

Malignant Mesothelioma

Pleural pathology • morphology • diagnostic reasoning

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Learning outcomes

- Connect asbestos exposure and the long latency period to pleural mesothelioma.
- Recognize diffuse pleural encasement and the three histologic patterns.
- Interpret mesothelial and epithelial immunohistochemical panels.
- Distinguish primary pleural mesothelioma from common mimics and apply WHO 2021 refinements.

Pleural neoplasia: Primary versus secondary

- Primary pleural malignancy includes mesothelioma; Primary mesothelial disease is uncommon.
- Secondary pleural involvement by tumors arising elsewhere is more frequent.
- Lung and breast primaries are common sources of metastatic pleural disease.
- A pleural mass or effusion therefore requires evaluation of tumor origin.

Primary pleural tumor
mesothelioma

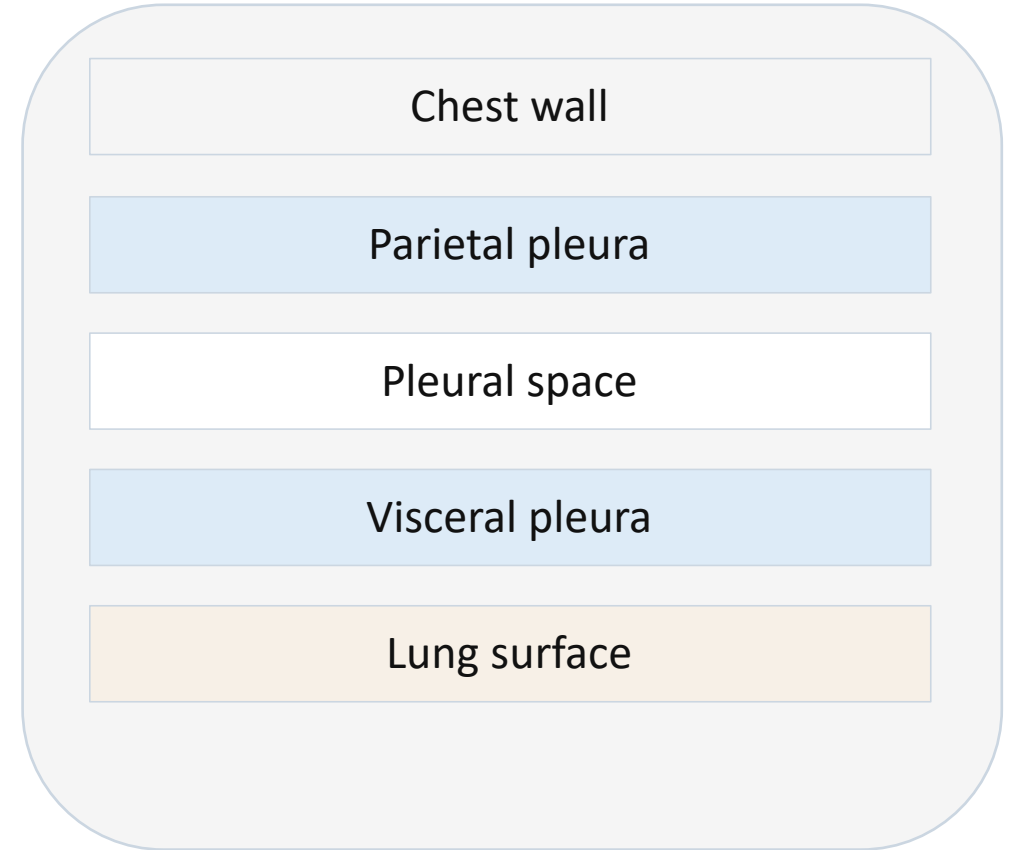
Versus

Secondary pleural deposits
metastatic carcinoma

Schematic — not a diagnostic specimen

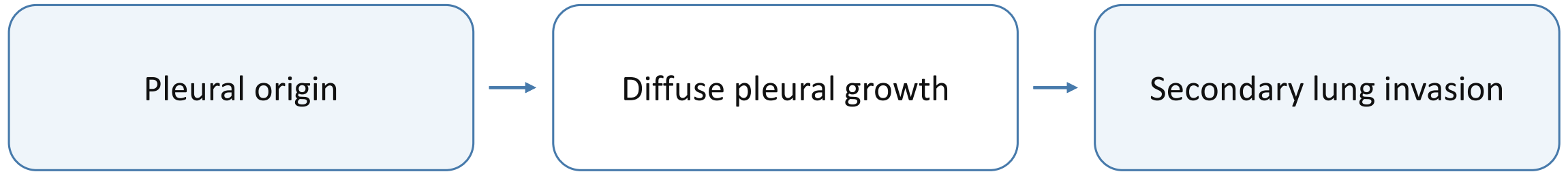
Mesothelial origin and pleural compartments

- Pleural mesothelioma can arise from visceral or parietal pleura.
- The visceral pleura covers the lung; The parietal pleura lines the thoracic cavity.
- Diffuse spread in the pleural space underlies the characteristic encasing pattern.



Schematic — not a diagnostic specimen

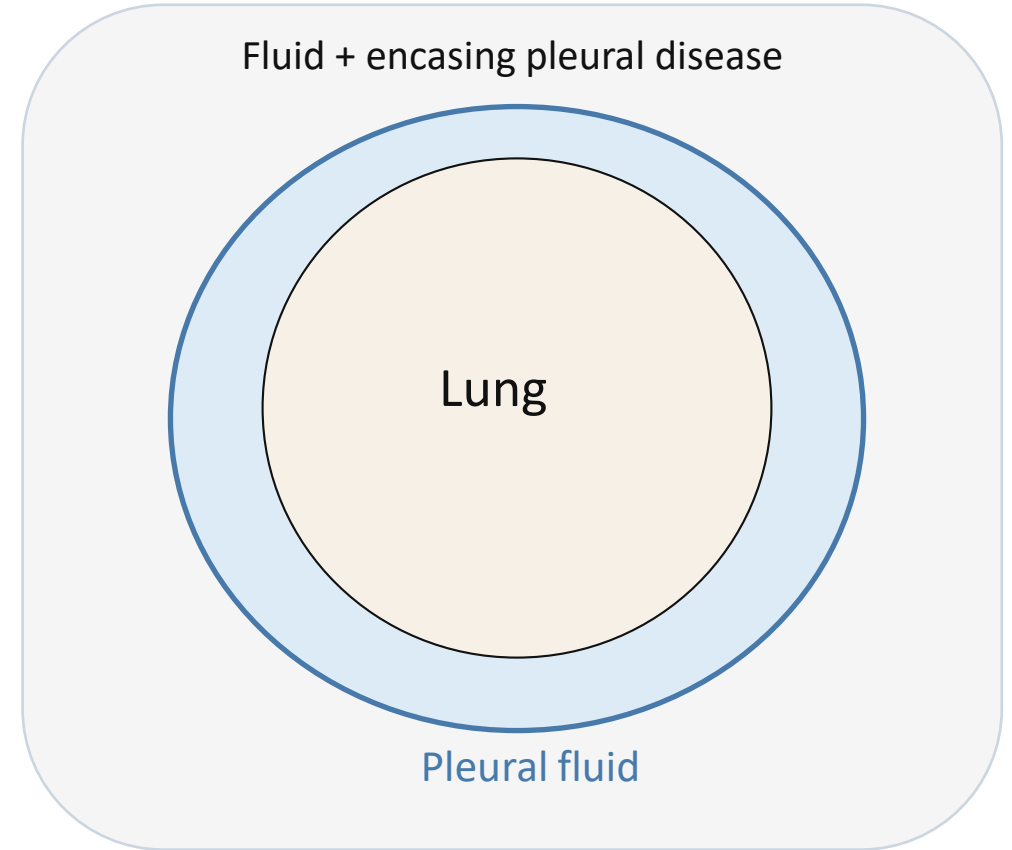
An anatomical rather than parenchymal cancer



- The primary lesion originates at the pleural lining, not in the pulmonary alveoli.
- Direct extension can subsequently invade the underlying lung.
- Differentiating site of origin matters when pleural carcinoma is in the differential.

Clinical entry point: A pleural syndrome

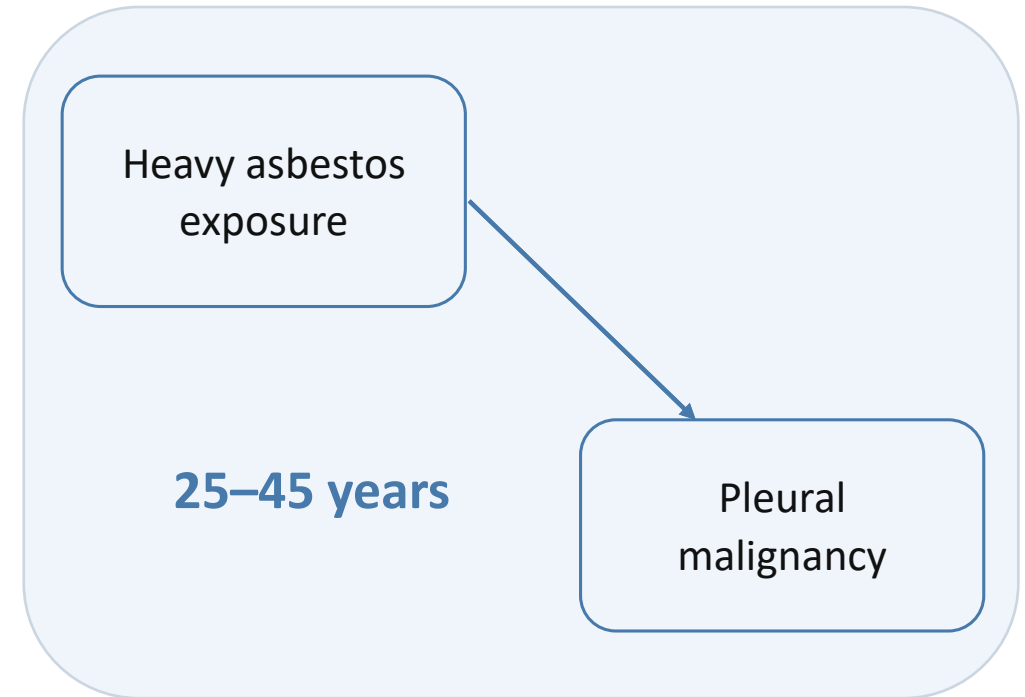
- Chest pain, dyspnea, and recurrent pleural effusion are typical presenting features.
- Symptoms reflect pleural disease and its effects on thoracic mechanics.
- The clinical presentation alone is not specific enough for a mesothelioma diagnosis.



Schematic — not a diagnostic specimen

Asbestos association is central to epidemiology

- Heavy asbestos exposure is the dominant documented etiologic association.
- Strong exposure links in historic shipbuilding and mining populations.
- Exposure history should be obtained with attention to industry and elapsed time.



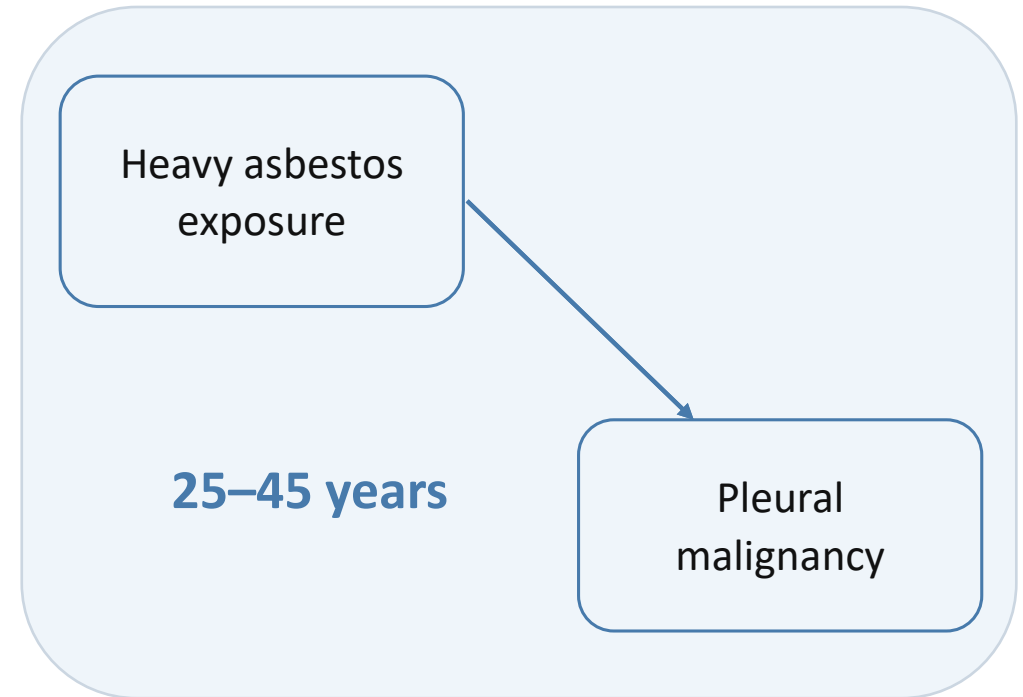
Schematic — not a diagnostic specimen

Historical occupational clusters

- Coastal shipping industries in the United States and Great Britain.
- Mining regions in Canada, Australia, and South Africa are also cited.
- In selected high-exposure populations, up to 90% of mesotheliomas were asbestos-related.
- The figure is context-specific; Do not generalize it to all contemporary patients.

Long latency is diagnostically important

- A 25–45-year interval for asbestos-associated mesothelioma.
- An exposure decades earlier remains relevant in a new pleural malignancy.
- The absence of recent exposure does not negate a historical asbestos link.



Schematic — not a diagnostic specimen

Exposure risk is not disease certainty

- A lifetime mesothelioma risk of up to 7–10% in heavily exposed persons.
- This estimate concerns heavily exposed groups, not the general population.
- Most exposed persons do not necessarily develop the disease; Individual risk cannot be assigned from this figure alone.

Smoking: A crucial etiologic distinction

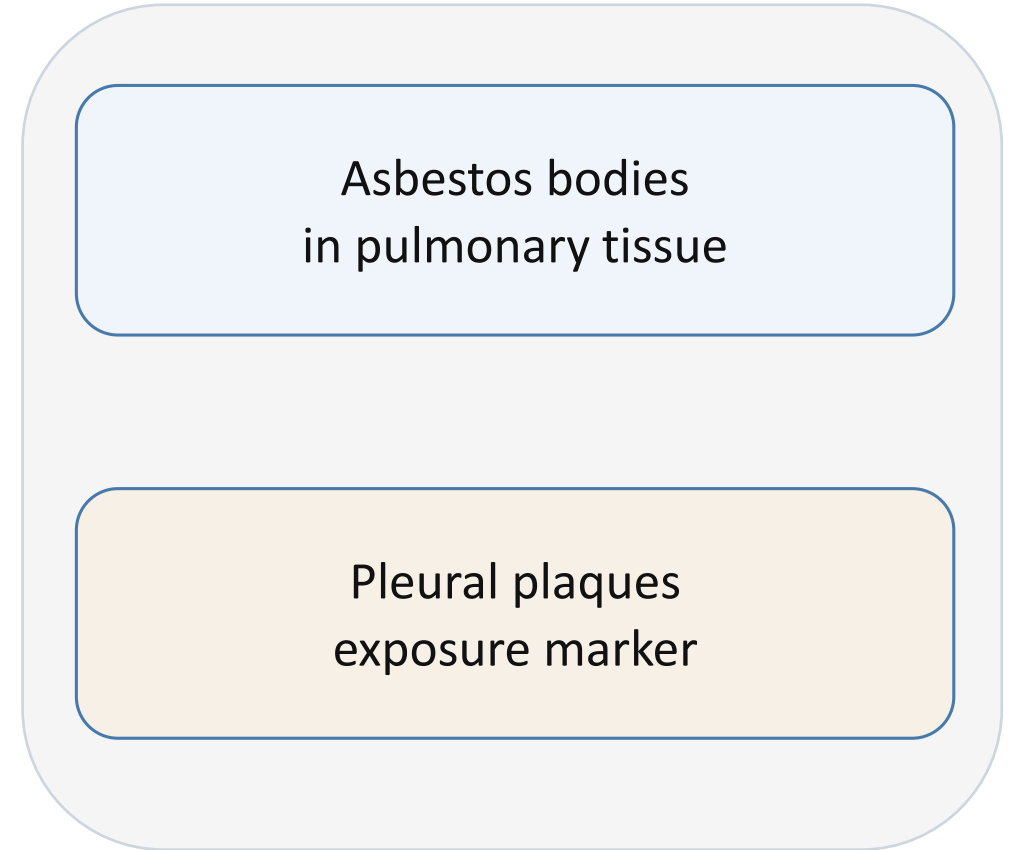
Question	Mesothelioma	Lung carcinoma
Heavy asbestos exposure	Strong association	Established association
Smoking interaction	No apparent increase reported	Risk markedly magnified
Primary site	Pleura	Lung parenchyma

Why asbestos workers may die of lung carcinoma

- Asbestos exposure predisposes to both mesothelioma and pulmonary carcinoma.
- The carcinogenic combination of asbestos and smoking is particularly strong for lung carcinoma.
- The textbook therefore notes higher lung carcinoma mortality than mesothelioma in asbestos workers, especially smokers.

Asbestos bodies and pleural plaques

- Increased asbestos bodies in lung tissue support prior exposure.
- Pleural plaques are another marker of asbestos exposure.
- These exposure markers should not be confused with the diagnosis of invasive mesothelioma.



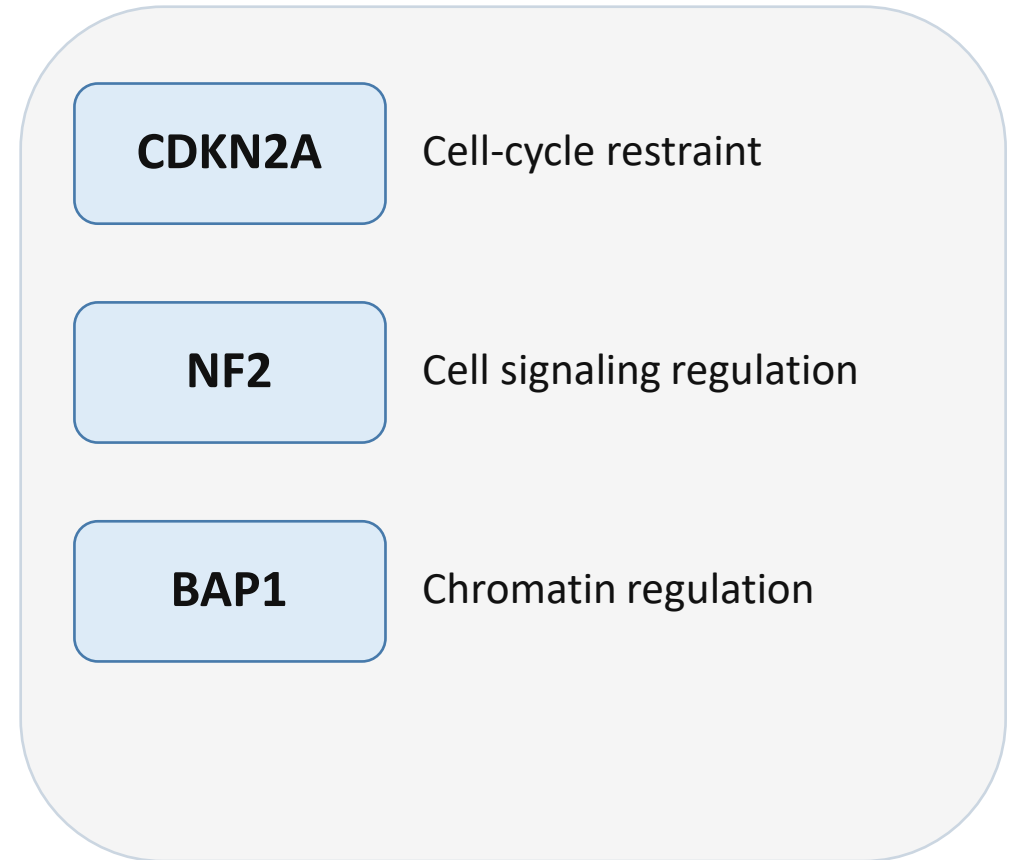
Schematic — not a diagnostic specimen

Asbestosis need not accompany mesothelioma

- Pulmonary asbestosis denotes associated interstitial fibrosis.
- Concurrent pulmonary asbestosis in only about 20% of pleural mesothelioma cases.
- Absence of interstitial fibrosis does not exclude a pleural mesothelioma.

Etiology and the molecular disease model

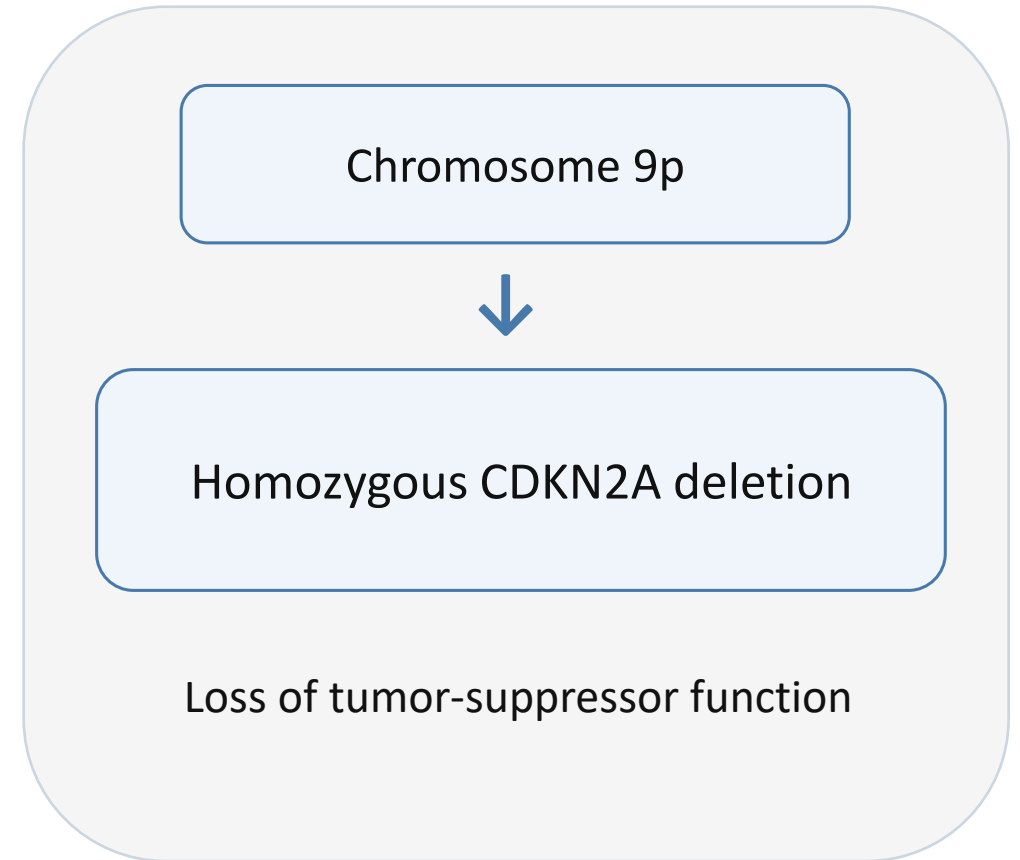
- Strong asbestos association identifies an exposure pathway at the population level.
- Mesotheliomas frequently show alterations of tumor-suppressor genes.
- CDKN2A, NF2, and BAP1 as central genetic abnormalities.
- The exact causal sequence from individual fiber exposure to each alteration is not established by this excerpt.



Schematic — not a diagnostic specimen

CDKN2A: A frequent deletion

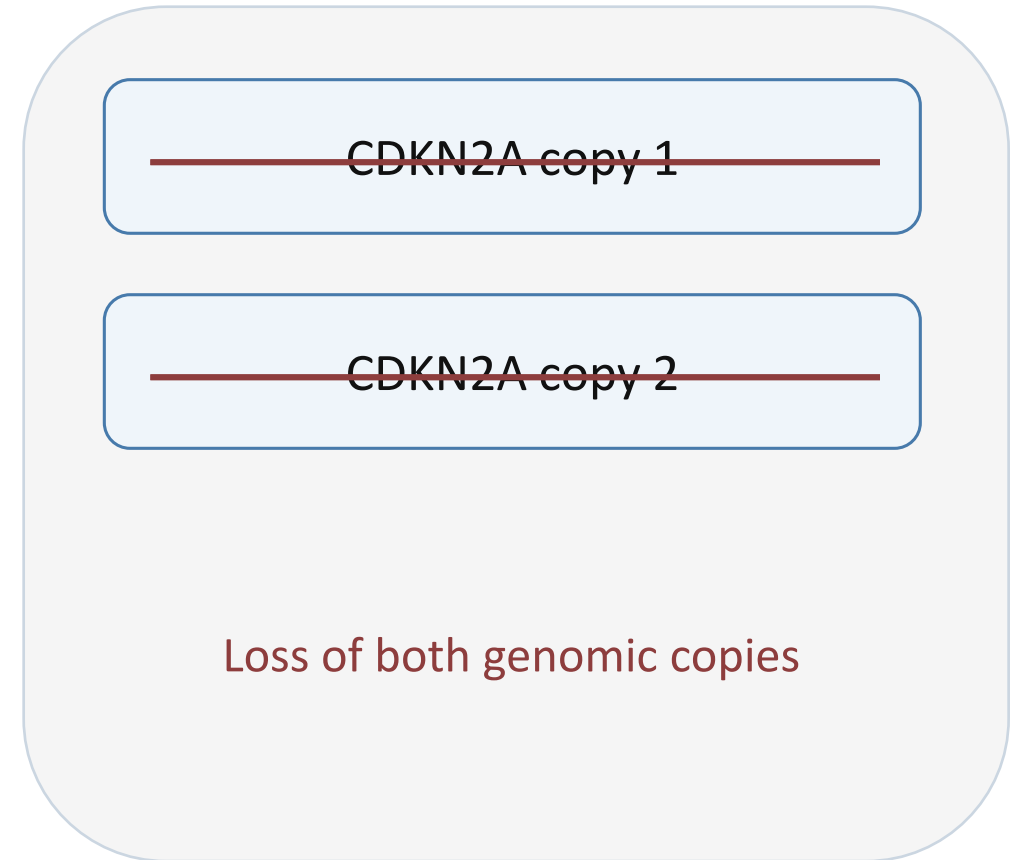
- Homozygous chromosome 9p deletion can eliminate the tumor suppressor CDKN2A.
- This event in about 80% of mesotheliomas.
- The 80% value is the textbook estimate, not a substitute for cohort-specific testing performance.



Schematic — not a diagnostic specimen

Why a homozygous deletion matters

- “Homozygous deletion” means loss of both genomic copies at the affected locus.
- Loss of a tumor-suppressor locus removes a key growth-restraining function.
- For diagnostics, gene deletion and absence of protein staining are different observations and assays.



Schematic — not a diagnostic specimen

NF2: Cell-signaling regulation

- NF2 is a recurrently altered gene in sequenced mesothelioma genomes.
- The NF2 product is a regulator of cell signaling.
- Its disruption supports a model of disordered growth control, rather than a single-pathway diagnosis.

CDKN2A

Cell-cycle restraint

NF2

Cell signaling regulation

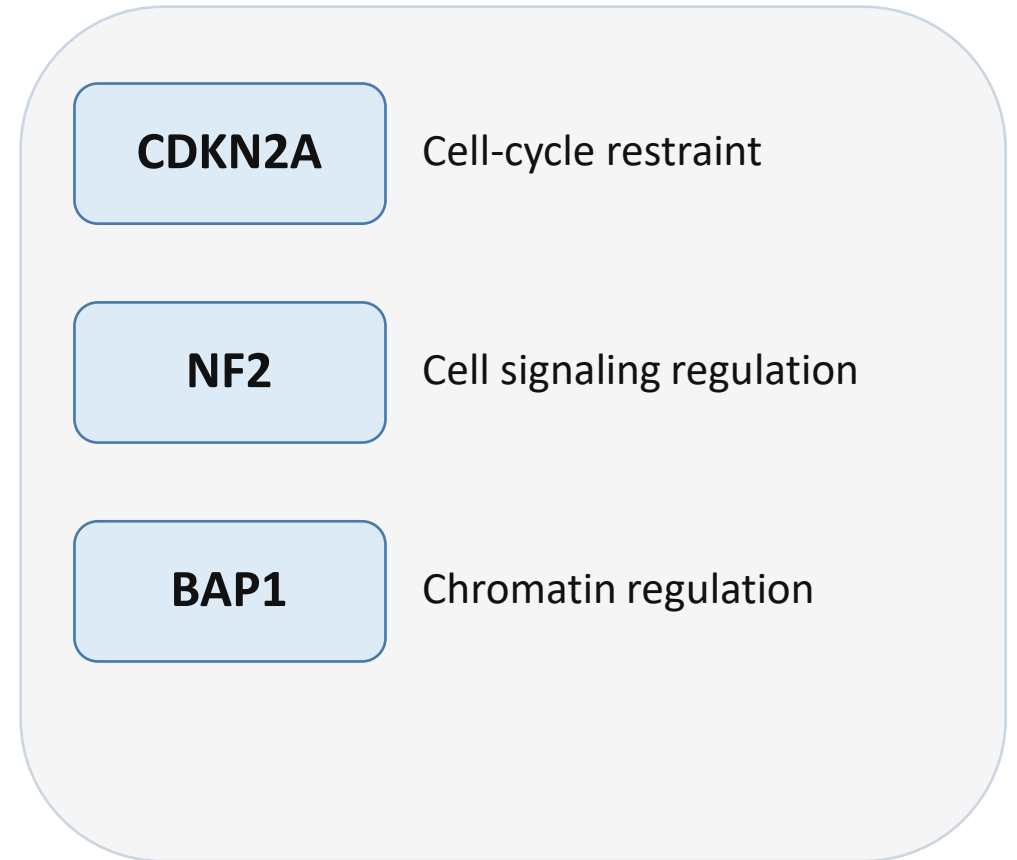
BAP1

Chromatin regulation

Schematic — not a diagnostic specimen

BAP1: Chromatin-associated tumor suppression

- BAP1 is a recurrent mesothelioma driver gene.
- The protein interacts with BRCA1 and participates in chromatin regulation.
- The genetic finding connects mesothelioma biology with altered gene-regulatory machinery.



Schematic — not a diagnostic specimen

Germline BAP1 and inherited susceptibility

Aspect	Germline BAP1	Somatic BAP1
Where present	Constitutional tissues	Tumor-acquired cells
Teaching relevance	Inherited predisposition	Tumor pathogenesis
Implication	Familial risk assessment	Tumor characterization

Molecular abnormalities are complementary

- CDKN2A loss, NF2 alterations, and BAP1 alterations affect different regulatory processes.
- No single alteration defines the entire morphologic spectrum.
- Integrate molecular information with gross pathology, microscopic morphology, and immunophenotype.

CDKN2A

Cell-cycle restraint

NF2

Cell signaling regulation

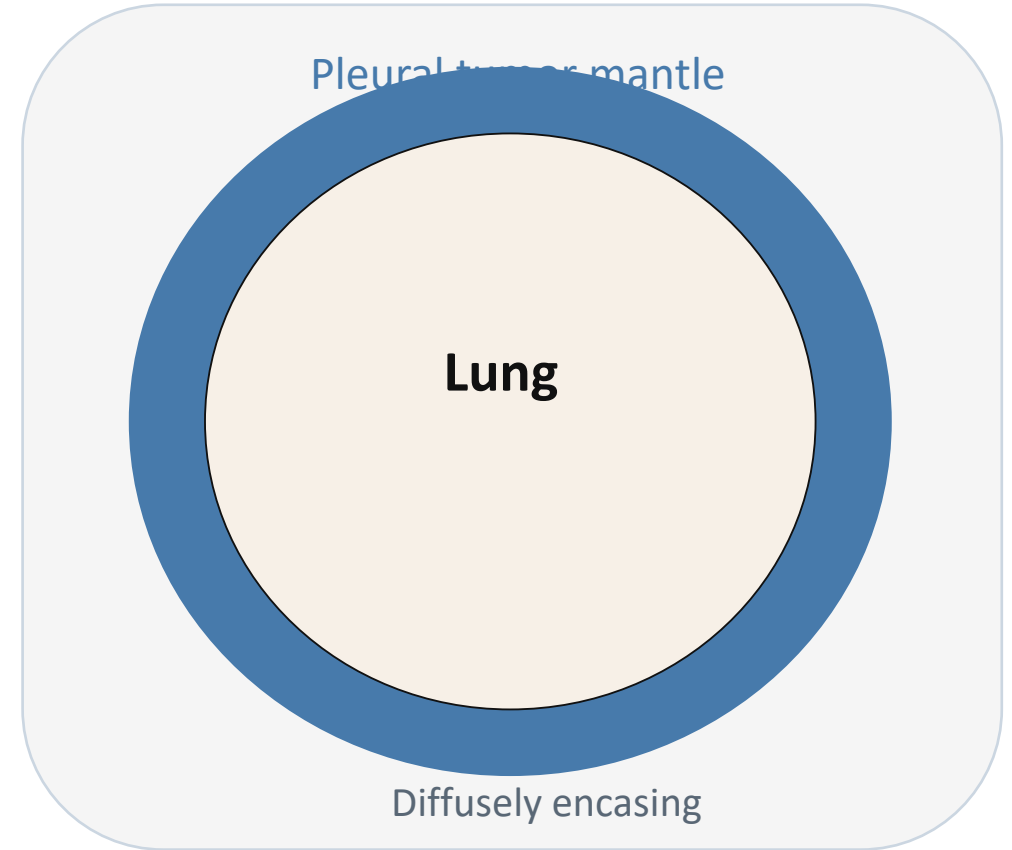
BAP1

Chromatin regulation

Schematic — not a diagnostic specimen

The distinctive gross growth pattern

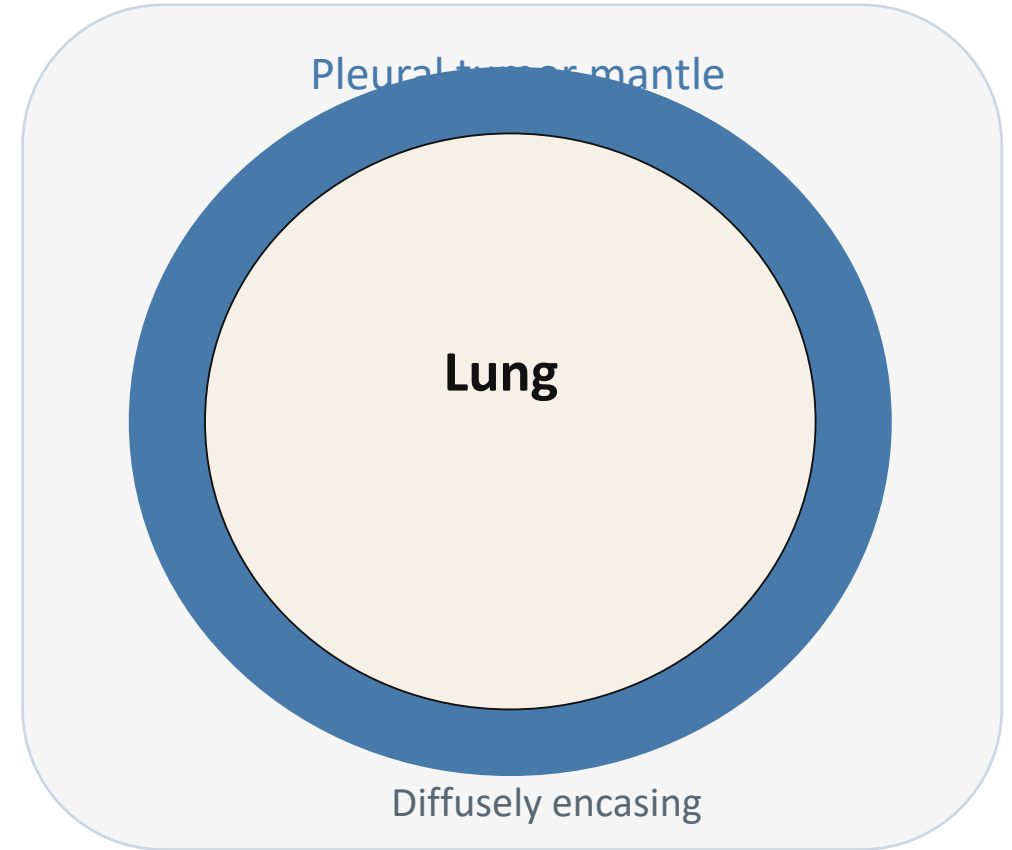
- Diffuse pleural mesothelioma spreads widely over pleural surfaces.
- Tumor tissue can form a thick mantle that ensheathes the lung.
- A soft, gelatinous, gray-pink gross appearance.
- Gross color and texture alone cannot establish tumor type.



Schematic — not a diagnostic specimen

A pleural rind restricts the enclosed lung

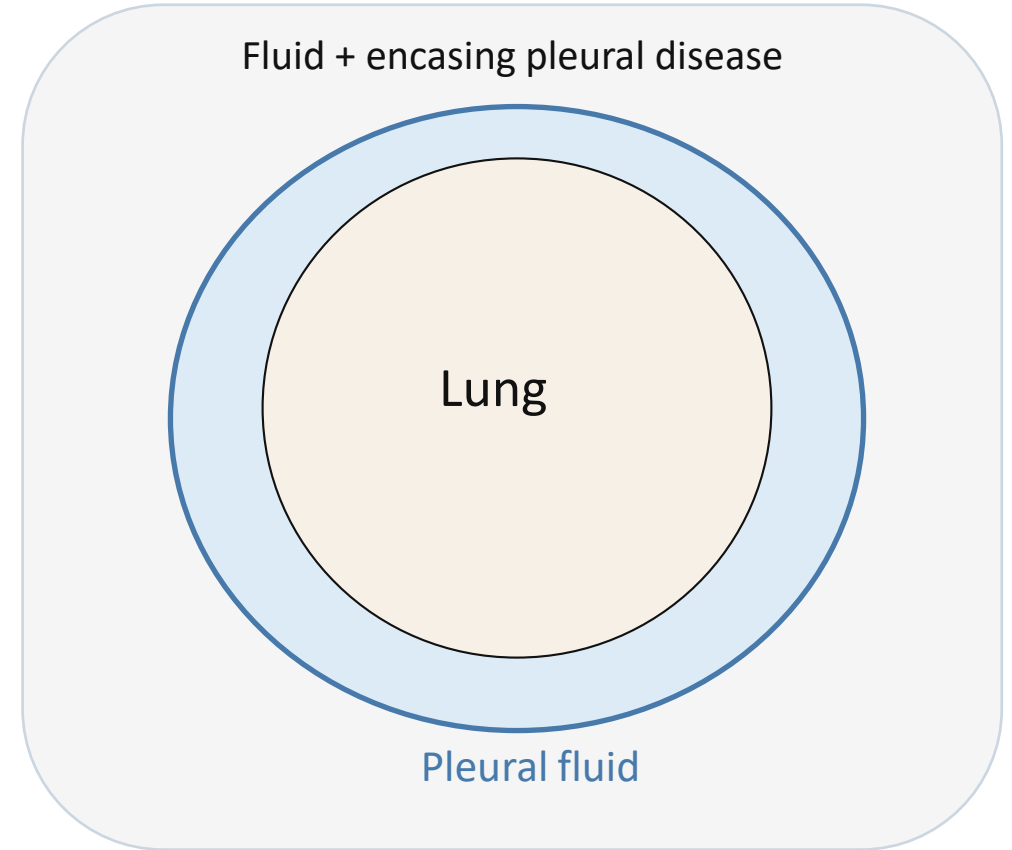
- The lesion grows along pleural surfaces instead of behaving as a solitary intrapulmonary nodule.
- An encasing pleural mantle anatomically constrains expansion of the underlying lung.
- This provides a clinicopathologic explanation for dyspnea alongside associated effusion.



Schematic — not a diagnostic specimen

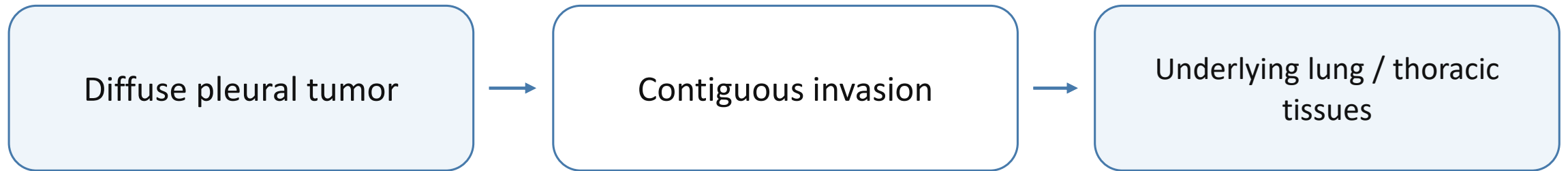
Pleural fluid is part of the gross phenotype

- Extensive pleural effusion frequently accompanies diffuse mesothelioma.
- Repeated fluid accumulation can become a major symptom-producing feature.
- The presence of effusion is not specific: Inflammation and metastatic tumors also cause pleural fluid.



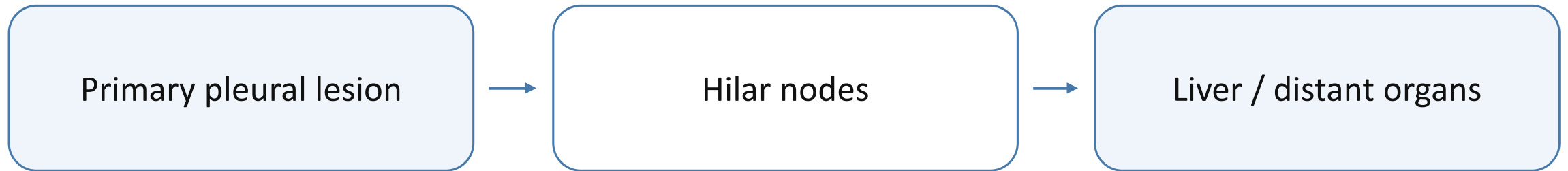
Schematic — not a diagnostic specimen

Direct invasion of neighboring structures



- Mesothelioma is locally aggressive and invades thoracic structures directly.
- Robbins specifically describes extension into the adjacent lung.
- Local anatomical spread should be distinguished from distant metastatic spread.

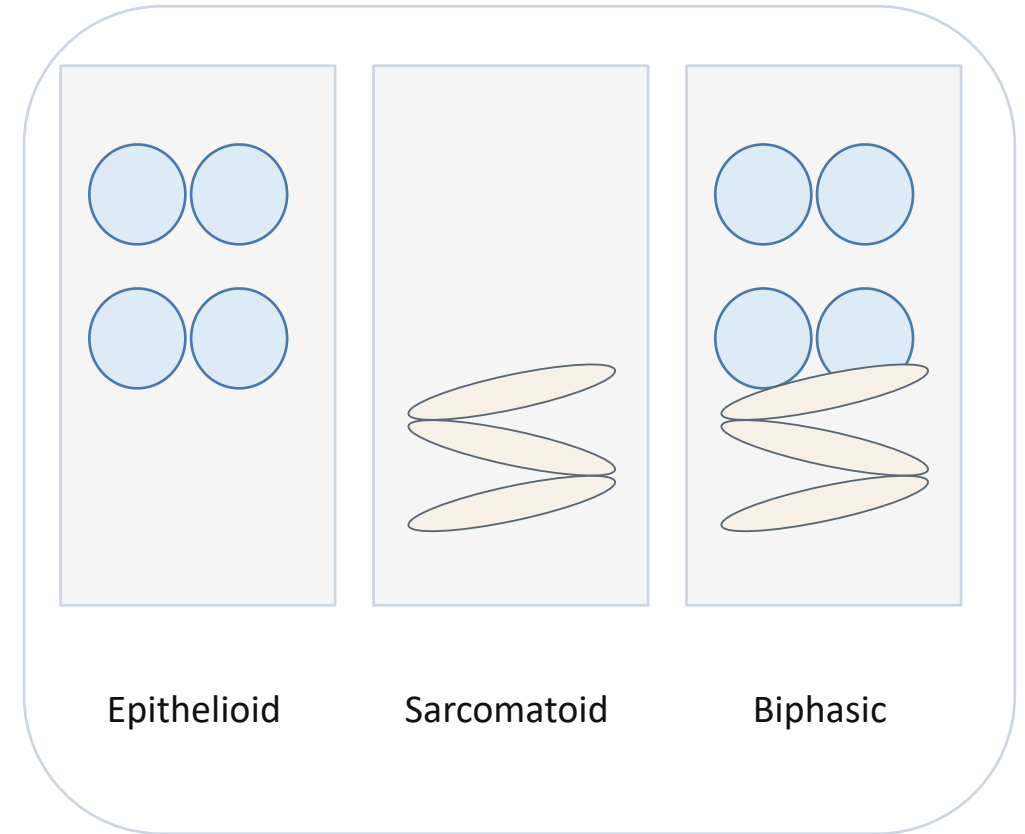
Distant spread occurs in advanced disease



- Hilar lymph nodes may be involved as disease progresses.
- Robbins also describes eventual spread to the liver and other distant sites.
- The pathologic description links regional and distant spread to aggressive clinical behavior.

Three principal microscopic patterns

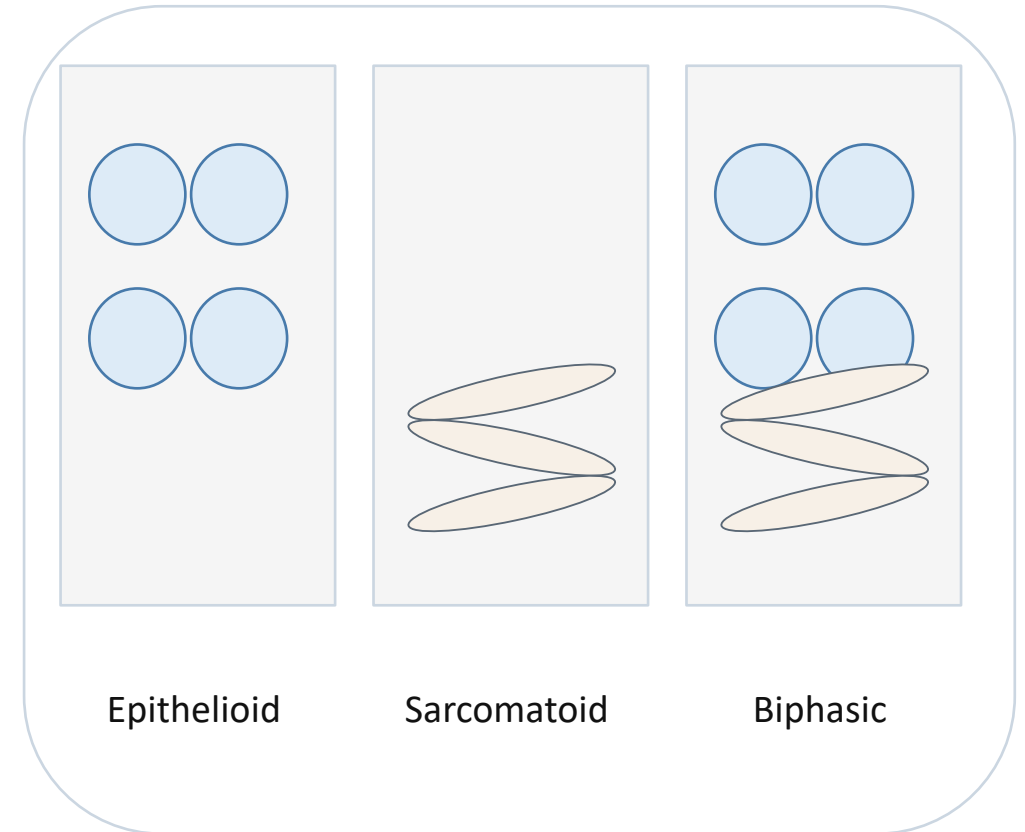
- Epithelioid, sarcomatoid, and biphasic are the three main histologic categories.
- Epithelioid as the dominant pattern (60–80%).
- Sarcomatoid (10–12%) and biphasic (10–15%) complete the textbook distribution.
- Percentages reflect the cited description and may vary by case series.



Schematic — not a diagnostic specimen

Mesothelial differentiation permits two patterns

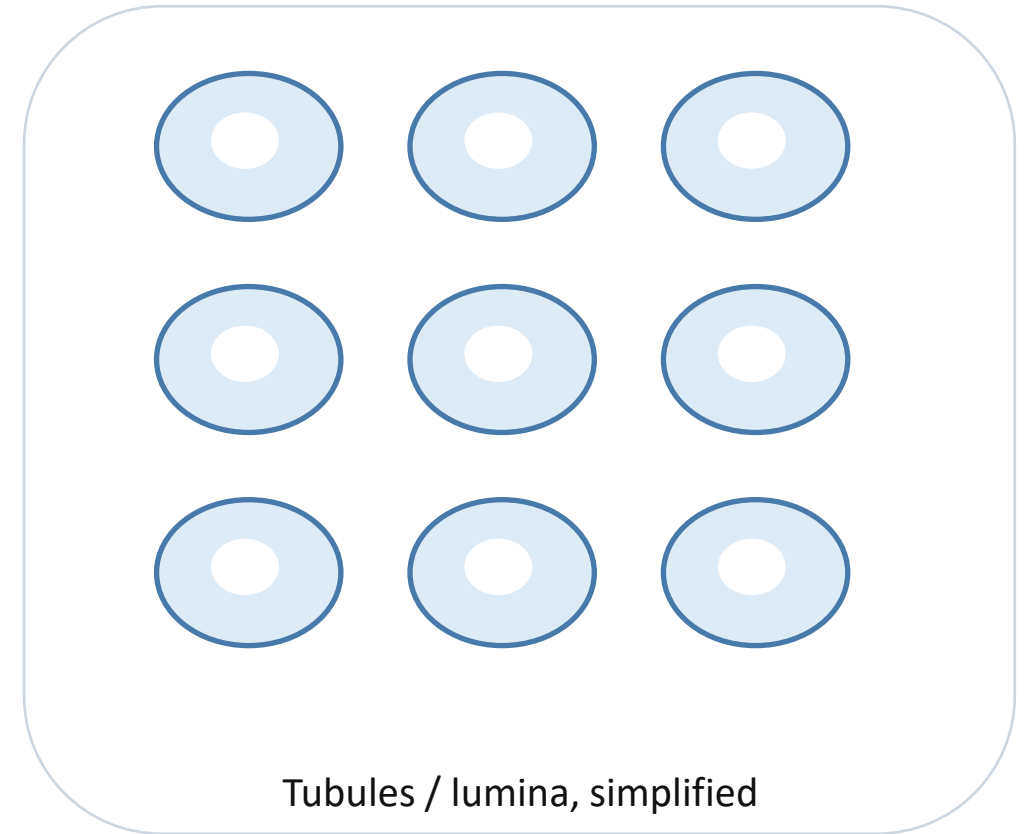
- Mesothelial tumor cells may adopt epithelium-like or mesenchymal-like morphologies.
- The epithelioid phenotype forms cohesive structures; The sarcomatoid phenotype is spindle-cell dominant.
- A biphasic tumor contains both histologic appearances.



Schematic — not a diagnostic specimen

Epithelioid mesothelioma: Cell shape

- Tumor cells may be cuboidal, columnar, or flattened.
- The cells can organize into structures resembling glandular epithelium.
- Cell shape by itself does not exclude pulmonary adenocarcinoma.

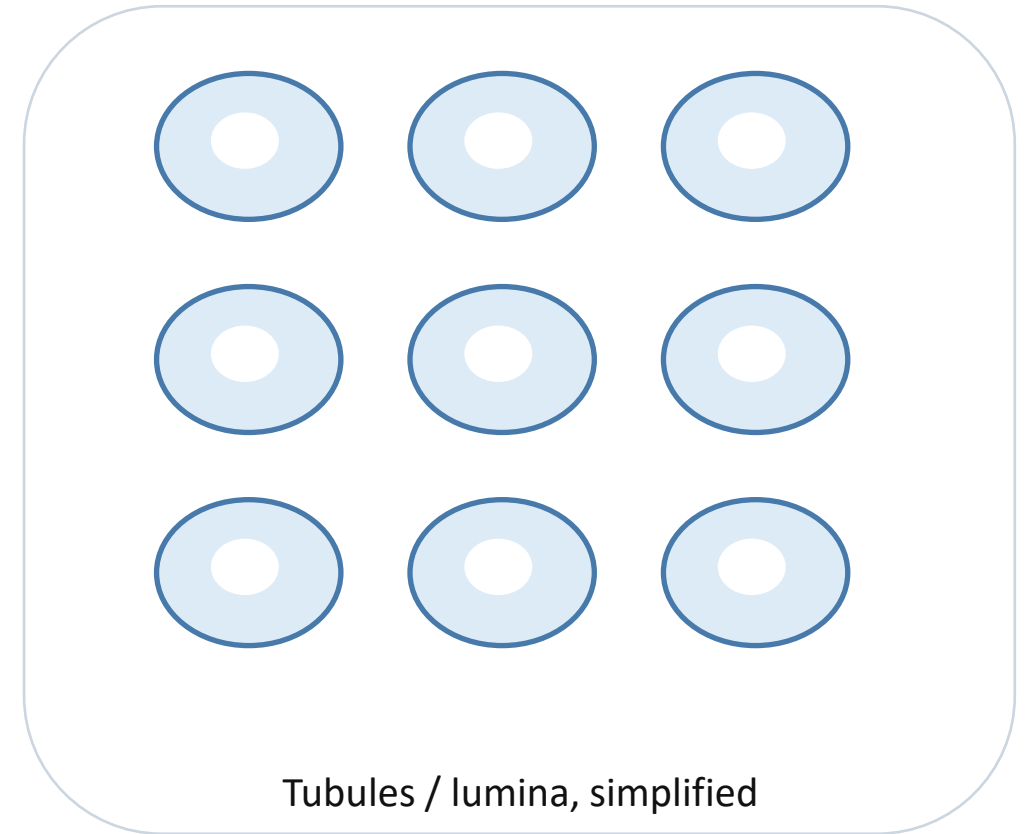


Tubules / lumina, simplified

Schematic — not a diagnostic specimen

Epithelioid mesothelioma: Architecture

- Tubular structures are a common epithelioid pattern in the Robbins description.
- Papillary architecture is another important pattern.
- These arrangements may mimic adenocarcinoma and motivate a discriminating immunopanel.



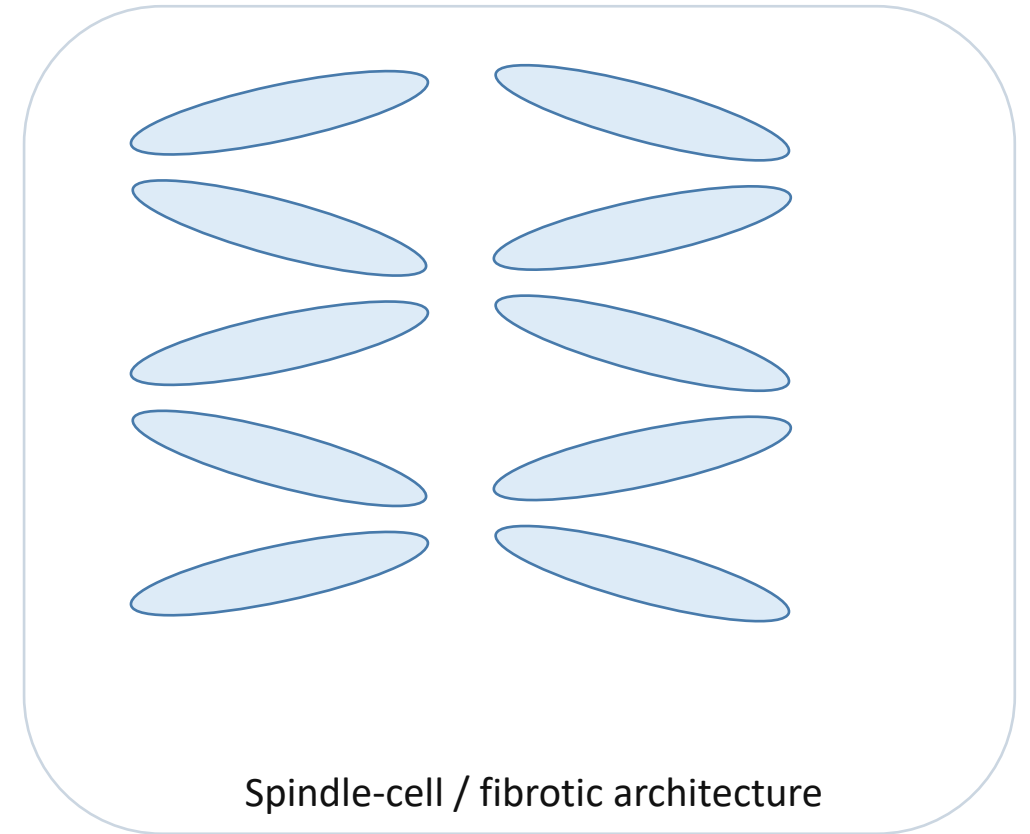
Schematic — not a diagnostic specimen

Why adenocarcinoma is a major mimic

Feature	Epithelioid mesothelioma	Pulmonary adenocarcinoma
Typical primary site	Pleura	Lung
Overlap	Tubules / papillae	Glandular morphology
Resolution	Mesothelial IHC + negative epithelial markers	Epithelial markers + clinical correlation

Sarcomatoid mesothelioma: Spindle phenotype

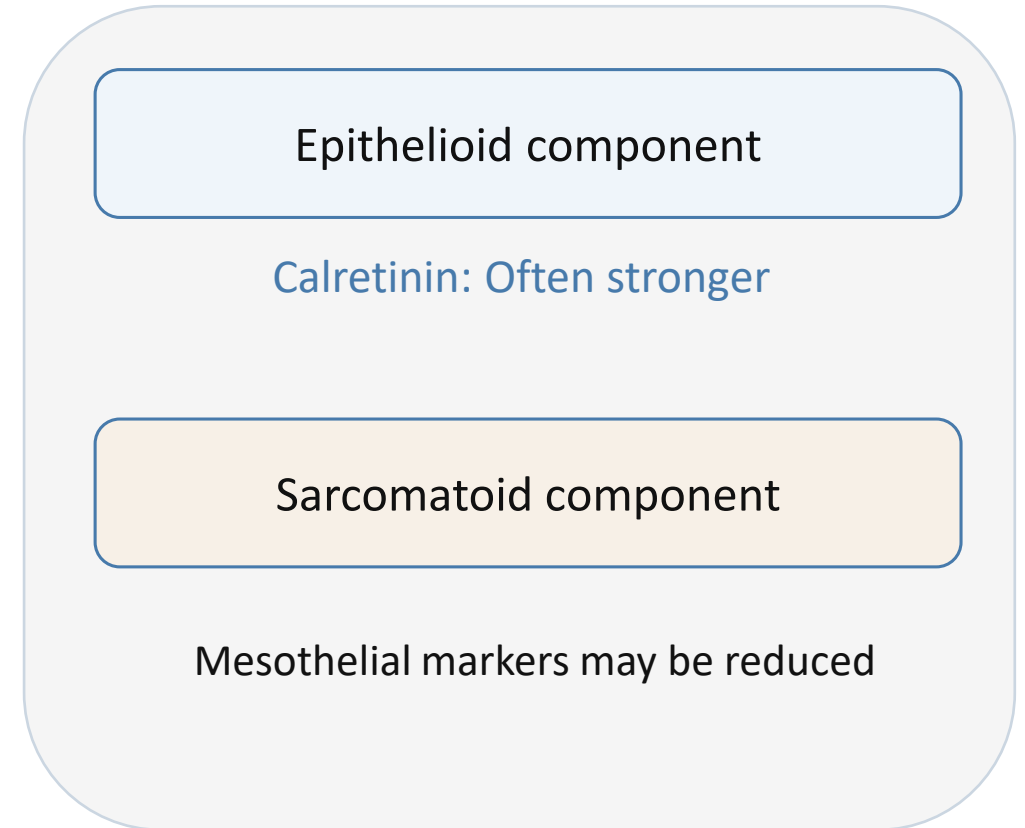
- Sarcomatoid mesothelioma resembles a fibrosarcoma microscopically.
- It is commonly extensively fibrotic and paucicellular.
- The spindle-cell phenotype can complicate both sampling and immunophenotypic recognition.



Schematic — not a diagnostic specimen

Sarcomatoid marker expression can be reduced

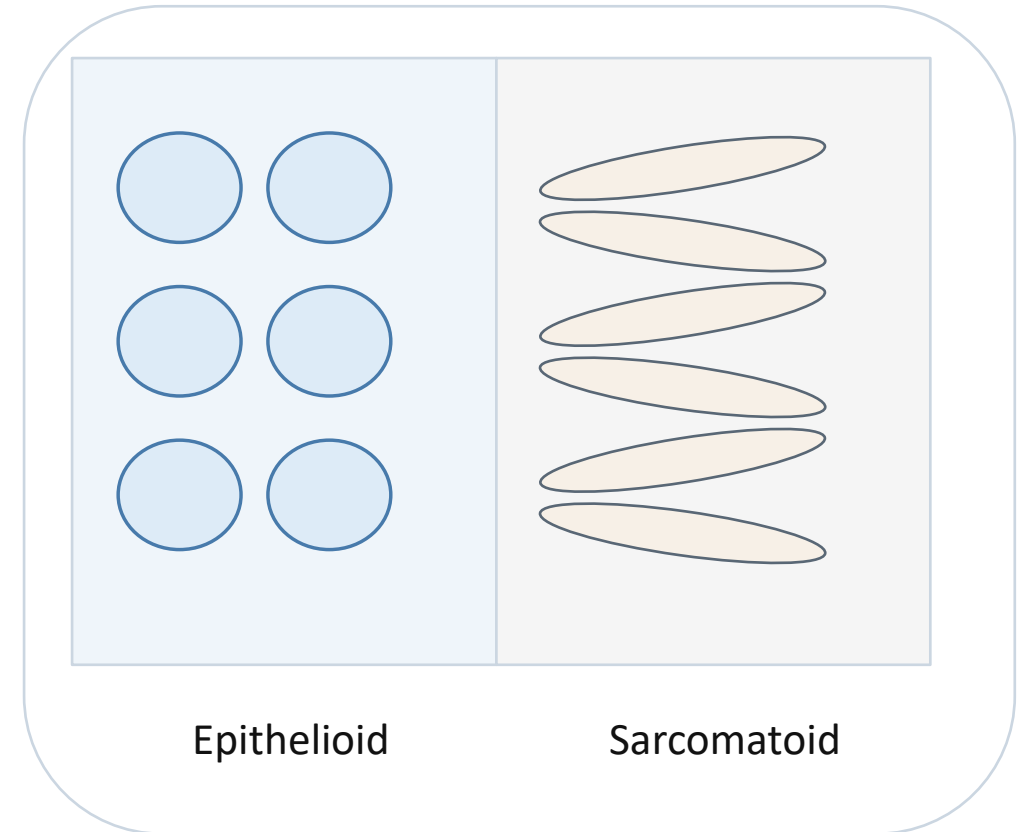
- Expression of many typical mesothelial markers is lower in sarcomatoid cases.
- Some tumors may show keratin staining while lacking the stronger mesothelial-marker profile.
- Negative calretinin or WT1 staining alone therefore does not exclude sarcomatoid mesothelioma.



Schematic — not a diagnostic specimen

Biphasic mesothelioma combines both components

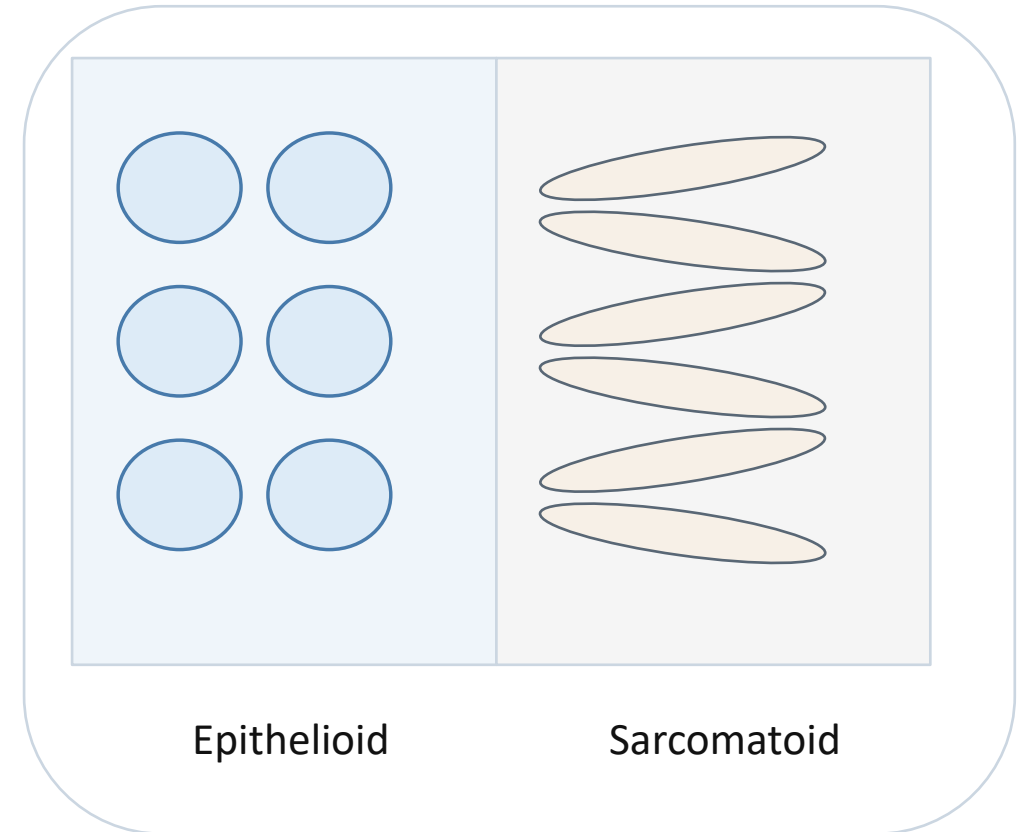
- The tumor has an epithelioid region and a sarcomatoid region.
- The relative proportions may vary across the sampled lesion.
- Robbins indicates clinical behavior resembling the sarcomatoid type.



Schematic — not a diagnostic specimen

Histologic sampling changes what is visible

- A limited biopsy may sample only one histologic compartment of a heterogeneous lesion.
- Finding both components changes the morphologic classification.
- WHO 2021 permits diagnosing biphasic mesothelioma on small biopsies with both components even when one is under 10%.

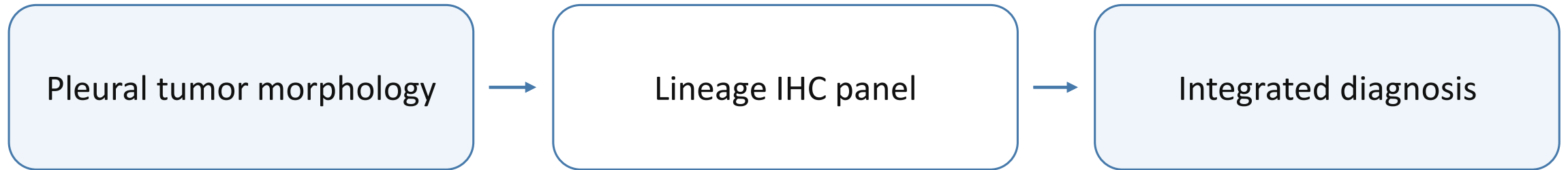


Schematic — not a diagnostic specimen

Morphologic pattern comparison

Pattern	Typical appearance	Pitfall
Epithelioid	Cuboidal / columnar cells; tubules, papillae	Mimics adenocarcinoma
Sarcomatoid	Spindle cells; fibrotic, paucicellular	Markers may be weak or absent
Biphasic	Epithelioid + sarcomatoid areas	Sampling may miss a component

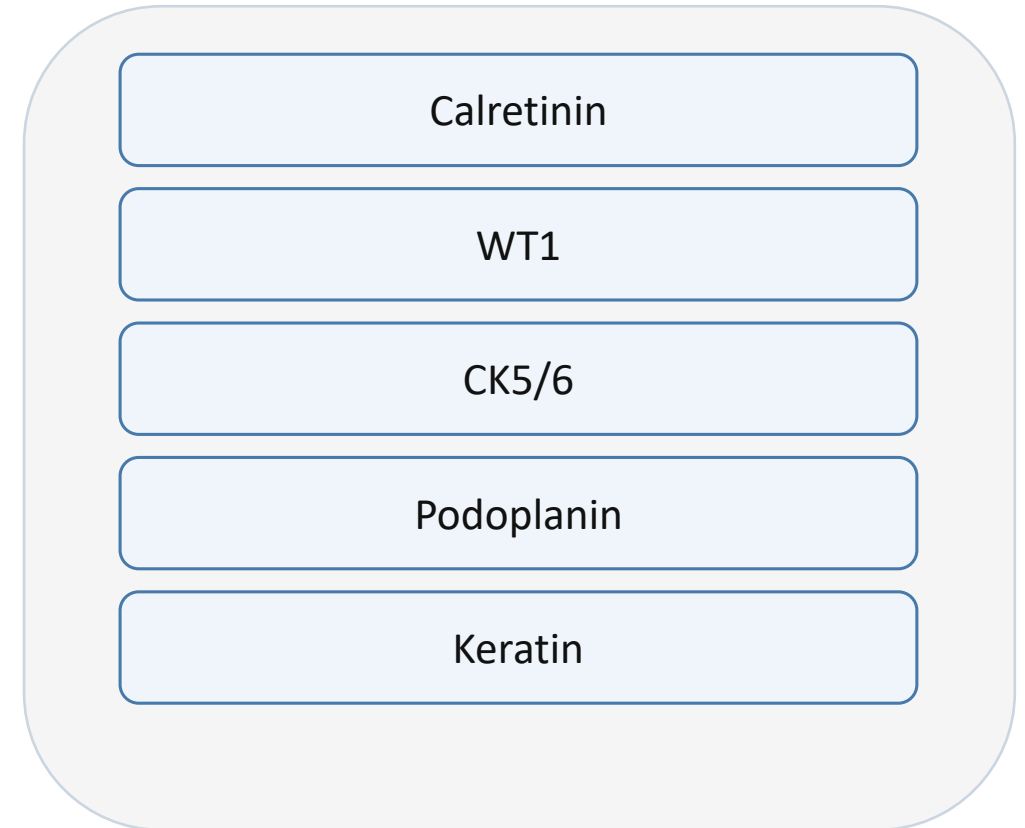
Immunohistochemistry answers a lineage question



- IHC is used to distinguish mesothelial differentiation from epithelial carcinoma.
- A diagnostic panel is more reliable than a single positive stain.
- Interpret marker distribution together with tissue morphology and the clinical setting.

Mesothelial-positive marker set

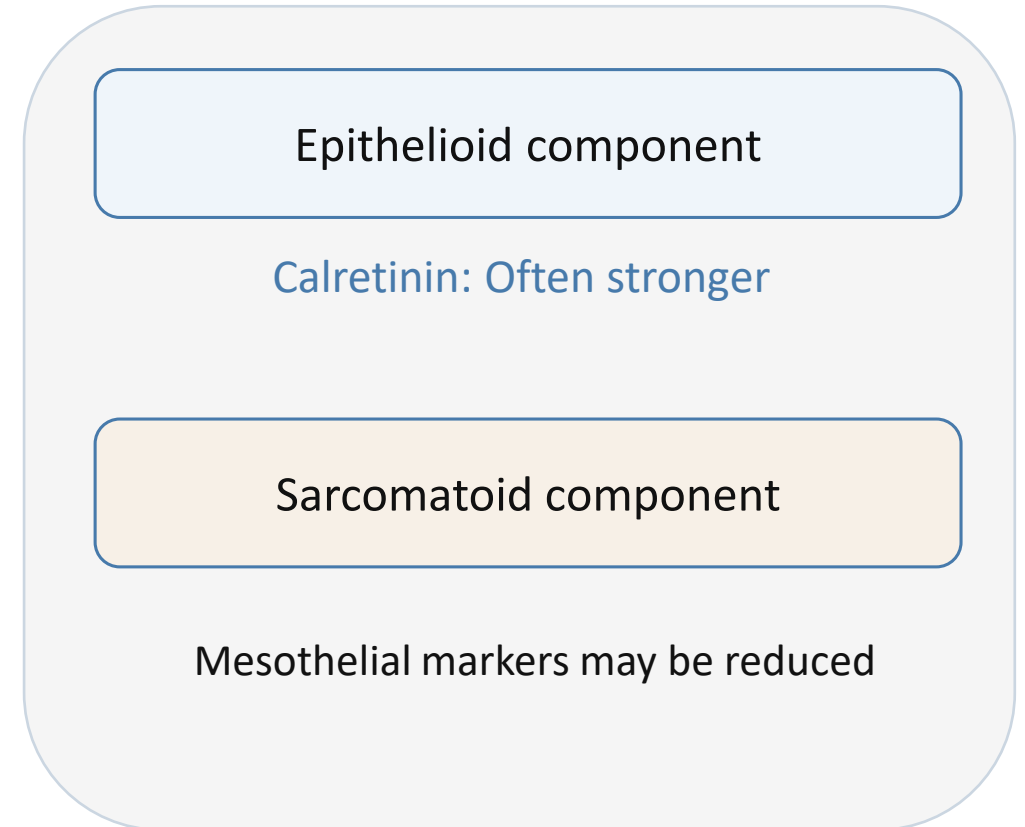
- Keratins, calretinin, WT1, cytokeratin 5/6, and podoplanin as commonly positive.
- These markers support mesothelial differentiation when their expected patterns are present.
- Sensitivity is context- and histologic-subtype-dependent.



Schematic — not a diagnostic specimen

Calretinin supports mesothelial differentiation

- Calretinin is usually expressed in epithelioid mesothelioma.
- The textbook illustration shows stronger staining in epithelioid than sarcomatoid areas.
- Stain interpretation must account for internal controls and tumor architecture.



Schematic — not a diagnostic specimen

WT1 is part of a composite mesothelial panel

- Wilms tumor protein 1 (WT1) is included among the main mesothelioma markers.
- A positive WT1 result is supportive, not uniquely diagnostic by itself.
- Correlation with keratin, calretinin, and epithelial-marker results remains necessary.

CK5/6 and podoplanin add complementary evidence

- Cytokeratin 5/6 and podoplanin are additional mesothelial-associated markers.
- Their value is greatest when concordant with the morphologic impression and other stains.
- Marker selection should consider the differential diagnosis rather than indiscriminate screening.

Keratins and lineage: A diagnostic nuance

- Mesotheliomas are typically keratin-positive despite their varied cell shapes.
- Keratin staining can remain useful when sarcomatoid tumors lose other mesothelial markers.
- Keratin positivity also occurs in carcinomas, so it cannot independently resolve lineage.

Claudin-4: An epithelial differentiation marker

Immunophenotype	Mesothelioma (typical)	Adenocarcinoma (typical)
Calretinin / WT1	Often positive	Not the characteristic mesothelial panel
Claudin-4	Negative	Often positive
Interpretation	Mesothelial lineage favored	Epithelial lineage favored

BerEP4 provides an additional exclusion signal

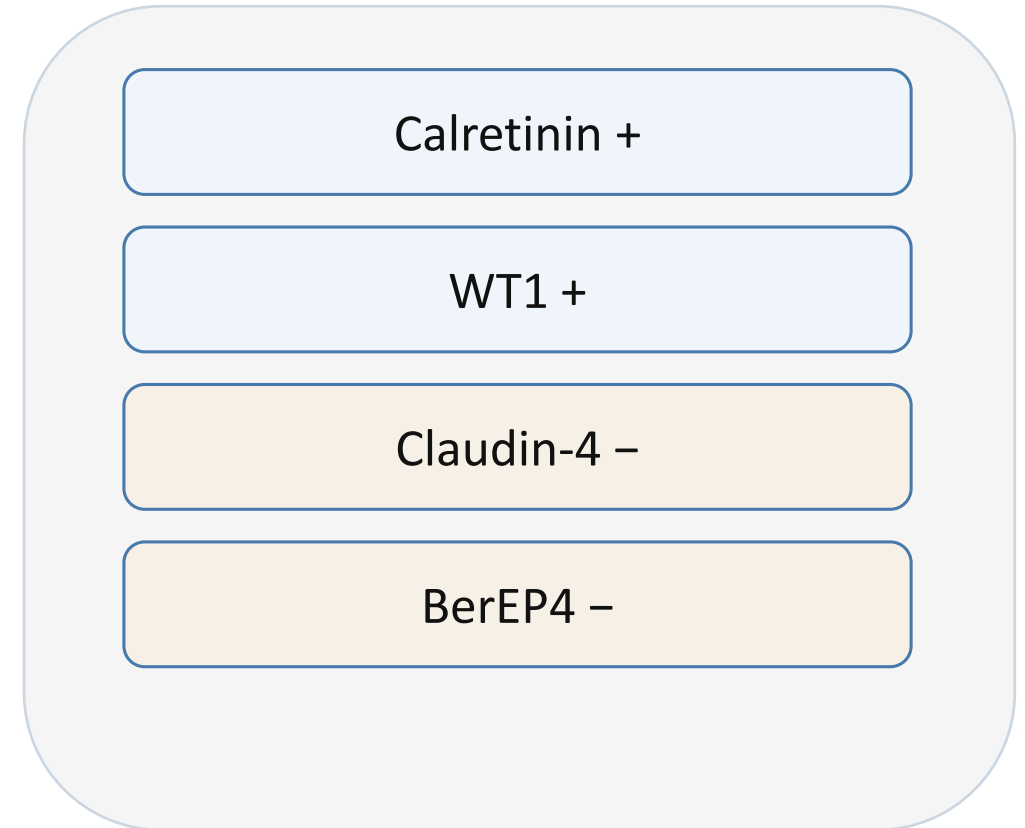
- BerEP4 is named by Robbins among epithelial differentiation markers.
- Mesotheliomas are usually negative while adenocarcinomas may be positive.
- Its diagnostic role complements other mesothelial-positive and epithelial-positive markers.

Two-sided IHC panels are more interpretable

Panel axis	Representative stains	Interpretive role
Mesothelial-associated	Calretinin, WT1, CK5/6, podoplanin	Support mesothelial differentiation
Epithelial-associated	Claudin-4, BerEP4	Favor carcinoma when expressed
Broad keratin	Pan-keratin	Supports epithelial/mesothelial nature; not discriminatory alone

Worked panel: A mesothelial profile

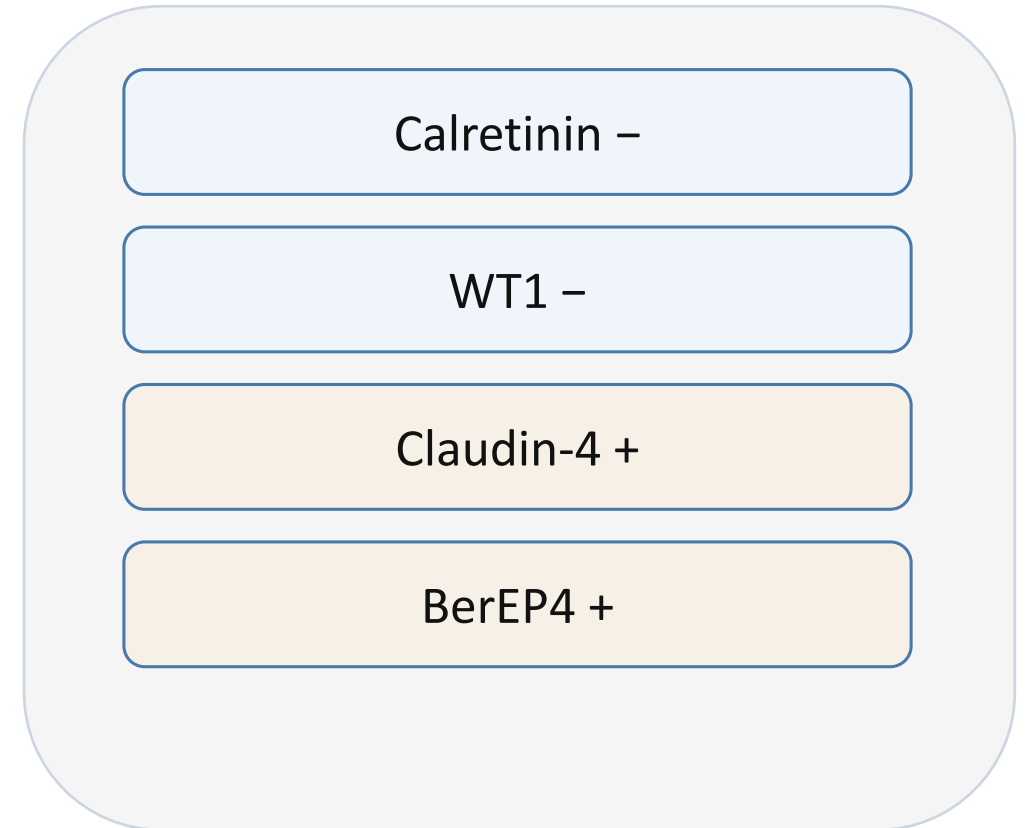
- Diffuse pleural tumor with epithelioid tubulopapillary architecture.
- Keratin, calretinin, and WT1 positive; Claudin-4 and BerEP4 negative.
- In the described context, the composite profile favors epithelioid mesothelioma.
- This is an educational composite, not a patient specimen.



Schematic — not a diagnostic specimen

Worked panel: An epithelial profile

- Pleural lesion with gland-forming malignant epithelial cells.
- Claudin-4 and BerEP4 positive without a convincing mesothelial marker profile.
- Adenocarcinoma becomes an important alternative diagnosis.
- Primary site still requires clinicopathologic correlation.



Schematic — not a diagnostic specimen

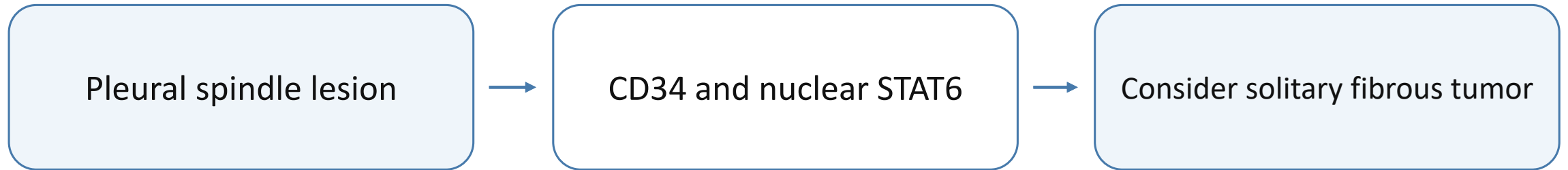
A solitary stain is not a diagnosis

- No single marker in the Robbins list is described as sufficient in every case.
- Weak or missing markers are especially problematic in sarcomatoid tumors.
- Avoid equating “keratin-positive spindle lesion” with mesothelioma without a differential work-up.

Solitary fibrous tumor: A pleural mimic

Feature	Mesothelioma	Solitary fibrous tumor
Distribution	Diffuse pleural spread	Often pedunculated / circumscribed
Keratin	Often positive	Typically negative
CD34 / STAT6	Not the characteristic profile	Typically positive
Asbestos relation	Strong association	No established relationship

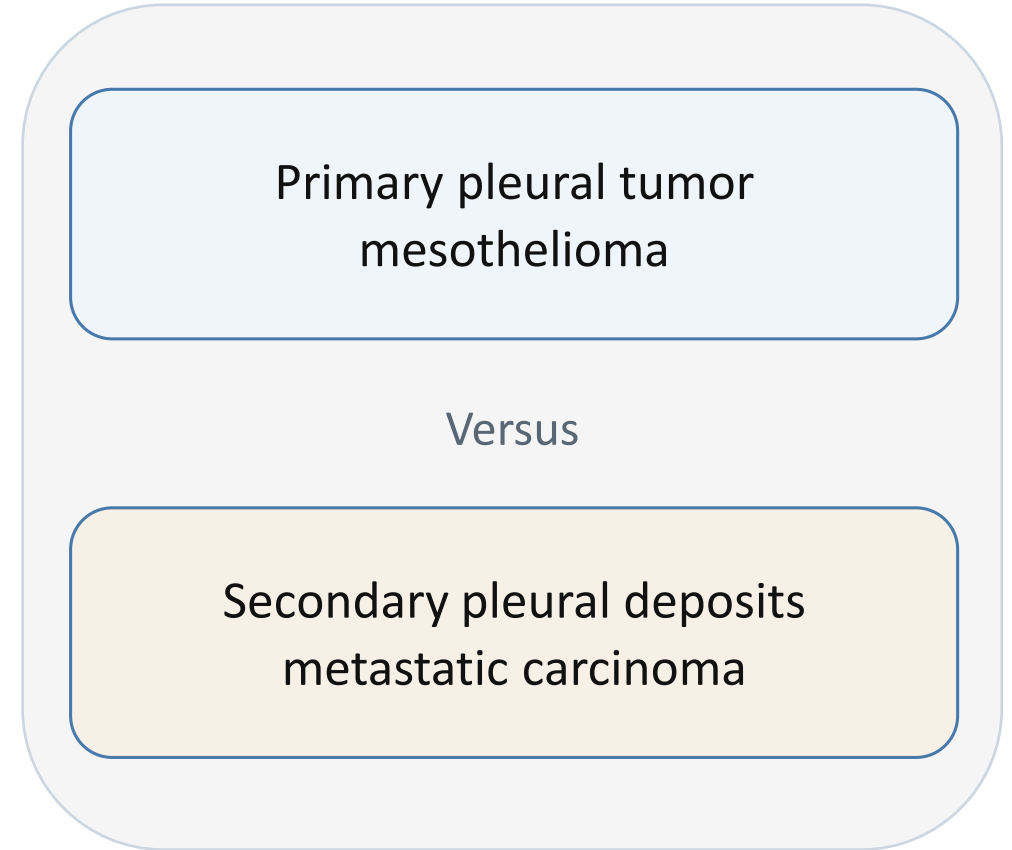
SFT carries NAB2::STAT6 rearrangement



- The adjacent Robbins section describes a characteristic NAB2::STAT6 fusion.
- SFT typically shows CD34 and STAT6 positivity with keratin negativity.
- These findings separate SFT from mesothelioma when morphology overlaps.

Metastatic pleural carcinoma remains common

- Secondary pleural tumors are far more common than primary pleural tumors overall.
- Lung and breast are frequent primary sites in the Robbins pleural-tumor discussion.
- Pleural implants often produce serous or serosanguineous fluid with neoplastic cells.



Schematic — not a diagnostic specimen

Effusion cytology: Useful but context-dependent

- Careful cytologic examination of fluid sediment when malignancy is suspected.
- Identifying neoplastic cells does not by itself settle whether a pleural lesion is primary or metastatic.
- Definitive tissue classification may require integrated morphologic and ancillary studies.

WHO 2021: Modern terminology

Robbins section terminology

WHO 2021 terminology

Malignant mesothelioma

Diffuse mesothelioma (invasive diffuse disease)

Epithelioid / sarcomatoid / biphasic

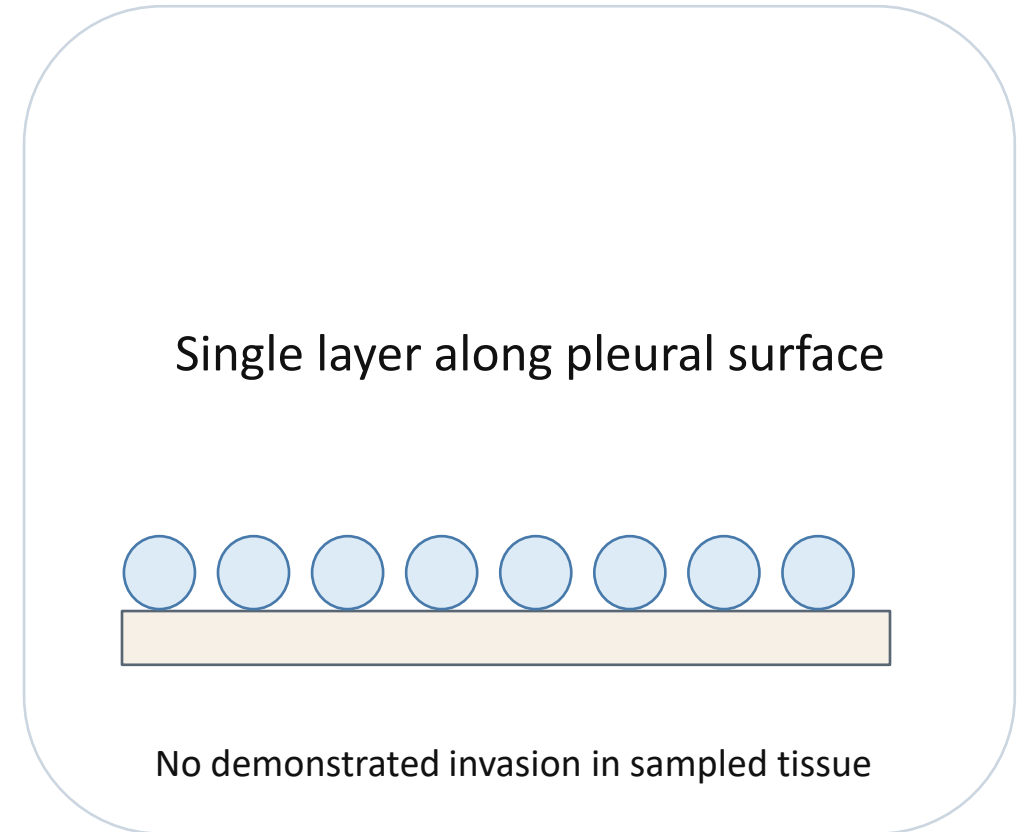
Same three main subtypes

Historical disease label

Contemporary classification wording

WHO 2021 recognizes mesothelioma in situ

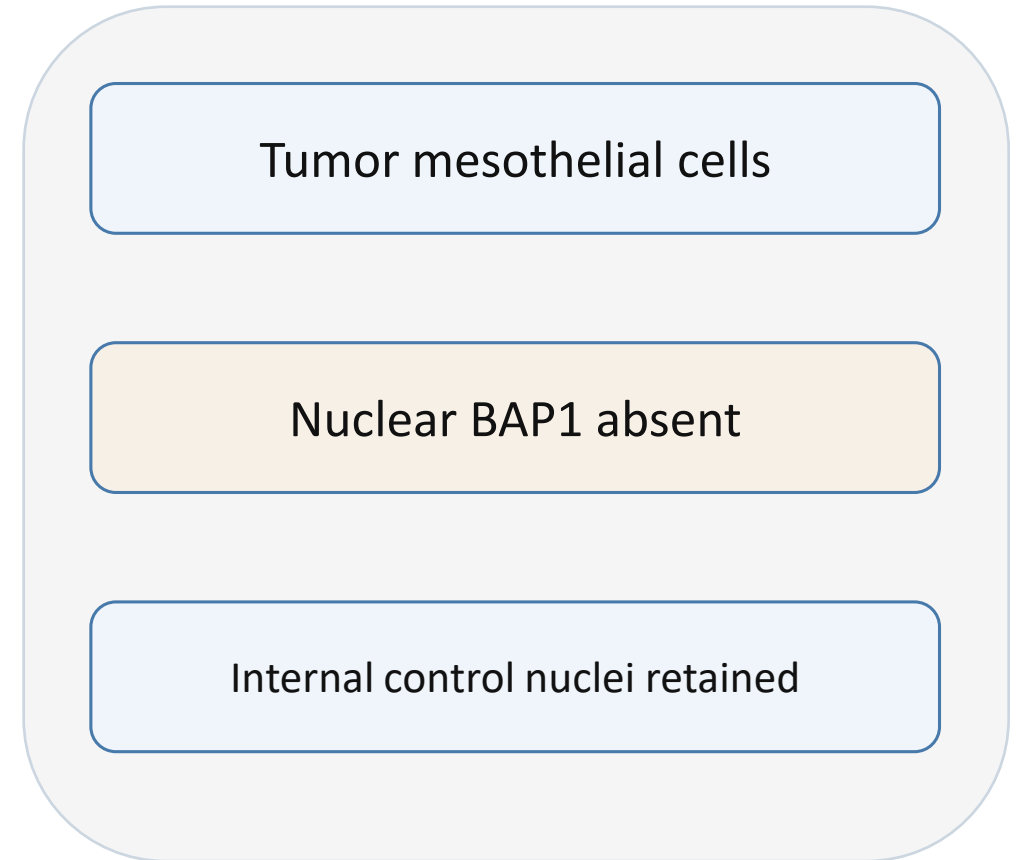
- Mesothelioma in situ is a preinvasive mesothelial lesion included in WHO 2021.
- Flat or minimally papillary mesothelial cells alone are insufficient for diagnosis.
- Molecularly supported malignant mesothelial proliferation must be assessed for invasion.



Schematic — not a diagnostic specimen

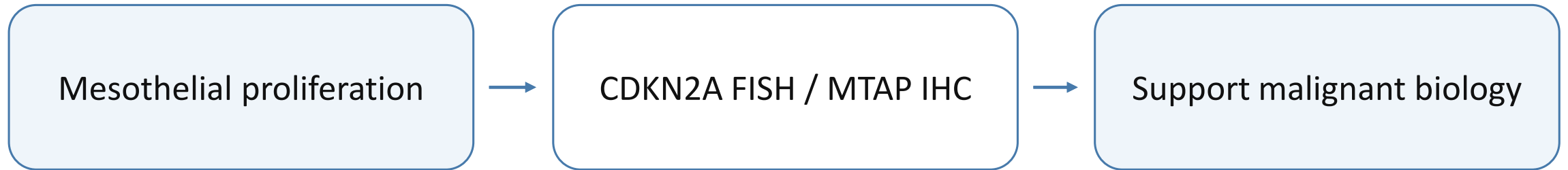
BAP1 loss as a marker of malignancy

- Loss of nuclear BAP1 expression can support a malignant mesothelial proliferation.
- Interpretation requires retained staining in appropriate internal control cells.
- BAP1 IHC loss is not equivalent to a demonstrated inherited BAP1 mutation.



Schematic — not a diagnostic specimen

CDKN2A deletion and MTAP IHC



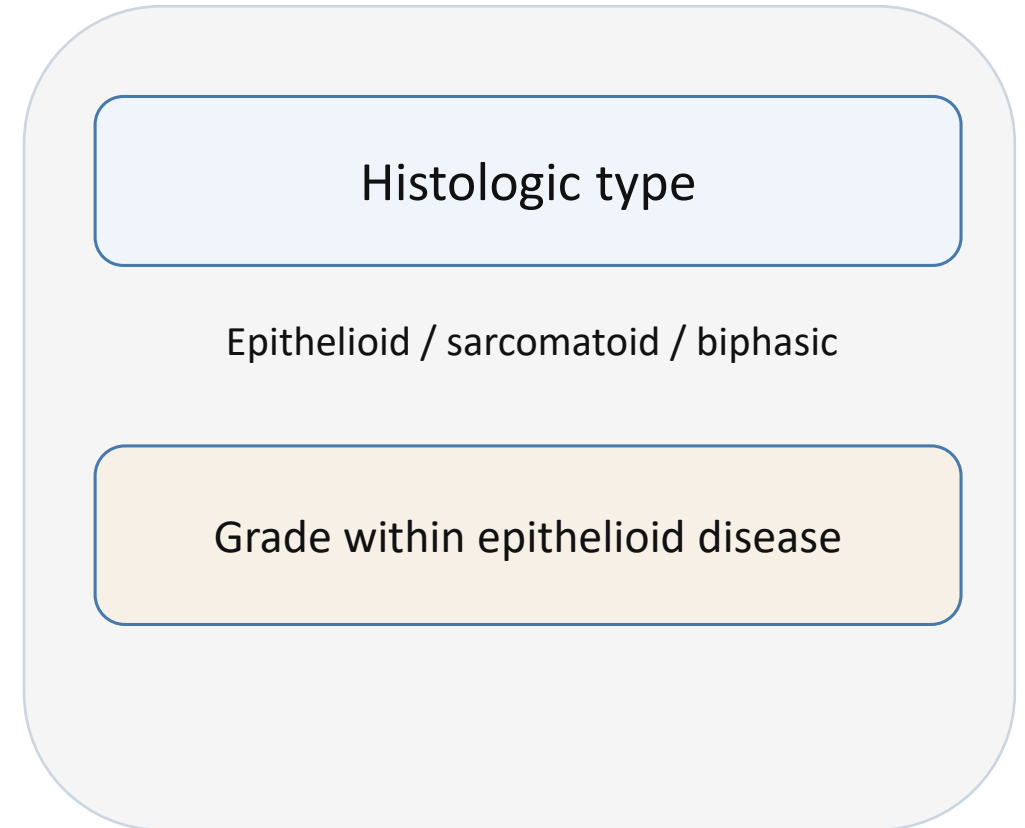
- Homozygous CDKN2A deletion can be detected by fluorescence in situ hybridization (FISH).
- Loss of MTAP by IHC can serve as a surrogate in validated settings.
- These assays address malignant-versus-reactive mesothelial proliferation rather than tumor lineage alone.

Why the in situ diagnosis needs tissue

Specimen	What it may establish	What it cannot alone exclude
Effusion / cytology	Abnormal mesothelial cells; molecular marker findings	Underlying invasive tumor
Pleural biopsy	Architecture and stromal interface	Complete disease extent when undersampled

WHO 2021 adds epithelioid grading

- The WHO update introduces nuclear grading for diffuse epithelioid mesothelioma.
- Architectural and cytologic/stromal features also carry prognostic relevance.
- Grading is distinct from histologic subtype; Exact criteria require the WHO framework.

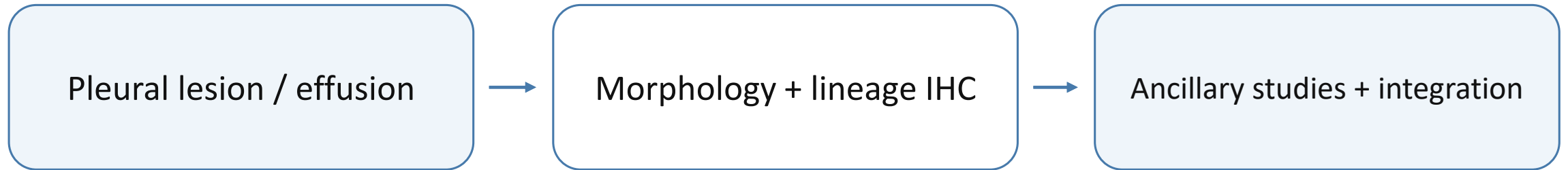


Schematic — not a diagnostic specimen

Prognosis varies by histologic subtype

- Histologic classification is clinically consequential, not merely descriptive.
- Biphasic disease behaving similarly to sarcomatoid disease.
- The WHO update also emphasizes prognostic heterogeneity within epithelioid disease.

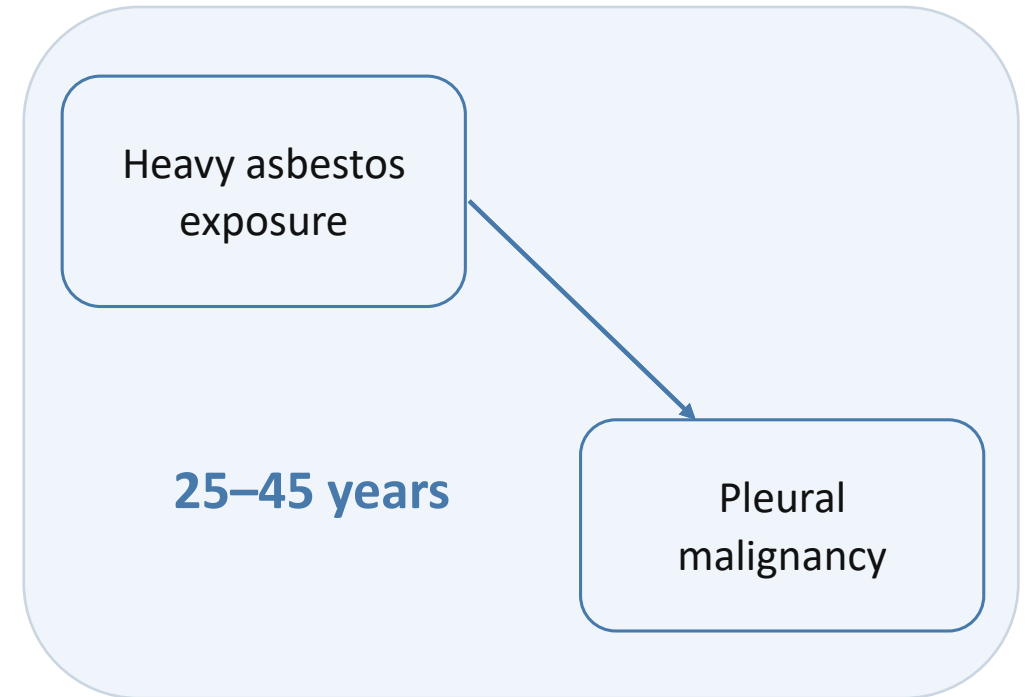
A practical integrated diagnostic pathway



- Start with pleural distribution and careful morphologic assessment.
- Establish lineage through a balanced IHC panel, with attention to subtype-related marker loss.
- Where needed, use validated BAP1/MTAP or CDKN2A assays to assess malignant mesothelial biology.
- Reconcile the full result with clinical and sampling limitations.

Clinical vignette: Remote shipyard exposure

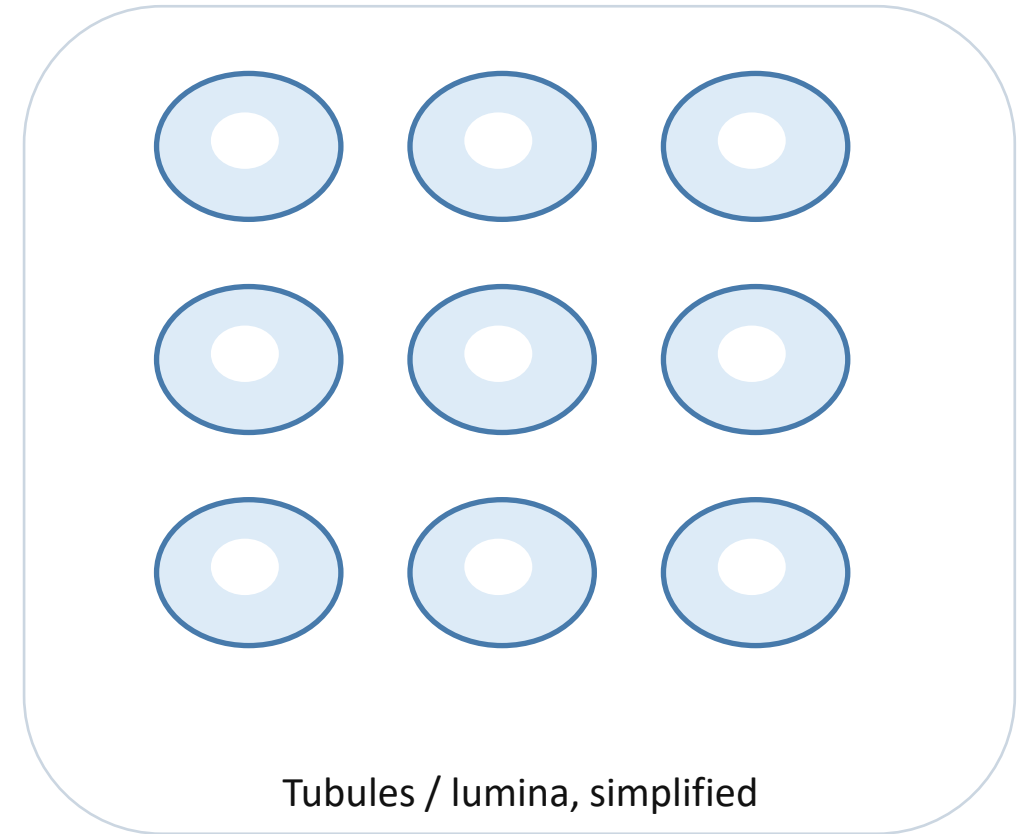
- A patient develops progressive dyspnea and recurrent unilateral pleural effusion.
- Occupational history reveals heavy shipyard asbestos exposure more than three decades earlier.
- The latency and pleural syndrome make mesothelioma a salient possibility.
- A tissue-based diagnosis is still required; Occupational history is not diagnostic.



Schematic — not a diagnostic specimen

Case interpretation: The diagnostic next question

- Pleural biopsy shows tubules formed by atypical epithelial-like cells.
- The pattern can be mesothelioma or metastatic/pulmonary adenocarcinoma.
- Apply a mesothelial-positive and epithelial-positive IHC panel before assigning origin.

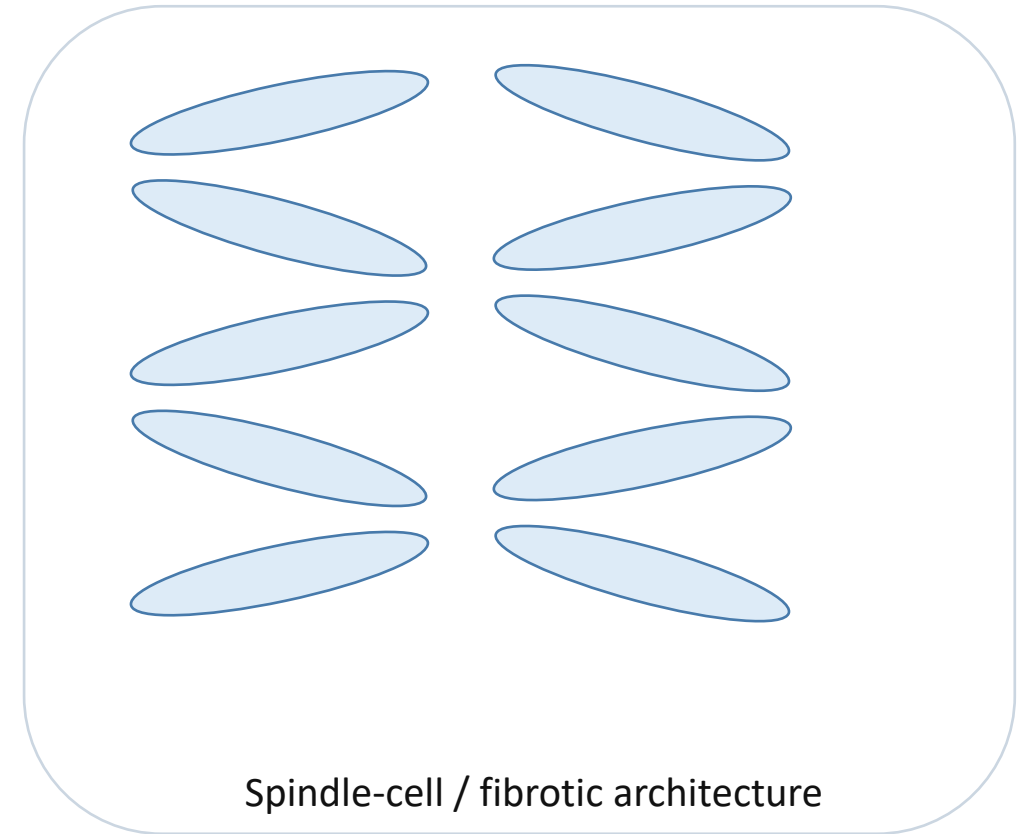


Tubules / lumina, simplified

Schematic — not a diagnostic specimen

Clinical vignette: Spindle-cell pleural tumor

- A fibrotic, paucicellular pleural tumor shows predominantly spindle-shaped cells.
- Sarcomatoid mesothelioma and solitary fibrous tumor are important considerations.
- Evaluate keratin alongside CD34/STAT6 and integrate gross distribution.

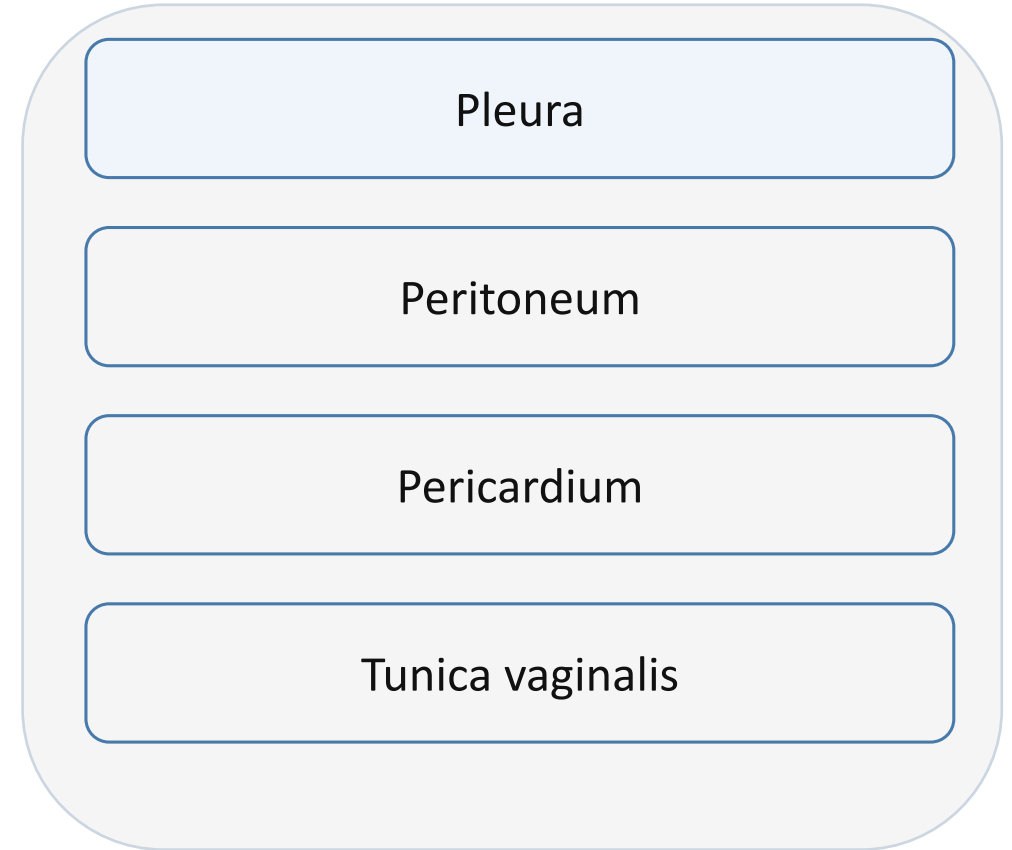


Spindle-cell / fibrotic architecture

Schematic — not a diagnostic specimen

Beyond the chest: Other serosal sites

- Mesothelioma also occurs in the peritoneum, pericardium, and tunica vaginalis.
- These locations should not be conflated with the usual pleural presentation.
- Robbins additionally mentions the benign adenomatoid tumor in a separate genital-tract context.



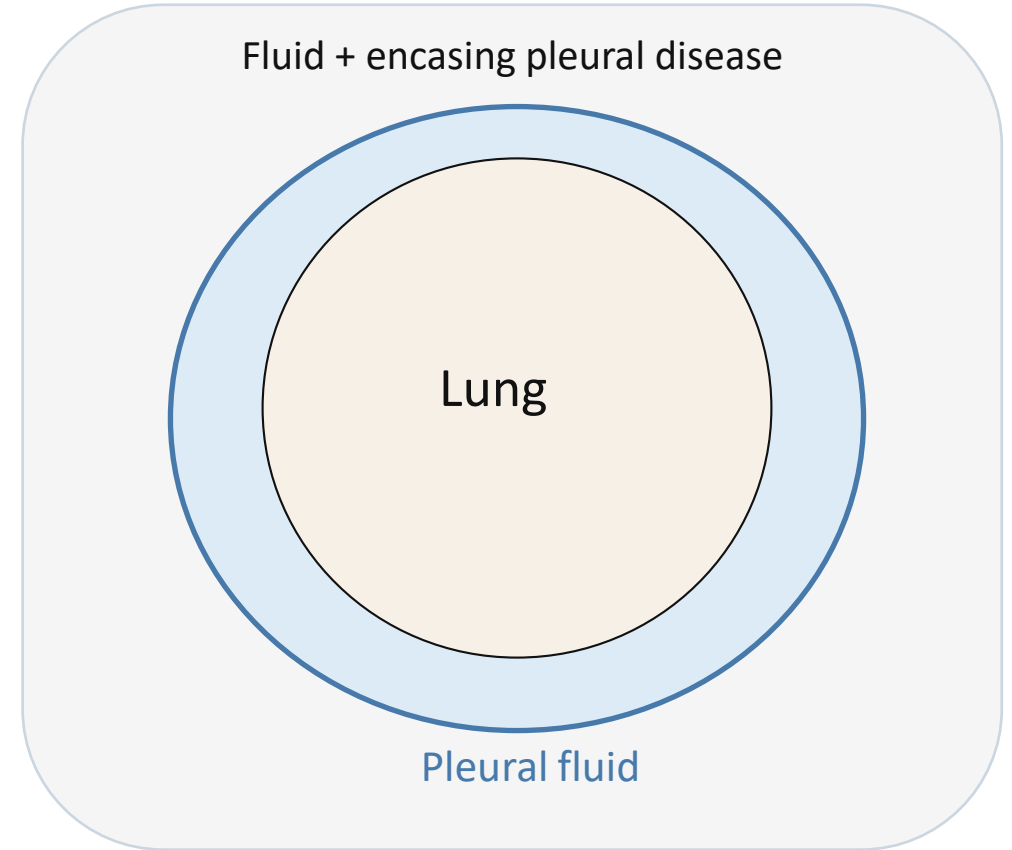
Schematic — not a diagnostic specimen

Peritoneal disease: Exposure and course

- Heavy asbestos association in 60% of male peritoneal cases, lower among women.
- In approximately half of cases, disease remains confined to the abdominal cavity.
- Intestinal involvement can cause obstruction and profound nutritional consequences.
- These are source-specific observations rather than contemporary staging criteria.

A clinicopathologic explanation of symptoms

- Chest pain is linked to the pleural site and invasive spread.
- Dyspnea reflects the combined consequences of effusion and an encasing pleural lesion.
- Recurrent effusions reflect continuing pleural disease rather than isolated fluid imbalance.



Schematic — not a diagnostic specimen

Prognosis description

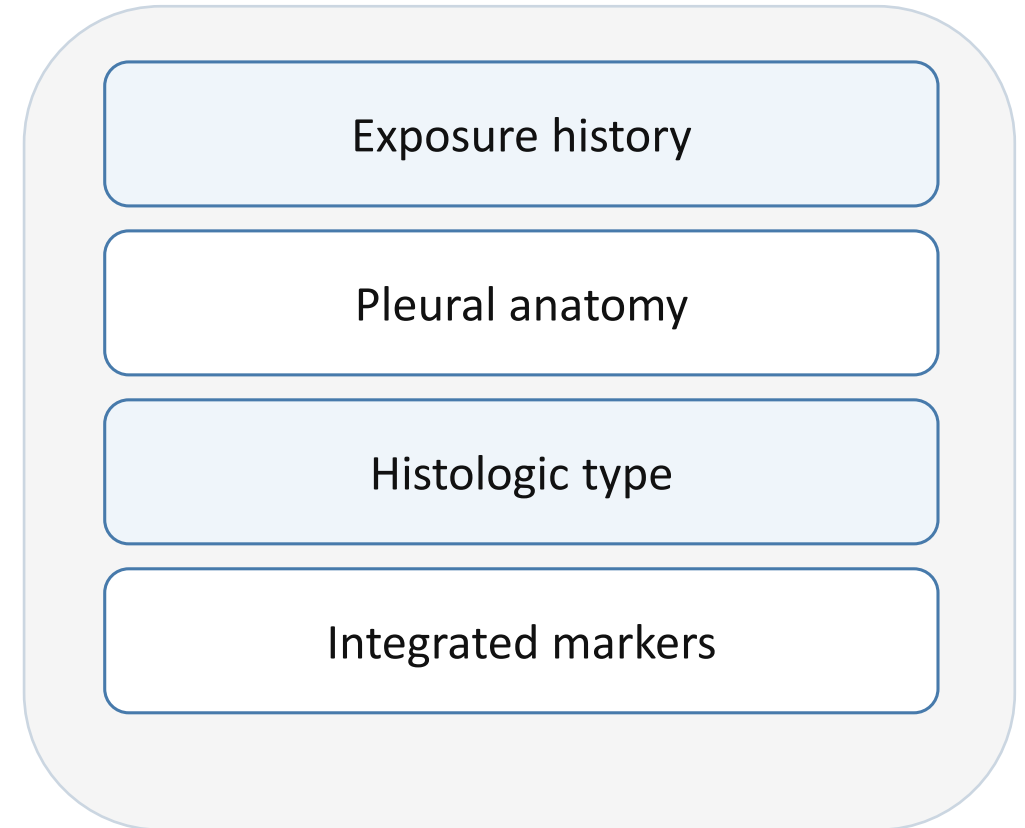
- Aggressive disease with a historically poor outcome.
- Its cited figures are approximately 50% mortality within 12 months and few survivors beyond two years.
- These figures must be understood as textbook historical estimates, not personalized modern survival predictions.

Management is multidisciplinary and evolving

- Surgery, chemotherapy, and radiation as approaches used in selected patients.
- Treatment selection depends on disease extent, histology, patient factors, and contemporary protocols.
- This pathology lecture does not present the textbook list as a current treatment guideline.

Four diagnostic anchors to retain

- Clinical context: Remote asbestos exposure plus a progressive pleural syndrome.
- Gross phenotype: Diffuse pleural spread and encasement of the lung.
- Microscopy: Epithelioid, sarcomatoid, or biphasic differentiation.
- Diagnosis: Integrate morphology with two-sided lineage IHC and appropriate ancillary testing.



Schematic — not a diagnostic specimen

Source documents and classification framework

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026), Chapter 15, pp. 660–662.
- Nicholson AG et al. 2021 WHO Classification of Tumors of the Pleura. J Thorac Oncol. 2022;17:608–622.
- Dacic S. Pleural mesothelioma classification—update and challenges. Mod Pathol. 2022;35:51–56.
- Diagnostic concepts should be checked against current local laboratory protocols and multidisciplinary guidance.