

Markers for sarcoma diagnosis: new and old.

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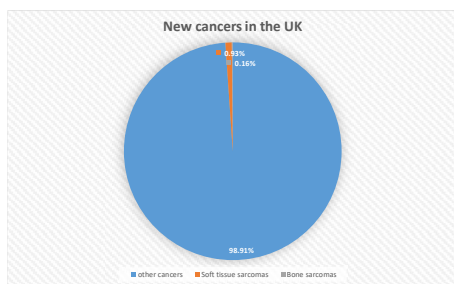
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Mesenchymal tumour

- Benign
 - much more common
 - incidence is difficult to estimate but the clinical presentation is estimate to 3000/ million pop.
- Malignant
 - Sarcomas, much rarer
 - 50 / million pop.

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Cancer research UK, 2014

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Sarcoma?

- Greek sarkoun 'to produce flesh'.
- Malignant mesenchymal tumour (connective or other non-epithelial tissue includes bone and cartilage)
- Display a large variety of histological subtypes ~ 100 different sub-types of sarcoma

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Soft tissue and bone tumours

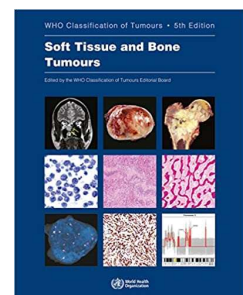
- Rare
- Over 200 subtypes
- Wide range of distribution

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WHO 2020

- Benign
- Intermediate (locally aggressive or rarely metastasizing)
- Malignant



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Tumours of bone: main groups

- Chodrogenic tumours
 - Osteogenic tumours
 - Fibrogenic tumours
 - Vascular tumours
 - Osteoclastic giant cell-rich tumours
 - Notochordal tumours
 - Other mesenchymal tumours of bone
-
- Undifferentiated small round cell sarcomas of bone and soft tissue
 - Ewing sarcoma
 - Round cell sarcomas with EWSR1-non-ETS fusions
 - CIC-rearranged sarcomas
 - Sarcomas with BCOR alterations

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WHO classification of bone tumours

[illegible]

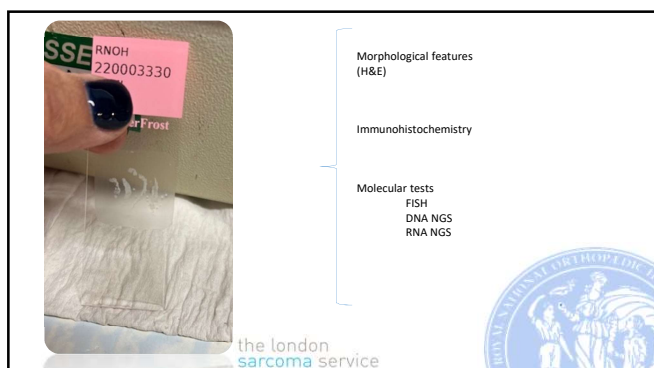
Tumours of soft tissue: main groups

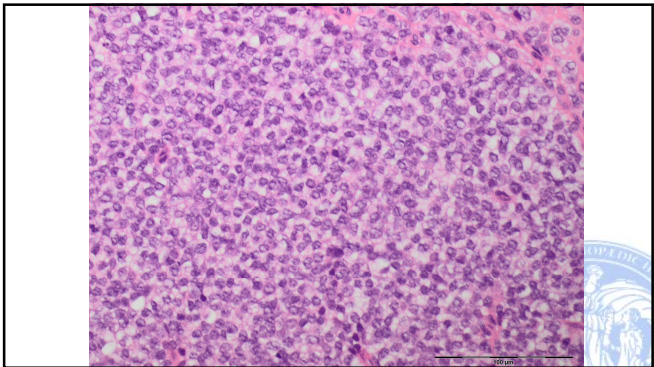
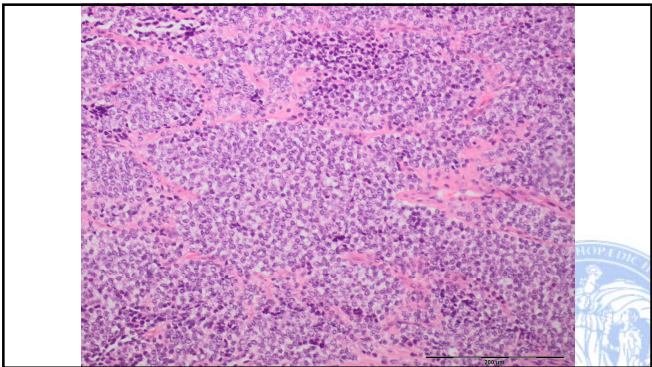
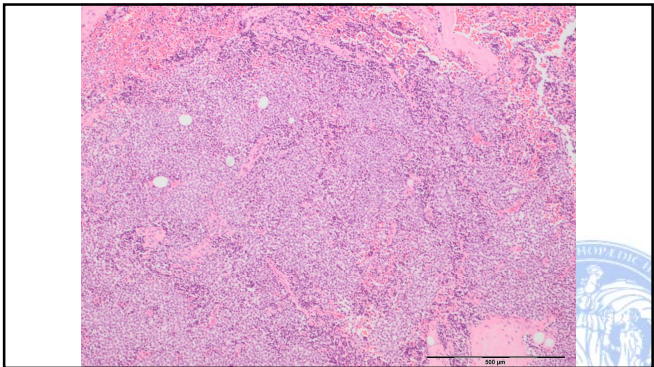
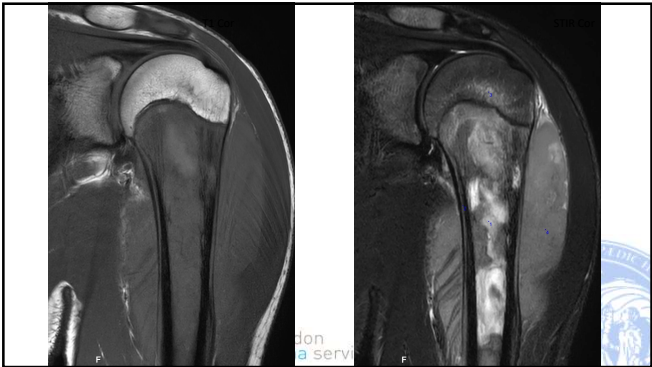
- Adipocytic tumours
- Fibroblastic /myofibroblastic tumours
- So-called Fibrohistiocytic tumours
- Vascular tumours of soft tissue
- Pericytic (Perivascular) tumours
- Smooth muscle tumours
- Skeletal muscle tumours
- Gastrointestinal stromal tumours
- Chondro-osseous tumours
- Peripheral Nerve Sheath tumours
- Tumours of uncertain differentiation

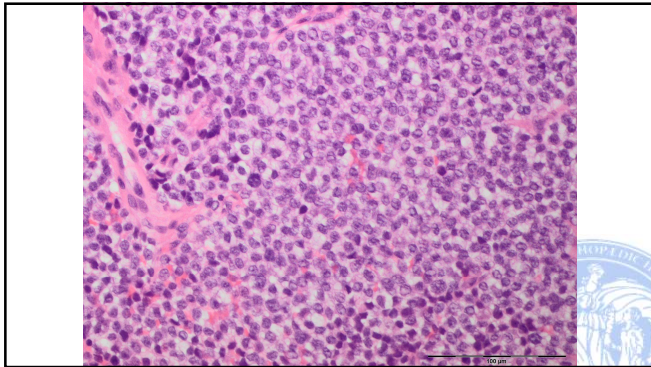
- Undifferentiated small round cell sarcomas of bone and soft tissue

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WHO classification of soft tissue tumours

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Diagnosis?

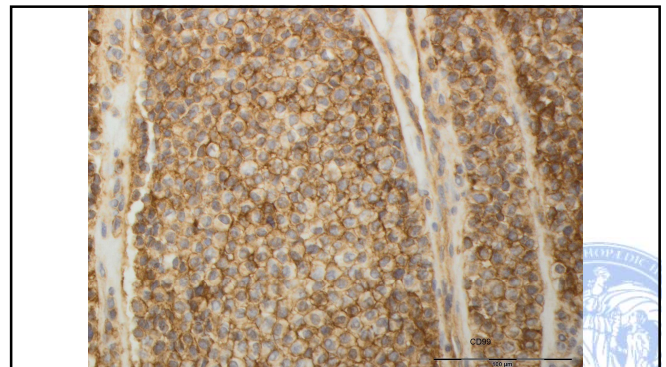
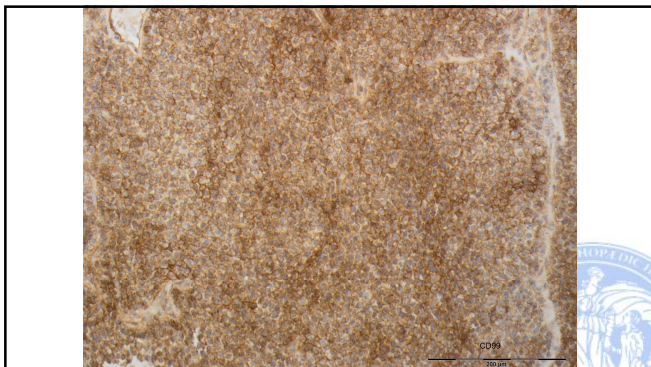
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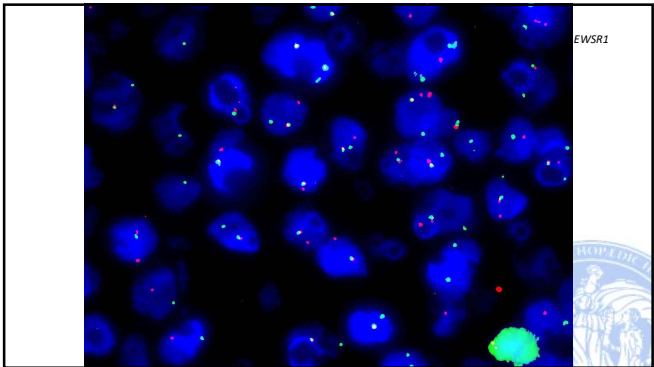
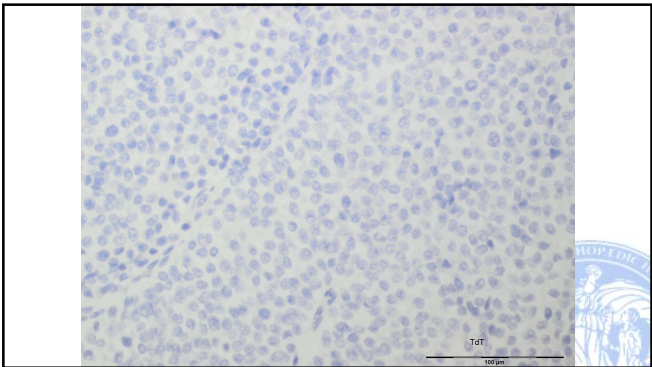
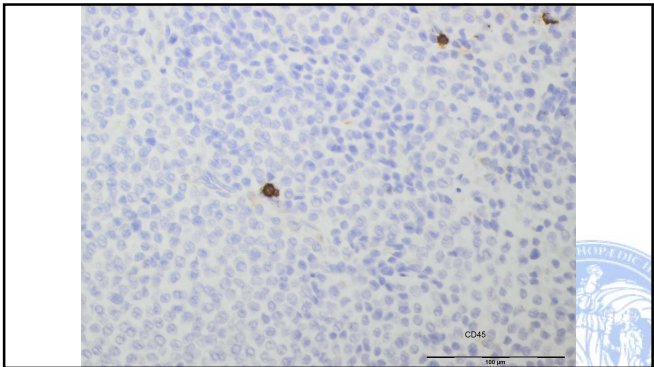
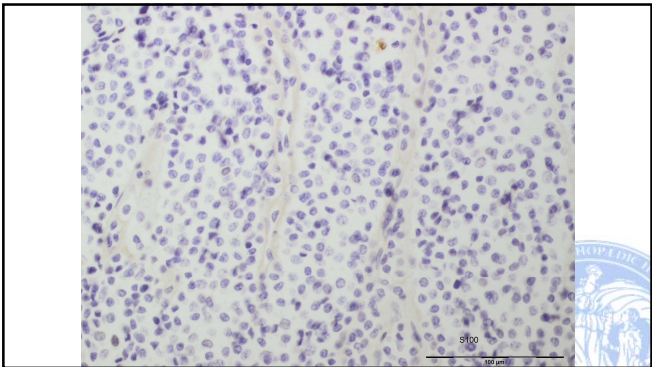
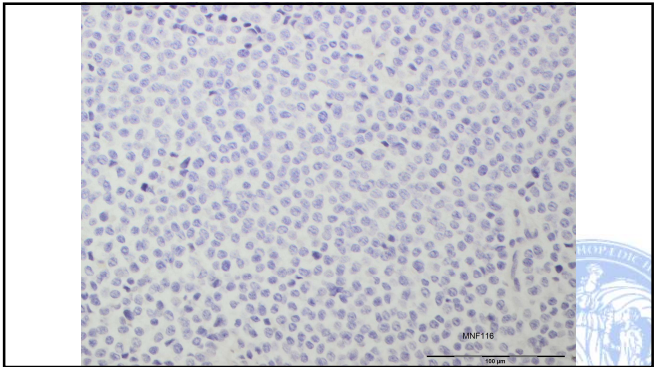
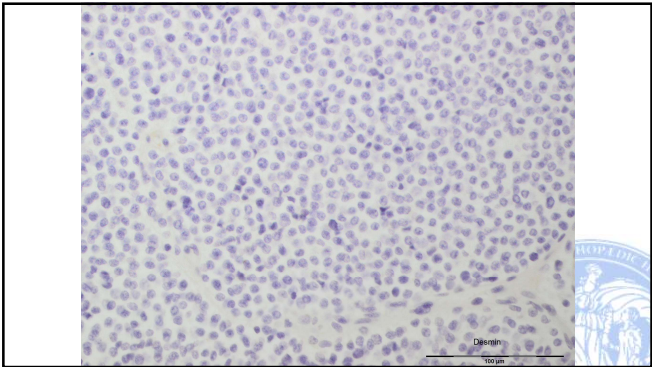


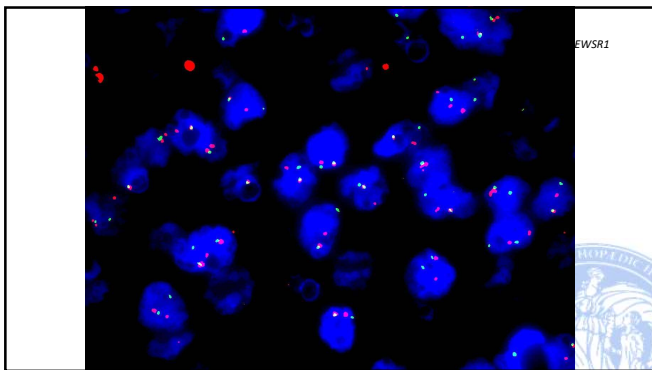
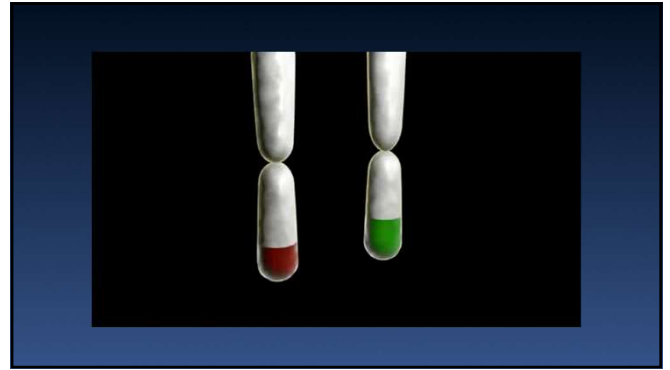
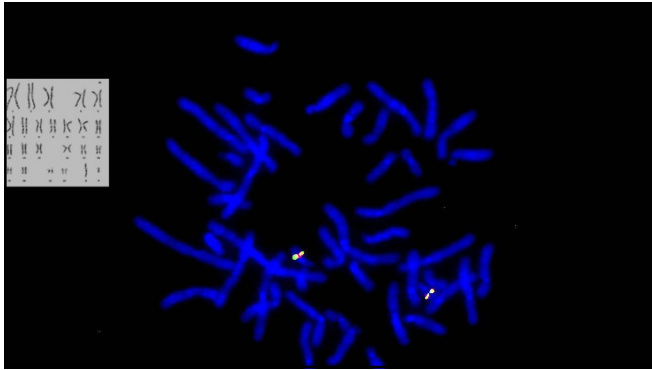
Immunohistochemistry

- CD99
- Desmin
- PanCK (MNf116)
- S100
- CD45
- TdT

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Ewing's sarcoma

- Children and adolescents: peak on 2nd decade of life
- 80% <20 yo
- 1.4M:1F
- Sites: any bone or soft tissue
 - metadiaphyseal in long bones
 - pelvis and ribs

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Ewing's sarcoma

- All cases associated with a fusion between a gene of the FET family and a gene of the ETS family
 - *EWSR1-FLI1* (~ 85%)
 - *EWSR1-ERG* (~ 10%)
 - *EWSR1-ETV1*
 - *EWSR1-ETV4*
 - *EWSR1-FEV*
 - *FUS-ERG*
 - *FUS-FEV*

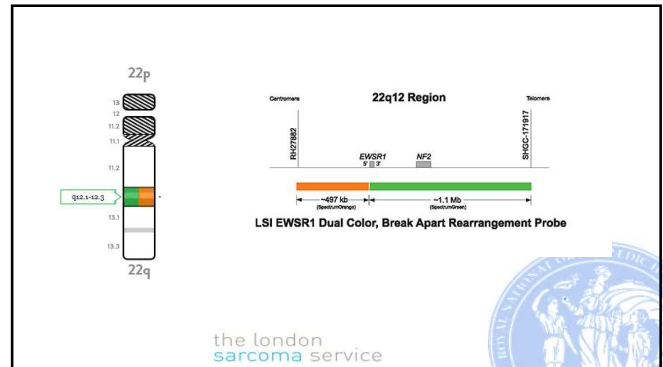
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Ewing's sarcoma

- Prognosis: 65-70% cure rate for localized disease
- Metastatic and early relapsing tumors = poor prognosis < 30% in 5y
- Histopathological assessment of tumour necrosis – cut off 10% residual viable tumour cells – some prognostic value

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Diagnosis of small round cell tumours

- Multidisciplinary approach:
 - Clinical information
 - Imaging
 - Pathology
 - Histological features
 - Immunohistochemistry
 - Molecular tests

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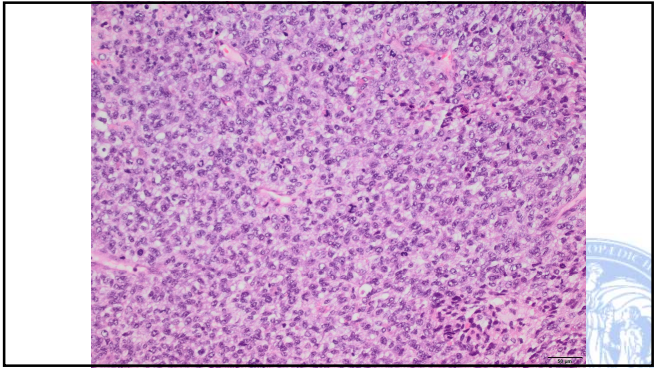
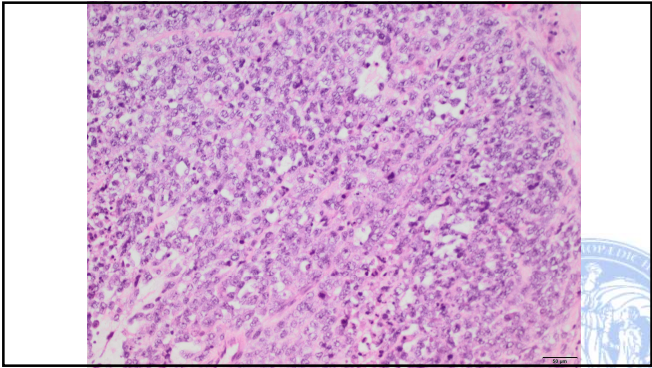
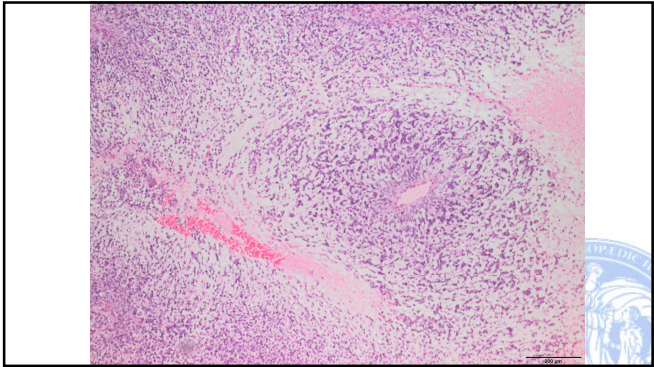
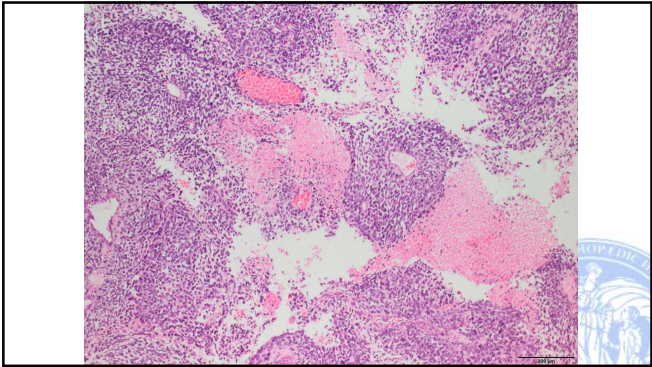
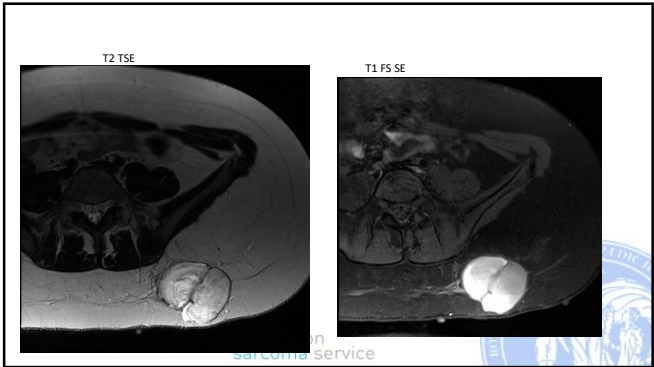


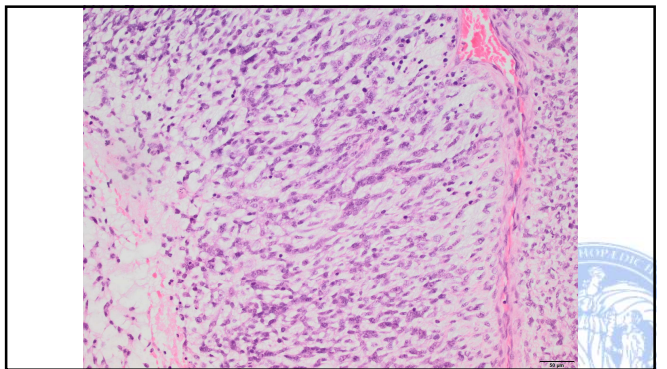
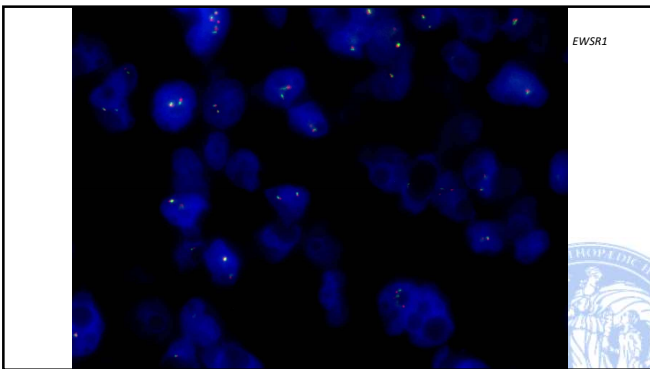
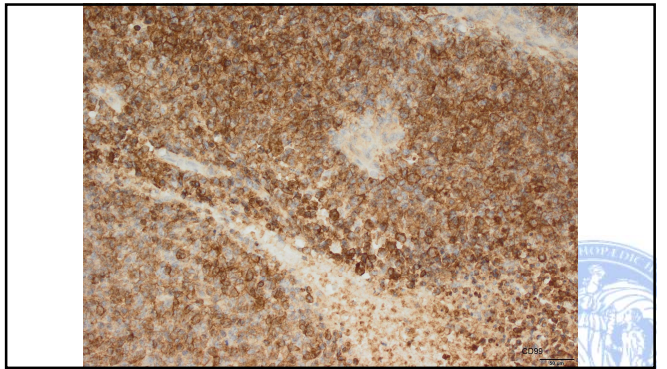
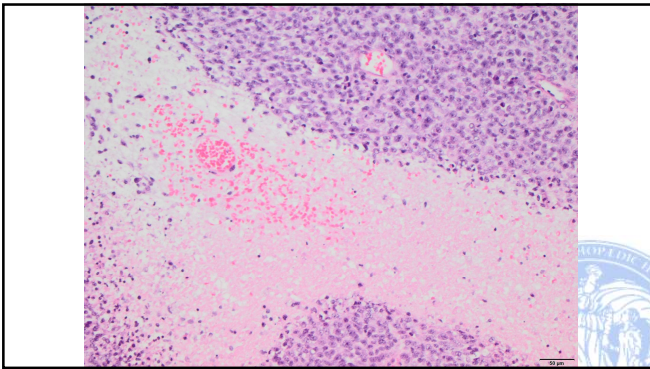
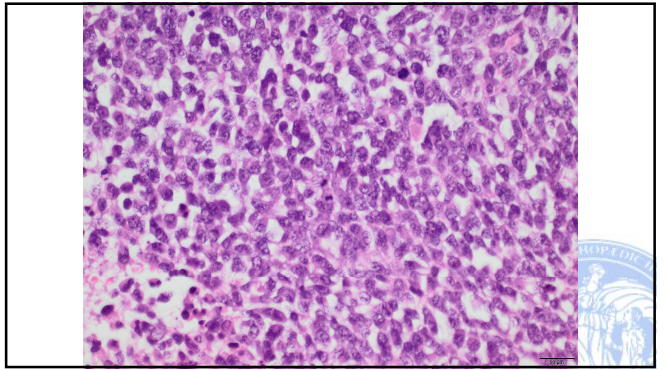
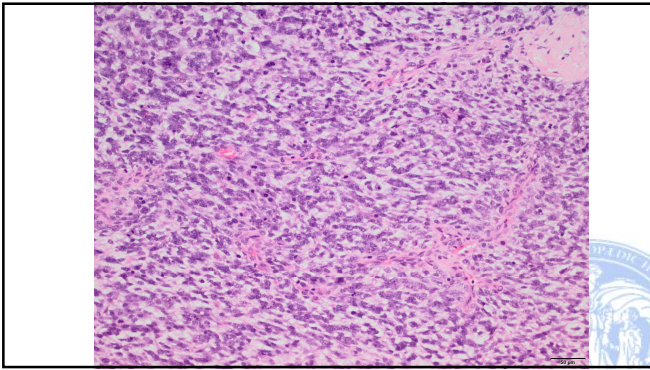
Case 2

15yo female presented with a lump in the left buttock

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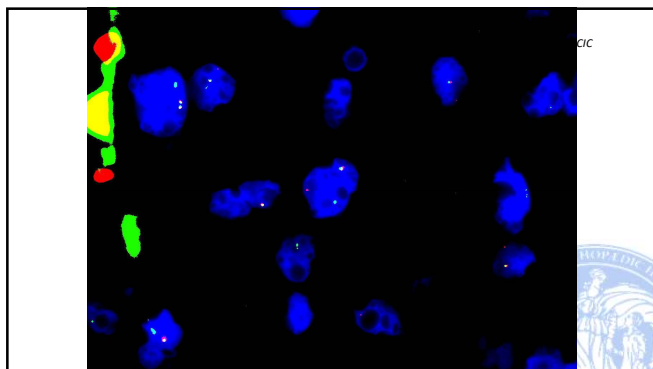
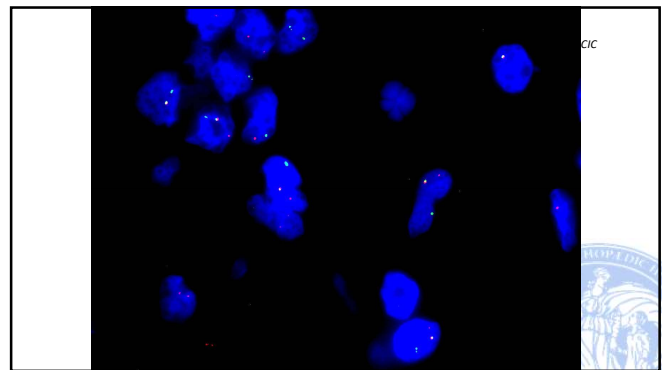
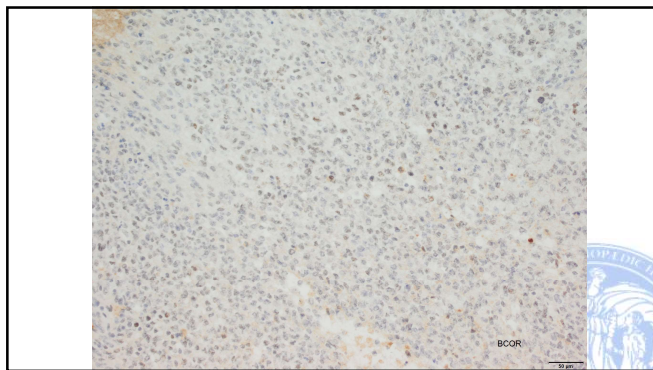
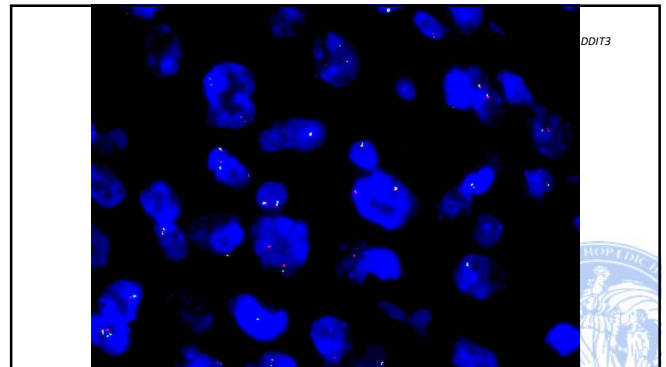


3.0: Undifferentiated small round cell sarcomas of bone and soft tissue

- 3.0.1: Ewing sarcoma
- 3.0.2: Round cell sarcoma with EWSR1-non-ETS fusions
- 3.0.3: CIC-rearranged sarcoma
- 3.0.4: Sarcoma with BCOR genetic alterations



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CIC-rearranged sarcoma

- High-grade round cell undifferentiated sarcoma defined by *CIC* gene (19q13) rearrangement.
- Any age group. Peak on young adults (25-35yo).
- Slight male predominance.
- Majority in the deep soft tissues of the extremities and trunk
Other sites include head&neck, pelvis, retroperitoneum. 10% in viscera and rare as primary in bone (<5%)

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CIC-rearranged sarcoma

- Undifferentiated round cells with at least focal multinodular pattern
- Minor spindle cell and/or epithelioid component
- A bit more atypical than Ewing, often with vesicular nuclei / nucleoli
- Pale eosinophilic cytoplasm
- Myxoid change with reticular or pseudo-acinar arrangement (1/3 of cases).
- CD99, often present, focal /patchy but may be diffuse.
- ERG can be positive – S100, CK, muscle markers are usually negative
- (WT1 and ETV-4 Positive . NKX2-2 negative)

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CIC-rearranged sarcoma

- 95% *CIC-DUX4*
As a result of either t(4;19)(q35;q13) or t(10;19)(q26;q13) translocation
- Rare other partners involved in the rearrangement with *CIC*:
 - *FOXO4*, *LEUTX*, *NUTM1*, and *NUTM2A*
- The gene expression profile of *CIC* sarcoma is distinct from that of Ewing sarcoma

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CIC-rearranged sarcoma

- Highly aggressive course with frequent metastases most commonly to the lung.
- 5-year overall survival rate varies from 17 to 43
- Poorer chemotherapy response when compared to Ewing sarcoma

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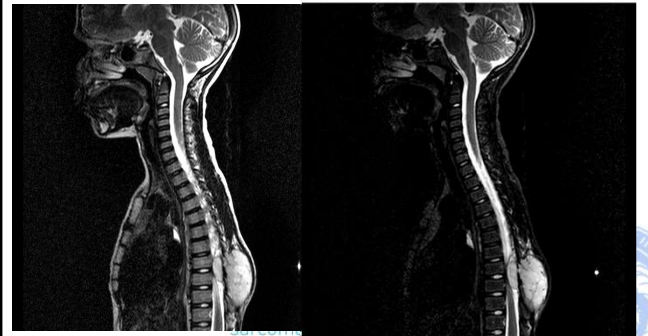
Case 3

10yo male presented with a lump on his back

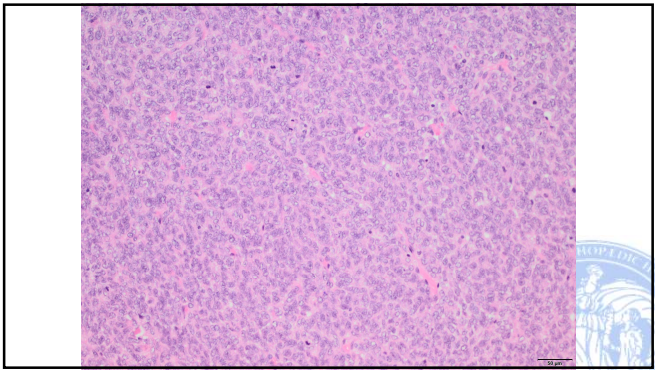
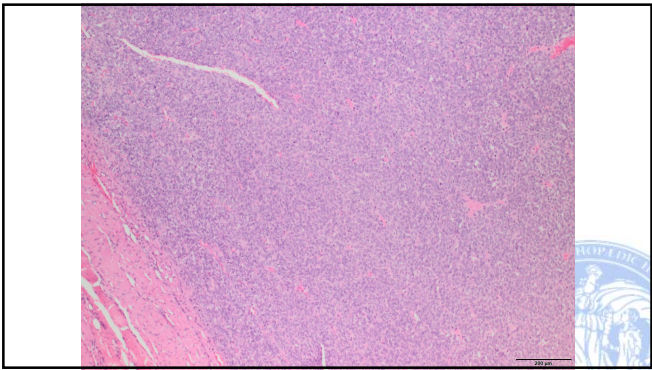
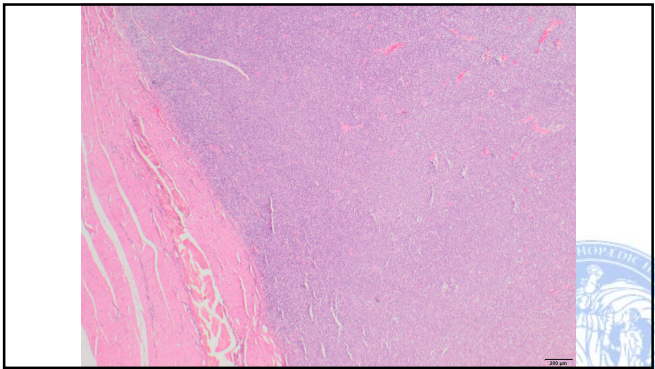
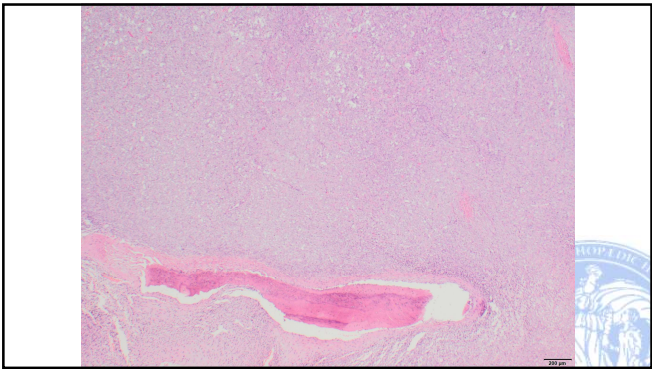
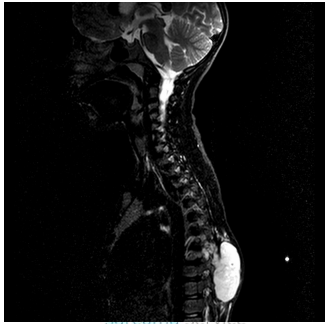
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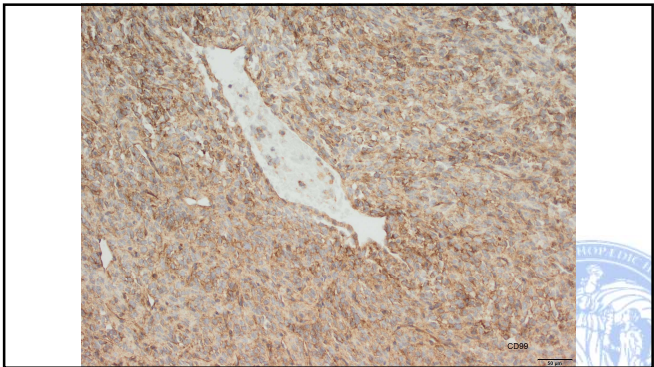
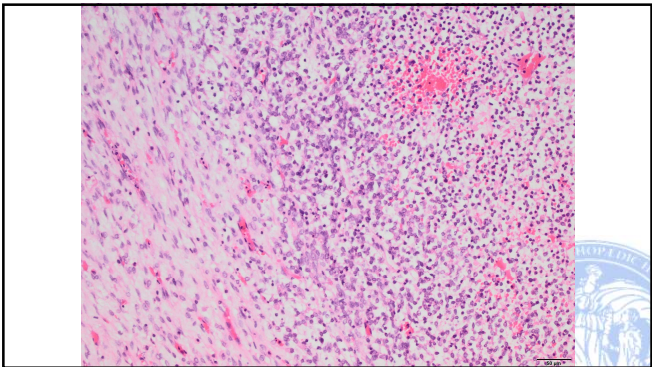
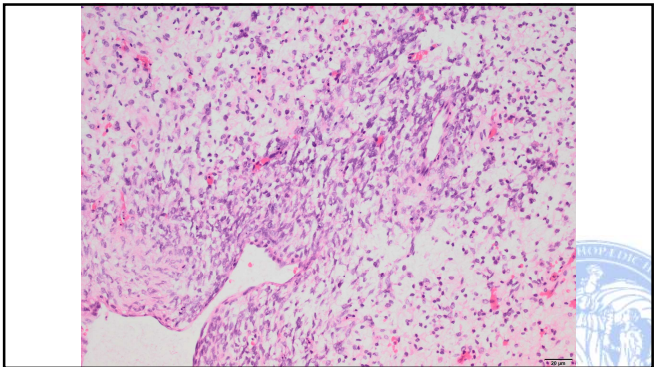
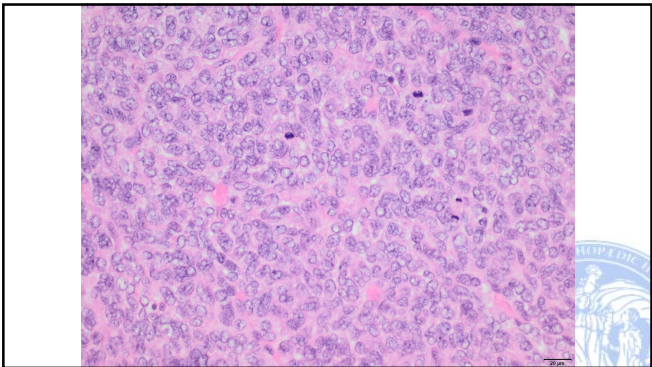
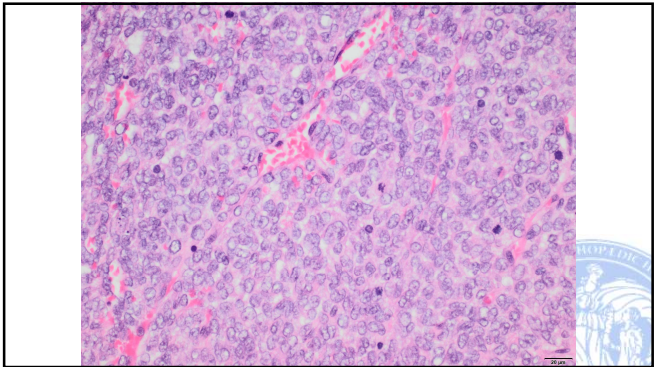
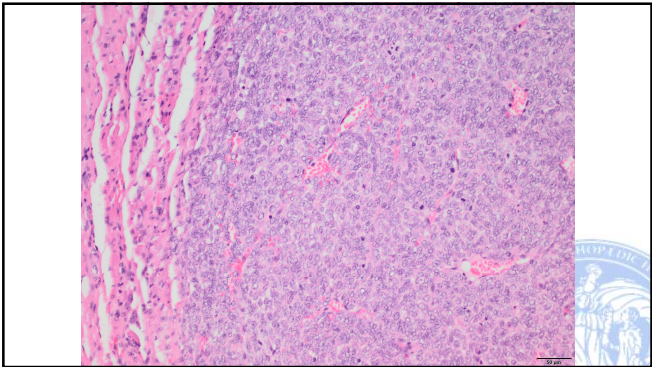


T2W TSE SAG



STIR TSE SAG – TUMOUR ARISING FROM THE SPINAL PROCESS T8

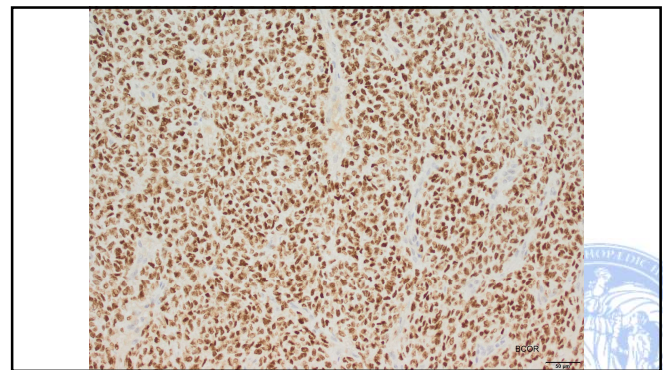
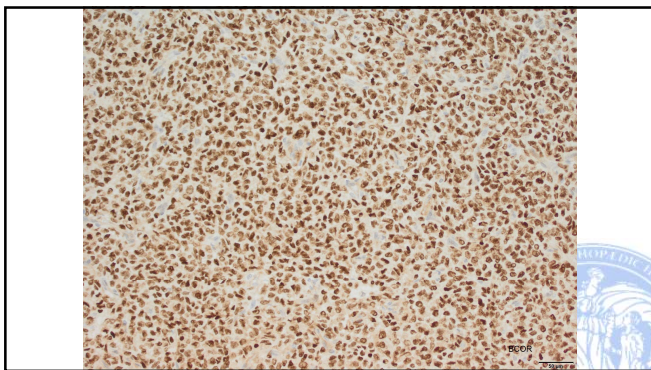
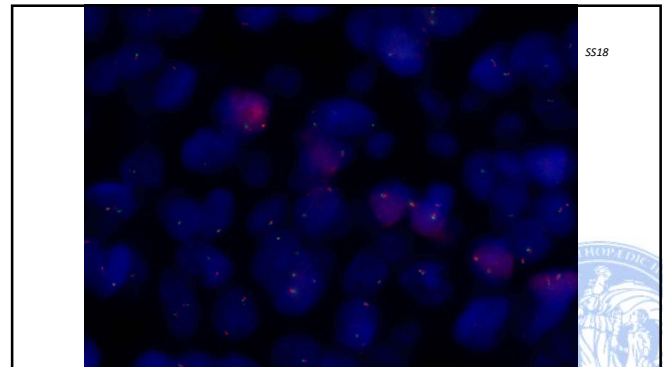




IHC

- Negative for MNF116, SMA, desmin, S100, CD45, TdT and CD34
- Scattered cells express EMA.

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Results: RNA was extracted. After reverse transcription, the housekeeping gene *GAPD* was successfully amplified (up to 200bp) indicating satisfactory RNA quality for the target fusion tested.

A fusion transcript for *BCOR-e15/CCNB3-e5* was detected.

Conclusion: *BCOR/CCNB3* fusion transcript is detected (Positive) in the above tested sample.

BCOR sequence reference: NM_001123383.1;
CCNB3 sequence reference: NM_033031.2

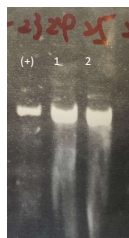
Interpretation of Results

- The integrity of the test sample is tested by amplifying a housekeeping gene *GAPD*.
- A positive result is reported when the test sample amplifies an appropriate sized band in both the housekeeping gene and test translocation
- A negative result is reported when the test sample successfully amplifies the housekeeping gene and is negative for the translocation test
- A non-informative result is reported when the housekeeping gene fails to amplify and no visible band is observed in the translocation test

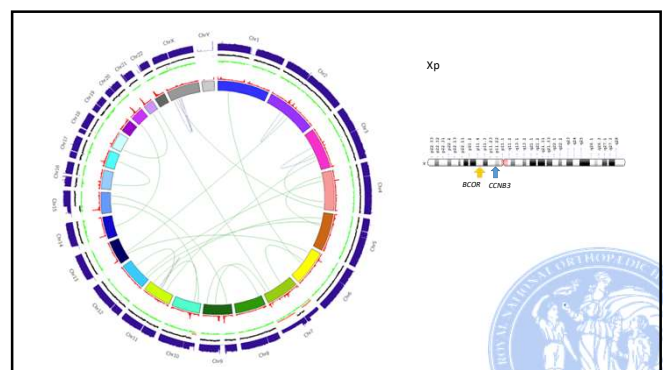
Reported by: Dr. Hongqiao Ye

Reviewed and authorized by: Dr. Francisco J. Mary

Date: 09/04/2018



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BCOR-CCNB3 undifferentiated sarcoma

- Bone and soft tissue (1.5bone:1ST)
- 90% of cases in patients under 20y of age
- 4.5M:1F
- Pelvis, lower limbs and paraspinal region
- IHC: BCOR (SATB2, TLE1, CyclinD1).
CD99 is half of the cases.

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Other BCOR associated sarcomas

- *BCOR-MAML3* or *BCOR-ZC3H7B* sarcomas
 - Wider age range when compared to *CCNB3* cases
- Tumours with *BCOR* internal tandem duplications.
 - Infantile undifferentiated sarcoma and primitive myxoid mesenchymal tumour of infancy.
 - First year of life, may be present at birth

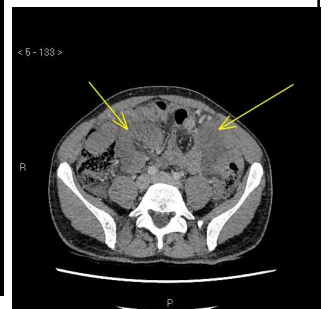
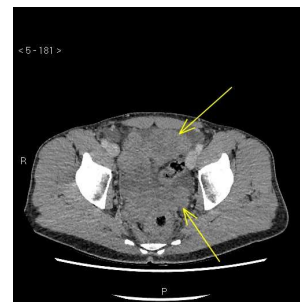
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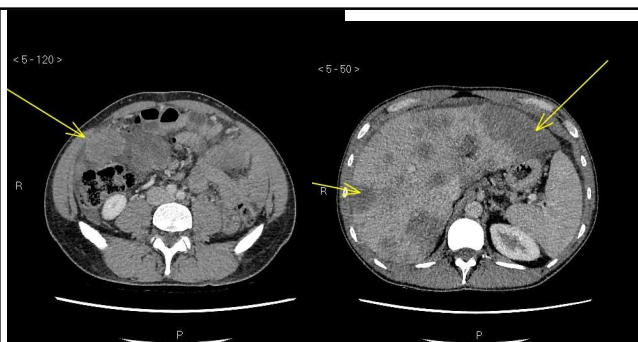
Case 4

41 yo male presented with abdominal pain

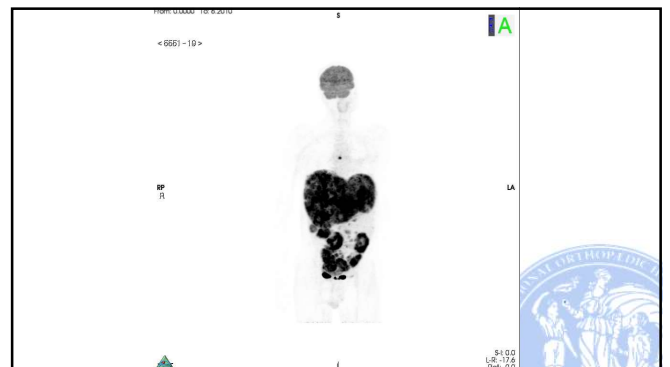
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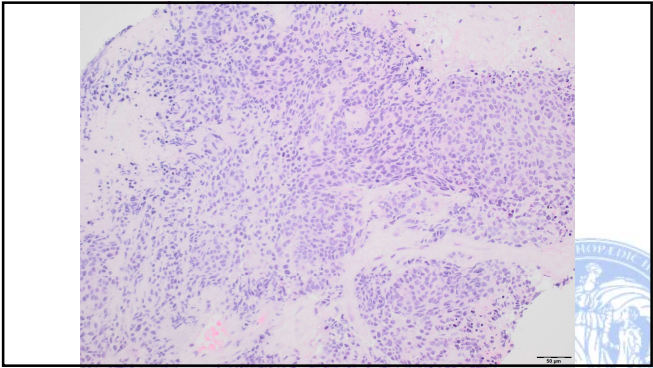
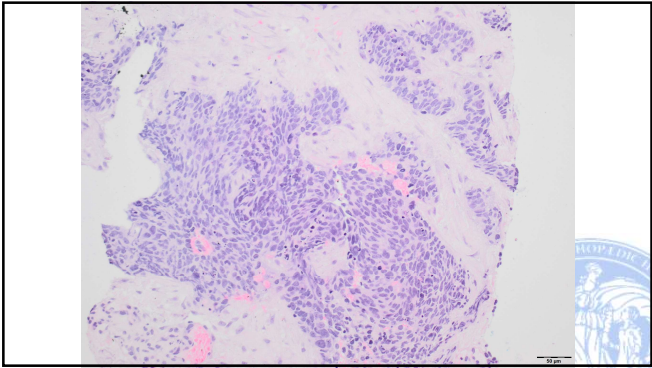
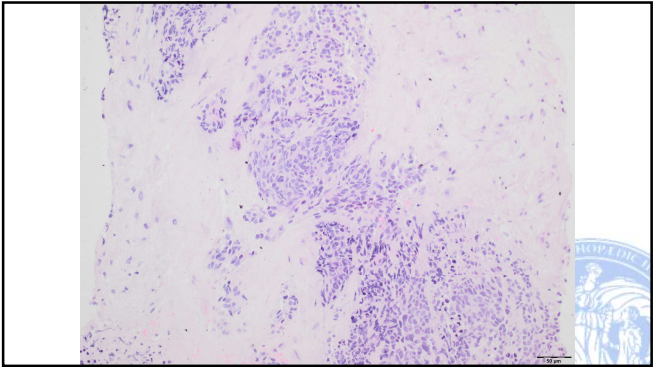
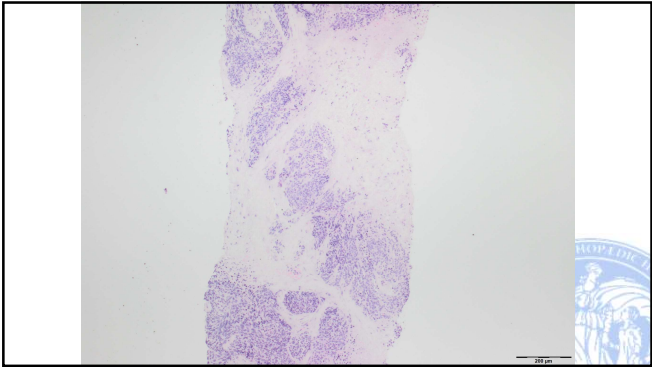
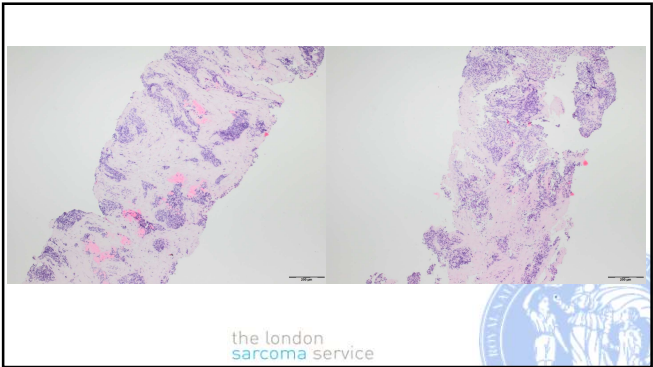
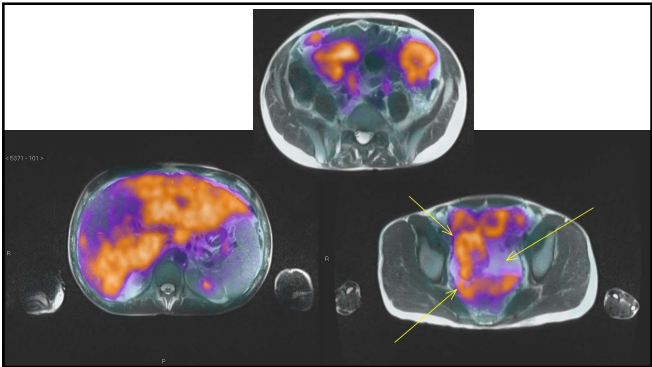
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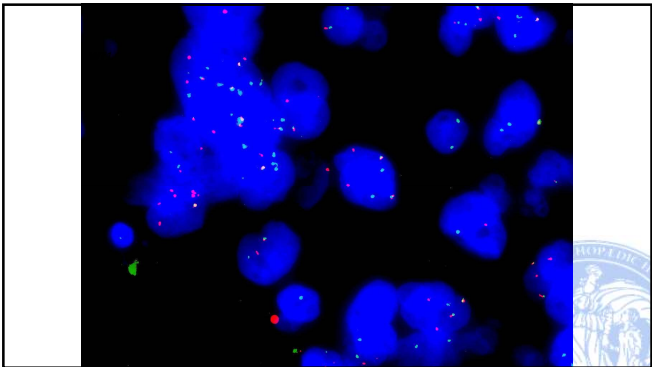
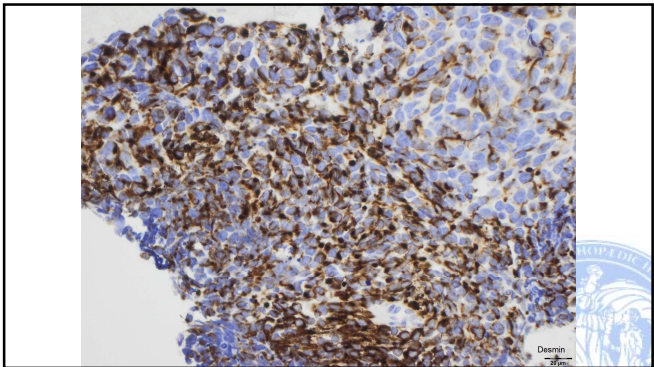
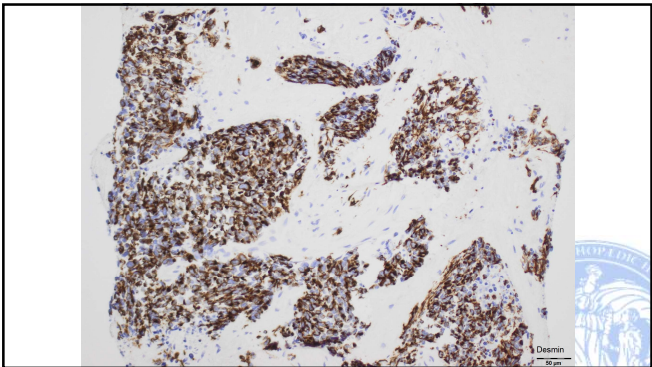
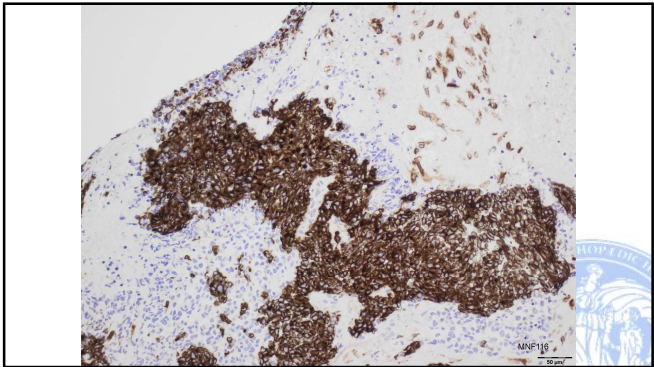
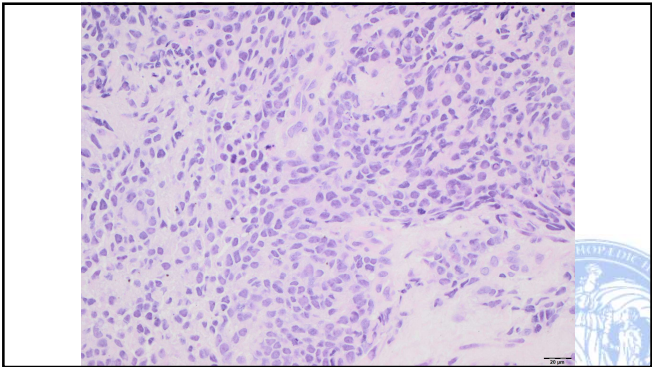


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S4:0.0
C4:0.0
S4:0.0





Results: RNA was extracted. After reverse transcription, the housekeeping gene *GAPDH* was successfully amplified (up to 200bp) indicating satisfactory RNA quality for the target fusion tested.

EWSR1-exon7/WT1-exon8 fusion transcripts were detected.

The fusion transcript for EWSR1-exon9/WT1-exon8 was not detected.

Conclusion: EWSR1-e7/WT1-e8 fusion transcript **is detected (Positive)** in the above tested sample.

EWSR1 sequence reference: NM_005243.3. WT1 sequence reference: NM_024426.4

Interpretation of Results

- The integrity of the test sample is tested by amplifying a housekeeping gene either *PCR* or *GAPDH*.
- A positive result is reported when the test sample amplifies an appropriate sized band in both the housekeeping gene and test translocation.
- A negative result is reported when the test sample successfully amplifies the housekeeping gene and is negative for the translocation test.
- A non-informative result is reported when the housekeeping gene fails to amplify and no visible band is observed in the translocation test.

Reported by: Fitim Benitha Reviewed and authorized by: Dr. Roberto Rodriguez Date: 28/03/2019

PCP18_Priori template_R1_PCR v1 21/03/2014 Page 1 of 1

Sarcoma Service

Desmoplastic small round cell tumour

- Abdominal / pelvic cavity
 - rare cases on thoracic cavity, paratesticular, limbs, head & neck
- Wide age range but predominantly in children and young adults
- Male predominance
- Small round cells on a desmoplastic stroma
 - pleomorphic areas, rosettes, rhabdoid cells, granular diff, may be seen.

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Desmoplastic small round cell tumour

- IHC – multiphenotypic
 - CK and desmin in most cases
 - Desmin distinctive dot-like cytoplasmic expression
 - WT1. (C-terminus)
 - stromal component is SMA positive
- *EWSR1-WT1* fusion - t(11;22)(p13;q12)
- Poor prognosis

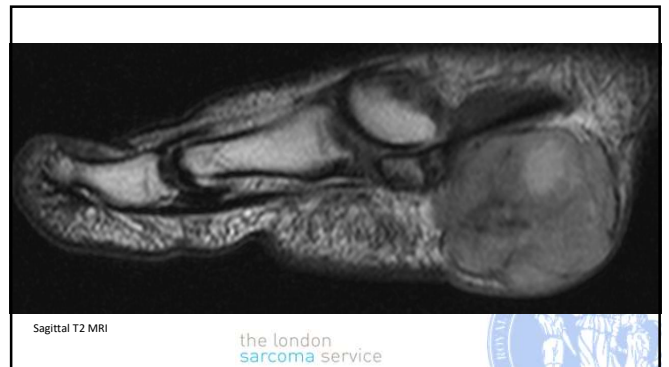
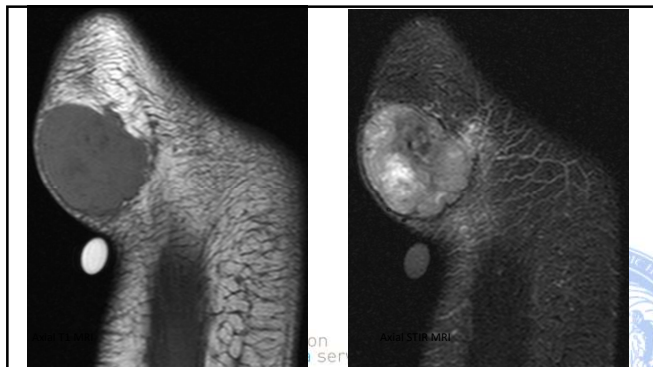
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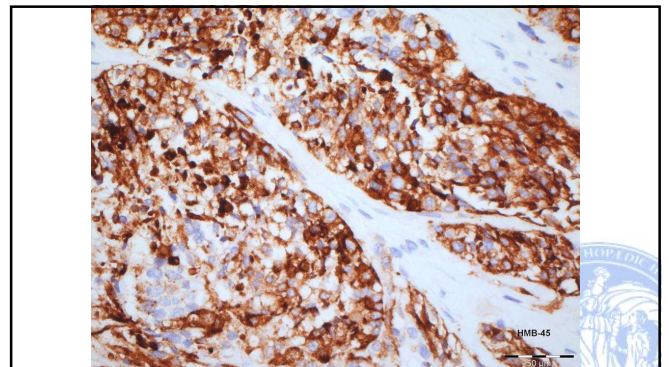
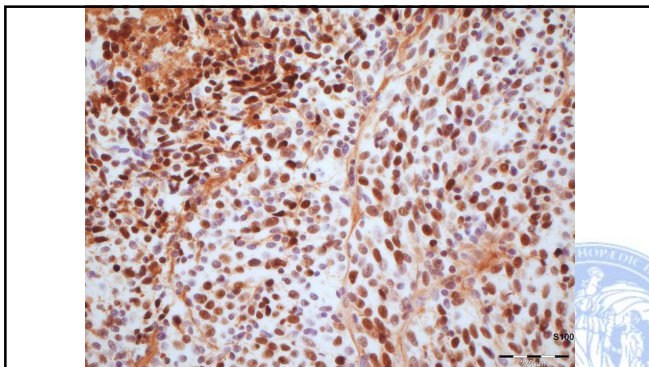
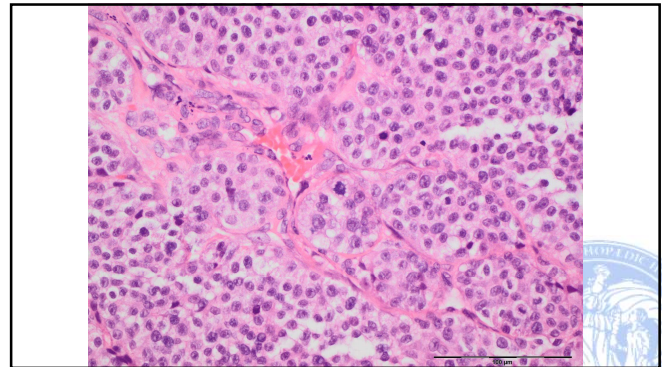
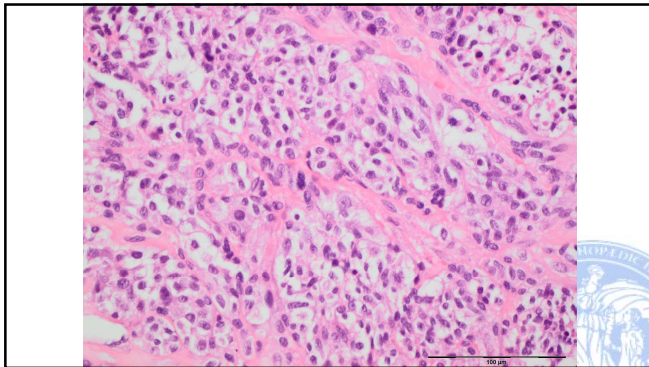
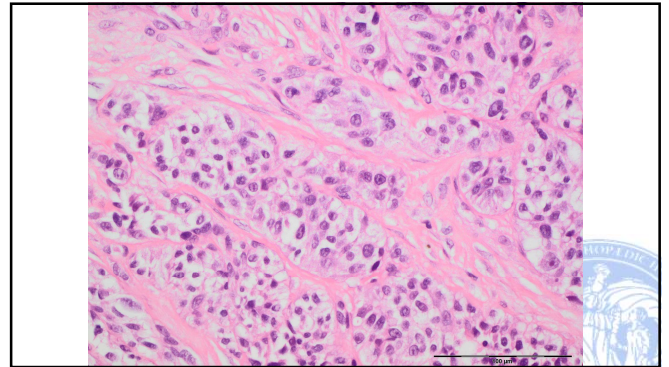
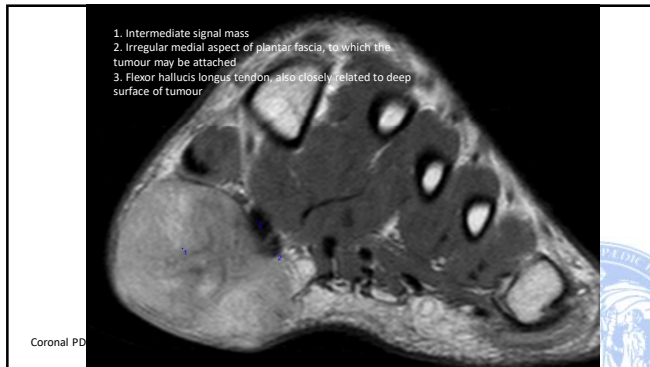


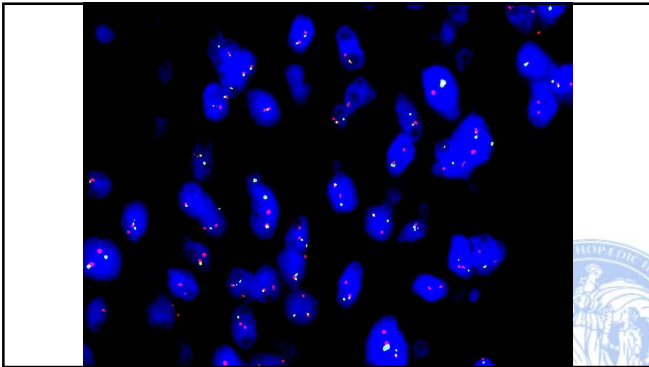
Case 5

31 yo male presented with a painless mass in the left foot

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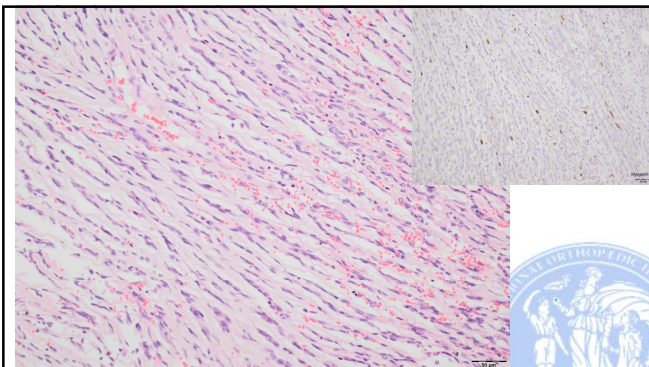
Clear cell sarcoma

BoSTT - Case 10
Bone and soft tissue tumours:
case studies.

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Case 6: 17 yo male - Base of tongue tumour extending into pharynx with obstruction of airway.

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Sclerosing
rhabdomyosarcoma

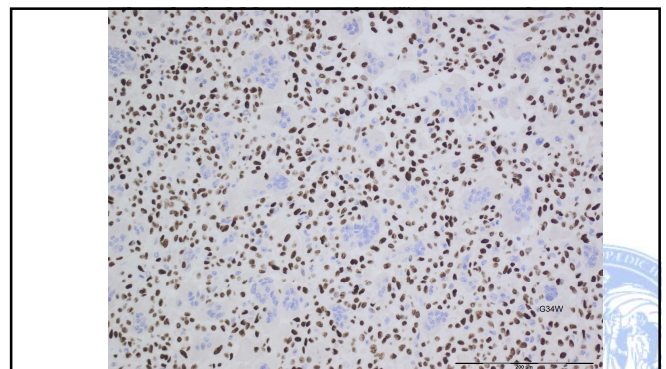
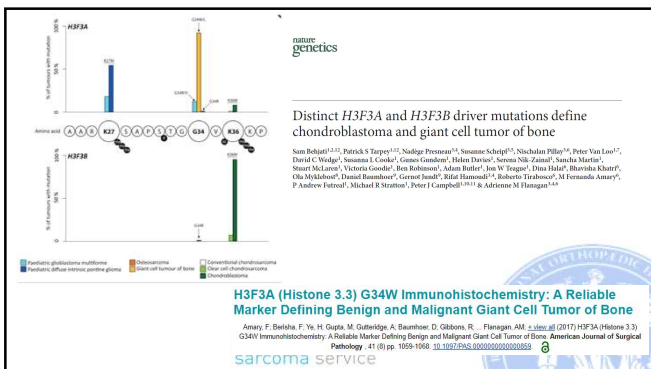
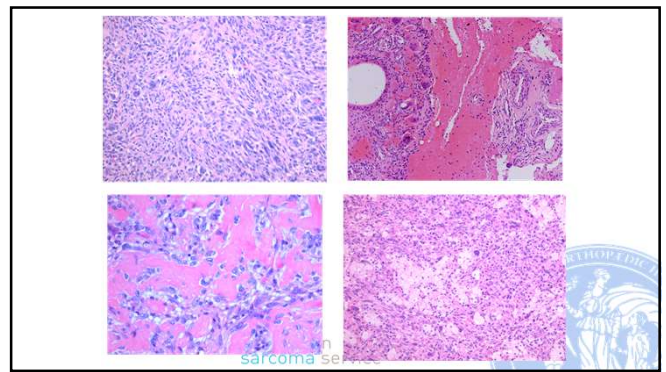
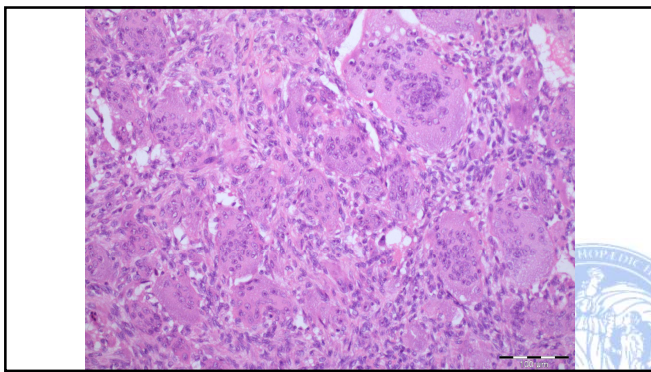
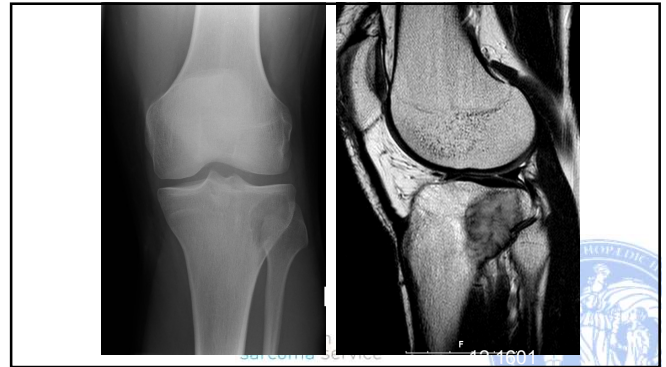
- *MyoD1* mutation (hotspot L122R)
- MyoD1 IHC – transcription factor
- Aggressive clinical course as compared to gene fusion Sclerosing rhabdos.

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Bone tumours

Subarticular

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Giant cell tumour of bone

- H3-3 G34W
- Example of IHC to targeting products of point mutation.

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Thank you!



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