

Undifferentiated soft tissue sarcoma

Morphology, genomic context, diagnostic exclusion and
clinicopathologic significance

Pathology lecture

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

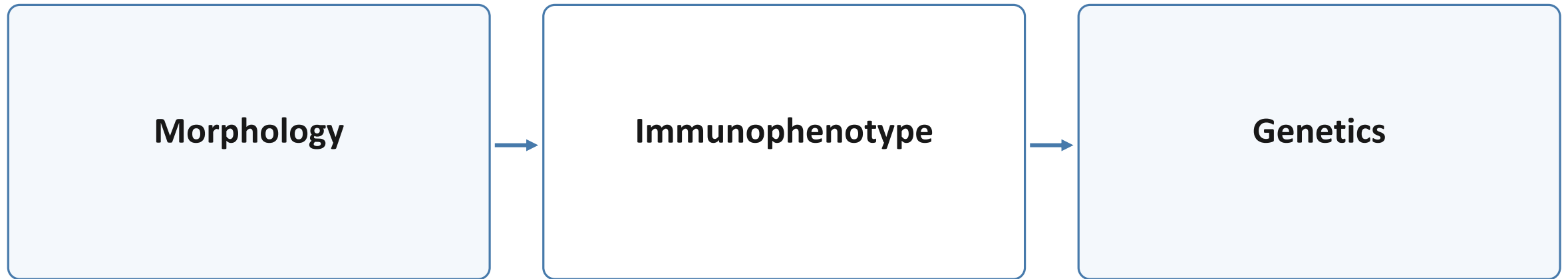
Learning objectives

- Define undifferentiated soft tissue sarcoma and its major pleomorphic subtype.
- Explain how morphology, immunophenotype and genetics contribute to classification.
- Recognize gross and microscopic patterns.
- Distinguish undifferentiated tumors from selected lineage-defined soft tissue sarcomas.
- Integrate aggressiveness, metastatic potential and management principles.

Where soft tissue pathology begins

- Soft tissue designates nonepithelial tissues outside the skeleton, joints, central nervous system and hematolymphoid system.
- Soft tissue tumors are heterogeneous neoplasms rather than one biologic disease.
- Classification depends on the recognizable differentiation and biological behavior of each lesion.

The three evidence domains in diagnosis



An undifferentiated label remains when these domains do not establish another category.

Undifferentiated is a diagnostic category

- The category includes malignant mesenchymal tumors not assignable to another entity.
- It is defined by failure to establish a particular lineage or specific tumor identity.
- An undifferentiated designation is not evidence of a new normal tissue counterpart.

Category and major subtype

Undifferentiated soft tissue sarcoma

Umbrella category: Malignant mesenchymal tumors remaining unclassified after integrated assessment.

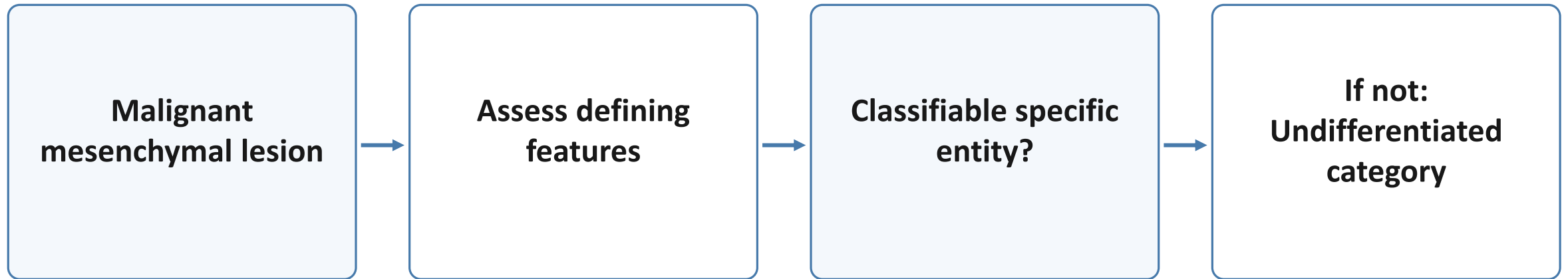
Undifferentiated pleomorphic sarcoma (UPS)

Major subtype: Anaplastic, often markedly pleomorphic and usually associated with a complex karyotype.

Why anaplasia is not an entity name

- Anaplastic cytology indicates severe loss of normal differentiation.
- Pronounced pleomorphism does not by itself identify a tissue lineage.
- Classification still requires evaluation for recognizable morphology, immunophenotype and genetic abnormalities.

A classification decision is hierarchical



Pedagogical decision schematic; Not a formal clinical testing algorithm.

Lineage information comes from distinct sources

Architecture

Fascicles, gland-like components, lipoblasts or differentiated cells may support a specific type.

Protein expression

An immunophenotypic pattern can help support differentiation.

Molecular features

Characteristic recurrent abnormalities may identify a particular sarcoma.

The limits of a negative diagnosis

- Absence of recognized differentiation is a definitional property of this category.
- An uninformative observation alone cannot prove every alternative has been excluded.
- Negative classification is a synthesis of the available morphological, immunophenotypic and genetic evidence.

Two different questions

Is the tumor malignant?

Marked cytologic atypia, abundant atypical mitoses, necrosis and clinical behavior inform malignant interpretation.

Which tumor is it?

Morphology, immunophenotype and genetic abnormalities are assessed for a defined sarcoma category.

Soft tissue tumor behavior is a spectrum

- Soft tissue lesions include benign tumors, locally aggressive intermediate lesions and highly aggressive malignancies.
- Sarcoma refers to the malignant end of this spectrum.
- Undifferentiated pleomorphic sarcoma is described as an aggressive malignant lesion.

Differentiated and undifferentiated patterns

Recognizable lineage

Some tumors recapitulate mature mesenchymal tissues such as smooth or skeletal muscle.

No recognizable lineage

Others lack a convincing normal tissue counterpart; UPS falls within this diagnostic problem.

Sarcoma precursors are generally undefined

- Sarcomas with carcinomas that may have recognized precursor lesions.
- Sarcoma precursor states are not well established.
- The parent chapter proposes a mesenchymal stem-cell origin after acquisition of oncogenic driver alterations.

Conceptual model of sarcomagenesis



General sarcoma model; Not a UPS-specific molecular pathway.

Predisposition: General sarcoma context

- Most sarcomas are sporadic with no identified predisposing cause.
- A minority arise in association with hereditary tumor-predisposition syndromes.
- The parent chapter also mentions radiation, burns, toxins and chronic inflammation for some sarcomas.
- These associations are not presented by Robbins as UPS-specific risk estimates.

Classification changes with molecular discovery

- That soft tissue tumor taxonomy continues to evolve.
- Distinctive molecular abnormalities may permit reassignment to defined categories.
- This is especially important for an undifferentiated diagnosis, which depends on available classification evidence.

Two broad sarcoma genomic patterns

Simple karyotype

A limited set of recurrent chromosomal alterations can define some tumors and assist classification.

Complex karyotype

Multiple chromosomal gains and losses indicate genomic instability and are common in adult pleomorphic tumors.

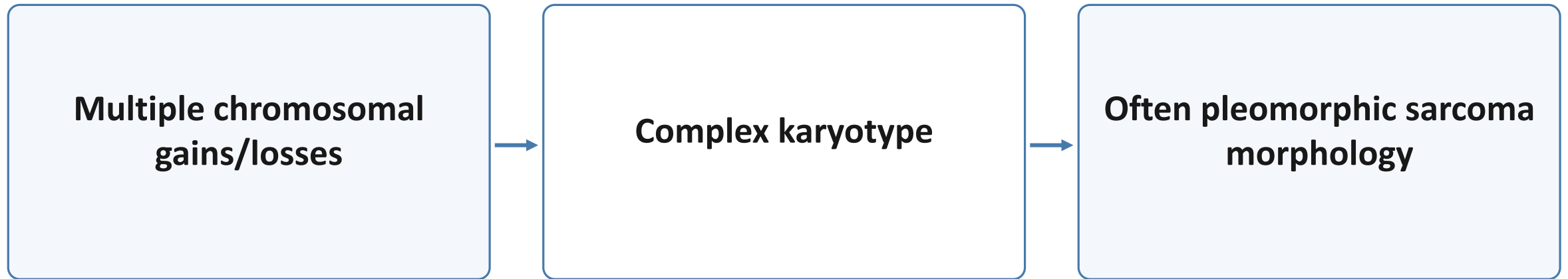
Simple karyotypes: A comparison group

- In selected sarcomas, a recurrent rearrangement yields a characteristic fusion gene.
- Such molecular events may have diagnostic utility.
- Synovial sarcoma provides the adjacent-chapter example, with an SS18::SSX fusion.

Complex karyotype: Genomic instability

- Complex-karyotype tumors typically show aneuploidy or polyploidy.
- Multiple chromosomal gains and losses imply underlying genomic instability.
- Adult sarcomas with this architecture often display pleomorphism.

Genomic instability and tumor phenotype



Association; Not a deterministic causal proof for any individual cell.

Genomics in undifferentiated pleomorphic sarcoma

- UPS typically has a complex karyotype.
- Its genomic instability is consistent with broad chromosomal heterogeneity.
- By definition, no diagnostic genetic abnormality identifies a more specific lineage or tumor type.

Complex is not the same as specific

Complex karyotype

Describes broad genomic disorganization, seen in multiple sarcoma types.

Diagnostic genetic abnormality

A characteristic change that directs classification to a defined tumor entity.

Typical patient profile

- UPS mainly affects middle-aged or older adults.
- It preferentially involves deep soft tissue.
- The extremities, especially the thigh, are emphasized description.

Typical anatomic pattern

Depth

Deep soft tissues rather than a superficial epidermal lesion.

Region

Extremity soft tissues; The thigh is a highlighted site.

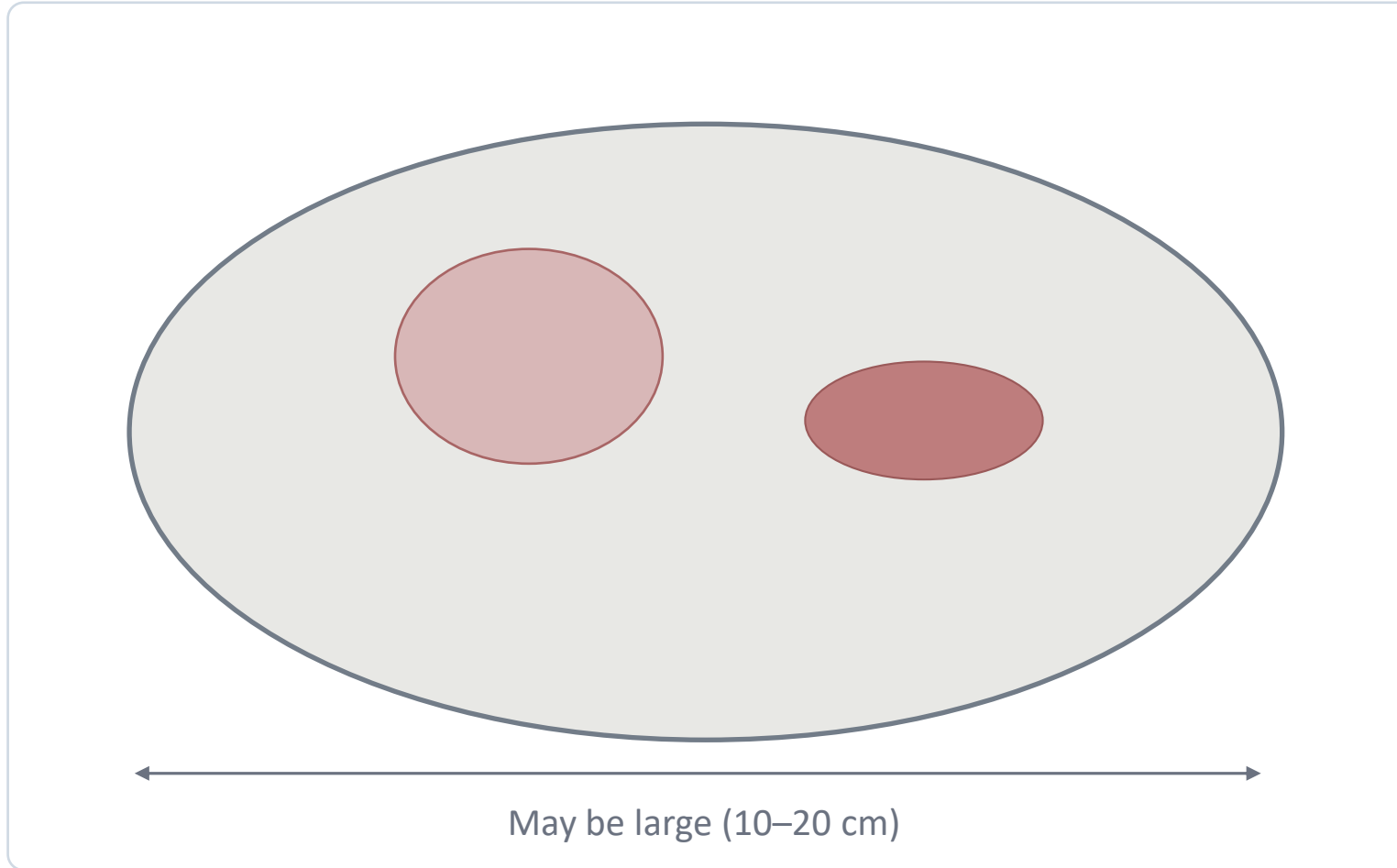
Age

Middle-aged and older adult patients predominate.

Anatomic pattern supports, but does not prove, UPS

- A large deep thigh tumor in an older adult is compatible with the reported profile.
- Smooth muscle and adipocytic sarcomas also occur in deep extremity tissues.
- Therefore, site and age help frame a differential rather than settle histologic type.

Gross morphology: Schematic overview



Gray-white

Fleshy

May reach 10–20 cm

Schematic tumor cross-section; Not a gross pathology photograph.

Size can be substantial

- Undifferentiated pleomorphic sarcomas may be large when examined grossly.
- Masses measuring approximately 10–20 cm.
- Size is a gross descriptor here, not a stand-alone criterion for diagnosing UPS.

Gross color and texture

- Masses are typically gray-white and fleshy.
- These descriptors capture the nonspecific macroscopic appearance of a high-grade soft tissue tumor.
- Final classification relies on microscopic and ancillary findings rather than color alone.

Two common gross secondary changes

Necrosis

Nonviable tumor regions are common within the gross mass.

Hemorrhage

Blood-filled or hemorrhagic areas may coexist with viable tumor.

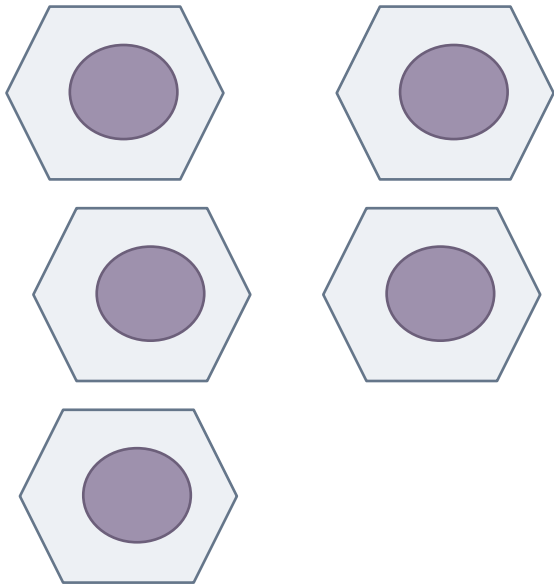
What gross heterogeneity means for interpretation

- Gross necrosis and hemorrhage are frequent in UPS.
- Viable and altered regions need not appear identical within one lesion.
- The gross appearance should be integrated with the microscopic description rather than treated as a unique signature.

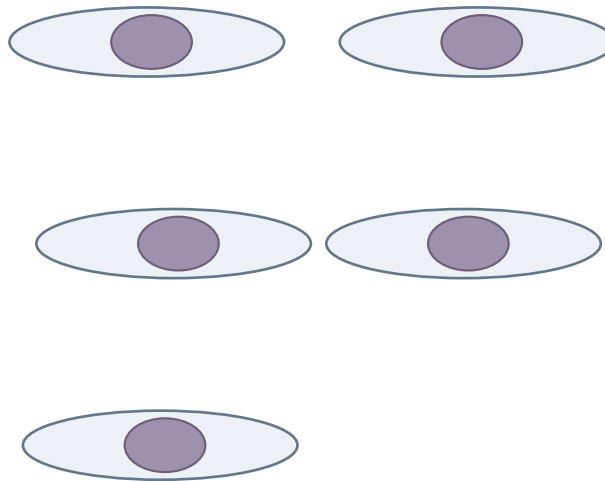
Last two statements are interpretation of the source morphology

Microscopic cell-shape diversity: Schematic

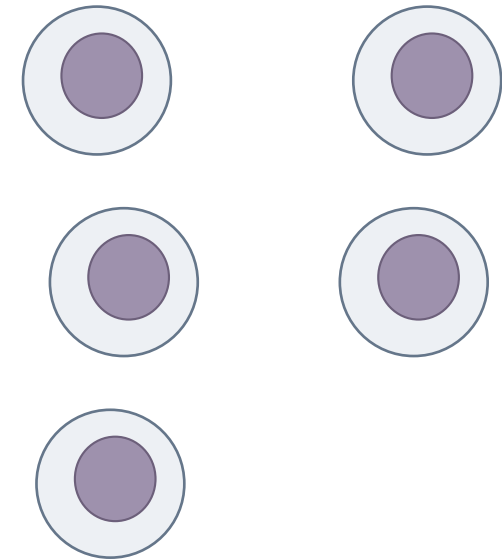
Polygonal cells



Spindle cells



Round cells



Cell-outline schematic only; Not histologic evidence.

Predominant UPS architecture

- The classic pleomorphic subtype frequently shows sheets of large anaplastic cells.
- Polygonal cellular contours are commonly described.
- Loss of orderly tissue differentiation is a central feature.

Nuclear hyperchromasia

- Neoplastic nuclei are typically hyperchromatic.
- Hyperchromasia occurs alongside marked variation in nuclear contour and size.
- This combination contributes to the cytologic impression of high-grade anaplasia.

Irregular and bizarre nuclei

- Nuclear outlines may be irregular and strikingly atypical.
- Some nuclei are described as bizarre.
- These nuclear changes are prominent features of the textbook illustration and description.

Pleomorphic versus other undifferentiated forms

Pleomorphic form

Sheets of large polygonal and markedly anaplastic cells dominate.

Other undifferentiated forms

Spindle-cell or round-cell populations can predominate; A different cell contour alone does not establish lineage.

Spindled undifferentiated tumors

- Robbins explicitly allows a predominantly spindle-cell pattern.
- Spindle morphology describes shape, not proven smooth-muscle or another mesenchymal lineage.
- Other evidence is needed to assign a specific spindle-cell sarcoma diagnosis.

Round-cell undifferentiated tumors

- Some undifferentiated soft tissue sarcomas contain predominantly round cells.
- Cell shape alone cannot identify a specific molecularly defined round-cell tumor.
- The unclassified category applies only when no specific diagnosis is established.

Mitoses are abundant

- Mitotic figures are numerous description.
- Abundance of mitoses complements marked nuclear atypia.
- This combination supports an actively proliferating malignant lesion.

Atypical versus ordinary mitotic figures

UPS

Atypical, nonsymmetric mitotic figures may be abundant.

Nodular fasciitis

Mitoses may occur, but atypical forms are notably absent in the parent chapter.

An integrated microscopic impression

Cellular architecture

Sheets of large anaplastic polygonal cells, with possible spindled or round-cell patterns.

Nuclear features

Hyperchromasia, irregularity and occasionally bizarre contours.

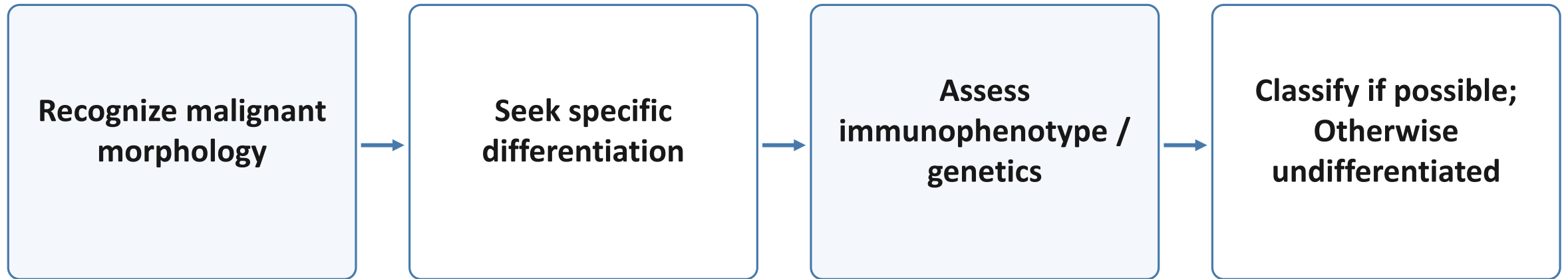
Proliferation

Numerous mitoses, including atypical forms; Necrosis may accompany the lesion.

Histomorphology has a limit

- The classic cytologic findings are characteristic of highly atypical malignant tissue.
- They do not independently establish the absence of every recognizable lineage.
- The undifferentiated category using morphology, immunophenotype and genetics together.

Integrated diagnostic reasoning



Conceptual sequence derived from the textbook definition.

Immunophenotype addresses a classification question

- Immunohistochemistry can support recognizable differentiation in selected tumors.
- The undifferentiated category lacks immunophenotypic evidence sufficient for another diagnosis.
- Robbins does not supply a positive lineage-specific UPS immunostain in this section.

Genetic testing addresses a different question

- Characteristic abnormalities can define some soft tissue sarcoma entities.
- Undifferentiated sarcoma lacks a diagnostic abnormality that establishes a specific alternative tumor.
- Complex chromosomal changes should not be confused with a unique tumor-defining rearrangement.

Synovial sarcoma: An instructive contrast

Synovial sarcoma

Monophasic tight uniform spindle cells or a biphasic pattern with gland-like epithelial structures.

Undifferentiated sarcoma

Markedly anaplastic, often pleomorphic tissue without a defining differentiated pattern.

Synovial sarcoma has a defining molecular clue

- The recurrent t(X;18) involving SS18 and SSX genes.
- Epithelial antigen expression can also support synovial sarcoma, especially the biphasic form.
- Such positive lineage or molecular evidence argues against leaving a tumor unclassified.

Leiomyosarcoma: A lineage-defined comparator

Leiomyosarcoma

Eosinophilic spindle cells with blunt-ended nuclei in interweaving fascicles.

Undifferentiated sarcoma

Markedly pleomorphic polygonal, spindle or round cells without established smooth-muscle differentiation.

Smooth-muscle protein evidence matters

- Smooth muscle actin, desmin and caldesmon as useful in diagnosing leiomyosarcoma.
- Their role is to support smooth-muscle differentiation in the appropriate context.
- No single marker or isolated stain result is presented here as a universal UPS exclusion test.

Pleomorphic liposarcoma: Another comparator

Pleomorphic liposarcoma

Anaplastic cells may occur with variable immature adipocytes (lipoblasts).

Undifferentiated sarcoma

No recognized adipocytic lineage or alternative specific diagnosis is established.

What the comparator tumors teach

- A very atypical soft tissue tumor may still belong to a defined lineage.
- Morphologic or molecular identity has priority over the generic term undifferentiated.
- The strength of a UPS diagnosis lies in the integrated exclusion of recognizable categories.

Selected diagnostic contrasts

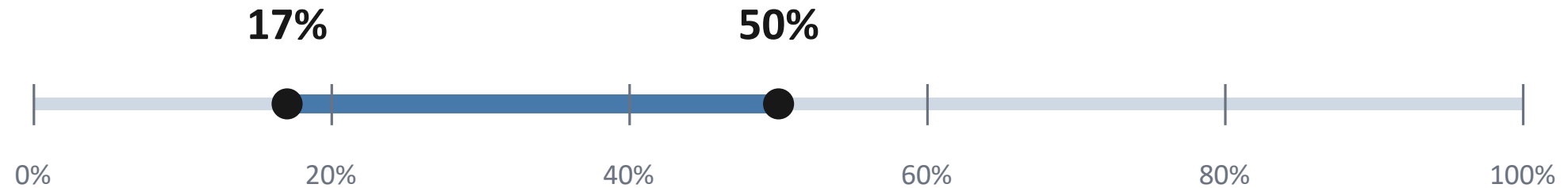
Tumor	Pattern supporting classification	Textbook distinguishing evidence
Undifferentiated sarcoma	Anaplastic, often pleomorphic	No lineage or diagnostic genetic identity
Leiomyosarcoma	Interweaving eosinophilic spindle fascicles	Smooth-muscle proteins
Synovial sarcoma	Uniform spindle $\pm$ gland-like epithelium	SS18::SSX; epithelial antigens
Pleomorphic liposarcoma	Anaplastic cells with lipoblasts	Adipocytic differentiation

Clinical behavior is aggressive

- Undifferentiated pleomorphic sarcoma is described as an aggressive malignancy.
- The tumor often presents as a large, deep soft tissue mass in its typical anatomic distribution.
- The morphologic severity is consistent with the clinically unfavorable behavior.

Metastatic risk: Reported range

Metastases occur in 17%–50% of UPS cases.



Reported range; Not a patient-specific probability estimate.

Prognosis is generally poor

- Robbins characterizes the prognosis of UPS as generally poor.
- Its potential to metastasize is clinically important.
- As with sarcomas more broadly, tumor grade and stage are relevant prognostic indicators.

Grade and stage describe different dimensions

Grade

Pathologic assessment of differentiation and other tumor features.

Stage

Extent of local disease and any metastatic spread.

The parent chapter identifies both as important prognostic indicators; No staging cutoffs are supplied.

Treatment modalities reported

Surgery

Local treatment central to management of UPS.

Radiation

May be used as an adjuvant modality.

Chemotherapy

May also be considered as adjuvant therapy.

The text gives options, not a patient-specific regimen or universal sequence.

Case study: Initial assessment

Illustrative scenario: An older adult has a deep thigh soft tissue mass.

Resection shows a gray-white, fleshy tumor with necrotic and hemorrhagic areas.

Histology reveals highly pleomorphic anaplastic cells and abundant atypical mitoses.

What features are compatible with UPS, and what information is still required?

Case study: Interpretation

- Age, depth and location match the pattern for UPS.
- Gross and histologic findings resemble the pleomorphic subtype.
- A final undifferentiated category still depends on not establishing a more specific diagnosis by morphology, immunophenotype or genetics.

Case study: Diagnostic redirection

Illustrative scenario: A pleomorphic spindle-cell tumor is suspected to represent UPS.

Additional analysis demonstrates a convincing smooth-muscle phenotype and compatible fascicular morphology.

The evidence now supports lineage-specific classification.

Should the tumor still be called undifferentiated?

Case study: Resolution

- No. Once convincing differentiation establishes a more specific sarcoma category, the undifferentiated designation is not appropriate.
- Smooth-muscle morphology and protein expression as diagnostic evidence for leiomyosarcoma.
- Cellular pleomorphism and genomic complexity do not negate positively established lineage.

Avoid four interpretive errors

- Calling every high-grade pleomorphic tumor UPS before evaluating specific differentiation.
- Equating spindle or round cell shape with a defined lineage.
- Using a complex karyotype as though it were a UPS-specific molecular signature.
- Interpreting a textbook metastasis range as an individualized prognosis.

Integrated conclusions

- Undifferentiated soft tissue sarcoma is an exclusion-based malignant mesenchymal category.
- UPS is the major subtype, classically arising in deep extremity soft tissues of older adults.
- Large gray-white masses, necrosis, hemorrhage, pleomorphism and atypical mitoses are prominent features.
- Complex genomics and absence of defining differentiation are central to its classification.
- Aggressive clinical behavior warrants careful clinicopathologic integration.

Principal reference

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th edition (2026).

Chapter: Bones, Joints, and Soft Tissue Tumors.

Primary sections: Soft Tissue Tumors; Tumors of Uncertain Origin; Undifferentiated Soft Tissue Sarcoma.

Comparative sections: Liposarcoma, Nodular Fasciitis, Leiomyosarcoma, Synovial Sarcoma.