

Skeletal Muscle Tumors

Rhabdomyoma · Rhabdomyosarcoma

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Learning objectives

- Distinguish the rare benign rhabdomyoma from rhabdomyosarcoma.
- Recognize four rhabdomyosarcoma subtypes by age, morphology, and molecular drivers.
- Connect differentiation, anatomic site, and histologic pattern with diagnosis and behavior.

Skeletal muscle neoplasia is predominantly malignant

- A contrast with most other mesenchymal tissue lineages.
- Most skeletal muscle neoplasms are malignant, represented by rhabdomyosarcoma.
- Rhabdomyoma is the uncommon benign counterpart.

Uncommon benign

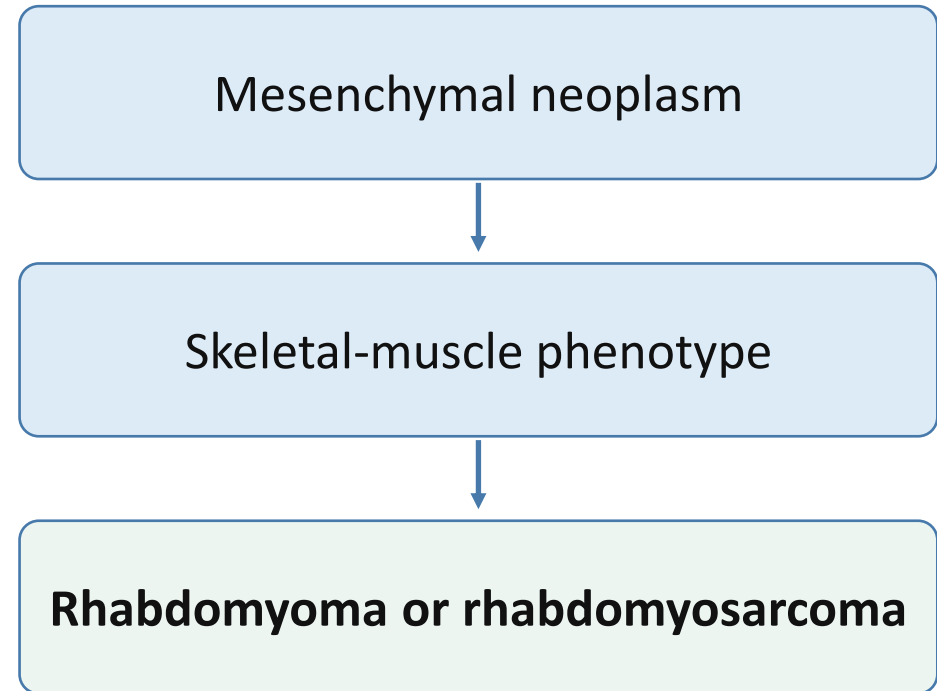
Rhabdomyoma
Benign designation

Predominant malignant

Rhabdomyosarcoma
Malignant skeletal-muscle differentiation

Place these tumors within soft-tissue pathology

- Soft-tissue tumors are mesenchymal neoplasms, not necessarily derived from a fully mature tissue cell.
- Skeletal muscle differentiation is a phenotype recognized in the tumor.
- Site of origin and line of differentiation must be considered separately.



Rhabdomyoma is the benign entity

- Rhabdomyoma is the benign skeletal-muscle-type neoplasm.
- The Robbins overview locates rhabdomyomas in the heart and in soft tissues.
- Its existence does not negate the predominance of malignancy in this category.

Skeletal-muscle differentiation

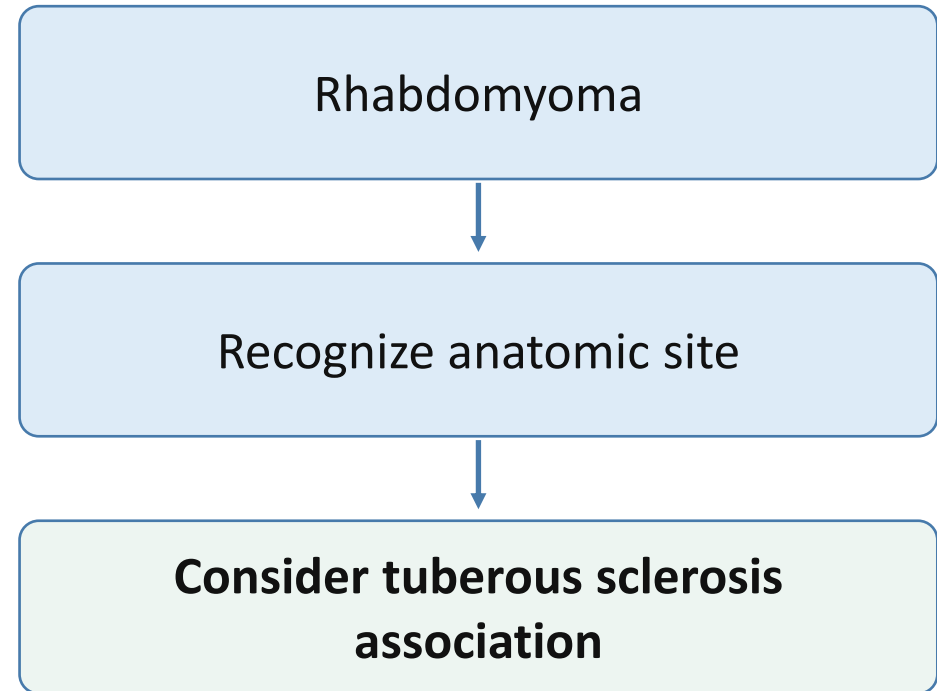


Simplified myogenic silhouette

Schematic — not a pathologic specimen

Rhabdomyoma and tuberous sclerosis

- A frequent association between rhabdomyoma and tuberous sclerosis.
- The association is especially relevant when interpreting cardiac rhabdomyomas.
- Do not assume that every anatomically distinct rhabdomyoma has the same syndromic association.



Rhabdomyoma occurs at distinct anatomic sites

- Cardiac location illustrates the association with a genetic syndrome.
- Soft-tissue lesions establish that benign rhabdomyomatous differentiation is not heart-restricted.
- Anatomic setting is essential when communicating a precise diagnosis.

Cardiac

Benign rhabdomyoma
Syndromic setting may be relevant

Soft tissue

Benign rhabdomyoma
Anatomic context remains essential

Benign versus malignant skeletal-muscle tumors

Feature	Rhabdomyoma	Rhabdomyosarcoma
Behavior	Benign	Malignant, aggressive
Frequency	Uncommon	Predominant category
Sites	Heart or soft tissues	Head and neck; genitourinary; other soft tissues

Rhabdomyosarcoma: Defining concept

- Malignant mesenchymal tumor exhibiting skeletal-muscle differentiation.
- It is not synonymous with a malignancy arising inside pre-existing skeletal muscle.
- Diagnosis integrates pathologic morphology with evidence of rhabdomyoblastic differentiation.

Skeletal-muscle differentiation

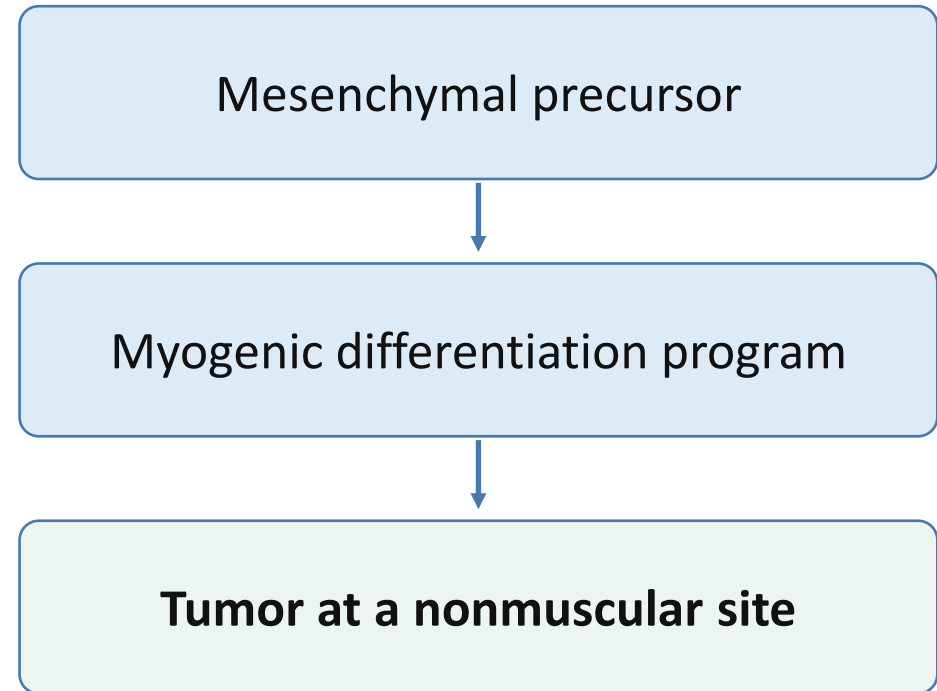


Simplified myogenic silhouette

Schematic — not a pathologic specimen

Differentiation describes a phenotype, not a postcode

- Pediatric tumors often occur at sites containing little normal skeletal muscle.
- Examples include sinuses, head and neck, and the genitourinary tract.
- This supports the model of an undifferentiated mesenchymal precursor acquiring myogenic identity.



Four recognized rhabdomyosarcoma subtypes

- Embryonal, alveolar, pleomorphic, and spindle cell/sclerosing types are described.
- Each subtype has characteristic clinical and morphologic associations.
- Molecular pathogenesis is heterogeneous across these groups.

Embryonal

Primitive cells;
Myxoid stroma

Alveolar

Septa; Central
dycohesion

Pleomorphic

Bizarre eosinophilic
cells

Spindle/sclerosing

Fascicles; Storiform
architecture

Subtype proportions

- Embryonal rhabdomyosarcoma accounts for 50% in the stated overview.
- Alveolar and pleomorphic types each account for 20%.
- Spindle cell/sclerosing type accounts for 10%.

Reported subtype distribution



- Embryonal: 50%
- Alveolar: 20%
- Pleomorphic: 20%
- Spindle/sclerosing: 10%

Age of onset helps contextualize the subtype

Subtype	Age pattern	Interpretive implication
Embryonal	Usually under 20 years	Pediatric differential
Alveolar	Usually under 20 years	Pediatric differential
Pleomorphic	Adults	Adult sarcoma work-up
Spindle/sclerosing	All ages	Age alone is insufficient

Childhood rhabdomyosarcoma is a major soft-tissue malignancy

- Embryonal and alveolar rhabdomyosarcoma as common pediatric soft-tissue sarcomas.
- Presentation is usually before 20 years of age.
- Subtype recognition is more informative than using a single undifferentiated label.

Pediatric emphasis

Embryonal / alveolar
Classically under 20 years

Adult emphasis

Pleomorphic
Most characteristic in adults

Frequent pediatric anatomic presentations

- Sinuses are a described site of pediatric rhabdomyosarcoma.
- Other head-and-neck sites are frequent.
- The genitourinary tract is another characteristic location.

Sinuses

Head and neck

Genitourinary tract

Tumors need not arise in mature skeletal muscle

- The sinonasal tract has relatively little native skeletal muscle.
- Nevertheless, rhabdomyosarcoma can arise there.
- Interpret lineage as differentiation acquired by a malignant mesenchymal cell, not simply tissue of origin.

Low native skeletal-muscle content



A myogenic sarcoma appears



Cell-of-origin $\neq$ mature myofiber

Subtype classification reflects distinct biology

- Clinical age and location differ by subtype.
- Architecture and cytology differ by subtype.
- Underlying recurrent fusions or other driver alterations also differ.

Clinical setting

Age and location

Morphology

Growth pattern and cytology

Genetics

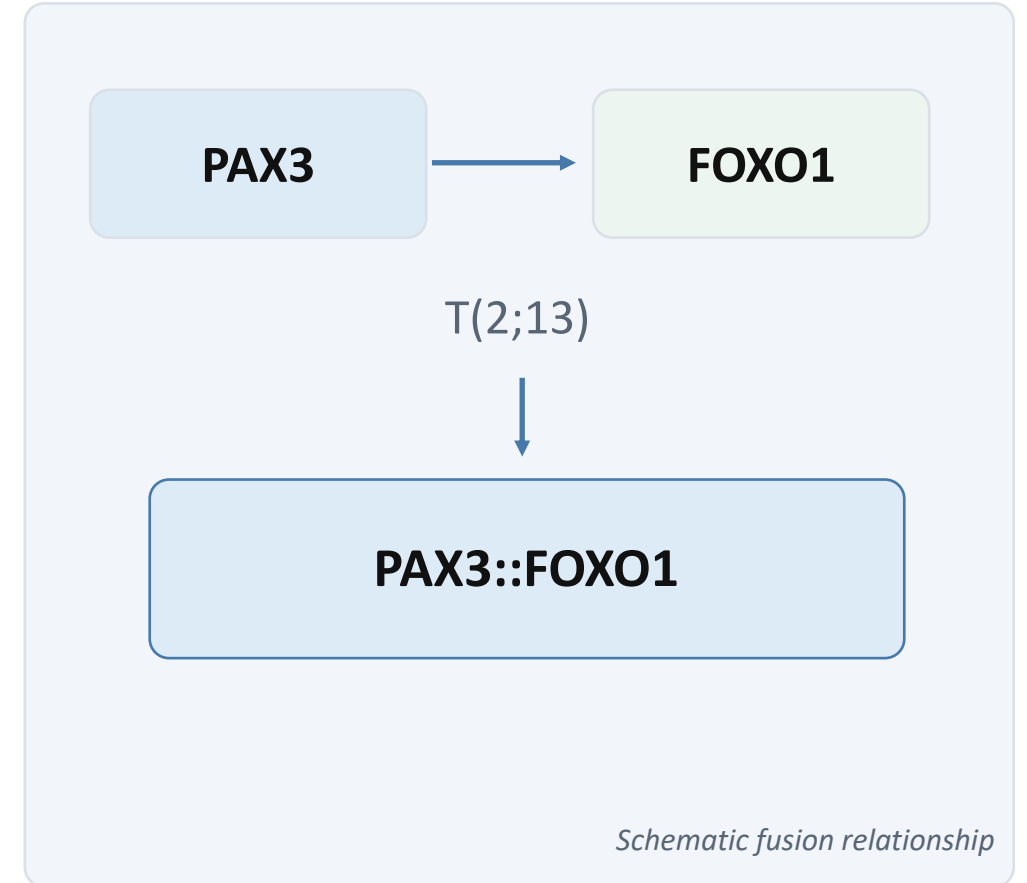
Fusion or other driver alterations

Molecular pathways vary across the four groups

Subtype	Reported alteration	Source-qualified frequency
Alveolar	PAX3/7::FOXO1 fusion	Frequent
Embryonal	RAS-pathway activation	Frequent
Spindle/sclerosing	MYOD1 mutation	Subset
Pleomorphic	Multiple diverse aberrations	Heterogeneous

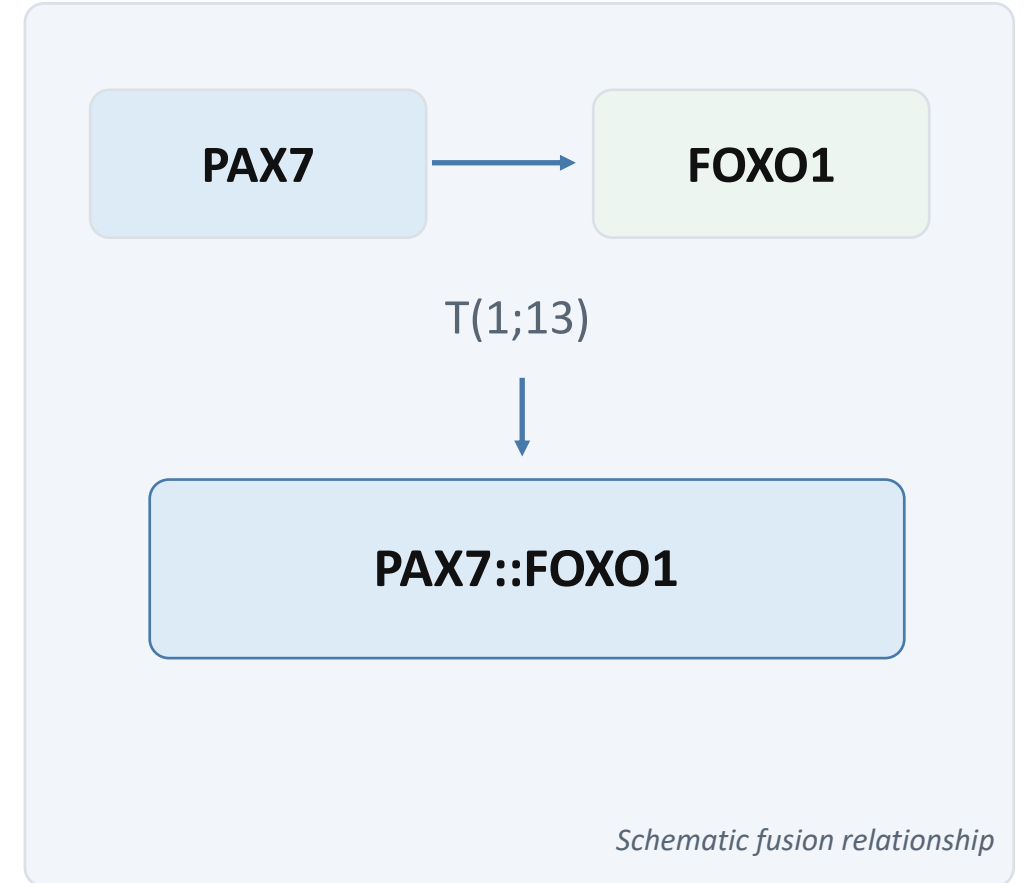
Alveolar RMS: PAX3::FOXO1 fusion

- The t(2;13) translocation can juxtapose PAX3 and FOXO1.
- PAX3 is a transcription factor involved in initiation of skeletal-muscle differentiation.
- The chimeric fusion product dysregulates the differentiation program.



Alveolar RMS: PAX7::FOXO1 fusion

- A second recurrent fusion pairs PAX7 with FOXO1.
- This to t(1;13).
- These fusion types are alternatives within the alveolar molecular spectrum.

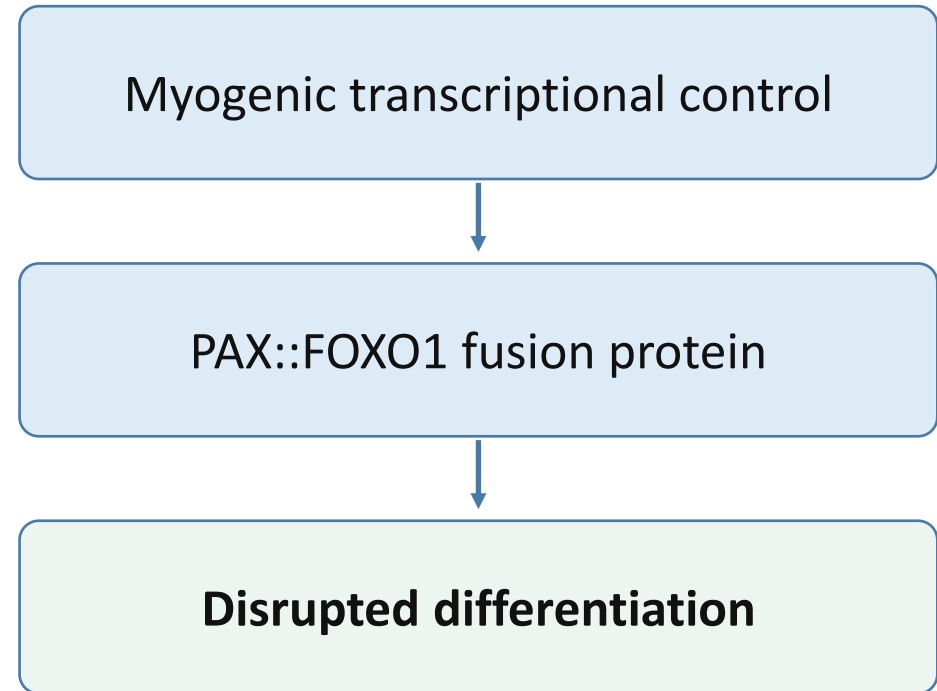


Translocations and fusion partners must match

Rearrangement	PAX partner	Fusion gene
t(2;13)	PAX3	PAX3::FOXO1
t(1;13)	PAX7	PAX7::FOXO1

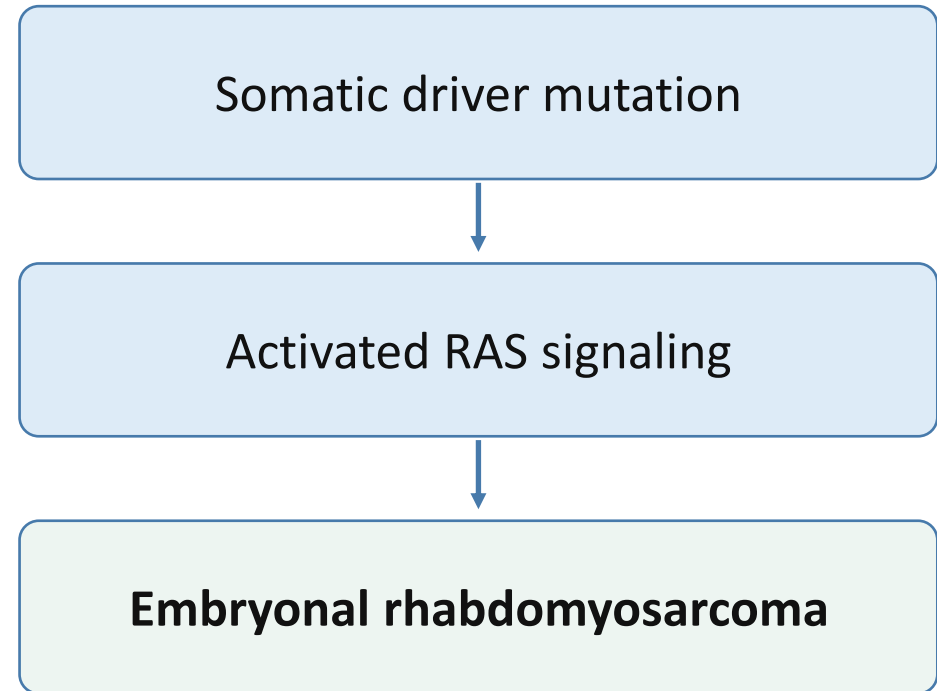
Fusion proteins disrupt differentiation

- Normal myogenic transcription factors help establish a differentiation program.
- A PAX::FOXO1 chimera is associated with interference in that program.
- The conceptual result is malignant proliferation without normal terminal maturation.



Embryonal RMS: Frequent RAS-pathway activation

- Embryonal tumors frequently contain acquired driver mutations.
- Those alterations activate the RAS signaling pathway.
- This differs mechanistically from the recurrent PAX::FOXO1 fusions of many alveolar tumors.



Embryonal and alveolar groups are molecularly distinct

- For embryonal RMS, the source emphasizes signaling-pathway activation.
- For alveolar RMS, the source emphasizes fusion transcription factors.
- Genetic mechanism and histologic appearance should be correlated—not treated as interchangeable.

Embryonal

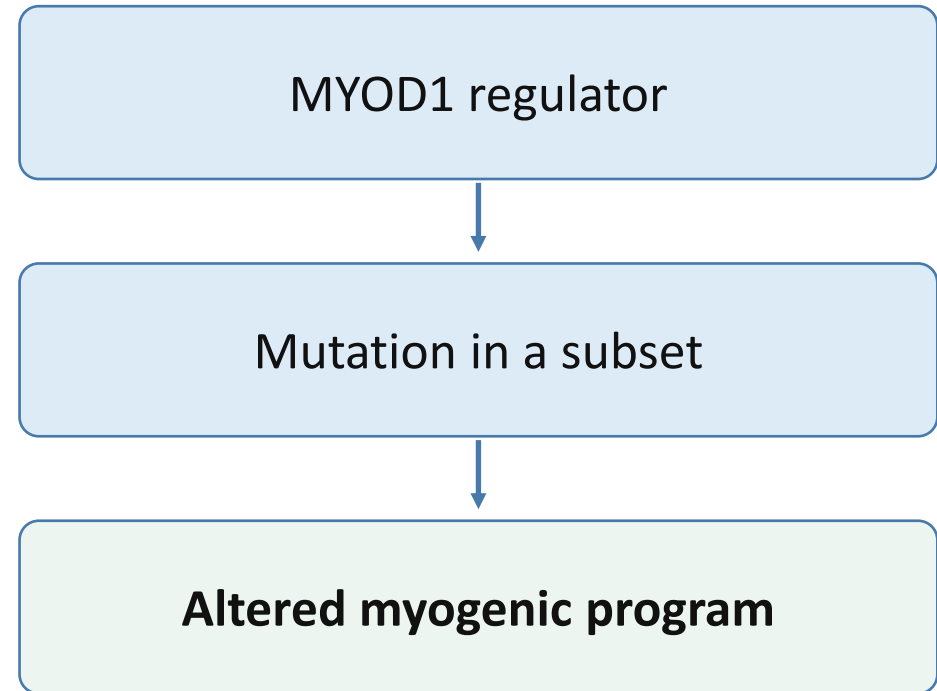
RAS-pathway drivers
Frequent; Somatic

Alveolar

PAX3/7::FOXO1 fusions
Frequent; Rearrangement-associated

Spindle cell/sclerosing RMS: MYOD1 subset

- A subset contains somatic alterations involving MYOD1.
- MYOD1 is a major regulator of skeletal muscle differentiation.
- The mutation is not described as universal for the entire spindle/sclerosing group.



The MYOD1 qualifier is diagnostically important

- “Subset” means a negative MYOD1 result would not logically exclude the category.
- The histologic subtype also rests on spindle/sclerotic architecture.
- Avoid equating all spindle-cell neoplasms with MYOD1-mutant rhabdomyosarcoma.

Supported inference

Some spindle/sclerosing RMS have MYOD1 alterations

Not every case must be MYOD1-mutant

Not supported

Architecture is characteristic

Spindling alone is not lineage proof

Pleomorphic RMS is genetically heterogeneous

- Multiple distinct genetic aberrations.
- No single recurrent defining fusion is stated for this group.
- Genetic diversity fits the importance of morphology plus myogenic differentiation evidence.

Adult predominance

Typical clinical setting

Marked pleomorphism

Characteristic histology

Diverse changes

Heterogeneous genomic background

Fusion-driven versus heterogeneous biology

Pattern	Representative subtype	Source example
Fusion transcription factor	Alveolar	PAX3::FOXO1; PAX7::FOXO1
Signaling activation	Embryonal	RAS pathway
Differentiation regulator	Spindle/sclerosing	MYOD1 subset
Heterogeneous aberrations	Pleomorphic	No uniform source-specified fusion

Microscopy: Recognize architecture and cytology

- Embryonal RMS: Primitive round/spindle cells in myxoid stroma.
- Alveolar RMS: Septated aggregates with poor central cohesion.
- Pleomorphic RMS: Bizarre eosinophilic cells;
Spindle/sclerosing RMS: Fascicles or storiform pattern.

Embryonal

Cellular diversity +
myxoid

Alveolar

Septa + dyscohesive
centers

Pleomorphic

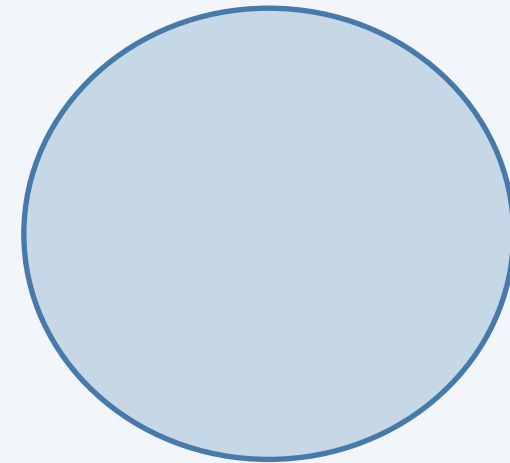
Large bizarre cells

Spindle/sclerosing

Fascicles + sclerosis

Embryonal RMS may be soft and infiltrative

- The gross tumor is typically described as soft and gray.
- Its margins may infiltrate surrounding tissues.
- Gross appearance gives context, but histology is needed for subtype recognition.

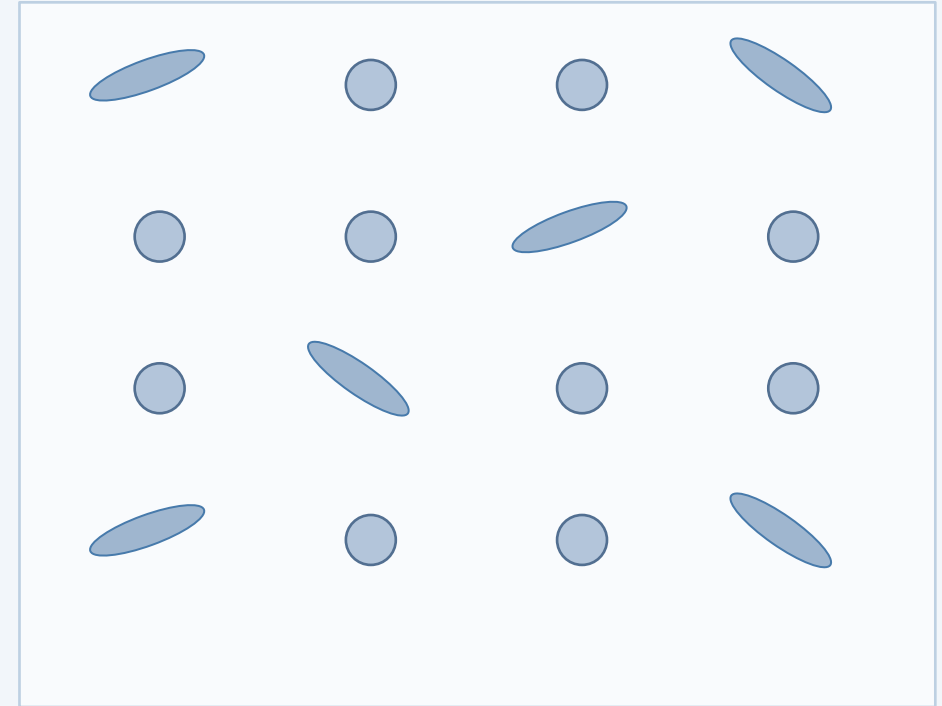


Soft, gray tumor mass

Schematic — not a pathologic specimen

Embryonal RMS has heterogeneous immature cells

- Primitive round cells form part of the neoplasm.
- Spindled immature cells coexist with the round population.
- This admixture reflects cells at multiple apparent stages of myogenic differentiation.

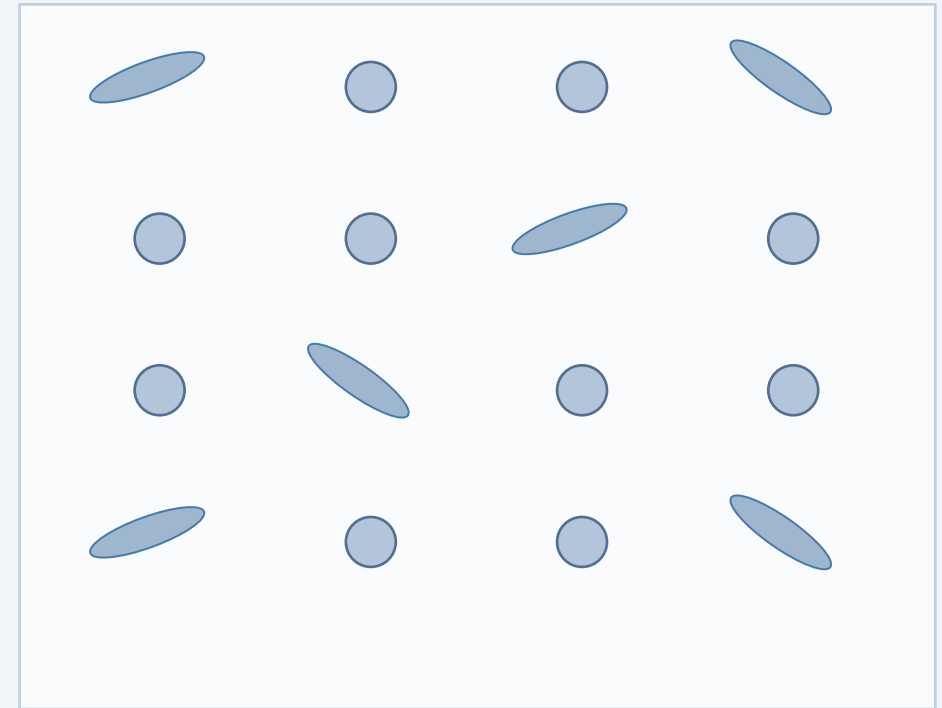


Mixed primitive round and spindle cells

Architecture schematic — not a histology image

Embryonal RMS often shows a myxoid background

- Primitive tumor cells may lie in loose myxoid stroma.
- A myxoid background is part of the characteristic tissue pattern.
- Interpret stroma together with cellular features—not in isolation.

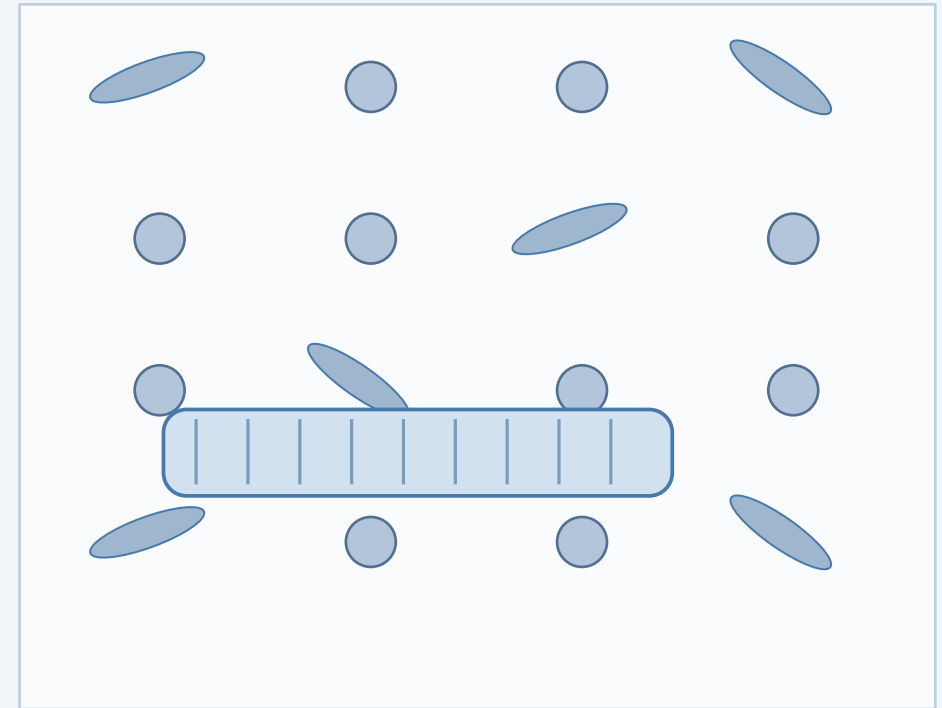


Immature cells in myxoid stroma

Architecture schematic — not a histology image

Rhabdomyoblasts signal muscle differentiation

- Some tumor cells develop recognizable rhabdomyoblastic features.
- Cross-striations can occasionally be visible in rhabdomyoblasts.
- Their presence provides morphologic support for skeletal-muscle differentiation.

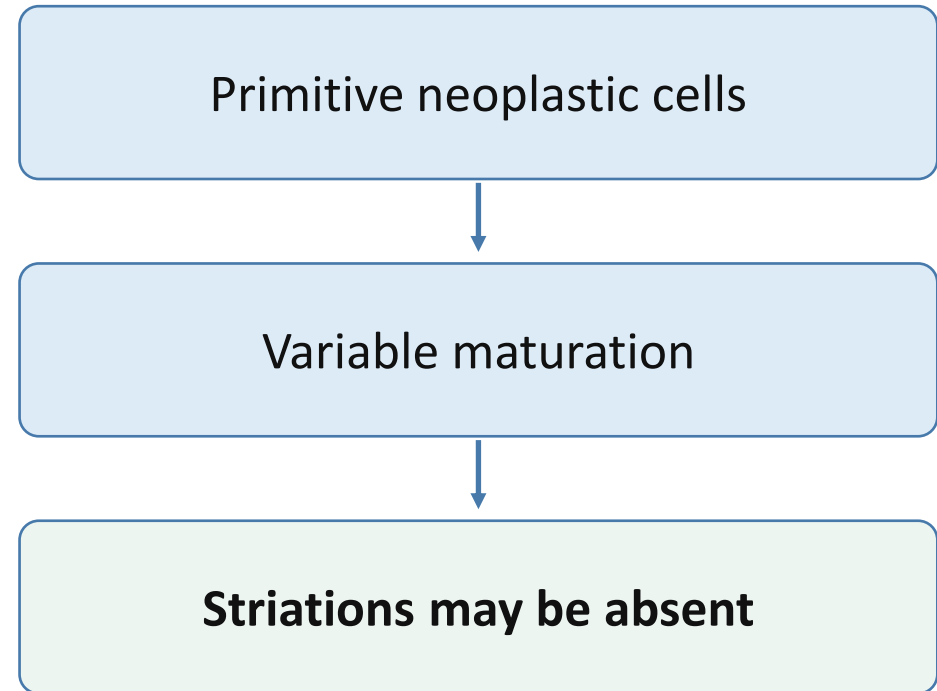


Variable rhabdomyoblast differentiation

Architecture schematic — not a histology image

Absent cross-striations do not erase the diagnosis

- Visible striations may be present, not that they must be present.
- Immature neoplastic cells need not recapitulate a fully differentiated myofiber.
- Use the complete morphologic and differentiation evidence.



Embryonal RMS: Integrate three morphologic clues

- Primitive round and spindle cells.
- Myxoid stroma.
- Occasional differentiated rhabdomyoblasts.

Cell type

Round + spindled

Stroma

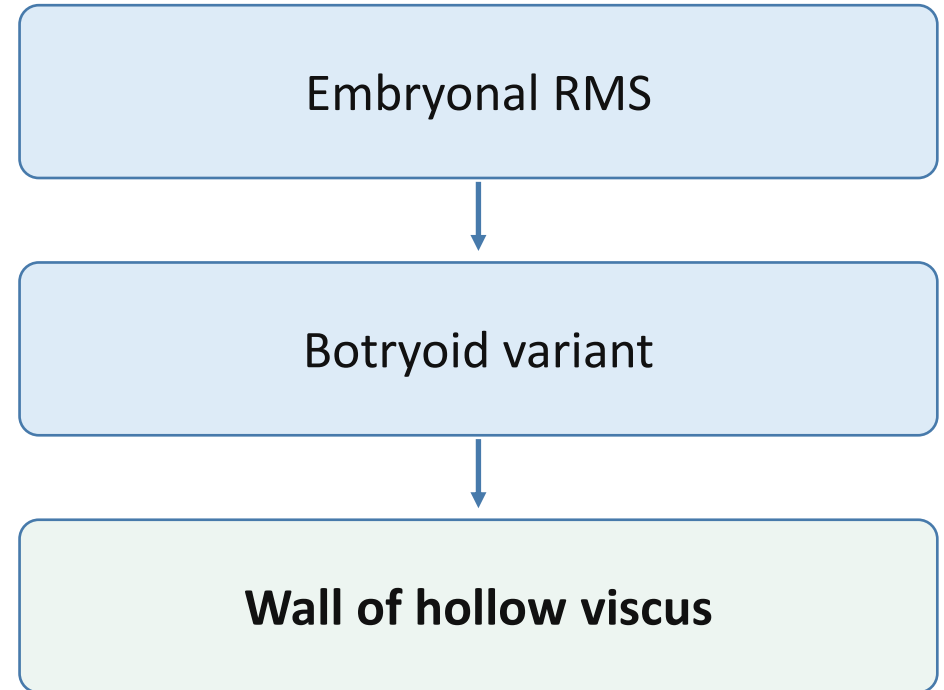
Myxoid

Differentiation

Rhabdomyoblasts; Possible striations

Sarcoma botryoides is an embryonal variant

- Botryoid RMS as a variant of embryonal RMS.
- Its site association is with walls of hollow viscera.
- The subtype and anatomic distribution must be documented together.



Botryoid RMS: Characteristic organ sites

- Urinary bladder is an explicitly cited location.
- Vagina is another explicitly cited site.
- The clinical scenario can bring a pediatric mass in a hollow viscus to attention.

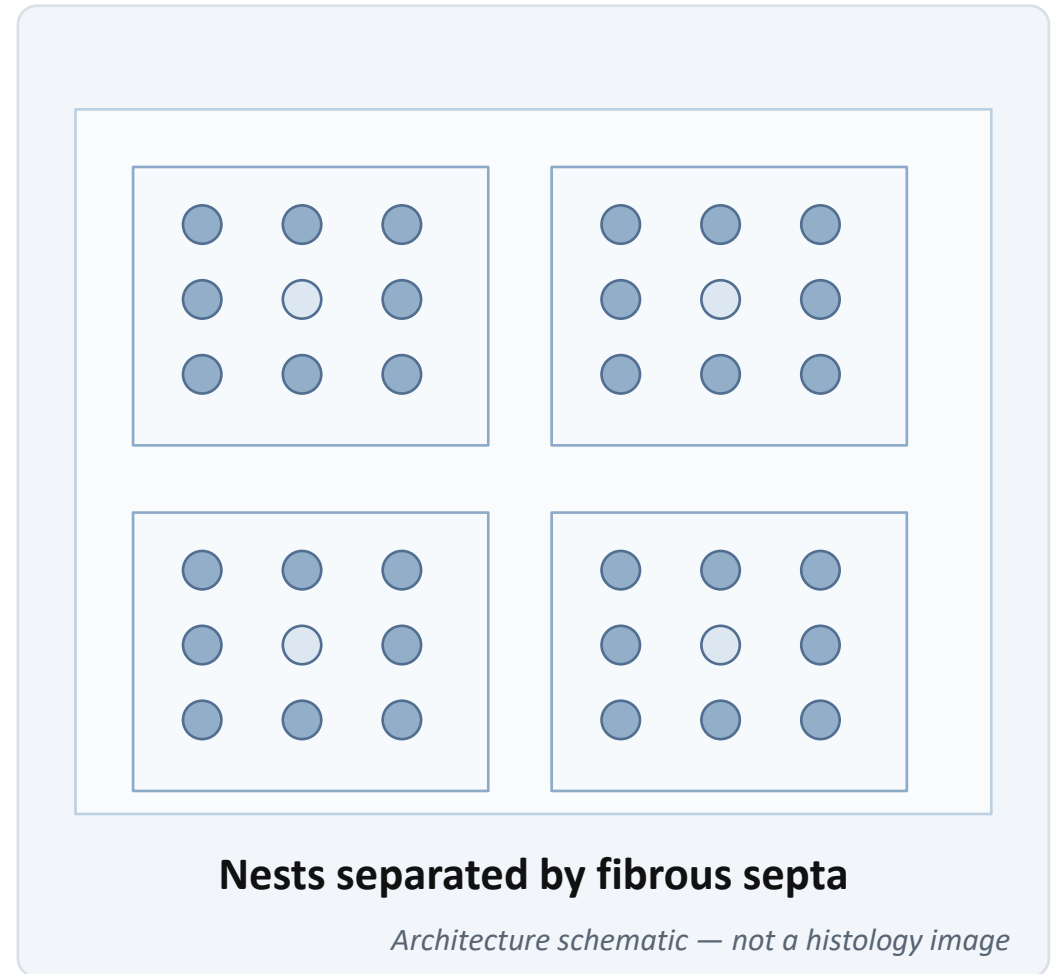
Urinary bladder

Vagina

Hollow visceral wall

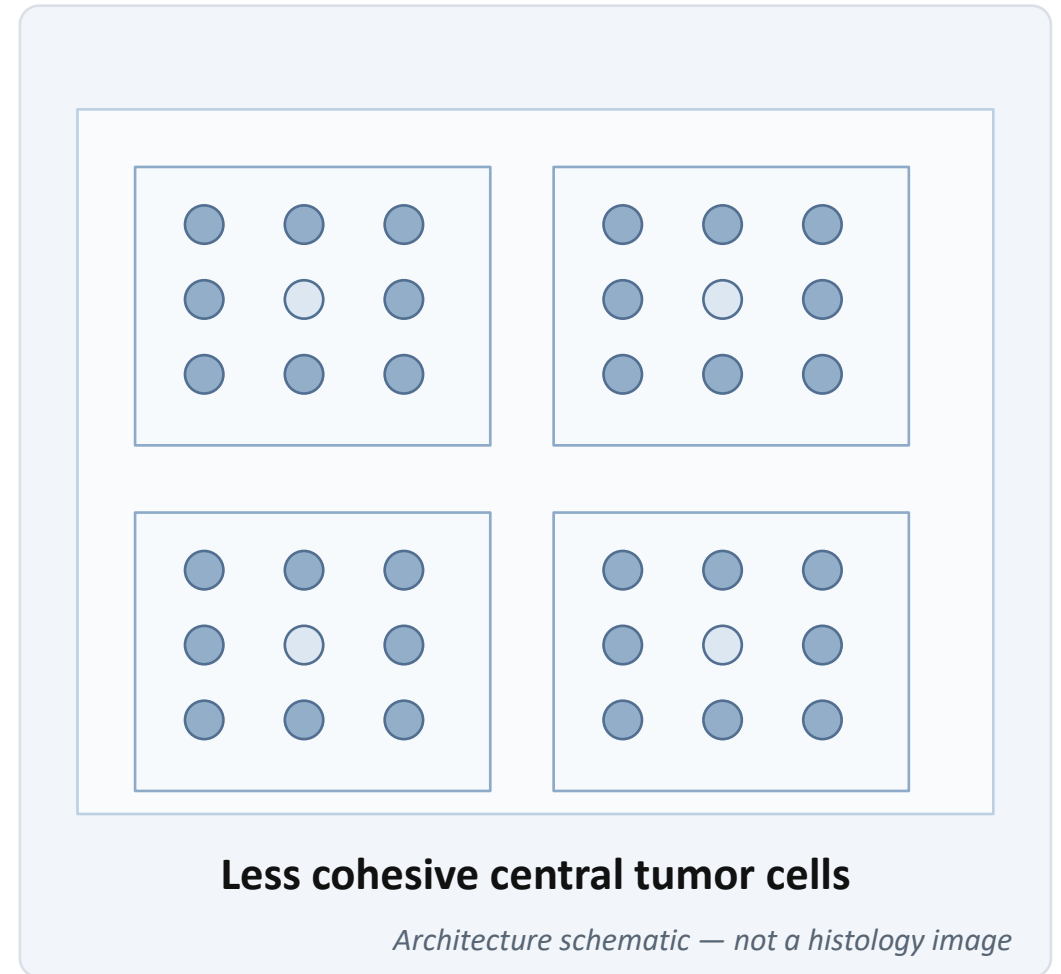
Alveolar RMS is organized by fibrous septa

- Fibrous partitions divide the tumor into cellular nests or aggregates.
- The architecture resembles pulmonary alveoli, explaining the designation.
- This is a pattern of growth, not actual lung epithelium.



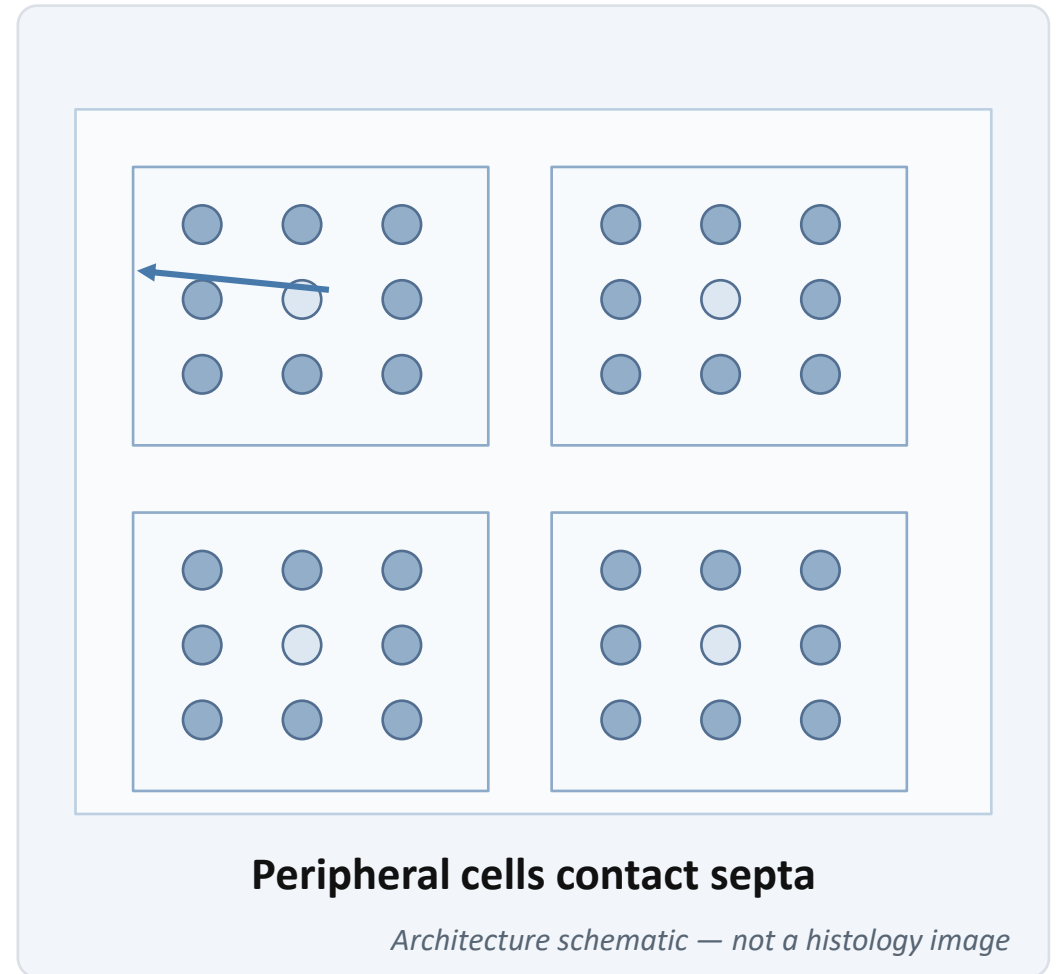
Alveolar RMS: Loss of central cohesion

- Cells near the centers of aggregates are minimally cohesive.
- The reduced cohesion produces open-looking spaces within nests.
- This structural relationship is more specific than the word “alveolar” alone.



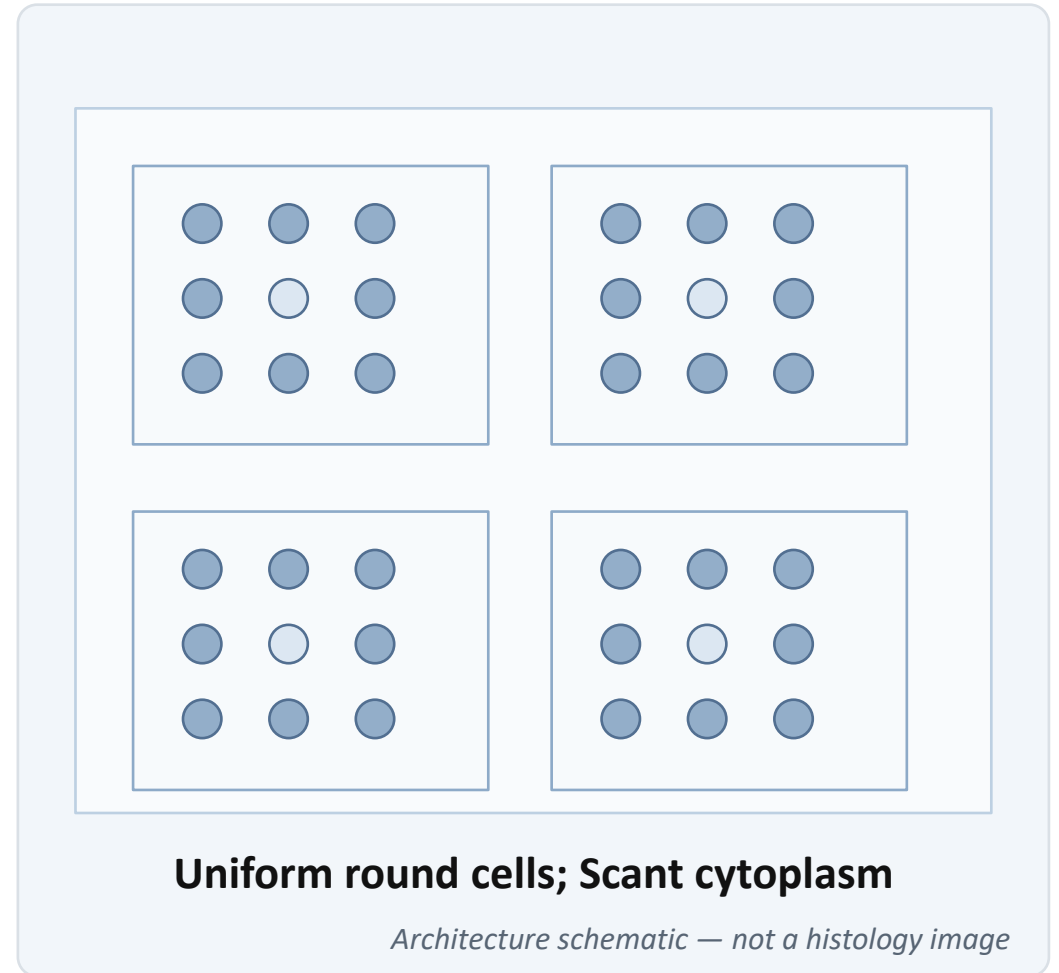
Alveolar RMS: Peripheral attachment

- Peripheral tumor cells retain an association with fibrous septa.
- Central cells show less cohesion than septal-adjacent cells.
- The center-versus-periphery contrast defines the source-described pattern.



Alveolar RMS: Relatively uniform cytology

- Tumor cells are often round and comparatively uniform.
- Cytoplasm is scant.
- Combine cytology with septated, dyscohesive architecture for pattern recognition.



Embryonal versus alveolar architecture

- Embryonal tumors contain primitive cell mixtures amid myxoid stroma.
- Alveolar tumors form nests separated by fibrous septa.
- Alveolar centers are less cohesive, while peripheral cells relate to the septa.

Embryonal morphology

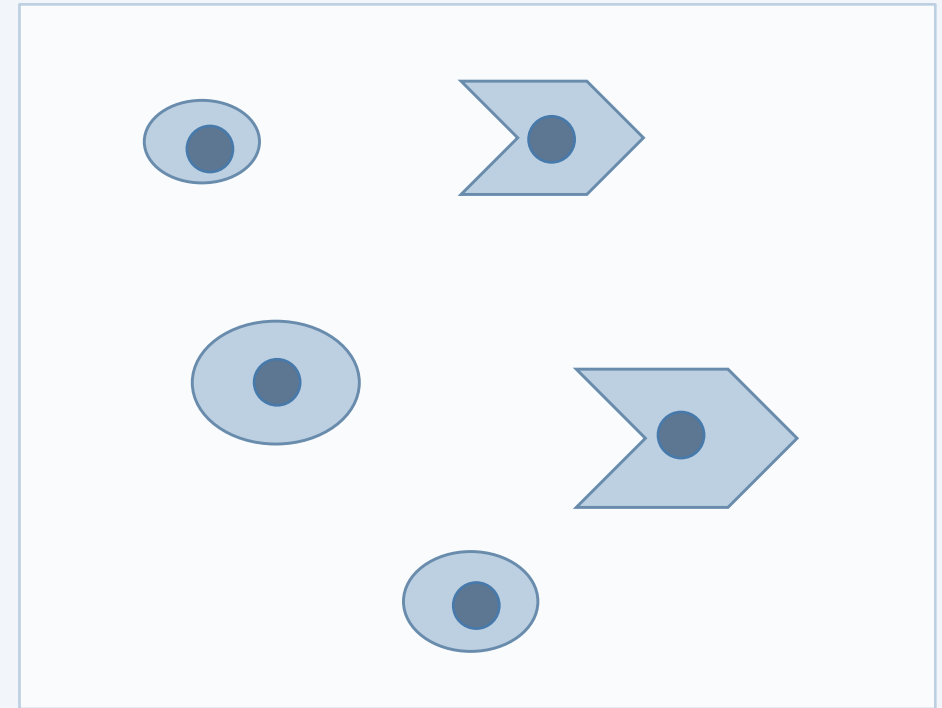
Mixed round and spindle cells
Myxoid tissue matrix

Alveolar morphology

Round uniform cells
Fibrous septa and dyscohesion

Pleomorphic RMS: Severe atypia

- Large eosinophilic tumor cells are conspicuous.
- Some cells are multinucleated and bizarre.
- This pattern can overlap with other pleomorphic sarcomas.

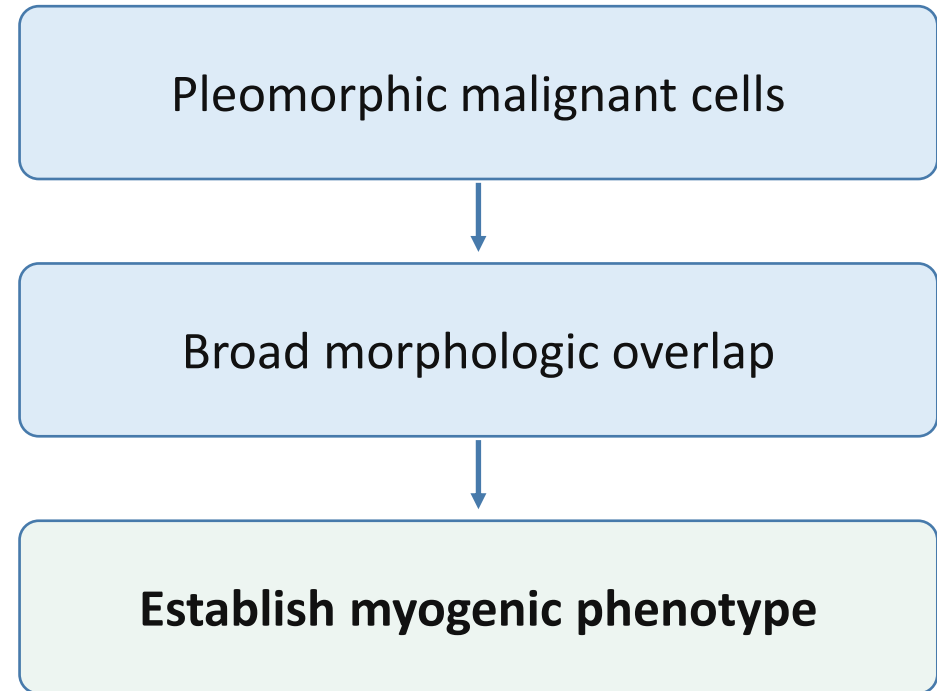


Bizarre, variably sized eosinophilic cells

Architecture schematic — not a histology image

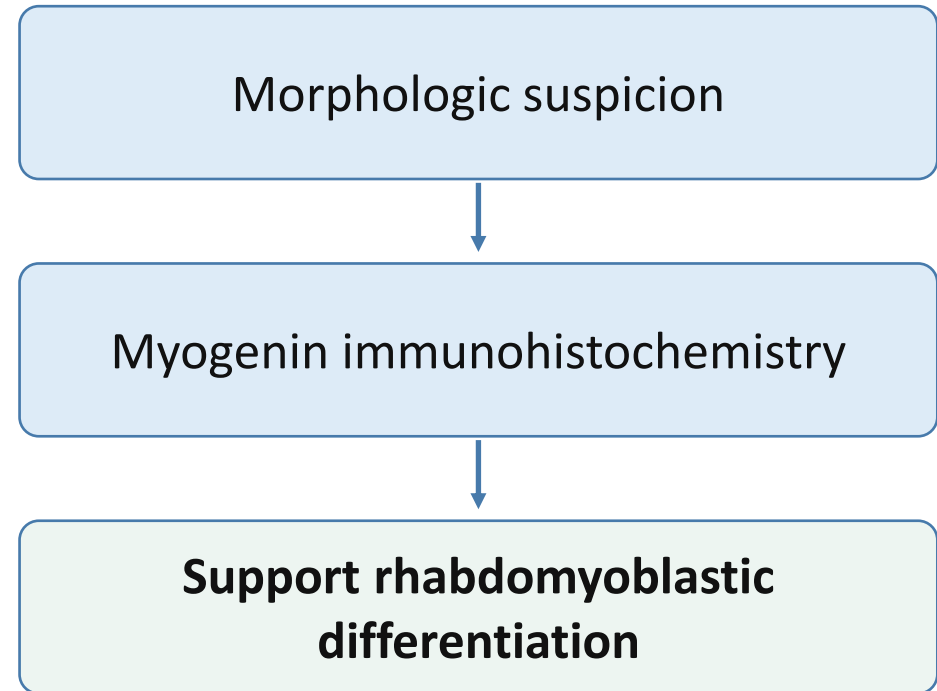
Pleomorphic morphology is not lineage-specific

- Bizarre sarcoma cells alone do not establish rhabdomyosarcoma.
- The source explicitly notes overlap with other pleomorphic sarcomas.
- Confirm skeletal-muscle differentiation rather than relying only on pleomorphism.



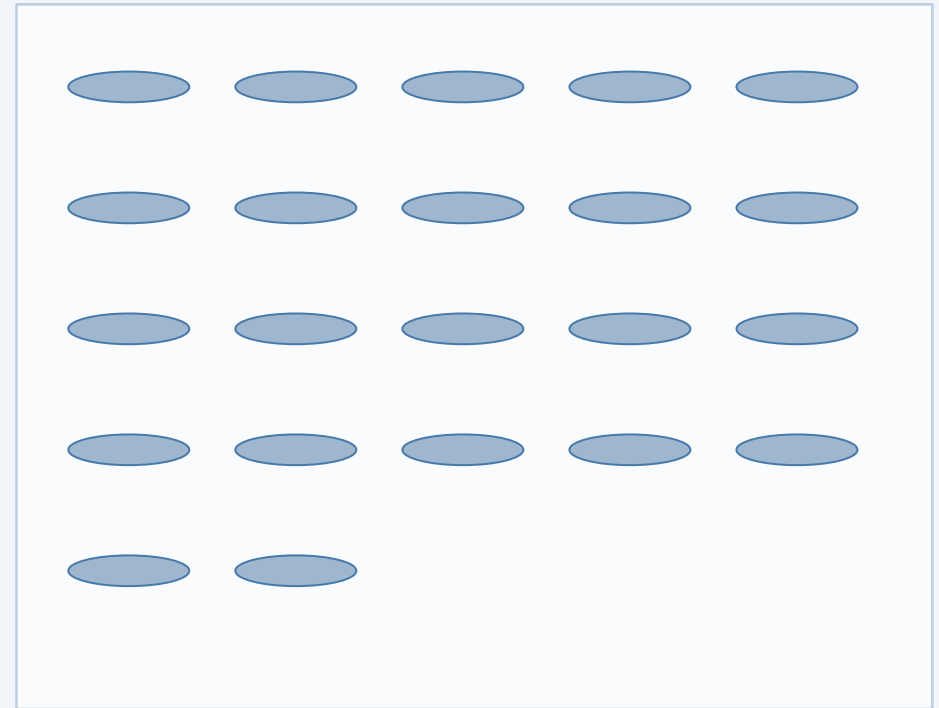
Myogenin immunohistochemistry supports lineage

- Myogenin as a skeletal-muscle-specific protein useful in diagnosis.
- Myogenin immunohistochemistry is usually needed to confirm rhabdomyoblastic differentiation in pleomorphic lesions.
- Immunostaining is interpreted in conjunction with architecture and cytology.



Spindle/sclerosing RMS: Fascicular architecture

- The tumor contains fusiform malignant cells.
- Nuclear chromatin can be vesicular.
- Cells may form extended, parallel fascicles.

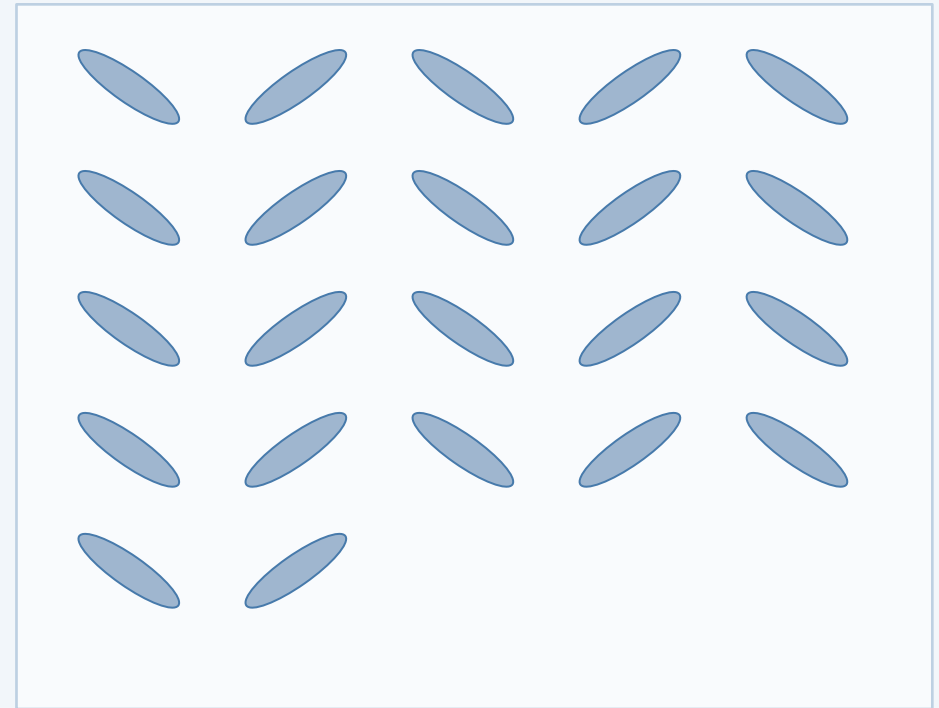


Spindle cells in long fascicles

Architecture schematic — not a histology image

Spindle/sclerosing RMS: Storiform pattern

- Spindle-cell fascicles may show storiform organization.
- A storiform pattern is a radiating, interlacing fascicular architecture.
- The pattern should be integrated with cytology and myogenic features.

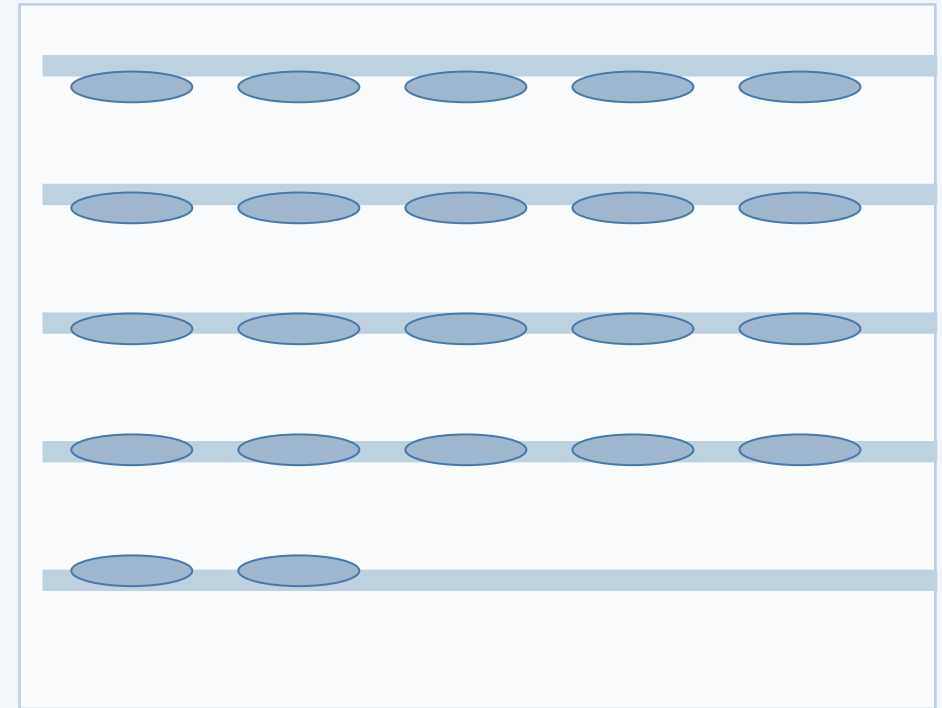


Interlacing storiform fascicles

Architecture schematic — not a histology image

Spindle/sclerosing RMS: Collagenous stroma

- Dense sclerotic collagen can accompany the neoplastic spindled cells.
- The source notes that sclerosis may be more common in adults.
- The amount of sclerosis is variable; It is not the only diagnostic feature.

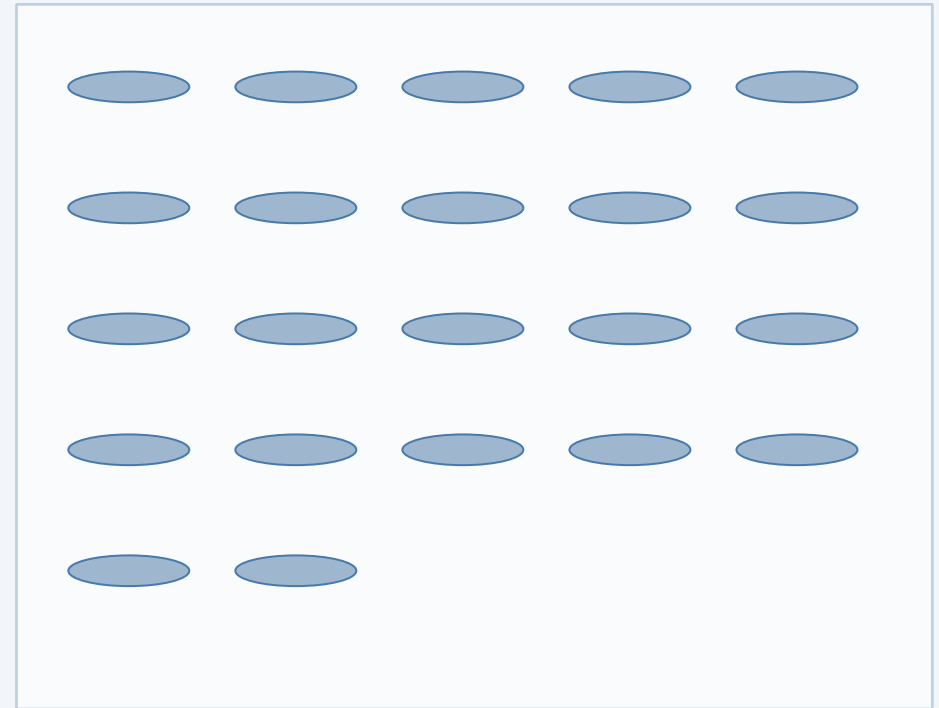


Spindle cells with collagenous sclerosis

Architecture schematic — not a histology image

Spindle/sclerosing RMS: Rhabdomyoblasts may be seen

- Recognizable rhabdomyoblasts are occasionally present.
- The dominant spindle-cell architecture may obscure the myogenic identity.
- A single favorable morphologic clue should be weighed with the whole lesion.



Occasional rhabdomyoblasts may occur

Architecture schematic — not a histology image

Histology comparison: Four diagnostic patterns

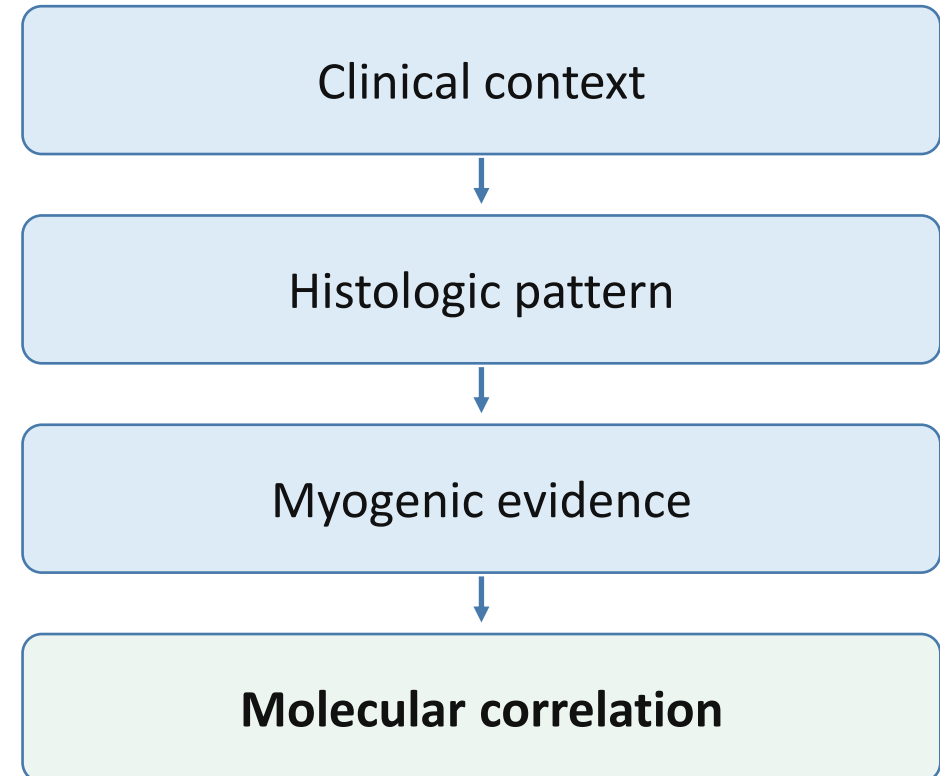
Subtype	Cells	Architecture / stroma
Embryonal	Primitive round + spindle	Myxoid; occasional rhabdomyoblasts
Alveolar	Uniform round; scant cytoplasm	Fibrous septa; central dyscohesion
Pleomorphic	Large, bizarre eosinophilic	Pleomorphic; possible giant cells
Spindle/sclerosing	Fusiform; vesicular chromatin	Fascicular or storiform; collagenous

Correlating morphology with molecular class

Histologic pattern	Molecular association
Alveolar	PAX3::FOXO1 or PAX7::FOXO1
Embryonal	RAS-pathway activation
Spindle/sclerosing	MYOD1 mutation in subset
Pleomorphic	Genetically heterogeneous

A pathology-oriented integration sequence

- Establish the clinical context: Age and anatomical site.
- Review growth pattern, cells, and background stroma.
- Use skeletal-muscle differentiation evidence and, where appropriate, the subtype-associated genetic mechanism.



Clinicopathologic patterns are informative—not rules

- Age and location can suggest a subtype.
- Microscopic architecture provides more direct phenotypic evidence.
- The Robbins associations do not make anatomic site or age independently diagnostic.

Age

Raises suspicion

Site

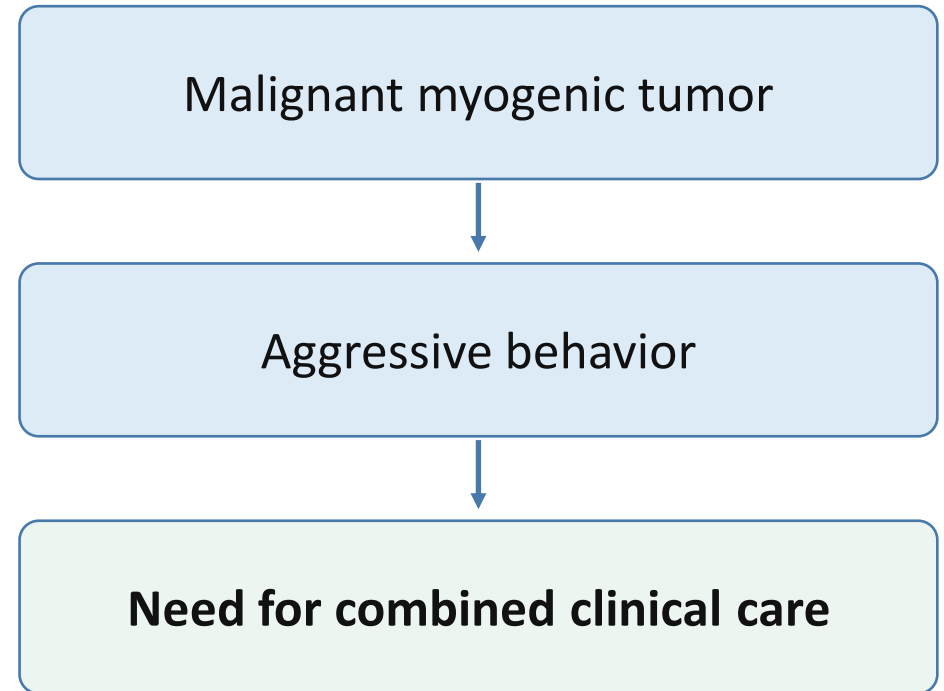
Adds context

Histology + phenotype

Supports classification

Rhabdomyosarcoma behaves aggressively

- The textbook characterizes rhabdomyosarcomas as aggressive tumors.
- Locoregional extent and other clinical factors matter in management planning.
- Histologic subtype and location correlate with survival.



Treatment in the Robbins overview is multimodal

- Surgical resection is one common component.
- Chemotherapy is generally included.
- Radiation therapy may be used, depending on the clinical situation.

Surgery

Local tumor control

Chemotherapy

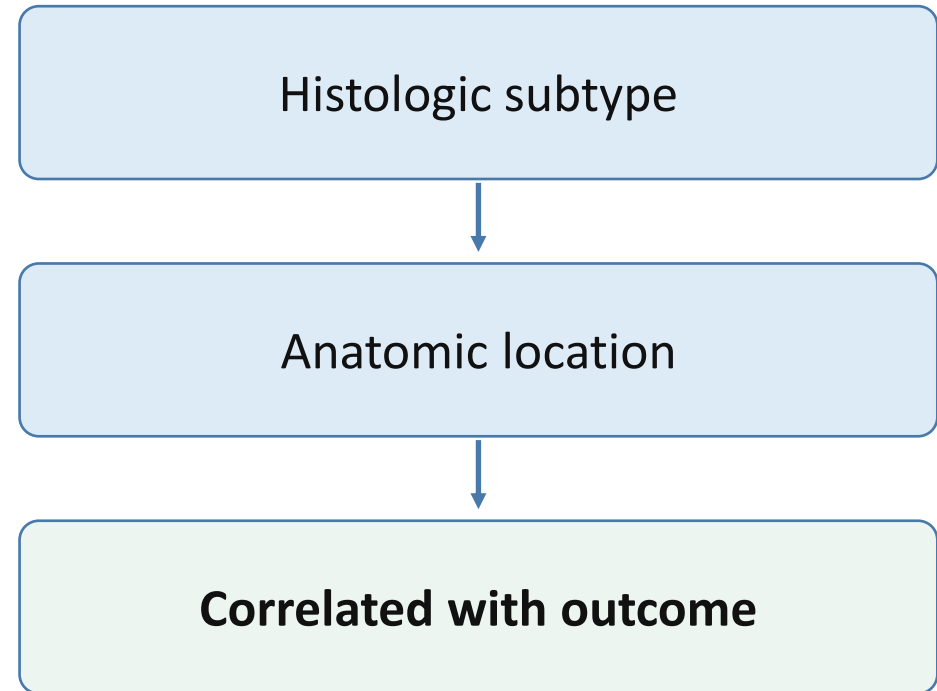
Systemic treatment

Radiation

May complement local treatment

Outcome differs by histologic type and location

- The source links patient survival with histologic subtype.
- Anatomic location is another prognostic correlate.
- These qualitative statements do not supply a universal survival percentage or staging algorithm.



Botryoid variant has a favorable relative prognosis

- Among the named morphologic types, botryoid RMS as most favorable.
- Botryoid tumors belong to the embryonal family.
- Prognosis should still be interpreted in the actual clinical context.

Variant

Botryoid RMS
Most favorable among described groups

Source prognostic statement

Pleomorphic RMS
Often fatal in the cited overview

Pleomorphic RMS has an adverse clinical course

- Pleomorphic rhabdomyosarcoma principally occurs in adults.
- It has marked cytologic atypia and genetic heterogeneity.
- The Robbins clinical summary describes pleomorphic RMS as often fatal.

Setting

Adulthood

Morphology

Bizarre eosinophilic cells

Clinical behavior

Often fatal (source description)

Teaching vignette: Pediatric hollow-viscus mass

- An illustrative pediatric mass arises in the wall of the urinary bladder.
- Biopsy shows primitive round/spindled cells in a myxoid background.
- Which subtype/variant should enter the differential first?

Interpretive answer

Embryonal rhabdomyosarcoma, with the botryoid variant considered in this anatomic context.

Illustrative teaching vignette—not patient data

Teaching vignette: Septated round-cell tumor

- An illustrative lesion contains round cells in nests divided by fibrous septa.
- Cells are less cohesive centrally but contact septa at the periphery.
- What is the characteristic histologic category and fusion class?

Interpretive answer

Alveolar RMS; PAX3::FOXO1 or PAX7::FOXO1 is a frequent molecular association.

Illustrative teaching vignette—not patient data

Teaching vignette: Adult pleomorphic sarcoma

- An illustrative adult lesion shows bizarre eosinophilic malignant cells.
- Histology overlaps with other pleomorphic sarcomas.
- What additional differentiation evidence is specifically highlighted by Robbins?

Interpretive answer

Myogenin immunohistochemistry to support rhabdomyoblastic differentiation.

Illustrative teaching vignette—not patient data

Avoid common interpretive errors

- Do not require visible striations in every rhabdomyosarcoma.
- Do not equate every spindle-cell tumor with MYOD1-mutant RMS.
- Do not reverse PAX3/PAX7 translocation mapping or mistake apparent “alveoli” for epithelial differentiation.

Morphologic overreach

Visible striations are optional

Molecular overreach

MYOD1 is a subset association

Extraction vigilance

PAX3 t(2;13), PAX7 t(1;13)

Integrated summary: Biologic classification

- Rhabdomyoma is benign; Skeletal-muscle neoplasms are otherwise predominantly malignant.
- Rhabdomyosarcoma is divided into embryonal, alveolar, pleomorphic, and spindle/sclerosing groups.
- The groups are distinguished by morphology, typical patient setting, and differing genetic events.

Embryonal

RAS frequently

Alveolar

PAX::FOXO1
frequently

Pleomorphic

Diverse aberrations

Spindle/sclerosing

MYOD1 in subset

Integrated summary: Microscopic recognition

- Myxoid primitive cell mixtures favor the embryonal pattern.
- Septate nests with dyscohesive centers favor the alveolar pattern.
- Bizarre eosinophilic cells or spindled/sclerotic patterns require evidence of myogenic differentiation.

Embryonal

Myxoid + immature

Alveolar

Septa + dyscohesion

Pleomorphic

Bizarre eosinophilic

Spindle/sclerosing

Fascicular;
Collagenous

Sources and scope

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Chapter 26: Bones, Joints, and Soft Tissue Tumors.

Primary passage: “Skeletal Muscle Tumors” (printed p. 1102); adjacent rhabdomyosarcoma morphology and clinical continuation (pp. 1102–1103).

All mechanisms and numeric subtype proportions follow the supplied Robbins text. No external staging criteria or quantitative outcomes are added.