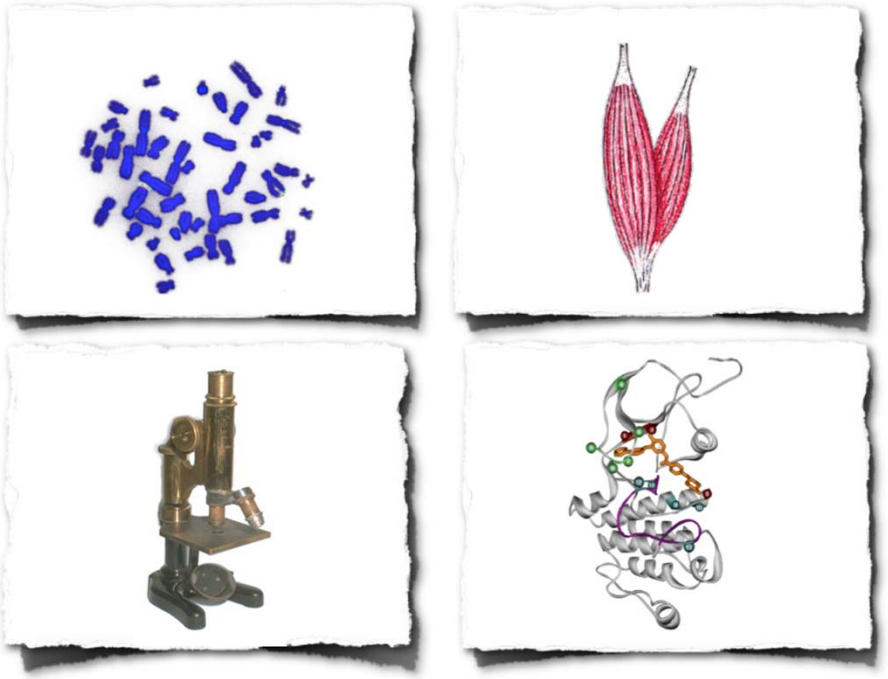
Maligne Weichteiltumoren – von der histologischen zur molekularen Klassifikation

Philipp Ströbel



Pathologisches Institut
Universitätsmedizin Mannheim

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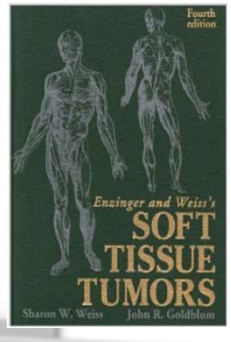
100 Jahre Sarkome

Albert C. Broders
Mayo Clinic

1925

Einführung des Tumor-Grading (CRC)

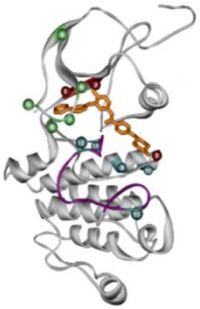


1983

Erstes wichtiges Textbook zu Sarkomen

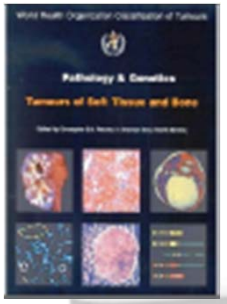
1984

FNCLCC grading (JM Coindre et al)



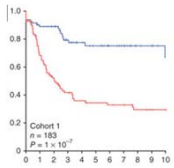
2001

Phase I Imatinib bei GIST (van Oosterom et al.)



2002

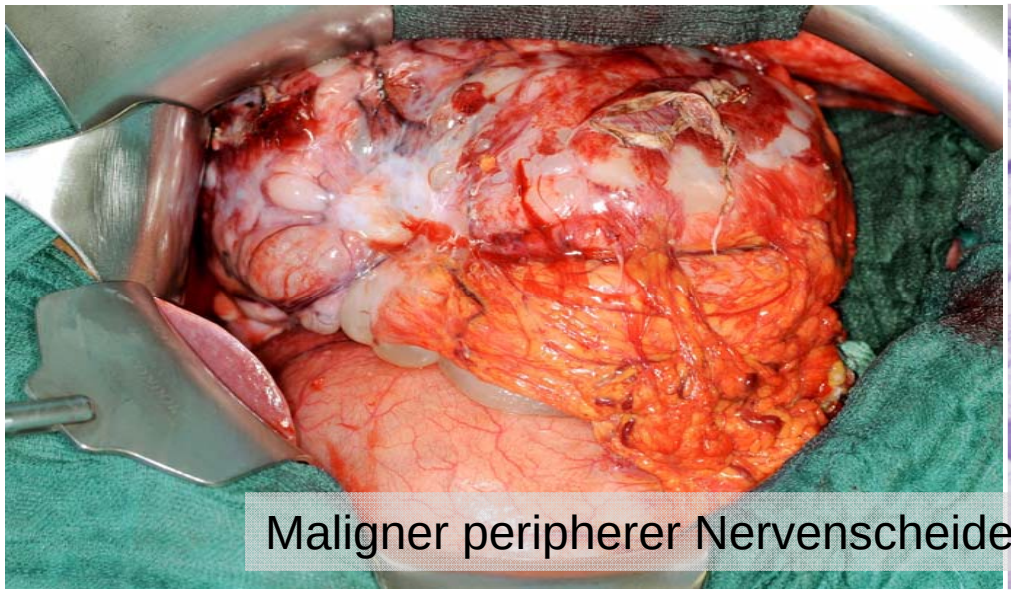
WHO Bluebook



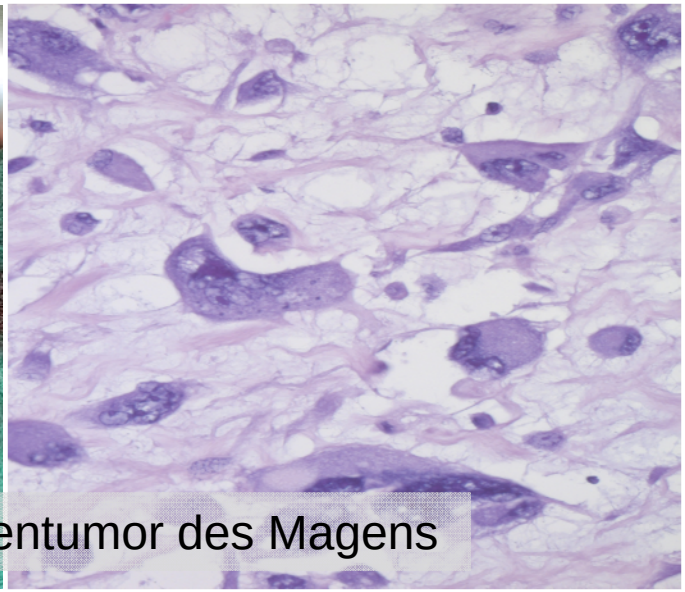
2010

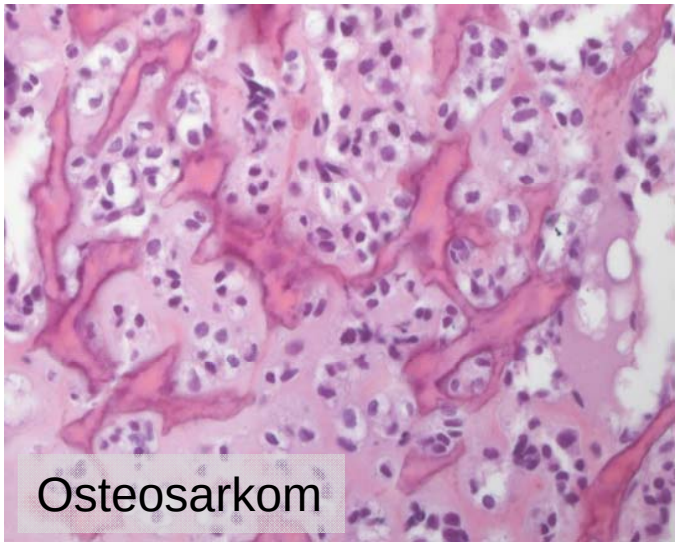
CINSARC Chibon et al.

Sarkome: maligne Tumoren der Binde- und Stützgewebe



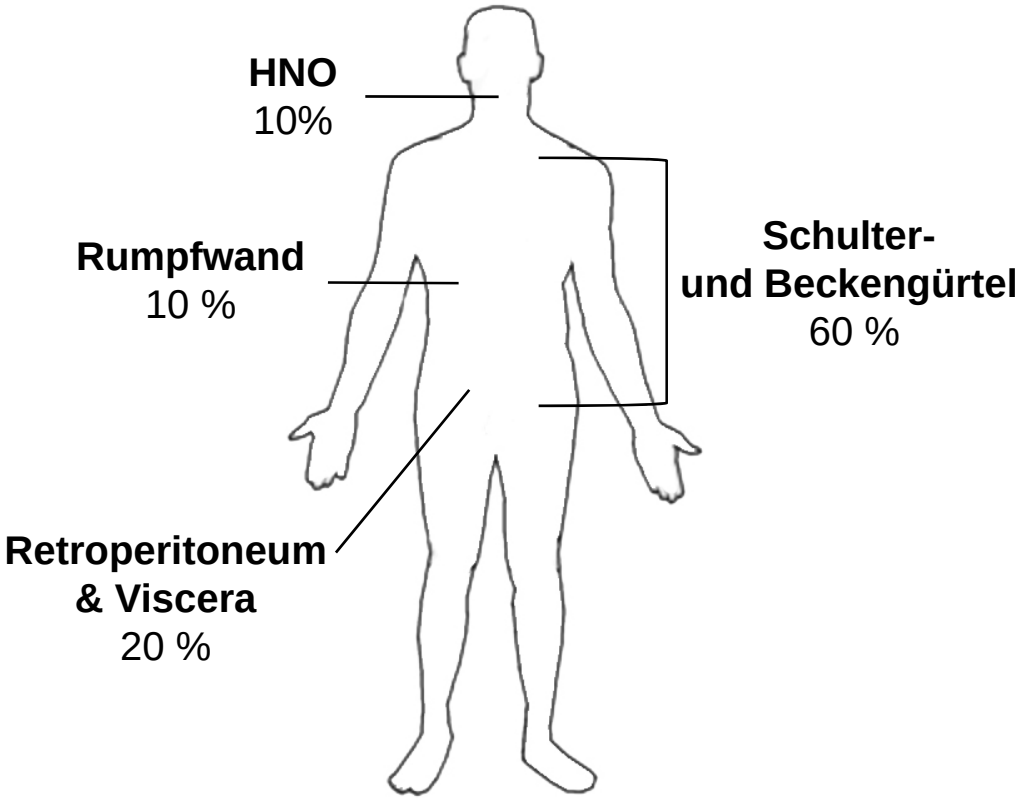
Maligner peripherer Nervenscheidentumor des Magens





Osteosarkom

Häufigkeit und Verteilung von Sarkomen

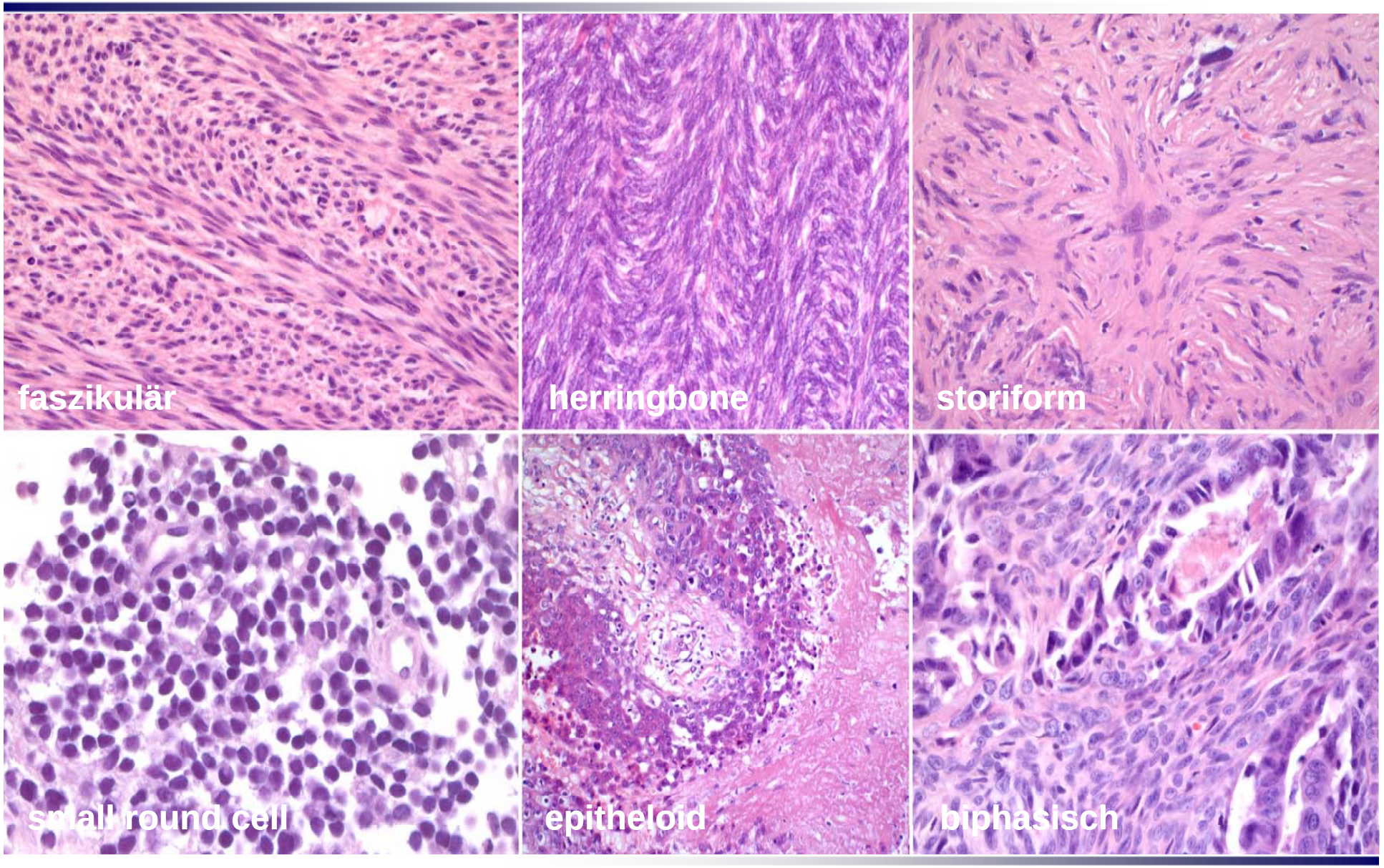


Inzidenz: **ca. 4/100.000**
15 % bei < 15 jährigen
75 % im höheren Erw. alter

<u>Mannheimer STS-Database</u>
(> 800 Fälle)

23 % Liposarkome
20 % Leiomyosarkome
14 % G3 NOS („MFH“)
7 % Osteosarkome
4 % Synovial-Sarkome

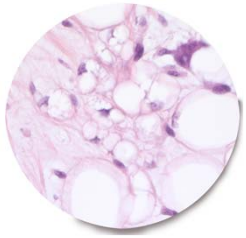
Klassische Wachstumsmuster von Sarkomen



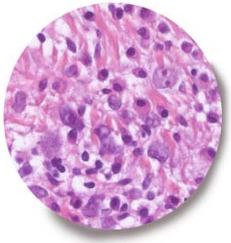
Immunhistochemie: limitierte Bedeutung !

Lipomatöse Differenzierung

(S100)



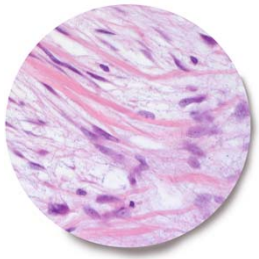
Fibrohistiozytäre Differenzierung



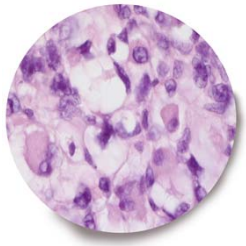
(CD68)

(Myo-)fibromatöse Differenzierung

Actin
Desmin



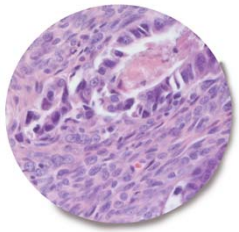
Muskuläre (glatt/qs.) Differenzierung



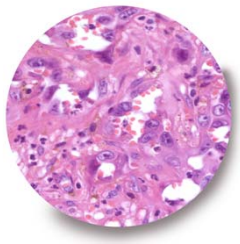
Actin
Desmin
Caldesmon
Myogenin

Sonstige

CD34
CK
EMA
CD117
CD99

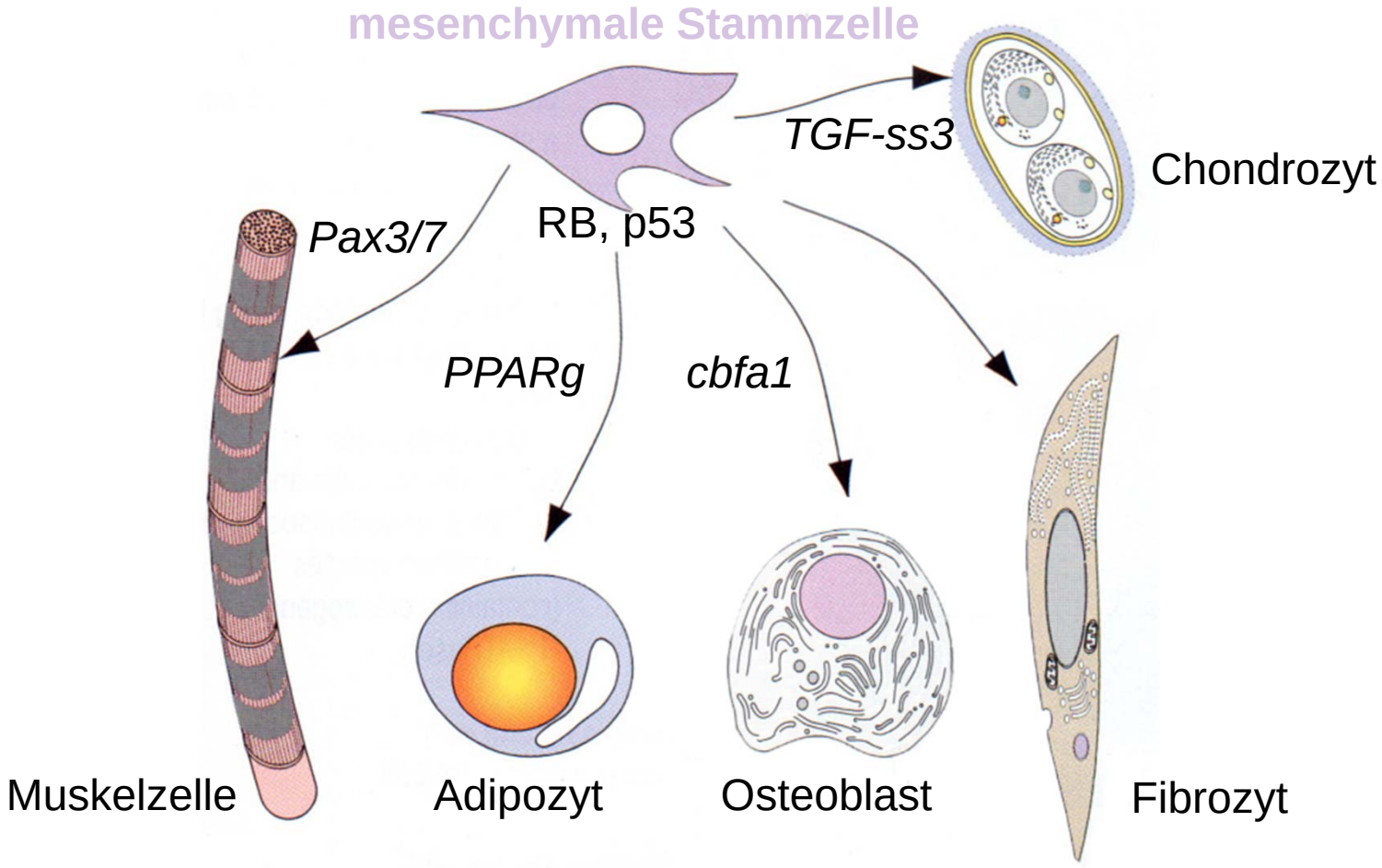


Vaskuläre Differenzierung



CD34
CD31

“Weichgewebe” leiten sich von einer mesenchymalen Stammzelle ab



Relaix et al., Nature 2005, Fajas et al. Dev Cell 2002, Calo et al. Nature 2010, Lee et al. Mol Cell Biol 2000

Sind Sarkome “Stammzelltumoren” ?

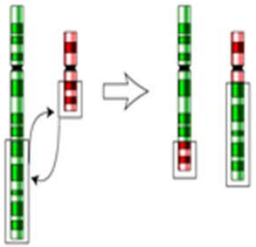
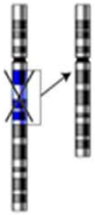
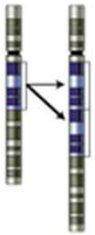
Aggressive Fibromatosis (Desmoid Tumor) Is Derived from Mesenchymal Progenitor Cells
Cancer Res; 70(19) October 1, 2010

Synovial Sarcoma Is a Stem Cell Malignancy
STEM CELLS 2010;28:1119–1131

Osteosarcoma originates from mesenchymal stem cells in consequence of aneuploidization and genomic loss of *Cdkn2*
J Pathol 2009; **219**: 294–305

A Differentiation-Based MicroRNA Signature Identifies Leiomyosarcoma as a Mesenchymal Stem Cell-Related Malignancy
AJP August 2010, Vol. 177, No. 2

Molekulare Klassifikation von Sarkomen

Translokation	Deletion/Mutation	Amplifikation	Komplex
			
15 %	**25 %**	**10 %**	**50 %**
EWS MLS ARMS Synovio ...	GIST Desmoid ...	WDLS	LMS ERMS MPNST OS CS

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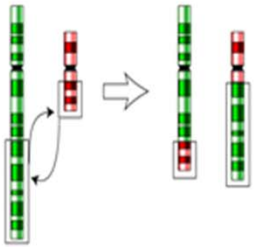
Molekulare Klassifikation von Sarkomen

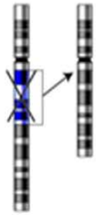
Translokation



15 %

EWS
MLS
ARMS
Synovio
...

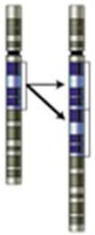
Deletion/Mutation



25 %

GIST
Desmoid
...

Amplifikation



10 %

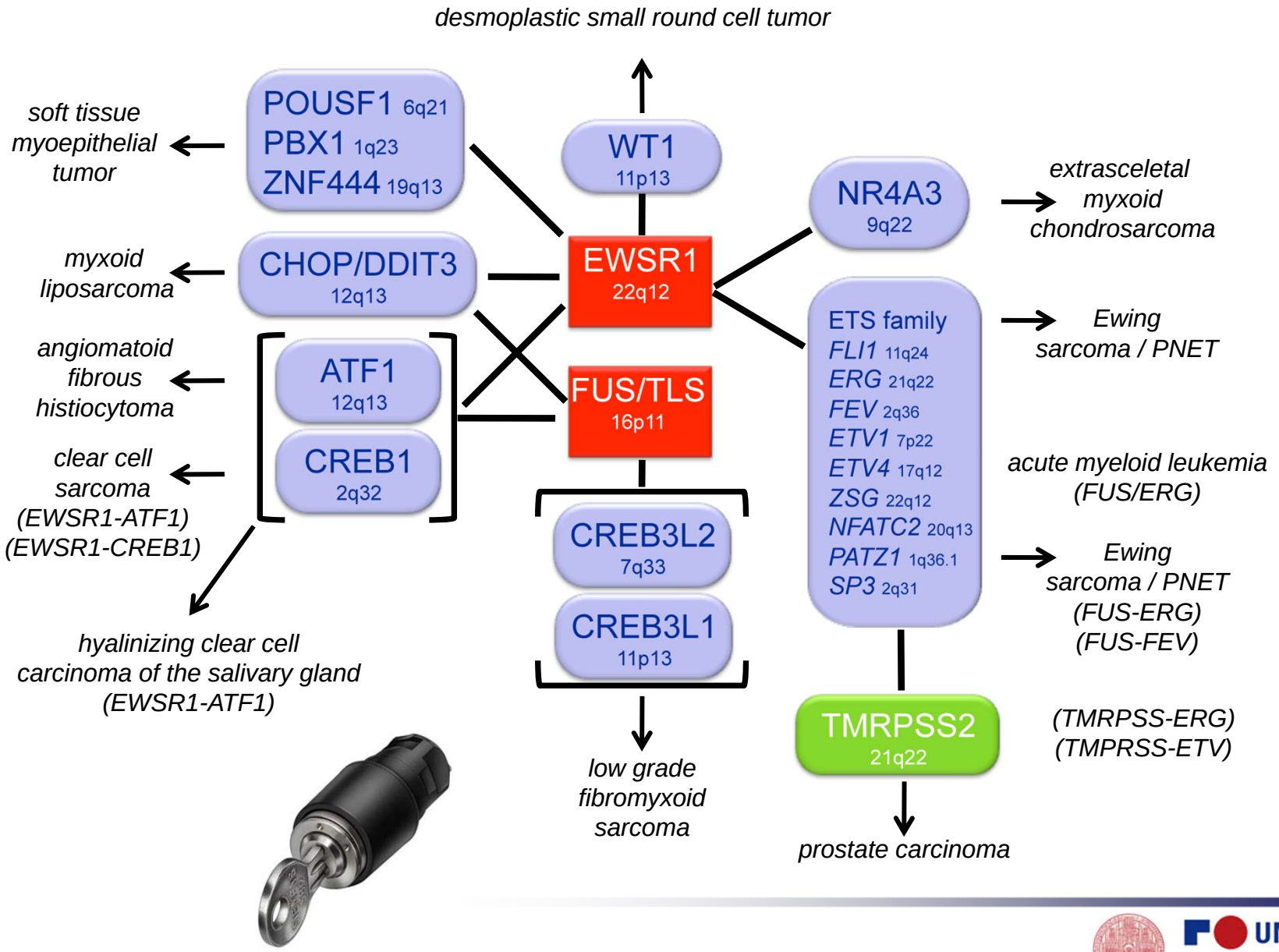
WDLS

Komplex

50 %

LMS
ERMS
MPNST
OS
CS

Komplexe Genetik auch bei Sarkomen mit Translokationen



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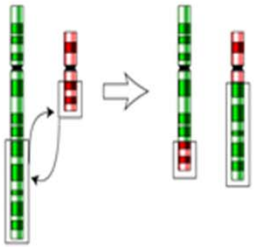
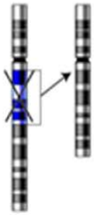
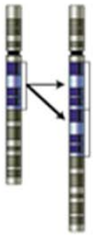
Molekulare Klassifikation von Sarkomen

Translokation	Deletion/Mutation	Amplifikation	Komplex
			
15 %	**25 %**	**10 %**	**50 %**
EWS MLS ARMS Synovio ...	GIST Desmoid ...	WDLS	LMS ERMS MPNST OS CS

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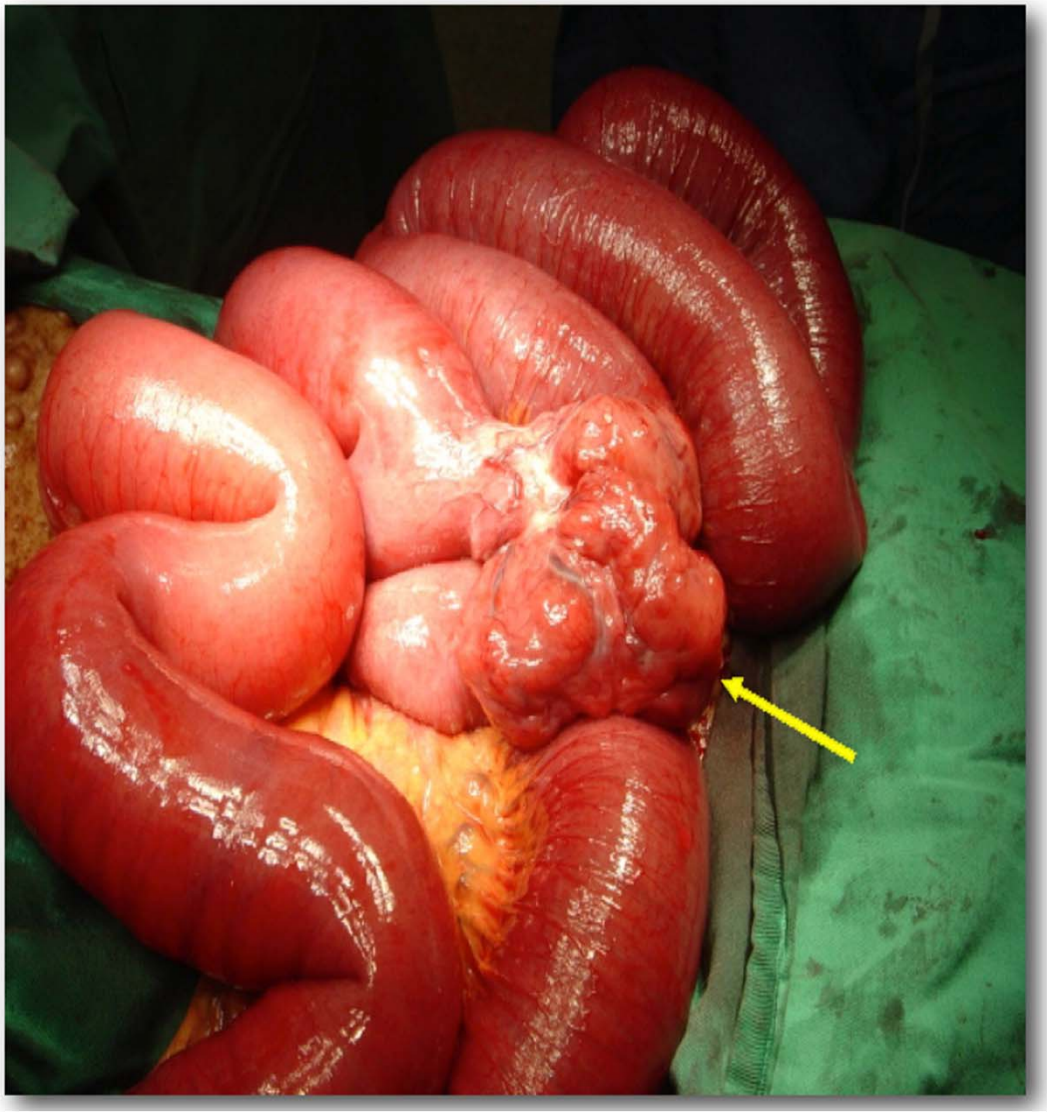
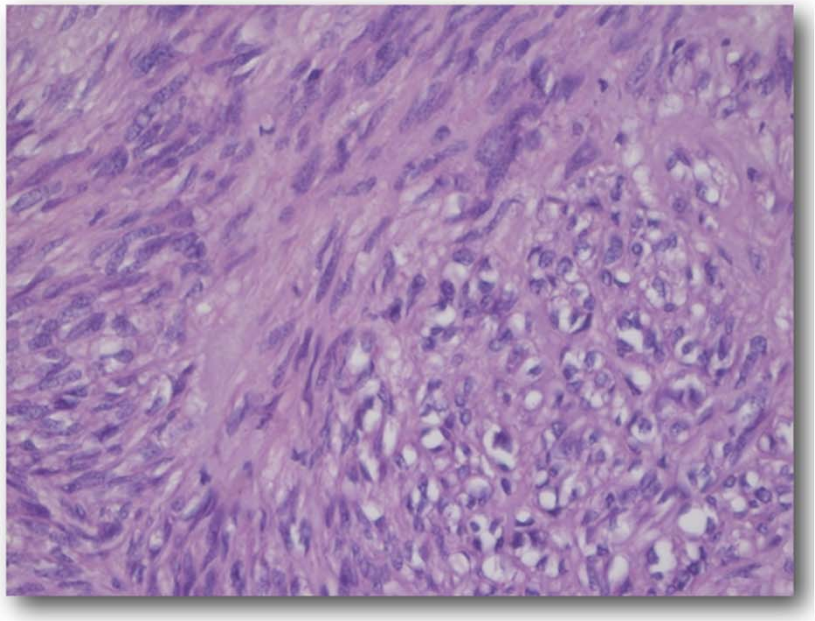
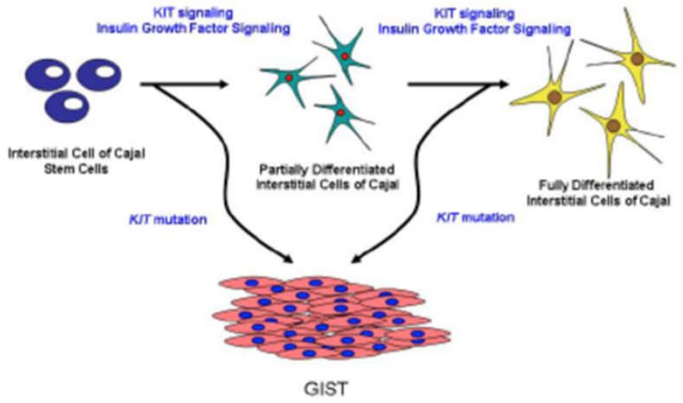
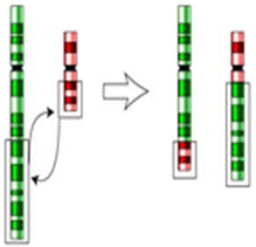
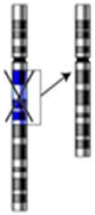
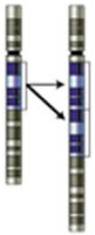
Mutationsassoziierte Sarkome: z.B. GIST







Molekulare Klassifikation von Sarkomen

Translokation	Deletion/Mutation	Amplifikation	Komplex
			
15 %	**25 %**	**10 %**	**50 %**
EWS MLS ARMS Synovio ...	GIST Desmoid ...	WDLS	LMS ERMS MPNST OS CS

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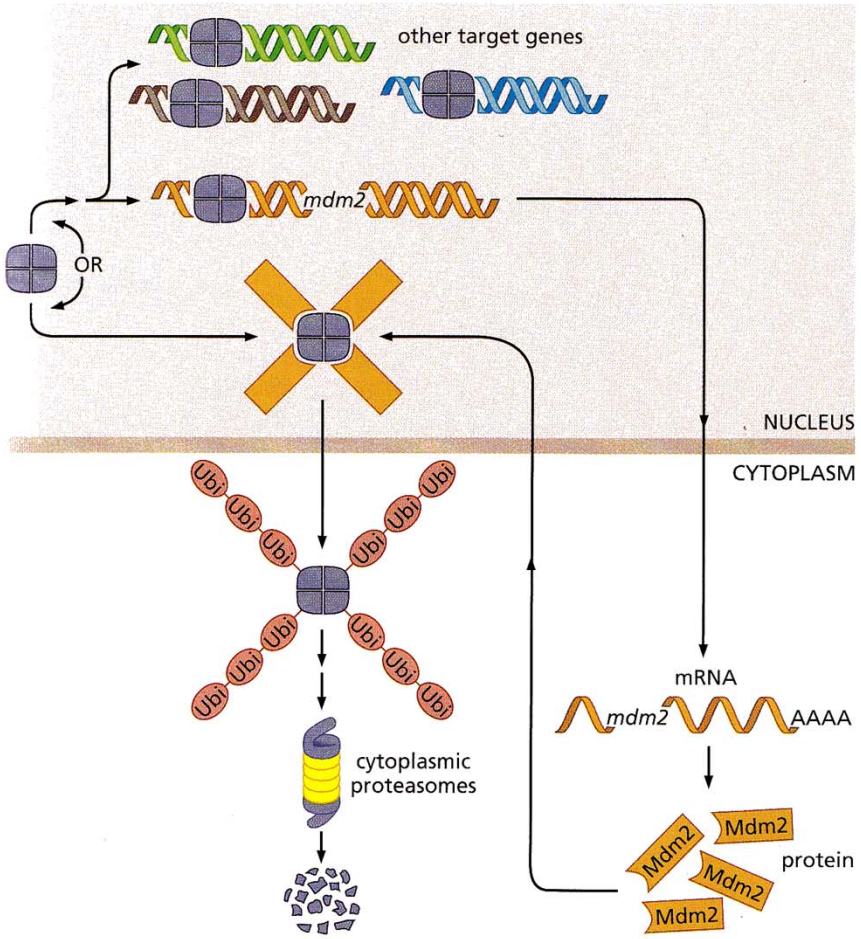
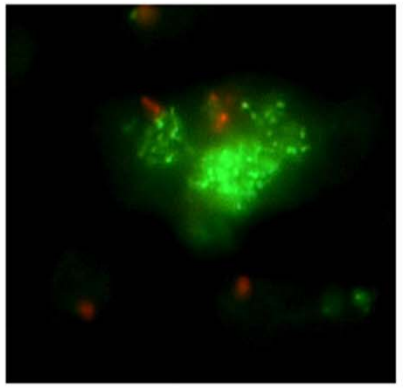
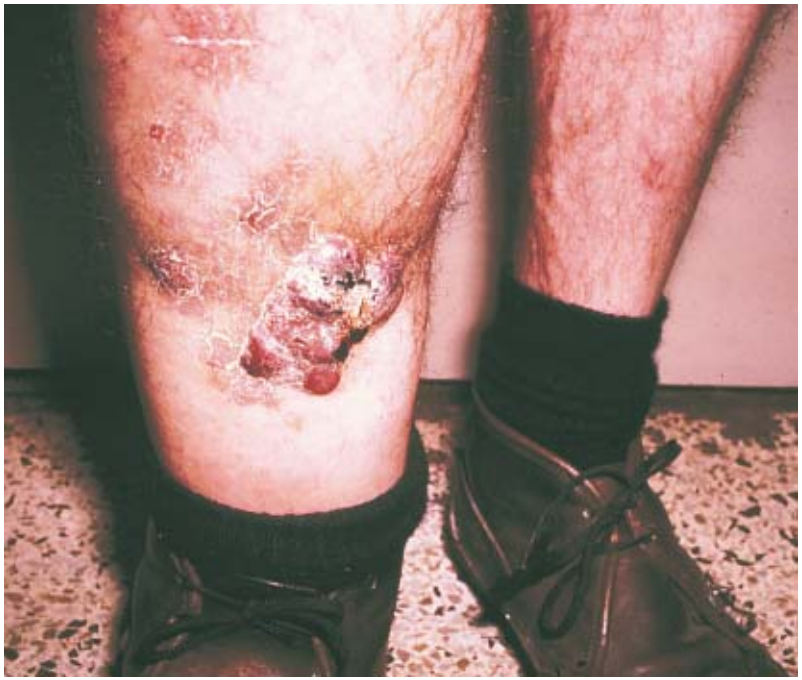
Mdm2 – Amplifikation beim hochdifferenzierten Liposarkom



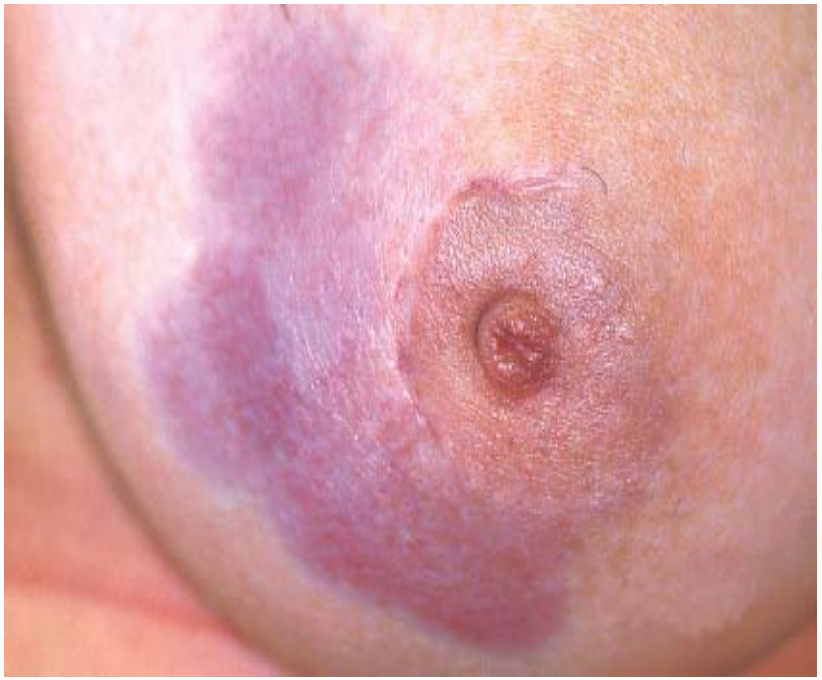


Ätiologie von Angiosarkomen

- primär
- sekundär (chron. Lymphödem, Bestrahlung)

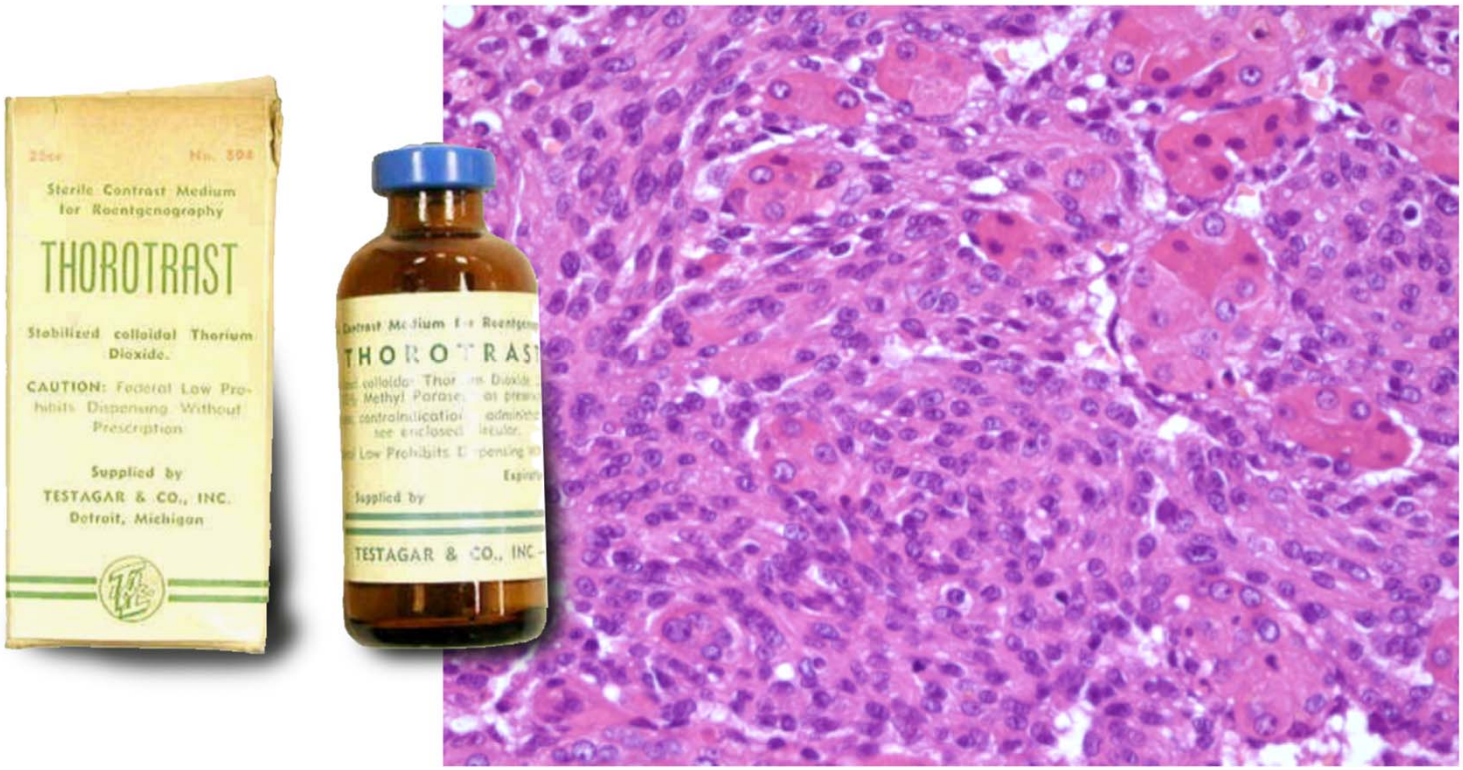


Lymphödem (Stewart-Treves-Syndrom)



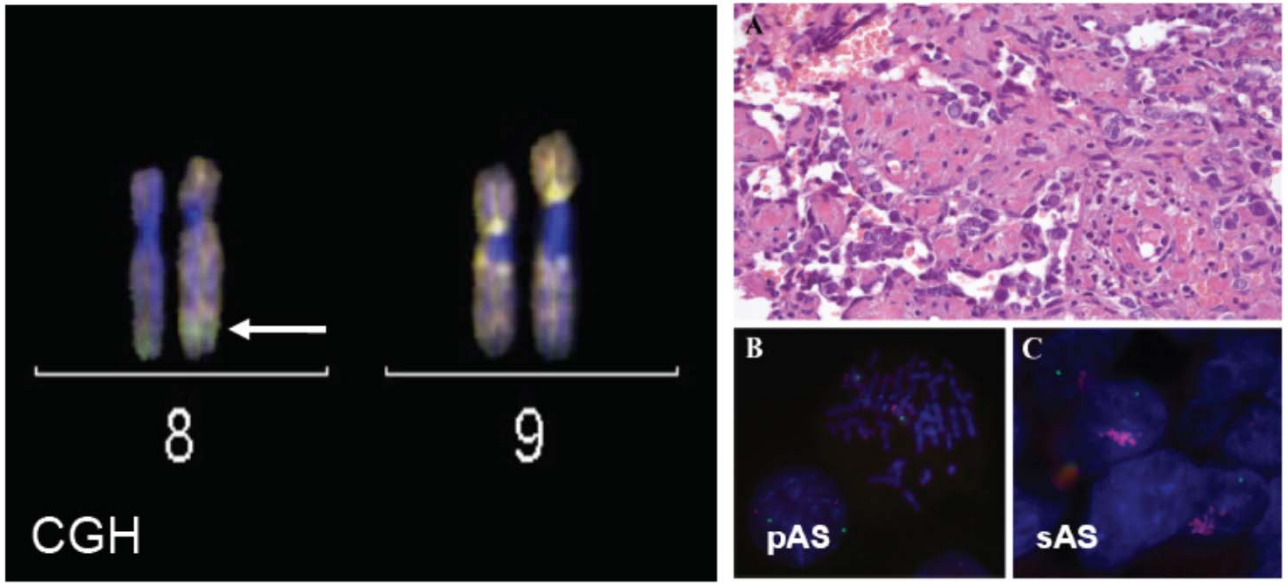
AS Bestrahlung wg. Mamma-CA

Thorotrast (1929 - 1955)



Thorotrast-induziertes Angiosarkom der Leber

MYC high level Amplifikationen ausschließlich in sekundären AS

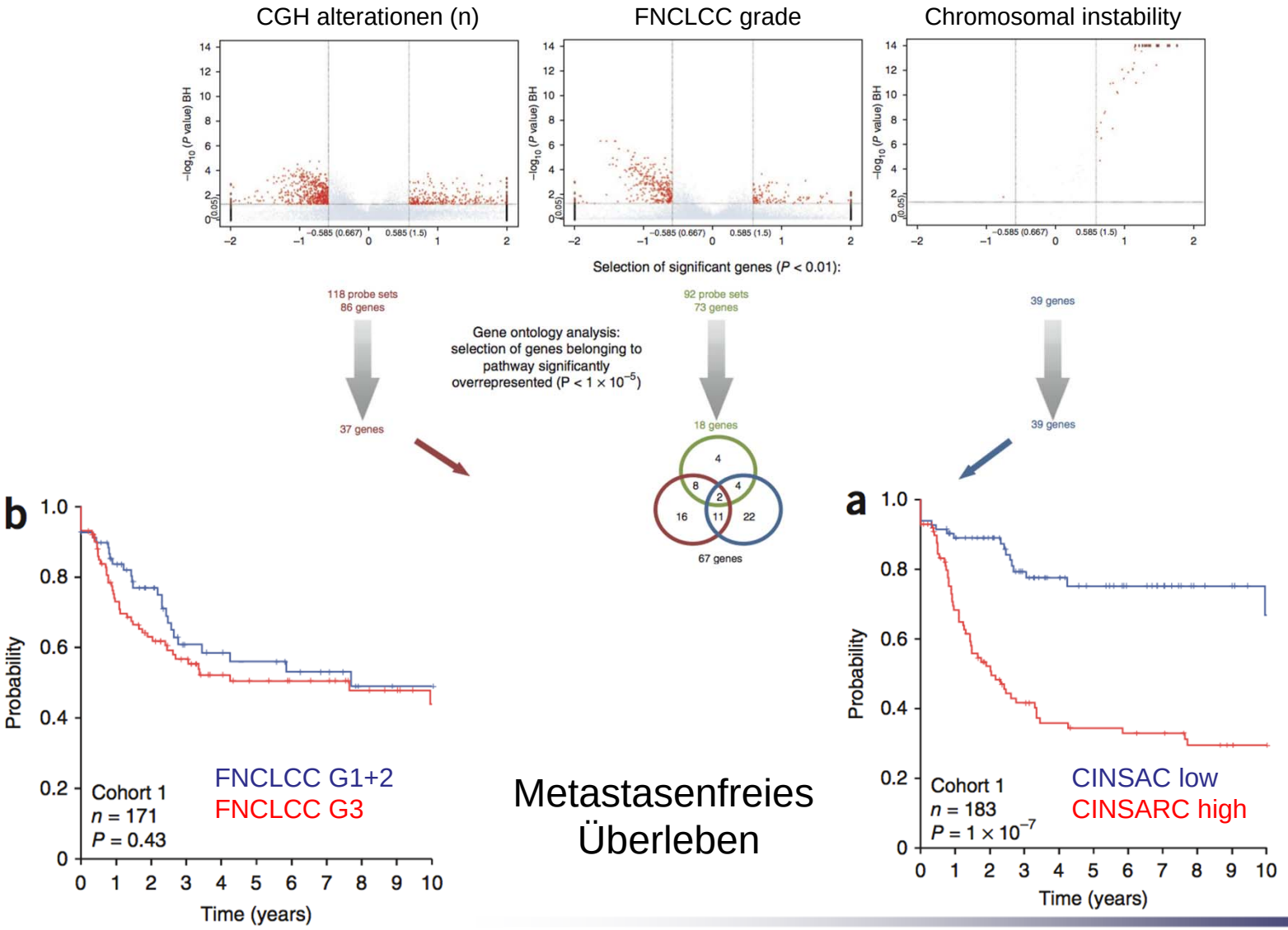


	MYC high level	MYC nc.	
pAS	0 (0%)	28 (100%)	28
sAS	18 (55%)	15 (45%)	33
	18	43	61

P • 0.0001

Manner et al. The American Journal of Pathology, 176, 2010

CINSARC: Molekulare Tumorgraduierung (Chibon et al. Nat Med 2010)



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Sarkome: von der histologischen zur molekularen Klassifikation

- Die Diagnose von Sarkomen beruht auf der Integration klinischer, histologischer, immunhistochemischer und molekularer Daten

- Etwa die Hälfte aller Sarkome weist spezifische molekulare Alterationen (Translokationen, Mutationen, Amplifikationen) auf

- Molekulare Parameter werden in Zukunft nicht nur die Diagnose, sondern auch die Tumorgraduierung (G1 vs. G2 vs. G3) und damit Therapie-entscheidungen beeinflussen

Dank an:

Katharina Mössinger

Christoph Käcker

Stefan Küffer

Carsten Stich

Li Li

Elena Hartmann (Wü)

Andreas Rosenwald (Wü)

Peter Hohenberger
Mannheim

JM Coindre
Bordeaux

Raf Sciot
Leuven

Alexander Marx
Mannheim

Euro Myasthenia

KO.SAR. Kompetenznetz SARKOME

Thymaide www.eurothymaide.org

MGTX

Conticanet

Deutsche Krebshilfe