

Gastrointestinal Stromal Tumor

Cell of origin • molecular drivers • morphology • clinicopathologic interpretation

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Learning outcomes

- Identify the cell of origin and major molecular classes of GIST.
- Distinguish gross and microscopic patterns and apply KIT/DOG1 staining.
- Integrate size, mitotic activity, and site when discussing prognosis.
- Connect genotype with targeted treatment and acquired resistance.

GIST is a mesenchymal neoplasm of the gut

Mesenchymal tumor — not an epithelial carcinoma

Most common mesenchymal tumor of the abdomen.

Biologically distinct from epithelial gastric cancers.

Origin is linked to interstitial cells of Cajal.

Gastric tumor families should not be conflated

Gastric tumor group	Examples	Diagnostic emphasis
Epithelial	Adenocarcinoma	Gland-forming epithelial neoplasm
Neuroendocrine	Neuroendocrine tumor	Neuroendocrine differentiation
Mesenchymal	GIST, leiomyoma, schwannoma	Morphology with lineage markers

The parent chapter distinguishes these tumor groups; Examples are not a complete classification.

More than half of GISTs occur in the stomach

$>1/2$

Occur in the stomach

Site

Is a prognostic variable

The stomach is the predominant site. GIST also occurs at other gastrointestinal locations.
Anatomic site matters when interpreting biological behavior.

GIST is uncommon in population terms

11–20

New cases per million people
annually

Annual incidence: 11–20 per million people. “Most common mesenchymal abdominal tumor” does not mean common among all neoplasms.

GIST is mainly diagnosed in older adults

~60

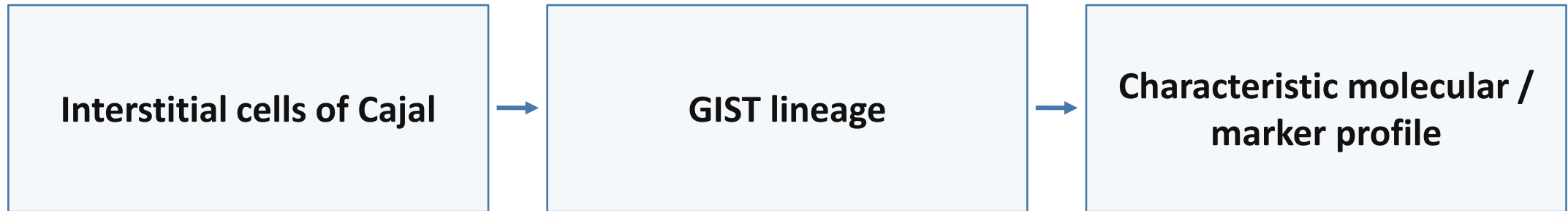
Peak age (years)

<10%

Diagnosed before 40 years

Peak age at diagnosis: About 60 years. Fewer than 10% occur before the age of 40. Pediatric GIST is distinctly uncommon.

Interstitial cells of Cajal provide the lineage context



Schematic lineage link; Not a literal progression sequence.

“Stromal” reflects a historical naming problem

Historical interpretation

- “Stromal” as nonspecific origin
- Overlapping mesenchymal appearances

Current interpretation

- Cajal-cell lineage recognized
- Molecular and immunophenotypic correlation

Other gastric mesenchymal tumors form key differentials

- Smooth muscle tumors: Leiomyoma and leiomyosarcoma.
- Nerve sheath tumor: Schwannoma.
- Glomus-body resembling tumor: Glomus tumor.
- These other mesenchymal neoplasms are uncommon in the gut.

Microscopic GIST-like proliferations can be silent

- Clinically silent microscopic foci are common.
- They may represent precursors to overt GIST.
- These small proliferations generally show low mitotic rates.

Precursor foci seldom progress

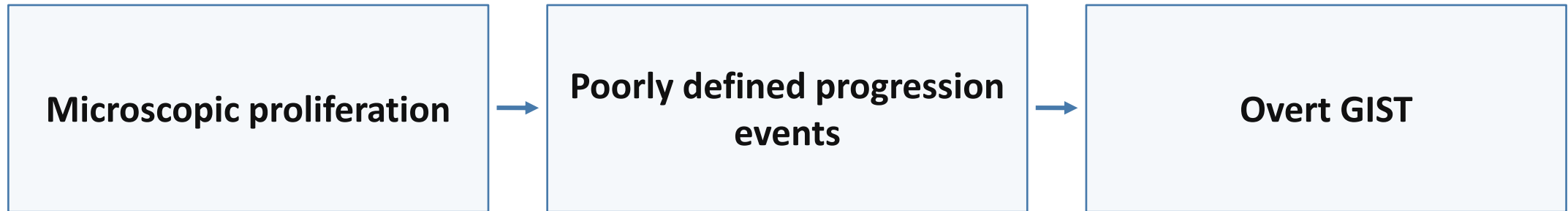
Precursor-like focus $\neq$ inevitable clinically significant GIST

Textbook characterizes the risk of neoplastic transformation as extremely low.

Presence of a microscopic focus does not imply inevitable tumor progression.

Events allowing progression to overt GIST remain poorly defined.

Chromosome losses accompany some progression



Loss/deletion of chromosomes 9, 14, or 22 may accompany progression; Causation is not fully established.

Some GISTs occur in inherited or syndromic settings

- Rare germline KIT or PDGFRA mutations may yield multiple GISTs.
- SDH-associated hereditary disease links GIST with paraganglioma.
- Neurofibromatosis type 1 has increased GIST incidence.
- Pediatric GIST may occur as part of the Carney triad.

Carney triad defines a distinct association

GIST

Gastrointestinal stromal
tumor

Paraganglioma

A second tumor type in the
triad

Pulmonary chondroma

Third characteristic tumor

Carney triad: Clinical demographic clues

- The syndrome is of unknown cause in the supplied Robbins description.
- It is usually reported in females.
- A subset of uncommon pediatric GISTs is associated with the triad.

Neurofibromatosis type 1 is a GIST-associated condition

- Individuals with NF1 show an increased incidence of GIST.
- Association with NF1 is distinct from the named Carney syndromes.
- Do not infer a specific mutation pattern from the provided passage.

The dominant GIST drivers are receptor kinases

~75%

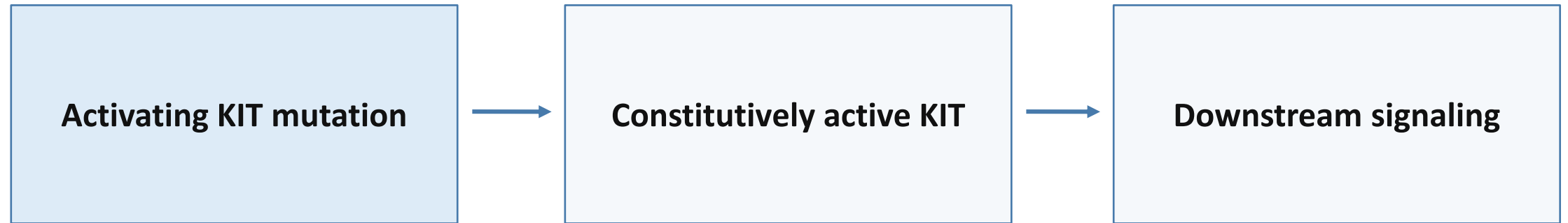
KIT gain-of-function

~8%

PDGFRA activating mutation

Approximately 75% carry activating KIT mutations. Another 8% carry activating PDGFRA mutations. Both proteins are receptor tyrosine kinases.

Mutant KIT is constitutively active



Simplified signaling relationship from the source; Individual effectors not specified.

Mutant PDGFRA activates a parallel kinase route



Schematic; The source does not enumerate individual downstream effectors.

KIT and PDGFRA driver mutations are mutually exclusive

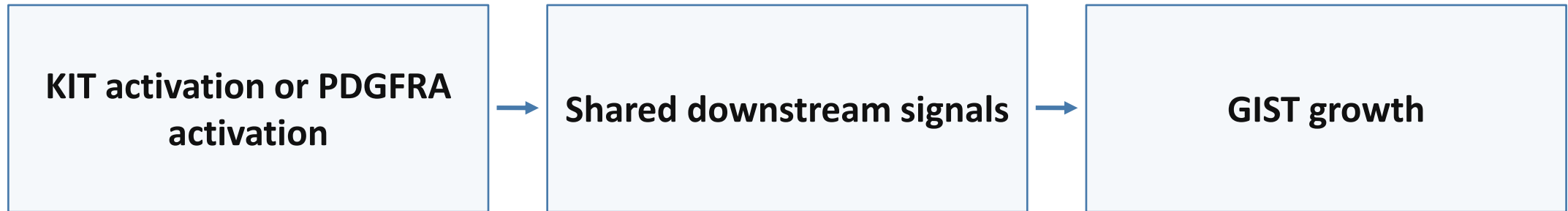
Molecular driver A

- KIT gain-of-function
- Receptor kinase signaling
- Dominant molecular class

Molecular driver B

- PDGFRA activation
- Overlapping downstream signaling
- Smaller molecular class

The shared pathway is more important than the receptor name



A conceptual map rather than a complete biochemical cascade.

Germline kinase mutations can yield multifocal disease

Germline KIT or PDGFRA mutation



Diffuse hyperplasia of interstitial cells of Cajal



Multiple GISTs may develop

Not all GISTs carry KIT or PDGFRA mutations

- A remaining subset lacks mutations of these two receptors.
- Some of those tumors instead harbor defects in succinate dehydrogenase genes.
- Molecular heterogeneity has practical consequences for treatment response.

SDH-related GIST involves a mitochondrial enzyme complex

SDHA

SDH subunit A

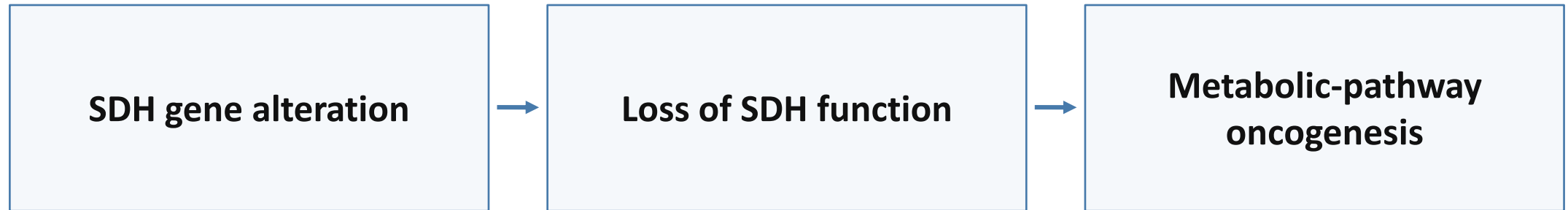
SDHB

SDH subunit B

SDHC / SDHD

SDH subunits C and D

SDH defects connect metabolism to oncogenesis



That mechanistic understanding remains incomplete.

Hereditary SDH-related GIST may follow a two-hit pattern

Inherited altered SDH gene copy



Tumor acquires mutation / loss of second copy



Functional SDH loss

Carney–Stratakis syndrome links GIST and paraganglioma

- The syndrome is associated with inherited SDH-complex mutations.
- The key tumor association is GIST plus paraganglioma.
- It should not be treated as synonymous with the Carney triad.

Carney triad and Carney–Stratakis differ

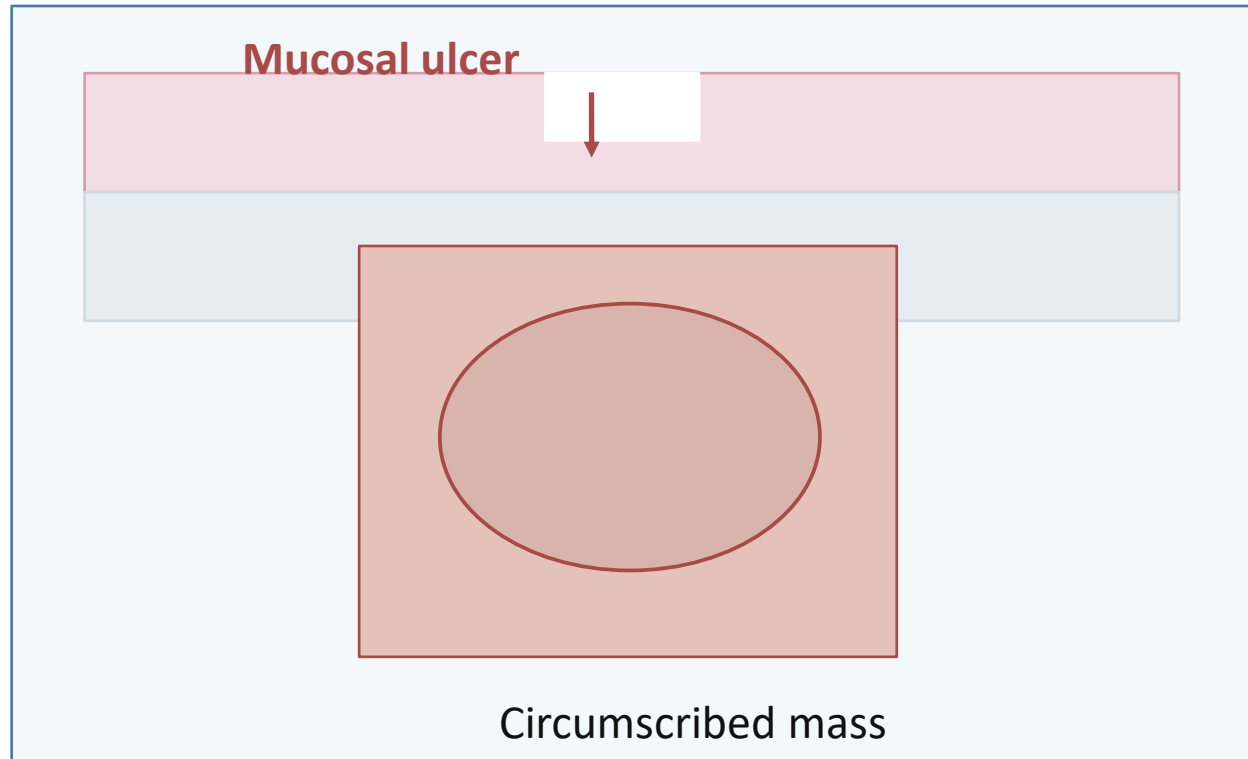
Feature	Carney triad	Carney–Stratakis
Tumor association	GIST + paraganglioma + pulmonary chondroma	GIST + paraganglioma
Cause	Unknown	Hereditary SDH deficiency
Teaching distinction	Three-tumor syndrome	GIST–paraganglioma dyad

Molecular drivers should be classified explicitly

Pathway class	Alteration	Key implication
KIT-driven	KIT gain-of-function	Common major GIST molecular group
PDGFRA-driven	PDGFRA activating mutation	Related tyrosine kinase mechanism
SDH-related	SDHA–D loss of function	Metabolic-pathway disease subset

This table deliberately excludes frequency estimates for molecular subsets not quantified.

Gastric GIST usually forms a discrete mass



Typically solitary and well circumscribed.

Gross cut surface is often fleshy.

A distinct lesion may be encountered at resection.

Schematic gastric wall (not a specimen)

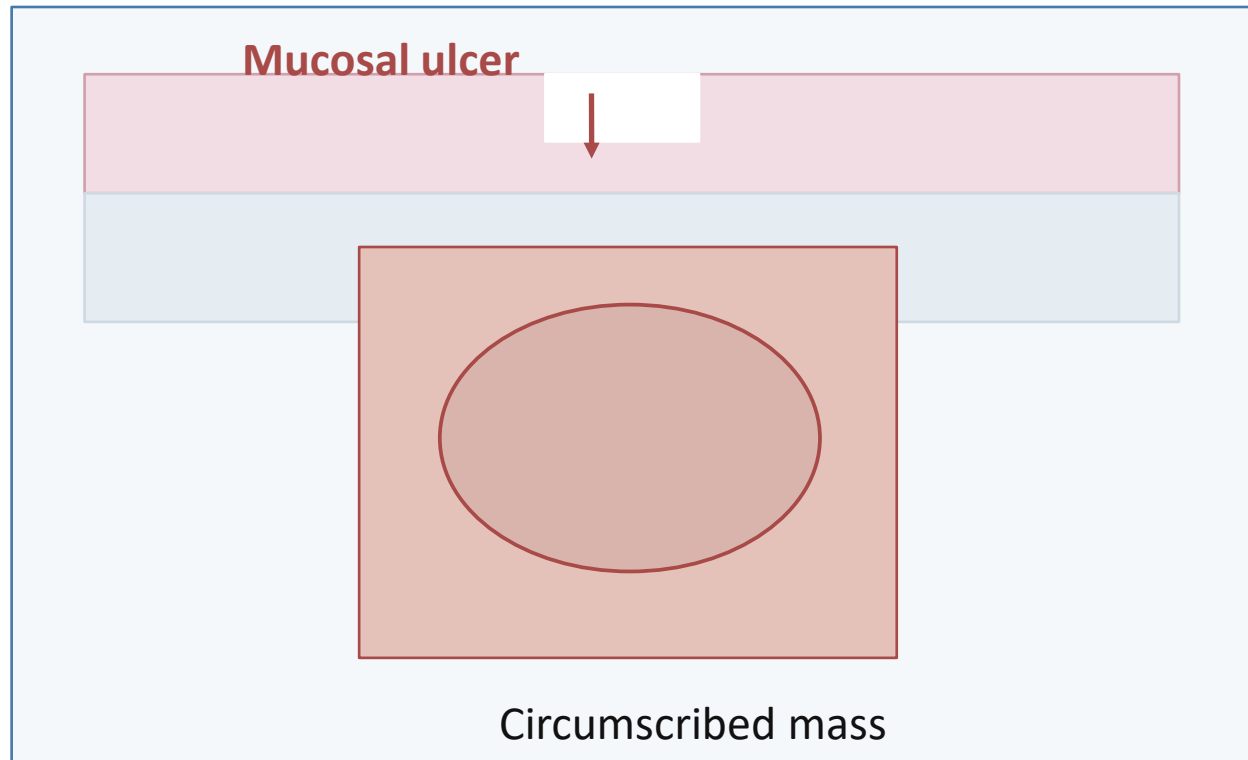
Large gastric GIST may remain circumscribed

Up to 30 cm

Described maximum primary
gastric GIST diameter

Gross size can be striking despite a defined border. Primary gastric GISTs as large as 30 cm.
The measurement alone does not replace mitotic activity and site in risk assessment.

Mucosal ulceration is a crucial gross finding



Mucosa overlying the mass is frequently ulcerated.

An ulcer provides a plausible route for tumor-related blood loss.

The gross appearance can explain anemia at presentation.

Schematic gastric wall (not a specimen)

The cut surface may have a whorled pattern

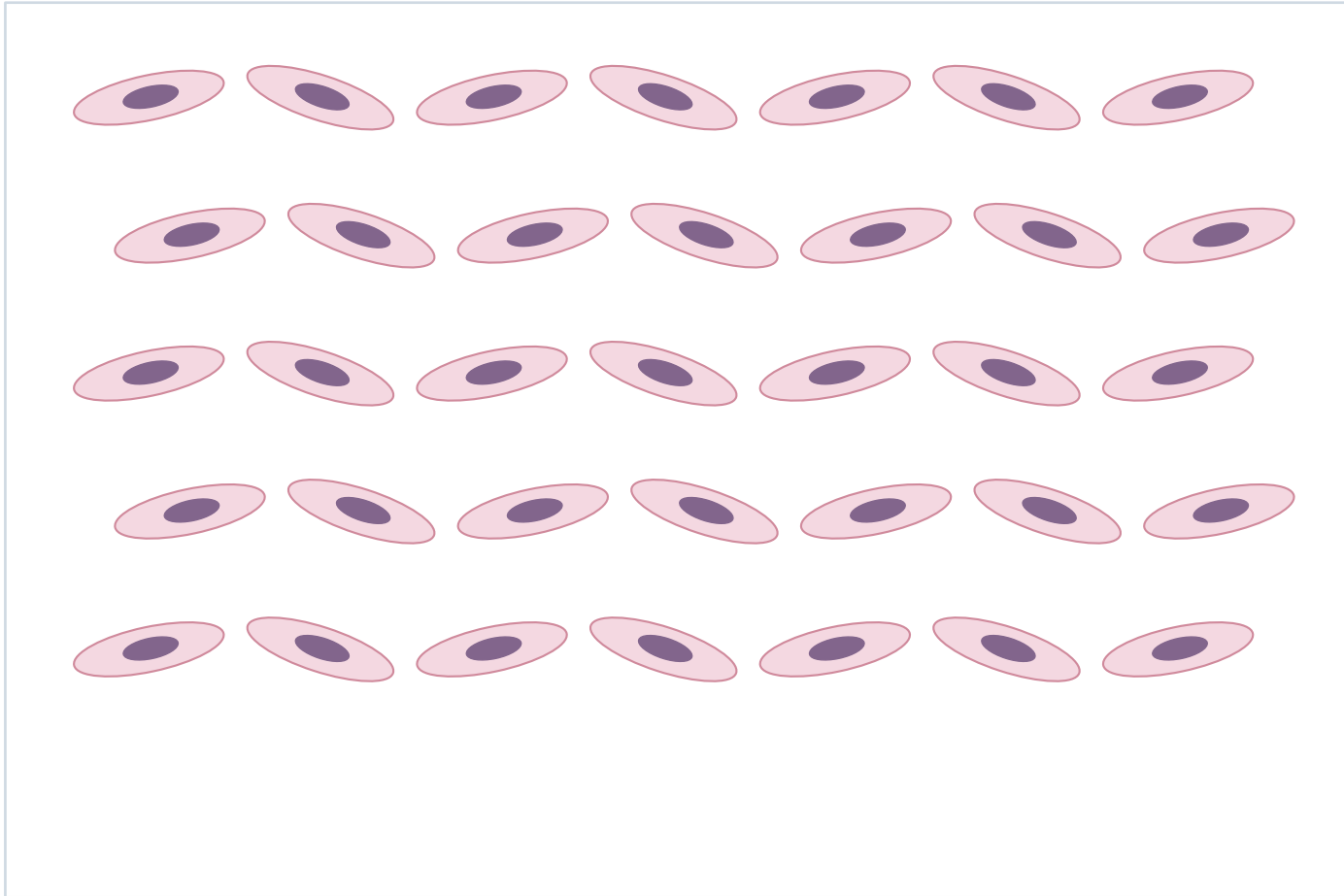
Describe the resection

- Solitary mass
- Defined circumscription
- Fleshy or whorled cut surface

Then classify the tumor

- Spindle or epithelioid histology
- KIT / DOG1 marker evaluation
- Clinical and molecular correlation

Spindle-cell GIST shows elongated cells in fascicles



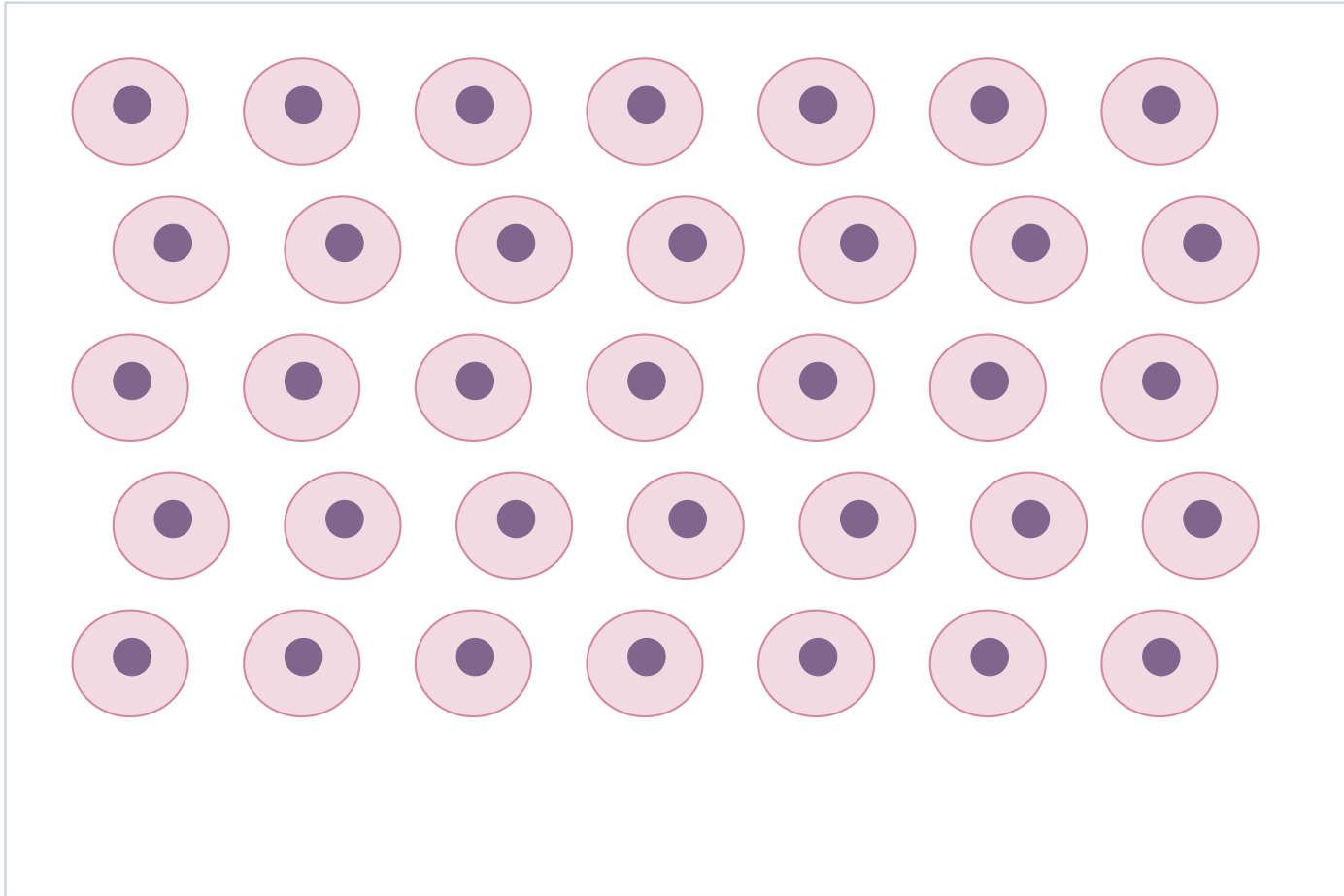
Thin, elongated neoplastic cells.

Organized into bundles or fascicles.

This is a histologic growth pattern, not a separate molecular diagnosis.

Original schematic — not H&E

Epithelioid GIST has plumper cells



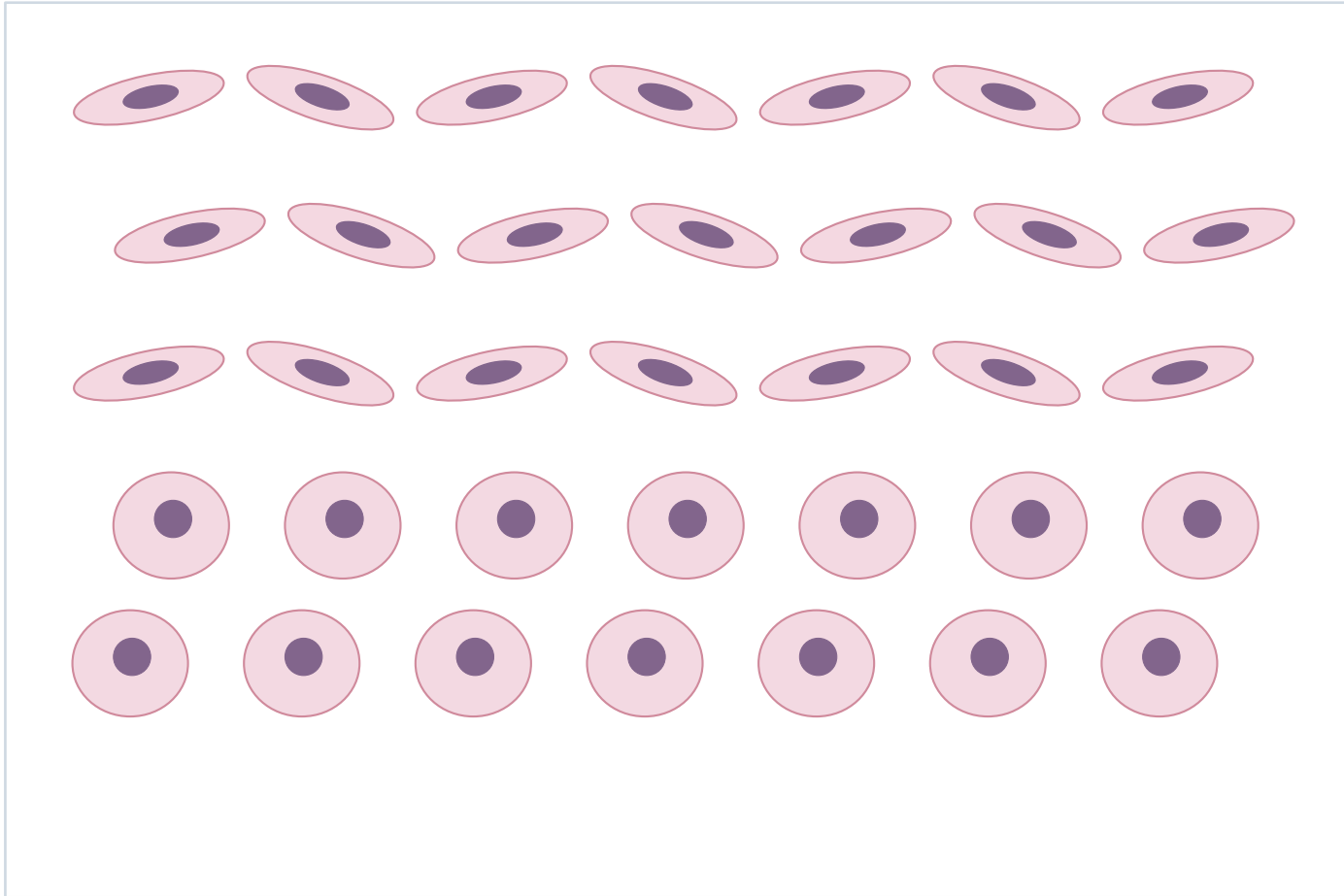
Original schematic — not H&E

Tumor cells are epithelial-appearing and rounded or plump.

Well-defined spindle-cell fascicles are absent.

The morphology can resemble gastric adenocarcinoma.

Spindle and epithelioid patterns may coexist



Mixed-pattern GIST contains both cell appearances.

Sampling may demonstrate different patterns within one tumor.

Recognition of either component directs lineage confirmation.

Original schematic — not H&E

Epithelioid GIST can mimic adenocarcinoma

Potential pitfall

- Plump epithelial-appearing cells
- Loose or absent fascicles
- Carcinoma-like first impression

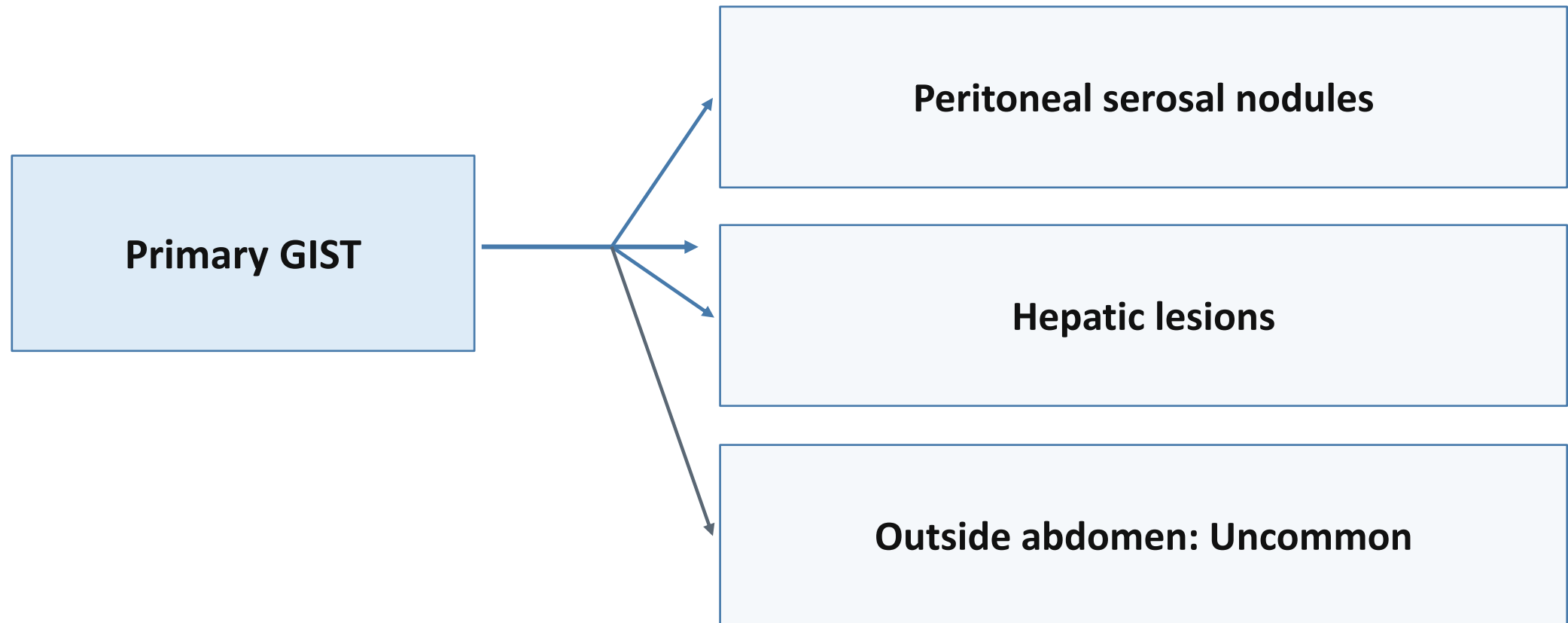
Diagnostic correction

- Maintain GIST in the differential
- Use morphology and immunohistochemistry
- Avoid lineage assignment from shape alone

Marked pleomorphism is not a defining feature

- Nuclear pleomorphism is uncommon in GIST.
- The diagnosis depends on an integrated morphological and immunophenotypic assessment.
- Pleomorphism alone is not the textbook's principal risk classifier.

Metastatic GIST commonly remains intra-abdominal



Serosal nodules may represent intraperitoneal deposits

Primary gastric GIST

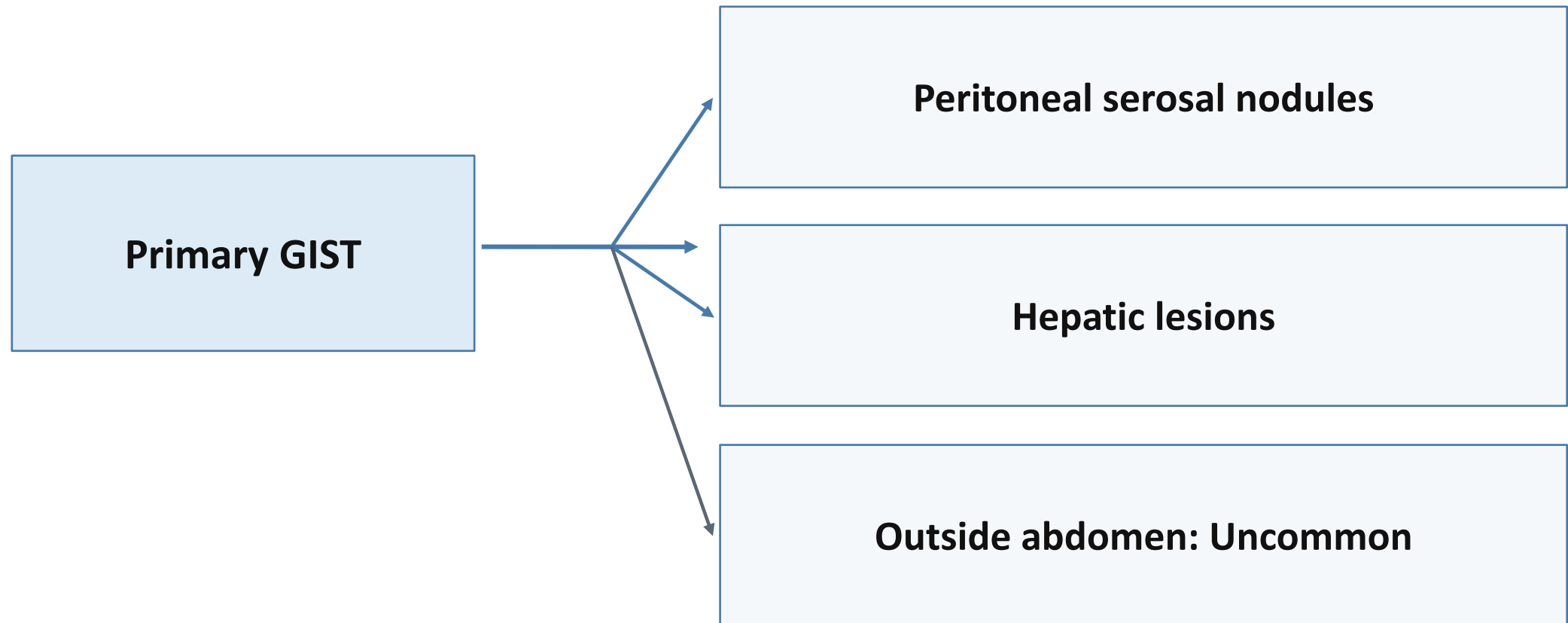


Peritoneal dissemination



Multiple serosal nodules

The liver is an important metastatic site



KIT (CD117) is a major diagnostic IHC marker

KIT gene

- Molecular sequence alteration
- Gain-of-function mutation in many GISTs
- Predictive relevance for kinase inhibitor use

KIT / CD117 protein

- Immunohistochemical expression
- Stains normal Cajal cells and many GISTs
- Diagnostic role distinct from mutation assay

Approximately 95% of gastric GISTs are KIT-positive

95%

Gastric GISTs show KIT IHC
staining

KIT immunoreactivity in 95% of gastric GISTs. The percentage applies specifically to gastric tumors in the cited description. A negative stain does not logically exclude the diagnosis.

Epithelioid GIST may be KIT-negative

- The source states that epithelioid-type GISTs are usually KIT-negative.
- An epithelioid pattern with negative KIT remains diagnostically possible.
- A second lineage marker is particularly useful in this setting.

DOG1 complements KIT in GIST diagnosis

95%

GISTs show DOG1 positivity

DOG1 means “discovered on GIST 1.” DOG1 positivity in 95% of GISTs. DOG1 includes the epithelioid-type tumors described as KIT-negative.

Diagnostic staining and gene sequencing answer different questions

Assessment	What it demonstrates	Primary teaching role
H&E morphology	Spindle / epithelioid architecture	Suggests tumor lineage
KIT / DOG1 IHC	Protein expression in tissue	Supports GIST diagnosis
KIT / PDGFRA genotype	Mutational driver status	Informs targeted treatment

An integrated GIST diagnosis has sequential steps

Recognize a mesenchymal gastric tumor pattern



Evaluate spindle / epithelioid morphology and KIT / DOG1 expression



Interpret molecular results when clinically relevant

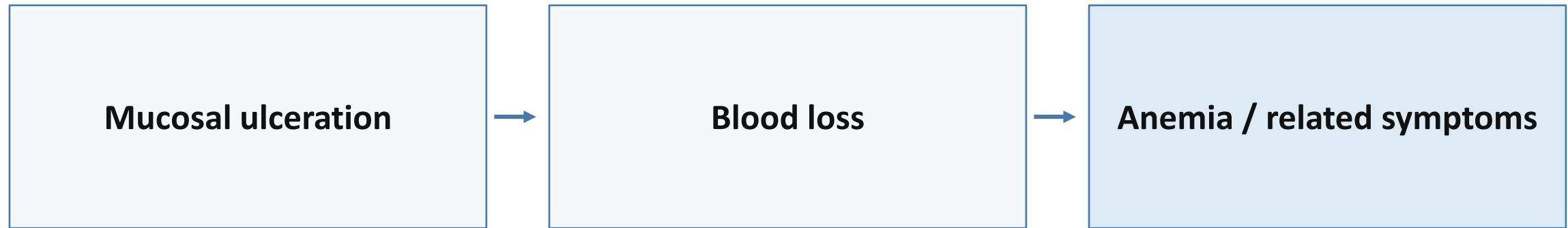
GIST is not synonymous with every gastric spindle-cell mass

Tumor type	Lineage cue from name	Why separation matters
GIST	Cajal-cell tumor	KIT / DOG1 and molecular phenotype
Leiomyoma / leiomyosarcoma	Smooth-muscle resemblance	Different mesenchymal entity
Schwannoma	Nerve-sheath resemblance	Different mesenchymal entity
Glomus tumor	Glomus-body resemblance	Different mesenchymal entity

Clinical symptoms often reflect mass effect

- Presenting complaints commonly reflect space-occupying effects.
- Symptomatic manifestations depend on what the growing mass affects.
- Some lesions remain asymptomatic and are discovered incidentally.

Mucosal ulceration creates a bleeding pathway



Schematic clinicopathologic chain; “approximately half” refers to the presenting anemia-related symptoms.

Incidental discovery is common enough to remember

Symptomatic route

- Mass effects
- Mucosal ulceration
- Blood loss / anemia

Incidental route

- Radiologic examination
- Endoscopy
- Surgery for another reason

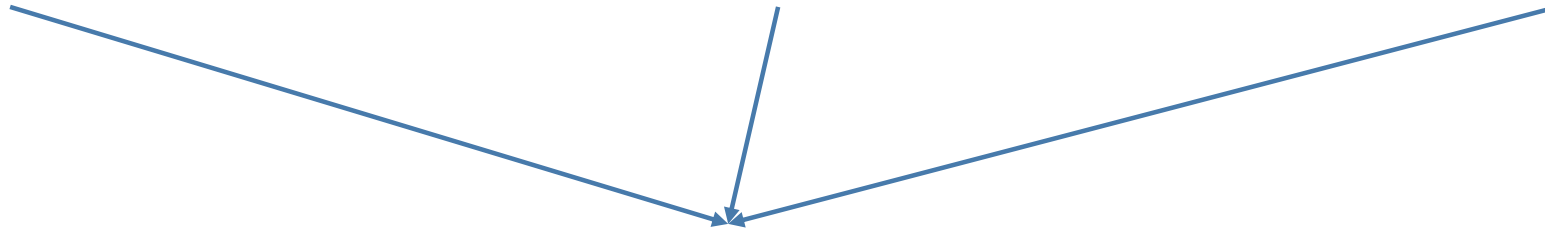
Prognosis requires multiple pathologic variables

Tumor size

Mitotic index

Anatomic location

Combined prognosis / risk assessment



Tumor size influences metastatic potential

<5 cm — gastric GIST

- Recurrence / metastasis rare
- Low risk is not identical to zero risk
- Other variables remain important

>10 cm — mitotically active

- Recurrence / metastasis common
- Mitotic activity is part of the statement
- Anatomic site must still be considered

Mitotic index modifies risk independently of size

Mitotic activity is essential to risk interpretation

Avoid inventing a numeric cutoff where the supplied source gives none.

Anatomic location changes GIST behavior

Stomach

- More than half of GISTs arise here
- Relatively less aggressive behavior
- Gastric-specific small-size example

Small intestine

- Another important site
- Relatively more aggressive behavior
- Cannot assume gastric risk is identical

Many GISTs have intermediate or uncertain potential

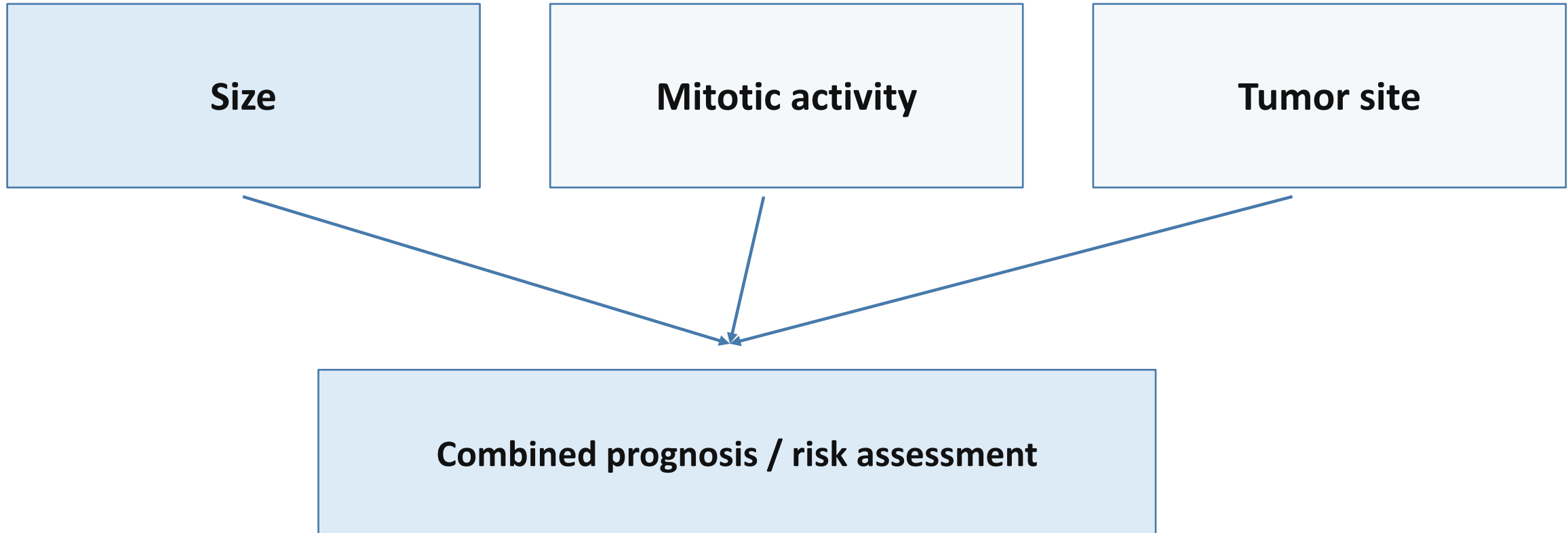
Risk assessment is probabilistic—not a binary label

Not every lesion falls clearly into a low- or high-risk group.

Robbins recognizes an intermediate group whose malignant potential cannot be predicted.

Communicate uncertainty rather than promising benign behavior.

Pathology reporting must integrate three risk axes



Localized gastric GIST is primarily treated by resection

Localized gastric GIST



Complete surgical resection



Pathologic risk assessment

Molecular phenotype becomes central in advanced disease

- Unresectable, recurrent, or metastatic GIST requires particular attention to molecular status.
- KIT- or PDGFRA-mutant GIST frequently responds to tyrosine kinase inhibition.
- Tumors lacking these mutations are generally resistant description.

Imatinib targets susceptible kinase-driven GIST

**KIT / PDGFRA mutant
tumor**



Tyrosine kinase inhibitor



Possible tumor response

Acquired imatinib resistance can involve new mutations

Susceptible mutant tumor receives imatinib



Secondary kinase mutation emerges

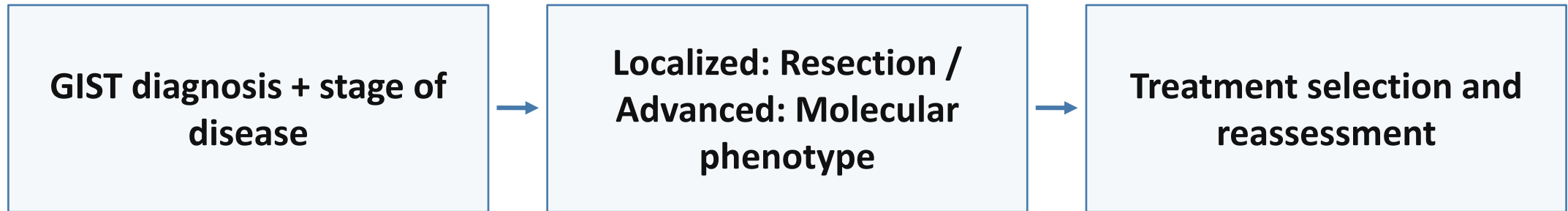


Clinical resistance may develop

Other kinase inhibitors may overcome some resistance

- Some resistant tumors respond to other tyrosine kinase inhibitors.
- The source describes agents that bypass resistance-producing mutations.
- Specific drug sequences and mutation-by-drug rules are not given in this excerpt.

The management logic runs from site to genotype



Simplified clinical framework derived; Not a complete guideline algorithm.

Case 1: Small gastric spindle-cell tumor

Teaching vignette

An older adult undergoes resection of a 3-cm, well-circumscribed gastric mass. Microscopy shows elongated cells in fascicles. Mitotic activity is low.

Interpretation tasks

Most likely tumor family?

What risk variables matter?

Which stains support diagnosis?

Case 1: Interpretation

Case interpretation

GIST is favored by the characteristic mesenchymal spindle pattern.

KIT / DOG1 help support the diagnosis.

The small gastric size is favorable; Full risk interpretation still includes mitotic index and site.

Case 2: Large, mitotically active gastric tumor

Teaching vignette

A patient presents with anemia. A 12-cm gastric mass is ulcerated and mitotically active; Nodules are also found on the peritoneal surface.

Interpretation tasks

Why anemia?

What does serosal spread suggest?

How does risk compare?

Case 2: Interpretation

Case interpretation

Ulceration provides the source-supported explanation for bleeding/anemia.

Serosal nodules indicate a metastatic distribution in this scenario.

Large size with mitotic activity is associated with frequent recurrence/metastasis.

Case 3: GIST with paraganglioma in a young patient

Teaching vignette

A young person is diagnosed with GIST and a paraganglioma. A hereditary predisposition is being considered; No pulmonary chondroma has been reported.

Interpretation tasks

Which gene complex is relevant?

What syndrome is suggested?

How does Carney triad differ?

Case 3: Interpretation

Case interpretation

Germline SDH-complex defects are linked to Carney–Stratakis syndrome.

Carney triad also includes pulmonary chondroma and is described as having unknown cause.

Tumor pairing alone does not establish a genetic diagnosis.

Case 4: KIT-negative epithelioid lesion

Teaching vignette

A gastric mass is composed of plump epithelioid tumor cells without clear fascicles. KIT immunostaining is negative and DOG1 is positive.

Interpretation tasks

Is GIST excluded?

What is the morphologic mimic?

Which result is informative?

Case 4: Interpretation

Case interpretation

Negative KIT does not exclude epithelioid GIST.

Adenocarcinoma is an important morphologic mimic.

DOG1 positivity supports GIST in this source-defined immunophenotypic setting.

Integrated summary: Recognize, classify, stratify, act

- Cajal-cell lineage, spindle/epithelioid morphology, and KIT/DOG1 establish the diagnostic framework.
- KIT/PDGFRα activation and SDH defects define biologically important molecular groups.
- Size, mitotic index, and location guide prognosis; Genotype guides advanced-disease therapy.

References and figure provenance

- Core text: Robbins, Cotran & Kumar, Pathologic Basis of Disease, 11th ed. (2026).
- Topic reading: Gastrointestinal Stromal Tumor.
- Cell illustrations in this lecture are conceptual schematics, not H&E microscopic specimens.