SOFT TISSUE TUMORS

Kenneth Alonso, MD, FACP

Table 26-9 Soft Tissue Tumors

Category	Behavior	Tumor Type	Common Locations	Age (yr)	Morphology
Adipose	Benign	Lipoma	Superficial extremity, trunk	40-60	Mature adipose tissue
	Malignant	Well-differentiated Liposarcoma	Deep extremity, retroperitoneum	50-60	Adipose tissue with scattered atypical spindle cells
		Myxoid liposarcoma	Thigh, leg	30s	Myxoid matrix, "chicken wire" vessels, round cells, lipoblasts
Fibrous	Benign	Nodular fasciitis	Arm, forearm	20-30	Tissue culture growth, extravasated erythrocytes,
		Deep fibromatosis	Abdominal wall	30-40	Dense collagen, long, unidirectional fascicles
Skeletal muscle	Benign	Rhabdomyoma	Head and neck	0-60	Polygonal rhabdomyoblasts, "spider" cells
	Malignant	Alveolar rhabdomyosarcoma	Extremities, sinuses	5-15	Uniform round discohesive cells between septae
		Embryonal rhabdomyosarcoma	Genitourinary tract	1-5	Primitive spindle cells, "strap" cells
Smooth muscle	Benign	Leiomyoma	Extremity	20s	Uniform, plump eosinophilic cells in fascicles
	Malignant	Leiomyosarcoma	Thigh, retroperitoneum	40-60	Pleomorphic eosinophilic cells
Vascular	Benign	Hemangioma	Head and neck	0-10	Circumscribed mass of capillary or venous channels
	Malignant	Angiosarcoma	Skin, deep lower extremity	50-80	Infiltrating capillary channels
Nerve sheath	Benign	Schwannoma	Head and neck	20-50	Encapsulated, fibrillar stroma, nuclear palisading
		Neurofibroma	Wide, cutaneous, subcutis	10-20+	Myxoid, ropy collagen, loose fascicles, mast cells
	Malignant	Malignant peripheral nerve sheath tumor	Extremities, shoulder girdle	20-50	Tight fascicles, atypia, mitotic activity, necrosis
Uncertain histotype	Benign	Solitary fibrous tumor	Pelvis, pleura	20-70	Branching ectatic vessels,
	Malignant	Synovial sarcoma	Thigh, leg	15-40	Tight fascicles of uniform basophilic spindle cells, Pseudoglandular structures
		Undifferentiated pleomorphic sarcoma	Thigh	40-70	High grade anaplastic polygonal, round or spindle cells Bizarre nuclei, atypical mitoses, necrosis
		Alveolar soft part sarcoma	Trunk, extremities	15-35	Multiple nodules of eosinophilic round cells, septae
		Clear cell sarcoma	Tendons, extremities	20-40	Sheets of pale or clear spindle cells, wreath-like giant cells

Table 26.7 Chromosomal Abnormalities in Soft Tissue Tumors

Tumor	Cytogenetic Abnormality	Gene Fusion	Proposed Function
Ewing sarcoma	t(11;22)(q24;q12) t(21;22)(q22;q12)	*EWS–FLI1* *EWS–ERG*	Disordered protein with multiple functions, including aberrant transcription, cell cycle regulation, RNA splicing, and telomerase
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12)	*EWS–CHN*	
Desmoplastic small round-cell tumor	t(11;22)(p13;q12)	*EWS–WT1*	
Clear-cell sarcoma	t(12;22)(q13;q12)	*EWS–ATF1*	
Liposarcoma—myxoid type	t(12;16)(q13;p11)	*FUS–DDIT3*	Arrests adipocytic differentiation
Synovial sarcoma	t(x;18)(p11;q11)	*SS18–SSX1* *SS18–SSX2* *SS18–SSX4*	Chimeric transcription factors, interrupts cell cycle control
Rhabdomyosarcoma—alveolar type	t(2;13)(q35;q14) t(1;13)(p36;q14)	*PAX3–FOXO1* *PAX7–FOXO1*	Chimeric transcription factors, disrupts skeletal muscle differentiation
Dermatofibrosarcoma protuberans	t(17;22)(q22;q15)	*COLA1–PDGFB*	Promoter driven overexpression of PDGF-β, autocrine stimulation
Alveolar soft-part sarcoma	t(X;17)(p11.2;q25)	*TFE3–ASPL*	Unknown
Infantile fibrosarcoma	t(12;15)(p13;q23)	*ETV6–NTRK3*	Chimeric tyrosine kinase leads to constitutively active Ras/MAPK pathway
Nodular fasciitis	t(22;17)	*MYH9–USP6*	Increased Wnt/β-catenin signaling

Genetic syndrome	Sarcoma	Gene
Neurofibromatosis type 1	MPNST, GIST	*NF1*
Retinoblastoma	STS, osteogenic	*Rb-1*
Li-Fraumeni syndrome	STS, osteogenic	*TP53*
Gardner syndrome	Fibromatosis, Fibrosarcoma	*APC*
Werner syndrome	STS	*WRN*
Gorlin syndrome	Fibrosarcoma, Rhabdomyosarcoma	*PTC*
Tuberous sclerosis	Rhabdomyosarcoma	*TSC1/TSC2*
Carney-Stratakis syndrome	GIST	*SDH* subunit genes

APC, adenomatous polyposis coli; GIST, gastrointestinal stromal tumour; MPNST, malignant peripheral nerve sheath tumour; SDH, succinate dehydrogenase; STS, soft tissue sarcoma; TSC1/2, tuberous sclerosis 1/2.

Fig. 5.5

Translocations resulting in chimeric transcription factors

Tumour type	Translocation	Gene(s)
Ewing sarcoma	*t(11;12)(q24;q12)* *t(21;22)(q22;q12)* *t(16;21)(p11;q22)*	*EWSR1-FLI1* *EWSR1-ERG* *FUS-ERG*
Angiomatoid fibrous histiocytoma	*t(12;22)(q13;q12)* *t(2;22)(q33;q12)*	*EWSR1-ATF1* *EWSR1-CREB1*
Clear cell sarcoma	*t(12;22)(q13;q12)* *t(2;22)(q33;q12)*	*EWSR1-ATF1* *EWSR1-CREB1*
Low-grade fibromyxoid sarcoma	*t(7;16)(q33;p11)* *t(11;16)(p11;p11)*	*FUS-CREB3L2* *FUS-CREB3L1*
Desmoplastic small round-cell tumour	*t(11;22)(p13;q12)*	*EWSR1-WT1*
Extraskeletal myxoid chondrosarcoma	*t(9;22)(q22;q12)* *t(9;17)(q22;q11)*	*EWSR1-NR4A3* *TAF2N-NR4A3*

EWSR1, Ewing sarcoma breakpoint region 1.

Fig. 6.2

Targeting DNA repair deficiencies in sarcomas

Repair Pathway	Sarcoma subtypes	Potential targets
Base excision repair (REF-1/PARP)	Osteosarcoma*/** Ewings sarcoma*/** Chondrosarcoma* Rhabdomyosarcoma* Liposarcoma*	PARP inhibitors **Trials:** COG ADVL1411 (**TMZ**)[1] Chov et al (**TMZ**)[2] TOMAS study (**trabectedin**)[3]
Nucleotide excision repair (ERCC1)	High expression in osteosarcoma, leiomyosarcoma	Increased susceptibility to **trabectedin**[4], **cisplatin**[5,6]
Mismatch repair (MSH2/MSH6)	Enriched in ESFT*, Osteosarcoma* worse prognosis	
Homologous repair (BRCA1/2, RADS1)	mBRCA2 (1% of STS) BRCAness signature in osteosarcoma* High expression RAD51 most STS[8]	Sensitivity to **trabectedin**[7] Imparts resistance to **doxorubicin**[8]
ATR/CHK1	UPS* Synovial sarcoma Ewing sarcoma osteosarcoma	Anti-ATR, Anti-CHK1 Sensitizes to **gemcitabine**[9, 10]

*preclinical, **clinical

Riyahi et al, in DNA-Damages and Repair Mechanisms, 2020. 1-Schafer et al, Ped Blood & Cancer 2019, 2-Choy et al, BMC Cancer 2014, 3-Grignani et al, Lancet Oncol 2018, 4-Moura et al, Cancers 2020, 5-Hattinger et al, Histopath 2015, 6-Obiedat et al, BMS Med Gen, 2018, 7-Monk et al, Canc Treat Rev 2016. 8-Hannay et al, Mol Canc Ther, 2007, 9-Laroche-Clary et al, Sci Rep 2020, 10-Laroche-Clary et al, Ann Oncol 2018

Immunohistochemical markers used to determine line of differentiation	
Muscle differentiation	Melanocyte-inducing desmin, smooth muscle actin (SMA), muscle specific actin (HHF35), MyoD1, Myf4 (myogenin), heavy caldesmon, calponin
Nerve sheath differentiation	S100, SOX10
Melanocytic differentiation	HMB-45, Melan-A (MART-1), tyrosinase, *MITF*
Endothelial differentiation	ERG, CD34, CD31
Fibrohistiocytic differentiation	CD68, Factor 13A, vimentin
Epithelial differentiation	Cytokeratins, EMA

Fig. 1.4

EMA, epithelial membrane antigen; MITF, melanocyte inducing transcription factor.

A panel of markers is employed.

Histological grading according to FNCLCC	
Tumour differentiation	
Score 1	Closely resembling normal tissue
Score 2	Histological typing is certain
Score 3	Embryonal or undifferentiated sarcomas
Mitotic count (per 1.7 mm²)	
Score 1	0-9 mitoses per 1.7 mm²
Score 2	10-19 mitoses per 1.7 mm²
Score 3	>19 mitoses per 1.7 mm²
Tumour necrosis	
Score 0	No necrosis
Score 1	<50% tumour necrosis
Score 2	≥50% tumour necrosis
Histological grade	**Grade 1: total score 2, 3** **Grade 2: total score 4, 5** **Grade 3: total score 6, 7, 8**

Fig. 1.7

FNCLCC, Fédération Nationale des Centres de Lutte Contre le Cancer.

Epithelioid sarcoma is high grade by definition.

Metastasis free survival correlates with histological grade.

TX		Primary tumour cannot be assessed			
T0		No evidence of primary tumour			
		Appendicular skeleton, trunk, facial bones			**Pelvis**
T1		Tumour ≤8 cm	T1		Tumour confined to 1 pelvic segment with no extraosseous extension
T2		Tumour >8 cm		T1a	Tumour ≤8 cm
T3		Discontinuous tumours in the primary bone site		T1b	Tumour >8 cm
		Spine	T2		Tumour confined to 1 pelvic segment with extraosseous extension or 2 segments without extension
T1		Tumour confined to 1 vertebral segment or 2 adjacent segments		T2a	Tumour ≤8 cm
T2		Tumour confined to 3 adjacent vertebral segment		T2b	Tumour >8 cm
T3		Tumour confined to 4 or more adjacent vertebral segments or any non-adjacent segments	T3		Tumour spanning 2 pelvic segments with extraosseous extension
T4		Extension into the spinal canal or great vessels		T3a	Tumour ≤8 cm
	T4a	Extension into the spinal canal		T3b	Tumour >8 cm
	T4b	Evidence of gross vascular invasion or tumour thrombus in the great vessels	T4		Tumour spanning 3 pelvic segments or crossing the sacroiliac joint
					Tumour ≤8 cm
					Tumour >8 cm
NX		Regional lymph nodes cannot be assessed			
N0		No regional lymph node metastases			
N1		Regional lymph node metastases			
MX		Distant metastases cannot be assessed			
M0		No distant metastases			
M1		Distant metastases			
	M1a	Lung			
	M1b	Secondary bone or other distant sites			

Fig. 4.6

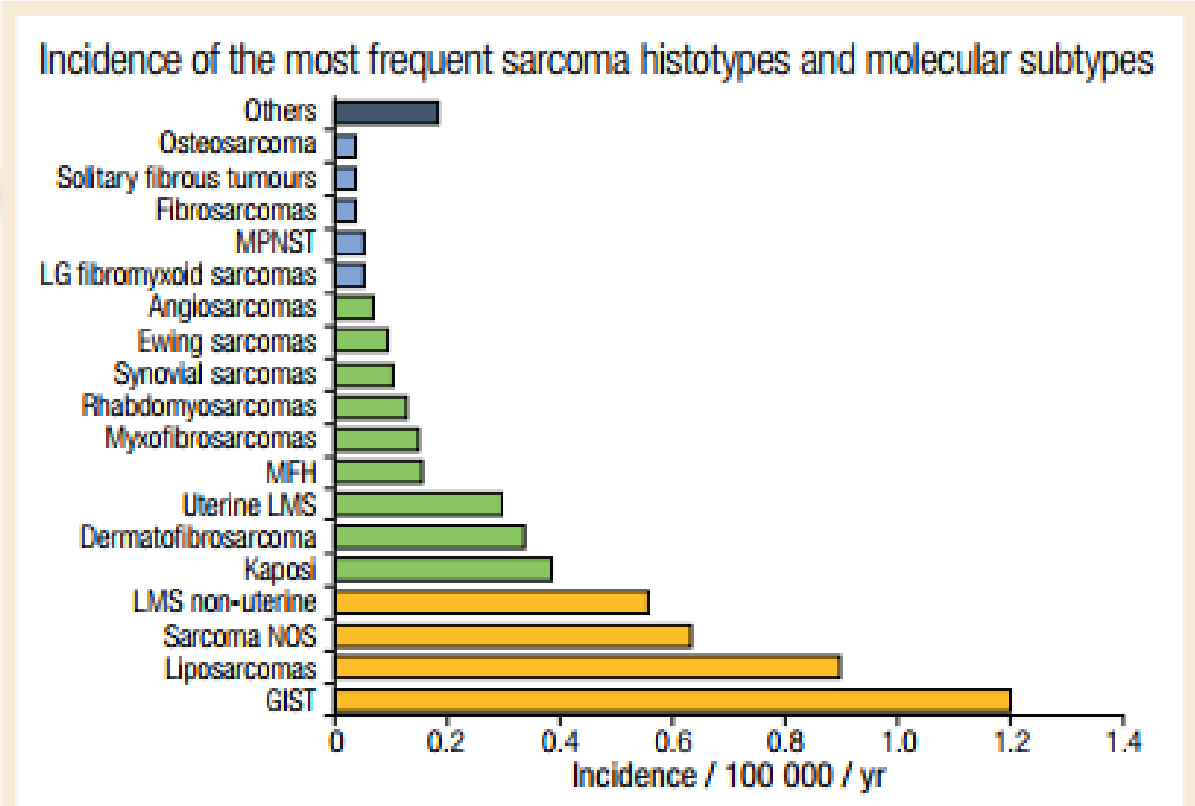
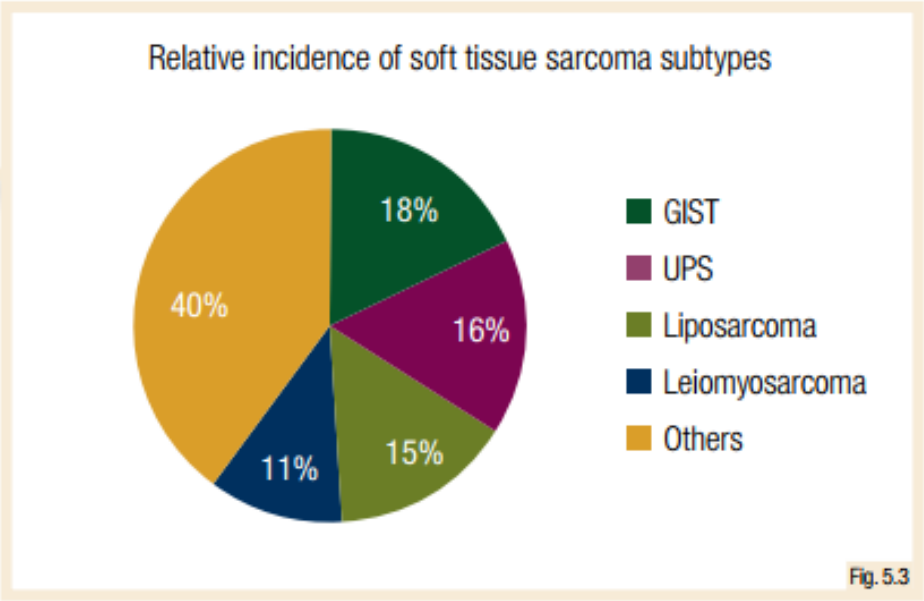
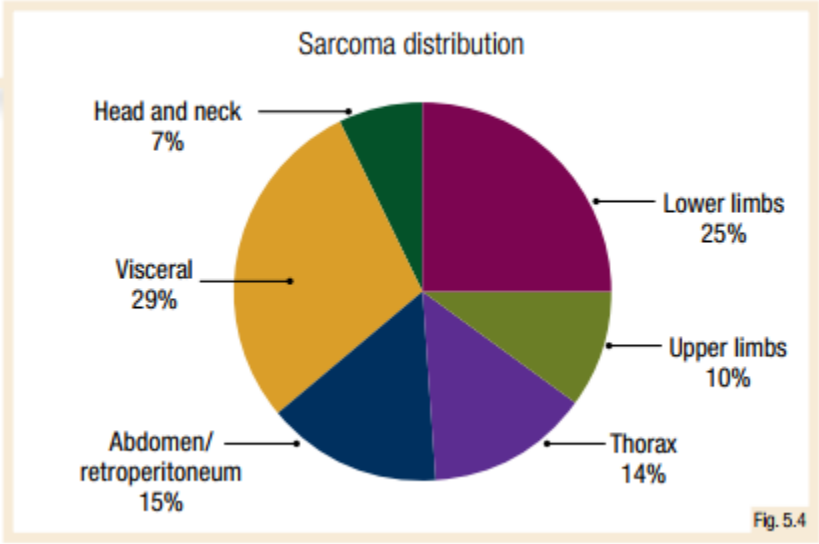


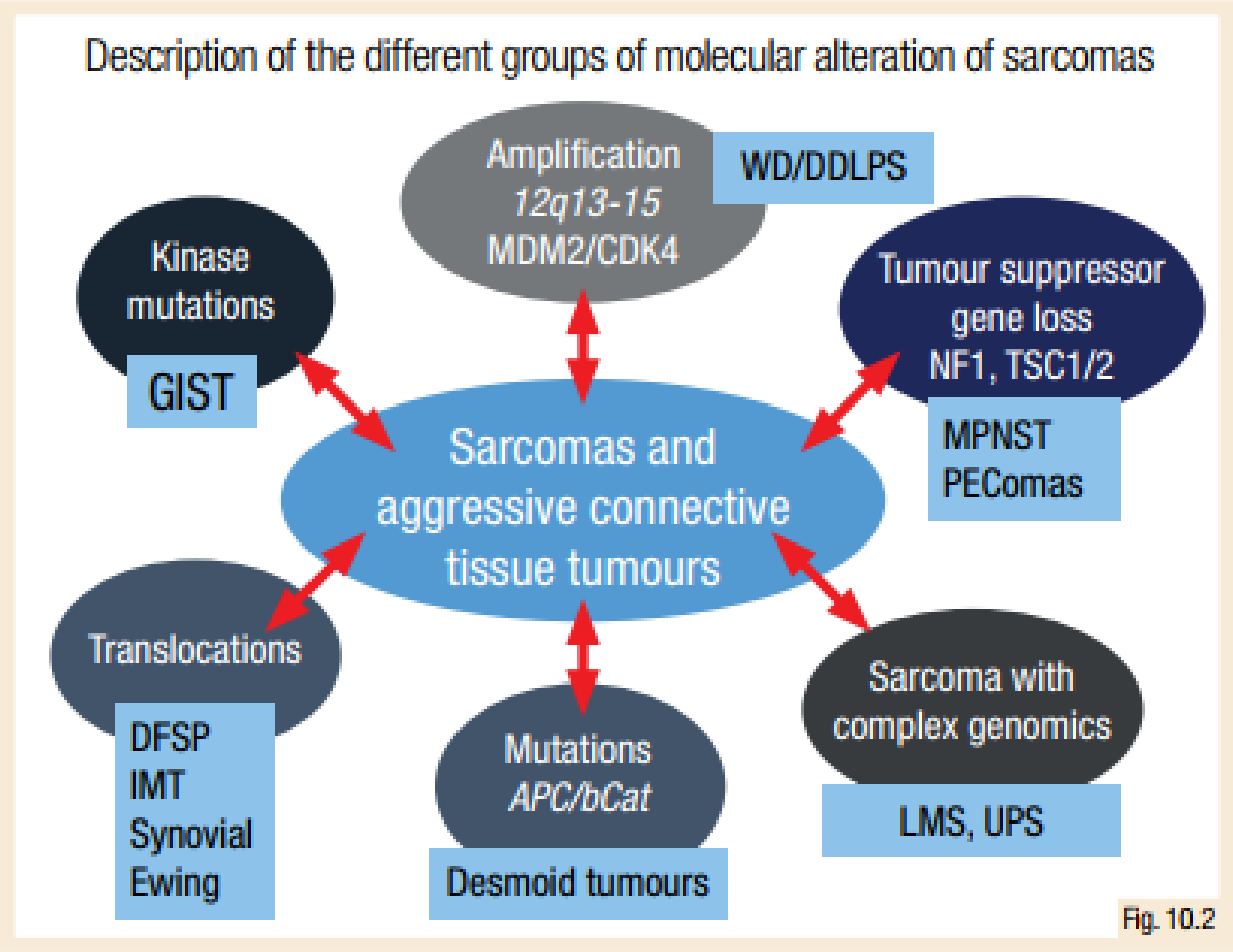
Fig. 10.1

GIST, gastrointestinal stromal tumour; LG, low grade; LMS, leiomyosarcoma; MFH, malignant fibrous histiocytoma; MPNST, malignant peripheral nerve sheath tumour; NOS, not otherwise specified.



GIST, gastrointestinal stromal tumour; UPS, undifferentiated pleomorphic sarcoma.





APC; adenomatous polyposis coli; DFSP, dermatofibrosarcoma protuberans; GIST, gastrointestinal stromal tumour; IMT, inflammatory myofibroblastic tumour; LMS, leiomyosarcoma; MPNST, malignant peripheral nerve sheath tumour; NF1, neurofibromatosis type 1; PEComa, perivascular epithelioid cell tumour; TSC 1/2, tuberous sclerosis 1/2; UPS, undifferentiated pleomorphic sarcoma; WD/DDLPS; well-differentiated/dedifferentiated liposarcoma.

Sarcomas

- Sarcomas cause 2% of all cancer deaths.
- Approximately 15% arise in children but the incidence increases with age.
- Sarcomas arise from pluripotent mesenchymal stem cells, which acquire somatic “driver” mutations.
- Liposarcoma, fibrosarcoma, pleomorphic sarcoma, and synovial cell carcinoma principally occur in the extremities.
- Metastasize generally to lung.

Sarcomas

- Liposarcoma and leiomyosarcoma are usually found in the retroperitoneum.
- Metastasize generally to liver and lung.
- The risk of local recurrence is elevated.
- Desmoid tumors (5q-, APC) liposarcoma, and leiomyosarcoma are the common soft tissue tumors of the chest wall.
- Leiomyosarcoma is the common soft tissue neoplasm found in the genitourinary tract.

Sarcomas

- In the gastrointestinal tract, GIST (leiomyosarcoma) or GANT (neural elements present) are the common soft tissue neoplasms.
- The risk of local recurrence is elevated.
- Metastases to the liver are common.

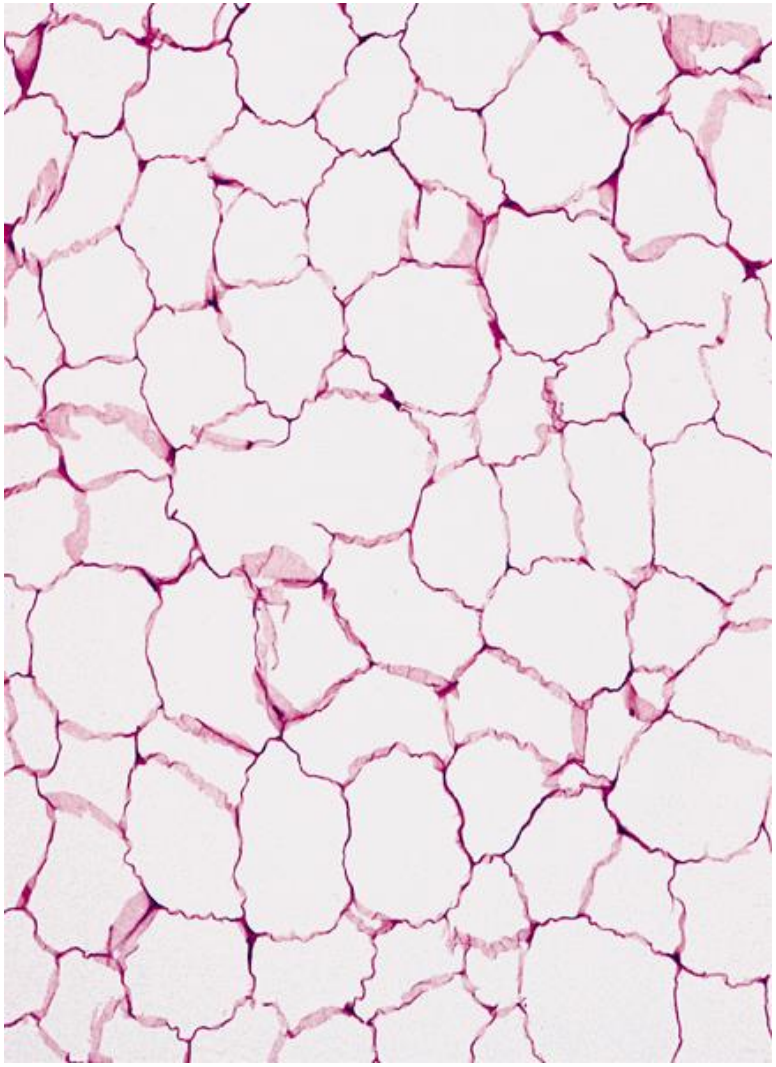
Lipoma

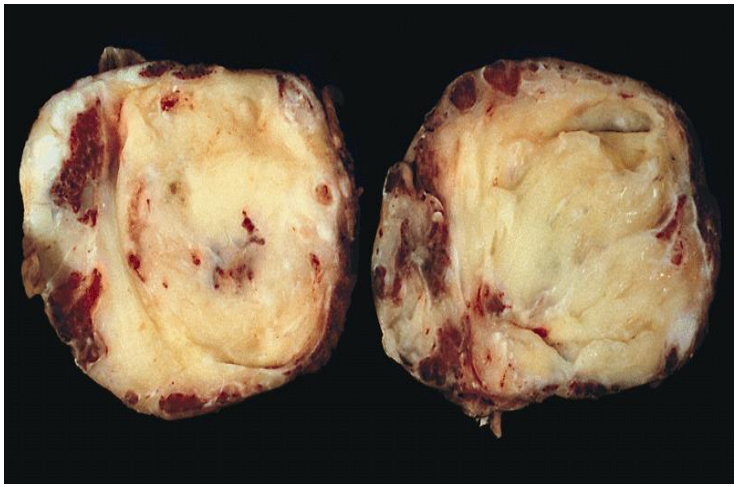
- The most common soft tissue tumor.
- They are well-encapsulated masses of mature adipocytes that arises in the subcutis of the proximal extremities and trunk, most frequently during mid-adulthood.
- Infrequently, lipomas are large, intramuscular, and poorly circumscribed.
- Lipomas are soft, mobile, and painless (except angiolipoma).

Lipoma

- Consist of mature white fat cells. No pleomorphism
- Conventional lipomas are the most common subtype and show rearrangements of 12q,14-15, 6p, and 13q.
- Spindle cell and pleomorphic lipomas have rearrangements of 16q and 13q.

Lipoma





Figs. 4-4 and 4-2 Kempson, Richard L., Fletcher, Christophr DM, Evans, Harry L, Hendrickson, Michael R, and Sibley, Richard K, Tumors of the Soft Tissues, Fascicle 30, Atlas of Tumor Pathology. 3rd Series. Armed Forces Institute of Pathology, Washington, DC (2001).

Liposarcoma

- Liposarcomas are the most common sarcomas of adulthood and appear in those in their forties to sixties;
- They are uncommon in children.
- They usually arise in the deep soft tissues of the proximal extremities and retroperitoneum.
- Retroperitoneal tumors may be large and bulky and cause abdominal symptoms.
- Liposarcomas can be divided into well-differentiated, myxoid, round cell, and pleomorphic variants.

Liposarcoma

- Well-differentiated liposarcoma contains adipocytes with scattered atypical spindle cells.
- Most common adipocytic malignancy (40 - 45% of all liposarcomas)
- Peak age in adults is between ages 40 - 60 years
- Lipoma-like subtype in deep thigh
- Sclerosing subtype in retroperitoneum or paratesticular location
- Molecularly characterized by ring or giant marker/rod chromosomes composed of material from 12q13-15.
- MDM2 amplifed, a potent suppressor of p53
- Do not metastasize

Liposarcoma

- Dedifferentiated liposarcoma is a non-lipogenic sarcoma that arises from a well-differentiated liposarcoma.
- 10% of well-differentiated liposarcomas
- Molecularly characterized by ring or giant marker/rod chromosomes composed of material from 12q13-15.
- First tumor to consider in a high grade sarcoma of the retroperitoneum in an adult
- Also occur in spermatic cord
- Recurs in 40 - 75%, metastasizes in 10 - 15% and is associated with a 28% mortality rate

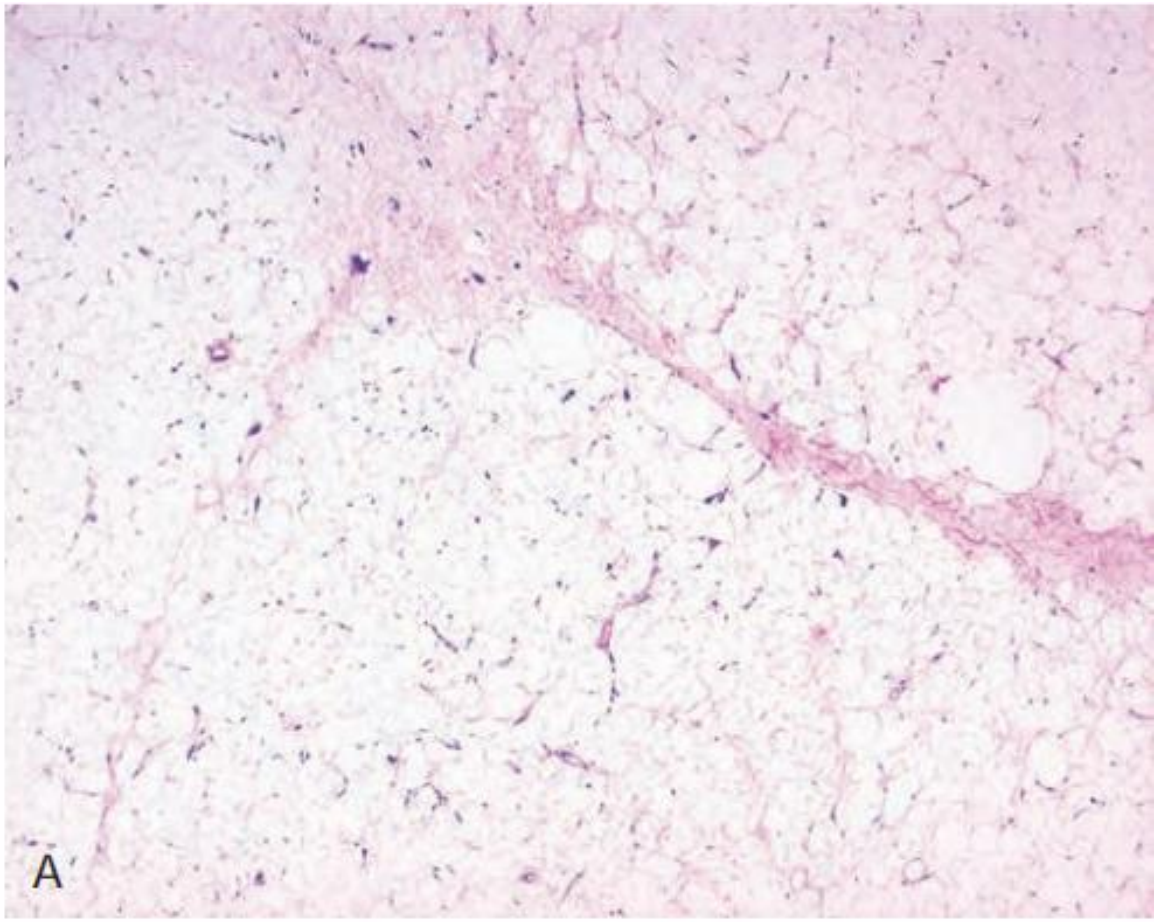
Liposarcoma

- Myxoid liposarcoma contains abundant basophilic extracellular matrix, arborizing capillaries and primitive cells at various stages of adipocyte differentiation reminiscent of fetal fat.
- If >5% round cells, high grade
- t(12;16)(q13;p11.2) FUS-DDIT3
- 2%, t(12;22)(q13;q12) EWSR1-DDIT3
- 4^{th}-5^{th} decade
- 5% of sarcomas
- Predilection for the thigh
- Rarely metastasize to lung

Liposarcoma

- Pleomorphic liposarcoma consists of sheets of anaplastic cells, bizarre nuclei and variable amounts of immature adipocytes (lipoblasts).
- Complex karyotypes
- 5% of liposarcomas
- 55-75 years of age
- Thigh, internal trunk, limb girdles, upper extremity, thoracoabdominal wall
- Recurs in 40%, metastasizes in 40%, causes death in 35%.

Well-differentiated liposarcoma



Dedifferentiated liposarcoma

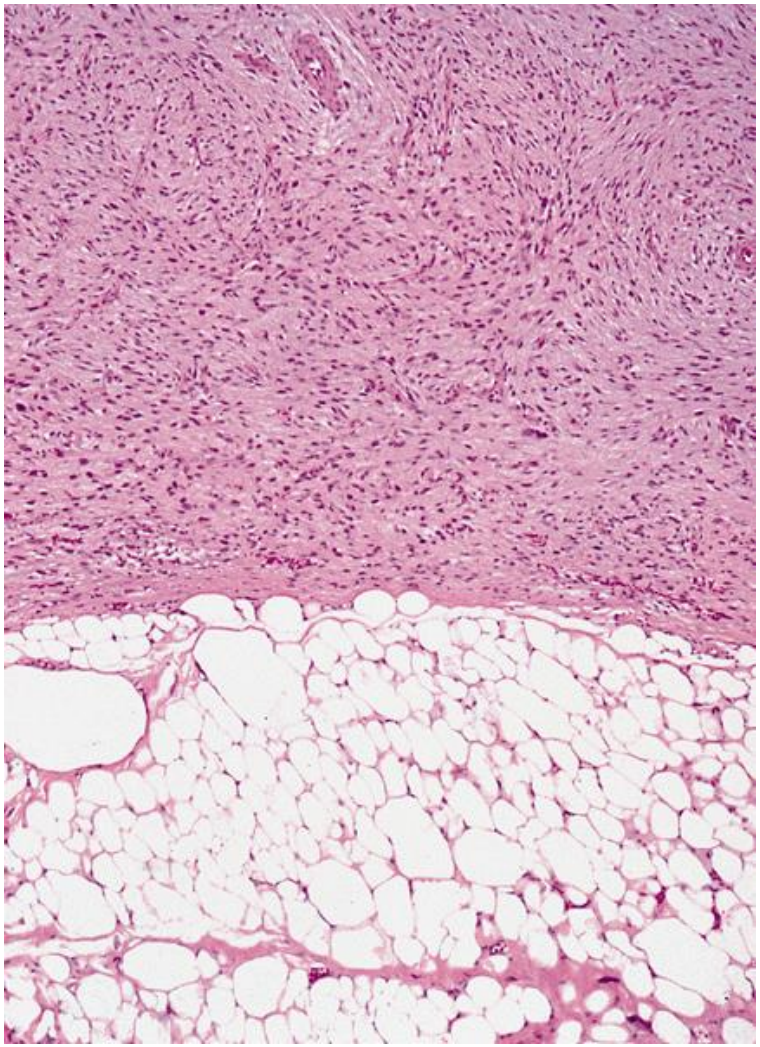


Fig. 4-37 Kempson, Richard L., Fletcher, Christophr DM, Evans, Harry L, Hendrickson, Michael R, and Sibley, Richard K, Tumors of the Soft Tissues, Fascicle 30, Atlas of Tumor Pathology. 3rd Series. Armed Forces Institute of Pathology, Washington, DC (2001).

Myxoid liposarcoma

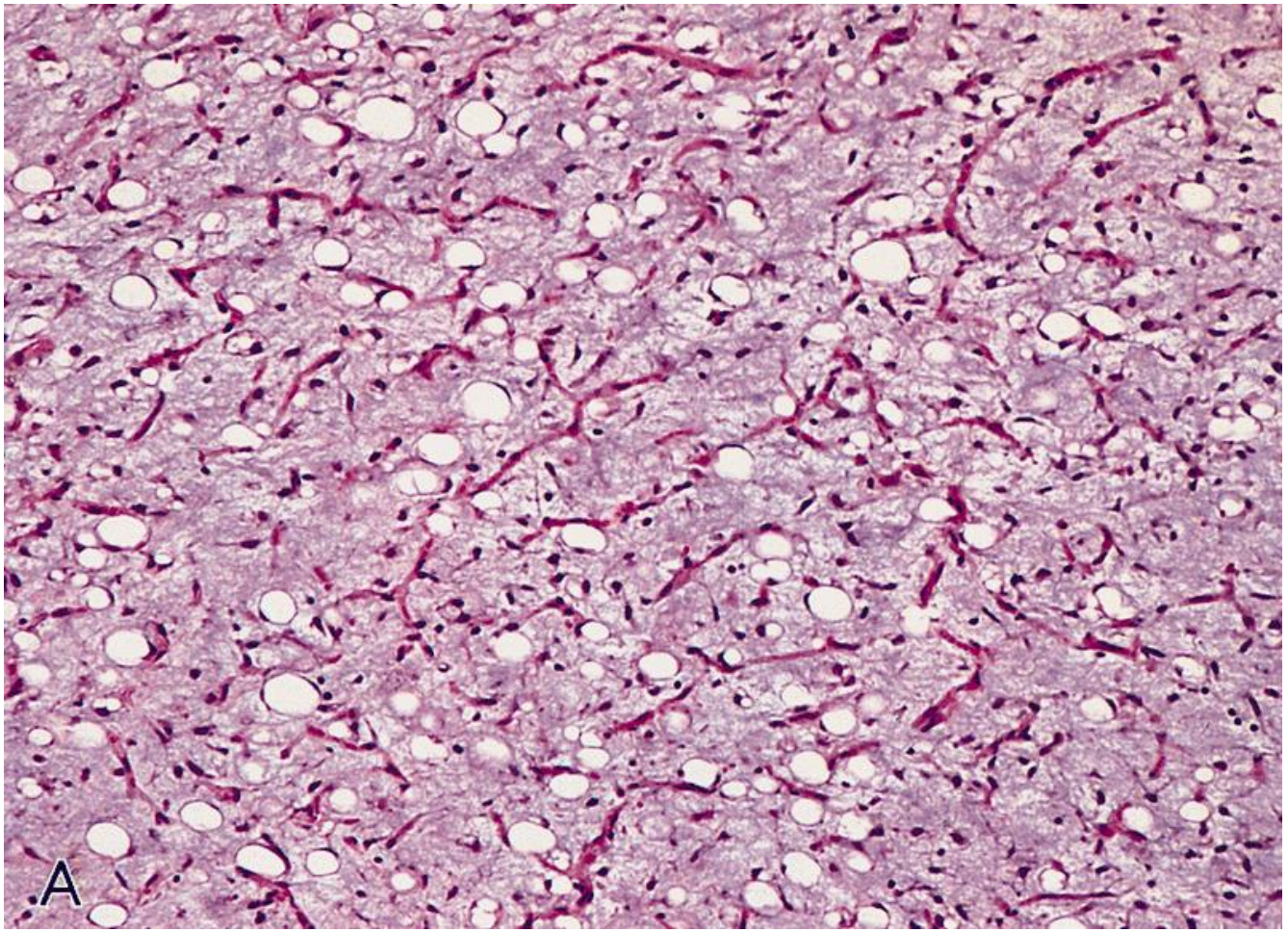
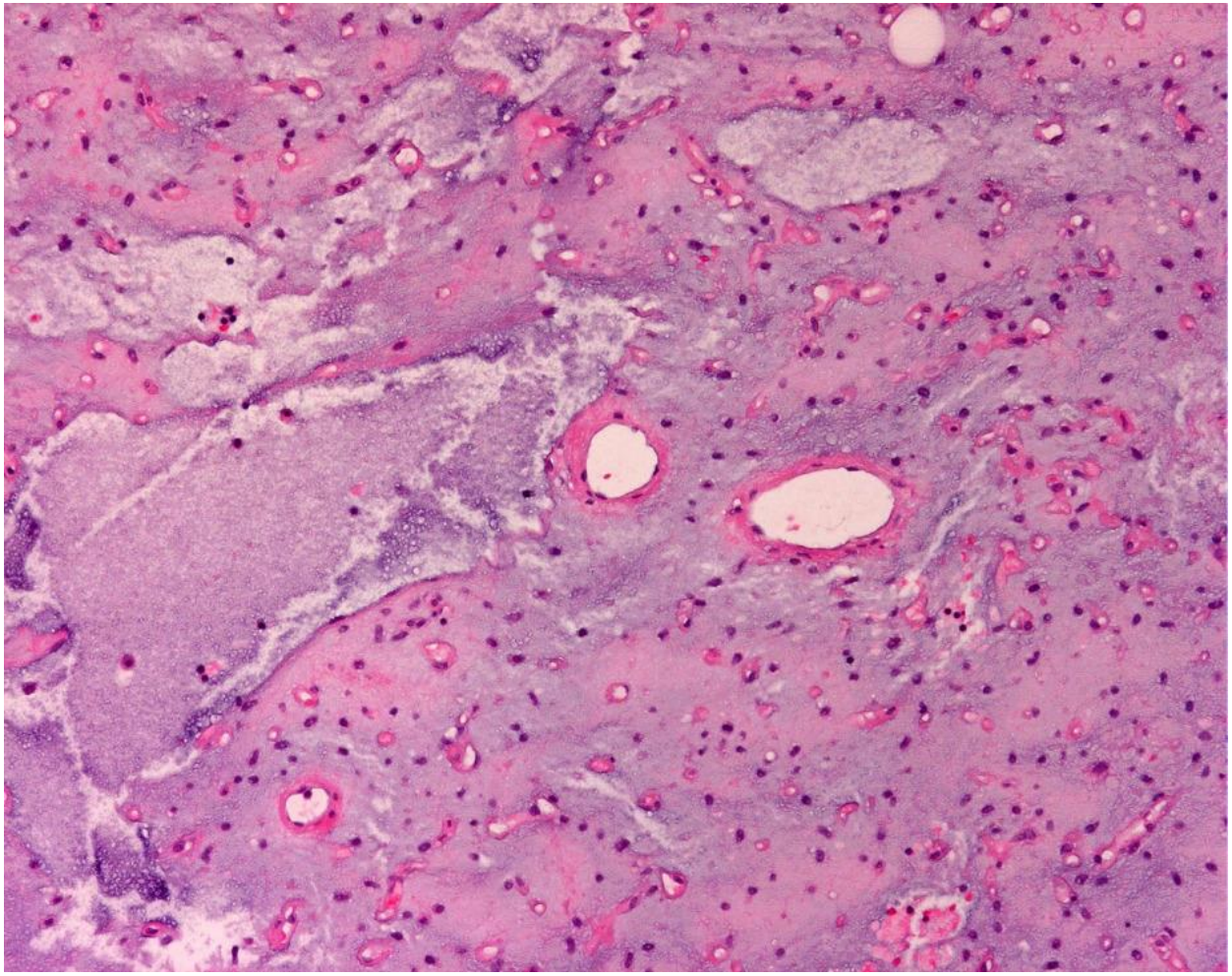


Fig. 4-45 Kempson, Richard L., Fletcher, Christophr DM, Evans, Harry L, Hendrickson, Michael R, and Sibley, Richard K, Tumors of the Soft Tissues, Fascicle 30, Atlas of Tumor Pathology. 3rd Series. Armed Forces Institute of Pathology, Washington, DC (2001).

High grade myxoid liposarcoma



Pulmonary edema pattern

http://www.pathologyoutlines.com/imgau/softtissuemyxoidliposarcomajenkins03_20180130-130844.jpg Accessed 06/10/2020

Pleomorphic liposarcoma

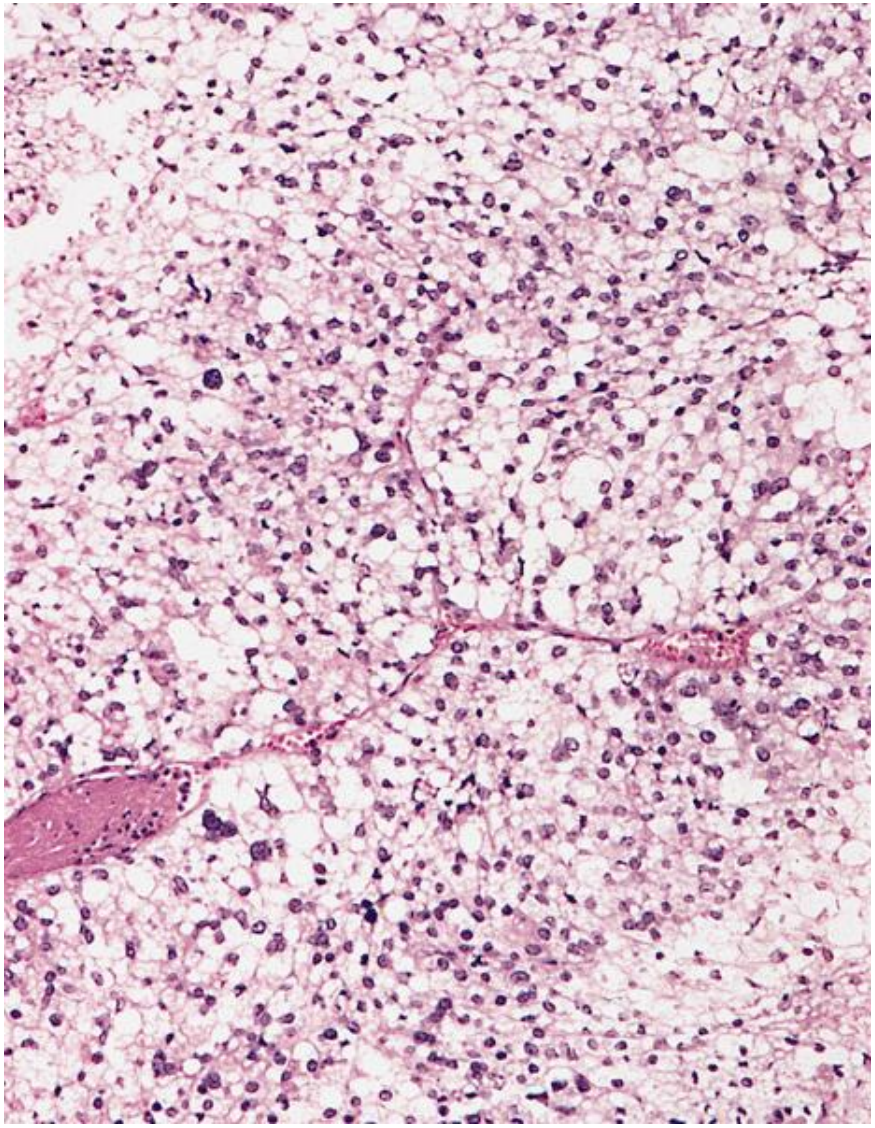


Fig. 4-61 Kempson, Richard L.,Fletcher, Christophr DM, Evans, Harry L, Hendrickson, Michael R, and Sibley, Richard K, Tumors of the Soft Tissues, Fascicle 30, Atlas of Tumor Pathology. 3rd Series. Armed Forces Institute of Pathology, Washington, DC (2001).

Nodular fasciitis

- Nodular fasciitis, also known as infiltrative or pseudosarcomatous fasciitis, is the most common of the reactive pseudosarcomas
- t(17;22) that produces a MYH9-USP6 fusion gene
- Cells avoid senescence
- Occurs on the volar aspect of the forearm, followed in order of frequency by the chest and back.
- Typically present with a several-week history of a solitary, rapidly growing, and sometimes painful mass.
- Proliferative fasciitis and proliferative myositis occur in slightly older patients and develop in the trunk or proximal extremities.

Nodular fasciitis

- Consists of plump, immature-appearing fibroblasts arranged randomly (simulating cells growing in tissue culture) or in short intersecting fascicles.
- The cells vary in shape from spindle to stellate and have conspicuous nucleoli.
- Mitoses abundant.
- Frequently the stroma is myxoid and contains lymphocytes and extravasated red blood cells.
- In proliferative fasciitis, the proliferating fibroblasts are often large and round, have prominent nucleoli, and resemble ganglion cells.
- Myositis ossificans contains metaplastic bone
- Rarely recur after excision.

Nodular fasciitis

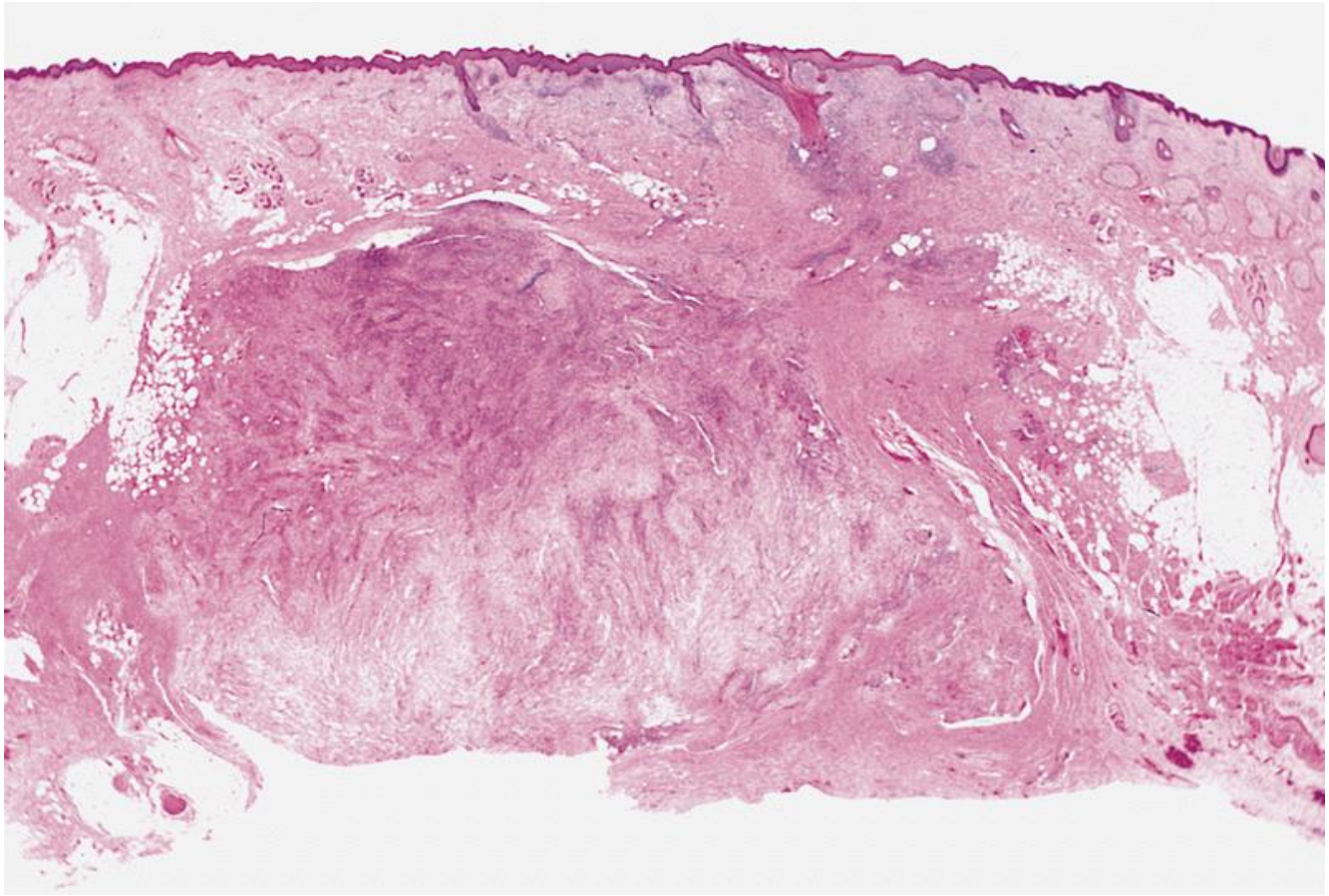


Fig. 2-1Kempson, Richard L., Fletcher, Christophr DM, Evans, Harry L, Hendrickson, Michael R, and Sibley, Richard K, Tumors of the Soft Tissues, Fascicle 30, Atlas of Tumor Pathology. 3rd Series. Armed Forces Institute of Pathology, Washington, DC (2001).

Fibromatoses

- The superficial fibromatoses are characterized by nodular or poorly defined broad fascicles of mature-appearing myofibroblasts surrounded by abundant dense collagen.
- Trisomy 3 and trisomy 18 common abnormalities.
- In the palmar variant (Dupuytren contracture), there is irregular or nodular thickening of the palmar fascia (bilaterally in 50%).
- Attachment to the overlying skin causes puckering and dimpling.
- At the same time, a slowly progressive flexion contracture develops, mainly of the fourth and fifth fingers of the hand.

Palmar fibromatosis

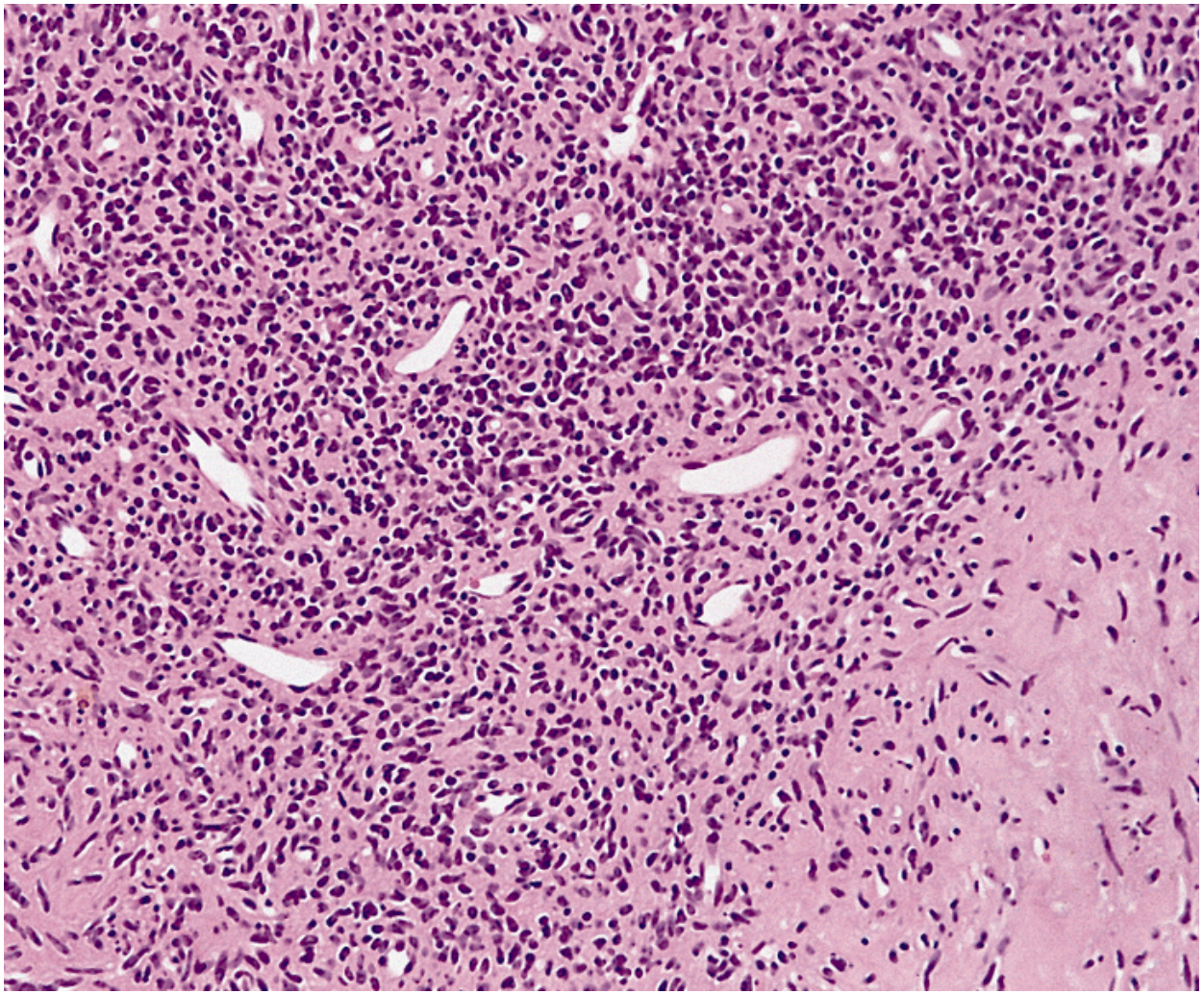


Fig. 2-45R Kempson, Richard L., Fletcher, Christophr DM, Evans, Harry L, Hendrickson, Michael R, and Sibley, Richard K, Tumors of the Soft Tissues, Fascicle 30, Atlas of Tumor Pathology. 3rd Series. Armed Forces Institute of Pathology, Washington, DC (2001).

Fibromatoses

- Essentially similar changes are seen with plantar fibromatosis, except that flexion contractures are uncommon and bilateral involvement is infrequent.
- Usually in preteen and teen boys.
- In penile fibromatosis (Peyronie disease), a palpable induration or mass appears usually on the dorsolateral aspect of the penis.
- It may cause eventually abnormal curvature of the shaft or constriction of the urethra, or both.
- 10% of all fibromatoses.

Fibromatoses

- Deep-seated fibromatoses (desmoid tumors) lie in the borderland between nonaggressive fibrous tumors and low-grade fibrosarcomas.
- Commonly present as large, infiltrative masses that frequently recur after incomplete excision.
- Composed of banal well-differentiated fibroblasts that do not metastasize.
- They may occur at any age but are most frequent in the teens to thirties.

Desmoid tumor

- Extra-abdominal arise principally in the musculature of the shoulder, chest wall, back, and thigh.
- No sex predilection.
- Abdominal desmoids generally arise in the musculo-aponeurotic structures of the anterior abdominal wall in women during or after pregnancy.
- Intra-abdominal desmoids tend to occur in the mesentery or pelvic walls, often in patients having familial adenomatous polyposis (Gardner syndrome).
- Mutations in the APC at 5q22.2 or CTNNB1
- Protein unable to bind to β-catenin and degrade

Desmoid tumor

- Desmoids are composed of plump fibroblasts arranged in broad sweeping fascicles that infiltrate to the adjacent tissue.
- Mitoses are usually infrequent.
- Regenerating muscle cells, when trapped within these lesions, may take on the appearance of multinucleated giant cells.

Desmoid

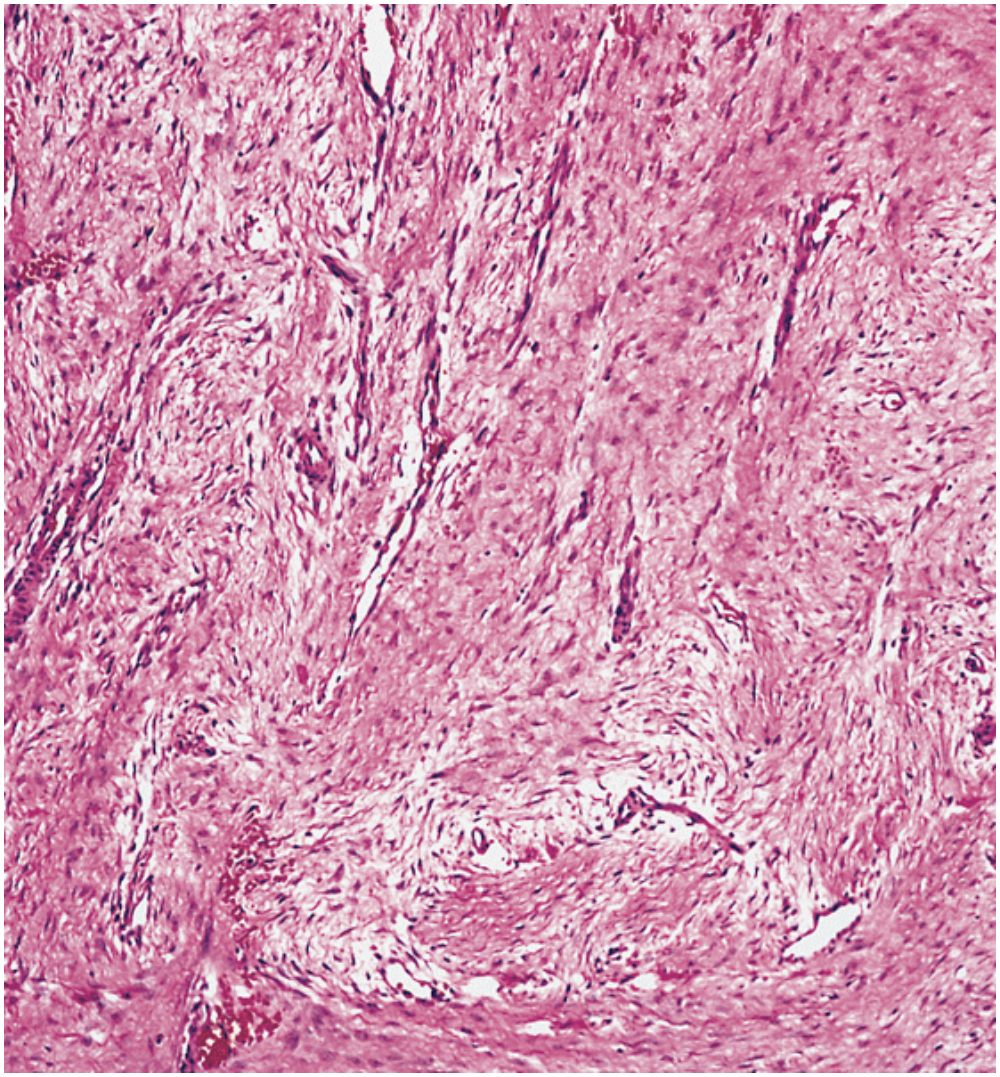


Fig. 2-49L Kempson, Richard L., Fletcher, Christophr DM, Evans, Harry L, Hendrickson, Michael R, and Sibley, Richard K, Tumors of the Soft Tissues, Fascicle 30, Atlas of Tumor Pathology. 3rd Series. Armed Forces Institute of Pathology, Washington, DC (2001).

Fibrous histiocytoma

- Most frequently arise in the dermis (dermatofibroma).
- Most benign fibrous histiocytomas consist of a proliferation of bland spindle cells arranged in a storiform pattern. These tumors have infiltrative margins.
- Common secondary findings include the presence of foam cells, hemosiderin deposits, multinucleated giant cells, and hyperplasia of the overlying epidermis.
- Adequate treatment is simple excision.

Fibrous histiocytoma

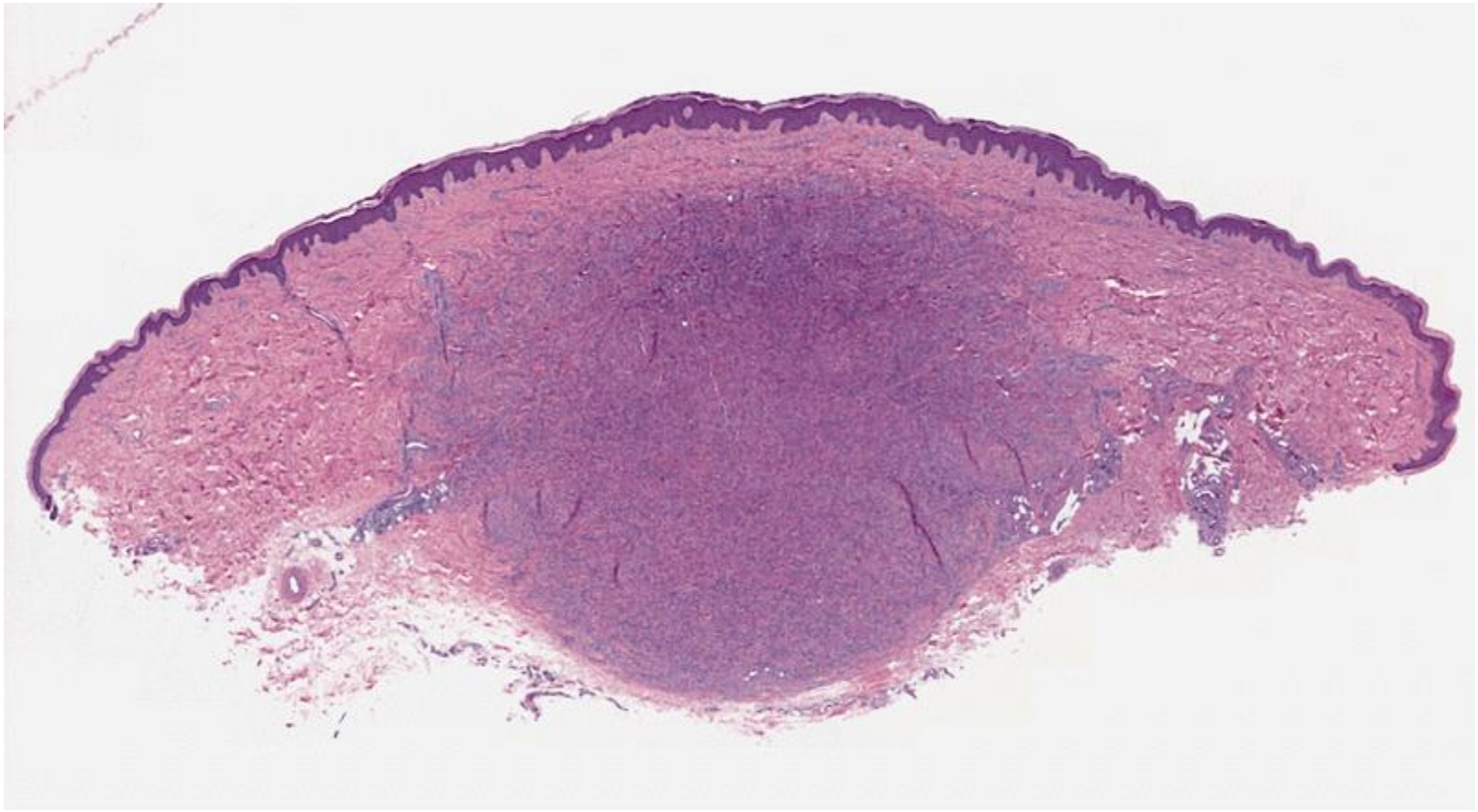


Fig. 3-1 Kempson, Richard L., Fletcher, Christophr DM, Evans, Harry L, Hendrickson, Michael R, and Sibley, Richard K, Tumors of the Soft Tissues, Fascicle 30, Atlas of Tumor Pathology. 3rd Series. Armed Forces Institute of Pathology, Washington, DC (2001).

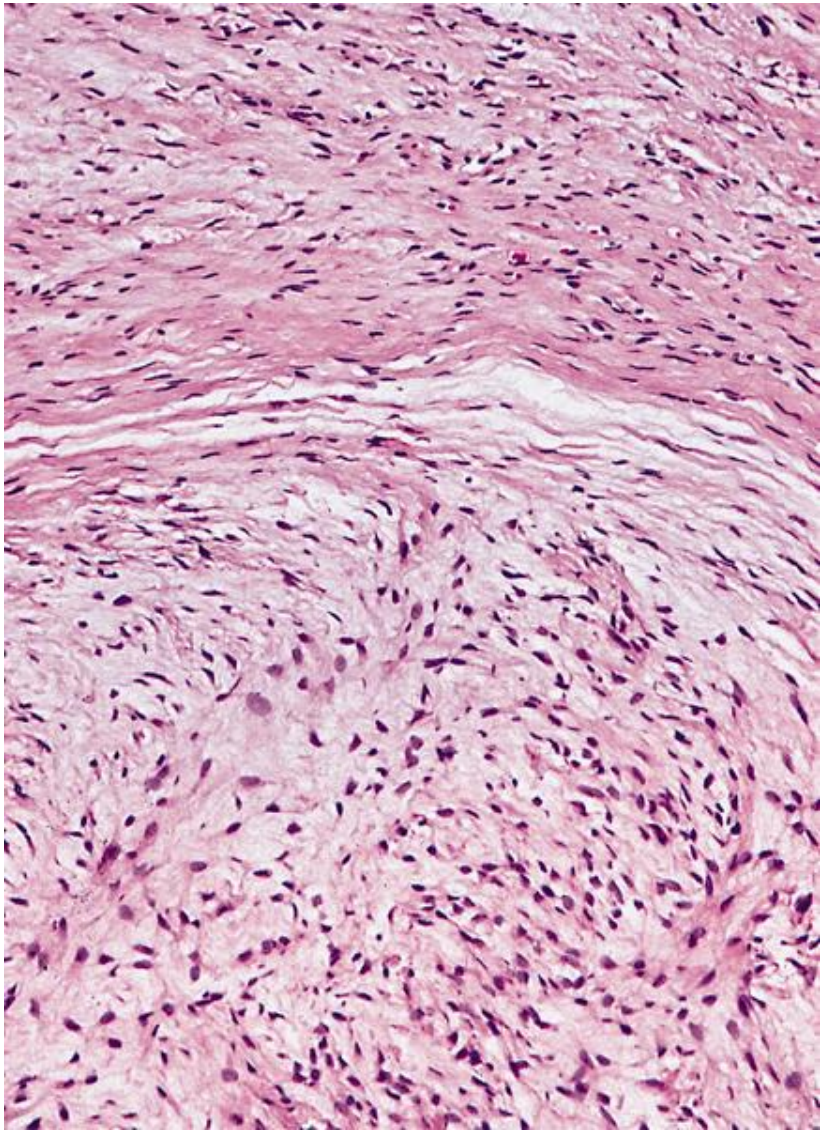
Fibrosarcoma

- Occurs in the middle decades and in the ederly. No sex predilection.
- Most commonly occur in the retroperitoneum, the thigh, the knee, and the distal extremities.
- In the bones, present as enlarging painful masses. Infiltrative, lytic. May extend into soft tissues. Pathologic fracture is a frequent complication.
- Retroperitoneal tumors may be large and bulky and cause abdominal symptoms.

Fibrosarcoma

- Composed of malignant fibroblasts arranged in a herringbone pattern.
- The level of differentiation determines the amount of collagen produced and the degree of cytologic atypia.
- Bizarre multinucleated cells are not common.
- Infantile fibrosarcoma
- < 2years old
- t(12;15)(p13;q23)
- Characterized by ETV6-NTRK3 fusion gene
- Constitutively active through RAS and PI3K/AKTpathways

Fibrosarcoma



Figs 2-73 Kempson, Richard L., Fletcher, Christophr DM, Evans, Harry L, Hendrickson, Michael R, and Sibley, Richard K, Tumors of the Soft Tissues, Fascicle 30, Atlas of Tumor Pathology. 3rd Series. Armed Forces Institute of Pathology, Washington, DC (2001).

Congenital-infantile fibrosarcoma

- Pathognomonic:
- t(12;15)(p13;q25
- ETV6-NTRK3 fusion transcript.
- Constitutively active
- Stimulates signaling through RAS and PI-3K/AKT pathways.
- Milder behavior than adult fibrosarcoma

Pleomorphic sarcoma

- Once known as malignant fibrous histiocytoma
- Occurs in middle decades and in the elderly.
- Men principally affected.
- Present as enlarging painful masses that usually arise in the metaphyses of long bones and pelvic flat bones.
- Infiltrative. May extend into soft tissues.
- Lytic.
- Pathologic fracture is a frequent complication.

Pleomorphic sarcoma

- May represent end stage of a variety of sarcomas.
- Immunohistochemistry is not helpful.
- Electron microscopy not helpful in detecting lineage.
- Consists of a background of spindled fibroblasts arranged in a storiform pattern admixed with large, ovoid, bizarre multinucleated tumor giant cells.
- Morphologically, some tumor cells resemble neoplastic histiocytes; however, they are fibroblasts.
- Complex karyotypes, usually triploid or tetraploid
- Often mutations in checkpoint genes
- 5-year survival is 50%

Malignant fibrous histiocytoma

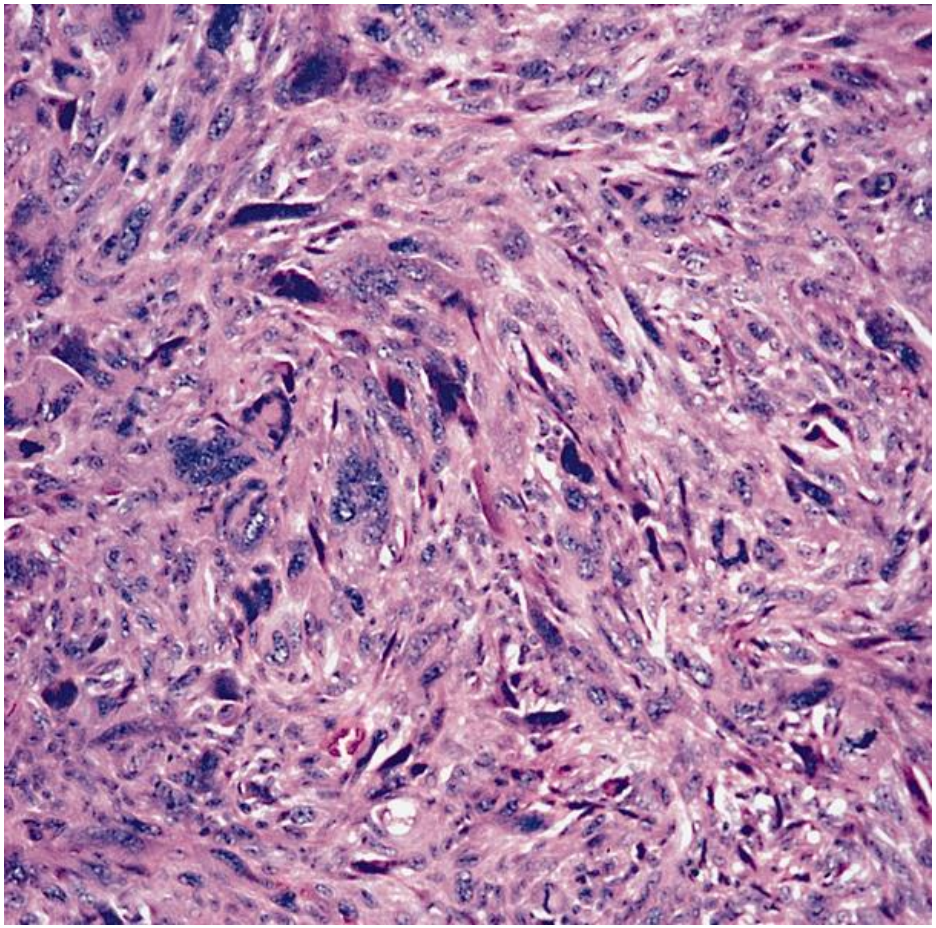


Fig. 3-46 Kempson, Richard L., Fletcher, Christophr DM, Evans, Harry L, Hendrickson, Michael R, and Sibley, Richard K, Tumors of the Soft Tissues, Fascicle 30, Atlas of Tumor Pathology. 3rd Series. Armed Forces Institute of Pathology, Washington, DC (2001).

Leiomyoma

- The most common tumor in humans.
- Usually occur in uterus but may also see in erector pili of skin (painful).
- Uteine leiomyoma present in 75% of females of reproductive age.
- Often multiple.
- Each uterine leiomyoma is a unique clonal neoplasm.
- t(12,14), del 7, trisomy 12 are common findings.
- Microscopically consists of whorled bundles of smooth muscle cells.

Leiomyoma

- Multiple leiomyomata occur following a germ-line loss of function mutation in the fumarate hydrase gene at 1q42.3.
- May also be associated with renal cell carcinoma.

Leiomyoma

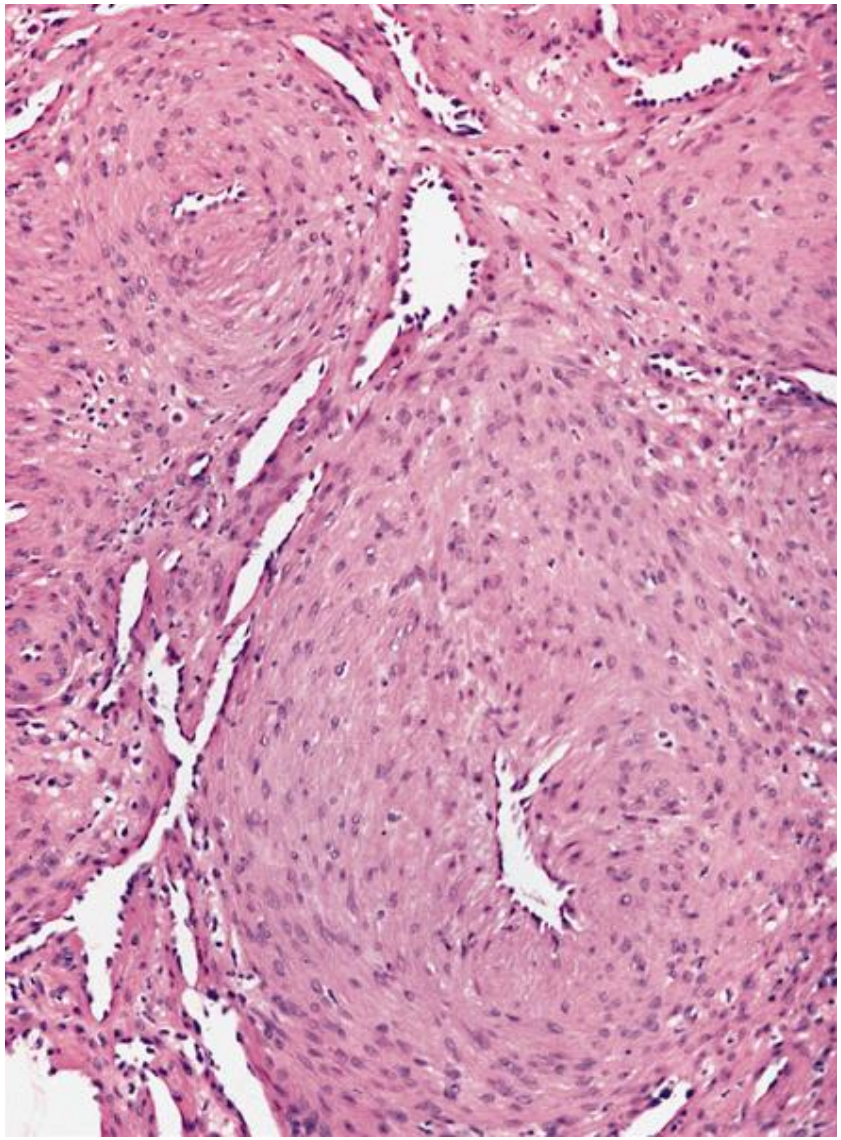


Fig. 5-2 Kempson, Richard L., Fletcher, Christophr DM, Evans, Harry L, Hendrickson, Michael R, and Sibley, Richard K, Tumors of the Soft Tissues, Fascicle 30, Atlas of Tumor Pathology. 3rd Series. Armed Forces Institute of Pathology, Washington, DC (2001).

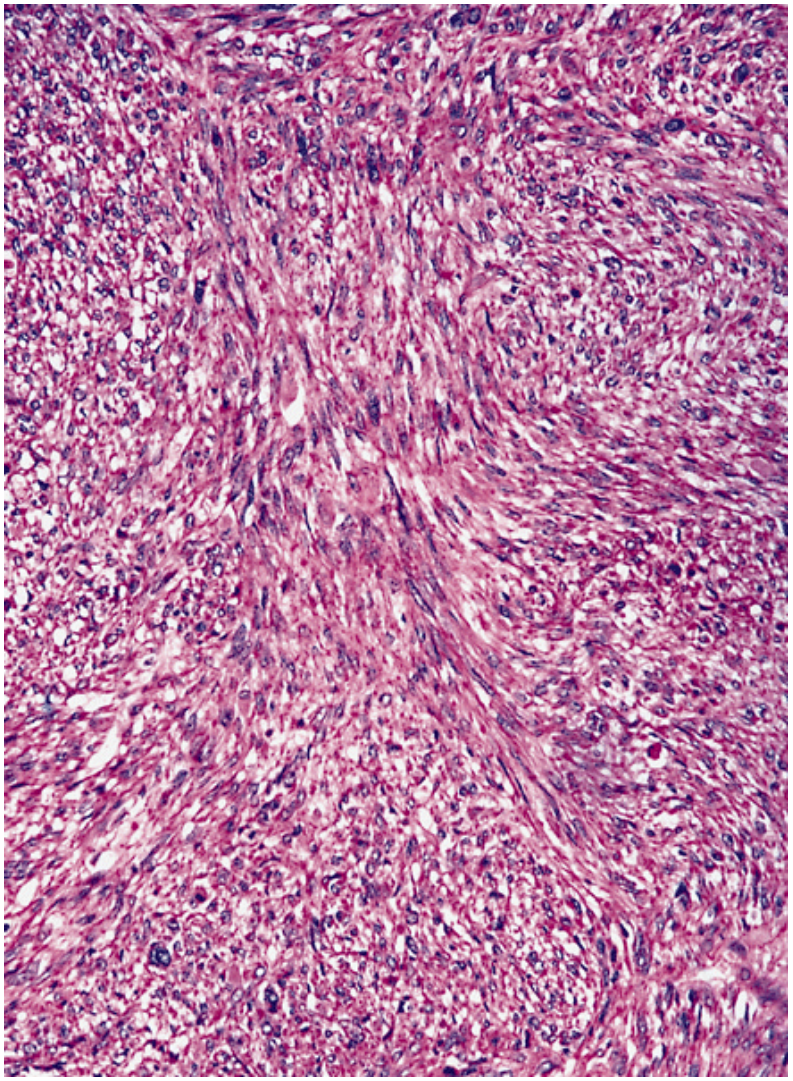
Leiomyosarcoma

- 10% to 20% of soft tissue sarcomas.
- Adults, principally women.
- Develop in the skin and deep soft tissues of the extremities and retroperitoneum.
- Painless firm masses.
- Retroperitoneal tumors may be large and bulky and cause abdominal symptoms.

Leiomyosarcoma

- Characterized by malignant spindle cells that have cigar-shaped nuclei arranged in interweaving fascicles.
- Morphologic variants include tumors with a prominent myxoid stroma and others, epithelioid

Leiomyosarcoma



Figs 5-3 Kempson, Richard L., Fletcher, Christophr DM, Evans, Harry L, Hendrickson, Michael R, and Sibley, Richard K, Tumors of the Soft Tissues, Fascicle 30, Atlas of Tumor Pathology. 3rd Series. Armed Forces Institute of Pathology, Washington, DC (2001).

Rhabdomyosarcoma

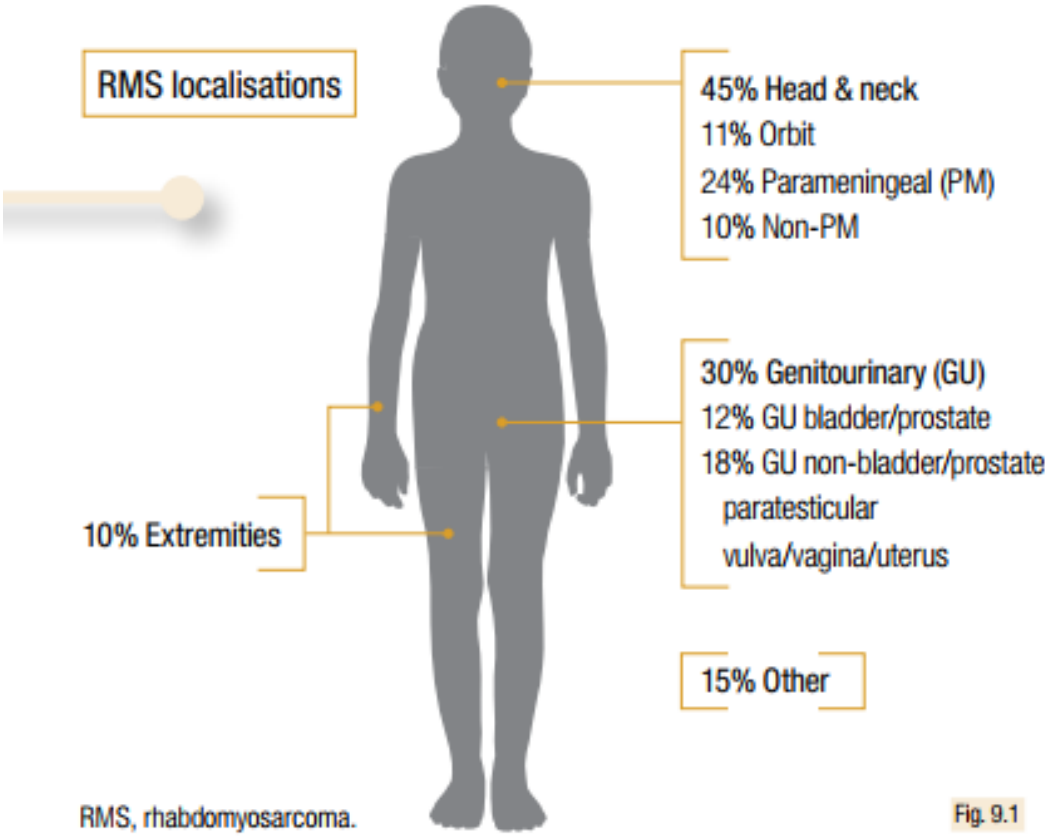
- The most common soft tissue sarcoma of childhood and adolescence.
- Most occur in the head and neck or genitourinary tract, where there is little, if any, skeletal muscle as a normal constituent.
- Only in the extremities do they appear in relation to skeletal muscle.
- t(2;13)(q35;14) is commonly found. PAX3-FOXO1 fusion (The PAX3 gene functions upstream of genes that control skeletal muscle differentiation).
- Less commonly found is t(1;13)(q36;q14); produces a PAX7-FOXO1 fusion gene

Rhabdomyosarcoma

- Rhabdomyosarcoma is histologically subclassified into the embryonal, alveolar, and pleomorphic variants.
- The rhabdomyoblast is the diagnostic cell in all types.
- It contains eccentric eosinophilic granular cytoplasm rich in thick and thin filaments.
- The rhabdomyoblasts may be round or elongate; the latter are known as tadpole or strap cells and may contain cross-striations visible by light microscopy.

Rhabdomyosarcoma

- Contain sarcomeres.
- Express the myogenic markers desmin, MYOD1, and myogenin.
- IGF-1R elevated in rhabdomyosarcoma



RMS, rhabdomyosarcoma.

Fig. 9.1

Two thirds of RMSs arise before the age of 6, but there is a second peak in adolescents and young adults.
20% metastatic

Rhabdomyosarcoma

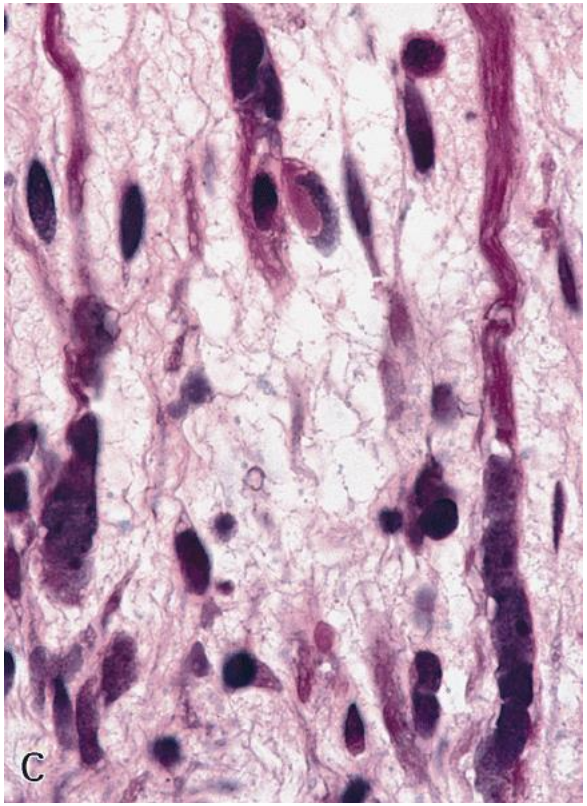
- Myogenin positivity defines myogenic differentiation
- Embryonal rhabdomyosarcoma (70%)
- Alveolar rhabdomyosarcoma (20%)
- FOXO1-PAX3 from t(2;13)(q35;q14)
- FOXO1-PAX7 from t(1;13)(p36;q14)

Rhabdomyosarcoma

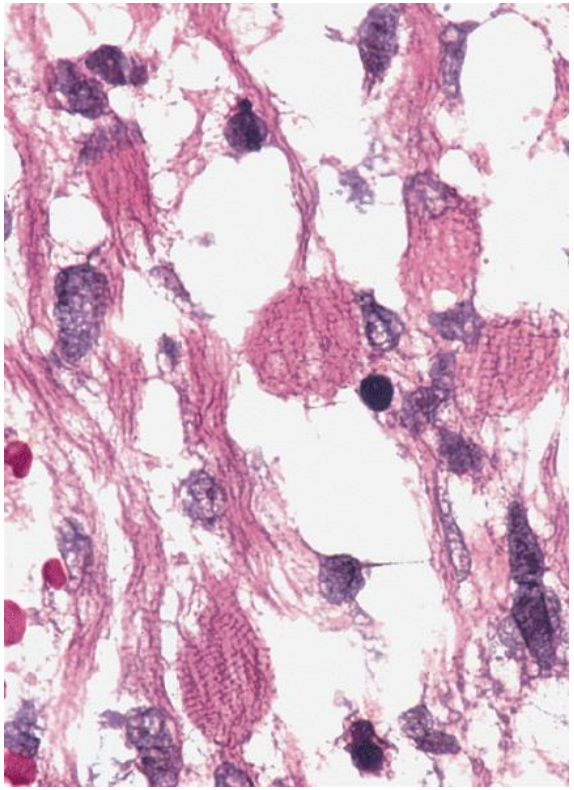
- Main prognostic factors:
- Histology
- Embryonal rhabdomyosarcoma better prognosis than alveolar rhabdomyosarcoma
- Age
- <10 years
- Size of the tumor
- ≤5 cm
- Nodes, metastases, and location(s).

Rhabdomyosarcoma

Nuclei in tandem (tadpole)



Cross-striations



Figs. 6-21C and 6-22 Kempson, Richard L., Fletcher, Christophr DM, Evans, Harry L, Hendrickson, Michael R, and Sibley, Richard K, Tumors of the Soft Tissues, Fascicle 30, Atlas of Tumor Pathology. 3rd Series. Armed Forces Institute of Pathology, Washington, DC (2001).

Embryonal rhabdomyosarcoma

- Most common type (66% of rhabdomyosarcomas).
- The tumor occurs in children under age 10 years and typically arises in the nasal cavity, orbit, middle ear, prostate, and paratesticular region.
- Commonly has allelic loss of chromosome 11p15.5 as its major genomic abnormality.
- The sarcoma botryoides subtype develops in the walls of hollow, mucosa-lined structures, such as the nasopharynx, common bile duct, bladder, and vagina.

Embryonal rhabdomyosarcoma

- Presents as soft gray infiltrative mass.
- The tumor cells mimic skeletal muscle at various stages of embryogenesis and consist of sheets of both primitive round and spindled cells in a myxoid stroma.
- Rhabdomyoblasts with visible cross-striations may be present.
- Where the tumors abut the mucosa of an organ, they form a submucosal zone of hypercellularity called the cambium layer.

Embryonal rhabdomyosarcoma

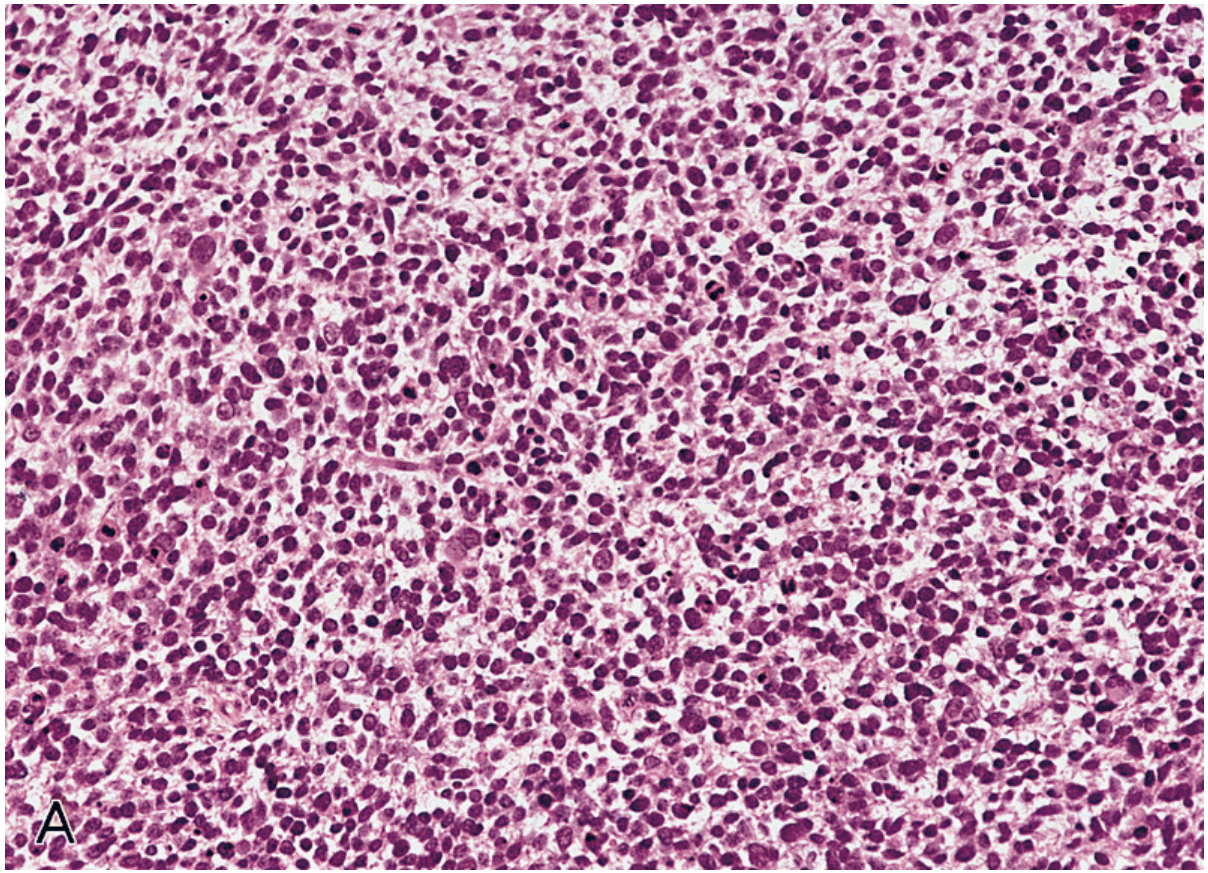


Fig. 6-17 Kempson, Richard L., Fletcher, Christophr DM, Evans, Harry L, Hendrickson, Michael R, and Sibley, Richard K, Tumors of the Soft Tissues, Fascicle 30, Atlas of Tumor Pathology. 3rd Series. Armed Forces Institute of Pathology, Washington, DC (2001).

Alveolar rhabdomyosarcoma

- Most common in early to mid-adolescence.
- Arise in the deep musculature of the extremities.
- The tumor is traversed by a network of fibrous septae that divide the cells into clusters or aggregates; as the central cells degenerate and drop out, a crude resemblance to pulmonary alveoli is created.
- The tumor cells are moderate in size, and many have little cytoplasm.
- Cells with cross-striations are identified in about 25% of cases.

Alveolar rhabdomyosarcoma

- t(2;13)(q35;14) is commonly found.
- PAX3-FOXO1 fusion gene.
- Less commonly found is t(1;13)(q36;q14)
- Produces a PAX7-FOXO1 fusion gene.

Alveolar rhabdomyosarcoma

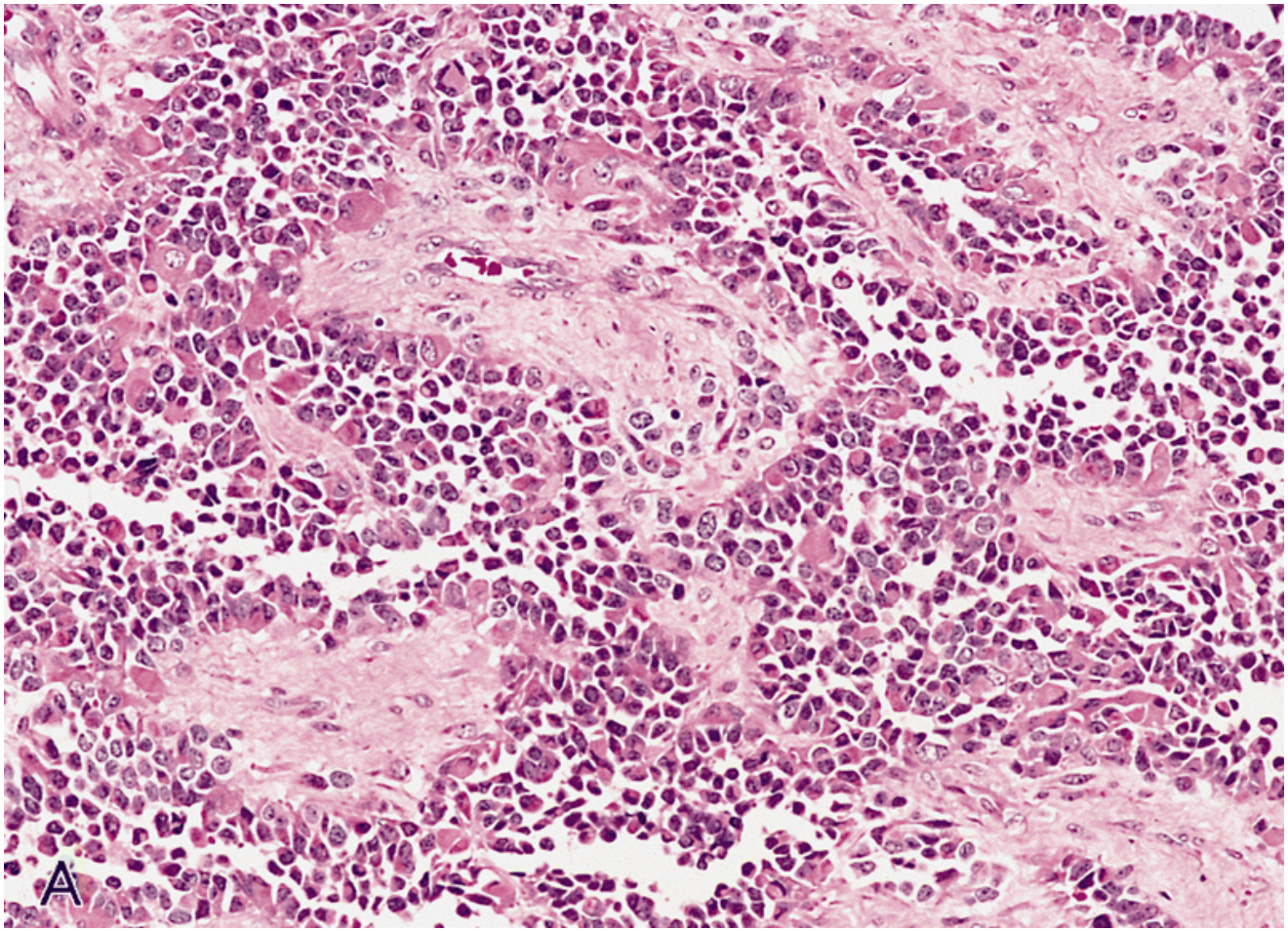


Fig. 6-35 Kempson, Richard L., Fletcher, Christophr DM, Evans, Harry L, Hendrickson, Michael R, and Sibley, Richard K, Tumors of the Soft Tissues, Fascicle 30, Atlas of Tumor Pathology. 3rd Series. Armed Forces Institute of Pathology, Washington, DC (2001).

Pleomorphic rhabdomyosarccoma

- Characterized by numerous large, sometimes multinucleated, bizarre eosinophilic tumor cells.
- This variant is rare, has a tendency to arise in the deep soft tissue of adults.
- Can resemble pleomorphic sarcoma microscopically.
- Immunohistochemistry (e.g., myogenin) is usually necessary to confirm rhabdomyoblastic differentiation.

Pleomorphic rhabdomyosarccoma

- The alveolar soft part sarcoma variant is characterized by TFE3-ASPL fusion gene;
- t(X;17)(p11.2;q25) abnormality.
- Upregulates MET.
- Young patients.
- Indolent
- But, >60% risk of metastases.

Pleomorphic rhabdomyosarcoma

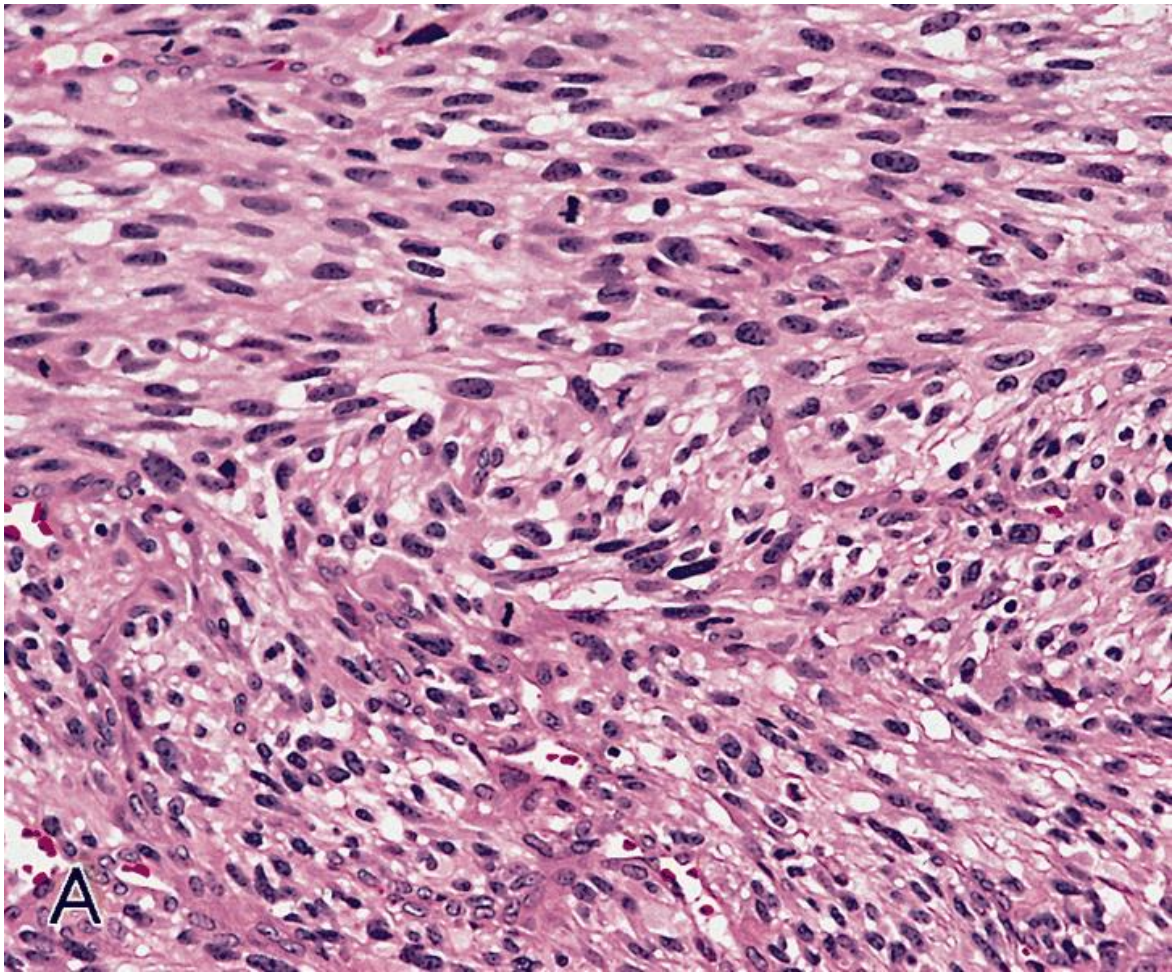


Fig. 6-34A Kempson, Richard L., Fletcher, Christophr DM, Evans, Harry L, Hendrickson, Michael R, and Sibley, Richard K, Tumors of the Soft Tissues, Fascicle 30, Atlas of Tumor Pathology. 3rd Series. Armed Forces Institute of Pathology, Washington, DC (2001).

Extracranial rhabdoid tumours

- Occur in infants and children as a fast-growing mass.
- Biallelic inactivating mutation of SMARCB1
- Poor prognosis

Molecular alterations

- FOXO1 gene at 13q14.11 fusion partner
- FOXO1 fusion-negative cases
- > 50% of cases, RAS pathway mutation
- RAS isoforms found in 64% of infants < 1 year old
- 21% had no putative driver mutation identified.
- FOXO1 fusion-positive cases
- 15%, BCOR
- 15%, NF1
- 13%, TP53

Molecular alterations

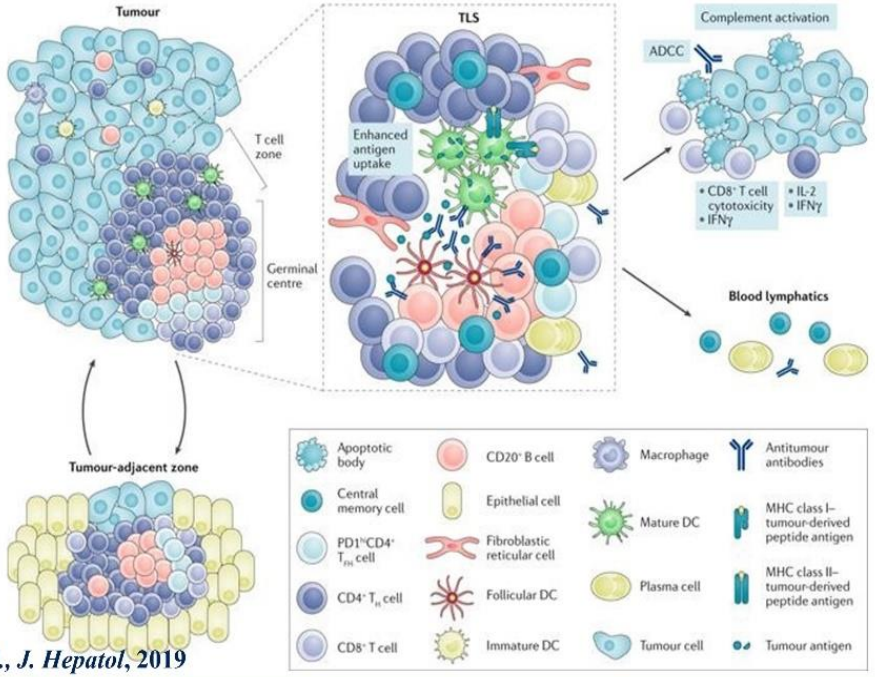
- TP53 mutations are associated with worse outcomes in both fusion-negative and FOXO1 fusion-positive cases
- MYOD1 is associated with older age, head and neck primary site, and a dismal survival.

Molecular alterations

- Embryonal rhabdomyosarcoma features point mutations and aneuploidy
- Alveolar rhabdomyosarcoma features gene fusions and amplifications.
- Pleomorphic rhabdomyosarcoma related to undifferentiated pleomorphic sarcoma

TLS are power houses of cellular and humoral immune responses in cancer

C Sautès-Fridman *et al, Nature Rev Cancer*, 2019



J. Calderaro *et al., J. Hepatol*, 2019

LOCAL

SYSTEMIC

memory cells

Dieu-Nosjean *et al., J Clin Oncol*, 2008
Platonova *et al., Cancer Res.*, 2011
De Chaisemartin *et al.*, Cancer Res., 2011
Germain *et al., Am J Resp Crit Care Med*, 2014
Goc *et al. Cancer Research* 2014
Dieu-Nosjean *et al., Immunol Rev* 2016
Sautès-Fridman *et al., Frontiers Immunol*, 2016

Tertiary lymphoid structures as biomarker for immune checkpoint therapy in soft tissue sarcoma

Gastrointestinal stromal cell tumor

- Most common mesenchymal tumor in gastrointestinal tract
- Stomach (60%) and jejunum and ileum (30%)
- Arise from interstitial cells of Cajal.
- 25% metastasize (gastric)
- 35-40% metastasize (small intestine)
- Mean age 60-65 years old

Gastrointestinal stromal cell tumor

- Familial:
- Germline mutations in KIT or PDGFRα
- Autosomal dominant
- Immunopositive for SDHB
- Neurofibromatosis:
- 7% of patients with NF1 develop one or more GIST, usually in small bowel
- Both C-KIT (75% of cases) and PDGFR (10% of cases) mutations lead to constitutive phosphorylation of tyrosine kinases (75% of cases)
- C-KIT and PDGFR mutations are mutually exclusive

Gastrointestinal stromal cell tumor

- Most cases of KIT or platelet-derived growth factor receptor alpha (PDGFRA) wild-type (WT) GIST are related to succinate dehydrogenase (SDH) deficiency.
- 95% cases are CD117 positive
- DOG1 (Anoctamin 1) identifies KIT-negative GIST patients while KIT and DOG1-negative GISTs are exceptional.
- Each type of mutation in exon 11 of the KIT gene clusters in different positions: (5´ region) deletions involve codons 550-572, duplications in codons 573-591 and missense mutations predominate in codons 559 and 560.

Gastrointestinal stromal tumor

- Succinate dehydrogenase deficient
- Young adults (before age 40)
- 1 - 2% of all GIST in pediatric patients
- Female preponderance (> 2:1)
- Almost exclusively in stomach (predilection for distal stomach and antrum)
- Minimal nuclear pleomorphism
- Epithelioid or mixed histology with frequent involvement of lymph nodes.
- Indolent course.

Gastrointestinal stromal tumor

- Succinate dehydrogenase (SDH) deficient:
- Carney triad:
- GIST, pulmonary chondroma, paraganglioma
- Nonhereditary
- SDHC promoter hypermethylation
- Small percentage have germline SDH mutations
- Carney-Stratakis syndrome:
- GIST and paraganglioma
- Autosomal dominant
- Germline mutations in SDHB, SDHC or SDHD subunit

Gastrointestinal stromal cell tumor

- 82% of gastric tumors are CD34+, but only 40% of small intestinal tumors
- SMA+ in 18% of gastric tumors, but 34% of small intestinal tumors
- Tumors that show features of enteric plexus (spindle cell) differentiation are often classified among GISTs.
- Gastrointestinal autonomic tumor (GIST)
- Vimentin, S100, and NSE+.

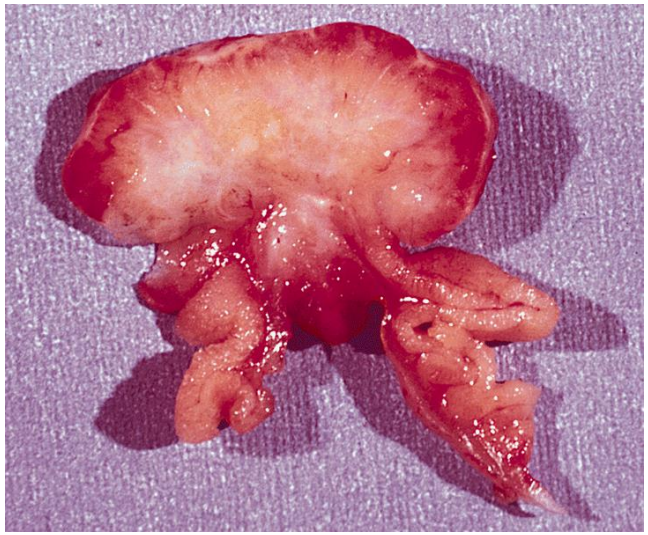
Gastrointestinal stromal cell tumor

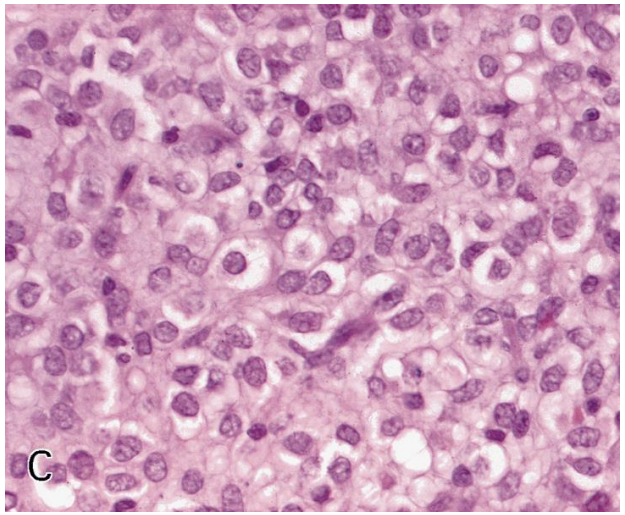
- Well circumscribed, intramural lesion, centered within the muscularis propria
- Fleshy, tan-pink cut surfaces, which may show hemorrhage or cystic degeneration
- Size >5cm associated with poor prognosis
- 3 morphologic types:
- Spindle (70%),
- Epithelioid (20%)
- Mixed (10%)

Gastrointestinal stromal cell tumor

- Spindle:
- Bland spindle cells with faintly eosinophilic cytoplasm in a syncytial pattern; elongated nuclei with inconspicuous nucleoli;
- Subtypes: sclerosing, palisaded, vacuolated, diffuse hypercellular, sarcomatoid features with significant nuclear atypia and mitotic activity

Gastrointestinal stromal tumor





Gross appearance of primarily submucosal tumor. Typical central nuclei and partially retracted cytoplasm are seen. Tumors vary in cellularity: those that are the most cellular tend to have smaller cells and larger nuclei. These are the areas where mitoses are most likely to be found.

Figs. 7-01R and 07-08C

Riddell, RH, Petras, RE, Williams, GT, Sobin, LH., "Tumors of the intestines." Atlas of Tumor Pathology, Third Series, Fascicle 32. Armed Forces Institute of Pathology, Washington, D.C. 2003.

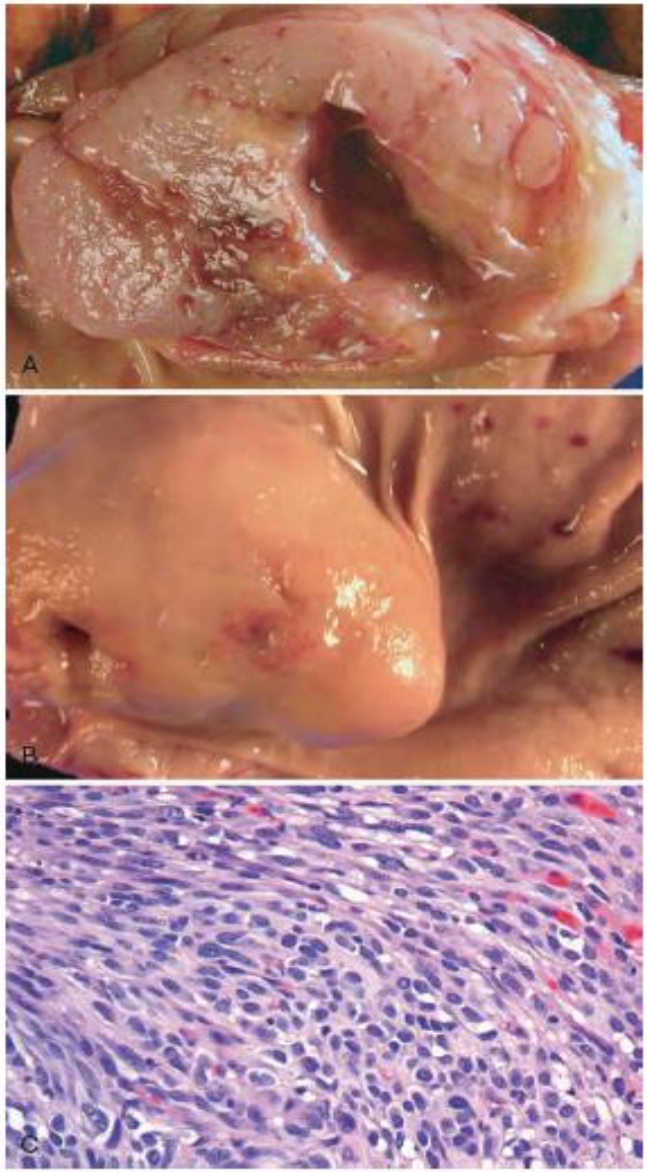
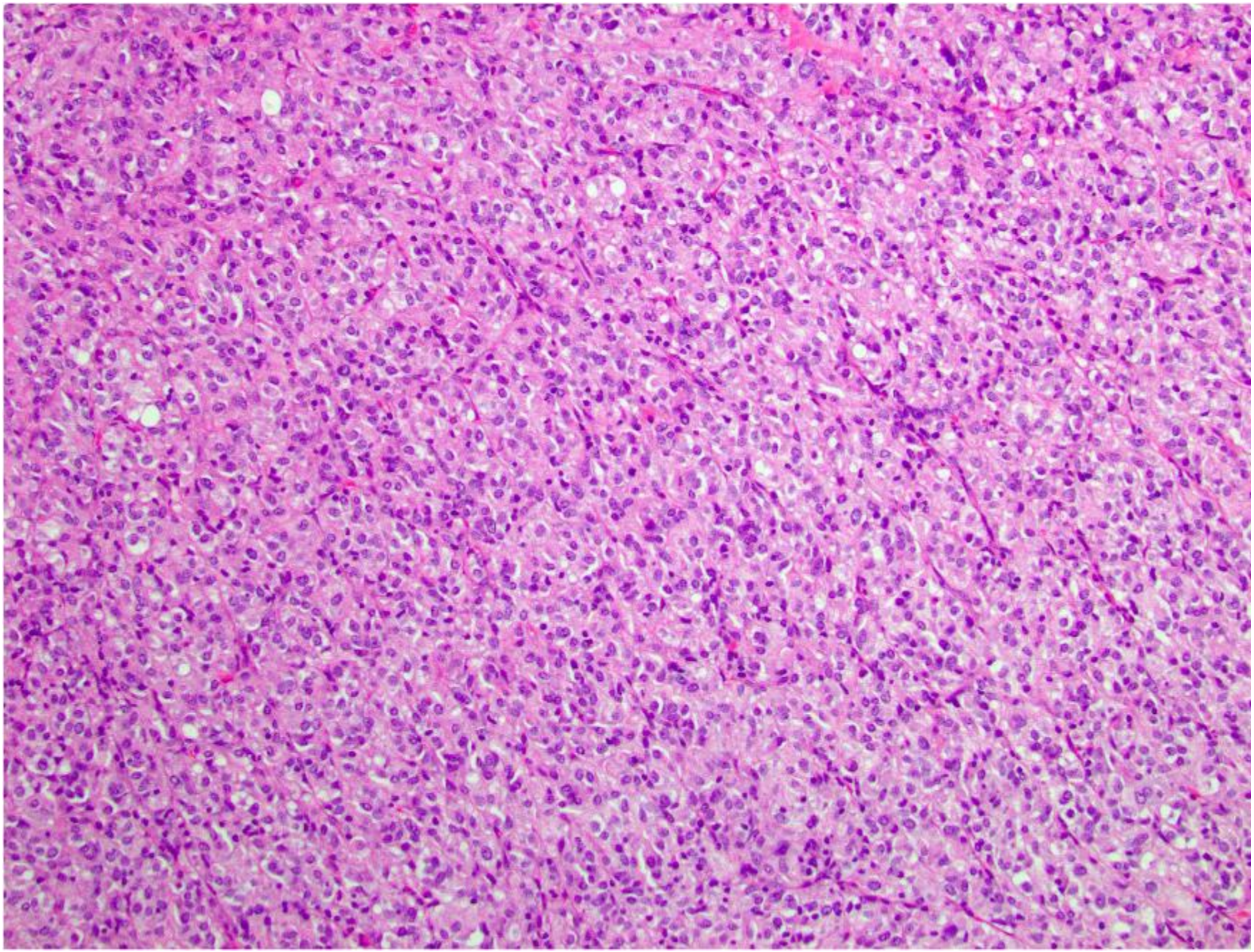
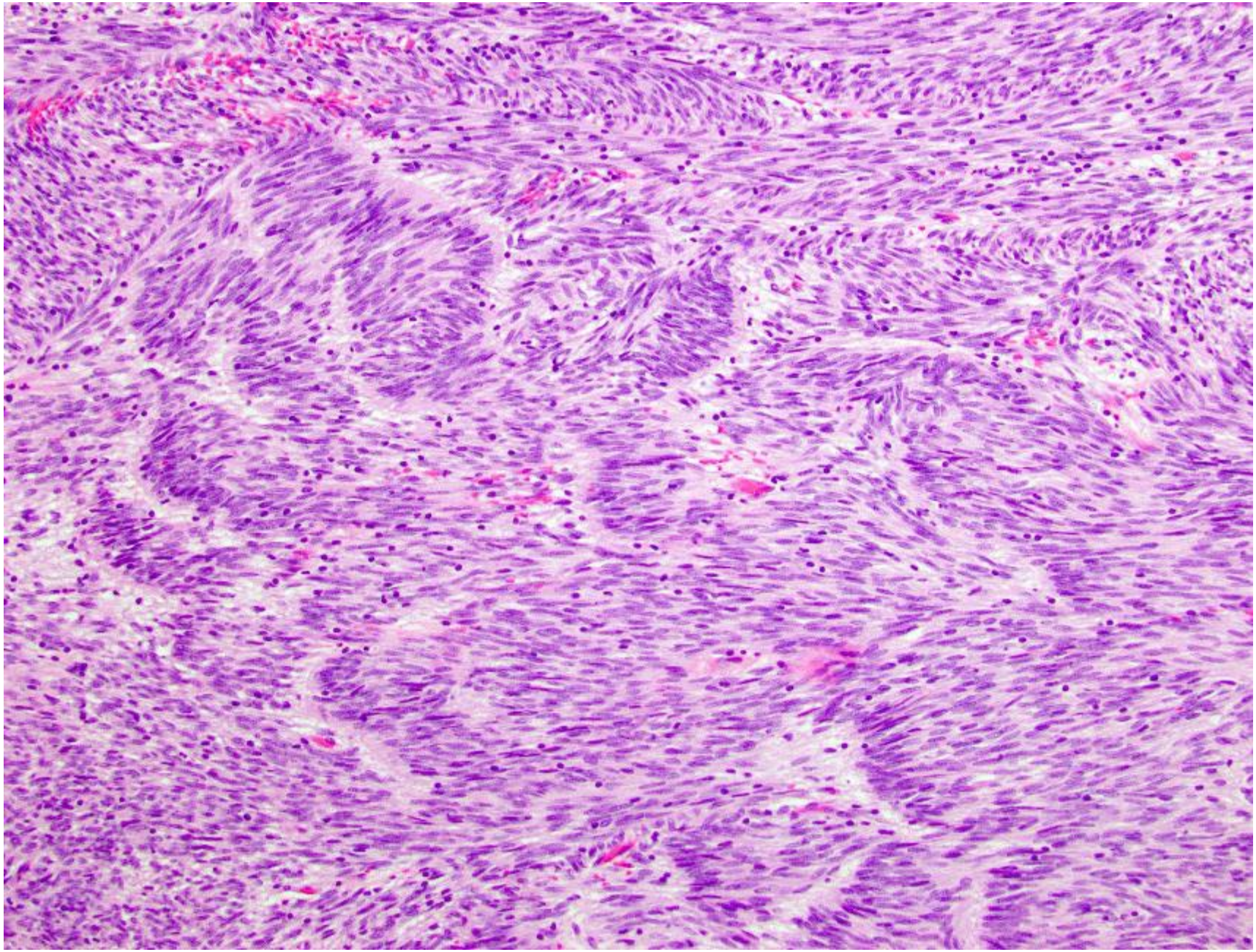


Figure 17-21 GI stromal tumor. **A,** On cross-section a whorled texture is evident within the white, fleshy tumor. **B,** The mass is covered by intact mucosa. **C,** Histologically the tumor is primarily composed of bundles, or fascicles, of spindle-shaped tumor cells. (Courtesy Dr. Christopher Weber, The University of Chicago, Chicago, Ill.)

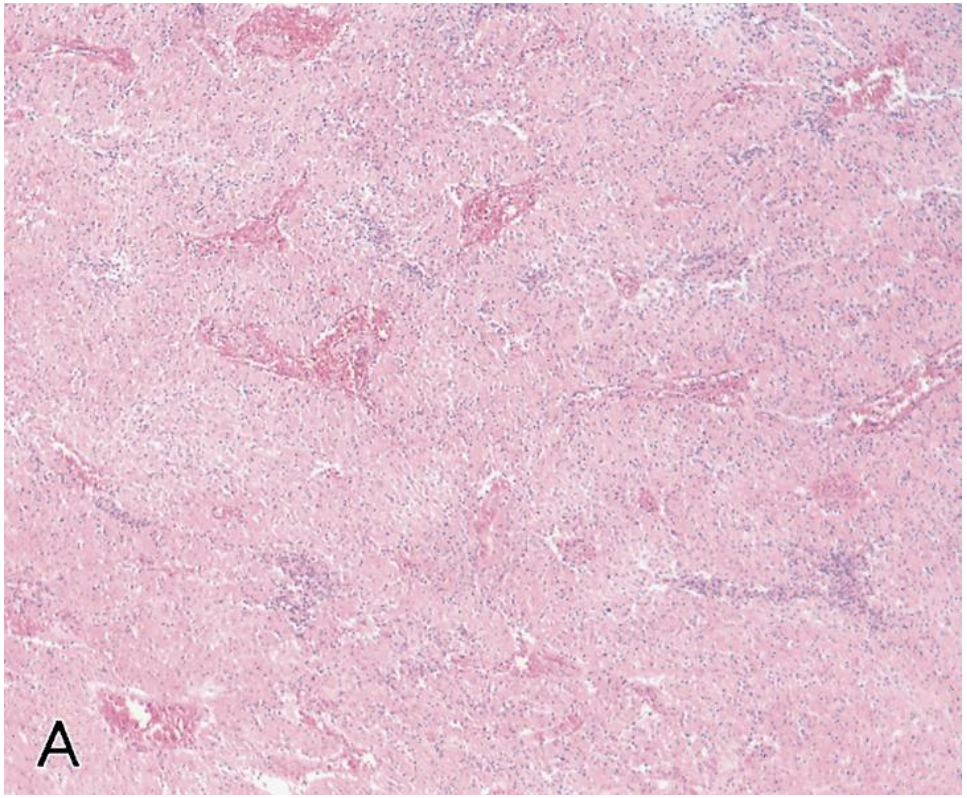


Gastrointestinal stromal cell tumor

- Epithelioid:
- Round cells with clear to eosinophilic cytoplasm in sheets or nests; increased tendency for pleomorphism versus spindle type
- Subtypes: sclerosing, discohesive, hypercellular, sarcomatous with significant atypia and mitotic activity
- Mixed:
- Tumor is composed of cells with spindle and epithelioid morphology



Gastrointestinal autonomic tumor



The more intact parts of the tumor are composed of uniform eosinophilic cells in which are seen occasional lymphoid aggregate

Fig. 7-11A

Riddell, RH, Petras, RE, Williams, GT, Sobin, LH., "Tumors of the intestines." Atlas of Tumor Pathology, Third Series, Fascicle 32. Armed Forces Institute of Pathology, Washington, D.C. 2003.

Gastrointestinal stromal tumor

- Dedifferentiated:
- Anaplastic appearance with an unusual phenotype (may lose expression of KIT or may aberrantly express other markers such as cytokeratin)
- Patients harboring D842V mutation in exon 18 of the PDGFRA gene do not respond to imatinib, sunitinib or regorafenib.
- Molecular biomarkers, such as KIT mutants involving codons 557-558 in exon 11 are independent prognostic factors.

Risk group	Size (cm)	Mitotic count (5 mm^2)	Location
Very low risk	2-5	≤5	Gastric
Low risk	>5 and ≤10	≤5	Gastric
	≤5	≤5	Intestinal
Intermediate risk	>10	≤5	Gastric
	>5 and ≤10	≤5	Intestinal
	2-5	>5	Gastric
High risk	2-5	>5	Intestinal
	>10	≤5	Intestinal
	>5 and ≤10	>5	Gastric
	>10	>5	Gastric
	>5 and ≤10	>5	Intestinal
	>10	>5	Intestinal

Fig. 2.7

Tumor rupture is a poor prognostic sign.

Choi criteria prognostic (dimensional and density changes on imaging).

Malignant peripheral nerve sheath tumor

- Once known as malignant schwannoma.
- 50% associated with NF1 gene mutaion at 17q11 abnormality. Often triploid.
- Vimentin, HAB71/O13+.
- May have glandular differentiation as well (positive for keratin, EMA, CEA, chromogranin)
- May have melanin in tumor cells, particularly if arise from spinal nerve roots (overlaps with primary melanoma of nerves)
- Predilection for Gallium uptake on MRI.
- Farnesyl transferase inhibitors block RAS activation.

Malignant peripheral nerve sheath tumor

- Monomorphic serpentine cells, palisading, large gaping vascular spaces, perivascular plump tumor cells, geographic necrosis with tumor palisading at edges, resembling glioblastoma multiforme
- Frequent mitotic figures
- May have bizarre cells
- 15% have metaplastic cartilage, bone, muscle

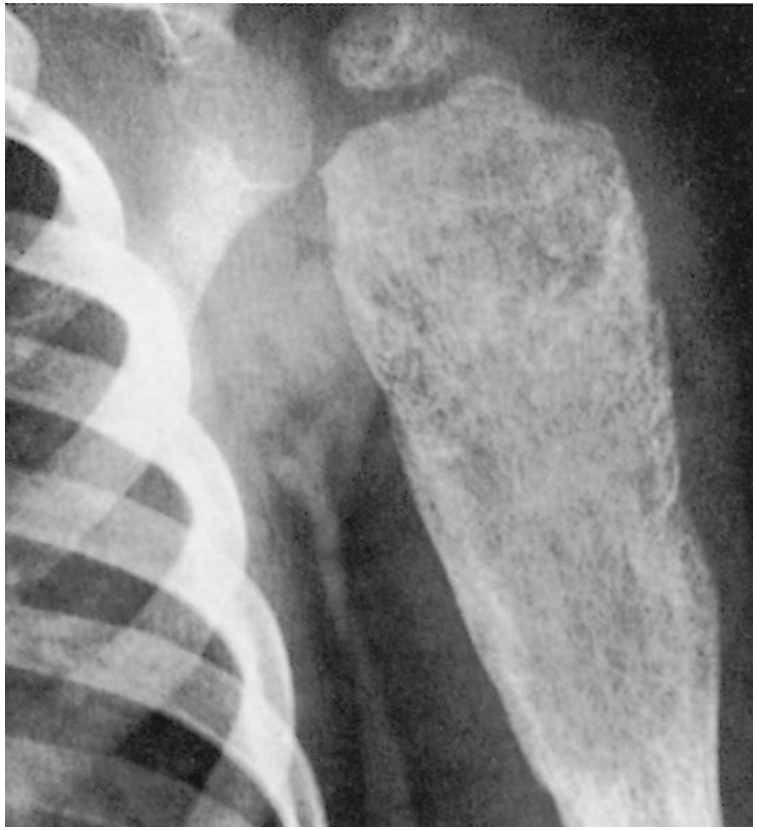
Ewing’s sarcoma

- Ewing’s sarcoma and primitive neuroectodermal tumor account for approximately 6% to 10% of primary malignant bone tumors.
- Follow osteosarcoma as the second most common group of bone sarcomas in children.
- Most patients are 10 to 15 years old. Unusual after age 20.
- Boys are affected slightly more frequently than girls, and there is a striking predilection for whites; those of sub-Saharan ancestry are rarely afflicted.

Ewing's sarcoma

- Usually arise in the diaphyses of long tubular bones, especially the femur and the flat bones of the pelvis.
- May be extraosseous.
- They present as painful enlarging masses, and the affected site is frequently tender, warm, and swollen. Some patients have systemic findings.
- Plain x-rays show a destructive lytic tumor that has permeative margins and extension into the surrounding soft tissues.
- The characteristic periosteal reaction produces layers of reactive bone deposited in an onionskin fashion.

Ewing’s sarcoma



Radiograph from a 2-year-old boy. There is diffuse loss of the normal contour of bone and destruction of the cortex. At operation, a large hemorrhagic, cystic cavity was encountered. Curettings from the wall revealed the primitive neuroectodermal cells of Ewing’s sarcoma.

Fig. 219

Fechner, FE, Mills, SE., “Tumors of the bones and joints.” Atlas of Tumor Pathology, Third Series, Fascicle 8. Armed Forces Institute of Pathology, Washington D.C.1992.

Ewing’s sarcoma

- 85% of cases, t(11;22)(q24;q12)
- 5%-10% of cases, t(21;22)(q21;q12)
- <1% of cases, t(7;22)(q22;q12)
- The most common fusion gene (FLI1-EWS) generated from the t(11;22) translocation acts as a dominant oncogene, and the fusion protein acts as a constitutively active transcription factor.
- ERG-EWS fusion gene in t(21;22); ETV1-EWS fusion gene in t(7;22).
- STEAP1 mutation associated with good prognosis.

Ewing's sarcoma

- Composed of sheets of uniform small, round cells that are slightly larger than lymphocytes. They have scant cytoplasm, which may appear clear because it is rich in glycogen.
- The presence of Homer-Wright rosettes (where the tumor cells are arranged in a circle about a central fibrillary space) is indicative of neural differentiation.
- There is generally little stroma, although the tumor contains fibrous septae. Necrosis may be prominent.
- Few mitotic figures in relation to the dense cellularity of the tumor.
- Nearly all patients have micro-metastases

Ewing's sarcoma

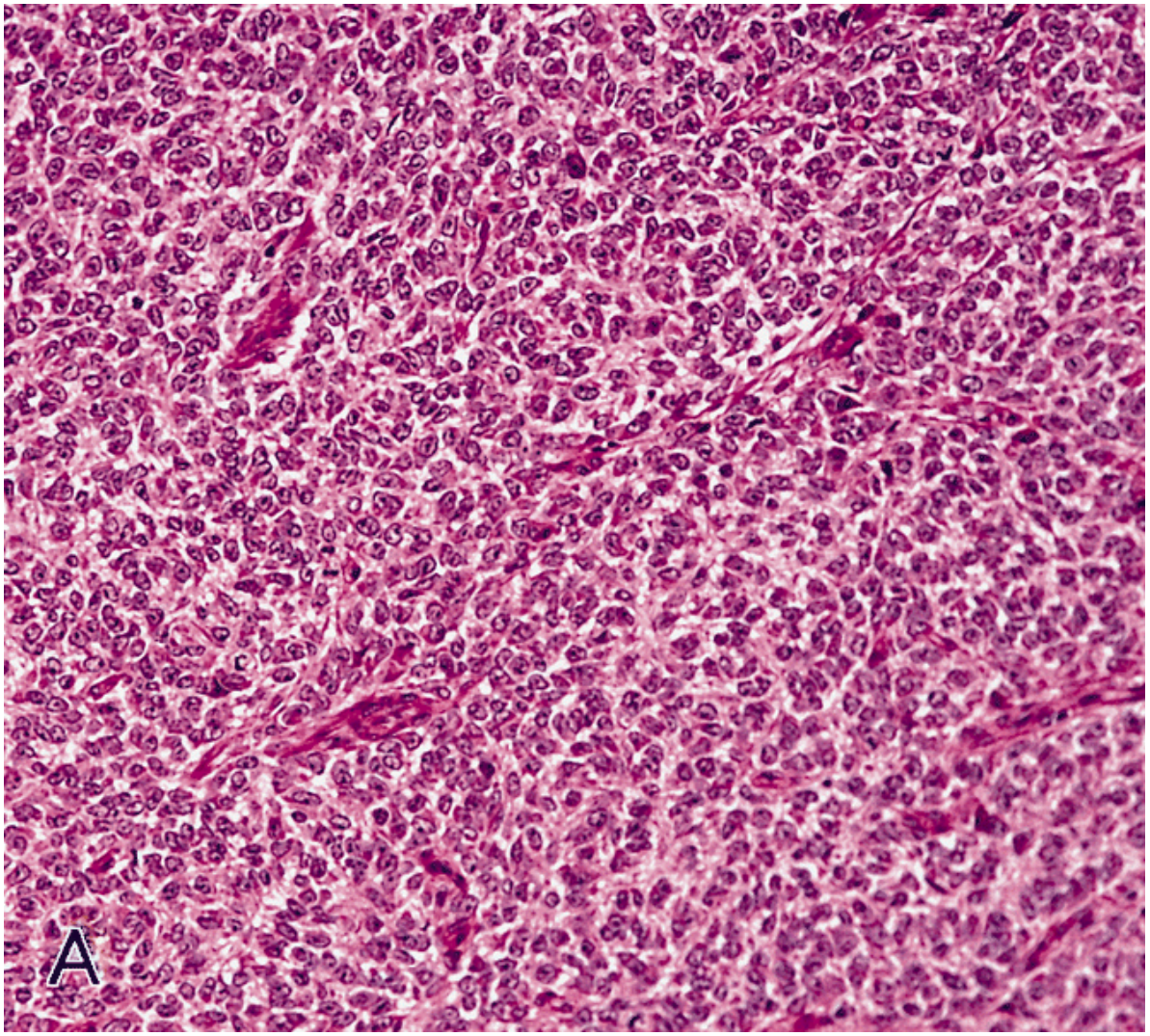


Fig. 11-47A Kempson, Richard L., Fletcher, Christophr DM, Evans, Harry L, Hendrickson, Michael R, and Sibley, Richard K, Tumors of the Soft Tissues, Fascicle 30, Atlas of Tumor Pathology. 3rd Series. Armed Forces Institute of Pathology, Washington, DC (2001).

Tenosynovial giant cell tumor

- It usually arises in patients in their twenties to forties.
- Monoarticular
- 80% of cases involve the knee.
- Hip, ankle and calcaneocuboid may also be involved.
- Once known as giant cell tumor of tendon sheath (localized) and as pigmented villonodular synovitis (diffuse)
- Nodular proliferation of synovial tissue
- Hyperplastic

Tenosynovial giant cell tumor

- Red-brown
- Composed of uniform oval mononuclear cells (CD68+) that have indistinct cell membranes and appear to grow in a syncytium.
- Mitoses are frequent.
- Scattered within this background are numerous giant cells (CD68+) believed to form via fusion of the mononuclear cells.
- RANKL present on cells
- Necrosis, hemorrhage, hemosiderin deposition, and reactive bone formation are common secondary features.

Tenosynovial giant cell tumors

- Recur
- Localized tumors are well circumscribed.
- May be locally invasive with bone cyst formation and loss of bone and cartilage
- In nodular tumors, the cells grow in a solid aggregate that may be attached to the synovium by a pedicle.
- In diffuse tumors the normally smooth joint synovium is converted into a tangled mat by red-brown folds, finger-like projections, and nodules.
- In the diffuse variant they spread along the surface and infiltrate the sub-synovial issue.

Tenosynovial giant cell tumors

- t(1;2)(p13;q37), resulting in fusion of the type VI collagen α-3 promoter upstream of the monocyte colony-stimulating factor (M-CSF) gene.
- Stimulates proliferation of macrophages

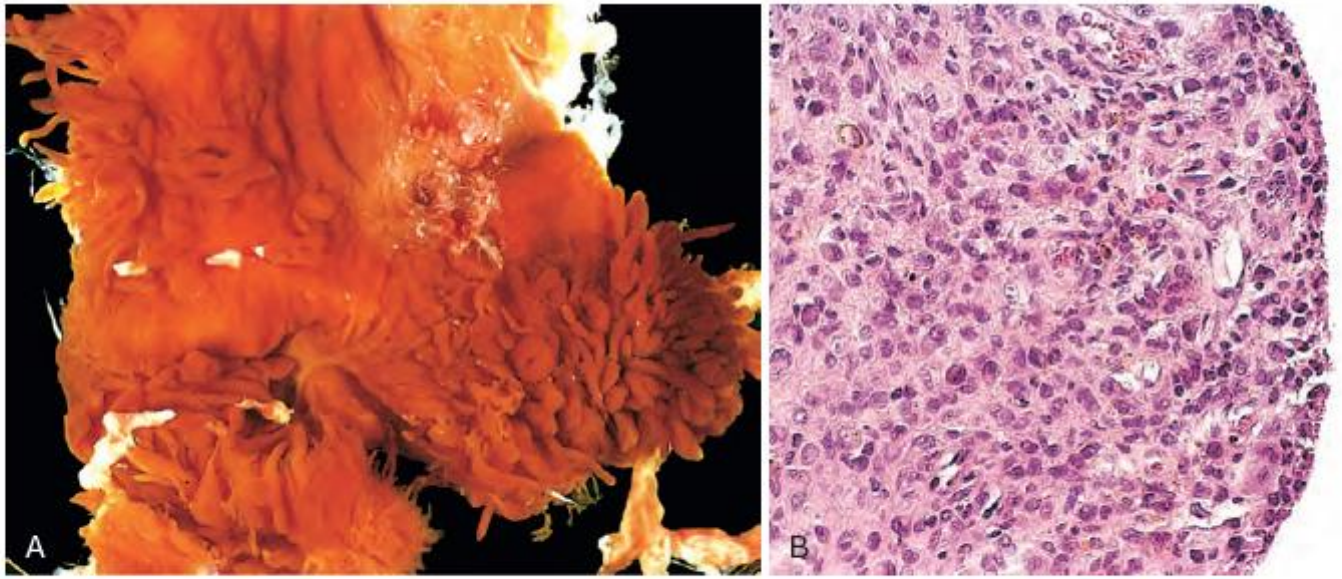


Figure 26-49 Tenosynovial giant cell tumor, diffuse type. **A,** Excised synovium with fronds and nodules typical of pigmented villonodular synovitis *(arrow)*. **B,** Sheets of proliferating cells in tenosynovial giant cell tumor bulging the synovial lining.

Tenosynovial tumor

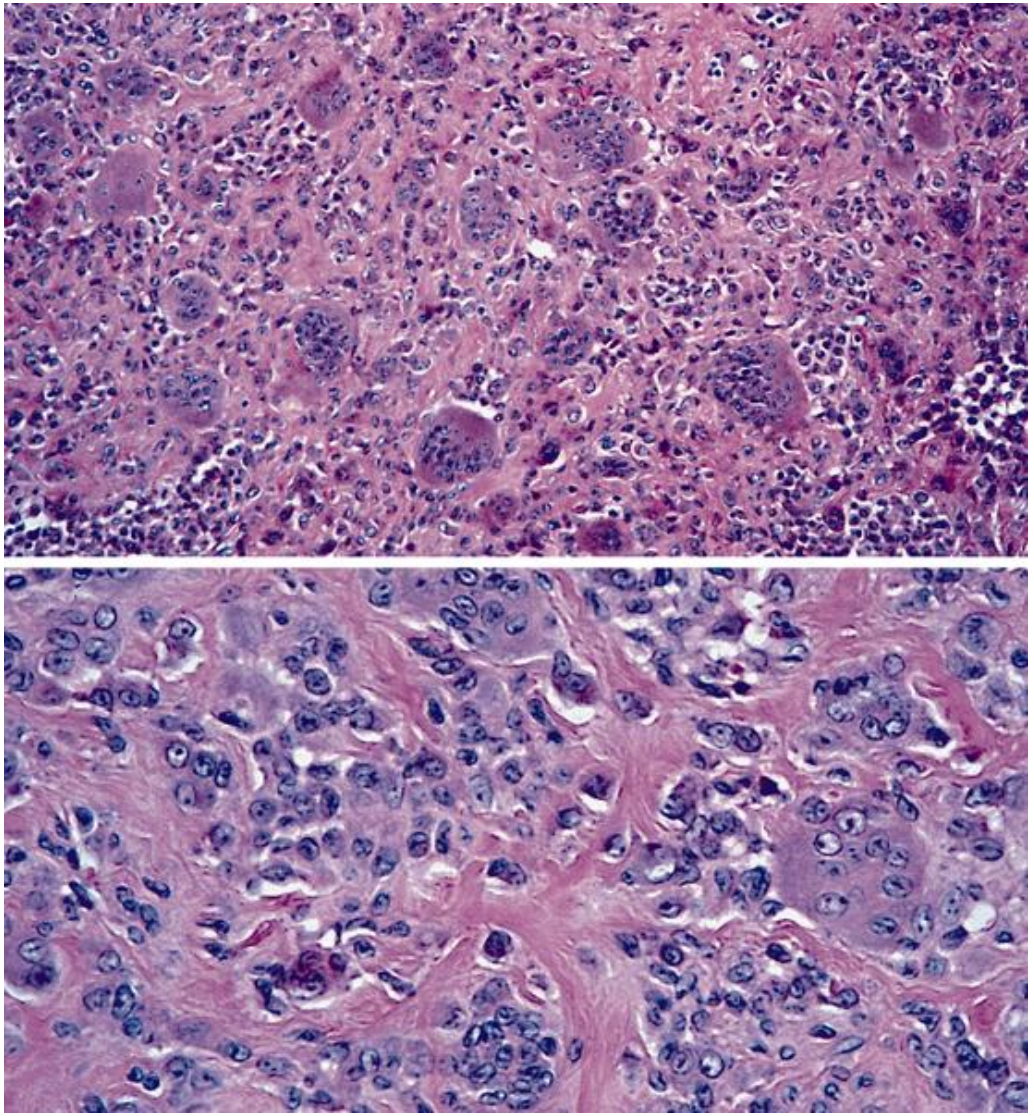


Fig. 9-3 Kempson, Richard L., Fletcher, Christophr DM, Evans, Harry L, Hendrickson, Michael R, and Sibley, Richard K, Tumors of the Soft Tissues, Fascicle 30, Atlas of Tumor Pathology. 3rd Series. Armed Forces Institute of Pathology, Washington, DC (2001).

Synovial sarcoma

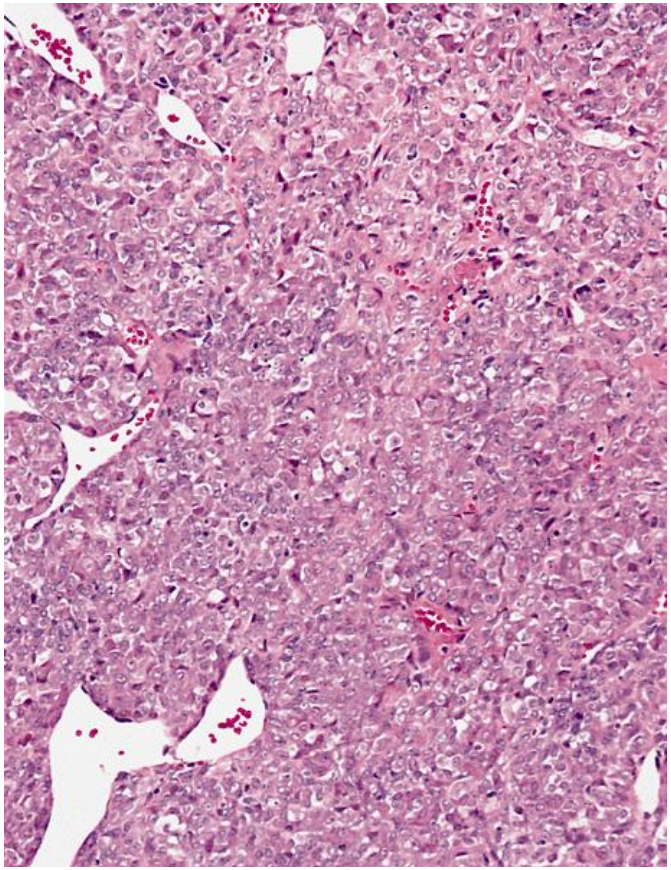
- 20-40 years of age
- 60-70% involve the deep tissues of the lower extremity about the knee and thigh
- Fewer than 10% are intra-articular.
- Myogenic origin.
- t(X;18)(p11;q11) with SYT-SSX fusion gene
- Monophasic (usually spindle cells) or biphasic (spindle and epithelial cells).

Synovial sarcoma

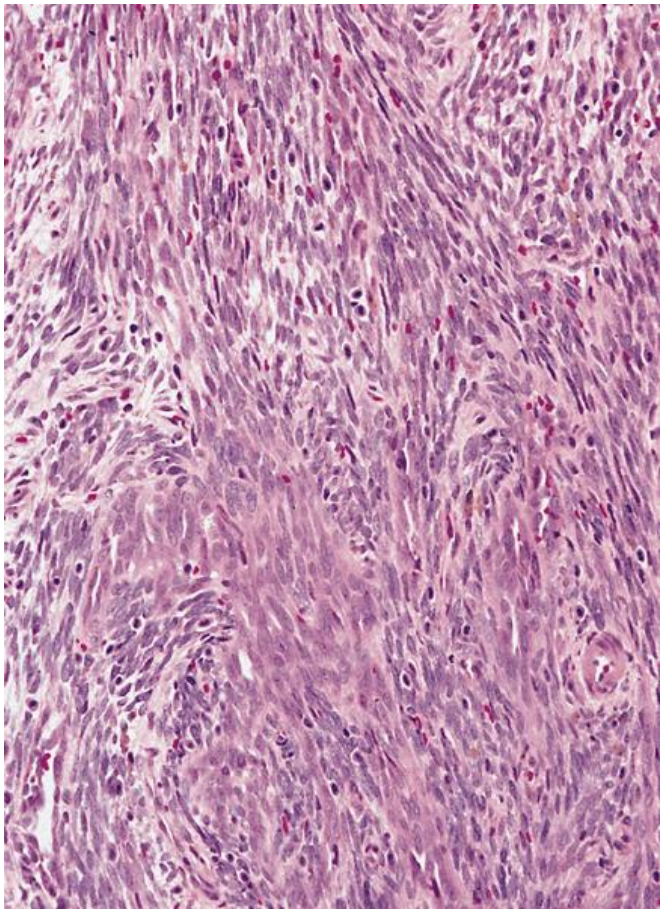
- Spindle cells are arranged in densely cellular fascicles (that may surround epithelial cells in biphasic tumors).
- Epithelial cells are cuboidal to columnar and form glands or grow in solid cords or aggregates.
- Lung metastases

Synovial sarcoma

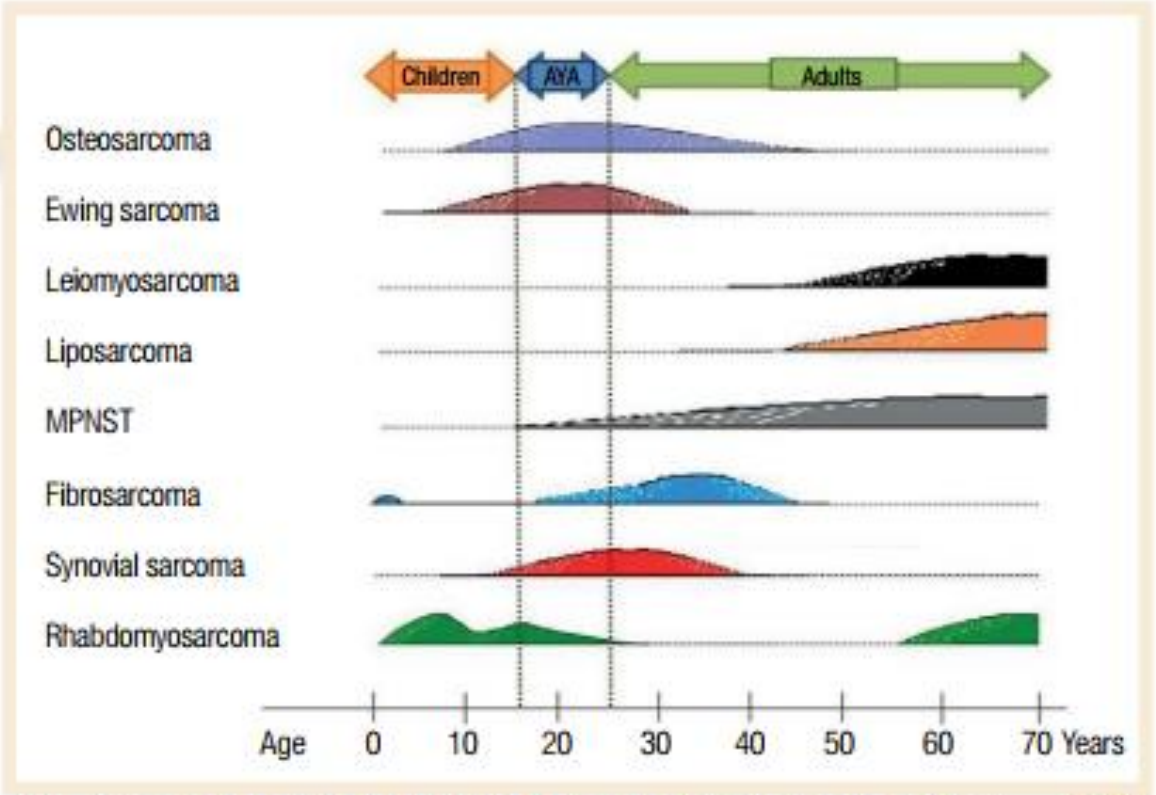
Monophasic



Biphasic



Figs. 11-88 and 11-78 Kempson, Richard L., Fletcher, Christophr DM, Evans, Harry L, Hendrickson, Michael R, and Sibley, Richard K, Tumors of the Soft Tissues, Fascicle 30, Atlas of Tumor Pathology. 3rd Series. Armed Forces Institute of Pathology, Washington, DC (2001).



AYA, adolescent and young adult; MPNST, malignant peripheral nerve sheath tumour.

Fig. 9.7

EpSSG classification (RMS 2005)						
Risk	**Groups**	**Histology**	**Surgery**	**Site**	**Nodes**	**Size and age**
LR	A	ERMS	I (R0)	Any	N0	Favourable
SR	B	ERMS	I (R0)	Any	N0	Unfavourable
	C	ERMS	II/III (R1/R2)	Favourable	N0	Any
	D	ERMS	II/III (R1/R2)	Unfavourable	N0	Favourable
HR	E	ERMS	II/III (R1/R2)	Unfavourable	N0	Unfavourable
	F	ERMS	II/III (R1/R2)	Any	N1	Any
	G	ARMS	I/II/III (R0/R1/R2)	Any	N0	Any
VHR	H	ARMS	II/III (R1/R2)	Any	N1	Any

Unfavourable site: parameningeal, extremities, genitourinary bladder-prostate; others.
Unfavourable size and age: ≥5 cm or 10 years or both

ARMS, alveolar RMS; EpSSG, European paediatric Soft tissue sarcoma Study Group; ERMS, embryonal RMS; HR, high risk; LR, low risk; RMS, rhabdomyosarcoma; SR, standard risk; VHR, very high risk.

Fig. 9.4

Vascular tumors

- Hemangiopericytomas (solitary fibrous tissue tumors) are derived from myofibroblast-like cells (pericytes) that are normally arranged around capillaries and venules.
- Numerous branching capillary channels and sinusoidal spaces enclosed within nests of spindle cells are found on microscopic examination.
- Slow growing.
- Painless.
- Common in lower extremities and in retroperitoneum.
- NAB2-STAT6 gene fusion.

Vascular tumors

- Angiosarcomas vary from anaplastic, plump endothelial cells producing vascular channels to tumors with solid spindle cell appearance but without blood vessels.
- Stain for CD31 or VWF.
- Consider taxanes.

Lymphangiomatosis

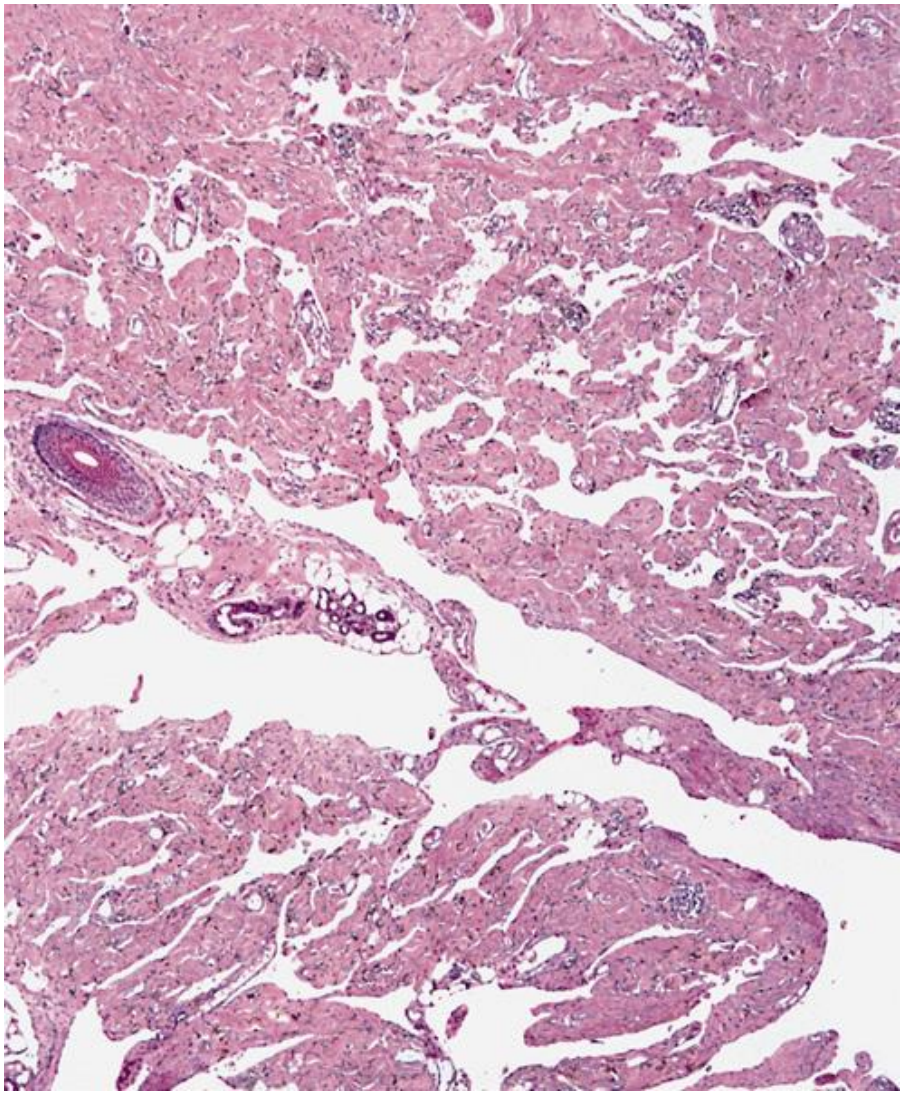


Fig. 7-79 Kempson, Richard L., Fletcher, Christophr DM, Evans, Harry L, Hendrickson, Michael R, and Sibley, Richard K, Tumors of the Soft Tissues, Fascicle 30, Atlas of Tumor Pathology. 3rd Series. Armed Forces Institute of Pathology, Washington, DC (2001).

Glomus tumor

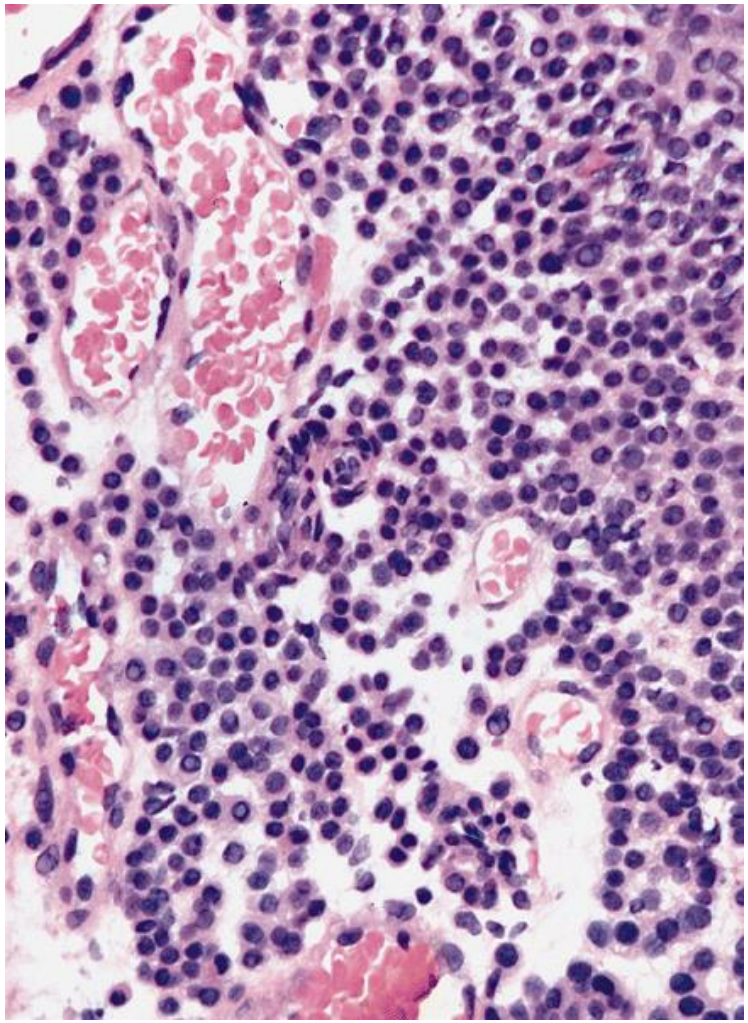
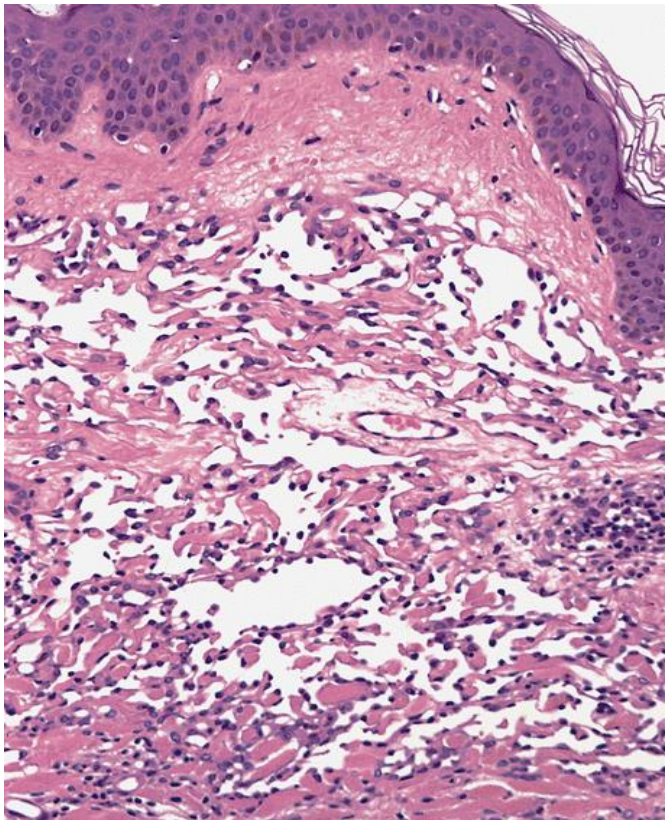


Fig. 8-6R Kempson, Richard L., Fletcher, Christophr DM, Evans, Harry L, Hendrickson, Michael R, and Sibley, Richard K, Tumors of the Soft Tissues, Fascicle 30, Atlas of Tumor Pathology. 3rd Series. Armed Forces Institute of Pathology, Washington, DC (2001).

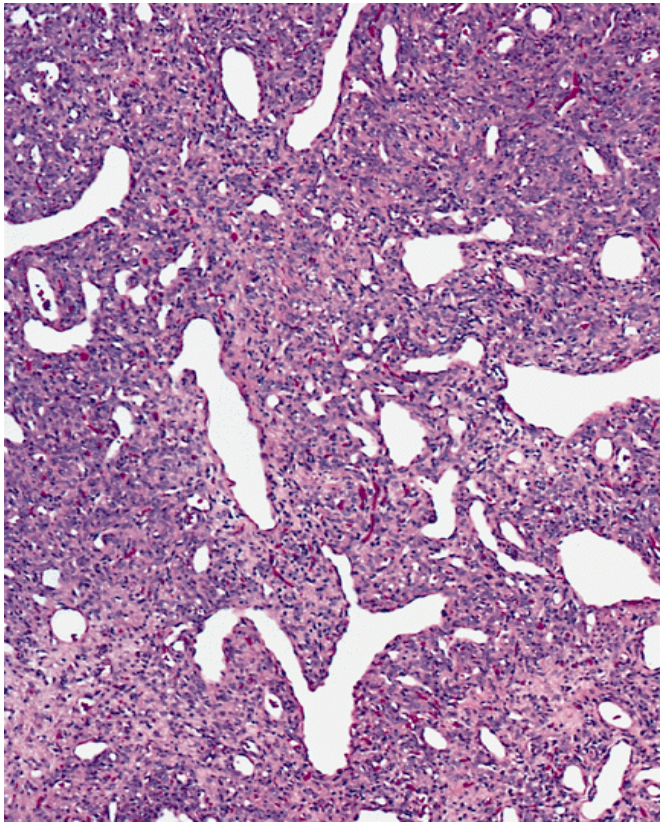
Benign, painful tumor arising from modified smooth muscle cells of the glomus body. Aggregates, nests and masses of glomus cells are associated with branching vascular channels.

Malignant vascular tumors

Angiosarcoma



Hemangiopericytoma



Figs 7-84 and 8-1 Kempson, Richard L., Fletcher, Christophr DM, Evans, Harry L, Hendrickson, Michael R, and Sibley, Richard K, Tumors of the Soft Tissues, Fascicle 30, Atlas of Tumor Pathology. 3rd Series. Armed Forces Institute of Pathology, Washington, DC (2001).

Malignant vascular tumors

Epithelioid hemangioendothelioma

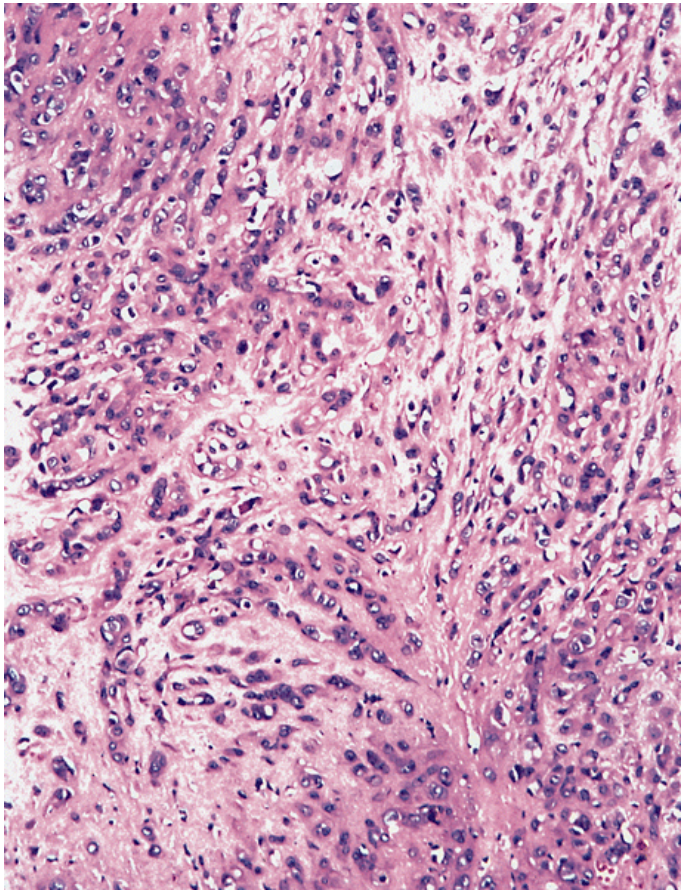


Fig. 7-78 Kempson, Richard L., Fletcher, Christophr DM, Evans, Harry L, Hendrickson, Michael R, and Sibley, Richard K, Tumors of the Soft Tissues, Fascicle 30, Atlas of Tumor Pathology. 3rd Series. Armed Forces Institute of Pathology, Washington, DC (2001).

Immunohistochemistry

- Kaposi's sarcoma, angiosarcoma, hemangioendothelioma are Factor VIII, CD34, and CD31 +.
- Up to 40% of patients present with tumor in the lymph nodes.
- Pericytoma is factor XIII and HLA-DR+.
- 12q13-15.
- Leiomyosarcoma is CD68-.
- However, are desmin, HAF35, and SMA+.
- 1p- and LOH 10 are common.
- Schwannoma is S100, Leu7 (CD57), laminin, and collagen 4 positive.
- Cellular if monosomy 22.

Immunohistochemistry

- Neuroblastoma is S100, NF+.
- 17q21 and 1q21-25 common.
- Paragangioma is S100 and chromogranin +.
- May be NSE-.
- Ewing's sarcoma is CD99 and MK2+.
- t(11;22)(q24;q12) is the EWS/FL11 gene.
- PNET is Leu7 (CD57), HBA71/O13, NF+ but may be NSE-.
- 10q23.
- Upregulates p27, leading to cell cycle arrest.

Immunohistochemistry

- Rhabdomyosarcoma is vimentin, desmin, NSE, HAF35, myoD1+.
- Leu7 (CD57) prominent.
- Alveolar type is tetraploid; +2q or +1q.
- Embryonal type, hyperdiploid. 11p
- Alveolar soft part sarcoma is desmin, myoD1, and sarcomeric actin +. t(1;13) or t(12;13).

Immunohistochemistry

- Extraskeletal chondrosarcoma is Vimentin, Leu7 (CD57), and NSE+.
- t(9;22) seen in myxoid lesions.
- Osteosarcoma is vimentin +.
- May see S100 + if small cell.
- LOH 3q. MDM2 if 17p53, 13q.

Immunohistochemistry

- Clear cell carcinoma is probably melanoma.
- S100 and HMB45+.
- t(12;22) found.
- Epithelioid (synovial) sarcoma
- EMA and keratin +.
- t(x;18)

MRI characteristics

- Weighted: T1 short (time to recovery, time to echo); T2 is long.
- Gradient echo inversion recovery compatible with fat saturation.
- Proton dense lesions have long TR, short TE.
- Fibrous dense have low T1, T2
- Cysts have low T1, bright T2
- Fat is bright T1, gray T2
- Marrow is brighter than muscle on T1
- Free water is iso-intense on T1, bright on T2 (usually this represents tumor)

Tumour type	Translocation	Drug
Gastrointestinal stromal cell tumour	*ETV6-NTRK*	Tropomyosin receptor kinase inhibitors
Dermatofibrosarcoma protuberans	*COL1A1-PDGFB*	Imatinib
Tenosynovial giant cell tumour	*COL6A3-CSF1*	Anti-CSF1
Inflammatory myofibroblastic tumour	*ALK* rearrangement	Crizotinib
Myxoid liposarcoma	*FUS-DDIT3*	Trabectedin
Alveolar rhabdomyosarcoma	*PAX3-FOXO1*	TKIs
Alveolar soft part sarcoma	*ASPSCR1-TFE3*	TKIs

Fig. 6.5

ALK, anaplastic lymphoma kinase; CSF1, colony stimulating factor 1; NTRK, neurotrophic tyrosine receptor kinase; PDGFB, platelet-derived growth factor beta; TKI, tyrosine kinase inhibitor.

Molecular profile	Clinical characteristics
Mutations of the *KIT* gene	80%-85% GISTs
Exon 11	The best response to imatinib; the most common mutation in sporadic GIST and in the GIST family
Exon 9	Limited response to imatinib (a starting dose of imatinib 800 mg is recommended); good response to sunitinib, more common in GISTs originating from the small intestine and the colon
Exon 13 and 17	Clinical responses to imatinib possible but these are very rare mutations
PDGFRA gene mutations	5%-8% of GIST
Exon 12	Possible clinical response to imatinib
Exon 14	Possible clinical response to imatinib, very rare mutation
Wild-type – or no *KIT* or *PDGFRA* mutations	Poor response to imatinib, better response to sunitinib; 12%-15% of cases; in paediatric GISTs, related to NF1, SDHB or Carney triad, possible *BRAF* mutations

GIST, gastrointestinal stromal tumour; NF1, neurofibromatosis type 1; *PDGFRA*, platelet-derived growth factor receptor alpha.

Fig. 7.7

Other translocations

- Translocations involving NTRK1-3 genes are observed in infantile fibrosarcoma (IFS) and adult sarcomas (e.g. GIST, undifferentiated pleomorphic sarcoma [UPS], IMT). They are mutually exclusive from other translocations.
- The NTRK1-3 genes have variable translocation partners. These translocations are found in 1% of all sarcomas, more frequently in specific rare histotypes (IFS, IMT, wild-type [WT] GIST).

Genetic characteristics and fusion proteins

- Alveolar rhabdomyosarcoma
  - t(2;13)(q35;q14) PAX3-FOXO1 fusion protein
  - t(1;13)(p36;q14) PAX7-FOXO1
  - t(X;2)(q13;q35) PAX3-AFX
- Alveolar soft part sarcoma
  - del(17)t(X;17)(p11;q25) ASPSCR1-TFE3 fusion protein
- Angiomatoid fibrous histiocytoma
  - t(12;22)(q13;q12) EWSR1-AFT1 fusion protein
  - t(2;22)(q32;q12) EWSR1-CREB1
  - t(12;16)(q13;q11) FUS-AFT1

Genetic characteristics and fusion proteins

- Dermatofibrosarcoma protuberans

  t(17;22)(q21;q13) and ring chromosomes

  COL1A1-PDGF8 fusion protein

  Enhanced MET signaling

- Desmoid

  Trisomy 8 or 20 or del 5q

  somatic CTNNB1 mutation

  APC mutation in deep tumors

- Desmoplastic small round cell tumor

  t(11;22)(p13;q12) EWSR1-WT1 fusion protein

Genetic characteristics and fusion proteins

- Elastofibroma

  1q abnormalities
- Embryonal rhabdomyosarcoma

  LOH 11p15
- Endometrial stromal sarcoma

  t(7;17)(p15;q11) JAZF1-JJAZ1(SUZ12) fusion protein

  t(6;7)(p21;p15) JAZF1-PHF1

  t(6;10)(p21;p11) EPC-PHF1
- Epithelioid Hemangioendothelioma

  t(1;3)(p36;q25) WWTR1-CAMTA1 fusion protein

Genetic characteristics and fusion proteins

- Epithelioid sarcoma

  22q11.2 alteration

  biallelic deactivation of hsNFS/INSI

- Ewing's sarcoma or PNET

  t(11;22)(q24;q12) EWSR1-FLI1 fusion protein

  t(21:22)(q22;q12) EWSR1-ERG

  t(7;22)(p22;q12) EWSR1-ETV1

  t(2;22)(q33;q12) EWSR1-FEV

  t(17;22)(q12;q12) EWSR1-E1AF

  inv(22)(q21;q12) EWSR1-ZSG

  t(16;21)9p11;q22) FUS-ERG

Genetic characteristics and fusion proteins

- Extrarenal malignant rhabdoid tumor

  22q11.22 alteration

  biallelic deactivation of hsNFS/INSI

- Extraskeletal myxoid chondrosarcoma

  t(9;22)(q22;q12) CHN-EWS

  t(9;17)(q22;q11.2) CHN-RBP56

  t(9;15)(q22;q21) CHN-TCF12

  t(3;9)(q11;q22) TGF-NR4A3

Genetic characteristics and fusion proteins

- Inflammatory myofibroblastic tumors
- 50% have ALK, NTRK, or ROS1 mutations
- Durable responses only if have said mutations
- Tenosynovial tumor
- t(1p13;2q35-37) CSF1-COL6A3

Genetic characteristics and fusion proteins

- Inflammatory myofibroblastoma

2p23 translocations	ALK fusion proteins
t(1;2)(q22;p23)	TMP3-ALK
t(2;19)(p23;p13)	TPM4-ALK
t(2;17)(p23;q23)	CTLC-ALK
t(2;2)(p23;q13)	RANBP2-ALK
t(2;11)(p23;p15)	CARS-ALK
inv(2)(p23;q35)	ATIC-ALK

- Leiomyosarcoma

CALAG1 fusions

Genetic characteristics and fusion proteins

- Lipoblastoma

  8q12 rearrangement CALAG1 fusions
- Low grade fibromyxoid sarcoma

  t(7;16)(q33;p11) FUS-CREB3L2 fusion protein

  t(11;16)(p11;p11) FUS-CREB3L1
- Malignant peripheral nerve sheath tumor

  del17q22 NF1
- Mesenchymal chondrosarcoma

  t(8;8)(q13;q21) HEY1-NCOA2 fusion protein

Genetic characteristics and fusion proteins

- Myxoid round cell liposarcoma

  t(12;16)(q13;p11) FUS-DD1T3 (TLS-CHOP) fusion protein

  t(12;22)(q13;q12) EWSR1-DD1T3 (CHOP)

Genetic characteristics and fusion proteins

- Myxoinflammatory fibrobastic sarcoma or hemosiderotic fibrolipomatous tumor

  t(1;10)(p22;q24) TGFBR3-MGEA5 fusion protein

  3p11-12 (ring chromosome)

  VGLL3, CHMP2B amplifications

- Nasopharyngeal angiofibroma

  gains 1p, 7q, 10q, 12q, 16p, 166q, 17q, 19p, 20q, 22q

  activating CTNNB1 mutations

Genetic characteristics and fusion proteins

- Osteosarcoma, low grade

  12q14-15 (ring chromosomes, giant marker chromosomes)

  CDK4, MDM2, HMGA2, GLI,
  SAS amplifications

Genetic characteristics and fusion proteins

- Pulmonary myxoid sarcoma

  t(2;22)(q34;q12) EWSR1-CREB1 fusion protein
- Radiation induced angiosarcoma

  8q24 MYC amplification
- Sclerosing epithelioid fibrosarcoma

  t(7;16)(p22;q24) FUS-CREB3L2 fusion protein

Genetic characteristics and fusion proteins

- Soft tissue myoepithelial tumor

  translocation 22q13 EWSR1 fusion proteins

  t(6;22)(p21;q12) EWSR1-POU5F1

  t(19;22)(q13;q12) EWSR1-ZNF444

  t(1;22)(q23;q12) EWSR1-PBX1

- Synovial sarcoma

  t(X;18)(p11;q11) SSX18 fusion products with SSX1, 2, or 4

- Undifferentiated small round blue cell tumor

  t(4;19)(q35;q13) CIC-DUX4 fusion protein

  t(10;19)(q26;q13)

Genetic characteristics and fusion proteins of benign tumors

- Aneurysmal bone cyst

7p13 rearrangements	USP6 fusion proteins
t(16;17)(q22;p13)	CDH11-USP6
t(1;17)(p34.3;p13)	THRAP3-USP6
t(3;17)(q21;p13)	CNBP-USP6
t(9;17)(q22;p13)	OMD-USP6
t(17;17)(q21;p13)	COL1A1-USP6

- Nodular Fasciitis

  t(17;22)(p13;q13) MYH9-USP6

Treatment strategy

- En bloc, macro- and microscopically complete surgical excision of the gross tumor encompassing the biopsy scar is the treatment of choice.
- Amputation is seldom used as limb sparing surgery with post-operative radiation yields similar results.
- Neoadjuvant chemotherapy may be employed to reduce tumor bulk to permit resection without amputation.
- Isolated limb perfusion with hyperthermia and tumor necrosis factor is another approach that may permit tumor resection without amputation.

Treatment strategy

- Following debulking:
- Dedifferentiated liposarcoma responds to ifosfamide.
- Trabectedin of promise in liposarcoma.
- Imanitib of use in treatment of dermatofibrosarcoma protuberans
- Gemcitabine and doxorubicin, dacarbazine (and temozolomide) preferred chemotherapy regimens for leiomyosarcoma.
- Trabectedin of promise as well.

Treatment strategy

- Rhabdomyosarcoma
- Low risk patients are those with embyronal tumors or orbital tumors.
- Those younger than 10 years of age with embryonal rhabdomyosarcoma and pulmonary metastases are not a high risk group.
- Resection of the primary tumor (except for orbital tumors) is followed by irradiation.
- Vincristine and dactinomycin chemotherapy is employed.
- 90-95% 5-year survival.

Treatment strategy

- Intermediate risk patients are treated with radiation and vincristine, dactinomycin, cyclophosphamide chemotherapy.
- 70-80% 5- year survival.
- High risk disease is defined as:
- >5cm
- High grade
- Deep soft tissue sarcomas
- High risk patients have metastatic disease.
- 20% 5-year survival following radiation and chemotherapy.

Treatment strategy

- High grade disease regardless of location should be considered for neo-adjuvant dose-intensive anthracycline and isofosfamide combination chemotherapy.
- Trabectedin is employed in all translocation related sarcomas
- Excluded are those patients unable to tolerate an aggressive regimen as well as those with alveolar soft-part sarcoma, clear cell sarcoma, epithelioid sarcoma, hemangiopericytoma, extraskeletal myxoid chondrosarcoma (resistant to chemotherapy generally).

Treatment strategy

- Surgical margins important.
- If >1mm, local recurrence 14% and death 16% at 5 years;
- if <1mm, local recurrence 38% and death 29% at 5 years
- Papzopanib (targets VEGF), brivanib (targets VEGF and FGF) use associated with improved survival.

Ewing’s sarcoma

- Vincristine, doxorubicin, ifosfamide induction chemotherapy followed by etoposide and cyclophosphamide with peripheral blood stem cell harvest.
- Surgical resection follows.
- Maintenance chemotherapy involves the same drugs and is followed by high dose busulfan and melphalan and return of the stem cells.

Ewing’s sarcoma

- Radiation therapy is reserved for patients who do not have a surgical option that preserves function or patients with inadequate margins of excision of the primary tumor.
- Even if pulmonary metastases disappear with chemotherapy, whole-lung radiation is provided.

Treatment strategy

- Tenosynovial giant cell tumors respond to tyrosine kinase inhibitors
- Synovial sarcoma is treated with ifosfamide. Synovial sarcoma may metastasize more than 5 years after presentation.
- Angiosarcoma responds to taxanes, gemcitabine
- Perivascular epithelioid cell tumors respond to mTOR inhibitors

Frequencies of *KIT* and *PDGFRA* mutations in GIST and sensitivity (S) or resistance (R) to tyrosine kinase inhibitors imatinib and sunitinib

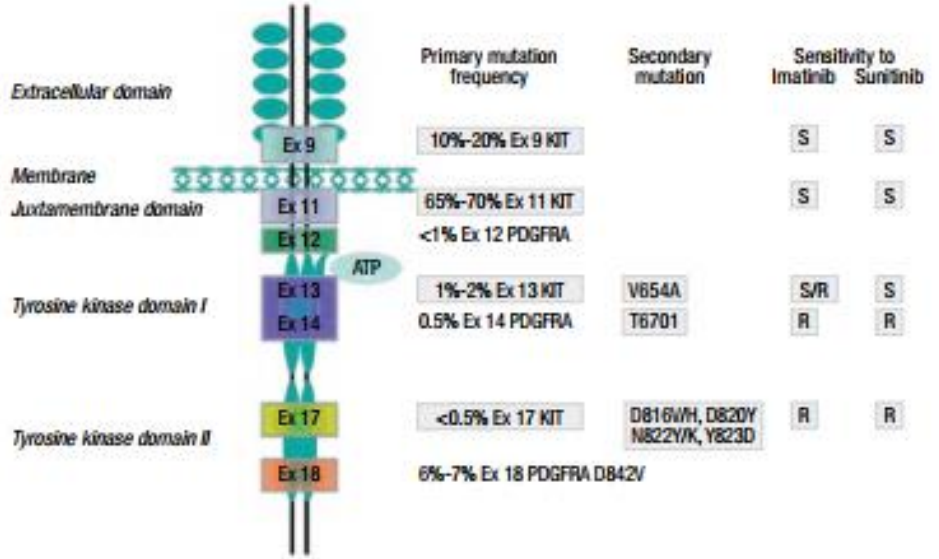


Fig. 6.6

GIST, gastrointestinal stromal tumour; PDGFRA, platelet-derived growth factor receptor alpha.

Response rates of different STS types for doxorubicin vs ifosfamide-containing regimen

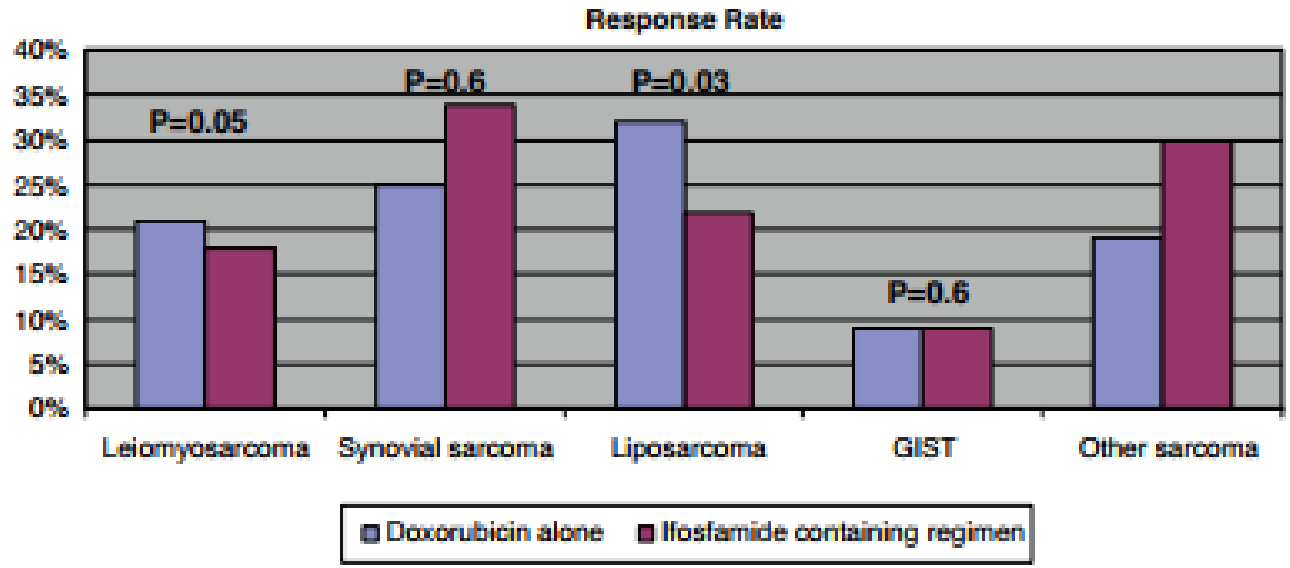


Fig. 3.7

GIST, gastrointestinal stromal tumour; STS, soft tissue sarcoma.

Tumour parameters		Risk for progressive disease*(%), based on site of origin			
Mitotic rate (HPF)	Size	Stomach	Jejunum/ ileum	Duodenum	Rectum
≤5/50	≤2 cm	None (0%)	None (0%)	None (0%)	None (0%)
	>2 cm, ≤5 cm	Very low (1.9%)	Low (4.3%)	Low (8.3%)	Low (8.5%)
	>5 cm, ≤10 cm	Low (3.6%)	Moderate (24%)	Insufficient data	Insufficient data
	>10 cm	Moderate (10%)	High (52%)	High (34%)	High (57%)
>5/50	≤2 cm	None[1]	High[1]	Insufficient data	High (54%)
	>2 cm, ≤5 cm	Moderate (16%)	High (73%)	High (50%)	High (52%)
	>5 cm, ≤10 cm	High (55%)	High (85%)	Insufficient data	Insufficient data
	>10 cm	High (86%)	High (90%)	High (86%)	High (71%)

Fig. 7.2

*Defined as metastasis or tumour-related death.

[1]Denotes small number of cases.

Data are based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal and 111 rectal GISTs.

GIST, gastrointestinal stromal tumour; HPF, high-power field.