

Urothelial Neoplasms

From benign papilloma to deeply invasive carcinoma

Papillary and flat pathways; morphology, grade, invasion, and clinical behavior

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Learning objectives

- Identify papillary and flat urothelial precursor lesions
- Compare papilloma, PUNLMP, and low-/high-grade papillary carcinoma
- Relate invasion depth to pT category and prognosis
- Integrate clinical presentation, recurrence, and surveillance

Urothelial tumors dominate bladder neoplasia

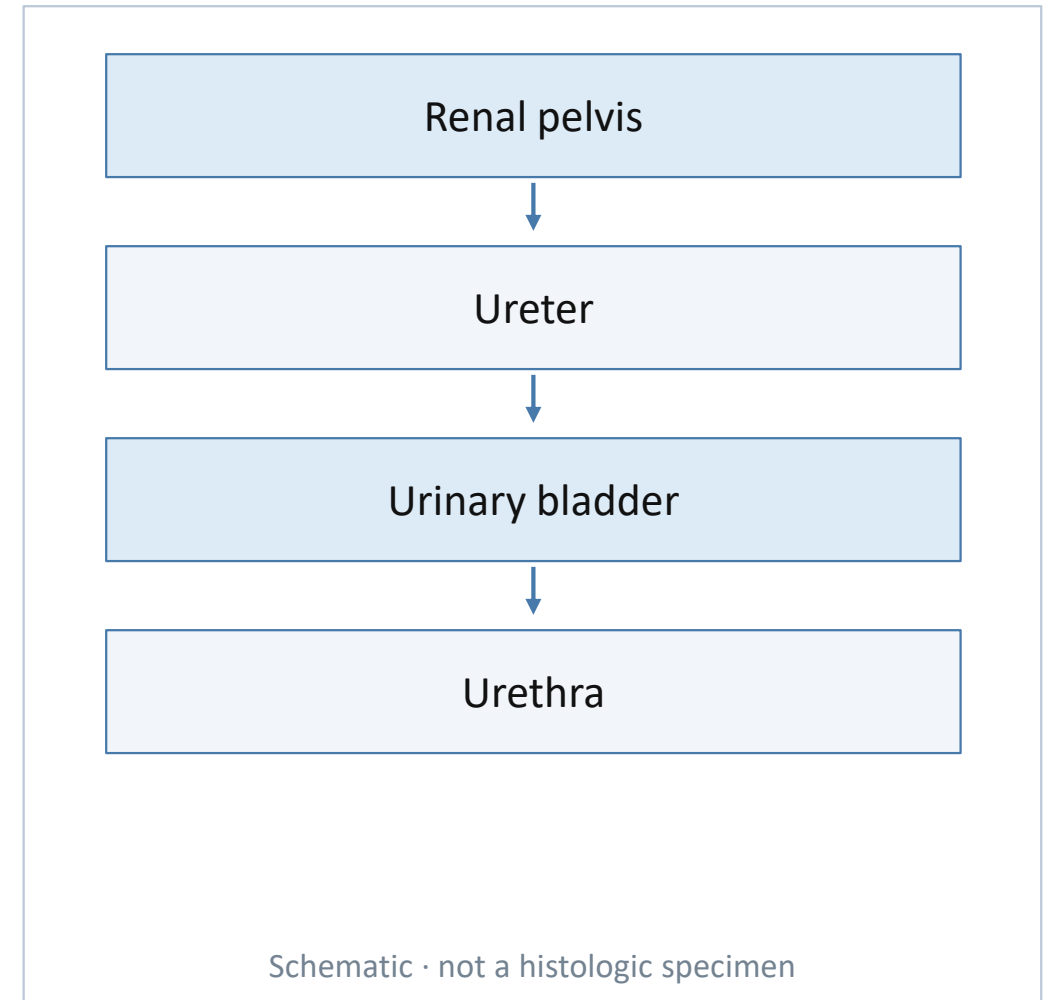
- Urothelial lesions account for approximately 90% of bladder tumors
- The biologic range extends from harmless papilloma to lethal invasive carcinoma
- Squamous, glandular, and other bladder tumors are separate categories

~90%

Of bladder tumors are urothelial

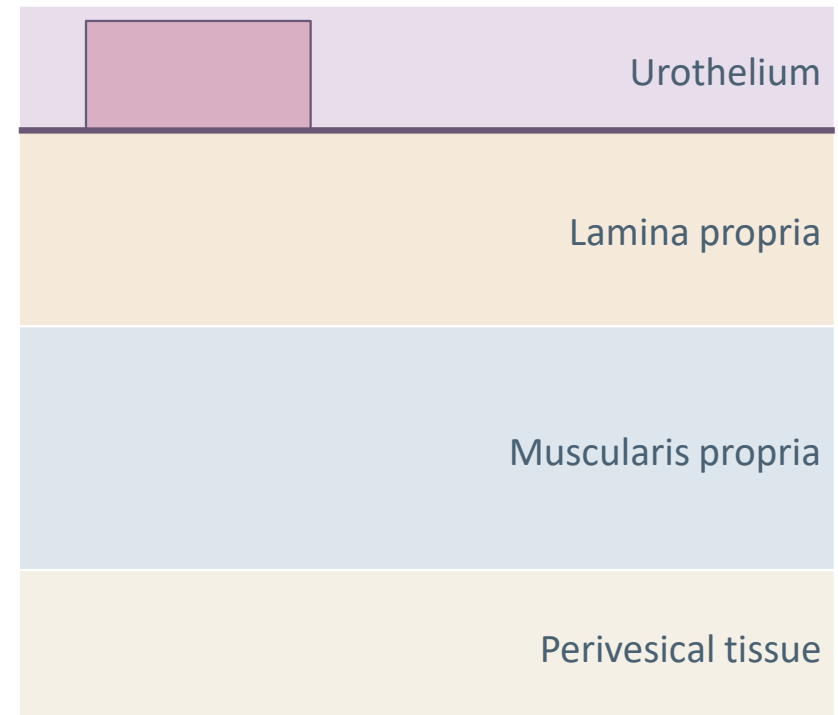
A disease of the entire urothelial tract

- Tumors are most common in the bladder
- Similar urothelial lesions can occur from renal pelvis to distal urethra
- Multifocal disease may be present at initial examination
- This distribution helps explain the clinical importance of field-wide evaluation



Normal bladder wall: Layers that matter

- Urothelium overlies the basement membrane
- Lamina propria is the subepithelial connective tissue
- Muscularis propria is the detrusor muscle
- Depth of invasion determines key stage boundaries



Basement membrane intact

Schematic · not a histologic specimen

Four broad growth patterns

- Exophytic noninvasive papillary neoplasm
- Flat noninvasive carcinoma in situ (CIS)
- Invasive papillary carcinoma
- Invasive carcinoma associated with flat CIS

Noninvasive growth

Papillary lesion

Flat CIS

Invasive growth

Papillary with
invasion

Flat CIS with
invasion

Two principal precursor routes

Papillary-enriched route

Growth signaling: FGFR3 / RAS



Noninvasive papillary neoplasm



Usually recurrence; Sometimes invasion

Flat CIS-enriched route

Checkpoint changes: TP53 / RB



Flat high-grade CIS



Potential invasion

Noninvasive is not synonymous with low grade

- Papillary lesions span multiple histologic grades
- Flat CIS is high-grade by definition
- Neither Ta papillary carcinoma nor Tis CIS crosses the basement membrane
- Grade and stage answer different questions

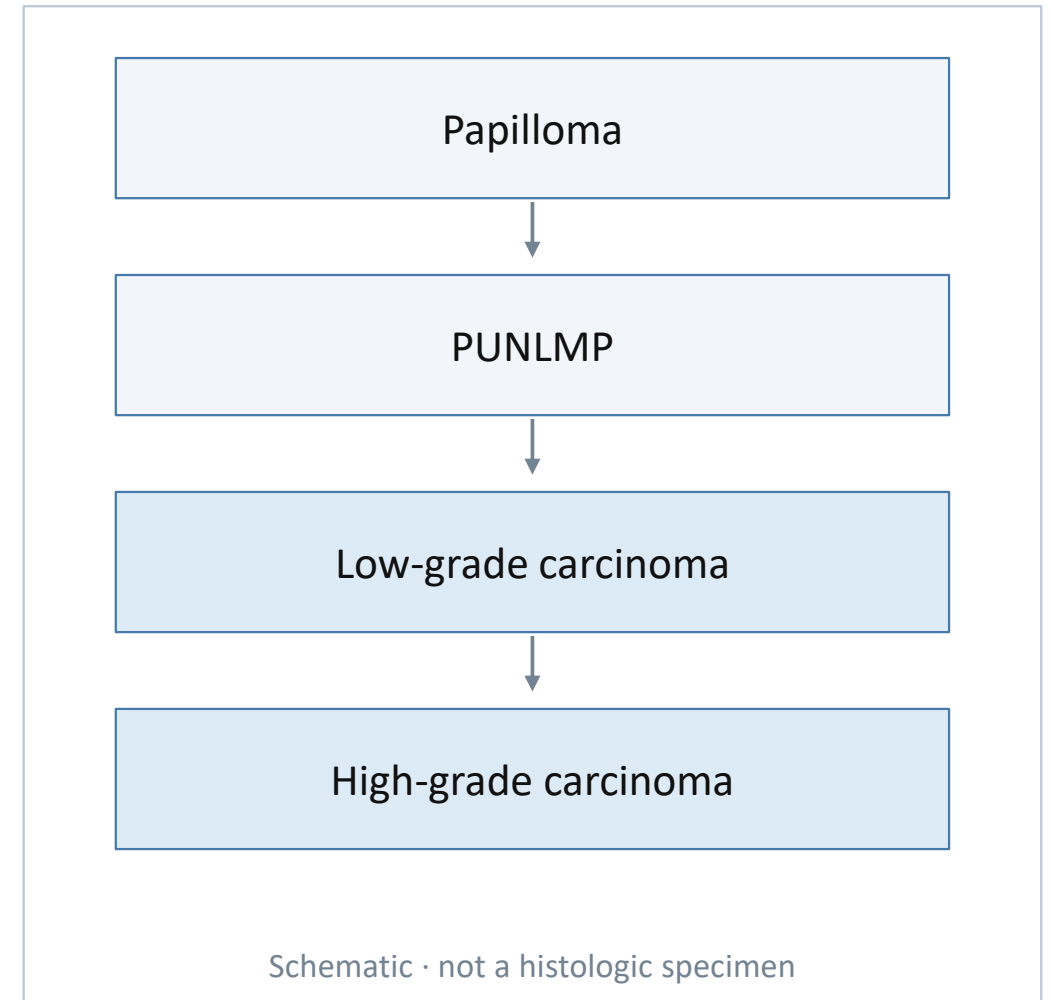
Grade	Stage
Cytologic/architectural atypia	Anatomic extent
Biologic aggressiveness	Basement membrane and depth

WHO 2022: Noninvasive flat lesions

Flat lesion	Key principle
Urothelial dysplasia	Flat atypical urothelial lesion
Urothelial CIS	Flat, high-grade noninvasive carcinoma

WHO 2022: Exophytic papillary lesions

- Papilloma
- Papillary urothelial neoplasm of low malignant potential (PUNLMP)
- Low-grade papillary urothelial carcinoma
- High-grade papillary urothelial carcinoma



Grade must be separated from invasion

- Low-grade papillary lesions often remain non-muscle-invasive
- High-grade papillary lesions have a substantially greater potential to progress
- CIS is high-grade but initially flat and noninvasive
- Muscularis propria invasion defines a major clinical transition

Microscopic grade

Low vs high
cytologic atypia

Order and cellular
polarity

Anatomic stage

Ta / Tis / T1

T2 and beyond

Epidemiology: Demographic pattern

- Male-to-female incidence ratio is approximately 3:1
- About 80% of patients are 50–80 years old
- Higher incidence in higher-income countries and urban populations
- Most bladder cancers are sporadic rather than familial

3 : 1

Male-to-female incidence ratio

Cigarette smoking: Dominant exposure

- Most important established risk factor
- Associated risk rises about three- to seven-fold
- Risk varies with duration and tobacco exposure type
- Cigarette-related carcinogenesis links environment and urothelial mutations

3–7×

Smoking-associated relative risk range

Smoking-attributable burden in males

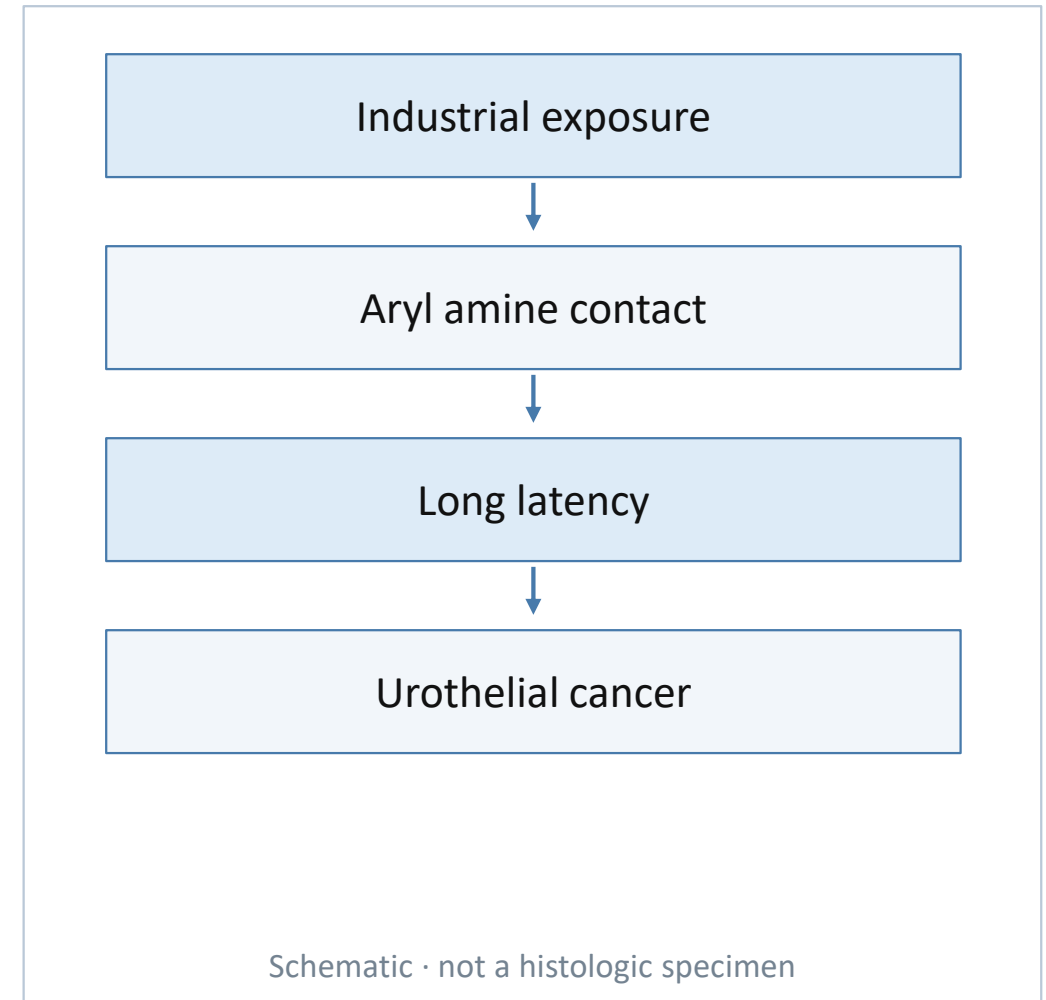
- Textbook estimates 50%–80% of bladder cancers among males are associated with cigarette use
- This is an epidemiologic association, not an individual diagnostic test
- Cigars, pipes, and smokeless tobacco show smaller associations than cigarettes

50–80%

Male bladder cancers associated with
cigarettes

Aryl amines and occupational exposure

- Industrial aryl amines are established urothelial carcinogens
- 2-Naphthylamine is the classic example
- Carcinogenic exposure can precede cancer by decades
- Exposure history should include remote occupations



Exposure-to-cancer latency

- The cited interval after initial industrial exposure is 15–40 years
- Remote exposures may be clinically relevant even after retirement
- Latency does not identify the grade or stage of an eventual tumor

15–40 y

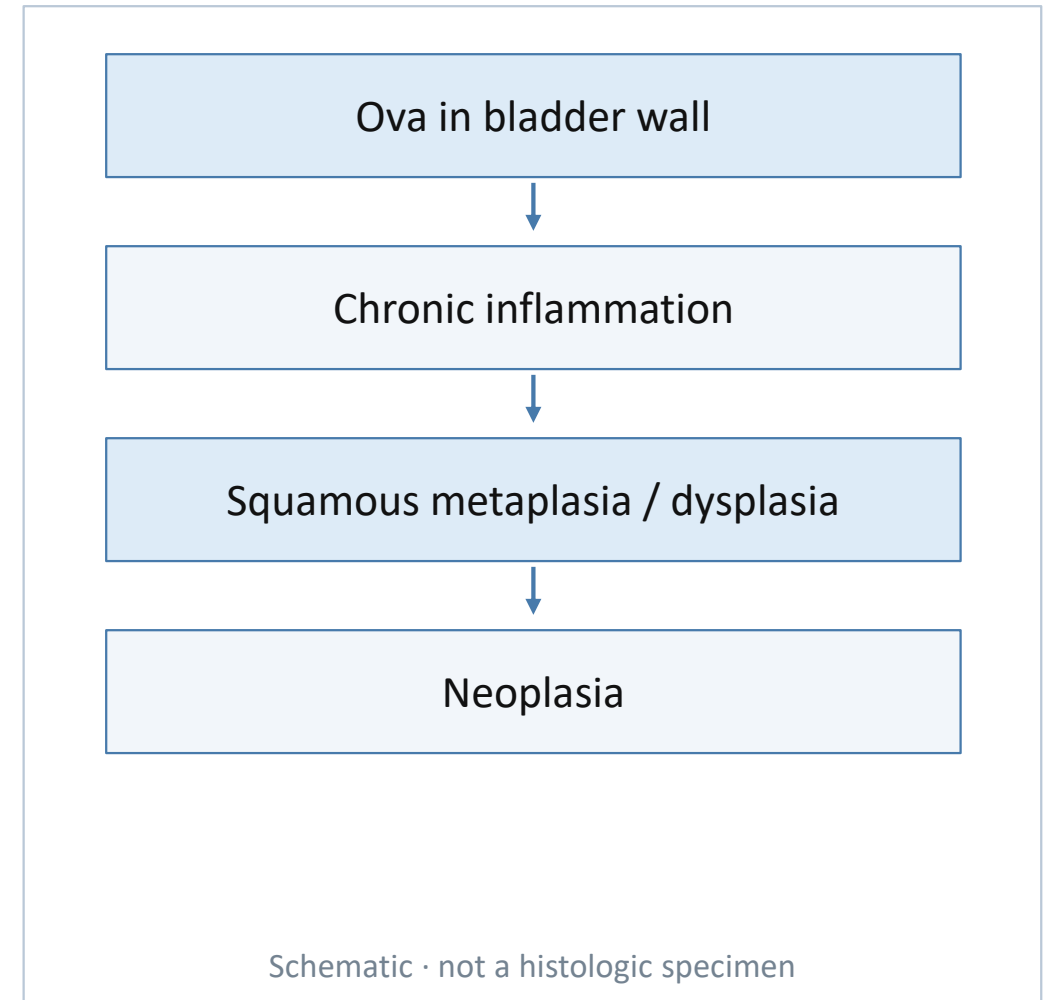
Reported interval after first aryl-amine
exposure

Other etiologic influences

Exposure	Relevant context
Cyclophosphamide	Hemorrhagic cystitis and later neoplasia
Pelvic irradiation	Cancer arising several years later
Analgesics	Long-term exposure implicated

Schistosomal bladder carcinogenesis

- Schistosoma haematobium eggs induce chronic bladder-wall inflammation
- Chronic injury can promote squamous metaplasia and dysplasia
- In endemic regions, associated cancers are more commonly squamous
- This is a differential-context risk factor, not the dominant papillary urothelial route



Epidemiology is not tumor classification

- Smoking and other exposures increase the probability of urothelial malignancy
- Morphology still establishes tumor type and grade
- Invasion determines stage independently of exposure history
- Avoid inferring subtype from a single risk factor

Pathogenesis: Two broad molecular routes

Papillary-enriched route

Growth signaling: FGFR3 / RAS



Noninvasive papillary neoplasm



Usually recurrence; Sometimes invasion

Flat CIS-enriched route

Checkpoint changes: TP53 / RB



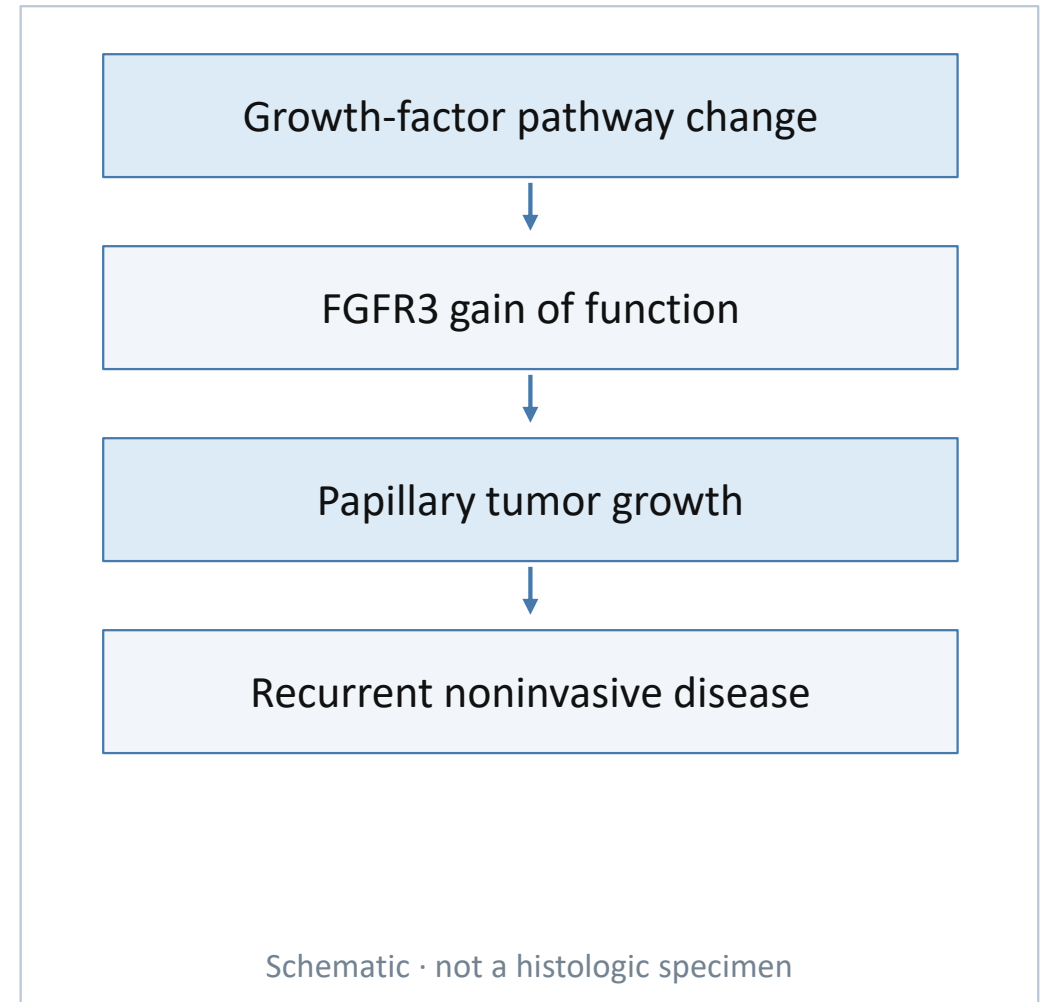
Flat high-grade CIS



Potential invasion

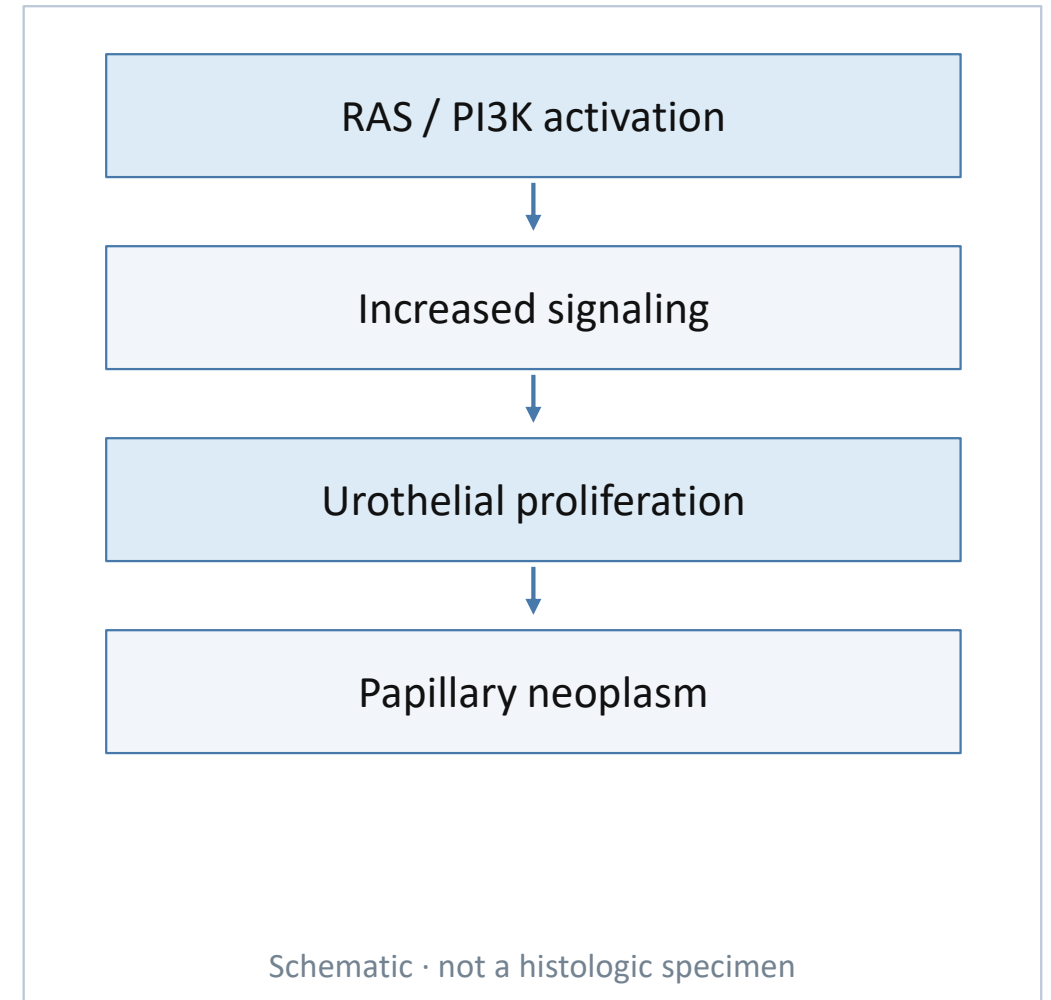
Papillary pathway: FGFR3 signaling

- Amplification or activation of FGFR3 is characteristic of a papillary pathway
- Enhanced receptor-driven growth contributes to papillary proliferation
- Many such tumors recur without becoming muscle-invasive
- FGFR3 is a biologic driver; Molecular status is not itself a pT category



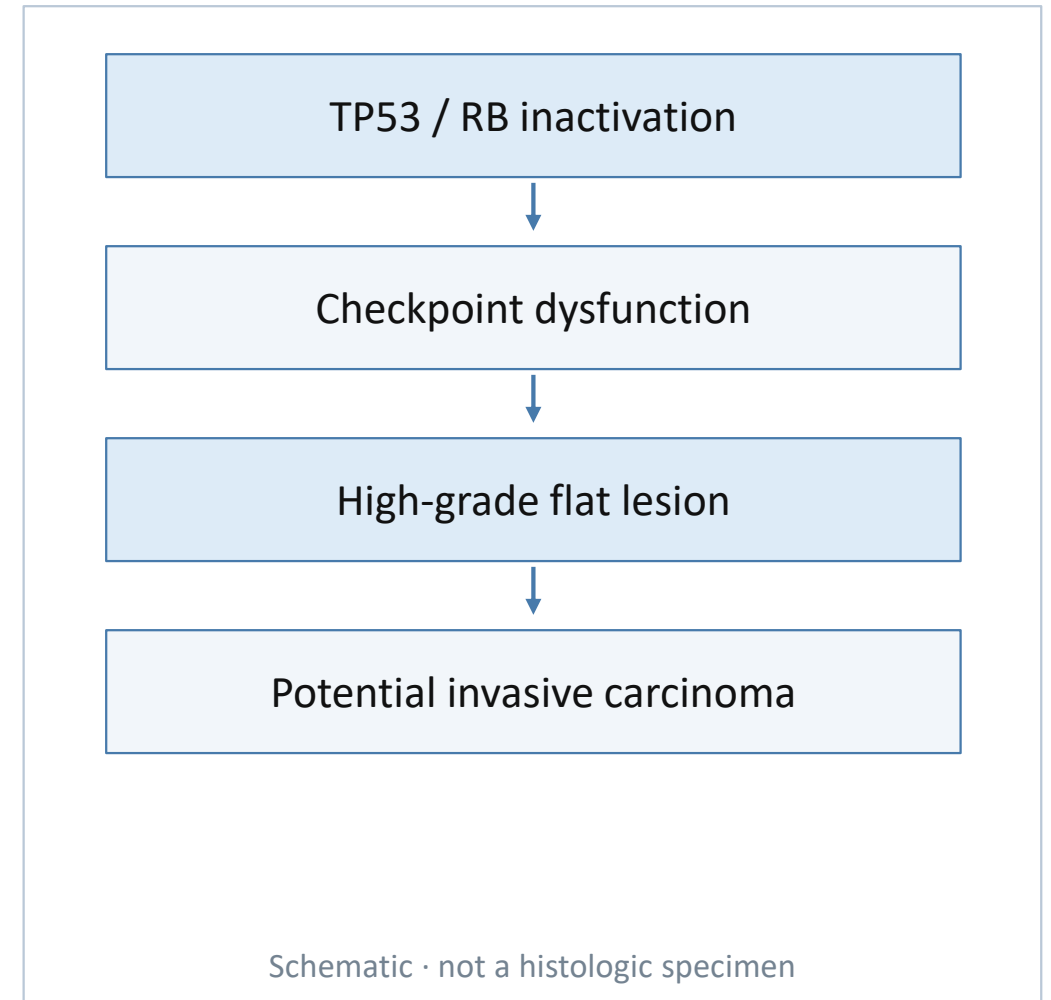
Papillary pathway: RAS and PI3K

- Activating RAS alterations are described
- PI 3-kinase pathway gene alterations can also enhance growth signaling
- These mechanisms converge on increased proliferative input
- Not every papillary lesion requires all of these events



CIS-associated pathway: TP53 and RB

- TP53 and RB disruption is prominent in muscle-invasive carcinoma
- These alterations may occur early in CIS development
- Comparable checkpoint disruption can appear later in some papillary cancers
- The route reflects impaired cell-cycle and genomic safeguards



Two routes are models, not absolutes

- Approximately 20% progression to muscle-invasive disease is cited for papillary non-muscle-invasive cancers in the molecular discussion
- The routes overlap as carcinomas accumulate alterations
- A high-grade papillary component may coexist with CIS
- Molecular findings must be interpreted beside morphology and invasion

Papillary-enriched route

FGFR3 / RAS / PI3K

Often NMIBC

CIS-enriched route

TP53 / RB disruption

Often precursor to MIBC

High somatic mutational burden

- Bladder cancers have substantial somatic mutation loads
- The textbook compares this burden with lung cancer and melanoma
- This pattern is consistent with important environmental carcinogenic effects
- Mutation burden alone does not specify stage or morphology

Broader molecular heterogeneity

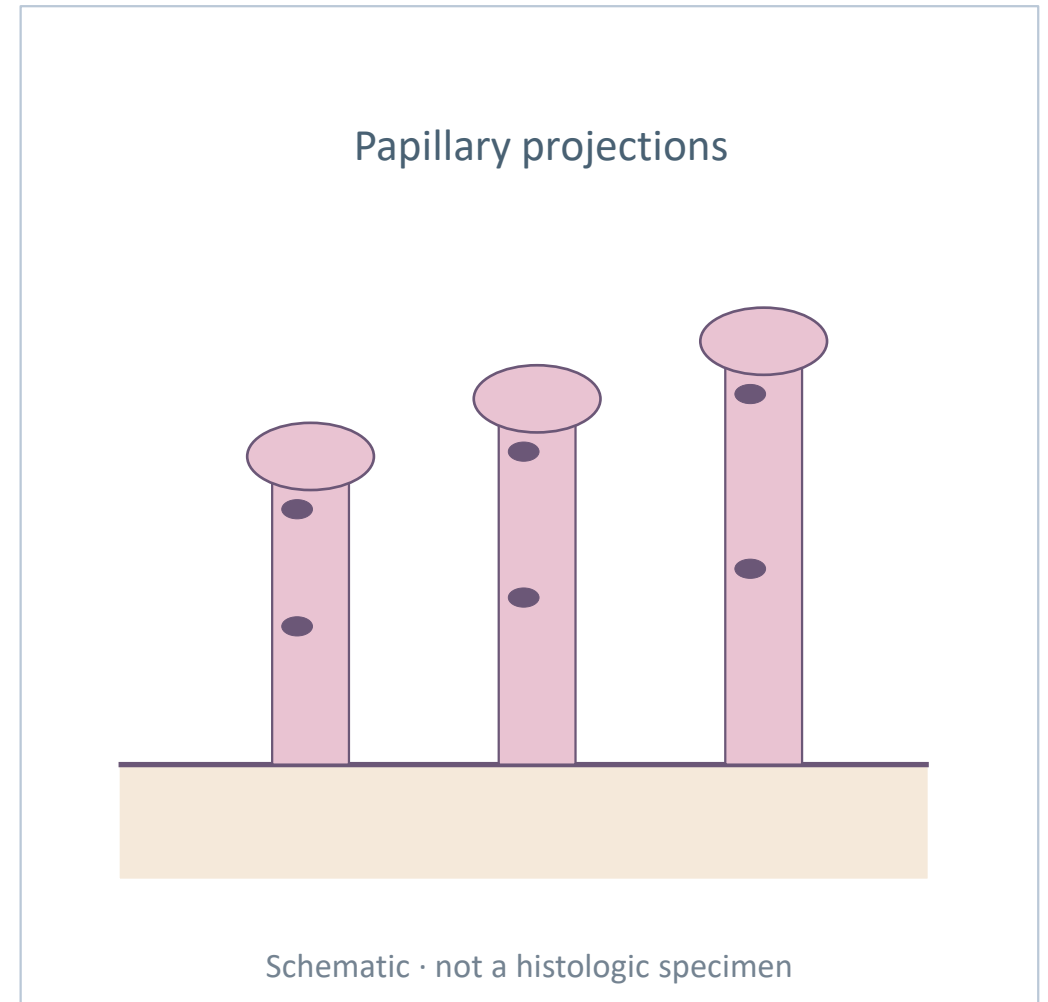
Altered cellular function	Illustrative category
Cell-cycle control	TP53 / RB-related checkpoint pathways
Growth signaling	FGFR3 / RAS / PI3K pathways
Other processes	Chromatin regulation; DNA repair

The diagnostic priority remains morphologic

- Molecular classification continues to develop
- The supplied source emphasizes tumor morphology, grade, and stage
- Do not substitute a mutation for demonstration of invasion
- Clinical interpretation integrates molecular and traditional pathology

Gross appearance: Papillary tumors

- Exophytic fronds project into the bladder lumen
- Tumors may be red and elevated
- Lesions from less than 1 cm to roughly 5 cm
- Multifocal, discrete papillary masses can occur



Papillary versus flat lesions at cystoscopy

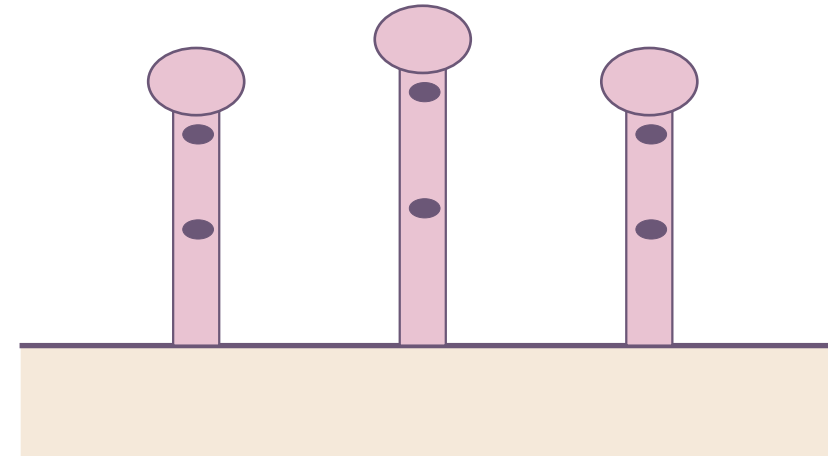
- Papillary tumors form protruding intraluminal lesions
- CIS typically gives erythema, granularity, or mucosal thickening
- CIS may not form a discrete mass
- Cystoscopic appearance alone cannot establish grade or invasion

Papillary	Flat CIS
Raised mucosal fronds	Red/granular surface
Visible projecting lesion	No obligatory luminal mass

Papilloma: Architecture of a benign frond

- Uncommon lesion, no more than about 1% of bladder tumors
- Often solitary and small, attached by a delicate stalk
- Finger-like fronds contain central fibrovascular cores
- Covering urothelium resembles normal urothelium

Bland fronds + fibrovascular cores



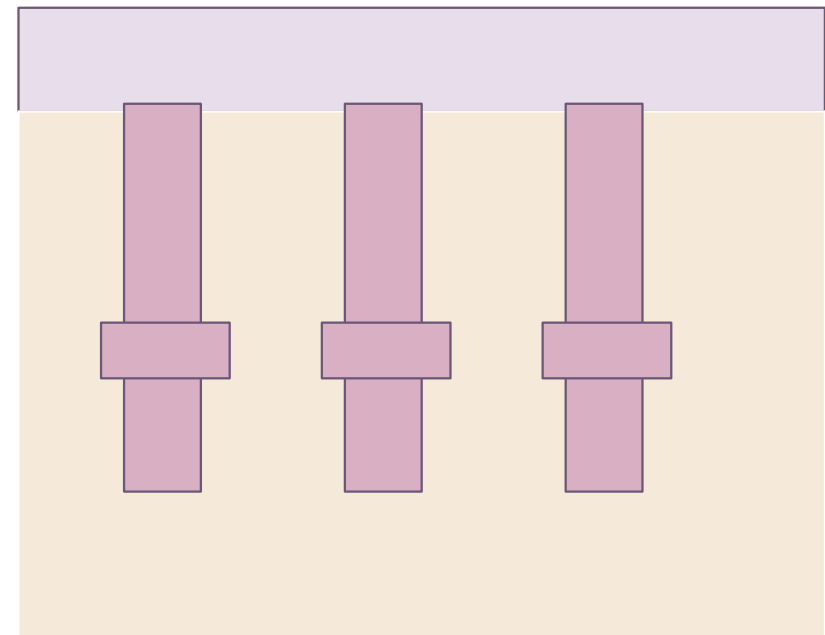
Schematic · not a histologic specimen

Papilloma: Expected behavior

- Typically seen in younger patients than ordinary bladder carcinoma
- Recurrence is unusual but can occur
- Progression is rare
- Morphologic distinction from thicker papillary lesions matters

Inverted papilloma: Deceptively endophytic

- Bland urothelial cords grow down into lamina propria
- Cords interanastomose rather than form external fronds
- Despite downward growth, this is considered benign
- It can mimic infiltrating carcinoma in a limited sample

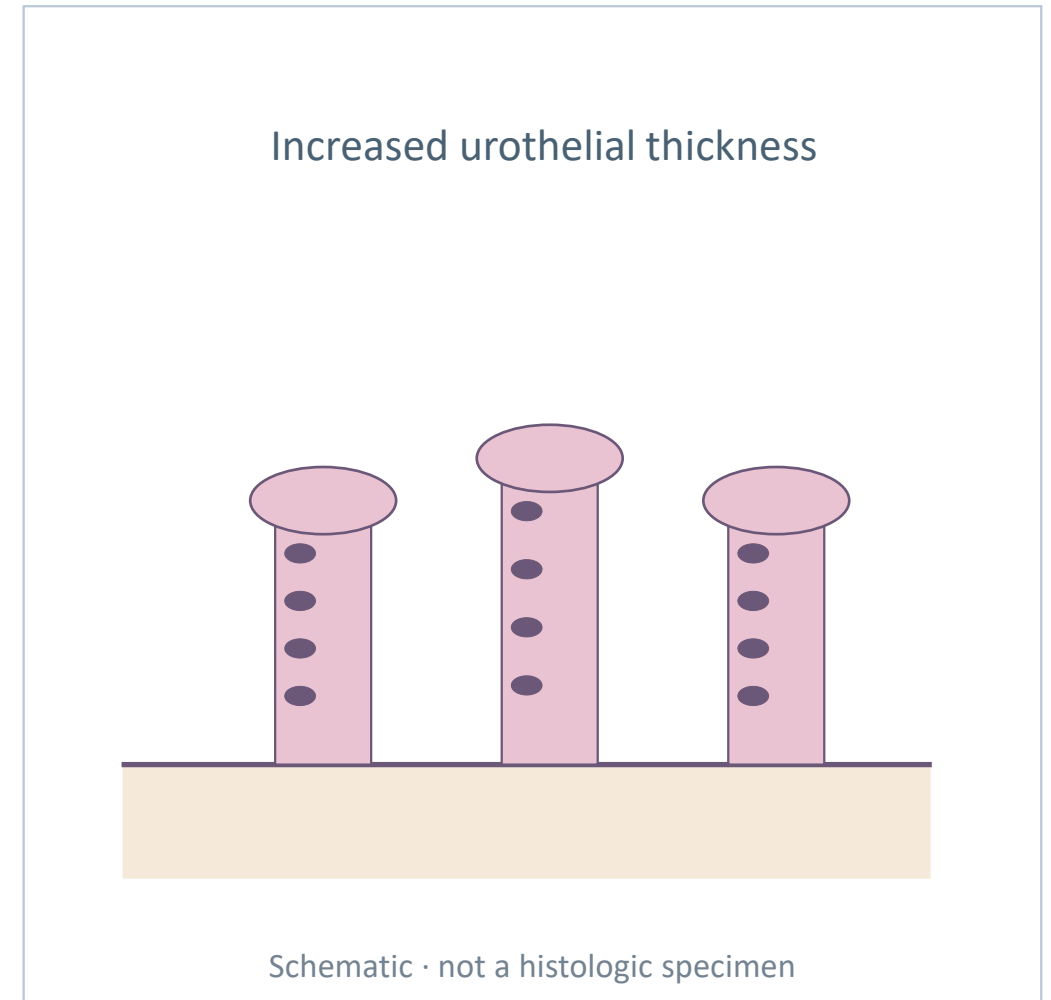


Bland endophytic, interconnected cords

Schematic · not a histologic specimen

PUNLMP: Increased urothelial thickness

- Thicker papillary epithelium with increased cell density
- Retains many features of papilloma
- May be grossly indistinguishable from papillary carcinoma
- Higher-grade progression is possible but uncommon



PUNLMP versus papilloma

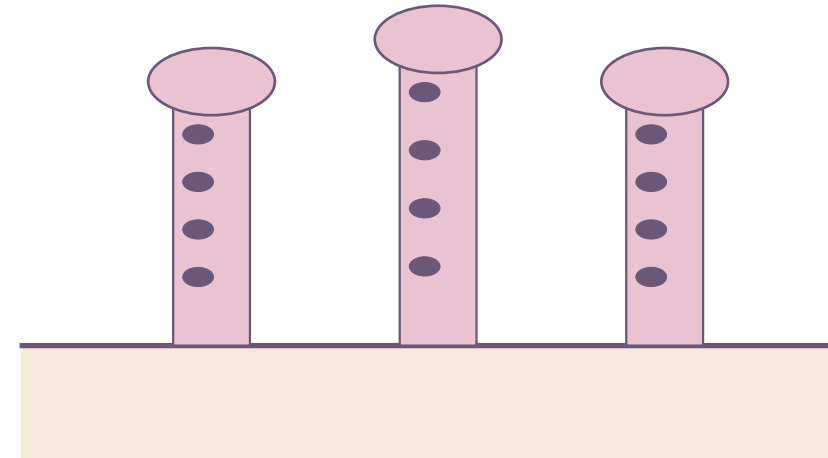
- The distinction turns on cellular density and epithelial thickness
- Both retain relatively bland cytology
- PUNLMP is not equivalent to high-grade carcinoma
- Histologic assessment is essential when gross features overlap

Papilloma	PUNLMP
Normal-like epithelial thickness	Increased epithelial thickness
Delicate fronds	Greater urothelial cellularity

Low-grade papillary carcinoma: Retained order

- Urothelial cells remain mostly cohesive
- Overall polarity and architectural order persist
- Nuclear size and shape vary mildly
- Hyperchromatic nuclei and mitoses may be scattered

Orderly cells; Mild nuclear atypia



Schematic · not a histologic specimen

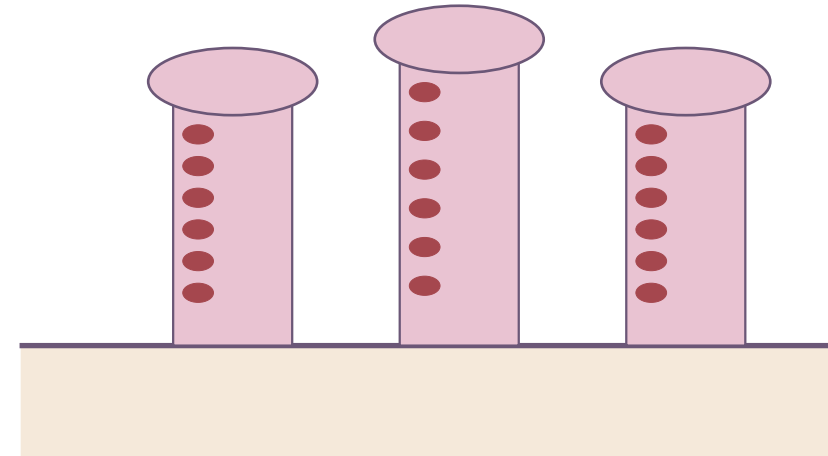
Low-grade carcinoma: Mitotic pattern

- Mitotic figures are infrequent
- When present, mitoses tend to occur toward the epithelial base
- Cytologic atypia is modest rather than absent
- The distinction from PUNLMP depends on integrated architecture and cytology

High-grade papillary carcinoma: Cytologic disorder

- Large hyperchromatic and irregular nuclei
- Prominent nucleoli and marked cellular atypia
- Frequent mitoses, sometimes atypical
- Cells may lose cohesiveness and normal polarity

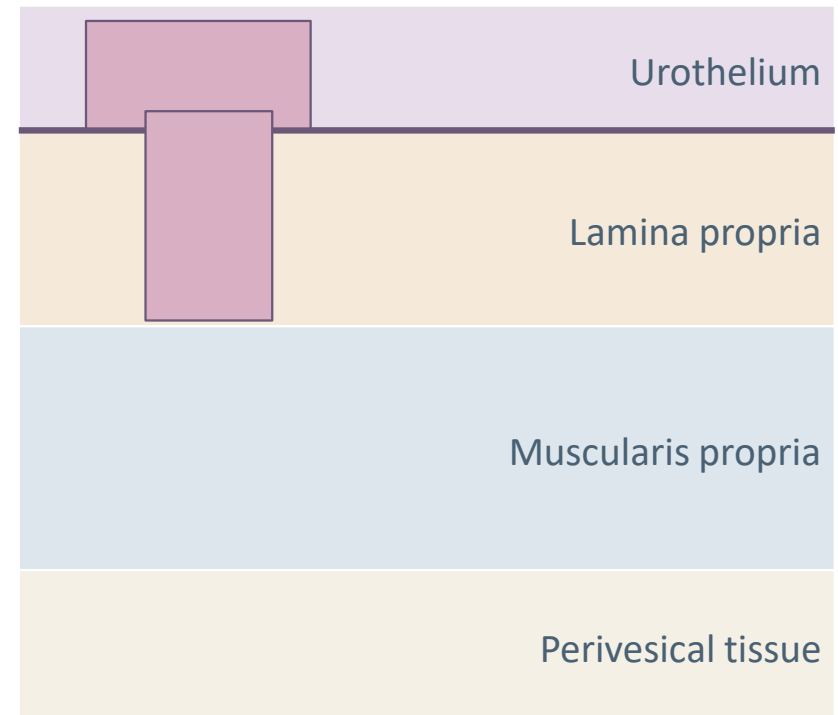
Crowding and marked atypia



Schematic · not a histologic specimen

High grade: Invasion is a separate question

- A very atypical papillary lesion can remain noninvasive (Ta)
- The same lesion may invade lamina propria or detrusor
- Grade predicts biologic behavior but cannot replace staging
- Report the presence and depth of invasion explicitly



Tumor enters lamina propria
Schematic · not a histologic specimen

Papillary grading: Integrated comparison

Lesion	Architecture / cytology
Papilloma	Delicate; Normal-like lining
PUNLMP	Thickened, crowded; Bland
Low-grade carcinoma	Mostly ordered; Mild atypia
High-grade carcinoma	Disordered; Severe atypia

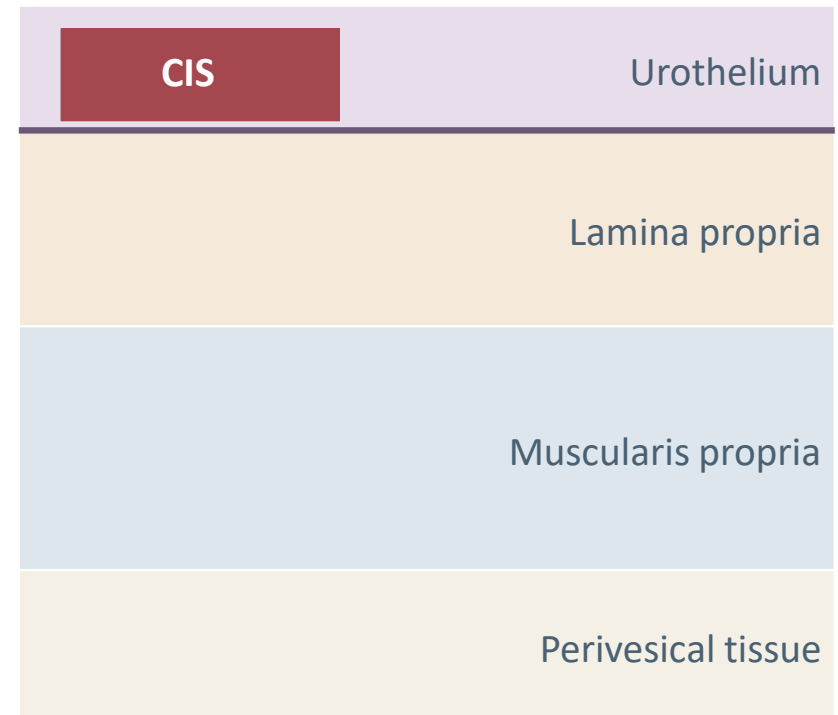
Recurrence does not equal progression

- Recurrence means a new detected lesion after treatment
- Progression implies greater grade and/or anatomic extent
- Low-grade tumors can recur repeatedly without becoming muscle-invasive
- High-grade papillary tumors have a greater progression risk

Recurrence	Progression
Tumor returns	Worsening biologic extent
May remain same grade / stage	New invasion or grade escalation

Carcinoma in situ: Flat and malignant

- CIS is high-grade urothelial carcinoma confined to epithelial lining
- It does not penetrate the basement membrane
- The affected surface can be subtle at cystoscopy
- CIS differs categorically from invasive carcinoma



Basement membrane intact

Schematic · not a histologic specimen

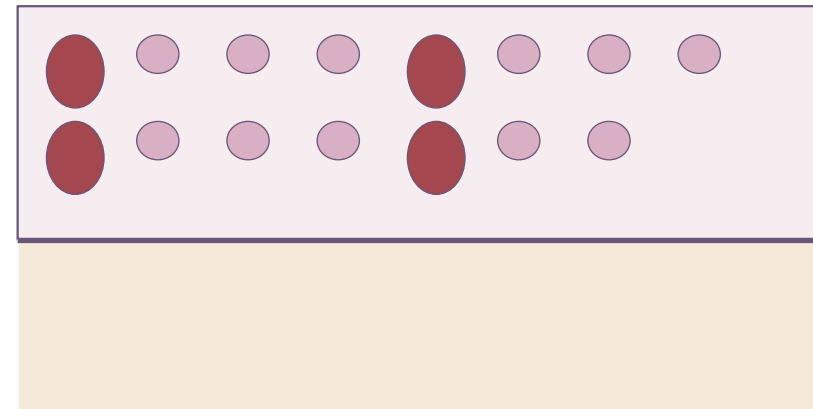
CIS: The cytologic hallmark

- Marked nuclear enlargement and pleomorphism
- Disorganization of the urothelial lining
- High-grade atypia may involve much or part of the epithelium
- Apparent flattening does not make the lesion biologically bland

Pagetoid CIS: Scattered malignant cells

- Malignant cells may be scattered among relatively normal urothelial cells
- The entire epithelium need not appear uniformly replaced
- Careful search is necessary in subtle lesions
- Pagetoid distribution still represents high-grade flat carcinoma

Scattered malignant cells within epithelium

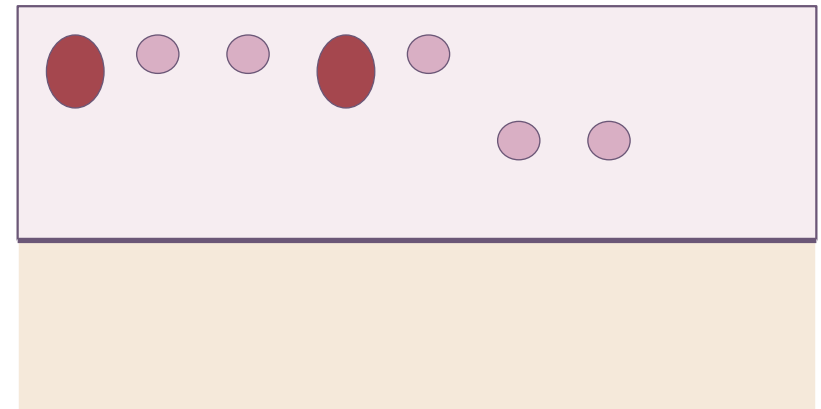


Schematic · not a histologic specimen

CIS can become denuded

- CIS cells often lose normal intercellular cohesion
- Malignant cells exfoliate into urine
- After extensive shedding, only a few abnormal cells may remain attached
- A denuded surface can complicate histologic interpretation

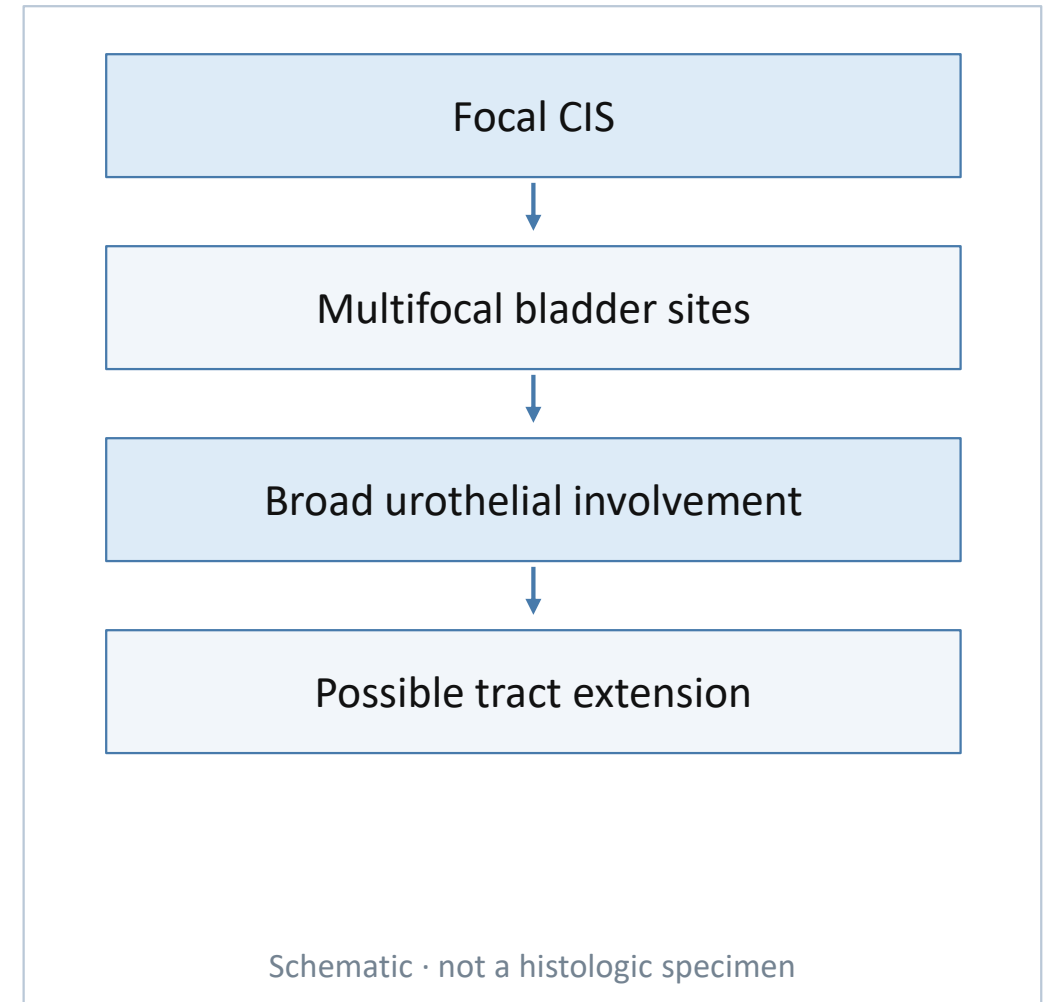
Surface denudation after loss of cohesion



Schematic · not a histologic specimen

CIS frequently involves a broad field

- CIS is commonly multifocal
- Bladder involvement may be extensive
- It can extend into ureters and urethra
- An isolated-looking mucosal abnormality may underestimate distribution



CIS: Risk of untreated progression

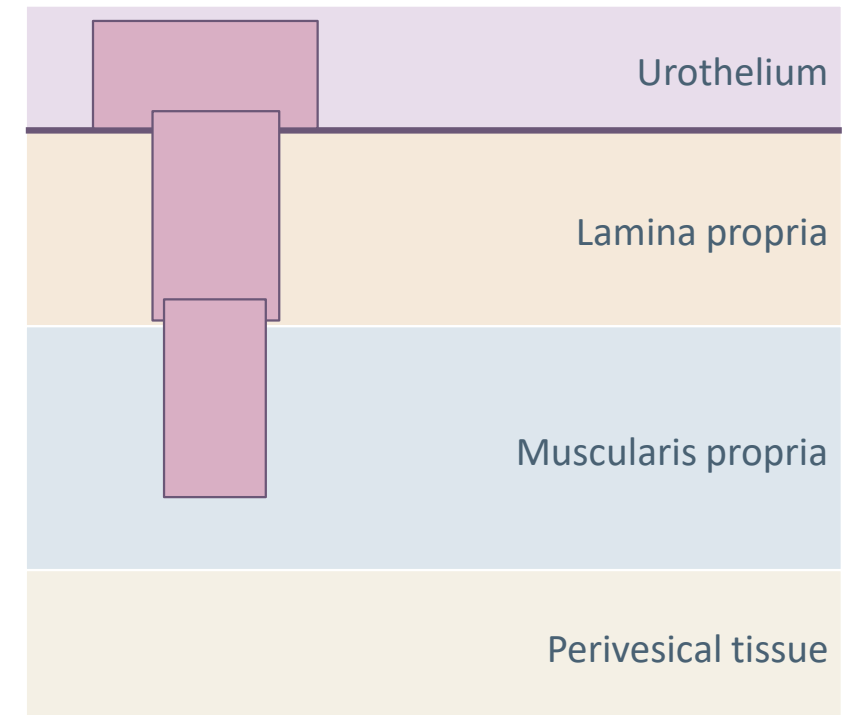
- 50%–75% progression to invasive carcinoma if untreated
- The quoted figure concerns untreated CIS, not any flat atypia
- Early recognition and appropriate clinical management are consequential

50–75%

Untreated CIS progressing to invasion
(textbook)

Invasive carcinoma: Loss of anatomic containment

- The epithelial basement membrane is crossed
- Tumor infiltrates lamina propria and can involve detrusor muscle
- Invasion must be distinguished from downgrowth of benign lesions
- Stage is defined by the deepest involved compartment

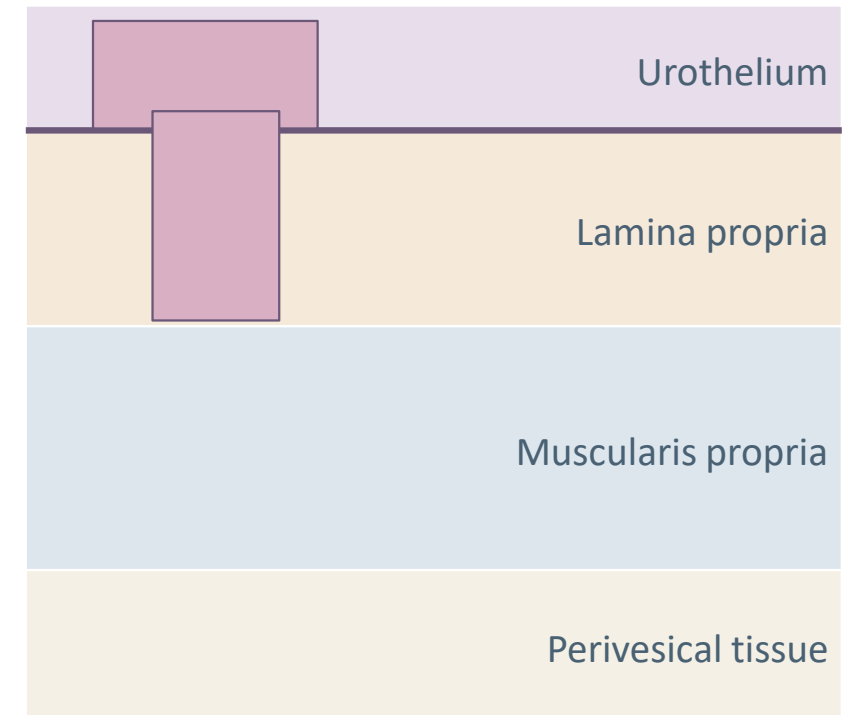


Tumor penetrates detrusor

Schematic · not a histologic specimen

Lamina propria invasion: T1

- Neoplastic cells extend into subepithelial connective tissue
- Muscularis propria is not invaded at T1
- This worsens prognosis compared with purely noninvasive disease
- T1 is still within the non–muscle-invasive management category

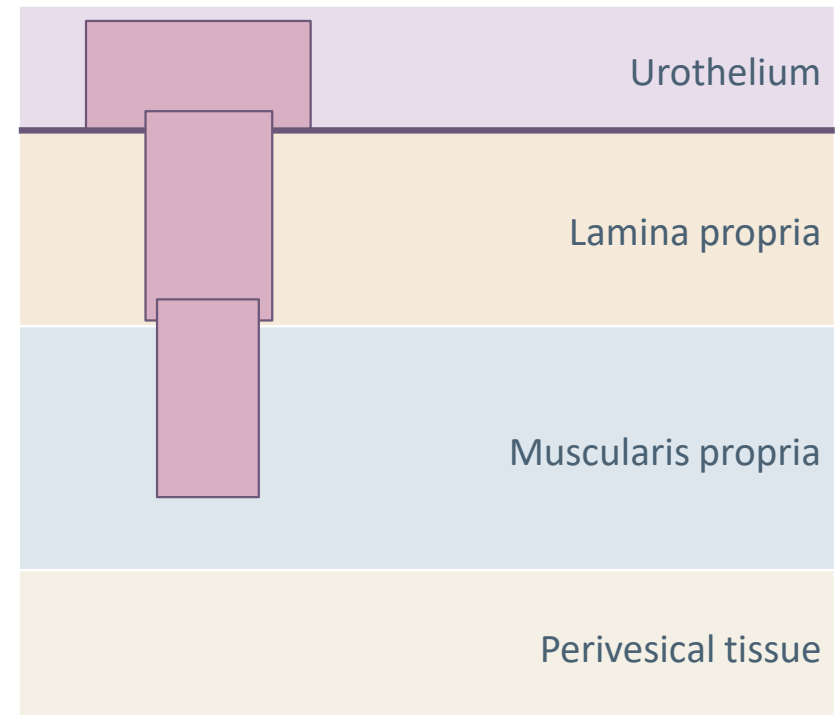


Tumor enters lamina propria

Schematic · not a histologic specimen

Muscularis propria invasion: T2

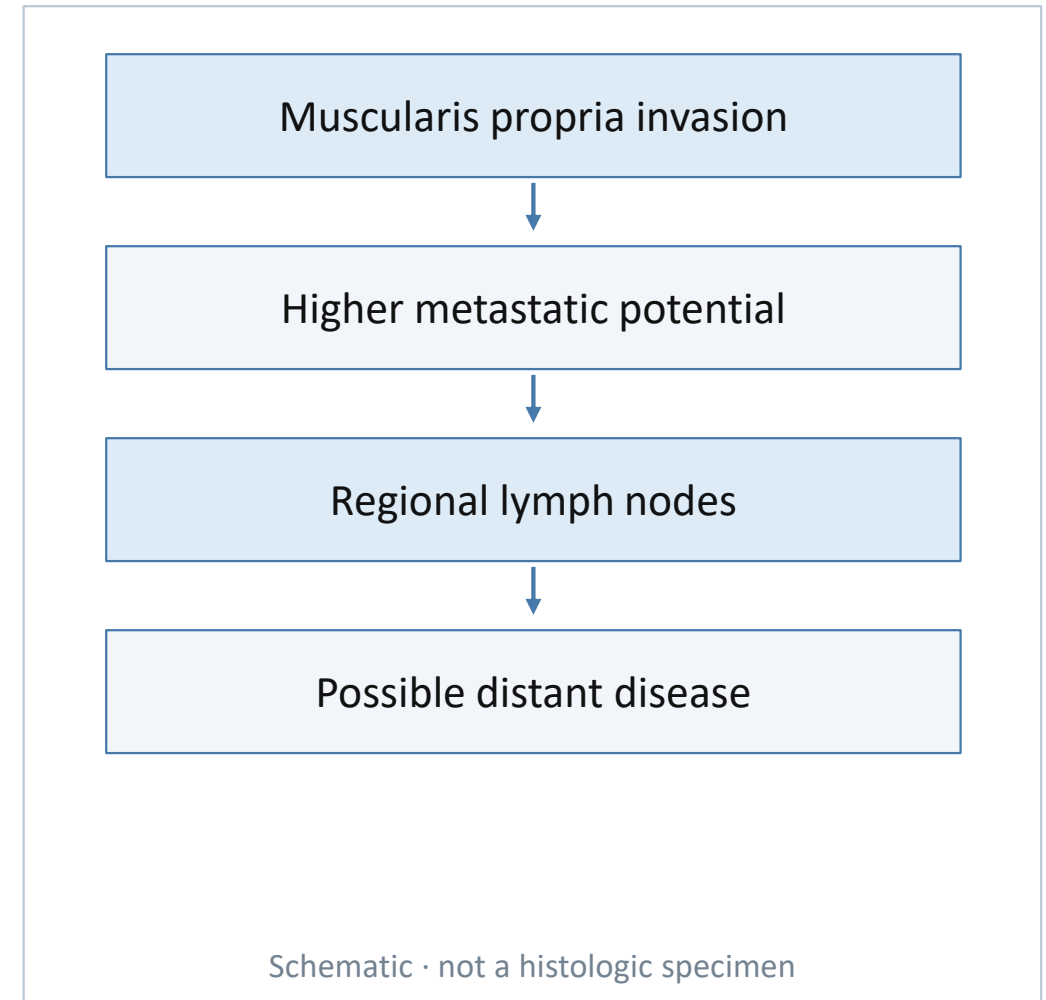
- Tumor reaches detrusor muscle
- This is the central stage distinction in clinical decision-making
- A marked decrease in survival with muscle invasion
- Involvement of muscularis mucosae alone is not equivalent to detrusor invasion



Tumor penetrates detrusor
Schematic · not a histologic specimen

Muscle invasion transforms the clinical problem

- Tumor has access to deeper bladder-wall structures
- Regional nodal and systemic spread become major concerns
- Source examples of distant deposits include liver and lung
- Accurate recognition of detrusor invasion is indispensable



Advanced invasive tumor: Gross features

- Large nodular or fungating masses can occur
- Ulceration and tumor necrosis may be present
- Infiltrative extension widens the tumor footprint
- An advanced mass may obscure the original precursor lesion

Variants: Architecture may mislead

Examples	Diagnostic significance
Nested / large nested	Bland-looking architecture can mislead
Micropapillary	Unusual growth pattern
Plasmacytoid / sarcomatoid	Nonconventional morphology
Other listed subtypes	Microcystic, tubular, giant-cell, etc.

Nested carcinoma: Benign-looking cytology trap

- A nested variant may have deceptively bland cellular features
- Infiltrative distribution is more informative than cytology alone
- Distinguish from benign inverted papilloma
- The correct diagnostic context requires full sampling and invasion assessment

Inverted papilloma

Bland
interconnecting
cords

Benign endophytic
lesion

Nested carcinoma

Bland appearance
may be deceptive

Infiltrative malignant
behavior

Variants do not replace stage

- A subtype name describes histologic differentiation or architecture
- Depth of invasion remains the primary staging determinant
- Clinical correlation requires both variant description and stage
- Avoid inferring exact prognostic percentages from subtype alone

AJCC 8th: Non–muscle-invasive pT categories

- Ta: Noninvasive papillary carcinoma
- Tis: Flat urothelial carcinoma in situ
- T1: Lamina propria invasion
- These all fall short of muscularis propria invasion

Ta/Tis	Urothelium
T1	Lamina propria
T2	Muscularis propria
T3	Perivesical tissue
T4	Adjacent structures

Schematic · not a histologic specimen

AJCC 8th: Muscle-invasive pT2

- T2: Muscularis propria invasion
- T2a: Inner half of detrusor muscle
- T2b: Outer half of detrusor muscle
- The distinction concerns detrusor depth, not histologic grade

Ta/Tis	Urothelium
T1	Lamina propria
T2	Muscularis propria
T3	Perivesical tissue
T4	Adjacent structures

Schematic · not a histologic specimen

AJCC 8th: Perivesical extension pT3

- T3 indicates spread into perivesical soft tissue
- T3a: Microscopic perivesical extension
- T3b: Grossly evident extravesical mass
- The tumor is now beyond the bladder muscle

Ta/Tis	Urothelium
T1	Lamina propria
T2	Muscularis propria
T3	Perivesical tissue
T4	Adjacent structures

Schematic · not a histologic specimen

AJCC 8th: PT4 invasion

- T4 denotes direct extension into defined adjacent structures
- T4a involves prostatic stroma, seminal vesicles, uterus, or vagina
- T4b involves pelvic wall or abdominal wall
- This is direct local spread rather than distant metastasis

Ta/Tis	Urothelium
T1	Lamina propria
T2	Muscularis propria
T3	Perivesical tissue
T4	Adjacent structures

Schematic · not a histologic specimen

Regional lymph nodes in AJCC 8th

N category	Regional lymph-node extent
N1	Single true-pelvic node
N2	Multiple true-pelvic nodes
N3	Common iliac node(s)

Distant metastatic staging

M category	Meaning
M1a	Distant nonregional nodes only
M1b	Distant deposits outside lymph nodes

Staging summary: What the pathologist answers

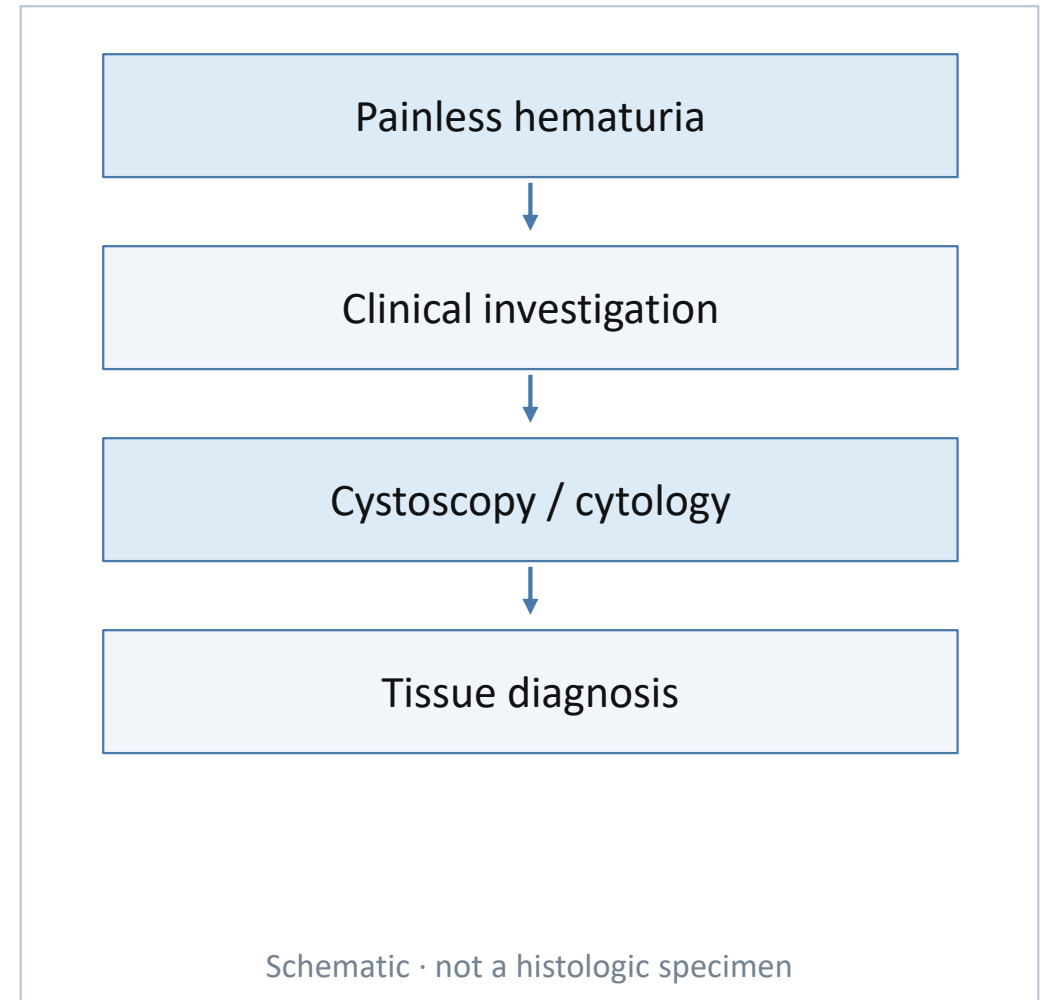
- Is the lesion flat or papillary and noninvasive?
- Does invasion involve lamina propria?
- Is muscularis propria actually present and involved?
- Is there extravesical or adjacent-organ involvement?

Ta/Tis	Urothelium
T1	Lamina propria
T2	Muscularis propria
T3	Perivesical tissue
T4	Adjacent structures

Schematic · not a histologic specimen

Painless hematuria: Classical presentation

- Most common presenting symptom of bladder carcinoma
- Absence of pain does not imply a benign lesion
- Textbook highlights investigation using cystoscopy and/or urine cytology
- Diagnosis requires tissue assessment when a suspicious lesion is found

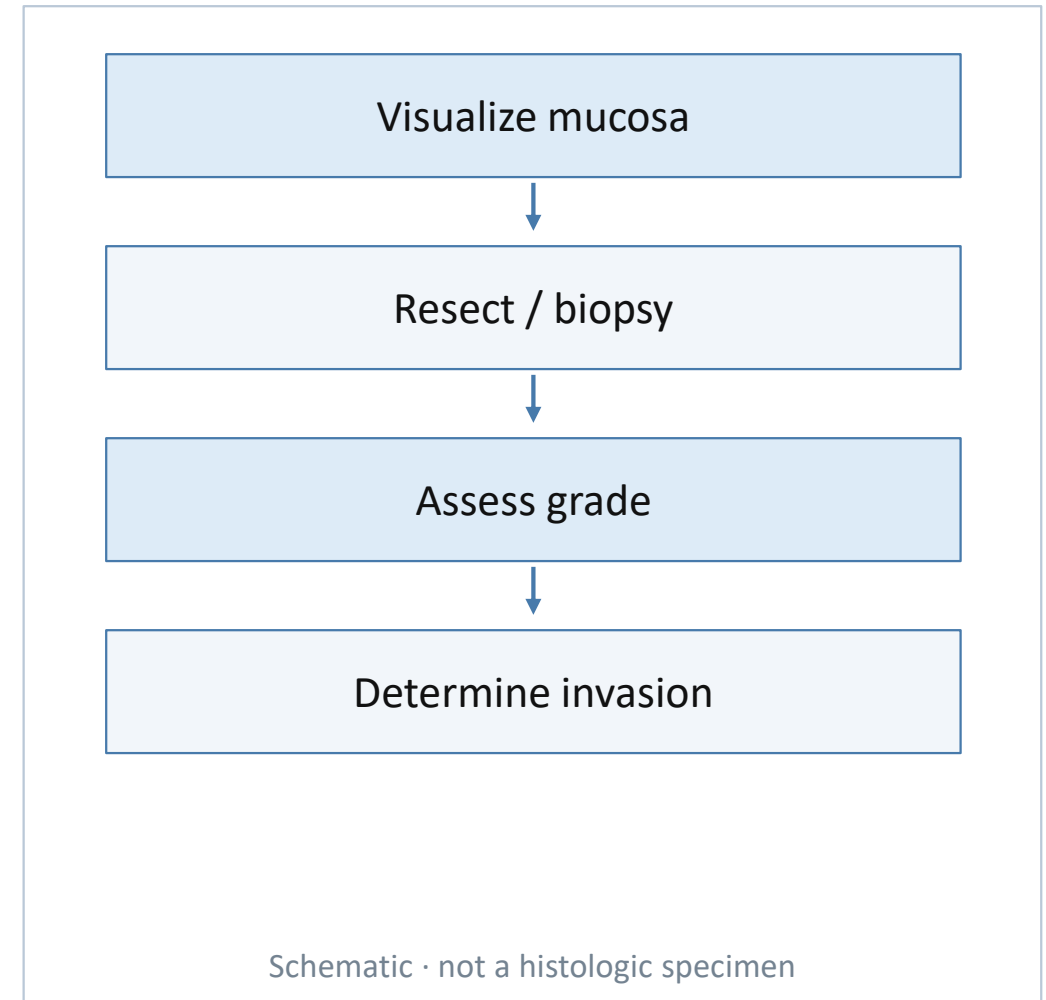


Irritative and obstructive manifestations

- Frequency, urgency, or dysuria can accompany hematuria
- Tumor near a ureteral orifice may cause obstruction
- Consequences can include hydronephrosis and pyelonephritis
- Symptoms do not establish stage in isolation

Cystoscopy, sampling, and histopathology

- Cystoscopy localizes visible papillary or flat mucosal abnormalities
- Transurethral resection provides tissue for grade and invasion assessment
- A specimen must be examined for lamina propria and detrusor involvement
- Urine-based assays do not replace anatomical tumor staging



What a useful pathology report resolves

- Histologic lesion type and urothelial grade
- Presence or absence of lamina propria invasion
- Whether muscularis propria is sampled and involved
- Additional patterns or variants when identified

Clinical categories: NMIBC versus MIBC

- Non–muscle-invasive cancer encompasses Ta, Tis, and T1 categories
- Textbook states about 70%–80% are non–muscle-invasive at presentation
- Approximately 20%–30% of bladder cancers are muscle-invasive
- This split strongly influences management and surveillance

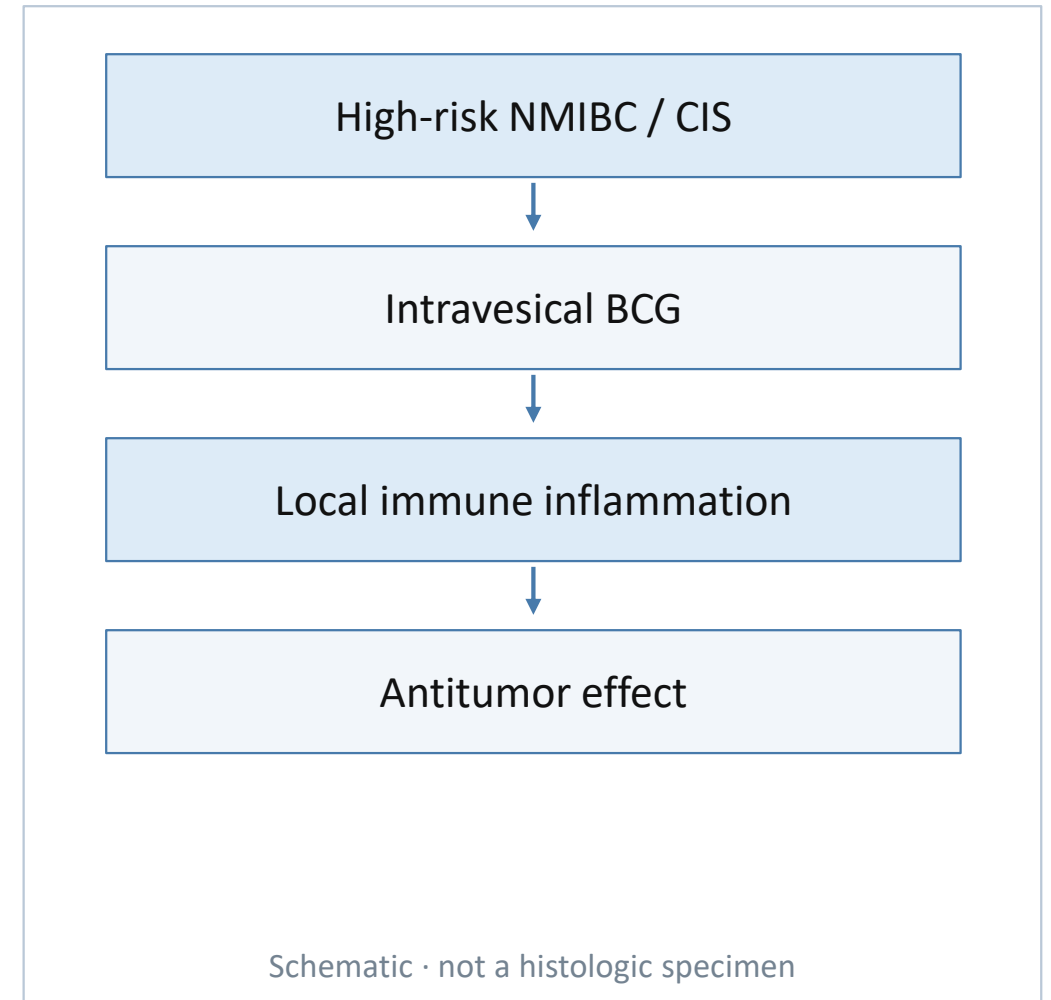
NMIBC	MIBC
Ta / Tis / T1	T2 and higher
No detrusor invasion	Detrusor or deeper invasion

Localized low-grade papillary disease

- Textbook describes diagnostic transurethral resection as sufficient for selected small localized low-grade tumors
- This description must not be mistaken for a universal modern treatment algorithm
- Appropriate treatment varies with grade, extent, recurrence, and stage

Intravesical BCG in higher-risk NMIBC

- BCG for CIS and selected higher-risk papillary disease
- Examples include large, high-grade, multifocal, recurrent, or T1 lesions
- BCG produces a local inflammatory antitumor response
- Treatment specifics depend on clinical risk stratification



Why non-muscle-invasive tumors recur

Clonally related recurrence

Tumor-cell shedding



Implantation elsewhere



Clonally related lesion

Independent second primary

New independent clone



Second primary tumor



Another bladder site

Surveillance is an essential part of care

- Even low-grade lesions may recur
- High-grade and CIS lesions have meaningful progression risk
- Lifelong follow-up is emphasized in the source
- No urine-based recurrence assay has replaced cystoscopy account

Management changes after detrusor invasion

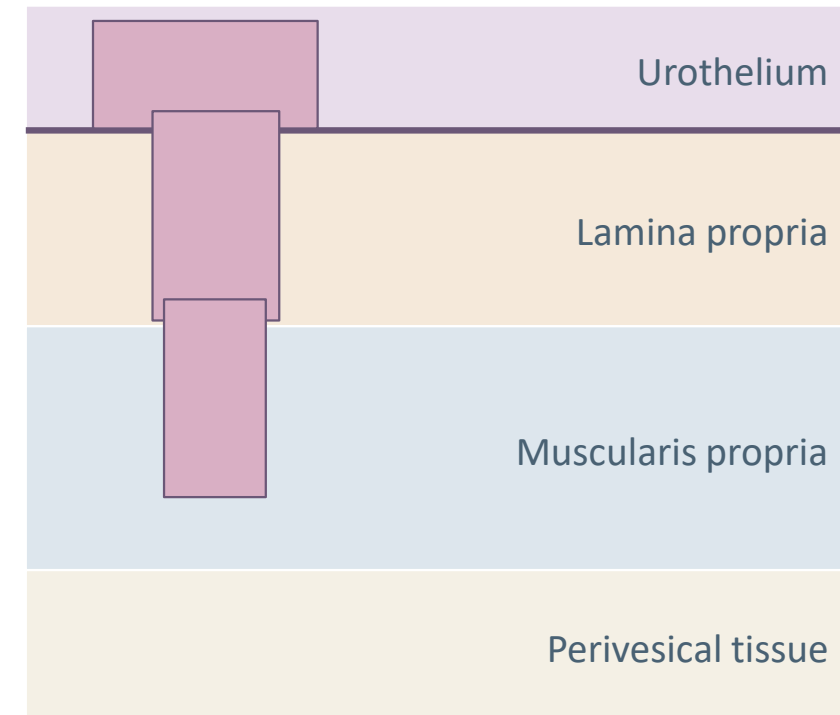
- Textbook describes radical cystectomy or selected radiation-based approaches
- Systemic chemotherapy is considered in the perioperative setting
- Muscle invasion creates substantial risk of nodal and systemic spread
- This is a source summary, not a current guideline prescription

Advanced or metastatic disease

- Regional nodes and distant organs may become involved
- Textbook discusses checkpoint blockade in a subset of metastatic tumors
- Antibody–drug conjugates and molecularly targeted approaches are noted
- Specific treatment recommendations require current oncology guidelines

Stage outweighs gross appearance for prognosis

- Papillary shape alone does not establish stage
- Depth of infiltration is the major determinant of prognosis
- Muscle invasion signals a substantial survival decrement
- Source survival figures are textbook cohort summaries, not individual predictions



Tumor penetrates detrusor

Schematic · not a histologic specimen

Case 1: A recurrent papillary lesion

- A small papillary lesion shows ordered cells, mild atypia, and no invasion
- Several years later, a morphologically similar lesion reappears elsewhere
- Question: Does this establish progression?
- Interpret recurrence separately from stage or grade progression

DISCUSSION

What observation determines the pathologic category?

Answer and rationale are recorded in the presenter notes.

Case 2: A flat erythematous mucosa

- Biopsy shows enlarged pleomorphic urothelial cells
- Tumor remains above an intact basement membrane
- Question: Is this benign because no invasion is visible?
- The morphologic diagnosis is high-grade carcinoma in situ

DISCUSSION

What observation determines the pathologic category?

Answer and rationale are recorded in the presenter notes.

Case 3: Papillary tumor with detrusor nests

- Histology identifies urothelial carcinoma within muscularis propria
- Even if the surface is papillary, depth determines a pT2 category
- Question: Which finding most changes clinical management?
- The presence of detrusor invasion is decisive

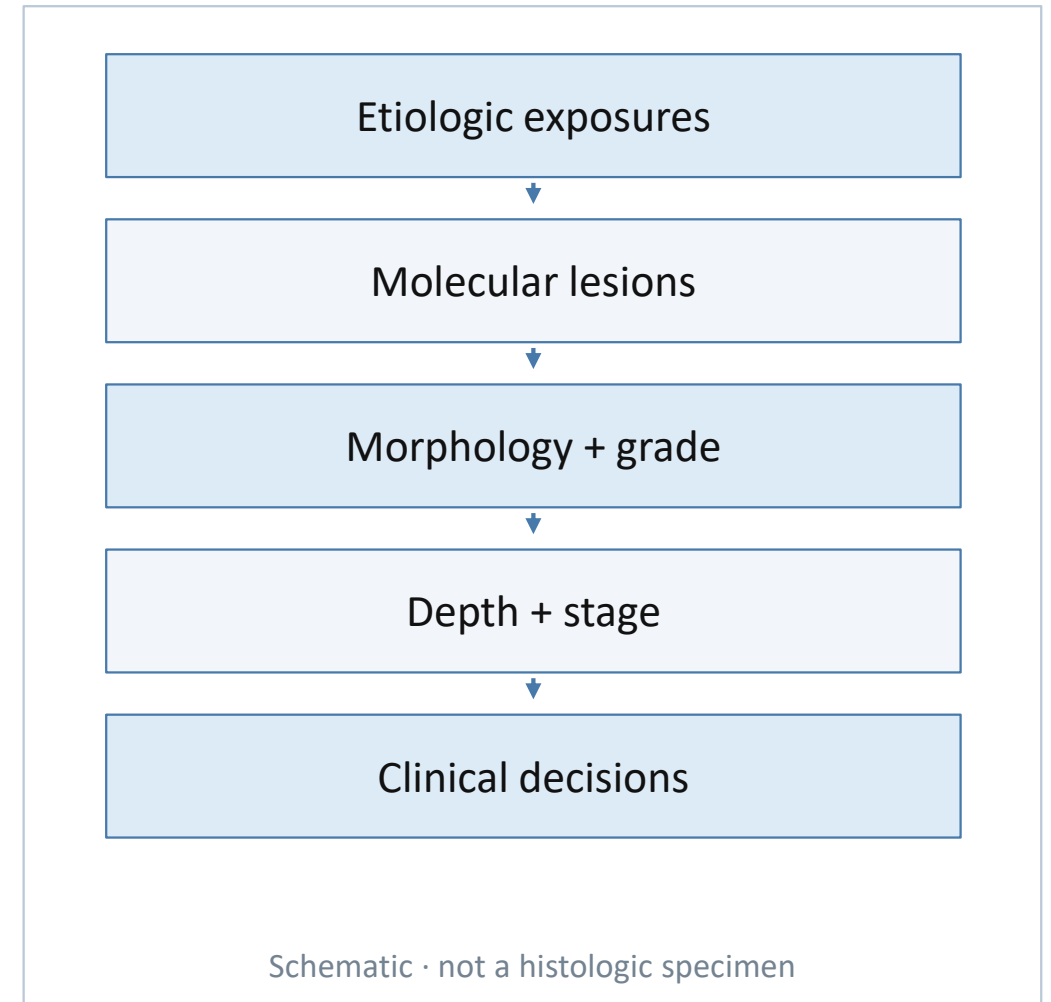
DISCUSSION

What observation determines the pathologic category?

Answer and rationale are recorded in the presenter notes.

Integrated clinicopathologic model

- Risk factors and molecular pathways create susceptibility
- Architecture and cytology classify the urothelial lesion
- Tissue layers determine anatomic pT stage
- Treatment and prognosis are guided chiefly by stage and grade



Five distinctions worth retaining

- Papillary versus flat describes growth pattern
- Low grade versus high grade describes malignancy-related cytology
- Noninvasive versus invasive describes basement membrane penetration
- T1 versus T2 separates lamina propria from detrusor invasion
- Recurrence versus progression describes distinct clinical events

Primary references and scope

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026), Ch. 21, pp. 870–874
- WHO Classification of Noninvasive Urothelial Tumors (2022), as reproduced in Robbins Table 21.3
- AJCC urinary bladder pTNM staging, 8th edition, as reproduced in Robbins Table 21.4
- Clinical treatment details are a textbook summary; confirm contemporary management separately