

Leiomyosarcoma

Uterine smooth muscle malignancy

Morphology • Differential diagnosis • Clinical behavior

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning outcomes for uterine smooth muscle tumors

- Explain why uterine leiomyosarcoma is biologically distinct from leiomyoma.
- Recognize the gross and microscopic features used in malignancy assessment.
- Explain STUMP and major benign diagnostic pitfalls.
- Relate tumor morphology to recurrence, metastasis, and prognosis.

The central diagnostic problem

Benign leiomyoma

- Common uterine smooth muscle neoplasm.
- Usually circumscribed; Low mitotic activity.
- May be large or morphologically atypical.

Leiomyosarcoma

- Uncommon malignant uterine smooth muscle neoplasm.
- Often invasive; Potentially marked atypia and tumor necrosis.
- Recurrence and distant spread are major concerns.

Three possible classifications

Leiomyoma

Benign smooth muscle tumor. Some variants show unusual nuclei or distribution.

STUMP

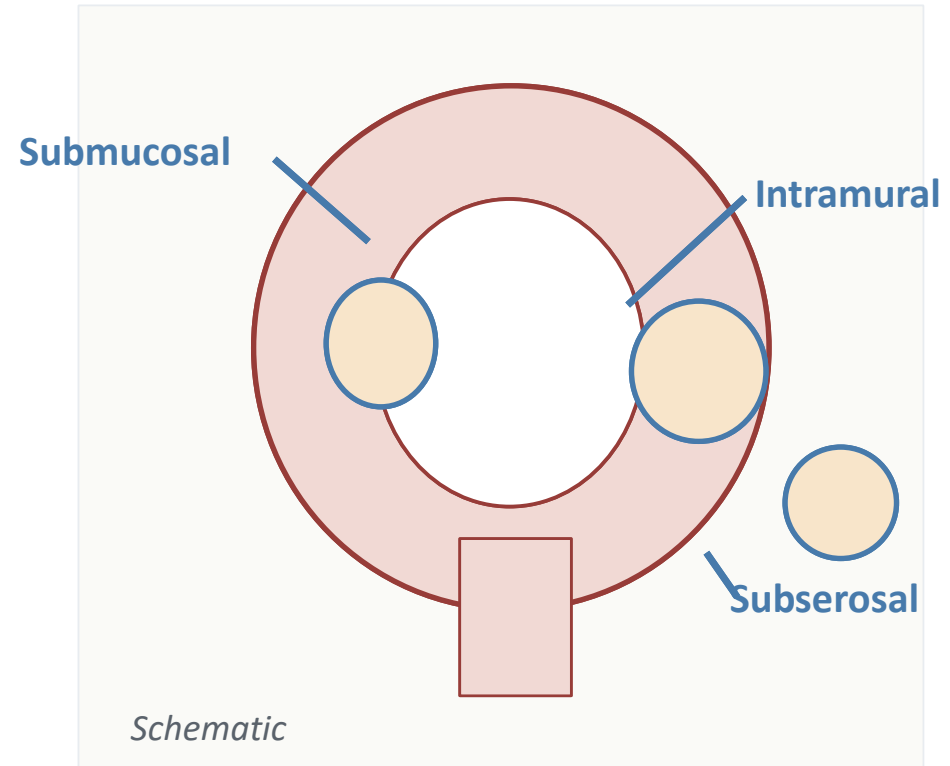
Smooth muscle tumor of uncertain malignant potential when definitive classification is not possible.

Leiomyosarcoma

Malignant smooth muscle tumor distinguished using morphology and clinical behavior.

Anatomic setting: Uterine myometrium

- The myometrium is the uterine smooth muscle layer.
- Leiomyomas usually develop within the corpus myometrium.
- Submucosal, intramural, and subserosal positions have different local effects.



Leiomyosarcoma is a malignant myometrial neoplasm

- Uterine leiomyosarcoma is uncommon compared with benign leiomyoma.
- Origin from myometrium or endometrial stromal precursor cells.
- The tumor is clinically important because of aggressive behavior.

Most leiomyosarcomas arise de novo



The usual model is not a stepwise transformation of an existing leiomyoma.

Why a leiomyoma is not the usual precursor

Leiomyoma

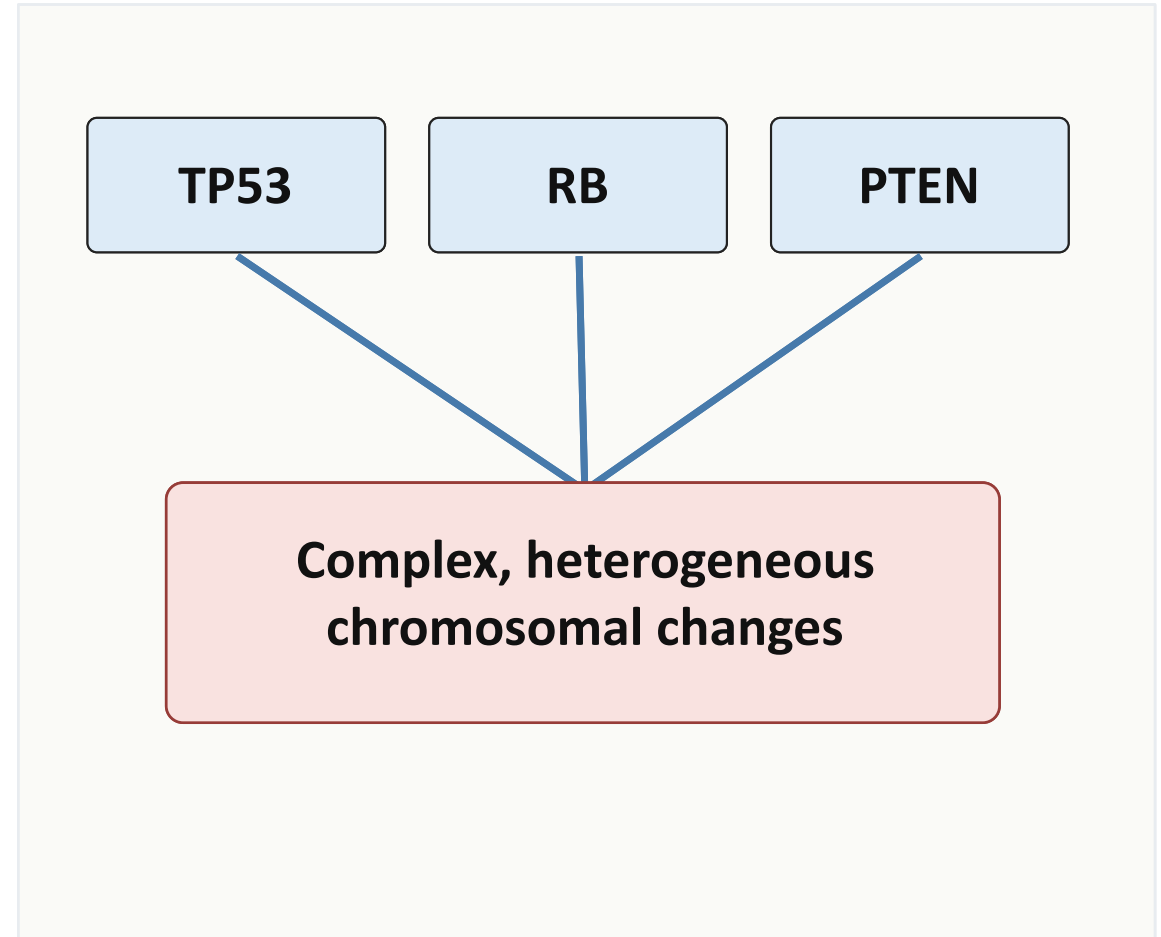
- Benign tumor of smooth muscle.
- Malignant transformation is extremely rare.
- Genetic changes often are limited.

Leiomyosarcoma

- Typically develops independently.
- Complex and variable karyotypes.
- Recurrent abnormalities in tumor-suppressor and oncogenic genes.

Genomic complexity is characteristic of leiomyosarcoma

- Leiomyosarcoma frequently has a complex, highly variable karyotype.
- Structural and numerical genomic changes are more extensive than in typical leiomyoma.
- The illustrated genes are associated abnormalities, not a single necessary pathway.



Genes highlighted by Robbins: TP53, RB, PTEN

TP53

A tumor suppressor gene included among alterations reported in leiomyosarcoma.

RB

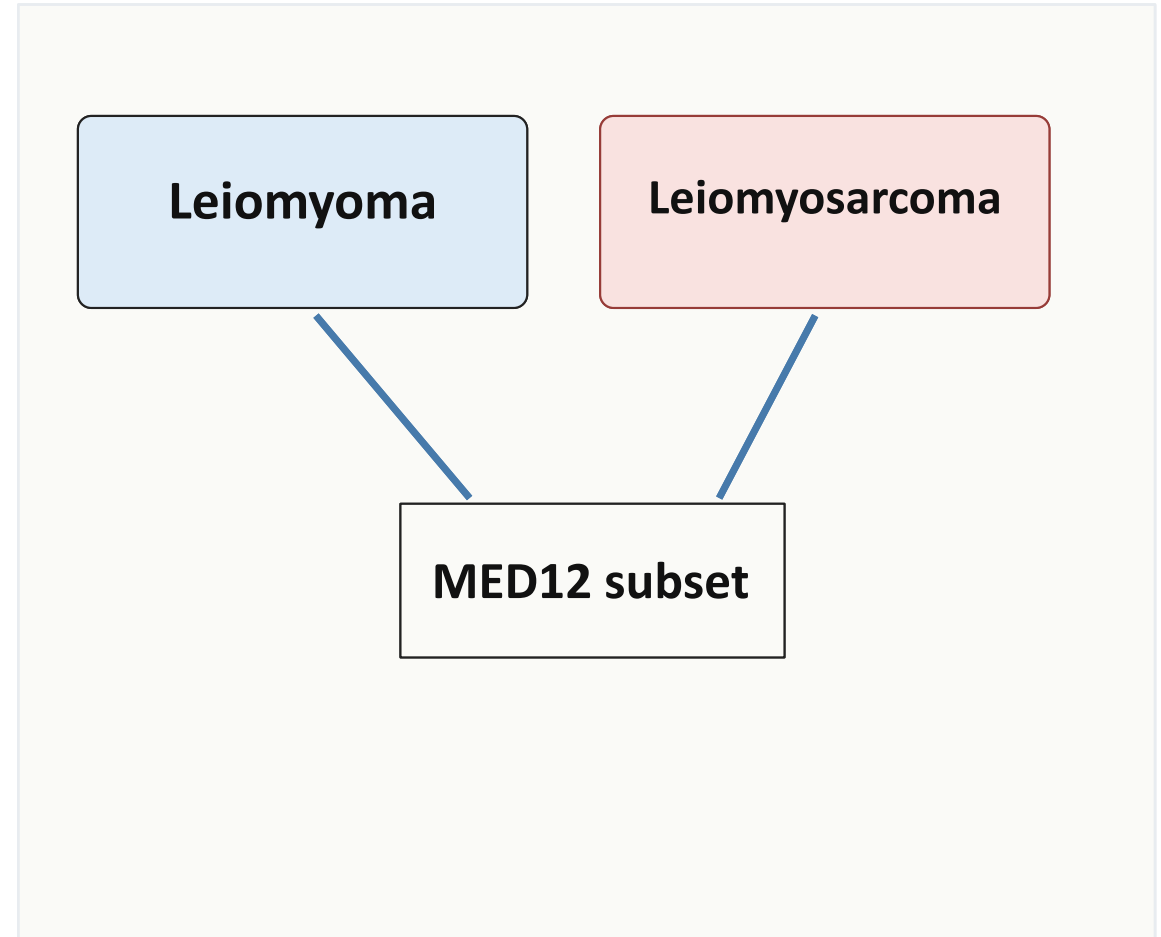
A tumor suppressor pathway component listed among recurrent genomic abnormalities.

PTEN

Another tumor suppressor gene affected in subsets of these tumors.

MED12 mutations do not separate benign and malignant

- A subset of leiomyosarcomas harbors MED12 mutations.
- MED12 mutations also occur in many leiomyomas.
- Shared mutation status does not demonstrate that a leiomyosarcoma arose from a fibroid.



Leiomyoma genetics provide the comparator

- Approximately 40% show simple chromosomal abnormalities in the Robbins text.
- Described cytogenetic groups include 12q14 and 6p rearrangements.
- MED12 mutations occur in roughly 70% of leiomyomas, per the textbook.

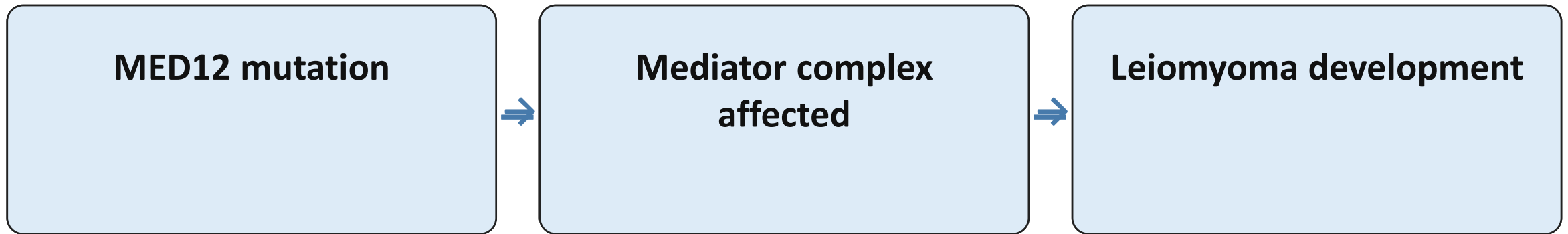
MED12

12q14 / HMGIC

6p / HMGIY

Distinct genetic subgroups

MED12 and transcription: What is known



The textbook supports a causal role in leiomyomas; The precise mechanism remains incompletely defined.

FH mutations define an important leiomyoma context

Inherited setting

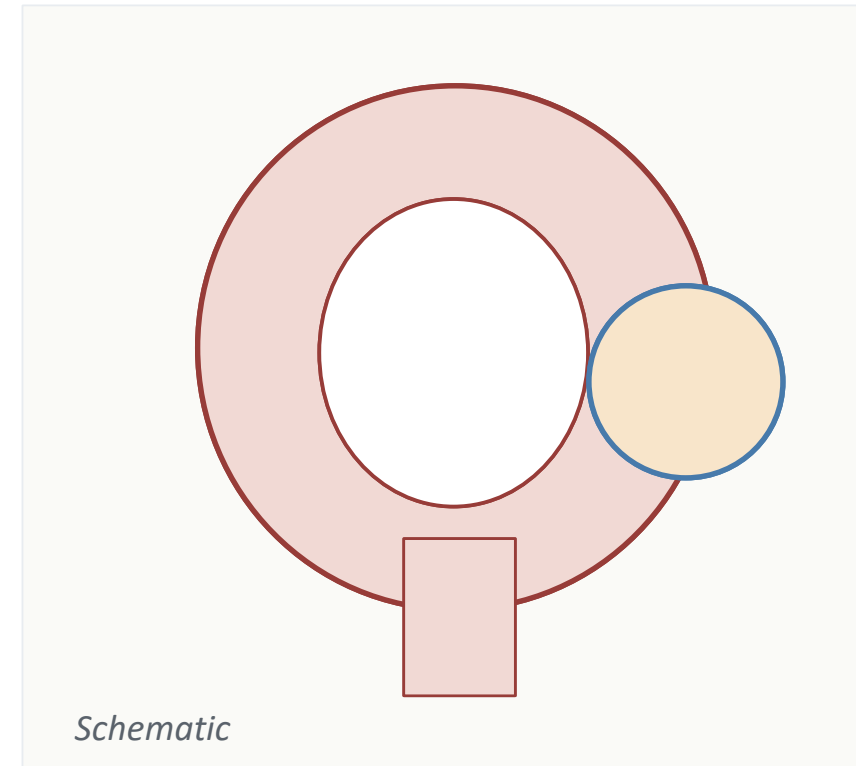
- HLRCC syndrome is associated with germline FH variants.
- Clinical significance extends beyond the uterine mass.

Sporadic setting

- Somatic FH mutations can occur in uterine leiomyomas.
- Bizarre nuclear morphology may be present in some FH-altered tumors.

Leiomyoma: Typical gross appearance

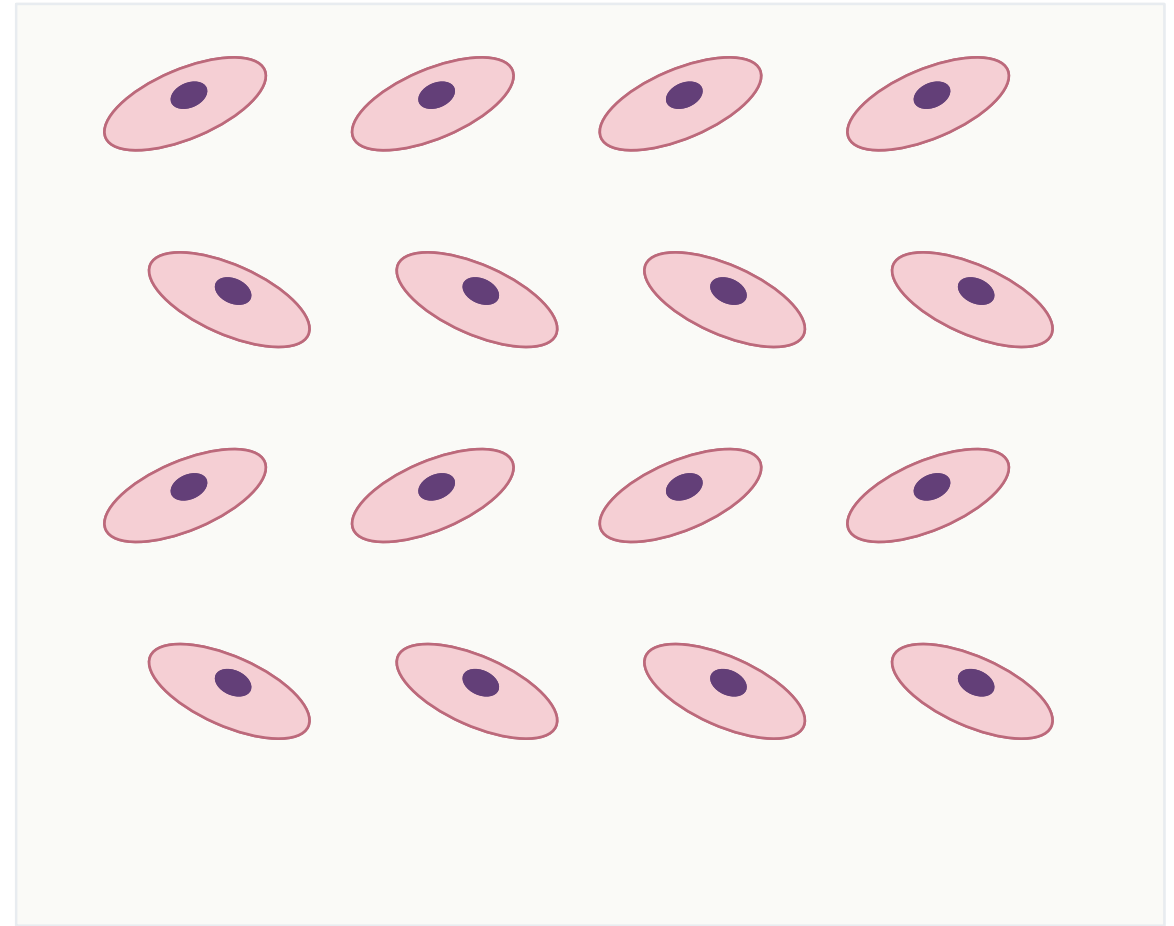
- Sharply circumscribed and discrete.
- Round, firm, gray-white nodules.
- A whorled appearance on the cut surface reflects organized smooth muscle bundles.



Circumscribed nodule

Leiomyoma morphology: Bland smooth muscle cells

- Intersecting bundles of smooth muscle resemble surrounding myometrium.
- Cells are relatively uniform with oval nuclei and elongated bipolar processes.
- Mitotic figures are usually scarce.



Conceptual cell schematic — not a photomicrograph

Large leiomyomas may undergo degenerative changes

- Large benign tumors can develop yellow-brown or red softening.
- The gross finding must be interpreted with the rest of the lesion.
- A single region of softening does not establish leiomyosarcoma.

Leiomyoma manifestations follow mass and location

Bleeding

Submucosal distortion can accompany abnormal uterine bleeding.

Pressure

Compression of adjacent structures may cause urinary frequency.

Fertility and pain

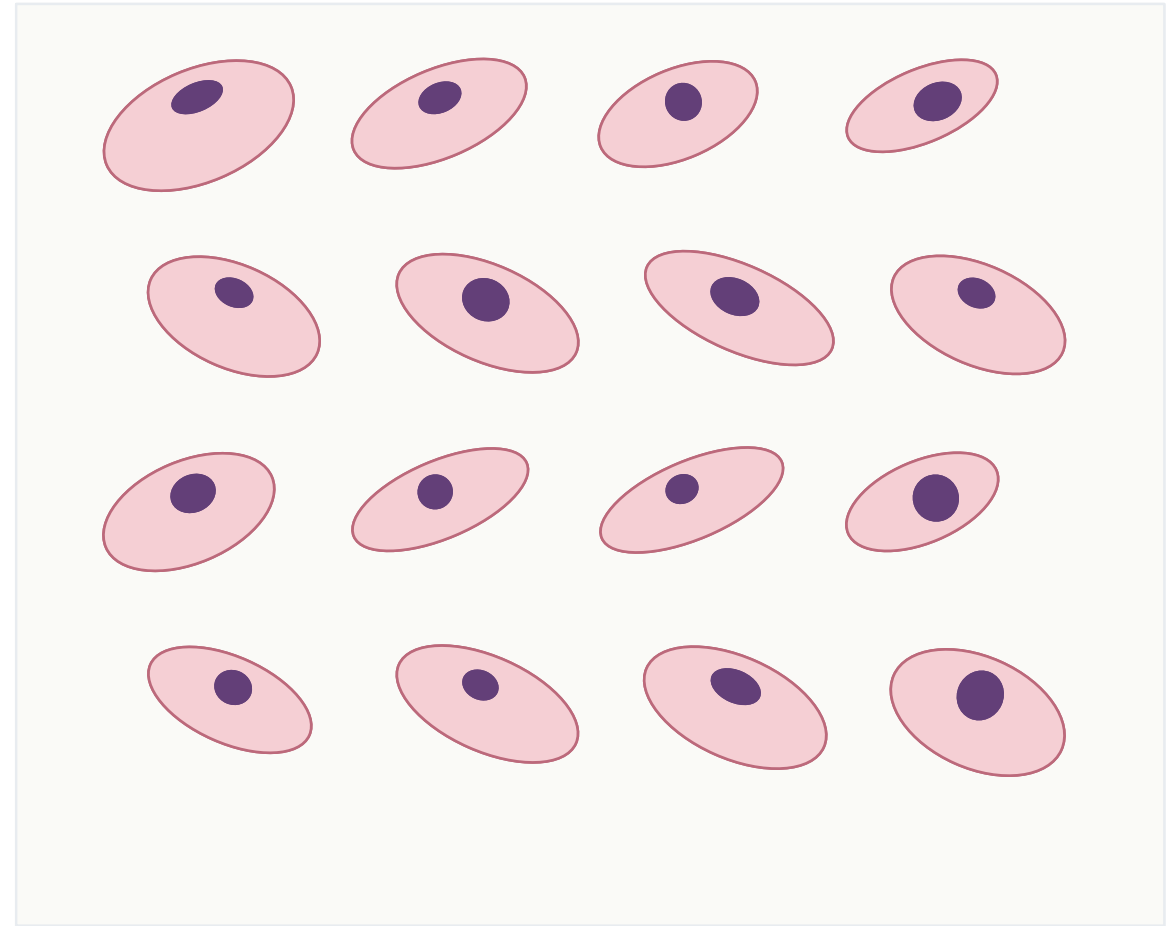
Impaired fertility or sudden pain with infarction may occur.

Pregnancy makes benign leiomyoma clinically important

- Leiomyomas may contribute to spontaneous abortion and malpresentation.
- Uterine inertia can impair effective contraction during labor.
- Postpartum hemorrhage is another recognized complication.
- Pregnancy also matters when interpreting a mitotically active smooth muscle tumor.

Leiomyoma with bizarre nuclei is a benign mimic

- Some leiomyomas contain marked nuclear atypia and giant cells.
- The mitotic index remains low in the described benign variant.
- Atypia in isolation must not determine malignant classification.



Conceptual cell schematic — not a photomicrograph

Cellular leiomyoma: Cellularity is not malignancy

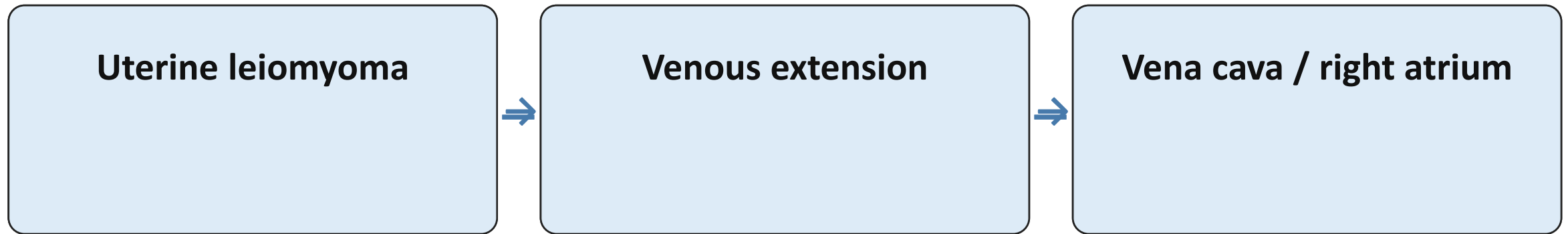
Cellular leiomyoma

- Increased cellular density is a recognized benign morphologic variant.
- Low mitotic index helps separate it from leiomyosarcoma.

Leiomyosarcoma

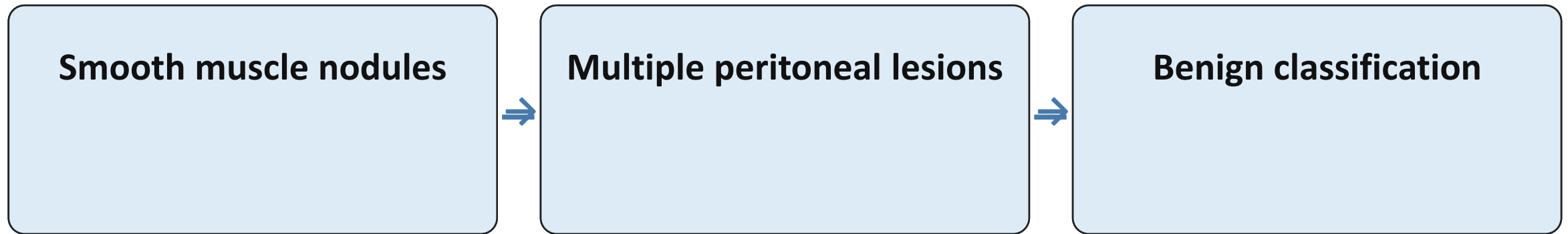
- Classification also considers nuclear atypia, mitotic activity, and tumor necrosis.
- No single descriptive adjective is sufficient.

Intravenous leiomyomatosis: Extension without malignancy



An exceptionally rare benign variant, despite its dramatic vascular distribution.

Disseminated peritoneal leiomyomatosis: Unusual benign spread



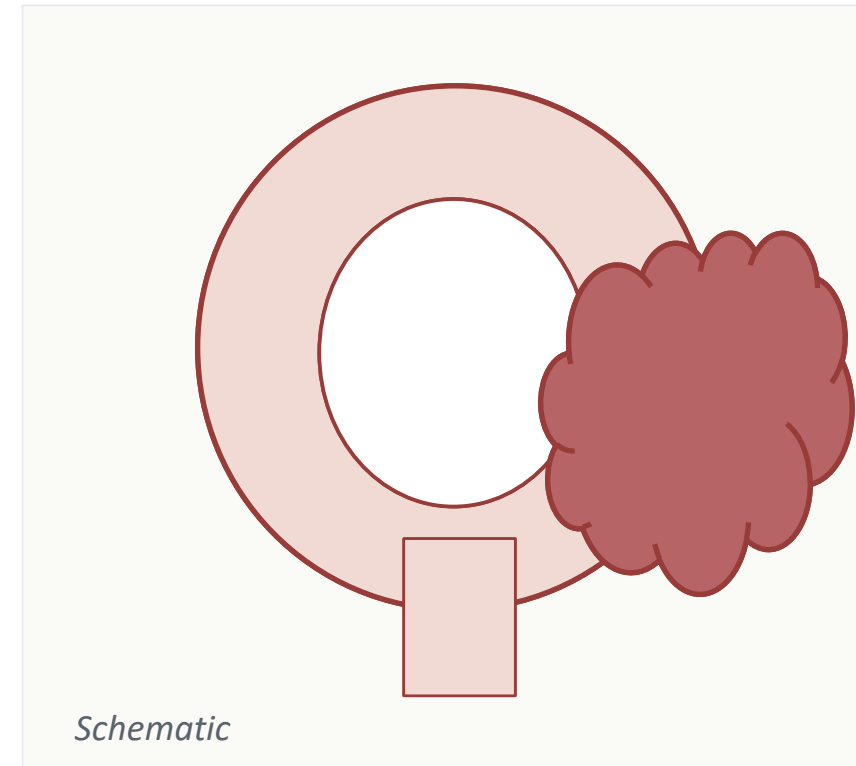
Distribution alone is not synonymous with leiomyosarcoma.

Contrast: Unusual benign behavior versus true sarcoma

Finding	Interpretation in context
Intravenous leiomyomatosis	Benign tumor despite vascular extension
Disseminated peritoneal leiomyomatosis	Benign process despite numerous nodules
Leiomyosarcoma	Malignant tumor with recurrent and metastatic potential

Gross leiomyosarcoma: Bulky, fleshy invasive mass

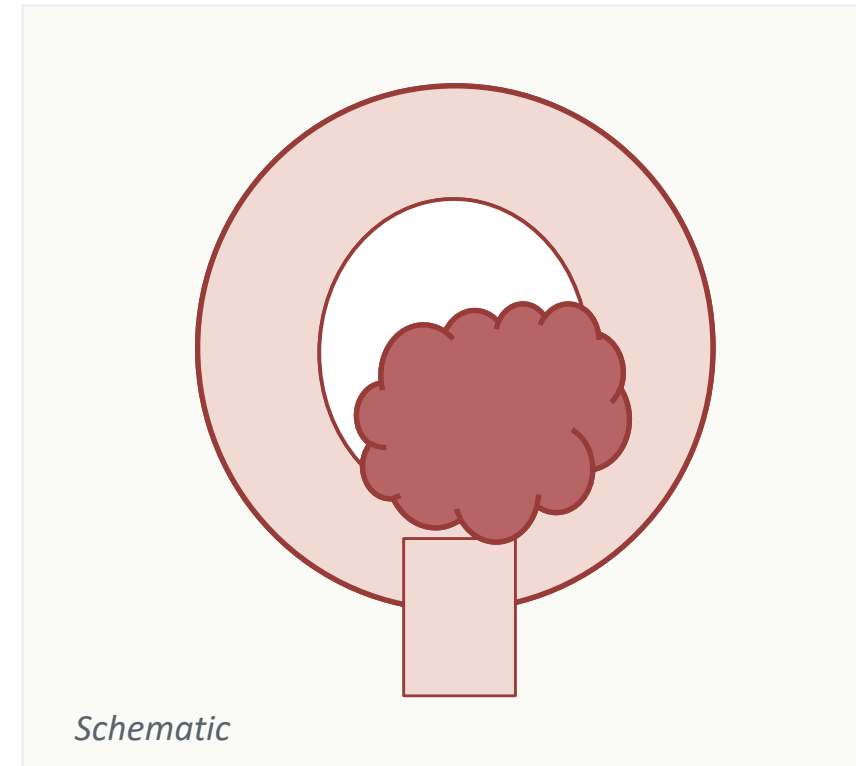
- One major growth pattern is a bulky, fleshy tumor.
- The lesion invades the uterine wall rather than remaining neatly circumscribed.
- Gross inspection directs histologic assessment but does not replace it.



Infiltrating wall

Gross leiomyosarcoma: Polypoid cavity mass

- The other described pattern protrudes into the uterine lumen.
- A polypoid configuration does not imply benign behavior.
- Assessment requires sampling and histologic evaluation.



Projects into cavity

Two growth patterns can represent the same malignancy

Infiltrative intramural growth

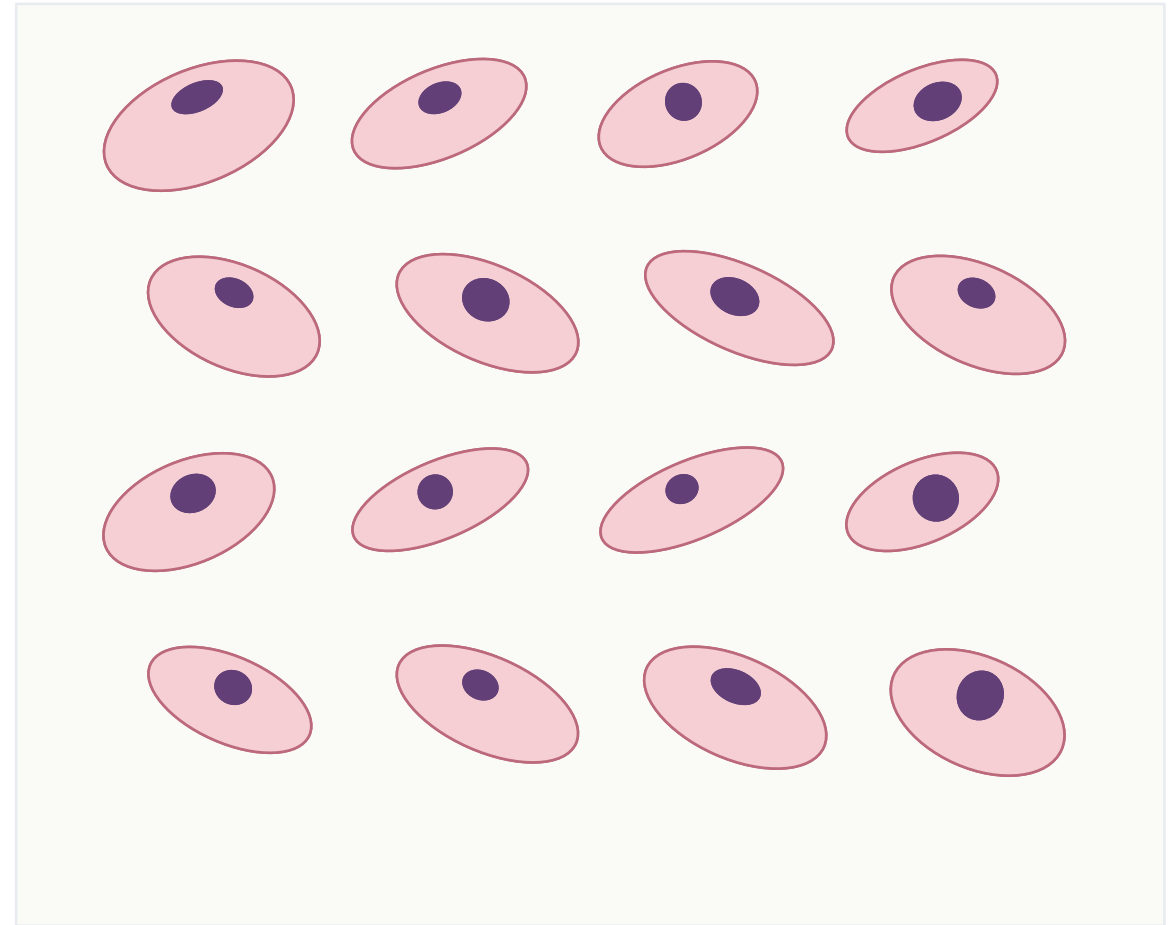
- Bulky fleshy expansion.
- Invasion of the uterine wall.
- Macroscopic focus is within the myometrium.

Polypoid intracavitary growth

- Tumor projects into the uterine cavity.
- Macroscopic presentation differs.
- Histologic malignant features remain decisive.

Cytologic differentiation ranges from bland to anaplastic

- Leiomyosarcoma shows a wide spectrum of atypia.
- Some tumors are very well differentiated.
- Others are highly anaplastic.
- Diagnostic evaluation therefore weighs multiple features.



Conceptual cell schematic — not a photomicrograph

The histologic diagnostic triad

Nuclear atypia

Morphologic variation and abnormal nuclei are weighed in context.

Mitotic activity

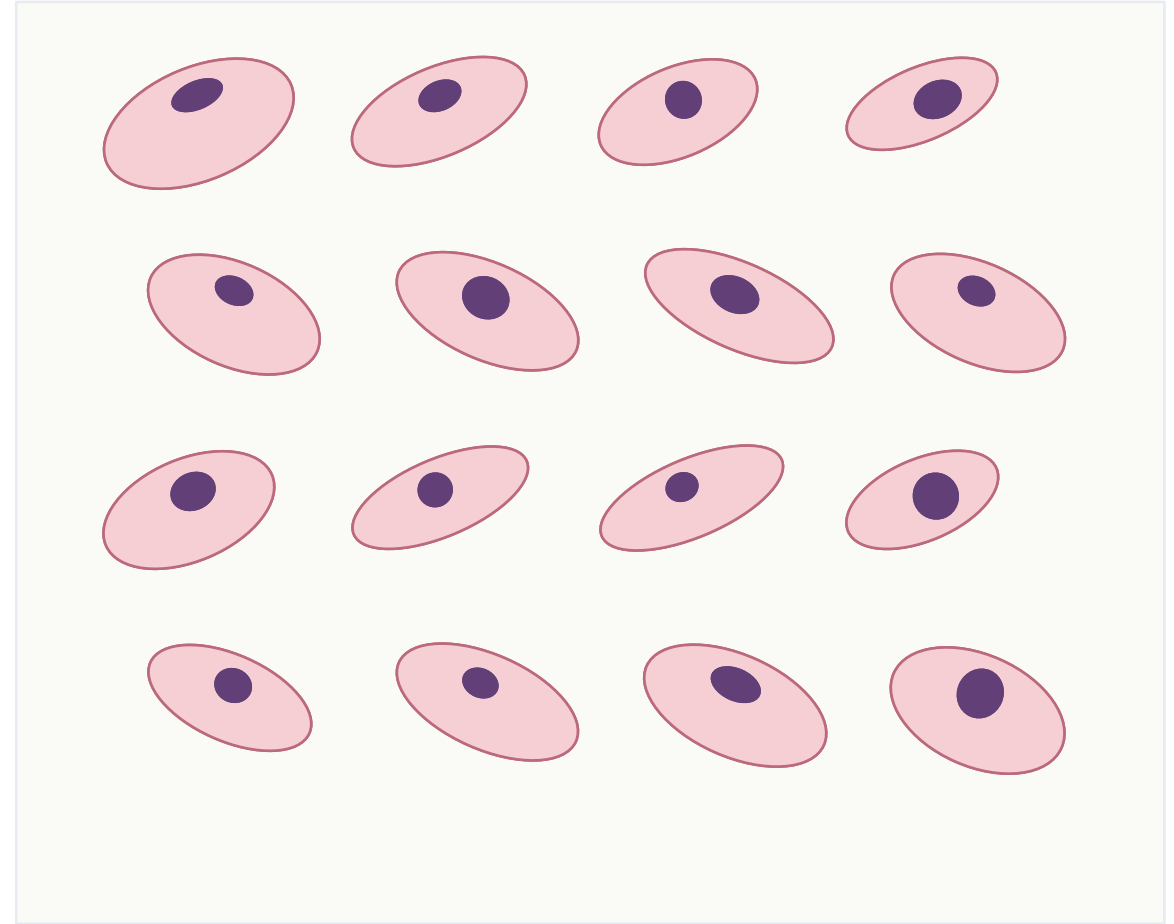
Increased mitoses support malignancy; Benign exceptions occur.

Tumor necrosis

Coagulative tumor necrosis contributes to the malignant pattern.

Nuclear atypia must be evaluated on its own terms

- Consider the severity and distribution of atypical nuclei.
- Marked atypia is part of the malignant morphologic pattern.
- Bizarre-nuclei leiomyoma illustrates why atypia alone can mislead.



Conceptual cell schematic — not a photomicrograph

Mitotic activity is important but not autonomous

- Mitotic figures reflect proliferative activity.
- Counts per 10 high-power fields in its diagnostic discussion.
- An increased count becomes more persuasive with cytologic atypia or coagulative necrosis.
- Age and pregnancy-related benign exceptions require caution.

Coagulative tumor necrosis strengthens malignancy assessment

Malignant-associated necrosis

- Coagulative tumor necrosis is one of the diagnostic discriminators identified by Robbins.
- Interpret with atypia and mitoses.

Benign degenerative change

- Large leiomyomas may show red or yellow-brown softening.
- The pathological meaning of altered tissue depends on context.

The three findings must be interpreted together

Atypia

Is nuclear atypia present, and how prominent is it?

Mitoses

How many mitotic figures are seen in the specified evaluated fields?

Necrosis

Is the pattern compatible with coagulative tumor necrosis?

Robbins threshold: At least 10 mitoses / 10 HPF

$\geq 10 / 10$ HPF

High-power fields (400× as printed)

- This threshold with malignancy in most situations.
- Accompanying nuclear atypia or coagulative necrosis strengthens the diagnosis.
- Exceptions exist; This is a textbook-level teaching rule, not a universal stand-alone algorithm.

Robbins threshold in atypical or epithelioid lesions

$\geq 4 / 10$ HPF

Textbook-described exception for
selected atypical or epithelioid tumors

- A lower threshold when nuclear atypia or large epithelioid cells are present.
- Histologic subtype and morphology matter when interpreting counts.
- Do not extend this simplification to every contemporary diagnostic variant.

Mitotically active leiomyoma is a diagnostic exception

Clinical setting

- Some leiomyomas in younger or pregnant females can show increased mitoses.
- The finding should trigger cautious assessment.

Diagnostic consequence

- An elevated count without the complete malignant context may be misleading.
- Do not reduce classification to one number.

Counting errors change diagnostic interpretation

- The denominator is 10 high-power fields.
- Field magnification, field area, and counting conventions are not specified in the extracted text.
- Avoid implying a laboratory-independent absolute cutoff without confirming the microscopy methodology.

STUMP: The category for unresolved classification

Leiomyoma

Available morphologic evidence supports benign classification.

STUMP

The evidence does not support confident benign versus malignant assignment.

Leiomyosarcoma

The combination of findings supports malignancy.

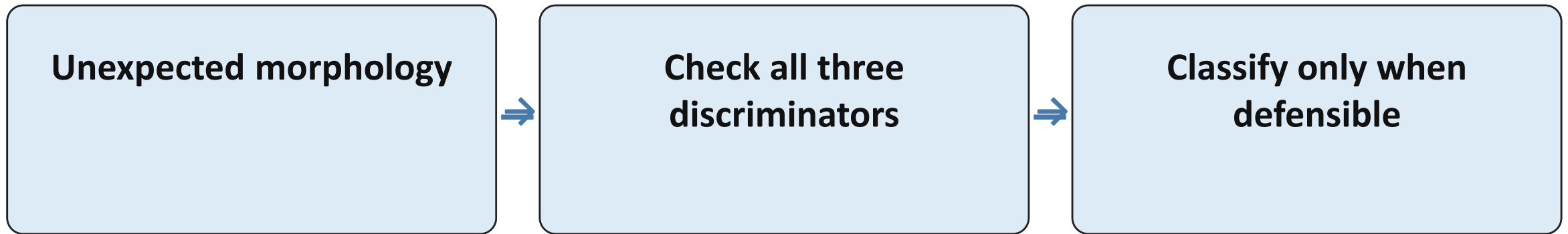
Why STUMP is not a histologic synonym for malignancy

- STUMP means smooth muscle tumor of uncertain malignant potential.
- It explicitly states that classification remains indeterminate.
- Neither a benign outcome nor definite sarcomatous behavior should be asserted on that label alone.

Benign, uncertain, and malignant tumors: Comparison

Domain	Leiomyoma	STUMP	Leiomyosarcoma
Nature	Benign	Uncertain	Malignant
Morphology	Usually bland	Indeterminate	Atypia/mitoses/necrosis considered
Clinical behavior	Usually local morbidity	Not predictable from label	Recurrent/metastatic potential
Genetics	Often simple changes	Not specified	Complex variable karyotype

A single abnormal finding can be a trap



Bizarre nuclei, cellularity, or mitoses alone may coexist with benign smooth muscle tumors.

Build a defensible morphologic description

- State the gross configuration: Circumscribed, infiltrative, or intracavitary.
- Describe nuclear atypia and overall cytologic differentiation.
- Document mitotic activity with the source-specific counting context.
- Record whether coagulative tumor necrosis is present.
- Explicitly preserve uncertainty when definitive classification is not possible.

The other uterine mesenchymal lineage is endometrial stroma

Smooth muscle lineage

- Leiomyoma and leiomyosarcoma.
- Myometrium is the principal anatomical setting.

Endometrial stromal lineage

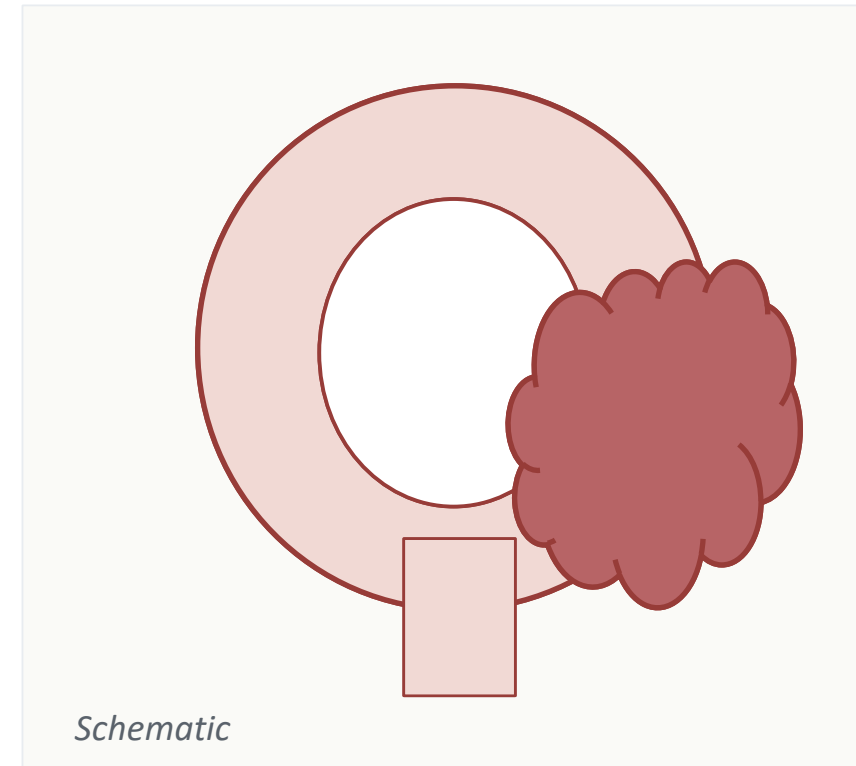
- Stromal nodule and low-/high-grade stromal sarcoma.
- Infiltration and molecular fusions enter their own classification.

Endometrial stromal nodule: Benign comparator

- Stromal nodules are described as well-circumscribed, benign tumors.
- They arise in the separate family of endometrial stromal neoplasms.
- Their classification cannot be inferred from leiomyosarcoma mitotic criteria.

Low-grade stromal sarcoma: Infiltration matters

- Low-grade endometrial stromal sarcoma resembles stromal nodule but infiltrates myometrium.
- A JAZF1 fusion involving SUZ12 or other polycomb factors is associated with many lesions.
- This context belongs to a distinct mesenchymal differential.



Conceptual wall infiltration

High-grade stromal sarcoma has distinct molecular associations

- High-grade endometrial stromal sarcoma is associated with marked atypia.
- YWHAE–NUTM2A/B and ZC3H7B–BCOR fusions.
- BCOR internal tandem duplication is also described.
- These alterations should not be recast as usual drivers of leiomyosarcoma.

Molecular contrast: Smooth muscle vs stromal sarcoma

Leiomyosarcoma context	Endometrial stromal sarcoma context
Highly variable karyotypes; TP53, RB, PTEN changes	Recurrent fusion-gene patterns provide clues to lineage
MED12 mutations in a subset	Low grade: JAZF1 / polycomb partners, often SUZ12
No single obligatory alteration listed	High grade: YWHAE–NUTM2A/B; BCOR-associated changes

Epidemiology: Peak between 40 and 60 years

40–60 years

Peak incidence

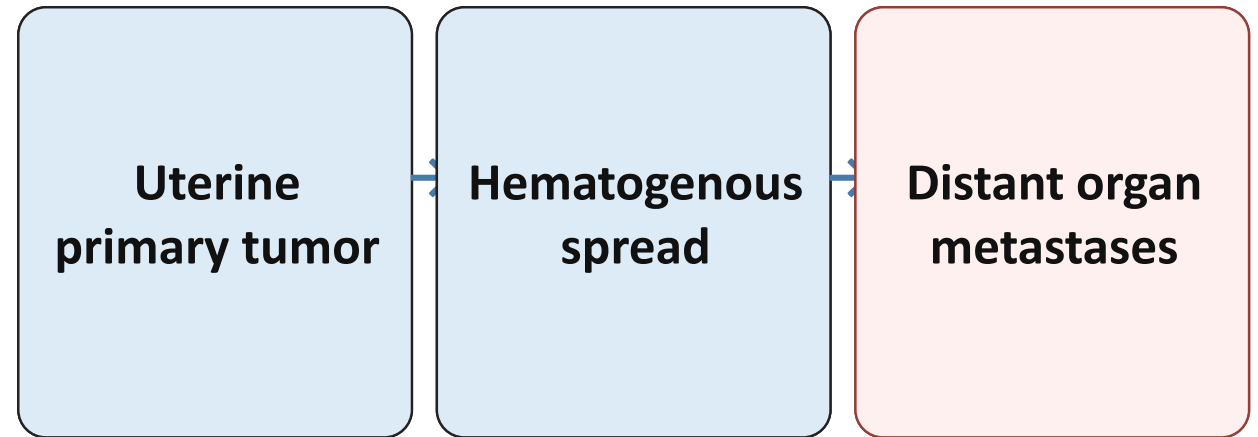
- Uterine leiomyosarcoma can occur before menopause.
- It also occurs after menopause.
- Age alone does not distinguish benign from malignant smooth muscle tumors.

Postoperative recurrence is a major clinical concern

- Leiomyosarcoma frequently recurs following surgery.
- Local treatment does not erase the risk of subsequent aggressive disease.
- Follow-up risk must be considered alongside primary morphologic diagnosis.

Hematogenous dissemination is a defining risk

- More than one-half of patients eventually develop distant hematogenous metastases,.
- Metastasis is not dependent on direct extension alone.
- The observed dissemination pattern reflects systemic malignant behavior.



Schematic route of spread

Metastatic targets include lung, bone, and brain

Lungs

A typical distant organ listed in the source.

Bone

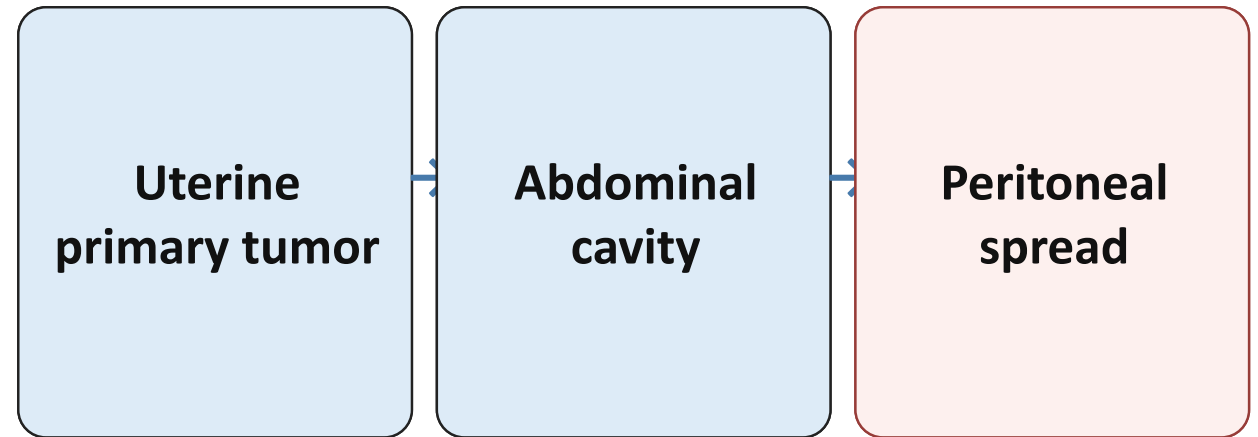
Another recognized destination for hematogenous metastasis.

Brain

Can be involved as part of distant metastatic disease.

Abdominal dissemination is another pattern

- Disease may disseminate throughout the abdominal cavity.
- This route adds to the burden beyond the primary uterine mass.
- Do not confuse sarcomatous dissemination with benign peritoneal leiomyomatosis.



Schematic route of spread

Overall survival illustrates the aggressive course

≈40%

Overall 5-year survival reported

- This estimate is taken from the 2026 textbook description.
- It is a cohort-level summary, not an individualized risk calculator.
- Do not infer a stage-specific survival rate from this number.

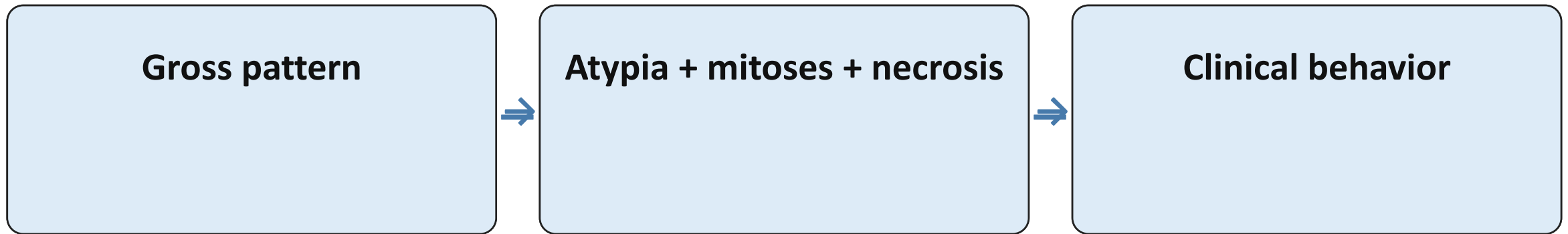
Anaplastic lesions have poorer reported outcomes

10–15%

**Textbook-reported 5-year survival
for anaplastic lesions**

- Highly anaplastic morphology with a poor prognosis.
- The figure is a historical textbook summary, not a personalized prediction.
- The text does not provide the contributing cohort or treatment-era details.

Why gross, microscopic, and clinical facts must align



Pathology classification and subsequent dissemination describe related, not interchangeable, disease attributes.

Application case: Circumscribed uterine nodule

A uterine mass is discrete, firm, gray-white, and whorled. Microscopy shows intersecting, relatively uniform smooth muscle cells with scarce mitotic figures.

Which primary category is most consistent with this pattern?

Application answer: Features favor leiomyoma

- Circumscription and the whorled, firm cut surface are typical benign gross features.
- Cellular uniformity and scarce mitoses favor leiomyoma.
- The vignette does not describe features that require calling this tumor leiomyosarcoma.

Application case: Invasive fleshy mass

A fleshy uterine tumor invades the wall. Histology shows marked nuclear atypia, prominent mitotic activity, and coagulative tumor necrosis.

Which constellation is most concerning for leiomyosarcoma?

Application answer: Malignant features converge

- Invasive fleshy growth conforms to the reported gross pattern.
- Nuclear atypia, mitoses, and coagulative necrosis reinforce one another.
- The combined pattern is substantially more informative than any isolated finding.

Application case: Atypia without a secure answer

A uterine smooth muscle tumor shows some worrisome features, but complete assessment does not permit a confident benign or malignant classification.

Which diagnostic label preserves that uncertainty?

Application answer: Preserve diagnostic uncertainty

- STUMP denotes a smooth muscle tumor of uncertain malignant potential.
- The label communicates unresolved classification rather than assured benignity.
- Avoid inventing a prognosis from the label when the source supplies none.

Five contrasts to retain

Domain	Leiomyoma	Leiomyosarcoma
Frequency	Very common	Uncommon
Origin	Benign smooth muscle	Usually de novo malignant tumor
Gross pattern	Well circumscribed; Whorled	Fleshy invasive or polypoid
Histology	Uniform cells; Scarce mitoses	Atypia, mitoses, necrosis evaluated
Clinical impact	Local morbidity	Recurrence and distant metastasis

Primary reference and interpretive limits

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. (2026), Chapter 22, “The Female Genital Tract,” pp. 920–922.
- The diagnostic count thresholds shown are the statements in this source edition; contemporary variant-specific criteria were not independently verified.
- All uterine and cellular drawings are native PowerPoint schematics, not gross or histologic specimens.
- The original textbook figure plates were not provided or reproduced.