

Other Epithelial Bladder Tumors

Squamous cell carcinoma | Adenocarcinoma | Small-cell carcinoma

Pathologic mechanisms · morphology · clinicopathologic interpretation

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Learning objectives

- Distinguish the three major non-urothelial epithelial bladder carcinoma categories.
- Explain the injury–metaplasia–dysplasia sequence associated with bladder squamous carcinoma.
- Relate morphology, precursor lesions, mixed histology, and invasion to diagnostic interpretation.
- Recognize what the Robbins excerpt does not establish about immunophenotype and therapy.

Tumors of the urinary bladder: Basic taxonomy

- Urothelial neoplasms form the dominant epithelial group.
- Other epithelial groups include squamous carcinoma, adenocarcinoma, mixed carcinoma, and small-cell carcinoma.
- Mesenchymal tumors are classified separately from epithelial tumors.

Tumor family	Included groups
Epithelial	Urothelial; squamous; adenocarcinoma; mixed; small cell
Mesenchymal	Leiomyoma, sarcoma and other stromal lesions
Secondary involvement	Extension/metastasis from nonbladder malignancy

Why non-urothelial tumors deserve separate recognition

- They are less frequent than urothelial carcinoma but have distinct differentiation.
- Pure tumors and mixed tumors with urothelial carcinoma must be distinguished.
- Morphology and the relationship to precursor change provide the starting classification.

Squamous	Glandular	Neuroendocrine / small cell
Keratinization and squamous differentiation	Gastrointestinal-like glandular morphology	Small-cell pulmonary-like tumor phenotype

Primary tumors versus secondary involvement

- An epithelial malignancy in the bladder is not automatically bladder-derived.
- Direct extension from cervix, uterus, prostate, or rectum is an important alternative.
- True solid-tumor metastases to the bladder are described as very rare.

Primary bladder lesion

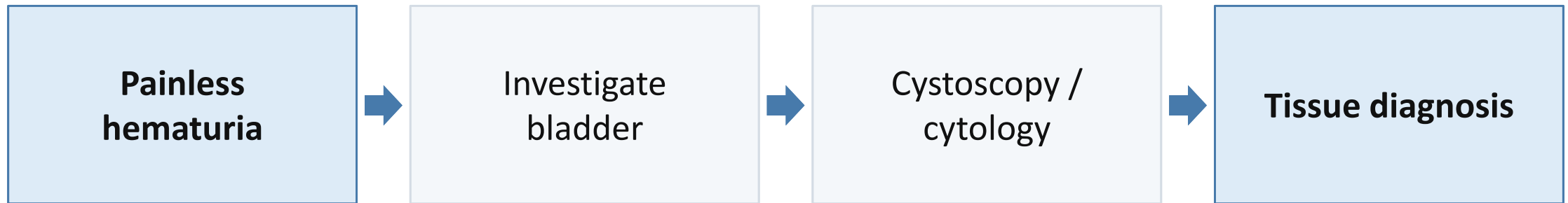
- Tumor originates in the bladder.
- Classification uses observed epithelial phenotype.
- Adjacent mucosal abnormalities may offer context.

Secondary bladder involvement

- Tumor extends from a neighboring organ.
- Cervix, uterus, prostate, and rectum are cited.
- The origin must be interpreted in anatomic context.

Clinical presentation: The common entry point

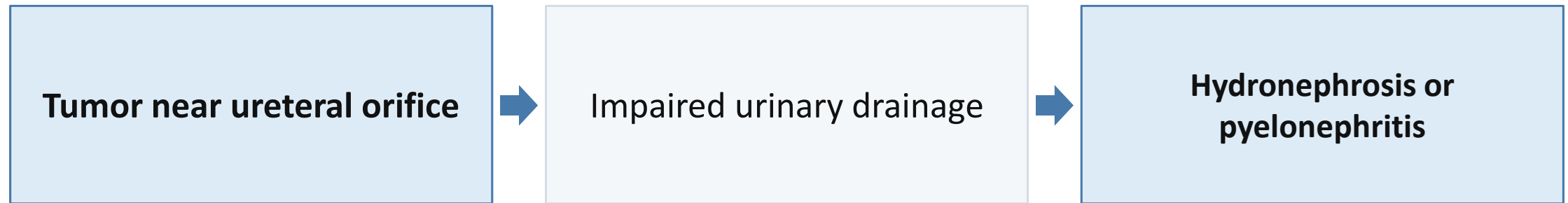
- Painless hematuria is the most common symptom of bladder cancer.
- Frequency, urgency, and dysuria can accompany hematuria.
- Symptoms alone cannot establish squamous, glandular, or small-cell differentiation.



Schematic — source-derived relationships; Not a clinical specimen

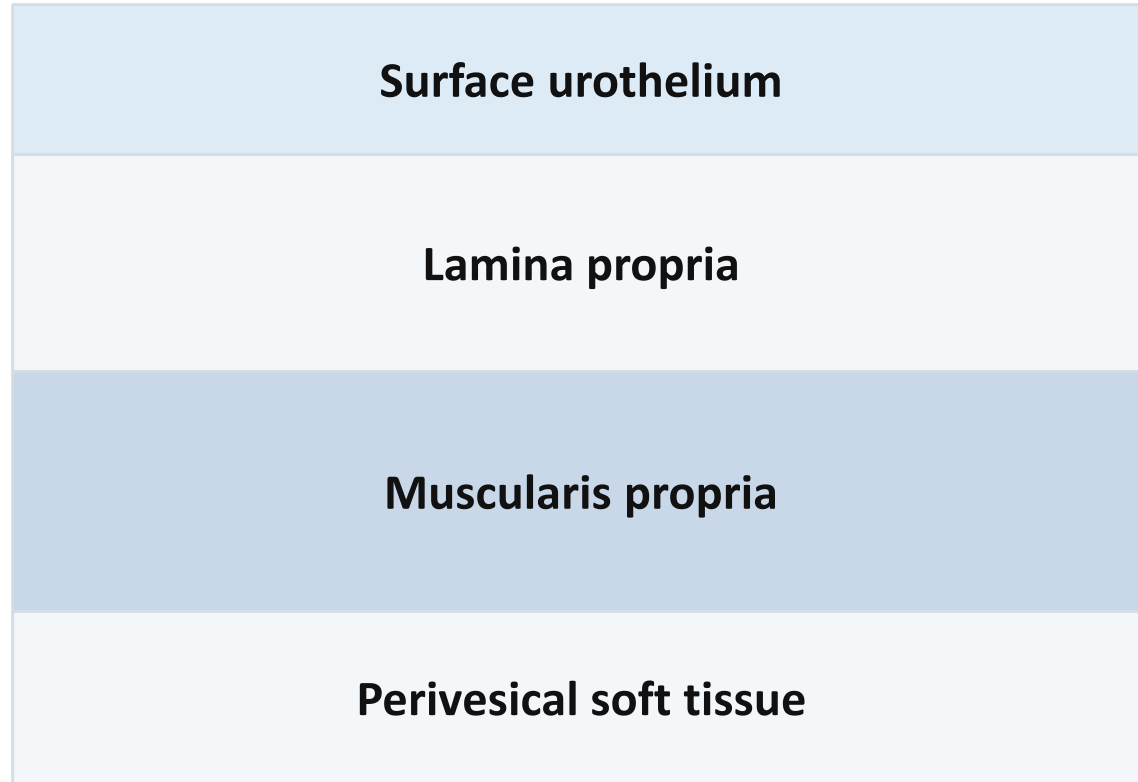
Local consequences may reflect the tumor location

- Bladder tumors may obstruct a ureteral orifice.
- Pyelonephritis or hydronephrosis may develop following obstruction.
- Symptoms and anatomic effects do not substitute for morphologic typing.



Schematic — source-derived relationships; Not a clinical specimen

Bladder wall layers frame tumor interpretation



Schematic of bladder wall compartments

- Urothelium covers the surface; Lamina propria lies beneath it.
- Muscularis propria is the detrusor muscle compartment.
- Depth of invasion is essential to pathologic stage and clinical course.

Different risk contexts require separate interpretation

- Cigarette smoking is a major risk factor for bladder cancer overall.
- Urinary schistosomiasis is specifically associated with squamous carcinoma in endemic areas.
- Cyclophosphamide and pelvic irradiation are other bladder cancer–related exposures.

Context	Robbins association
Smoking	Major bladder cancer risk; also noted with small-cell carcinoma
S. haematobium	Chronic injury, squamous metaplasia, squamous carcinoma
Cyclophosphamide	Hemorrhagic cystitis and increased bladder cancer risk
Pelvic irradiation	Later urothelial carcinoma risk

Squamous cell carcinoma: Defining context

- Bladder squamous carcinoma resembles squamous malignancy at other anatomic sites.
- Pure squamous carcinoma is different from urothelial carcinoma containing a squamous component.
- An association with chronic irritation and infection.

Squamous carcinoma is uncommon in the United States

- That squamous carcinomas comprise 3%–7% of bladder cancers in the United States.
- This is a United States estimate—not a global proportion.
- Regional prevalence changes in settings where urinary schistosomiasis is endemic.

United States

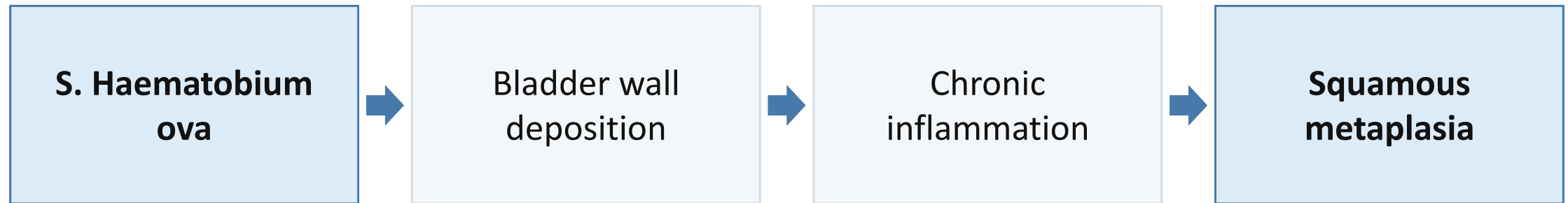
- Squamous carcinoma: 3%–7%.
- Urothelial carcinoma predominates.

Schistosomiasis-endemic regions

- Bladder squamous carcinoma is much more frequent.
- The change is associated with *S. Haematobium* infection.

Urinary schistosomiasis creates sustained epithelial injury

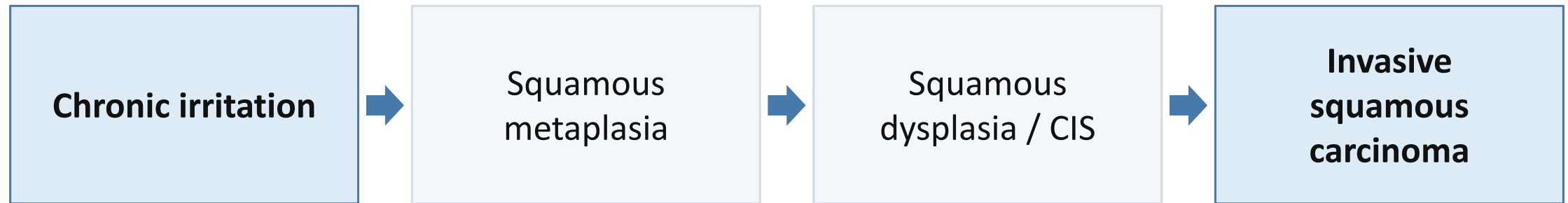
- Schistosoma haematobium ova are deposited in the bladder wall.
- The ova incite chronic inflammation.
- Chronic mucosal injury sets the context for progressive squamous alteration.



Schematic — source-derived relationships; Not a clinical specimen

A multistep squamous precursor sequence

- The textbook links chronic inflammation with squamous metaplasia, dysplasia, and neoplasia.
- Progression is possible; Metaplasia alone does not imply that carcinoma is already present.
- Represent the morphologic steps separately when examining a specimen.



Schematic — source-derived relationships; Not a clinical specimen

Squamous metaplasia is an adaptive epithelial change

- Urothelium can be replaced by squamous epithelium in response to chronic injury.
- The replacement as a more durable lining.
- The change may be keratinizing or nonkeratinizing.

Normal urothelium

- Specialized urinary lining.
- An umbrella cell layer is a normal surface feature.

Squamous metaplasia

- Squamous epithelium replaces urothelium.
- A more durable response to chronic injury.

Not all squamous epithelium in the bladder is abnormal

- Glycogenated squamous epithelium normally occurs at the female bladder trigone.
- It must be separated from injury-related keratinizing squamous metaplasia.
- Anatomic site and type of epithelial maturation therefore matter.

Normal trigonal finding

- Glycogenated squamous epithelium.
- Recognized in females.

Injury-associated lesion

- Keratinizing squamous metaplasia.
- May be extensive and multifocal.

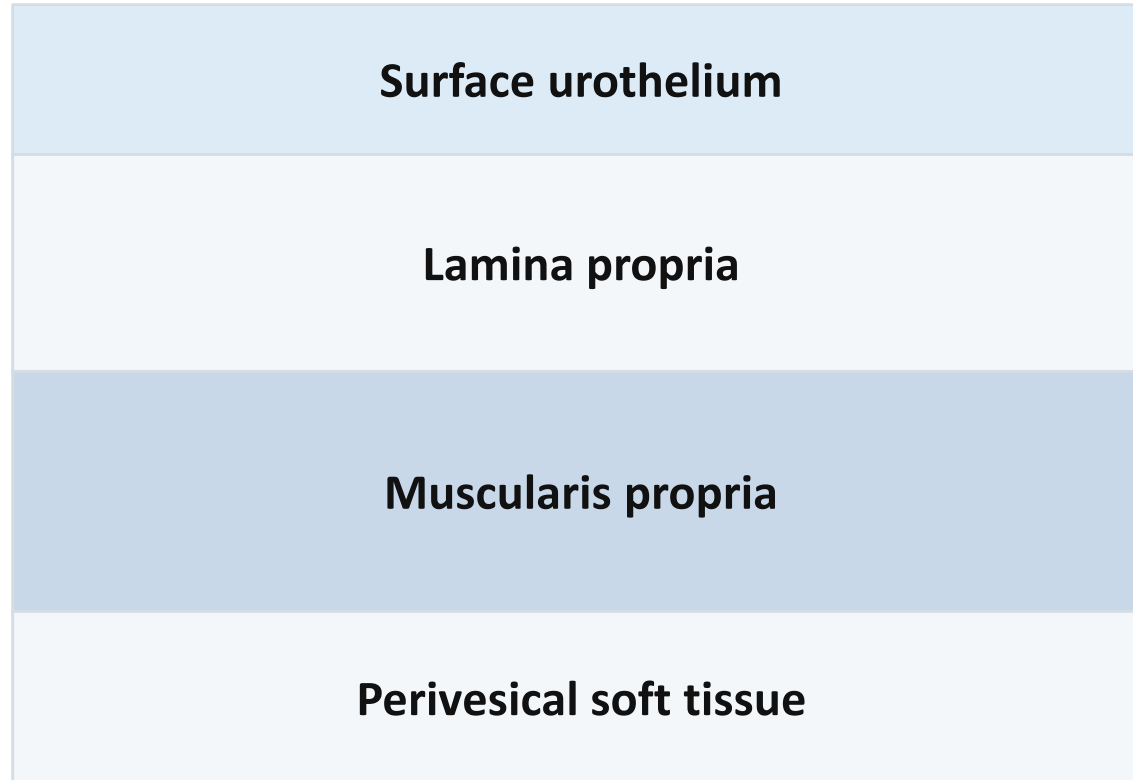
Keratinizing squamous metaplasia and malignant potential

- Extensive multifocal keratinizing metaplasia is a precursor to squamous dysplasia and carcinoma.
- Both in situ and invasive squamous carcinoma as possible downstream lesions.
- Keratinizing metaplasia therefore merits distinction from physiologic trigonal squamous epithelium.



Schematic — source-derived relationships; Not a clinical specimen

Squamous dysplasia versus in situ carcinoma

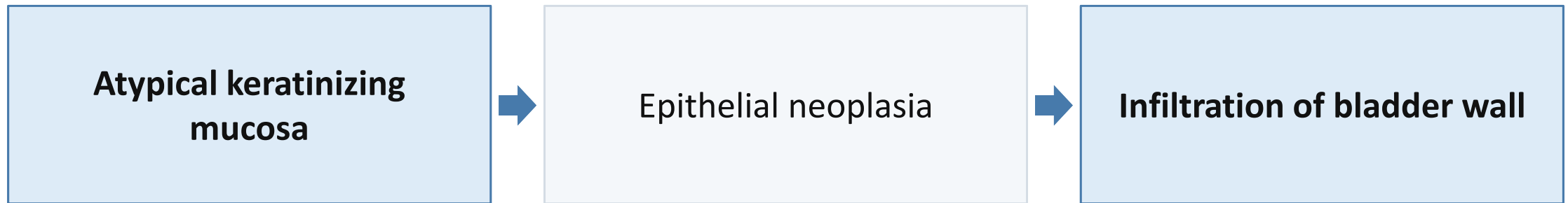


Schematic of bladder wall compartments

- Both lie on the dysplastic precursor spectrum.
- Carcinoma in situ indicates cytologic malignancy confined to the epithelial compartment.
- Invasion requires malignant cells to extend beyond the epithelial basement membrane.

Why precursor mapping matters in squamous carcinoma

- Atypical keratinizing mucosa can provide a mucosal precursor adjacent to a tumor.
- Identify dysplasia or in situ change separately from invasive tumor.
- The presence of a precursor helps interpret the injury-associated sequence.



Schematic — source-derived relationships; Not a clinical specimen

Two different bladder cancer developmental pathways

- Non–muscle-invasive papillary urothelial cancers commonly involve growth-factor signaling activation.
- The CIS-associated muscle-invasive pathway often involves disruption of TP53 and RB.
- These general urothelial patterns should not be imposed automatically on every non-urothelial tumor.

Papillary urothelial pathway

- FGFR3, RAS, PI 3-kinase alterations.
- Often recurs; Less often becomes muscle invasive.

CIS-associated invasive pathway

- TP53 and RB pathway disruption.
- Associated with muscle-invasive disease.

Pure squamous carcinoma versus mixed carcinoma

- Mixed urothelial carcinoma containing areas of squamous carcinoma is more common than pure squamous carcinoma.
- A diagnosis of a purely squamous tumor depends on assessment of the sampled neoplasm.
- Do not assume any squamous differentiation excludes an accompanying urothelial component.

Pure squamous carcinoma

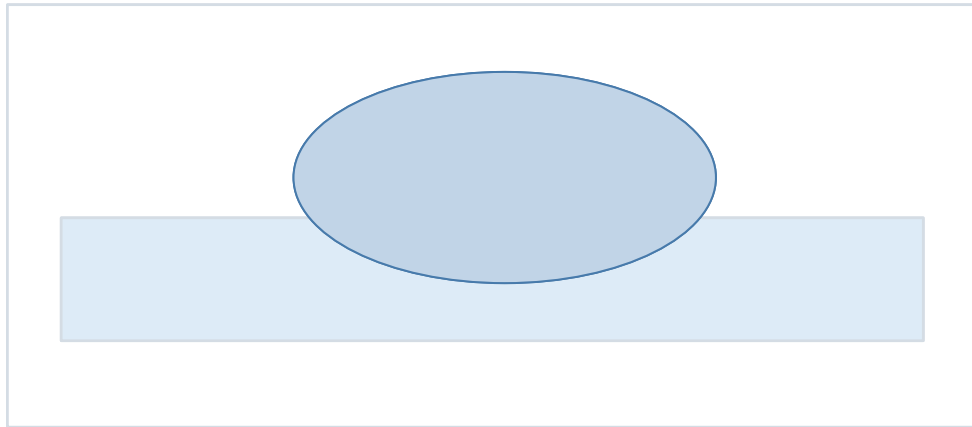
- Squamous phenotype constitutes the described tumor.
- No urothelial carcinoma component identified in evaluated tissue.

Mixed urothelial / squamous tumor

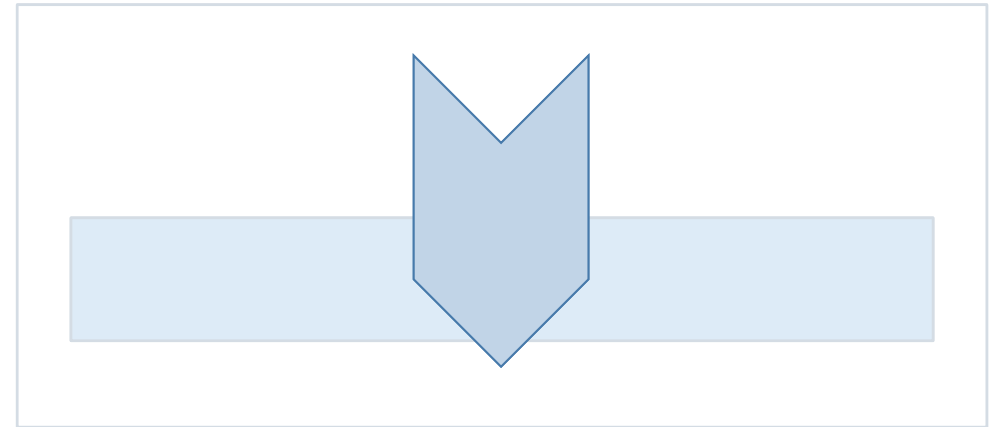
- Urothelial carcinoma and squamous areas coexist.
- Recognizing both components changes descriptive classification.

The gross appearance of squamous carcinoma is often invasive

- Most squamous carcinomas as invasive lesions.
- One macroscopic form is a fungating mass protruding into the bladder lumen.
- An alternative pattern is infiltrative and ulcerative.



Fungating projection

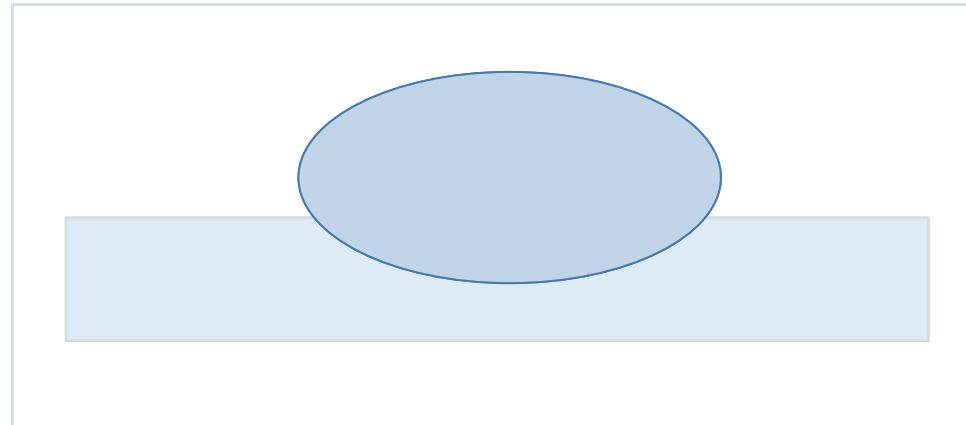


Infiltrative / ulcerative

Conceptual gross-pattern schematics — not clinical specimen images

Fungating tumors: An exophytic invasive pattern

- A fungating mass projects into the lumen.
- Gross projection does not by itself determine whether the muscularis propria is involved.
- Histologic evaluation is still needed to establish invasion depth.

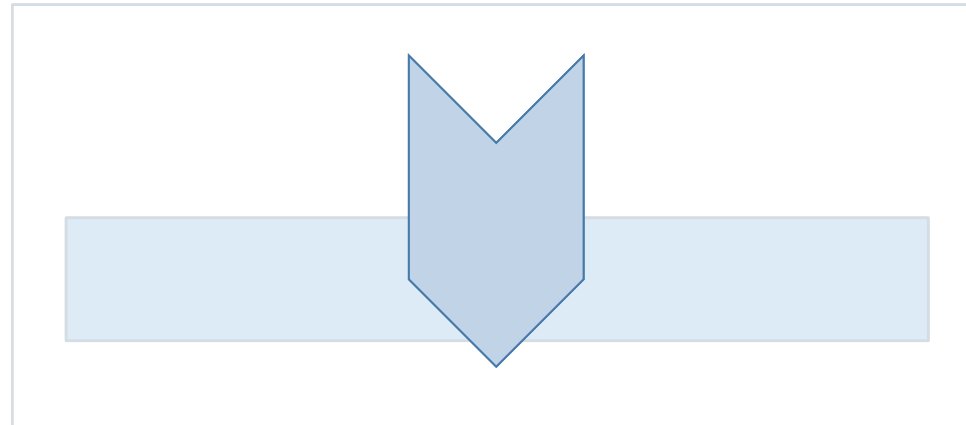


Fungating projection

Conceptual gross-pattern schematics — not clinical specimen images

Infiltrative and ulcerative squamous tumors

- The lesion may extend within the bladder wall and ulcerate the overlying surface.
- Surface ulceration is not a substitute for histologic staging.
- The wall layers provide the anatomic framework for reporting extent.

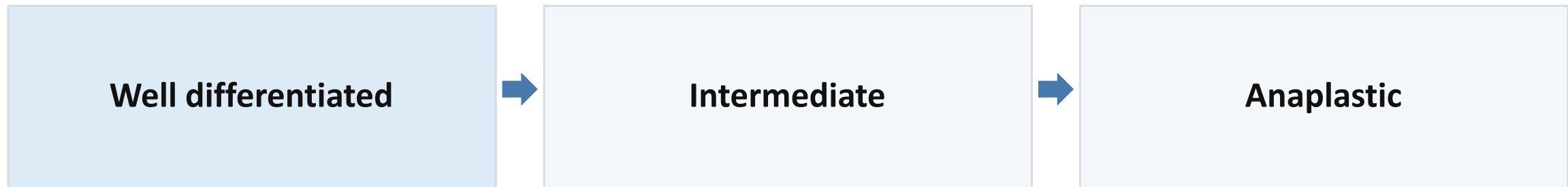


Infiltrative / ulcerative

Conceptual gross-pattern schematics — not clinical specimen images

Squamous histology spans a differentiation spectrum

- Well-differentiated tumors produce abundant keratin.
- At the anaplastic end, squamous differentiation may only be focal.
- The degree of differentiation is not uniform among all squamous carcinomas.



Progressively less overt keratinizing differentiation

Well-differentiated squamous carcinoma

- Abundant keratin formation is emphasized in the Robbins description.
- Keratin production is a morphologic expression of squamous differentiation.
- The assessment still requires attention to invasion and any nonsquamous tumor component.

Anaplastic squamous carcinoma: Sparse clues

- Some tumors show only focal evidence of squamous differentiation.
- Limited squamous foci are easier to overlook than abundant keratin production.
- A restricted sample may not reveal the full differentiation spectrum.

Extensive squamous differentiation

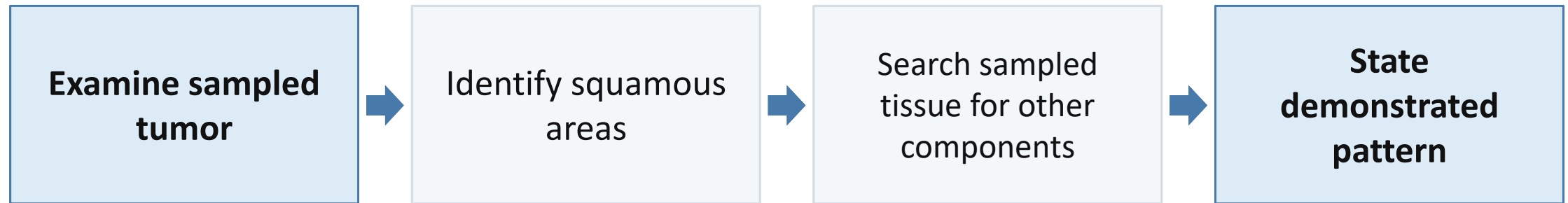
- Abundant keratin; Conspicuous squamous identity.

Focal squamous differentiation

- Only limited areas may establish phenotype.
- Evaluate other available tumor regions.

Morphology and tumor sampling: An interpretive boundary

- The source explicitly recognizes mixed tumors and focal squamous differentiation.
- Accordingly, phenotype in a limited fragment may not represent the entire mass.
- Interpretation should distinguish observed findings from claims about unsampled tissue.



Schematic — source-derived relationships; Not a clinical specimen

Teaching case: Chronic irritative disease and a bladder mass

HYPOTHETICAL TEACHING CASE

- Hypothetical: An older patient from a schistosomiasis-endemic region has hematuria and an ulcerated bladder mass.
- Tissue shows keratinizing carcinoma next to atypical keratinizing mucosa.
- Question: Which pathogenetic sequence is most consistent with these observations?

Interpretation requires separating observed evidence from diagnostic inference.

Case interpretation: Separate evidence from inference

- Observed evidence: Keratinizing carcinoma, adjacent atypical mucosa, and an ulcerated mass.
- Source-supported inference: The pattern is compatible with squamous carcinoma arising in an injury-related metaplastic field.
- Do not infer a specific infection in an individual patient solely from tumor morphology.

Observed

- Squamous differentiation.
- Atypical keratinizing epithelium.
- Ulcerated lesion.

Interpretation

- Compatible precursor sequence.
- Etiologic attribution requires clinical evidence.

Adenocarcinoma of the bladder is rare

- Adenocarcinoma is listed as a distinct bladder epithelial tumor category.
- Bladder adenocarcinoma is rare.
- Its morphology closely resembles adenocarcinoma in the gastrointestinal tract.

Adenocarcinoma: The glandular differentiation problem

- The textbook stresses histologic identity with gastrointestinal adenocarcinomas.
- Glandular appearance establishes a phenotype, not automatically the organ of origin.
- Bladder-primary disease must be separated from extension by a nearby gastrointestinal tumor.

Morphologic question

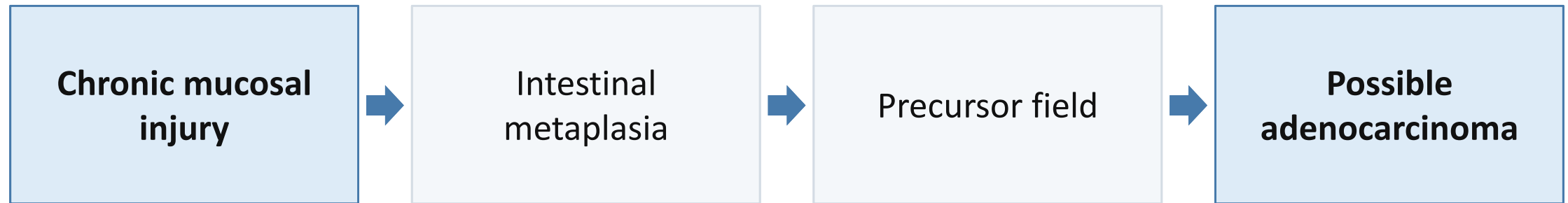
- Is the tumor gland-forming / adenocarcinomatous?
- How closely does it resemble intestinal cancer?

Anatomic origin question

- Does the lesion arise in the bladder?
- Could it extend from the rectum or another organ?

Intestinal metaplasia is a relevant epithelial precursor

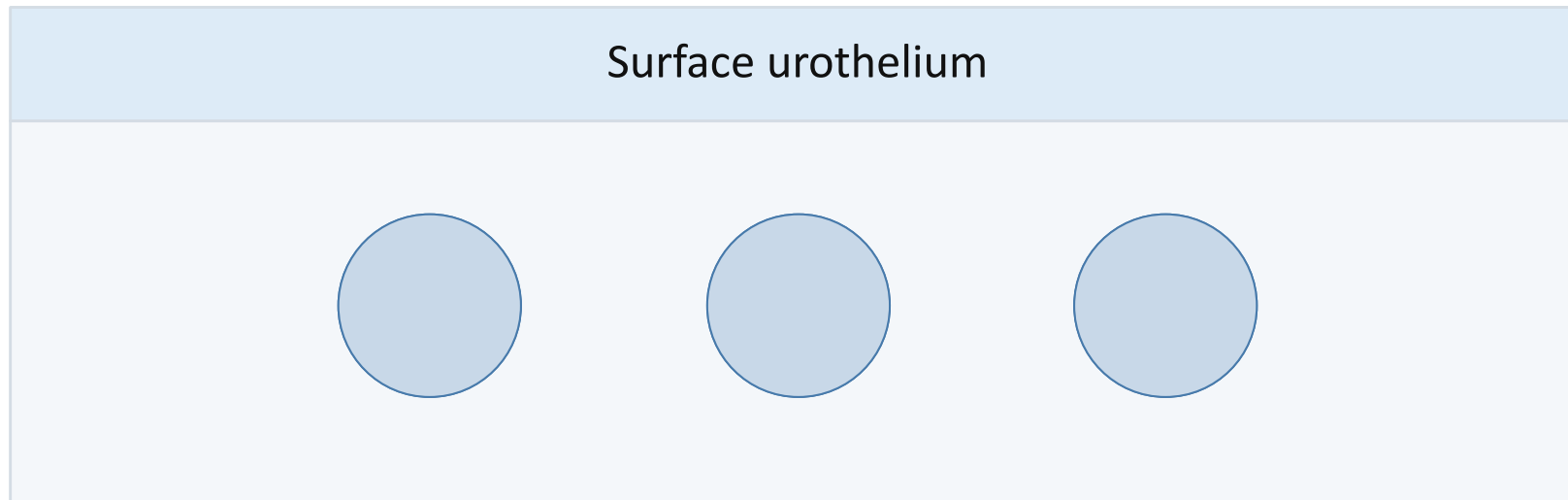
- Extensive, multifocal intestinal metaplasia as a precursor to bladder adenocarcinoma.
- The precursor is addressed in the related section on metaplastic lesions.
- This is a risk relationship—not a claim that every glandular lesion becomes malignant.



Schematic — source-derived relationships; Not a clinical specimen

Von Brunn nests: The starting epithelial architecture

- Urothelial nests can extend downward into the lamina propria.
- These are termed von Brunn nests.
- Their centers may later undergo glandular change or cystic retraction.

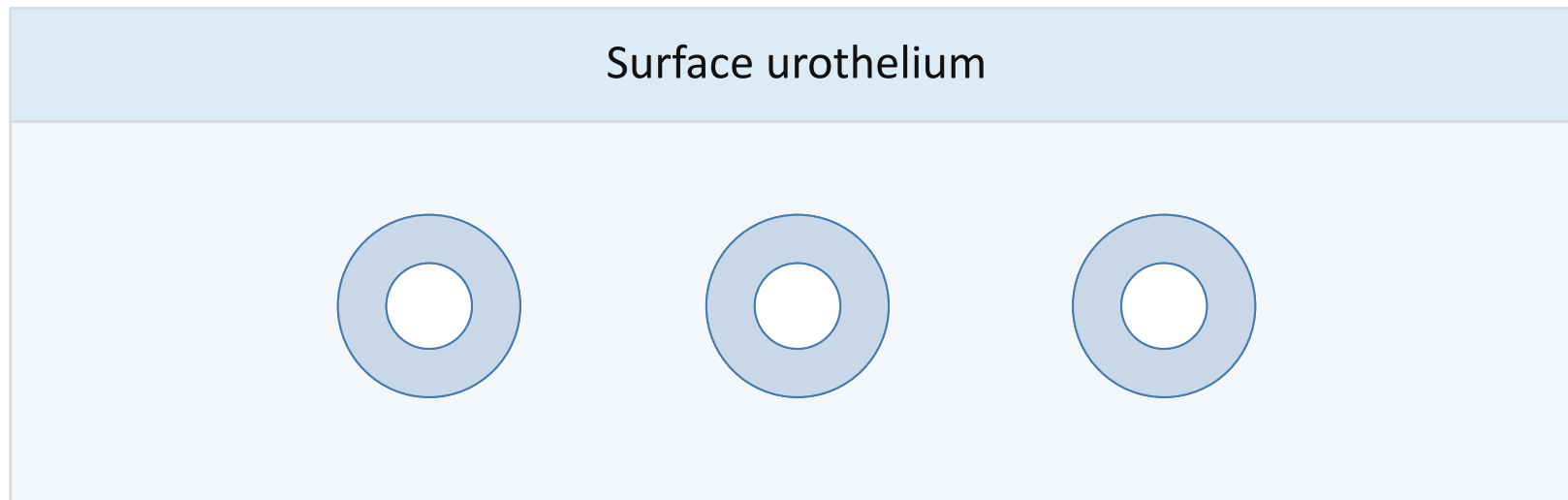


Downward urothelial nests

Schematic (not histology)

Cystitis glandularis: A benign glandular mimic

- Central cells within urothelial nests acquire a cuboidal or columnar appearance.
- Robbins calls this cystitis glandularis.
- A glandular lining in the bladder is therefore not synonymous with invasive adenocarcinoma.

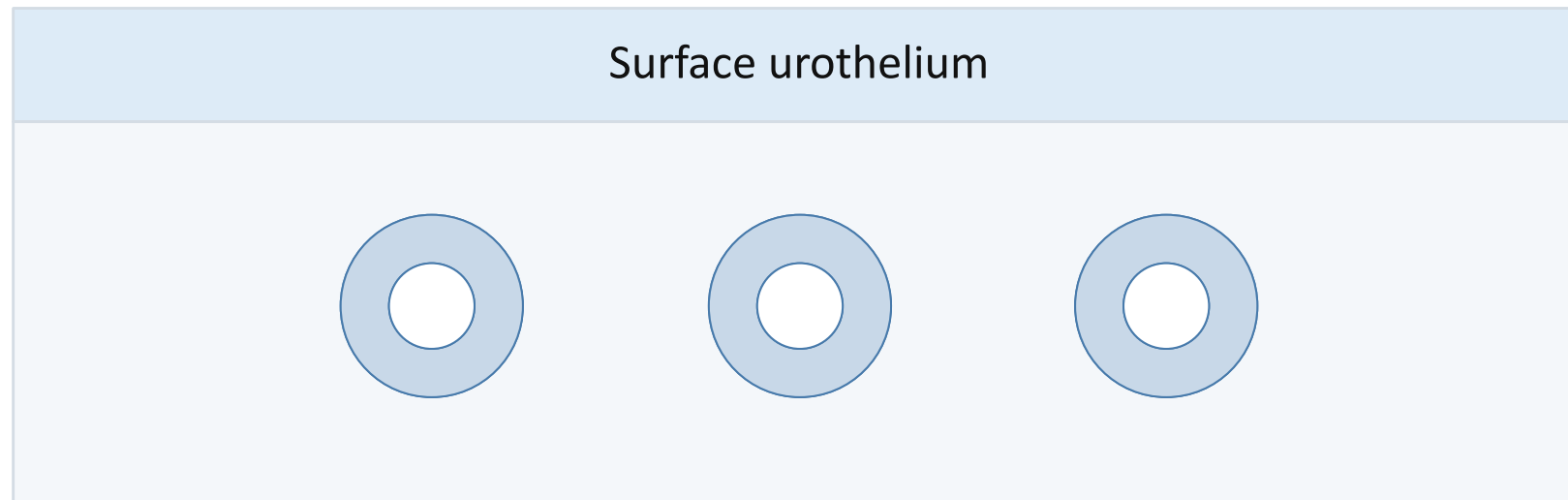


Cuboidal / columnar central metaplasia

Schematic (not histology)

Cystitis cystica: A cystic rather than glandular pattern

- Central nest cells retract, leaving cystic spaces.
- The resulting spaces are lined by flattened urothelium.
- The lesion can coexist with cystitis glandularis.



Cystic central retraction

Schematic (not histology)

Cystitis cystica et glandularis: Frequent coexistence

- The cystic and glandular metaplastic processes often coexist.
- The combined term cystitis cystica et glandularis reflects this overlap.
- Histologic context prevents overcalling a benign reactive process as cancer.

Cystitis cystica

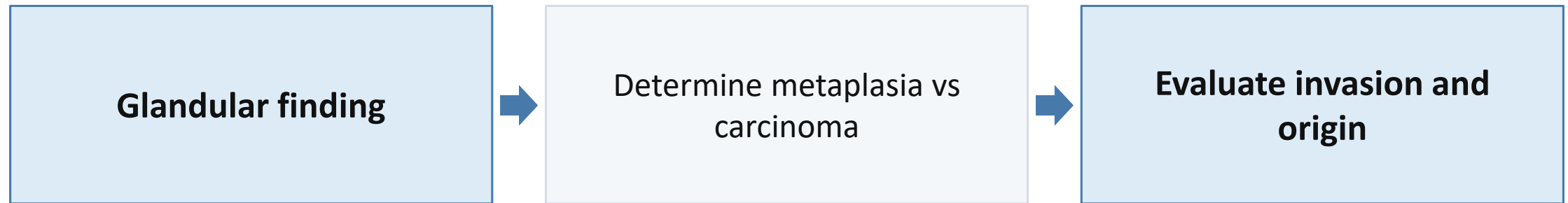
- Retracted nest centers.
- Cystic space with flattened lining.

Cystitis glandularis

- Cuboidal or columnar metaplasia.
- Glandular-appearing epithelial nests.

Glandular change and carcinoma require distinction

- Benign glandular metaplasia is not itself a diagnosis of adenocarcinoma.
- Extensive multifocal intestinal metaplasia has a recognized precursor association.
- An invasive adenocarcinoma must be characterized on its own malignant architecture and context.



Schematic — source-derived relationships; Not a clinical specimen

Primary bladder adenocarcinoma versus rectal extension

- A glandular tumor in the bladder can resemble a gastrointestinal primary histologically.
- The rectum among common adjacent sources of direct malignant extension.
- Anatomic relationship is therefore indispensable to assigning primary site.

Possible bladder primary

- Bladder epithelial tumor with adenocarcinoma morphology.
- Evaluate associated bladder mucosa.

Possible rectal extension

- Rectal tumor directly involving bladder.
- Morphologic similarity alone cannot settle the origin.

Teaching case: A gland-forming bladder tumor

HYPOTHETICAL TEACHING CASE

- Hypothetical: Bladder biopsy contains carcinoma with intestinal-type glandular morphology.
- Imaging also shows a mass adjacent to the rectum.
- Question: What does morphology establish, and what remains unresolved?

Interpretation requires separating observed evidence from diagnostic inference.

Adenocarcinoma case: Scope the conclusion correctly

- The gland-forming pattern supports a diagnosis of adenocarcinoma.
- It cannot alone demonstrate whether the lesion started in bladder or rectum.
- Correlate pathology with the tumor epicenter and adjacent-organ findings.

Small-cell carcinoma: A distinct epithelial malignancy

- Small-cell carcinoma occasionally arises in the urinary bladder.
- Robbins says its histologic appearance is indistinguishable from small-cell carcinoma of the lung.
- It should not be conflated with urothelial carcinoma solely because both occur in the bladder.

Small-cell appearance does not prove lung origin

- The term “small-cell carcinoma” denotes a morphologic tumor phenotype.
- The textbook explicitly recognizes primary bladder occurrence.
- Anatomic and clinical context remains necessary when assessing site of origin.

Morphology

- Small-cell phenotype analogous to pulmonary small-cell carcinoma.

Site attribution

- Bladder may be the primary site.
- Morphology alone is not site-specific.

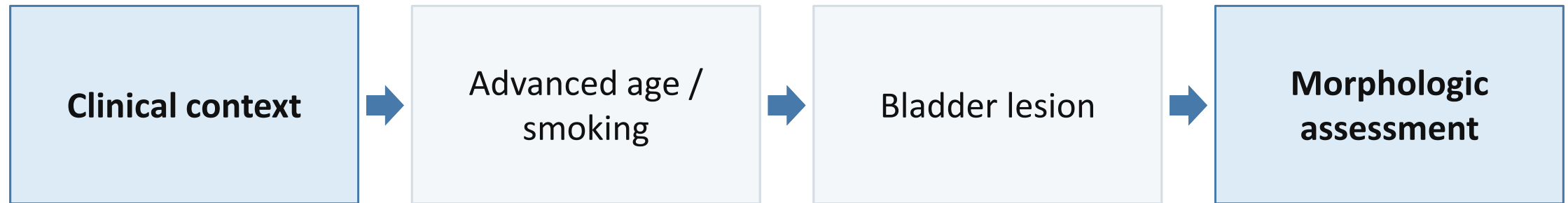
Small-cell carcinoma often has mixed histology

- Bladder small-cell carcinoma often arises adjacent to urothelial carcinoma.
- Squamous carcinoma or adenocarcinoma may also be present alongside it.
- Such admixture should be recognized rather than flattened into one generic tumor label.

Urothelial area	Squamous / glandular area	Small-cell area
One possible associated epithelial component	Other epithelial components may coexist	Distinct small-cell phenotype

Age and smoking association in small-cell carcinoma

- Bladder small-cell carcinoma with advanced age and smoking.
- Smoking is also a major bladder cancer risk factor overall.
- An exposure association does not replace histologic diagnosis.



Schematic — source-derived relationships; Not a clinical specimen

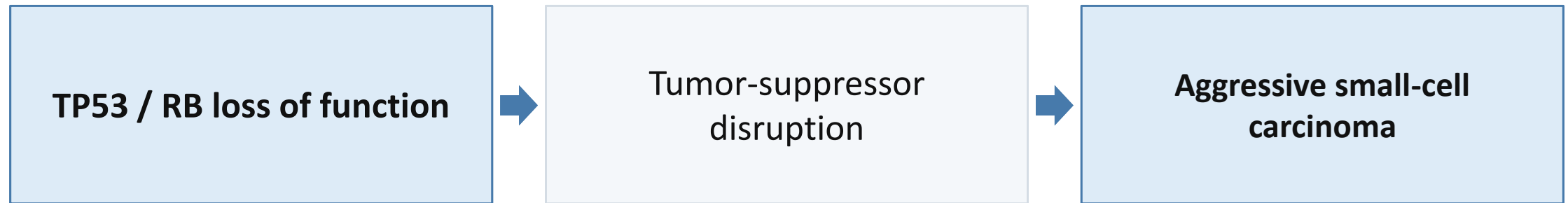
Neuroendocrine differentiation as a conceptual origin

- Bladder small-cell carcinoma as arising from neuroendocrine cells.
- This distinguishes its stated origin from ordinary squamous or glandular epithelial differentiation.
- No specific immunohistochemical panel is provided in the supplied passage.

Squamous	Glandular	Neuroendocrine
Squamous differentiation	Adenocarcinomatous differentiation	Small-cell carcinoma lineage

TP53 and RB alterations in small-cell carcinoma

- Very aggressive bladder small-cell carcinomas commonly harbor loss-of-function mutations in TP53 and RB.
- The altered tumor suppressors are also highlighted in the muscle-invasive urothelial pathway.
- A shared molecular alteration does not mean the tumor types are identical.



Schematic — source-derived relationships; Not a clinical specimen

Compare two major molecular themes

- Papillary non–muscle-invasive urothelial cancer: Activating growth-factor pathway alterations.
- Bladder small-cell carcinoma: Common TP53 and RB loss-of-function alterations.
- Robbins does not supply a defining molecular signature for every squamous or glandular bladder carcinoma.

Tumor pattern	Highlighted molecular alteration
Non–muscle-invasive papillary urothelial	FGFR3, RAS, PI 3-kinase pathway activation
Muscle-invasive urothelial / CIS pathway	TP53 and RB disruption
Bladder small-cell	Common TP53 and RB loss of function
Pure squamous / bladder adenocarcinoma	Not specified in the targeted textbook excerpt

Clinical meaning of an aggressive small-cell phenotype

- Robbins explicitly describes bladder small-cell carcinoma as very aggressive.
- Its occurrence with other epithelial components makes careful morphologic recognition essential.
- General urothelial carcinoma survival figures must not be assigned to small-cell carcinoma without supporting data.

Teaching case: A bladder carcinoma with two patterns

HYPOTHETICAL TEACHING CASE

- Hypothetical: A bladder tumor shows small-cell carcinoma adjacent to an otherwise recognizable urothelial carcinoma.
- The patient has a long smoking history.
- Question: Which two source-supported features should be recorded?

Interpretation requires separating observed evidence from diagnostic inference.

Case interpretation: Document both components

- A small-cell component is a separate morphologic finding.
- Coexisting urothelial carcinoma should not be hidden by a broad “bladder cancer” label.
- The tumor can be contextualized by age and smoking without making unsupported molecular or treatment claims.

Reportable observations

- Small-cell carcinoma phenotype.
- Associated urothelial carcinoma.

Context, not proof

- Age and smoking association.
- TP53/RB alterations are common, not obligatory.

Three tumor types: An integrated comparison

- The three categories are defined by different epithelial phenotypes.
- Mixed histology and overlapping clinical features complicate classification.

Feature	Squamous cell	Adenocarcinoma	Small cell
Frequency	3%–7% of US bladder cancers	Rare	Occasional
Characteristic context	Chronic irritation; schistosomiasis	Intestinal metaplasia precursor	Advanced age; smoking
Typical description	Keratinization; invasive mass	GI-like histology	Lung small-cell–like
Other components	Often mixed with urothelial	May appear in mixed carcinoma	Often adjacent to other epithelial types

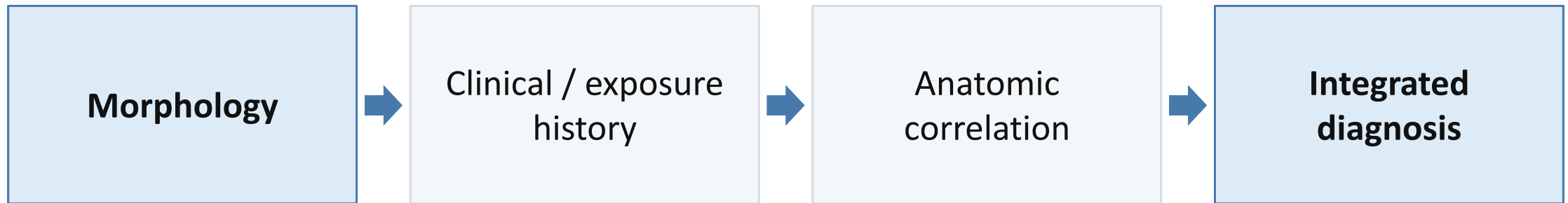
Precursor associations should not be generalized

- Keratinizing squamous metaplasia can precede dysplasia and squamous carcinoma.
- Extensive multifocal intestinal metaplasia is a precursor to adenocarcinoma.
- The small-cell passage provides no corresponding metaplastic precursor sequence.

Histotype	Precursor information supported by Robbins
Squamous cell carcinoma	Keratinizing metaplasia → dysplasia / CIS
Adenocarcinoma	Extensive multifocal intestinal metaplasia
Small-cell carcinoma	No precursor sequence specified in passage

Phenotype, risk, and primary site are different questions

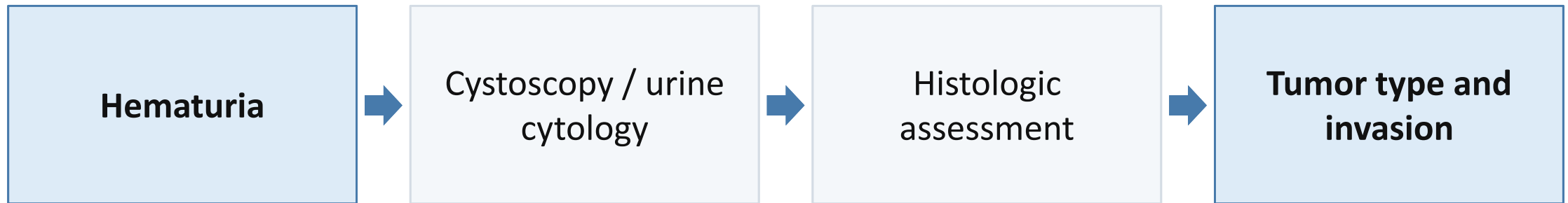
- Phenotype: What differentiation is present in the tumor?
- Risk context: Which exposures or injury patterns are linked with that histotype?
- Primary site: Did the tumor originate in the bladder or extend from elsewhere?



Schematic — source-derived relationships; Not a clinical specimen

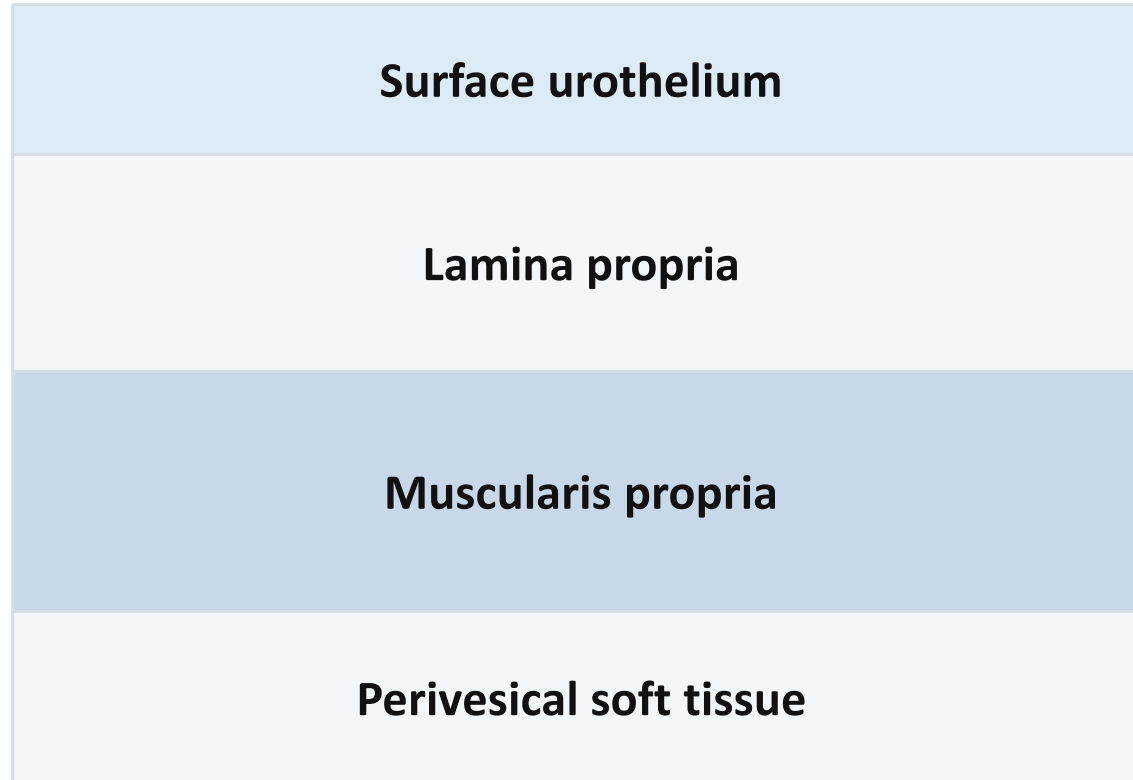
Cystoscopy and urine cytology: Roles and limits

- Painless hematuria prompts clinical investigation by cystoscopy and/or urine cytology.
- Cystoscopy assesses visible bladder mucosal abnormalities.
- The specific epithelial histotype and depth of invasion require tissue-based interpretation.



Schematic — source-derived relationships; Not a clinical specimen

Invasion is defined relative to the bladder wall



Schematic of bladder wall compartments

- Lamina propria invasion corresponds to pT1 in the supplied AJCC 8th-edition staging table.
- Muscularis propria involvement corresponds to pT2.
- Perivesical soft-tissue invasion is pT3; Specified adjacent-organ or pelvic-wall involvement is pT4.

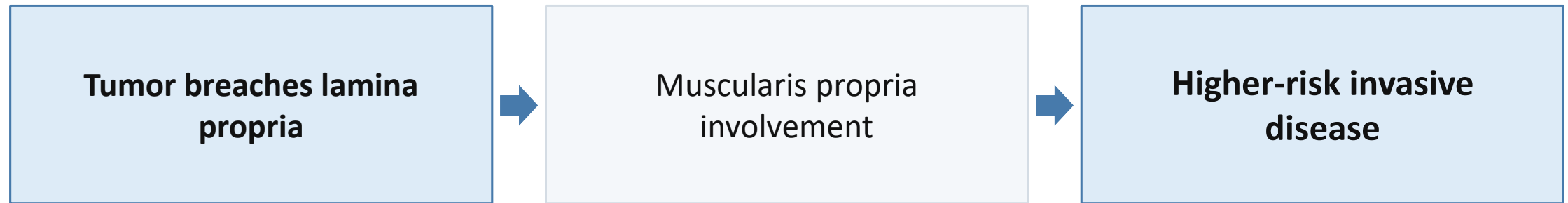
Selected pT categories from the supplied AJCC 8th edition

- The table concerns depth/anatomic extent, not epithelial differentiation.
- It provides a common staging language for carcinoma of the urinary bladder.

Primary tumor category	Meaning
Ta / Tis	Noninvasive papillary carcinoma / flat urothelial CIS
T1	Lamina propria invasion
T2	Muscularis propria invasion
T3	Perivesical soft-tissue invasion
T4	Extension into specified adjacent organs or walls

Why muscularis propria invasion changes the discussion

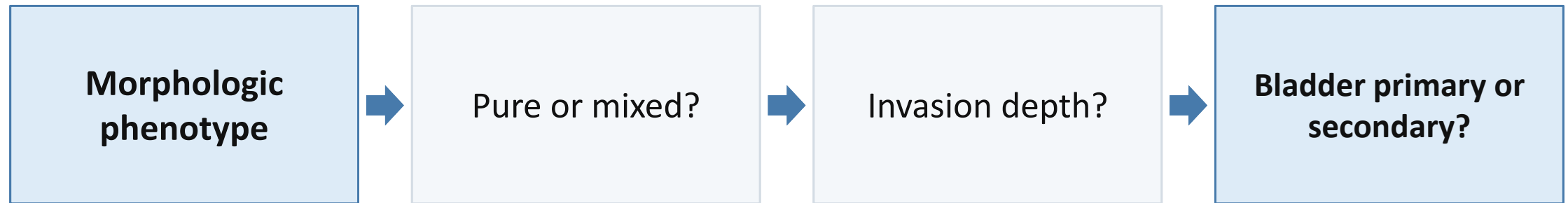
- Depth of invasion as the most important prognostic factor in invasive bladder cancer.
- Muscle-invasive disease has substantially greater potential for regional and distant spread.
- Staging must be recorded independently of histologic subtype.



Schematic — source-derived relationships; Not a clinical specimen

Mixed epithelial tumors: A structured examination

- Identify each demonstrated epithelial component rather than assuming a pure histotype.
- Document squamous, glandular, urothelial, or small-cell features actually seen.
- Separate cell type from depth of invasion and primary-site attribution.



Schematic — source-derived relationships; Not a clinical specimen

Interpretive pitfalls to avoid

- Do not mistake physiologic glycogenated trigonal squamous epithelium for high-risk keratinizing metaplasia.
- Do not equate cystitis glandularis with adenocarcinoma.
- Do not classify a mixed urothelial–squamous carcinoma as necessarily pure squamous.

Pitfall	Correct discriminating question
Trigonal squamous lining	Physiologic glycogenated or keratinizing injury related?
Glandular epithelium	Metaplastic or invasive adenocarcinoma?
Squamous tumor area	Pure squamous or mixed with urothelial cancer?
Small-cell tumor	Primary bladder or involvement from elsewhere?

Integrated teaching case: Classify without overreaching

HYPOTHETICAL TEACHING CASE

- Hypothetical: A bladder lesion contains invasive carcinoma with extensive keratin production, focal urothelial carcinoma, and muscularis propria invasion.
- There is a history of chronic bladder irritation.
- Question: What should be distinguished in histotype, risk context, and stage?

Interpretation requires separating observed evidence from diagnostic inference.

Integrated case: A defensible interpretation

- Histotype: Both urothelial and squamous components are observed, so avoid claiming pure squamous carcinoma.
- Risk context: Chronic irritation is associated with squamous differentiation but is not uniquely causal.
- Extent: Muscularis propria invasion is the defining feature of pT2 in the supplied staging system.

Tumor classification	Predisposing context	Anatomic extent
Mixed urothelial and squamous carcinoma	Chronic irritation is associated, not diagnostic	Muscularis propria involved: PT2

Essential conclusions

- Squamous carcinoma is linked to chronic injury, especially schistosomiasis, and spans a wide differentiation spectrum.
- Bladder adenocarcinoma is rare, resembles gastrointestinal adenocarcinoma, and requires attention to glandular mimics and site of origin.
- Small-cell carcinoma is an aggressive, often mixed tumor associated with smoking and common TP53/RB loss.
- Morphologic type, precursor field, anatomic origin, and invasion depth are complementary—not interchangeable—diagnostic dimensions.

Primary reading and scope of evidence

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026). Chapter 21: The Lower Urinary Tract and Male Genital System.
- Principal section: “Other Epithelial Bladder Tumors”; related bladder neoplasm, metaplasia, secondary tumor and staging material.
- Conceptual schematics and hypothetical cases are original teaching constructions; no synthetic microscopy is presented as diagnostic evidence.
- The supplied material does not provide a validated immunohistochemical panel or treatment algorithm for each of these uncommon histotypes.