COST-EFFECTIVE DIAGNOSIS OF SOFT TISSUE TUMORS

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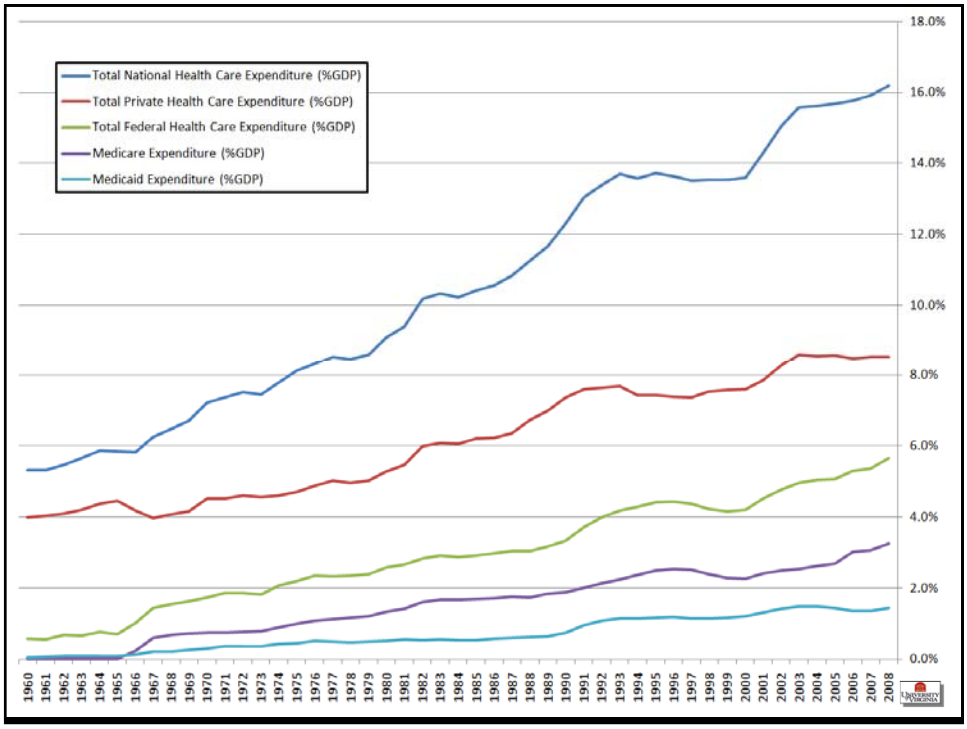
The Age of "Accountable Care"

- **An "Accountable Care Organization" is a healthcare entity typified by a payment and care-delivery model that ties provider-reimbursement to "quality metrics" and *reductions in the total cost of care.***
- **A group of providers forms an ACO, which provides care to a subscribed group of patients**
- **The ACO is accountable to the patients and all third-party payers for the quality, appropriateness, & efficiency of the care provided.**
- **Success depends on the ability of the ACO to incentivize hospitals, physicians, clinics, and other parts of the organization to coordinate care and limit costs**
- **According to CMS, *a minimum savings rate must exceed a predefined benchmark by at least 2% for an ACO to qualify for further participation in the system***



Future Nightmare or Possible Reality?

What is the Principle of Prior Probability, & Why is it Germane to ACOs?

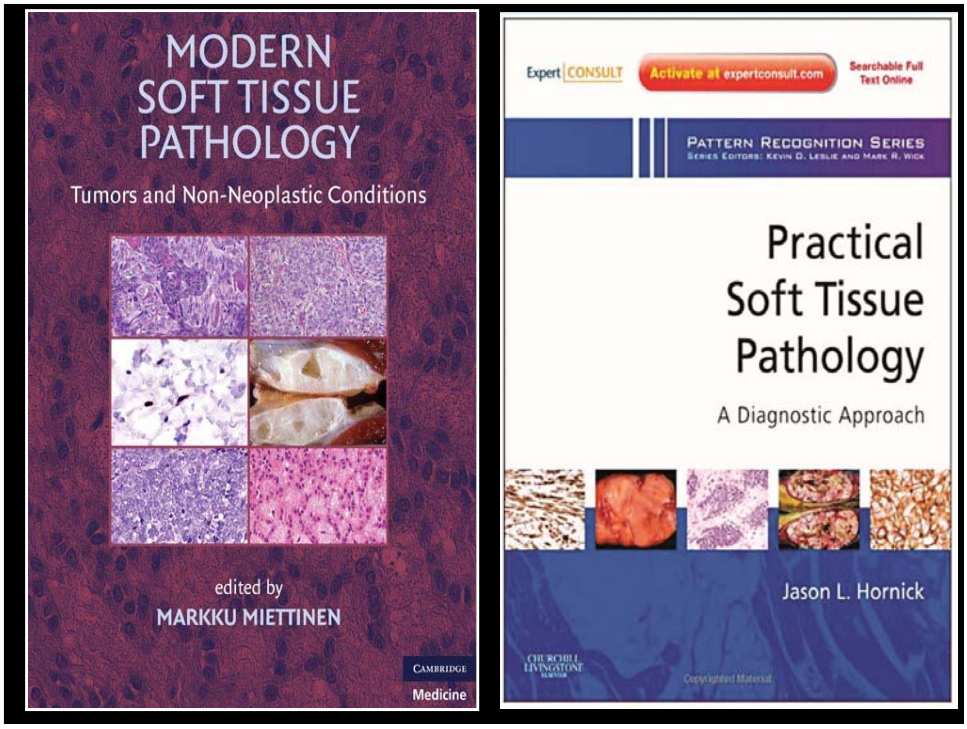
- As defined in the internet-reference Wikipedia, *"a prior probability distribution, often called simply the 'prior,' of an uncertain quantity p (for example, suppose p is the proportion of voters who will vote for…a particular…[sic] politician in a future election) is the probability distribution that would express one's uncertainty about p before the 'data' (for example, an opinion poll) is taken into account.* It is meant to attribute uncertainty rather than randomness to the uncertain quantity"
- In reference to the current discussion, the "prior" could be defined as the *level of diagnostic or prognostic certainty-- based on morphological analysis and clinical correlation-- that is attached to a particular case before additional data (e.g., generated by adjunctive pathologic studies) are obtained.*
- If one is already certain of a conclusion, the procurement of more information can only be obfuscatory, and the cost of getting it is unnecessary

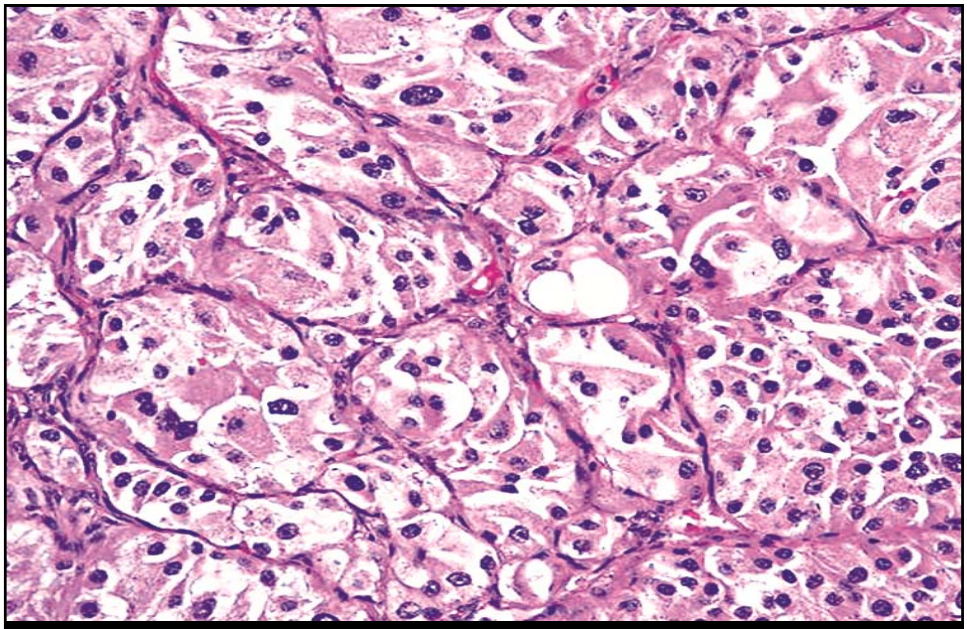
Pathologic Methods Used for the Study of Soft Tissue Tumors (STT)

- Traditional morphological evaluation
- Histochemistry
- Electron microscopy
- Immunohistology
- Molecular analyses

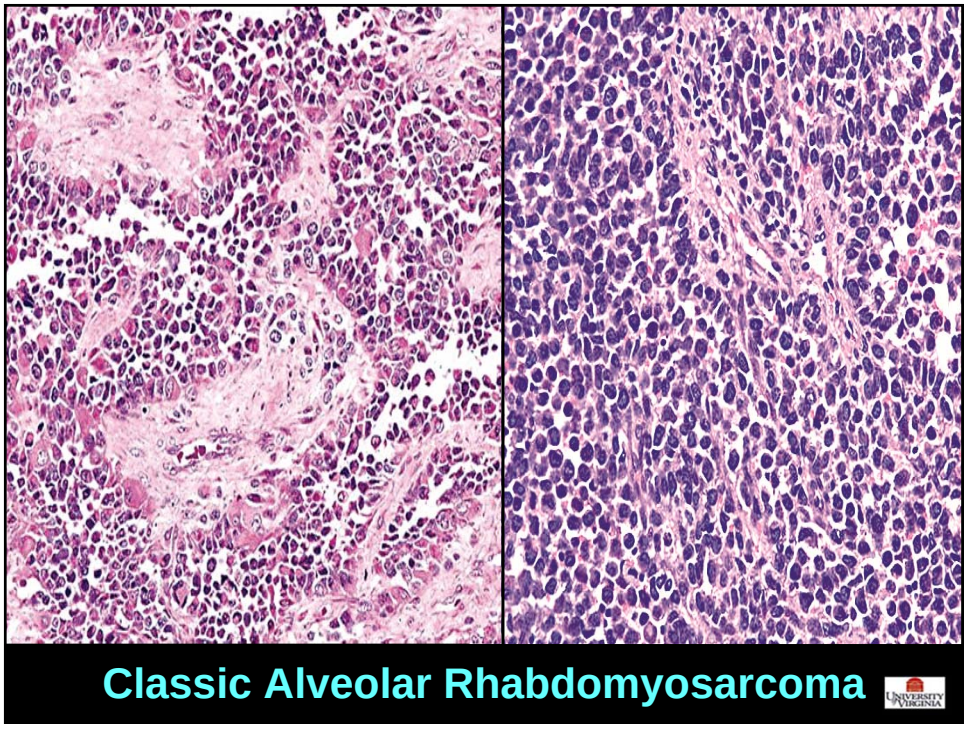
- Step-wise evaluation of diagnostic certainty is needed for each of these techniques, relative to the diagnosis & prognosis of STT. It has not yet been done, but is crucial to assessment of cost-effectiveness in this area
- *Kappa statistics pertaining to the interlaboratory reproducibility of these methods are also unavailable generally, and in specific reference to STT*

Exemplary STT with a Characteristic Morphotype

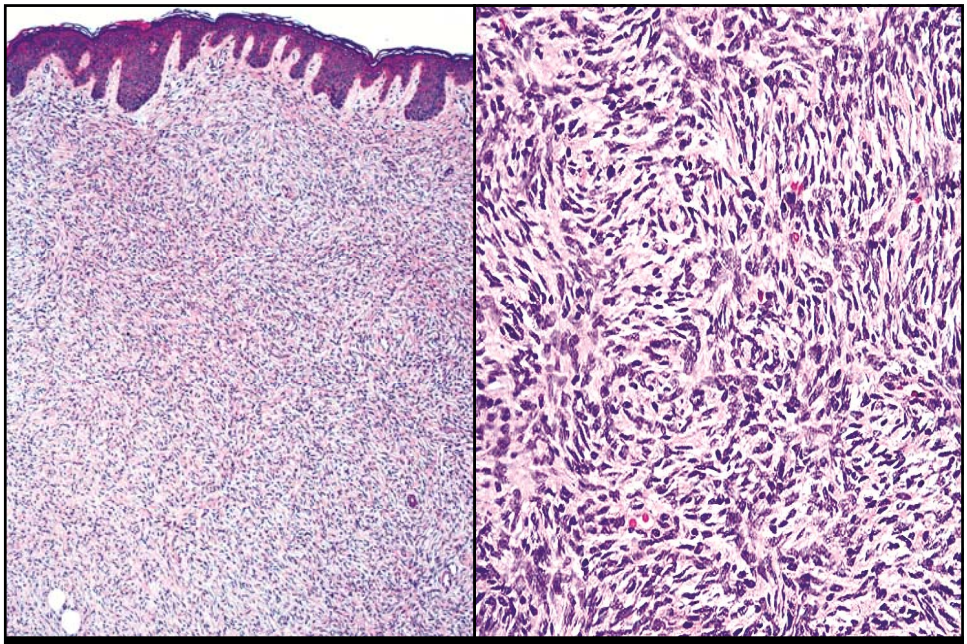




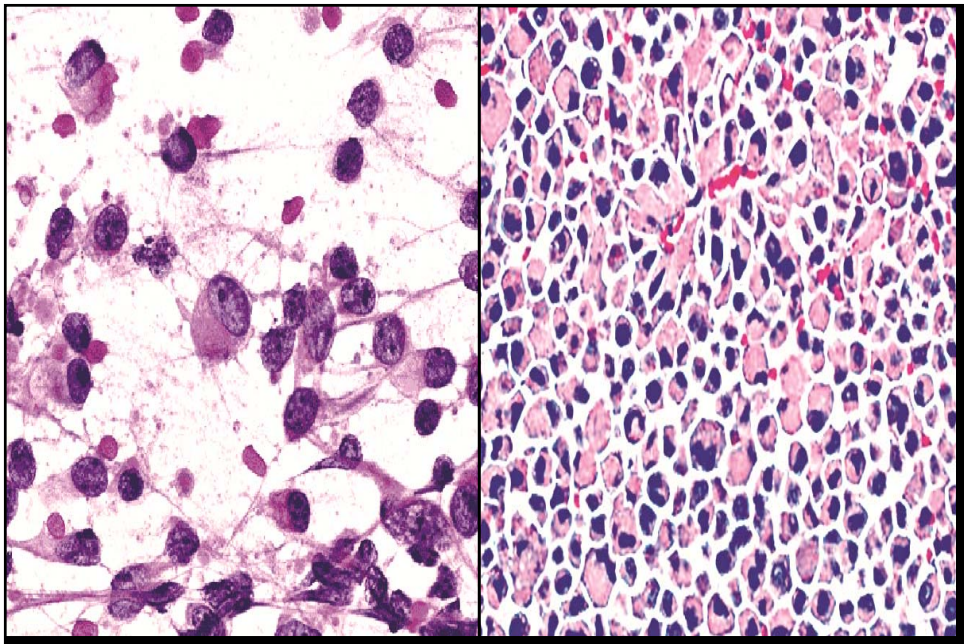
Alveolar Soft Parts Sarcoma



Classic Alveolar Rhabdomyosarcoma

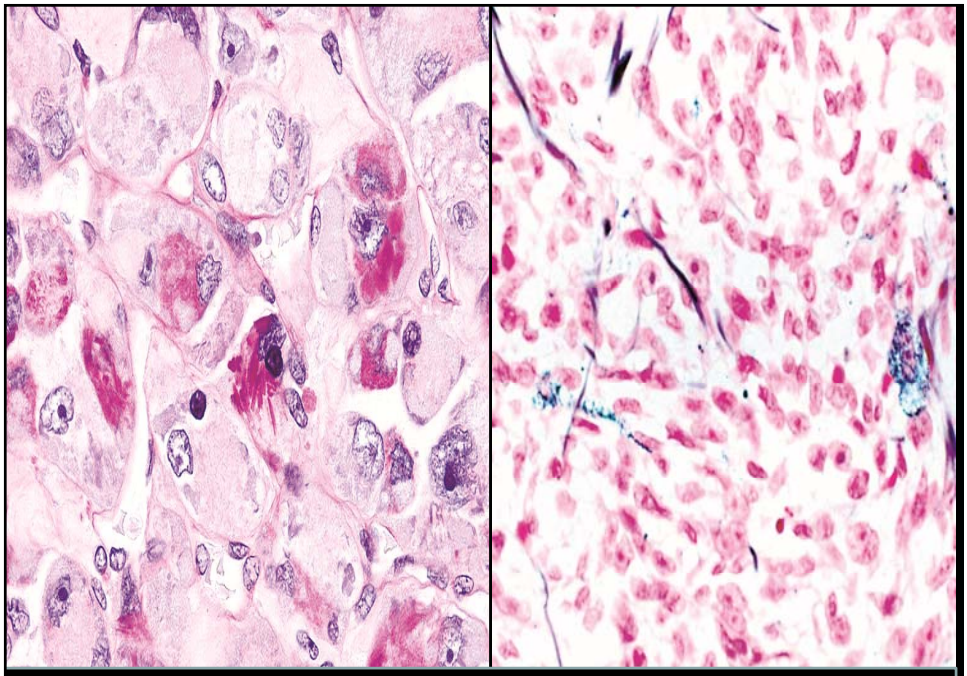


Dermatofibrosarcoma



Malignant Extrarenal Rhabdoid Tumor

Exemplary STT with Characteristic Histochemical Features

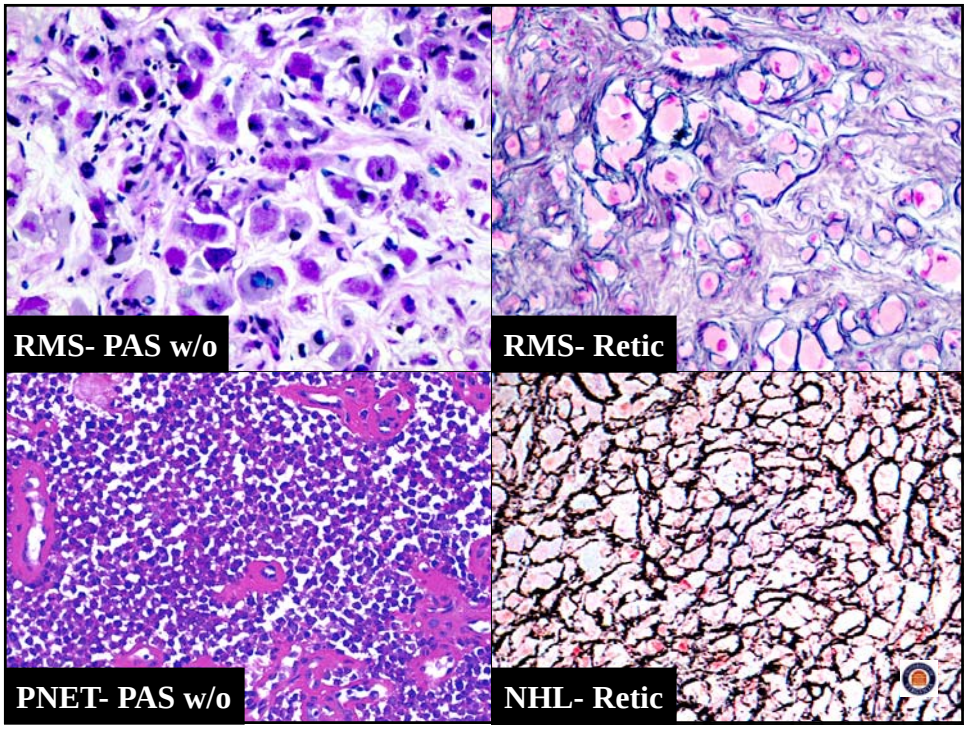


Alveolar soft parts sarcoma– PAS stain

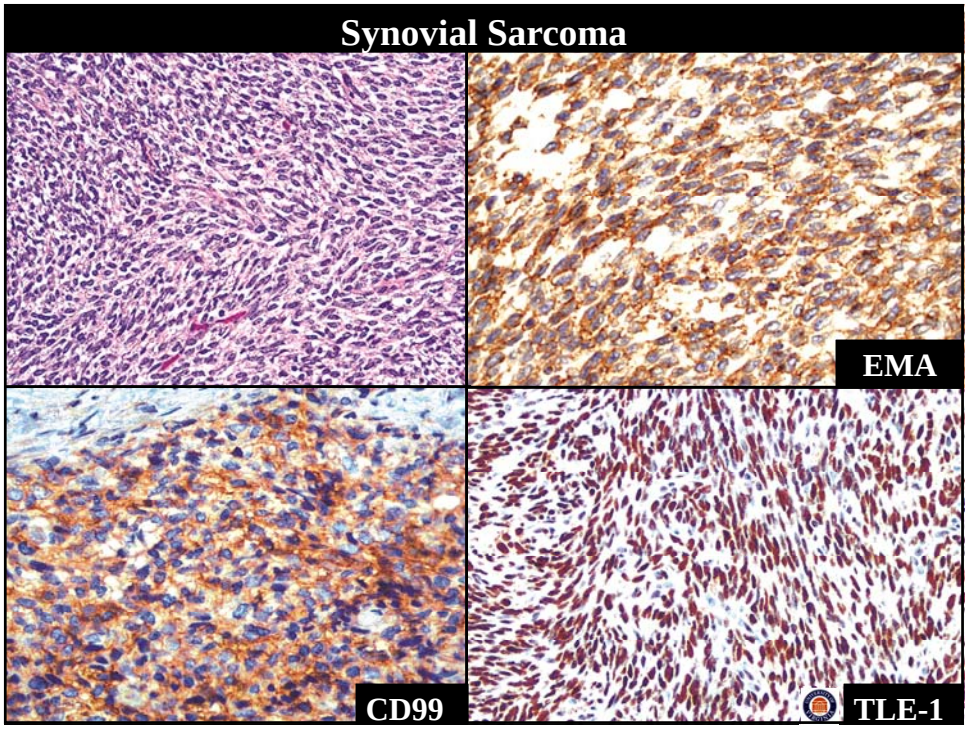
Clear Cell sarcoma– Fontana stain

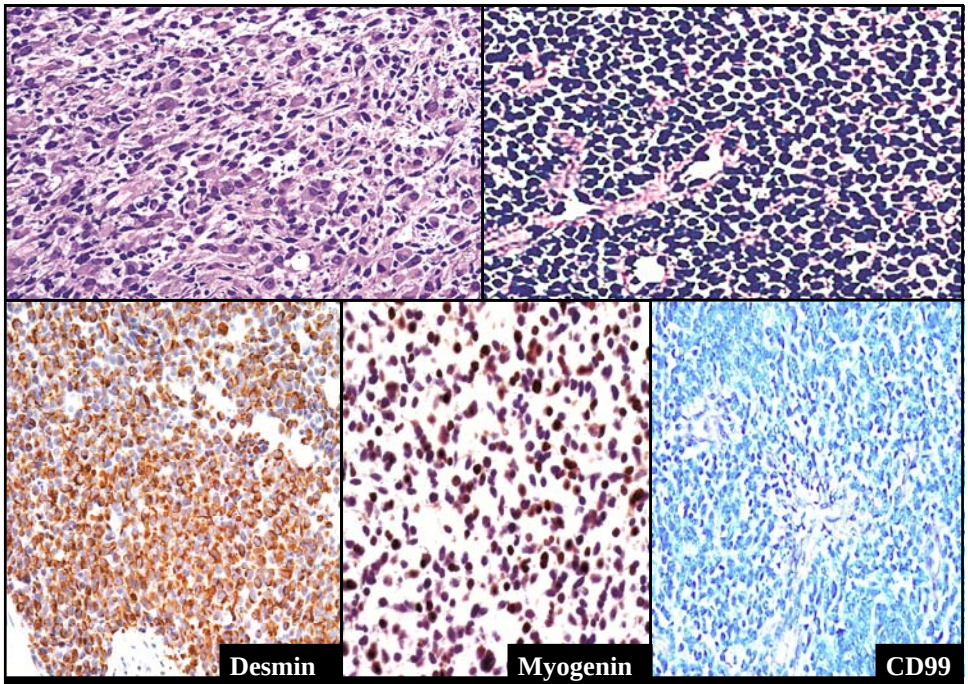
Expected Staining Patterns of Pediatric Small Round-Cell Tumors

Tumor	PAS w/o	Pericellular Reticulin
PNET	+ to +++	0
RMS	+ to +++	+
Lymphoma	0	+ to ++
Neuroblastoma	0	0



Exemplary STT with Characteristic Immunophenotypes



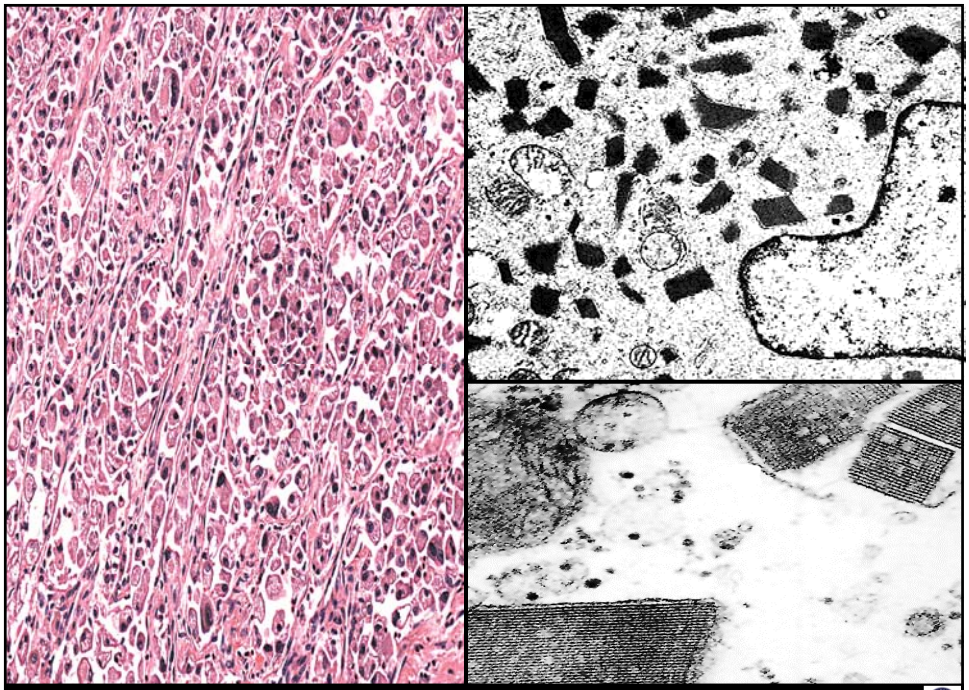


Small-cell (Embryonal & Alveolar) Rhabdomyosarcomas

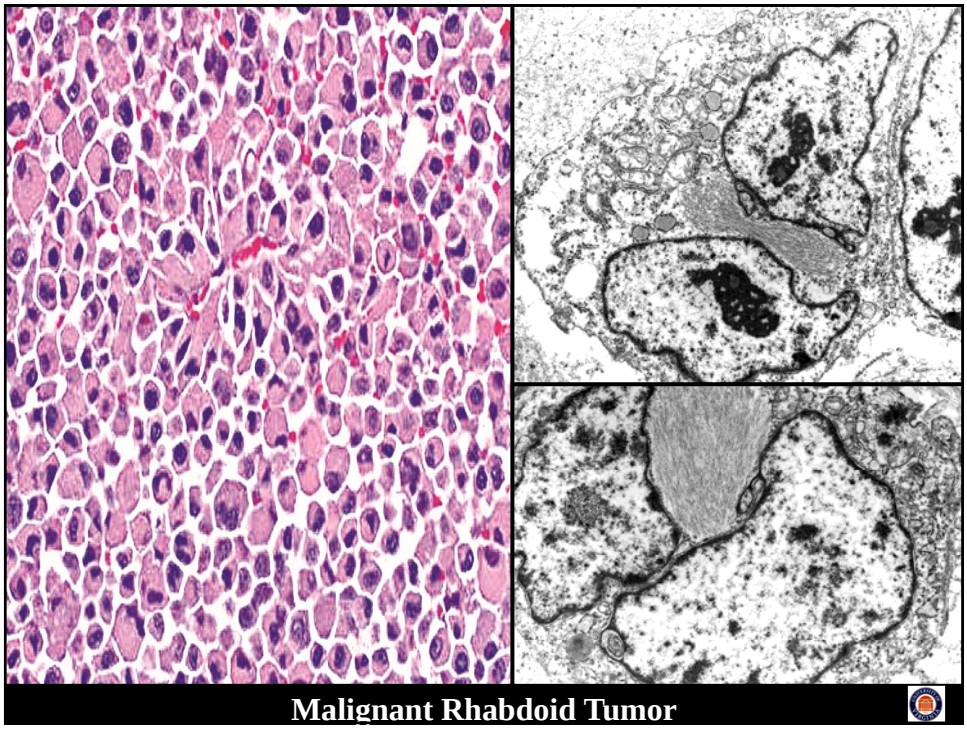
Exemplary STT with a Characteristic Ultrastructural Appearance

Electron Microscopy in 2013

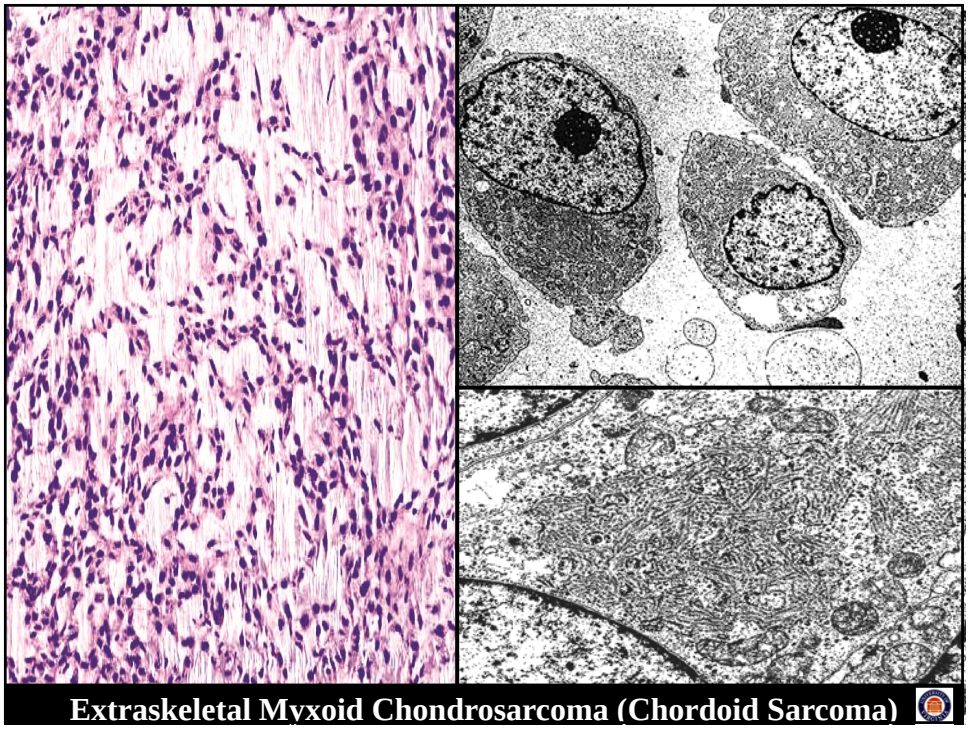
- Ultrastructural studies are still viable in the current atmosphere of anatomic pathology, and they are particularly highly-reimbursed by most third-party payers in the medical insurance business
- The cost-benefit ratio of maintaining an EM facility depends on the volume of cases (pathologist-gated) and the experience of pathologists in ultrastructural interpretation



Alveolar Soft Parts Sarcoma



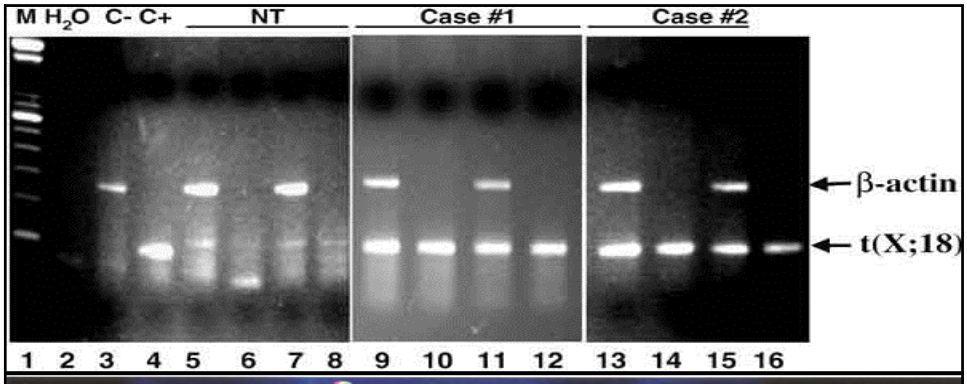
Malignant Rhabdoid Tumor



Extraskeletal Myxoid Chondrosarcoma (Chordoid Sarcoma)

Exemplary STT with a Characteristic Cytogenetic "Signature"

Tumor Type	Cytogenetic Abnormality	Genes Involved
Ewing's sarcoma/primitive neuroectodermal tumor	t(11;22)(q24;q12)	*FLI-1-EWSR1*
	t(21;22)(q22;q12)	*ERG-EWSR1*
	t(7;22)(p22;q12)	*ETV1-EWSR1*
	t(17;22)(q12;q12)	*EIAF-EWSR1*
	t(2;22)(q33;q12)	*FEV-EWSR1*
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14)	*PAX3-FOXO1A*
	t(1;13)(p36;q14)	*PAX7-FOXO1A*
Myxoid/round cell liposarcoma	t(12:16)(q13;q11)	*DDIT3-FUS*
	t(12;22)(q13;q11-12)	*DDIT3-EWSR1*
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	*WT1-EWSR1*
Synovial sarcoma	t(X;18)(p11.2;q11.2)	*SSX1-SYT*
		SSX2-SYT
Clear cell sarcoma	t(12;22)(q13;q12)	*ATF-1-EWSR1*
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12)	*NR4A3-EWSR1*
Dermatofibrosarcoma protuberans/ giant cell fibroblastoma	t(17;22)(q22;q13)	*PDGFB-COL1A1*
Infantile fibrosarcoma	t(12;15)(p13;q25)	*ETV6-NTRK3*
Alveolar soft part sarcoma	t(X;17)(p11;q25)	*ASPL-TFE3*
Low grade fibromyxoid sarcoma	t(7;16)(q33;p11)	*FUS-BBF2H7*



Methods for Cytogenetic Analysis– RT-PCR & *In-Situ* Hybridization

How "Complete" Does a Workup for STT Need to Be?– Pertinent Questions

- Does a specific treatment regimen exist that is tailored narrowly to the diagnosis in question?
- Even more specifically, is a "targeted" therapy possible that would depend on the presence of particular cytogenetic variant of the tumor type *(e.g.*, a specific mutation)*?*

Decision Tables & Diagnostic Evaluation of Soft Tissue Tumors

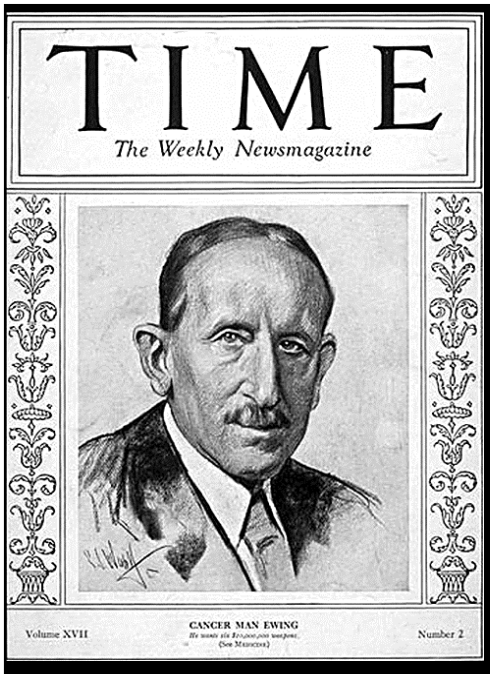
STT Decision Table

Histology	Histochemistry	IHC	Cytogenetics
Characteristic? Degree of diagnostic certainty? If above 95%, stop.	Needed or only confirmatory? Degree of Dx certainty? If above 95%, stop.	Needed or only confirmatory? Degree of Dx certainty? If above 95%, stop.	Needed or only confirmatory? Degree of Dx certainty? If above 95%, stop.
Cumulative Cost of Pathologic Evaluation?			
$ X	$ X +	$ X + +	$ X + + +

"I had my accounting department run a cost-benefit analysis on you and I have some bad news."

Selected Soft Tissue Tumors with Characteristic Cytogenetic Signatures: What is Their Relative Diagnostic Value?

The "Ewing Family" of Small Round-Cell Neoplasms

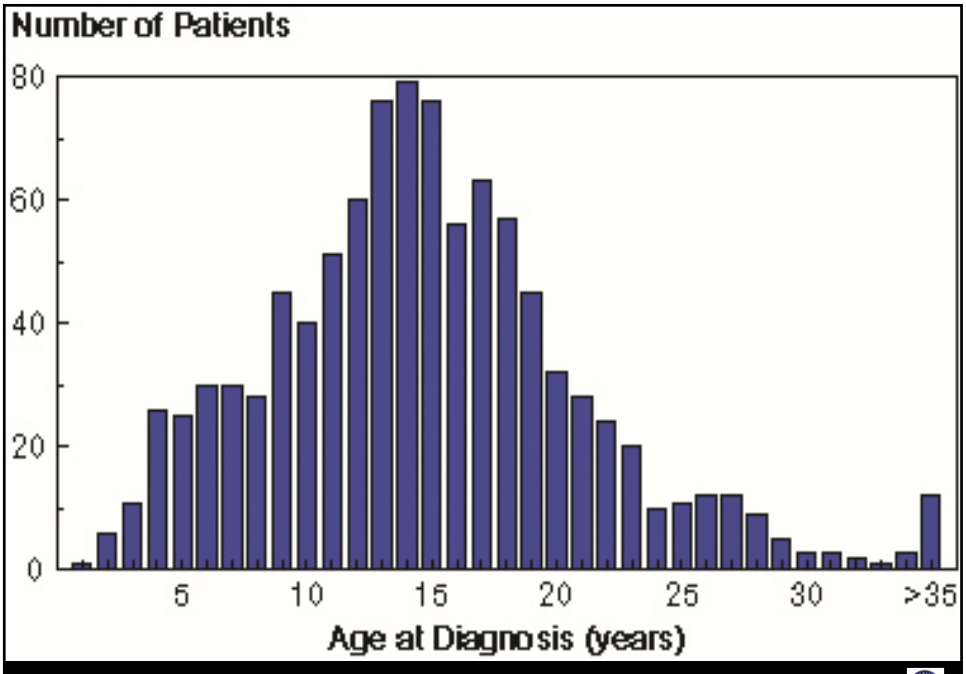


January 12, 1931

James Ewing, M.D.: Diffuse endothelioma of bone. *Proc N Y Pathol Soc* 1921; 21: 17-24.

Primitive Neuroectodermal Tumors

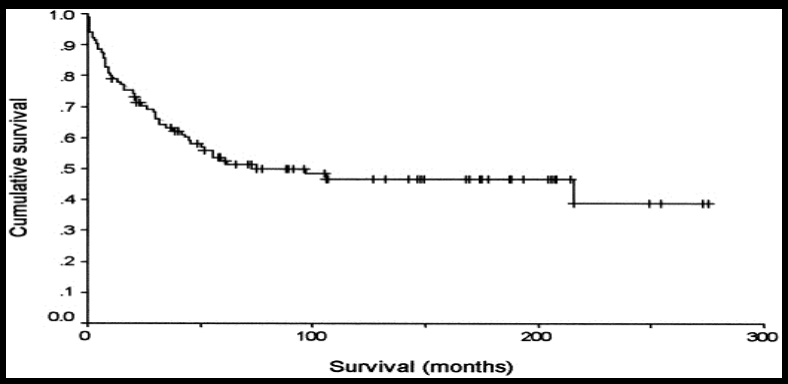
- Blastoma-like, group II neuroendocrine neoplasms, principally seen in children & young adults
- Distributed throughout the body, with a predilection for the diaphyses of long bones (Ewing sarcomas) and the soft tissues of the proximal limbs & trunk
- Constituted by monomorphic small round cells with high nucleocytoplasmic ratios, dispersed chromatin, & a rich fibrovascular stroma
- Necrosis and mitotic activity are paradoxically scarce in untreated neoplasms in this group
- Undigested PAS stains are positive in the majority of cases; reticulin stains show no investment of tumor cells



Age Distribution of Ewing Family Tumors

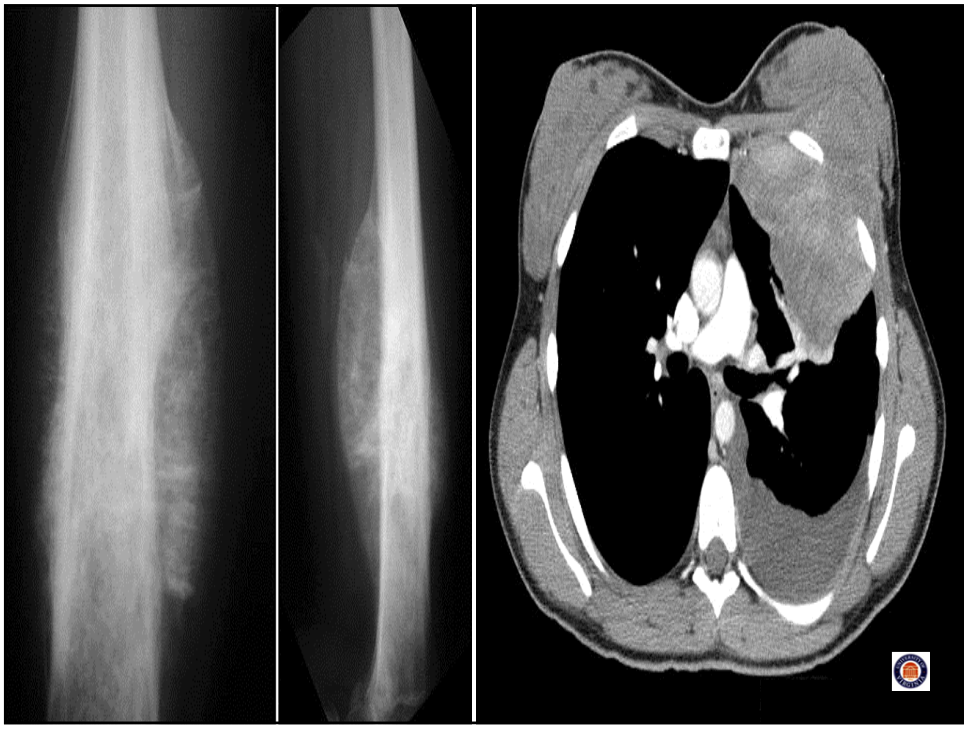
Primitive Neuroectodermal Tumors

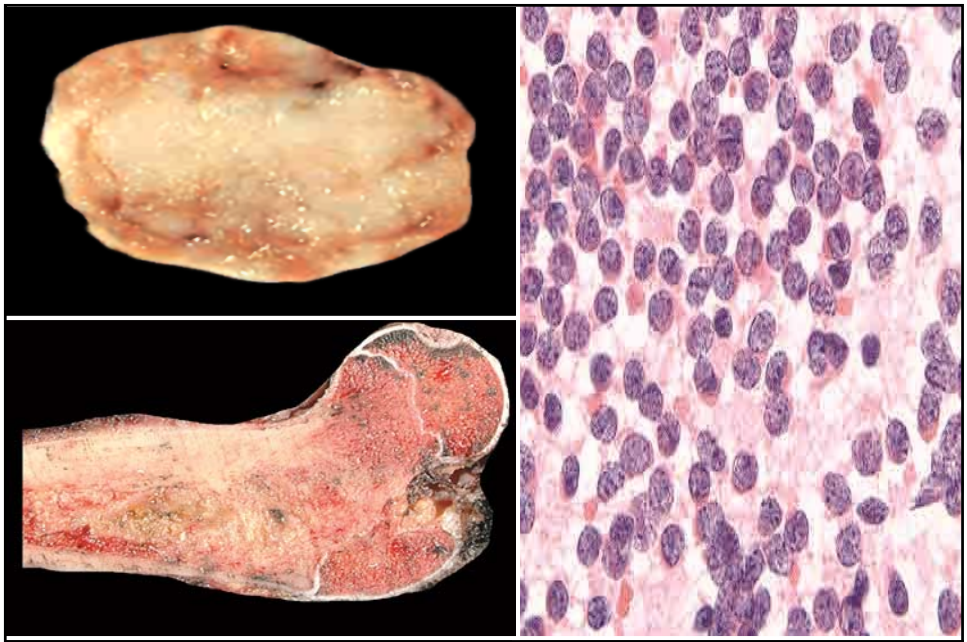
- Best treated with an aggressive combination of surgery, irradiation, and chemotherapy
- Even under optimal circumstances, long-term survival is seen in only ~50% of cases



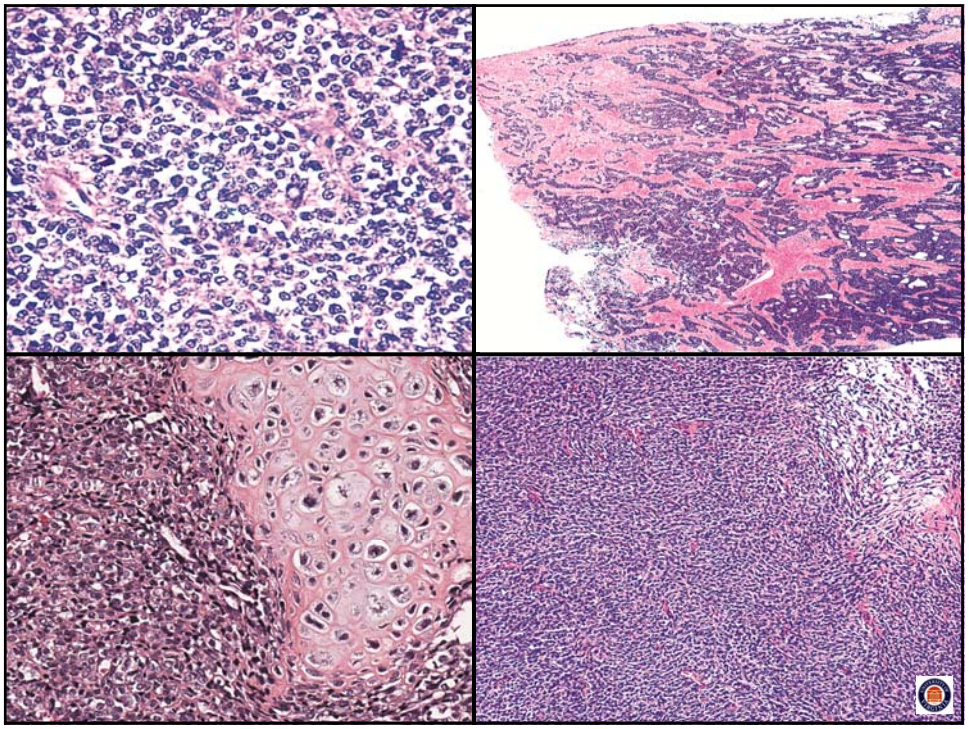
MEMBERS OF THE "EWING FAMILY" OF SMALL ROUND-CELL TUMORS

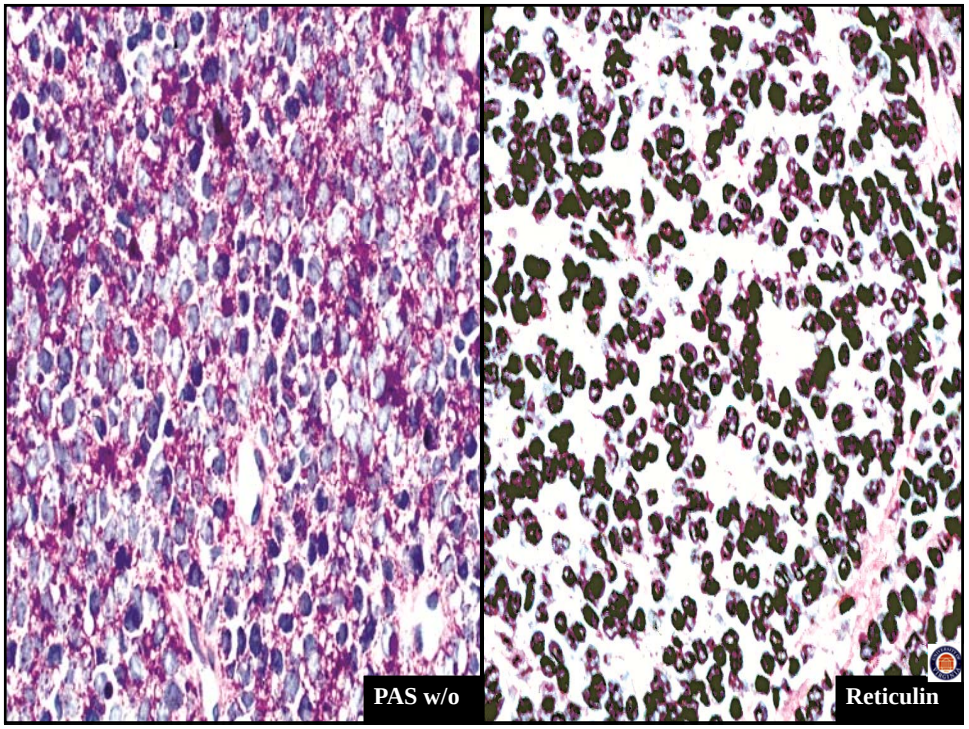
- Prototypic Ewing's tumor/Primitive neuroectodermal tumor (monophenotypic)
- Peripheral and central polyphenotypic small cell tumors (including desmoplastic small round-cell tumor)
- Mesenchymal chondrosarcoma
- Small-cell osteosarcoma

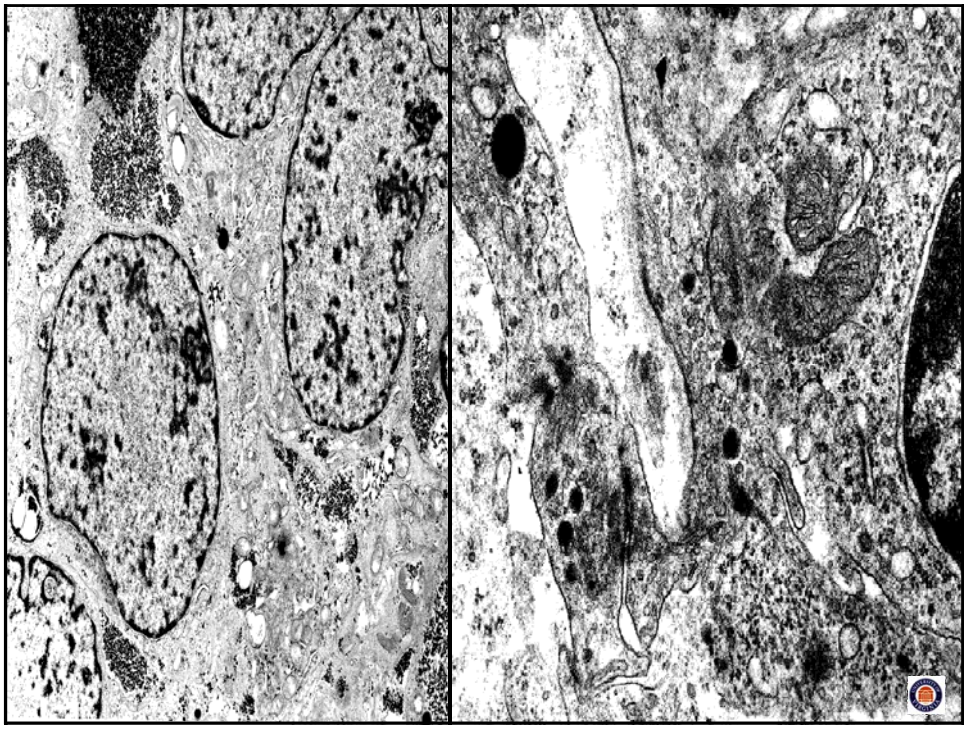




Primitive Neuroectodermal Tumor/ Ewing's Sarcoma

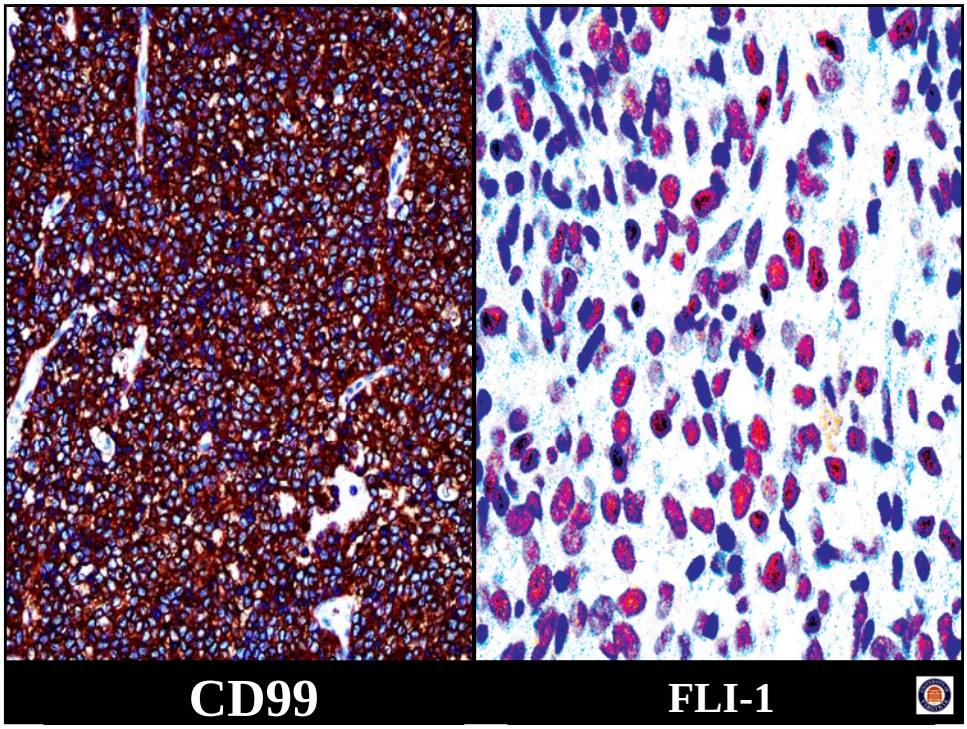


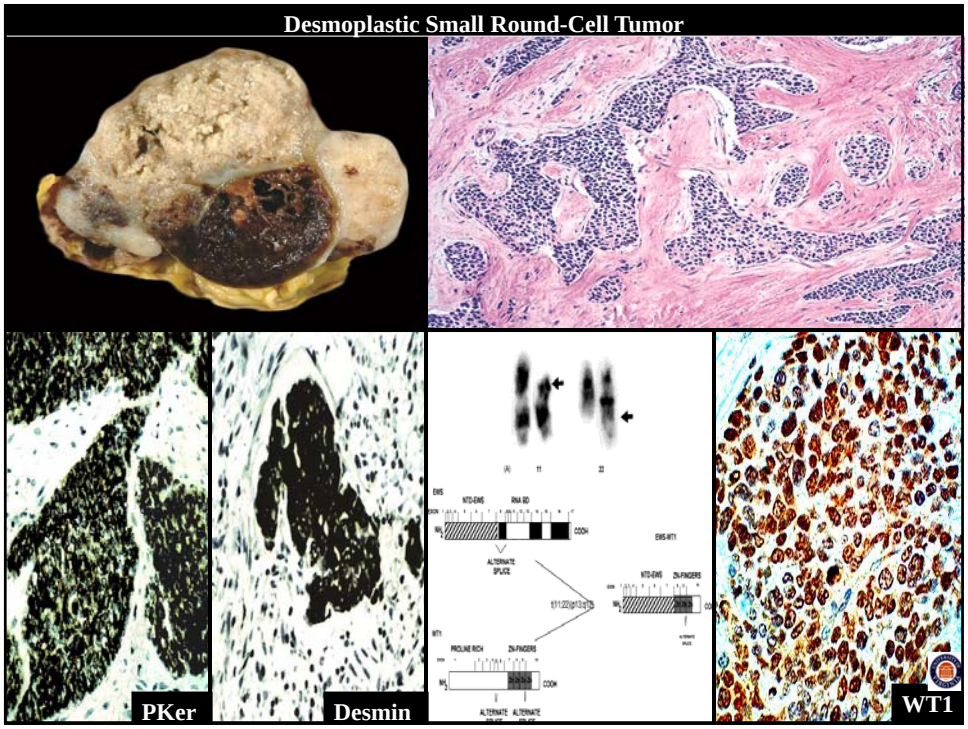

PAS w/o
Reticulin

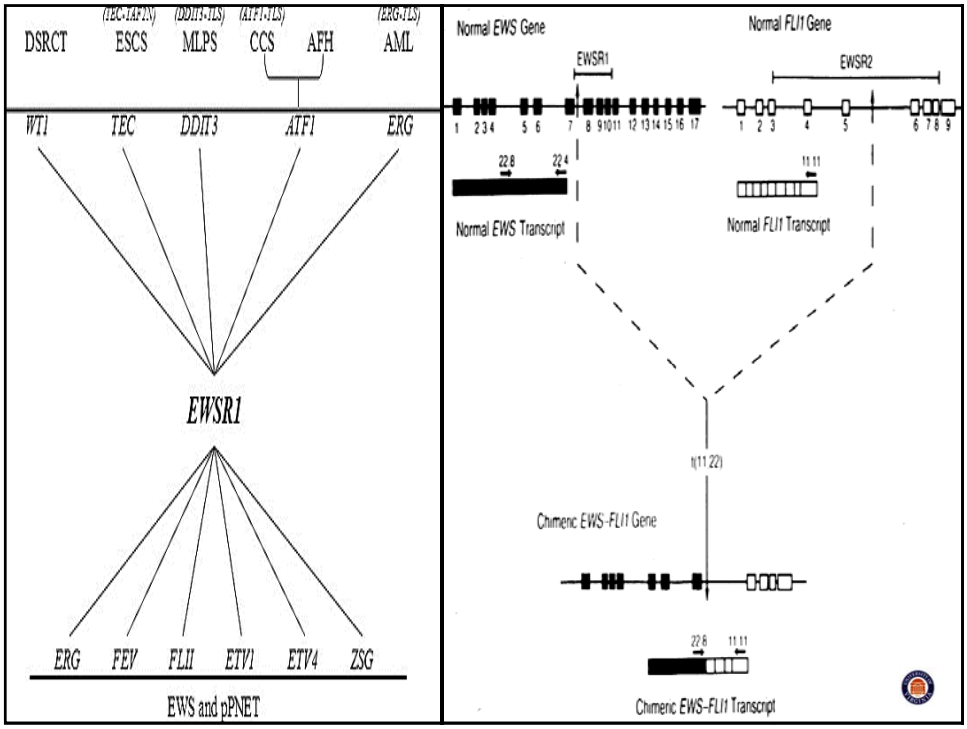


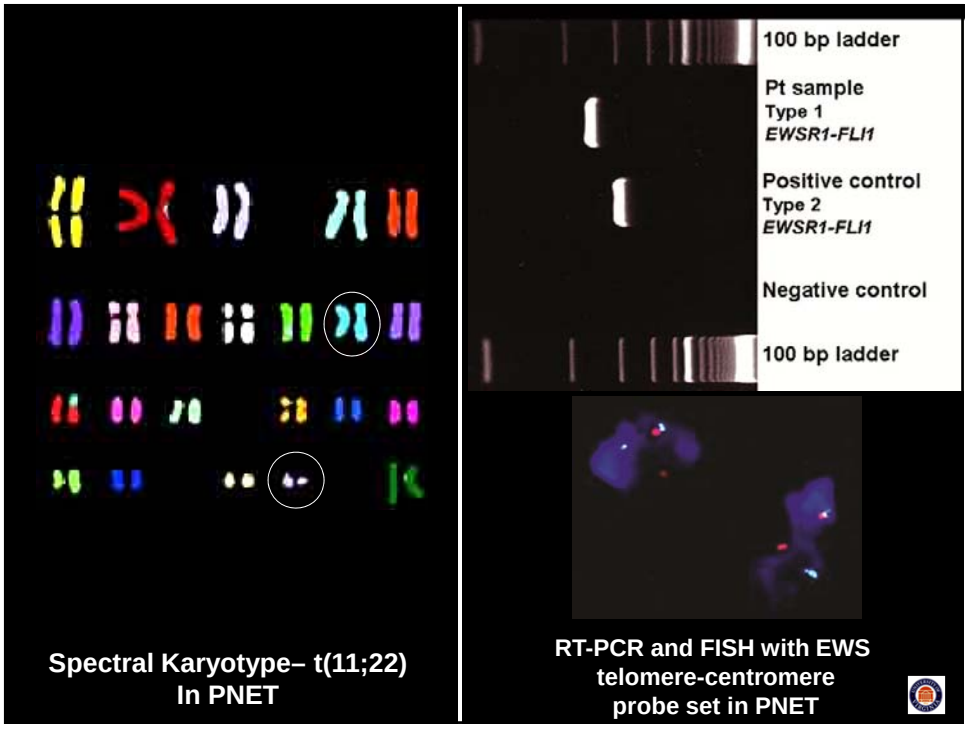
IMMUNOHISTOLOGY OF CLASSIC PNET

- **Keratin (-)**
- **Vimentin (+)**
- **Desmin (-)**
- **Muscle-specific actin (-)**
- **Neuron-specific enolase (+)**
- **CD56 or 57 (+/-)**
- **Synaptophysin (+/-)**
- **NB84 (+/-)**
- ***CD99/MIC-2 (+)***
- ***FLI-1 (+)***


CD99
FLI-1

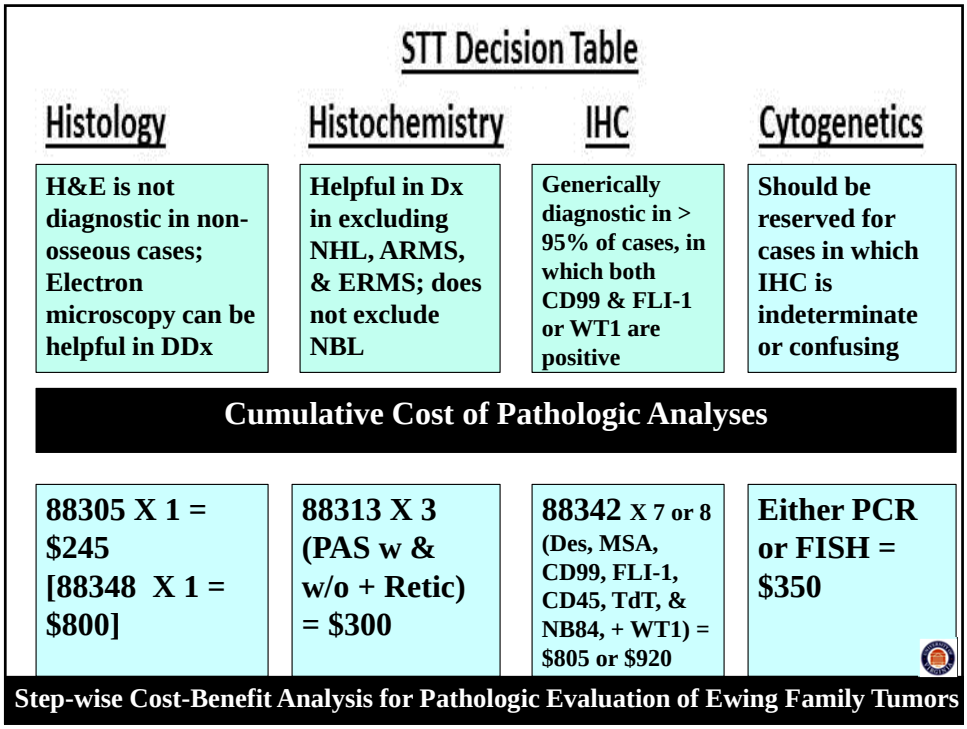

Desmoplastic Small Round-Cell Tumor
PKer
Desmin
WT1





Spectral Karyotype– t(11;22) In PNET

RT-PCR and FISH with EWS telomere-centromere probe set in PNET



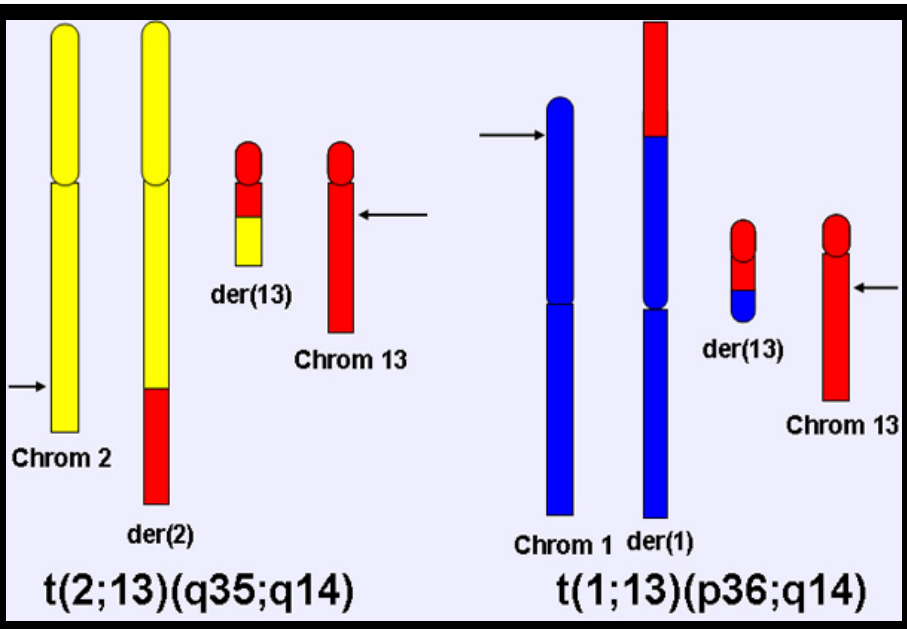
Step-wise Cost-Benefit Analysis for Pathologic Evaluation of Ewing Family Tumors

Alveolar & Embryonal Rhabdomyosarcoma

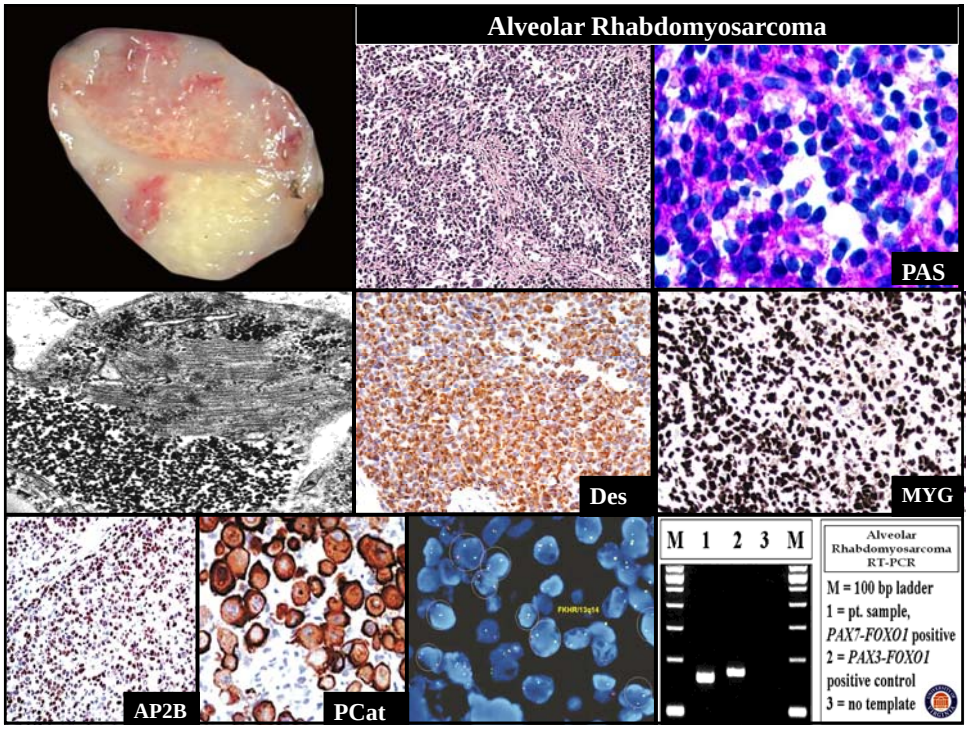
- ARMS accounts for 20-30% of all RMS tumors, ~1% of all malignancies in children & adolescents. A subset of ARMSs also occur in young or middle-aged adults; these are usually PAX3-FKHR. In contrast, PAX7-FKHR-positive ARMS as well as fusion-negative tumors tend to occur in young children (< 5 years old).
- ARMS often occurs in the skeletal muscles of the extremities but can also be seen in other sites including the trunk, and head and neck. It presents as a painless mass, or with symptoms produced by compression of anatomic structures.
- 25-30% of patients have metastatic disease at diagnosis. ARMS most frequently involves bone marrow, nodes, and bone. Standard treatment for ARMS is a combination of surgery, radiation, and intensive chemotherapy.

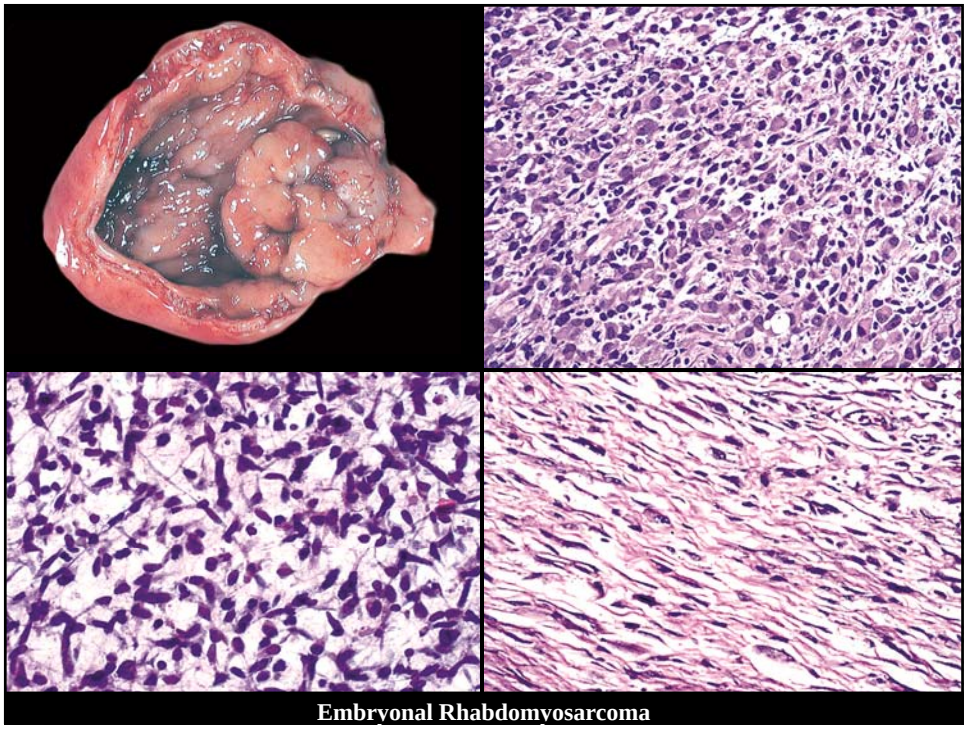
Alveolar & Embryonal Rhabdomyosarcoma

- **Desmin and muscle-specific actin are present immunohistologically in >95% of ARMS cases. Staining for myogenin and MyoD1 shows different patterns in ARMS and embryonal rhabdomyosarcoma (ERMS); most cells in ARMS label for both markers, whereas scattered cells in ERMS are positive.**
- **Microarray studies have shown that *activating enhancer-binding protein 2-beta (AP2β) and p-cadherin are specific markers for fusion-positive ARMS cases* immunohistologically. Epidermal growth factor receptor (EGFR) and fibrillin-2 are markers for ERMS.**
- **Immunolabeling for EGFR + fibrillin-2 = ERMS with specificity of 76% & sensitivity of 90%. The combination of AP2beta and P-cadherin = ARMS with specificity of 97% and sensitivity of 90%.**



Characteristic Chromosomal Translocations in ARMS


Alveolar Rhabdomyosarcoma
PAS
Des
MYG
AP2B
PCat
M 1 2 3 M
Alveolar Rhabdomyosarcoma RT-PCR
M = 100 bp ladder
1 = pt. sample, PAX7-FOXO1 positive
2 = PAX3-FOXO1 positive control
3 = no template


Embryonal Rhabdomyosarcoma

STT Decision Table

Histology	Histochemistry	IHC	Cytogenetics
- Diagnostic in ~ 90% of cases– exceptions = "solid" ARMS & spindle-cell ERMS - EM may be helpful in DDx	Helpful in Dx in excluding NHL, PNET, & NBL; does not separate ARMS from ERMS	Generically diagnostic in > 95% of cases; if AP2b + p-Cad are positive, 97% of cases are translocated	Should be reserved for AP2b + P-cad-negative cases; Either FISH or RT-PCR
Cumulative Cost of Pathologic Analyses			
88305 X 1 = $245 [88348 X 1 = $800]	88313 X 3 (PAS w & w/o + Retic) = $300	88342 X 5 (Des, MSA, MYG, AP2b, & P-Cat = $575	Either PCR or FISH = $350

Step-wise Cost-Benefit Analysis for Pathologic Evaluation of Rhabdomyosarcoma

Dermatofibrosarcoma

- Translocation between chromosomes 17 and 22 t(17;22) fuses the *COL1A1* gene on chromosome 17 with the *PDGFB* gene on chromosome 22. The translocation can be either linear or circular (supernumerary ring chromosomes).
- *COL1A1-PDGFB* fusion gene transcribes an abnormal protein that functions somewhat like *PDGFB* protein.

Dermatofibrosarcoma

- Dermatofibrosarcoma protuberans (DFSP) is a 1 to 5 cm in diameter, purple-red or flesh-colored cutaneous nodule. Rarely can be a flat or depressed plaque form. Most common on torso, arms, legs, head, or neck. Most often presents in individuals aged 20-30 yrs, but children can also be affected.
- Microscopic subtypes:
  - Classic storiform DFSP
  - Myxoid DFSP
  - Atrophic DFSP
  - Pigmented DFSP (Bednar tumor)
  - Fibrosarcomatous DFSP

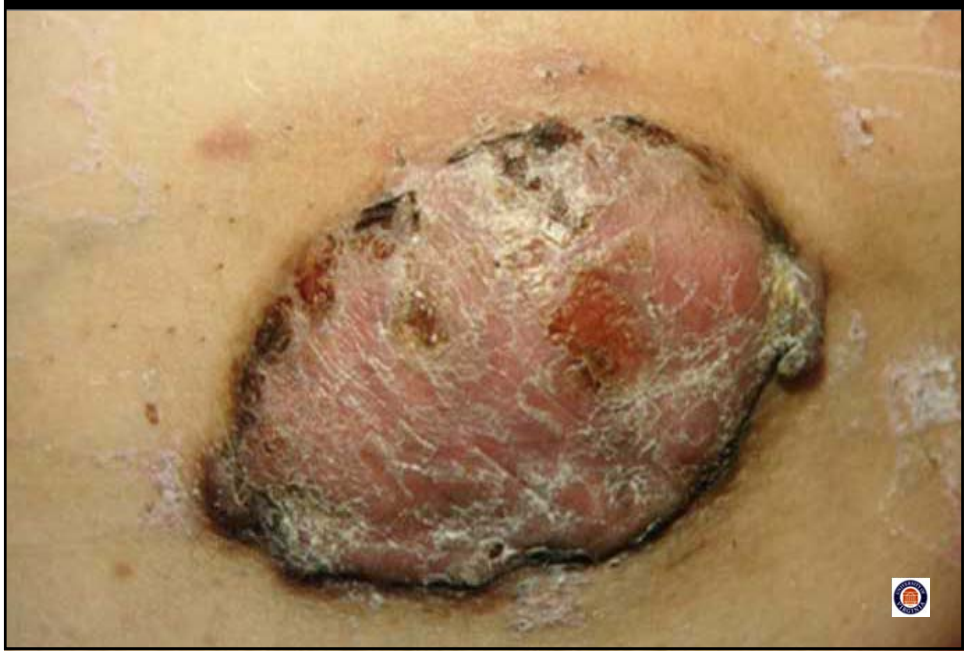
GIANT CELL FIBROBLASTOMA: Clinical Features

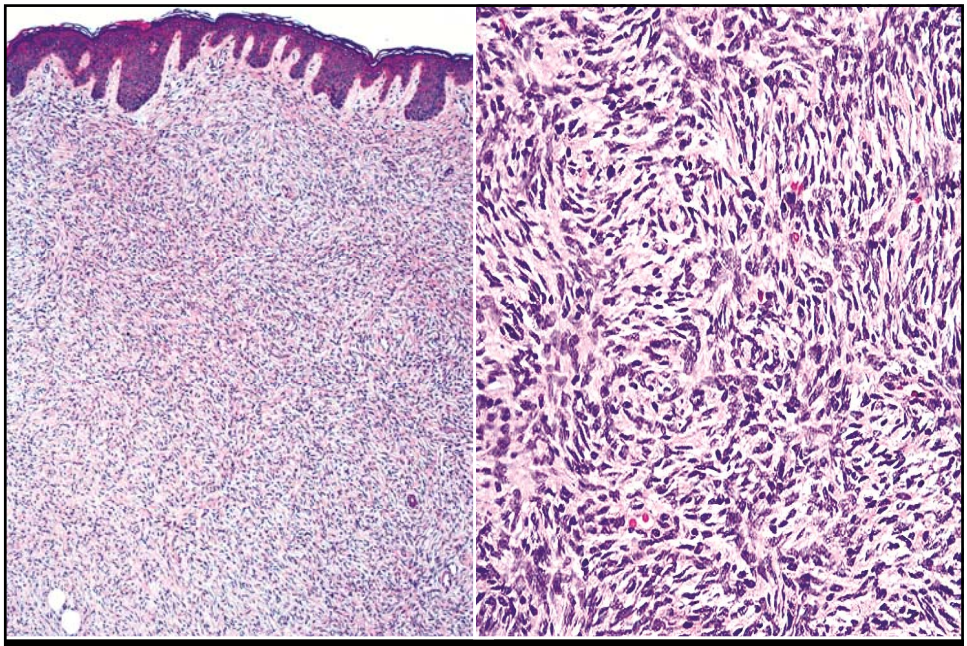
- Rare lesion; a juvenile form of DFSP
- Males under 15 yrs. of age favored
- Superficial tumor of deep dermis & subcutis, on trunk & extremities
- Often mistaken for lipoma or lymphangioma clinically
- Long evolution (months to yrs.) before diagnosis

GIANT CELL FIBROBLASTOMA:
Pathologic Features

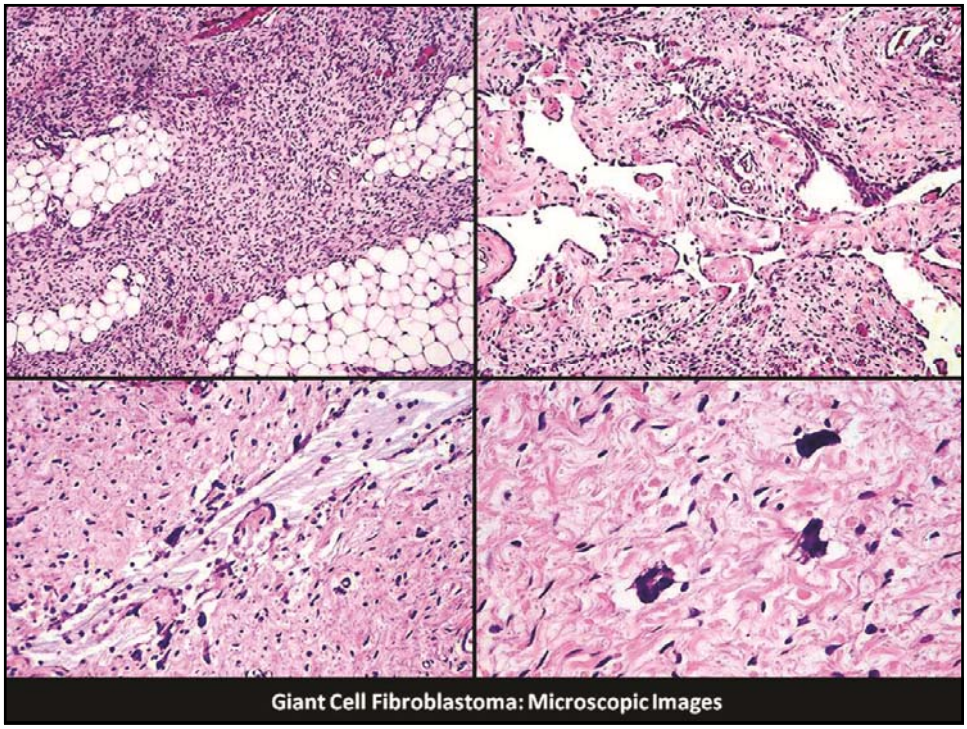
- **Biphasic appearance--superficial "solid" areas composed of stellate & fusiform cells, admixed with floret giant cells; deep component shows "angiectoid" spaces lined by giant cells**
- **Cytologically bland**
- **Mitotic activity is sparse**

DFSP & Giant Cell Fibroblastoma: Clinical Image

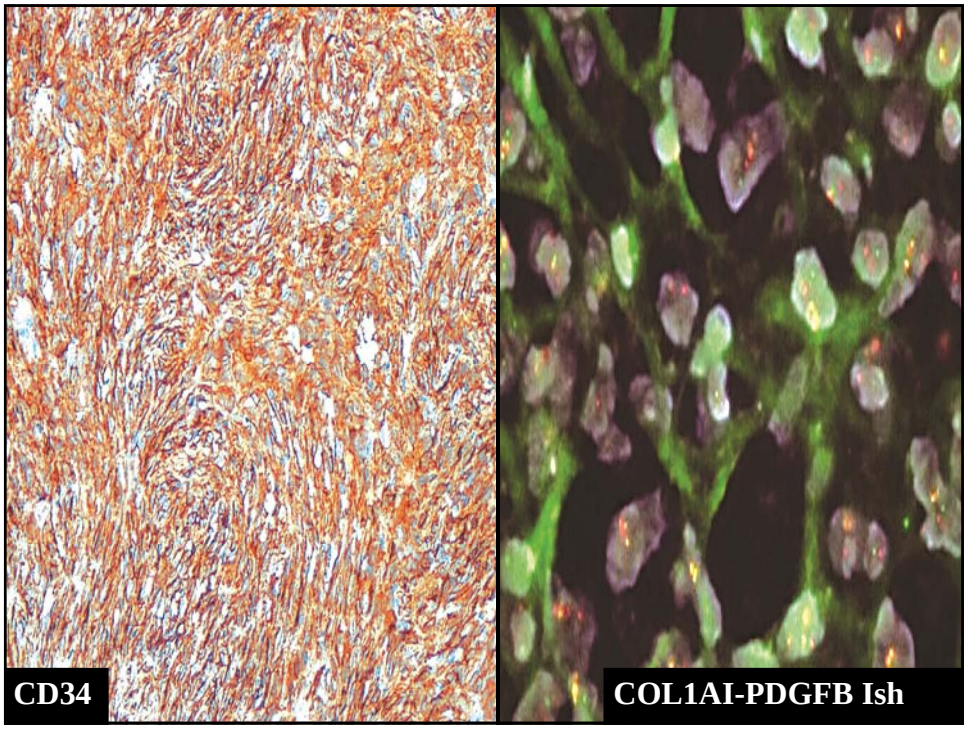




Dermatofibrosarcoma– Typical Image



Giant Cell Fibroblastoma: Microscopic Images



STT Decision Table

Histology	Histochemistry	IHC	Cytogenetics
Diagnostic in approximately 95% of cases– exceptions = myxoid & atrophic DFSP	Helpful in identifying the pigmented (melanotic) variant of DFSP	CD34+ is generically diagnostic in > 95% of cases, especially if podoplanin stain is negative	Generally not needed for diagnosis; prediction of response to targeted therapy also does not require it
Cumulative Cost of Pathologic Analyses			
88305 X 1 = $245	Generally not used	88342 X 2 (CD34 & Podoplanin = $230	Either PCR or FISH = $350

Step-wise Cost-Benefit Analysis for Pathologic Evaluation of Dermatofibrosarcoma/Giant Cell Fibroblastoma

Synovial Sarcoma (SS)

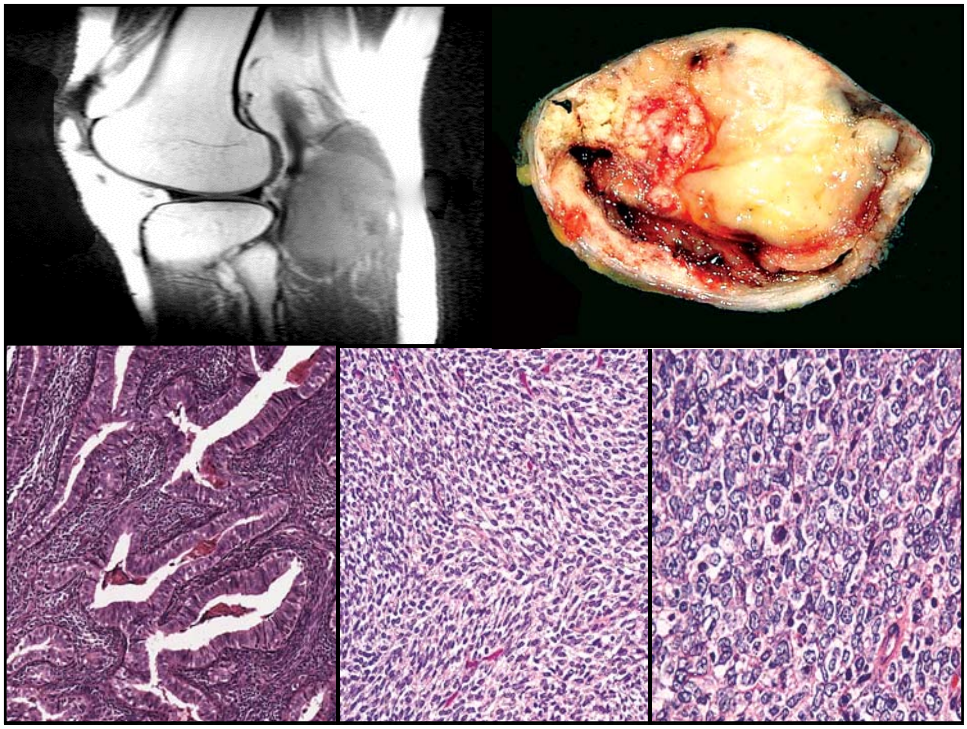
- Seen over a wide range of patient ages, from 15 to 90, in many body locations including viscera. Favored sites are extremities and trunk
- Generally presents as a non-painful mass; visceral lesions may interfere with organ function
- Several microscopic iterations on the theme of monophasic & biphasic growth patterns (*e.g.*, small-cell epithelial-predominant; gland-like, myxoid, sclerotic, squamoid, metaplastic)
- Monophasic SS shows a prototypical "herringbone" growth pattern, often with "staghorn"-shaped blood vessels throughout the lesion

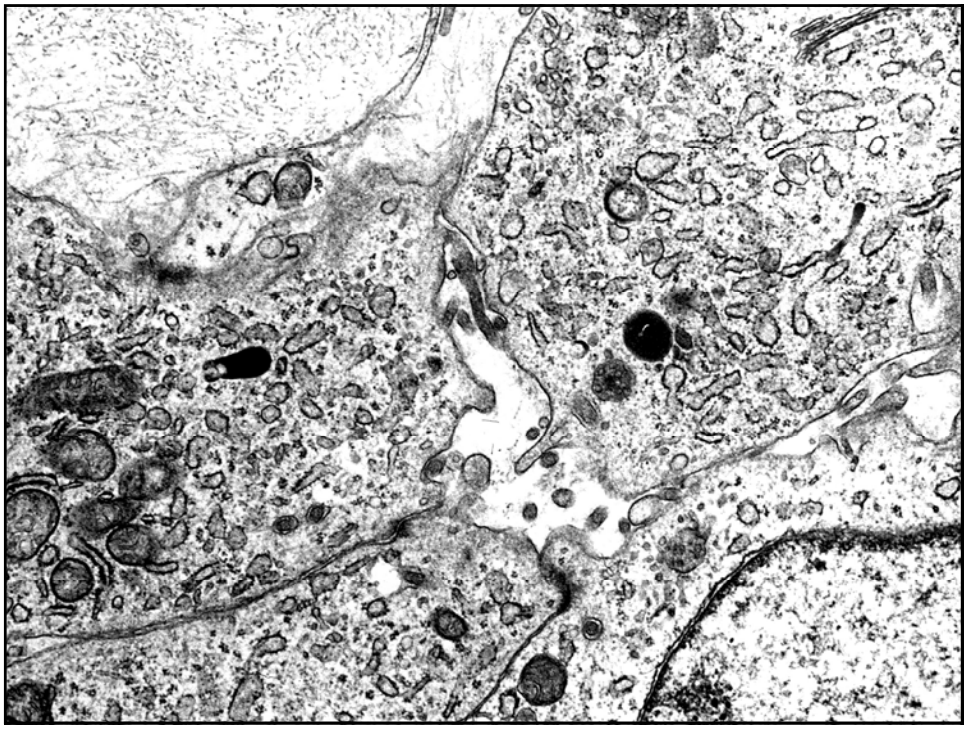
Synovial Sarcoma (SS)

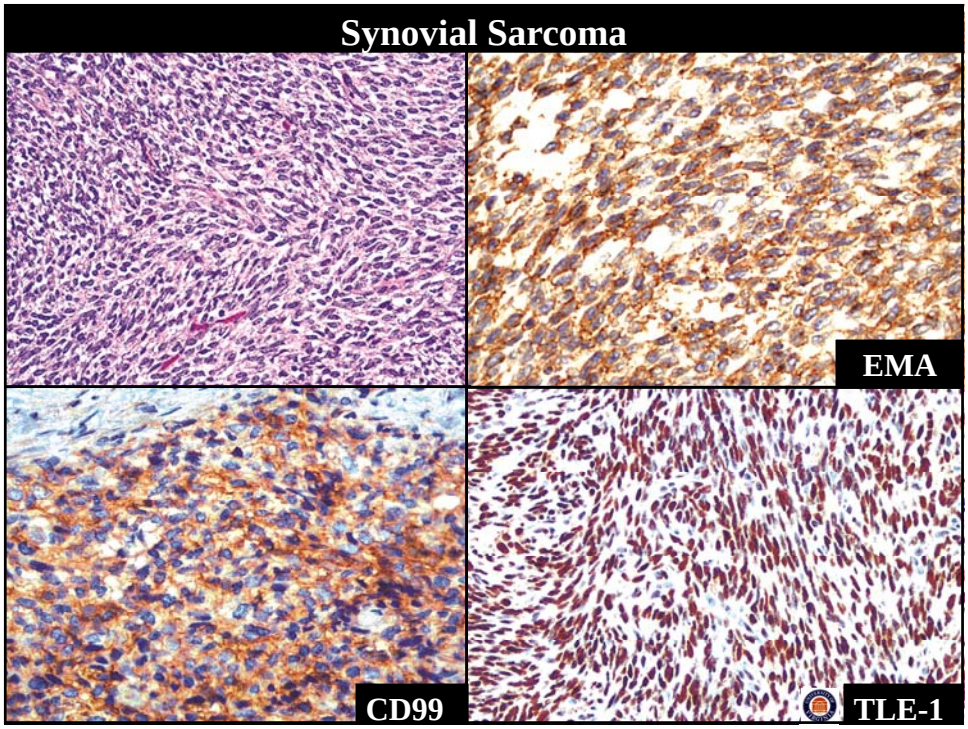
- Electron microscopy shows well-formed intercellular junctions in SS, especially in the biphasic and epithelial-predominant forms of the tumor.
- Immunohistologic studies demonstrate labeling for pankeratin and/or EMA/CD99/*bcl-2* in >95% of cases; CD56 and/or CD57 in ~70%; & S100 protein in ~5% of tumors. Myogenic markers are absent.
- In a recent study by Foo et al., 82% of SSs were positive for transducer-like enhancer of split 1 (TLE1)– 78% of biphasic; 79% of monophasic; & 91% of small-cell (poorly differentiated) tumors. Among other tumors, 15% of MPNSTs and 8% of solitary fibrous tumors were TLE1-reactive, with weak staining.

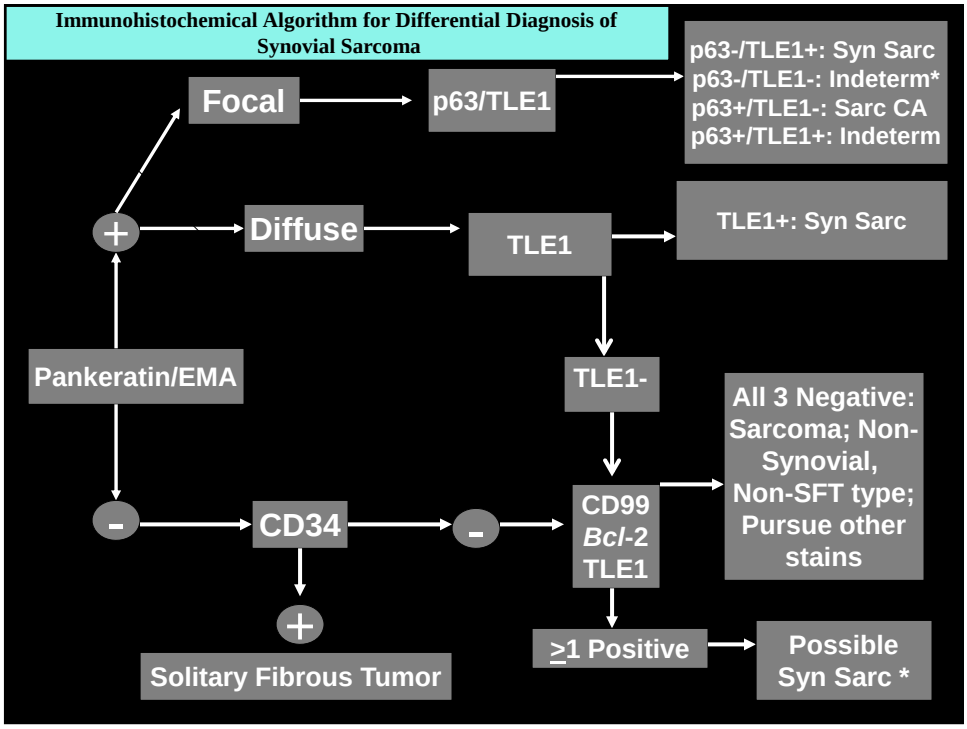
Synovial Sarcoma (SS)

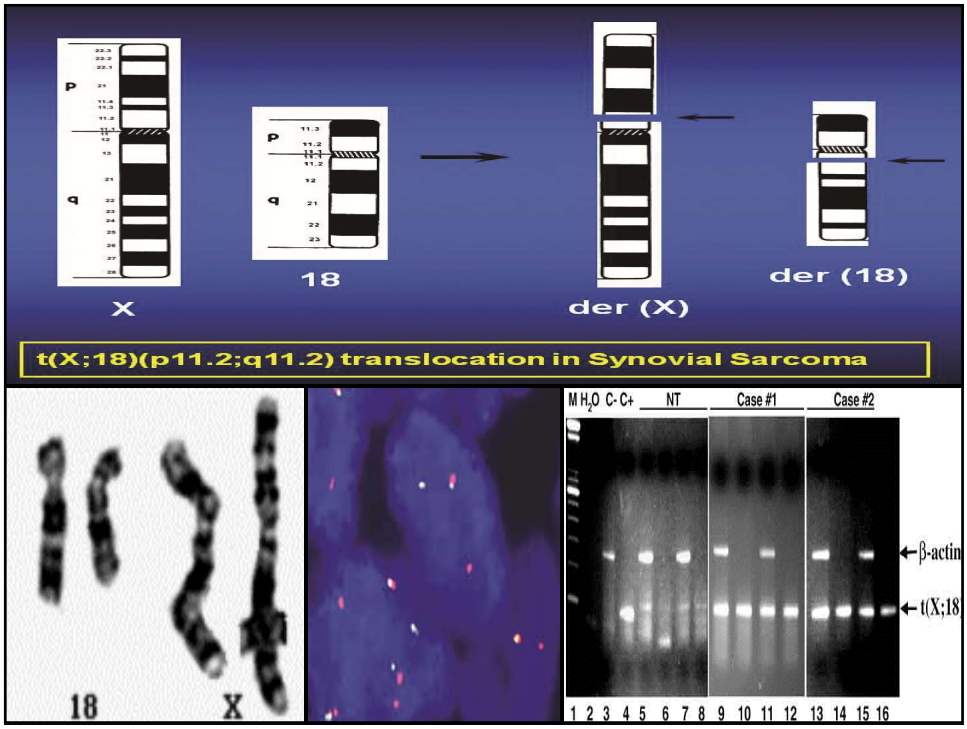
- **The chromosomal aberration which characterizes SS is t(X;18;p11;q11), resulting in *SS18-SSX1*, *SS18-SSX2*, & rarely, *SS18-SSX4* fusion transcripts.**
- **The translocation is present in ~95% of SS cases in which optimal tissue substrates are available; however, technical problems (poor preservation of nucleic acid) may cause false-negativity in up to 20% of cases overall.**
- **TLE-1-immunoreactivity has been shown to demonstrate excellent correlation with the presence of t(X;18).**
- ***In-situ* hybridization or RT-PCR can be used to assess lesions for the translocation, using paraffinized material.**






Synovial Sarcoma
EMA
CD99
TLE-1


Immunohistochemical Algorithm for Differential Diagnosis of Synovial Sarcoma
Focal
p63/TLE1
p63-/TLE1+: Syn Sarc
p63-/TLE1-: Indeterm*
p63+/TLE1-: Sarc CA
p63+/TLE1+: Indeterm
+
Diffuse
TLE1
TLE1+: Syn Sarc
Pankeratin/EMA
TLE1-
All 3 Negative: Sarcoma; Non-Synovial, Non-SFT type; Pursue other stains
-
CD34
-
CD99
Bcl-2
TLE1
+
Solitary Fibrous Tumor
≥1 Positive
Possible Syn Sarc *


X
18
der (X)
der (18)
t(X;18)(p11.2;q11.2) translocation in Synovial Sarcoma
18
X
M H2O C- C+
NT
Case #1
Case #2
β-actin
t(X;18)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16

STT Decision Table

Histology	Histochemistry	IHC	Cytogenetics
Diagnostic in approximately 35% of cases, (diffuse biphasic pattern); EM may be helpful	Rarely helpful– only if mucicarmine or PAS-D+	Immunostaining is dispositive in >90% of cases, using the specified algorithmic approach	Principally needed in TLE1– cases and those in which immunohistologic findings are confusing
Cumulative Cost of Pathologic Analyses			
88305 X 1 = $245 [88348 X 1 = $800]	88313 X 2 = $200	88342 X 7 (Pankeratin, EMA, CD99, *bcl-2*, CD34, p63, TLE1) = $795	Either PCR or FISH = $350

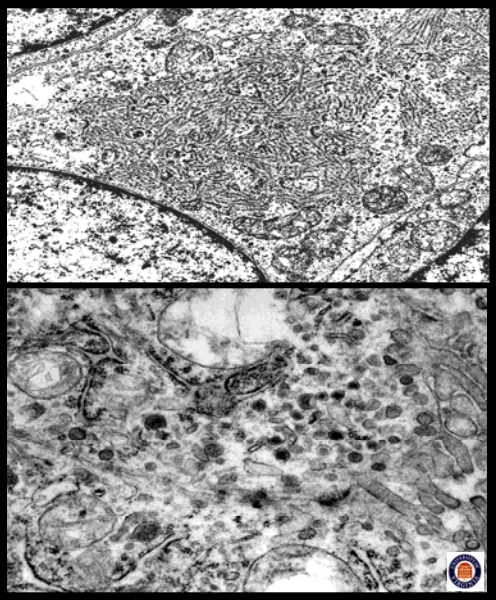
Step-wise Cost-Benefit Analysis for Pathologic Evaluation of Synovial Sarcoma

Extraskeletal Myxoid Chondrosarcoma

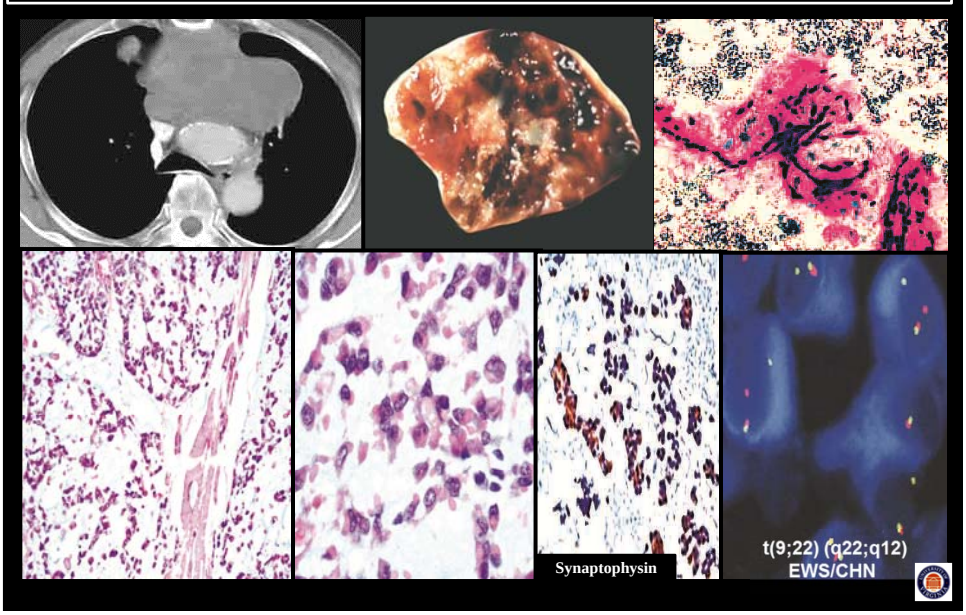
- Tumor of adults, usually in the legs; may rarely arise in the pleura, pericardium, or other soft tissue sites.
- Cords of compact polygonal cells, separated by myxomucinous stroma– cellularity is variable, as is the degree of nuclear atypicality and mitotic activity
- Resemblance to chordoma yielded the older term for this tumor of "chordoid sarcoma"
- Much less often immunoreactive for S100 protein and CD57 than conventional skeletal chondrosarcoma; may also show EMA-positivity in some cases; brachyurin- and pankeratin- negative
- > 70% of cases show immunohistologic evidence of "occult" neuroendocrine differentiation, especially for synaptophysin

Extraskeletal Myxoid Chondrosarcoma

- Characteristically shows the presence of cytoplasmic microtubular complexes by electron microscopy, and may contain neurosecretory granules as well; these are distinctive findings in ESMC

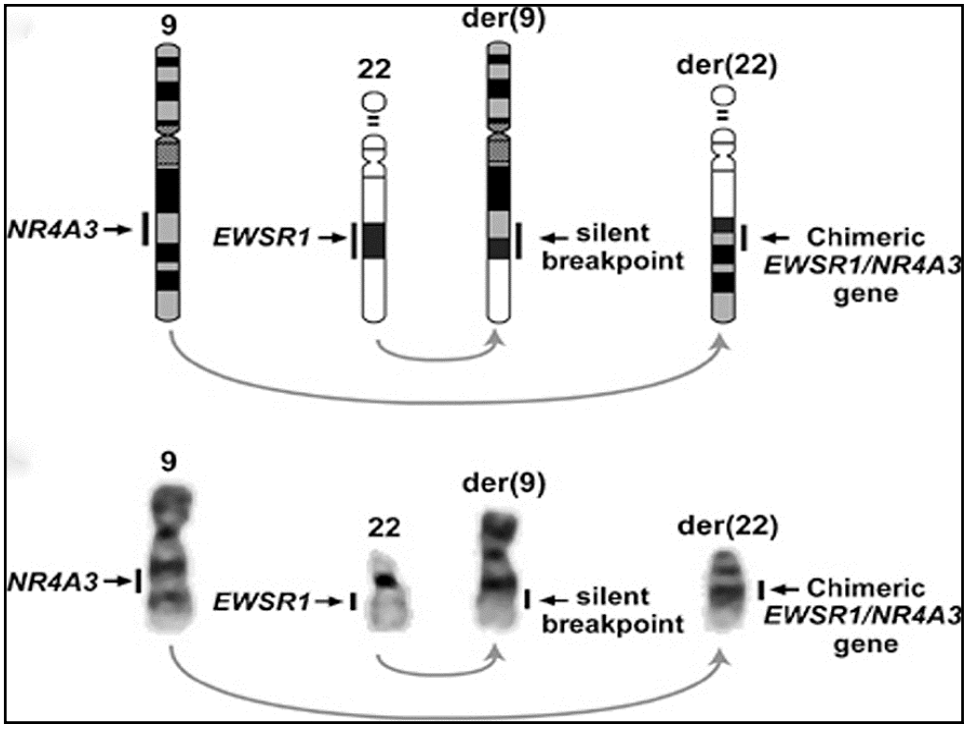


Extraskeletal Myxoid Chondrosarcoma



Extraskeletal Myxoid Chondrosarcoma

- Genotyping is used in excluding the elusive entity of "parachordoma", which may resemble ESMC histologically
- t(9;22) (q22;q12) is the most common translocation seen in ESMC, producing fusion of the *EWSR1* and *NR4A3* genes
- t(9;12) & t(9;17) have also been reported in some cases
- The translocation in ESMC involves different breakpoints than the t(9;22) defect of chronic myelogenous leukemia
- All of these specific fusion genes can be assessed via karyotyping, FISH or RT-PCR



Extraskeletal Myxoid Chondrosarcoma

- **Typically an indolent tumor that may recur but uncommonly metastasizes; the latter behavior is seen in only ~20% of cases**
- **Large tumor size (>10 cm), patient age ≥ 45 yrs, male gender, high tumor cellularity, and mitotic activity > 2/10 high-power fields were all negative prognosticators in a study by Oliveira et al. (*Mod Pathol*, 2000)**

Factor	*P* Value	
	Metastasis-free Survival	Overall Survival
Age (≥45 years old)	0.783	0.126
Male sex	0.077	0.068
Tumor ≥10 cm	0.027	0.033
High cellularity	0.429	0.044
Mitotic activity (>2/10 HPF)	0.037	0.099

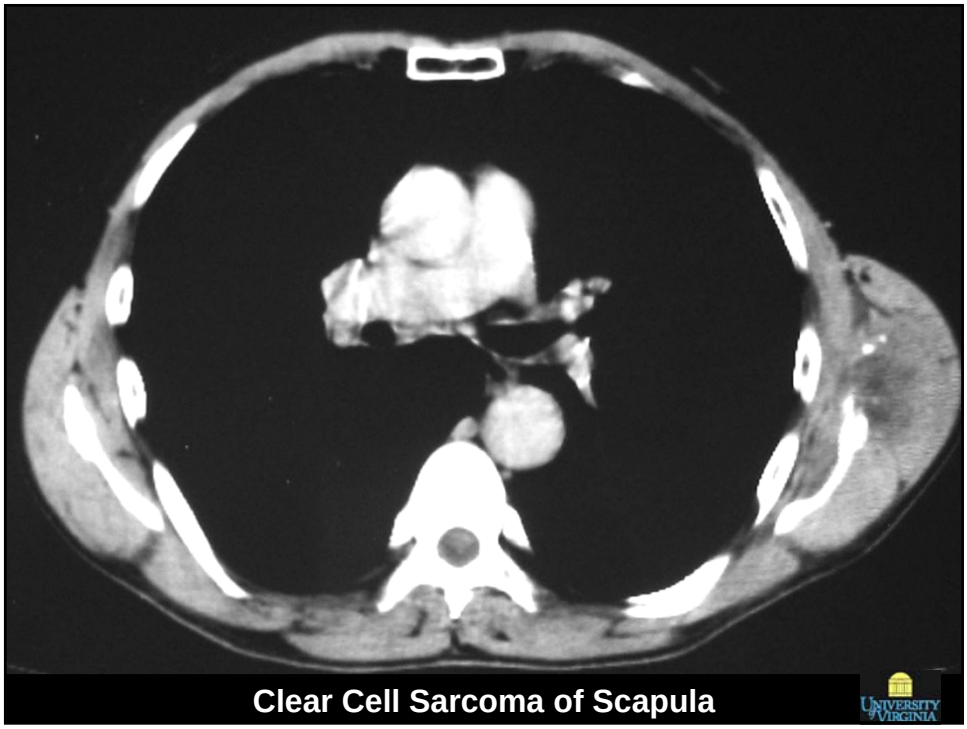
STT Decision Table

Histology	Histochemistry	IHC	Cytogenetics
H&Es are not dispositive diagnostically, but electron microscopy may be diagnostic	Rarely helpful–only if mucicarmine or PAS-D+	Immunostaining is diagnostic in ~70% of cases, which show neuroendocrine markers	Principally needed in synaptophysin & chromogranin-negative cases
Cumulative Cost of Pathologic Analyses			
88305 X1 = $245 [88348 X1 = $800]	88313 X 2 = $200	88342 X 5 (Pankeratin, EMA, S100, synaptophysin, chromogranin-A) = $575	Either PCR or FISH = $350

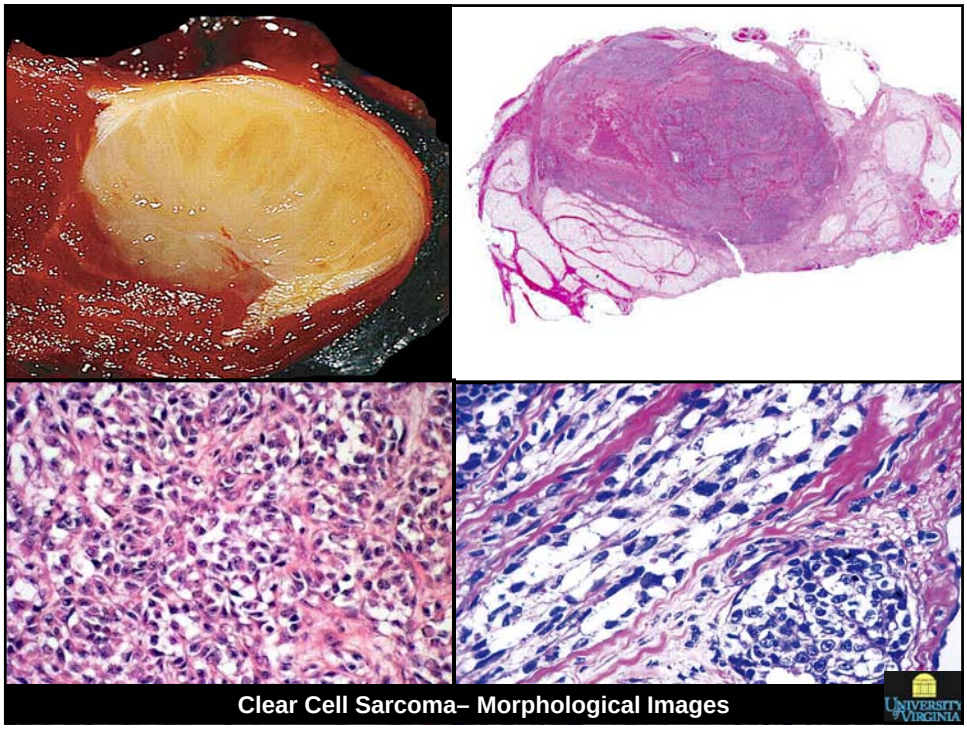
Step-wise Cost-Benefit Analysis for Pathologic Evaluation of ESMC

Clear-Cell Sarcoma (CCS)

- Like synovial sarcoma & epithelioid sarcoma, CCS is principally a tumor of adolescents and young adults; male predominance of 2:1
- Preference for deep soft tissues of the extremities and trunk
- *Infiltrative*, fascicular or alveolar growth of epithelioid & spindle cells, with variable clearing of cytoplasm, necrosis, and mitotic activity

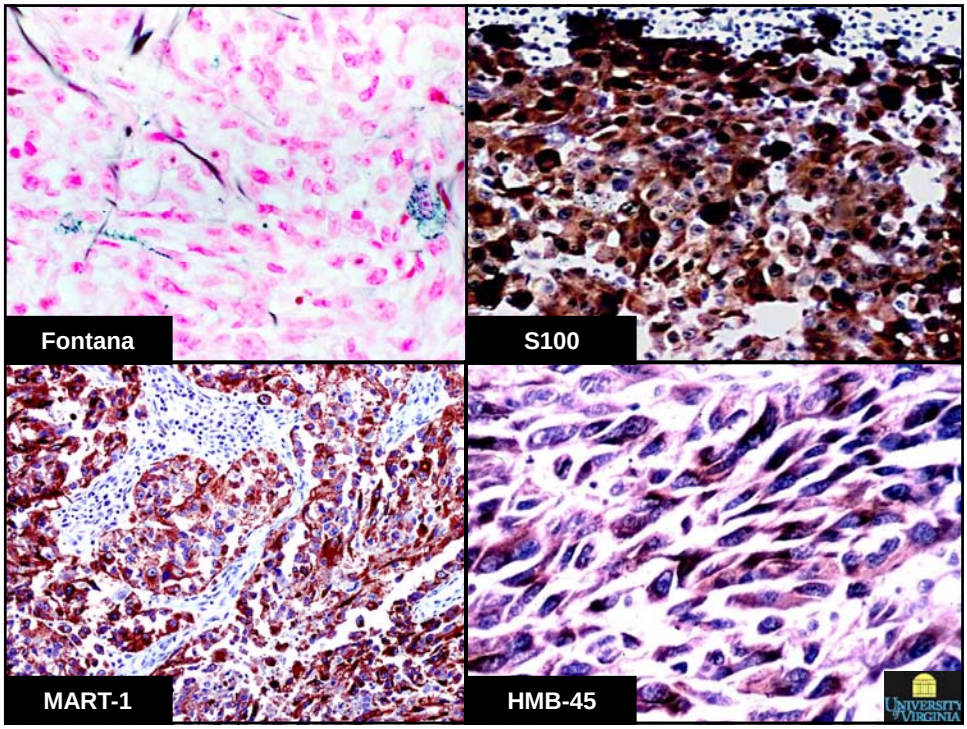


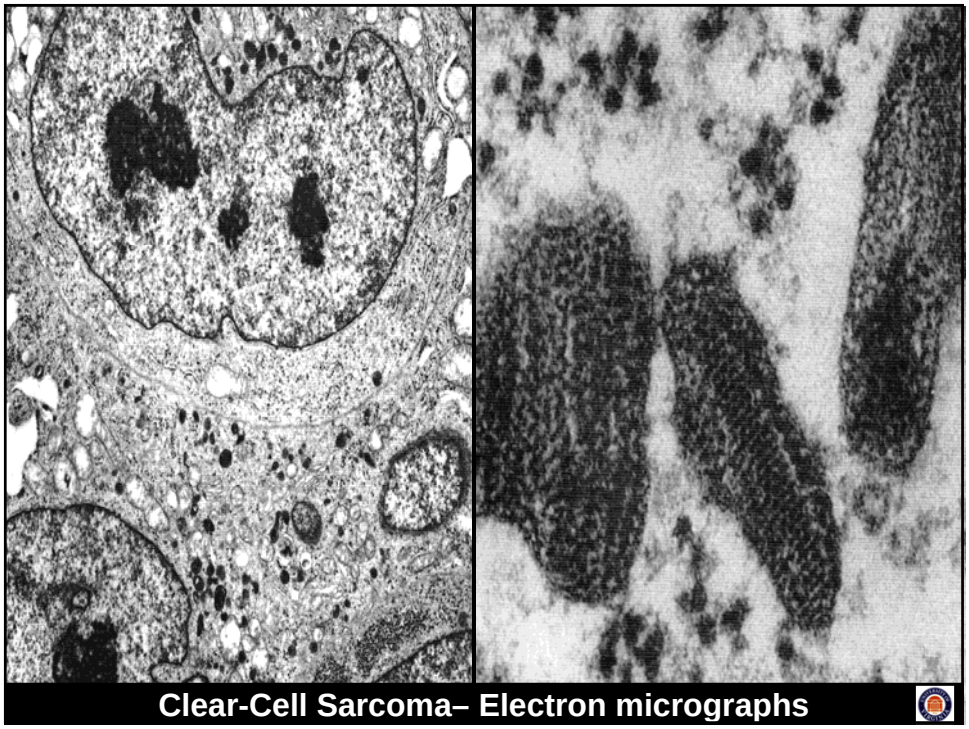
Clear Cell Sarcoma of Scapula



Clear-Cell Sarcoma (CCS)

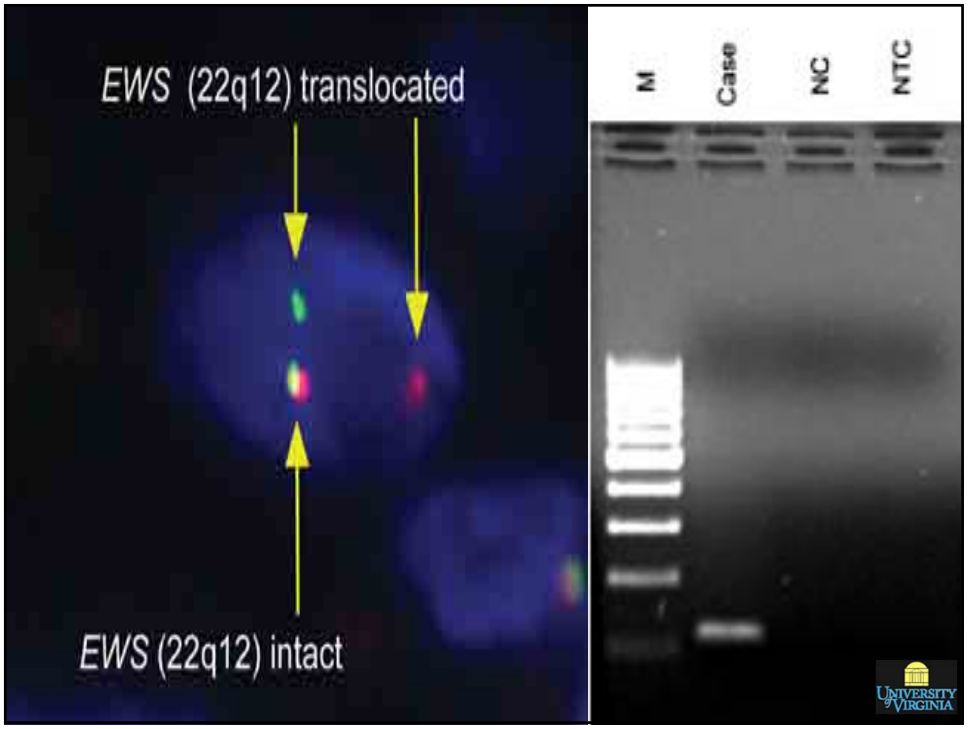
- **CCS shows melanocytic differentiation at a number of levels, including histochemical positivity with the Fontana-Masson method & immunoreactivity for vimentin, S100 protein, MART-1, MITF, HMB-45, tyrosinase, & PNL2; keratin & desmin are absent, but EMA may be seen in 1/3 of cases**
- **Electron microscopy demonstrates the presence of intracellular premelanosomes**


Fontana
S100
MART-1
HMB-45

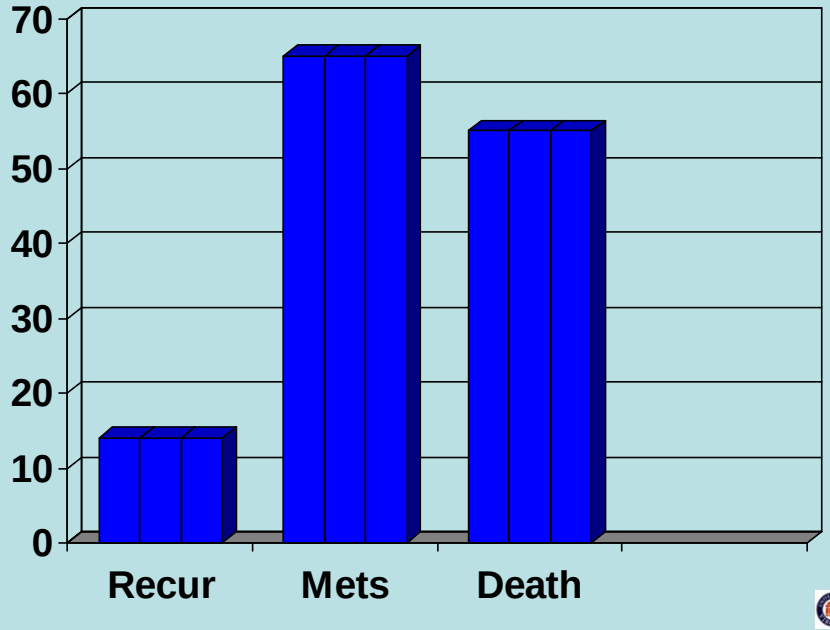

Clear-Cell Sarcoma– Electron micrographs

Clear-Cell Sarcoma: Molecular Features

- **Reproducible t(12;22)(q13;q12) translocation, fusing the *EWS* and *ATF1* genes on chromosomes 22q12 and 12q13, respectively.**
- **This can be visualized by fluorescent in-situ hybridization, using a "break-apart" probe for visualization of *EWS* (22q.12) gene rearrangement, or RT-PCR**
- **Melanoma essentially *never* demonstrates this cytogenetic aberration**



Behavior of Clear Cell Sarcoma



STT Decision Table

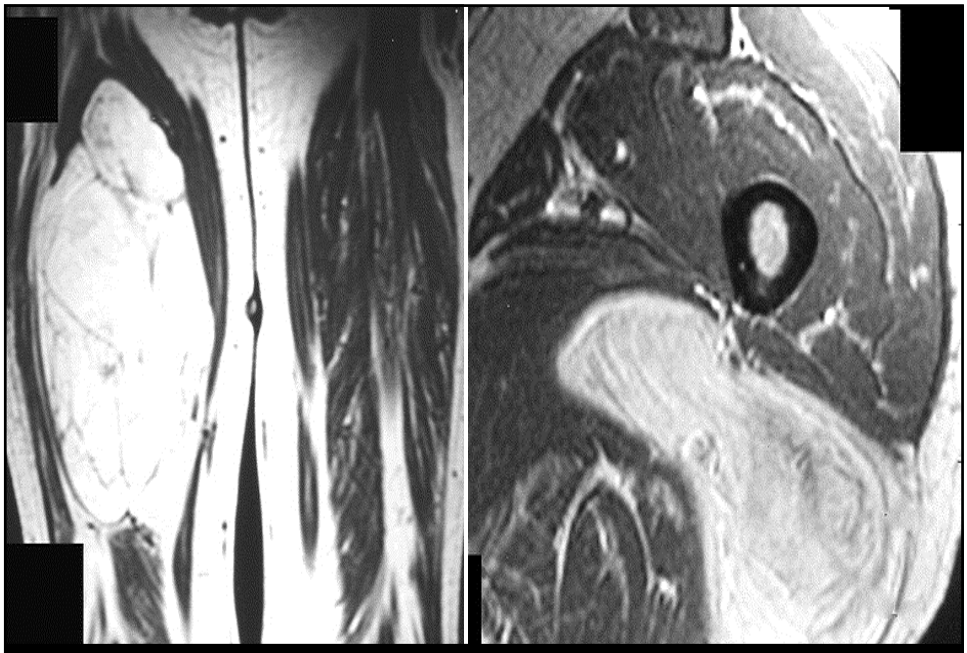
Histology	Histochemistry	IHC	Cytogenetics
H&Es are not dispositive diagnostically, but electron microscopy may be diagnostic	Helpful if Fontana-Masson or Schmorl stain is positive (35% of cases)	Immunostaining is diagnostic of melanocytic differentiation in all cases	Principally needed in cases where clinical history & histologic growth pattern cannot exclude the Dx of metastatic melanoma
Cumulative Cost of Pathologic Analyses			
88305 X1 = $245 [88348 X1 = $800]	88313 X 1 = $100	88342 X 4 (Pankeratin, EMA, S100, MART1 or PNL2) = $460	Either PCR or FISH = $350

Step-wise Cost-Benefit Analysis for Pathologic Evaluation of Clear-Cell Sarcoma

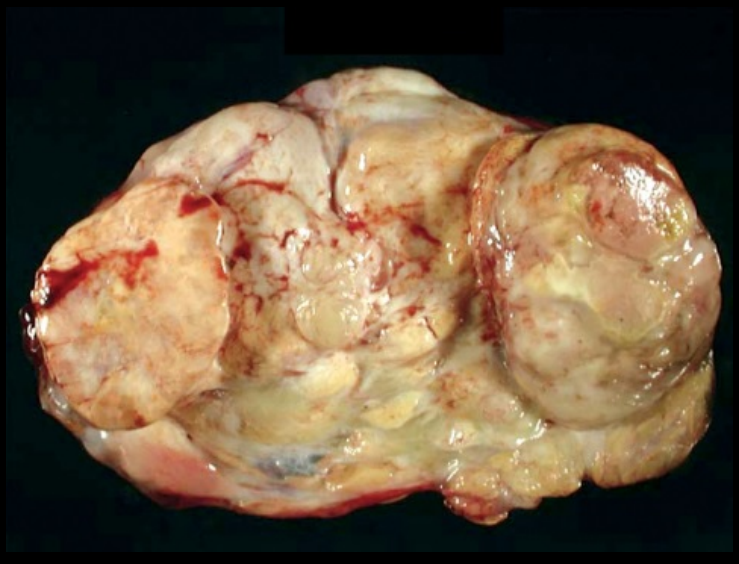
Liposarcomas

Lipoma-like Liposarcoma Variants

- **Liposarcoma (LPS) variants are among the most commonly-encountered soft tissue sarcomas; they favor deep sites in the extremities and trunk in patients > 35 years old**
- **Retroperitoneal and intrathoracic examples may attain huge dimensions (> 25 cm in maximal diameter)**
- **Well-differentiated LPS (also called "atypical lipomatous tumor" [ALT]) is distinguished from lipoma because it shows more nuclear atypicality than the latter; anatomic location also important in DDx of those entities.**
- **The adipocytic nature of well-differentiated LPS/ALT is typically obvious in imaging studies and gross examination**



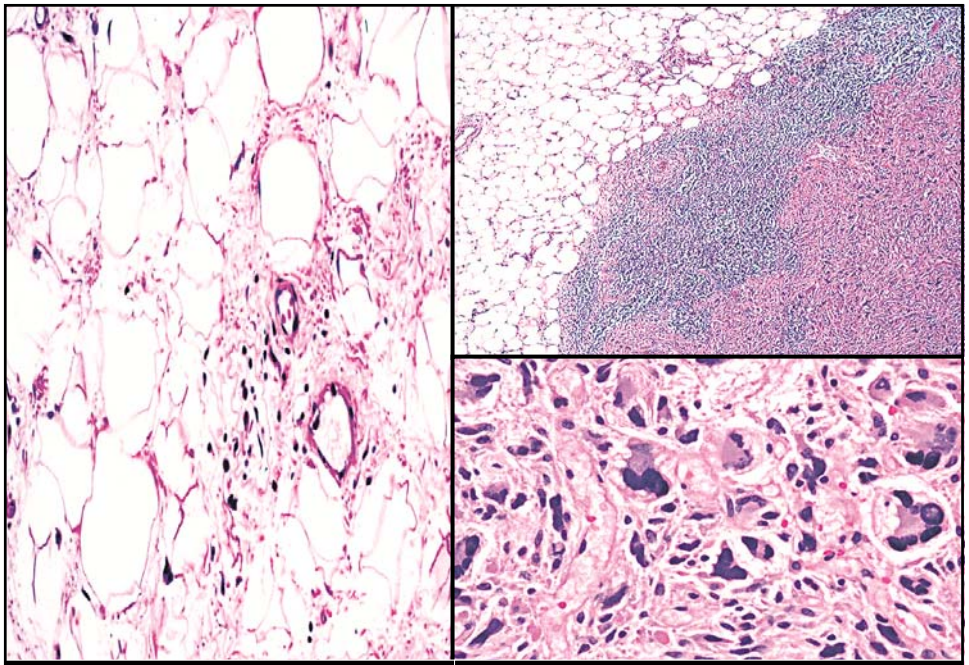
MRI scan (left) & Contrast-enhanced computed tomogram (right) of well-differentiated liposarcoma in the right thigh



Well-Differentiated Liposarcoma– Gross Photograph

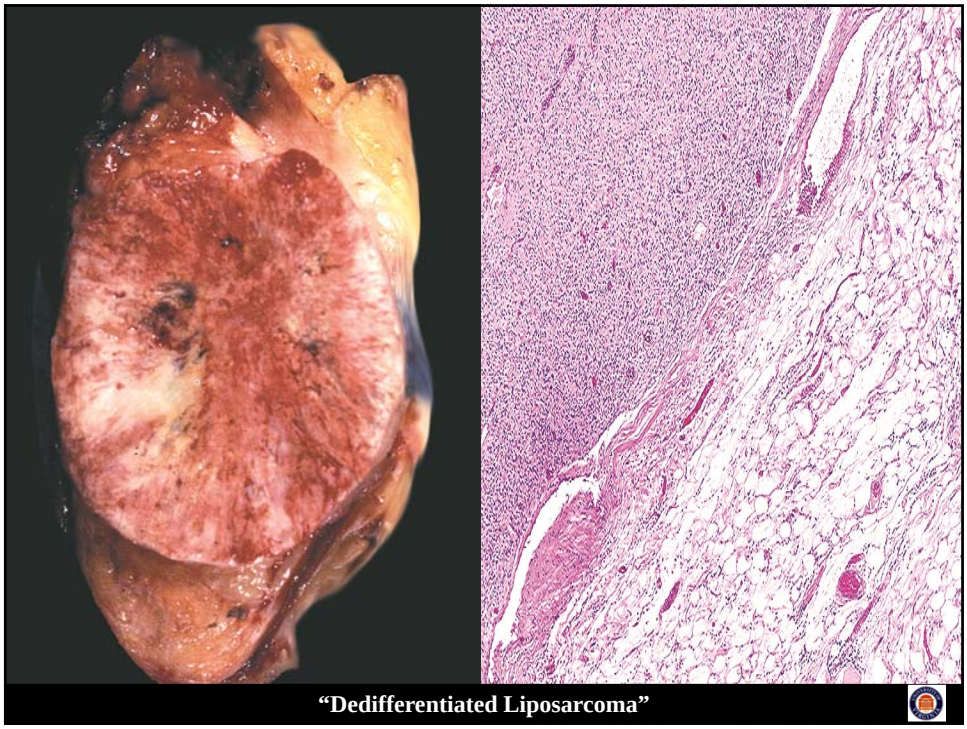
"Dedifferentiated" Liposarcoma

- Clonal evolution of a well-differentiated lipomatous tumor, with the secondary appearance of a higher-grade sarcoma morphotype. The latter may resemble MFH, pleomorphic LPS, osteosarcoma, rhabdomyosarcoma, angiosarcoma, and other sarcoma types
- The two tumor components are typically sharply demarcated from one another on scanning microscopy
- "Dedifferentiation" increases the aggressiveness of liposarcoma



Well-differentiated liposarcoma/AKA "Atypical lipomatous tumor"

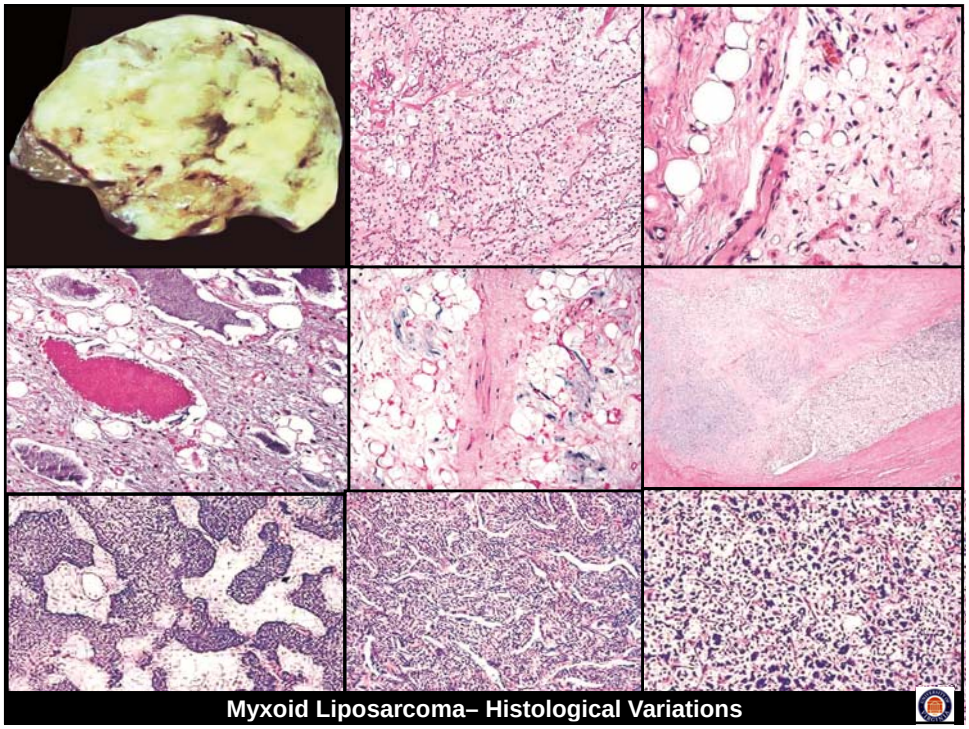
"Dedifferentiated" liposarcoma



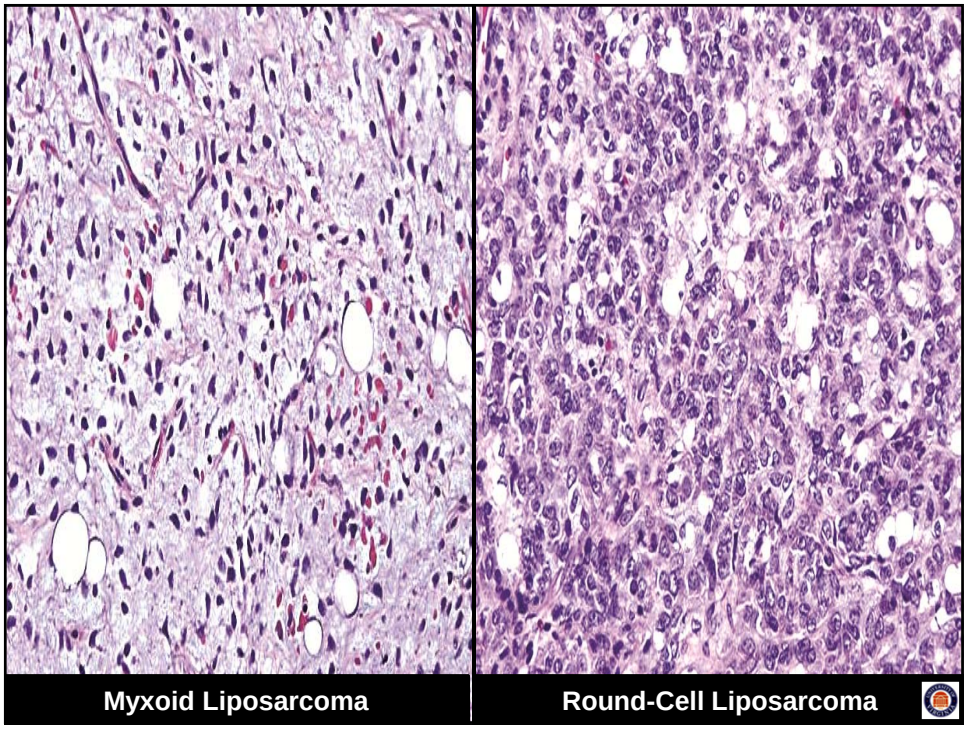
"Dedifferentiated Liposarcoma"

Myxoid/Round-Cell Liposarcoma

- A second "class" of LPS, seen in middle-aged to elderly adults
- Favored location = deep soft tissue of extremities; intrathoracic tumors of this type are uncommon but not rare; retroperitoneal MRC-LPS are seen very infrequently
- Low grade tumor comprising fusiform or stellate non-lipogenic mesenchymal cells, signet ring lipoblasts, & prominent myxoid stroma with a branching vascular pattern
- Round-cell areas represent a high-grade element, and they have little morphologic resemblance to other liposarcoma morphotypes



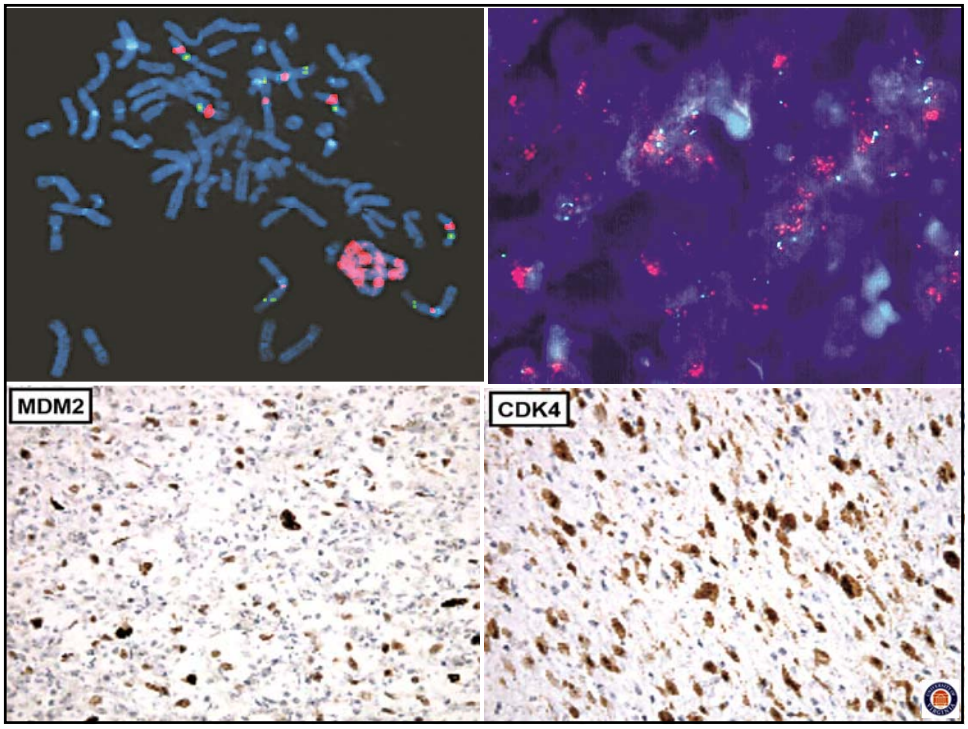
Myxoid Liposarcoma– Histological Variations

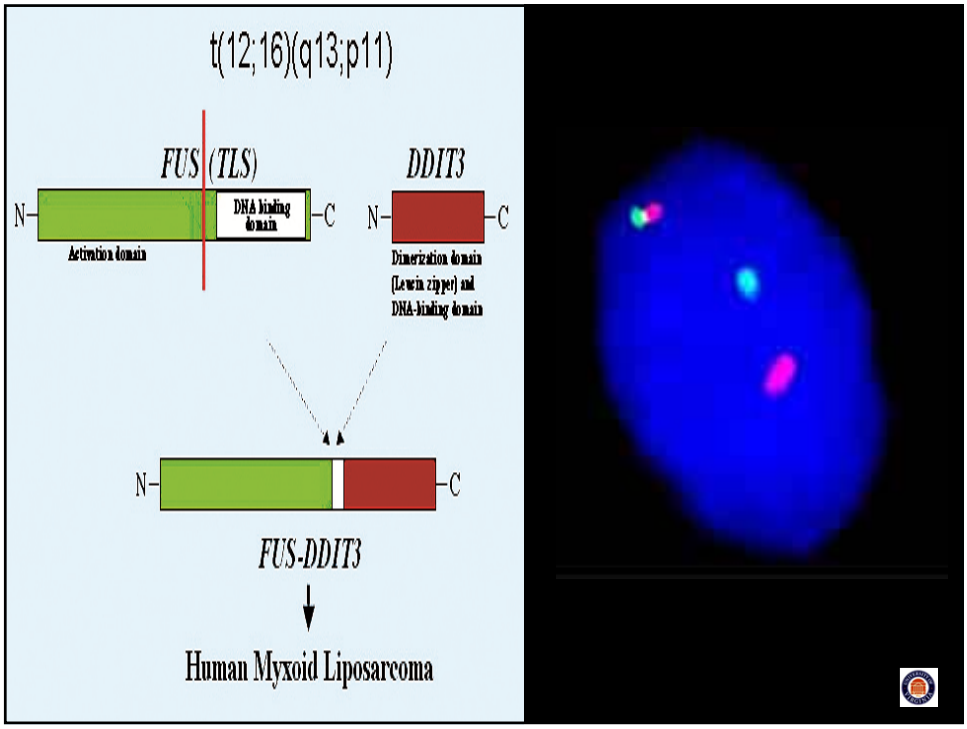


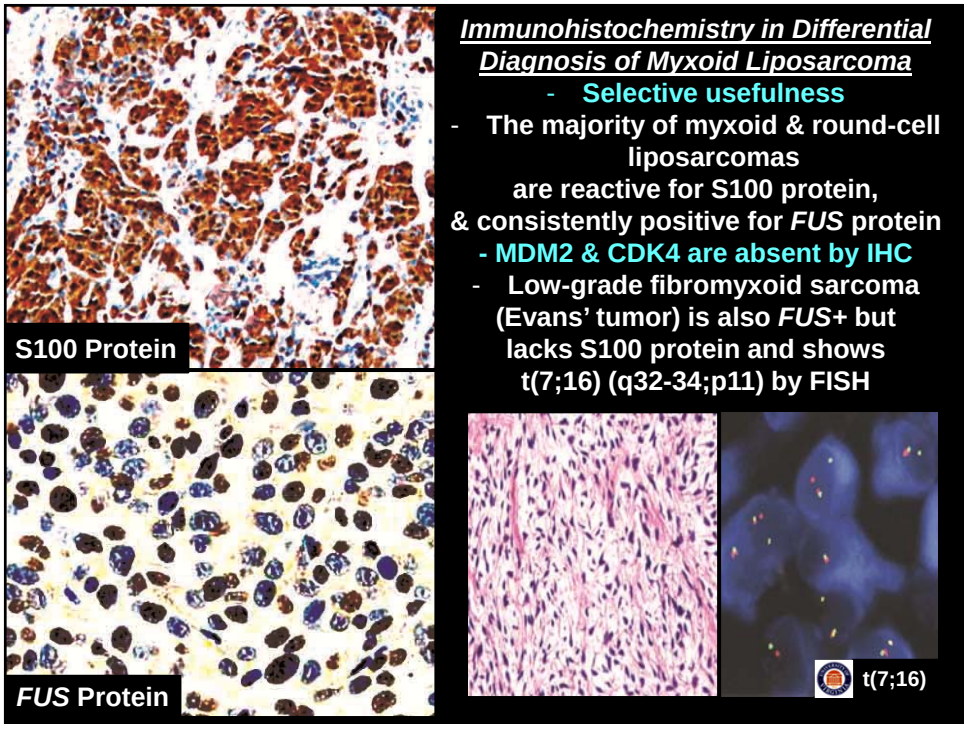
Myxoid Liposarcoma | Round-Cell Liposarcoma

Liposarcomas: Genetic Pathways

- **Most liposarcomas appear to segregate themselves genetically into two groups:**
  - **Mouse double minute 2 homolog (MDM2) is a negative regulator of the p53 tumor suppressor gene. Cyclin-dependent kinase 4 (CDK4) is part of the cyclin-dependent kinase family, which is important for cell cycle G1 phase-progression. The C*INK4a* gene produces p16 protein, which also functions in regulation of the cell cycle.**
- **Any or all 3 of those genes are amplified in well-differentiated LPS/ALT, as well as both components of "dedifferentiated" LPS**
- **In contrast, myxoid/round-cell LPS shows a balanced t(12;16)(q13;p11) translocation in ~90% of cases, joining portions of the *FUS* and *DDIT* genes**




t(12;16)(q13;p11)
FUS (TLS)
DDIT3
N
C
DNA binding domain
Activation domain
Dimerization domain (Leucin zipper) and DNA-binding domain
FUS-DDIT3
Human Myxoid Liposarcoma


S100 Protein
FUS Protein
Immunohistochemistry in Differential Diagnosis of Myxoid Liposarcoma
- Selective usefulness
- The majority of myxoid & round-cell liposarcomas are reactive for S100 protein, & consistently positive for FUS protein
- MDM2 & CDK4 are absent by IHC
- Low-grade fibromyxoid sarcoma (Evans' tumor) is also FUS+ but lacks S100 protein and shows t(7;16) (q32-34;p11) by FISH
t(7;16)

Are Adjunctive Studies Beyond H&E Examination Needed in All Cases of Liposarcoma?

- Certainly not. In the speaker's opinion, 90% of all lipocytic tumors can be identified confidently by morphological analysis.
- In cases where only small biopsies of large masses are obtained, the best course of action is to recommend excision; one may wish to use the term "adipocytic neoplasm of uncertain biologic potential" in those instances for the biopsy diagnosis
- Immunohistologic or cytogenetic studies are best reserved for diagnosis of round-cell LPS and the high-grade element of a suspected "dedifferentiated" LPS
- *De novo* pleomorphic LPS has no characteristic cytogenetic signature

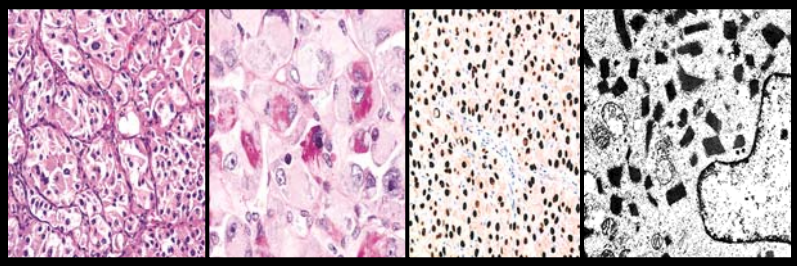
STT Decision Table

Histology	Histochemistry	IHC	Cytogenetics
H&Es are dispositive diagnostically in approximately 90% of cases	Not usually helpful	Immunostaining is for *FUS*, or MDM2, p16, and CDK4 proteins can be useful in the 2 LPS groups	Principally needed in cases of suspected round-cell LPS and "dedifferentiated" LPS
Cumulative Cost of Pathologic Analyses			
88305 X1 = $245	$0	88342 X 1 or 3 = $115 or $345	Either PCR or FISH = $350

Step-wise Cost-Benefit Analysis for Pathologic Evaluation of Liposarcomas

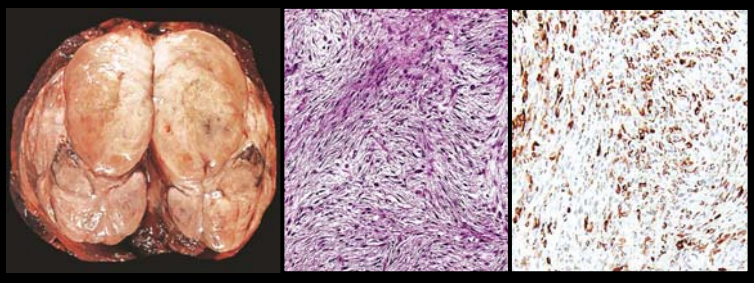
Other Soft Tissue Sarcomas with Characteristic Genotypes, but for Which Cytogenetic Studies are Usually Superfluous

- **Alveolar soft parts sarcoma [der(17)t(X:17)(p11;p25), producing *ASPL-TFE3* fusion genes] – Histology & histochemistry (PAS) are typically sufficient; immunohistology for TFE3 & electron microscopy are helpful adjuncts when necessary**



Other Soft Tissue Sarcomas with Characteristic Genotypes, but for Which Cytogenetic Studies are Usually Superfluous

- **Low-grade fibromyxoid sarcoma (Evans' tumor) [t(7;16)(q34;p11), producing *FUS/CREB3L2* fusion gene] – Histology & immunohistochemistry (for MUC4) are diagnostically sufficient in virtually all cases**



Soft Tissue Tumors with Inconsistent, Variable, or Non-Diagnostic Genotypes

- Desmoid-type fibromatosis
- Embryonal rhabdomyosarcoma
- Malignant rhabdoid tumor
- Epithelioid sarcomas (both proximal & distal)
- Inflammatory myofibroblastic tumor
- Adult-type fibrosarcoma
- Angiosarcoma
- *De novo* pleomorphic sarcomas
- Malignant peripheral nerve sheath tumors
- Solitary fibrous tumor/hemangiopericytoma
- Extraskeletal osteosarcoma & chondrosarcoma
- Low-grade myxofibrosarcoma (Angervall's tumor)
- Acral myxoinflammatory fibroblastic sarcoma

Summary

- Cost-effective pathological evaluation of soft tissue tumors is NOT formulaic– this presentation offers only a philosophical model for how to approach that topic
- Whether or not one uses any or all of the adjunctive studies that can be done for STT depends on individual levels of morphologic-diagnostic confidence, familiarity with the additional techniques, and their institutional availability, as well as the specific differential diagnoses being considered
- HOWEVER, some general conclusions can be reached on this subject:
  - 1. Morphological expertise continues to represent a powerful diagnostic tool; the better one is at refining that skill, the more cost-effective one will be
  - 2. In a purely pragmatic sense, the combination of morphological excellence + molecular technology is the most cost-effective one. Nevertheless, requirements of differential diagnosis make that approach a tenuous, "all or none" pathway
  - 3. Systematic future studies are greatly needed to identify which pathologic assays are the most optimal ones, relative to the diagnosis and prognostication of specific soft tissue tumors