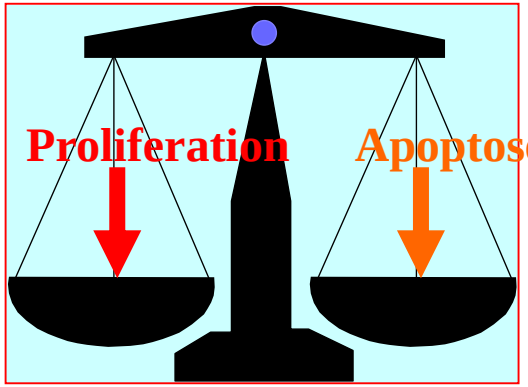
- Progression - Proliferation veränderter Zellklone

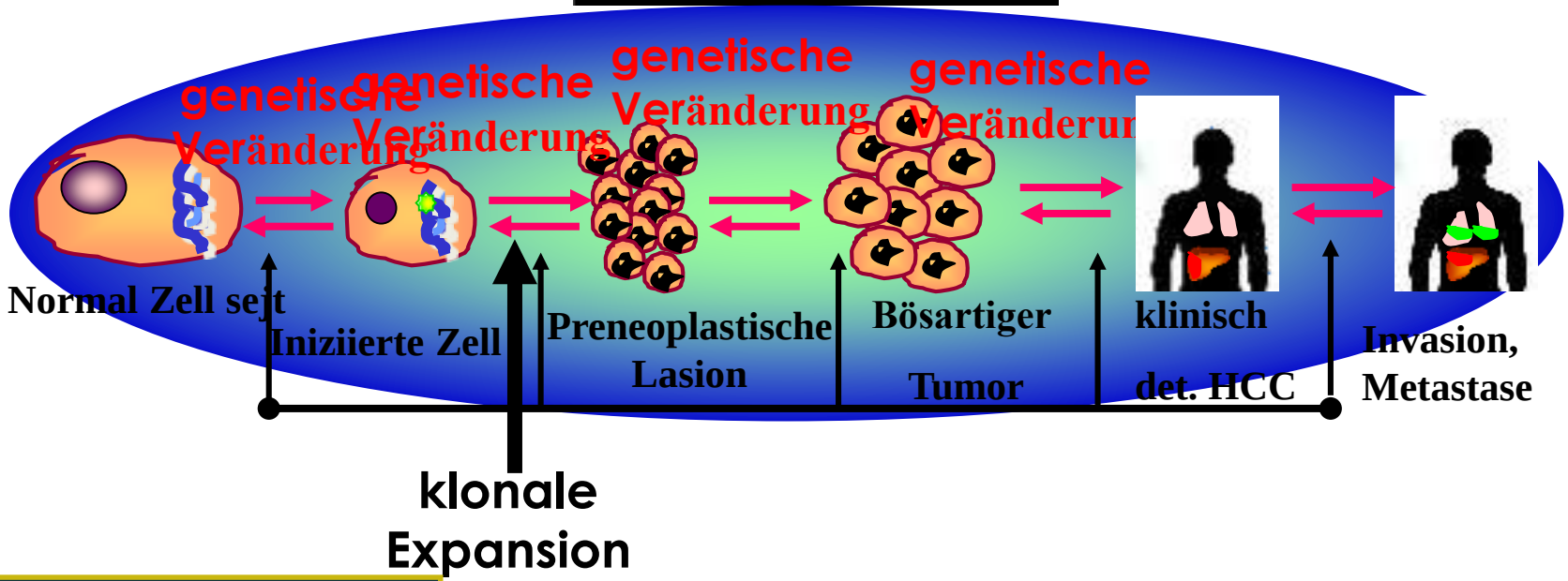
Initiation

Promotion

Progression

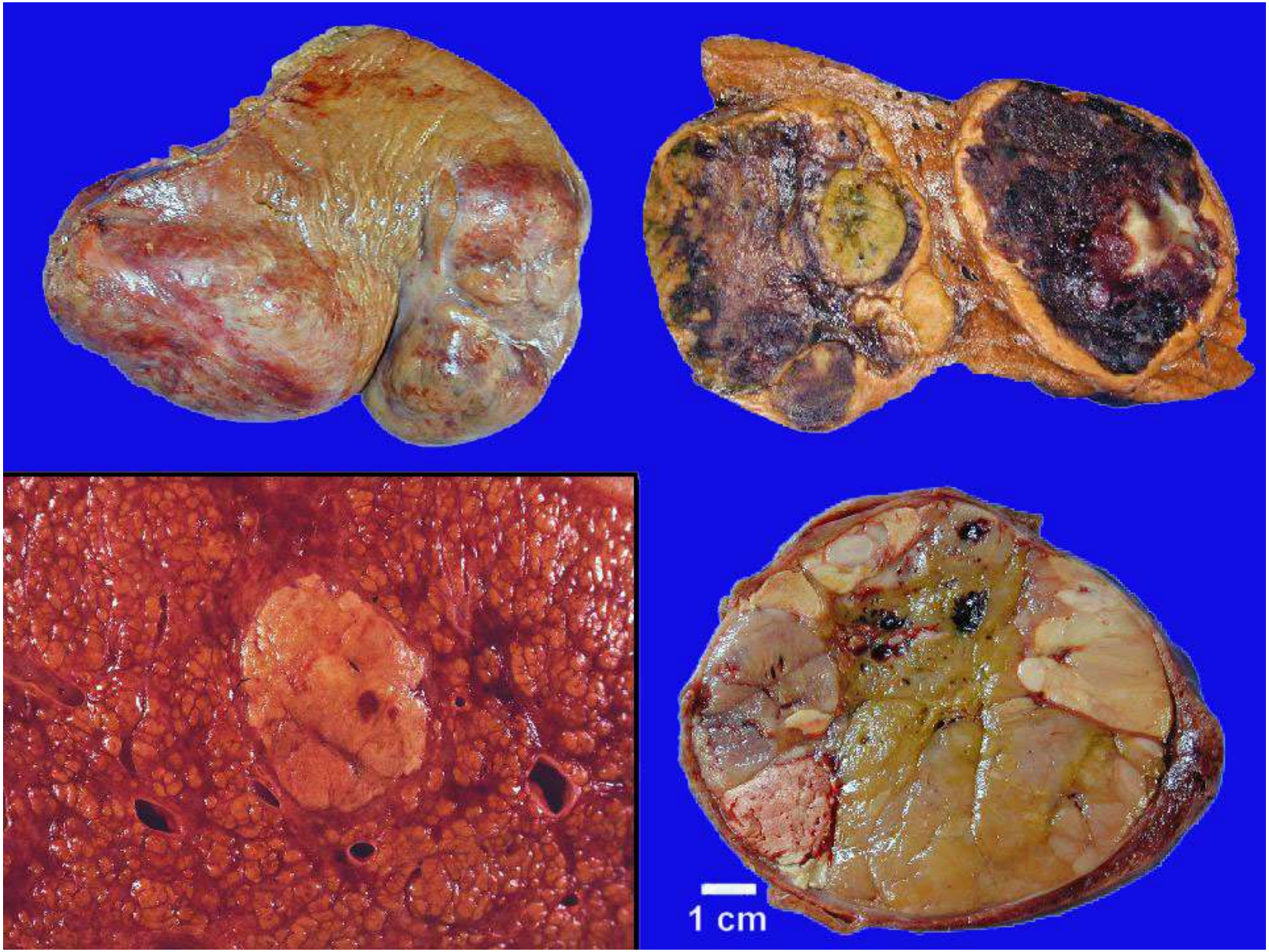
Genalterationen: deletio, amplificatio; *cis*-activatio (HBV); demethylatio



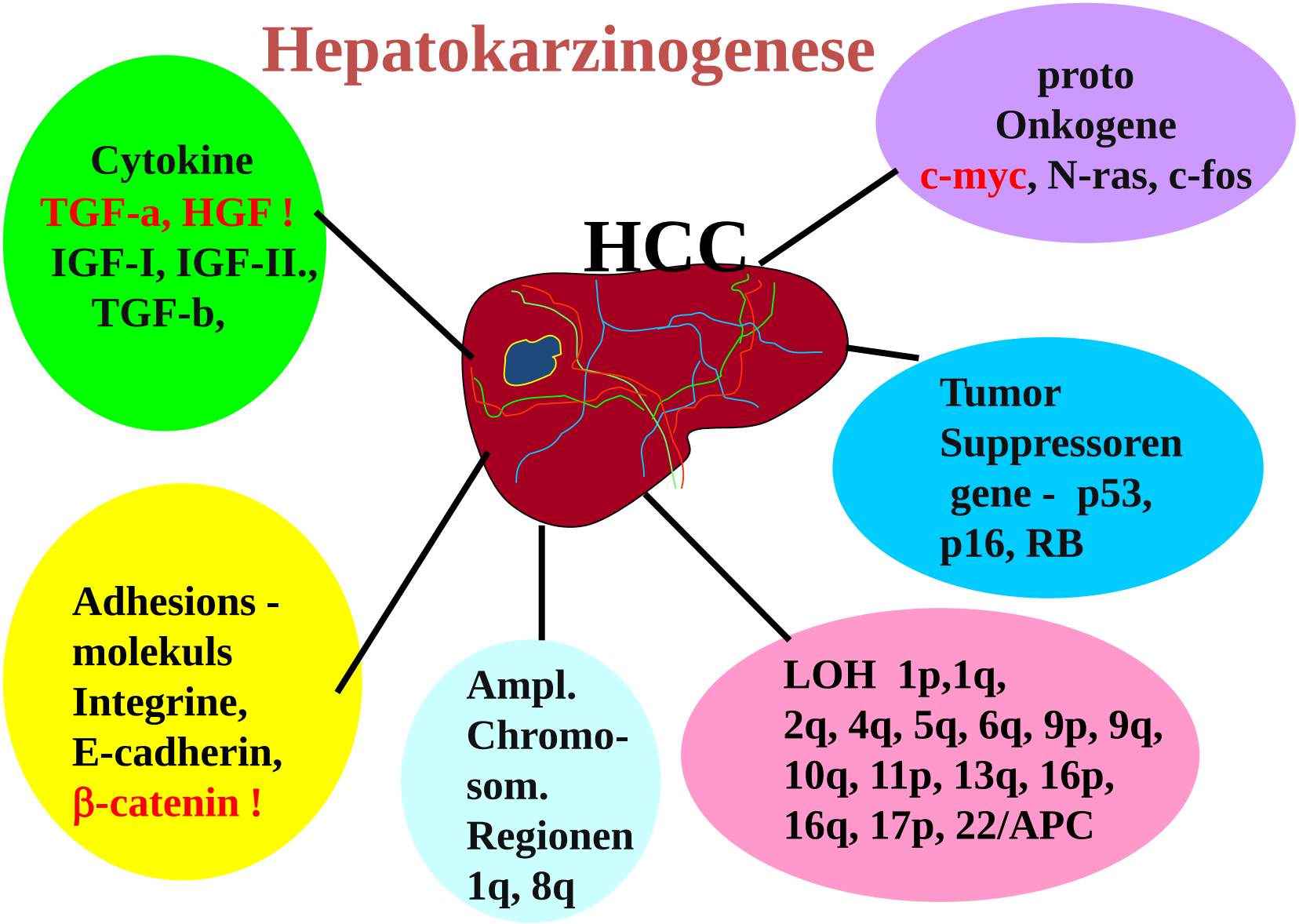


HCV
core, E2, NS3, NS5A

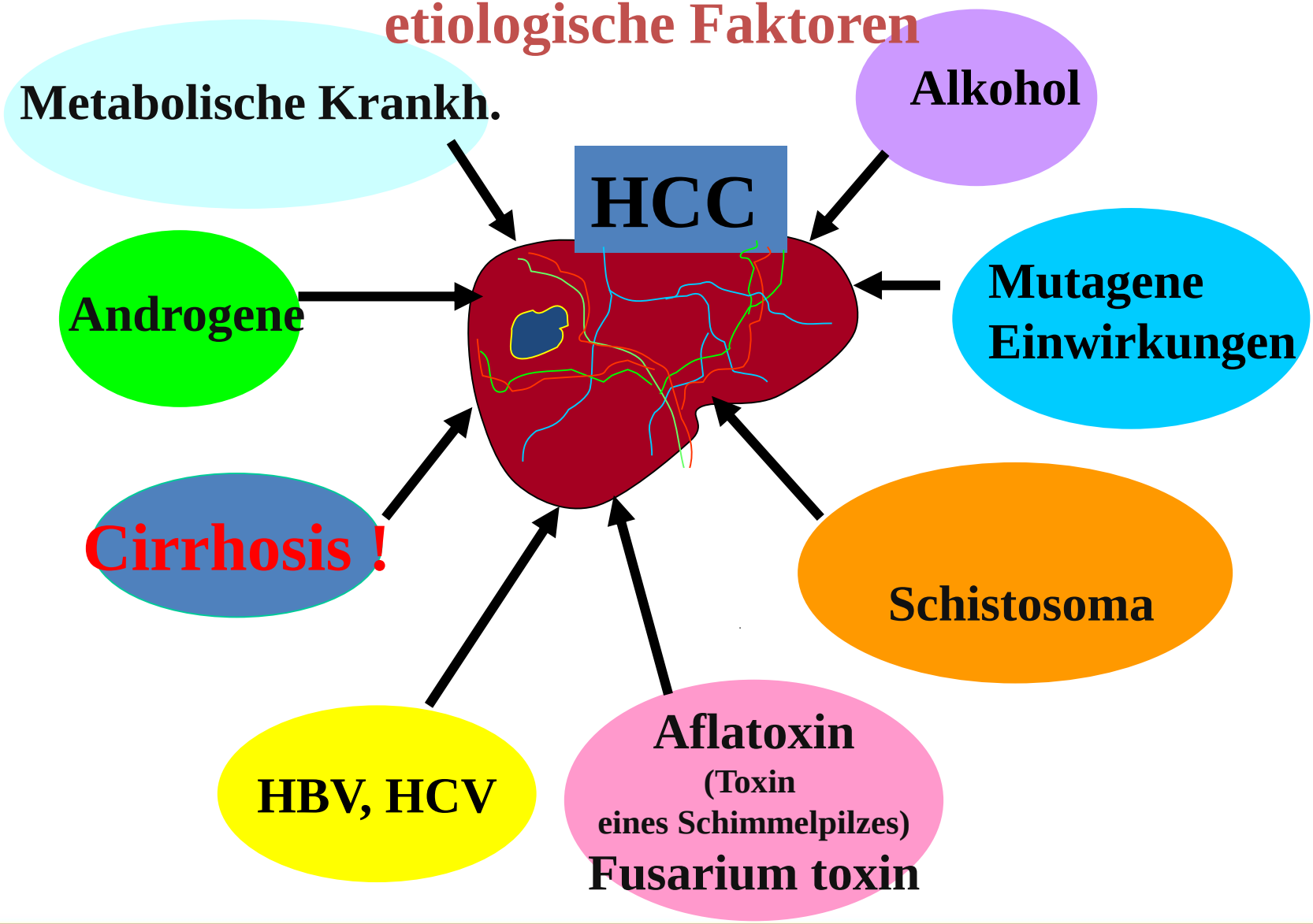
HBV
HBx, HBsAg; PreS2; Integration

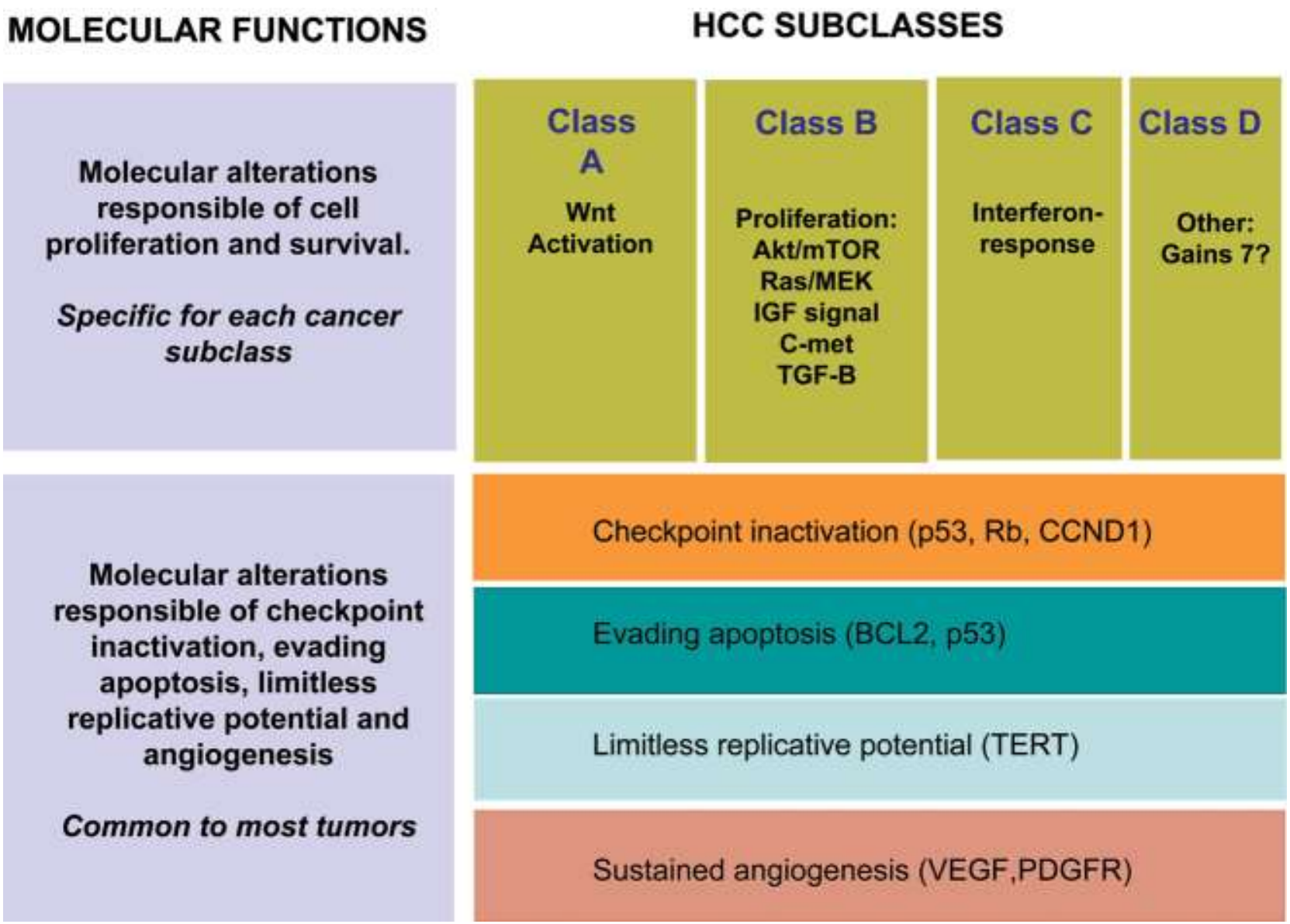

1 cm

Hepatokarzinogenese



Hepatokarzinogenese
etiologische Faktoren





Llovet J.M., Bruix J. Hepatology 2008.48:1312-27

Gastroenterology 2015;■:1–14

Genetic Landscape and Biomarkers of Hepatocellular Carcinoma

Jessica Zucman-Rossi[1,2,3,4], Augustin Villanueva[5,6], Jean-Charles Nault[1,2,3], Josep M. Llovet[5,6,7,8]

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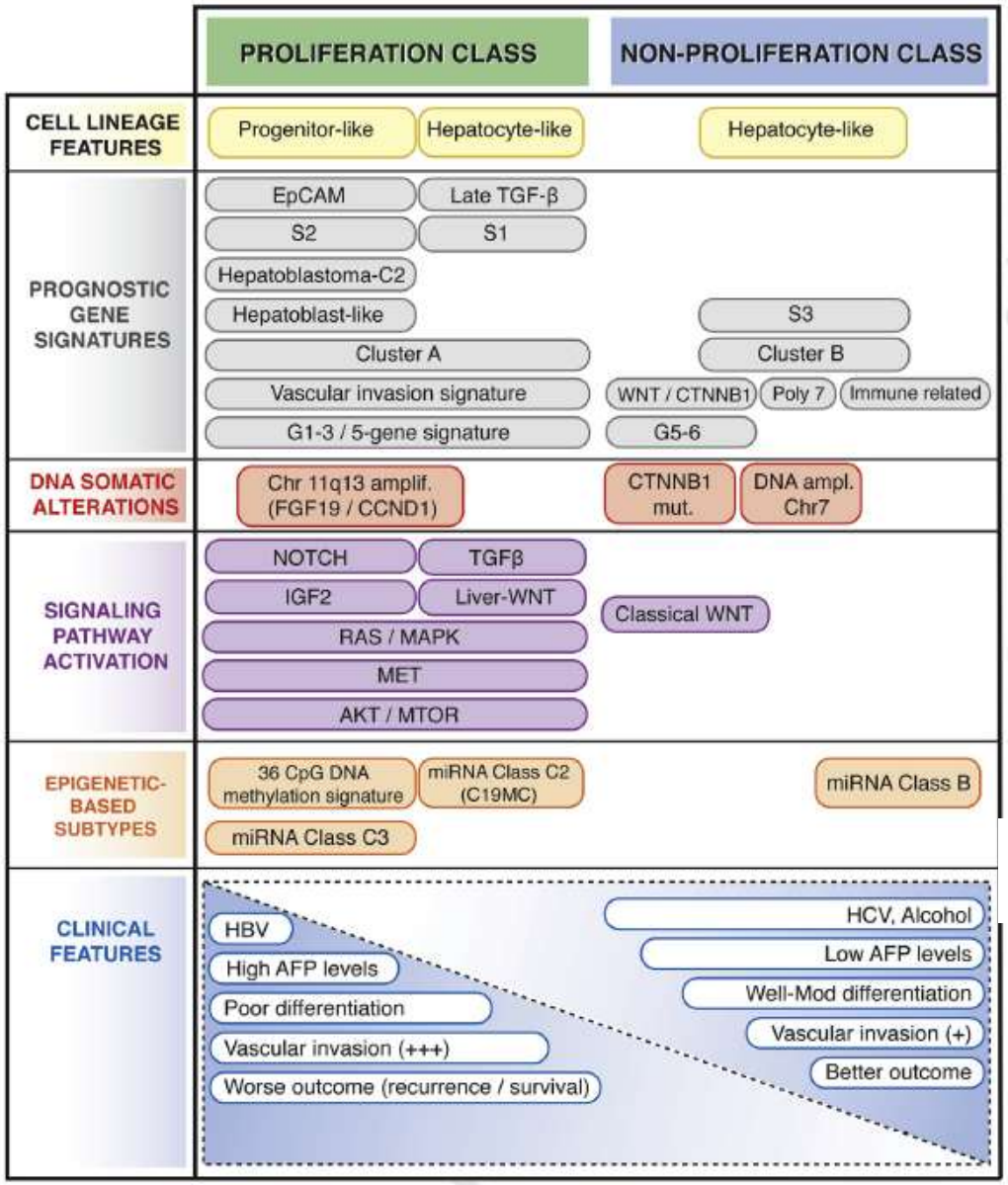
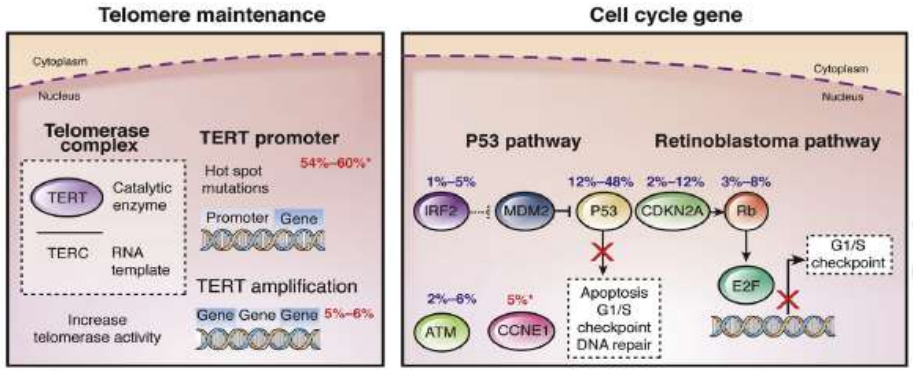
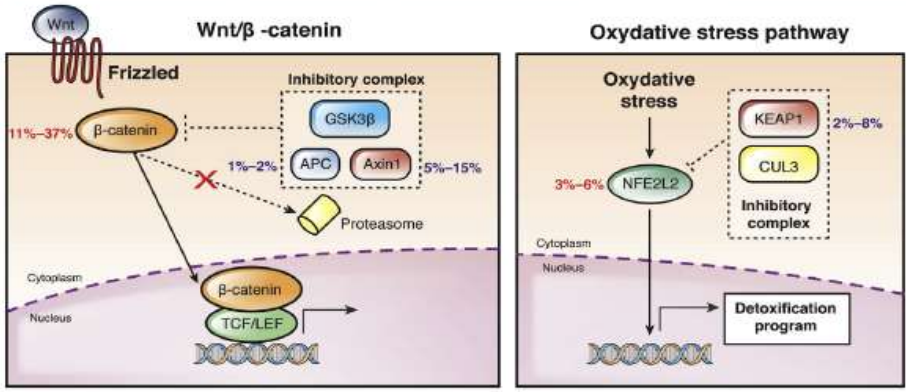
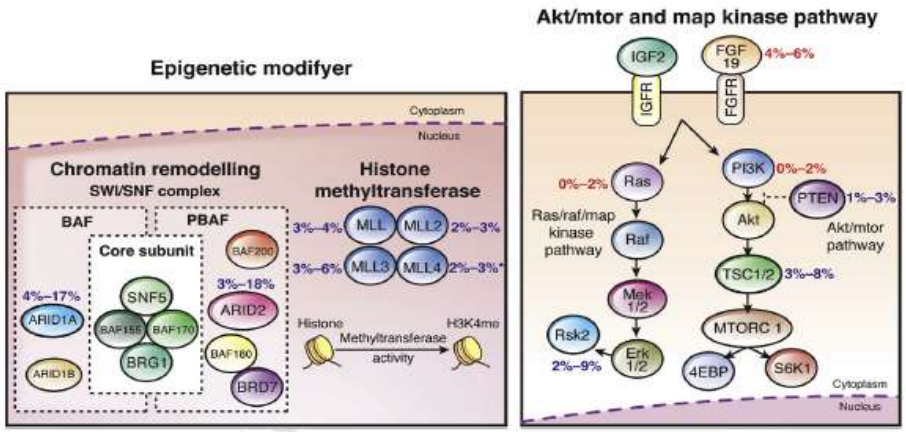


Summary of molecular classification of HCC. Major classes (proliferation and nonproliferation) are depicted based on messenger RNA expression profiling. Additional molecular features affecting DNA structure, pathway deregulation and epigenetics are overlapped.







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Genetic Landscape and Biomarkers of Hepatocellular Carcinoma

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The genetic landscape of HCC. *Red*, activating mutations of oncogenes, *blue*, inactivating mutations of tumor suppressors. *Gene was recurrently targeted by HBV integration.

Article | Open Access | Published: 05 February 2020

Pan-cancer analysis of whole genomes

The ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium

Nature **578**, 82–93(2020) | Cite this article

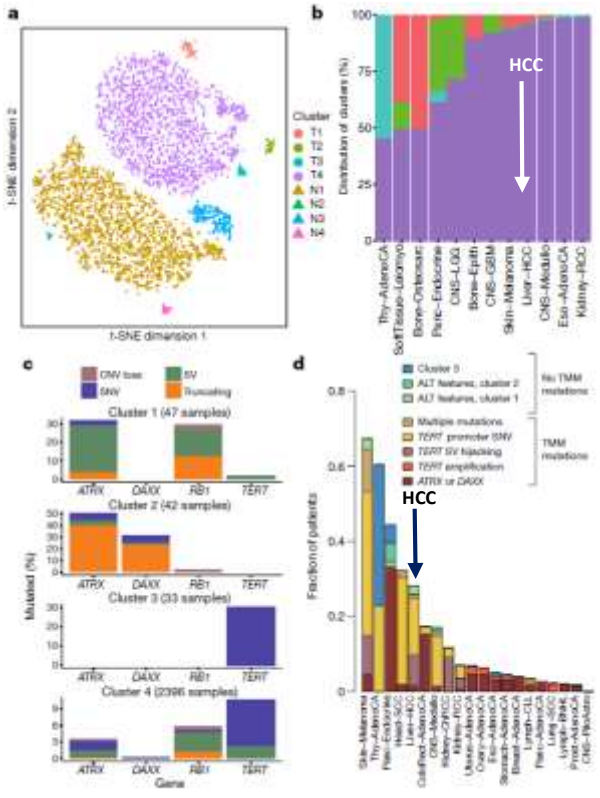


Fig. 7 | Telomere sequence patterns across PCAWG. a, Scatter plot of the clusters of telomere patterns identified across PCAWG using *t*-distributed

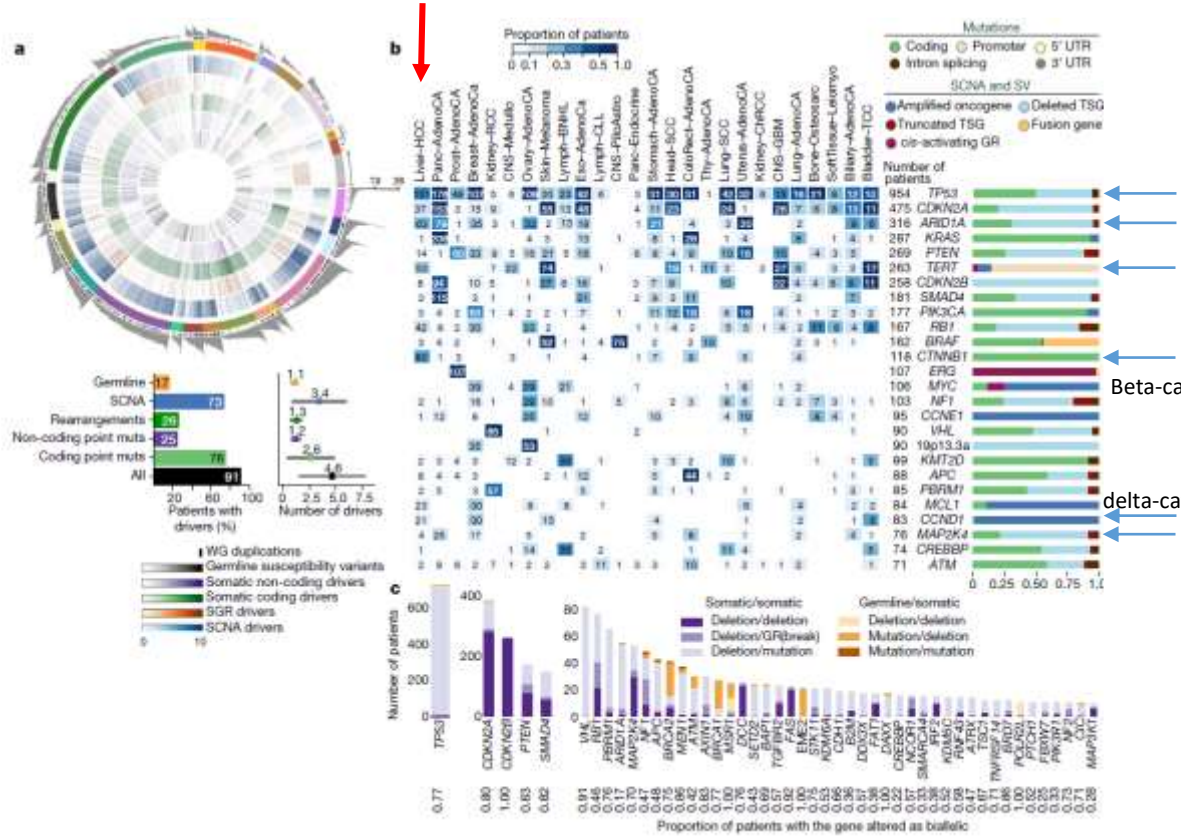
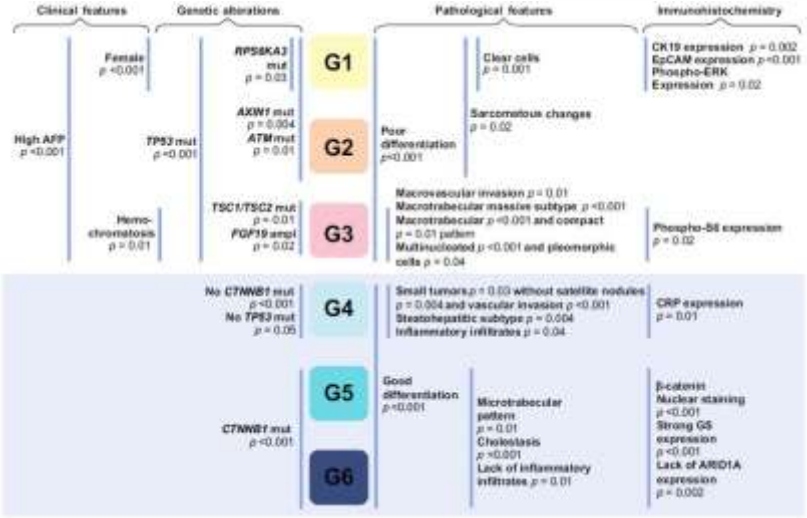


Fig. 2 | Panorama of driver mutations in PCAWG. a, Top, putative driver patients. **b**, Genomic elements targeted by different types of mutations in the

Molekuläre HCC Subtypen ?

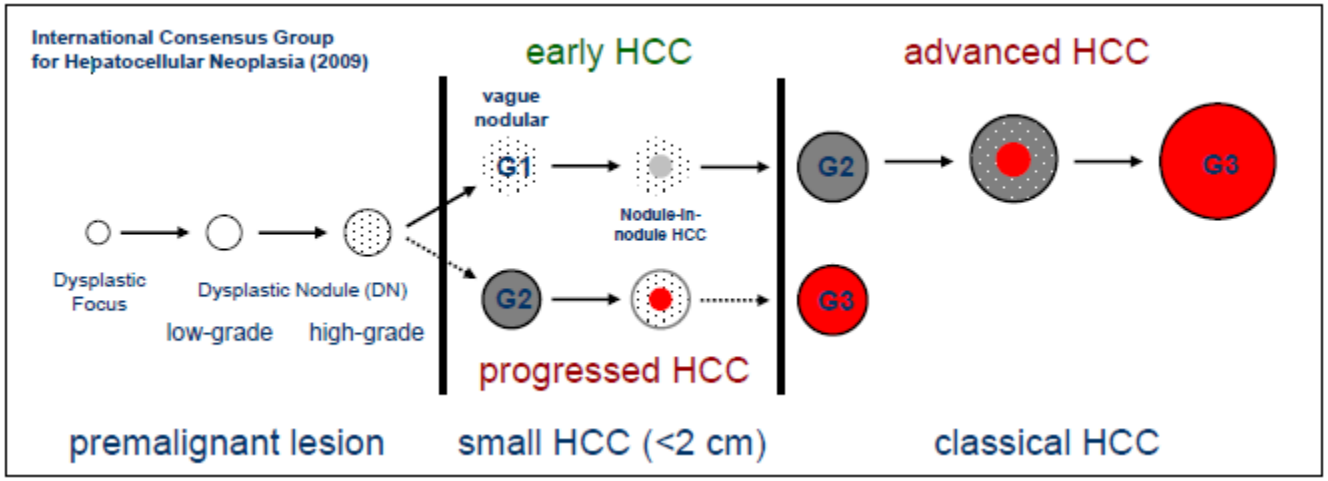


Calderaro, J. et al, J. Hepatol. 2017

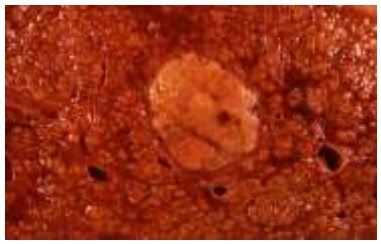
Frage:

- es charakteriziert eher Subtypen oder Stadien ?
- nur für Stage I/II Tumoren ?
- Relation/Hierarchie Analyse der Muster kann N Status ändern
- überlappende Gruppen
- einige Sonderaltypen sind nicht beschrieben

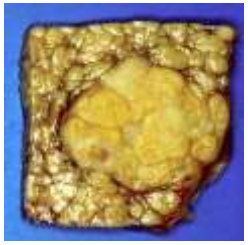
Entwicklung und Progression der HCC



dysplastisches Nodulus



frühes (early) HCC



progrediiertes, kleines (progressed small) HCC

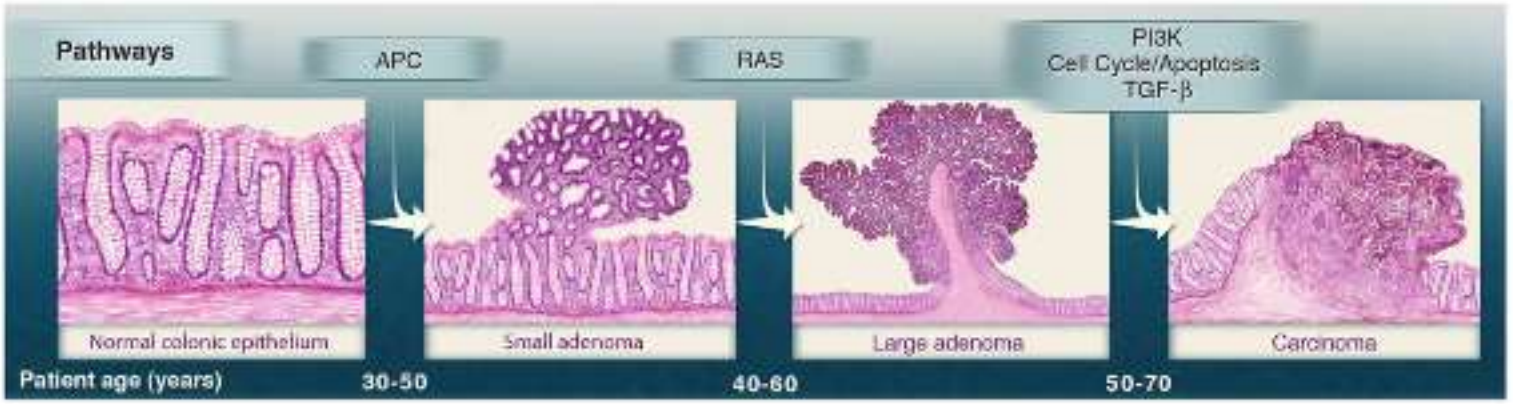
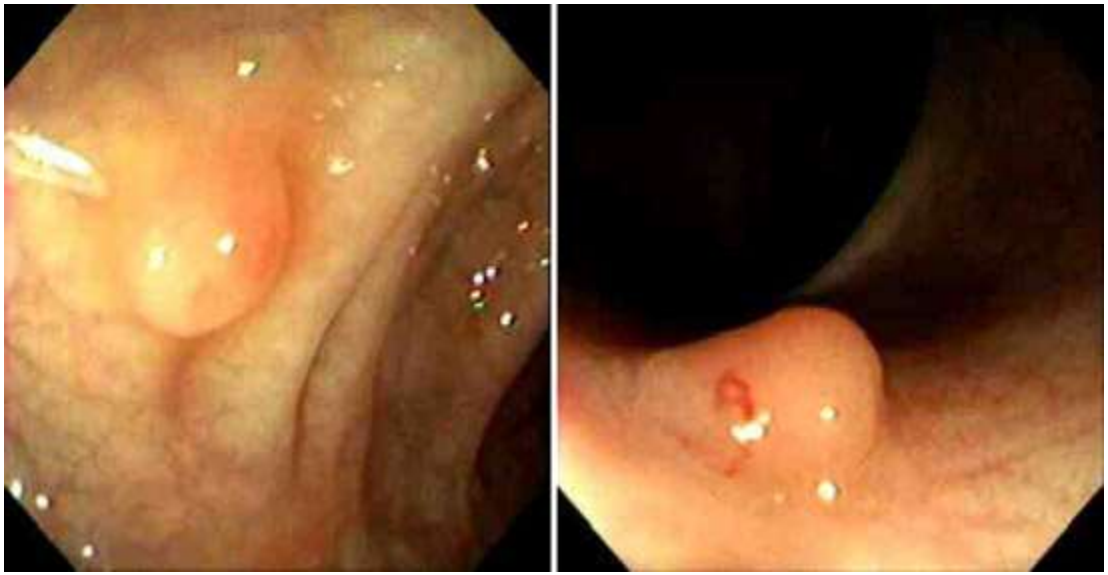
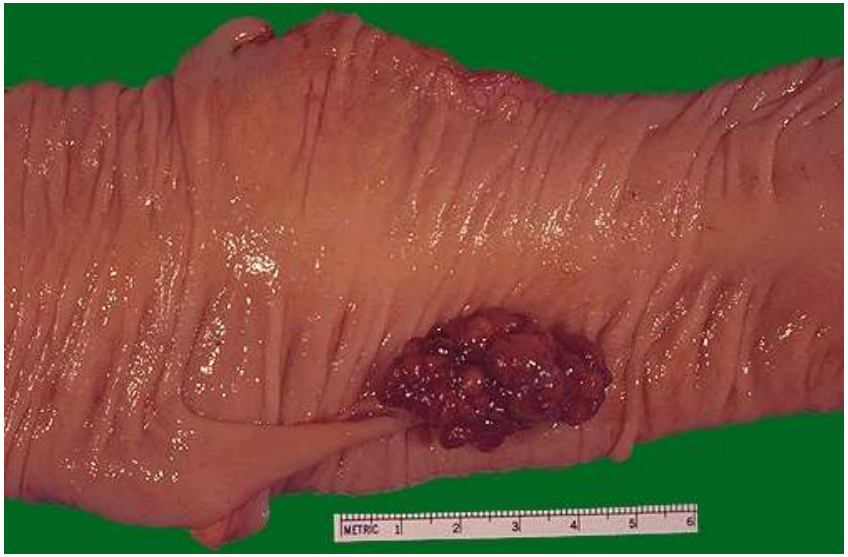


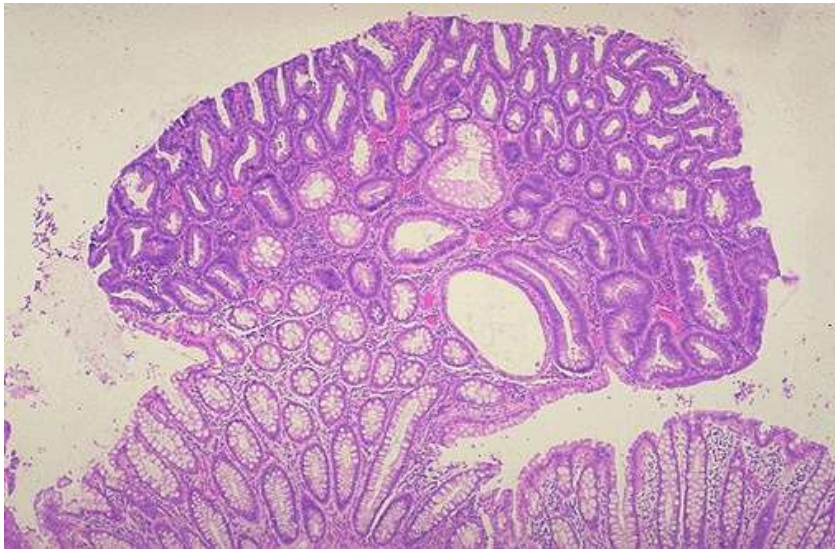
Fig. 2. Genetic alterations and the progression of colorectal cancer

The major signaling pathways that drive tumorigenesis are shown at the transitions between each tumor stage. One of several driver genes that encode components of these pathways can be altered in any individual tumor. Patient age indicates the time intervals during which the driver genes are usually mutated. Note that this model may not apply to all tumor types. TGF-β, transforming growth factor–β.

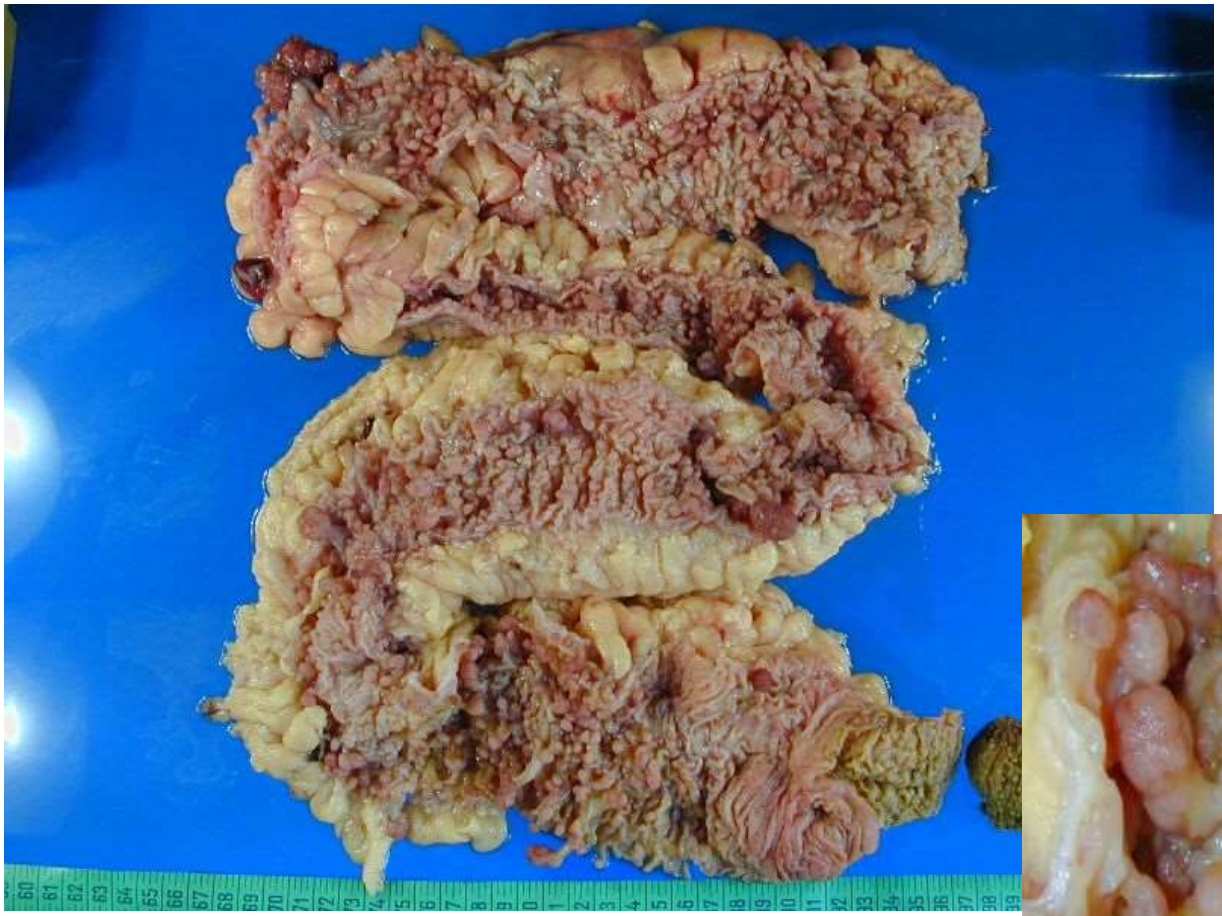
Polyp - Adenom in Dickdarm

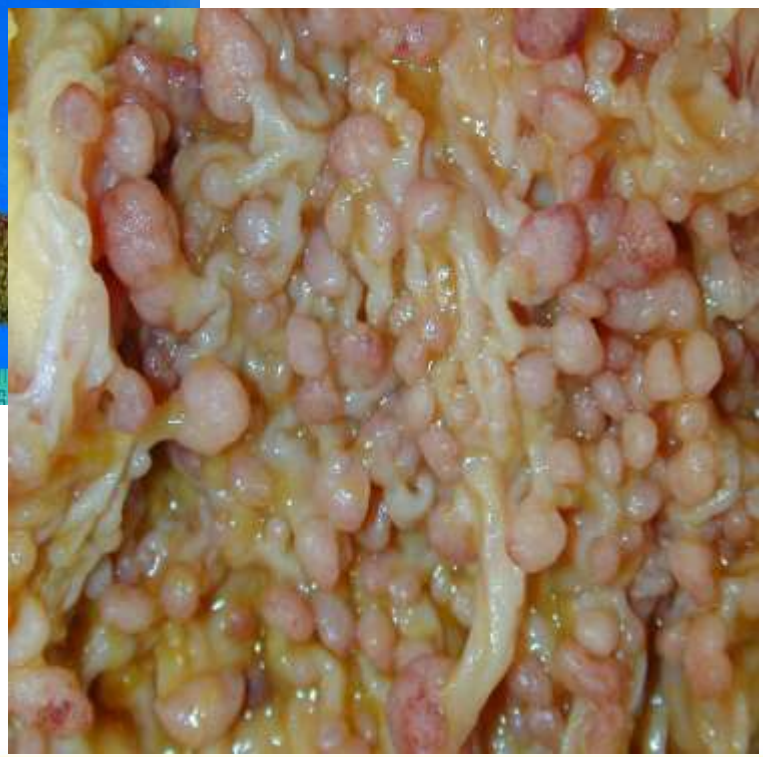


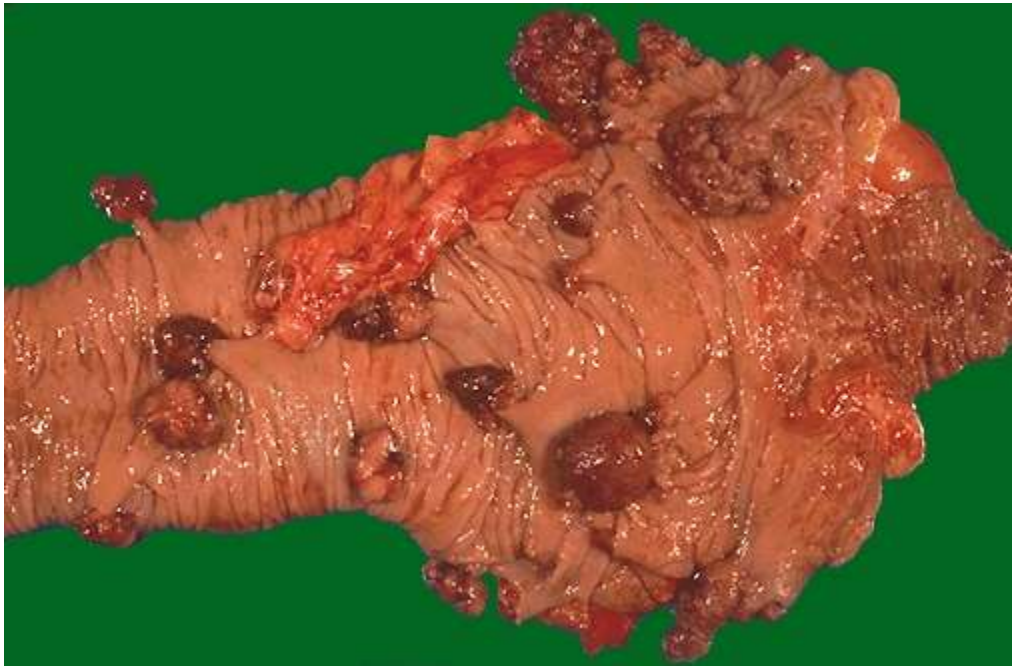




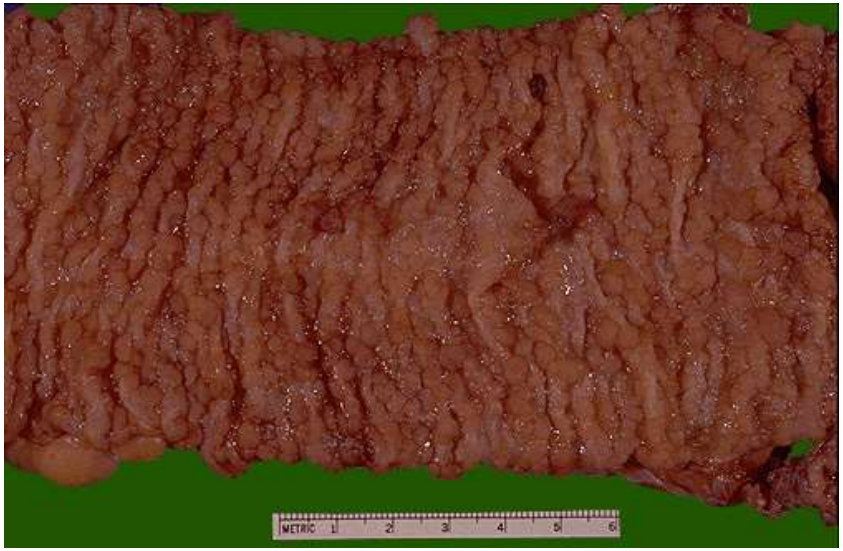
FAP

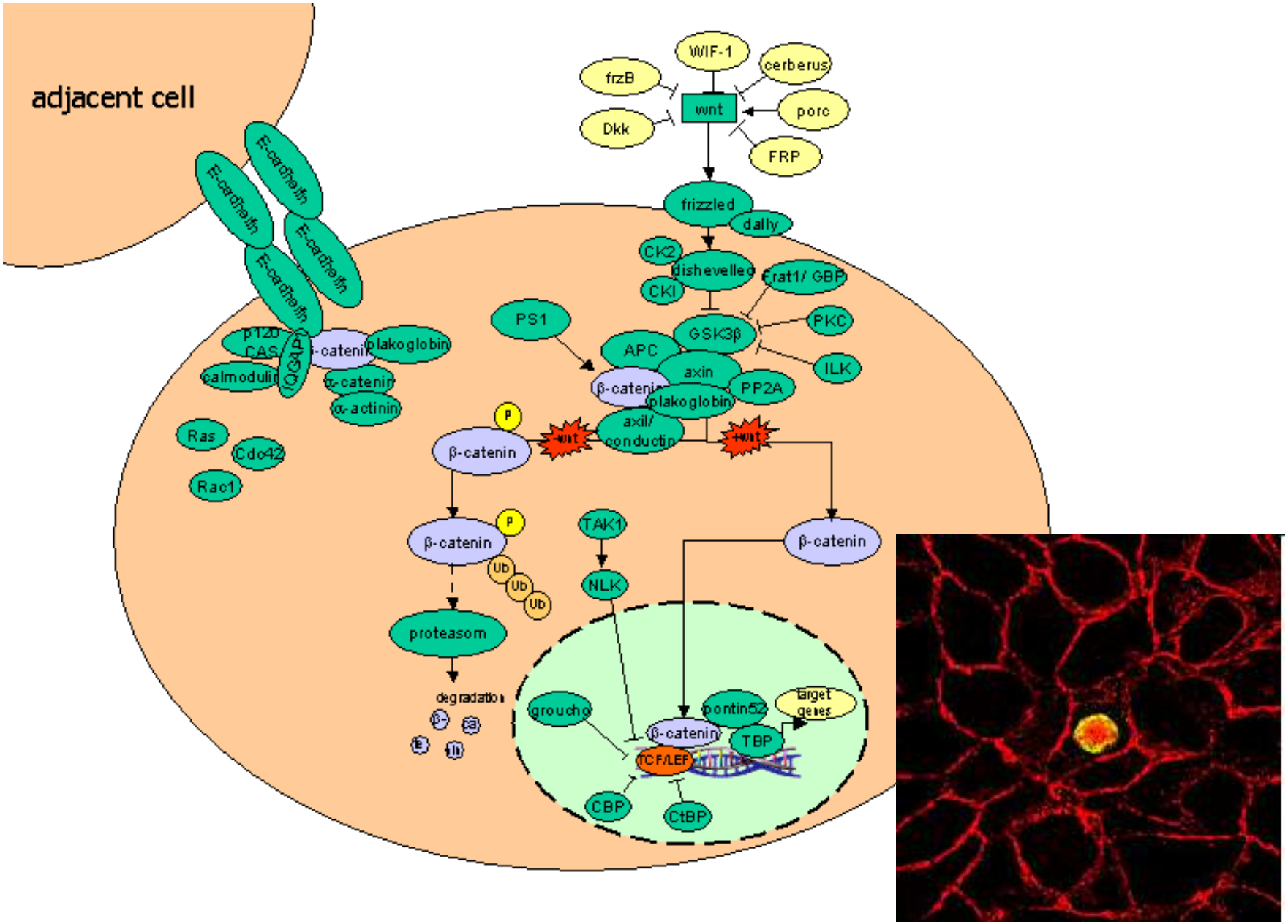






FAP




adjacent cell
WIF-1
cerberus
frzB
wnt
porc
Dkk
FRP
frizzled
dally
CK2
dishevelled
rat1/ GBP
CKI
PKC
PS1
GSK3β
APC
ILK
axin
β-catenin
PP2A
plakoglobin
axil/
conductin
wnt
wnt
P
β-catenin
Ras
Cdc42
Rac1
β-catenin
TAK1
β-catenin
P
Ub
Ub
Ub
NLK
proteasom
degradation
groucho
pontin52
target
genes
β-catenin
TBP
TCF/LEF
CBP
CtBP

NEOPLASIA

- Lancet 2002 Feb 2;359(9304):403-4

Detection of proximal colorectal cancers through analysis of faecal DNA.

Traverso G, Shuber A, Olsson L, Levin B, Johnson C, Hamilton SR, Boynton K, Kinzler KW, Vogelstein B.

BIOLOGIE der TUMORWACHSTUM

- Transformation
- Wachstum des transformierten Klones
- Lokale Invasion
- METASTASE

HCC Präkurzoren und Markers der malignen Transformation

Histological features / diagnostic tools	LGDN	HGDN	Early HCC
Cytology			
Small-cell change	–	+	+
Large-cell change	±	±	–
Foci with clonal appearance	–	+	+
Growth patterns			
Increased cell density over surrounding liver parenchyma	< 1.3 times	1.3–2 times	> 2 times
Pseudoglandular/acinar changes	–	±	+
Architectural changes			
Portal tracts	Present	Present	Often absent
Reticulin framework[a]	Intact	Intact	Usually at least focal loss
Unpaired (non-triadal) arteries and sinusoidal capillarization (CD34)	±	±	+
Additional diagnostic tools			
Stromal invasion and loss of ductular reaction (CK7/CK19)[a]	–	–	±
Overexpression[a] (of ≥ 2 among HSP70[b], GPC3[b], and GS[b]) [776,2919A]	–	–	+ (most)
Nodule-in-nodule growth[a]	–	–	±

–, absent; ±, may be present but not necessarily detectable in biopsy; +, present and usually detectable in biopsy; HGDN, high-grade dysplastic nodule; LGDN, low-grade dysplastic nodule.
[a]High discriminatory value; helpful immunohistochemical stain. [b]Recommended in international guidelines [885].

WHO-Classification of Tumours (5th ed), Digestive System Tumours

Invasion

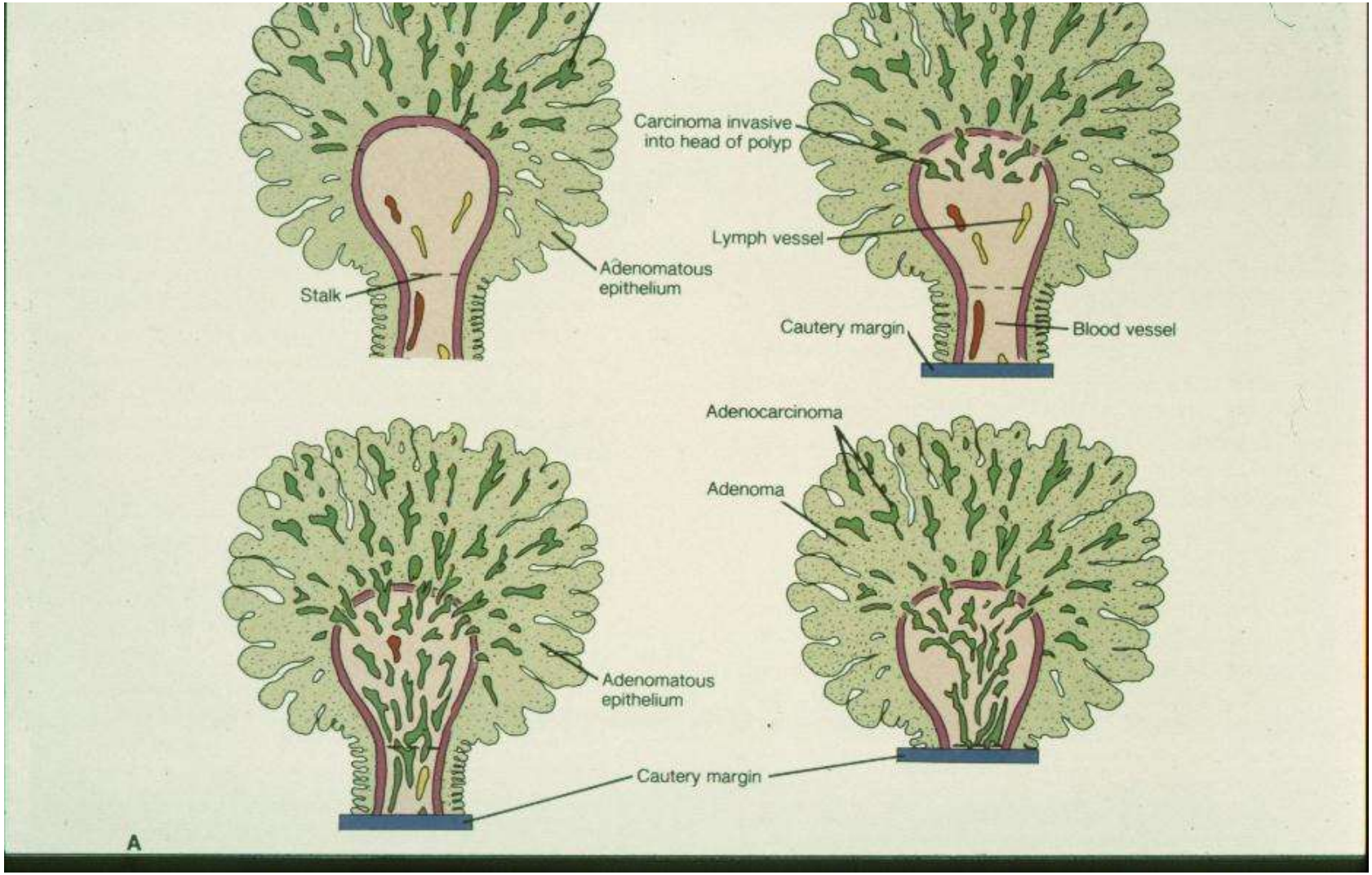
- Lokale Invasion: Neben Metastasen, die Invasion ist das zuverlassigste Zeichen der Malignitat !!
- In situ Karzinom: Maligne Tumoren entwickeln haufig von einem Prekursor-Lasion (pramaligne, prainvasive, in situ). Dysplastische/anaplastische Zellen können das ganzes Epithelium ersetzen (zytologische Eigenschaften der Malignitat)

  OHNE INVASION des Basalmembrans !

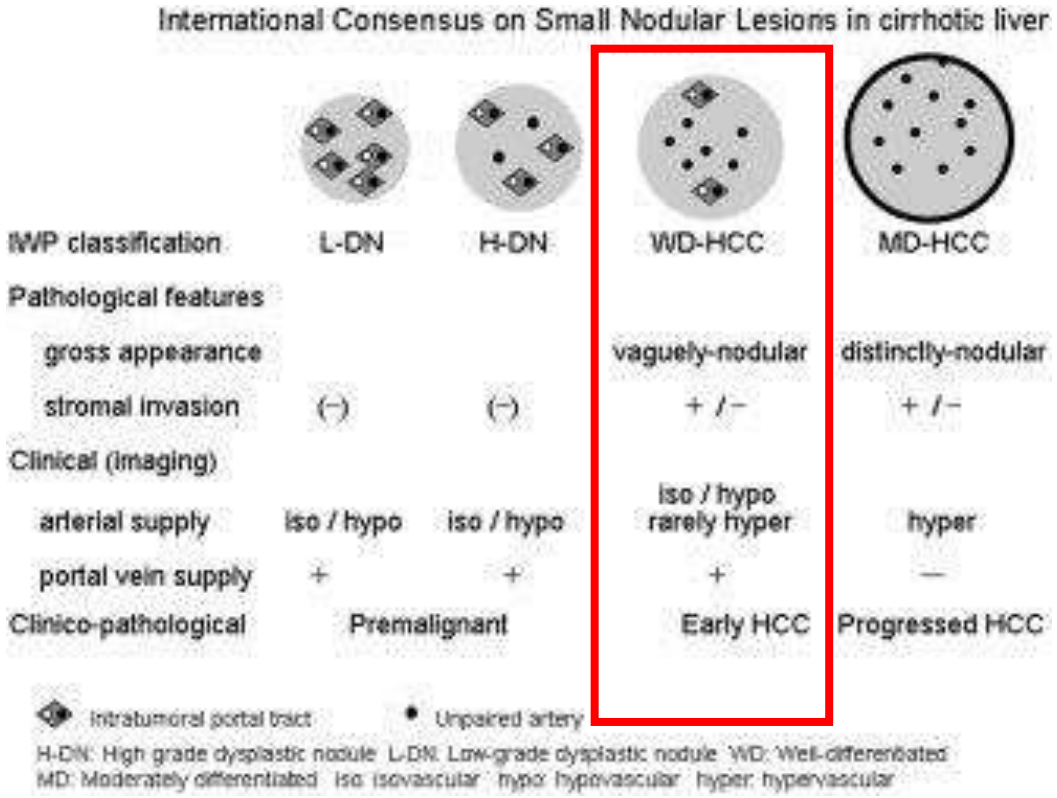
Carcinoma in situ, „Frühkarzinom”

- Zervix cc. (CIN 1, 2, 3, CIS)
- Mundhöhle
- Esophagus cc.
- Pancreas cc. (PanIn1,2,3)
- Magen
- Usw. ....

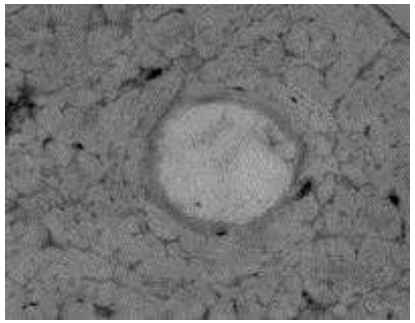
Carcinoma in polypo.



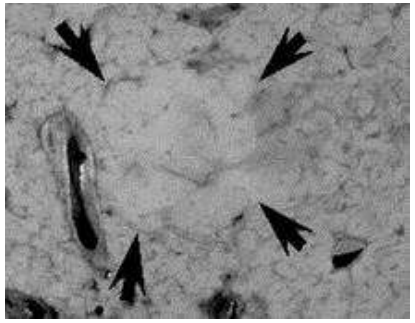
Small HCCs



International Consensus Group; Hepatology 49 (2009) 658-664



Distinct: progressed! (12 mm)



Vaguely nodular: early HCC

Features of Early and Small Progressed HCC

Feature	Early HCC	Small progressed HCC
Gross margins	Indistinct	Distinct
Type of growth	Replacing	Expansive/infiltrative
Capsule	Absent	Common (> 50%)
Differentiation	Very well to well differentiated	Well to moderately differentiated
Fatty change	Frequent (up to 40%)	Rare
Intratumoural portal tracts	Rare	Absent
Sinusoidal capillarization	Scattered/low density	Diffuse/high density
Stromal invasion	Focal/subtle	Obvious
Morphology	Non-tumoural liver mimic (low magnification), but increased cell density or cytological atypia deserves attention Little cellular and structural atypia (high magnification) requires careful distinction from HGDN	Increased cellular and structural atypia compared with early HCC Nodule-in-nodule pattern when arising within early HCC or HGDN

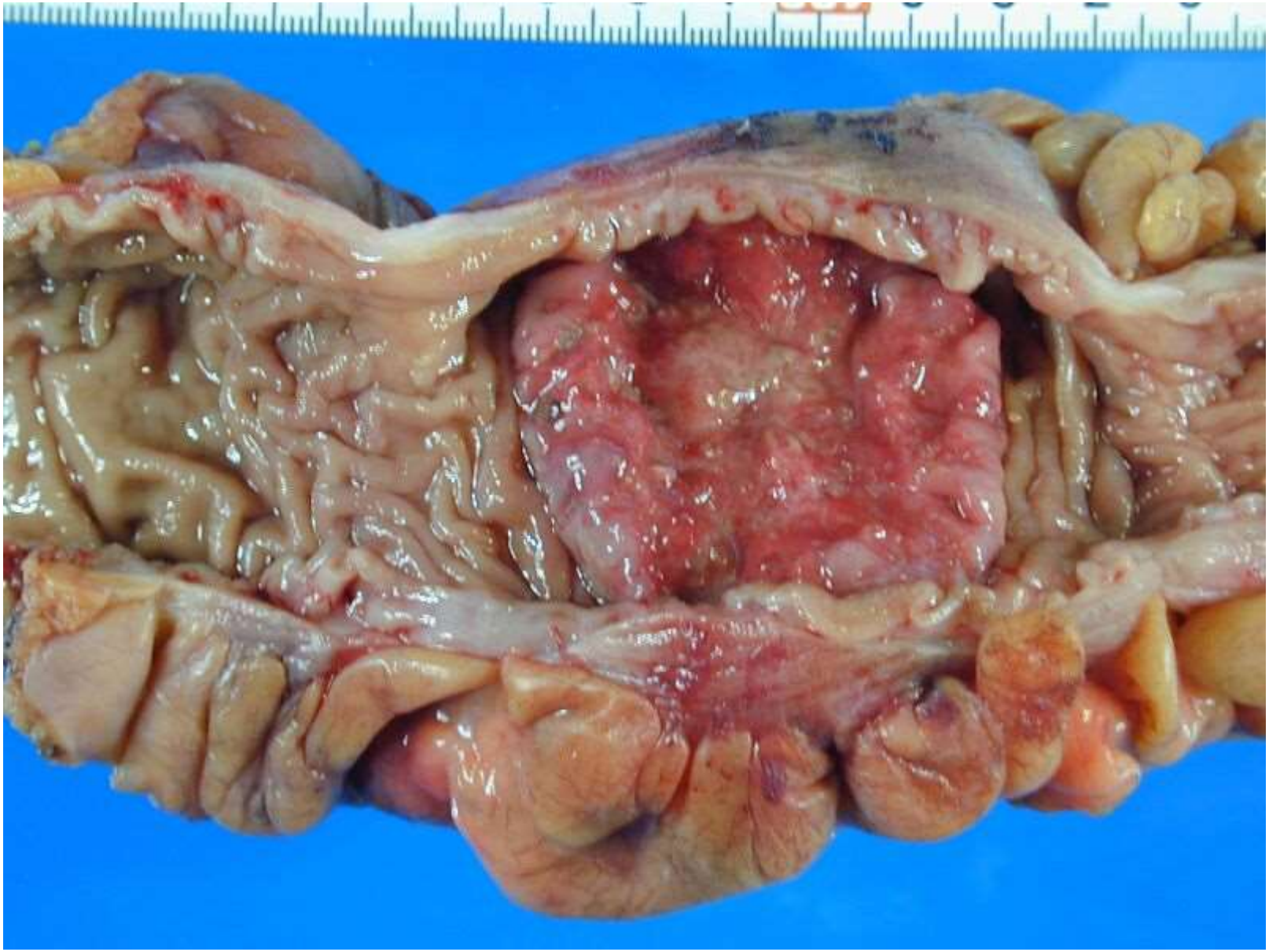
HGDN, high-grade dysplastic nodule.

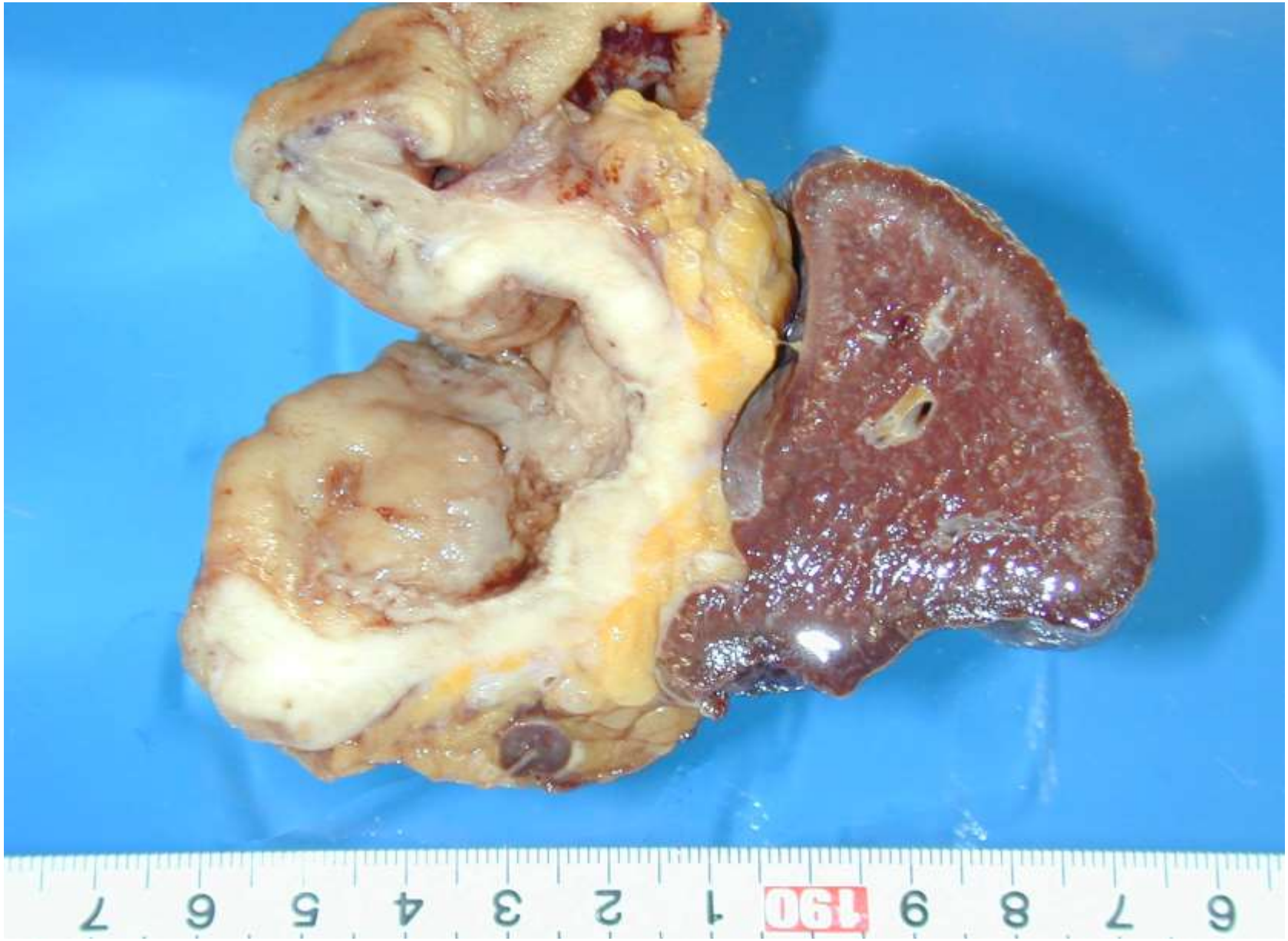
WHO-Classification of Tumours (5th ed), Digestive System Tumours

NEOPLASIE

Im General: attach the suffix: -oma nach dem originial Gewebe.

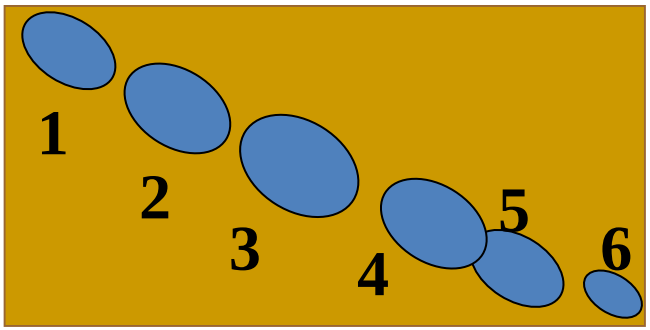
gutartig	bösartig
gut differenziert	• schlecht diff. zu undiff. anaplasia !!
• Langsames Wachstum	• rapides Wachstum
• KEINE lokale Invasion !!!	• invasiv !!
• KEINE Metastase !!!	• Metastase !!

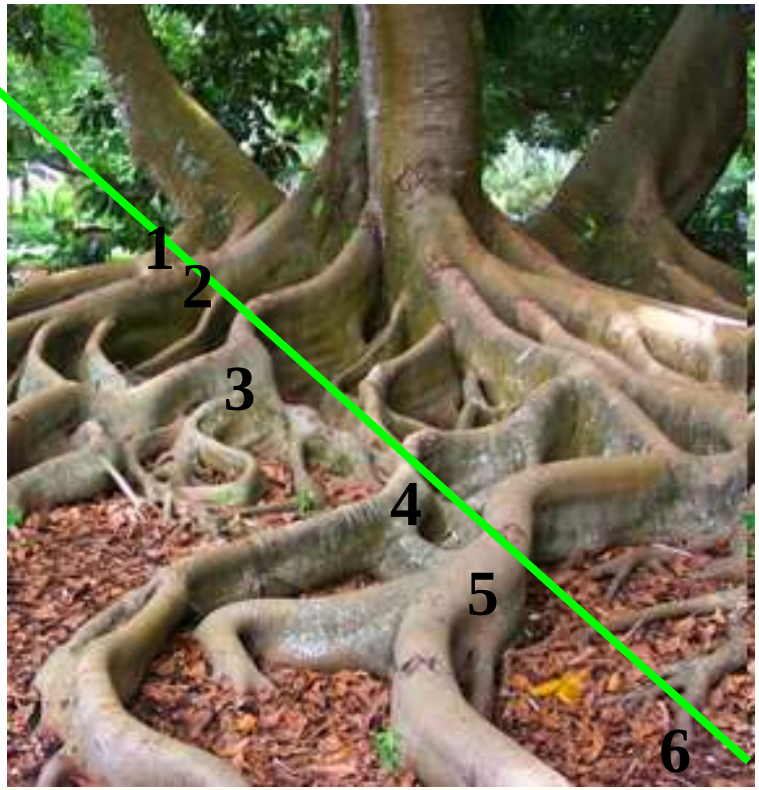


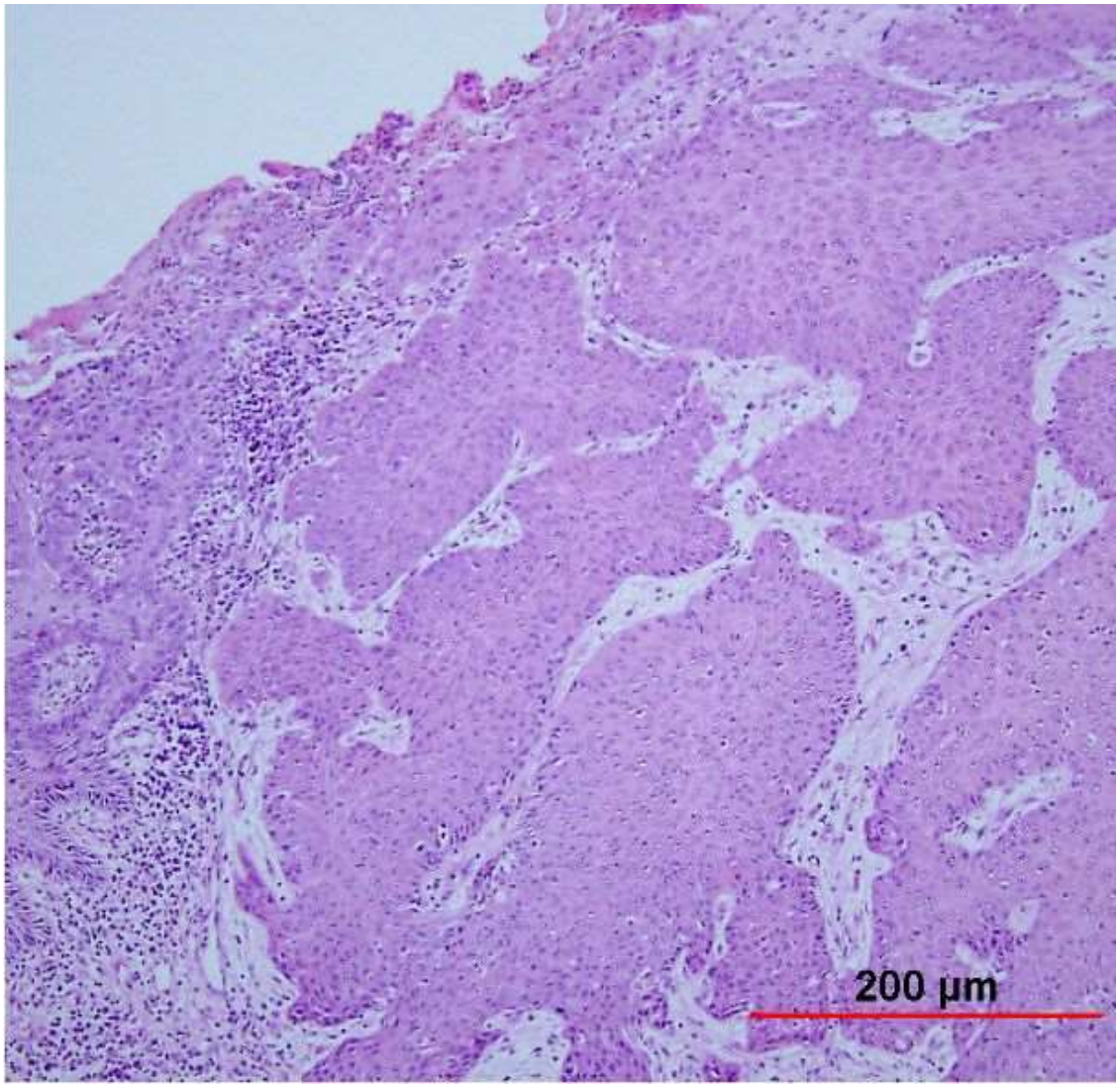


Schnitte : 2 D !!

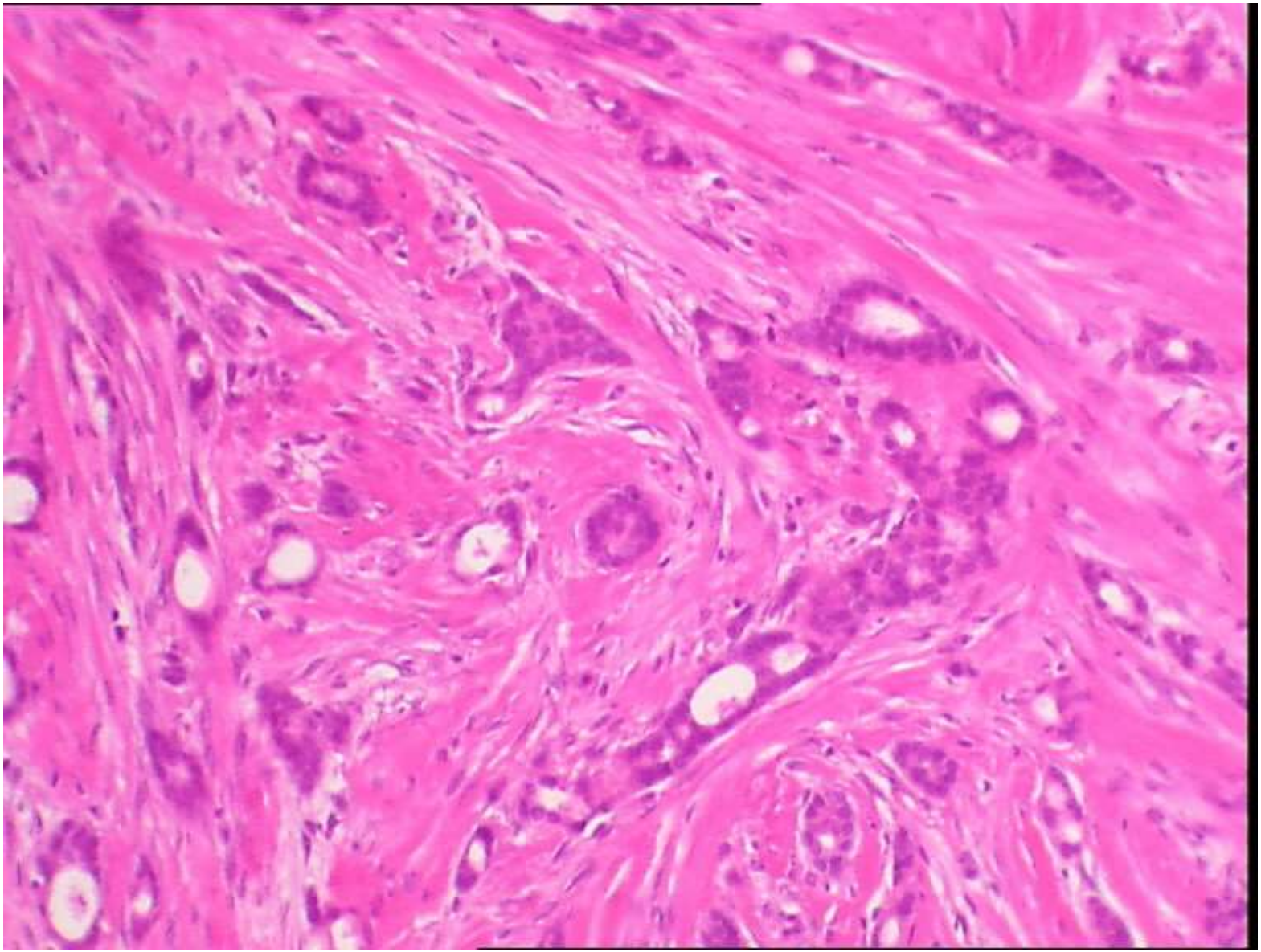
Biologische Strukturen: 3 D !!





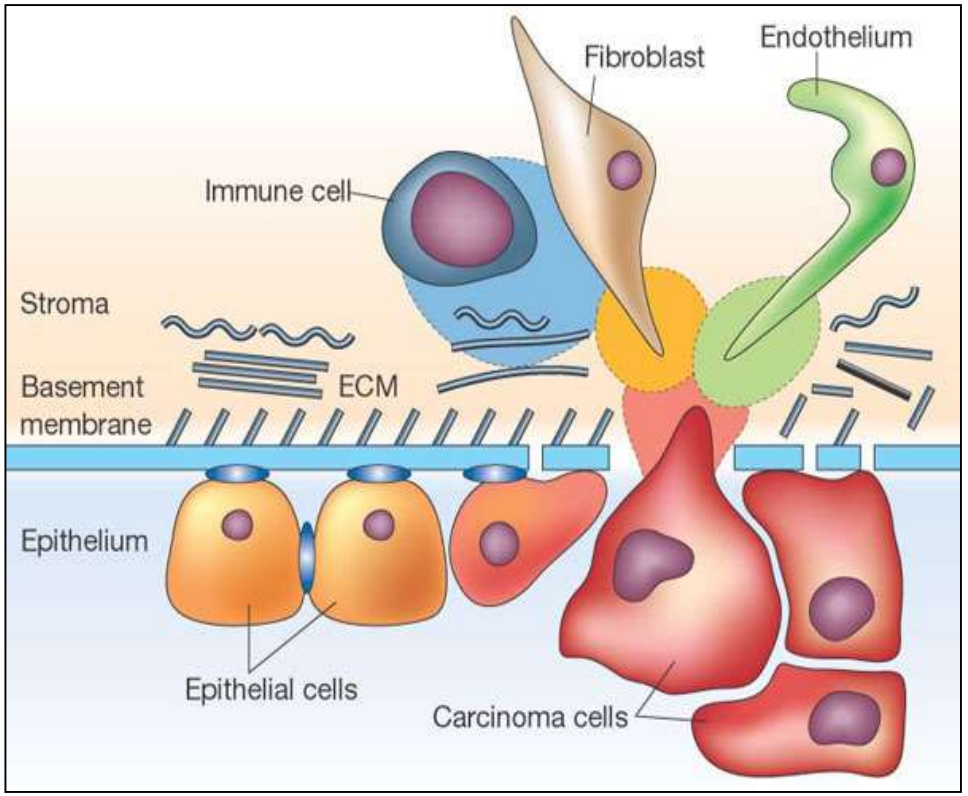


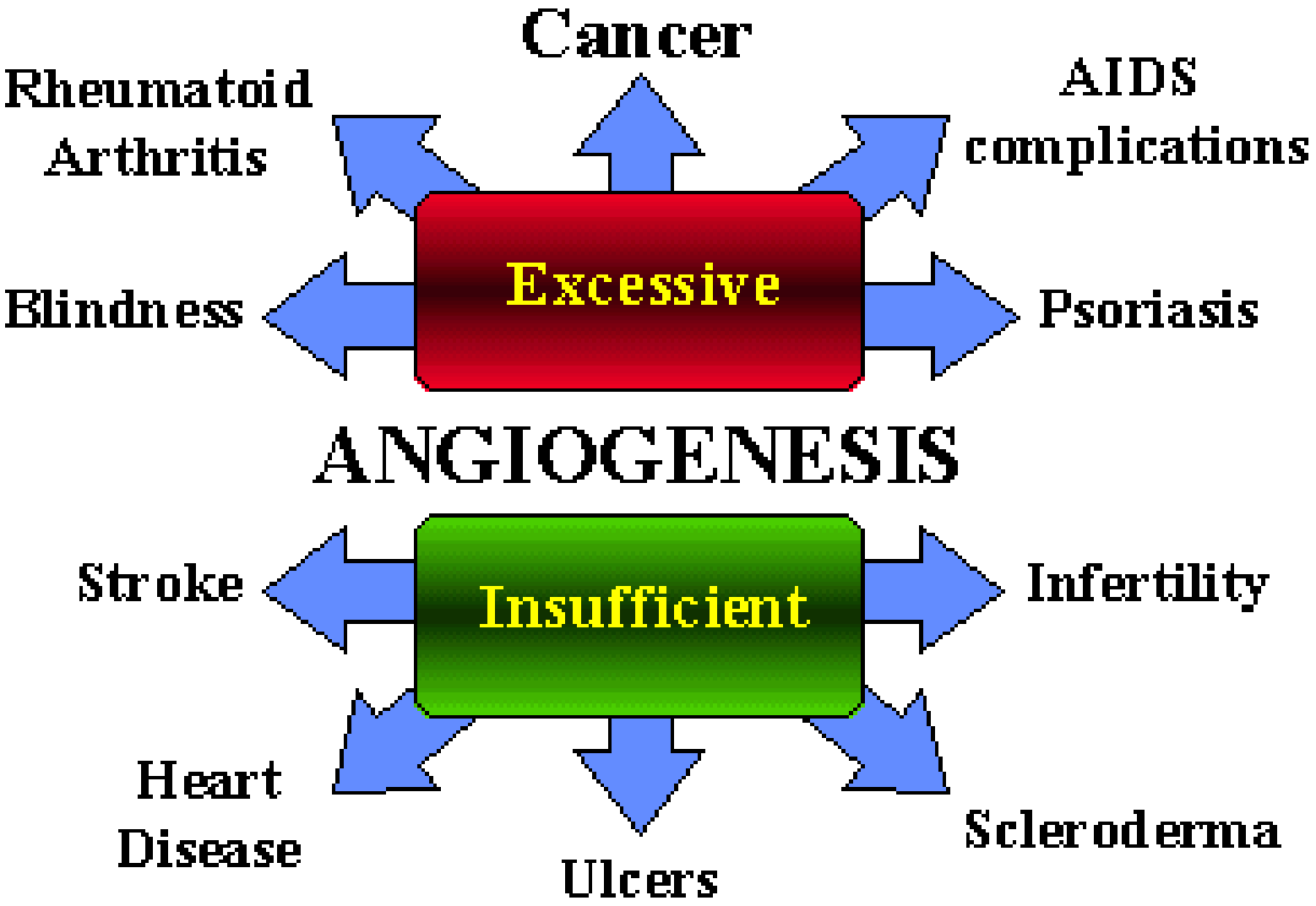
Invazves Karzinom -cervix

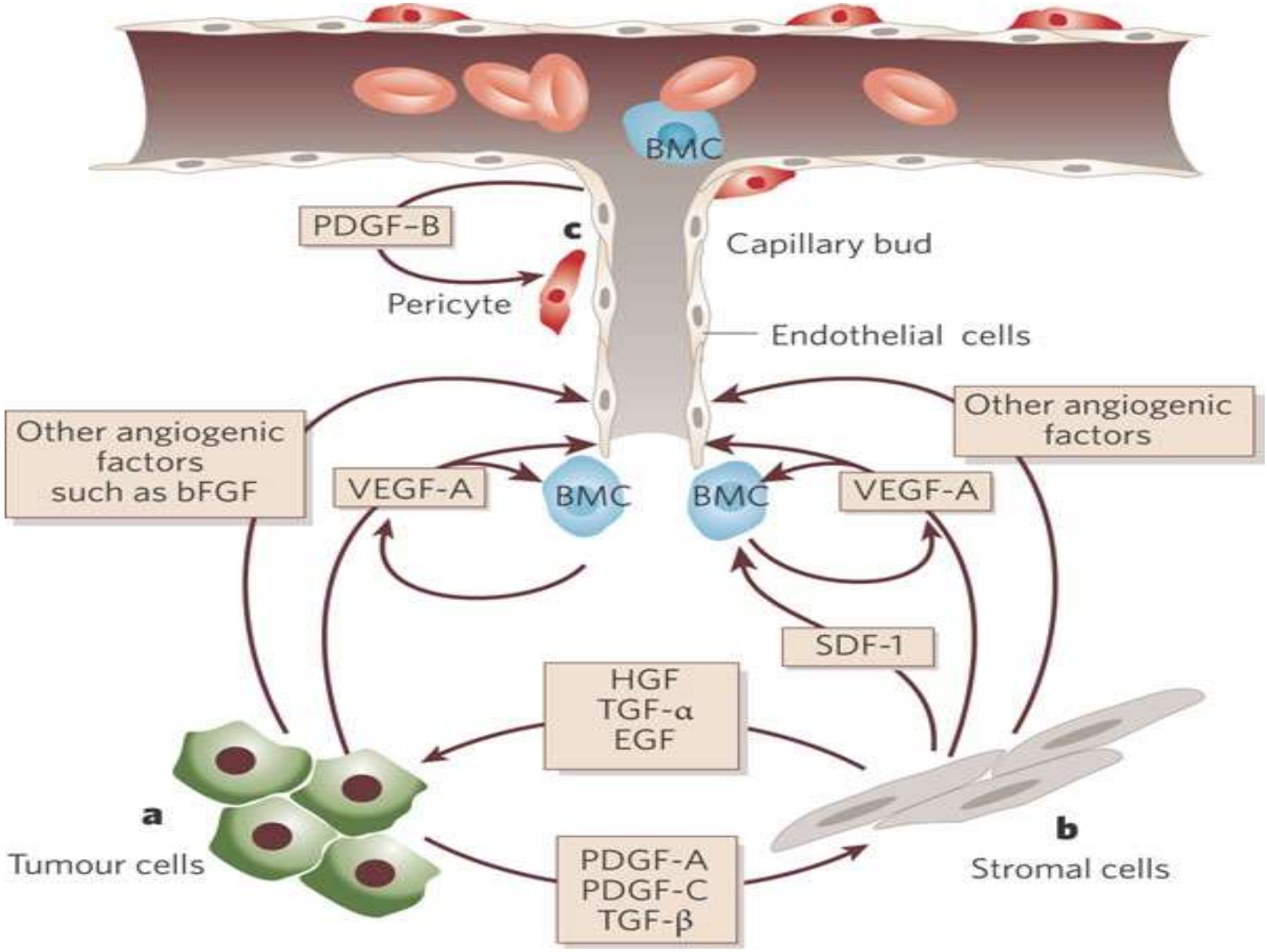


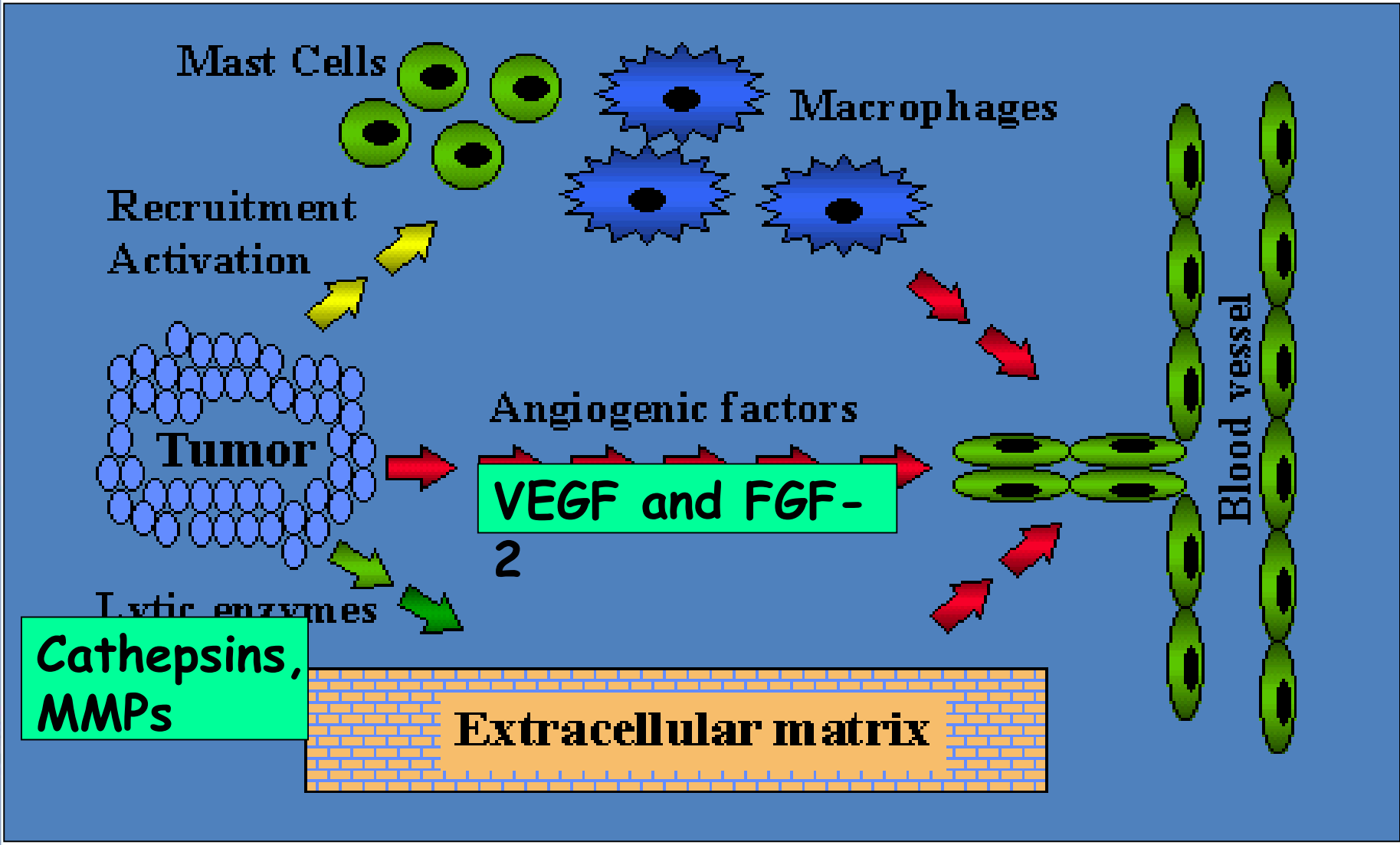
Eigenschaften der Tumorzellen

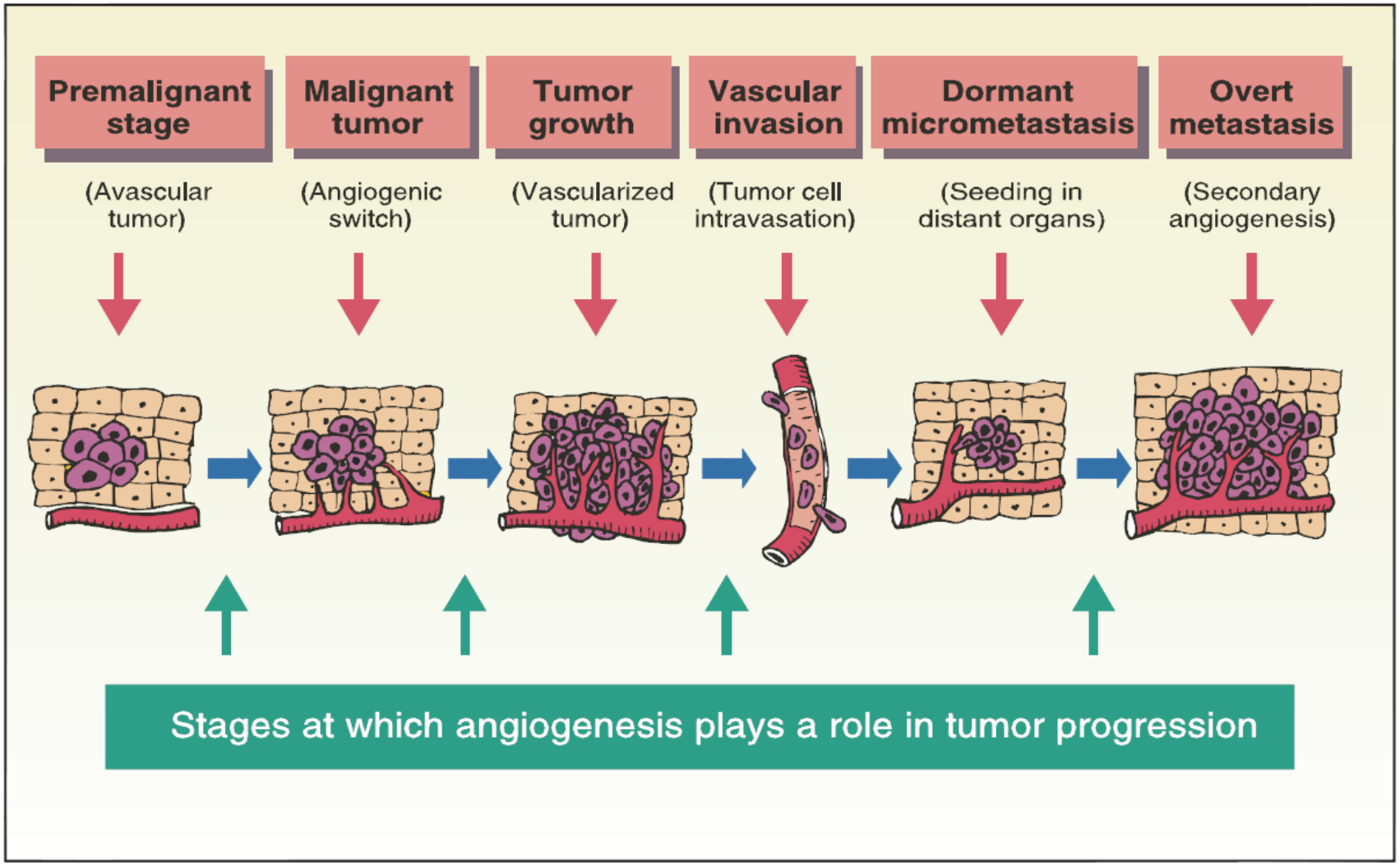
- Die können Neoangiogenese induzieren
- Die sind fahig für Invasion und Metastase
- Die Angiogenese ist die nötige Eigenschaft der Malignitat !!




Cancer
Rheumatoid Arthritis
AIDS complications
Excessive
Blindness
Psoriasis
ANGIOGENESIS
Stroke
Insufficient
Infertility
Heart Disease
Ulcers
Scleroderma

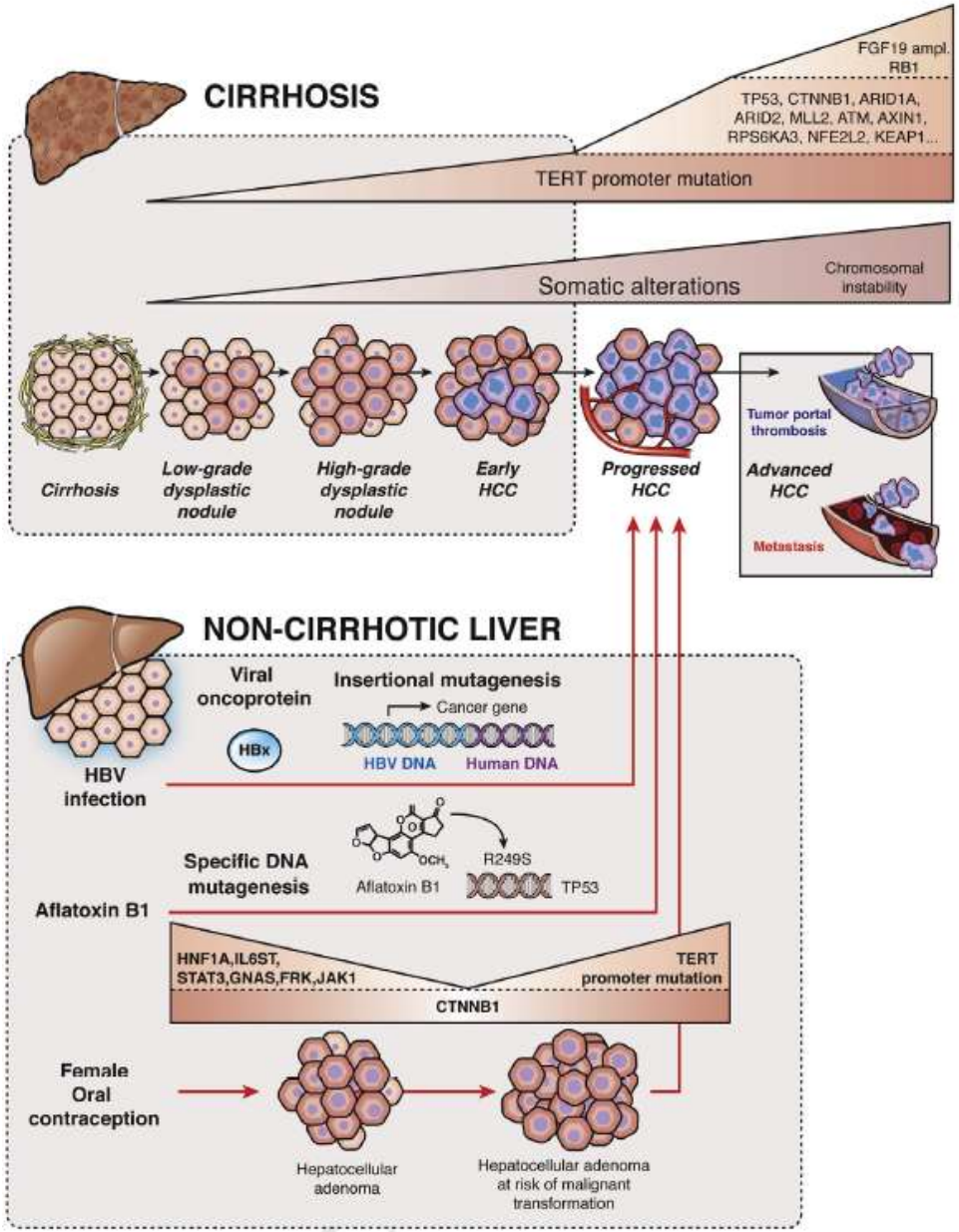

BMC
PDGF–B
c
Capillary bud
Pericyte
Endothelial cells
Other angiogenic factors such as bFGF
Other angiogenic factors
VEGF-A
BMC
BMC
VEGF-A
SDF-1
HGF
TGF-α
EGF
a
Tumour cells
b
Stromal cells
PDGF-A
PDGF-C
TGF-β


Mast Cells
Macrophages
Recruitment
Activation
Tumor
Angiogenic factors
VEGF and FGF-2
Blood vessel
Lytic enzymes
Cathepsins, MMPs
Extracellular matrix



Angiogenesis and antiangiogenic therapy in hepatocellular carcinoma

Roberta Pang [a], Ronnie T.P. Poon [b,a]

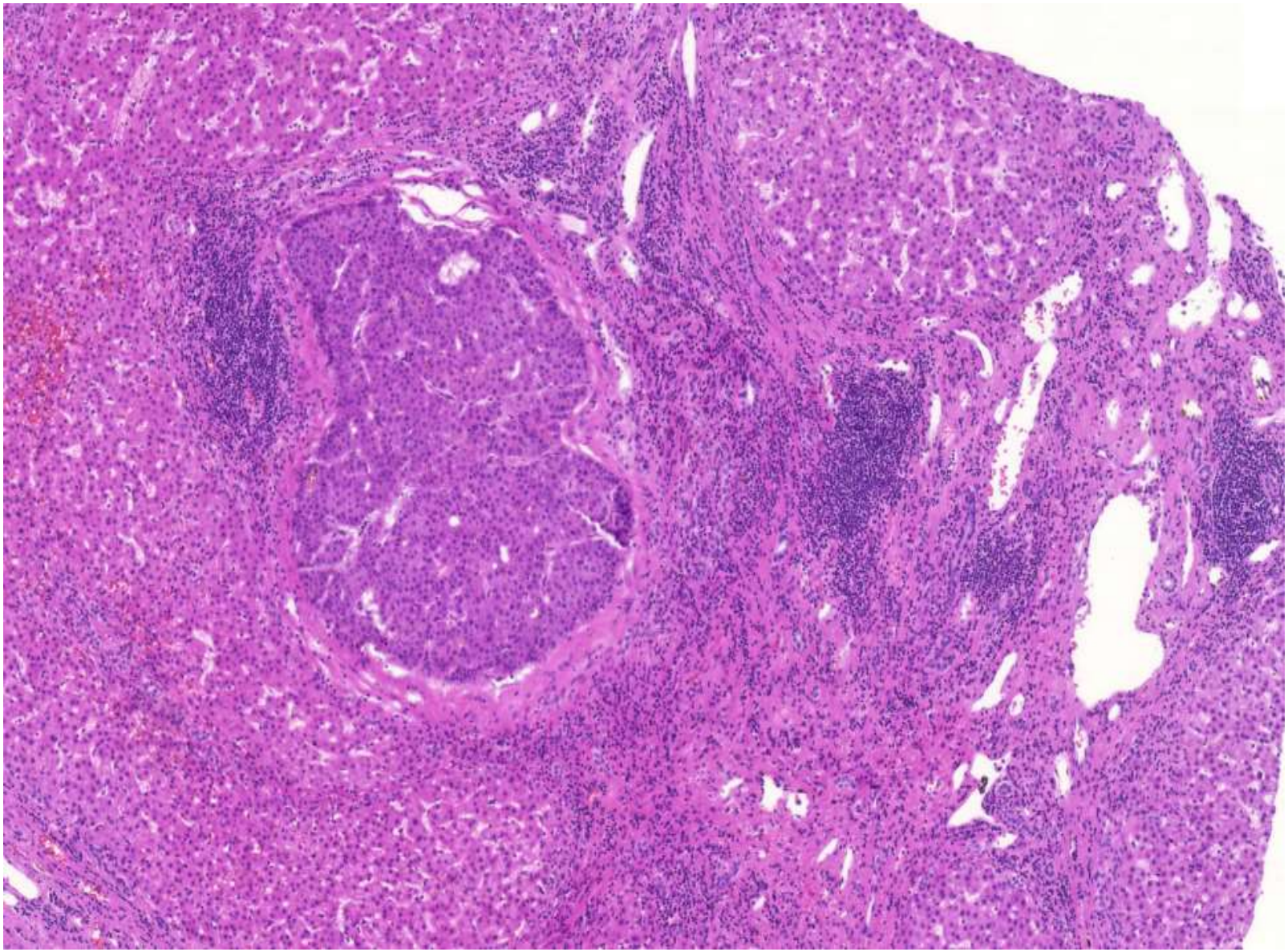


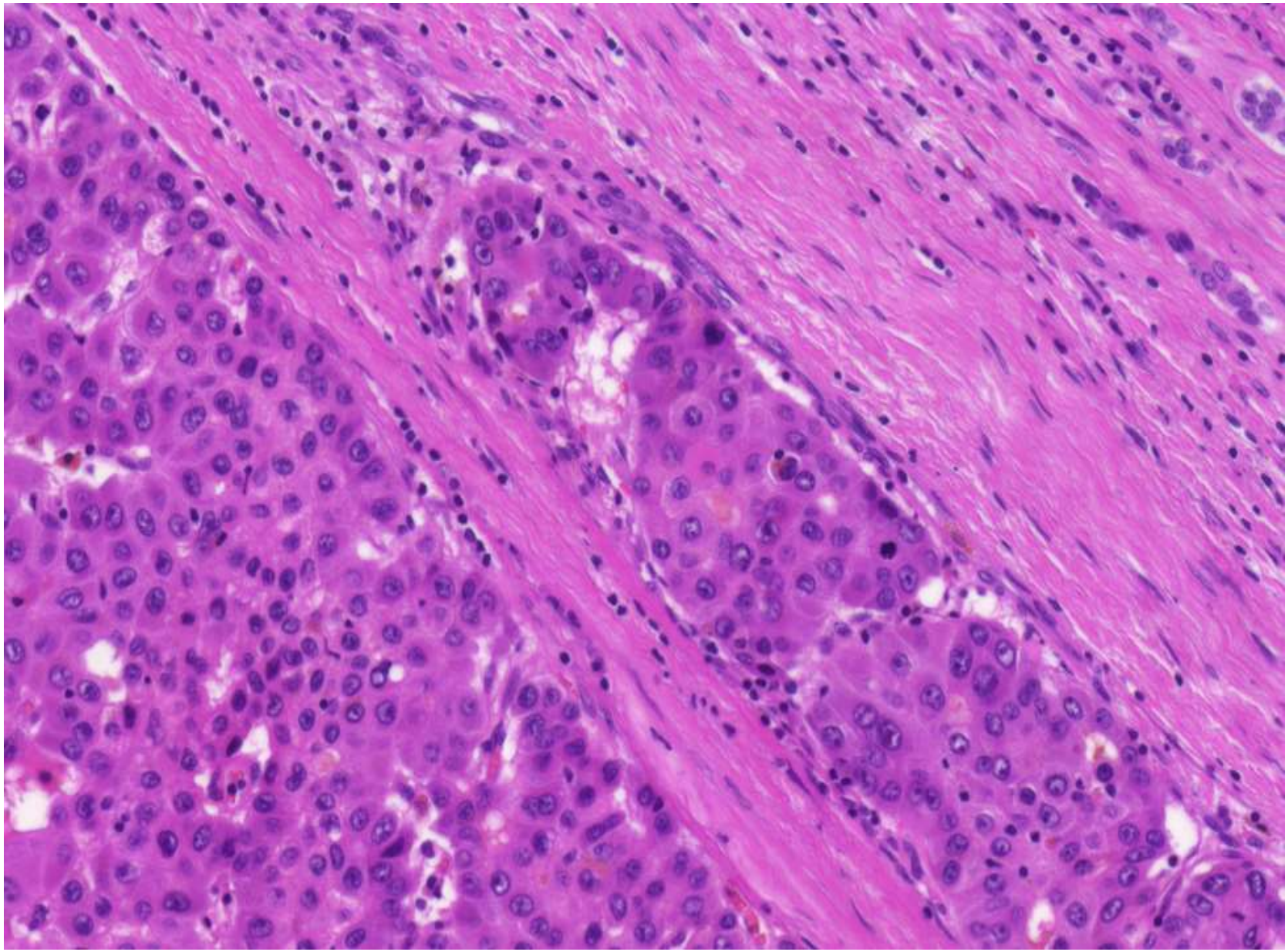
Mechanisms of malignant transformation in HCC.

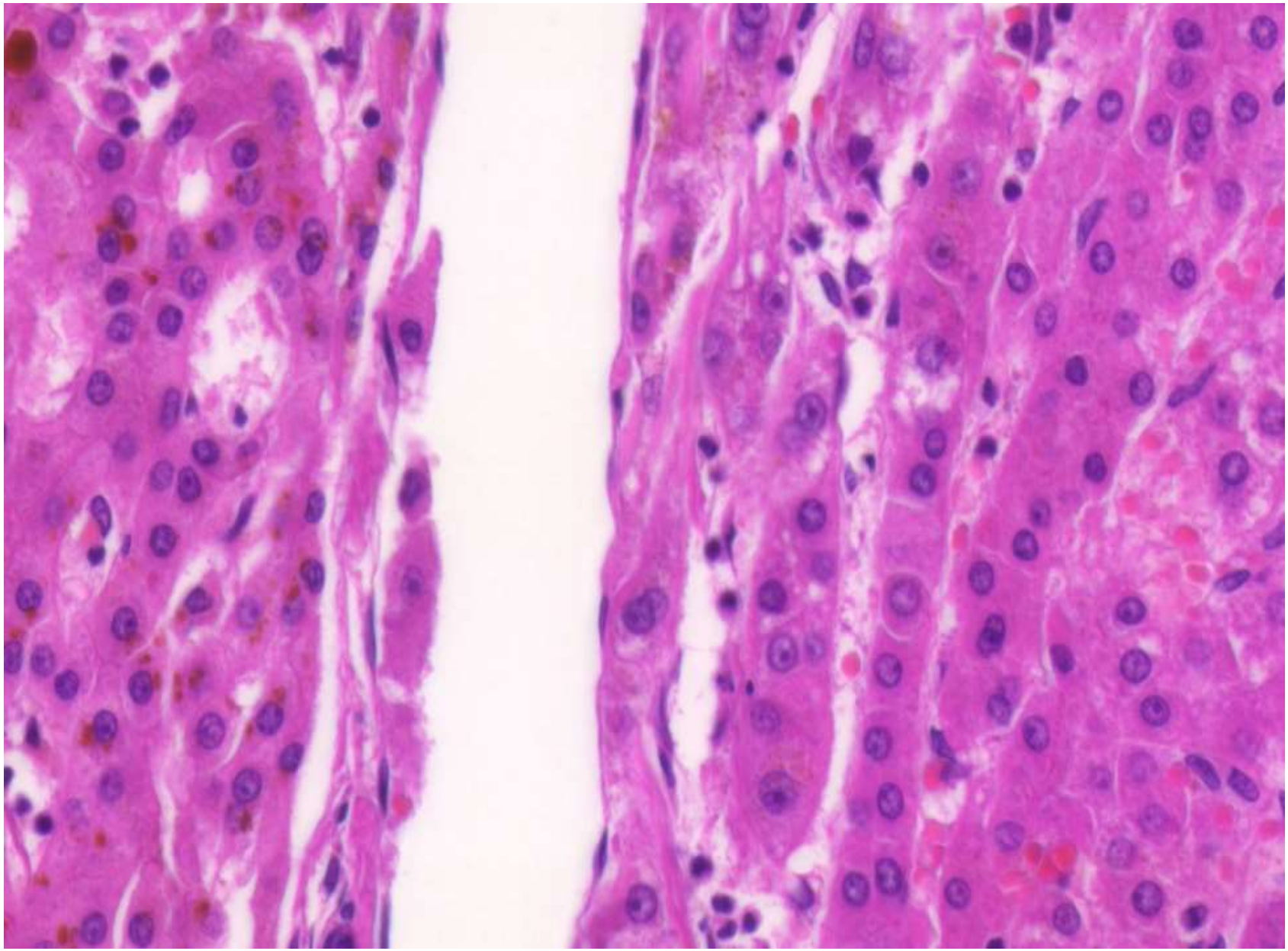
Gastroenterology 2015;■:1–14

Genetic Landscape and Biomarkers of Hepatocellular Carcinoma

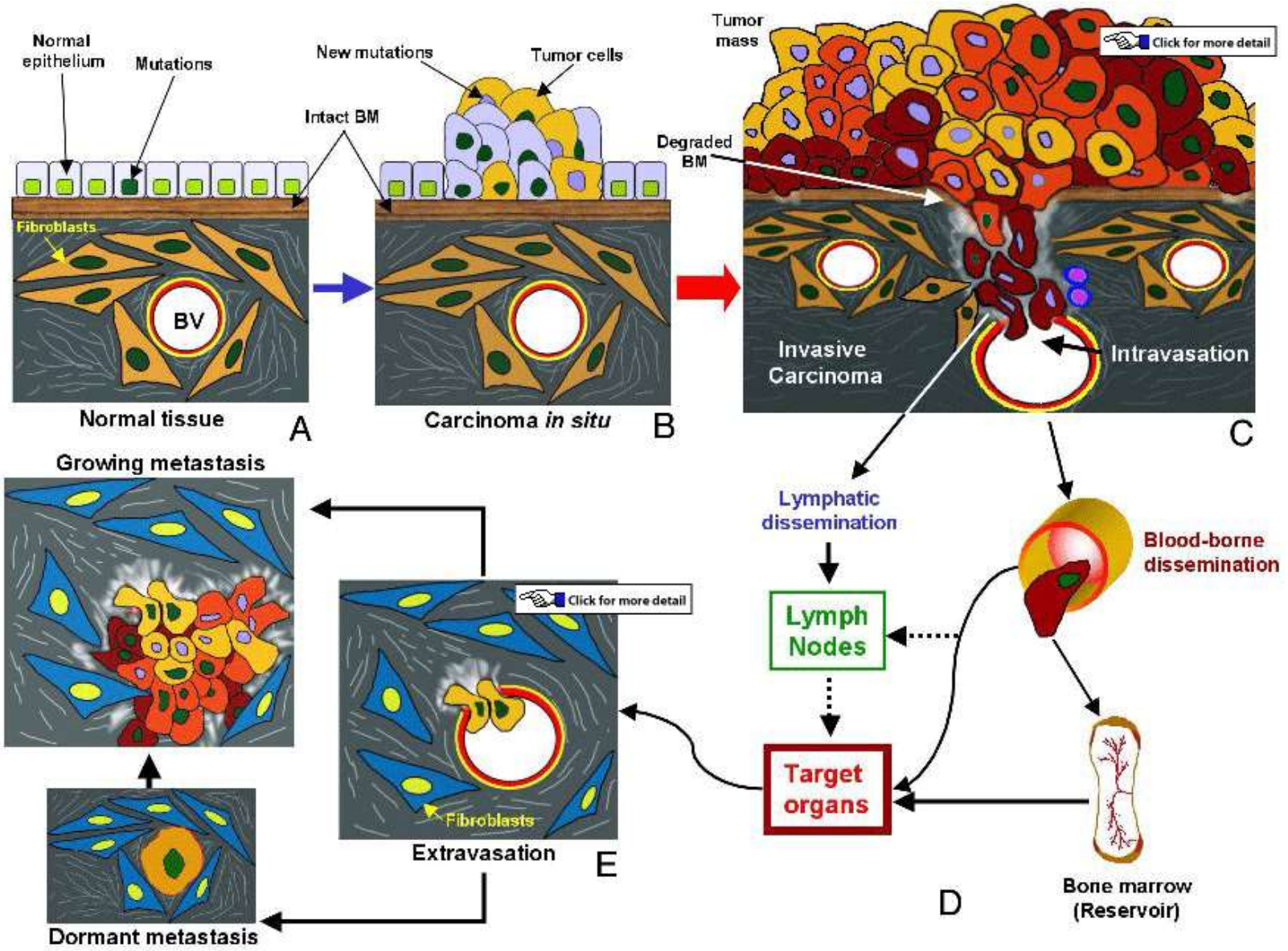
[1]Inserm, UMR-1162, Génomique Fonctionnelle des Tumeurs Solides, Equipe Labellisée Ligue Contre le Cancer, Institut Universitaire d'Hématologie, Paris, France; [2]Université Paris Descartes, Labex Immuno-Oncology, Sorbonne Paris Cité, Faculté de Médecine, Paris, France; [3]Université Paris 13, Sorbonne Paris Cité, Unité de Formation et de Recherche Santé, Médecine, Biologie Humaine, Bobigny, France; [4]Université Paris Diderot, Paris; [5]Liver Cancer Program, Division of Liver Diseases, Department of Medicine, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, New York; [6]Division of Hematology and Medical Oncology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York; [7]Service d'hépatologie, Hôpital Jean Verdier, Hôpitaux Universitaires Paris-Seine-Saint-Denis, Assistance-Publique Hôpitaux de Paris, Bondy, France; [8]Liver Cancer Translational Research Laboratory, Barcelona-Clinic Liver Cancer Group, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Liver Unit, CIBERehd, Hospital Clínic, Barcelona, Catalonia, Spain; [9]Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Catalonia, Spain

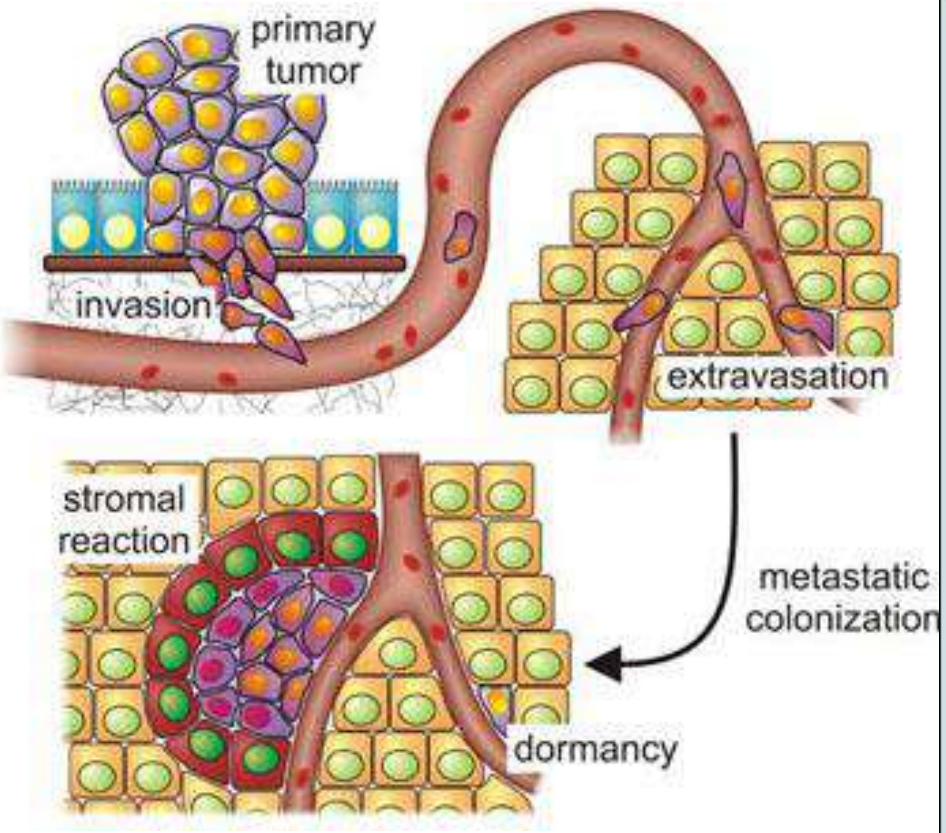


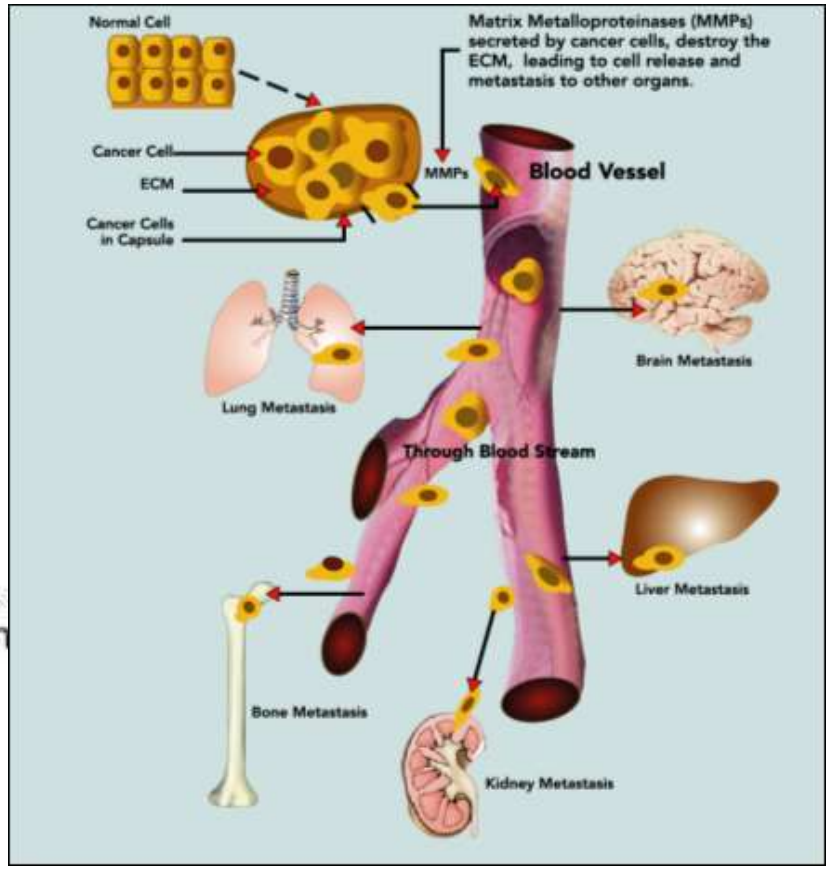


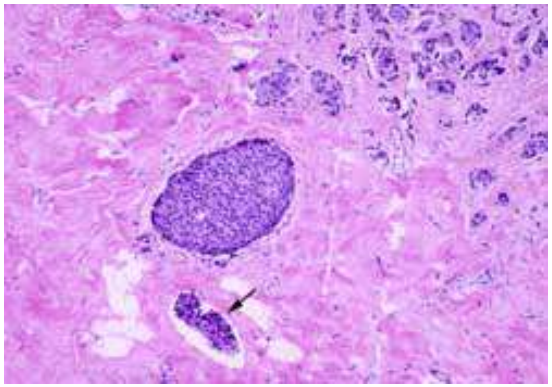


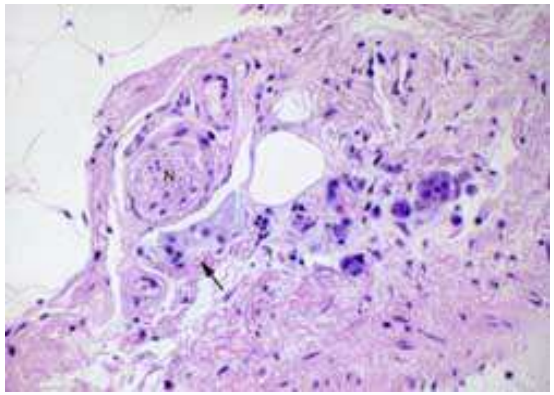
TUMOR ANGIOGENESE


Normal epithelium
Mutations
New mutations
Tumor cells
Intact BM
Tumor mass
Click for more detail
Degraded BM
Fibroblasts
BV
Invasive Carcinoma
Intravasation
Normal tissue
A
Carcinoma in situ
B
C
Growing metastasis
Lymphatic dissemination
Blood-borne dissemination
Lymph Nodes
Click for more detail
Target organs
Fibroblasts
Extravasation
E
D
Bone marrow (Reservoir)
Dormant metastasis


primary tumor
invasion
extravasation
stromal reaction
metastatic colonization
dormancy

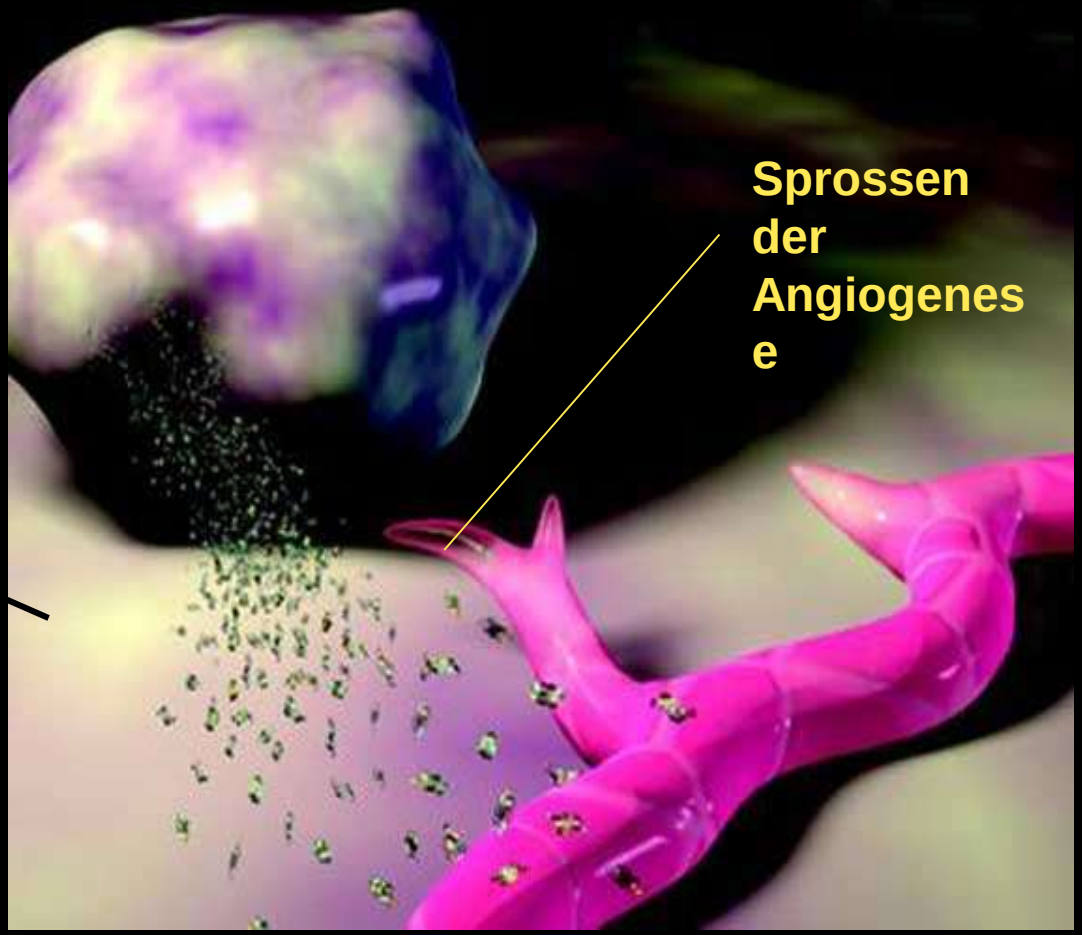

Normal Cell
Matrix Metalloproteinases (MMPs) secreted by cancer cells, destroy the ECM, leading to cell release and metastasis to other organs.
Cancer Cell
ECM
Cancer Cells in Capsule
MMPs
Blood Vessel
Brain Metastasis
Lung Metastasis
Through Blood Stream
Liver Metastasis
Bone Metastasis
Kidney Metastasis



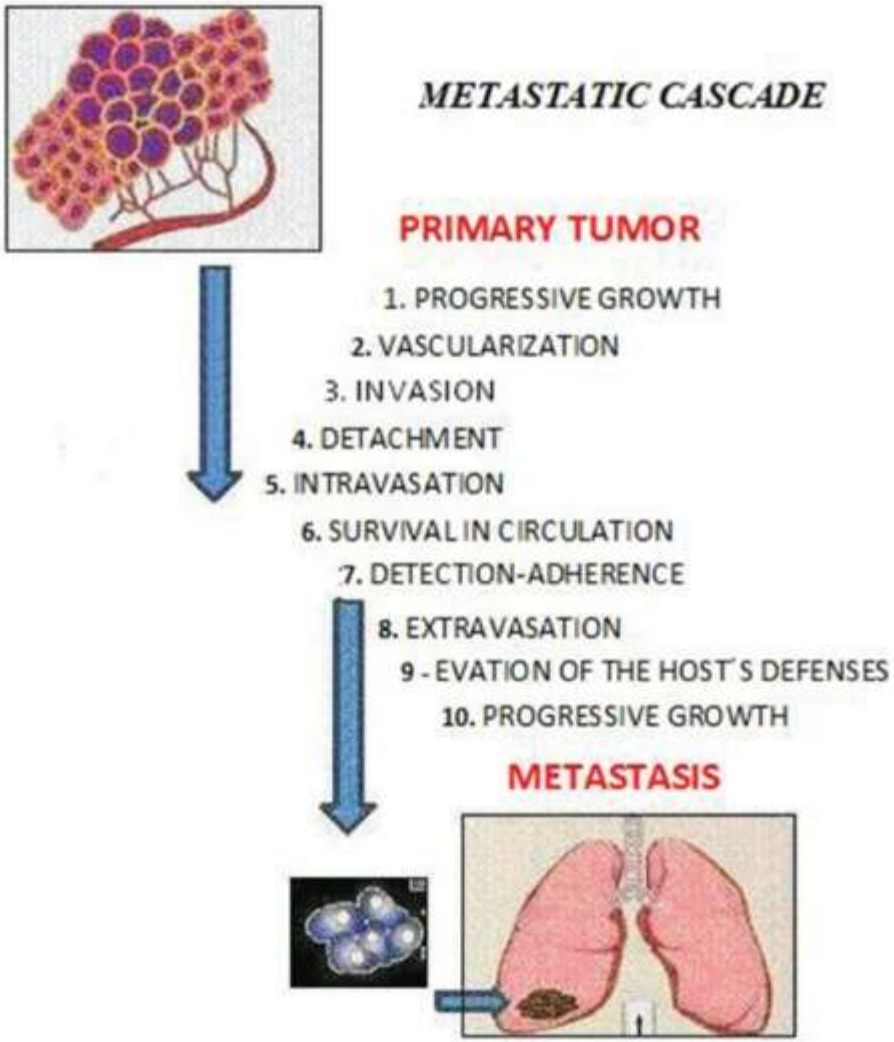


TUMOR ANGIOGENESE

Gowth factors Eg., basic fibroblast growth factor, bFGF, Placental growth factor, PlGF, Vascular endothelial growth factor, VEGF



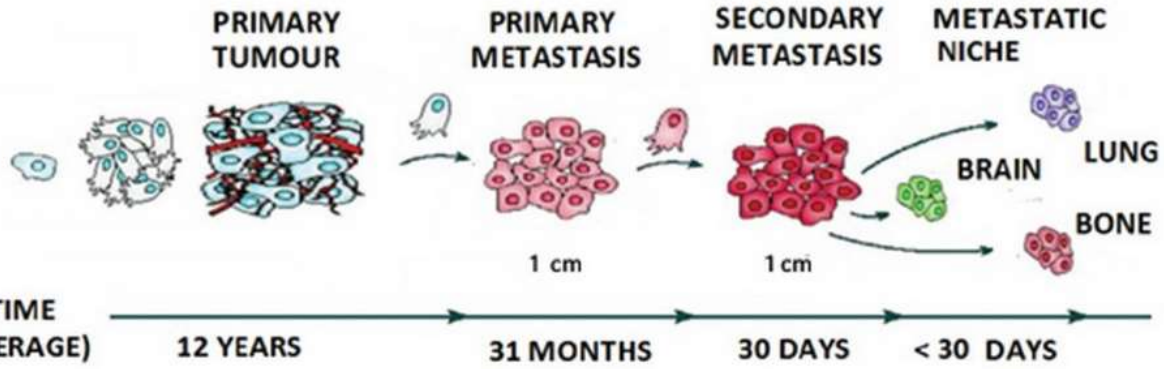
TUMOR ANGIOGENESE



Francisco Arvelo,[1,2] Felipe Sojo,[1,2] and Carlos Cotte[2]:
Tumour progression and metastasis Ecancermedicalscience. 2016; 10: 617.

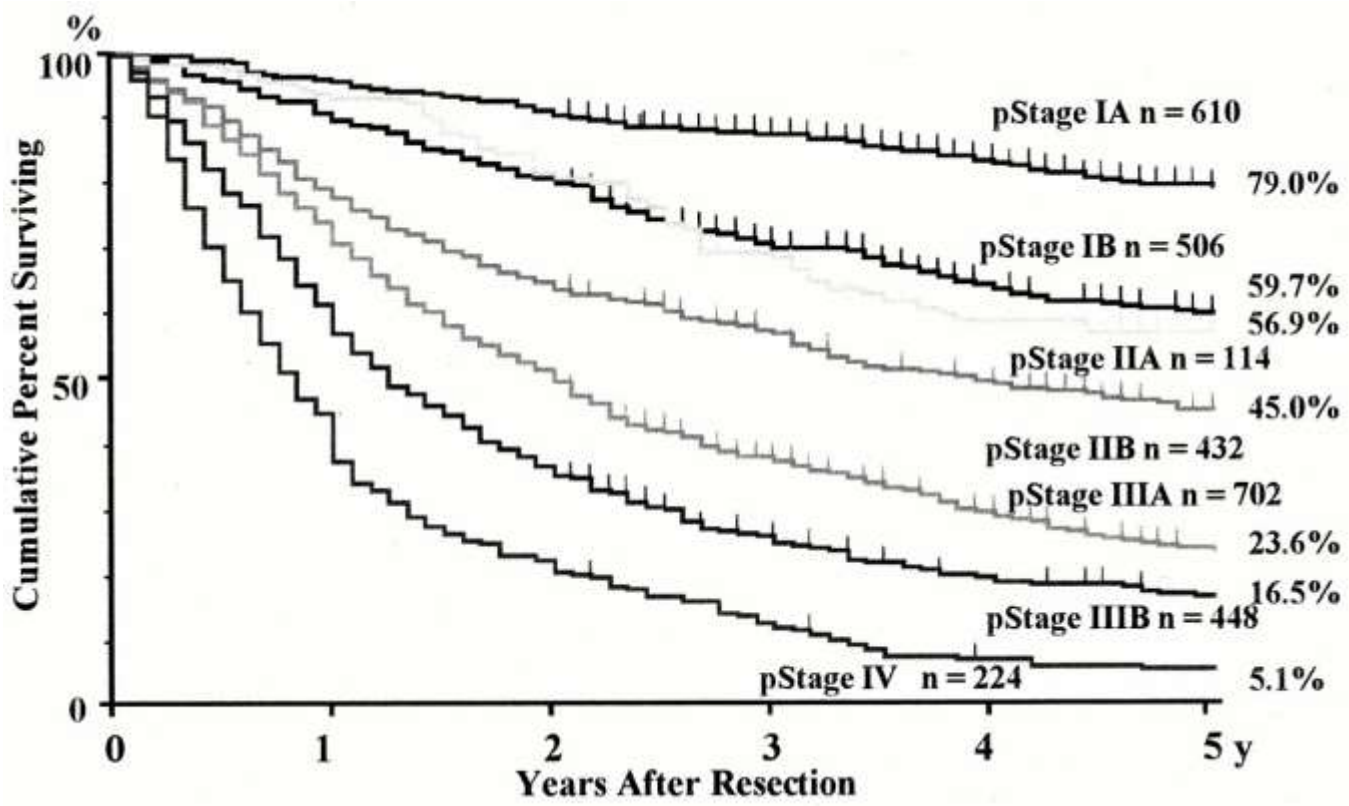
METASTASIS, TIME AND FAILURE FACTORS IN CANCER TREATMENT

- DELAYED DIAGNOSIS DUE TO:
  - ✓ INOPERABLE TUMORS
  - ✓ EARLY DISSEMINATION
  - ✓ OCCULT PRIMARY METASTASIS
- LOCATION OF THE TUMOR AND/OR METASTASIS IN VITAL ORGANS
- DAMAGE FROM:
  - ✓ COMPRESSION
  - ✓ LOCAL INVASION
  - ✓ LOSS OF FUNCTION
- TOXICITY OF TREATMENTS
- TUMOR HETEROGENEITY
  - ✓ GENE INESTABILITY AND GENERATION OF MORE MALIGNANT CELLS
  - ✓ METASTATIC PROGRESSION AND THE RESPONSE TO TREATMENTS CAN CAUSE CHANGES Y THE PRIMARY TUMOUR CELLS AND THE METASYTASES



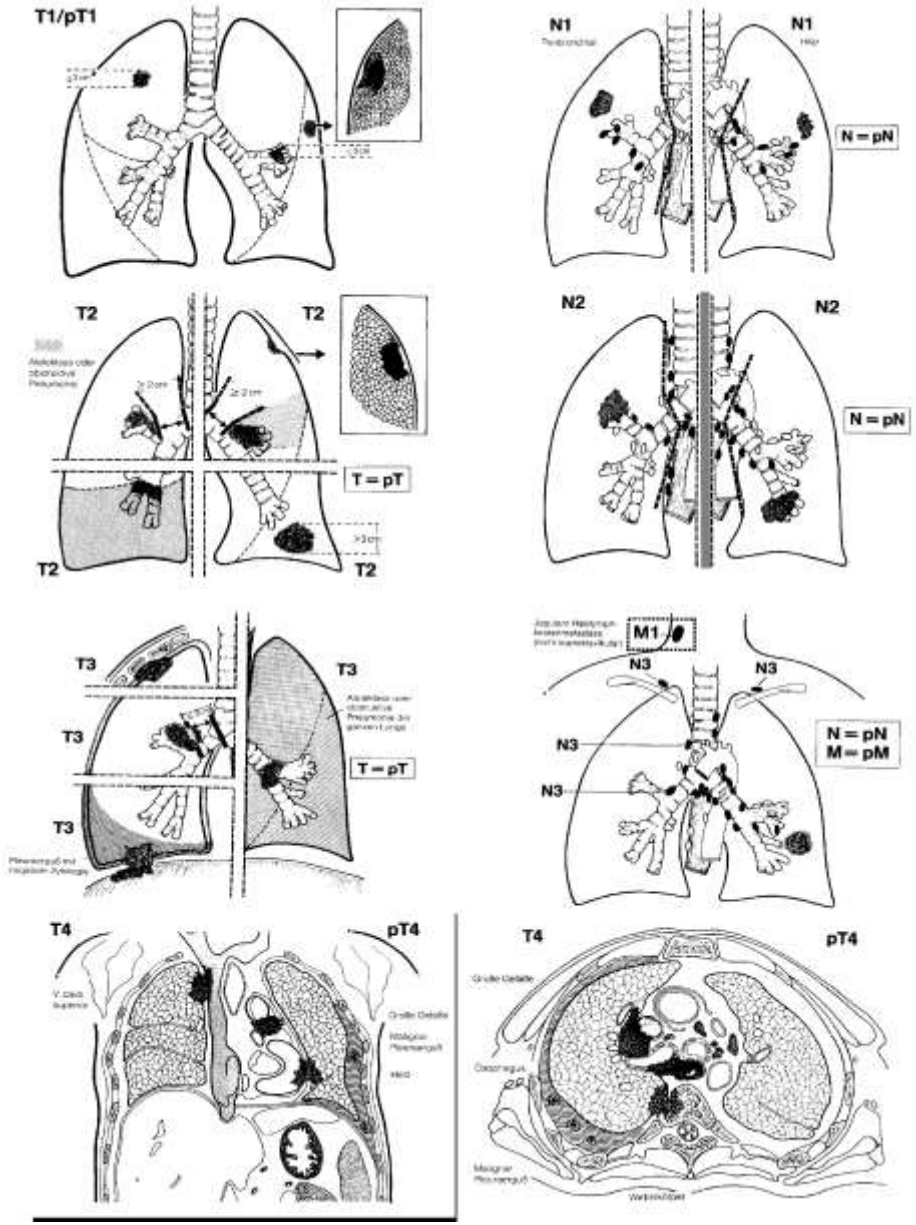
Francisco Arvelo,[1,2] Felipe Sojo,[1,2] and Carlos Cotte[2]:
Tumour progression and metastasis Ecancermedicalscience. 2016; 10: 617.

Stadienabhängiges Überleben Kaplan Meier



Survival rates for 3,043 patients after resection of lung cancer according to postoperative stage

Beispiele zur TNM Klassifikation



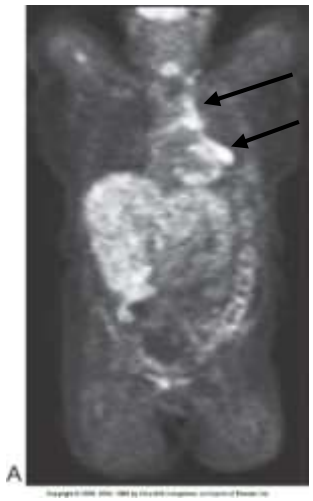
Bronchialkarzinom

<u>Diagnostik:</u> Staging zur Klärung der Operabilität

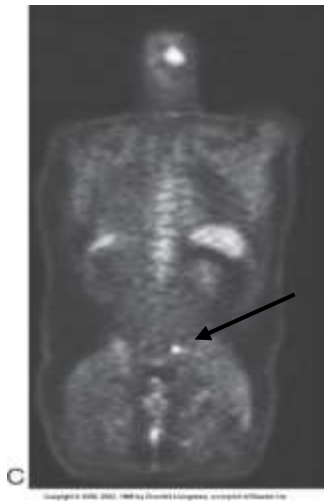
Ausschluß von Fernmetastasen **(kontralat. Lunge, Knochen, Leber, Hirn, Nebenniere)**

Beurteilung des Lymphknotenstatus **(N3 Lymphknoten)**

Bei Fernmetastasen / N3 LK (Stage IIIb) hat der Patient von einer operativen Therapie keinen prognostischen Vorteil



Befall mediastinale LK



Knochenmetastase OS Sacrum

CT: -Schädel, -Thorax, -Abdomen

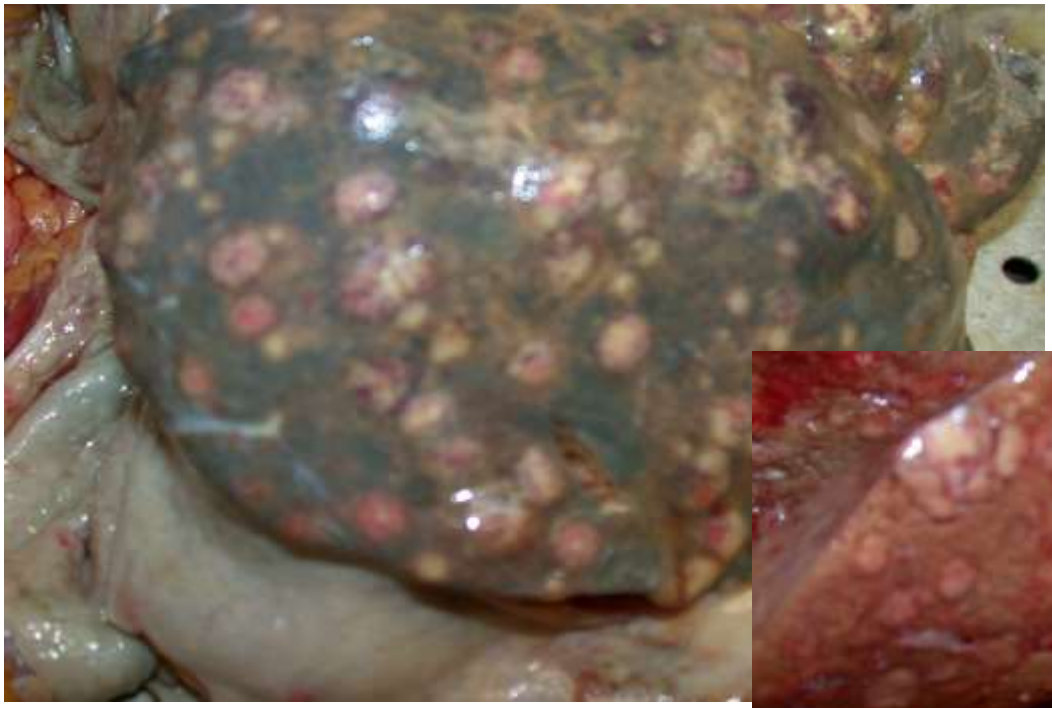
Skelett-Szintigraphie

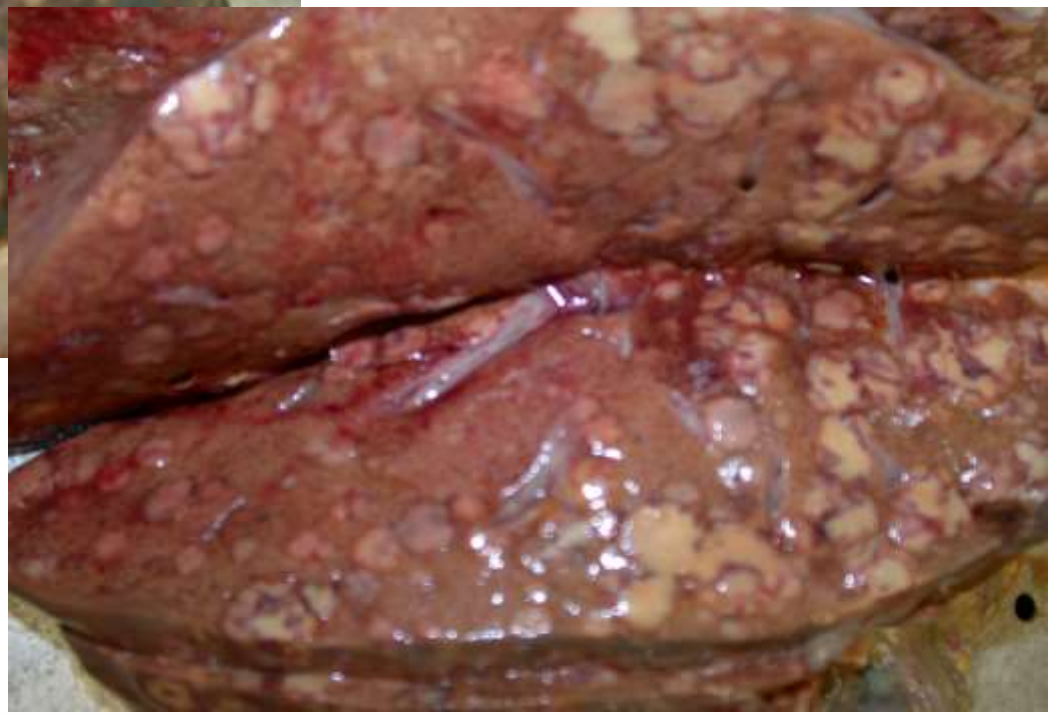
PET/CT

EUS

Mediastinoskopie

Metastase





METASTASE

- 30 %- neuer Falle
- Todesursache in meisten Falle

Direkte Verbreitung in Körperraumen (pseudomyxoma peritonei)

Lymphatische Verbreitung (cc. und Sarkomen) – cave: Reaktive Lymphknote

Haematogen Metastase (Sarkomen und cc. /Niere/)

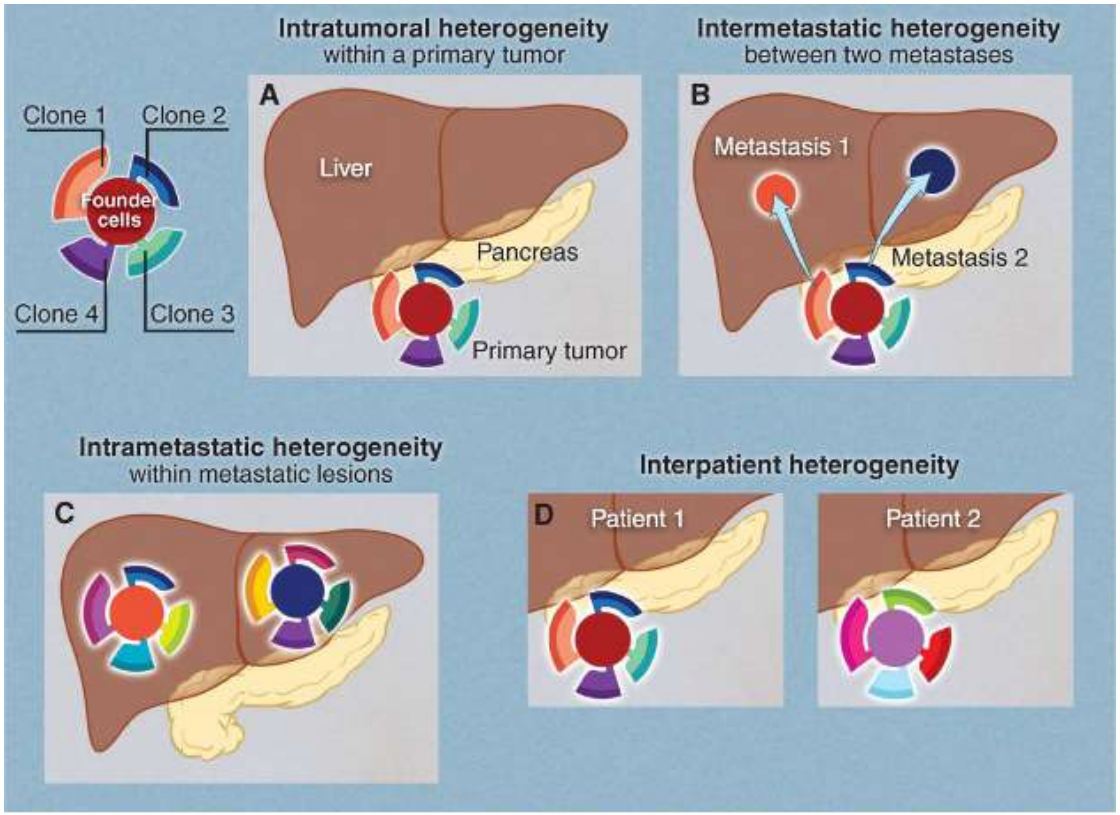


Fig. 6. Four types of genetic heterogeneity in tumors, illustrated by a primary tumor in the pancreas and its metastatic lesions in the liver

Mutations introduced during primary tumor cell growth result in clonal heterogeneity. At the top left, a typical tumor is represented by cells with a large fraction of the total mutations (founder cells) from which subclones are derived. The differently colored regions in the subclones represent stages of evolution within a subclone. (**A**) Intratumoral: heterogeneity among the cells of the primary tumor. (**B**) Intermetastatic: heterogeneity among different metastatic lesions in the same patient. In the case illustrated here, each metastasis was derived from a different subclone. (**C**) Intrametastatic: heterogeneity among the cells of each metastasis develops as the metastases grow. (**D**) Interpatient: heterogeneity among the tumors of different patients. The mutations in the founder cells of the tumors of these two

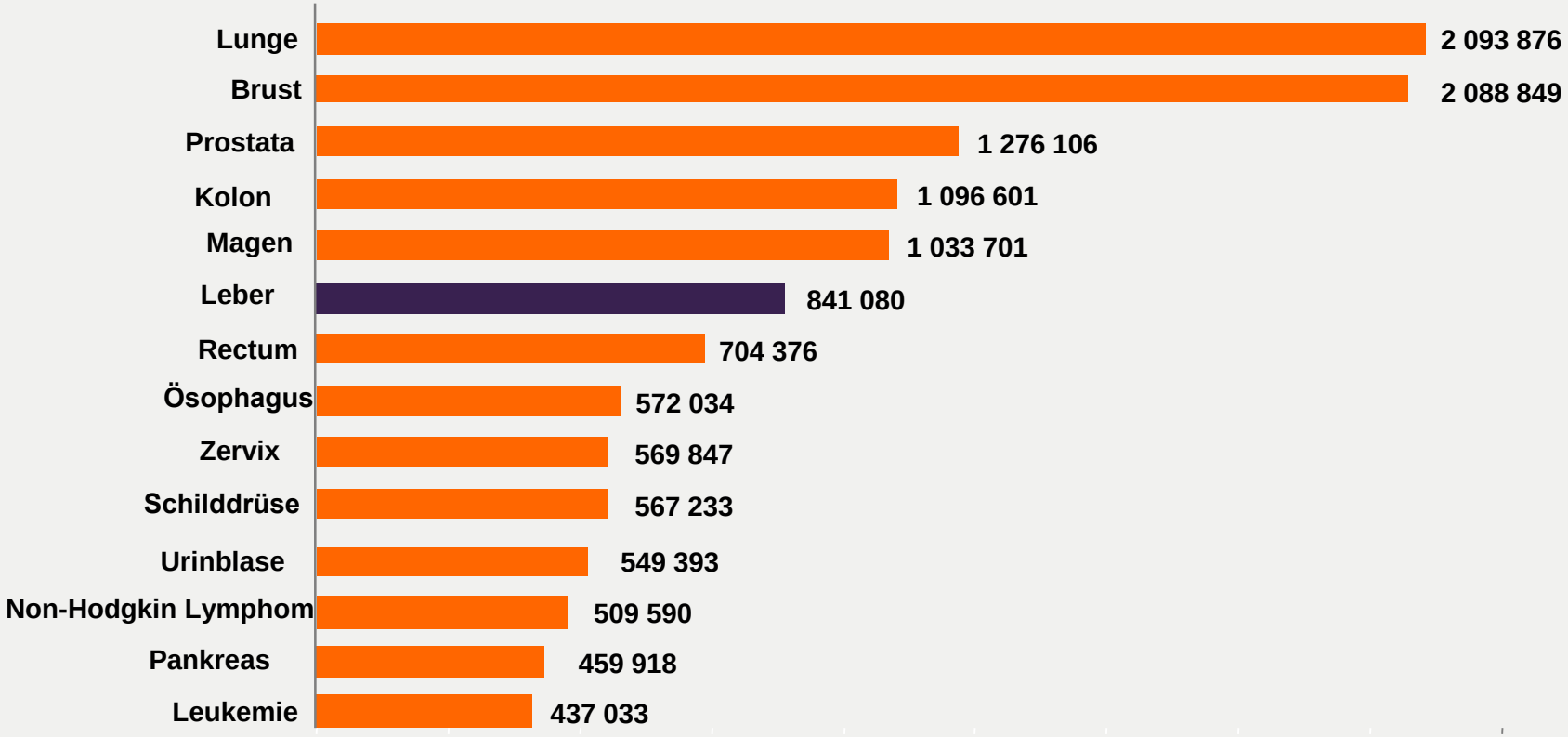
Ungarische Tumor Inzidenz- und Mortalitatsdaten verglichen in Europa (Ranking - 40 Lander)

Lokalization	Inzidenz Ranking	Mortalitat Ranking
Összes	10.	**1.**
Lunge	1.	1.
Colorektal	2.	1.
Brust	28.	18.
Prostata	27.	27.
Hamatologische und Lymphorgan Malignitaten	28.	11.
Lippe und oral	1.	1.
Urinblase	4.	9.
Niere	12.	15.
Pankreas	3.	1.
Magen	17.	15.
Larynx	1.	3.
Pharynx, nasopharynx	1.	1.

Quelle:
GLOBOCAN 2012
http://globocan.iarc.fr

Epidemiologie

(2018 geschatzte Daten)



Bray et al. CA Cancer J Clin. 2018 Sep 12. doi: 10.3322/caac.21492. [Epub ahead of print]

Haufigste Malignitaten

- Brustkrebs
- Bronchialkarzinom

Diese Malignitaten können:

- Lungenmetastase
- Lebermetastase
- Knochenmetastase
- Gehirnmetastase geben

(+ fast jede zweite Bronchialkarzinome metastasieren in Nebennieren)

Melanom kann überall metastasieren !!

Hauptwegen der Metastasen (Walther schemes, 1948 – „metastasis cascade”)

- Vena portae (gastrointestinal) Typ
- Vena hepatica (liver) Typ
- Vena cava Typ
- Vena pulmonalis (Lunge) Typ
- Durch die Batson Venen (paravertebral)

Metastasenbildung

- **Lymphogene**: im allgemeine Karzinomen
  - Ductus thoracicus: hämatogen Dissemination
  - Virchow Lymphknoten

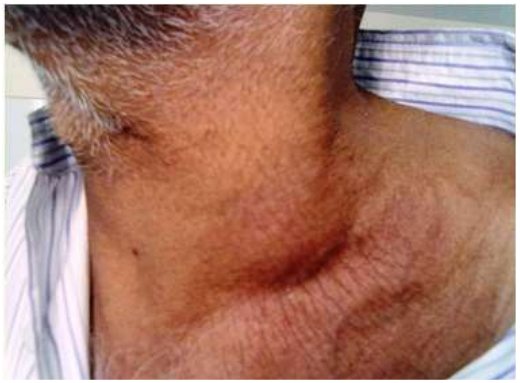


Fig. 1. links supraklavikulär vergrösserte LK

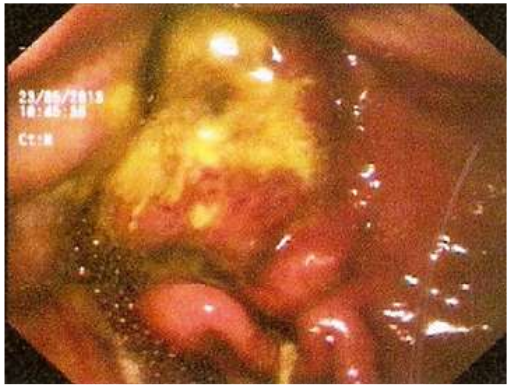
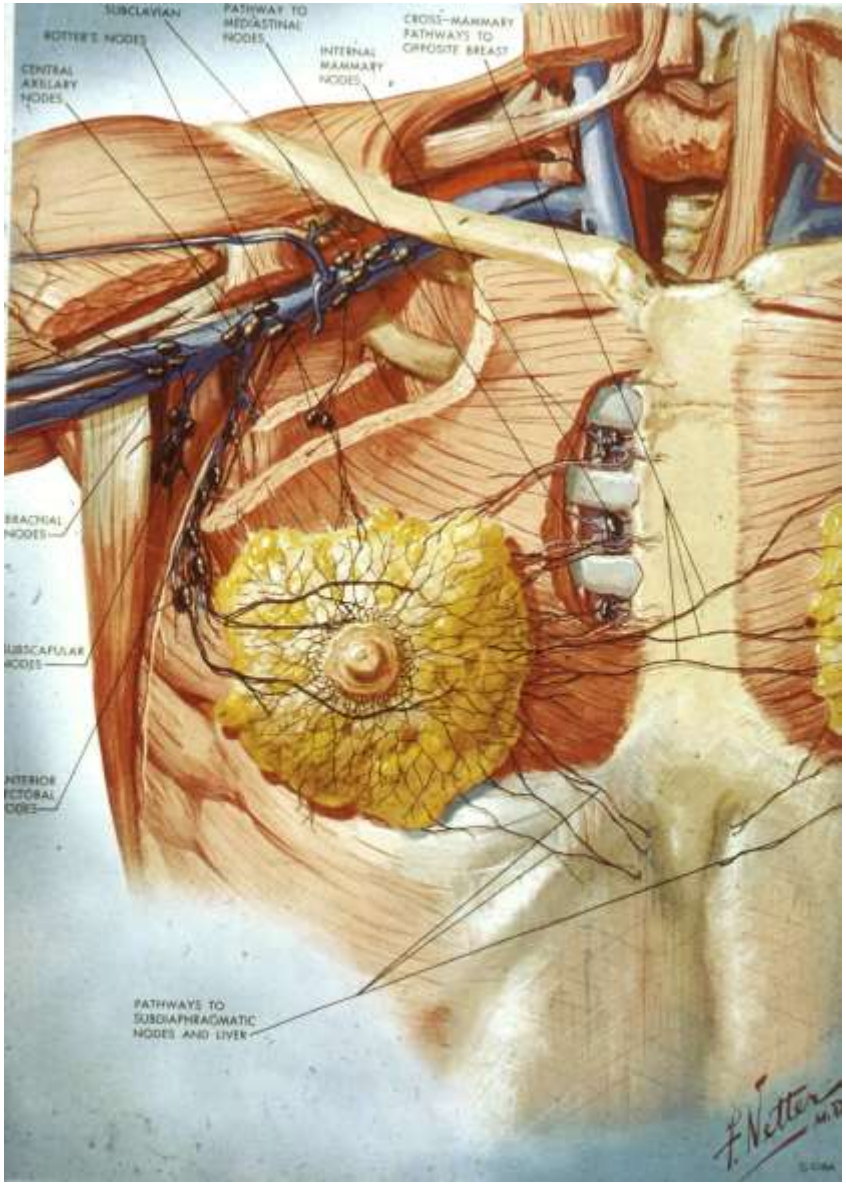


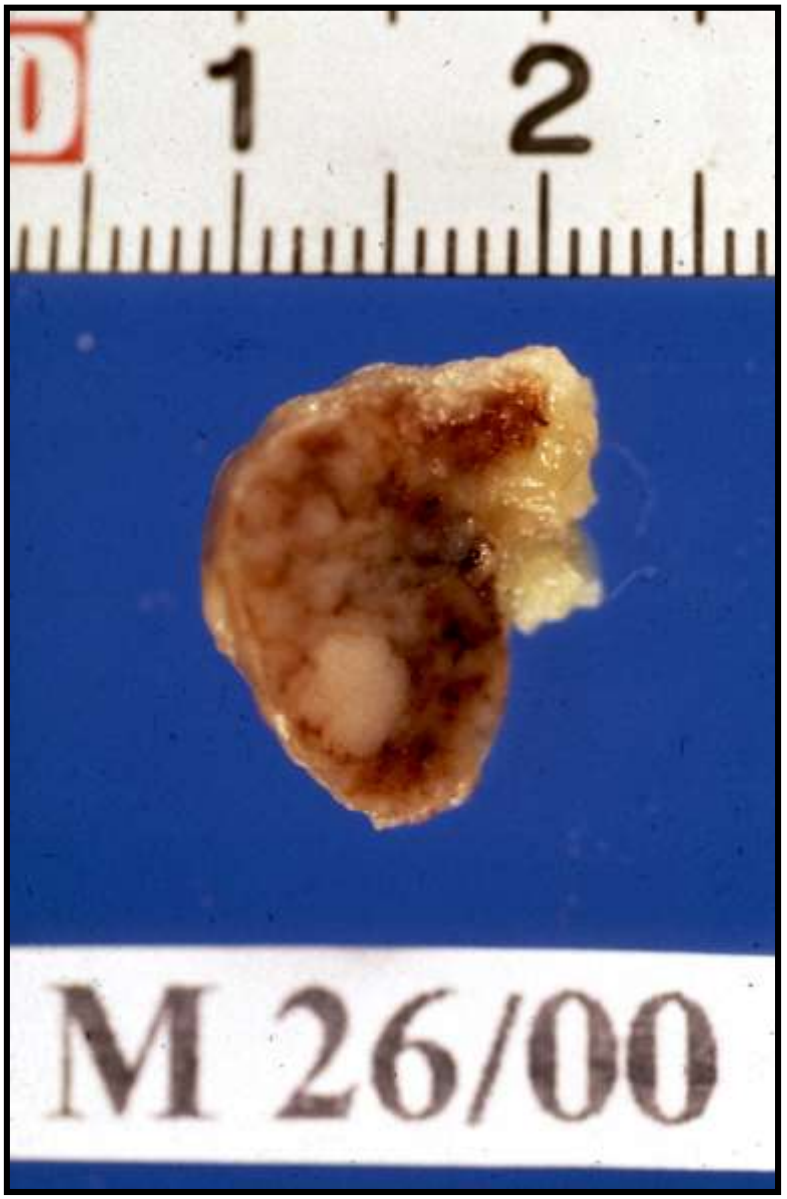
Fig. 2. oberer Gastrointestinaltrakt Endoskopie

A 57-year-old man presented to us with epigastric pain, decreased appetite, weight loss (8 kg) for 2 months prior to presentation. He noted a lump on the left side of the neck for 15 days. He was a chronic smoker, smoking two packs of bidi per day for about 20 years. On examination, he had a 3.5×4 cm, firm, non-tender lump in the left supraclavicular region between the two heads of the sterno-cleidomastoid muscle, that is, Virchow's node (figure 1). Systemic examination was normal. An upper gastrointestinal (GI) endoscopy revealed an ulceroproliferative growth in the antrum (figure 2). A histopathological examination following the biopsy was consistent with adenocarcinoma.

  - Wächterknoten (sentinel)

- **Hämatogene**: im allgemeine Sarkomen
  - Karzinomen auch: Lunge, Mamma, Niere, Prostata, Schilddrüse


SUBCLAVIAN
PATHWAY TO MEDIASTINAL NODES
CROSS-MAMMARY PATHWAYS TO OPPOSITE BREAST
INTERNAL MAMMARY NODES
CENTRAL AXILLARY NODES
PATHWAYS TO SUBDIAPHRAGMATIC NODES AND LIVER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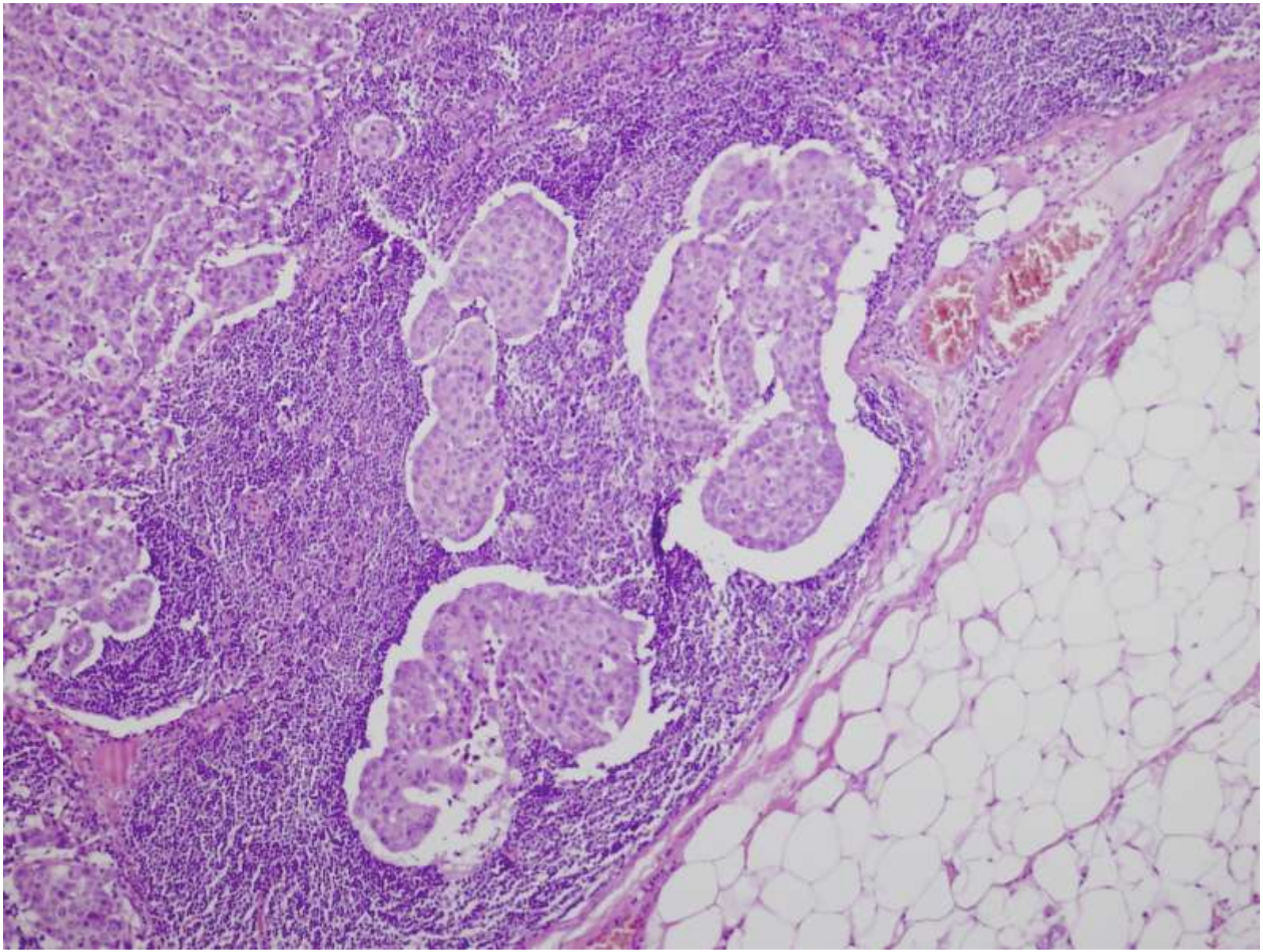

Sentinel (Wache) Lymknoten

- 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

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

A Randomized Clinical Trial

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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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nagement of Axillary Lymph Node tastasis in Breast Cancer

ing Progress

ter Carlson, MD
. Wood, MD

IS MORE"—SO GOES THE ADAGE, AND THAT CER- nly has been the case for breast cancer. Forty years o, the standard treatment for this disease was the ilsted radical mastectomy, an aggressive opera- involved removal of not only the breast but also nt musculature and axillary lymph nodes. Better ding of breast cancer biology revealed that aggres- cal therapy alone was inadequate. As treatment s evolved away from extensive surgery, axillary de dissection (ALND) remained part of the treat- men to detect nodal disease. Axillary lymph node s were considered an indicator that systemic dis- resent, identifying a need for chemotherapy. with breast cancer have benefitted greatly from carefully performed randomized controlled trials. essive trial showed that less surgery was better, tcomes were the same and less surgical interven- ed in fewer surgical complications. In the first ma- the National Surgical Adjuvant Breast and Bowel NSABP) B-04 trial, which began in 1971, 1765 ith breast cancer were randomized into 3 treat- ps. Those with palpable lymph nodes were ran- o receive a Halsted radical mastectomy or a total ny (removal of the breast only without the under- cle or lymph nodes) along with regional radia- py. Women with breast cancer without palpable mph nodes were randomized into 1 of 3 study alsted radical mastectomy with ALND, total mas- ith regional radiation treatment, or mastectomy h delayed ALND if nodal recurrences were ob- ere was a 40% incidence of occult nodal metas- e radical mastectomy group. Despite an axillary failure rate of 19% in the total mastectomy group, al was similar between the groups after 25 years up.[2] In general, women with clinically palpable mph nodes had worse survival than those with- ally evident lymph nodes. Local treatment of oc- r in axillary lymph nodes had no effect on over- al.

p 569.

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[3] 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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METASTASE MUSTER / TYP
VERSCHIEDENE ORGANE mit VERSCHIEDENEN FERNMETASTASENLOKALISATIONEN

v. Cava-Typ: (venös)

- **Primärtumoren die venös von v. cava versorgt** sind – metastasieren **in die Lunge**, dann weiter Skelett, Gehirn, Leber und Milz. Pfortadertyp ***Lebermetastasen können auch weiter in die Lunge metastasieren***.

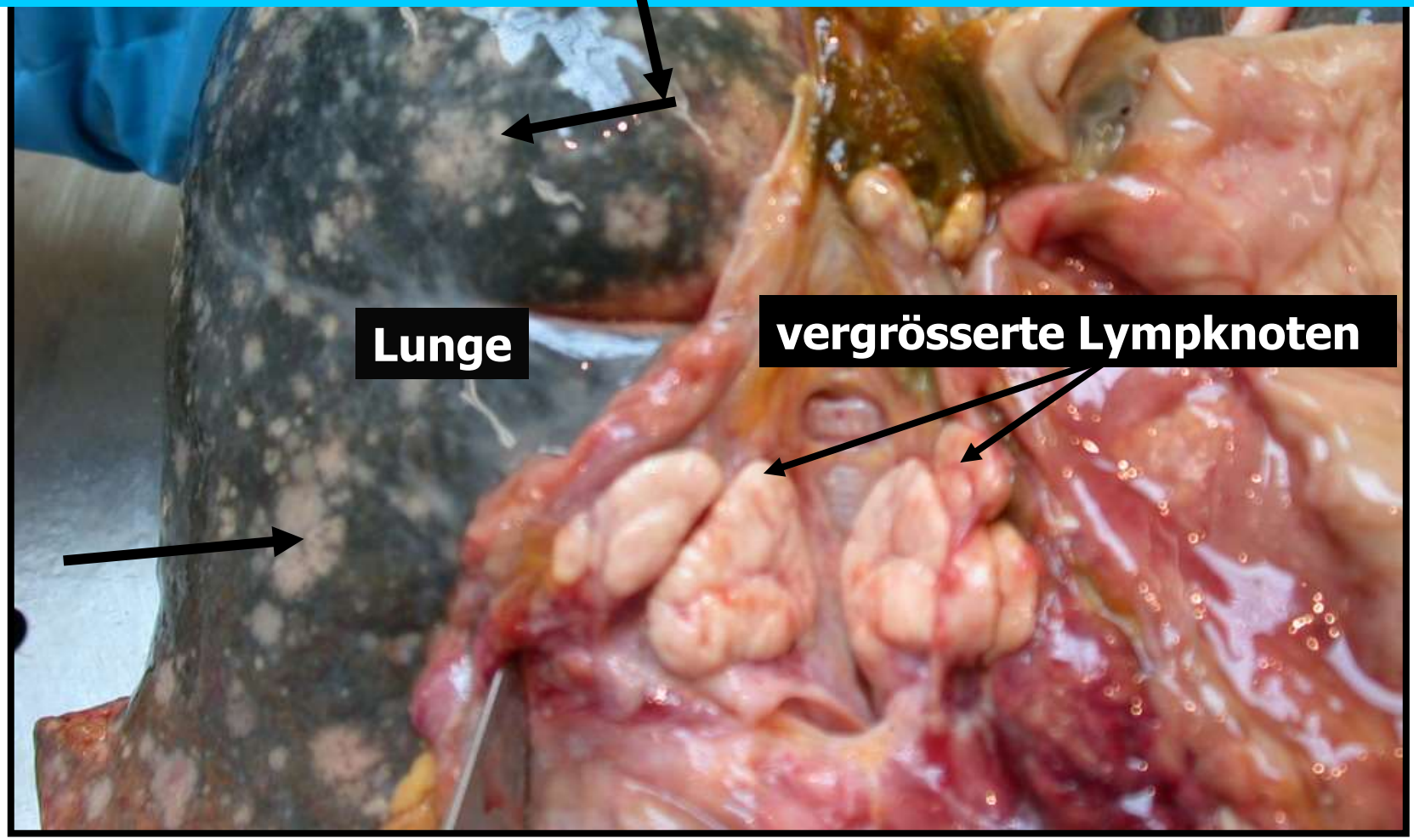
Lungen Typ: (arteriell): Lungentumoren (primär oder sekundär) Metastasieren – ins Gehirn, in die Leber, in die Knochen

-

Pfortader Typ (v. portae Typ): (venös)

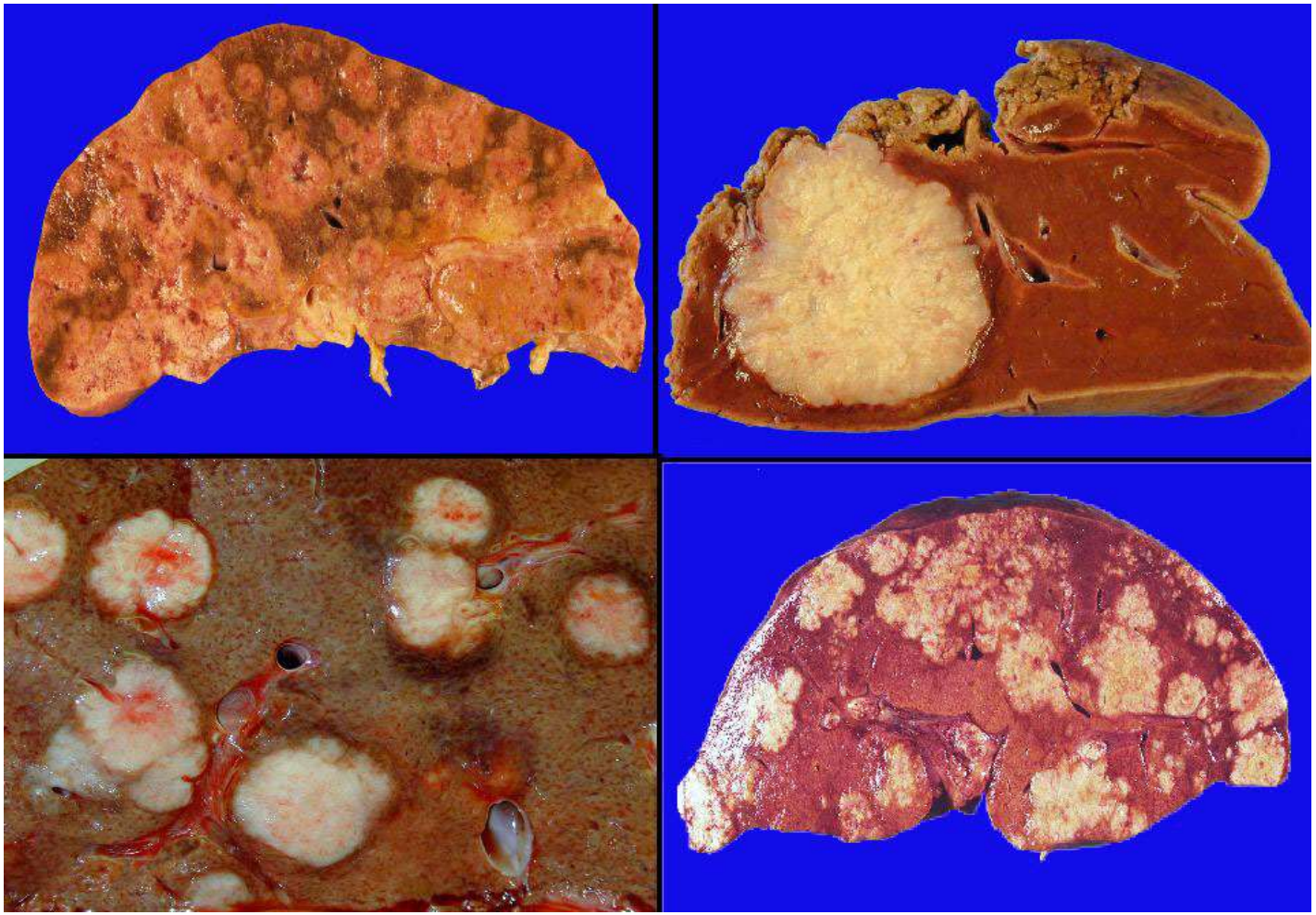
- Organe des Verdauungstraktes (untere Speiseröhre, Magen, Bauchspeicheldrüse, Dünn- und Dickdarm, oberer Teil des Rektums (Mastdarm) metastasieren erstmal **in die Leber**, dann Lebermetastasen können in die Lunge weitermtastasieren

v. cava Typ Metastase: Primartumor stammt from von der the venösen Sammelgebiet von V. cava: unterer Teil des Rectums, Nieren, Nebennieren, Uterus, usw.)



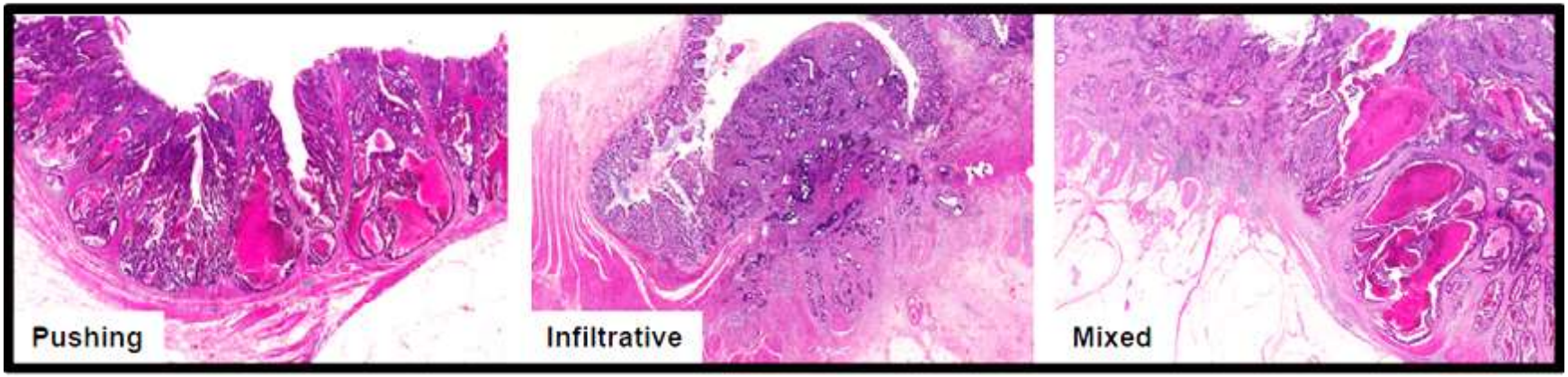
Vena portae (gastrointestinal) Typ der Metastasen

Primar bösartiger Tumor entwickelt sich in der gastrointestinalen Systeme (Magen, Dickdarm, Pankreas) und verbreitet sich durch („Fluss”) der v.portae und metastaziert in die Leber.



Auswertung des Wachstumsmusters

Tumor border configuration (10x)



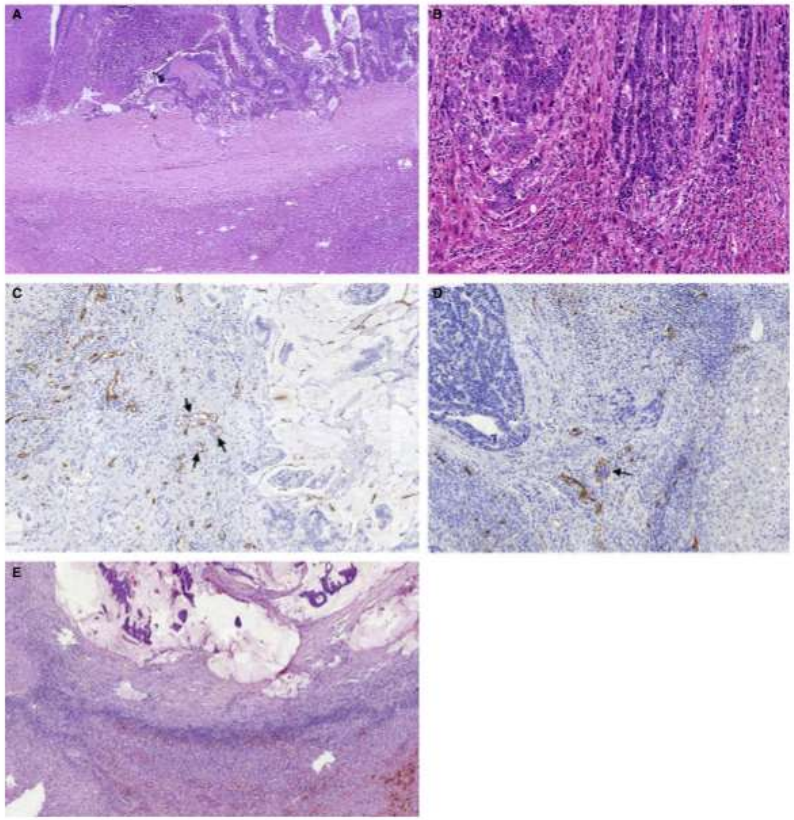
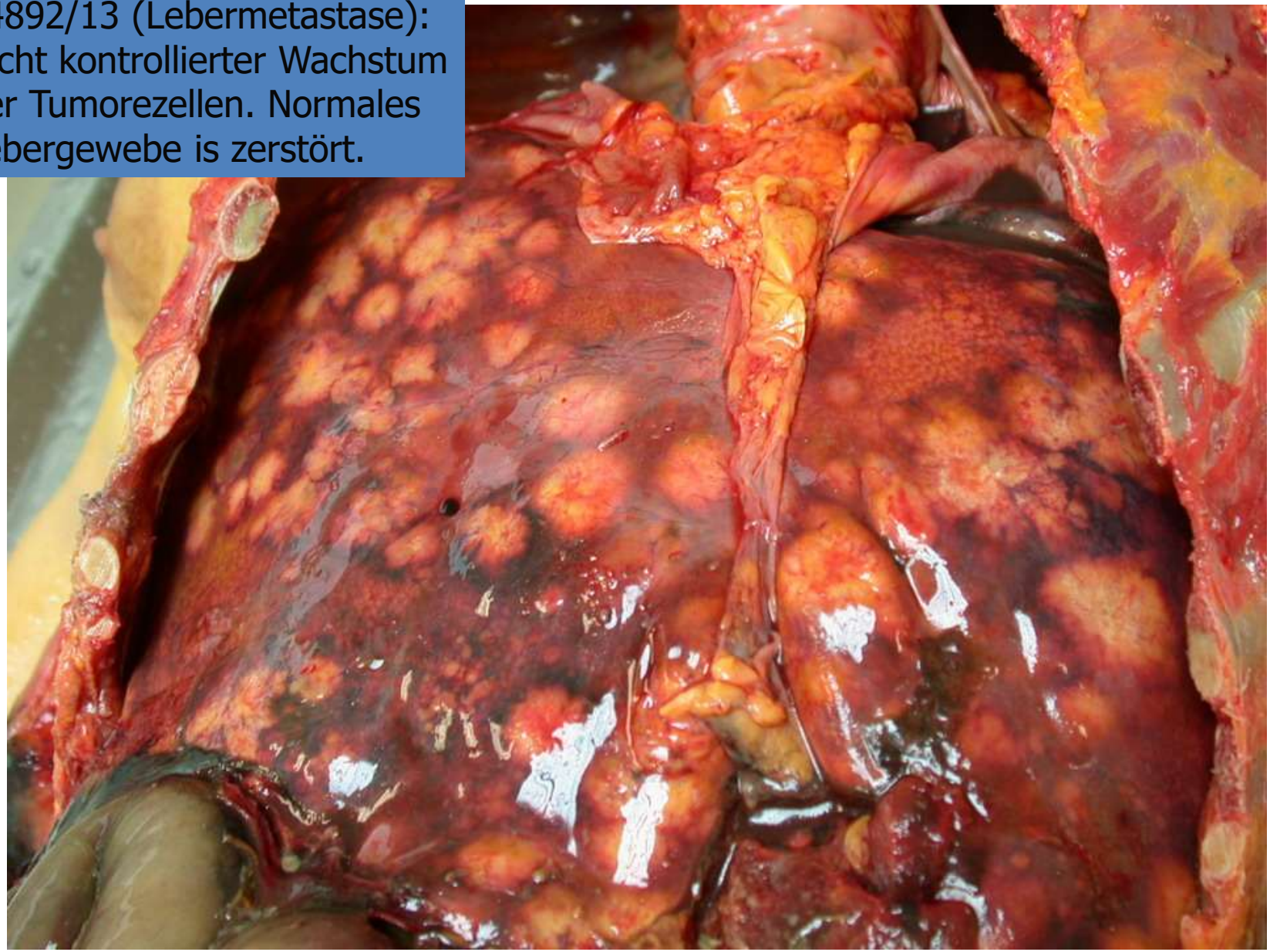


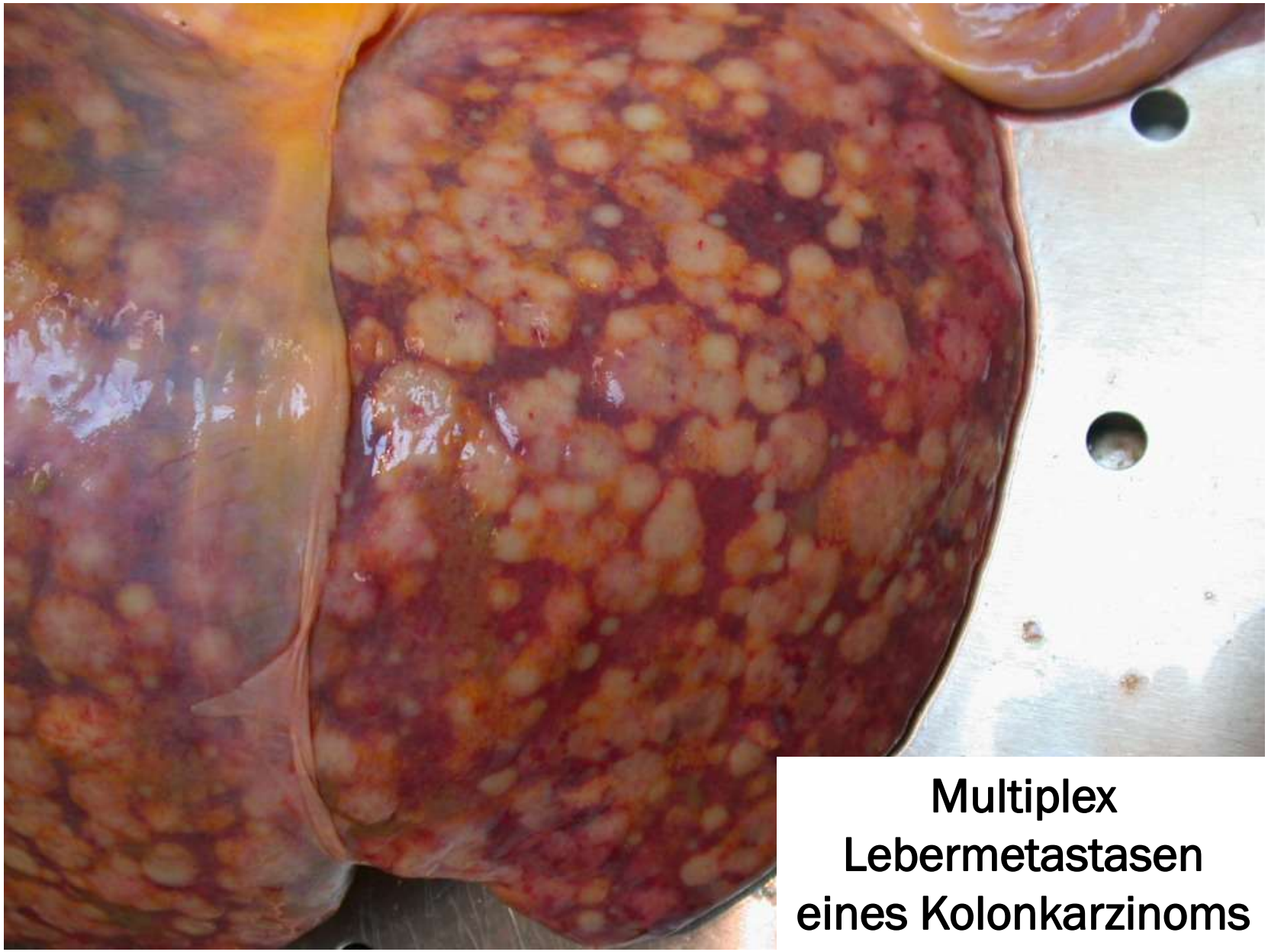
Figure 1. Illustration of histopathological findings in colorectal liver metastasis. A, A pushing growth pattern showing a thick fibrous pseudocapsule (haematoxylin and eosin). B, An infiltrative growth pattern characterised by tumour cells infiltrating the adjacent hepatic parenchyma (haematoxylin and eosin). C, Positive staining for CD34 in endothelial cells of blood vessels (arrow), demonstrating portal vein invasion. D, A cluster of tumour cells within the lumen lined by endothelial cells with immunoreactivity for D2-40 (arrow), characterising lymphatic invasion. E, Cancer cell clusters and malignant glandular structures floating in large mucin pools. Marked fibrosis and a dense inflammatory infiltrate can be seen in the periphery of the tumour (haematoxylin and eosin).

Biliary invasion

Yamamoto *et al.*[68] reported that biliary invasion among patients with CRLMs was associated with a higher incidence of recurrence after liver resection when the margin size was <2 mm. Paradoxically, Okano *et al.*[67,69] reported that macroscopic bile duct invasion was an independent favourable prognostic factor after

44892/13 (Lebermetastase): Nicht kontrollierter Wachstum der Tumorezellen. Normales Lebergewebe is zerstört.





Multiplex Lebermetastasen eines Kolonkarzinoms

weitere METASTASE MUSTER / TYP

VERSCHIEDENE ORGANE mit VERSCHIEDENEN FERNMETASTASENLOKALISATIONEN

Leber Typ: (venös)

- Lebertumoren oder Tumoren von der Leber metastasieren erstmal in die Lunge, dann es kann als Lungetyp weitere Metastasen geben

Paravertebral oder retrograd (venös)

- Durch Batson-sche paravertebrale Venen: von Nebenniere (Neuroblastom), Pancreas, Prostata: Knöchernes Becken, Wirbelkörper Schilddrüse: Wirbelkörper
- Abdominelle Druckerhöhung: retrograd Strom: Wirbel, Schulter, Schädel und Becken Knochen

Abklatsch, Abtropfen/Implantationsmetastasen:

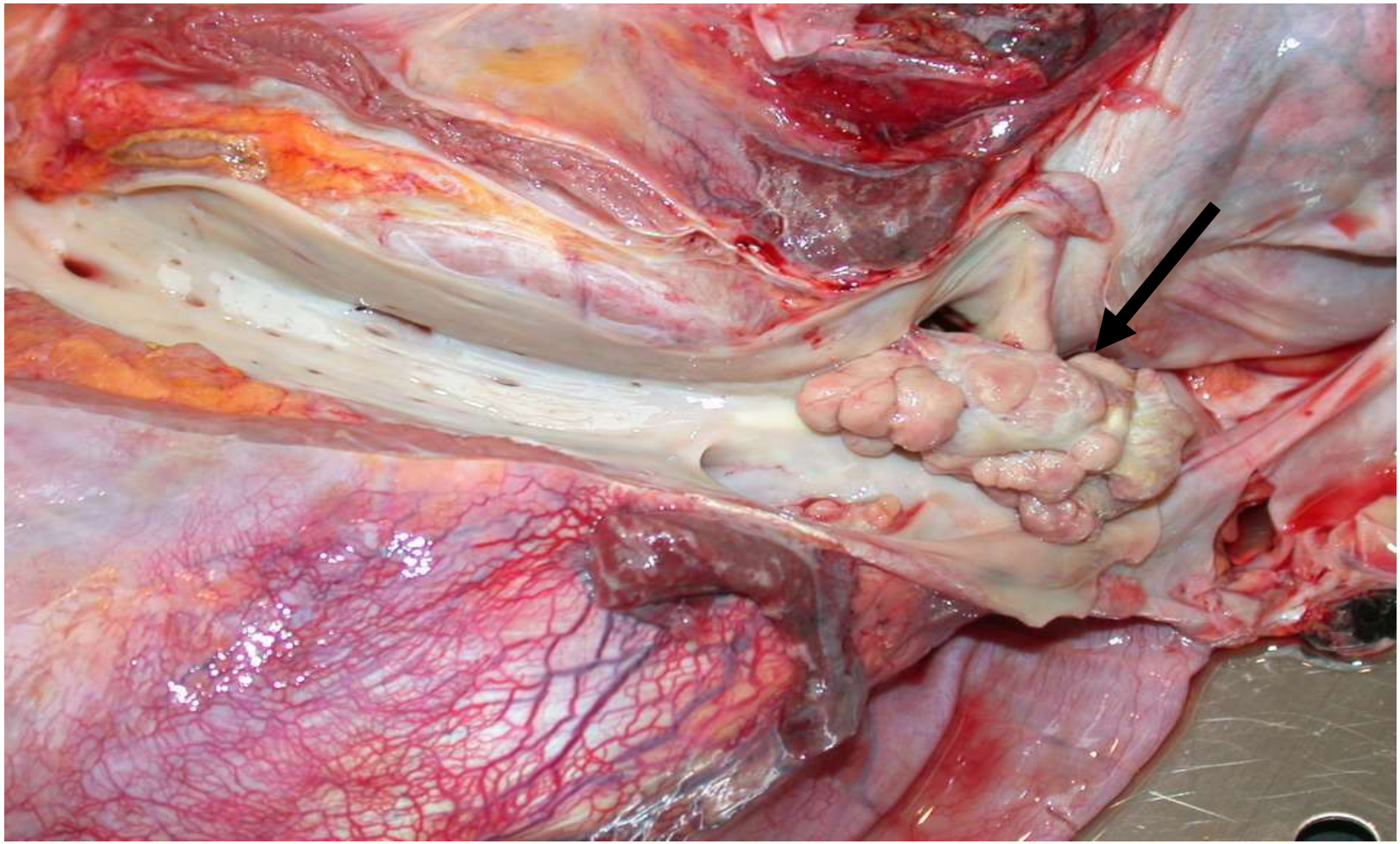
Peritoneum, Pleura

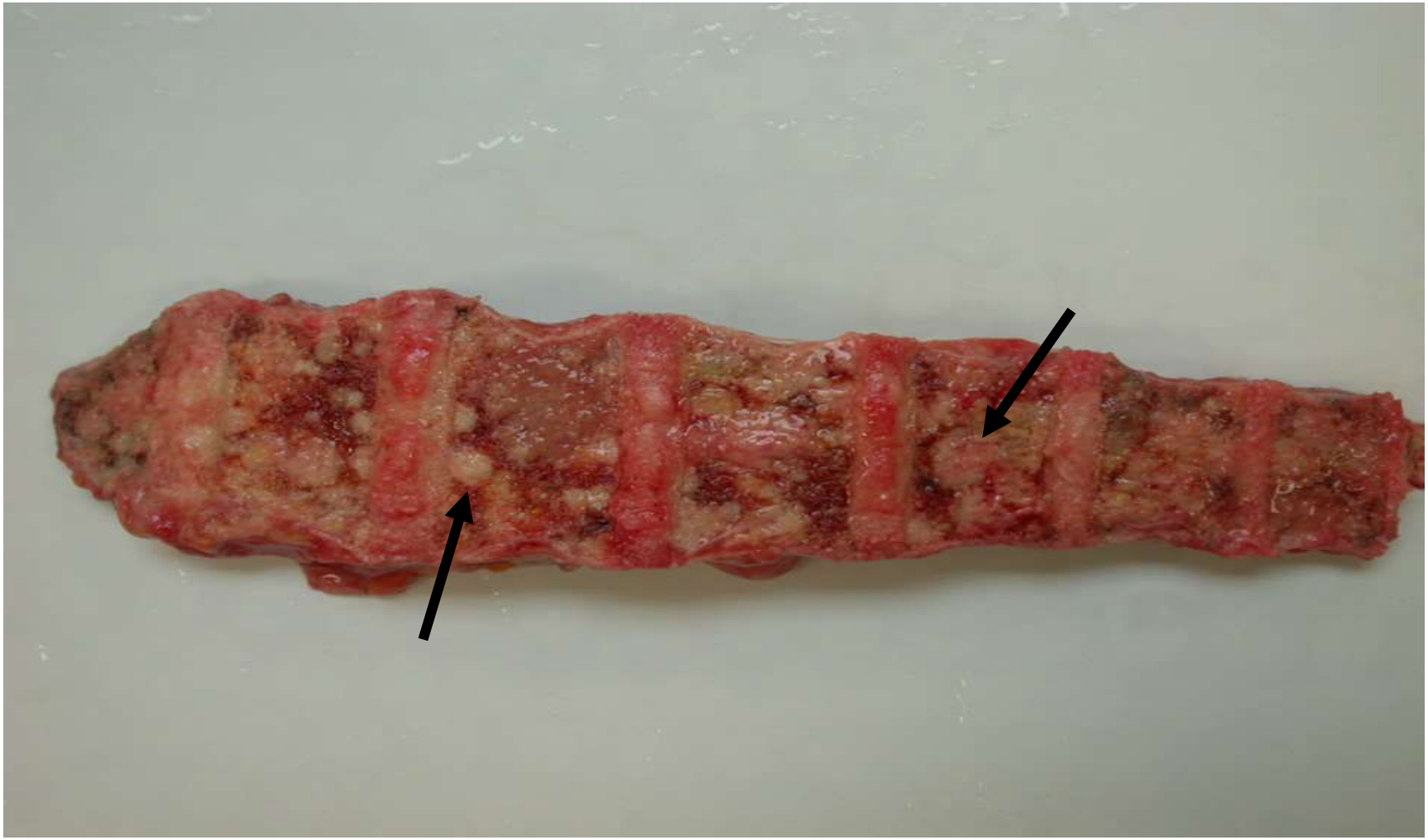
Krukenberg Tumor: (muzinöse Karzinome der Brust oder des Magens geben Ovarium Metastasen)

Kanalikulär: ZNS, Lumen

Haut: Hauttumoren (Mal. Melanom), Leukämien, Lymphomen

V.Hepatica (Leber) Typ Metastase. **Metastazierende Tumorzellen stammen (primar oder sekundar) von der Leber, brechen in doe V. hepaticae ein und strönebn in die V.cava und Metastase entwickelt sich in der Lunge.**

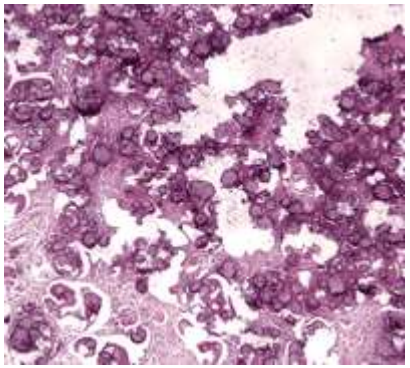


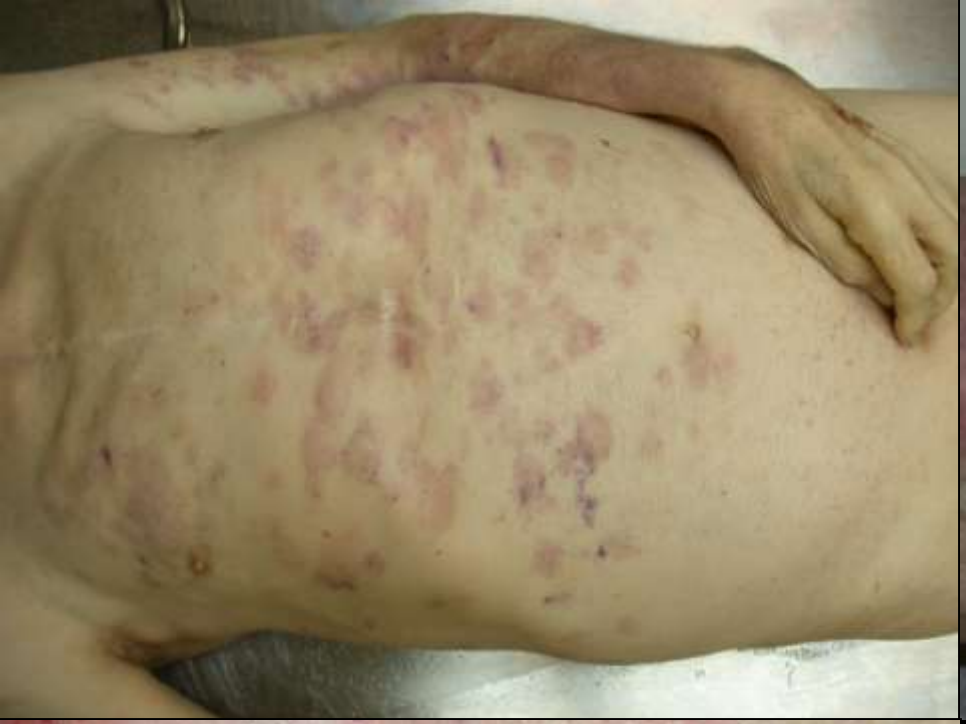


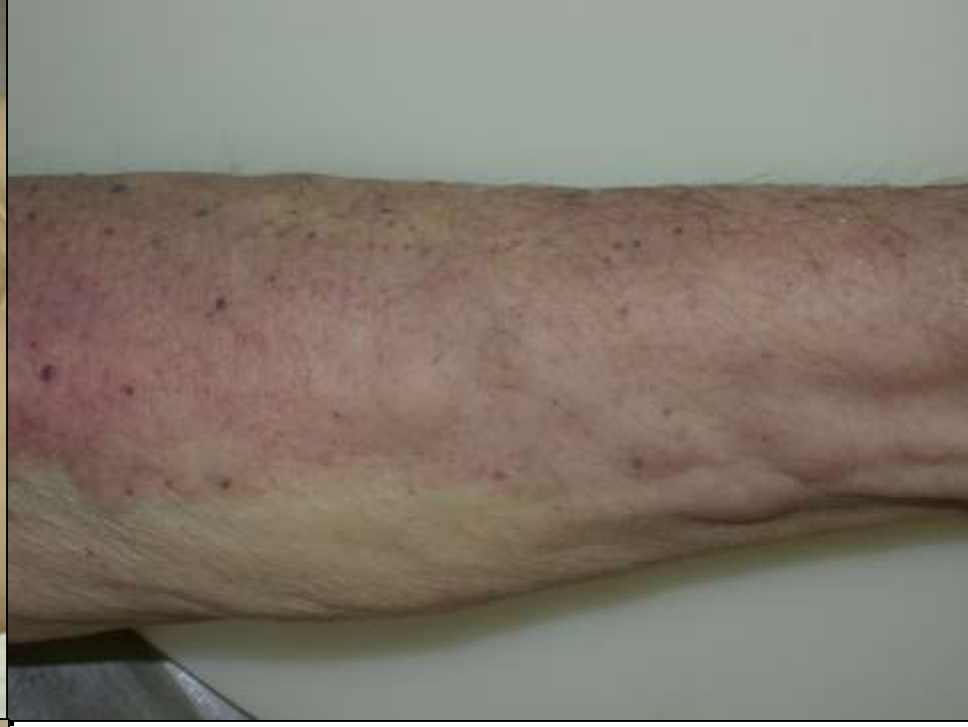
44800/02. Vertebrale Metastasen eines Prostatakarzinoms.

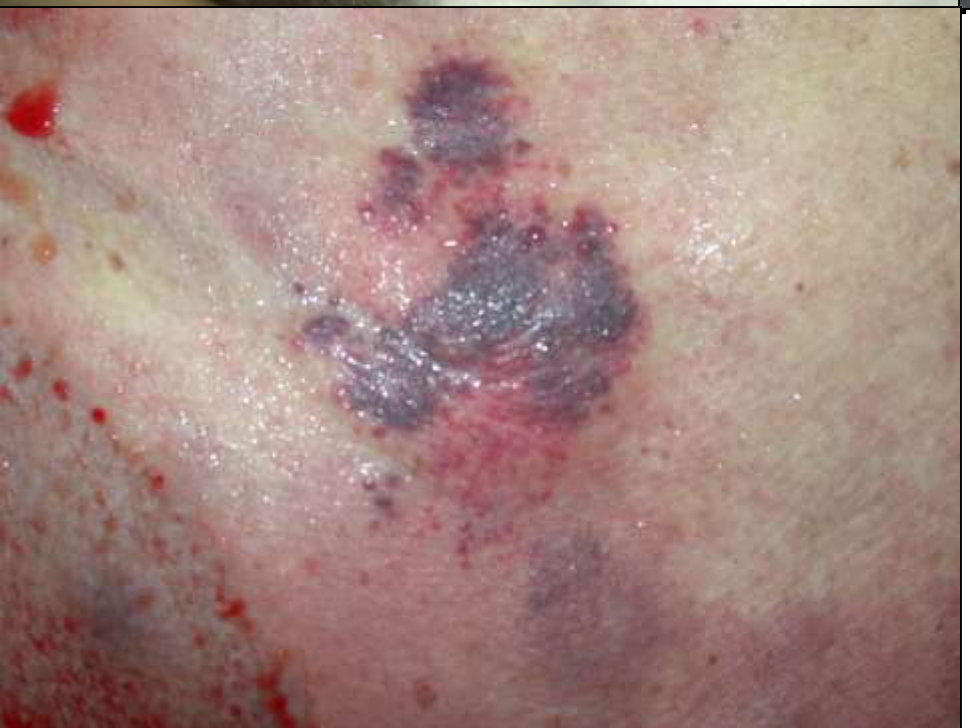
Tumoren die in der Nähe des Columna Vertebralis embolizieren häfig durch die paravertebrale Plexen

Ovar Karzinom



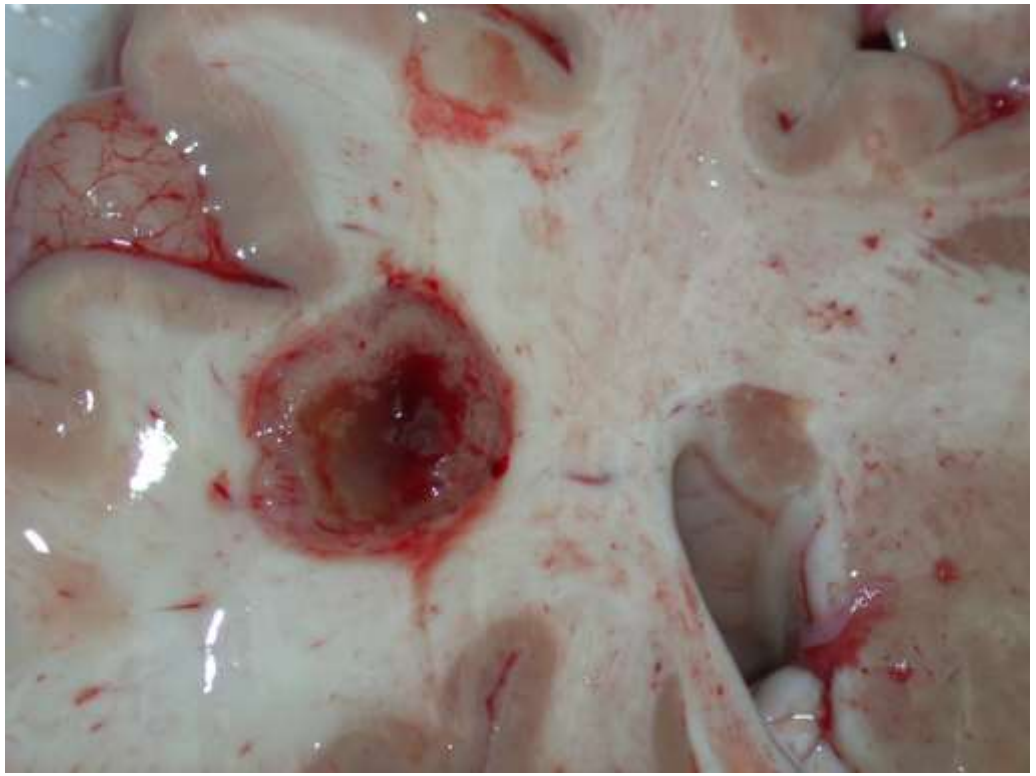






Nk zelliges Lymphom

GEHIRNMETASTASE



LUNGE
MAMMA
MALIGNES MELANOM

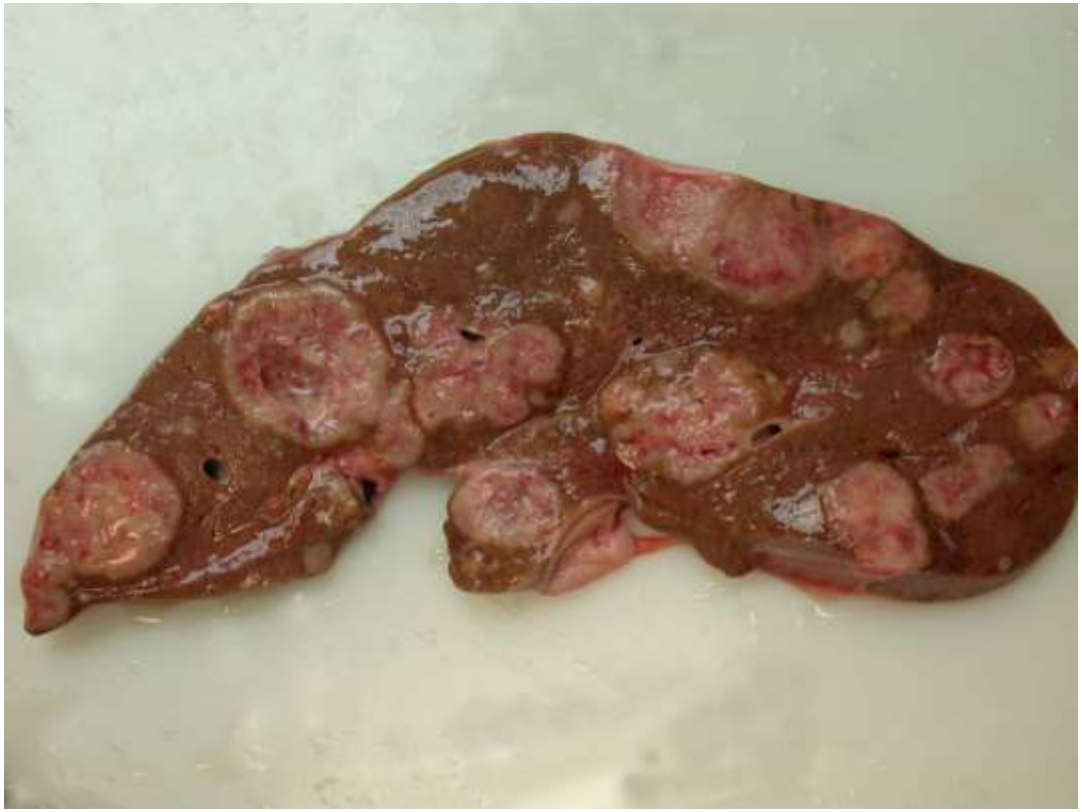
Primär Gehirntumoren geben niemals extrakraniale Metastase!

KNOCHENMETASTASE

LUNGE –
MAMMA –
SCHILDDRÜSE –
PROSTATA –
NIERENZELL K.

Prostata Karzinoma gibt Wirbelmetastase durch die Batson Venen.

LEBERMETASTASE



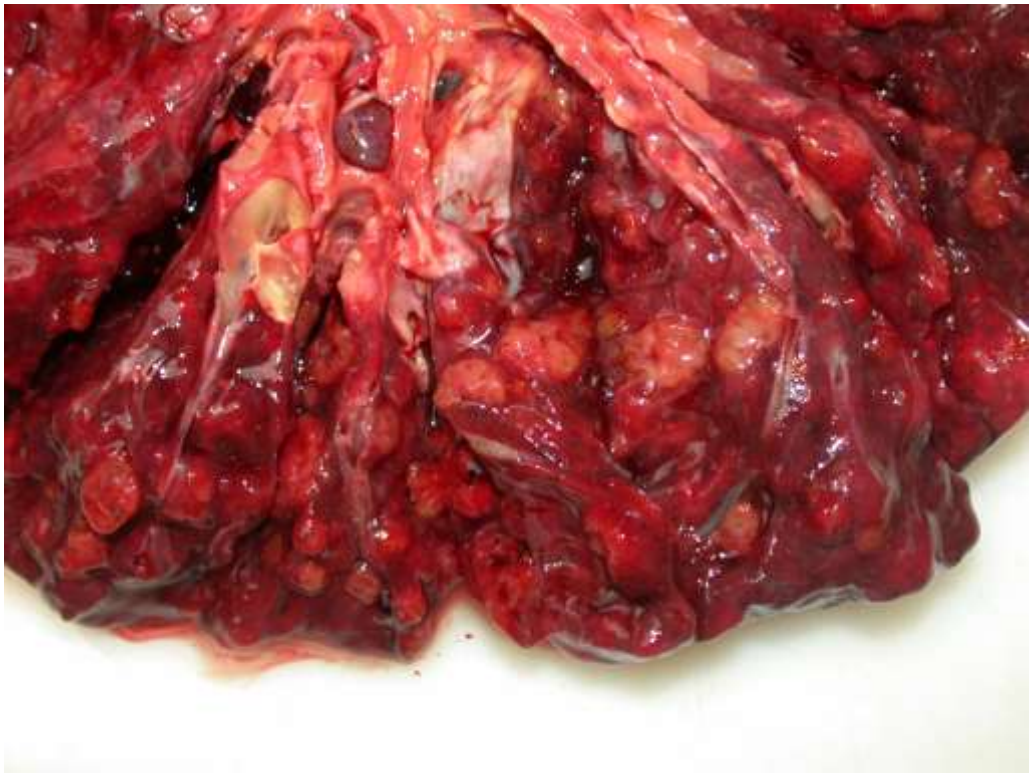
GASTROINTESTINALE –
LUNGE –
MAMMA

MELANOMA

NEUROBLASTOMA

USW.

LUNGENMETASTASE



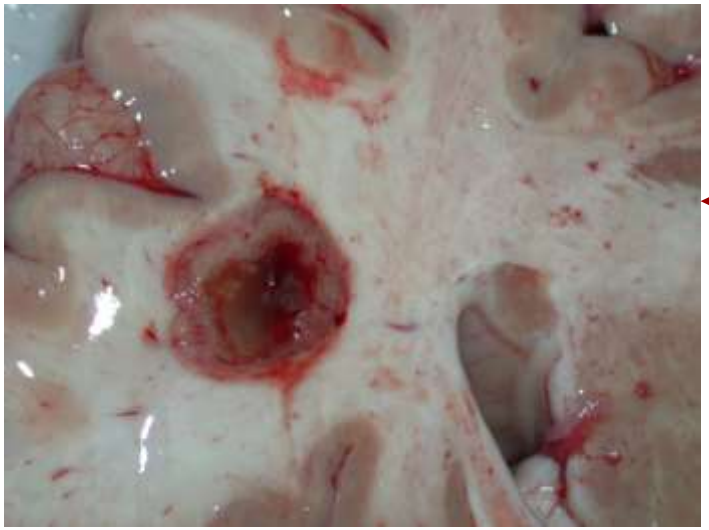
MAMMA –
LEBER –
NIERE -
REKTUM KARZINOM

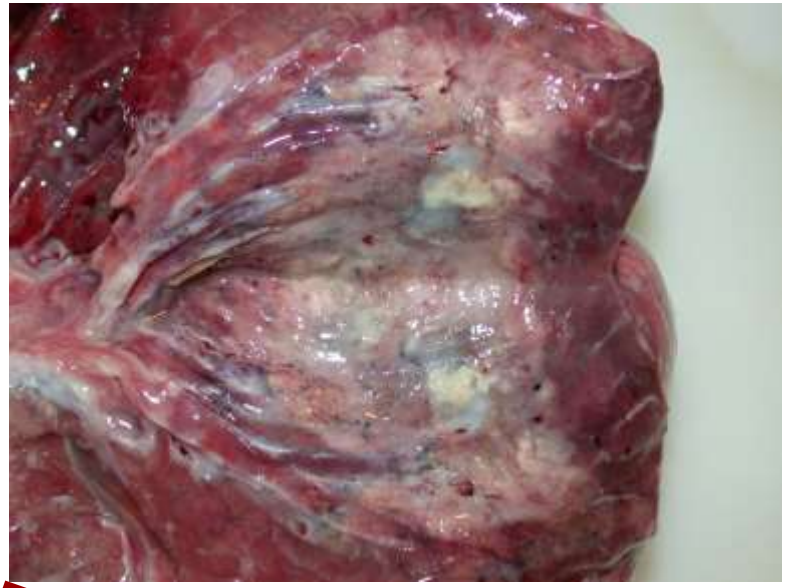
KEIMZELL TUMOREN

WEICHGEWEBSSARKOMEN

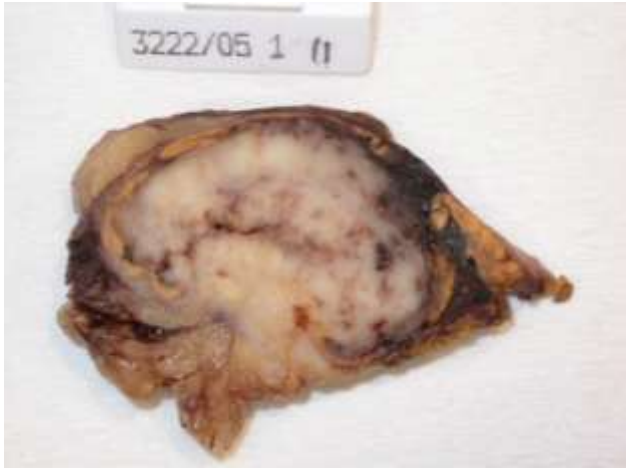
OSTEOSARCOM

ÜBERALL Lungentumoren

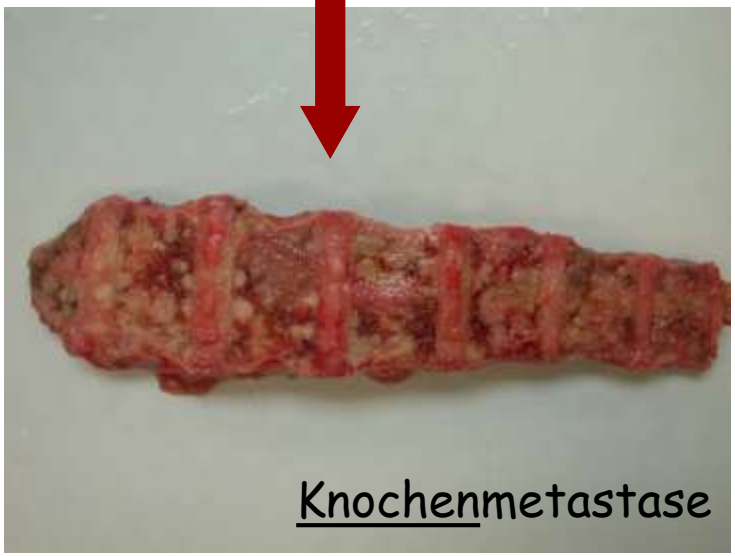




Gehirn Metastase

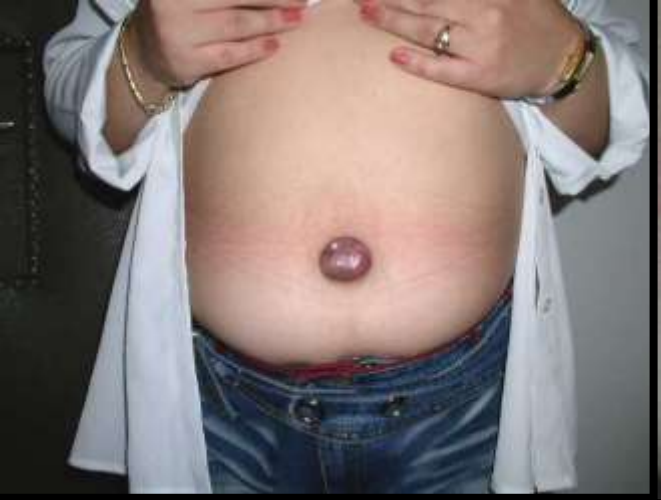


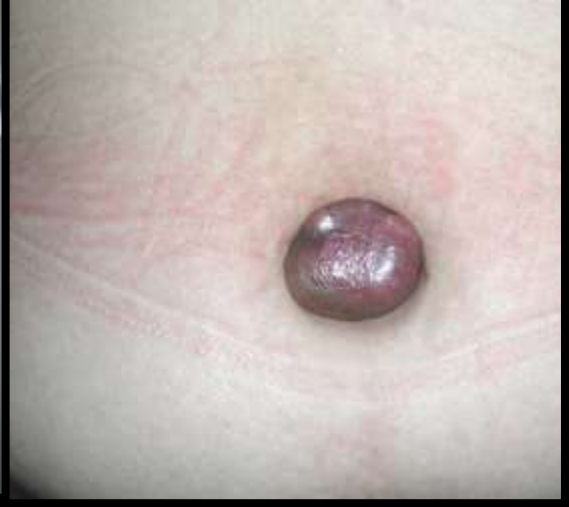
Leber Met.

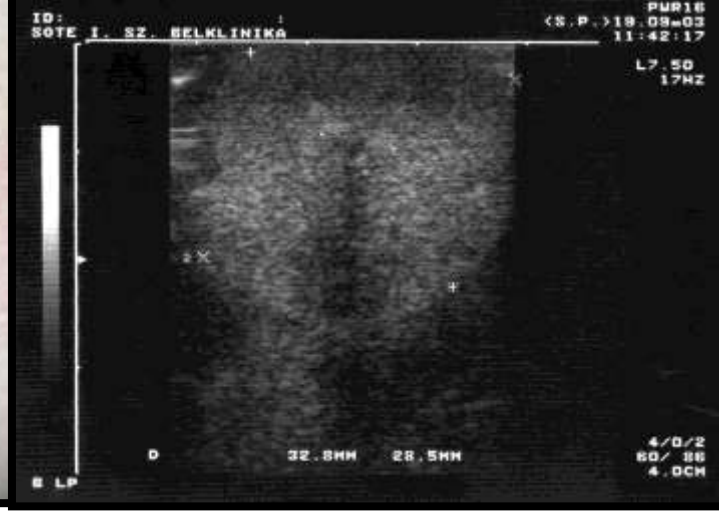


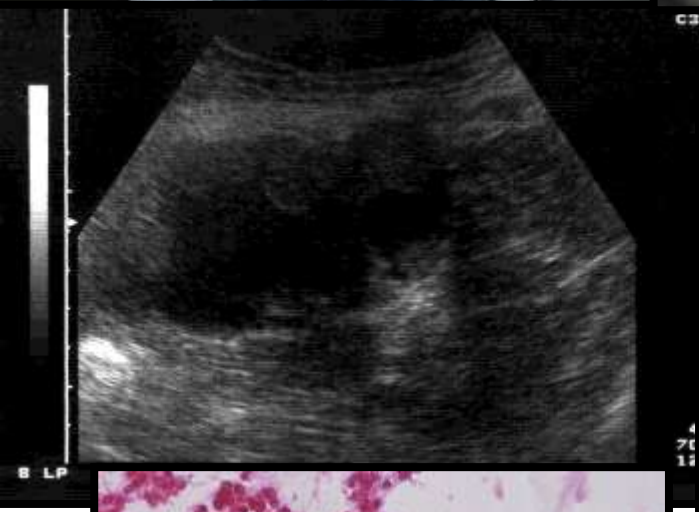
Knochenmetastase

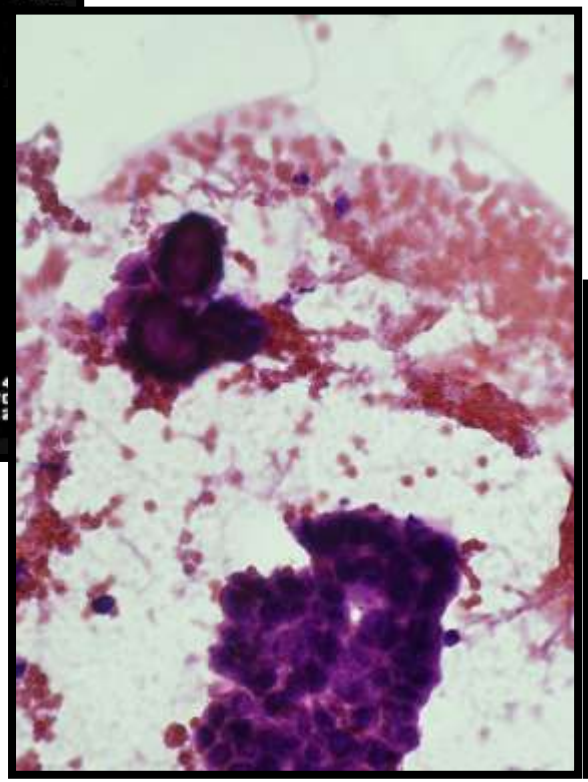
Beidseitige Nebenniere - Metastase

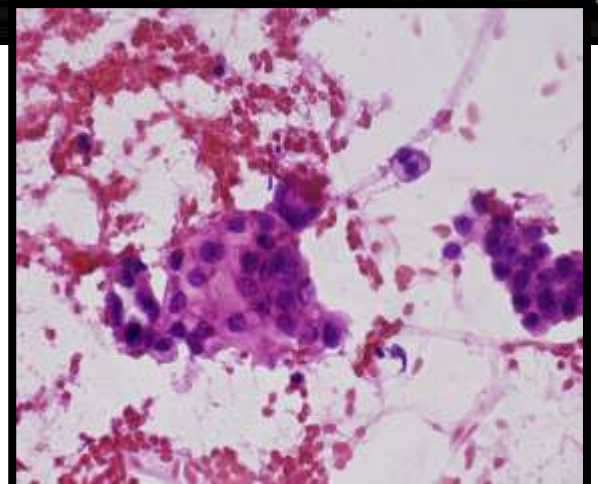


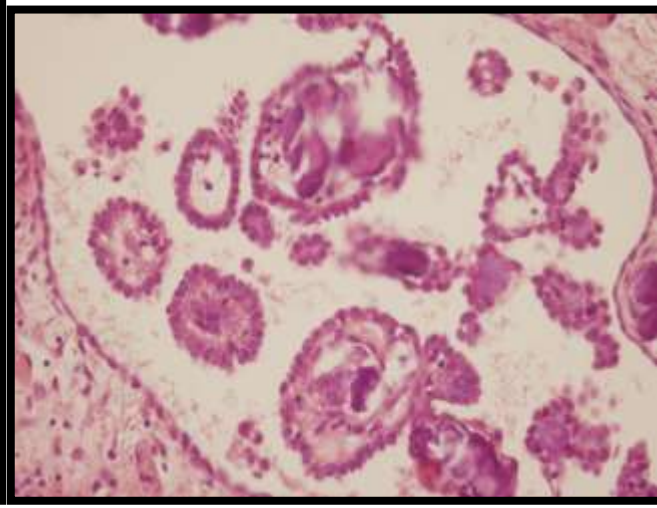












Sister Mary Joseph nodule - Nabelmetastase

- Gastrointestinale Tumoren
- Gynekologische Tumoren
- Karzinom bei unbekanntem Primärtumor
  - Unknown primary tumors (CUP)
- Urothelial Tumoren, Respiratorische Trakt

Transperitoneale Infiltratio

V. umbilicalis, lymphogen / hämatogen Weg

Sister Mary Joseph Dempsey (born Julia Dempsey; 1856-1939) was the surgical assistant of William J. Mayo at St. Mary's Hospital in Rochester, Minnesota from 1890 to 1915. She drew Mayo's attention to the phenomenon, and he published an article about it in 1928. The eponymous term Sister Mary Joseph nodule was coined in 1949 by Hamilton Bailey.

Danke für Ihre Aufmerksamkeit !