Histopathology and Molecular Pathology of SCOS - Distinction from Fusion-Driven RCS and Implications for Clinical Practice

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OS subtypes

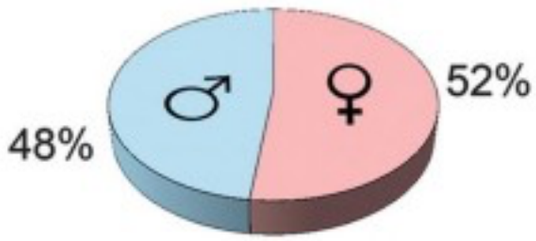
Subtype	Location	Grade	Histology
Low-grade central osteosarcoma	Medulla	Low grade	Spindle cells with low-grade nuclear atypia and well-formed neoplastic woven bone trabeculae, often 12q13 amplification
Parosteal osteosarcoma	Surface	Low grade	Spindle cell proliferation, often with cartilaginous differentiation, and 12q13 amplification
Periosteal osteosarcoma	Surface (typically underneath the periosteum)	Intermediate grade	Predominantly chondroblastic bone-forming sarcoma
Conventional osteosarcoma Fibroblastic Chondroblastic Osteoblastic	Medulla	High grade	High-grade sarcoma in which the tumour cells produce bone. Tumour cells can be fibroblastic, chondroblast- or osteoblast-like
Small-cell osteosarcoma	Medulla	High grade	Small cells with scant cytoplasm, associated with variable osteoid formation; may resemble Ewing sarcoma
Telangiectatic osteosarcoma	Medulla	High grade	Osteosarcoma composed of blood-filled or empty cystic spaces closely simulating aneurysmal bone cyst
High-grade surface osteosarcoma	Surface	High grade	Similar to conventional osteosarcoma

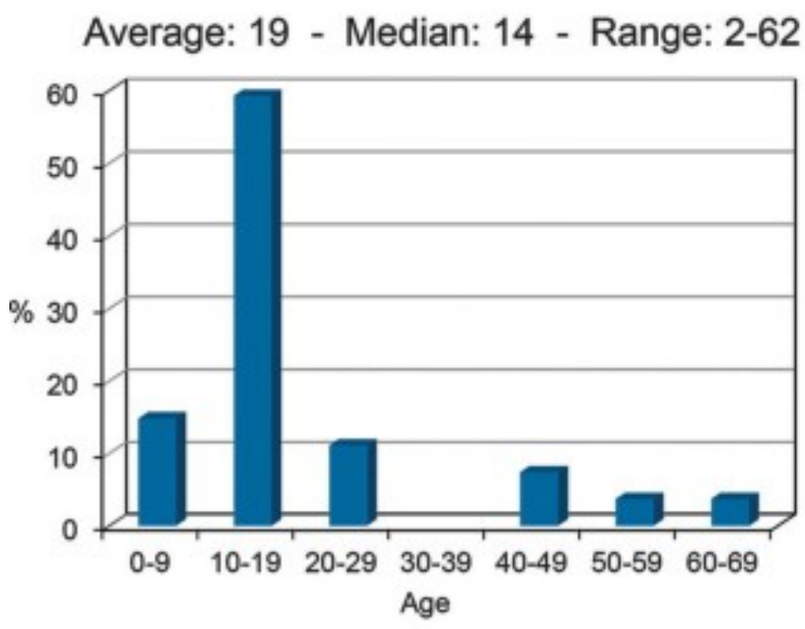
COS

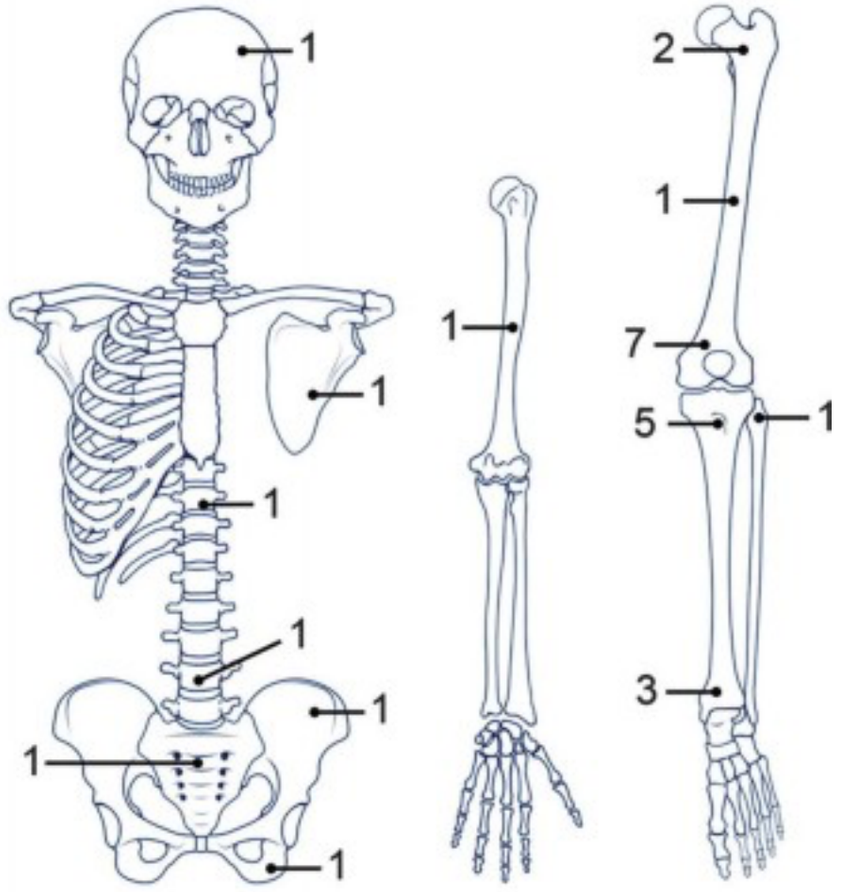
WHO, Blue Books, 5th Ed., 2019; Virchows Arch 2020

Small Cell Osteosarcoma

SCOS (1.5%) (G3/HG)







HG Osteosarcomas are tumors with highly complex karyotypes

They have **complex karyotypes** lacking specific genetic aberrations and recognisable chromosomal patterns

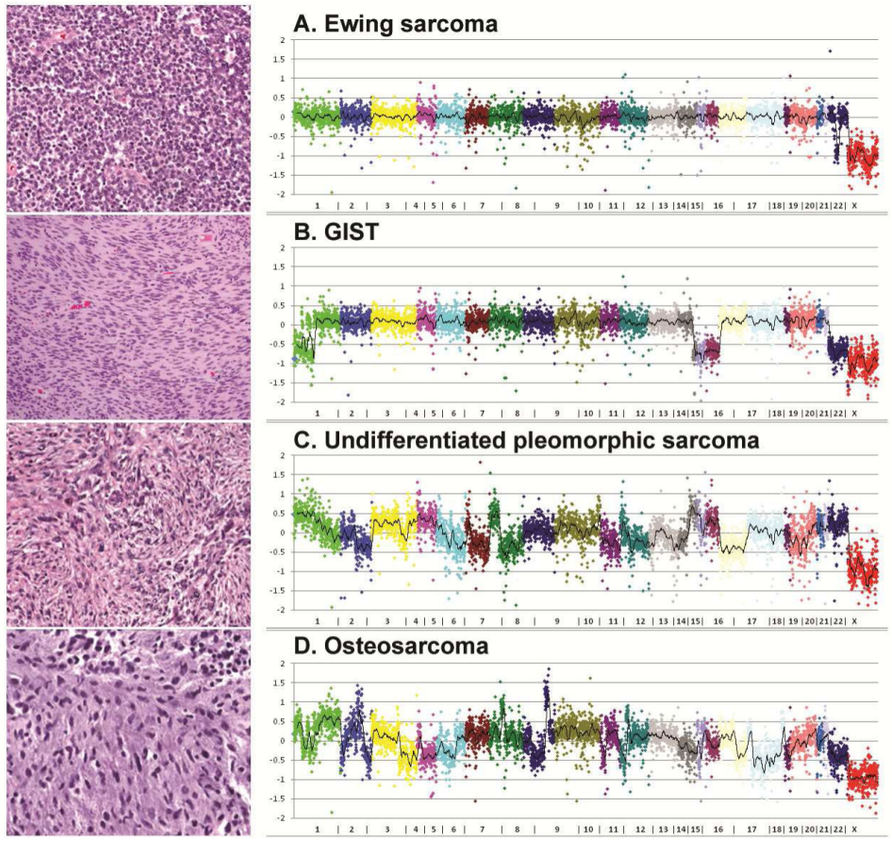
They harbour aberrations in the ***Rb1*** **(50%) or** ***p53*** (>90%)

Pleomorohic tumors from a histopathological standpoint

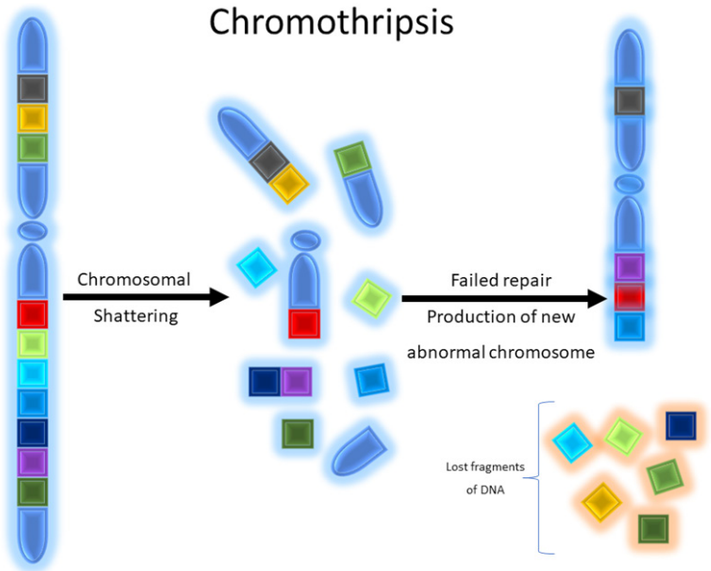
High risk of **metastasis**

Extremely unstable with many translocations, amplifications, mutations and deletions

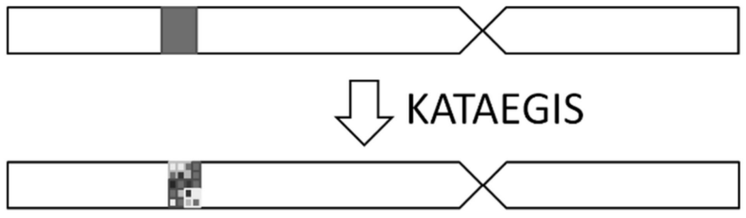
The detection of specific driver genes and pathways is **extremely difficult**



Copy number profiles of sarcomas with simple and complex genome (Surg Pathol Clin, 2017)



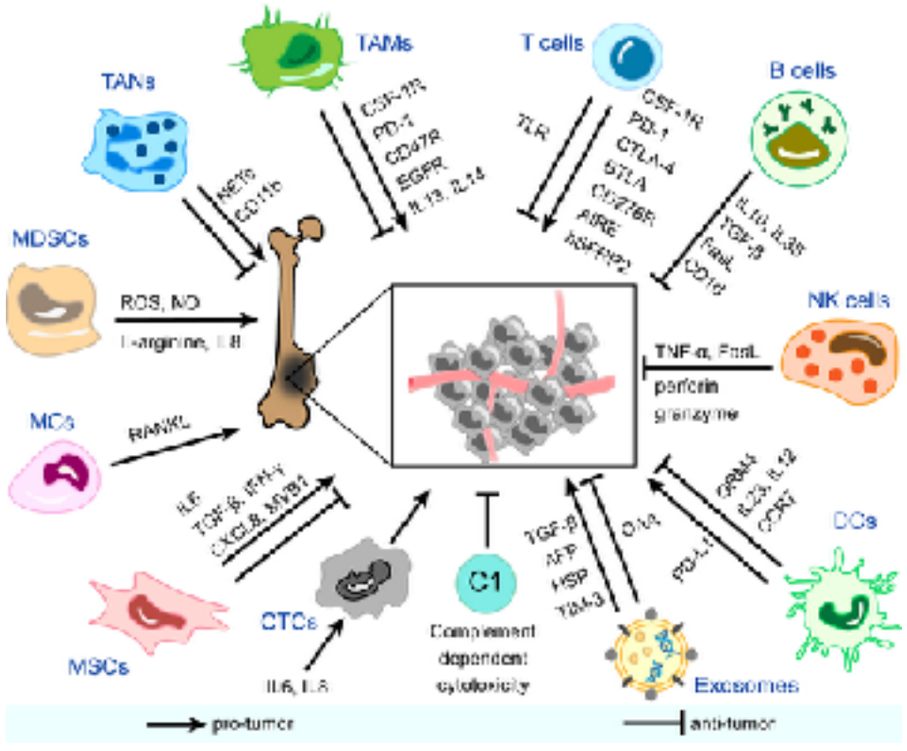
77% of COS



50-85% of COS

Hypermutated region

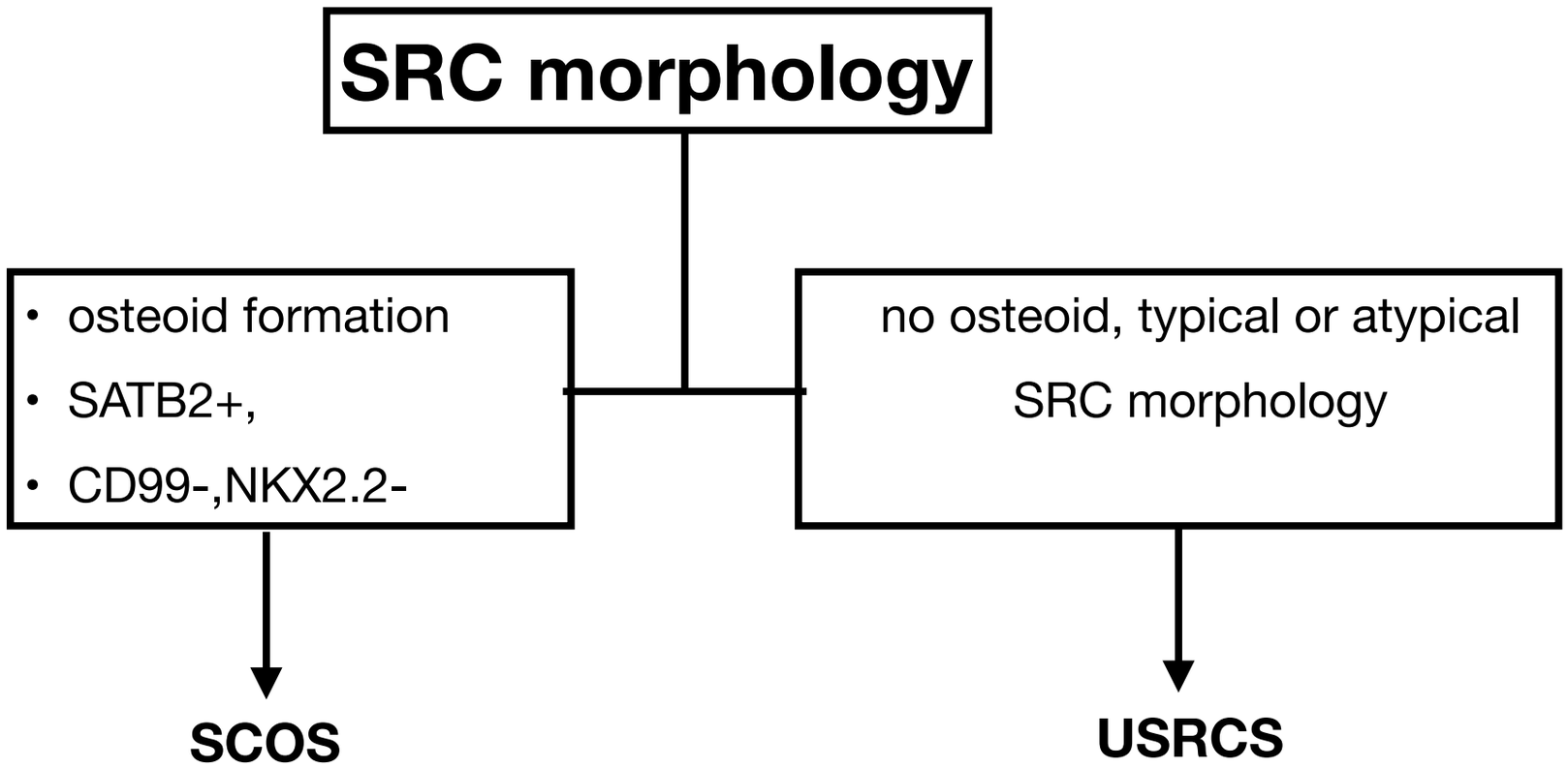
Microenvironmental factors



J Cancer Metastasis Treat 2021, Cancers 2020

DDX of SCOS

- Lymphoma
- Neuroblastoma
- Rhabdomyosarcoma
- Mesenchymal CHS
- Myoepithelial tumor
- Monophasic SS
- **Undifferentiated SRCS**


SRC morphology
• osteoid formation
• SATB2+,
• CD99-,NKX2.2-
SCOS
no osteoid, typical or atypical SRC morphology
USRCS

Undif/ted SRCS: focus on Bone

Virchows Arch (2020) 476:109–119

Histotype	Molecular alteration	Gene fusion
Ewing sarcoma	t(11;22)(q24;q12)	EWSR1-FLI1 (85%)
	t(21;22)(q22;q12)	EWSR1-ERG (10%)
		EWSR1-ETS gene family
		FUS-ETS gene family
EWSR1 RCS-non-ETS partners	t(20;22)(q13.2;q12)	EWSR1-NFATC2
	t(20;16)(q13.2;p11.2)	FUS-NFATC2
	inv(22)(q12; q12)	EWSR1-PATZ1
CIC sarcomas	t(4;19)(q35;q13)	CIC-DUX4
	t(10;19)(q26;q13)	CIC-DUX4
	t(x;19)(q13;q13.3)	CIC-FOXO4
	t(;19)()	CIC-LEUTX
	t(15;19)(q14;q13.2)	CIC-NUTM1
	t(10;19)(q23.3;q13)	CIC-NUTM2B
BCOR sarcomas	inv(x)(p11;p11)	BCOR-CCNB3
	BCOR-ITD	BCOR-ITD
	T(10;17)(q23.3;p13.3)	YWHAE1-NUTM2B
	t(4;x)(p11;q31)	BCOR-MAML3
	t(x;22;)(p11;q13.2)	ZC3H7B-BCOR

I. Ewing's Sarcoma

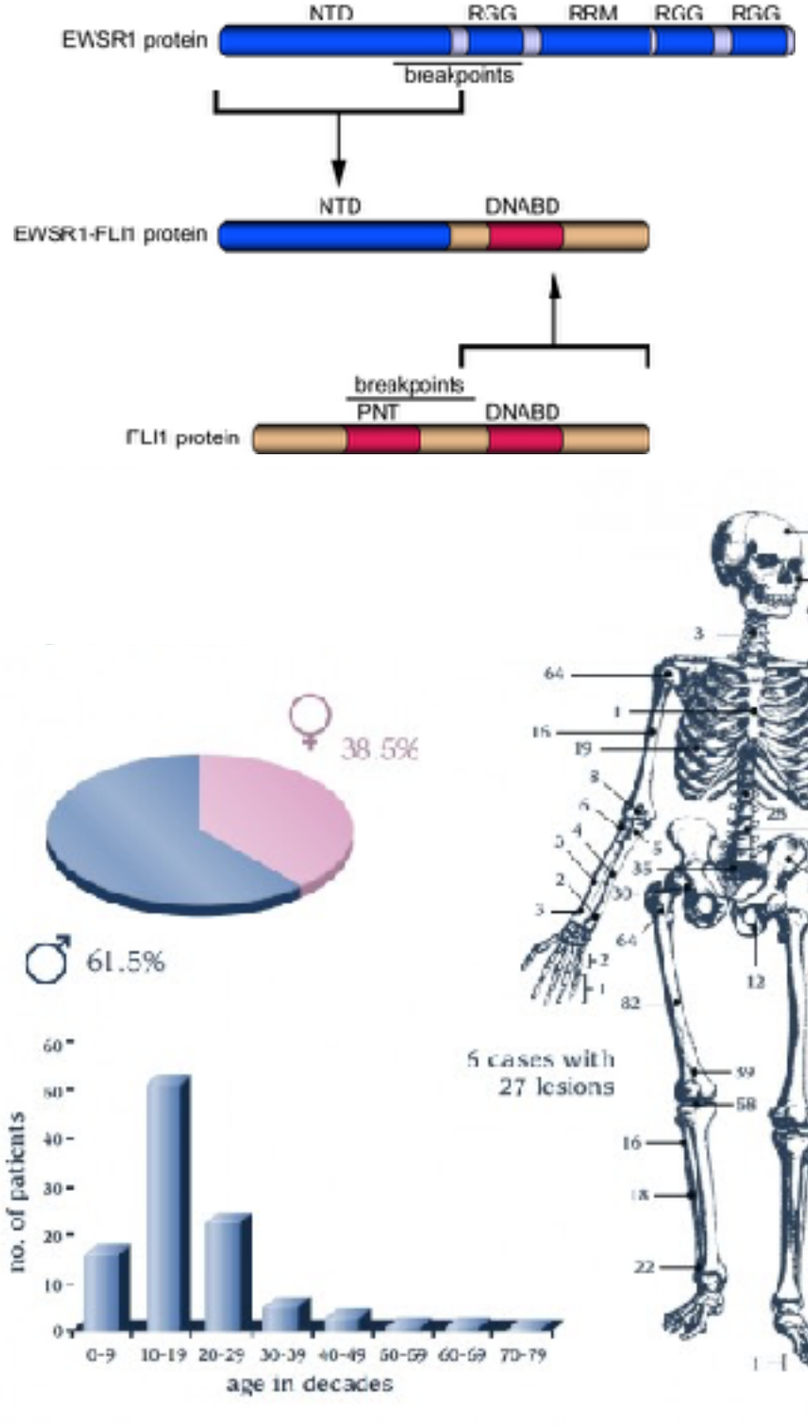
WHO: gene fusions involving **FET** family of genes (usually *EWSR1, FUS*) and a member of the **ETS** family of transcription factors (FLI1, ERG).

Location:

- Diaphysis - metadiaphysis of long bones
- Central skeleton

Immunohistochemistry:

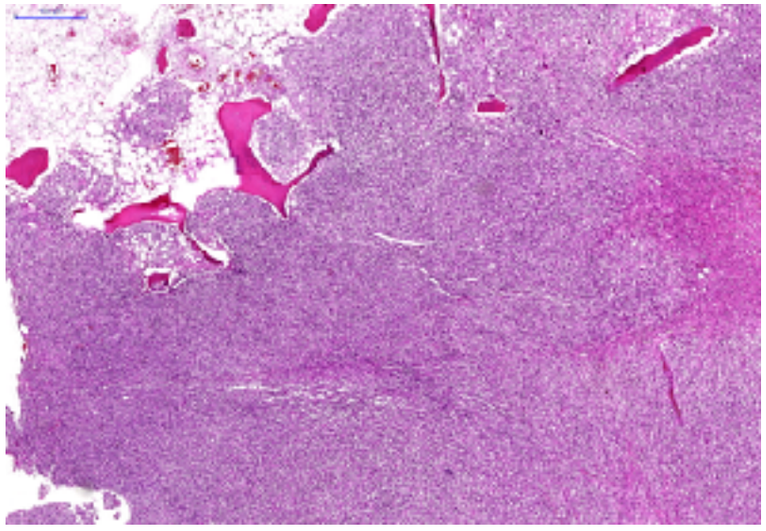
- **CD99**: Strong, diffuse membranous expression in 95% of Ewing sarcomas
- **NKX2.2**: higher specificity than CD99.
- Keratins: +approximately 25% of cases
- FLI1 and ERG: often expressed in the cases with the corresponding gene fusions.
- Neuroendocrine markers and/or S100
- SATB2: usually neg.

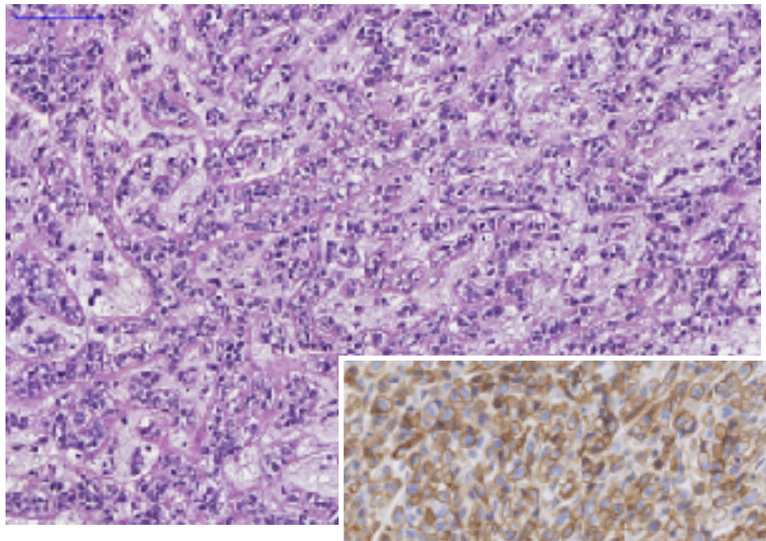


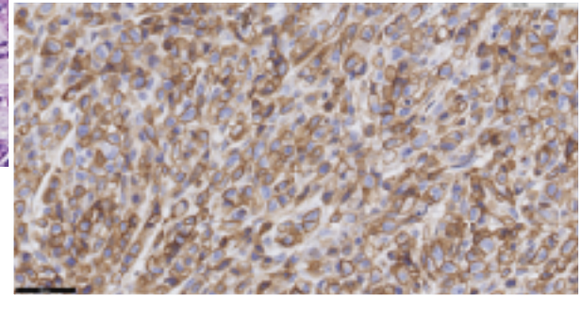
II. SRCS with *EWSR1-non-ETS* fusions:

EWSR1::NFATC2 sarcoma

- Children - adults (range: 12-67; MA=32.3yrs)
- male predominance (M:F=5:1) primarily bone (long bones: metaphysis-diaphysyis)
- ***FUS-NFATC2* tumours have been reported exclusively in long bones**
- variable micro-morphology, multifocal pleomorphism, carcinoma mimicker
- **IHC:** CD99+ (50%), dot-like CK expression, NKX2.2 +/-
- Late mets
- Little or no response to neoadjuvant ChTx

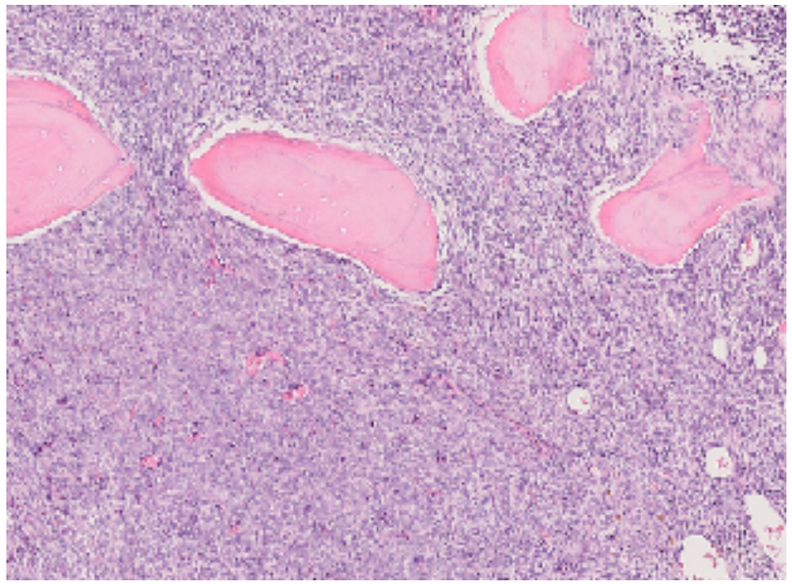


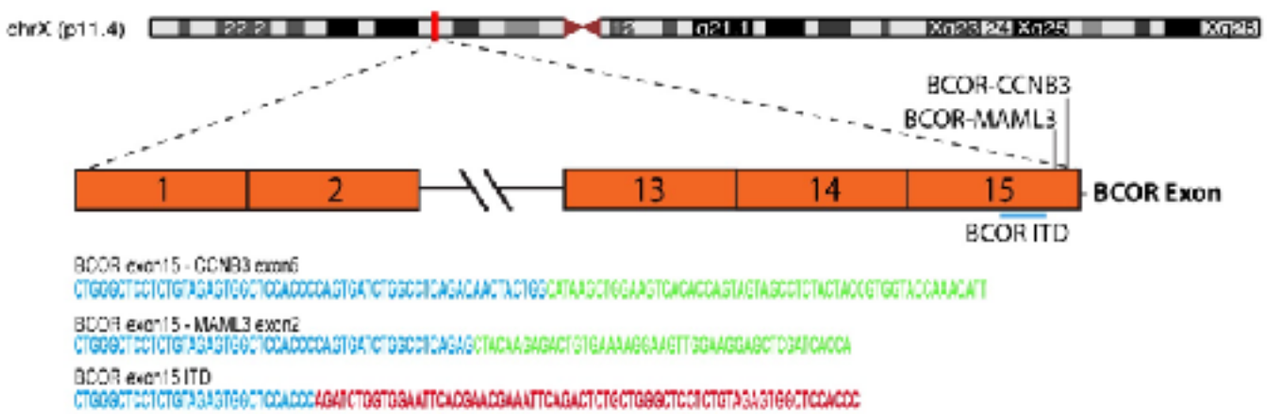


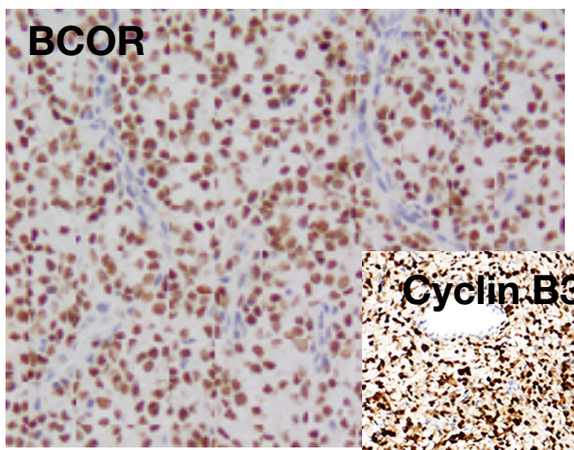


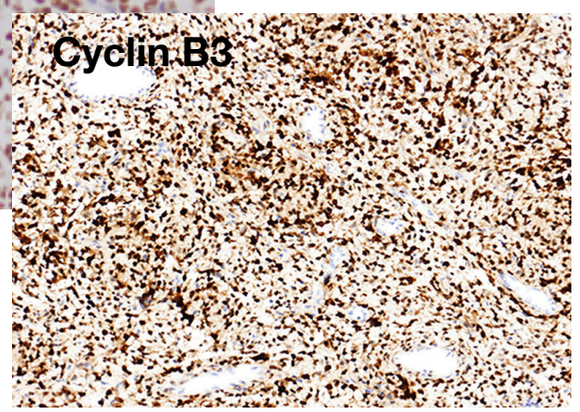
III. Sarcoma with BCOR genetic alterations

- ***BCOR-CCNB3* sarcoma (88%)**
- slightly more often in bone than in soft tissue (ratio: 1.5:1)
- > 90% of patients aged **< 20 years**
- **M:F ratio: 4.5:1**
- **Morphology**: round and spindle cell component (st prominent)
- **IHC**: BCOR+, CD99+ (50%), SATB2+, TLE1+, CyclinD1+, CCNB3+, *BCOR-CCNB3* sarcoma: **Cyclin B3** (not expressed in other BCOR sarcomas)
- **Px**: similar to EWS, may give mets
- Histological response to EWS-based Tx





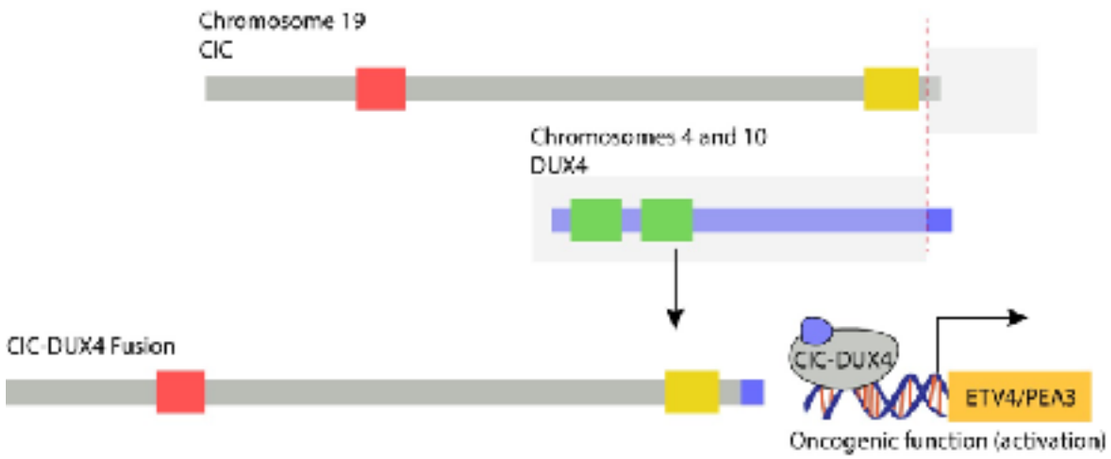


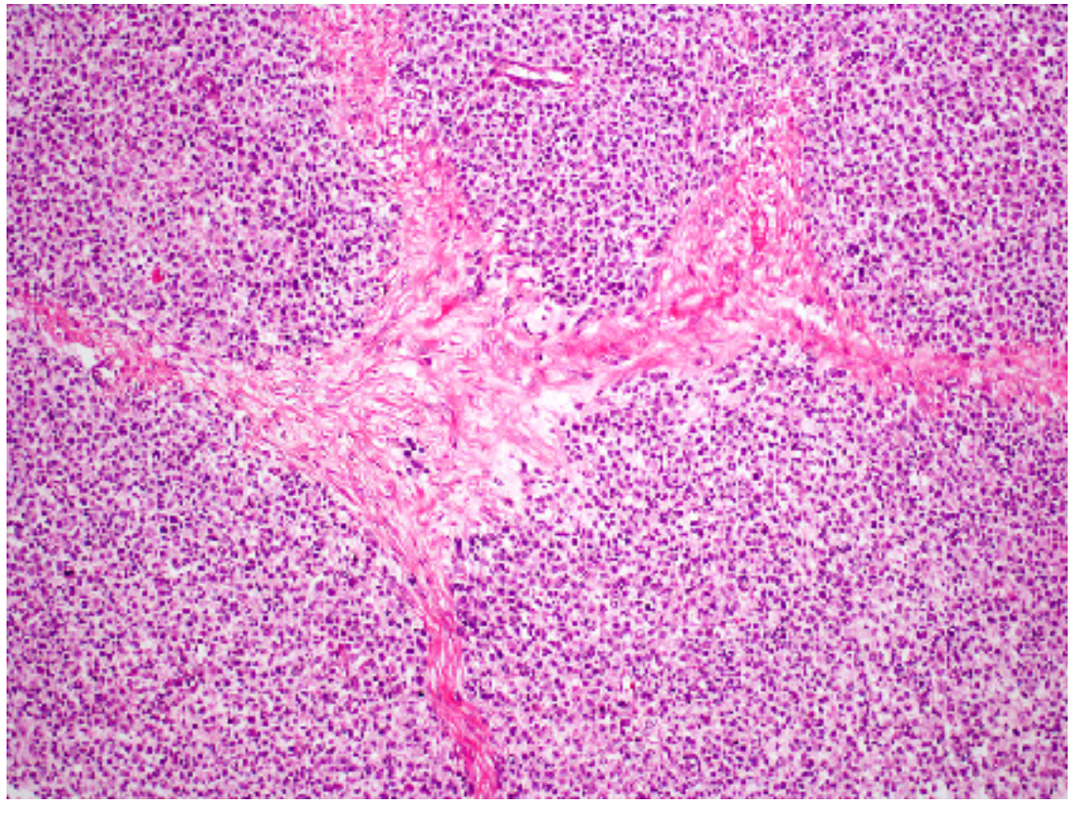


WHO, 5th Ed

IV. CIC-sarcomas

- most often ***CIC::DUX4*** **t(4;19) or t(10;19) (95%)**.
- the deep soft tissues of the limbs or trunk
- Primary osseous involvement is rare **(< 5%)**
- striking predilection for young adults (**median age: 25–35 years)**, and < 25% of cases present in the paediatric age group
- **IHC:**
  - CD99+ (patsy/variable)
  - WT1 (90–95%)
  - ETV4 (95–100%)
- **5-year overall survival rate is 17–43%,** significantly worse than that of Ewing sarcoma
- **Poor** response to EWS Tx





SCOS *vs* fusion-driven SRCS

- osteoid formation
- SATB2+,
- CD99-,NKX2.2-

SCOS

no osteoid, typical or atypical SRC morphology

Fusion-driven SRCS

Clinical & Imaging Data

Histomorphology

Immunohistochemistry

Molecular Analysis

Final Diagnosis

Histomorphology	Immunohistochemistry	Molecular Analysis	Final Diagnosis
Small round cell morphology, bland	CD99: +++ NKX2.2: +++ ERG: +/- FLI1: +/- Keratin: +/- p40: +/-	FISH for *EWSR1* or *FUS*	*EWSR1/FUS::FLI1/ERG/FTV4/FEV1*	Ewing Sarcoma
Small round cell morphology, pleomorphic	CD99: +/++ WT1: +++ SATB2: +/++ ERG: +/++		*CIC::DUX4/DUX4L/FOXO4*	CIC-rearranged sarcoma
Spindle and round cell, microcystic, hyalinized vessel	CD99: -/+ Desmin: +/++ S100: +/++ GFAP: -+/+++ Keratin: +/++	NGS	*EWSR1::PATZ1*	*EWSR1::PATZ1*-rearranged sarcoma
Fibrohyaline stroma	CD99: -/+ NKX2.2: -+ Keratin: +/++ (dot-like)		*EWSR1/FUS::NFATc2*	*EWSR1/FUS::NFATc2*-rearranged sarcoma
Spindle to round cell, myxoid stroma, prominent capillary network	CD99: +/++ BCOR: +++ Cyclin D1: +++ SATB2: +++		*BCOR::CCNB3* BCOR ITD*	*BCOR*-rearranged sarcoma

Human Pathology 147 (2024) 101–113

…key takeaways!

- Distinction between SCOS and RCS (fusion-driven) might be **challenging** especially in small Bx

- **Morphology-IHC-molecular analysis:** help (in association with Clinical and Imaging Data)

- Importance of **pre-analytical phase** (esp. decalcification: EDTA/Nitric Acid/Formic Acid)

- **Multidisciplinary** approach

- **Clinical relevance**?