THE EVOLVING CLASSIFICATION OF SOFT TISSUE TUMORS

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MAJOR STRENGTHS

Broad consensus view
New approach to authorship
More extensive text / illustrations
Inclusion of genetics
Timeliness
SIGNIFICANT CHANGES FROM 1994 CLASSIFICATION

Approach to biologic potential
Approach to fibrohistiocytic tumours
Approach to haemangiopericytoma
Recategorisation of ‘intermediate’ vascular tumours
Numerous ‘new’ entities
More tumours of ‘uncertain differentiation’
Most benign soft tissue tumours do not recur locally. Those that do recur do so in a non-destructive fashion and are almost always readily cured by complete local excision. Exceedingly rarely (almost certainly <1/50,000 cases, and probably even less than that), a morphologically benign lesion may give rise to distant metastases. This is entirely unpredictable on the basis of conventional histological examination and, to date, has been best documented in cutaneous benign fibrous histiocytoma.
INTERMEDIATE CATEGORY
(Locally aggressive)

Soft tissue tumours in this category often recur locally and are associated with an infiltrative and locally destructive growth pattern. Lesions in this category do not have any evident potential to metastasise but typically require wide excision with a margin of normal tissue in order to ensure local control. The prototypical lesion in this category is desmoid fibromatosis.
Soft tissue tumours in this category are often locally aggressive but, in addition, show the well documented ability to give rise to distant metastases in occasional cases. The risk of such metastases appears to be <2% and is not reliably predictable on the basis of histomorphology. Metastasis in such lesions is usually to lymph node or lung. Prototypical examples in this category include plexiform fibrohistiocytic tumour and so-called angiomatoid fibrous histiocytoma.
In addition to the potential for locally destructive growth and recurrence, malignant soft tissue tumours (known as soft tissue sarcomas) have significant risk of distant metastasis, ranging in most instances from 20% to almost 100%, depending upon histological type and grade. Some (but not all) histologically low grade sarcomas have a metastatic risk of only 2-10%, but such lesions may advance in grade in a local recurrence, and thereby acquire a higher risk of distant spread (e.g., myxofibrosarcoma and leiomyosarcoma).
World Health Organization Classification of Tumours

Pathology & Genetics

Tumours of Soft Tissue and Bone

Edited by Christopher D.M. Fletcher, K. Krishnan Unni, Fredrik Mertens
CONTEMPORARY CONCENSUS CLASSIFICATION

- NOT A TEXTBOOK
REASONS TO HAVE CLASSIFICATIONS

- Reproducible diagnostic criteria
- Better determine biologic potential
- Better understand intrinsic biology
- Reflect conceptual evolution
SIGNIFICANT CHANGES FROM 2002 CLASSIFICATION

- ‘MFH’ is gone
- ‘Haemangiopericytoma’ is gone
- Pericytic (perivascular) tumours better defined
- GIST and nerve sheath tumours now allocated to this volume
- Category of undifferentiated sarcomas introduced
- Some “new entities” added
- More genetic data added
World Health Organization (2013) Classification of Tumours of Soft Tissue

“NEW ENTITIES”

Pseudomyogenic (ES-like) haemangioendothelioma

Hybrid nerve sheath tumours

Acral (digital) fibromyxoma

Haemosiderotic fibrolipomatous tumour

Phosphaturic mesenchymal tumour
World Health Organization (2013)
Classification of Tumours of Soft Tissue

ADIPOCYTIC TUMOURS

Benign

Lipoma
Lipomatosis
Lipomatosis of nerve
Lipoblastoma(tosis)
Angiolipoma

Myolipoma
Chondroid lipoma
Extrarenal angiomyolipoma
Extra-adrenal myelolipoma
Spindle cell/pleomorphic lipoma
Hibernoma
Intermediate (locally aggressive)

Atypical lipomatous tumour / well differentiated liposarcoma

Malignant

Dedifferentiated liposarcoma
Myxoid liposarcoma
Pleomorphic liposarcoma
Liposarcoma, not otherwise specified
### FIBROBLASTIC / MYOFIBROBLASTIC TUMOURS

**Benign (1)**

<table>
<thead>
<tr>
<th>Benign Tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodular fasciitis</td>
</tr>
<tr>
<td>Proliferative fasciitis (?)</td>
</tr>
<tr>
<td>Proliferative myositis (?)</td>
</tr>
<tr>
<td>Myositis ossificans and fibro-osseous pseudotumour of digits</td>
</tr>
<tr>
<td>Ischaemic fasciitis</td>
</tr>
<tr>
<td>Elastofibroma</td>
</tr>
<tr>
<td>Fibrous hamartoma of infancy</td>
</tr>
<tr>
<td>Fibromatosis colli</td>
</tr>
<tr>
<td>Juvenile hyaline fibromatosis</td>
</tr>
<tr>
<td>Inclusion body fibromatosis</td>
</tr>
</tbody>
</table>

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*World Health Organization (2013) Classification of Tumours of Soft Tissue*
NODULAR FASCIITIS

t(17;22)(p13;q12.3) (cryptic)

USP6-MYH9

ICD-0: 8828/0
Never had a code before!
FIBROBLASTIC / MYOFIBROBLASTIC TUMOURS

Benign (2)

Fibroma of tendon sheath
Desmoplastic fibroblastoma
Mammary-type myofibroblastoma
Calcifying aponeurotic fibroma
Angiomyofibroblastoma

Cellular angiofibroma
Nuchal-type fibroma
Gardner fibroma
Calcifying fibrous tumour
World Health Organization (2013)
Classification of Tumours of Soft Tissue

FIBROBLASTIC / MYOFIBROBLASTIC TUMOURS

Intermediate category

Locally aggressive
Superficial fibromatoses
Desmoid-type fibromatoses
Lipofibromatosis
Giant cell fibroblastoma

Rarely metastasising
Dermatofibrosarcoma protuberans
Solitary fibrous tumour
Inflammatory myofibroblastic tumour
Low grade myofibroblastic sarcoma
Myxoinflammatory fibroblastic sarcoma/atypical myxoinflammatory fibroblastic tumour
Infantile fibrosarcoma
FIBROBLASTIC / MYOFIBROBLASTIC TUMOURS

Malignant

Adult fibrosarcoma
Myxofibrosarcoma
Low grade fibromyxoid sarcoma
Sclerosing epithelioid fibrosarcoma
LGFMS/SEF
MOLECULAR GENETICS

**PURE LGFMS**
Most have t(11;16)(q33;p11) *FUS-CREB3L2*
Few have t(11;16)(p11;p11) *FUS-CREB3L1*
Basically all are MUC4 immunopositive

**PURE SEF**
If MUC4 +ve (70%) – ? Up to 90% have *EWSR1-CREB3L1*
? 30-40% have *FUS* rearrangement
(some with *CREB3L1* or *CREB3L2*)

MUC4 -ve – *FUS* negative, otherwise unknown

**HYBRID LGFMS/SEF**
All are MUC4 +ve – Most have either *FUS* or *EWSR1*
rearrangement (usually with *CREB3L2*)
SO-CALLED FIBROHISTIOCYTIC TUMOURS

**Benign**

Tenosynovial giant cell tumour
- localised
- diffuse

Deep benign fibrous histiocytoma

**Intermediate (rarely metastasising)**

Plexiform fibrohistiocytic tumour
Giant cell tumour of soft tissues

World Health Organization (2013)
Classification of Tumours of Soft Tissue
SMOOTH MUSCLE TUMOURS

Deep leiomyoma

Leiomyosarcoma (excluding skin)
PERICYTIC (PERIVASCULAR) TUMOURS

Glomus tumour (and variants)
  Glomangiomatosis
  Malignant glomus tumour
Myopericytoma
  Myofibroma
  Myofibromatosis
Angioleiomyoma

World Health Organization (2013)
Classification of Tumours of Soft Tissue
Multiple familial glomus tumours result from germline \textit{GLMN} mutation

NF-1 may be associated with multiple digital glomus tumours (which show \textit{NF-1} inactivation)

\textit{NOTCH2} or \textit{NOTCH3} rearrangement identified in 60% of sporadic soft tissue glomus tumours

\textit{BRAF} (10%) and \textit{KRAS} (rare) mutations identified in sporadic glomus tumours
PERICYTIC (PERIVASCULAR) TUMOURS

KEY POINTS

• Morphologic continuum, includes myofibroma
• Angioleiomyoma fits better here
• Could ultimately be renamed as haemangiopericytoma!
## SKELETAL MUSCLE TUMOURS

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhabdomyoma</td>
<td>Embryonal rhabdomyosarcoma</td>
</tr>
<tr>
<td>adult type</td>
<td>(incl. botryoid, anaplastic)</td>
</tr>
<tr>
<td>fetal type</td>
<td>Alveolar rhabdomyosarcoma</td>
</tr>
<tr>
<td>genital type</td>
<td>(incl. solid, anaplastic)</td>
</tr>
<tr>
<td></td>
<td>Pleomorphic rhabdomyosarcoma</td>
</tr>
<tr>
<td></td>
<td>Spindle cell/sclerosing rhabdomyosarcoma</td>
</tr>
</tbody>
</table>
SPINDLE CELL RHABDOMYOSARCOMA

- 1st described 1992 / 1993
- Long regarded as variant of embryonal
- Commonest in children / adolescents
- Mainly paratesticular
- 5 year survival > 90% in children
- Easily confused with other spindle cell sarcomas
SPINDLE CELL RHABDOMYOSARCOMA IN ADULTS

• Mainly 3\textsuperscript{rd} / 4\textsuperscript{th} decades
• Males > females
• Head and neck commonest (50%) - but wide range of sites
• More aggressive than in children

? Relationship to sclerosing rhabdo Morphologic overlap in 15-20\% of cases
SCLEROSING RHABDOMYOSARCOMA

- 1st described 2000 / 2002 (Mentzel et al; Folpe et al)
- Affects adults & children / adolescents
- Head & neck = Limbs
- Prognosis still somewhat uncertain
- No clear genetic data until recently
- Easily confused with angiosarcoma or perhaps even osteosarcoma
SPINDLE CELL / SCLEROSING RHABDOMYOSARCOMA
POST-WHO GENETIC FINDINGS

- *NCOA2* gene rearrangements in congenital/infantile spindle cell rhabdo (Mosquera et al)
- *MYOD1* mutations in spindle cell rhabdo in adults (Szuhai et al)
- *MYOD1* (+PI3K) mutations in BOTH spindle cell and sclerosing rhabdoses in children and adults (distinct from *NCOA2* group) (Agaram et al)
- *MYOD1* (+PI3K) mutations in “aggressive embryonal” rhabdoses (Kohsaka et al)
SPINDLE CELL / SCLEROSING RHABDOMYOSARCOMA

KEY POINTS

- No clear relationship to embryonal rhabdomyosarcoma
- Form a morphologic continuum
- Affect both children (paratesticular ++) and adults (head/neck > limbs)
- Worse prognosis in adults
- Treatment uncertain
- Recent genetic data very informative and support separate classification
VASCULAR TUMOURS

Benign

Haemangiomas
  synovial
  venous
  arteriovenous (malformation)
  intramuscular

Epithelioid haemangioma

Angiomatosis

Lymphangioma
VASCULAR TUMOURS

Intermediate (locally aggressive)
Kaposiform haemangioendothelioma

Intermediate (rarely metastasising)
Retiform haemangioendothelioma
Papillary intralymphatic angioendothelioma

Composite
haemangioendothelioma

Pseudomyogenic (epithelioid sarcoma-like)
haemangioendothelioma
Kaposi sarcoma

Malignant
Epithelioid
haemangioendothelioma
Angiosarcoma of soft tissue

NB NEW GENETIC DATA
PSEUDOMYOGENIC (‘EPITHELIOID SARCOMA-LIKE’) HAEMANGIOENDOTHELIOMA

CLINICAL FEATURES

Young adults
Males > females ++
80% limbs – leg > arm
Multiple nodules – usually < 3 cm
Multiple planes – skin > subcutis > muscle > bone
Often painful

Metastasis infrequent - ? Indolent / delayed
World Health Organization (2013) Classification of Tumours of Soft Tissue

CHONDRO-OSSEOUS TUMOURS

Soft tissue chondroma
Extraskeletal mesenchymal chondrosarcoma
Extraskeletal osteosarcoma
GASTROINTESTINAL STROMAL TUMOURS

GIST, benign
GIST, uncertain malignant potential
GIST, malignant
## Proposed Guidelines for Defining Risk of Aggressive Behaviour in GISTs (NCI 2002)

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Size</th>
<th>Mitotic Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low risk</td>
<td>&lt; 2 cm</td>
<td>&lt; 5 per 50 HPF</td>
</tr>
<tr>
<td>Low risk</td>
<td>2-5 cm</td>
<td>≤ 5 per 50 HPF</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>≤ 5 cm</td>
<td>6-10 per 50 HPF</td>
</tr>
<tr>
<td></td>
<td>5-10 cm</td>
<td>≤ 5 per 50 HPF</td>
</tr>
<tr>
<td></td>
<td>&gt; 5 cm</td>
<td>&gt; 5 per 50 HPF</td>
</tr>
<tr>
<td>High risk</td>
<td>&gt; 10 cm</td>
<td>Any mitotic rate</td>
</tr>
<tr>
<td></td>
<td>&gt; Any size</td>
<td>&gt; 10 per 50 HPF</td>
</tr>
</tbody>
</table>
Management of GIST

Table 1  Risk Stratification of Primary GIST by Mitotic Index, Size, and Site

<table>
<thead>
<tr>
<th>Tumor Parameters</th>
<th>Mitotic Rate ≤ 5 per 50 HPF</th>
<th>Size ≤ 2 cm</th>
<th>Mitotic Rate &gt; 5 per 50 HPF</th>
<th>Size &gt; 2, ≤ 5 cm</th>
<th>Mitotic Rate &gt; 5, ≤ 10 cm</th>
<th>Size &gt; 5, ≤ 10 cm</th>
<th>Mitotic Rate &gt; 10 cm</th>
<th>Size &gt; 10 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Stomach</td>
<td>Risk for Progressive Disease* (%)</td>
<td>Stomach</td>
<td>Jejunum/Ileum</td>
<td>Low (4.3%)</td>
<td>Insufficient data</td>
<td>High (57%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>None (0%)</td>
<td>Low (3.6%)</td>
<td>Moderate (24%)</td>
<td>Insufficient data</td>
<td>High (52%)</td>
<td>Insufficient data</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Very low (1.9%)</td>
<td>Low (10%)</td>
<td>Moderate (10%)</td>
<td>Insufficient data</td>
<td>High (34%)</td>
<td>Insufficient data</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>None†</td>
<td>High†</td>
<td>Insufficient data</td>
<td>High (54%)</td>
<td>High (52%)</td>
<td>Insufficient data</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Moderate (16%)</td>
<td>Insufficient data</td>
<td>High (50%)</td>
<td>High (50%)</td>
<td>High (85%)</td>
<td>High (71%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High (55%)</td>
<td>High (86%)</td>
<td>Insufficient data</td>
<td>High (90%)</td>
<td>High (90%)</td>
<td>High (86%)</td>
</tr>
</tbody>
</table>

Data are based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal GISTs. Abbreviations: GIST, gastrointestinal stromal tumor; HPF, high-power field.

*Defined as metastasis or tumor-related death.

†Denotes small numbers of cases.

Adapted from Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Sem Diagn Pathol 2006;23:70–83.
<table>
<thead>
<tr>
<th>Prognostic group</th>
<th>Size</th>
<th>Mitotic rate per 50 HPFs</th>
<th>Progressive disease during follow-up (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≤ 2</td>
<td>≤ 5</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>&gt; 2 ≤ 5</td>
<td>≤ 5</td>
<td>1.9 (Gastric GISTs) 4.3 (Small-intestinal GISTs)</td>
</tr>
<tr>
<td>3a</td>
<td>&gt; 5 ≤ 10</td>
<td>≤ 5</td>
<td>3.6 (Gastric GISTs) 24 (Small-intestinal GISTs)</td>
</tr>
<tr>
<td>3b</td>
<td>&gt; 10</td>
<td>≤ 5</td>
<td>12 (Gastric GISTs) 52 (Small-intestinal GISTs)</td>
</tr>
<tr>
<td>4</td>
<td>≤ 2</td>
<td>&gt; 5</td>
<td>0 (Gastric GISTs) 50 (Small-intestinal GISTs)</td>
</tr>
<tr>
<td>5</td>
<td>&gt; 2 ≤ 5</td>
<td>&gt; 5</td>
<td>16 (Gastric GISTs) 73 (Small-intestinal GISTs)</td>
</tr>
<tr>
<td>6a</td>
<td>&gt; 5 ≤ 10</td>
<td>&gt; 5</td>
<td>55 (Gastric GISTs) 85 (Small-intestinal GISTs)</td>
</tr>
<tr>
<td>6b</td>
<td>&gt; 10</td>
<td>&gt; 5</td>
<td>86 (Gastric GISTs) 90 (Small-intestinal GISTs)</td>
</tr>
</tbody>
</table>

HPF, high-power field

- Based on observation of 1784 patients in studies carried out by the Armed Force Institute of Pathology (AFIP). Intestinal GISTs generally follow the behaviour of small-intestinal GISTs.
- Denotes tumour categories with very small numbers of cases. Data based on reference (1885).

WHO 2013
SDH-DEFICIENT GISTS

KEY POINTS REGARDING A NEW GROUP

• Approx. 5-7% of gastric GISTs
• Wild-type KIT and PDGFRA
• Distinct subsets of GIST – pediatric-type, Carney-Stratakis syndrome, Carney triad
• Epithelioid, multinodular, show LVI
• Frequent nodal mets – but v. indolent
• All SDHB-neg by IHC – but few mutations
• 25% also SDHA-neg – predicts mutation
NERVE SHEATH TUMOURS

Benign (1)

Schwannoma (including variants)
  Melanotic schwannoma

Neurofibroma (including variants)
  Plexiform neurofibroma

Perineurioma

Granular cell tumour
NERVE SHEATH TUMOURS

Benign (2)

Dermal nerve sheath myxoma
Solitary circumscribed neuroma
Ectopic meningioma
Nasal glial heterotopia
Benign Triton tumour

Hybrid nerve sheath tumours
HYBRID NERVE SHEATH TUMOURS

Hybrid schwannoma / perineurioma
Hybrid neurofibroma / schwannoma
Hybrid granular cell tumour / perineurioma
Hybrid neurofibroma / perineurioma (?)
NERVE SHEATH TUMOURS

Malignant

Malignant peripheral nerve sheath tumour
Epithelioid malignant peripheral nerve sheath tumour
Malignant Triton tumour
Malignant granular cell tumour
Ectomesenchymoma
TUMOURS OF UNCERTAIN DIFFERENTIATION

Benign

Acral fibromyxoma
Intramuscular myxoma
  (incl. cellular variant)
Juxta-articular myxoma
Deep ‘aggressive’ angiomyxoma
Pleomorphic hyalinizing angiectatic tumour
Ectopic hamartomatous thymoma
ACRAL (DIGITAL) FIBROMYXOMA

CLINICAL FEATURES

Adults; M > F
Toes / fingers ++
Often adjacent to nail bed
Dermal / subcutaneous nodule
Most < 2 cm
Local recurrence ~ 10%
TUMOURS OF UNCERTAIN DIFFERENTIATION

Intermediate (locally aggressive)
Haemosiderotic fibrolipomatous tumour

Intermediate (rarely metastasising)
Atypical fibroxanthoma
Angiomatoid fibrous histiocytoma
Ossifying fibromyxoid tumour
  (incl. atypical / malignant)
Mixed tumour / Myoepithelioma / Myoep. Carcinoma
Phosphaturic mesenchymal tumour
HAEMOSIDEROTIC FIBROLIPOMATOUS TUMOUR
(aka “haemosiderotic fibrohistiocytic lipomatous lesion”)

CLINICAL FEATURES

Adults > children
Females slightly > males
Ankle / foot ++
Subcutaneous / poorly marginated
Usually < 5 cm
Local recurrence 30%
Possible potential to progress (?)
HAEMOSIDEROPTIC FIBROLIPOMATOUS TUMOUR
(aka “haemosiderotic fibrohistiocytic lipomatous lesion”)

PATHOLOGIC FEATURES
Admixture, in variable proportions, of:
- Fibroblastic spindle cells
- Mature adipocytes
Fascicular or whorled pattern
Usually prominent haemosiderin
Scattered osteoclastic giant cells
Mitoses scarce
Occasional atypia / pleomorphism
HAEMOSIDEROTIC FIBROLIPOMATOUS TUMOUR
(aka “haemosiderotic fibrohistiocytic lipomatous lesion”)

ISSUES OF INTEREST

Reactive (??) vs. neoplastic
Significance of atypia
Biologic potential
Relationship to other entities ??
Female aged 46 with lesion on dorsum of foot – 2 different components
MYXOINFLAMMATORY FIBROBLASTIC SARCOMA

CLINICAL FEATURES

Adults, wide age range
Equal sex distribution
Slowly growing, ill-defined mass
Distal extremities
- especially hands and feet
Subcutaneous / tenosynovial
Usually < 5 cm
Local recurrence common
Metastasis very rare
MYXOINFLAMMATORY FIBROBLASTIC SARCOMA
AND
HEMOSIDEROTIC FIBROLIPOMATOUS TUMOR
SHARED CLINICOPATHOLOGIC & GENETIC FEATURES

Predilection for distal extremities, esp. feet
Recur ++ - but ? almost never metastasise
Isolated cases show hybrid morphologic features
Both show reciprocal t(1;10)(p22;q24)
Gene fusion TGFBR3 – MGEA5
Leads to up-regulation of FGF8
Also amplified 3p in ring chromosomes

Lambert et al, Virchows Arch 2001; 438:509-512
Wettach et al, Cancer Genet Cytogenet 2008; 182:140-143
Hallor et al, J Pathol 2009; 217:716-727
Antonescu et al, Genes Chromosomes & Cancer 2011; 50:757-764
ATYPICAL FIBROXANTHOMA

CLINICAL FEATURES

Mainly elderly patients
Males > females
Head and neck++ / limbs rare
Rapidly enlarging exophytic
Sometimes multiple / asynchronous

Recurrence infrequent
No metastasis if carefully diagnosed
PHOSPHATURIC MESENCHYMAL TUMOUR

KEY POINTS

• Mostly middle-aged adults – almost any site
• Most assoc. with tumour-induced osteomalacia due to FGF23 production
• Varied morphology but most are myoid or myopericytoma-like with blueish matrix and granular calcification
• Vast majority are benign
TUMOURS OF UNCERTAIN DIFFERENTIATION

Malignant

Synovial sarcoma
Epithelioid sarcoma
Alveolar soft part sarcoma
Clear cell sarcoma of soft tissue
Extraskeletal myxoid chondrosarcoma
Extraskeletal Ewing sarcoma

Desmoplastic small round cell tumour
Extra-renal rhabdoid tumour
PEComa
Intimal sarcoma
UNDIFFERENTIATED / UNCLASSIFIED SARCOMAS

Undifferentiated spindle cell sarcoma
Undifferentiated pleomorphic sarcoma
Undifferentiated round cell sarcoma
Undifferentiated epithelioid sarcoma
Undifferentiated sarcoma NOS
NEW GENETICS (1)

*Fibroblastic / Myofibroblastic tumours*

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Chromosome Translocation</th>
<th>Gene Pair</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodular fasciitis</td>
<td>t(17;22)(p13;q12.3)</td>
<td><em>USP6-MYH9</em></td>
</tr>
<tr>
<td>Myxoinflammatory fibroblastic sarcoma</td>
<td>t(1;10)(p22;q24)</td>
<td><em>TGFBR3-MGEA5</em></td>
</tr>
<tr>
<td>Low grade fibromyxoid sarcoma</td>
<td>t(7;16)(q33;p11)</td>
<td><em>FUS-CREB3L2</em></td>
</tr>
<tr>
<td></td>
<td>t(11;16)(p13;p11)</td>
<td><em>FUS-CREB3L1</em></td>
</tr>
</tbody>
</table>

- also seen in HFLT and hybrid lesions

(Post-WHO – Solitary fibrous tumor  inv12(q13q13)  *NAB2-STAT6*)
### World Health Organization (2013)
**Classification of Tumours of Soft Tissue**

#### NEW GENETICS (2)

**Vascular tumours**

<table>
<thead>
<tr>
<th>Type</th>
<th>Chromosomal Abnormality</th>
<th>Gene Fusion(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomyogenic haemangioendothelioma</td>
<td>t(7;19)(q22;q13)</td>
<td>SERPINE1-FOSB</td>
</tr>
<tr>
<td>Epithelioid haemangioendothelioma</td>
<td>t(1;13)(p36.3;q25)</td>
<td>WWTR1-CAMTA1</td>
</tr>
<tr>
<td>Angiosarcoma (breast)</td>
<td></td>
<td>KDR mutation (25%)</td>
</tr>
<tr>
<td>Angiosarcoma (secondary)</td>
<td></td>
<td>MYC amplification (100%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FLT4 coamplification (25%)</td>
</tr>
</tbody>
</table>

(Post-WHO – EHE – new subset with **YAP1-TFE3** gene fusion)
EHE Subset with *TFE3* gene overexpression
### NEW GENETICS (3)

**Tumours of Uncertain Differentiation**

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Genomic Alteration</th>
<th>Partner Gene</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiomatoid ‘FH’</td>
<td>t(2;22)(q33;q12)</td>
<td>EWSR1-CREB1</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td></td>
<td>t(12;22)(q13;q12)</td>
<td>EWSR1-ATF1</td>
<td>(rare)</td>
</tr>
<tr>
<td></td>
<td>t(12;16)(q13;p11)</td>
<td>FUS-ATF1</td>
<td>(rare)</td>
</tr>
<tr>
<td>OFMT</td>
<td>PHF1 rearrangement (on 6p21)</td>
<td>(80%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- fused with EP400 (55%) or EPC1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myoepithelial tumours (mainly malignant)</td>
<td>EWSR1 rearrangement</td>
<td>(45% of cases)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>with various partners</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEComa</td>
<td>TSC2 deletion/rearrangement</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TFE3 rearrangement (rare, distinct subset)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undifferentiated round cell sarcoma</td>
<td>t(4;19)(q35;q13.1)</td>
<td>CIC-DUX4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(10;19)(q35;q26)</td>
<td>CIC-DUX4</td>
<td></td>
</tr>
</tbody>
</table>
ISSUES STILL TO ADDRESS

- Outdated diagnostic concepts
- Nomenclatural anomalies
- Lack of biologic understanding in some broad areas
- Genetic uncertainties
ADULT FIBROSARCOMA
CURRENT STATUS

• Most lesions so classified in the past would nowadays be relabelled synovial sarcoma or MPNST
• Malignant fibroblastic tumors in adults do exist – eg myxofibrosarcoma, LGFMS, fibrosarcomatous DFSP
• Other less well-defined tumors may well belong in this category, but fibrosarcoma NOS is not currently a useful concept
• Our ability to define fibroblasts/fibroblastic neoplasms is still very limited
• The fact that some but not all fibroblastic tumors form a continuum with myofibroblastic tumors adds another level of complexity
FIBROBLASTIC SARCOMAS
PROBLEMS TO CONSIDER

• Virtual non-existence of adult-type fibrosarcoma as presently defined
• Difficulties in reproducibly defining fibroblastic differentiation
• Undoubted existence of fibroblastic sarcomas, some with reproducible features, some without
NOMENCLATURAL ANOMALIES

Practical considerations vs scientific accuracy
How best to define nomenclature?
Historical precedent vs line of differentiation
(which may be unknown) vs genetics
Potential consequences for patient care
(Isn’t it our job to re-educate clinicians?)
Fossilising sociologic issues …..

Is there another branch of science that is quite so slow to change?
SYNOVIAL SARCOMA
EXTRASKEL MYXOID CHONDROSARCOMA
ANGIOMATOID “MFH”
CLEAR CELL SARCOMA
NOMENCLATURAL ANOMALIES
POSSIBLE WAYS FORWARD

- Openness to gradual revision on the basis of good/rational evidence
- Willingness to accept genetic definitions (as with leukemias)
- Commitment to bringing clinicians along with us (perhaps thro’ concensus conferences)
- ‘Radical’ approaches, dismissing time-honored terminology - ? Less likely to succeed
- WHO Working Groups should formally validate terminology
LACK OF BIOLOGIC UNDERSTANDING

Vascular tumours – par excellence!
Neoplasm vs malformation / hamartoma
How to define a neoplasm?
Relevance of clonality / mixed cell types
Limited genetic data
Blood vascular vs lymphovascular
Potential to be overtaken by clinicoradiologic classification
SOFT TISSUE TUMORS
EXAMPLES OF GENETIC OVERLAP

• Tumors with similar morphology
• Tumors that may show hybrid morphology
• Seemingly totally unrelated tumors
• Tumors of different lineages
EXAMPLES OF GENETIC OVERLAP

- Tumors with similar morphology
  e.g. spindle cell lipoma, cellular angiofibroma, mammary-type myofibroblastoma
- Tumors that may show hybrid morphology
  e.g. DFSP and giant cell fibroblastoma
- Seemingly totally unrelated tumors
  e.g. clear cell sarcoma and angiomatoid “MFH”
- Tumors of different lineages
  e.g. infantile fibrosarcoma and secretory carcinoma
Generally different anatomic sites - does this influence the phenotype?
Morphologic overlap with subtle differences
Immunophenotypic differences
Same rearrangement/loss of 13q14 (Rb)
All benign/rarely recur
Cellular angiofibroma may perhaps have potential for progression
SOFT TISSUE TUMORS
TYPES OF GENETIC OVERLAP

- Frequently involved genes in multiple different tumor types, e.g. *EWSR1*, *HMGA2*
- Interchangeable genes in multiple distinct tumor types, e.g. *EWSR1* and *FUS*
- Shared fusion genes in tumors thought to be distinct entities, e.g. *TGFBR3-MGEA5*
- Shared fusion genes in tumors which appear totally unrelated, e.g. *EWSR1-ATF1*
IMPACT OF GENETICS

SHARED GENE REARRANGEMENTS

• EWSR1
• FUS
• CREB1
• ATF1
• HMG A-2
Schematic representation of frequent structural aberrations of chromosome 12 in benign solid tumors

- $t(3;12)(q27;q14-15)$
- $t(12;14)(q14-15;q24)$
- $\text{inv}(12)(p11.2q14-15)$

[Dal Cin 1995]
Ewing’s sarcoma
FLI1 >80%
ERG 10-15%
ETV1 (<5%)
E1AF (<5%)
FEV (<5%)

DSRCT
WT1

Clear cell sarcoma
ATF1

Extraskel myxoid chondrosarc
CHN & others

[2001]
SHARED FUSION GENES IN SOFT TISSUE SARCOMAS

Szuhai & Bovee, 2012
ETV6-NTRK3

- Infantile fibrosarcoma
- Cellular mesoblastic nephroma
- Secretory carcinoma of breast (and salivary gland)
- Rare cases of AML, CML & ALL
- Radiation-associated thyroid carcinomas
**EWSR1-ATF1**

**EWSR1-CREB1**

- Clear cell sarcoma
- Melanocytic
- Deep soft tissue/GI
- Adults (mainly young)
- > 50% metastasise

- Angiomatoid “MFH”
- Lineage unknown
- ?? dendritic cell
- Mostly subcutaneous
- Commonest < 20 years
- < 2% metastasise
• Evidence of relationship?
• Biologic / mechanistic significance?
• Impact on classification schemes?
• Variants of a single ‘molecular’ entity?
• Potential impact on diagnosis
IMPACT OF GENETICS
WHERE NEXT?

• Need to more sharply define diagnostic role
• Need to reassess role in classification – how best to reconcile/prioritise genotype with phenotype?
• Need to determine significance (pathogenetic and ?? clinical) of such prominently shared fusion genes – are the downstream signaling events the same?
• Need to keep up this work!
OTHER UNANSWERED QUESTIONS WHICH MIGHT IMPACT TAXONOMY

- Cell of origin in many/most tumor types?
- Line of differentiation in many tumor types?
- Nature of multistep process in mesenchymal tumorigenesis?
WHO CLASSIFICATION OF SOFT TISSUE TUMOURS 2013

WEAKNESSES

• Some ‘newer’ entities or genetic findings left out
• Continued nomenclatural anomalies
• Rigidity of ICD-0 coding system
• Increasing problem/challenge of genetic overlap
CONCLUSIONS

- There remain important opportunities to improve the classification of soft tissue tumours
- Objectivity and diagnostic reproducibility are both the goals as well as the validation of any classification scheme
- Cytogenetics / molecular genetics have been invaluable thus far, but their impact has become more complex and confusing
- Old habits die hard ........ Need to maintain open-mindedness to allow ongoing evolution