Urinary Tract Pathology: Urinary Bladder, Renal Pelvis & Urethra

APPROVED

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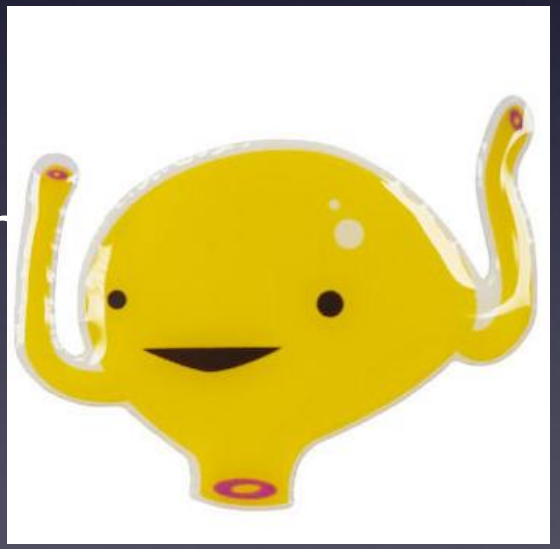


First set of benign conditions to discuss.

Cystitis

Infectious cystitis

- "Ascending" infection due to enteric bacteria
  - >95% of cases due to *E. coli*
  - *Klebsiella, Proteus,* etc. in predisposed pts
  - Yeast, viruses (CMV, polyoma, adenovirus) with immunosuppression
- Favored by obstruction
- Prostatism, congenital anomalies, stones

Most conditions of ureteritis and pyelonephritis are also ascending infections

important for patients on immunosuppression (transplant patients, neutropenic patients)

Fungal cystitis is unusual except in chronic catherization and patients on multiple antibiotics. Usually develop yeast (candida) infection.

We keep bacteria out of urinary tract by peeing. Therefore obstruct the urinary flow = infection. Female anatomy (shorter urethra) puts them at greater risk. Risk for males is obstruction of the prostate

Older men due to BPH are at risk of obstruction and cystitis

Stones favors infectious cystitis.

Urethral colonization

UTI is a spectrum of degrees across which ascending infection has assembled itself across various areas of the urinary tract

Pathogenetic sequence is reflective in the diagnostic sequence. On wards diagnosing cystitis is done by a urine culture and quantitatively determine the diagnosis.

Asymptomatic bacteriuria ($<10^4$/ml)

Occurs for various reasons, but does not warrant treatment

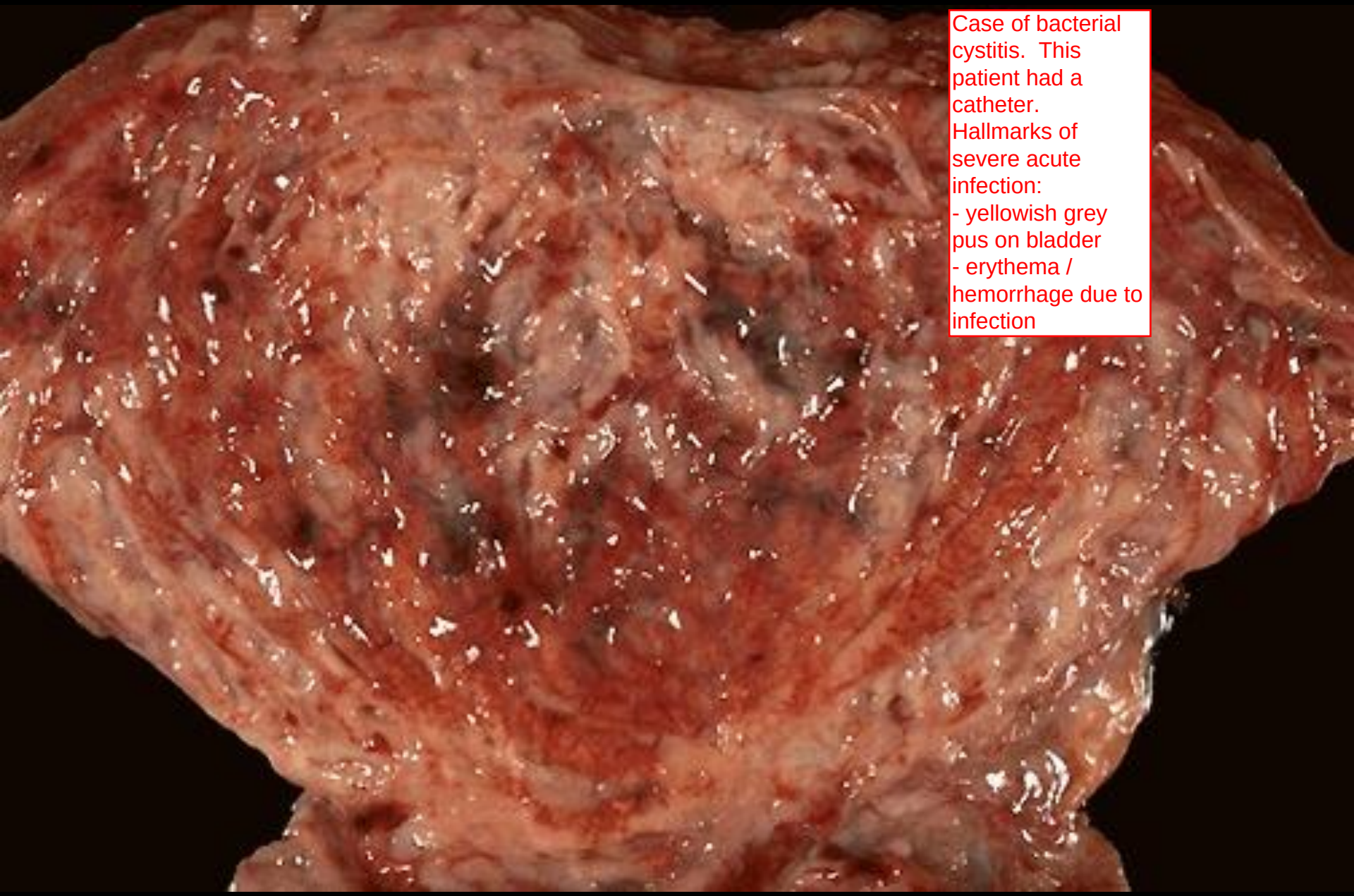
"Urethral syndrome" (10^4–10^5/ml)

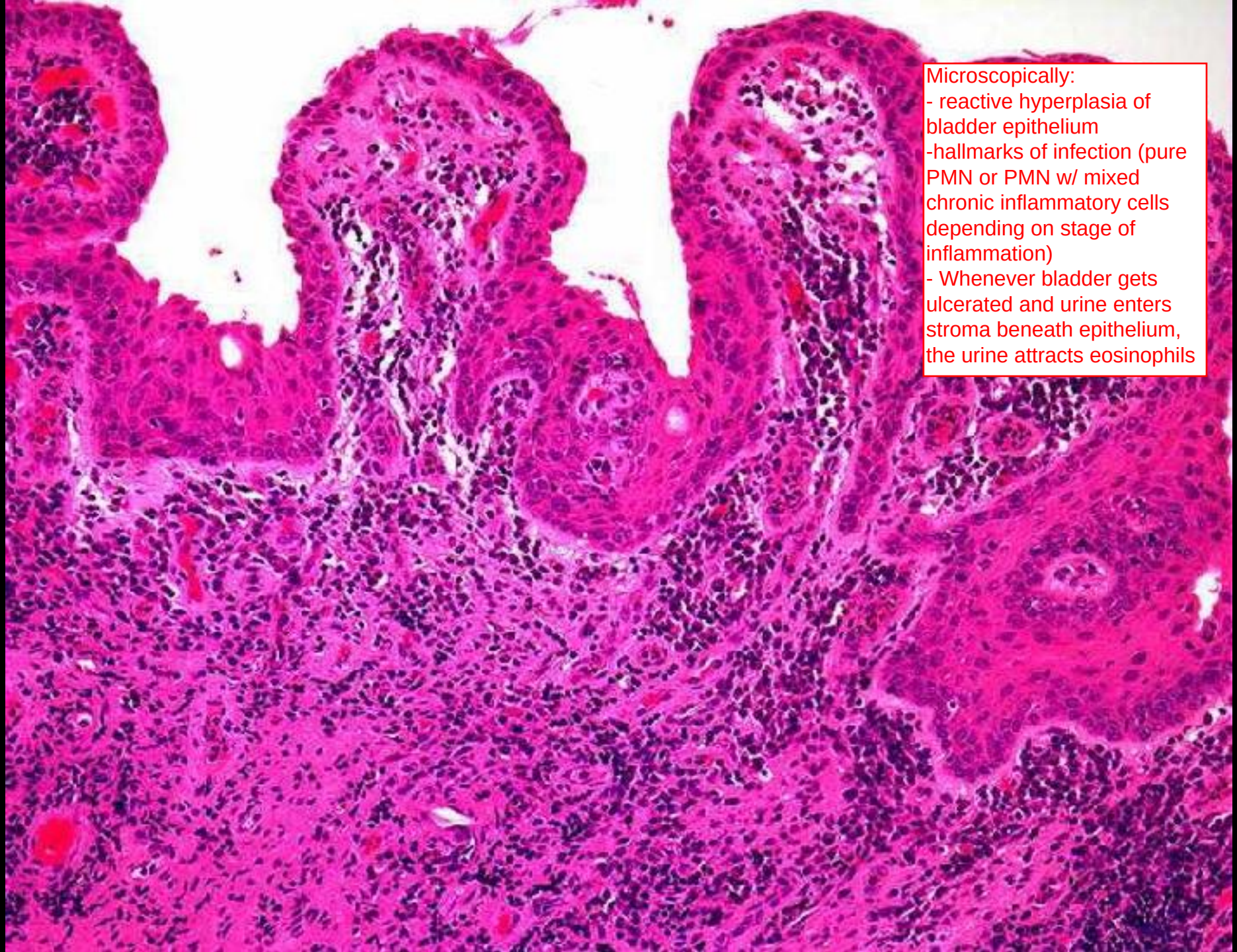
Numerical criteria to diagnose cystitis. This number is of a single species.

Grey zone often associated with burning symptoms. So, often urethritis ("urethral syndrome") precedes cystitis.

Cystitis ($\geq 10^5$/ml)

Pyelonephritis


Case of bacterial cystitis. This patient had a catheter.
Hallmarks of severe acute infection:
- yellowish grey pus on bladder
- erythema / hemorrhage due to infection


Microscopically:
- reactive hyperplasia of bladder epithelium
-hallmarks of infection (pure PMN or PMN w/ mixed chronic inflammatory cells depending on stage of inflammation)
- Whenever bladder gets ulcerated and urine enters stroma beneath epithelium, the urine attracts eosinophils

Interstitial (“Hunner’s”) cystitis

AKA "Bladder Pain Syndrome"

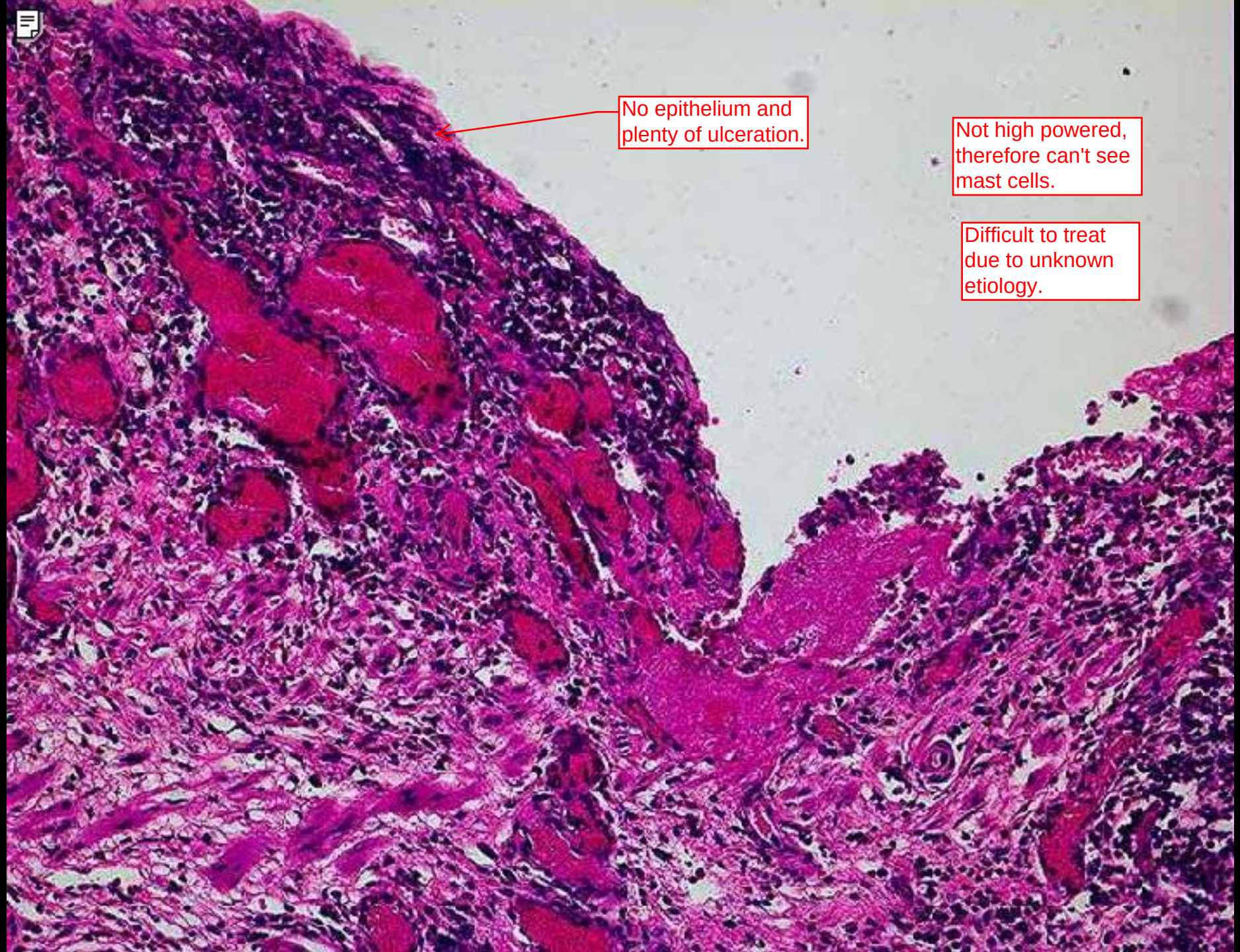
There are a couple of other non-infectious kinds of cystitis. Interstitial cystitis is one of them. Frustrating diagnosis / unknown etiology

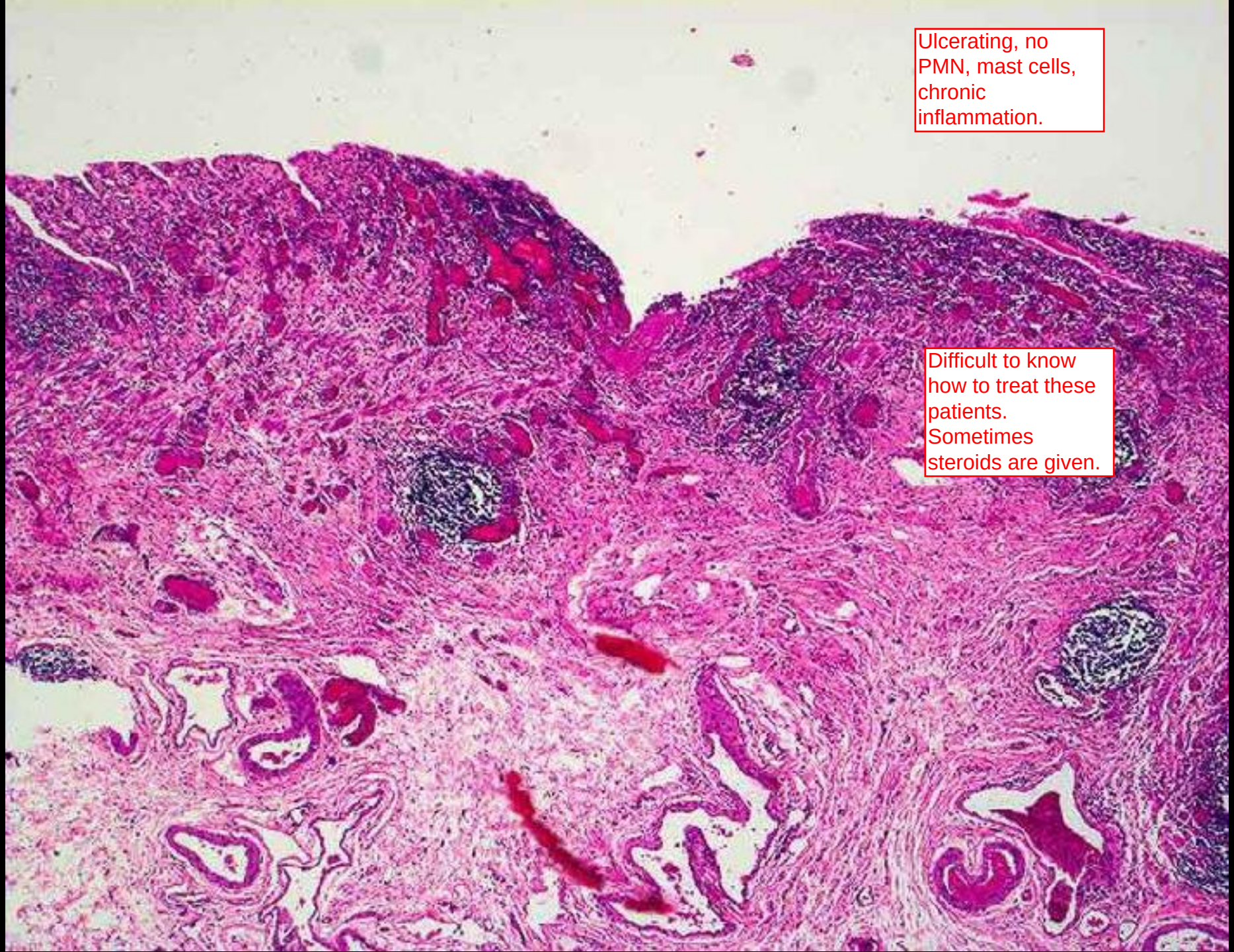
- Idiopathic (? autoimmune, mast cell dysfunction) cystitis
- Typically, women in later adulthood
- Hematuria, pain
- Extensive ulceration, often transmural, with fibrosis
- dDx: infection, cancer

Superficial to transmural ulceration

Chronic, recurrent, mild to severe w/possible transmural ulceratoin. Supposedly an autoimmune process

Many mast cells found in infiltrate.


No epithelium and plenty of ulceration.
Not high powered, therefore can't see mast cells.
Difficult to treat due to unknown etiology.


Ulcerating, no PMN, mast cells, chronic inflammation.
Difficult to know how to treat these patients. Sometimes steroids are given.

Hemorrhagic cystitis

Kind of cystitis associated with cytotoxic chemotherapy agents / RT. Blood found in urine.

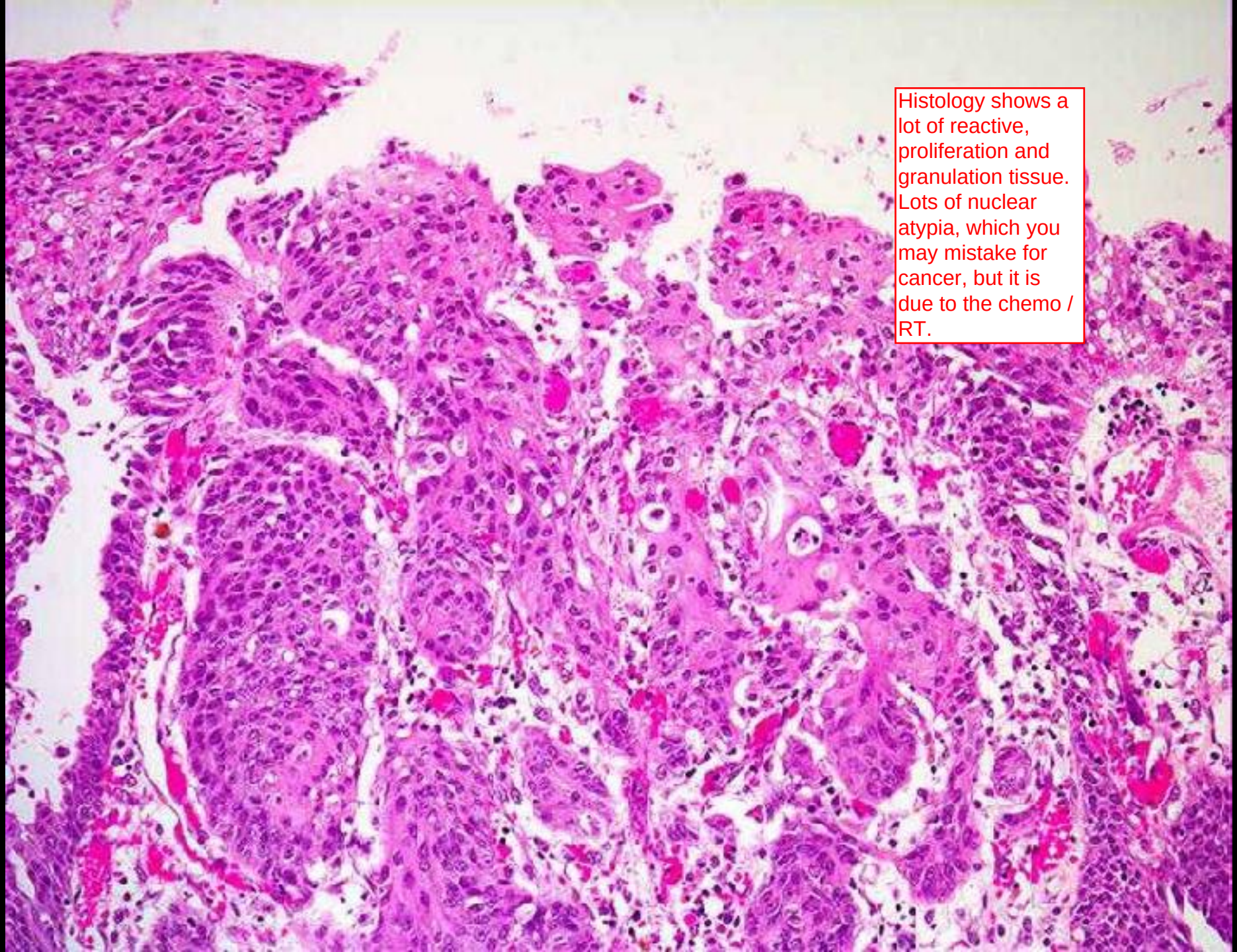
Another kind of cystitis. Inpatient and outpatient chemotherapy patients are the prime target.

- Complication of chemo-therapy or therapeutic pelvic irradiation
- Cyclophosphamide, others
- Can cause severe hemorrhage

Can be PO therapy (such as cyclophosphamide) or intravenous. Both can cause hemorrhagic cystitis.

Often require a cystectomy to control the bleeding


Severe hemorrhagic cystitis. Surgical case where the patient was losing lots of blood and a cystectomy was necessary.
A


Histology shows a lot of reactive, proliferation and granulation tissue. Lots of nuclear atypia, which you may mistake for cancer, but it is due to the chemo / RT.

Malakoplakia & Xanthogranulomatous pyelonephritis

- Chronic bacterial infection with ineffective clearance of organisms
  - *Proteus* often involved
- "Pseudotumor"
- Sheets of histiocytes packed lysosomes
- Malakoplakia has Michaelis-Gutmann bodies

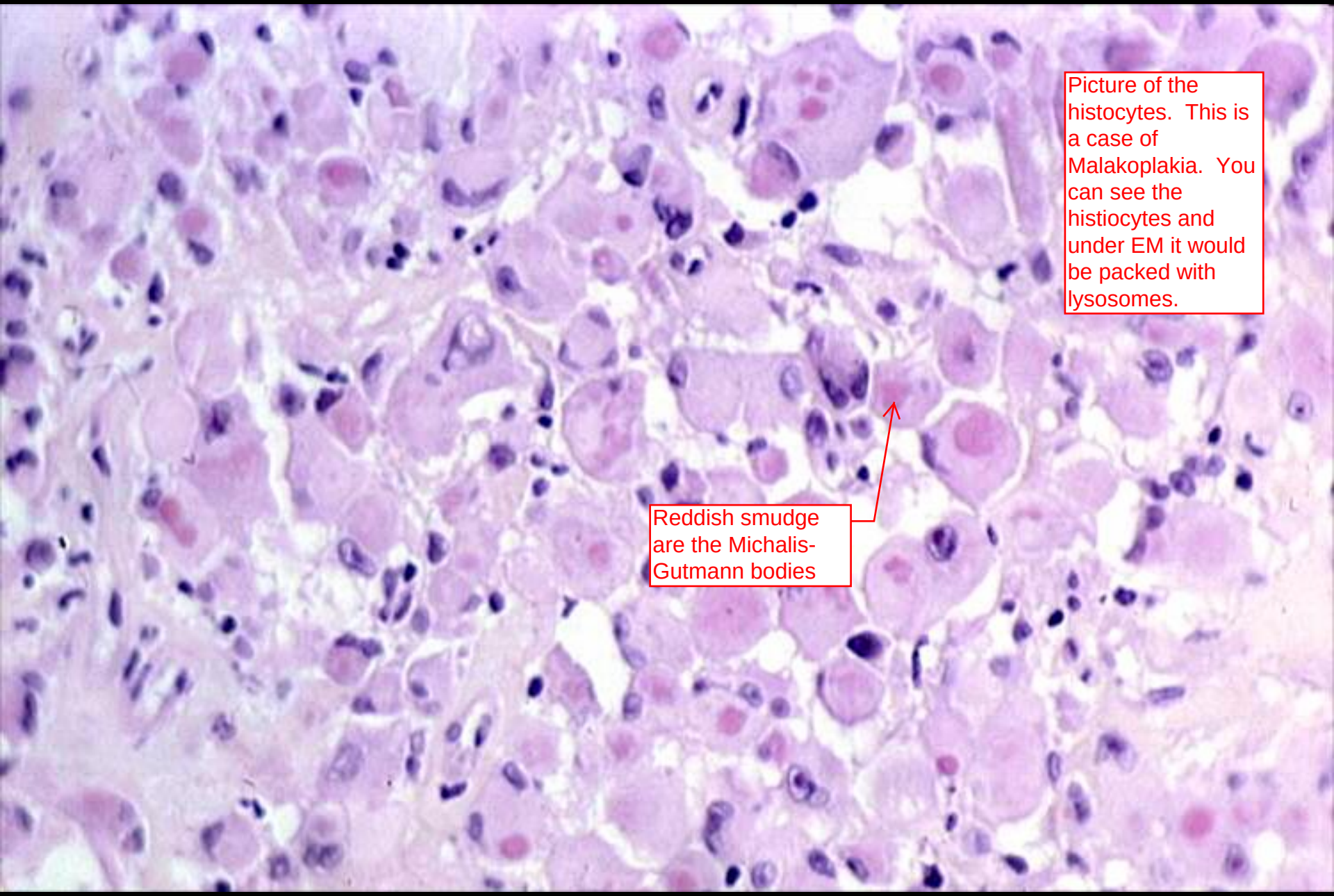
Xanthogranulomatous pyelo is similar to Malakoplakia of the urinary bladder. Both are entities that result from chronic bacterial infection and ineffective clearance of bacteria. Occurs often when you have stones in the renal pelvis or patients who are paraplegic w/o bladder control who constantly develop cystitis.

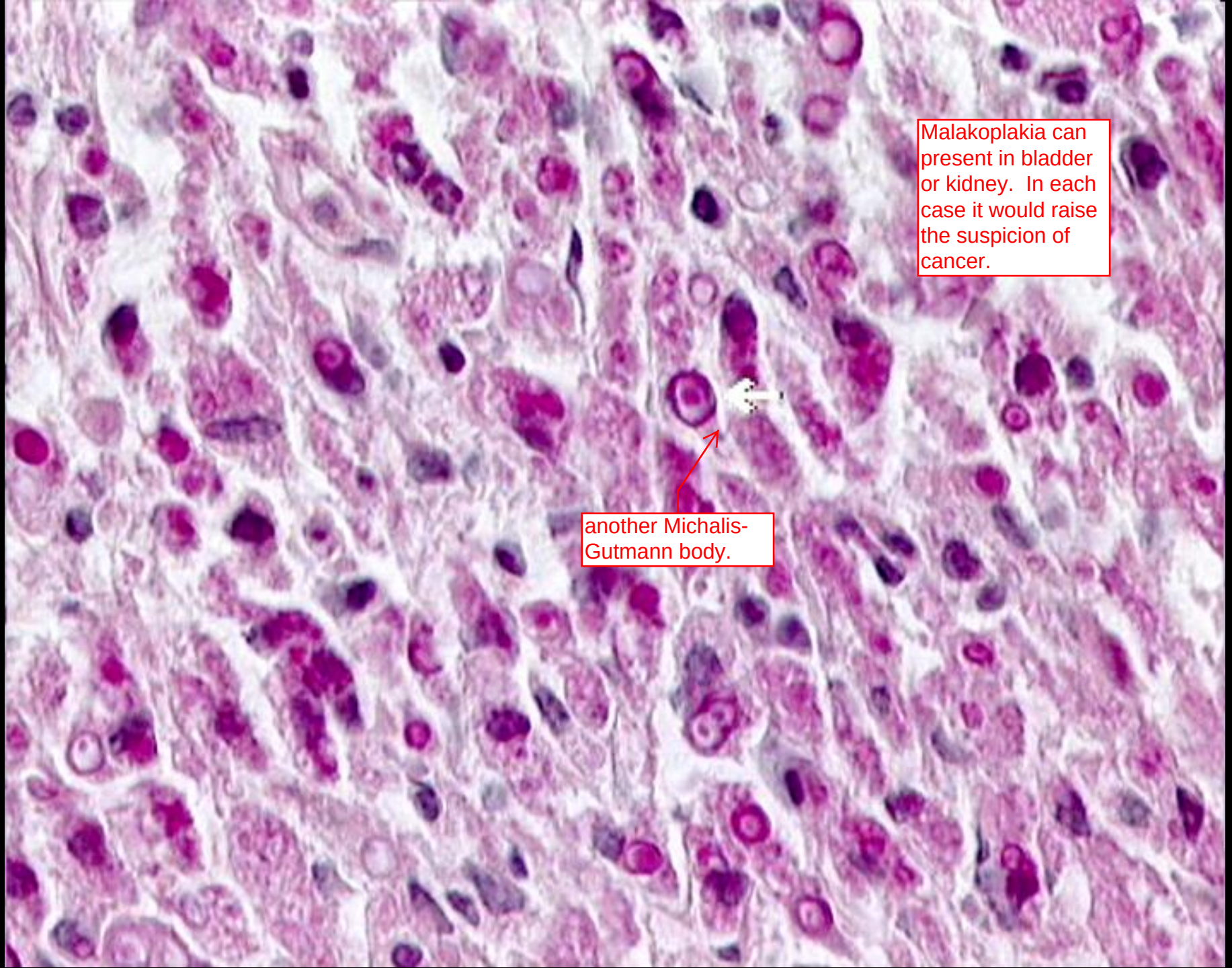
Difference between the two is that Malakoplakia have calcified / fossilized bacteria in the lysosomes creating these bodies.

Lysosomes have shreds of partially digested bacteria

Case of xanthogranulomatous pyelonephritis presenting as a renal tumor. This patient had the kidney removed. The physician thought this was clear cell RCC, but it is simply a mass of histocytes mimicking a tumor. Entirely reasonable to excise this kidney, although a partial nephrectomy would be more advisable.

These people usually have large renal calculi


Picture of the histocytes. This is a case of Malakoplakia. You can see the histiocytes and under EM it would be packed with lysosomes.
Reddish smudge are the Michalis-Gutmann bodies

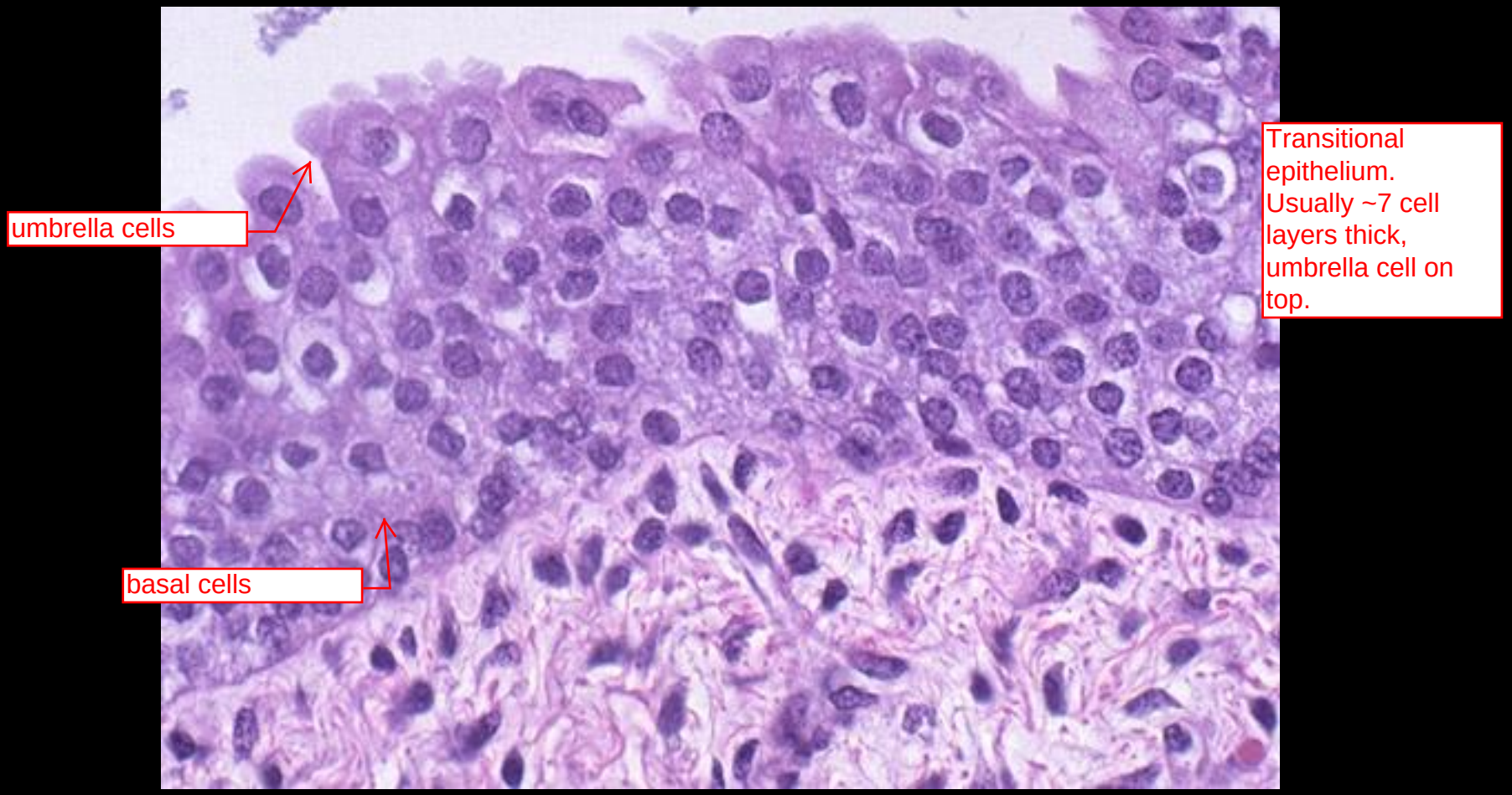

Malakoplakia can present in bladder or kidney. In each case it would raise the suspicion of cancer.
another Michalis-Gutmann body.

When a normal cell type undergoes differentiation to another cell type = metaplasia. It does so due to insults. At times these areas undergo biopsy and report states "squamous cell metaplasia". It is a common benign change and you don't want to mistake it for a carcinoma. Metaplasia is not neoplasia. It is not cancerous and does not necessarily precede cancer.

Urothelial metaplasia

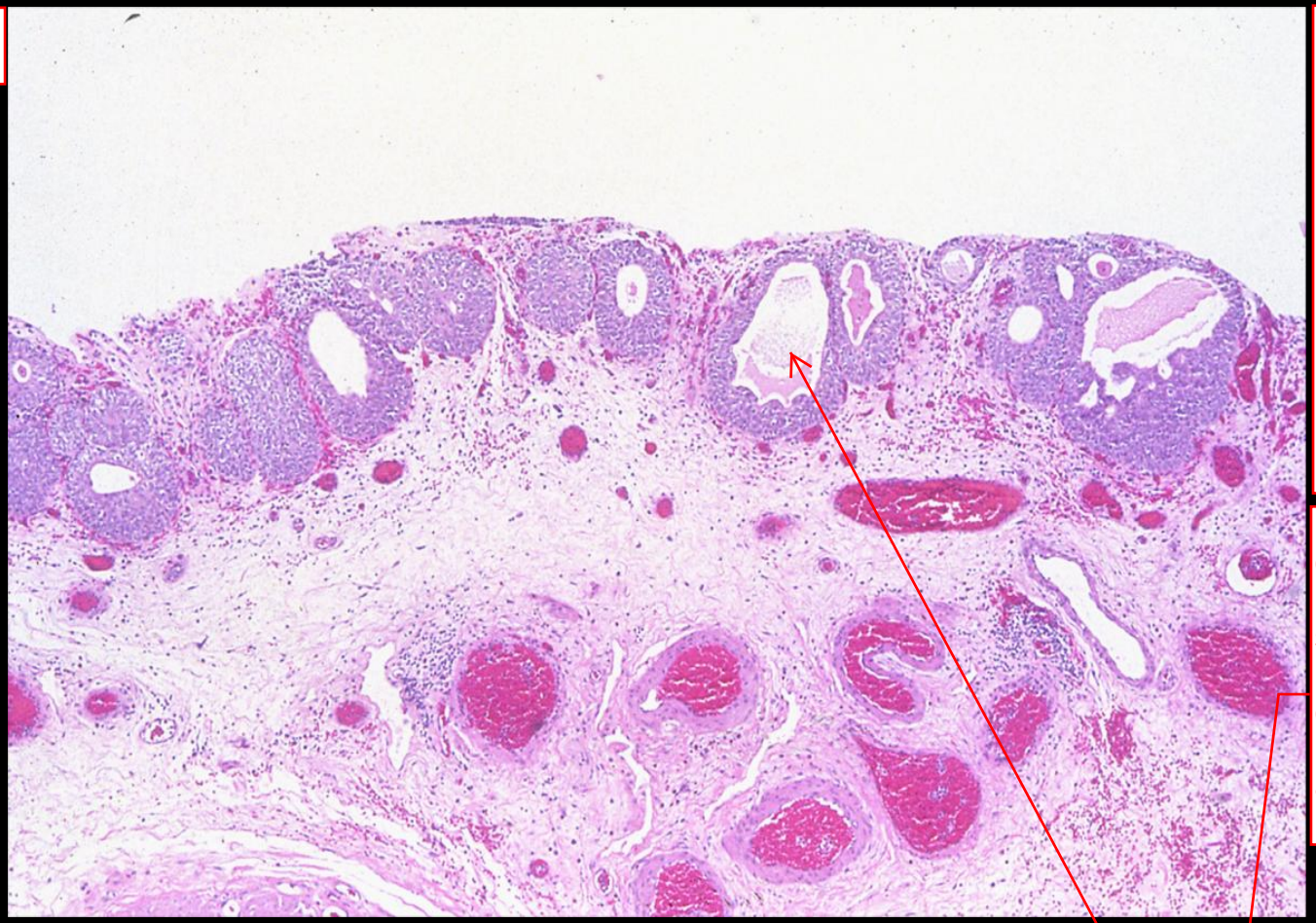
Urothelium has incredible ability to undergo

- Urothelium takes on characteristics of some other type of epithelium
- Often a response to chronic inflammation
- Benign



Normal urothelium

Benign metaplastic change.

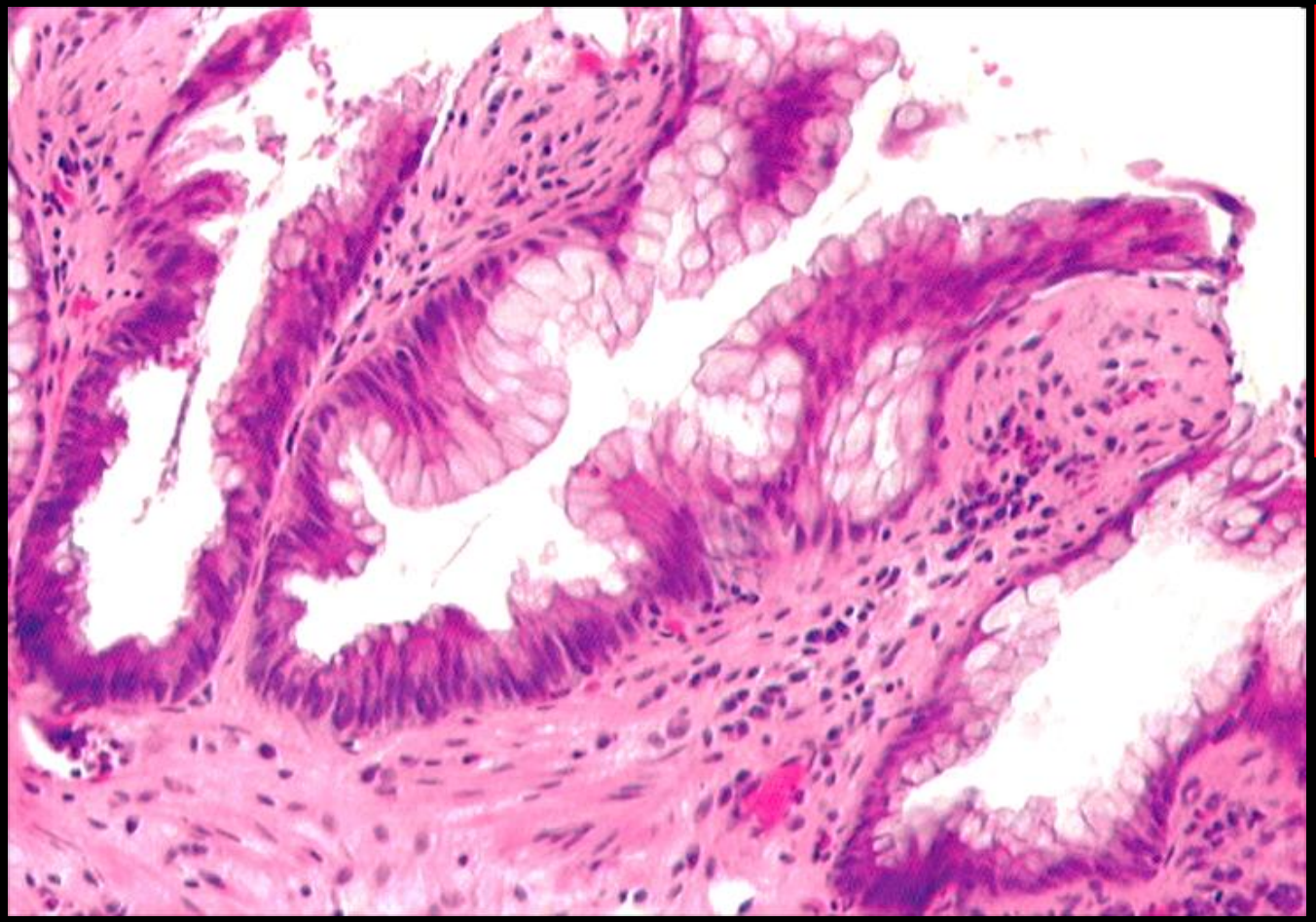


Sort of metaplasia that is common in the bladder and appears as a domed mass on the bladder and is often biopsied in fear of cancer. Odd name since we frequently have no cystitis, but do have a cystic change.

Normal invagination of the urothelium underneath submucosa that undergoes central cystic change, inflates, and causes a mass.

Cystitis cystica

Normal submucosal nests of urothelium (“von Brunn’s nests”) develop central cystic change

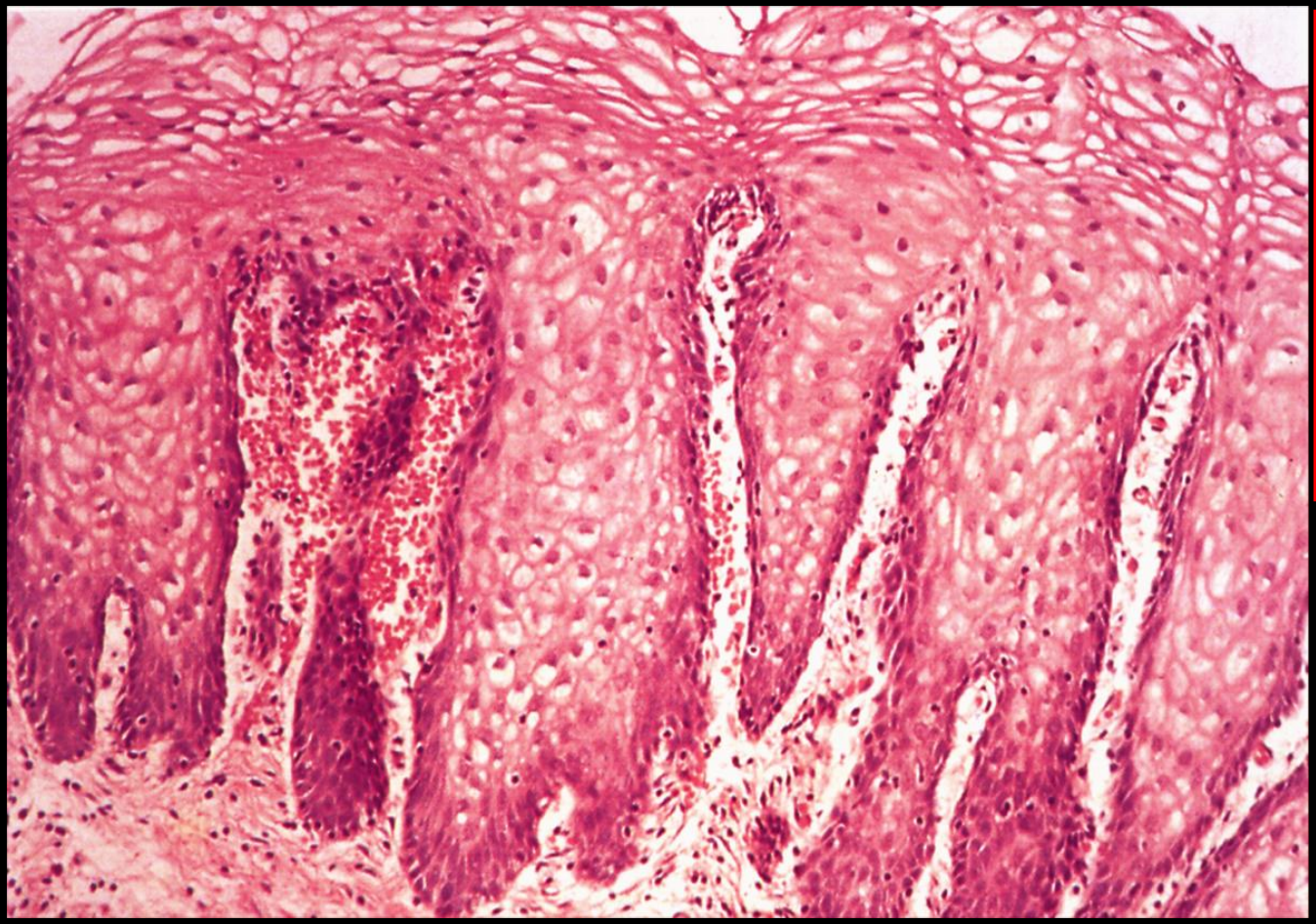


Cystitis cystica can undergo secondary metaplasis to look like colon. Causing cystitis glandularis. Negative for malignancy. May be spontaneous or associated w/ inflammation.

Most bladder cancers are those of urothelium. We may see adenocarcinoma arising due to this type of metaplasia.

Cystitis glandularis

Transitional cells convert to mucinous columnar type

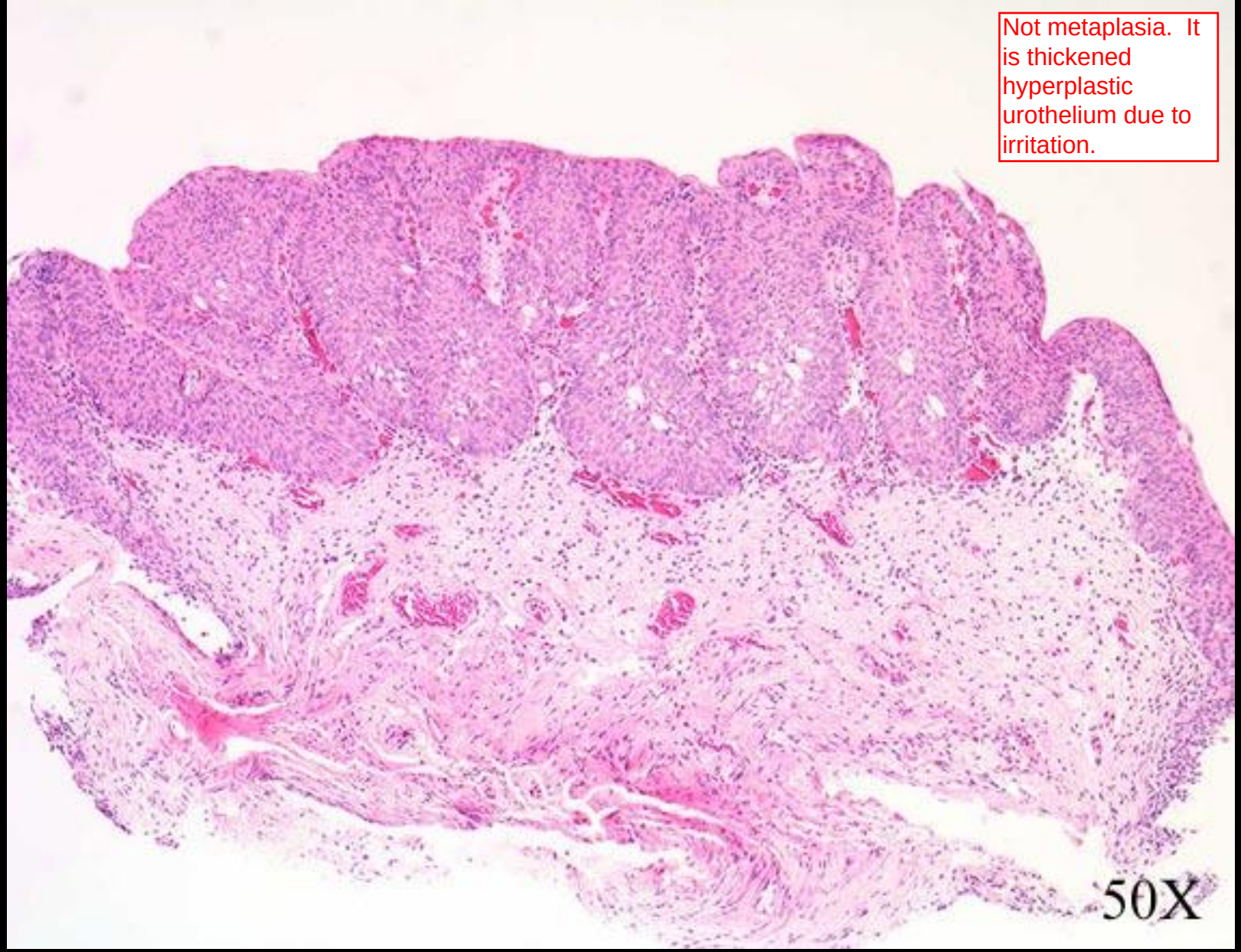


Common in bladder, especially w/ patients who have schistosomiasis. Theory is that the squamous epithelium is more protective than the typical urothelium, hence the metaplasia during chronic irritation.

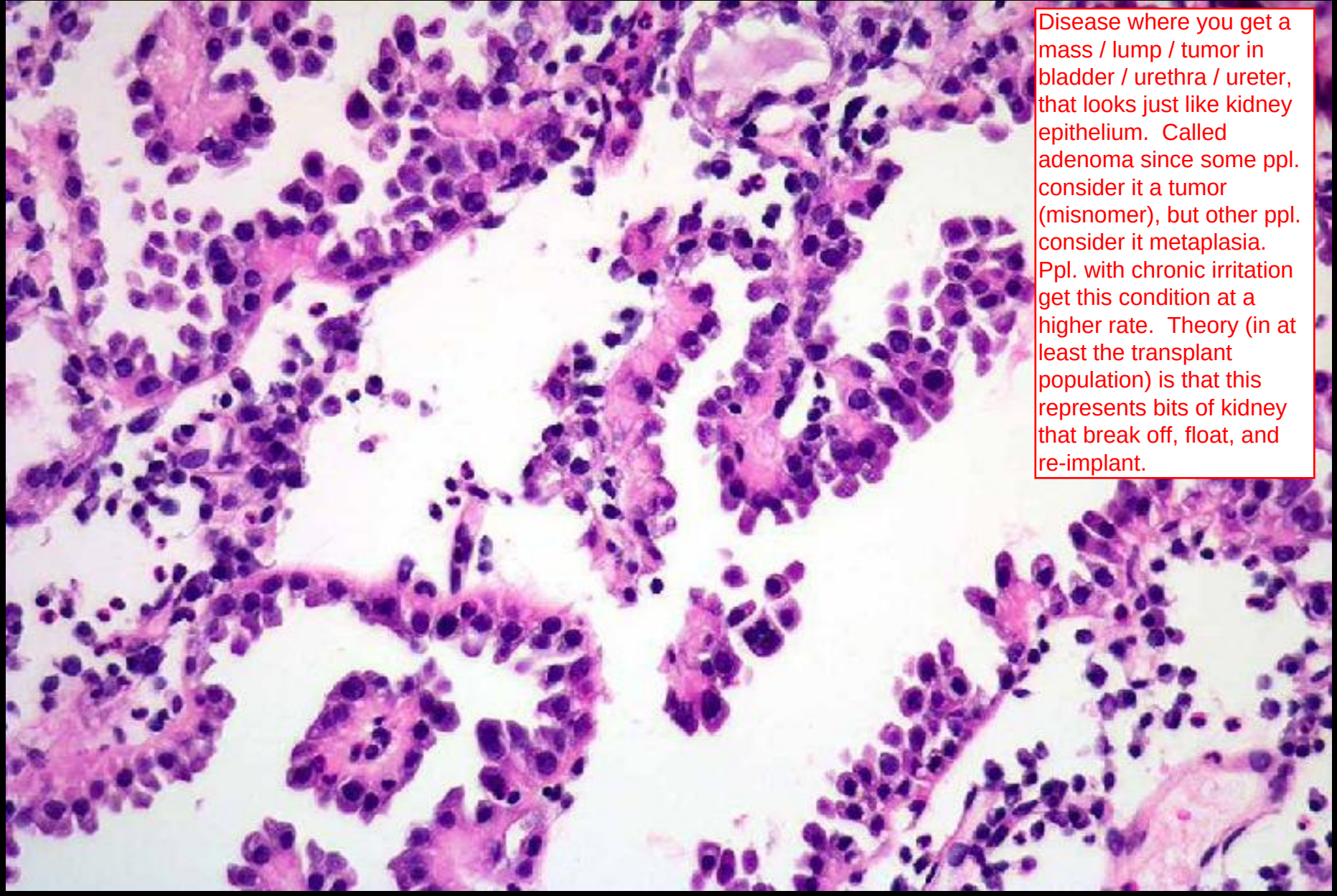
Again, rarely we see squamous carcinoma of the bladder due to underlying squamous metaplasia

Squamous metaplasia

Transitional cells convert to squamous cells under chronic irritation



Urothelial hyperplasia



Disease where you get a mass / lump / tumor in bladder / urethra / ureter, that looks just like kidney epithelium. Called adenoma since some ppl. consider it a tumor (misnomer), but other ppl. consider it metaplasia. Ppl. with chronic irritation get this condition at a higher rate. Theory (in at least the transplant population) is that this represents bits of kidney that break off, float, and re-implant.

“Nephrogenic adenoma”

Urothelial (transitional cell)carcinoma

Bladder carcinoma. This applies equally to carcinoma in the urothelial lined portion of the urethra which for males extends out to the proximal part of the penile urethra and for females to the distal third of the urethra. After that point squamous epithelium takes over. The ureters and renal pelvis are also lined with urothelium.

- Most common carcinoma of urinary bladder (85%)
- Y > X, white > black
- Known risk factors
  - Smoking → ~50% of U.S. cases
  - Aromatic amines
  - Some occupations
  - Schistosomiasis (squamous>TCC)

Various exposures to environmental carcinogens is typically the cause. Unlike RCC, which seems to just occur.

More common in males. More common in the white race.

Single most important risk factor for bladder cancer

Hair dye (in the past), no longer permitted.

Nickel industry.

Most of the cancer is squamous in these patients, but some are urothelial

So, most bladder cancer are urothelial carcinoma (90-95%), the remaining are squamous, adeno. (due to the metaplasia as explained previously

Bladder cancer is described by the term "polychronotropism" (historically) due to the following factors:

- Tends to occur multifocally
- Tends to recur

Because it is so closely related to chemical exposure, the chemical gets concentrated in the urine and is stirred around in the bladder = multifocal. In addition, it is typically triggered by numerous genetic hits = high reoccurrence

- Molecular alterations in multiple regulatory pathways are seen (Ras-MAPK, p53, Rb)

There is no one knockout genetic change / gene involved in bladder cancer.

- Abnormalities of chromosome 9 (mostly del 9) are a consistent, early finding

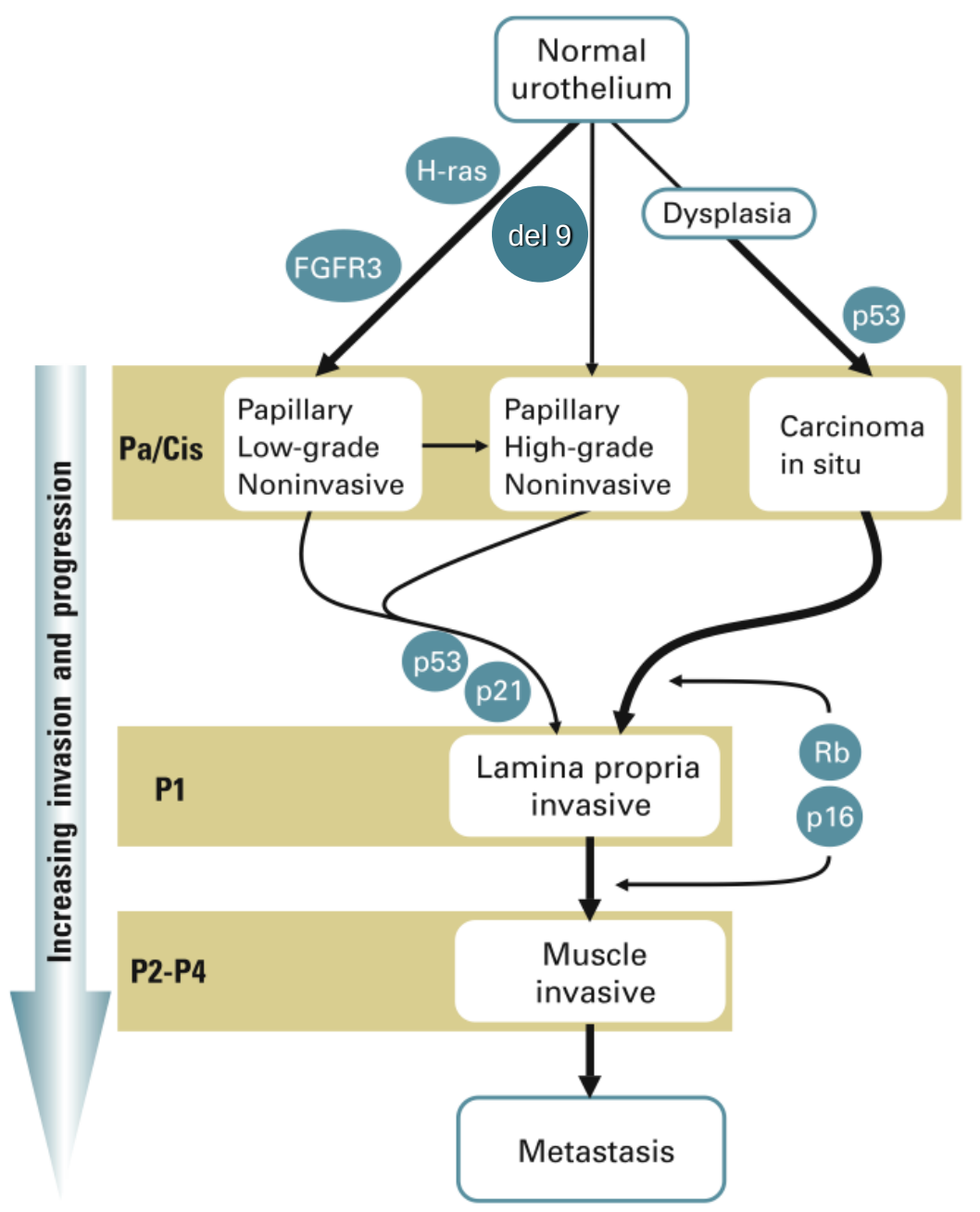
very common

  - p16 (CDKN2A) underexpression (9p21-) (Rb pathway) especially common

Also common

- One FDA-approved ancillary test (UroVysion™ Abbott) detects aneuploidy 3, 7, 17, and loss of the 9p21 via fluorescence in situ hybridization (FISH) in urine

UroVysion is used as a screening test for bladder cancer.



Not all that important. For those interested it shows an early view of where some of these genetic changes occur. Early cancers at top and more invasive cancers at bottom

Molecular Pathways in Invasive Bladder Cancer:
New Insights Into Mechanisms, Progression, and Target Identification

Anirban P. Mitra, Ram H. Datar, and Richard J. Cote
From the Departments of Pathology

JOURNAL OF CLINICAL ONCOLOGY REVIEWA RTICLE
VOLUME24 NUMBER35 DECEMBER102006

Bladder cancer: clinical

- Symptoms
  - Painless hematuria (80%)
- Diagnostic evaluation
  - Urinary cytology
    - Sensitivity modest, detects mainly high grade lesions
    - Okay for following patients with established Dx
  - Molecular tests

In 80% of patients Bladder cancer presents to medical attention with painless hematuria (text obscured by slide title)

Least invasive way to start workup is a urine sample.

If you have cystitis there is blood in the urine with pain. Unlike bladder cancer which causes blood and no pain

Urine cytology is not good for early / low grade cancer

You can perform the molecular test as mention on previous slide (UroVysion)

Gold Standard is **cystoscopy with biopsy**

Bladder cancer in two broad categories by extent of invasion

Several ways to subcategorize bladder cancer. One important way is based on how deeply invasive it is. Two groups:
1. Superficial
2. Muscle Invasive

- Superficial
  - Non-invasive *or* Invasive into lamina propria only
  - Traditionally, treated by transurethral resection
- Muscle-invasive

Much worse prognosis

  - Invasion into or through muscularis propria
  - Treated by cystectomy and/or radiation

Superficial is lower grade, less aggressive

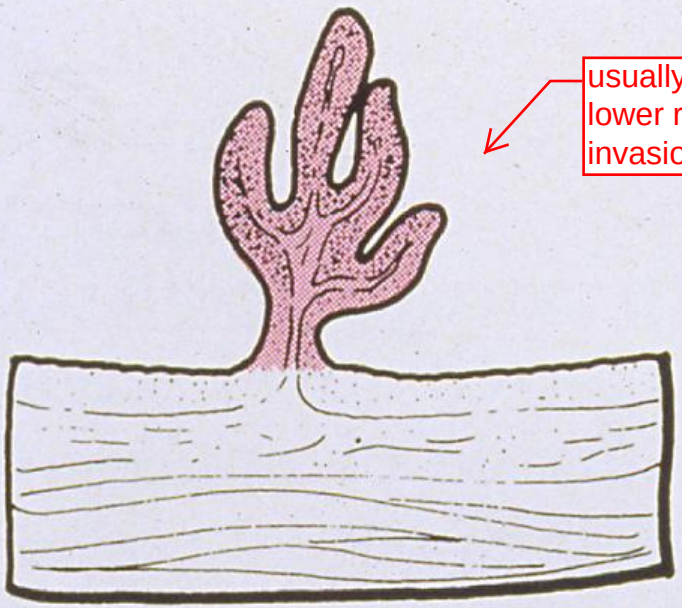
Superficial urothelial neoplasia: two histologic types

Two main histo subtypes:
1. Papillary: Cauliflower mass (lower grade risk)
2. Non-papillary: analogous to dysplasia in the cervix, flat lesion (higher grade risk)

- Papillary
  - Majority of urothelial cancers
  - Exophytic, cystoscopic resection often possible
  - On average, lower grade
- Non-papillary

More aggressive, high grade

  - 10-40% of urothelial cancers
  - Cystoscopically occult



usually low grade / lower risk of invasion

Papilloma-papillary carcinoma

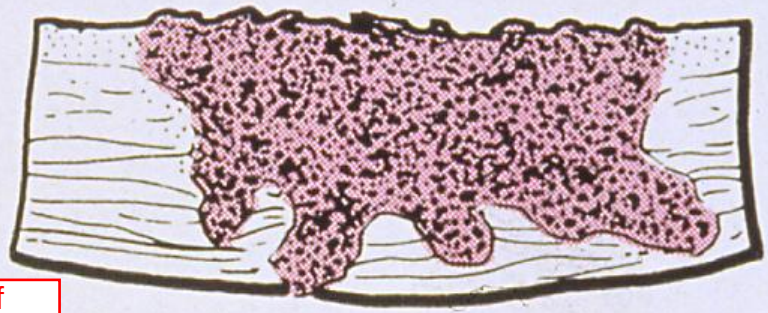
Episodic twisting off papillary tumor can lead to random hematuria.

Invasive papillary carcinoma

flat carcinoma are higher grade / high risk of becoming invasive

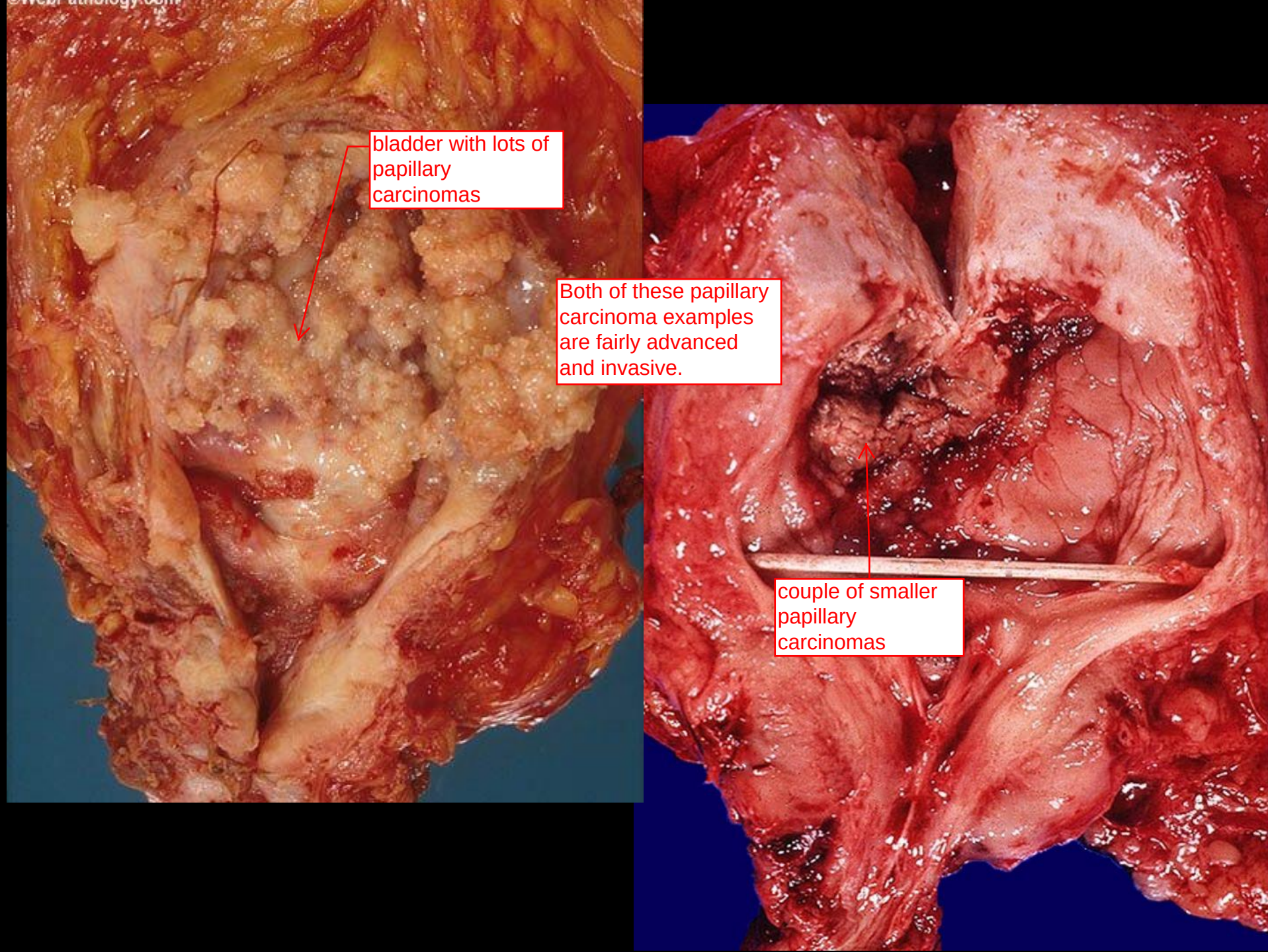
Flat noninvasive carcinoma

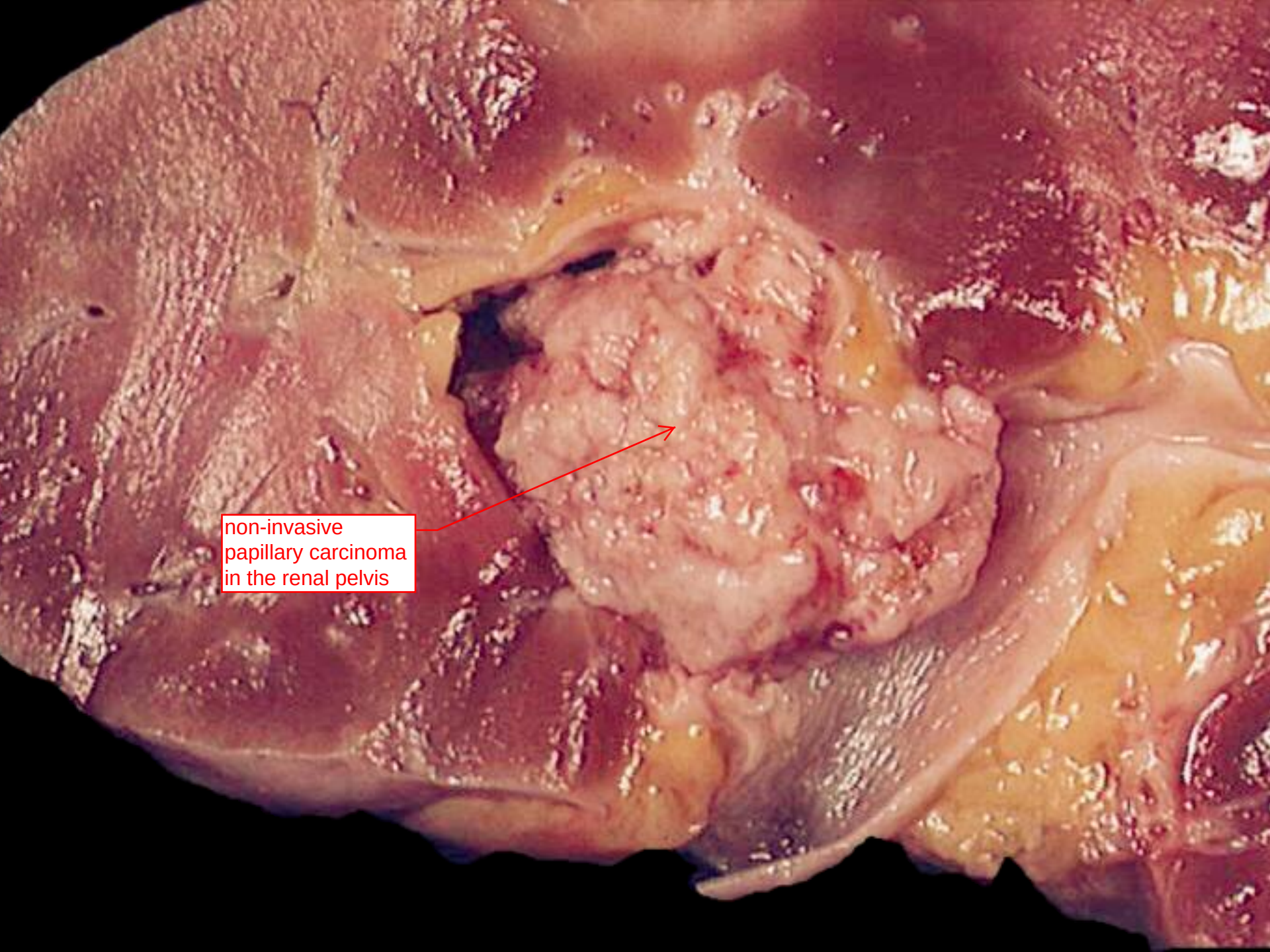
Roughly 25% of pts belong to the bottom two "flat" kind. These are more aggressive



Flat invasive carcinoma

Superficial papillary urothelial neoplasia

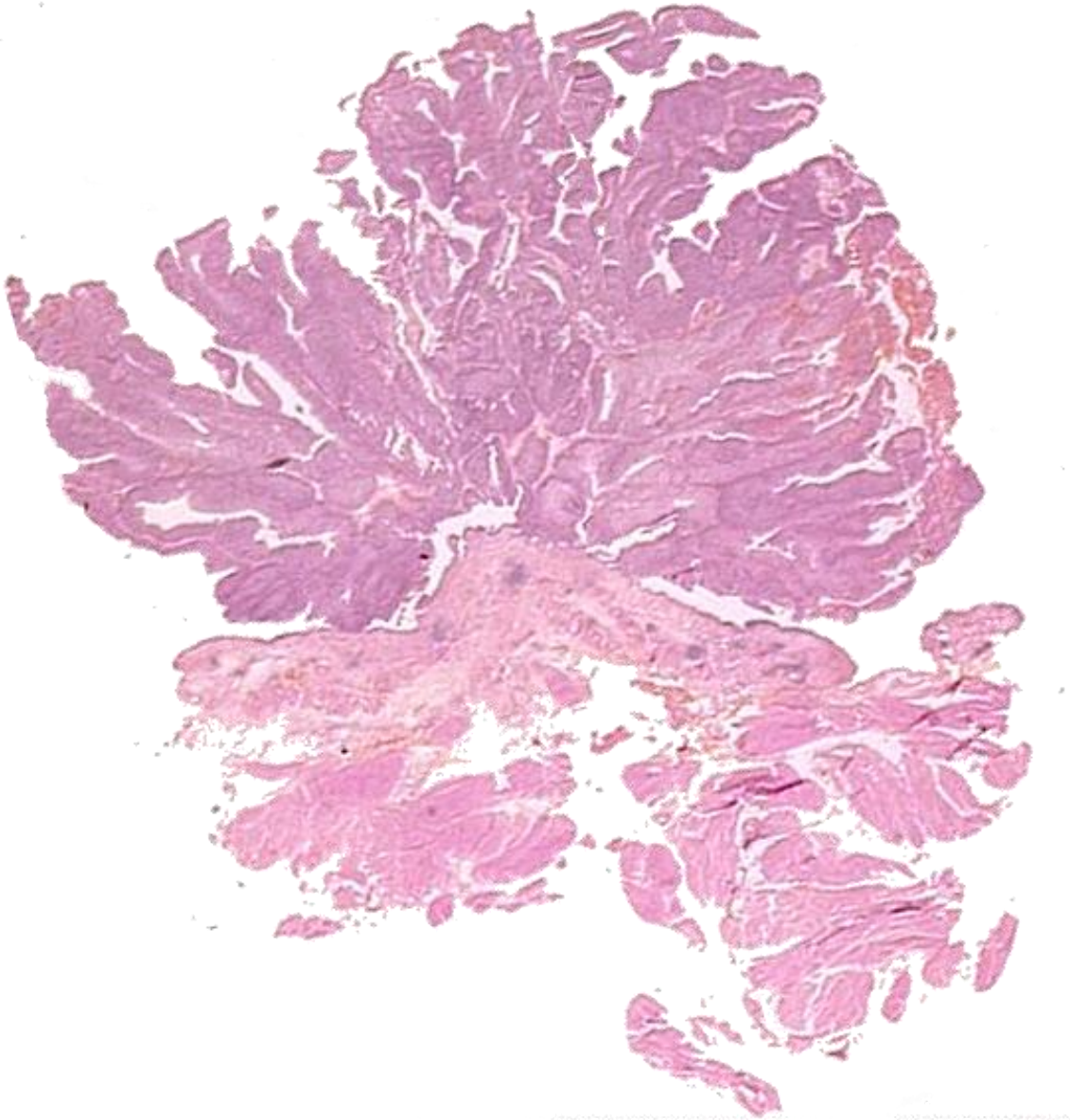

bladder with lots of papillary carcinomas
Both of these papillary carcinoma examples are fairly advanced and invasive.
couple of smaller papillary carcinomas


non-invasive
papillary carcinoma
in the renal pelvis

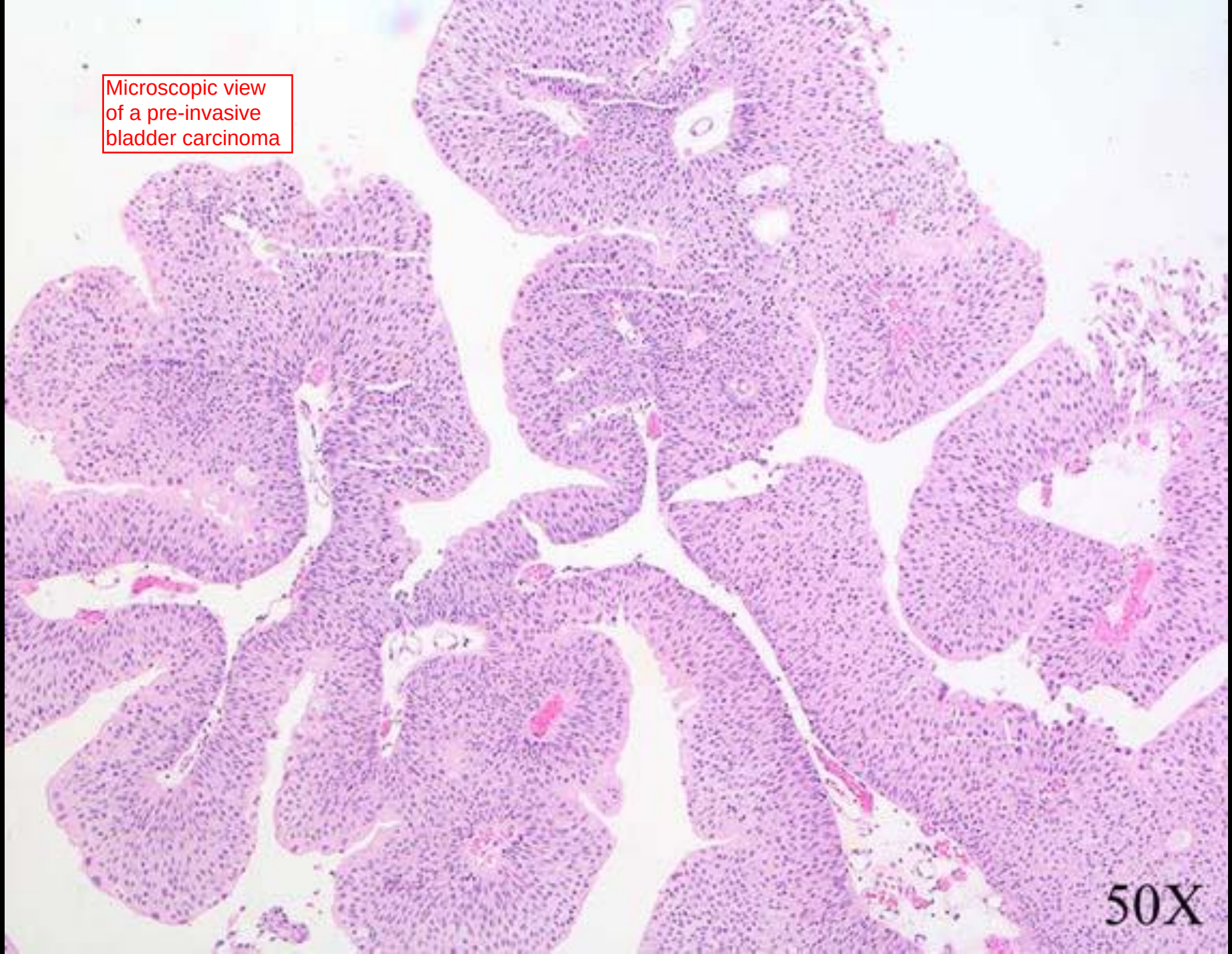
Bladder cancer exception (for historic reasons): Whether invasive or pre-invasive, lesions of the bladder are called cancer. Pre- or non-invasive "cancer" have very good prognosis and rarely progress to invasive disease.

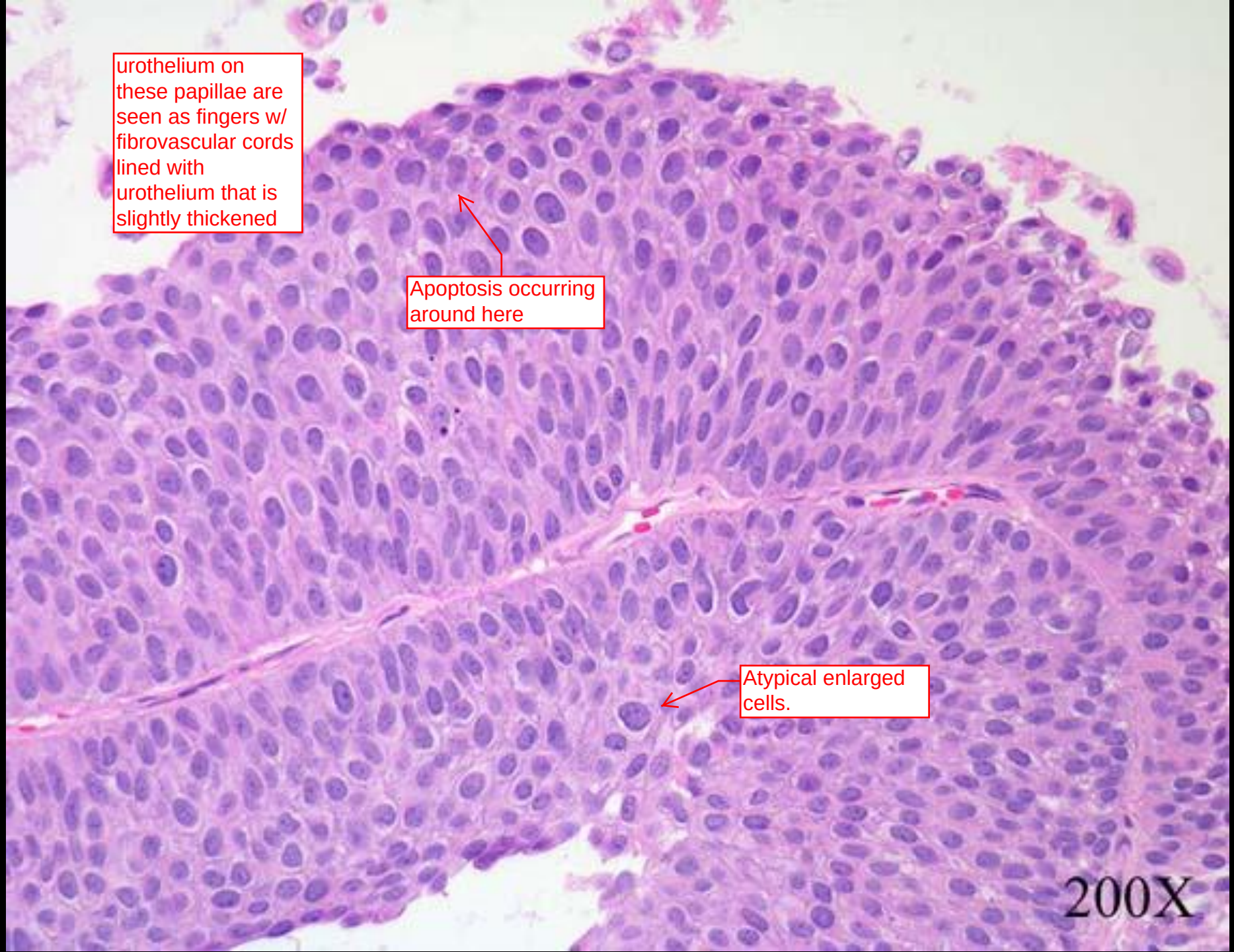
Warning!

- By convention, papillary neoplasms of urothelium are always called "carcinoma" *even if non-invasive*
- Why call this "carcinoma"?
  - Comparison with colonic adenoma



Superficial non-invasive papillary "carcinoma" of the bladder, low grade, excised cystoscopically.


Microscopic view
of a pre-invasive
bladder carcinoma
50X

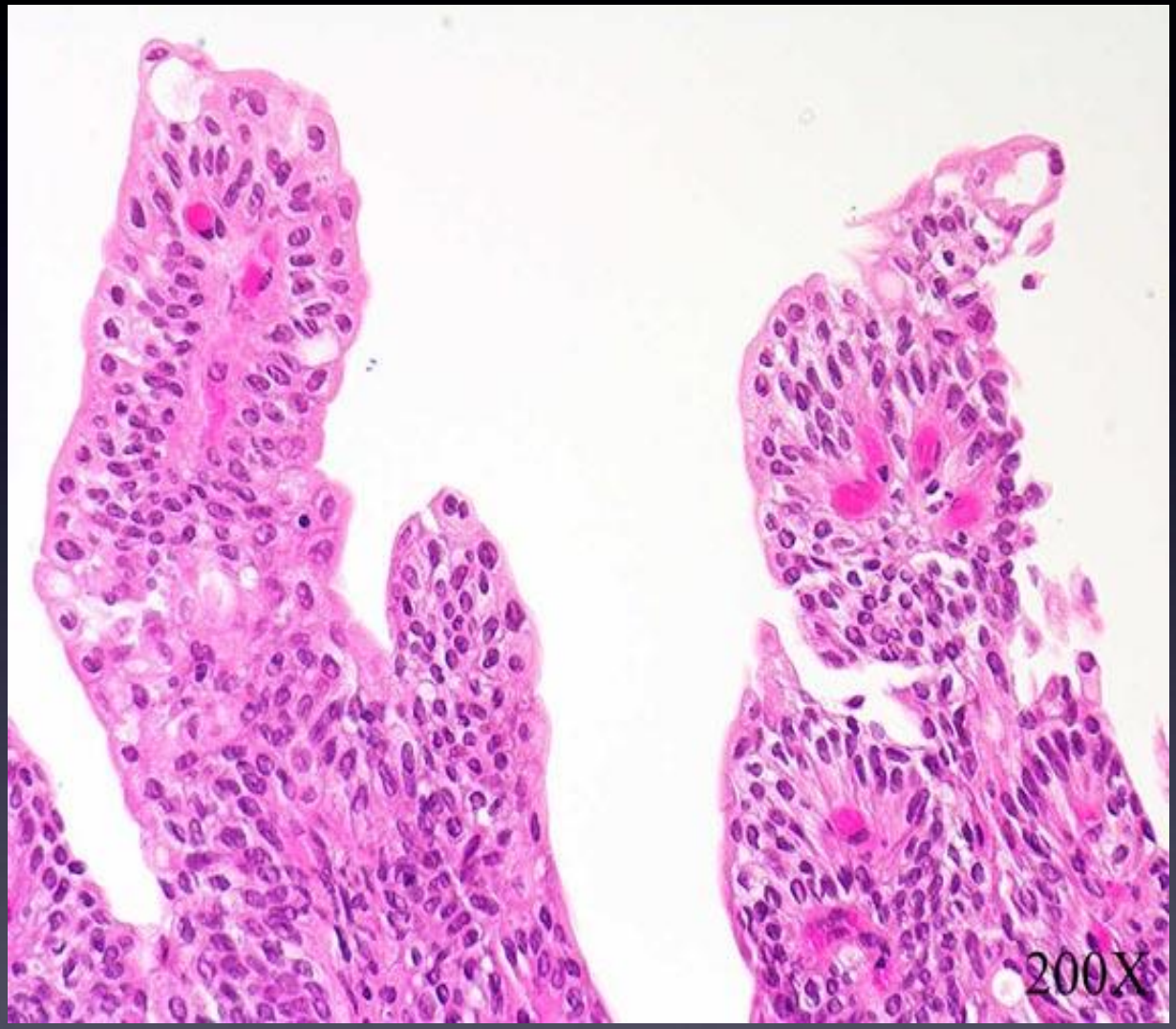

urothelium on these papillae are seen as fingers w/ fibrovascular cords lined with urothelium that is slightly thickened
Apoptosis occurring around here
Atypical enlarged cells.
200X

Papillary urothelial neoplasia: grading

- Papilloma
- (Low malignant potential)
- Low grade UC
- High grade UC

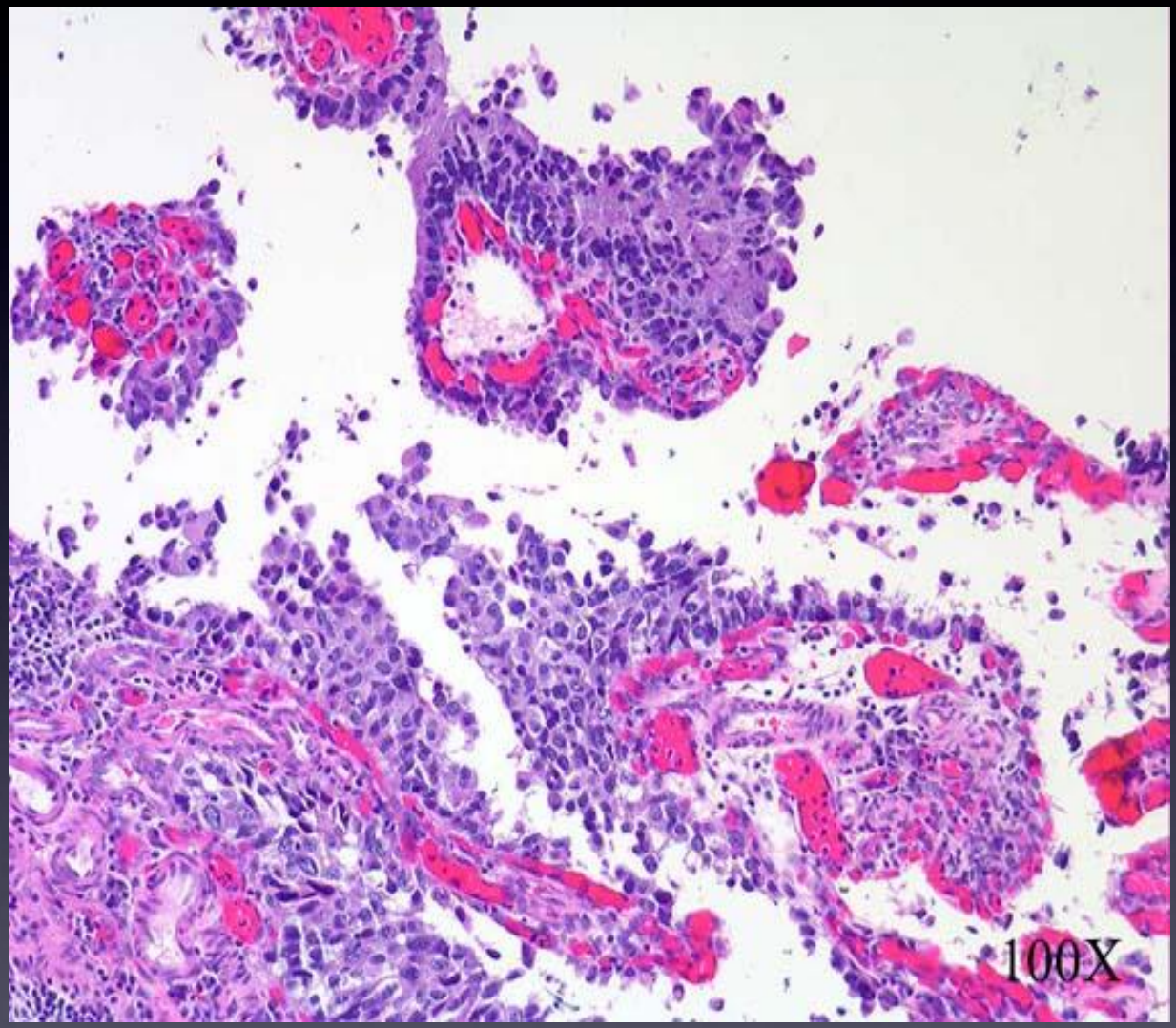
When these papillary urothelial neoplasms are pre-invasive can be divided into low grade and high grade. The majority of the papillary are low grade and don't progress.

Example of a low grade one



Another example
of a low grade one

Example of a high grade one

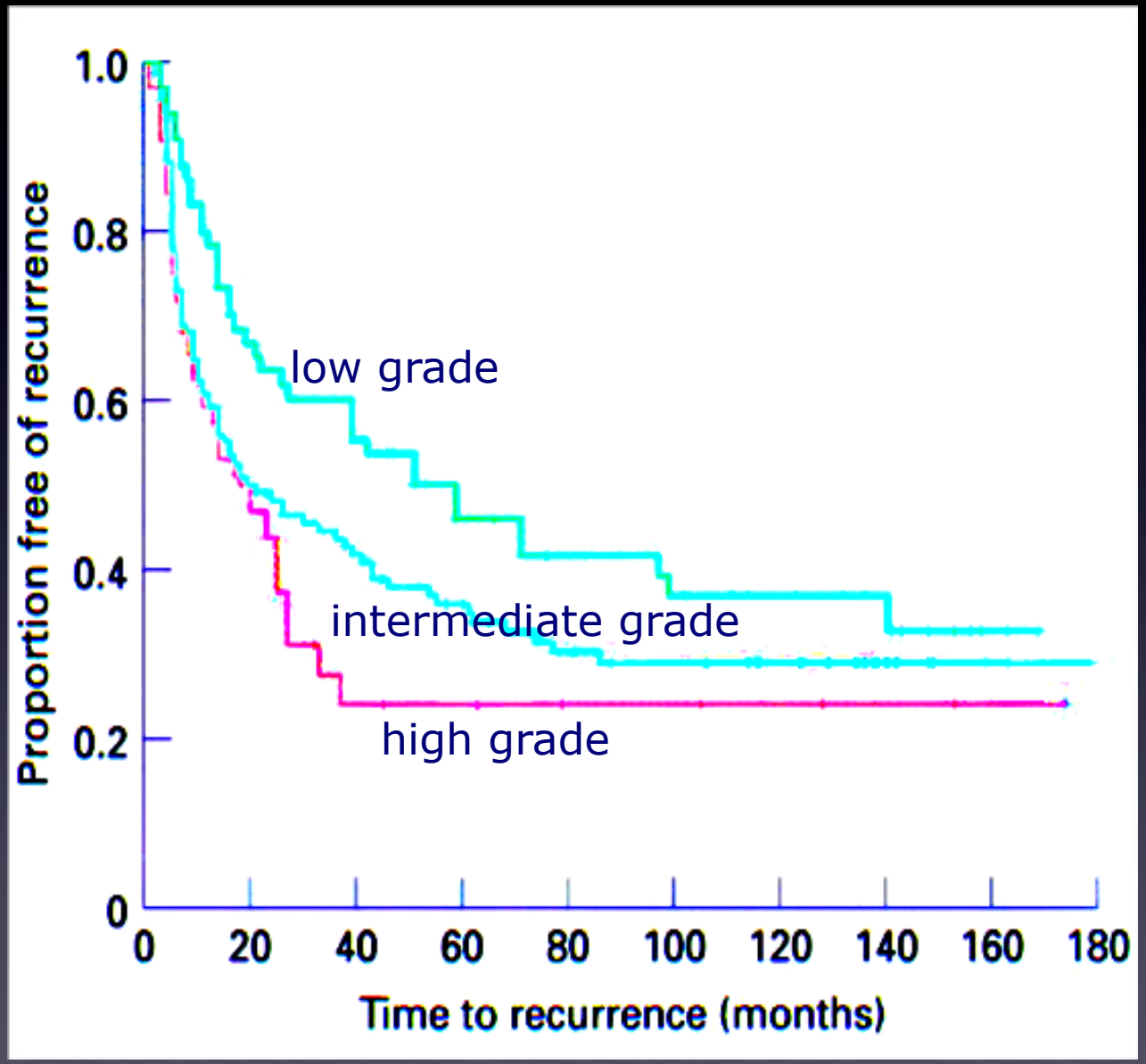


Superficial papillary urothelial neoplasia: natural history

- Frequent recurrence
- Infrequent progression or invasion

Since papillary neoplasia is usually low grade and doesn't progress, they typically present as episodic hematuria, urologist will perform a cystoscopy, snips the cauliflower lesion, pathologist labels it as low grade, and it may recur. None of these tumors develop an invasive component. So this patient must keep coming back to have these papillae snipped out every six months.

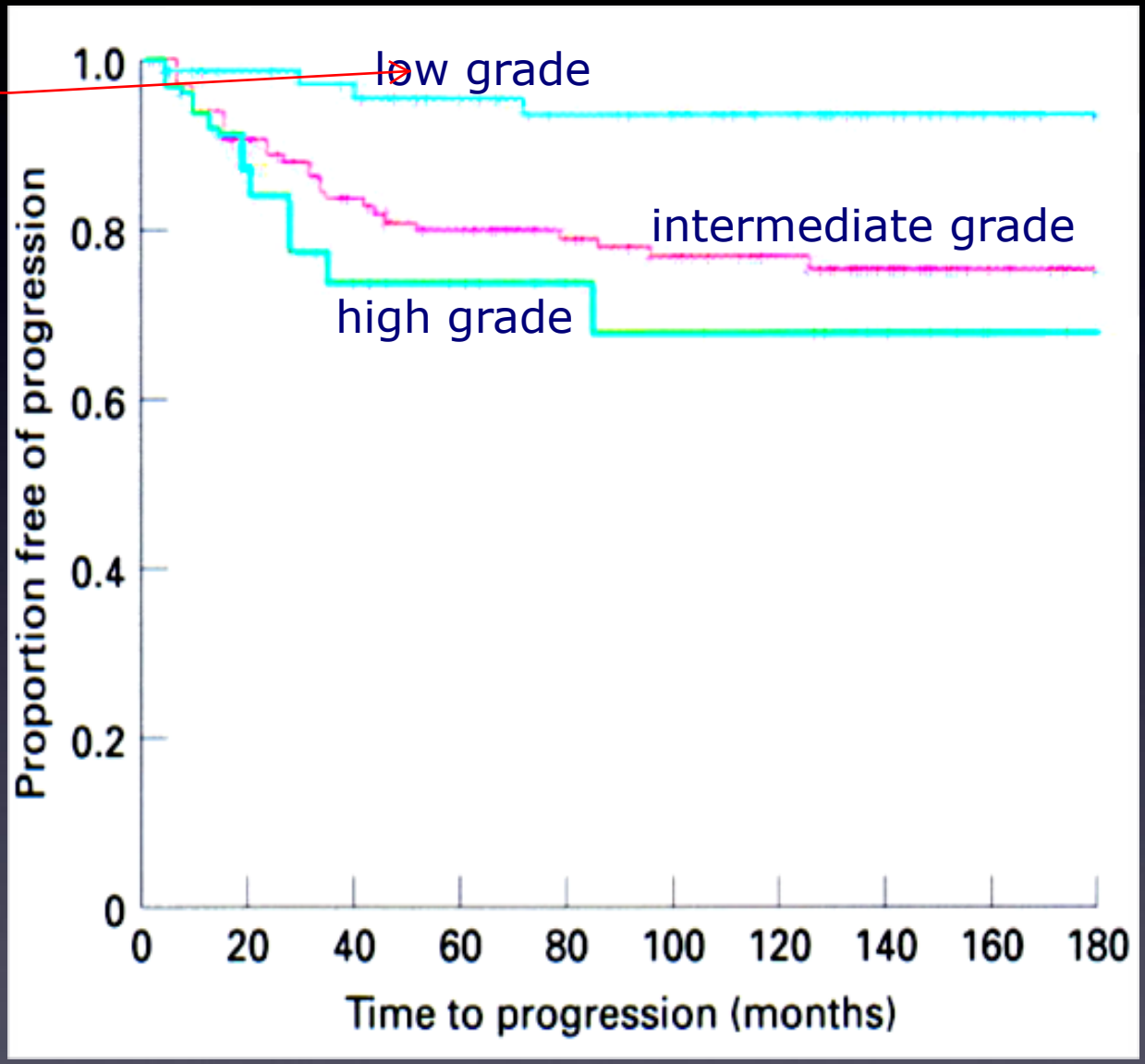
Superficial papillary urothelial neoplasia: recurrence



All grades of papillary neoplasia tend to recur. After a couple of years at least half of the ppl have had recurrence of the tumor.

Superficial papillary urothelial neoplasia: progression

Low grade (out to 15 years) well over half have recurred, but 5% have progressed



Progression (development of invasive component) is uncommon in these patients

Therapy for superficial papillary urothelial neoplasia

- Cystoscopic resection
- Periodic (lifelong) follow-up
  - Urine cytology
  - Cystoscopy
- Intravesical therapy
- Partial cystectomy for high-grade tumors

Alluded to on previous slide. Keep snipping the papillae out.

Routine for urologist to give single dose of mitomycin (intravesically) following cystoscopic resection of a papillary urothelium neoplasm. This pushes out the time to recurrence.

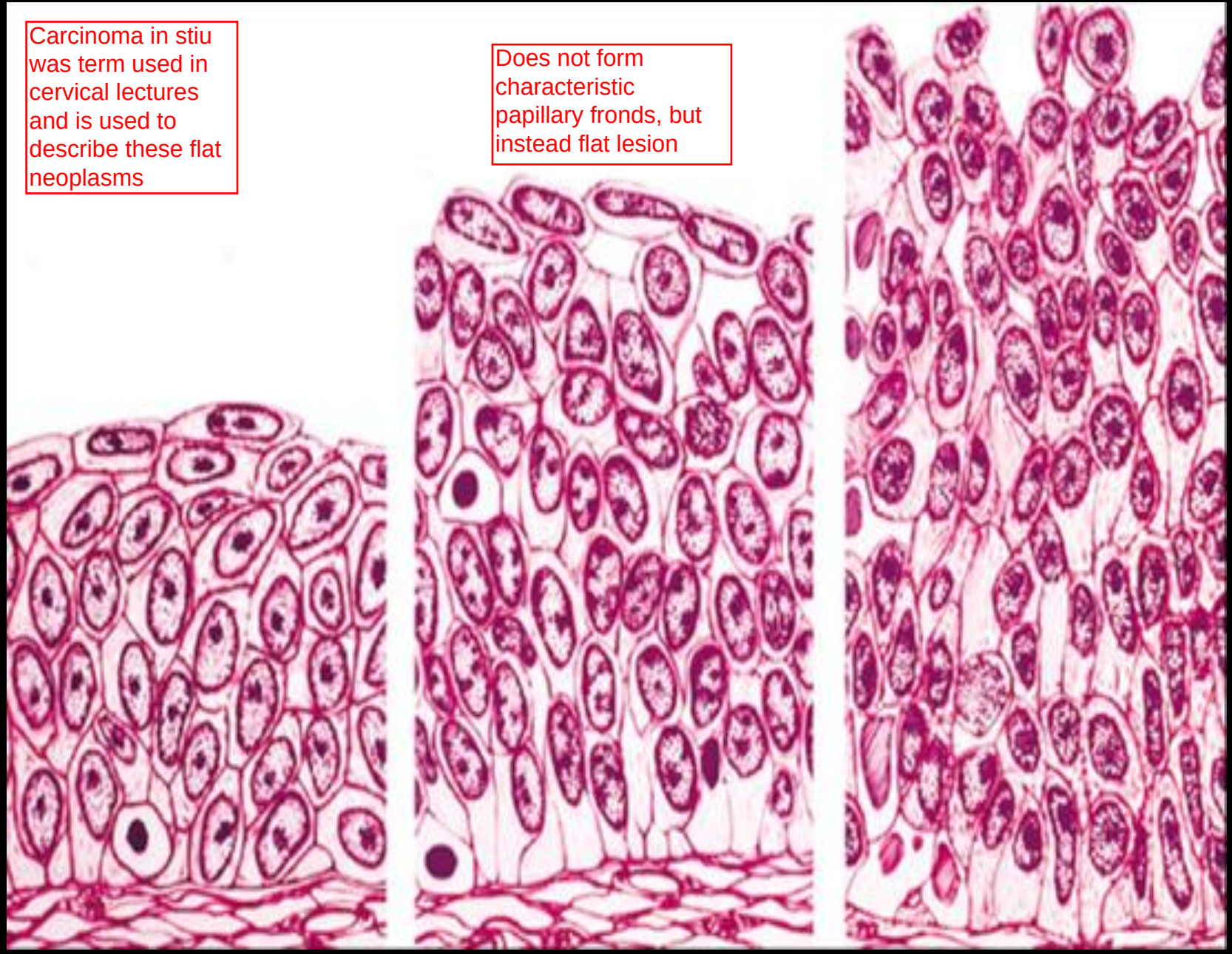
Bladder-sparring surgery is not really done

So ... we have two histological types. The papillary ones that we just discussed, and here we have the "flat" ones. These are rather aggressive.

Superficial “flat” urothelial neoplasia

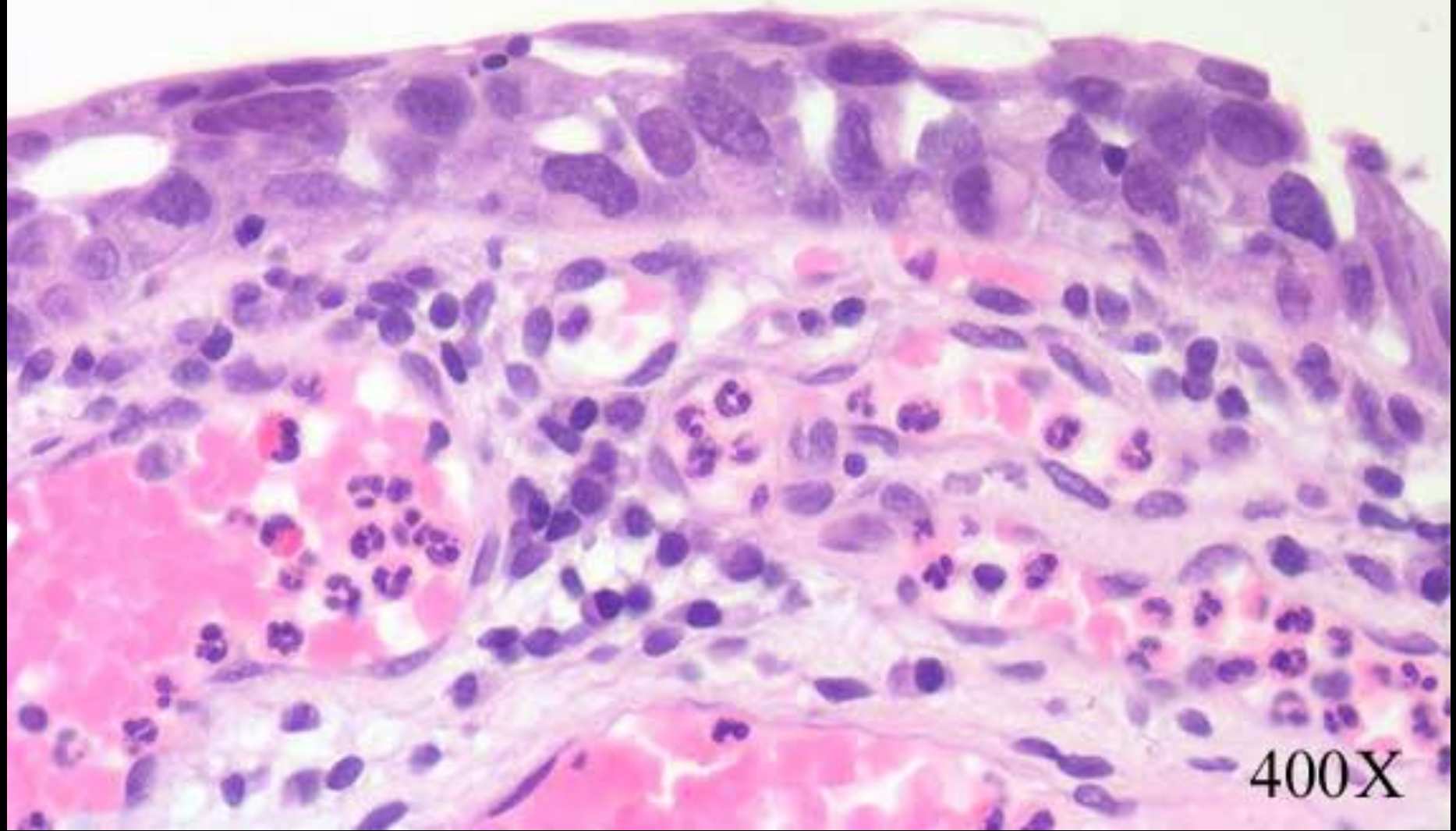
Carcinoma in stiu was term used in cervical lectures and is used to describe these flat neoplasms

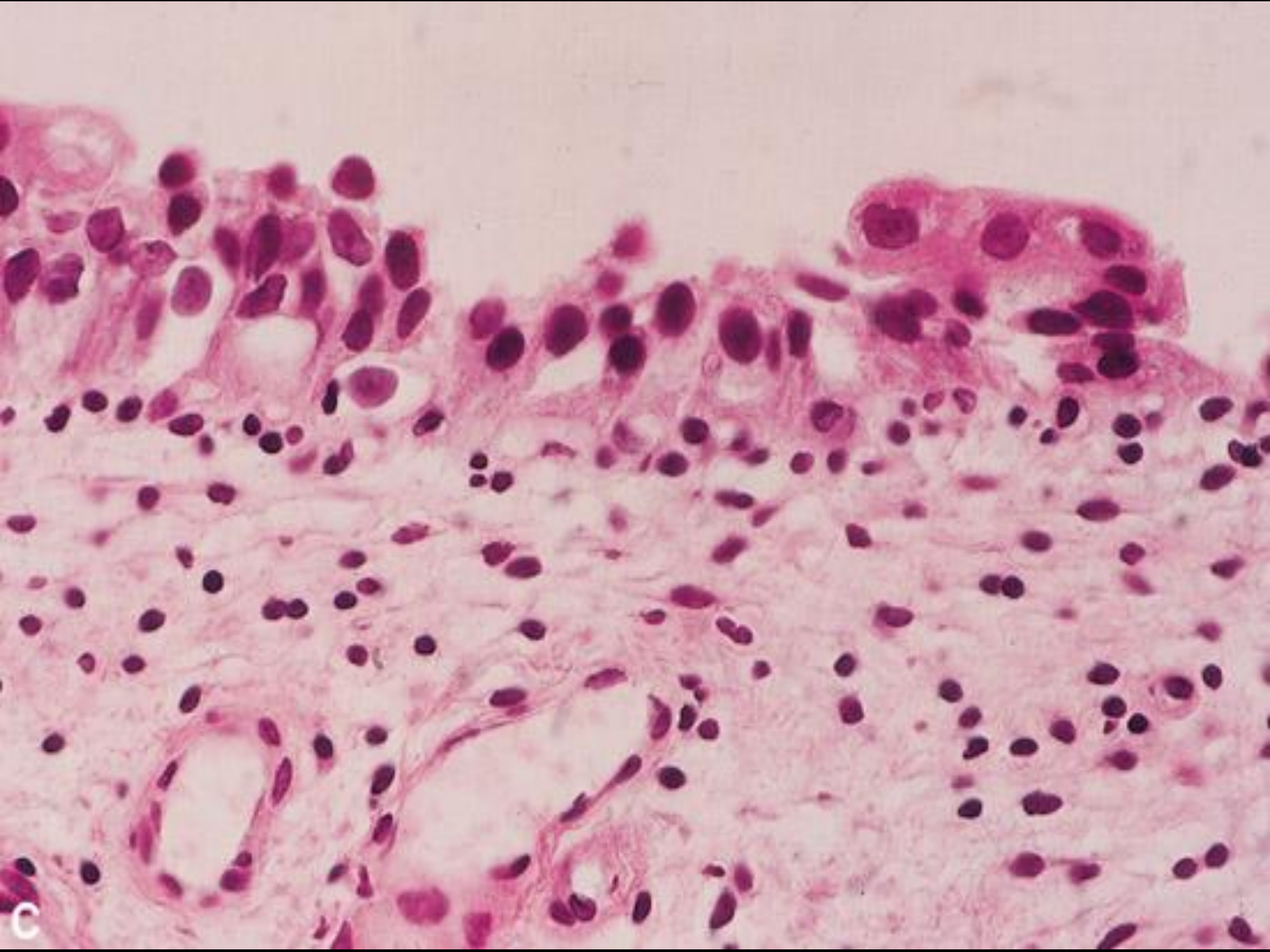
Does not form characteristic papillary fronds, but instead flat lesion



Atypia Dysplasia CIS

Carcinoma in situ of the bladder. It does not form papillae, but has nasty looking cytologically atypical cells, nuclear enlargement, and nuclear pleomorphism.

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Non-papillary ("Flat") urothelial neoplasia (urothelial carcinoma-in-situ): natural history

For "flat" urothelial neoplasia pre-invasive or in situ, the situation is very different than that for papillary neoplasm. Read the slide.

- Over 70% have diffuse disease at diagnosis
- Over 30% of CIS have undiagnosed invasive disease at cystectomy
- Over 5% dead of (metastatic) disease in 5 years after cystectomy for CIS

“Flat” urothelial neoplasia (urothelial carcinoma-in-situ): therapy

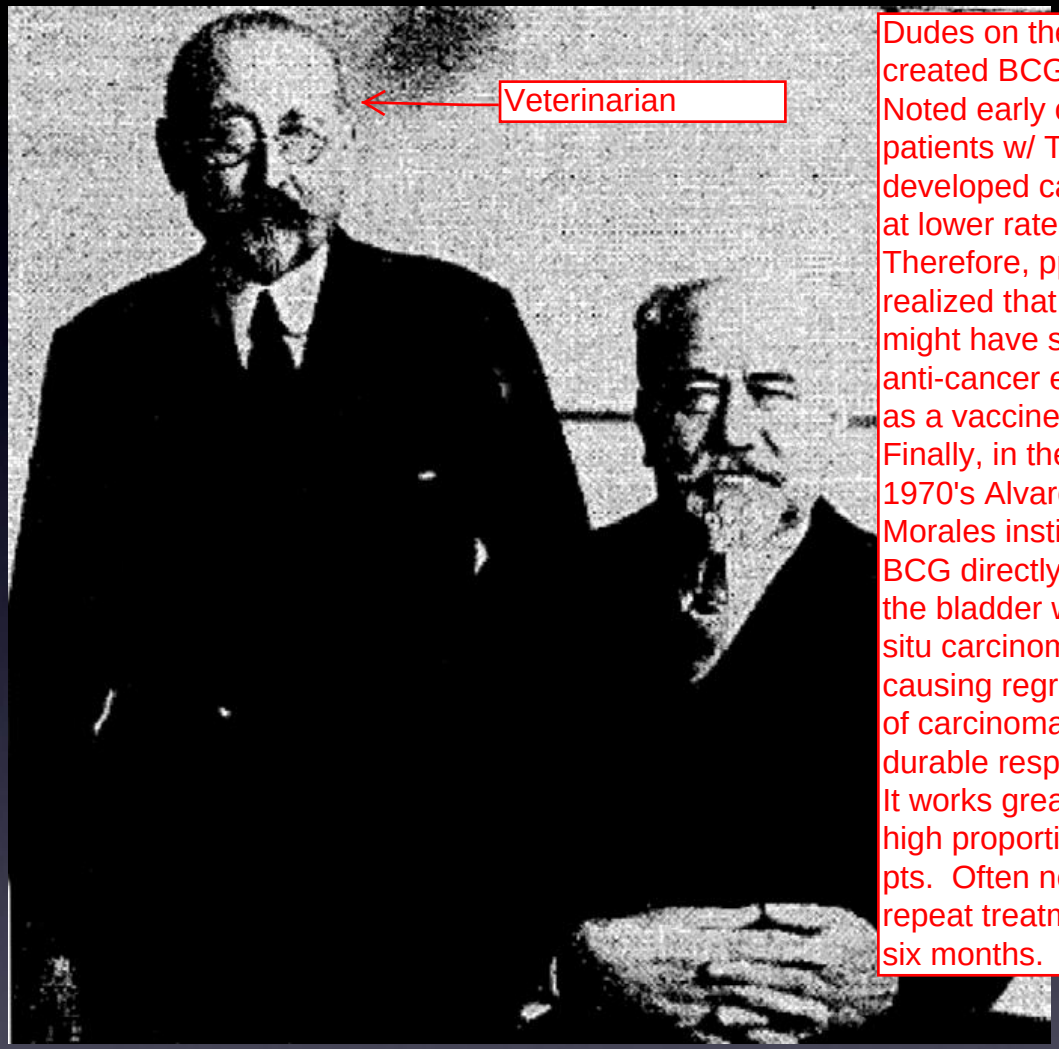
- BCG
  - >70% durable response in CIS
- Intravesical chemotherapy
  - Thiotepa/doxorubicin/mitomycin
- Interferon
- Cystectomy

immunotherapeutic agent. Attenuated form of mycobacterium TB.

BCG works not only for flat urothelium neoplasia, but also papillary type.

What do we do if we catch it early? We can biopsy, but can't resect b/c it's multifocal. Therefore use intravesical chemotherapy / immunotherapeutic agent or cystectomy.

cytotoxic



Guerin & Calmette

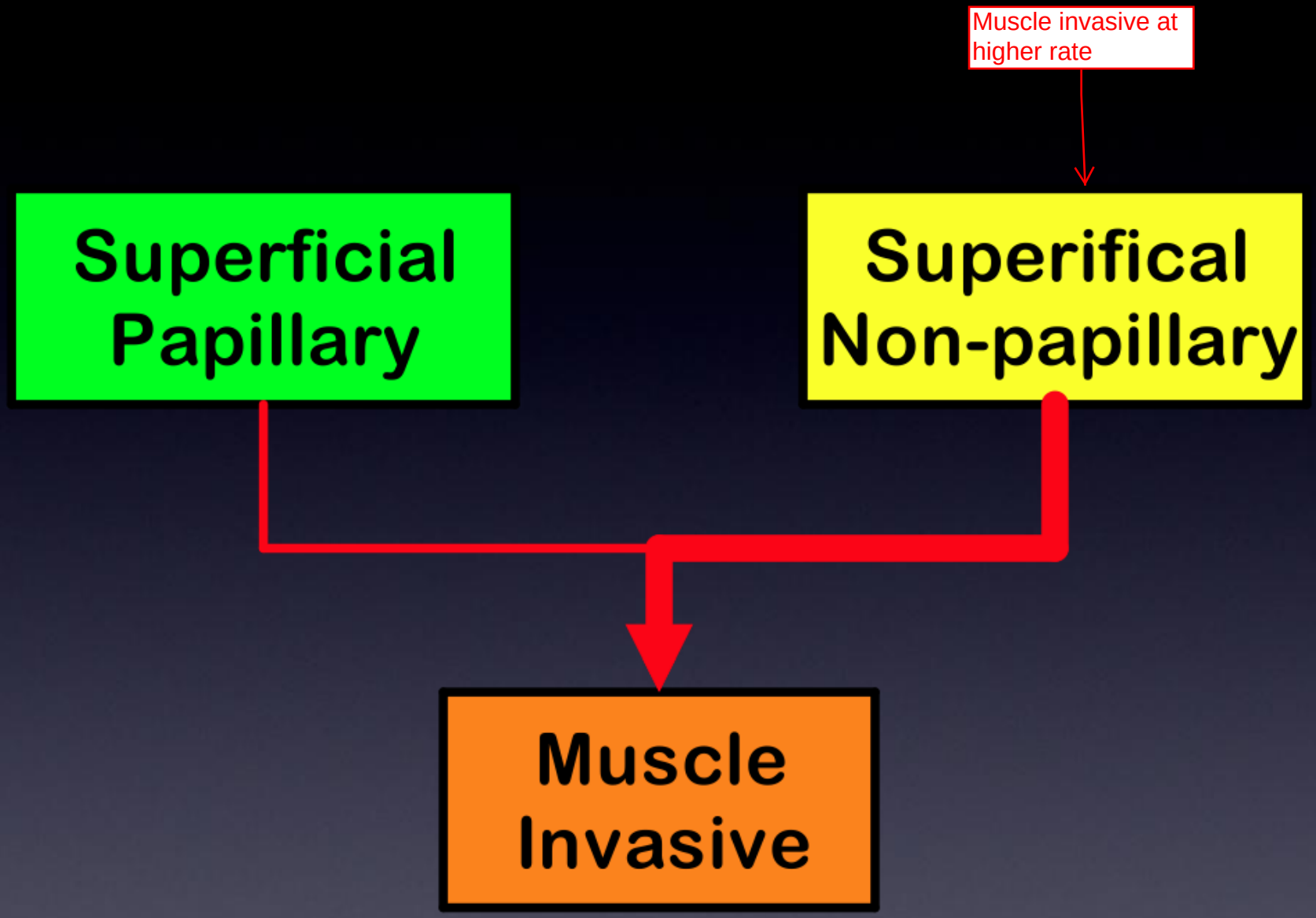
Dudes on the left created BCG. Noted early on that patients w/ TB developed cancer at lower rates. Therefore, ppl realized that BCG might have some anti-cancer effects as a vaccine. Finally, in the 1970's Alvaro Morales instilled BCG directly into the bladder with in-situ carcinoma causing regression of carcinoma and durable responses. It works great in high proportion of pts. Often need to repeat treatment in six months.

Spanish urologist from Canada.

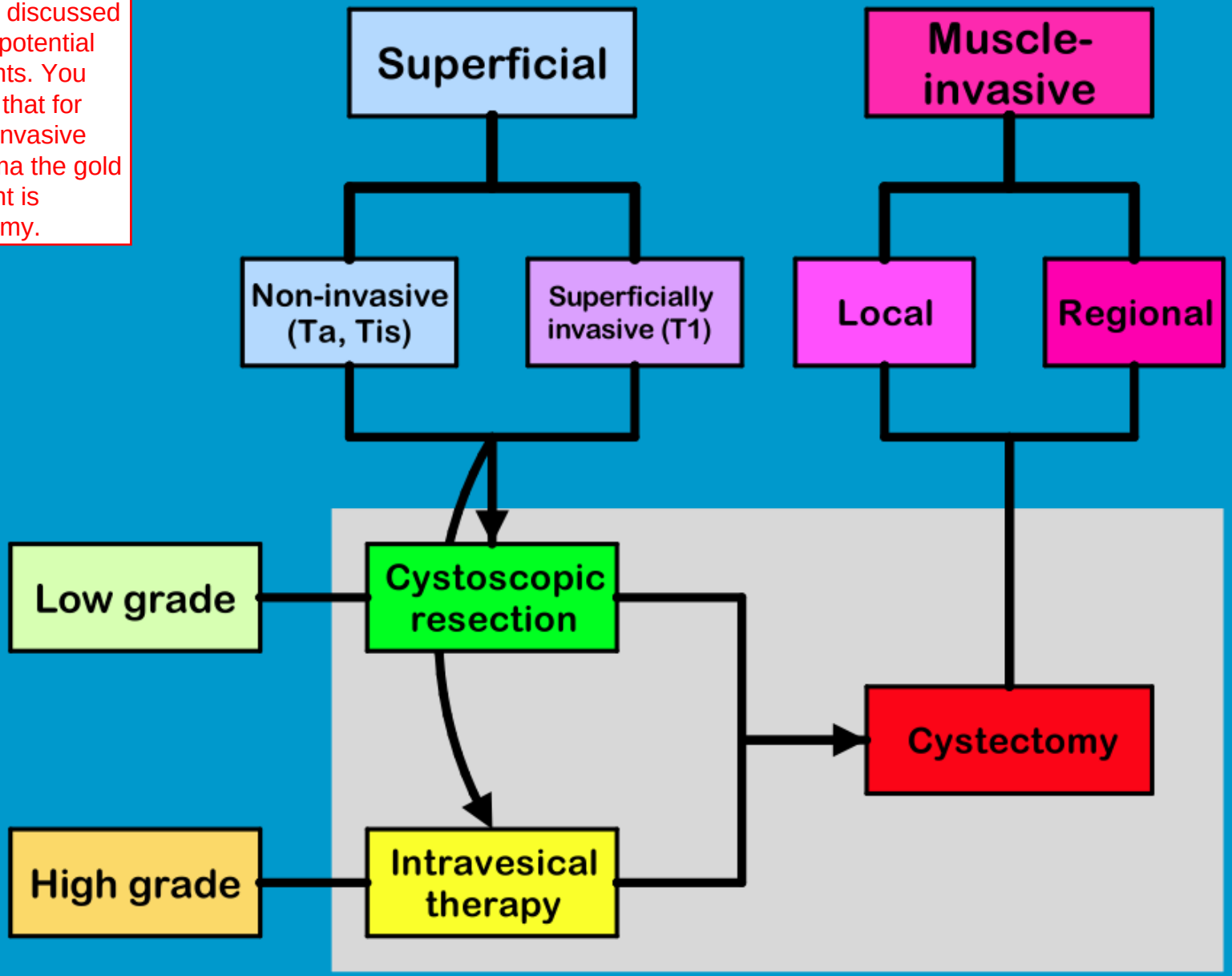
Alvaro Morales

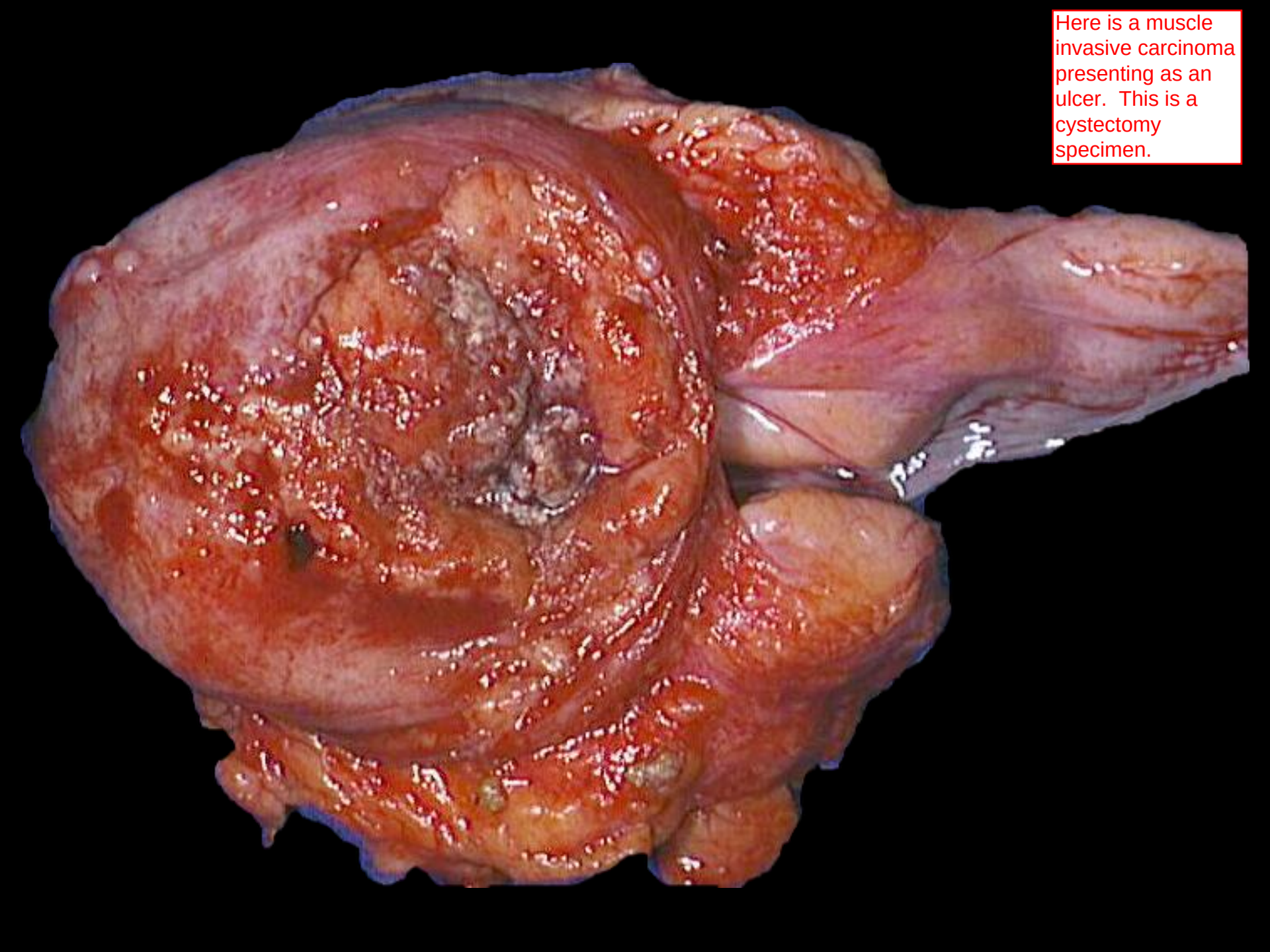
We discussed the lower grade papillary type and higher grade flat type. Either of these two types can evolve into muscle-invasive urothelial carcinoma (the flat kind at a higher rate). Once muscle involvement occurs it is very hard to distinguish papillary versus flat type.

Muscle-invasive urothelial carcinoma

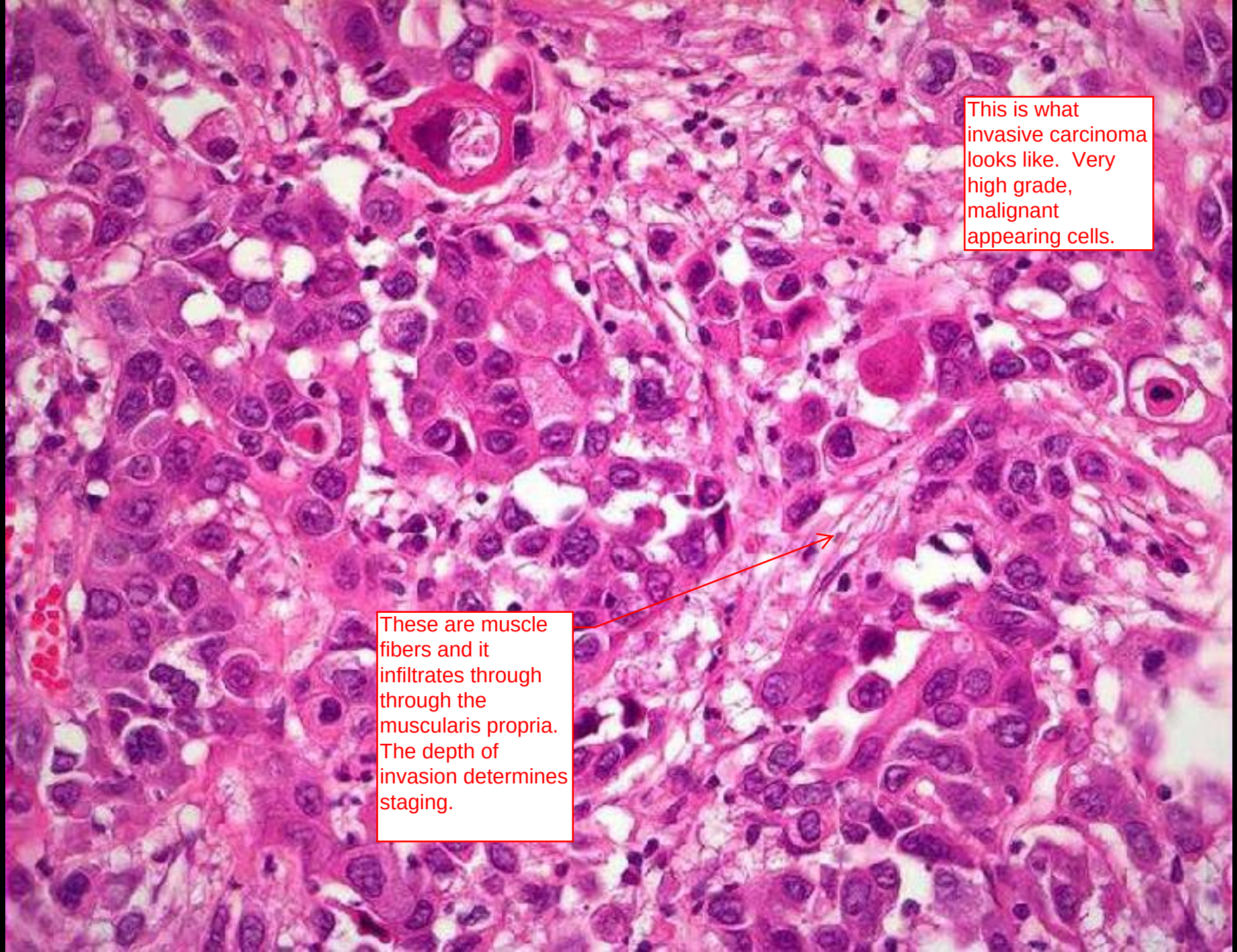

Muscle invasive at higher rate
Superficial Papillary
Superifical Non-papillary
Muscle Invasive

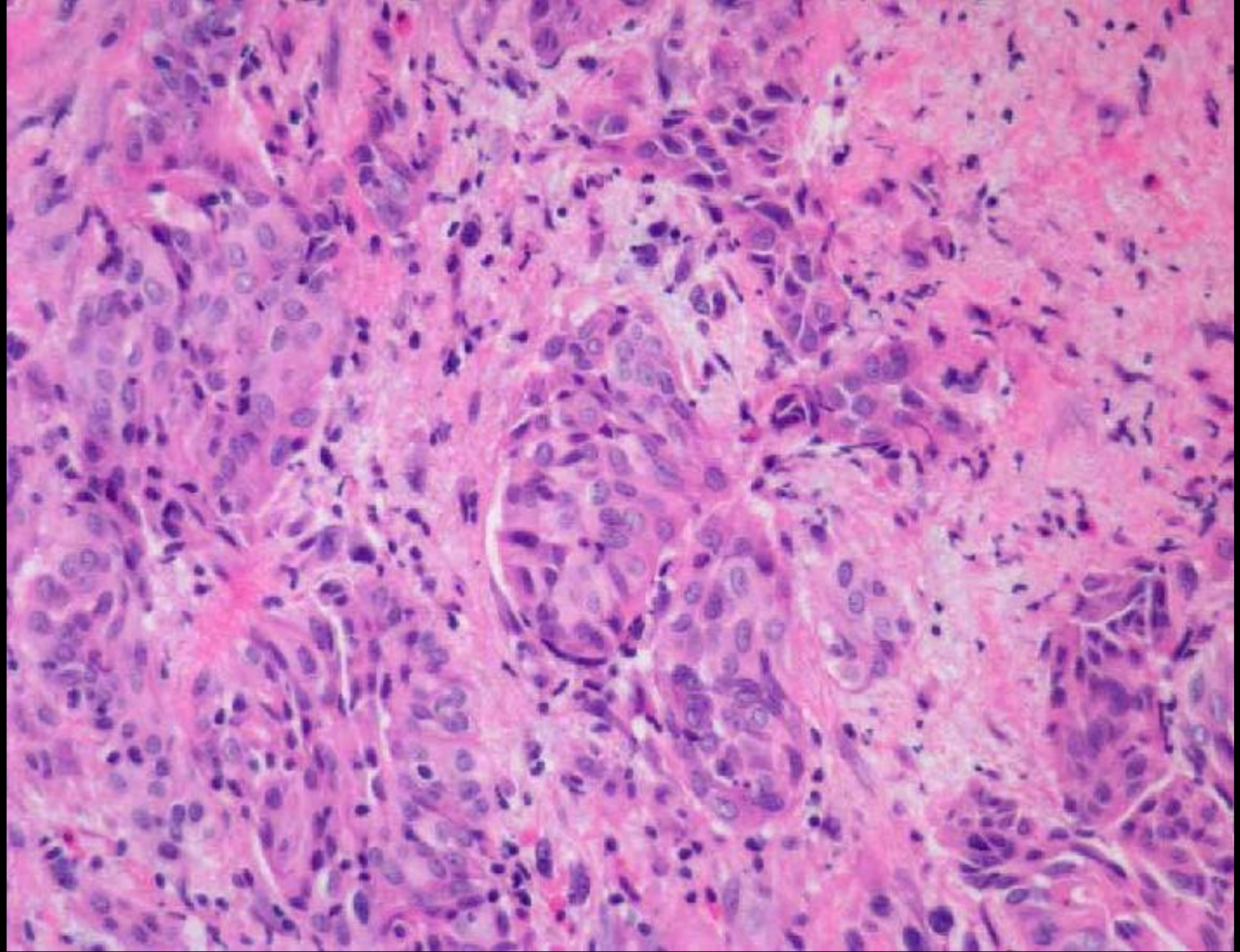
Visual flow chart of what we discussed and the potential treatments. You can see that for muscle invasive carcinoma the gold treatment is cystectomy.

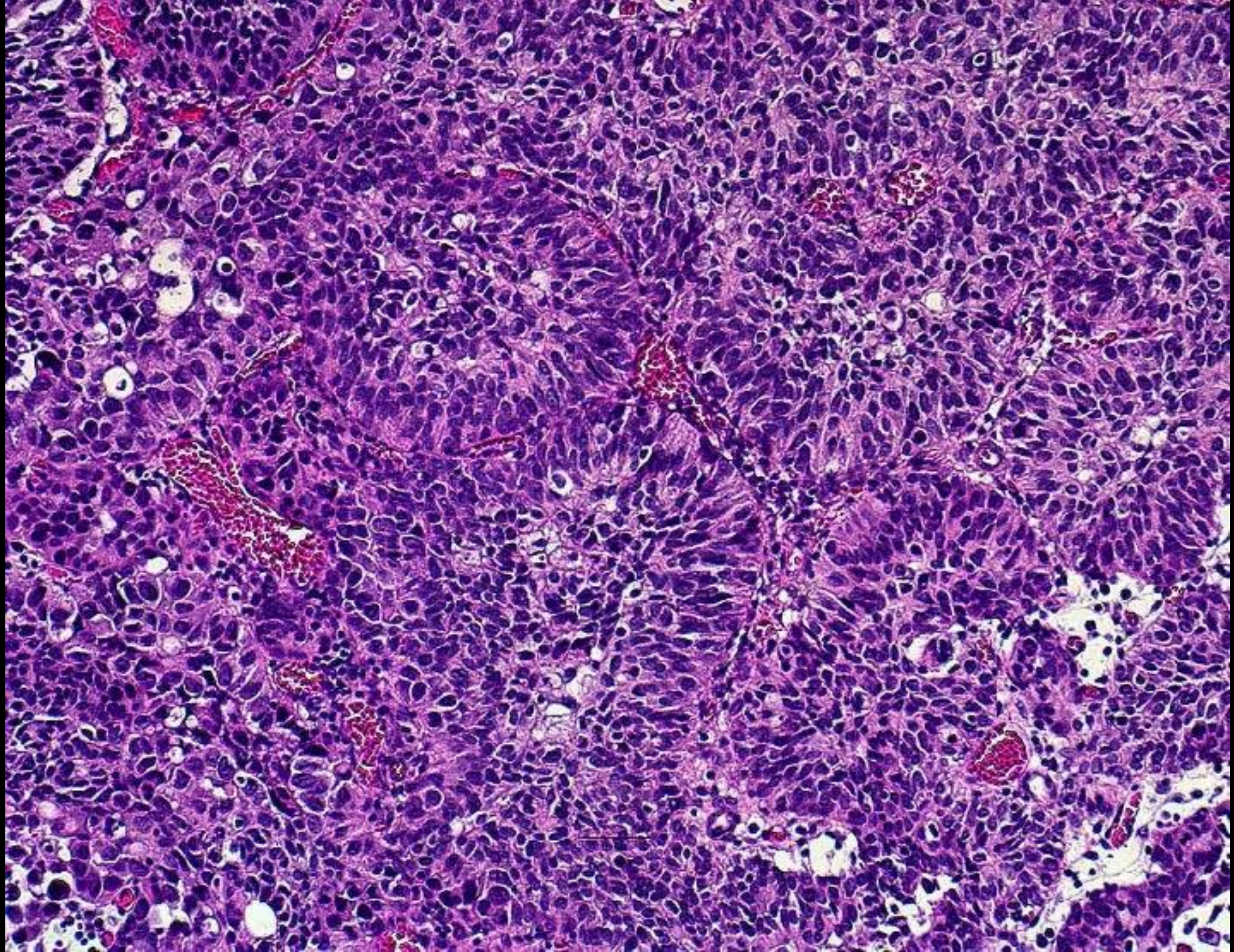



Here is a muscle invasive carcinoma presenting as an ulcer. This is a cystectomy specimen.


Here is an invasive carcinoma of the bladder that probably started as a papillary carcinoma and evolved into a large carcinoma which invades muscle.


This is what invasive carcinoma looks like. Very high grade, malignant appearing cells.
These are muscle fibers and it infiltrates through through the muscularis propria. The depth of invasion determines staging.

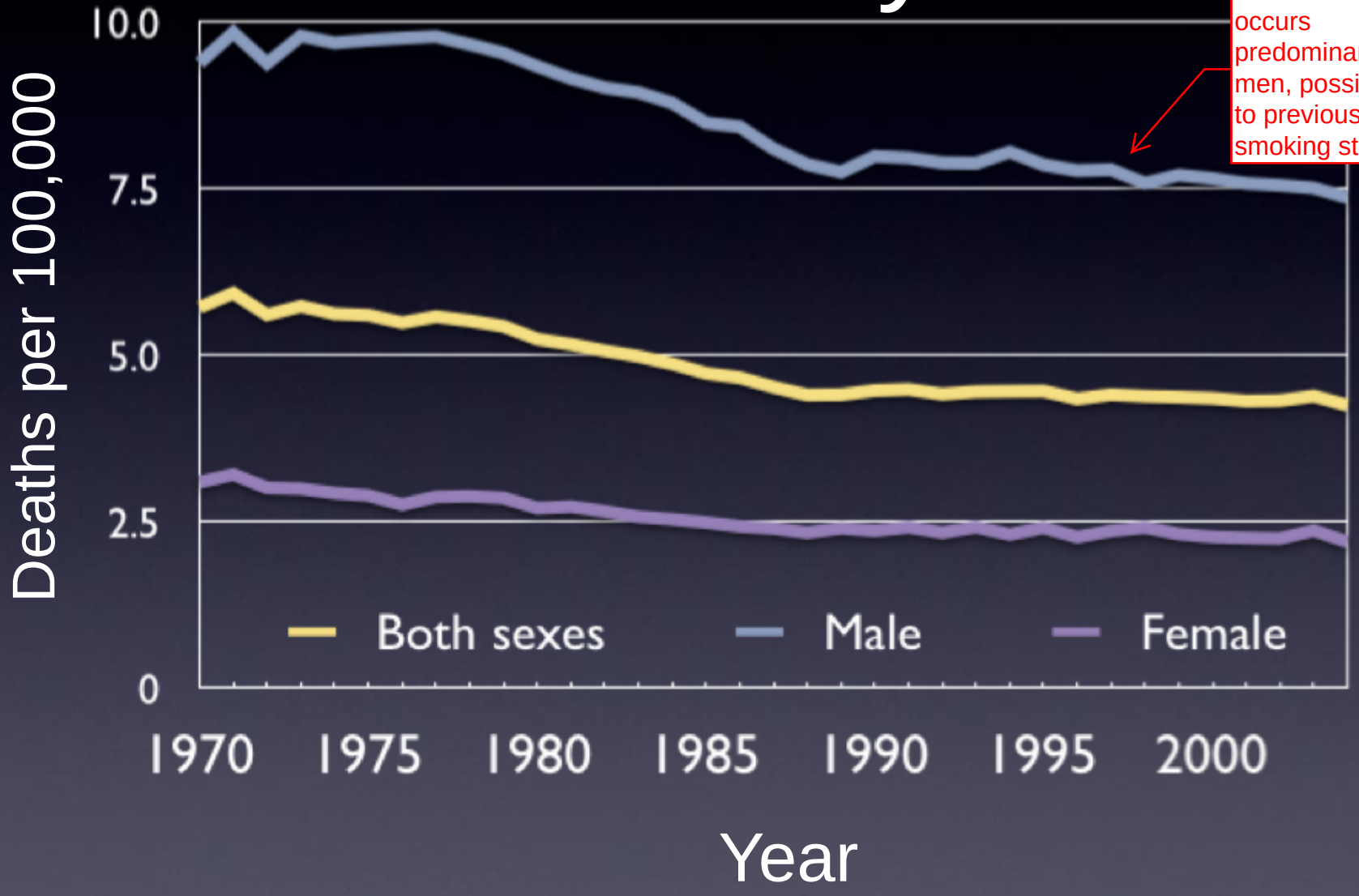




Bladder cancer mortality

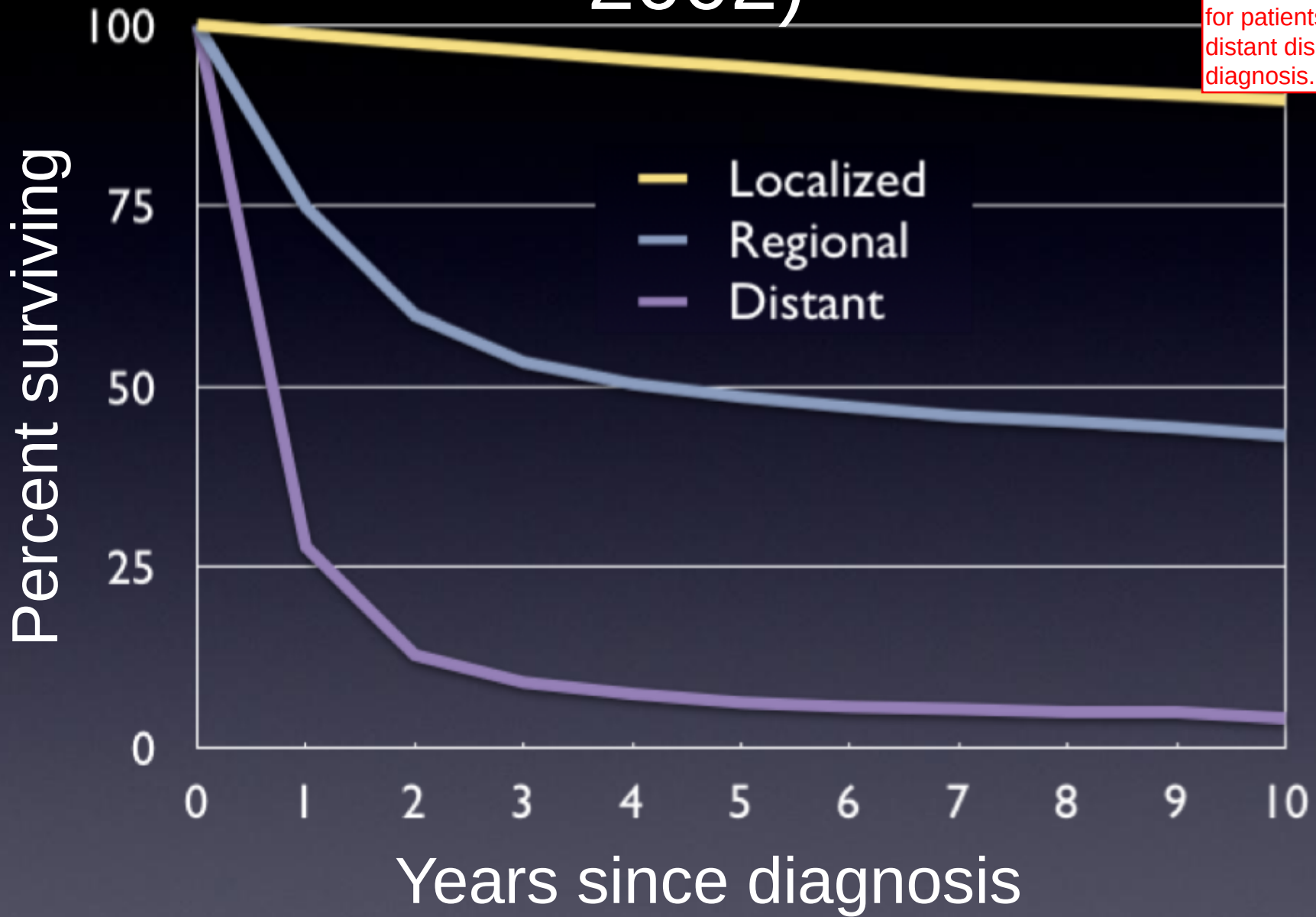
Over the years the mortality has been decreasing due to better chemical hygiene and better diagnosis.

Bladder cancer occurs predominantly in men, possibly due to previous smoking statistics



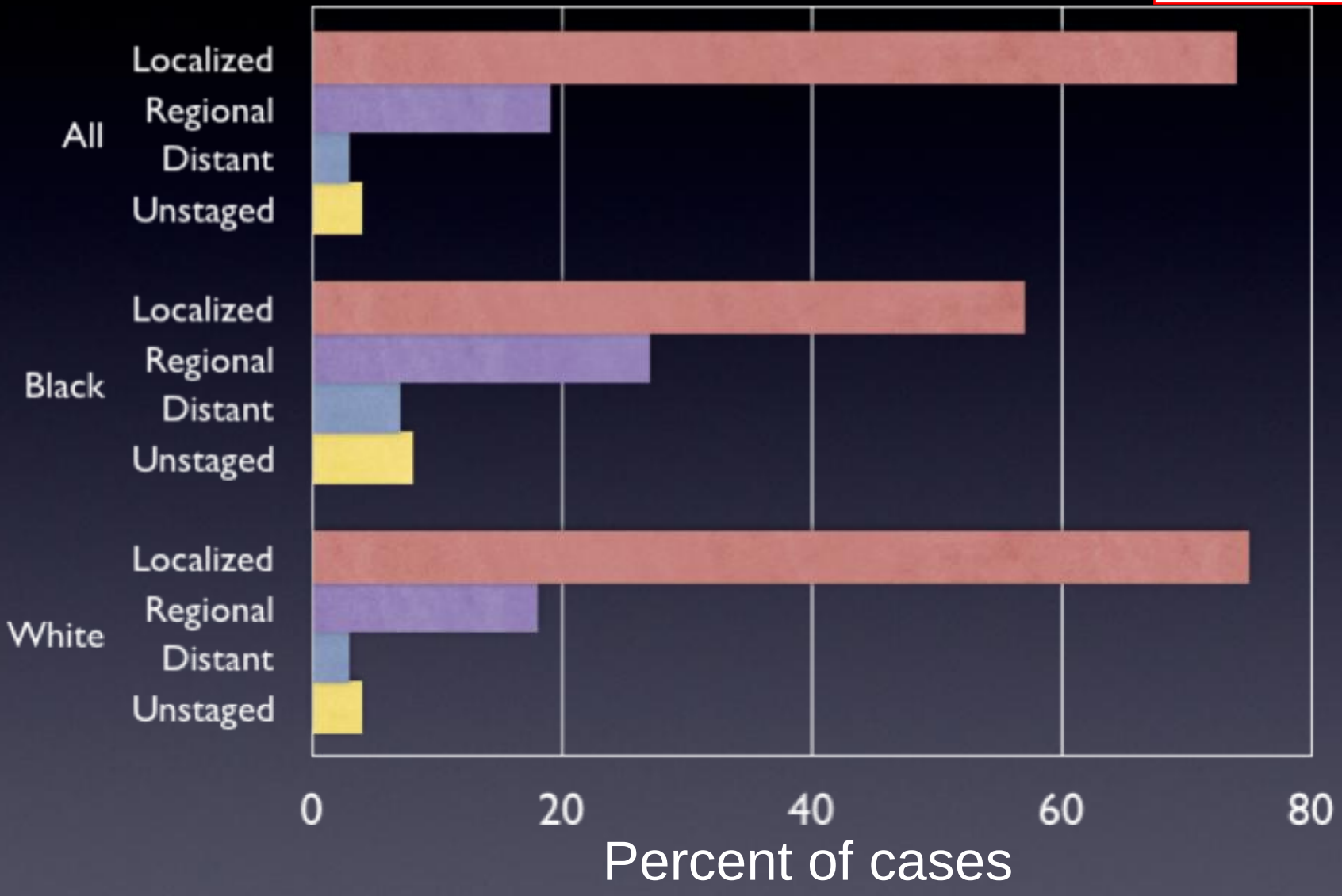
Bladder cancer survival (1988-2002)

Survival is great for low grade papillary disease and dismal for patients with distant disease at diagnosis.



Bladder cancer stage distribution (1988-2002)

Fortunately most are diagnosed at time when it is localized. Good alarm is the hematuria.



Therapy for invasive urothelial carcinoma

- Radical cystectomy

Therapy for invasive urothelial carcinoma (gold standard) is radical cystectomy.

- Partial cystectomy
  - Transurethral resection

Should be called bladder sparring. They resect as much tumor as possible via the transurethral approach and then the person gets systemic and intravesical therapy.

- Chemotherapy
  - MVAC (methotrexate +

Deleted on bottom of slide: MVAC (methotrexate + vinblastine + adriamycin + cysplatin)