Practical diagnostic approach of bladder tumors

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A few abbreviations

- UBC : urothelial bladder carcinoma
- TURB : transurethral resection of bladder
- MIBC : muscle invasive bladder cancer
- NMIBC : non muscle invasive bladder cancer

Outline

- Normal features in bladder
- Natural history of UBC
- Diagnosis and prognosis of UBC on TURB
- Histological subtypes of UBC
- Differential diagnosis of UBC
- Prognosis features on cystectomy

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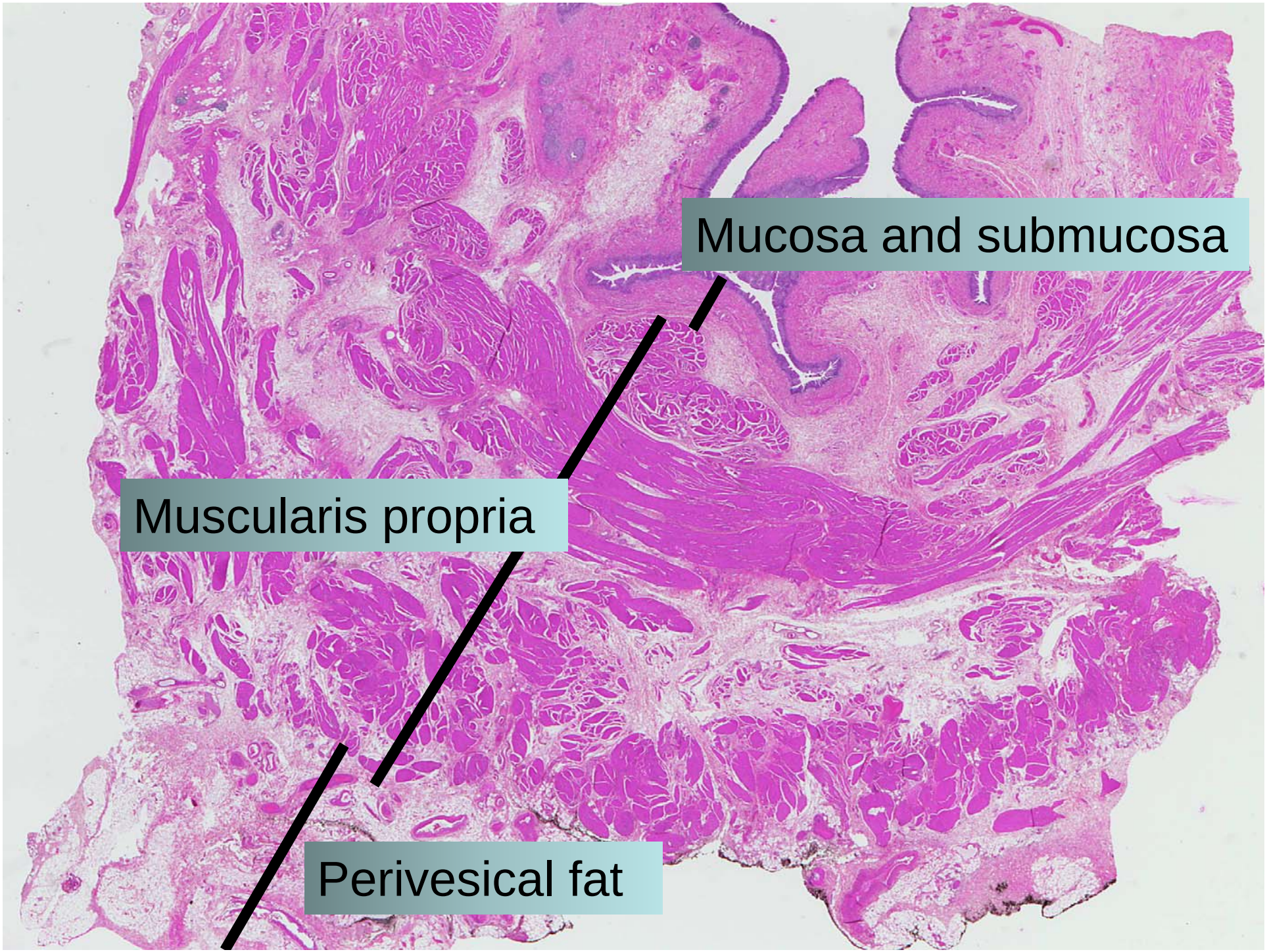
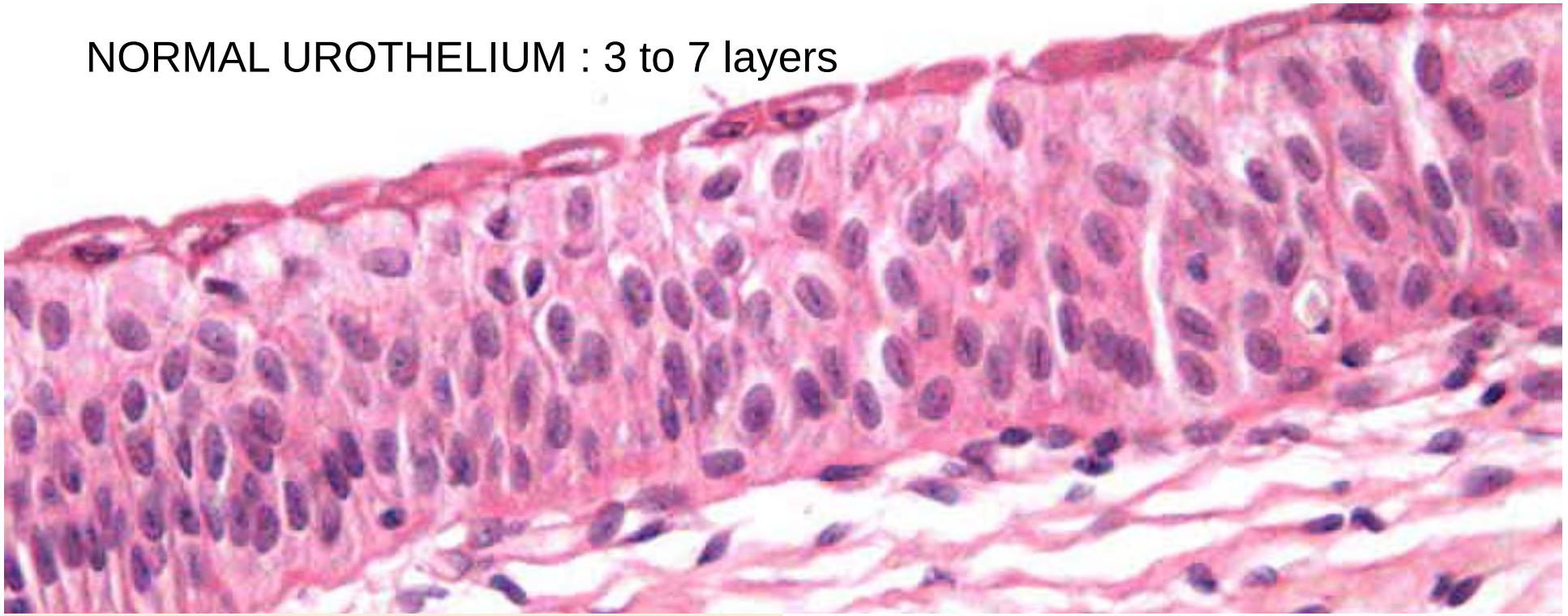
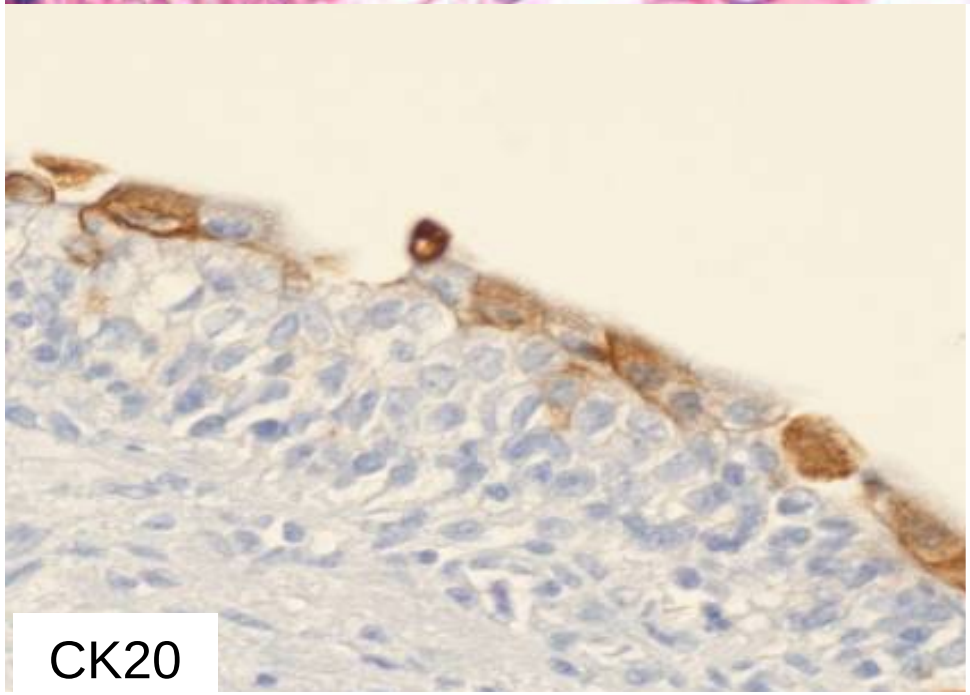
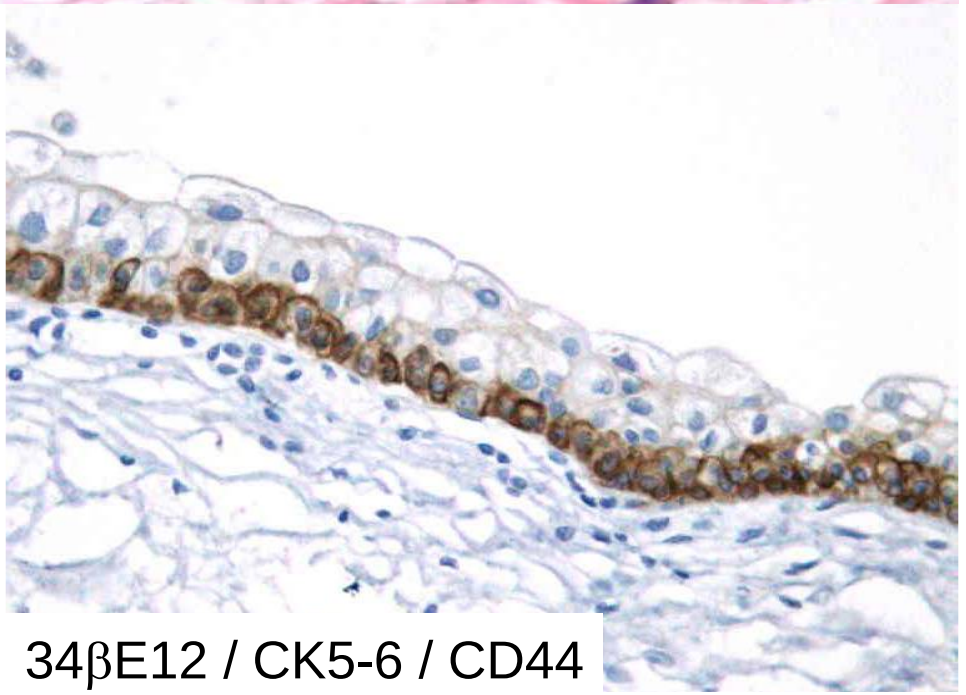

Mucosa and submucosa
Muscularis propria
Perivesical fat

NORMAL UROTHELIUM : 3 to 7 layers



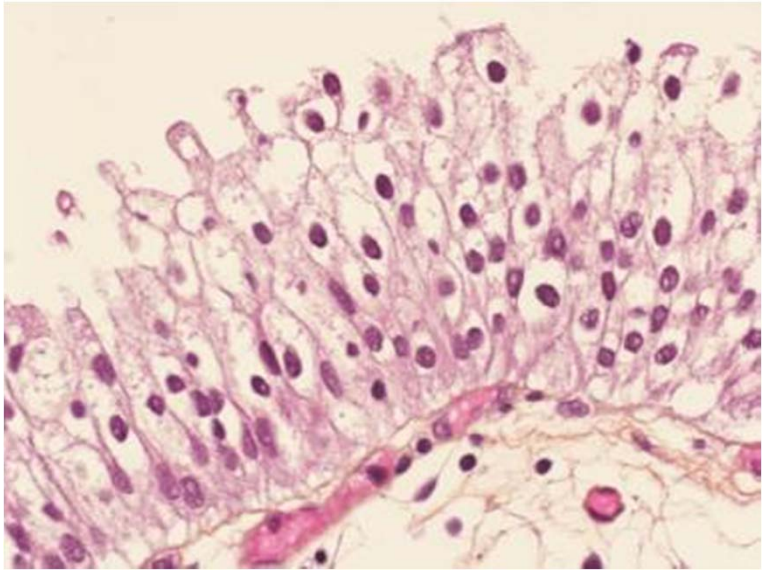


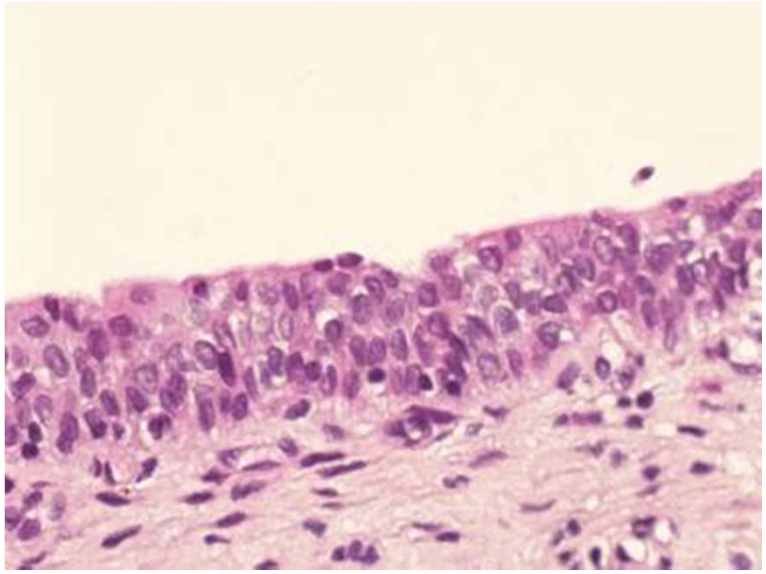
CK20



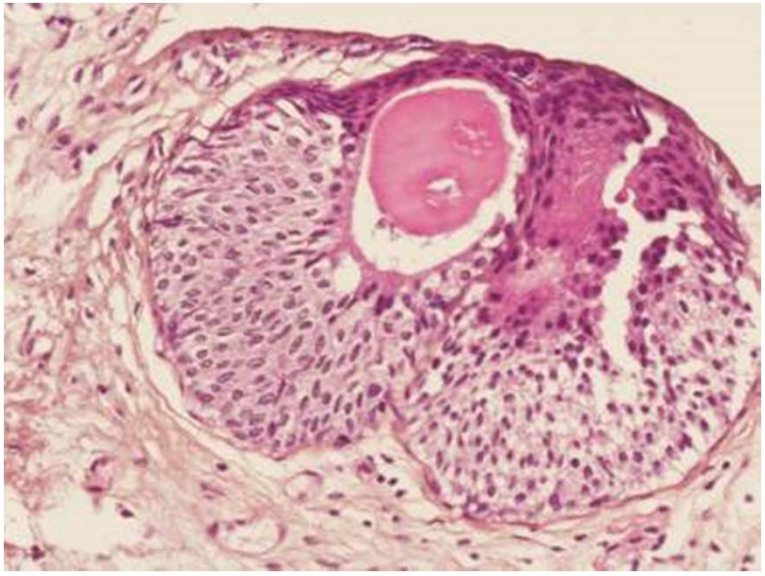
34βE12 / CK5-6 / CD44

Normal urothelium with variations !!

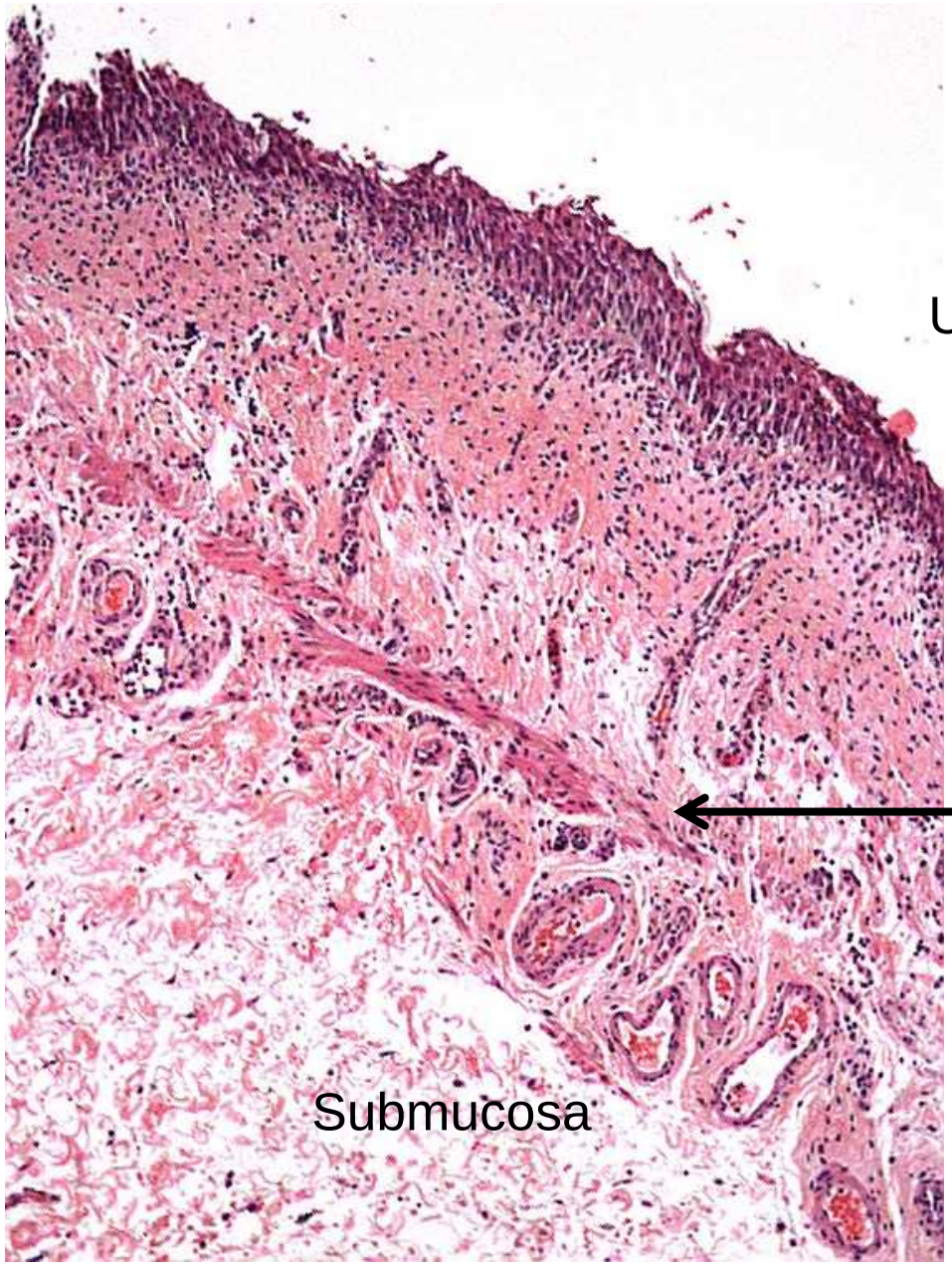




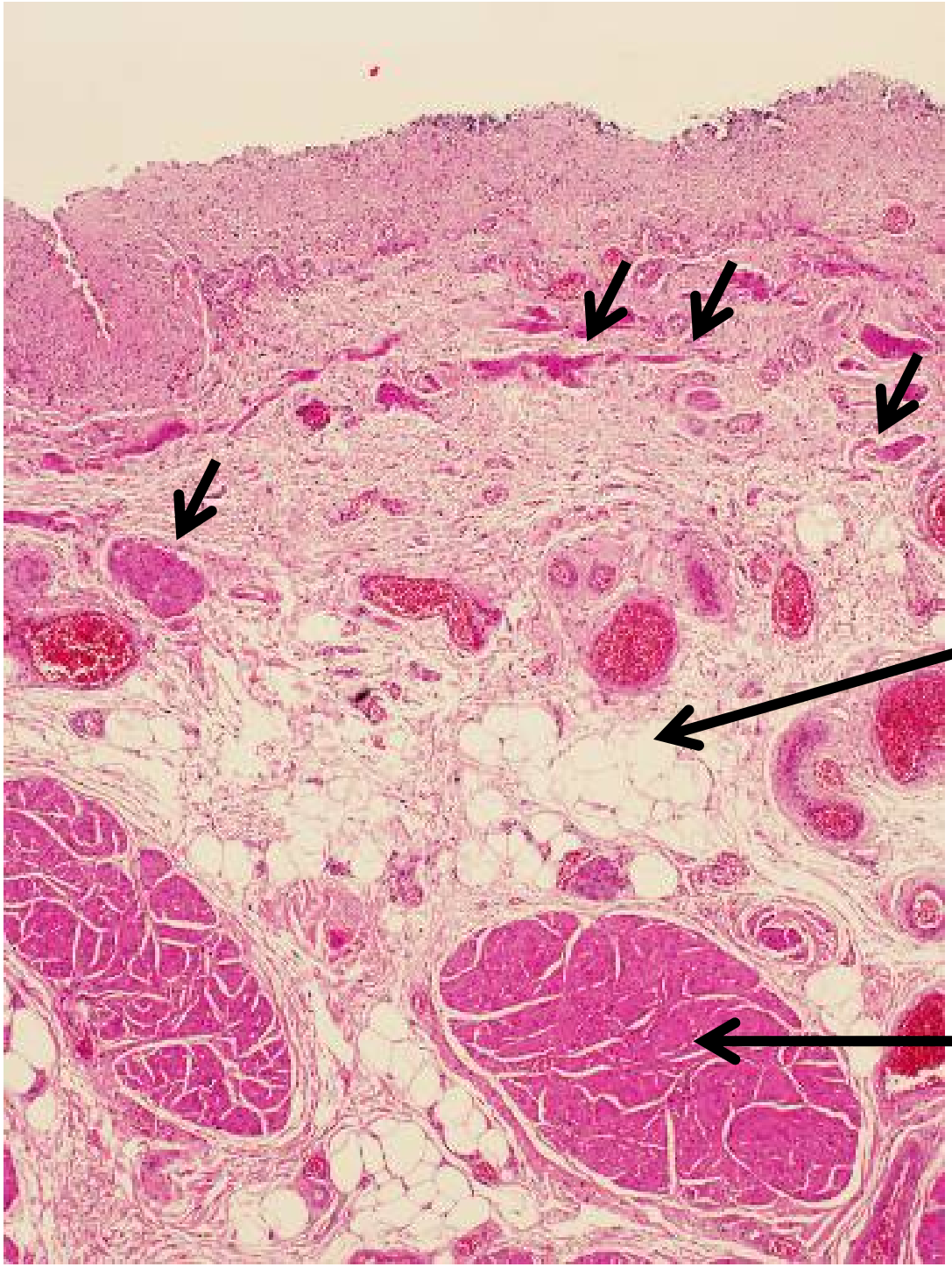
Von Brunn nest



Subepithelial connective tissue



Complete..... 3%
Discontinous... .20%
Scattered..... 71%
Absent..... 6%
frequently hyperplastic
in dome location



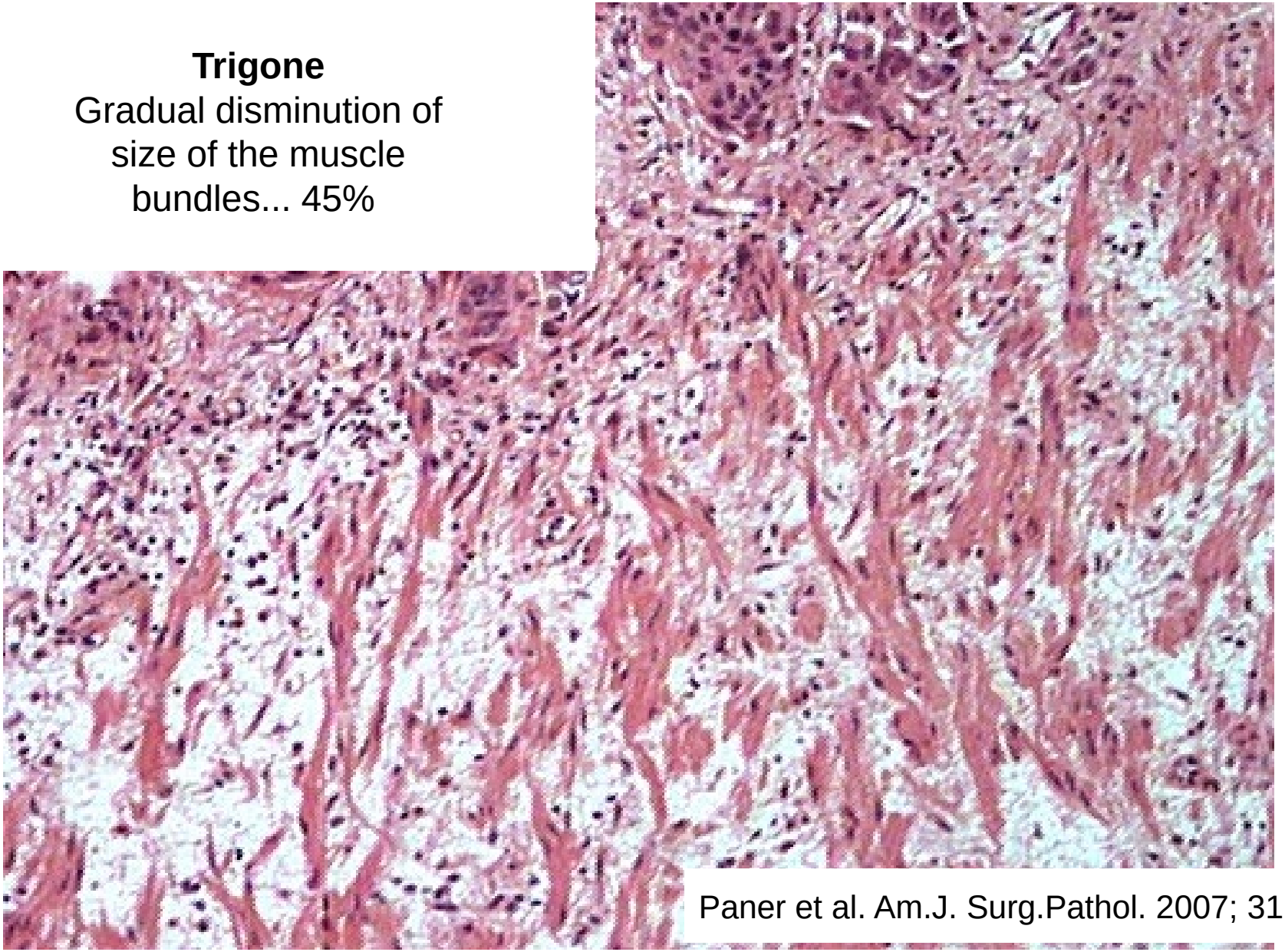
Muscularis mucosa

Fat tissue

Muscularis propria (Thick, dense bundles smooth muscle fibers)

Muscularis propia variations

Trigone
Gradual disminution of size of the muscle bundles... 45%



Paner et al. Am.J. Surg.Pathol. 2007; 31: 1420

Muscularis mucosae vs muscularis propria

The immunostaining by smoothelin or desmin is not discriminant enough to help in the distinction in difficult cases

Paner et al. Am. J. Surg. Pathol. 2009; 33: 91
Miyamoto et al. Am. J.- Surg. Pathol. 2010; 34: 418

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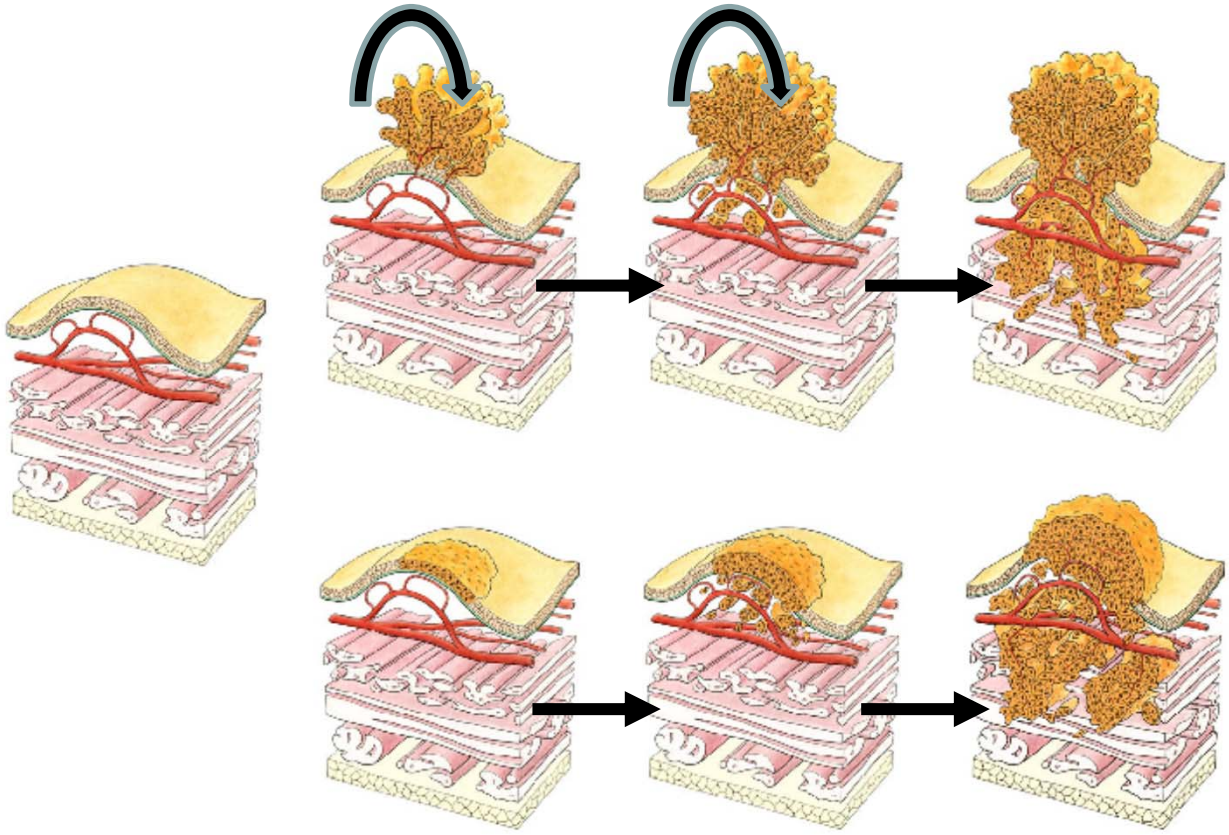
WHO 2004 bladder tumor classification

- Urothelial tumors
- Squamous tumors
- Glandular tumors
- Neuroendocrine tumors
- Melanocytic tumors
- Mesenchymal tumors
- Hematopoeitic tumors
- Secondary tumors

Urothelial tumor classification (WHO 2004)

- Non invasive urothelial tumors
  - Carcinoma in situ
  - Non invasive papillary urothelial carcinoma , high grade
  - Non invasive papillary urothelial carcinoma , low grade
  - Non invasive papillary urothelial low malignant potential tumor
  - Urothelial papilloma
  - Inverted papilloma
- Invasive urothelial tumors
  - subtypes



Non invasive tumors

Invasive tumors

Non muscle invasive bladder cancer NMIBC

Muscle invasive bladder cancer MIBC

Treatment of UBC after initial TURB depends on the estimated risk of progression

- MIBC : high risk of metastasis and specific death, treatment by radical cystectomy (unfrequently by radiotherapy and chemotherapy)

- NMIBC aggressive: significant risk of progression to muscle invasion and specific death, treatment by BCG (cystectomy can be proposed for T1 with high risk)

- NMIBC indolent: low risk of progression, recurrences treated by TURB

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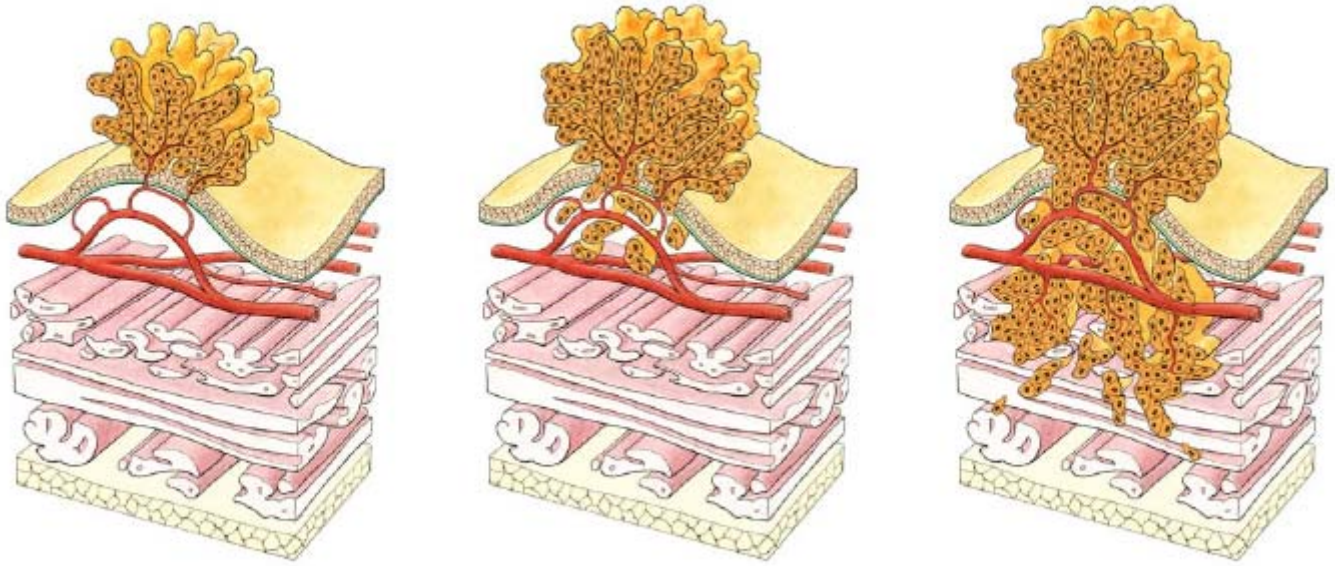
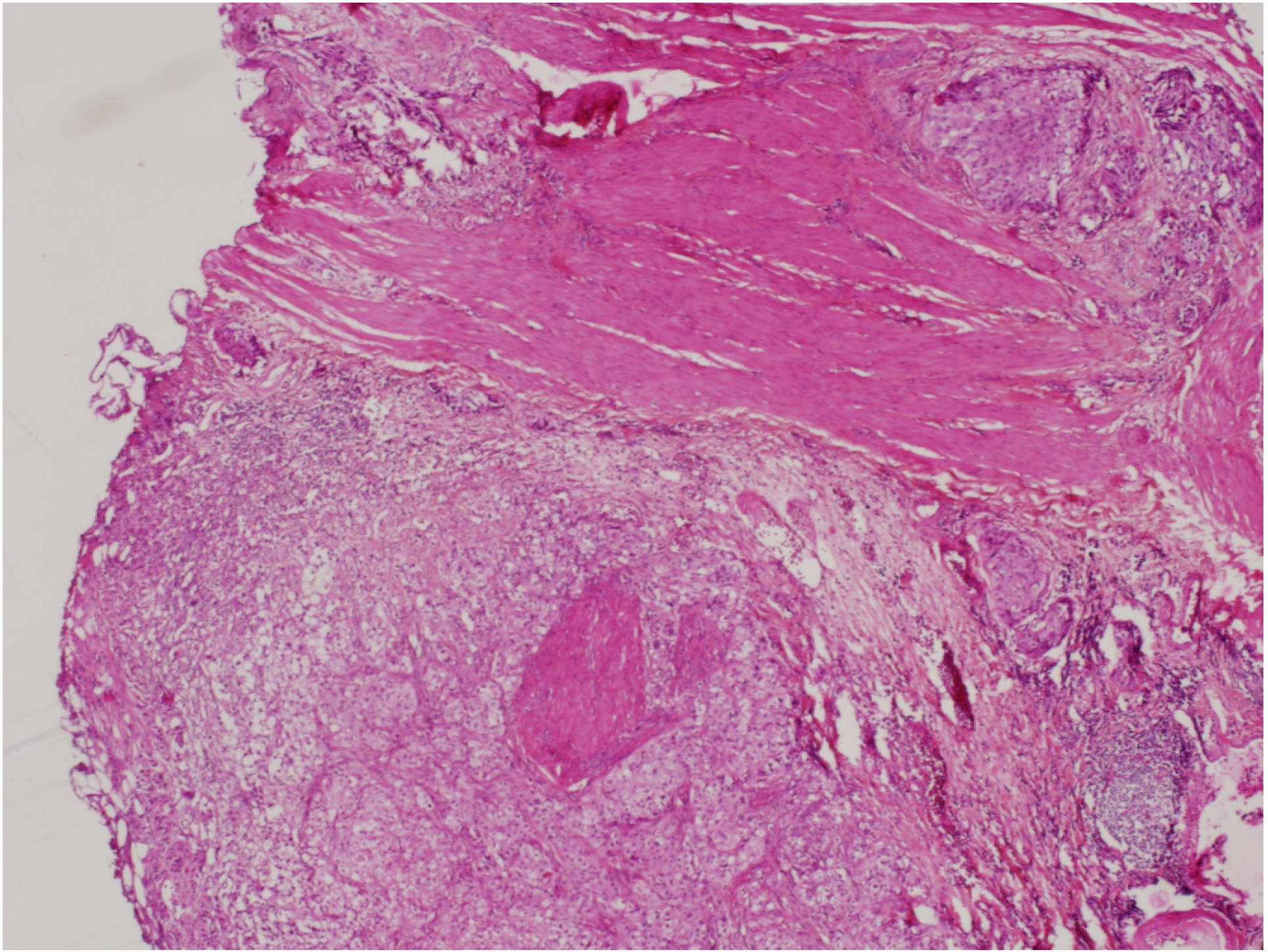
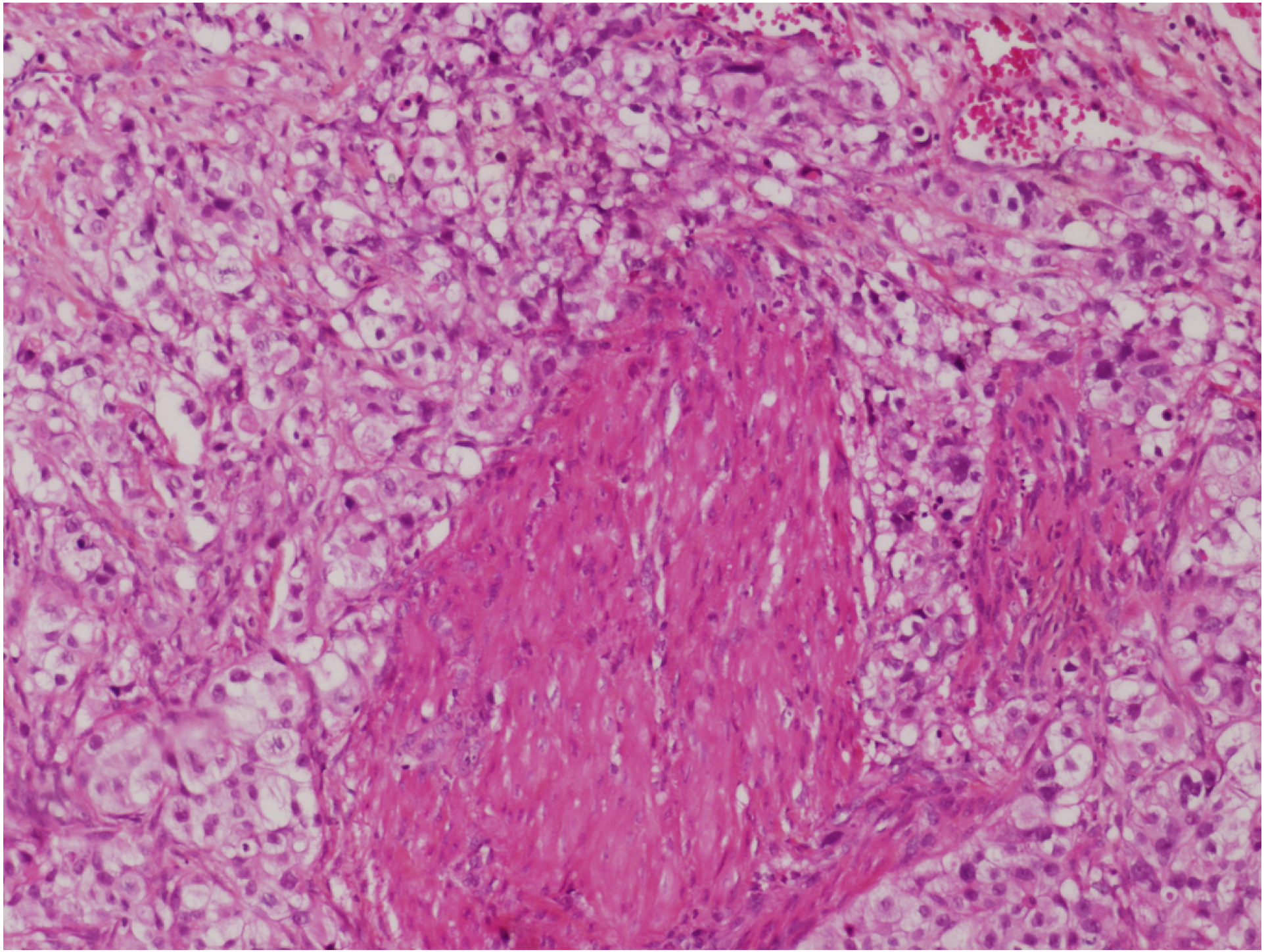
Eliminate muscle invasion, then determine Ta vs T1



Ta T1 T2

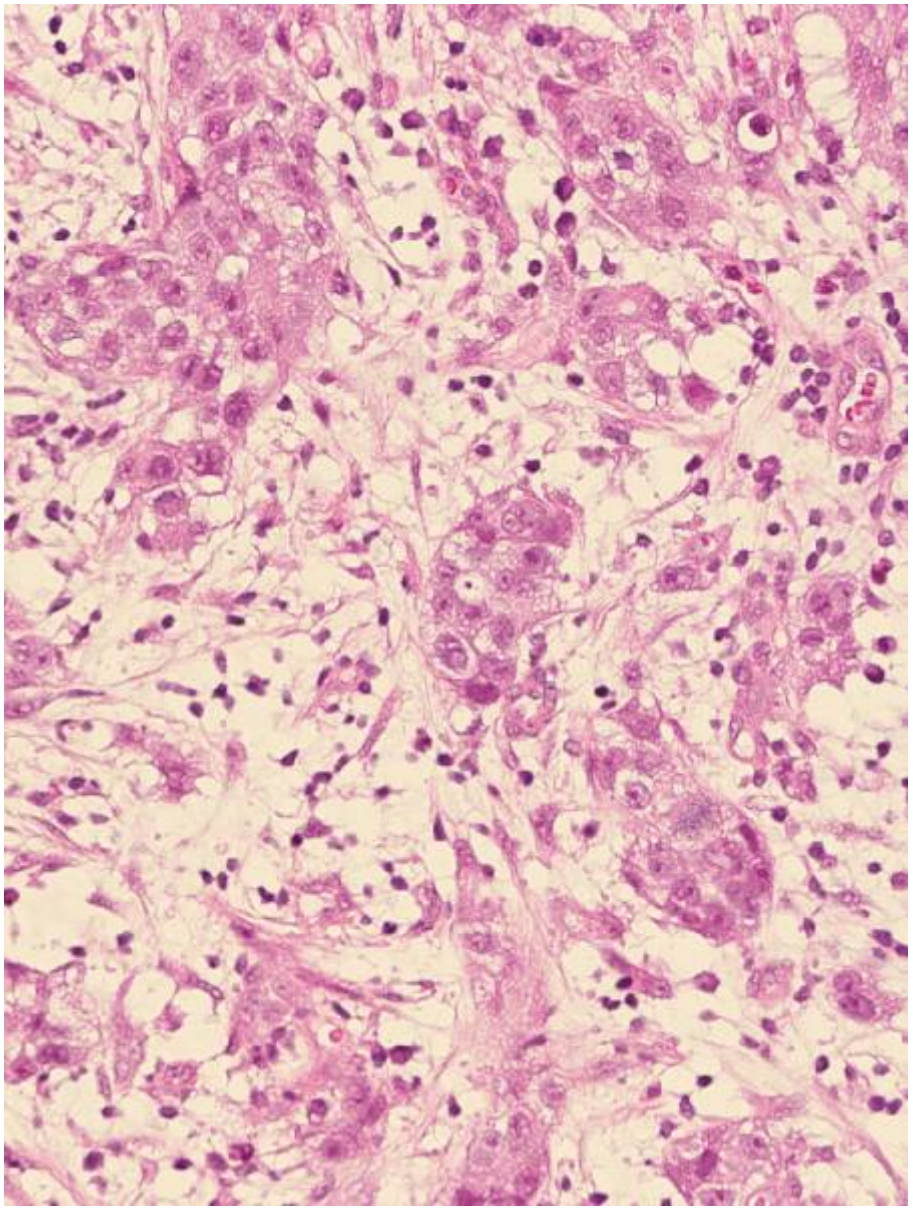
- The tumor stage is a major prognostic feature
- The presence or absence of muscle on TURB must be precised
- Pitfalls : sub- and overstaging





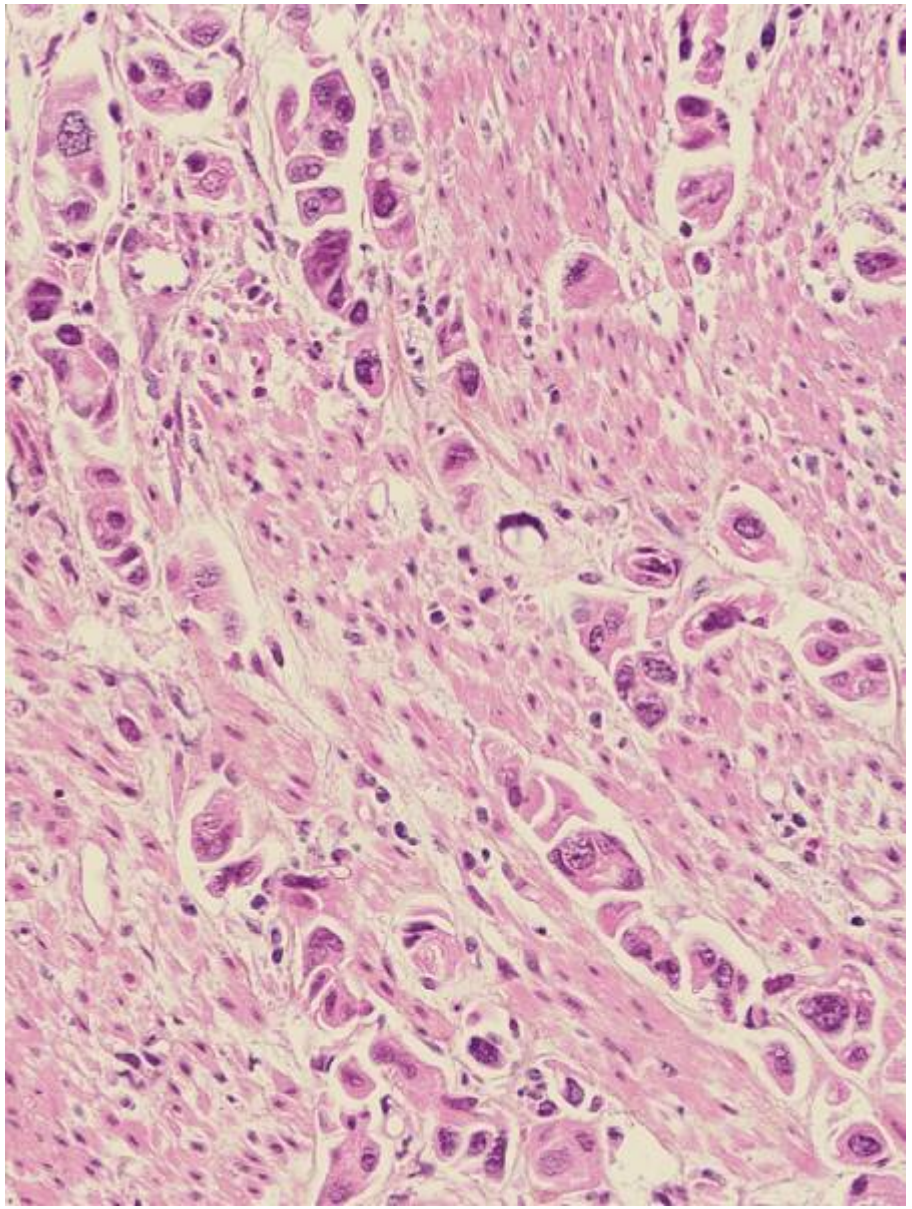
Muscle not observed

T1b at least



Muscle present

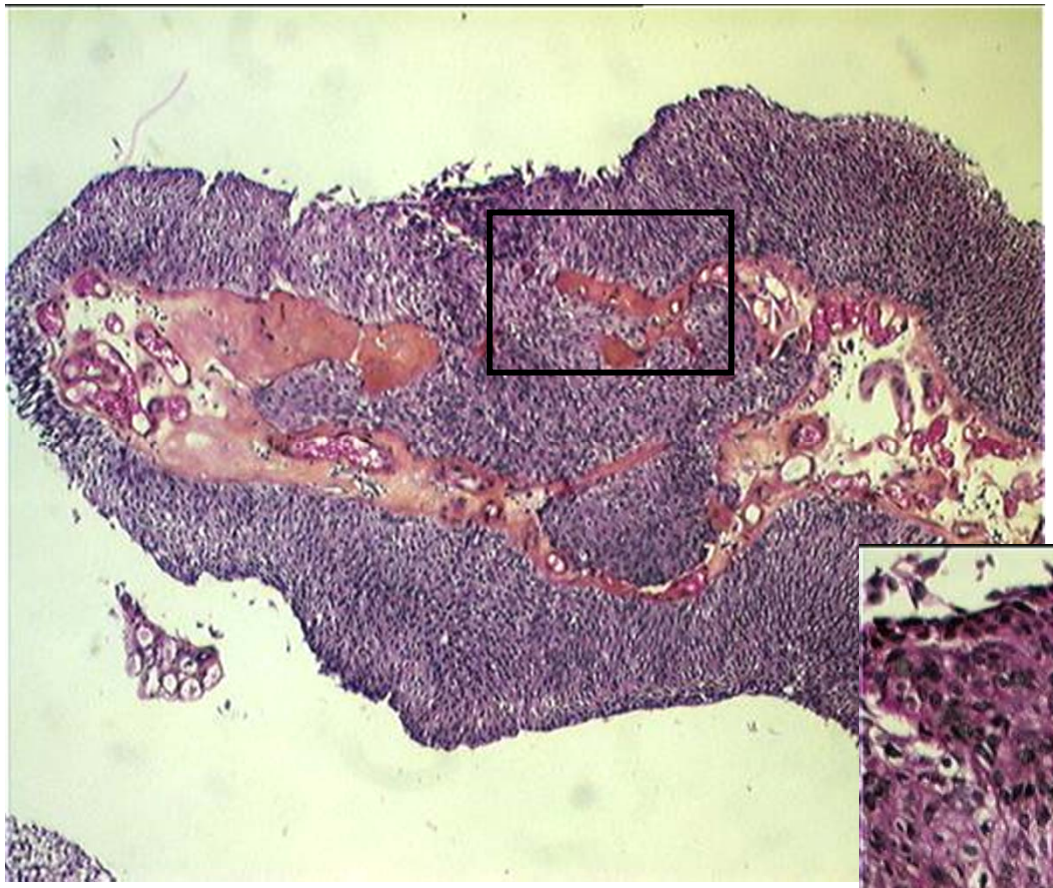
T2



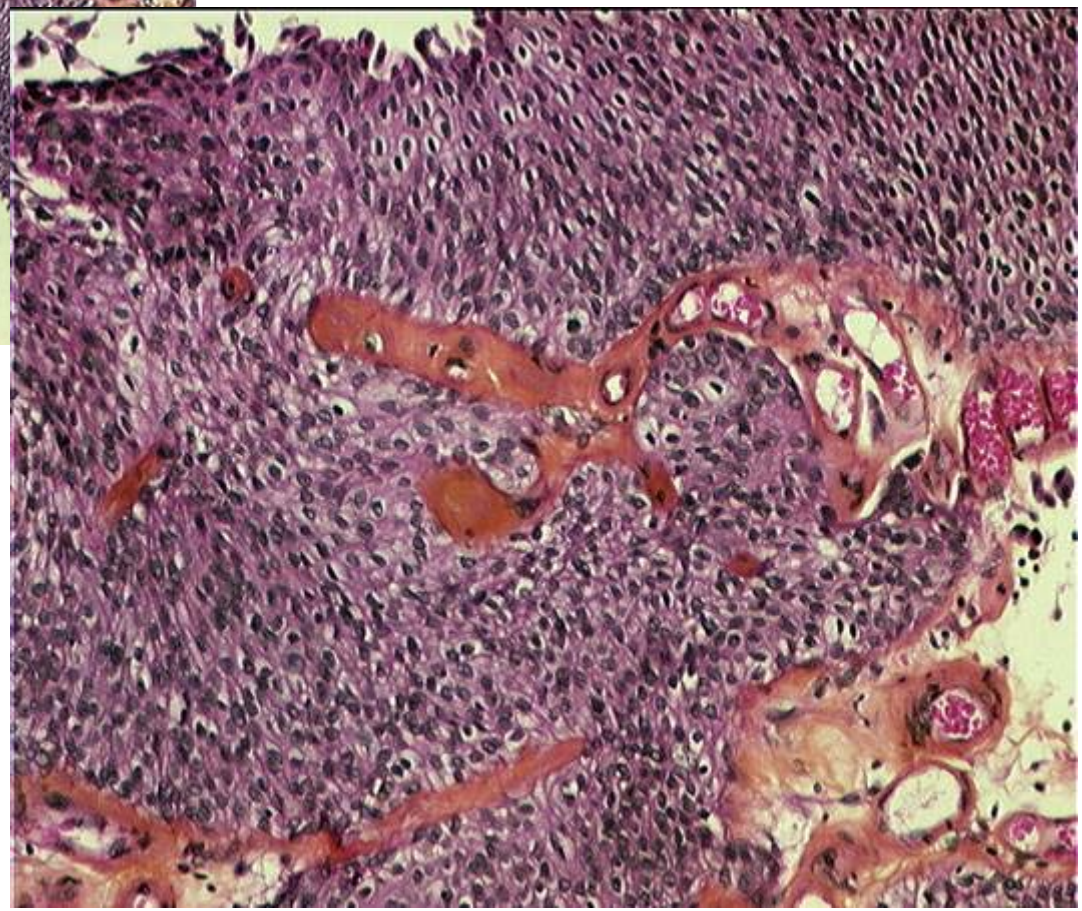
Issues with muscle invasion evaluation

- Absence of muscle sampling
- Myofibroblastic stroma
- Muscle not apparent due to massive destruction by the tumor
- T1 vs T2 ?
  - muscularis mucosa vs muscularis propria (trigone, dome+++)
  - T1 depth vs T2 superficial
- Can be associated with papillary component or not in surface

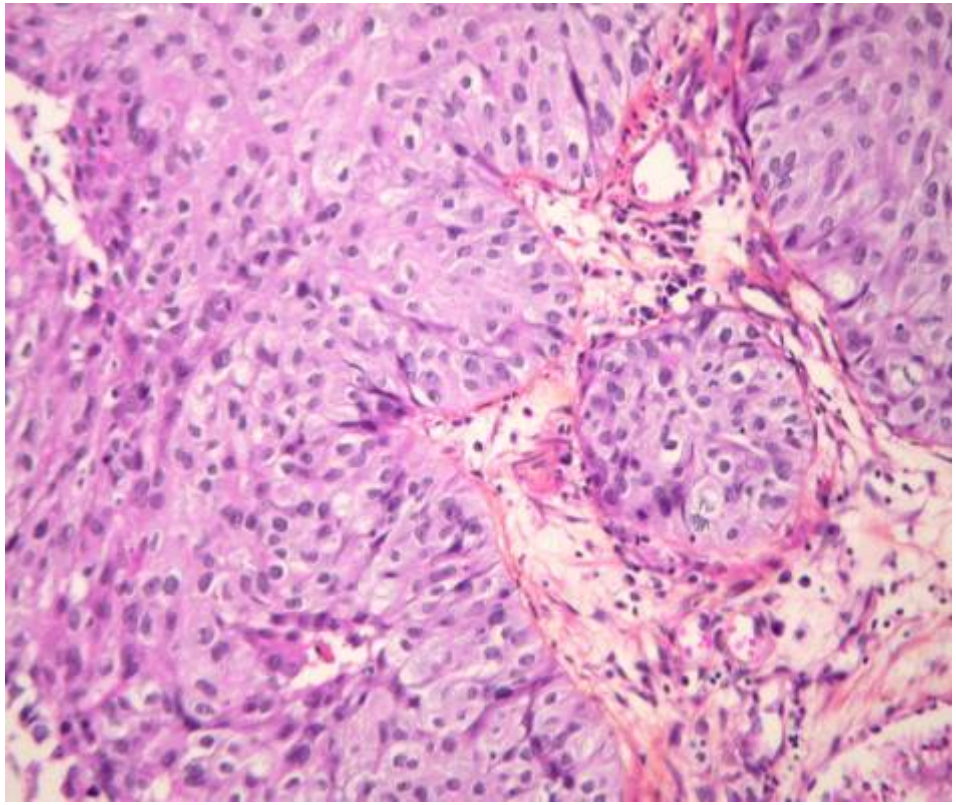
Ta versus T1

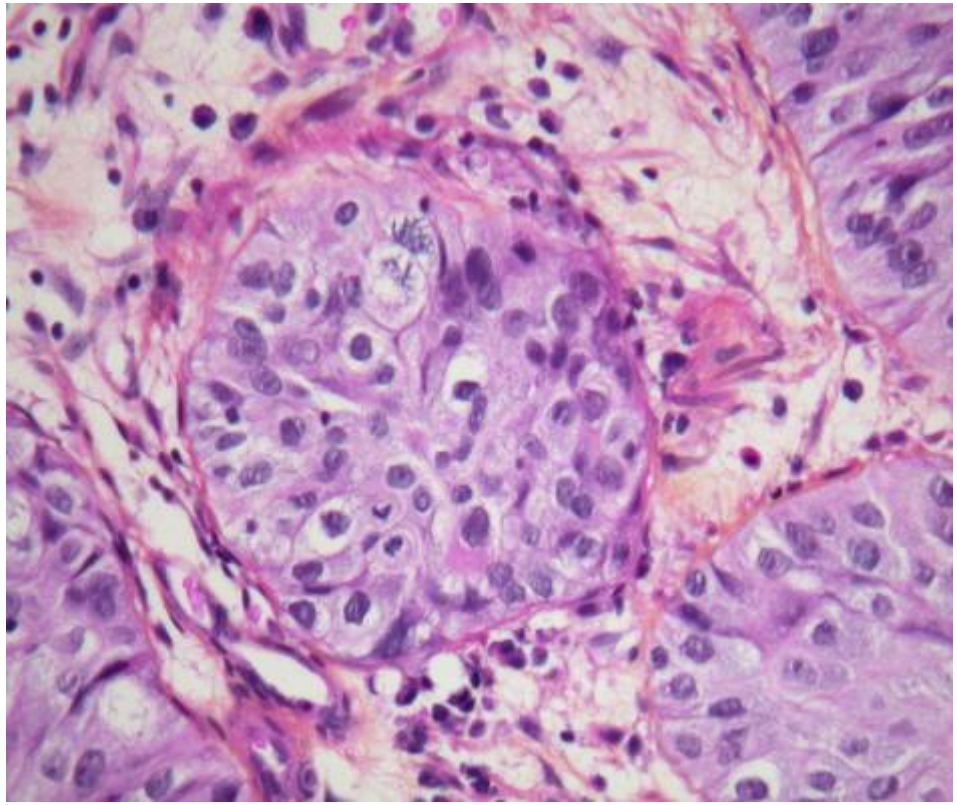


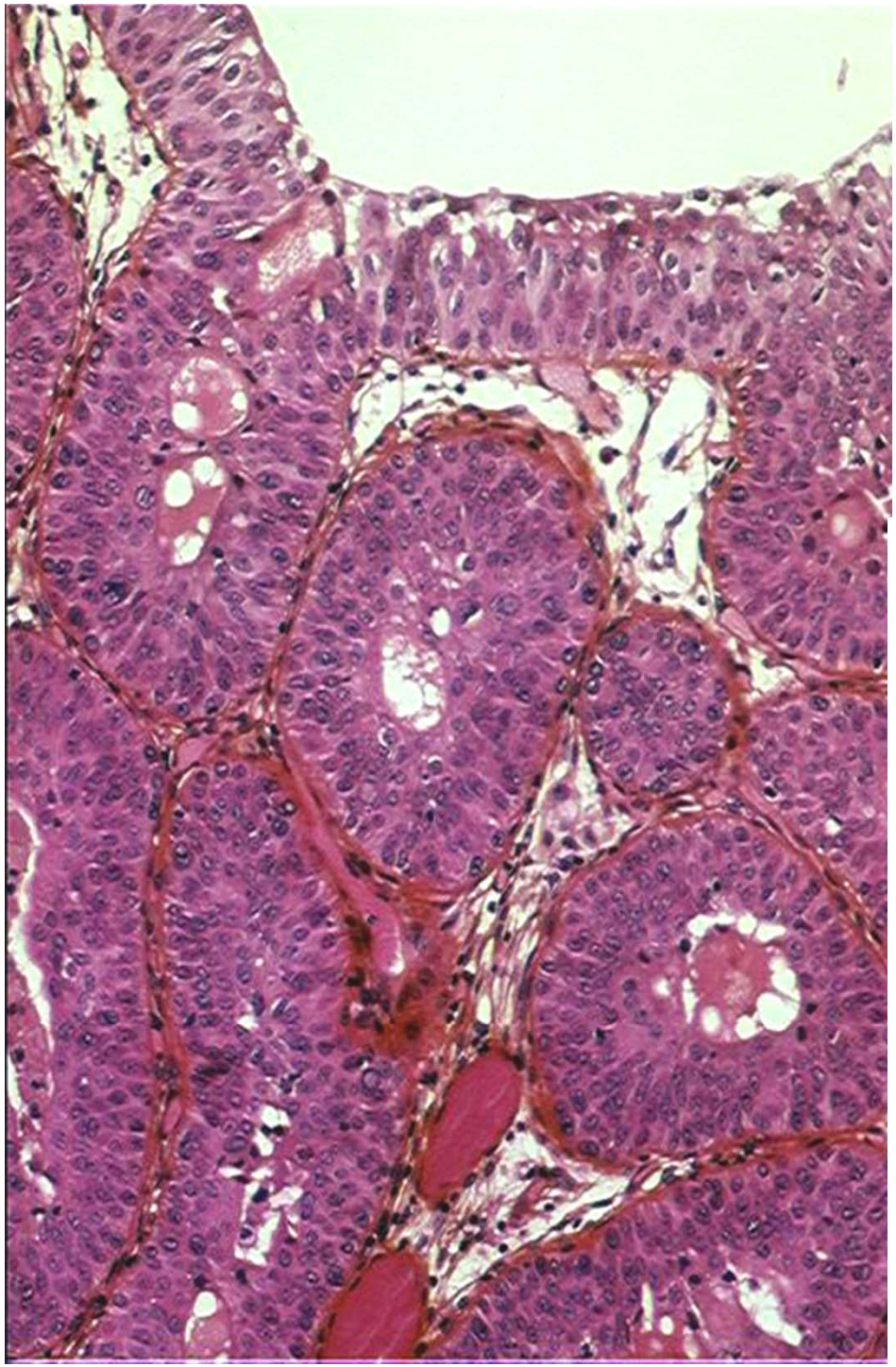
Ta with
endophytic growth



Ta, with well rounded structure

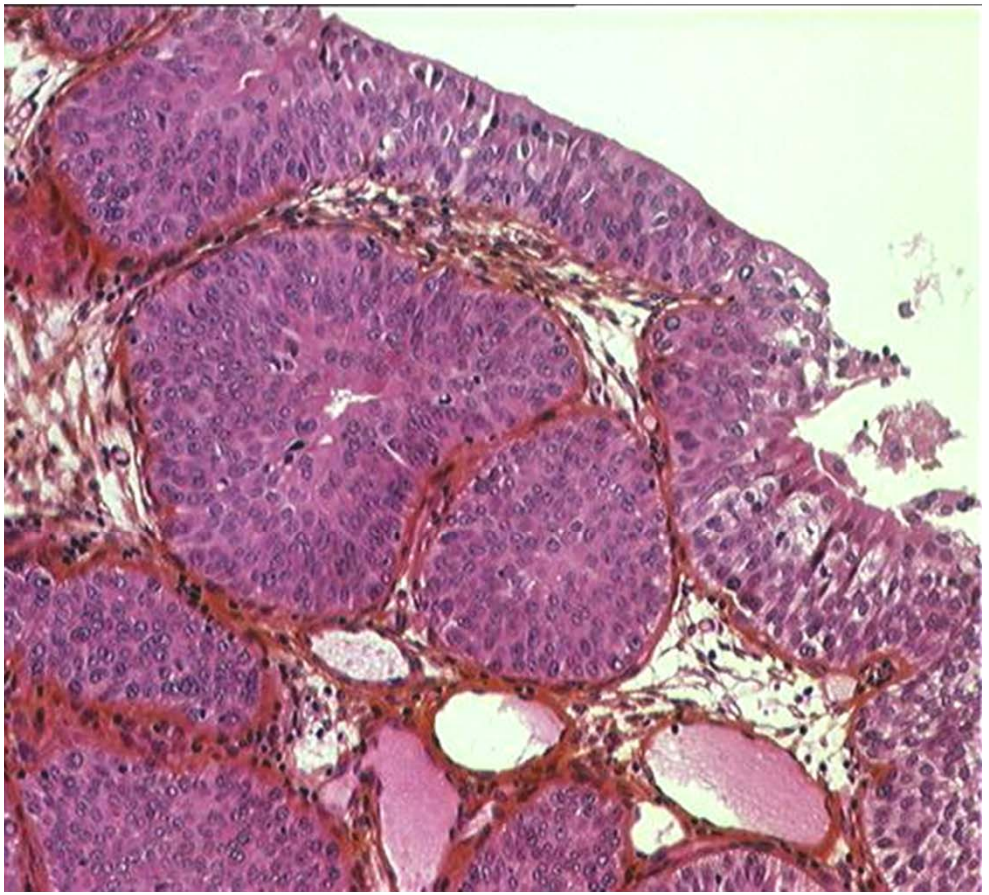




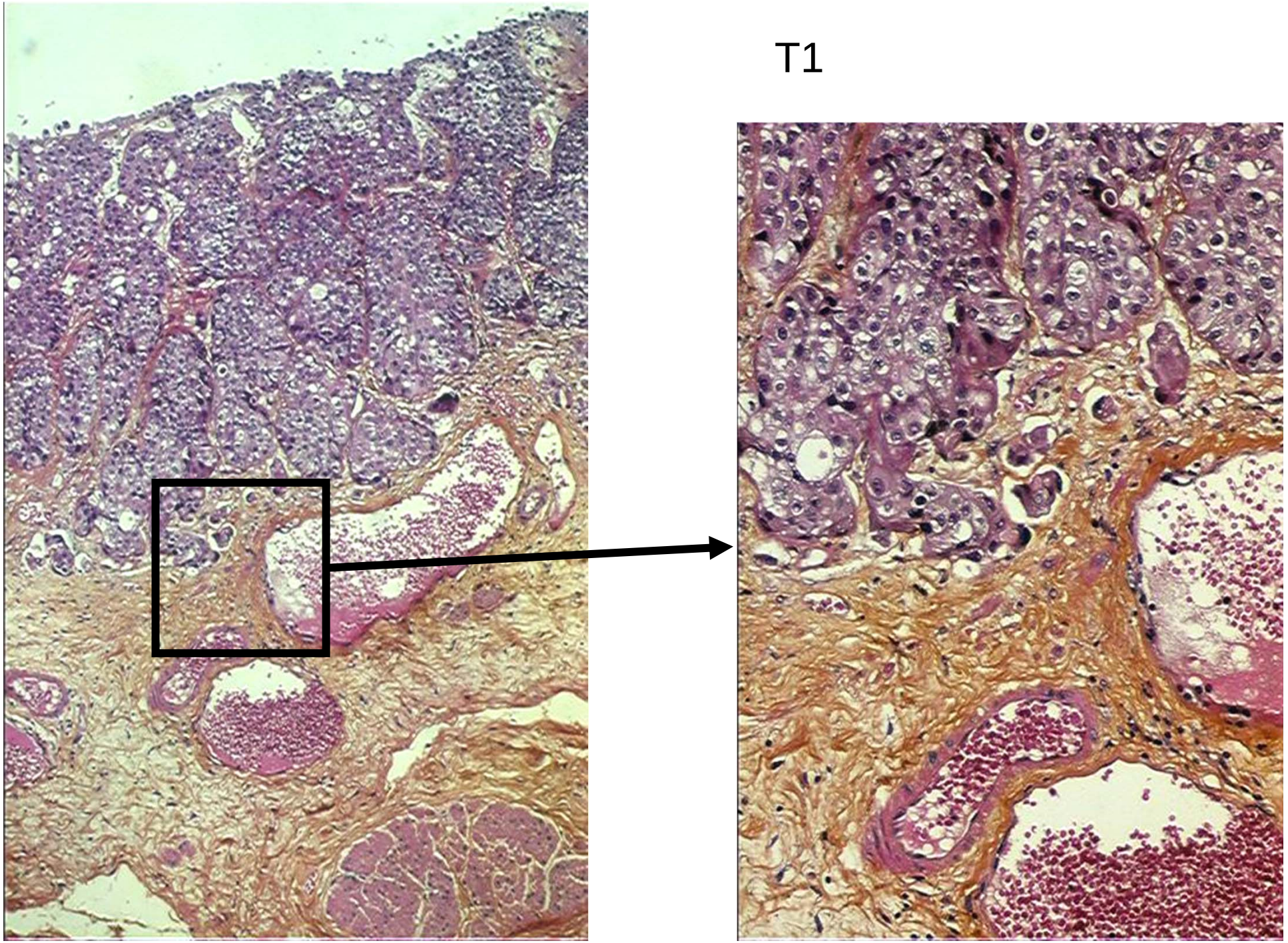


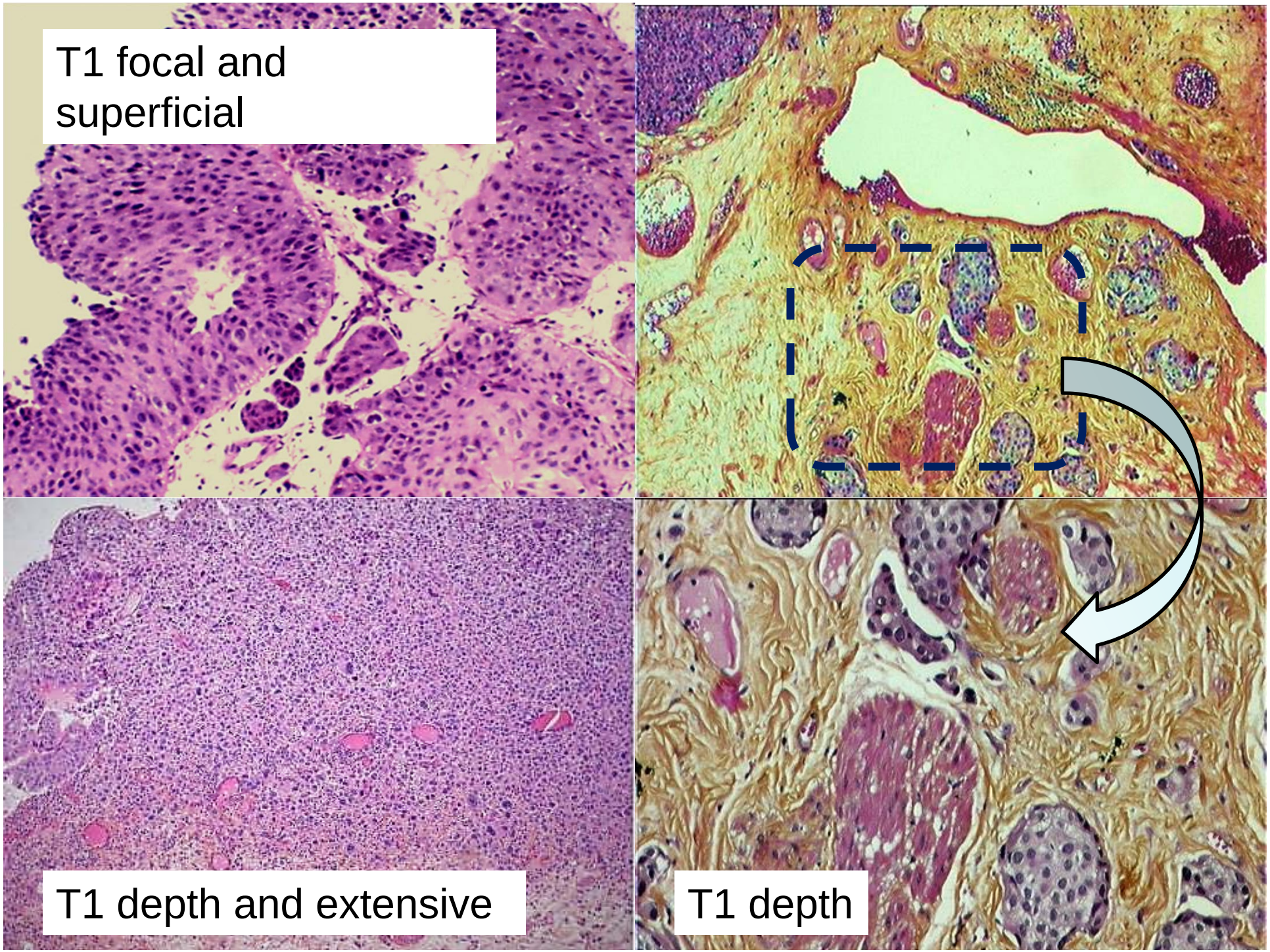
Ta

Inverted growth



T1




T1 focal and superficial
T1 depth and extensive
T1 depth

Substaging T1

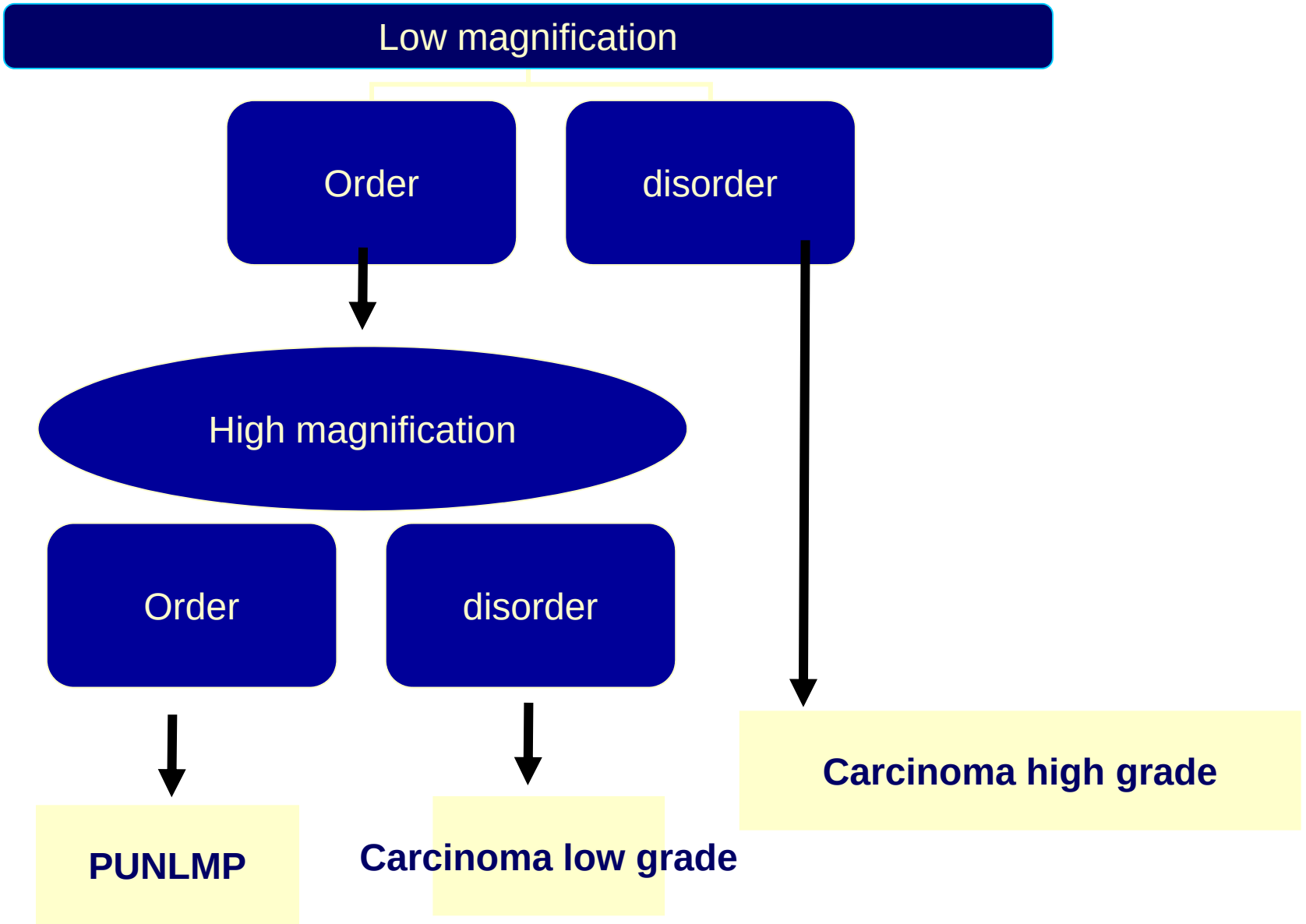
- Different systems proposed:
  - T1a/T1b/T1c
  - T1a/T1b (superficial/depth)
  - Measurement of depth of invasion
  - Focal / extensive
- Lack of reproductibility or validation
- Still it is recommended to provide information regarding the importance of T1 involvement

Amin Eur Urol 2013

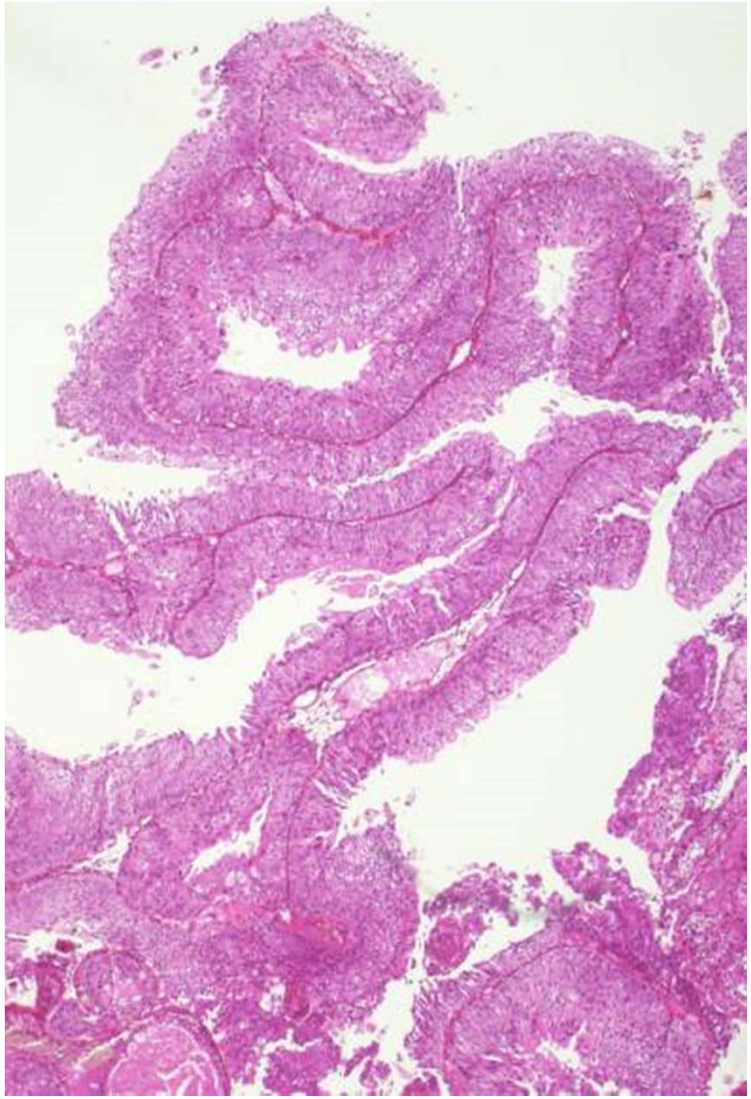
WHO 1973 grading

- Papilloma (Grade 0)
- Grade 1 : « the least degree of anaplasia compatible with the diagnosis of malignancy »
- Grade 2 : « in between »
- Grade 3 : « the more severe degrees of cellular anaplasia »

WHO 2004


Low magnification
Order
disorder
High magnification
Order
disorder
PUNLMP
Carcinoma low grade
Carcinoma high grade

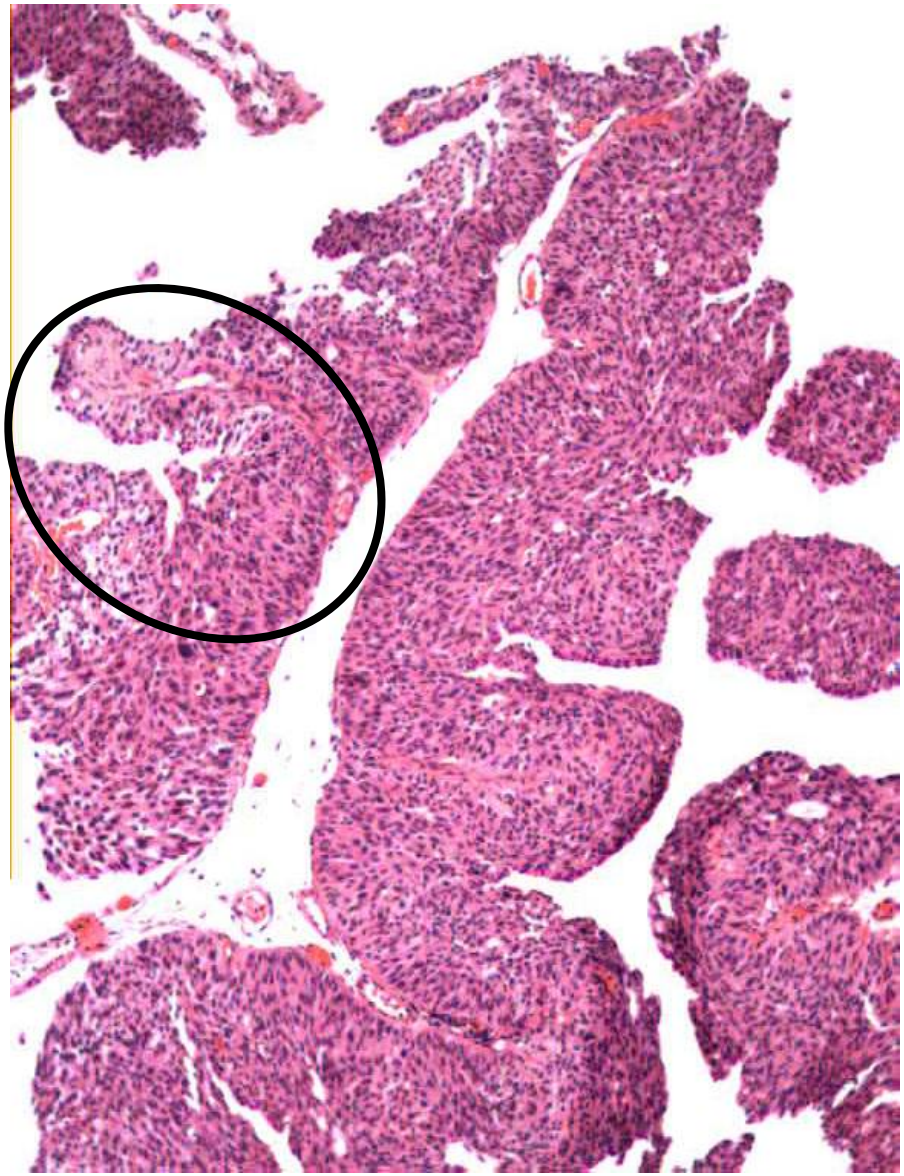
Papilloma

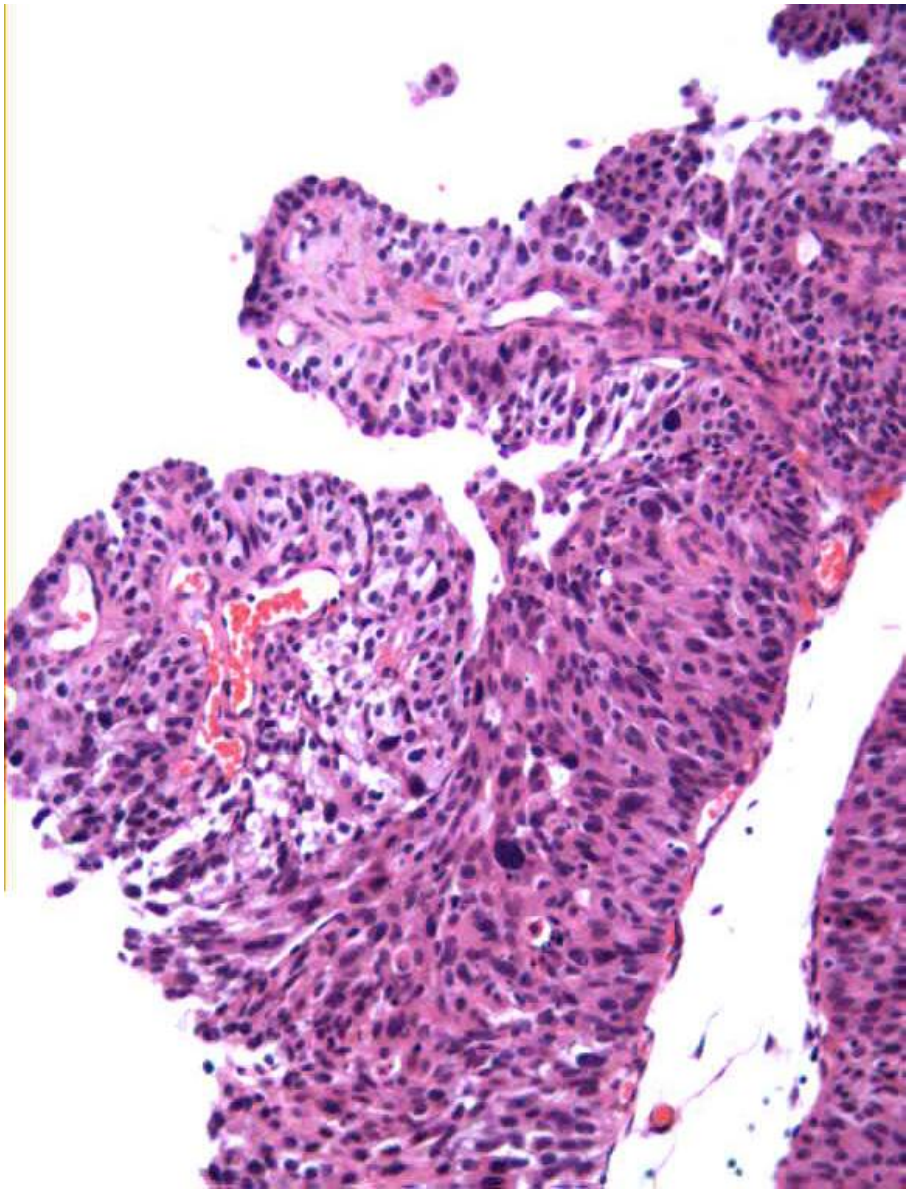


- Very rare
- Benign
- No hyperplasia, no atypia
- Unique lesion
- Papillary architecture

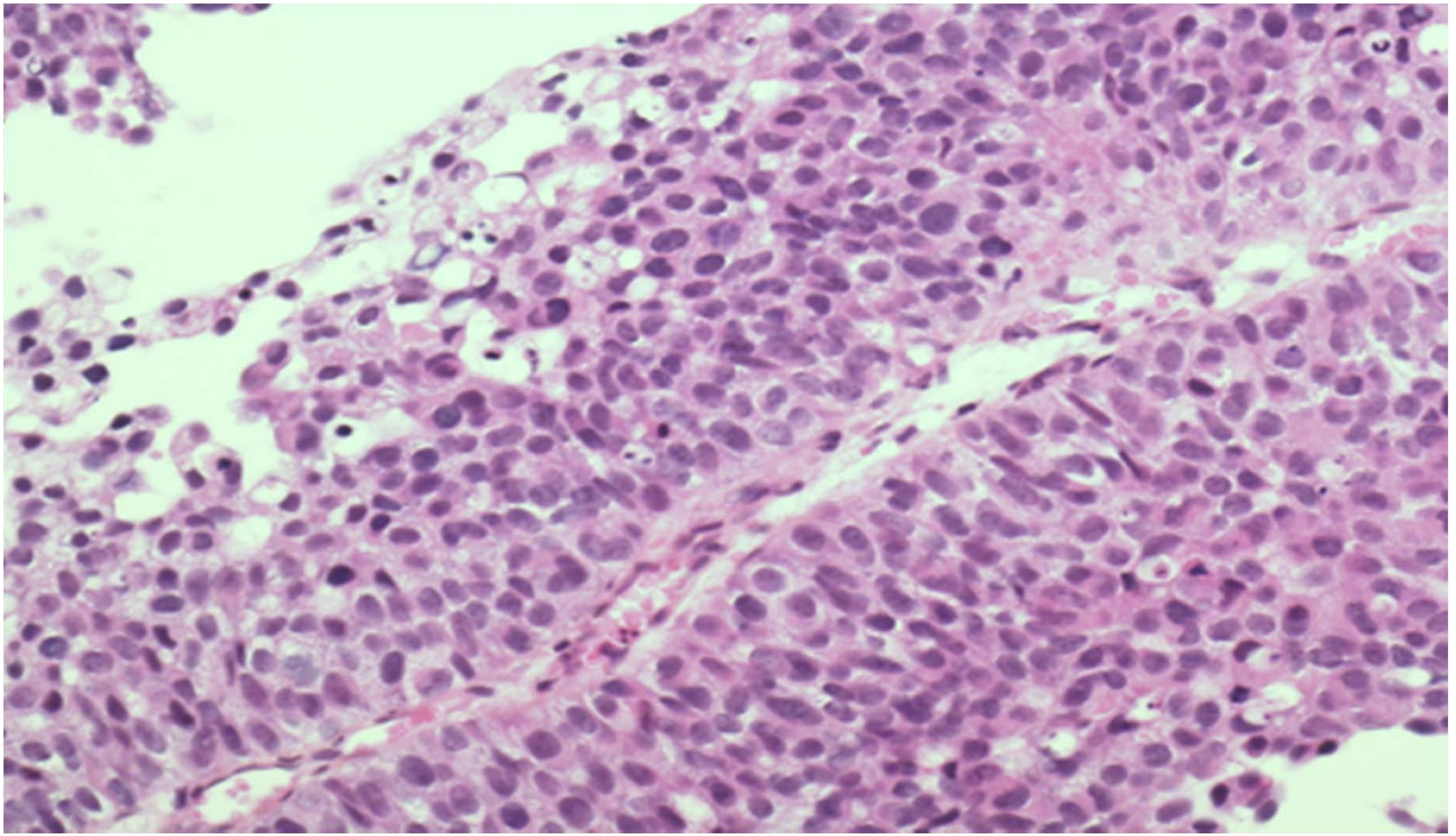
- All other urothelial tumors are currently considered as malignant or with a potential of malignancy, and should be graded and staged.

LOW MAGNIFICATION → DISORDER → **HIGH GRADE CARCINOMA**





Non invasive high grade carcinoma



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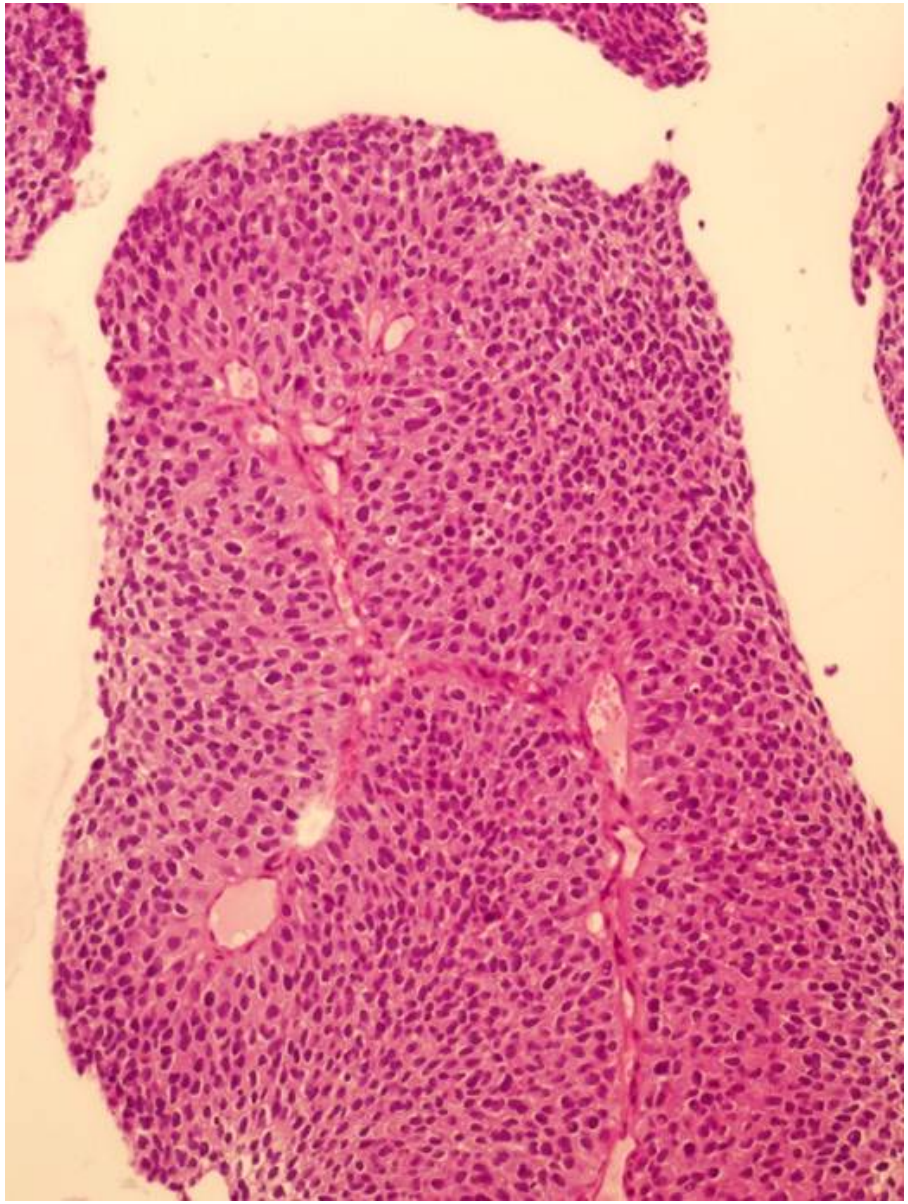
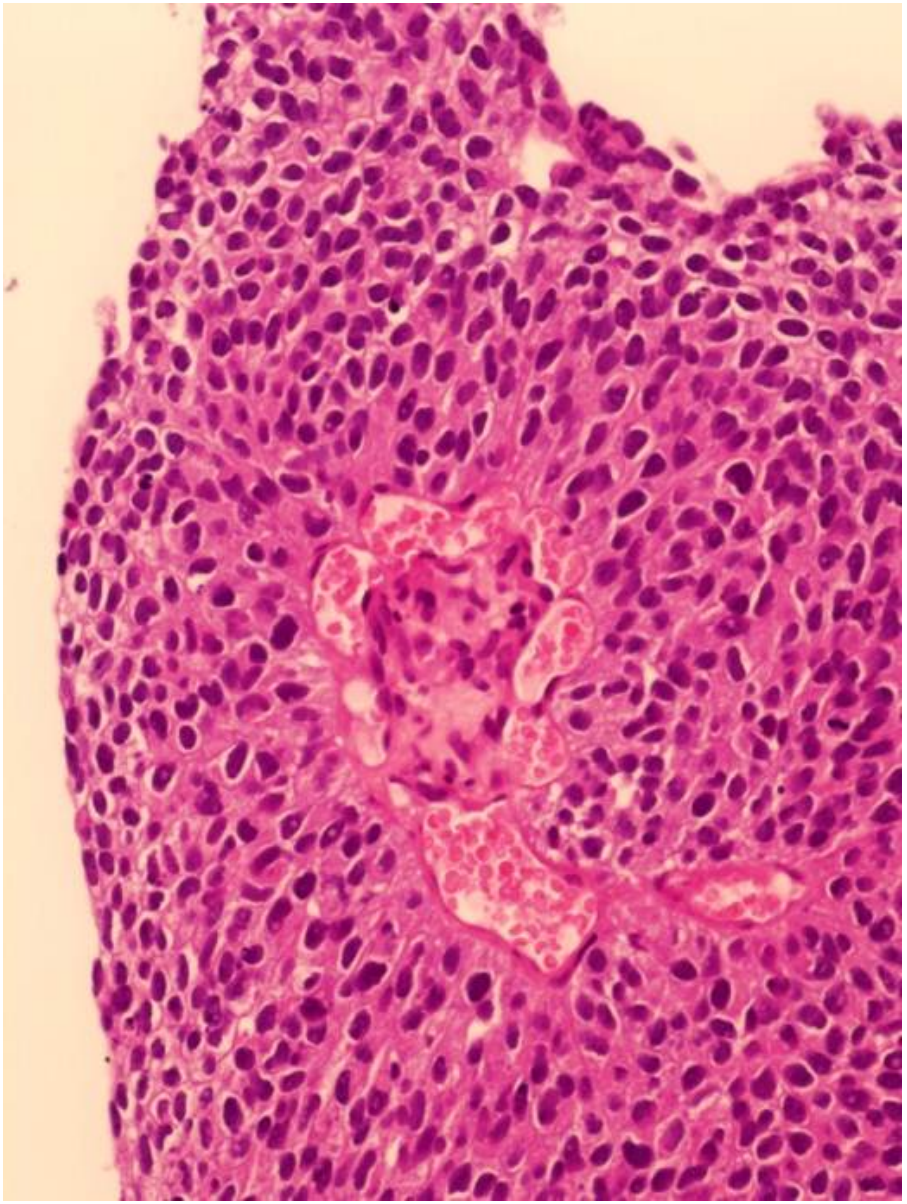
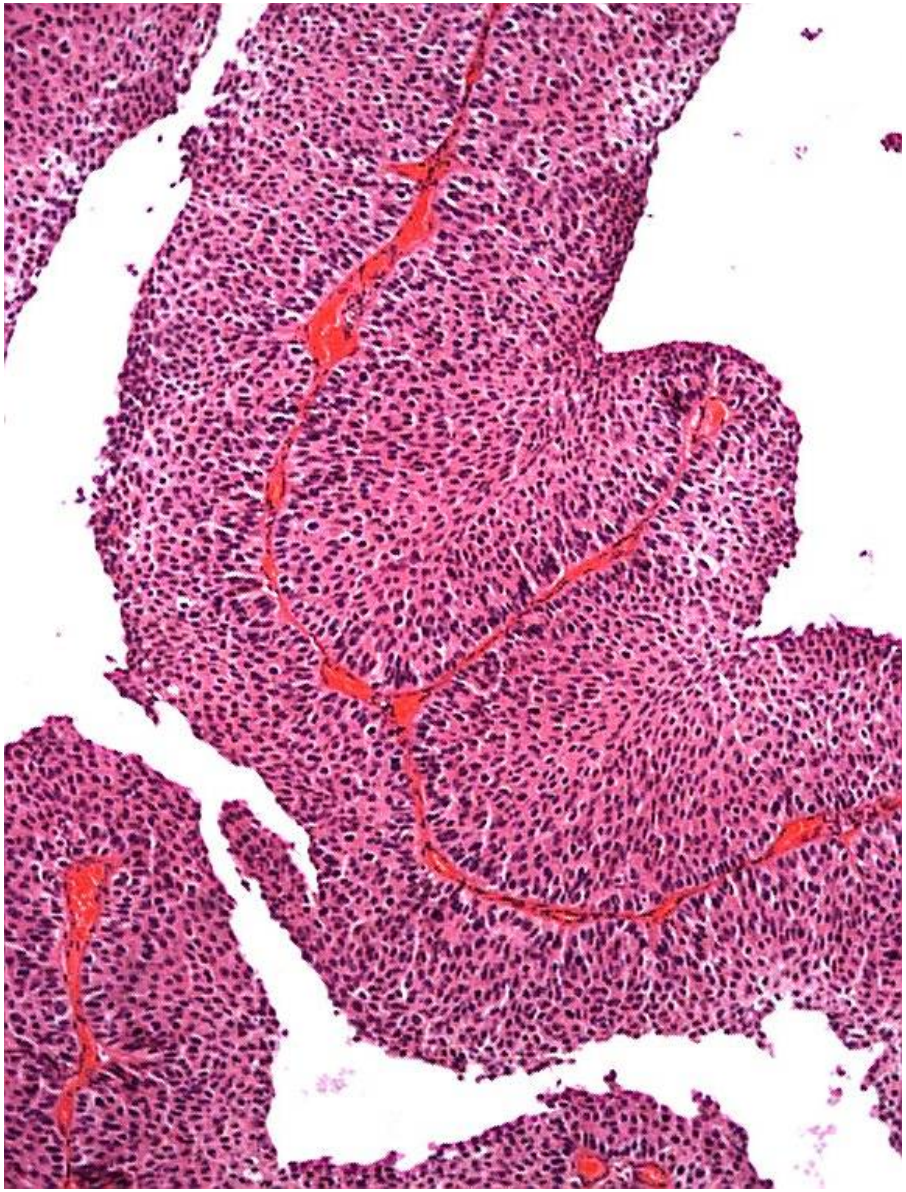
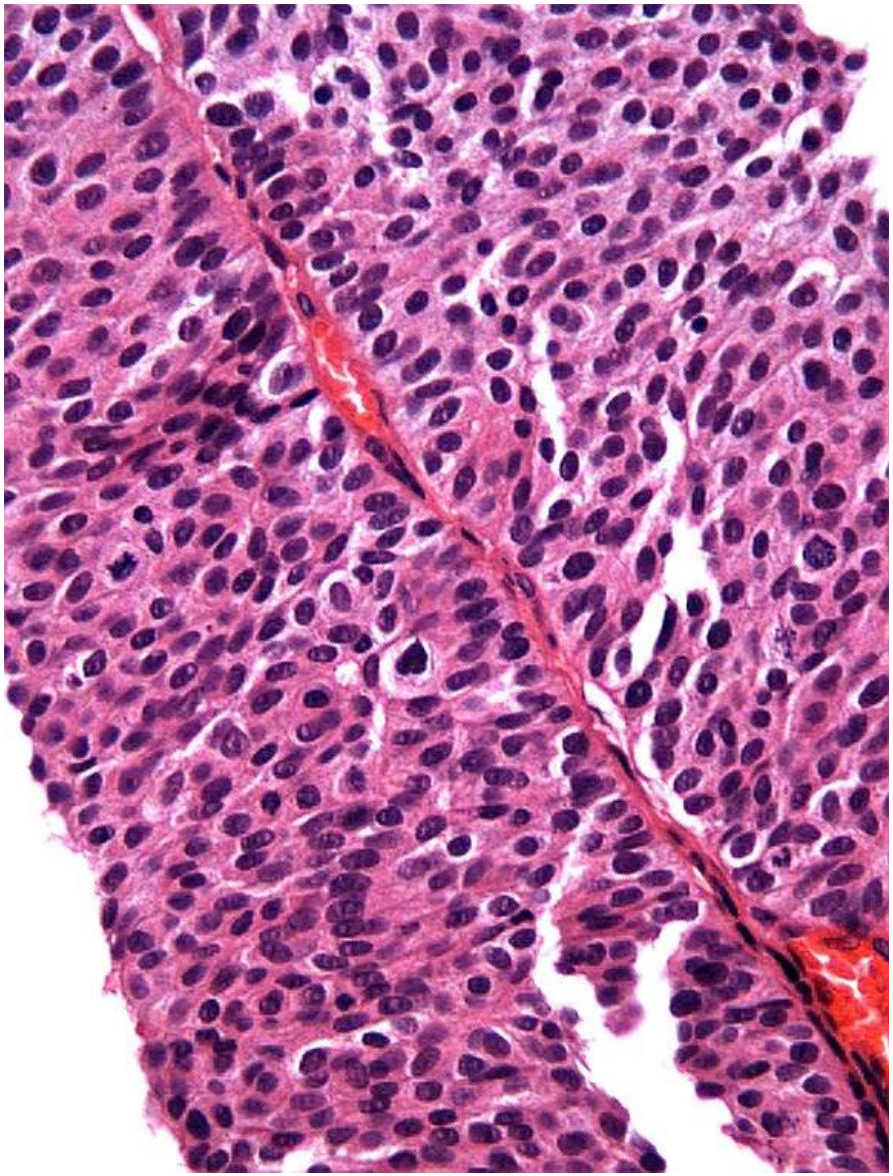


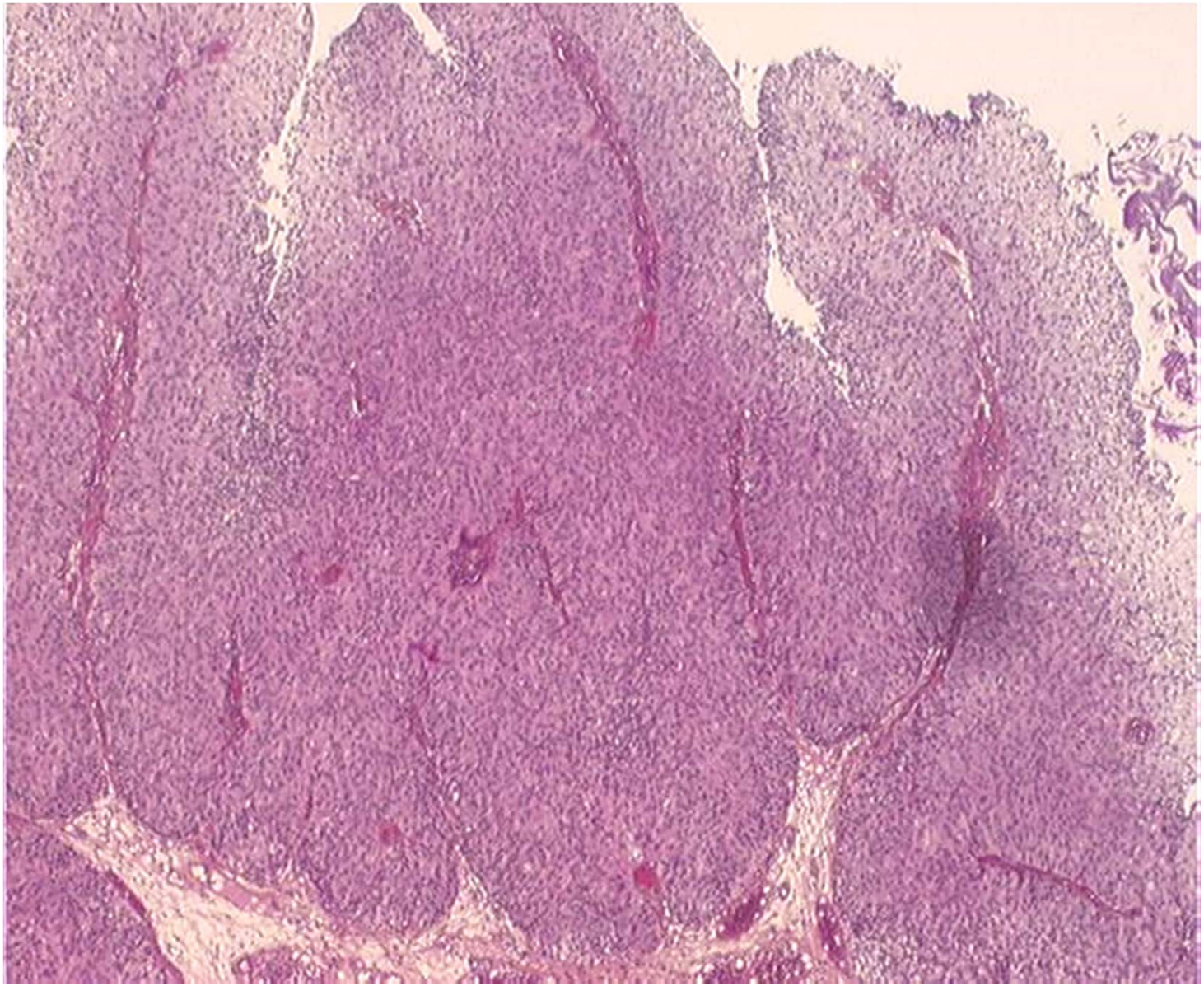


LOW MAGNIFICATION → ORDER → **HIGH MAGNIFICATION** → DISORDER → **LOW GRADE CARCINOMA**





Low grade carcinoma with thick papillae



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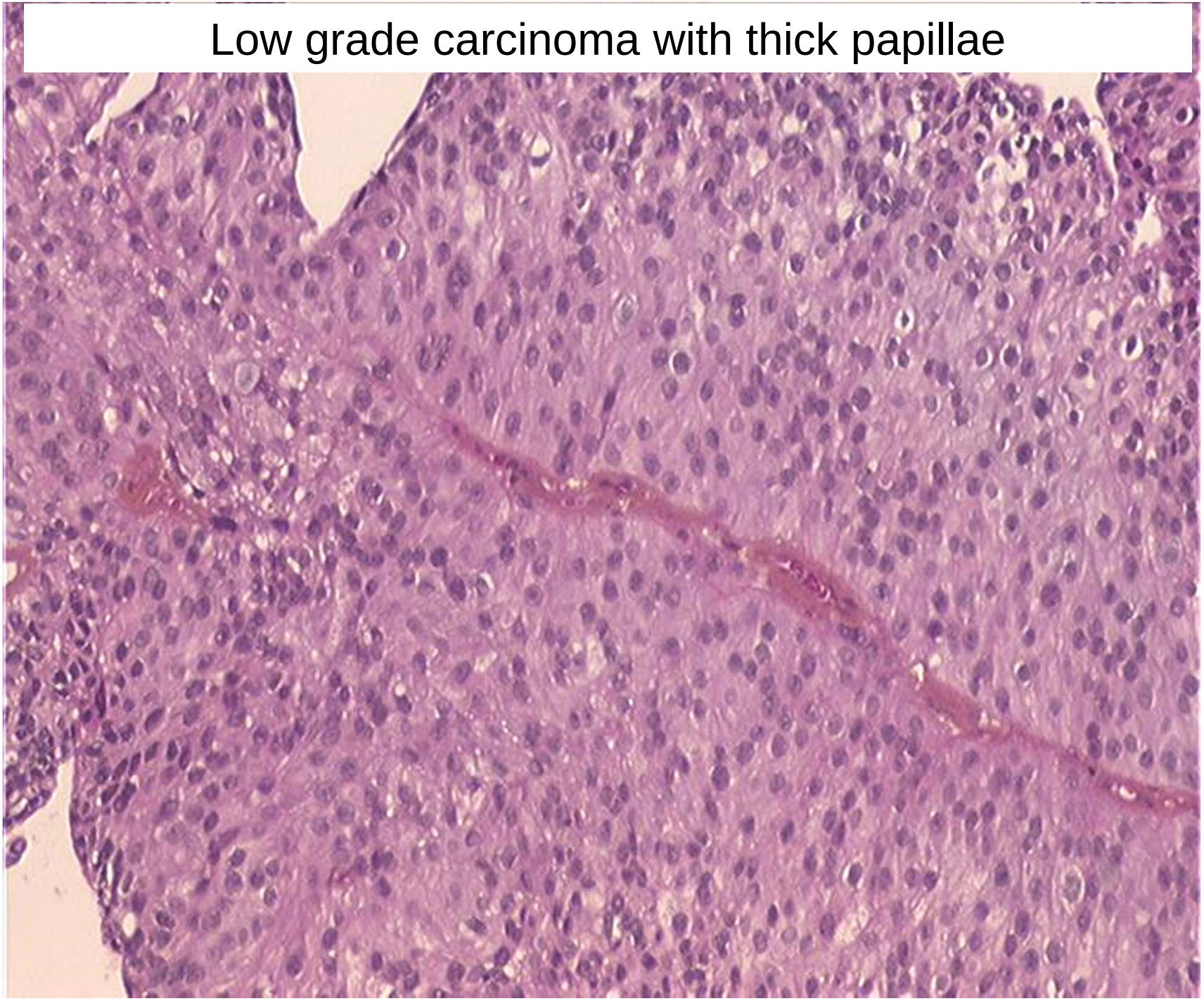
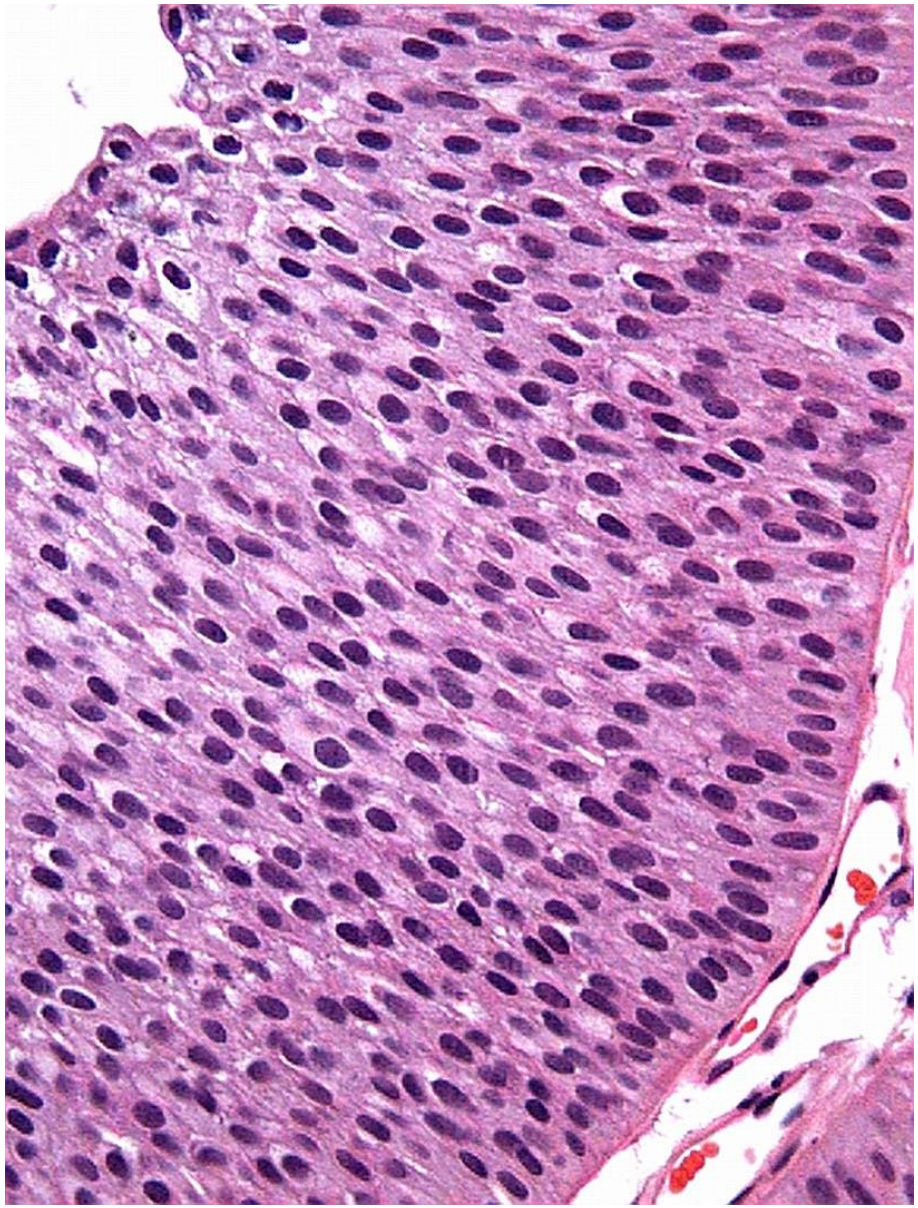
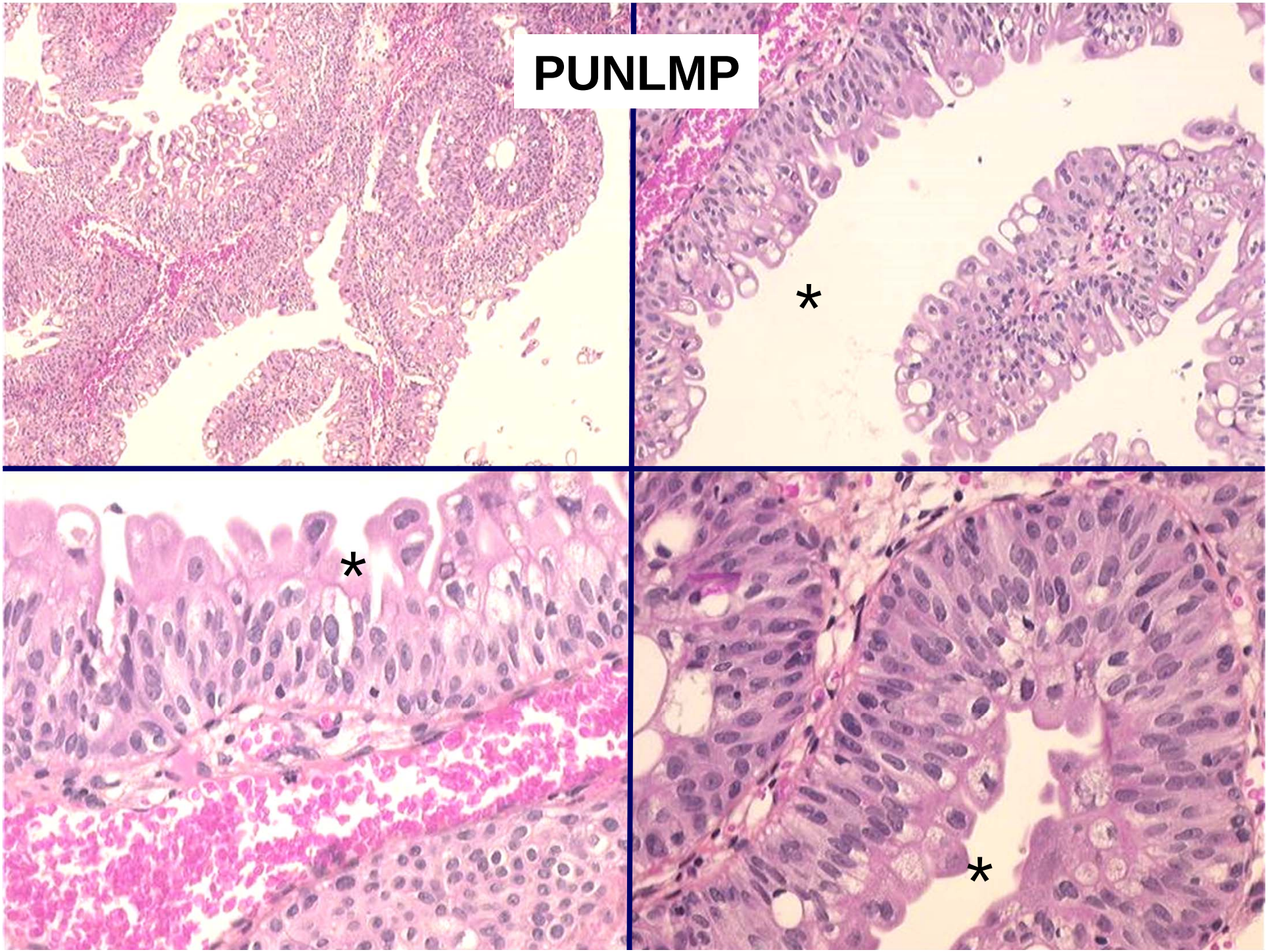
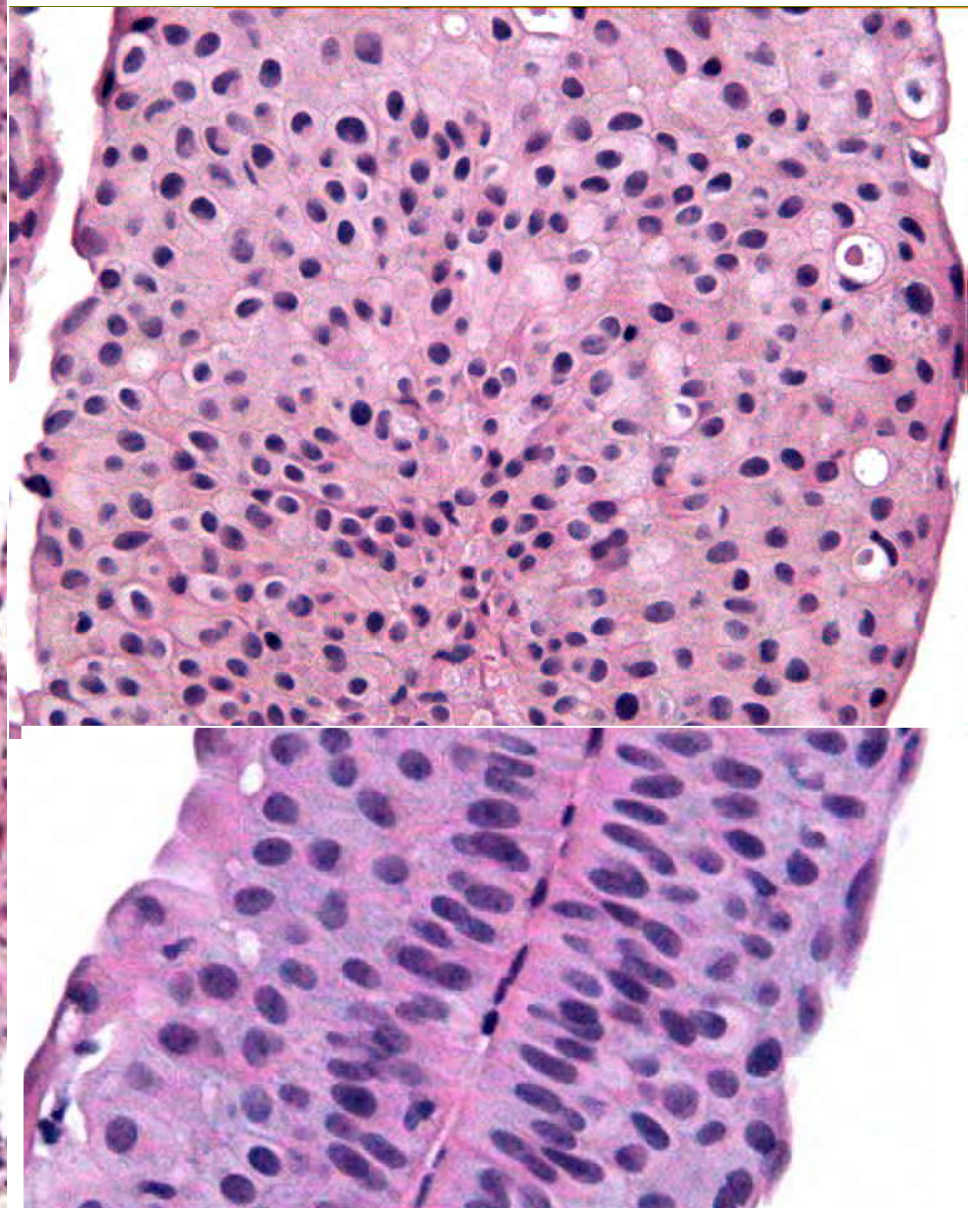


LOW MAGNIFICATION → ORDER → **HIGH MAGNIFICATION** → ORDER → **PUNLMP**

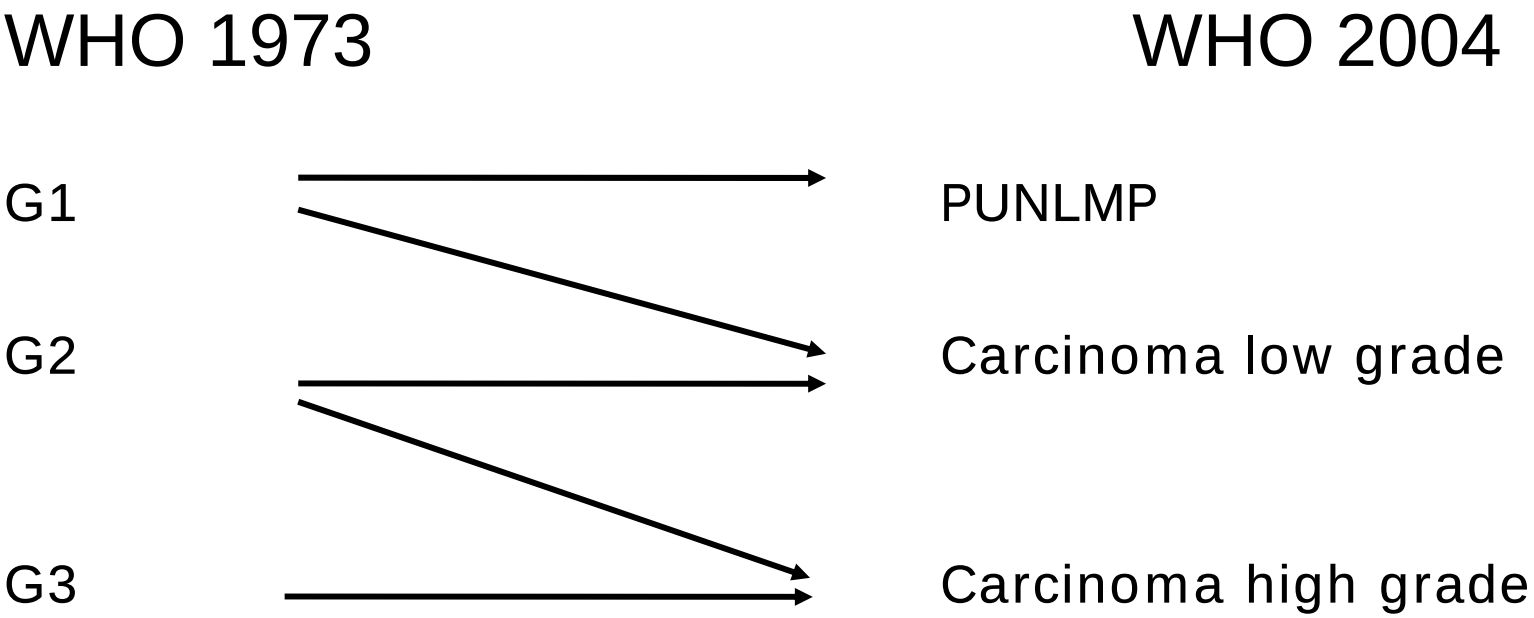



PUNLMP
*
*
*

NO EVALUATION



Relationships WHO 1973 and WHO 2004



Concerns about bladder grading

- PUNLMP has a poor reproducibility, and is treated like carcinoma low grade
- No more prognostic value for WHO 2004 over WHO1973
- Prognostic interest to subdivide in T1 high grade tumors two categories

Tuna Virchows 2011, Cheng Hum Pathol 2012,
Chen PlosOne 2012, Amin Eur Urol 2013

Recommendations for the grade

- Specify the system used (1973 or 2004)
- Ensure a good comprehension between clinician pathologist
- Unfrequent or none low grade in T1

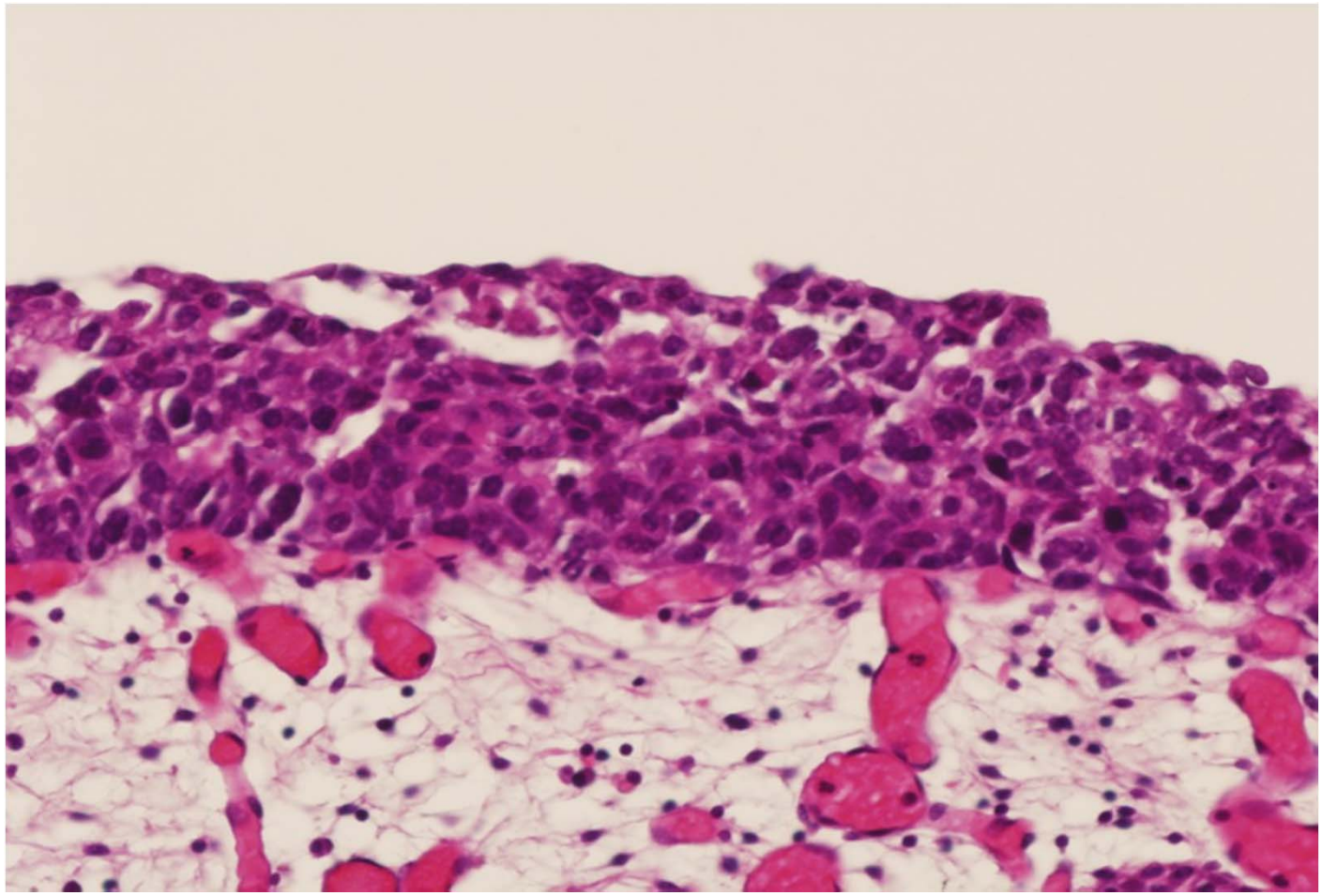
Circumstances to discover a flat lesion of carcinoma *in situ*

- At initial diagnosis in association with a papillary tumor
- During the follow-up of a patient with prior papillary tumor

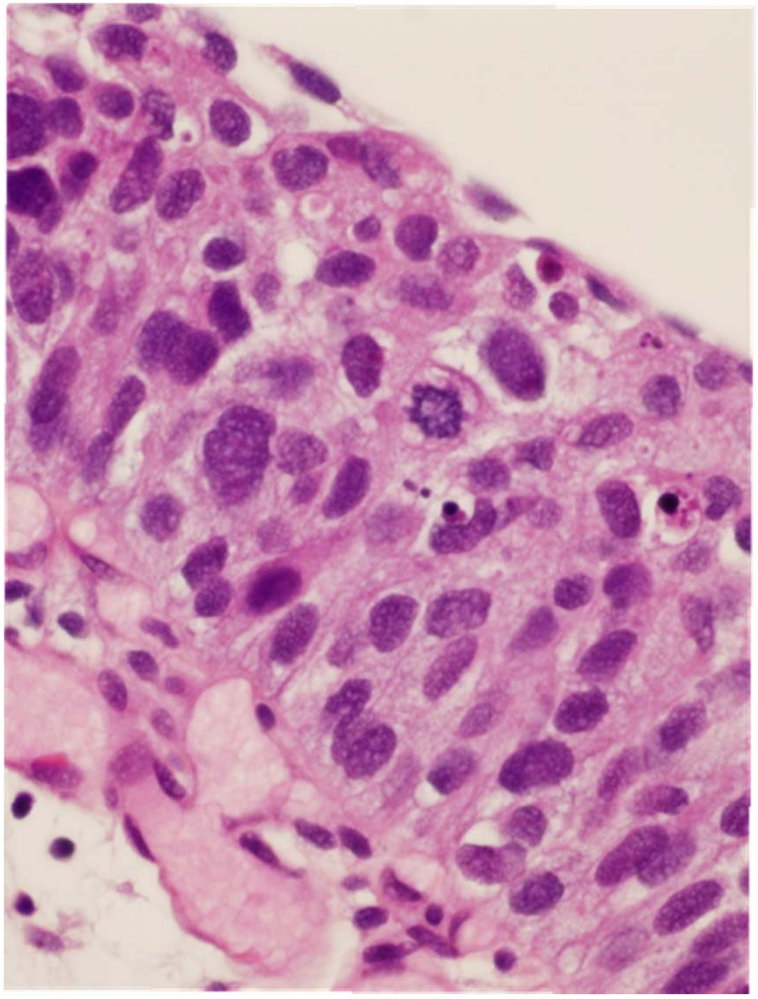
  Carcinoma *in situ* is associated with genomic instability , and its presence increases the risk of progression to muscle invasion.

- At initial diagnosis as an isolated lesion. This is rare event, but is revealed rather by irritative symptoms than hematuria.

Carcinome *in situ*

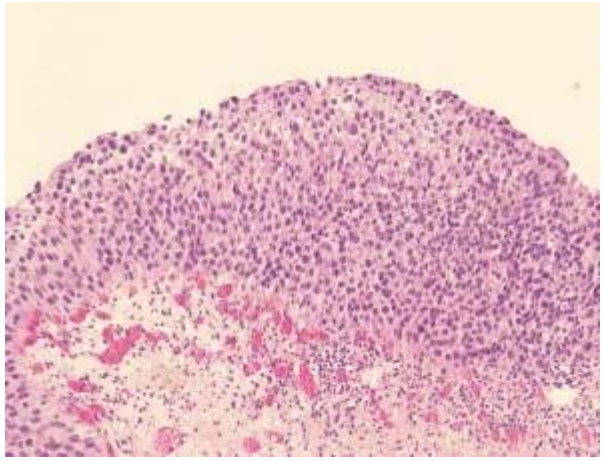
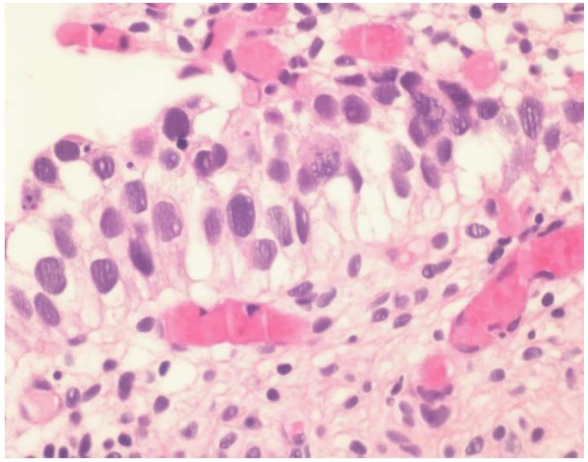
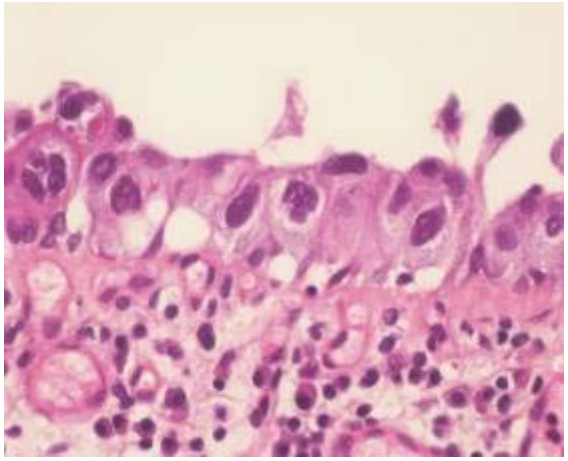


Carcinoma *in situ* (pleomorphic)

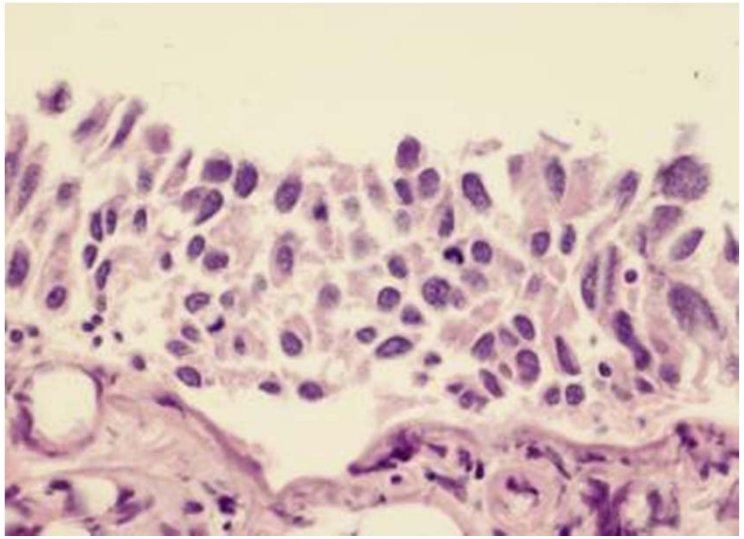


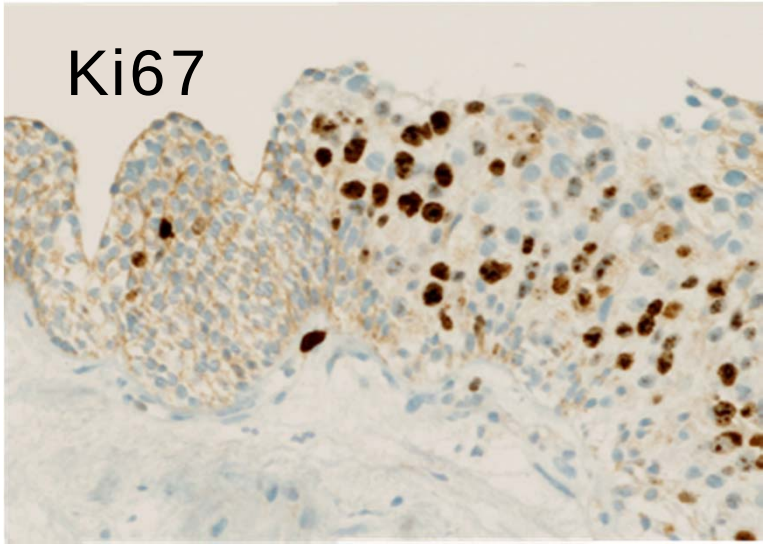
- Major cytological atypia
- Loss of cell polarity
- Large, irregular, hyperchromatic nuclei
- Mitoses in upper layers, with atypia

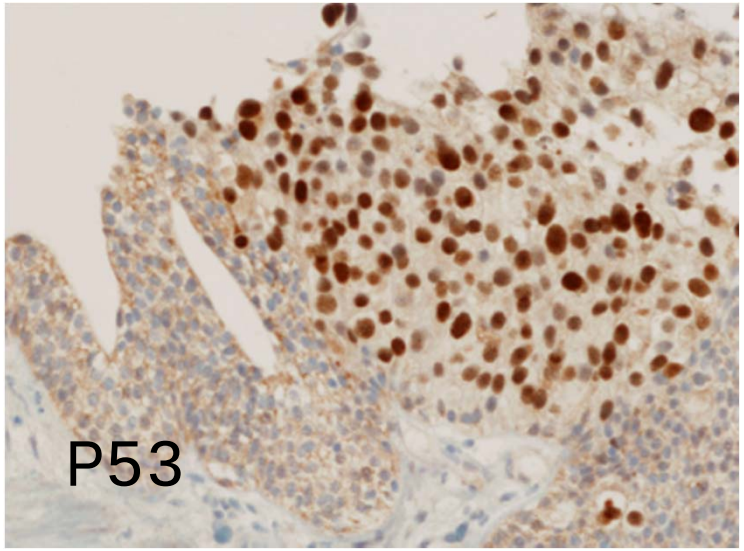
Carcinoma *in situ:* the urothelium thickness can be increased, normal or decreased

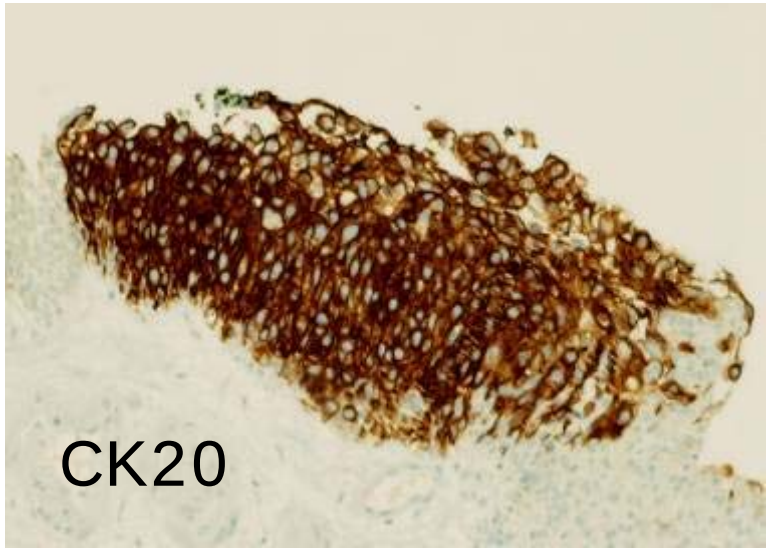




Carcinoma *in situ*, markers ?





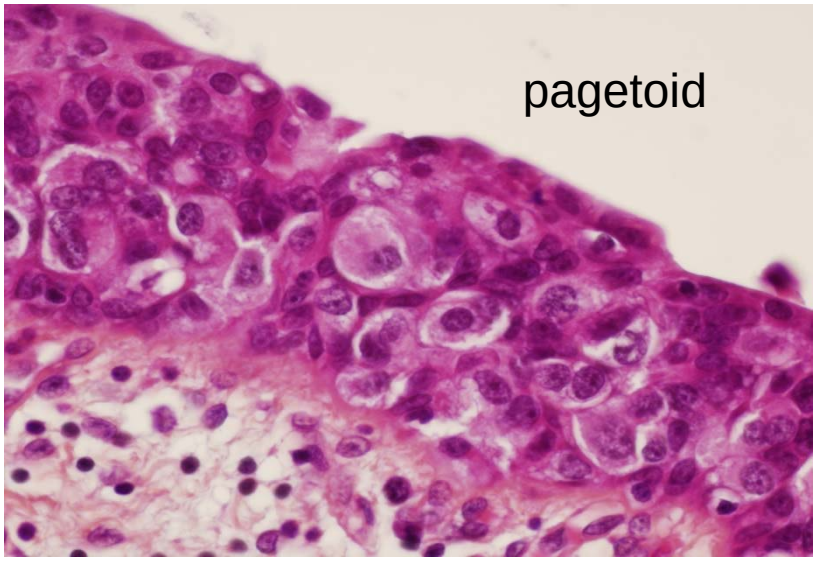


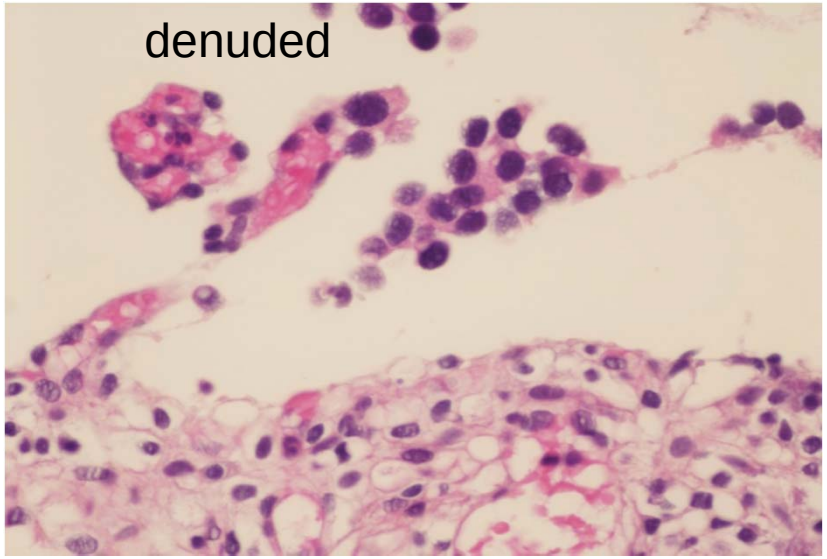


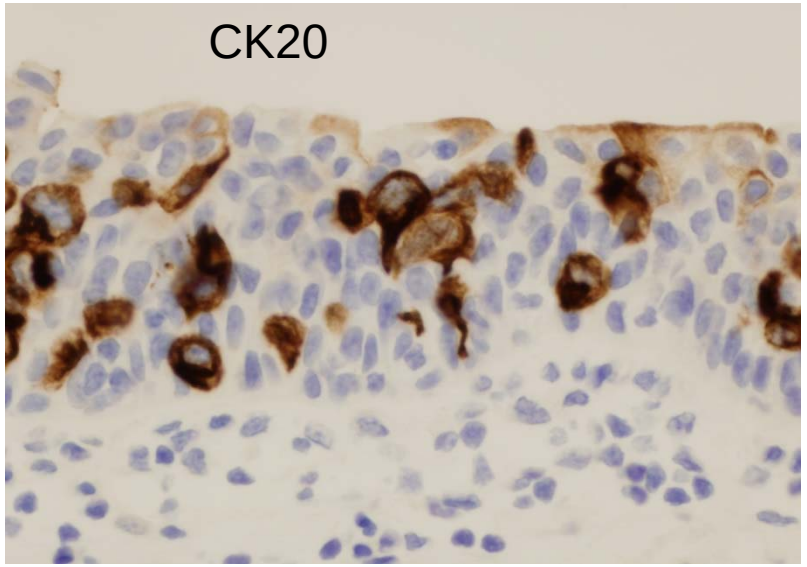
Carcinoma *in situ*, morphological variants

- Classical, pleomorphic with large cells
- Monomorphic with large cells
- Monomorphic with small cells
- Denuded, clinging
- Pagetoid

Carcinoma *in situ*, morphological variants







Recommendations for carcinoma *in situ*

- Precise if its presence is assessable (flat urothelium prsent), and if it is present or no
- Specify if it is present in prostatic ducts/glands or in urethra

Amin Eur Urol 2013

NMIBC

- Recurrence 60- 80 %
- 15 à 20 % evolve to muscle invasion, with the following risk factors (tumor size, multifocality, grade, CIS associated, stage, prior recurrence)

Factor	Recurrence	Progression
Number of tumours		
Single	0	0
2 to 7	3	3
≥8	6	3
Tumour diameter		
<3 cm	0	0
≥3 cm	3	3
Prior recurrence rate		
Primary	0	0
≤1 recurrence/yr	2	2
>1 recurrence/yr	4	2
Category		
Ta	0	0
T1	1	4
Concomitant CIS		
No	0	0
Yes	1	6
Grade (1973 WHO)		
G1	0	0
G2	1	0
G3	2	5
Total score	0–17	0–23

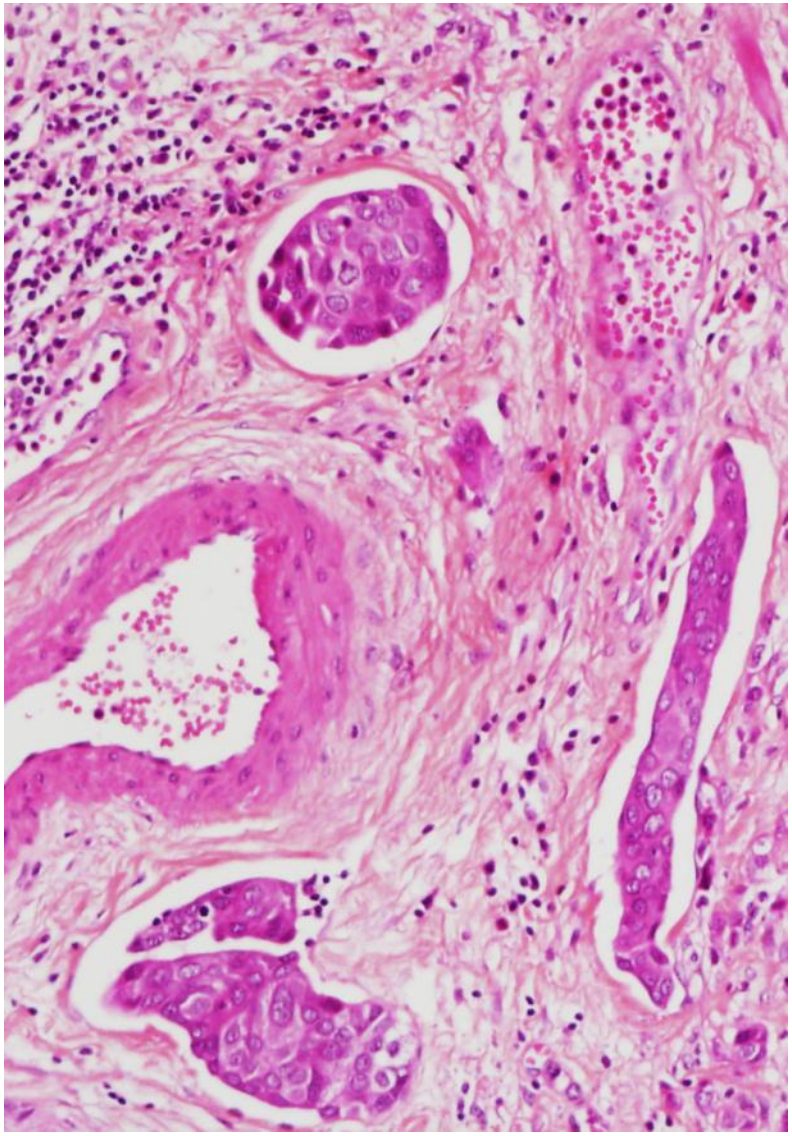
Bajuk, European Urology 2008

TVNIM

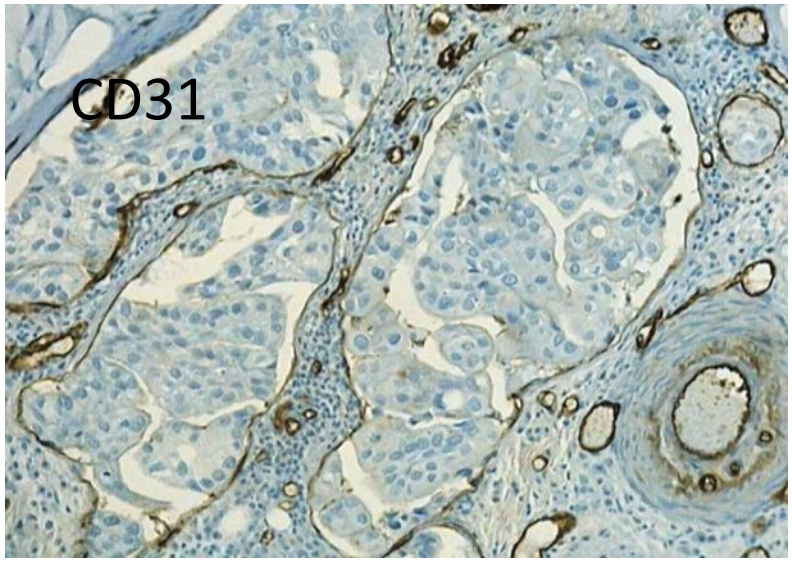
Recurrence score	Probability of recurrence at 1 yr		Probability of recurrence at 5 yr		Recurrence risk group
	%	(95% CI)	%	(95% CI)	
0	15	(10–19)	31	(24–37)	Low risk
1–4	24	(21–26)	46	(42–49)	Intermediate risk
5–9	38	(35–41)	62	(58–65)	Intermediate risk
10–17	61	(55–67)	78	(73–84)	High risk
Progression score	**Probability of progression at 1 yr**		**Probability of progression at 5 yr**		**Progression risk group**
	%	(95% CI)	%	(95% CI)	
0	0.2	(0–0.7)	0.8	(0–1.7)	Low risk
2–6	1	(0.4–1.6)	6	(5–8)	Intermediate risk
7–13	5	(4–7)	17	(14–20)	High risk
14–23	17	(10–24)	45	(35–55)	High risk

Bajuk, European Urology 2008

Lymphovascular invasion and NMIBC



- Diagnostic issue (help with CD31, D2-40)
- Concordance TURB cystectomy?
- Reproductibility?



Algaba Curr Opin Urol. 2006, Streeper BJU Int 2008, Kunju J Urol 2008, Resnick BJU Int 2011, Mazzucchelli Anal Quant Cytol Histol. 2012, Xie Int J Urol Nephrol 2012

Invasions lymphovasculaires and NMIBC

In retrospective studies, they are associated with

- the risk of progression and metastatic outcome for tumor T1 (stage on TURB)
- specific survival after cystectomy for pT1N0 (stade final)
- The risk to underestimate the stage of tumor initally cT1N0

They should be reported.

Cho J Urol 2009, Streeper BJU Int 2009, Ku Tumori 2010, Tilki BJUI 2012, Xie Int Urol Nephrol 2012, Olsson Scand J Urol Nephrol 2012

Outline

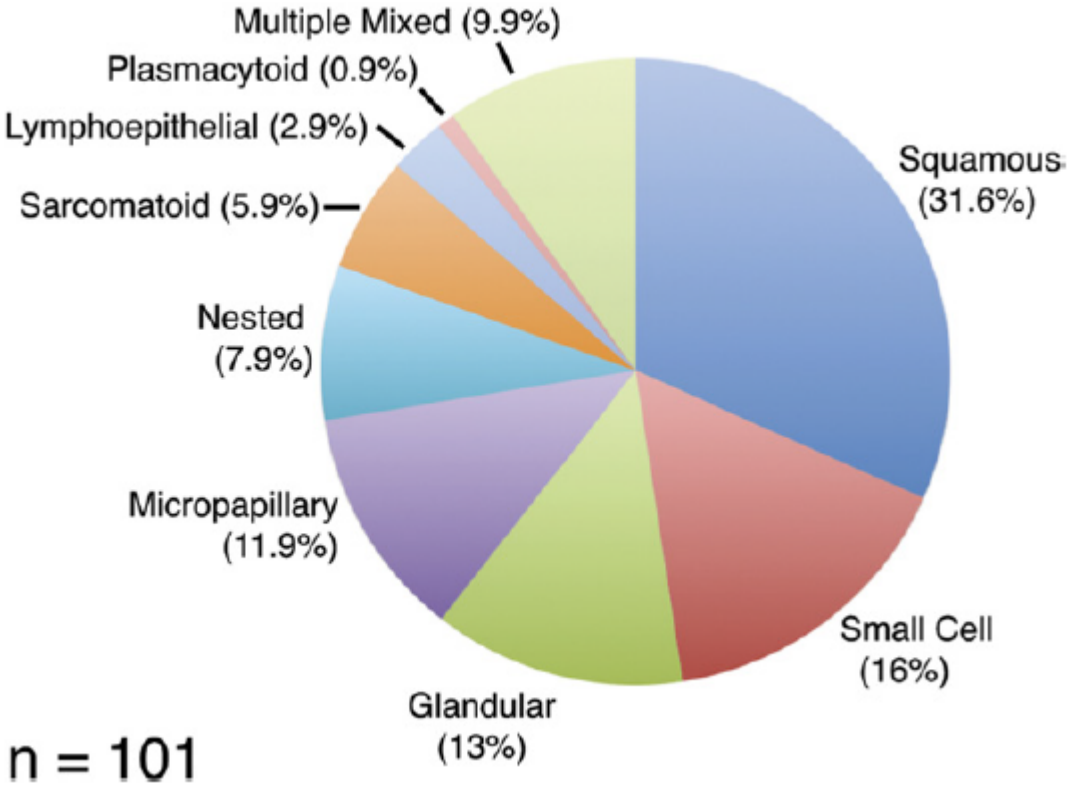
- Normal features in bladder
- Natural history of UBC
- Diagnosis and prognosis of UBC on TURB
- Histological subtypes of UBC
- Differential diagnosis of UBC
- Prognosis features on cystectomy

Urothelial variants / histological subtypes

- With squamous differentiation
- With glandular differentiation
- Micropapillary
- Nested
- Microcystic
- Sarcomatoïd
- Giant cell
- Trophoblastic differentiation
- Lympho-epithelioma type (lymphoid stroma)
- Plasmocytoid (independent cell)

Histological variant estimates

N=589 TURB reviewed: 19.5% variants, with 69% de TVIM



(*Shah Urol Oncol 2012*)

Histological variant estimates

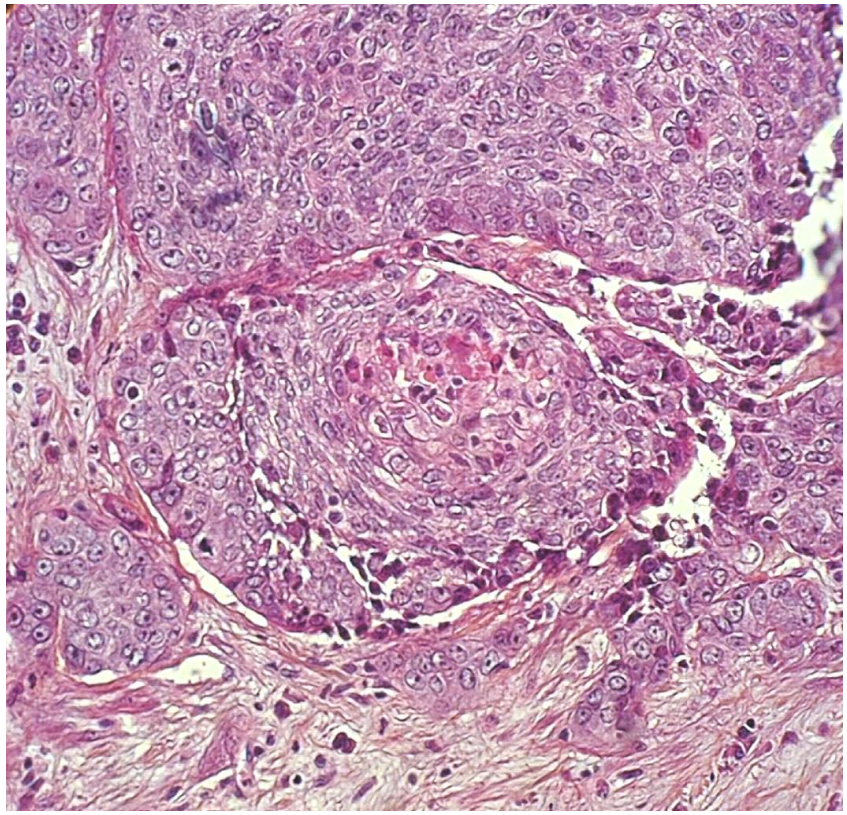
Frequencies under-estimated

- by resections (sampling, tumor heterogeneity)
  (sensibility 39%)
- by lack of expertise ?

Abd El-Latif J Urol 2012, Shah Urol Oncol 2012

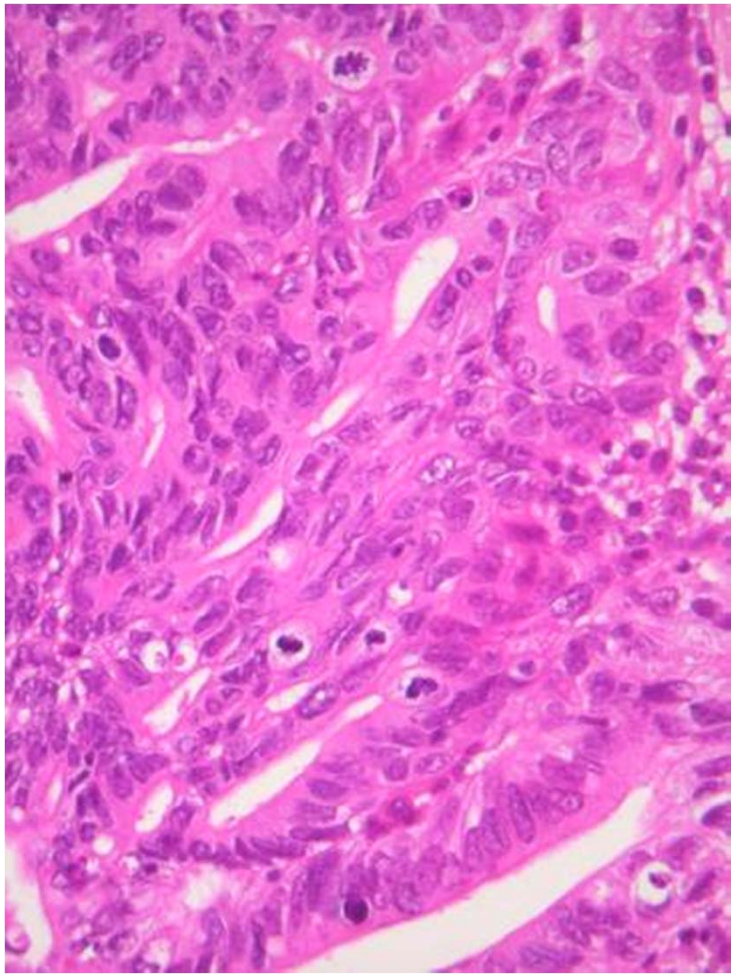
Urothelial carcinoma with squamous differentiation

- 10 - 60% of cases
- Threshold to define ? (>10% ?)
- The % of squamous component has to be precised
- CK5/6 +
- Associated with high grade, and advanced stages (pT3-pT4, N+)



Urothelial carcinoma with glandular differentiation

- <10 % cases ?
- Threshold to define ?
- The % of glandular component has to be precised
- Pronostic no specifically studied but jointly with UC with squamous differentiation



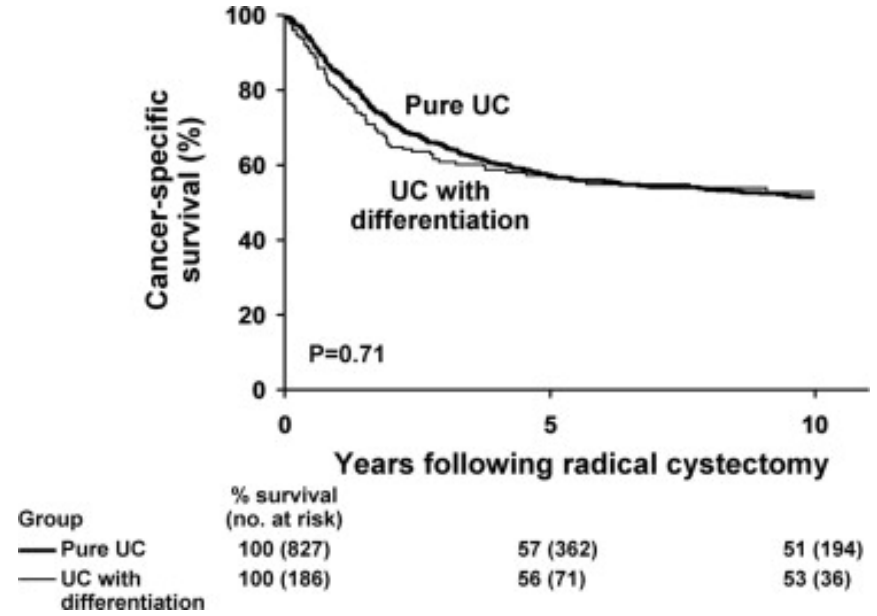
Impact of squamous or glandular differentiation in UC on survival after cystectomy

1013 patients : 827 (72%) pur UC and 186 (18%) with squamous differentiation(132), glandular (41) or both (13)

UC with vs without differentiation

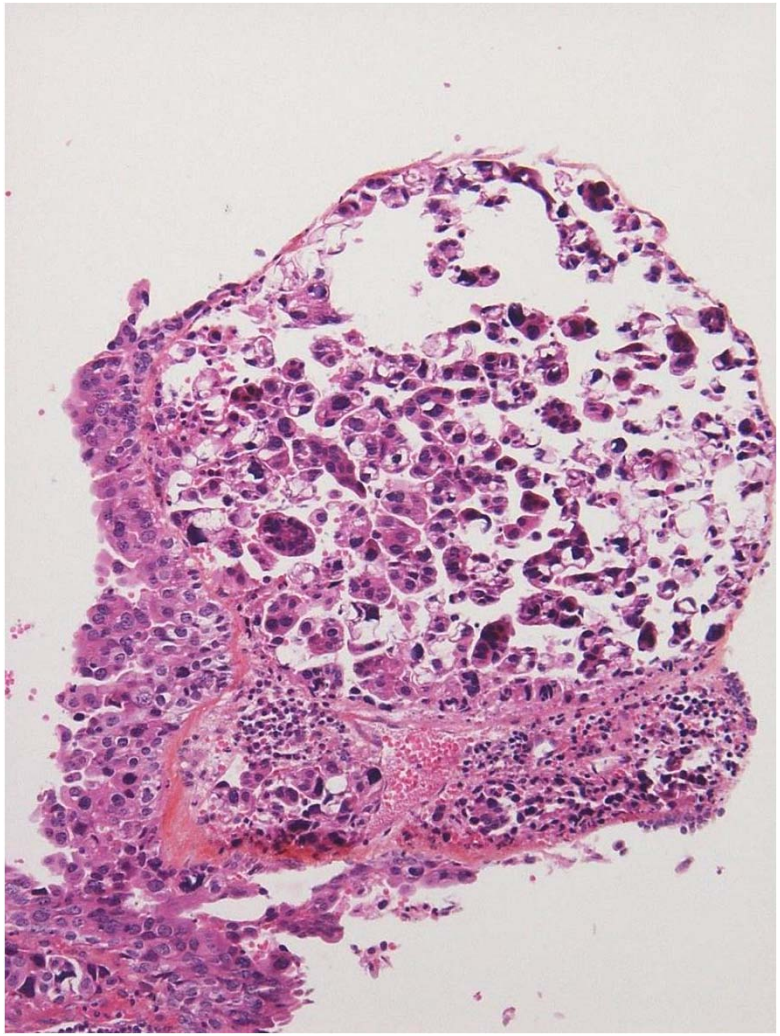
- pT3-T4 (70% vs 38%, p <0.0001)
- pN+ (20% vs 15%, p = 0.05)

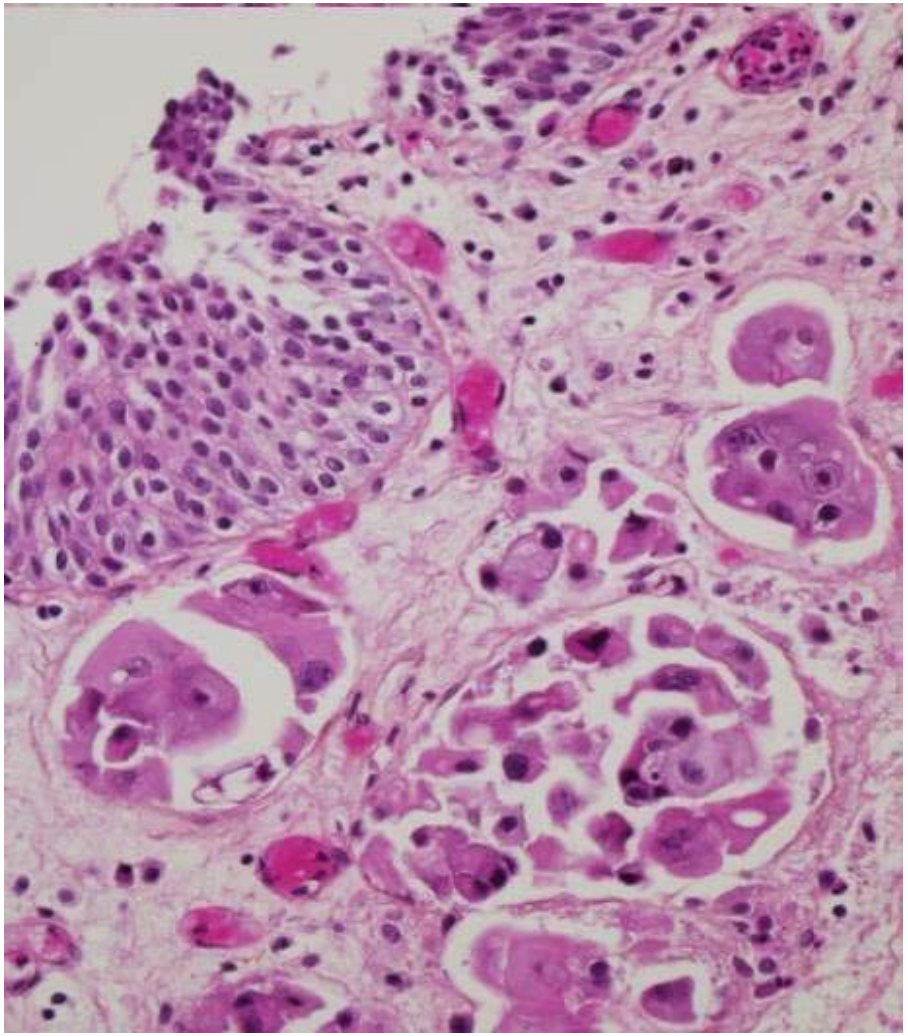
But, after adjustment for the stage, no difference of specific survival.



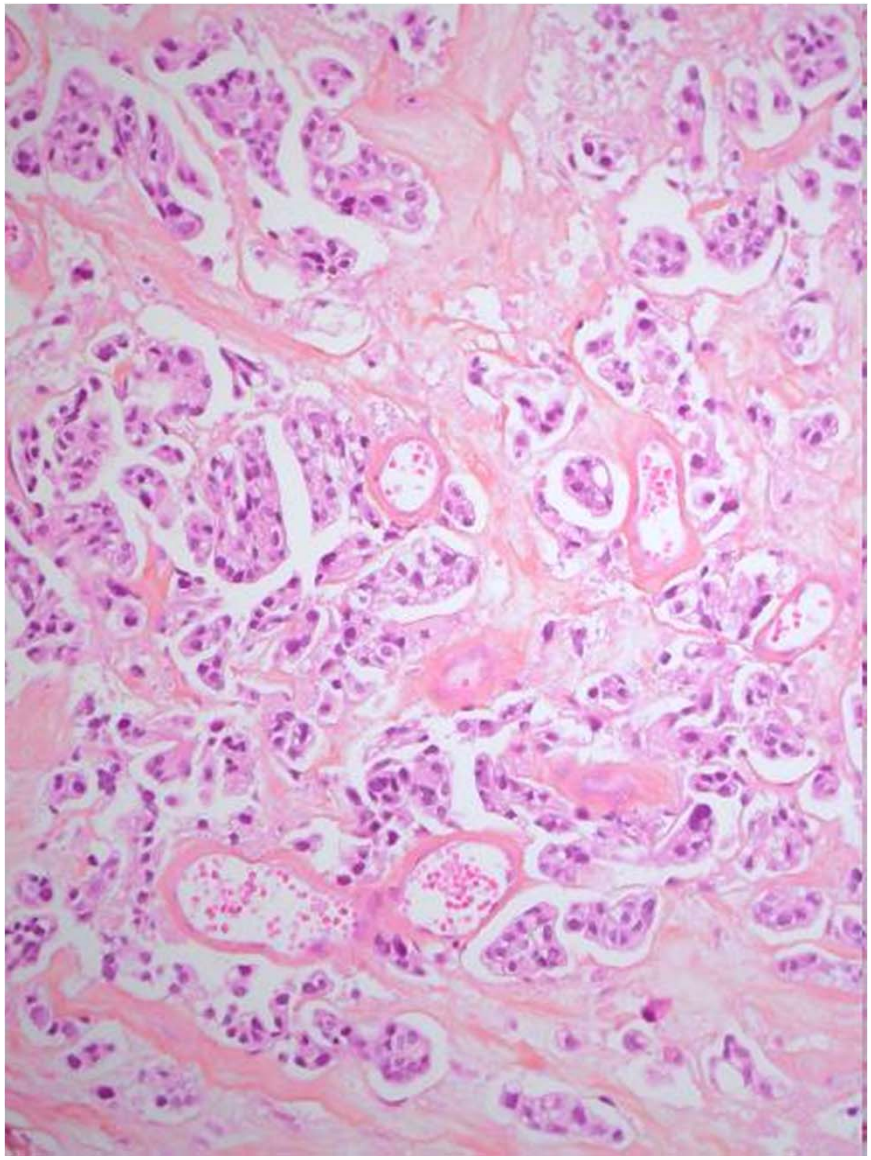
Kim J Urol 2012

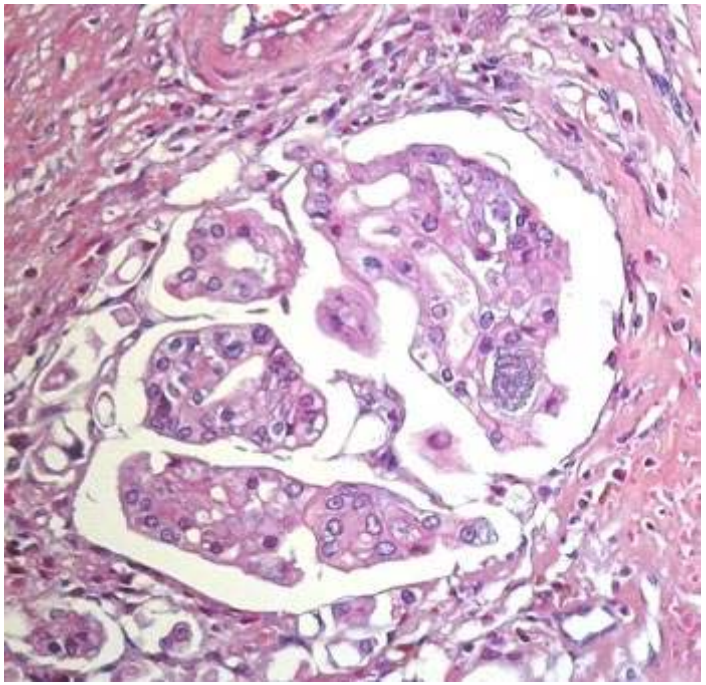
Micropapillary carcinoma

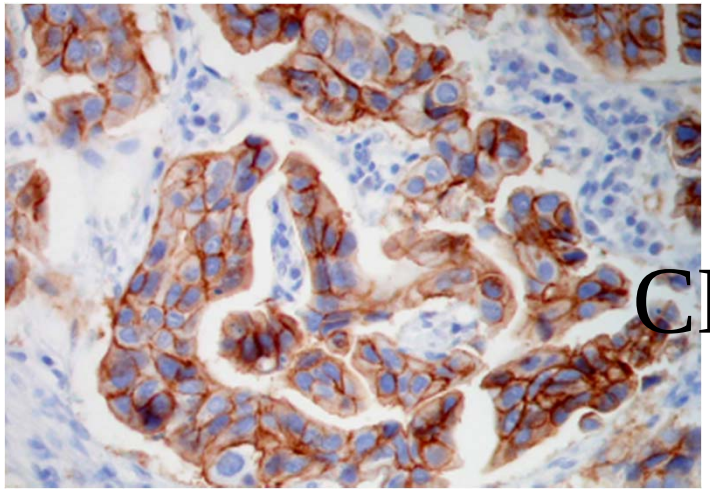




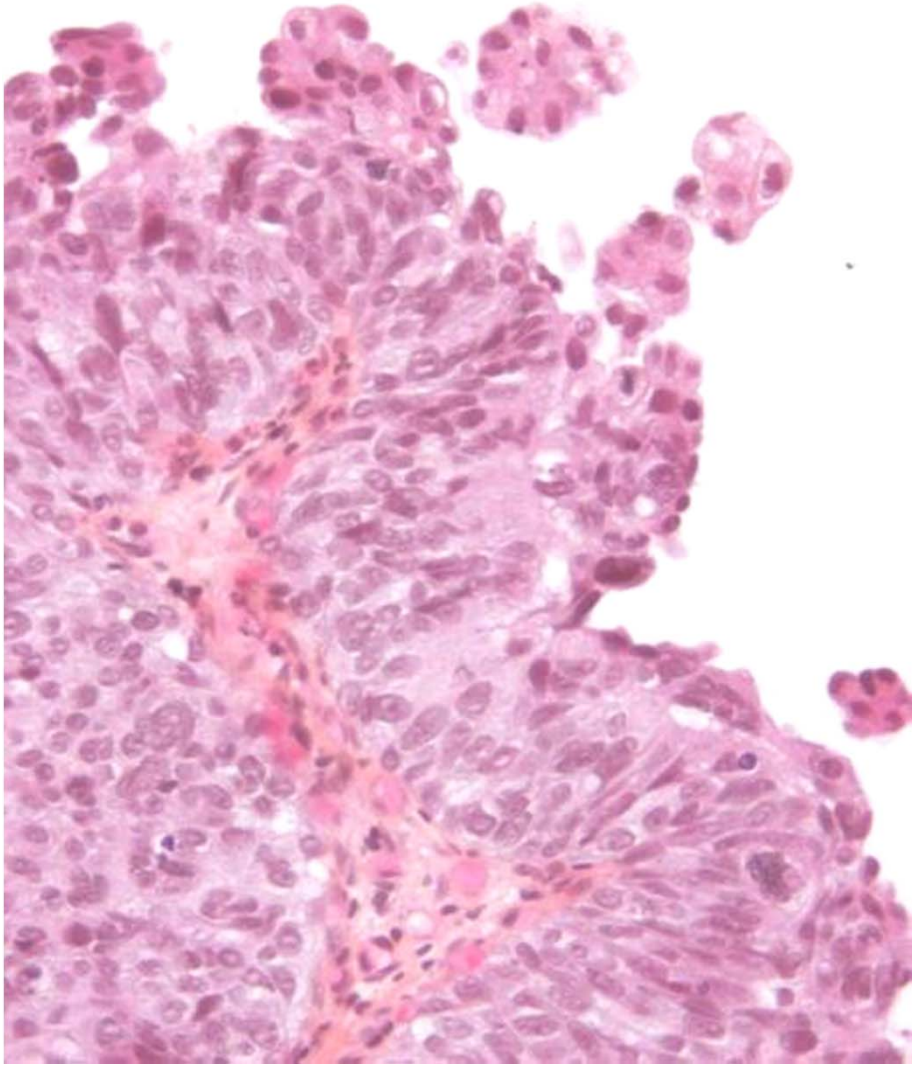
Micropapillary carcinoma

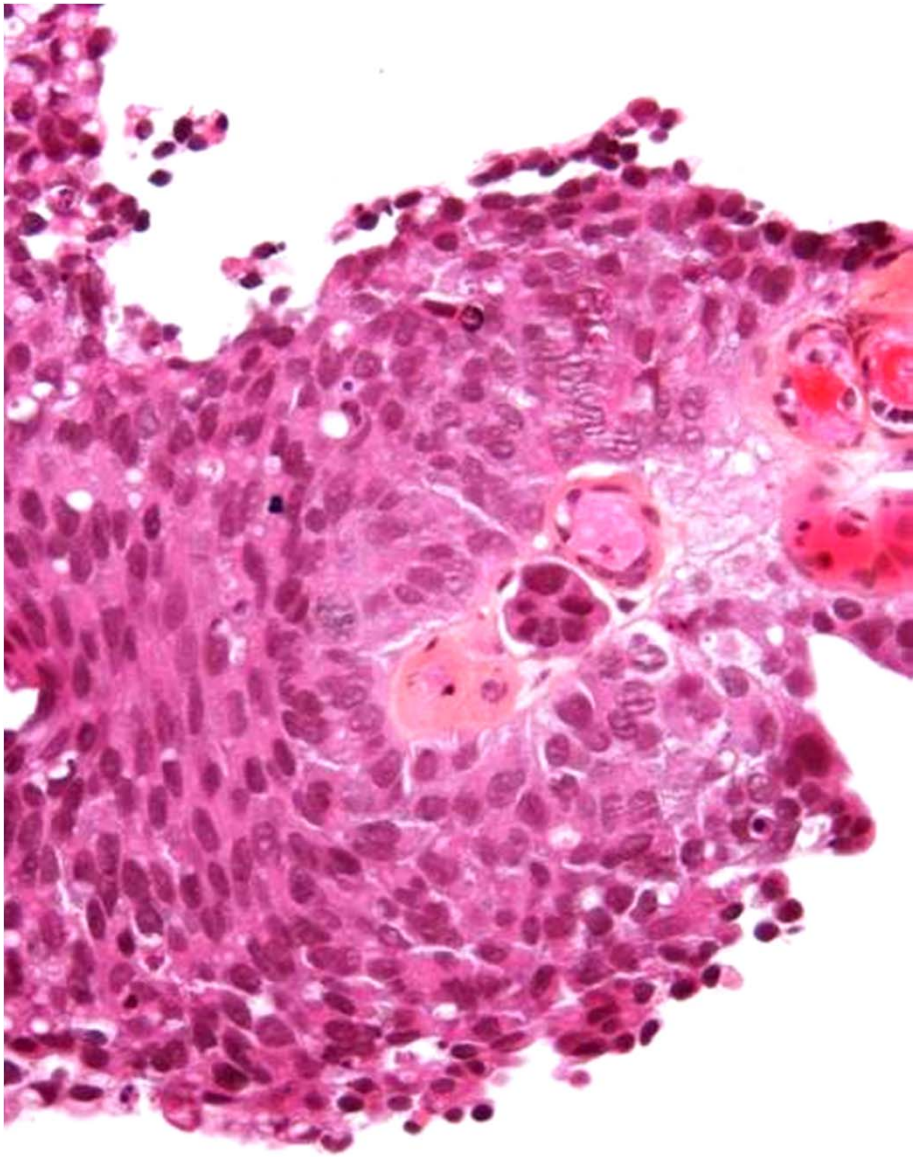






CK7

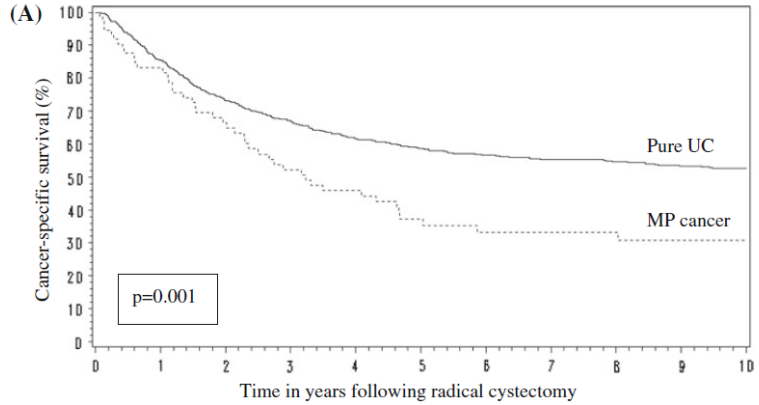




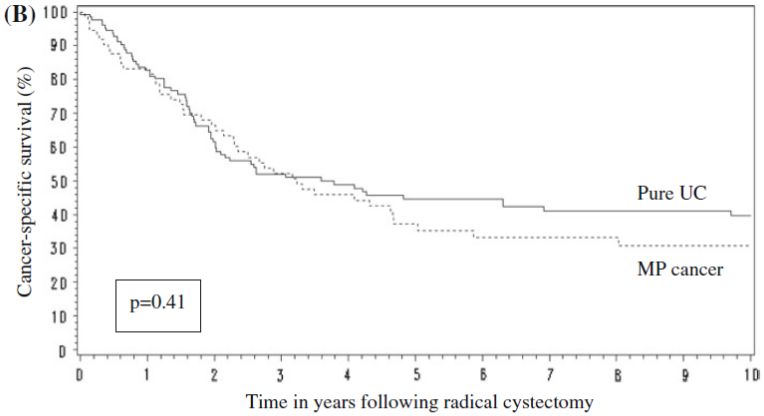
Micropapillary CIS

Courtesy Eva Compérat

Micropapillary carcinoma



	Number at risk		
Histology	0 years	5 years	10 years
MP cancer	73	19	10
Pure UC	748	340	182



	Number at risk		
Histology	0 years	5 years	10 years
MP cancer	73	19	10
Pure UC	136	40	26

Control group not paired

Control group paired according to stage pTN

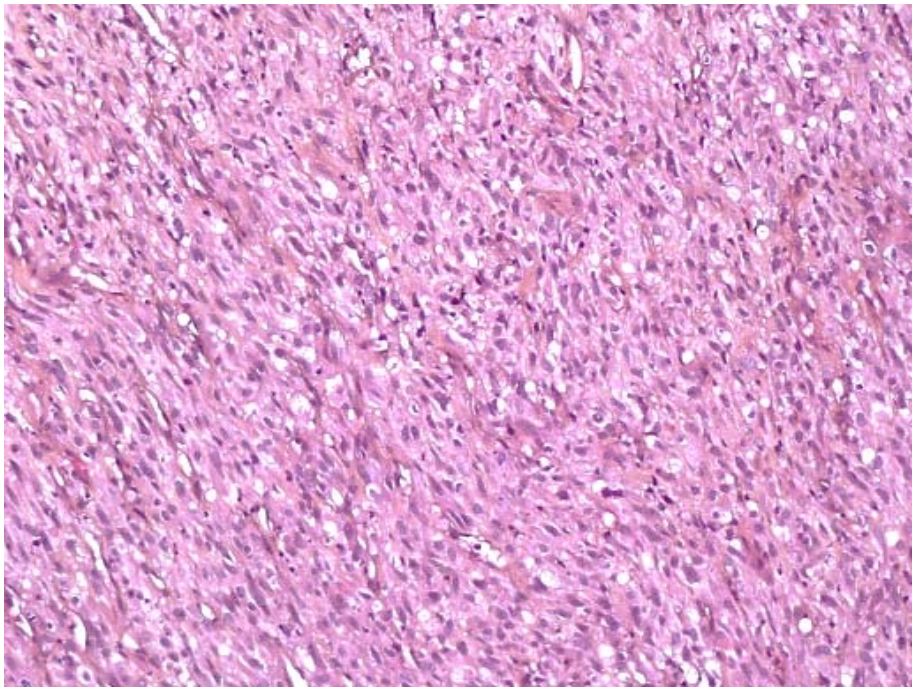
- Confirm association with advanced stage, des invasions lymphovascular invasions and LN invasion,
- Without difference with classical UC after pairement according to stage pTN

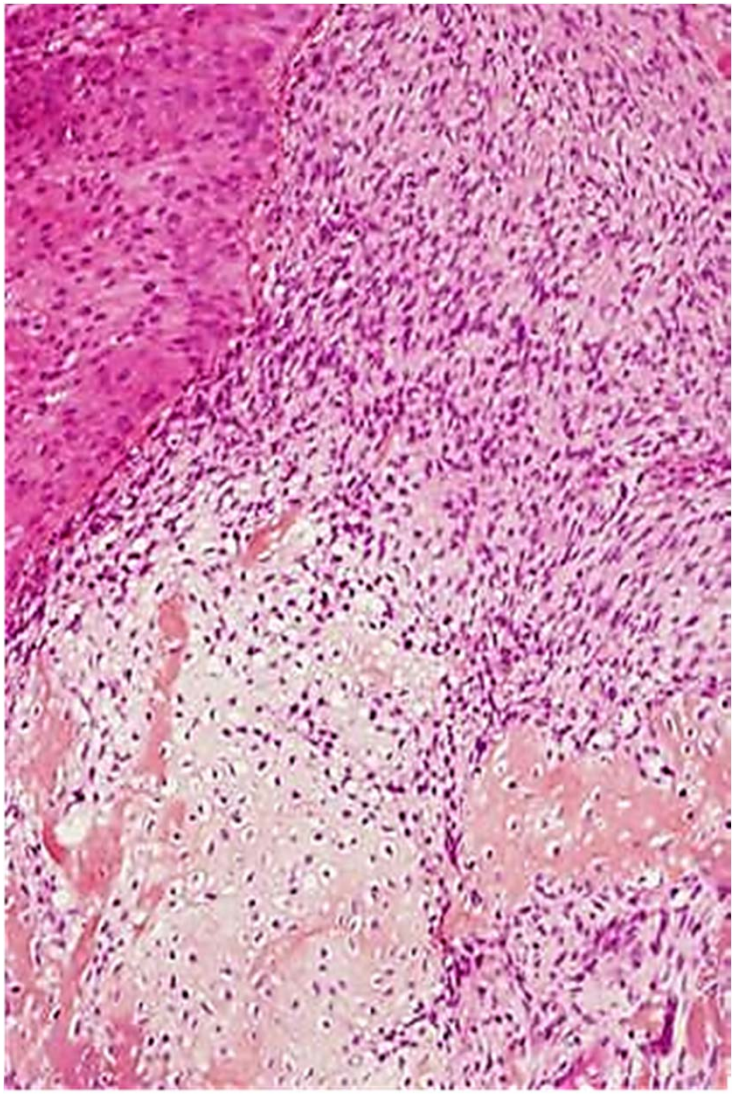
Wang World J Urol 2012

Sarcomatoid carcinoma

- The most frequent bladder spindle cell tumor in elderly people

- Indifferentiated (sarcomatoid carcinoma), or carcinosarcoma with specific differentiation (leiomyomatous, chondromatous, ...)

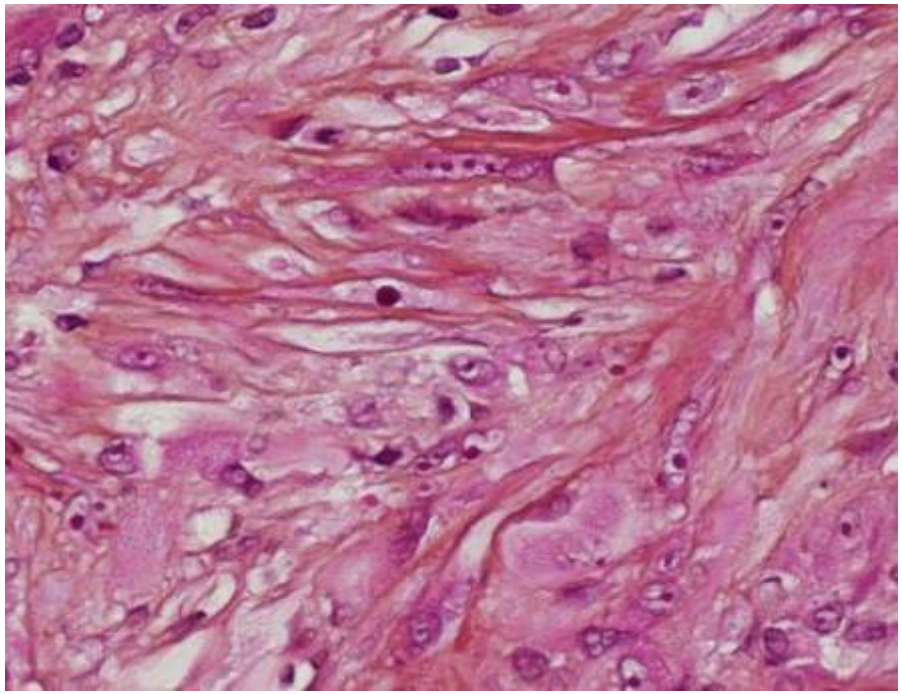


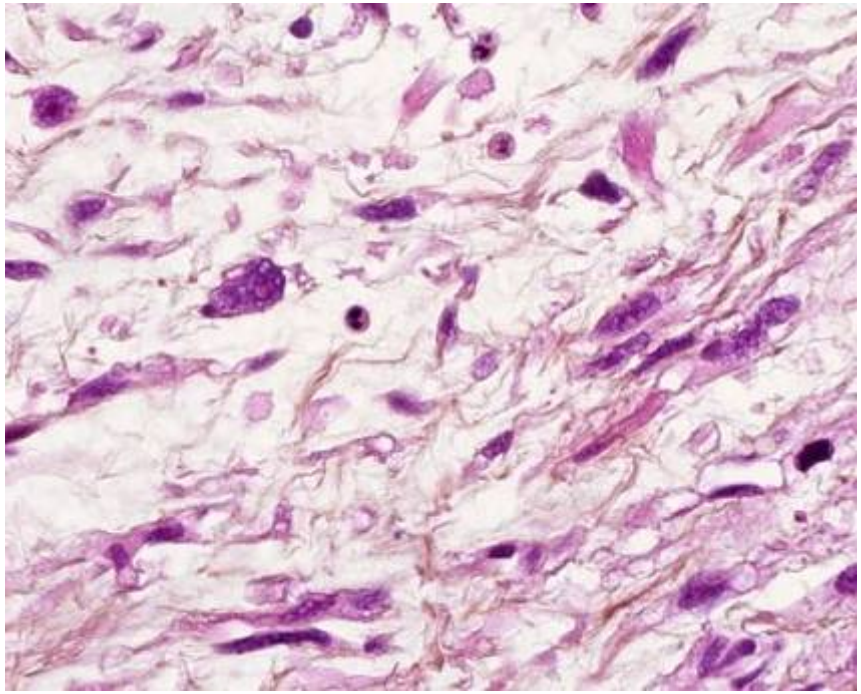


Lott Human Pathol 2007; Mc Kenney Adv Anat Pathol 2005; Ikegami Human Pathol 2000, Lopez-Beltran J Urol 1998

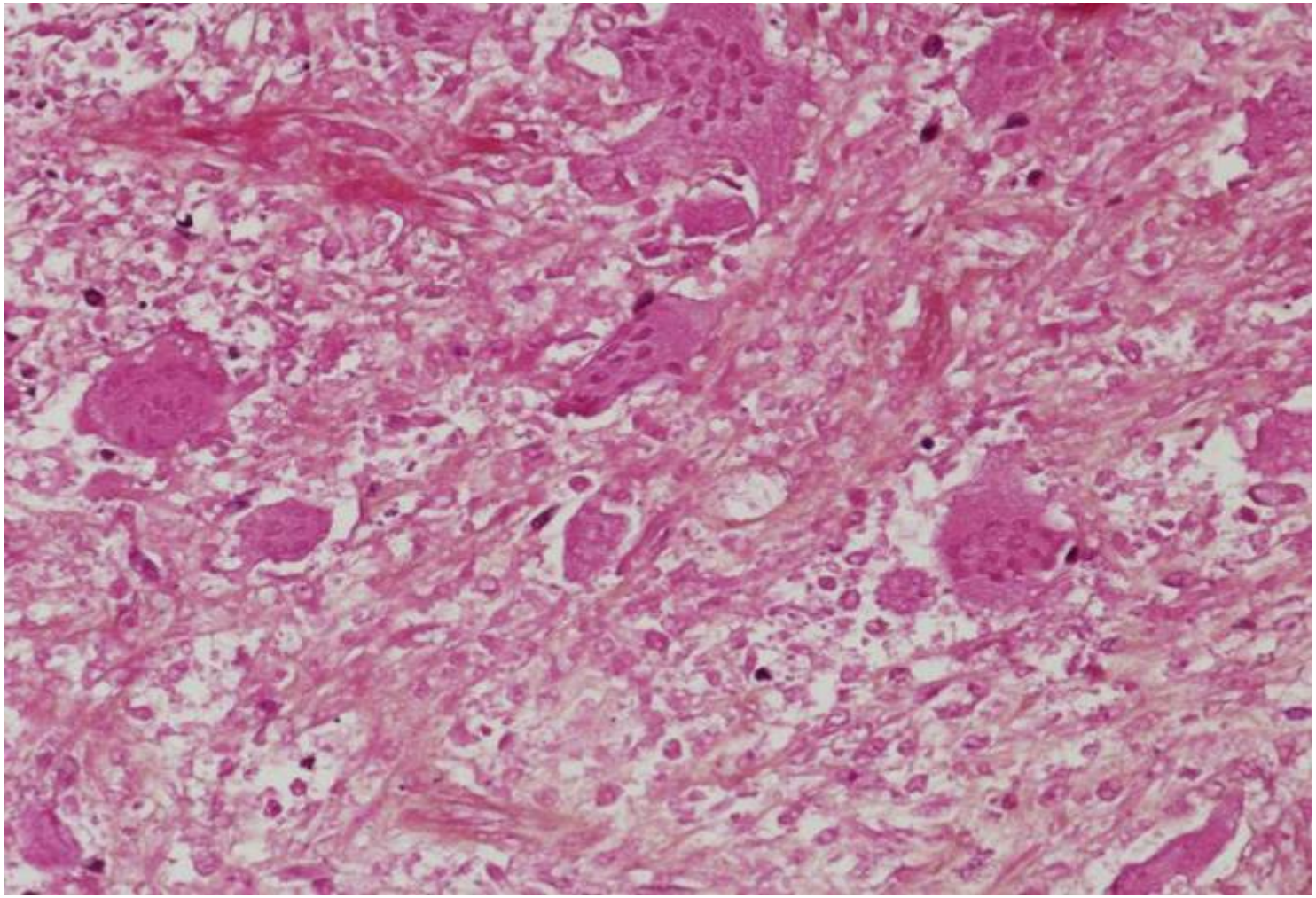
Sarcomatoid carcinoma

- Spindle cell arranged in fascicles or dispersed in a myxoid background
- Abnormal mitosis, pleomorphism, extensive necrosis, giant cell associated are frequent.





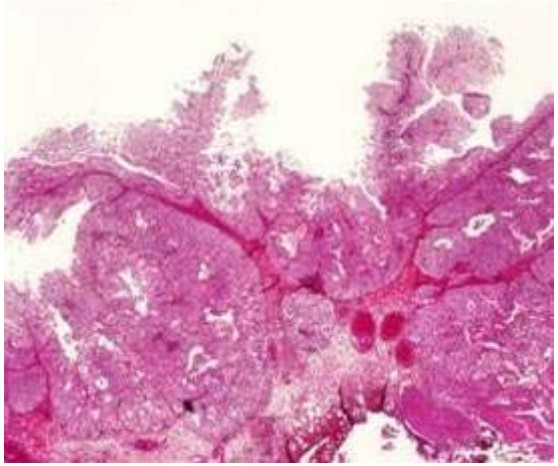
Sarcomatoid carcinoma with extensive necrosis



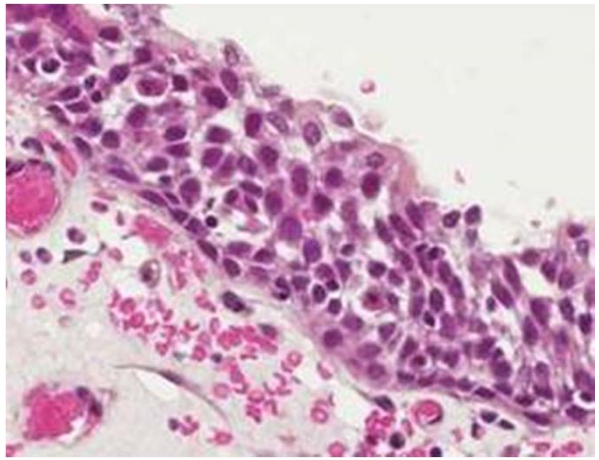
Sarcomatoid carcinoma

To confirm diagnosis, find an epithelial component

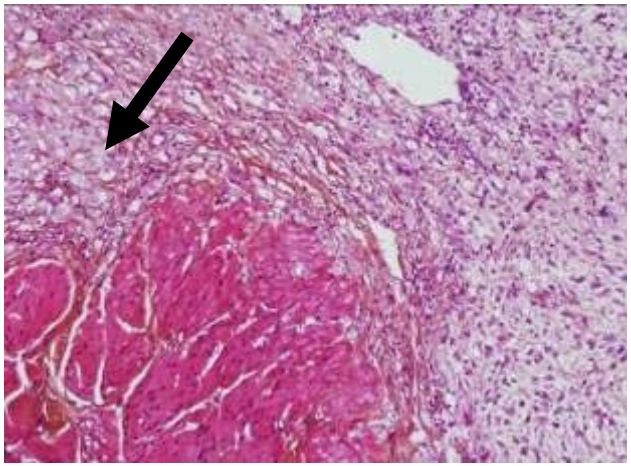
Papillae



Carcinoma *in situ*



Epithelio-mesenchymal transition



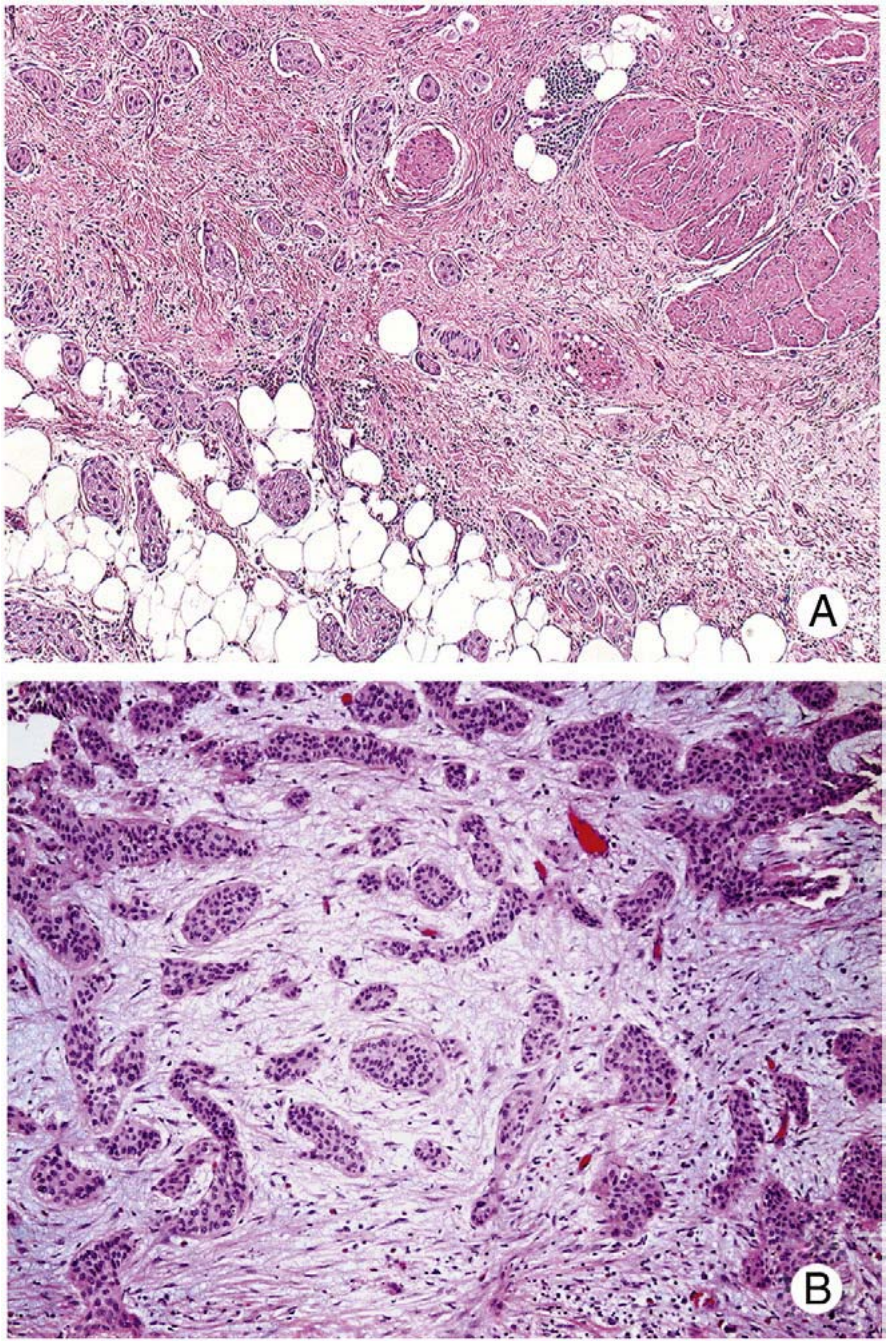
Sarcomatoid carcinoma and prognosis

- A study with 135 sarcomatoid carcinoma , 166 carcinosarcoma, and 46515 invasive UC ,
- Overall survival 37%, 17% and 47% at 5 years,
- In comparaison with classical UC, the stage T is higher, and LN and metastasis are more frequent for the sarcomatoid carcinoma and carcinosarcoma.
- In multivariate analysis, the specific risk of death is also higher.

Black J Urol. 2007.

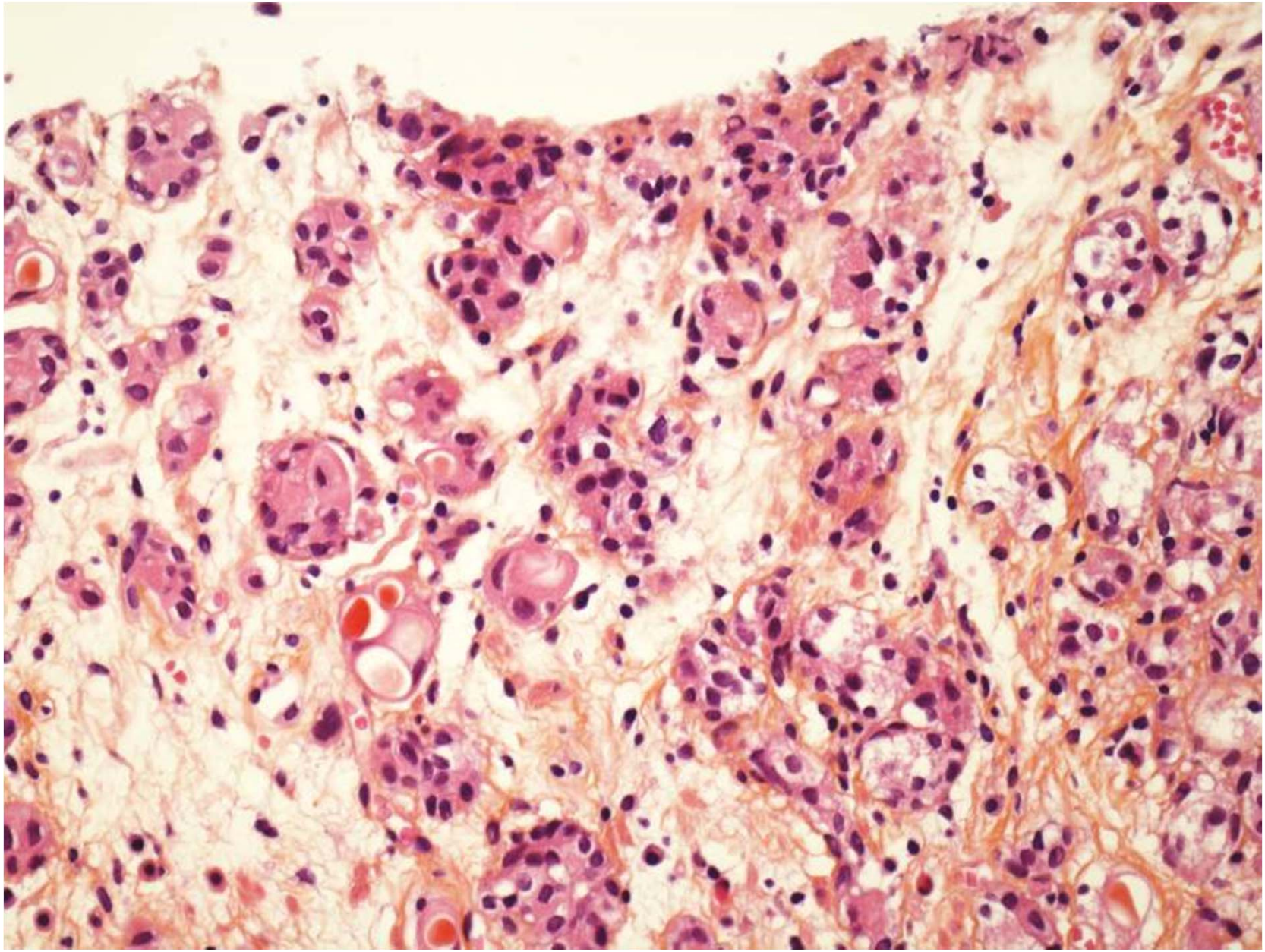
Nested variant

- Differential diagnosis with von Brunn nests
- Pure or associated with classical UC
- Associated with muscle invasion, extravesical invasion, and metastasis
- After ajustment for the stage, the prognosis is not different from classical UC.

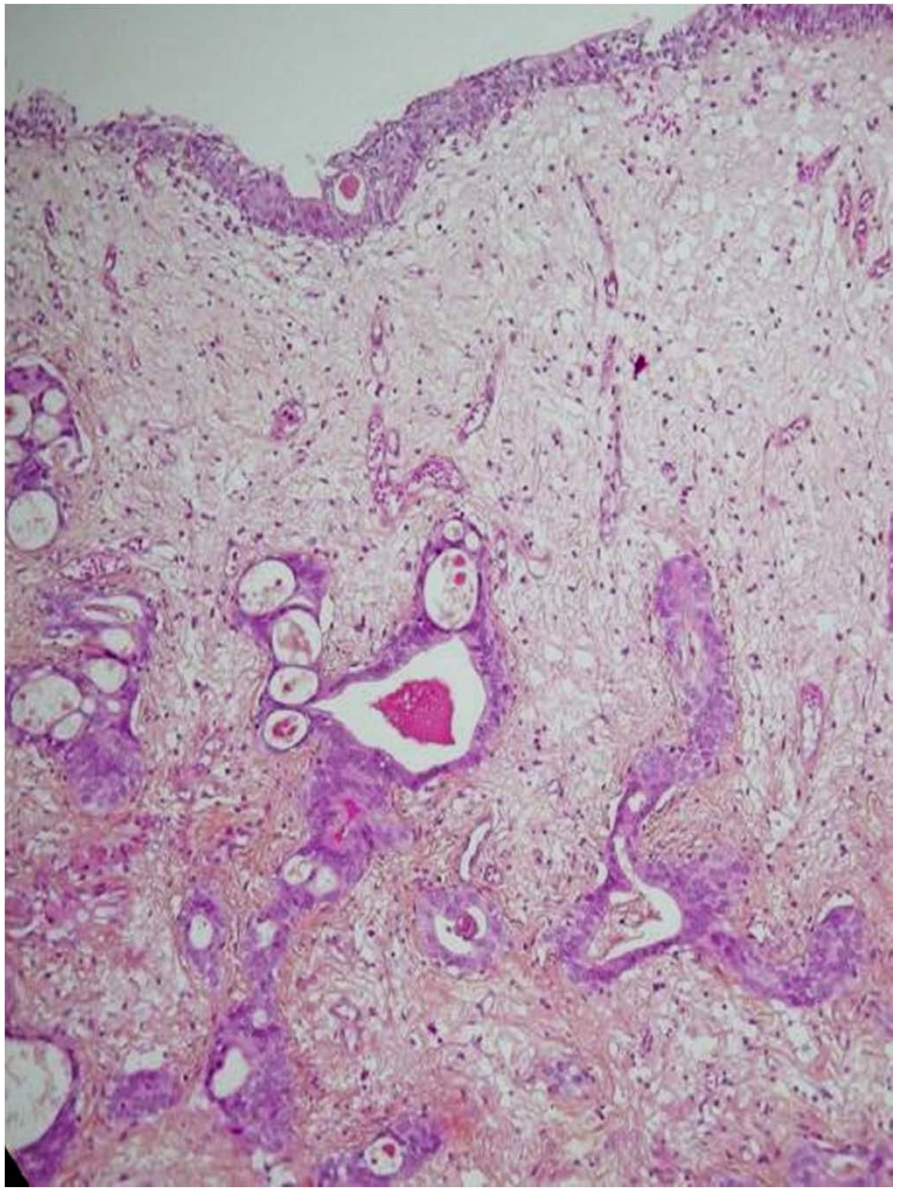


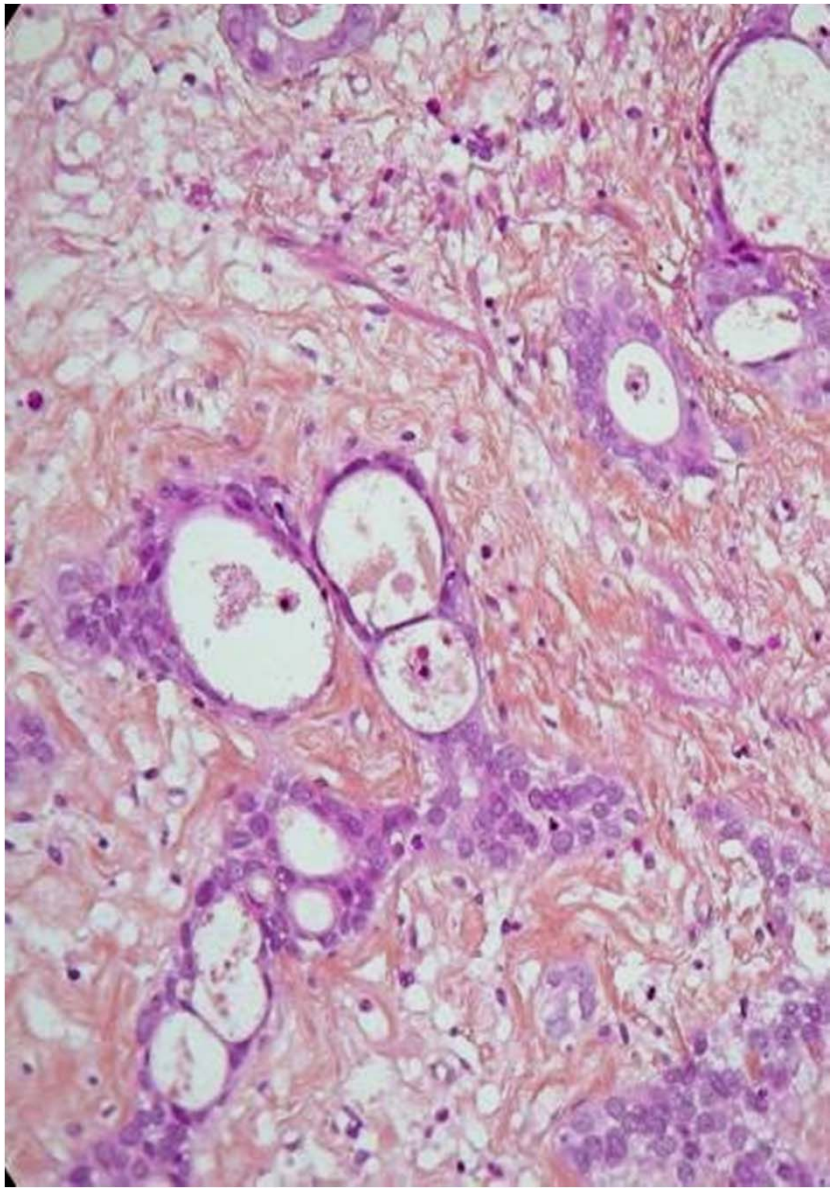
Wasco Human Pathol 2009,
Linder J Urol 2012

Nested carcinoma



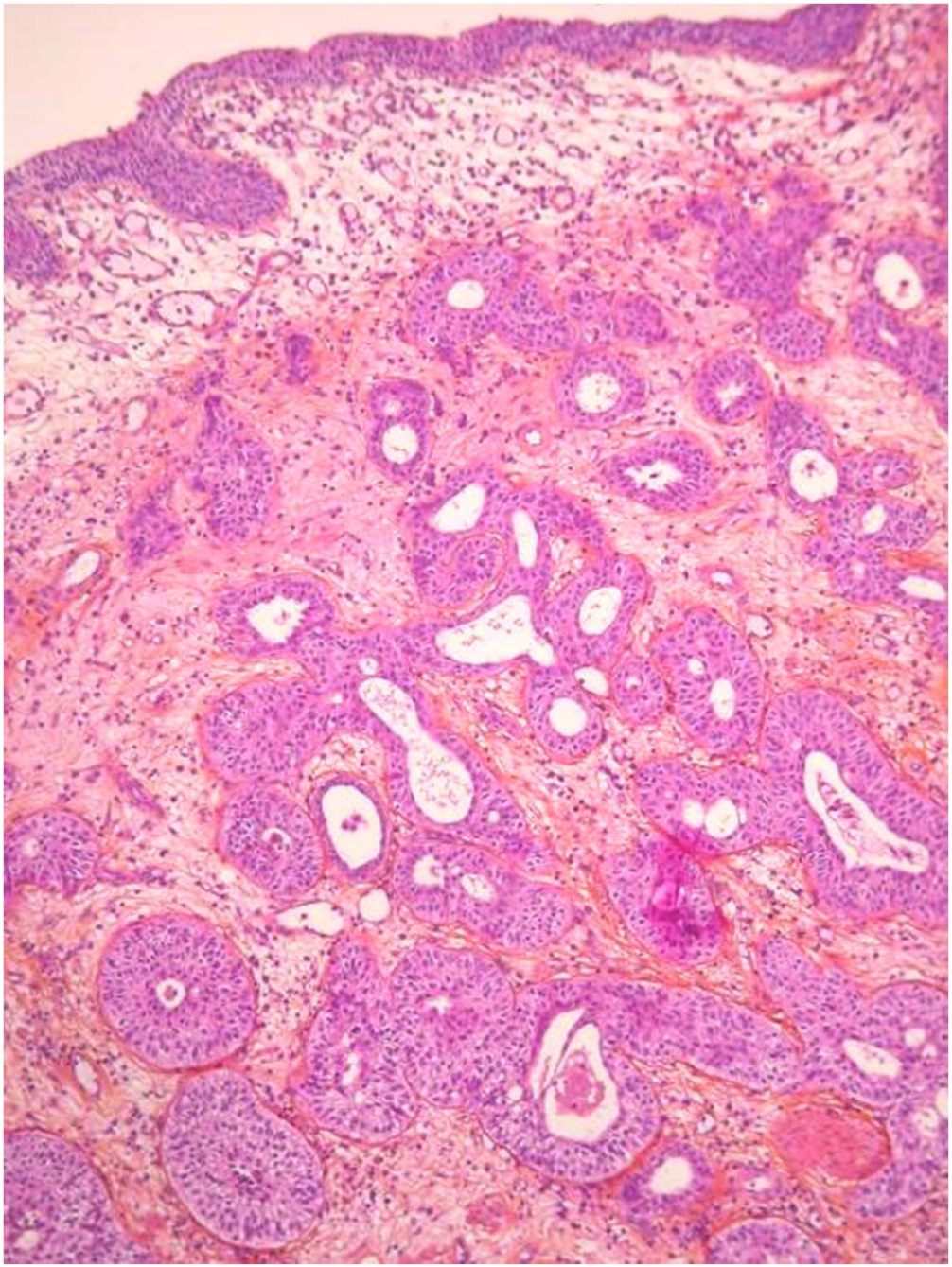
Microcystic carcinoma



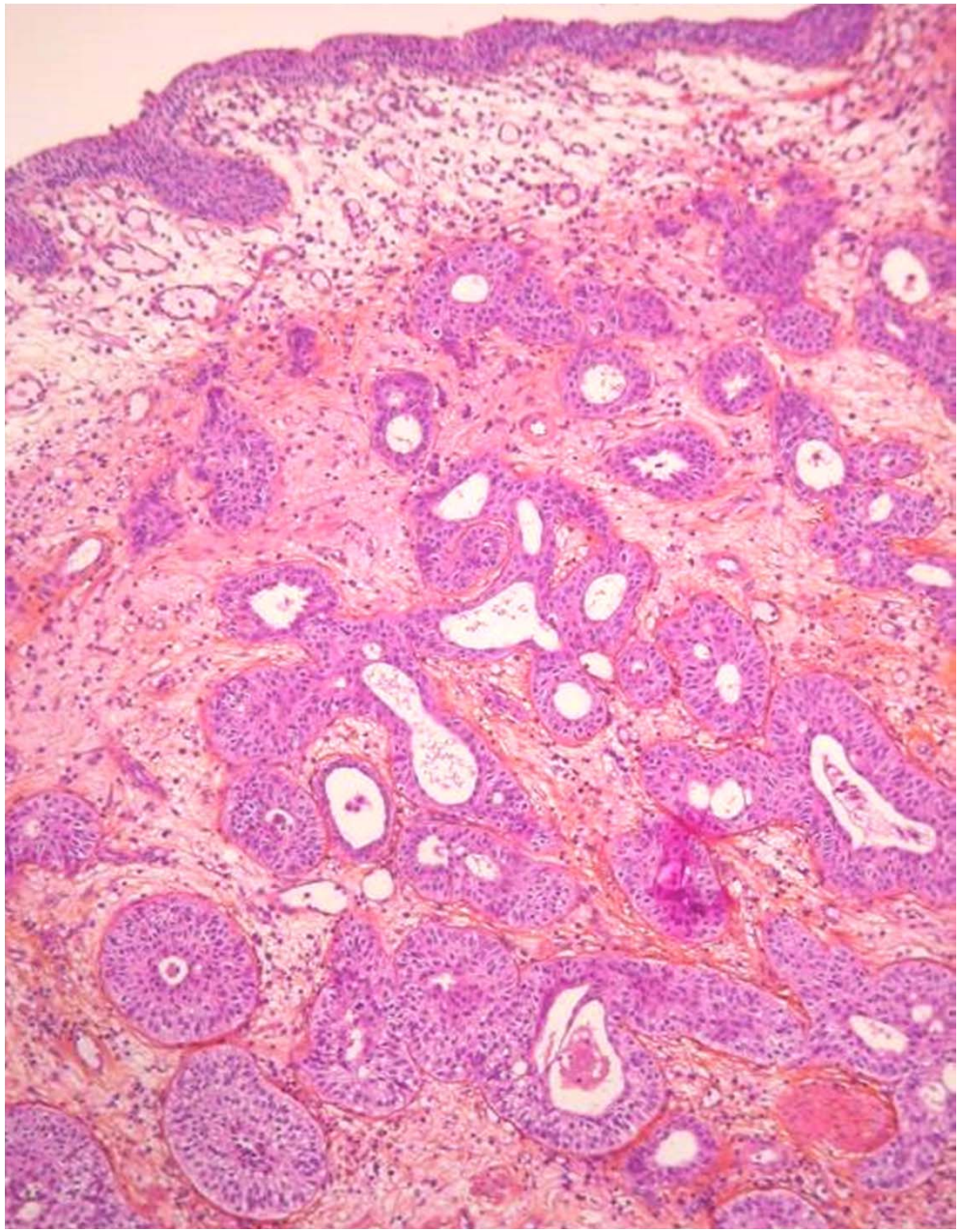


Microcystic carcinoma

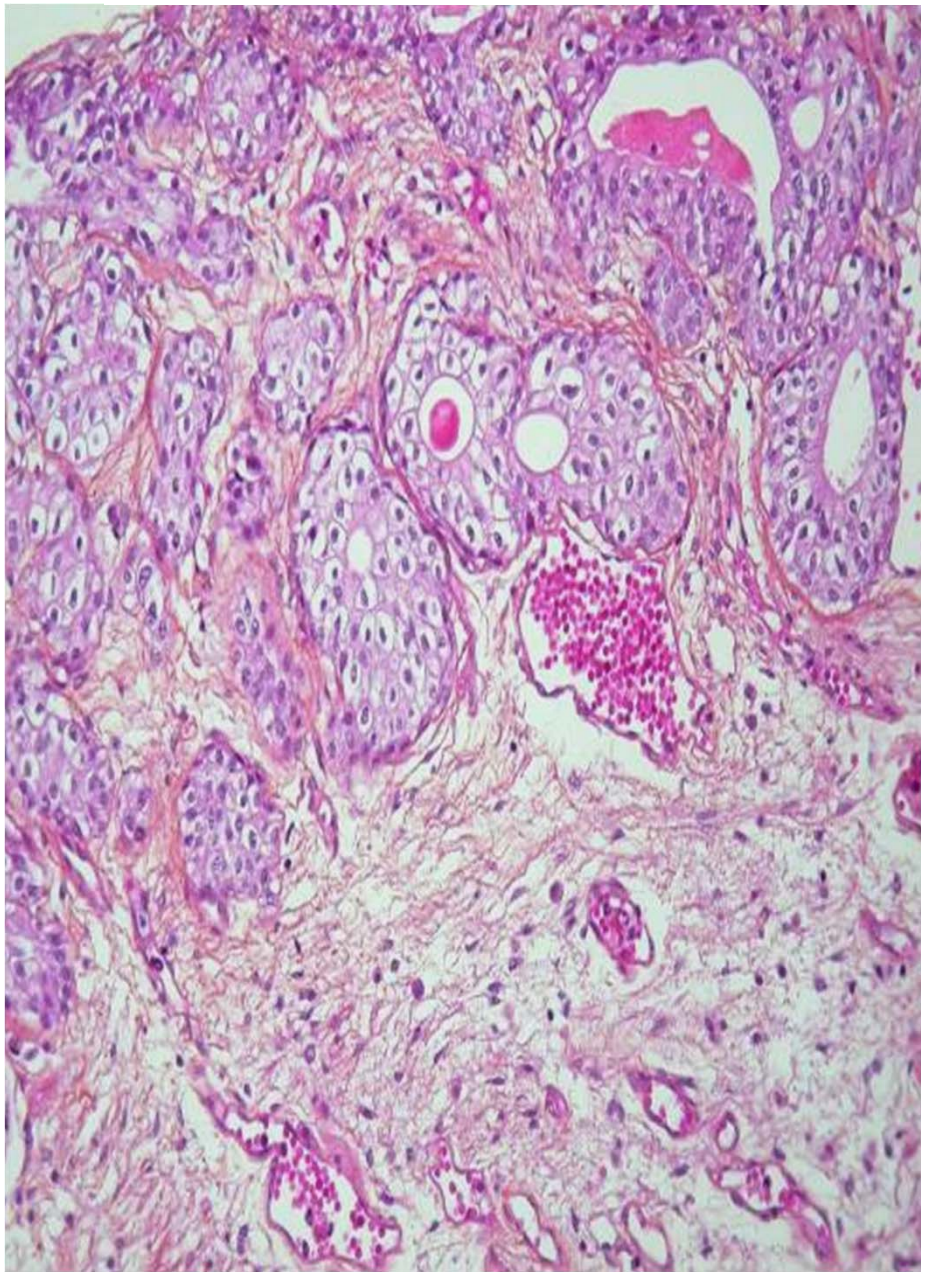
Shares some features with the nested variant and can be associated with it

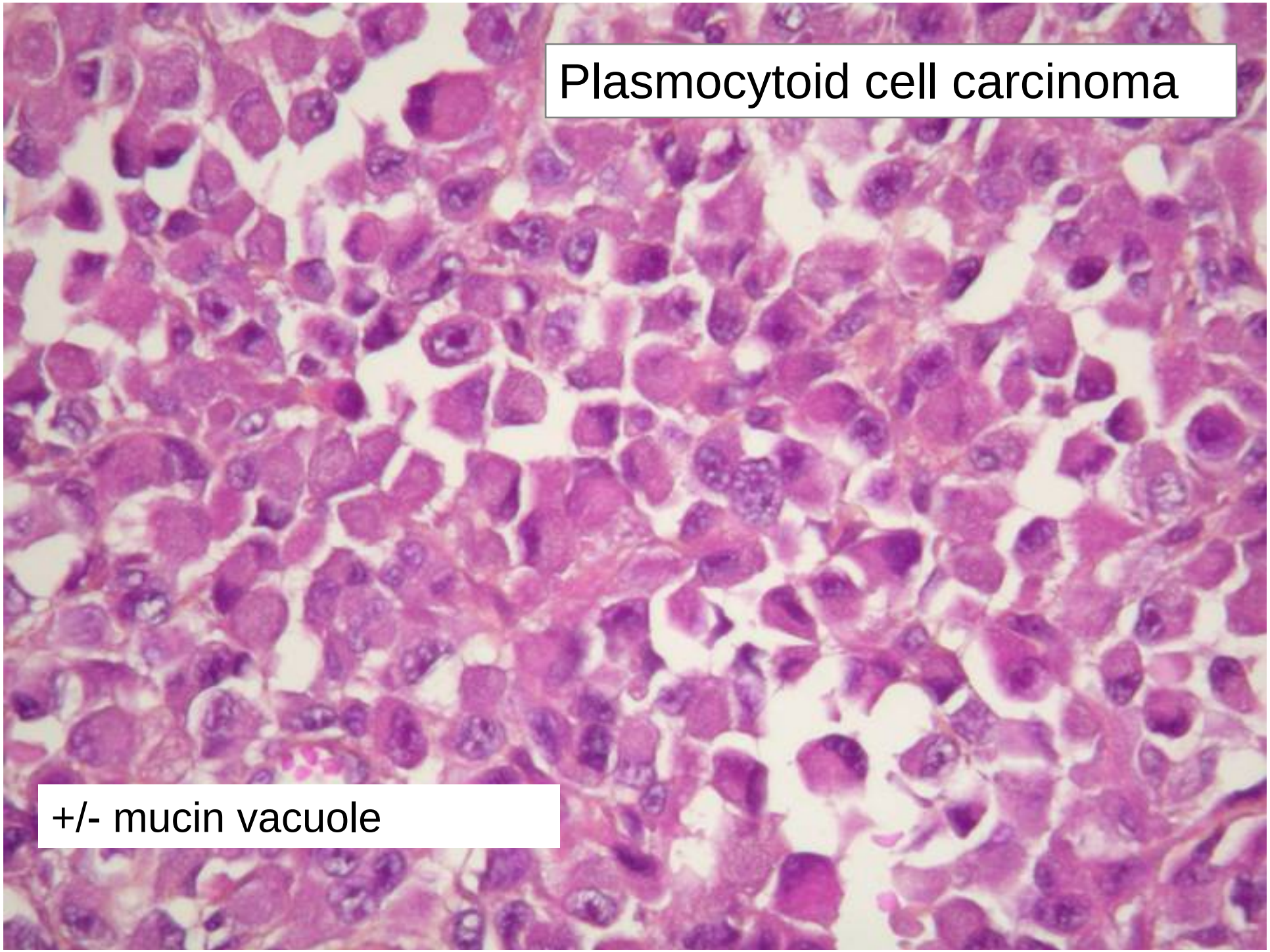


Microcystic carcinoma



Von Brünn nests with cystic pattern




Plasmocytoid cell carcinoma
+/- mucin vacuole

For these variants, there is no relevant prognostic study due to their very low frequency.

- Plasmocytoid carcinoma
- Microcystic carcinoma
- Carcinoma lympho-epithelioma like
- Carcinoma with giant cells
- Carcinoma with trophoblastic differentiation
- Undifferentiated carcinoma

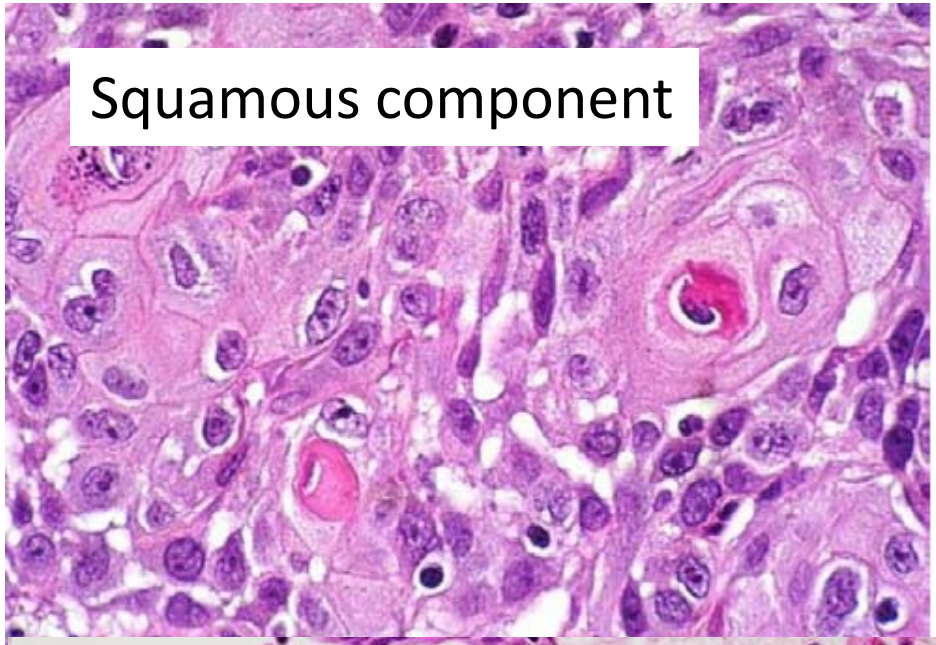
Nigwekar Am J Surg Pathol 2009

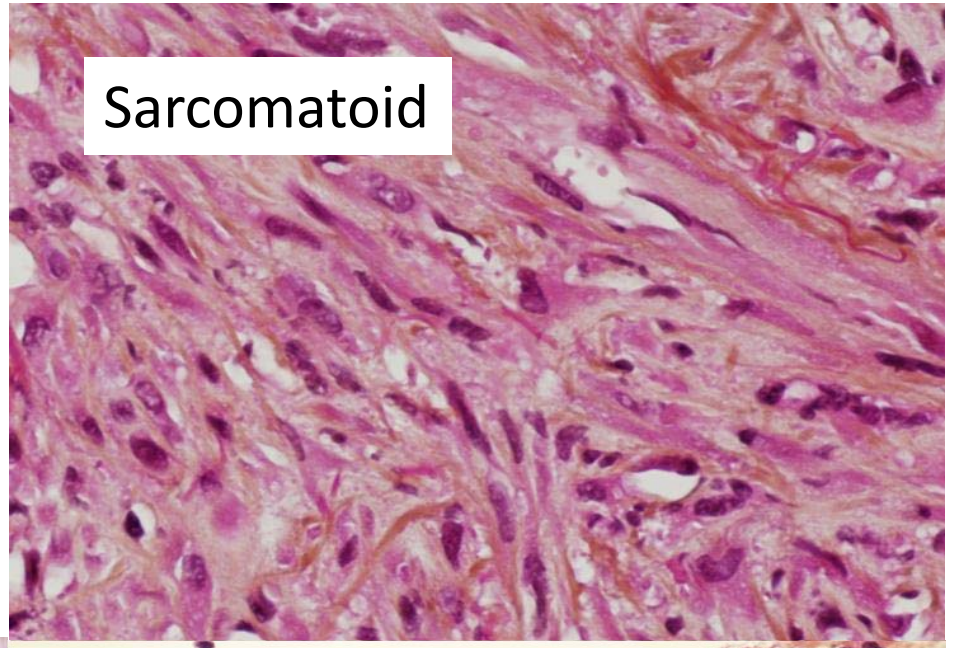
Impact of identifying histological subtypes in UC?

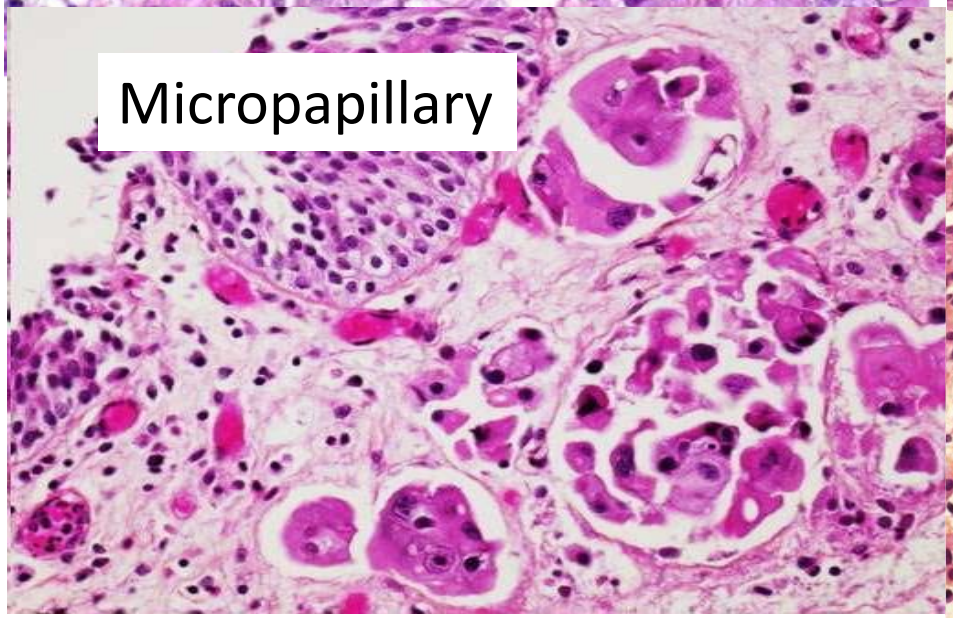
- The histological variants increase the risk of locally advanced or metastatic disease
- There is also an increased risk of under-stadification and occult micrometastatic disease at diagnosis
- For some groups, it is an evidence to support neoadjuvant chemotherapy
- The possibility of specific targeted therapies related to these subtypes remains undetermined.

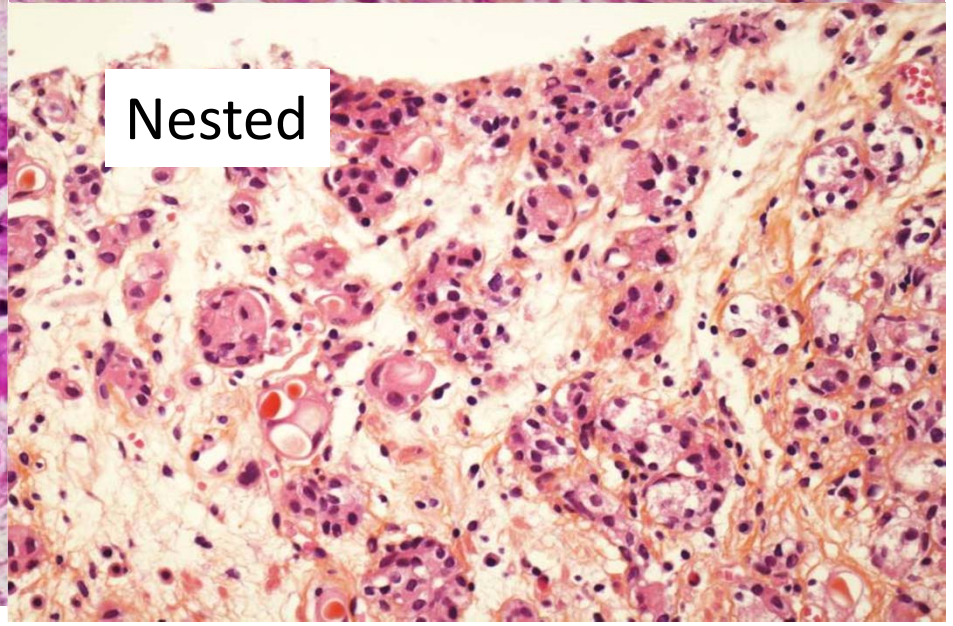
Black Urol Oncol 2009, Turker BJU Int 2012,
Amin Eur Urol 2013

Histological subtypes and NMIBC









Histological subtypes and NMIBC

Associated with a risk of underestimate the stage and with the risk of progression

They should be noticed in the report

A second look is mandatory to check the stage

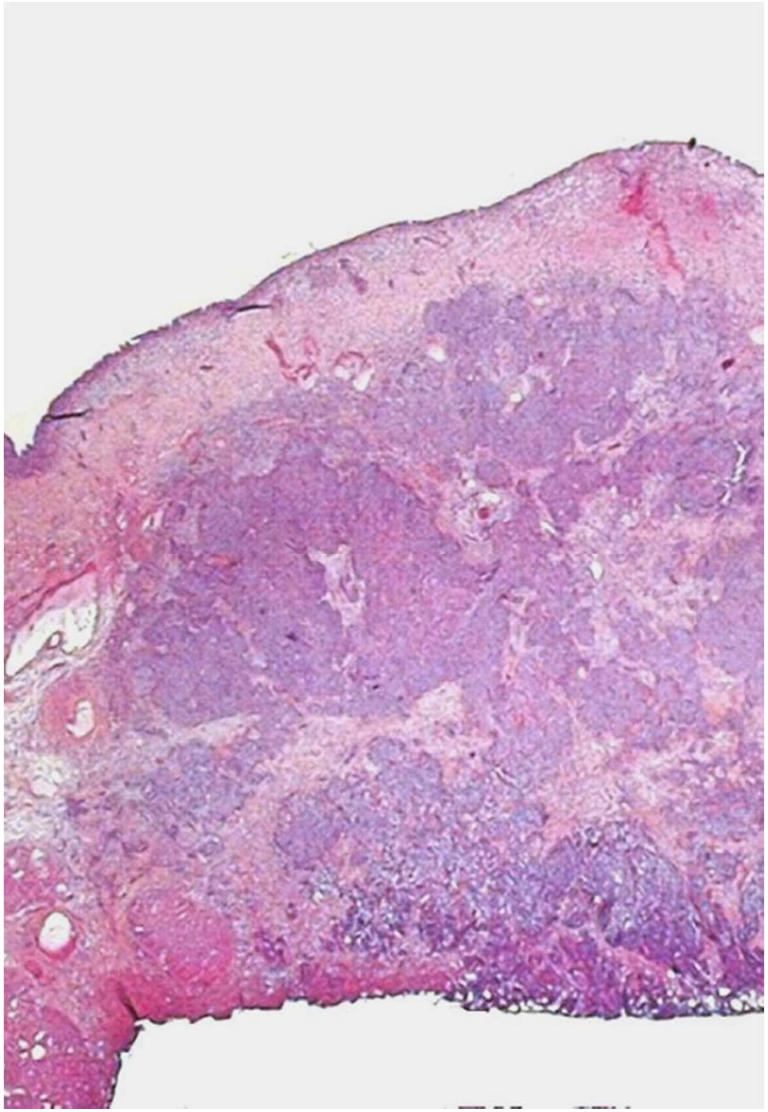
For some teams, it is a criteria to favor cystectomy rather than conservative TURB+BCG.

Kamat J Urol 2006, Black Urol Oncol 2009

Outline

- Normal features in bladder
- Natural history of UBC
- Diagnosis and prognosis of UBC on TURB
- Histological subtypes of UBC
- Differential diagnosis of UBC
- Prognosis features on cystectomy

Main differential diagnosis for invasive urothelial carcinoma



1) Primary bladder tumors
   Pure squamous cell carcinoma
   Pure adenocarcinoma (bladder or ouraque)
   Neuroendocrine carcinoma poorly differentiated

2) 2) Regional extension
   Prostate adenocarcinoma +++
   Uterine cervix carcinoma +
   Rectal adenocarcinoma
   Ovarian tumor

3) metastases
   Breast adenocarcinoma other

Differential diagnosis for papillary urothelial tumor in bladder

- Non tumoral lesions (papillary hyperplasia)

- Non urothelial tumor :
  - Rare pure squamous tumor
  - Prostatic carcinoma extended to bladder
  - All non-bladder tumor invading the surface of the bladder are prone to develop a papillary or pseudo-papillary pattern

Differential diagnosis of flat CIS

- Flat hyperplasia without atypia
- Reactive changes (inflammation, radiotherapy, cyclophosphamide)
- Dysplasia

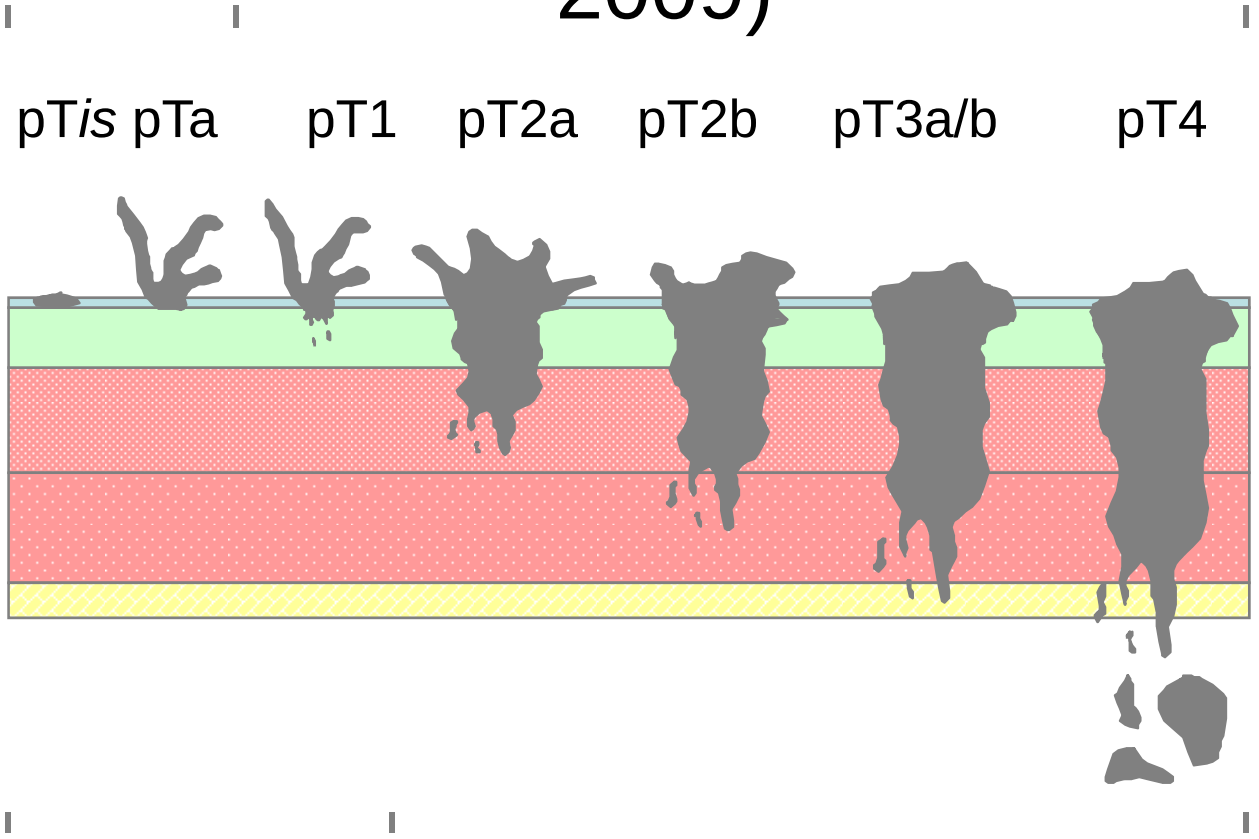
Outline

- Normal features in bladder
- Natural history of UBC
- Diagnosis and prognosis of UBC on TURB
- Histological subtypes of UBC
- Differential diagnosis of UBC
- Prognosis features on cystectomy

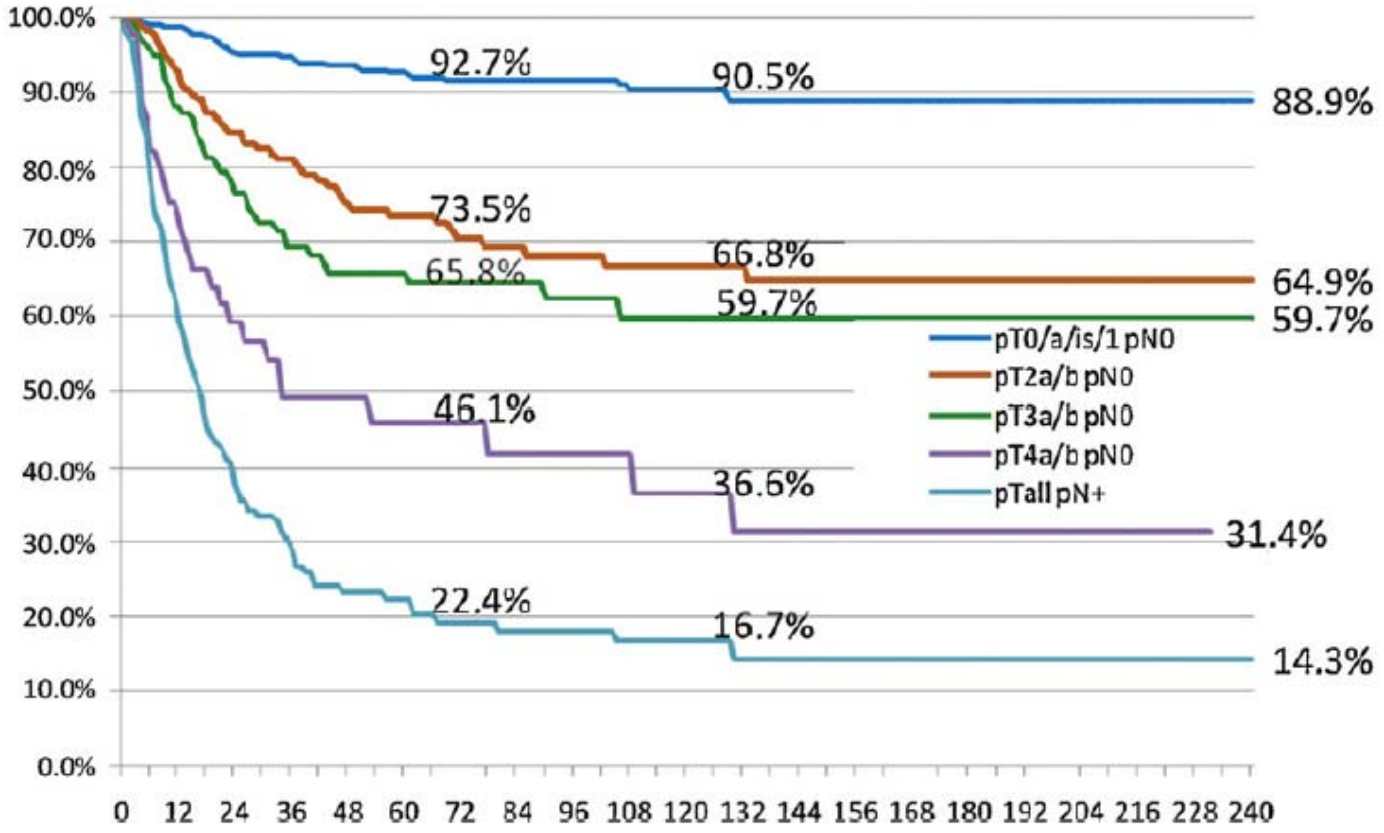
Prognosis evaluation on cystectomy

- Staging pT (cystectomy specimen) and pN (lymphadenectomy)
- Margins
- Lympho-vascular invasion
- Patterns of infiltration
- Histological sub-type
- For men, prostate and seminal vesicle invasion
- In case of neoadjuvant treatment , response?

Tumor stage (TNM 2009)



Courtesy F. Larousserie



Cancer specific survival (n=1,100)

Hautmann et al. Eur Urol 2012

Classification TNM 2009 regional lymph nodes

- Nx : non evaluable
- N0 : no sign of LN invasion
- N1 : one pelvic LN invaded
- N2 : > 1 pelvic LN invaded
- N3 : one or more extra-pelvic LN invaded

Lymph nodes (TNM 2002)

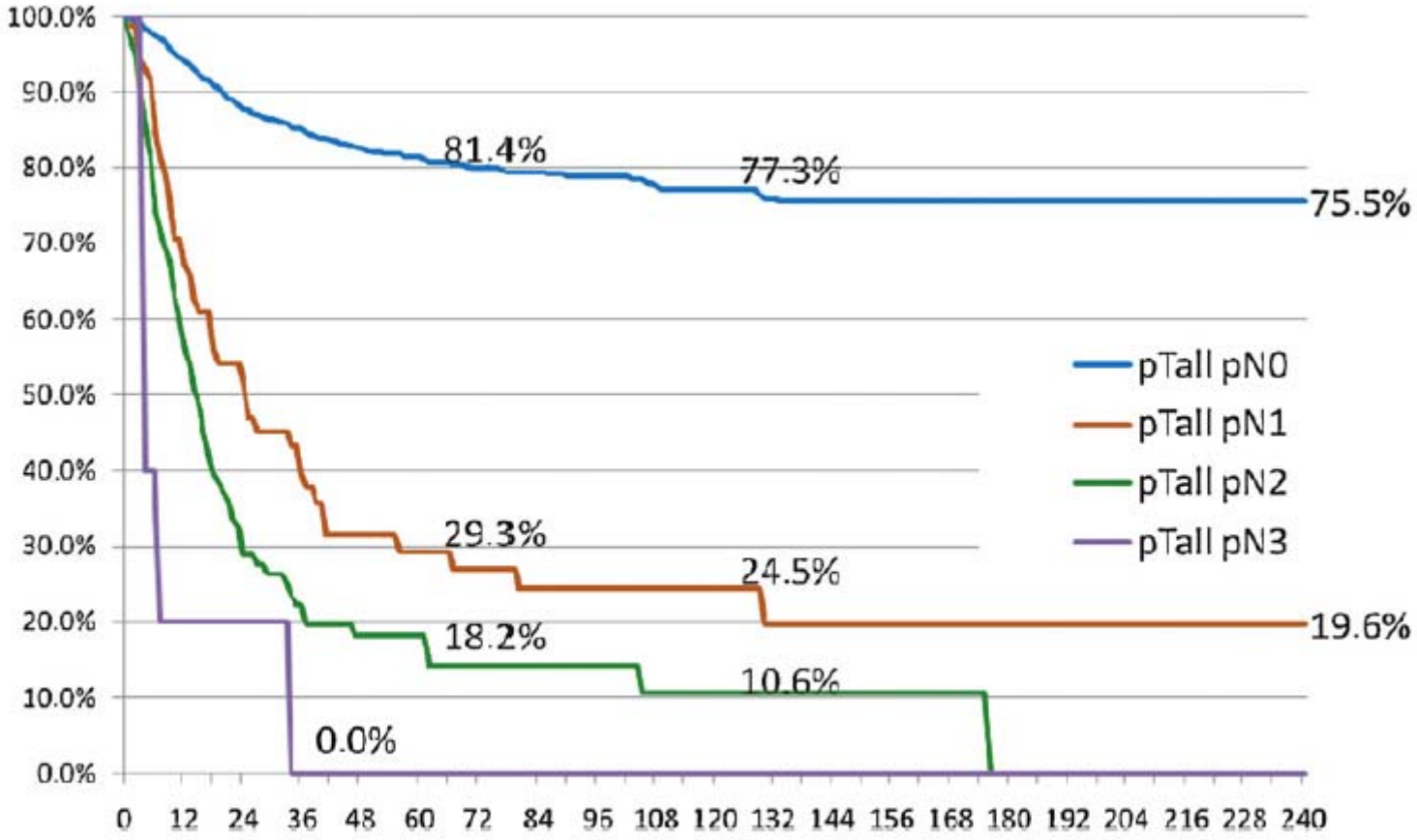


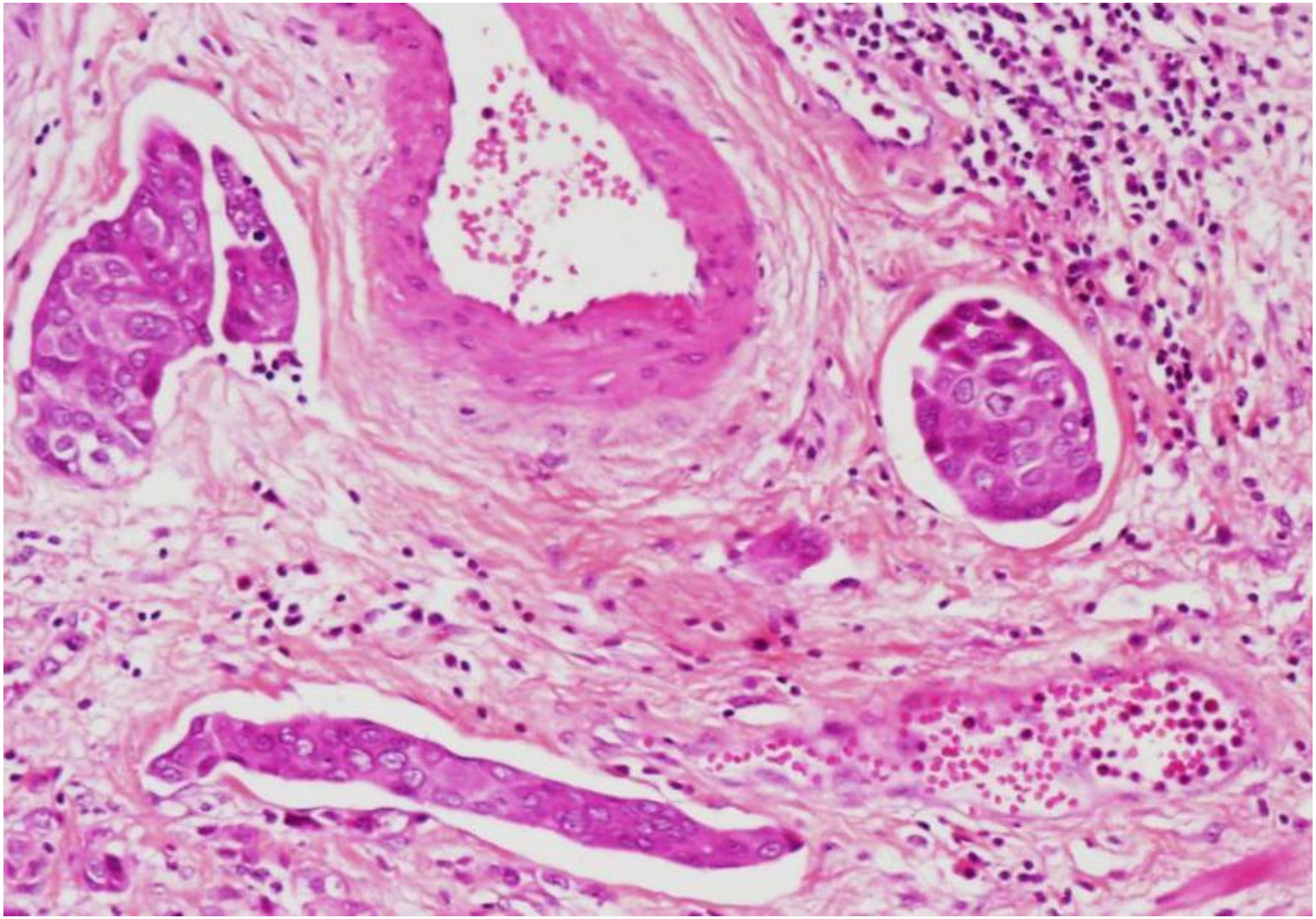
Fig. 11 – Disease-specific survival according to the lymph node status.

Lymph nodes

Prognostic value for

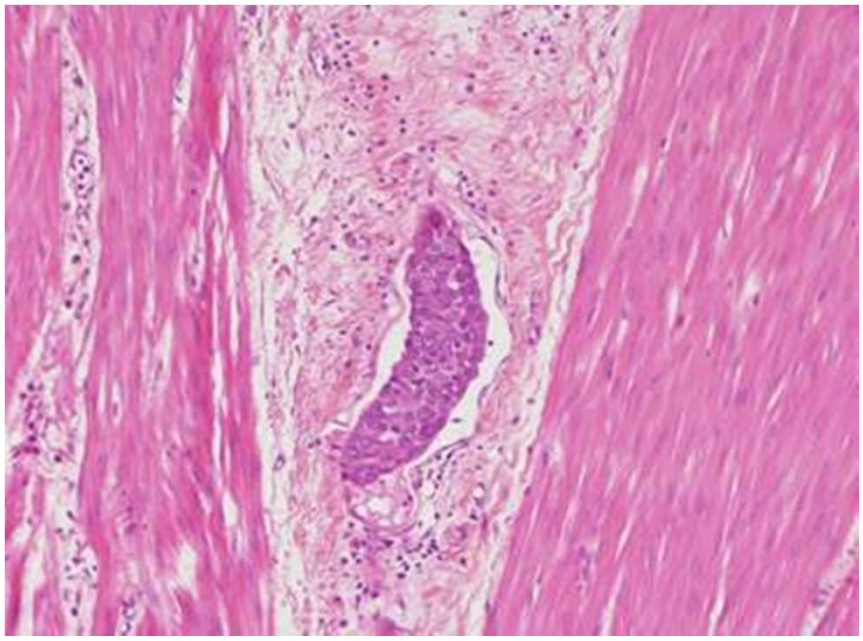
- the lymph node density ?
- the extranodal extension ?
- the peri-nodal lymphovascular invasion ?

May et al. Eur urol 2011
Fajkovic et al. Eur Urol 2012
Masson-Lecomte A et al. Ann Surg Oncol 2013
Fritsche et al. Eur Urol 2013



Lymphovascular invasion on cystectomy specimen

- Prognostic factor , at least in uni-variate analysis, in particular in pN0 patients.

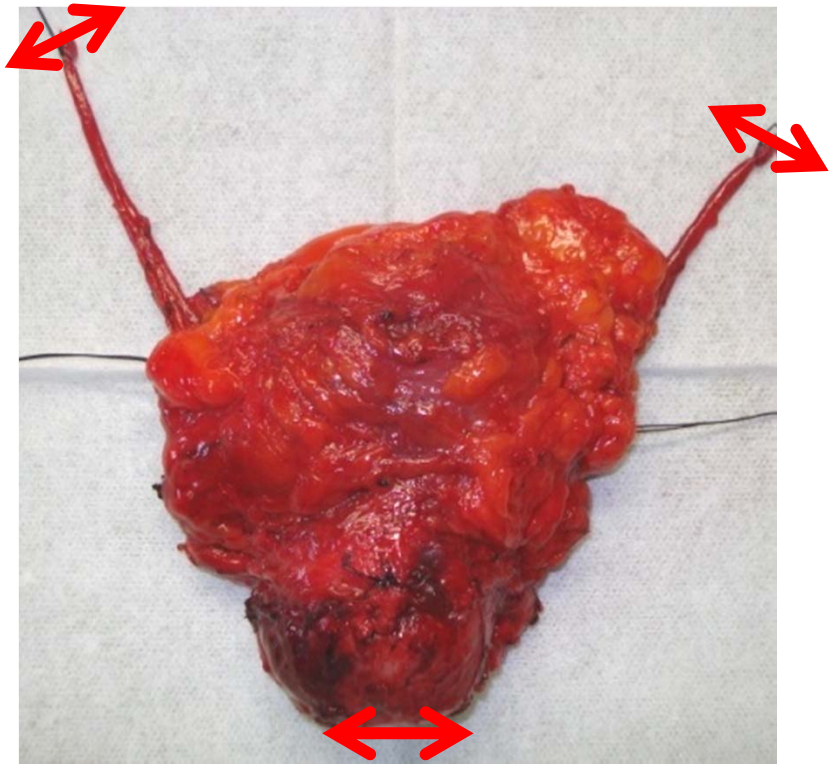


Immunostaining (CD31, CD34, D2-40) may help, but is not recommended systematically

Shariat et al. BJU Int 2010
Xylinas et al. Br J Cancer 2012

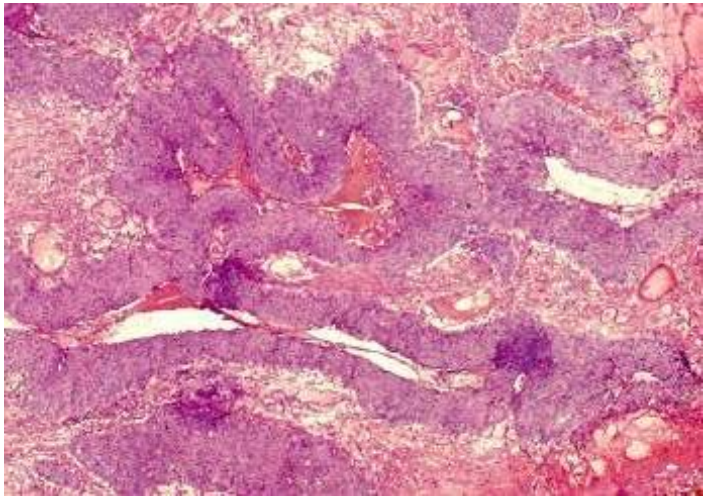
Margins

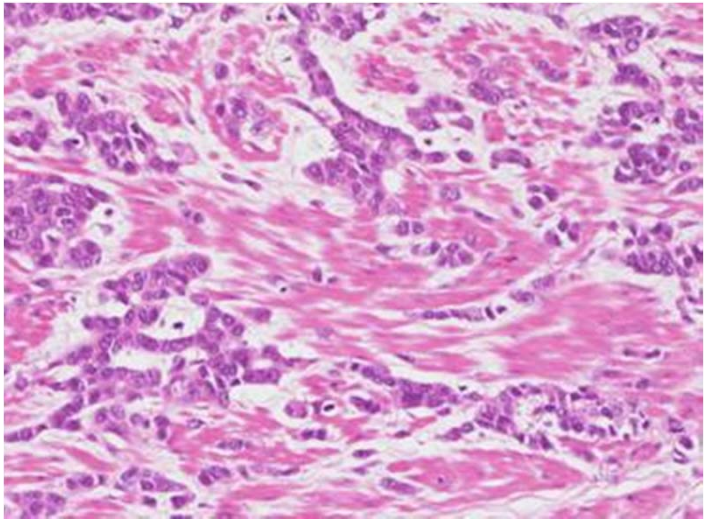
- Ureteral margins (carcinoma in situ?)
- Urethral margin (carcinoma in situ?) +
- Peri-vesical (soft tissue margin) +++



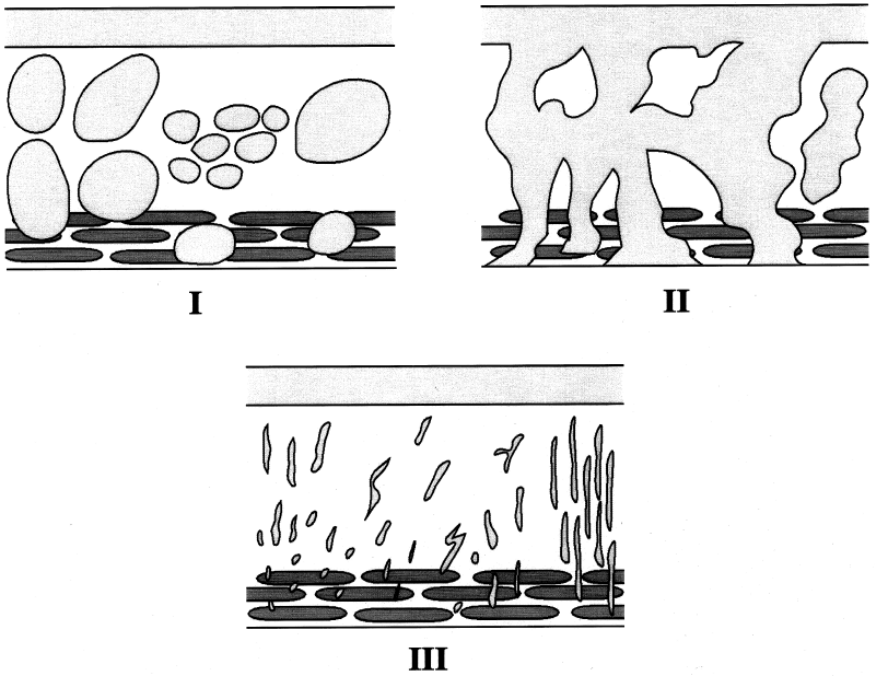
Neuzillet et al. BJU Int 2013

Patterns of invasion



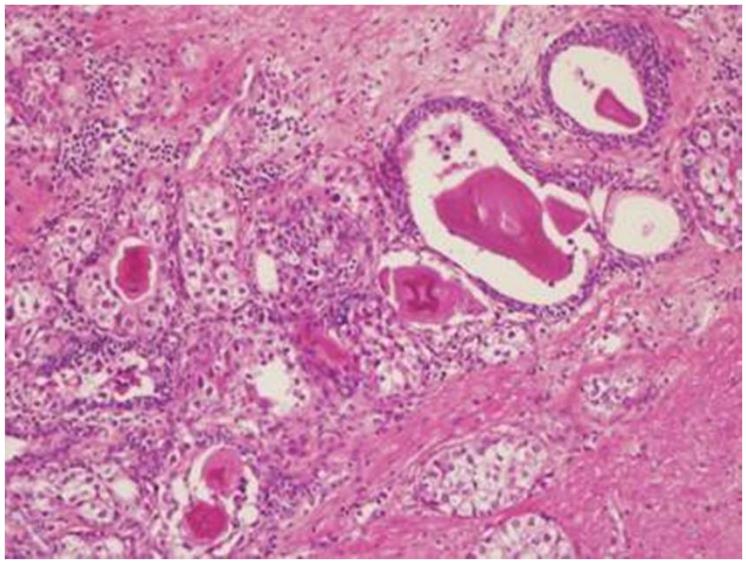


A pronostic classification according to the pattern of invasion has been proposed but remains to be validated.



Jimenez et al. Am J Surg Pathol 2000

Prostatic invasion



- Prostatic involvement may occur via direct extension from an extravesical bladder mass, direct invasion from an in situ lesion within the prostatic urethra, or colonization of the prostatic ducts followed by invasion.

Hansel et al. Eur Uorl 2013

- The prognosis is different (5-year OS rates were 21% through bladder wall and 55% through urethra)

- It is recommended to assign T4a only prostate invasion from the bladder wall and assign T1 or T2 extension from urethra (use urethra tumor classification).

Seminal vesicle invasion

- A survey suggested that seminal vesicle invasion is of poor prognosis, mimicking pT4b behaviour

You et al. BJU Int 2010

Treatment response

- Resection extensive :
  - downstaging with an impact on prognosis
- Chemotherapy neoadjuvant
  - ypT0 is associated with better OS
- Additional sampling on the area previously resected is warranted to ensure ypT0

Hautmann et al Eur Urol 2012
Rosenblatt et al. Eur Urol 2012