Review of the New World Health Organization (WHO) Classification of Soft Tissue Tumours (no time for bone)

Sarcoma Classification

- Can be challenging
- Heterogeneous group of tumors with >50 histological subtypes, each with varying clinical phenotypes and behavior
- Some tumors are unclassifiable
- Many benign entities (100:1), some of which can be confused for sarcomas
Sarcoma Classification: Morphology

- Round cell tumor, epithelioid, spindle cell sarcoma
- Useful in unclassifiable tumors
- Does not always provide information on behavior or nature of tumor
- Important to determine malignant potential if possible

Sarcoma Classification: Histogenesis/Line of Differentiation

- Osteosarcoma
- Chondrosarcoma
- Angiosarcoma
- Liposarcoma
- Synovial Sarcoma
- MFH
- MFH
- Leiomyosarcoma
- Rhabdomyosarcoma
- MPNST

Sarcoma Classification: Line of Differentiation

- Morphologically or by immunohistochemical studies
- Beware of mimics
- Some tumors lack a normal counterpart (i.e. synovial sarcoma)
- Not all tumors with similar differentiation will behave the same
Sarcoma Classification: Biological Potential

- **Benign:**
  - Usually do not recur and if do so in a non-destructive fashion, almost never metastasizes

- **Intermediate (locally aggressive):**
  - Often recur, infiltrative and destructive

- **Intermediate (rarely metastasizing):**
  - Locally aggressive but can give rise to metastasis (<2%)

- **Malignant:**
  - Recurs, destructive, high risk of metastasis

<table>
<thead>
<tr>
<th>Lipoma</th>
<th>Desmoid</th>
<th>Angiomatoid FH</th>
<th>Synovial Sarcoma</th>
</tr>
</thead>
</table>

Introduction

- The 2013 book surpasses the previous 2002 edition in regards to:
  - Number of pages
  - Illustrations
  - Authors (159 authors, 24 different countries)

Major Changes

- The addition of two entirely new chapters:
  - Gastrointestinal stromal tumours
  - Nerve sheath tumours
- Incorporation of more detailed cytogenetic and molecular data.
- The designation of two distinct types of intermediate malignancy in terms of biological potential:
  - The “locally aggressive”
  - The “rarely metastasizing”
Minor Changes

• Tumors moved into new sections (angiomatoid MFH/FH and extraskeletal myxoid chondrosarcoma moved to “Tumors of Uncertain differentiation”)
• Multiple newly described entities recognized
• A few skin tumour entries were added
• A few entities likely representing morphologic variants of other tumours were deleted

Grading systems
French Federation of Cancer Centers Sarcoma Group

General
Grade 1: total score of 2-3 points
Grade 2: total score of 4-5 points
Grade 3: total score of 6-8 points

Tumor differentiation:
1 point: resembles normal adult mesenchymal tissue, may be confused with a benign lesion, such as well differentiated liposarcoma
2 points: histologic typing is certain, such as myxoid liposarcoma
3 points: several sarcomas, liposarcoma, being’s sarcoma/HKB, sarcomas of doubtful tumor type, embryonal sarcoma

Mitotic count (count 10 successive high power fields [area of 0.17 mm squared] in most mitotically active area):
1 point: 0-9 mitoses
2 points: 10-19 mitoses
3 points: 20 or more mitoses

Tumor necrosis:
0 points: no necrosis on any slides
1 point: no more 50% necrosis for all examined tumor surface
2 points: tumor necrosis of 50% or more of examined tumor surface

Liposarcoma – Tumor Differentiation Score

1. ALTWD LPS
2. Myxoid LPS
3. Round Cell LPS

De-Diff LPS

De-Diff LPS

De-Diff LPS

De-Diff LPS

De-Diff LPS
### Leiomyosarcoma – Tumor Differentiation Score

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<th>Grade</th>
<th>Score</th>
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<tr>
<td>Conventional</td>
<td>2</td>
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<tr>
<td>Epithelioid</td>
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</table>

### FNCLCC Grading

- **Mitotic Count**: In the most mitotically active area, ten successive high-power fields (at 400x magnification) using a 40x objective.
  - Grade 1: 0-9 mitoses per 10 HPFs
  - Grade 2: 10-19 mitoses per 10 HPFs
  - Grade 3: >20 mitoses per 10 HPFs

- **Tumor necrosis**: Evaluated on gross examination and validated with histological sections.
  - Grade 0: No tumor necrosis
  - Grade 1: <50% tumor necrosis
  - Grade 2: >50% tumor necrosis

- **Degree of Differentiation**: 1-3

### French Federation of Cancer Centers Sarcoma Group

**Grades of common sarcoma types**

- Fibrosarcoma – well differentiated – 1
- Liposarcoma – well differentiated – 1
- Liposarcoma – conventional – 2
- UPS/MFH – pleomorphic with storiform pattern – 2
- Fibrosarcoma – conventional – 2
- Liposarcoma – myxoid – 2
- Liposarcoma – round cell – 3
- Malignant triton tumor – 3
- Diffuse large B-cell lymphoma – 3
- MFH – pleomorphic without storiform pattern – 3
- Myxofibrosarcoma – 2
- Chondrosarcoma – mesenchymal – 3
- Clear cell sarcoma – 3
- Epithelioid sarcoma – 3
- Chondrosarcoma – poorly differentiated – 3
- Myxoid liposarcoma – 3
- Synovial sarcoma – 3
- PNET – 3
- Angiosarcoma – poorly differentiated / epithelioid – 3
- Angiosarcoma – myxoid / epithelioid / pleomorphic – 3
- Chondrosarcoma – poorly differentiated / epithelioid – 3
- Malignant peripheral nerve sheath tumor – 3
- Synovial sarcoma – mesenchymal – 3
- Synovial sarcoma – epithelioid / poorly differentiated / pleomorphic – 3
- MFH – giant cell – 3
- Rhabdomyosarcoma – alveolar / embryonal – 3
- Ewing sarcoma – 3
- Ewing sarcoma – alveolar / embryonal – 3
- Ewing sarcoma – pleomorphic – 3
- Ewing sarcoma – epithelioid – 3
- Ewing sarcoma – poorly differentiated – 3
- Extraosseous Ewing sarcoma – 3
- Glomus tumor – 3
- Chordoma – 3
- Chondrosarcoma – 3
- Chondrosarcoma – myxoid / epithelioid – 3
- Chondrosarcoma – round cell – 3
- Chondrosarcoma – well differentiated – 3
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- Chondrosarcoma – 2
FNCLCC Grading

- Three tiered grading system
- Based on mitotic activity, necrosis and differentiated but also requires assessment of cellularity & pleomorphism for certain subtypes
- Also proven to correlate with prognosis

FNCLCC vs. NCI

- Both three-tiered and prognostic of metastasis development and tumor mortality
- FNCLCC considered slightly better (classifies less tumors as grade 2) with better reproducibility
- FNCLCC recommended over NCI by CAP guidelines and now adopted by the AJCC 7th edition
National Cancer Institute tumor grading system

Grade 1:
- Well differentiated liposarcoma
- Myxoid liposarcoma
- Subcutaneous myxoid MMT
- Well differentiated malignant hemangiopericytoma
- Well differentiated fibrosarcoma
- Well differentiated leiomyosarcoma
- Malignant schwannoma (MPNST) if resembles neurofibroma
- Myxoid chondrosarcoma

Grade 2:
- Other histologic types with less than 15% necrosis

Grade 3:
- Extraskeletal Ewing sarcoma / PNET
- Extraskeletal osteosarcoma
- Mesenchymal chondrosarcoma
- Malignant triton tumor
- Other histologic types with 15% or more necrosis

Molecular classification of soft tissue tumours

- More detailed molecular and genetic studies of soft tissue tumours are now incorporated with the current WHO classification.
- This resulted in recognition of new separate entities and omission and reclassification of others.
- More strict criteria are now applied to the “undifferentiated sarcoma” category.
Major Molecular and genetic advances

- **MYH9-USP6** gene recurrent fusion in nodular fasciitis has confirmed its previously controversial neoplastic nature.
- **MUC4** in low-grade fibromyxoid sarcoma highly sensitive and specific; linked to the presence of the FUS-CREB3L1 fusion gene.
- Cytogenetic analysis of gene-expression profiling datasets identified multiple molecular subgroups of leiomyosarcoma, including a “muscle-enriched” subtype and less differentiated group with varying prognoses.
- Some tumours classified as UPS cluster closely with a subset of leiomyosarcoma suggesting the existence of “dedifferentiated leiomyosarcoma.”
- Tumours with mixed embryonal and alveolar pattern were previously considered to be variants of ARMS, but most of these lack PAX3-FKHR fusions, thus appearing to be clinically and biologically more akin to embryonal rhabdomyosarcoma.

### Liposarcoma Classification

- **Well differentiated Liposarcoma**
  - (Dedifferentiated)
    - Genetic amplification: 12q13~15
- **Myxoid Liposarcoma**
  - (Round Cell)
    - Translocation: t(12;16)(q13p11)  
      - DDIT3 & FUS (EWSR1)
- **Pleomorphic Liposarcoma**
  - Complex karyotype
  - **PS3** mutations

### Adipocytic Tumours

<table>
<thead>
<tr>
<th>2002</th>
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<tbody>
<tr>
<td>Benign</td>
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<tr>
<td>Lipoma</td>
<td>Lipoma</td>
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<td>Lipomatosis of nerve</td>
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<td>Liposarcoma / liposarcomatosis</td>
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<td>Angiomyxoma</td>
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<td>Myelolipoma</td>
<td>Myelolipoma of soft tissue</td>
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<table>
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<td>Liposarcoma / dermatofibrosarcoma</td>
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<td>Pleomorphic liposarcoma</td>
<td>Pleomorphic liposarcoma</td>
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<td>Mixed-type liposarcoma</td>
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<tr>
<td>Liposarcoma, not otherwise specified</td>
<td>Liposarcoma, not otherwise specified</td>
</tr>
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</table>
Adipocytic tumours

General Changes

- Mixed-type liposarcoma deleted.
- Molecular testing almost always leads to reclassifying of “mixed-type liposarcoma” into a specific liposarcoma.
- Myxolipoma deleted.
- Most of the so-called myxolipomas are now considered variants of spindle cell lipoma.

Adipocytic tumours

Atypical lipomatous tumour (ALT)

- ALT is divided into 3 main subgroups (rather than 4):
  - (1) adipocytic (lipoma-like)
  - (2) sclerosing
  - (3) inflammatory types
- The lack of MDM2 immunopositivity or 12q15 amplification in spindle cell liposarcoma, suggests that it is a separate group.
Adipocytic tumours
Dedifferentiated liposarcoma

“Homologous lipoblastic dedifferentiation” or “pleomorphic liposarcoma-like features”:
A rare situation of homologous dedifferentiation resembling pleomorphic liposarcoma
As for heterologous differentiation, this is not known to affect disease progression

Fibroblastic / myofibroblastic tumours

2002

- Nodular fasciitis
  - Benign
  - Proliferative
  - Proliferative myositis
  - Myositis ossificans
  - Fibro-osseous pseudotumour of digits
  - Ischemic fasciitis
  - Elastofibroma
  - Fibrous hamartoma of infancy
  - Fibromatosis coli
  - Juvenile hyaline fibromatosis
  - Inclusion body fibromatosis
  - Fibroma of tendon sheath
  - Desmoplastic fibroblastoma
  - Mammary-type myofibroblastoma
  - Calcifying aponeurotic fibroma
  - Angiomyofibroblastoma
  - Cellular angiofibroma
  - Nuchal-type fibroma
  - Gardner fibroma
  - Calcifying fibrous tumour
  - Giant cell angiofibroma

2013

- Benign
  - Nodular fasciitis
  - Proliferative fasciitis
  - Proliferative myositis
  - Myositis ossificans
  - Fibro-osseous pseudotumour of digits
  - Ischemic fasciitis
  - Elastofibroma
  - Fibrous hamartoma of infancy
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  - Calcifying aponeurotic fibroma
  - Angiomyofibroblastoma
  - Cellular angiofibroma
  - Nuchal-type fibroma
  - Gardner fibroma
  - Calcifying fibrous tumour
  - Giant cell fibroblastoma

- Intermediate (locally aggressive)
  - Palmar/plantar fibromatosis
  - Desmoid-type fibromatosis
  - Lipofibromatosis
  - Giant cell fibroblastoma

- Intermediate (rarely metastasizing)
  - Dermatofibrosarcoma protuberans
  - Pigmented dermatofibrosarcoma protuberans
  - Solitary fibrous tumour, malignant
  - Inflammatory myofibroblastic tumour
  - Low grade myofibroblastic sarcoma
  - Myxoinflammatory fibroblastic sarcoma
  - Infantile fibrosarcoma
  - Malignant adult fibrosarcoma
  - Myxofibrosarcoma
  - Low-grade fibromyxoid sarcoma
  - Hyalinized spindle cell tumour
  - Sclerosing epithelioid fibrosarcoma

- Inflammatory myofibroblastic tumour

Fibroblastic / myofibroblastic tumours
Extrapleural solitary fibrous tumour

- The term “haemangiopericytoma” is obsolete.
- “Haemangiopericytoma” is a morphological pattern that is shared by different entities.
- “Extrapleural solitary fibrous tumour”/ “giant cell angiofibroma” category includes:
  - solitary fibrous tumour
  - Haemangiopericytoma
  - Lipomatous haemangiopericytoma
**Background**

*Low-Grade Fibromyxoid Sarcoma (LGFMS)*

- Harry L Evans (1987)
- Banal appearing but metastasizes
- N=12 – 58% metastasize, 33% died of disease with long-term follow-up
- Hyalinizing spindle cell tumor with giant rosettes (HSCTGR) – variant of LGFMS
- LGFMS and HSCTGR can have prominent epithelioid cells & sclerosis that mimic SEF

**Background**

*Sclerosing Epithelioid Fibrosarcoma (SEF)*

- Meis, Kindblom & Enzinger (1995)
- Nests and cords of epithelioid cells with prominent hyaline sclerosis
- 50% recurrence, 43% metastasis, 25% mortality (n=16)
- Other series: metastasis of 86% and mortality of up to 57%
- Can have fibromyxoid areas reminiscent of low-grade fibromyxoid sarcoma (LGFMS)
Background

SEF and LGFMS

- Reid et al. described t(7;16)(q34;p11) in LGFMS and HSCTGR including one case with SEF-like area
- Guillou et al. identified FUS-CREBL2/1 chimeric transcripts by RT-PCR in LGFMS with and without SEF-like areas and SEF
- Suggest a connection with SEF and LGFMS

Reid et al. AJSP (2003) 27(9):1229-1236
Material and Methods

Fluorescence in-situ hybridization

MUC4 & LGFMS
Conclusions

- Cytogenetically confirmed LGFMS can have SEF-like areas
  - FUS rearrangement can be detected in both components
- Vast majority of pure SEF lack FUS rearrangement by FISH (but often express MUC4)
- Despite SEF-like areas in LGFMS, unclear if all pure SEF and LGFMS are necessarily related genetically
  - SEF more aggressive than LGFMS
  - Prognosis:
    * SEF-like areas in LGFMS
    * Fusion status in pure SEF
So-called fibrohistiocytic tumours

2002
Benign
- Giant cell tumour of tendon sheath
- Diffuse-type giant cell tumour
- Deep benign fibrous histiocytoma

Intermediate (rarely metastasizing)
- Plexiform fibrohistiocytic tumour
- Giant cell tumour of soft tissue

Malignant
- Pleomorphic MFH / Undifferentiated pleomorphic sarcoma with giant cells
- Inflammatory MFH / Undifferentiated pleomorphic sarcoma with prominent inflammation

2013
Benign
- Tenosynovial giant cell tumour
- Localised type
- Diffuse type
- Inflammatory

Deep benign fibrous histiocytoma

Intermediate (rarely metastasizing)
- Plexiform fibrohistiocytic tumour
- Giant cell tumour of soft tissue

Smooth-muscle tumours

2002
Benign
- Angioleiomyoma
- Deep leiomyoma
- Genital leiomyoma

Malignant
- Leiomyosarcoma (excluding skin)

2013
Benign
- Leiomyoma of deep soft tissue

Malignant
- Leiomyosarcoma (excluding skin)
74 year old male with leg lesion

SMA

Desmin
### Pericytic (perivascular) tumours

<table>
<thead>
<tr>
<th>Year</th>
<th>Tumour Type</th>
<th>Variants</th>
<th>Tumour Type</th>
<th>Variants</th>
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<tbody>
<tr>
<td>2002</td>
<td>Glomus tumour (and variants)</td>
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<td>Glomus tumour (and variants)</td>
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### Skeletal-muscle tumours

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<td>rhabdomyosarcoma</td>
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### Vascular tumours

**2002**
- Benign
  - Haemangioma of cutaneous/subcutaneous/epithelial
  - Cavernous
  - Arteriovenous
  - Venous
  - Epithelioid

- Intermediate (locally aggressive)
  - Kaposiform haemangioendothelioma
  - Synovial

- Malignant
  - Synovial haemangioendothelioma
  - Angiosarcoma

**2013**
- Benign
  - Haemangioma
  - Arteriovenous
  - Venous
  - Epithelioid
  - Angiomatosis
  - Lymphangioma

- Intermediate (locally aggressive)
  - Kaposiform haemangioendothelioma

- Malignant
  - Synovial haemangioendothelioma
  - Angiosarcoma
  - Epithelioid (epithelioid sarcoma-like)
  - Kaposi sarcoma

- Pseudomyogenic (epithelioid sarcoma-like) haemangioendothelioma was added to the intermediate (rarely metastasizing) subgroup.
- Two intermediate vascular neoplasms that the Working Group had previously considered for inclusion in the 2002 classification, namely giant cell angiolymphoid haemangioendothelioma and polymorphous haemangioendothelioma, were not added to the current classification due to lack of cases and data.

### Gastrointestinal stromal tumours

**2013**
- Gastrointestinal stromal tumour
  - Benign
  - Uncertain malignant potential
  - Malignant
Risk of Aggressive Behavior in GISTs (Fletcher et al, 2002)

<table>
<thead>
<tr>
<th>Size</th>
<th>Mitotic count</th>
</tr>
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<tbody>
<tr>
<td>very low</td>
<td>&lt;2 cm</td>
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<td>low</td>
<td>&lt;5 cm</td>
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<tr>
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<td></td>
<td>&gt;10 cm</td>
</tr>
</tbody>
</table>

AFIP-Miettinen System

<table>
<thead>
<tr>
<th>Tumor Parameters</th>
<th>Risk of Progressive Disease (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitotic index</td>
<td>Gastric</td>
</tr>
<tr>
<td>≤ 5 per 50 hpf</td>
<td>None (0%)</td>
</tr>
<tr>
<td>&lt; 2 cm</td>
<td>None (0%)</td>
</tr>
<tr>
<td>≤ 2 ≤ 5 cm</td>
<td>Low (1.6%)</td>
</tr>
<tr>
<td>&gt; 5 ≤ 10 cm</td>
<td>Moderate (24%)</td>
</tr>
<tr>
<td>&gt; 10 cm</td>
<td>High (52%)</td>
</tr>
<tr>
<td>&gt; 5 per 50 hpf</td>
<td>None (0%)</td>
</tr>
<tr>
<td>&lt; 2 cm ≤ 5 cm</td>
<td>High (16%)</td>
</tr>
<tr>
<td>&gt; 5 ≤ 10 cm</td>
<td>High (55%)</td>
</tr>
<tr>
<td>&gt; 10 cm</td>
<td>High (86%)</td>
</tr>
</tbody>
</table>

Nerve sheath tumours

<table>
<thead>
<tr>
<th>Year</th>
<th>Tumour Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>Nasal glial heterotopia</td>
</tr>
<tr>
<td></td>
<td>Benign Triton tumour</td>
</tr>
<tr>
<td></td>
<td>Hybrid nerve sheath tumours</td>
</tr>
<tr>
<td></td>
<td>Schwannoma (including variants)</td>
</tr>
<tr>
<td></td>
<td>Melanotic schwannoma</td>
</tr>
<tr>
<td></td>
<td>Neurofibroma (including variants)</td>
</tr>
<tr>
<td></td>
<td>Plexiform neurofibroma</td>
</tr>
<tr>
<td></td>
<td>Perineuroma</td>
</tr>
<tr>
<td></td>
<td>Malignant perineuroma</td>
</tr>
<tr>
<td></td>
<td>Granular cell tumour</td>
</tr>
<tr>
<td></td>
<td>Dermal nerve sheath myxoma</td>
</tr>
<tr>
<td></td>
<td>Solitary circumscribed neuroma</td>
</tr>
<tr>
<td></td>
<td>Ectopic meningioma</td>
</tr>
<tr>
<td></td>
<td>Malignant peripheral nerve sheath tumour</td>
</tr>
<tr>
<td></td>
<td>Epithelioid malignant nerve sheath tumour</td>
</tr>
<tr>
<td></td>
<td>Malignant Triton tumour</td>
</tr>
<tr>
<td></td>
<td>Malignant granular cell tumour</td>
</tr>
<tr>
<td></td>
<td>Ectomesenchymoma</td>
</tr>
</tbody>
</table>
Nerve sheath tumours

New added entities

- Granular cell tumor
- Dermal nerve sheath myxoma
- Solitary circumscribed neuroma
- Ectopic meningioma / meningothelial hamartoma
- Nasal glial heterotopia
- Benign Triton tumor
- Hybrid nerve sheath tumors
- Malignant Triton tumor
- Malignant granular cell tumor
- Ectomesenchymoma

Tumours of uncertain differentiation

- Malignant mesenchymoma deleted
- Likely heterologous line of differentiation in specific sarcomas such as:
  - myxoid liposarcomas with cartilaginous metaplasia
  - ALT and dedifferentiated liposarcomas with osseous, cartilaginous, smooth muscle or skeletal muscle elements,
  - MPNST with heterologous elements
Undifferentiated / unclassified sarcomas

2013
Undifferentiated spindle cell sarcoma
Undifferentiated pleomorphic sarcoma
Undifferentiated round cell sarcoma
Undifferentiated epithelioid sarcoma
Undifferentiated sarcoma NOS

Undifferentiated / unclassified sarcomas

• Previously included in the fibrohistiocytic tumours, namely “malignant fibrous histiocytomas”
• Lack identifiable line of differentiation when characterized by presently available technology
• Dedifferentiated types of specific sarcomas are not included in this category
• Lack distinct clinical or morphological characteristics
• Genetic subgroups are emerging within this family......stay tuned

Undifferentiated round cell and spindle cell sarcoma

• EWSR1 involved in non-ETS fusions with: PATZ1, POU5F1, SMARCA5, NFATC2 or SP3
• Another recurrent rearrangement involves CIC- DUX4 fusion gene/protein upregulates genes of the PEA3 subclass of ETS family
• One or more separate entities, or best classified as variants of Ewing sarcoma?
Undifferentiated pleomorphic sarcoma (UPS)

- UPS was most often called malignant fibrous histiocytoma in the past
- Difficult to evaluate due to shifting diagnostic criteria throughout the years
- Highly complex karyotype with no specific recurrent aberrations
- Undifferentiated sarcomas with 12q13~15 amplification best classified as dedifferentiated liposarcomas
- Relationship with undifferentiated/unclassified tumors with spindle cell morphology is evolving and problematic in practice

Aligning the Stars

- Raph Pollock, Chair
- Path: Lazar, Weiss, Krausz (CAP)
- WHO (2002, now 2013) nomenclature
  - Prior carcinoma-like: WD, MD, PD
- FNCLCC adopted (NIH as alternative)
- CAP Protocol (B. Rubin)
- All aligned to details; complete compatibility
- Amongst first tumor systems to do this

CAP Soft Tissue (& GIST) Authors

- Brian Rubin
- Cristina Antonescu
- Kum Cooper
- Ron Dematteo (Surgery)
- George Demetri (Oncology)
- Chris Fletcher
- Andrew Folpe
- John Goldblum
- Alex Lazar
- Bob Maki (Oncology)
- Markku Miettinen
- Tony Montag
- Raph Pollock (Surgery; AJCC)
- John Reith
- Stephen Qualman
- Sharon Weiss
- Thomas Krausz
Summary

• The 2013 WHO Classification of tumors of soft tissue and bone contains major modifications to the previous one through:
  – The addition of new chapters
  – The inclusion of new entities
  – The deletion of some entities
  – The reclassification of some entities

• It also has minor changes such as renaming of some tumors and updates of molecular and genetic findings