Pathologic Assessment of Invasion in TUR Specimens

A. Lopez-Beltran

T1 (cT1)

Prognostic factors for progression/invasive disease Ta,T1,CIS- NMIBC :TNM 2017

- ESSENTIAL:
- Grade
- T stage
- CIS
- Number of lesions
- Previous recurrences
- ADDITIONAL
- Recurrence at 3 month check
- Tumor size>> 3 cm

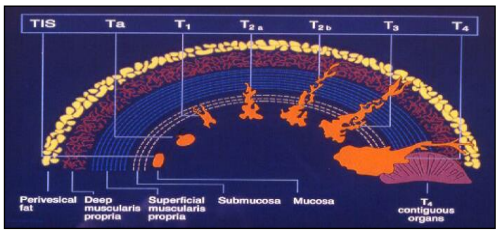
Prognostic factors metastasis risk/Survival MIBC T2-4No-1 :TNM 2017

- ESSENTIAL:
- T category
- N category
- ADDITIONAL
- Grade
- Histological type
- LVI
- Concomitant CIS
- Tumor size
- Hydronephrosis

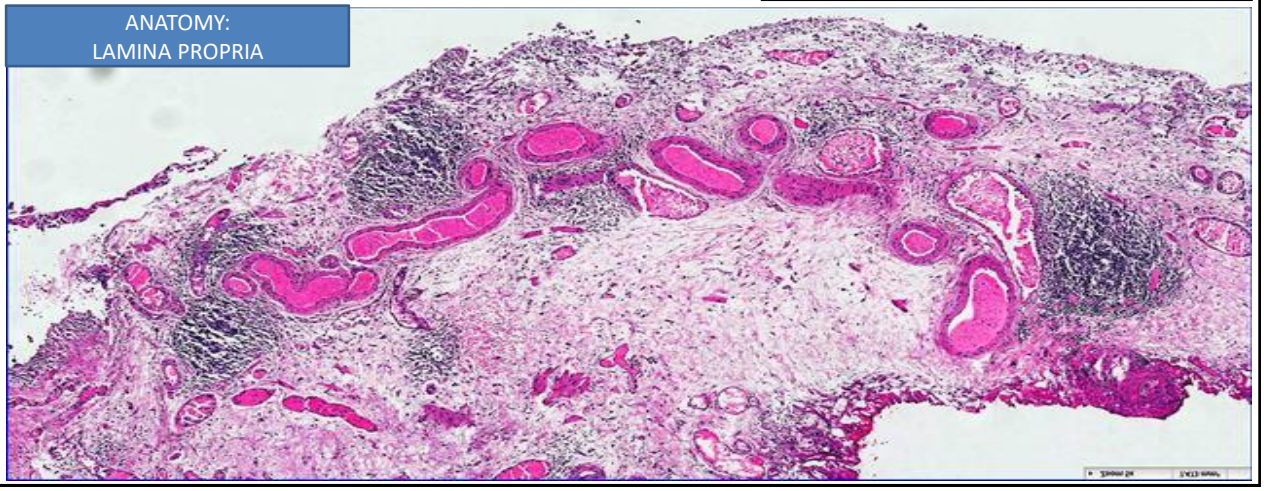
Background

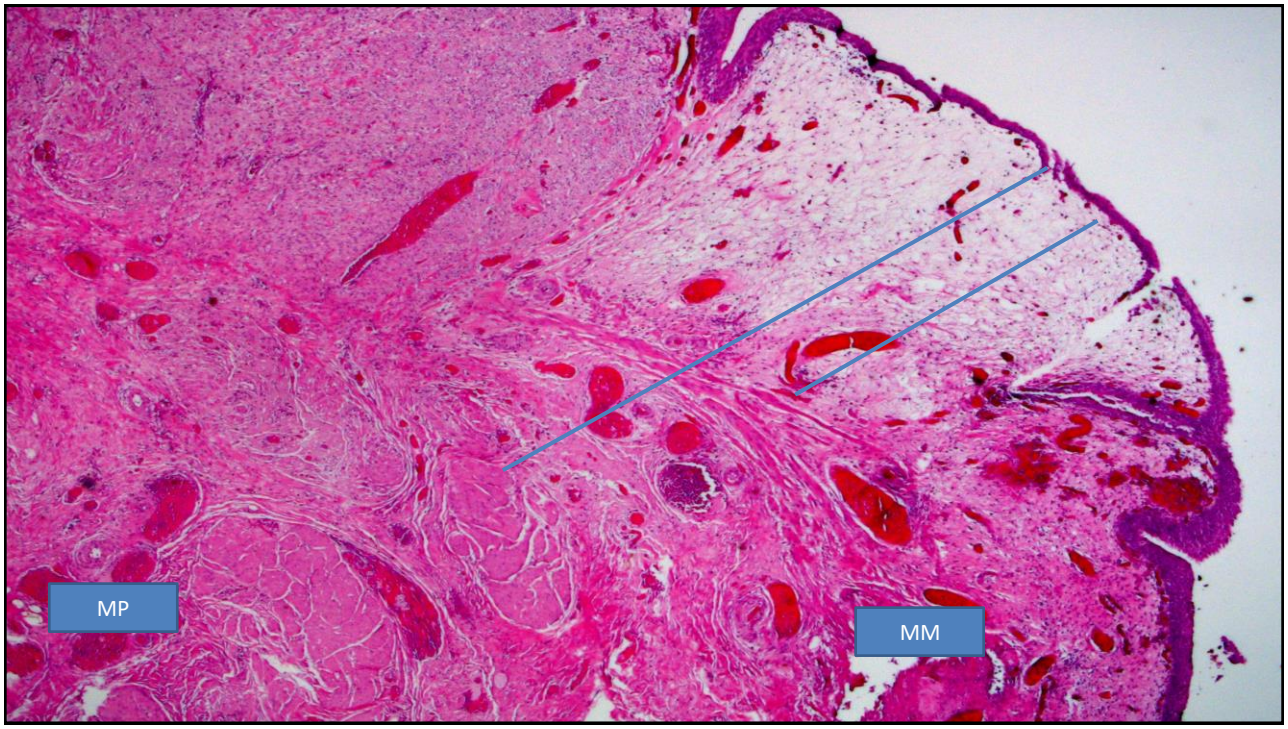
- T1 assessment and pitfalls
- T1 substaging-Proposals
- T2 assessment and pitfalls
- AJCC/TNM 2017

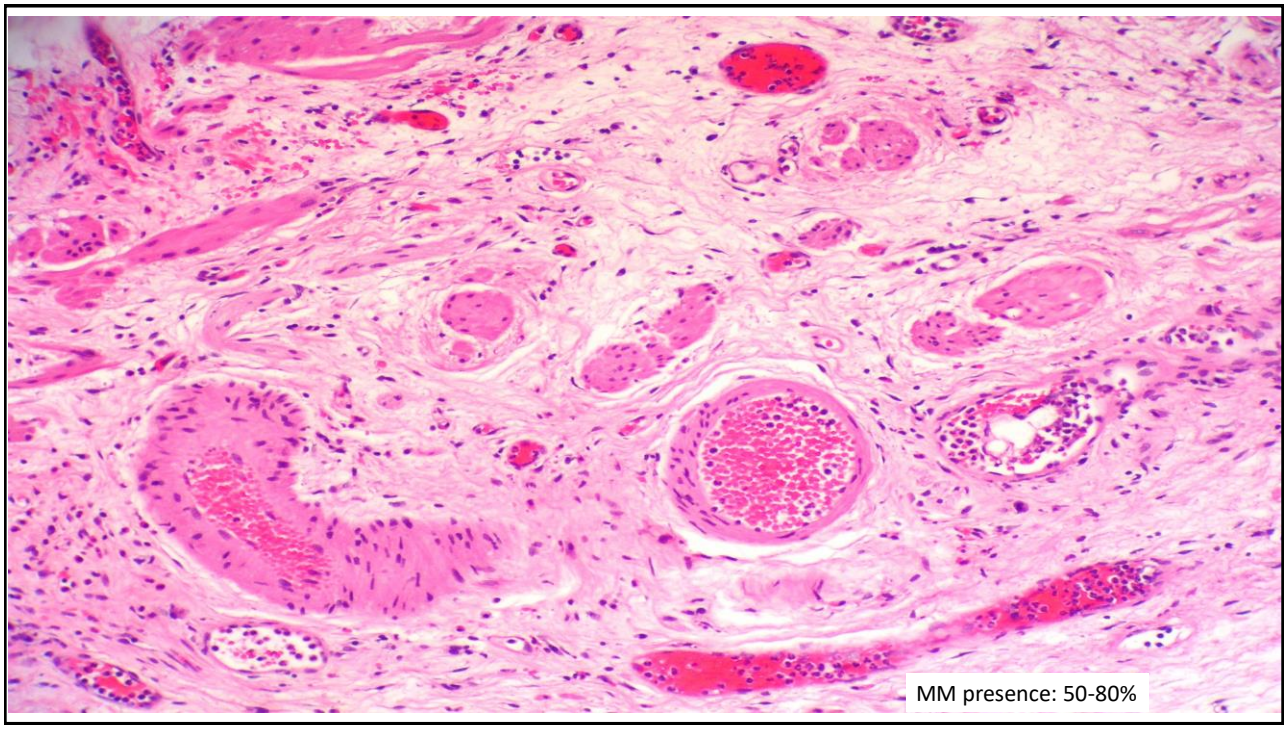
Definition T1 (AJCC/TNM 2017):
Tumor invading subepithelial connective tissue

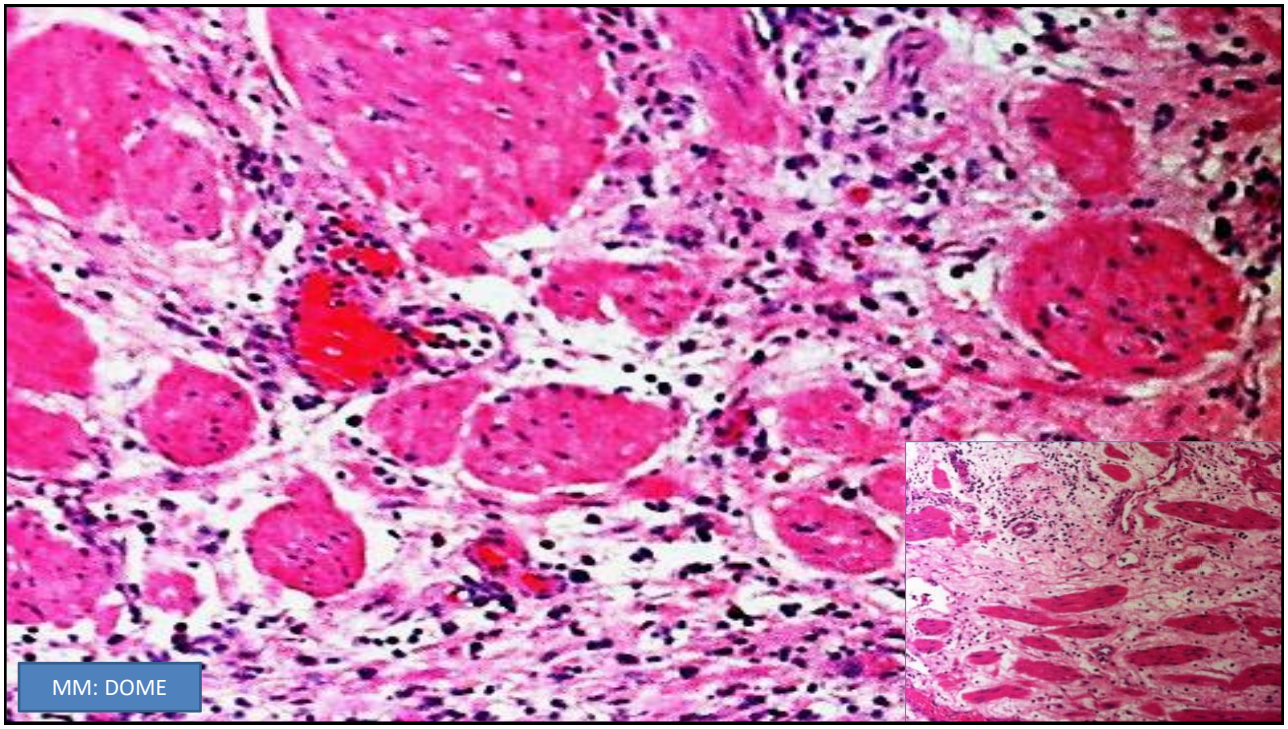


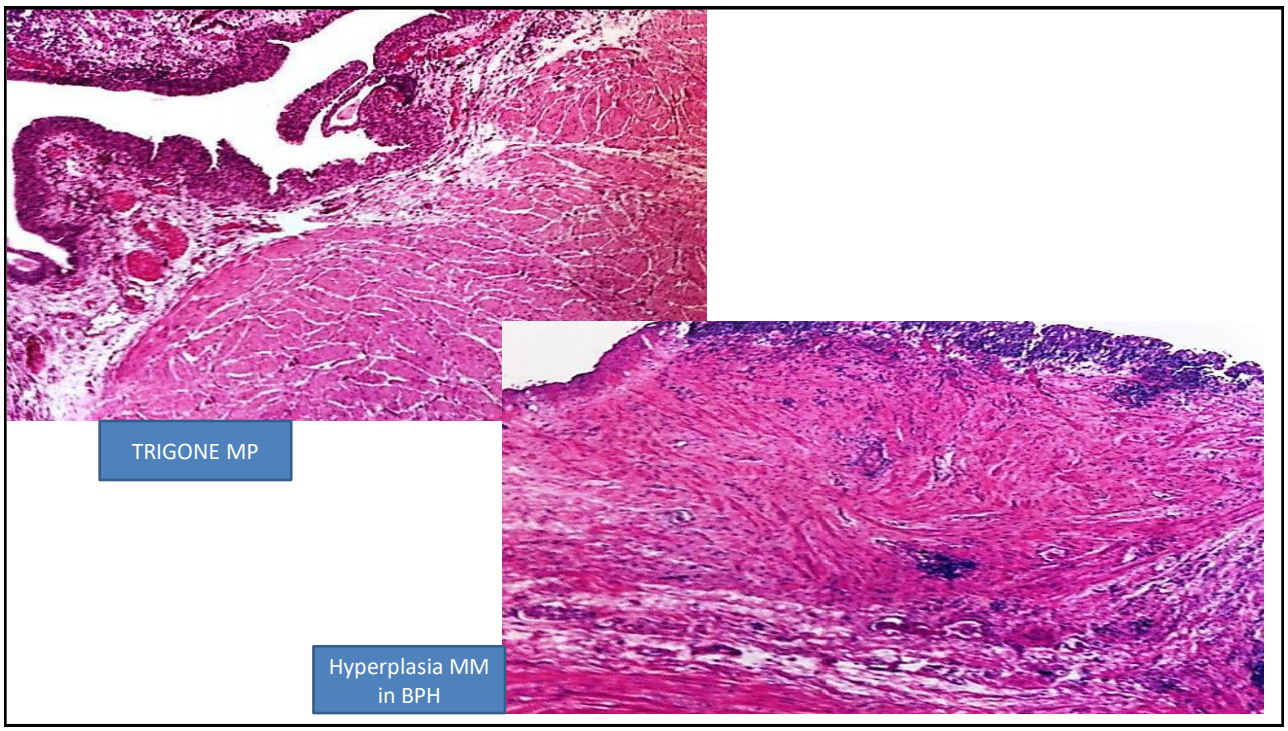
ANATOMY:
LAMINA PROPRIA

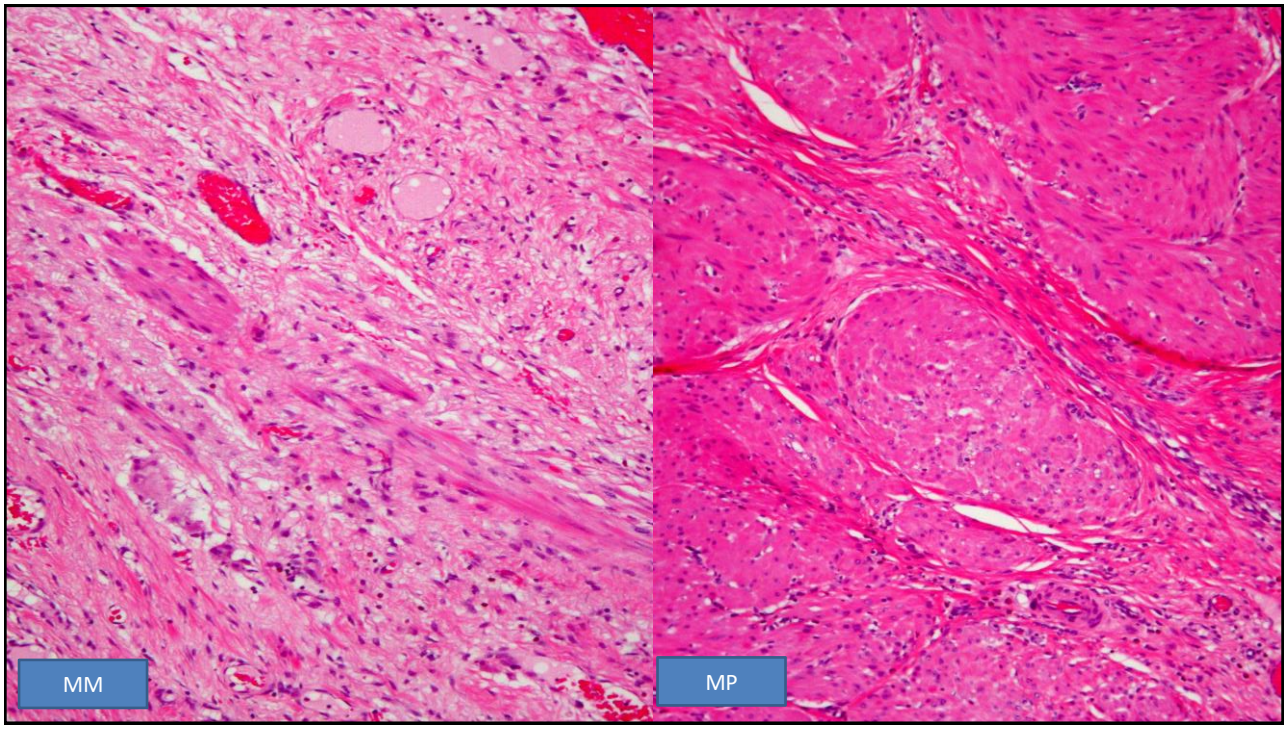


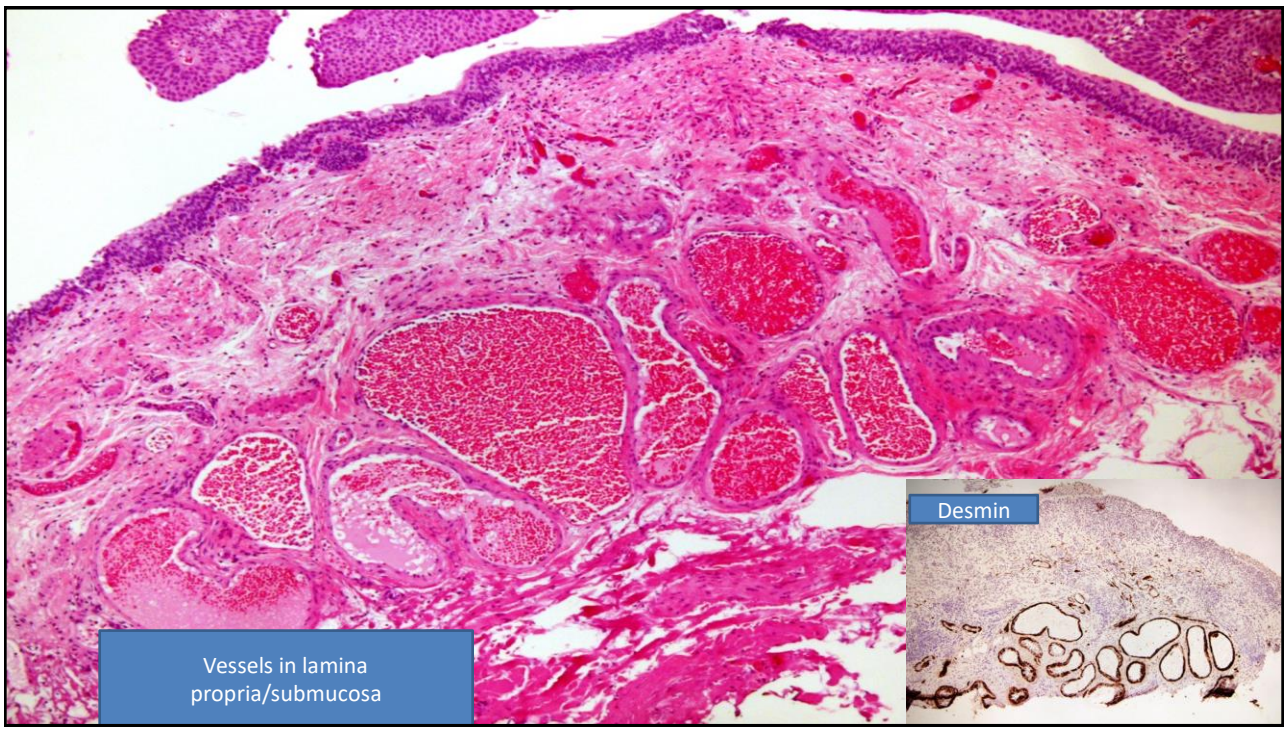

MP
MM


MM presence: 50-80%

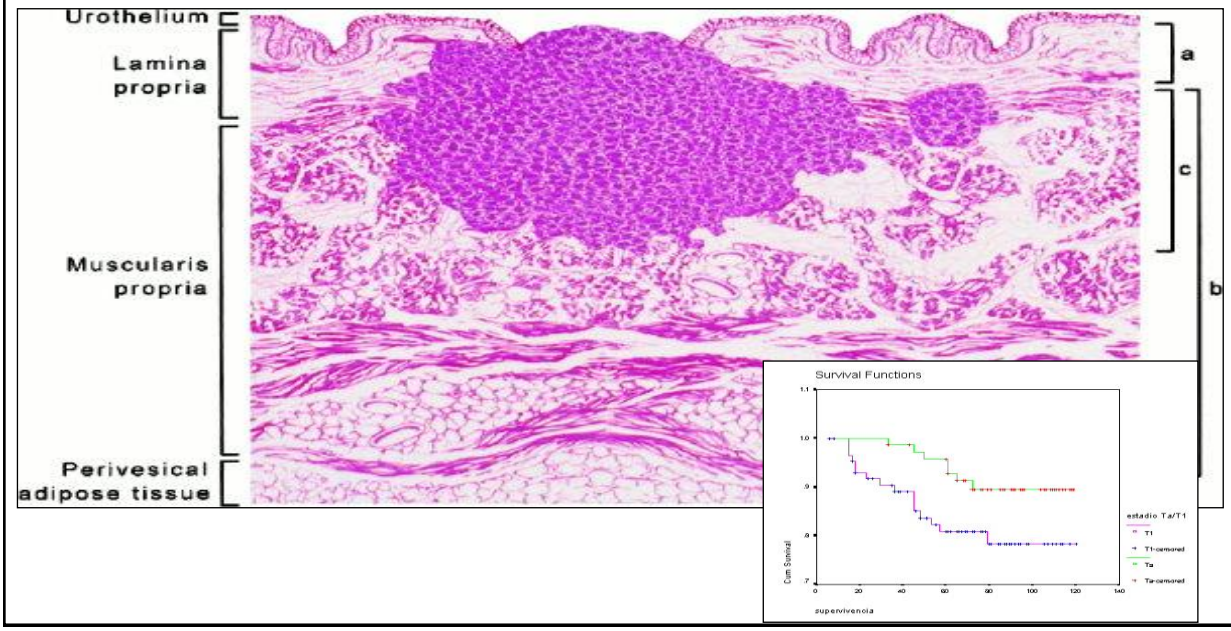

MM: DOME

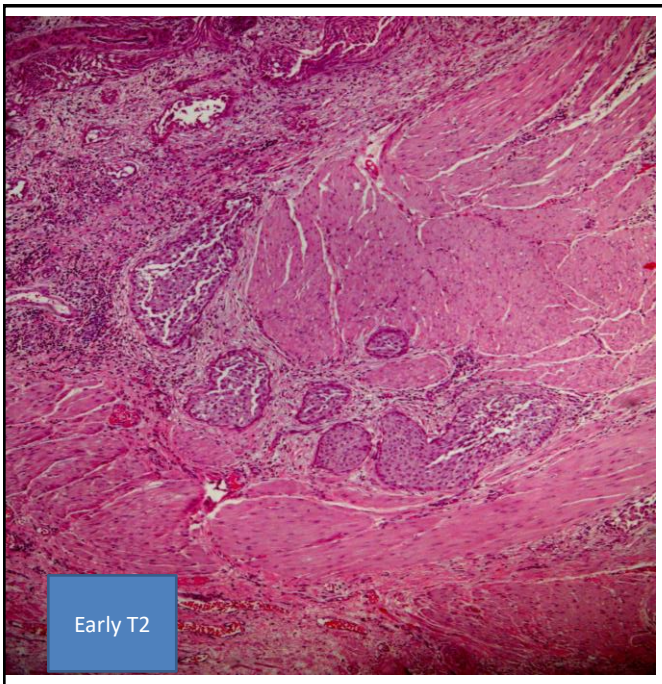

TRIGONE MP
Hyperplasia MM in BPH

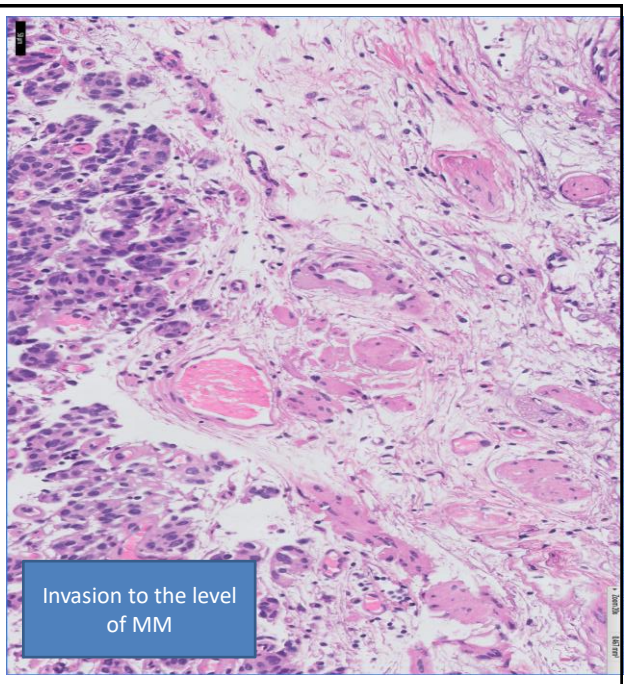

MM
MP

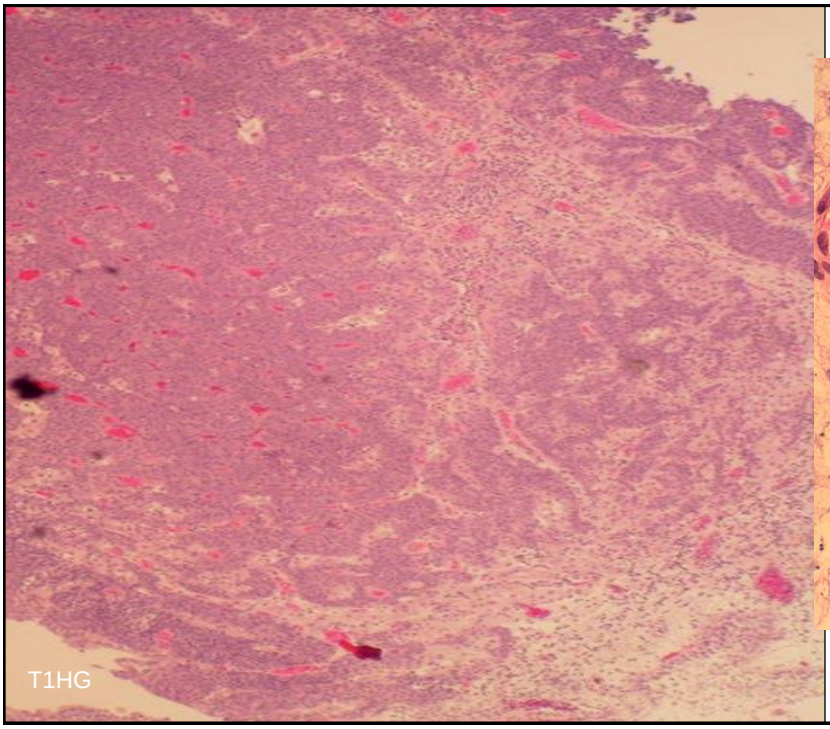

Desmin
Vessels in lamina propria/submucosa

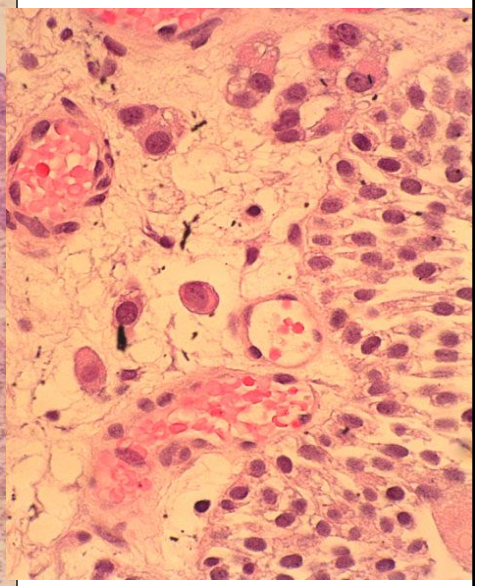
Lamina propria invasion











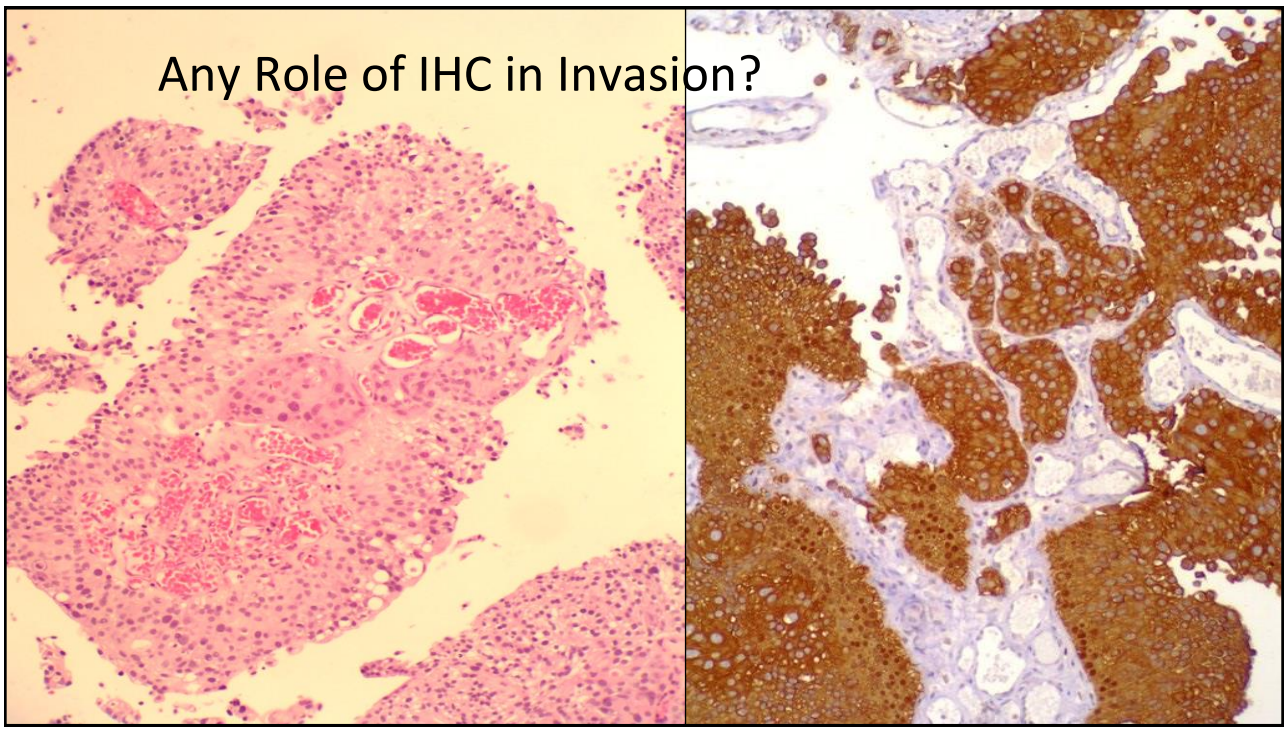
T1HG: Early-single cells

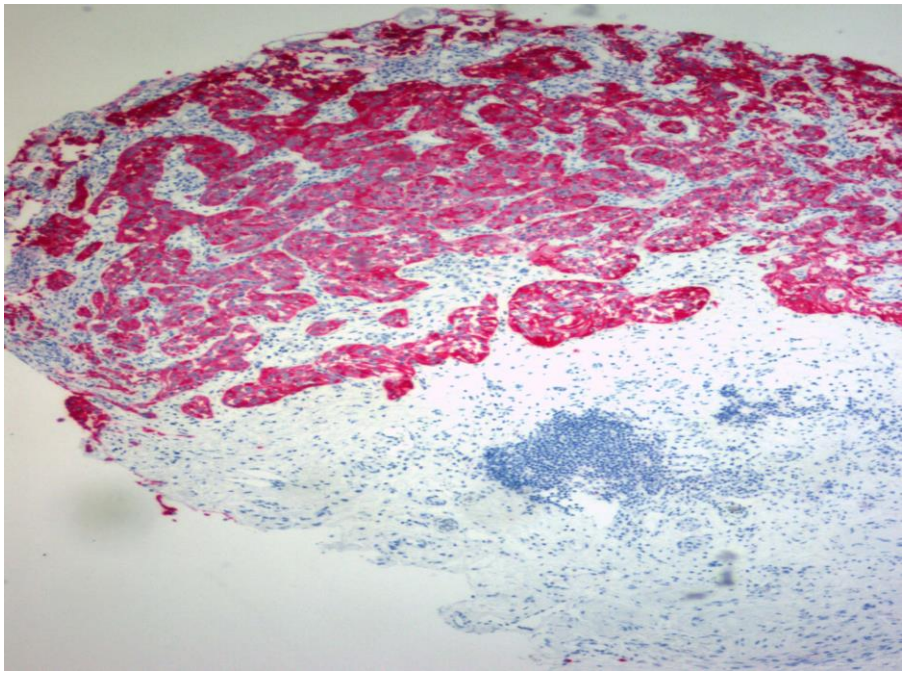
Important pathologic problem:
Reproducibility in pT1

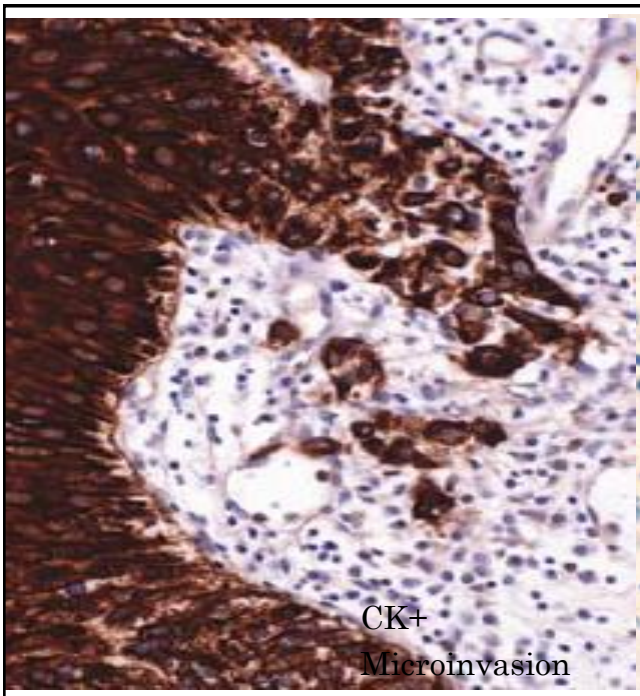
Reproducibility of lamina propria invasion

(reviewed by Lopez-Beltran and Cheng, 2003

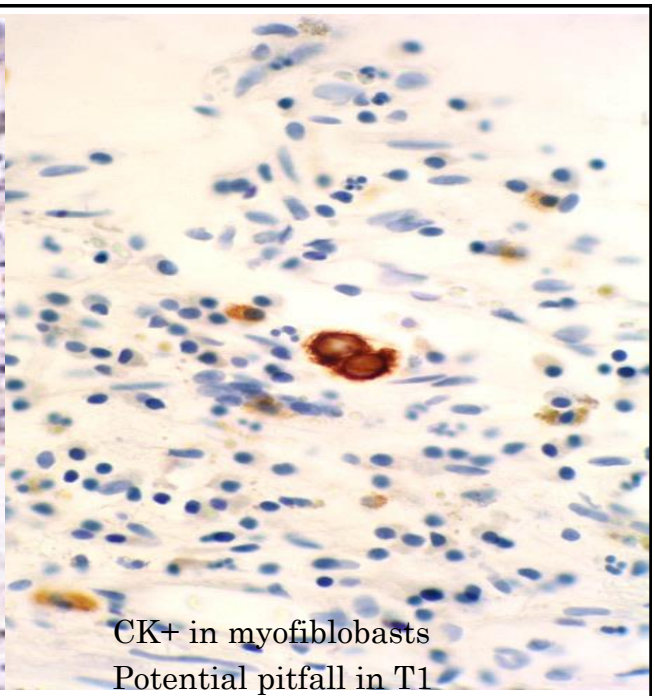
- 61% agreement; 10% NO consensus after 4 rounds
- 15% of pT1 down-staged as pTa
- 22% of pT2 down-staged to pT1 or pTa
- 80% agreement; 88% after a 2nd round
- 35% pT1 to pTa; 3% to pT2-T3
- 2nd TURBT found: 2-28% pT1 to be at least pT2
- **pT1 (experts) study**: (Histopathology 2013)
- Full agreement (44%)
- Majority consensus (72%)
- *Kappa* ~ 50%



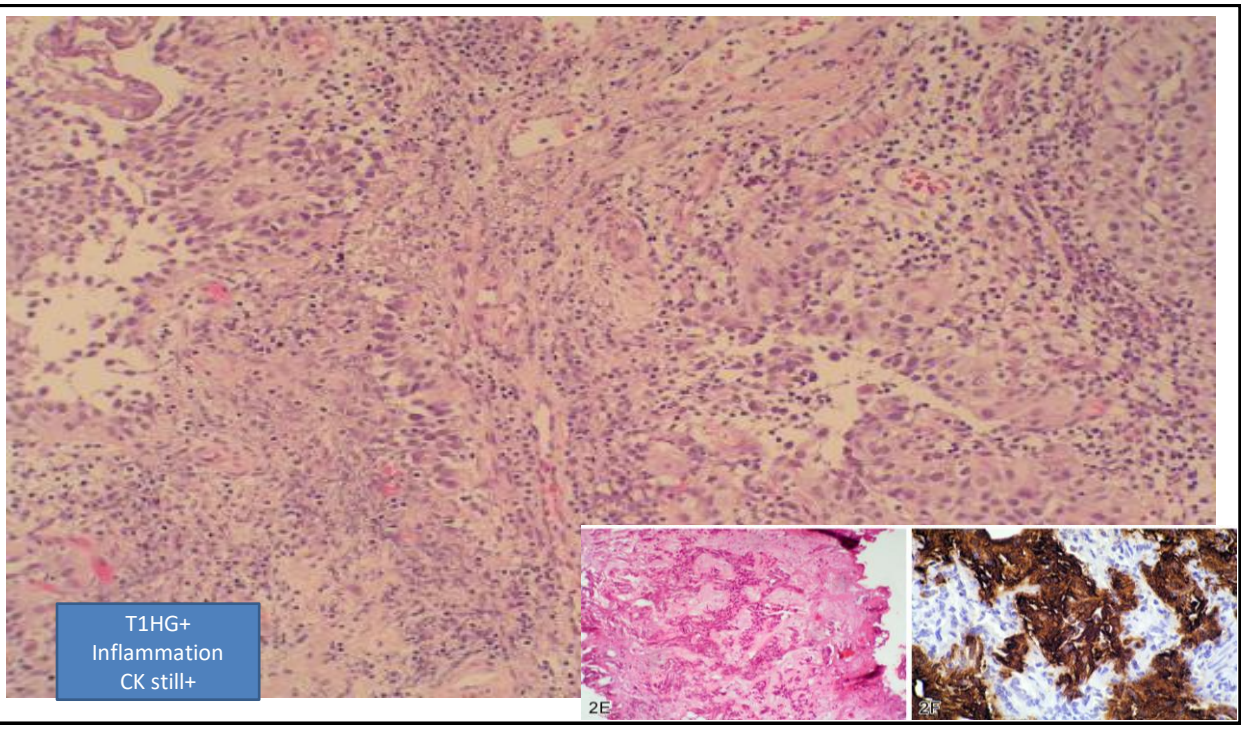




CK+
Microinvasion



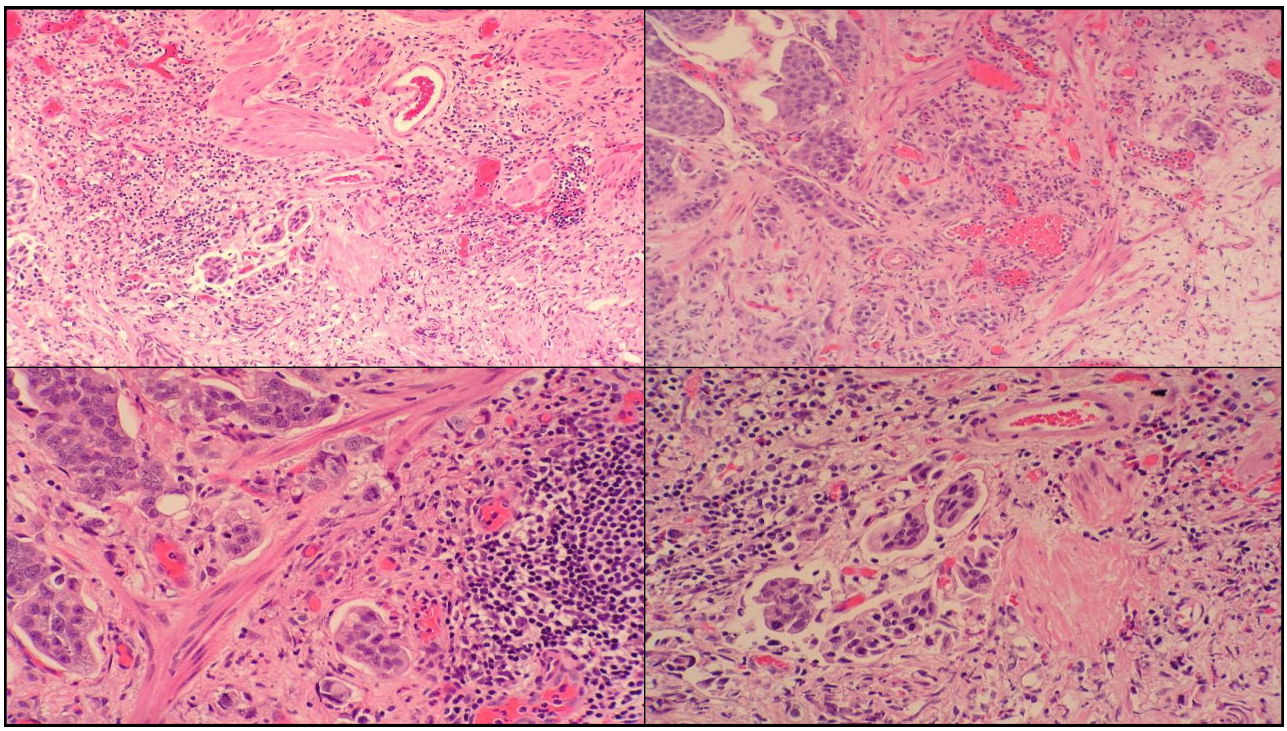
CK+ in myofiblobasts
Potential pitfall in T1

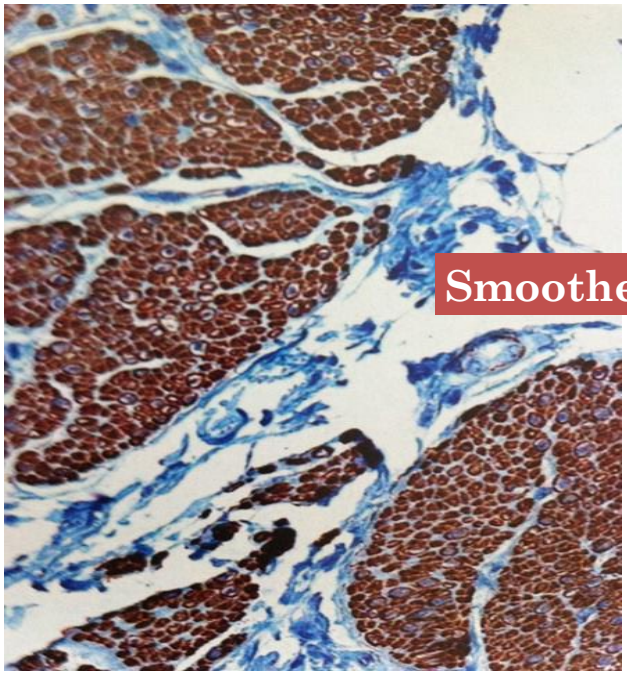


T1 Substaging

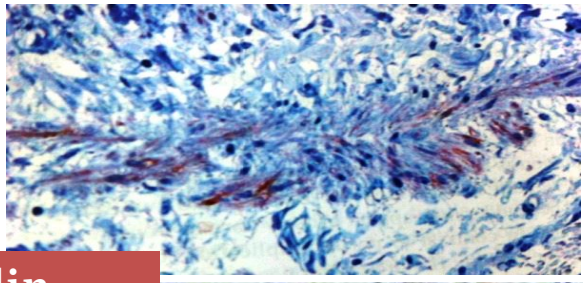
Review of previous reports on depth of lamina propria involvement as a prognostic factor for disease progression in T1 bladder tumors

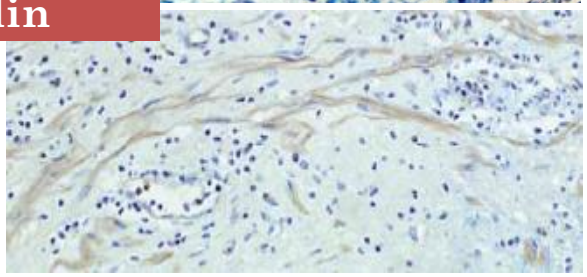
Year	Author	Staging system	Number of cases	Progression (%)	Survival (%)
1990	Younes et al. [6]	T1a (lamina propria)	15	NA	75
		T1b (into MM)	3		
		T1c (across MM)	14		11
1994	Hasui et al. [8]	T1a (Younes T1a)	60[a]	6.7	95
		T1b (Younes T1b and c)	28[a]	53.5	82
1995	Angulo et al. [21]	T1a (Younes T1a and b)	50[a]	NA	86
		T1b (Younes T1c)	49[a]	NA	52
1997	Holmäng et al. [9]	T1a (Younes T1a)	26	36	58
		T1b (Younes T1b and c)	38	58	42
1998	Smits et al. [10]	T1a		6	NA
		T1b	119 total[a]	33	NA
		T1c		55	NA
1998	Hermann et al. [22]	T1a	31[b]	NA	79
		T1b	60[b]	NA	70
		T1c	52[b]	NA	57
1999	Cheng et al. [11]	T1 above MM	23[a]	11	NA
		T1 into or below MM	21[a]	32	NA
2000	Kondylis et al. [7]	T1a into MM	32[b]	22	NA
		T1b beyond MM	17[b]	29	NA
2001	Bernardini et al. [20]	T1a (Younes T1a)	54[a]		NA
		T1b (Younes T1b and c)	40[a]	[c]	NA
2003	Trias et al. [12]	T1a (Younes T1a)	11	9	NA
		T1b (Younes T1b and c)	13	30.7	NA



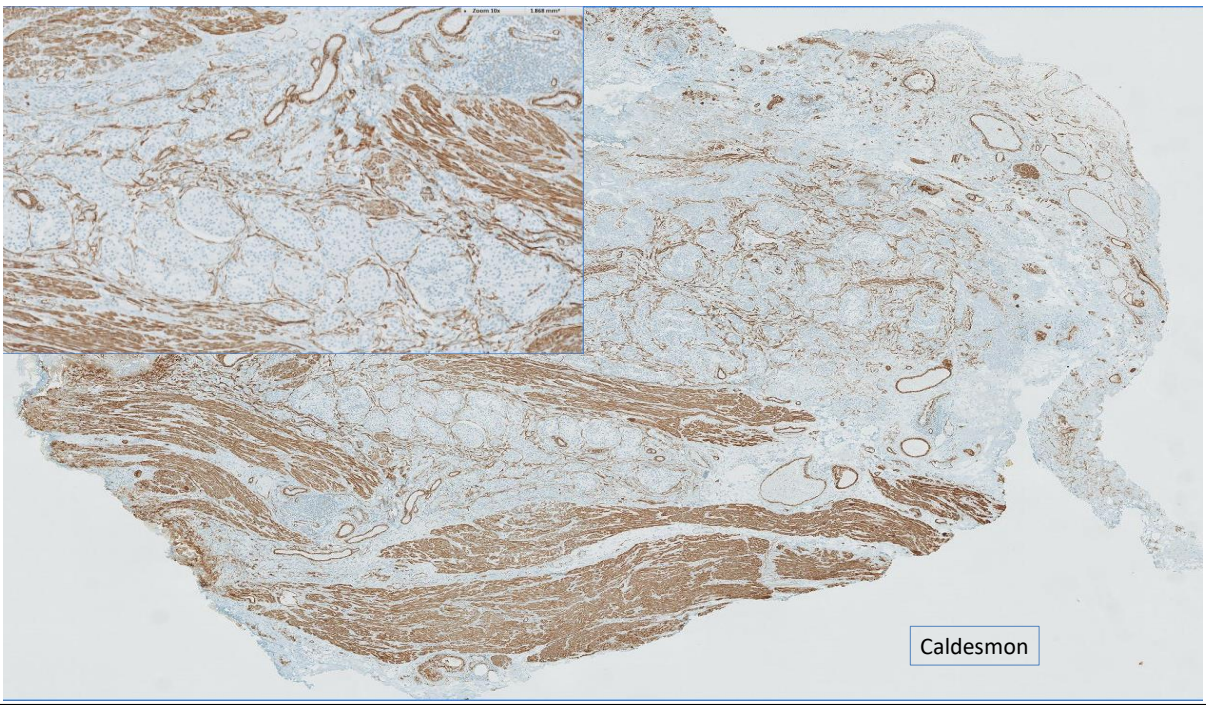


Smoothelin

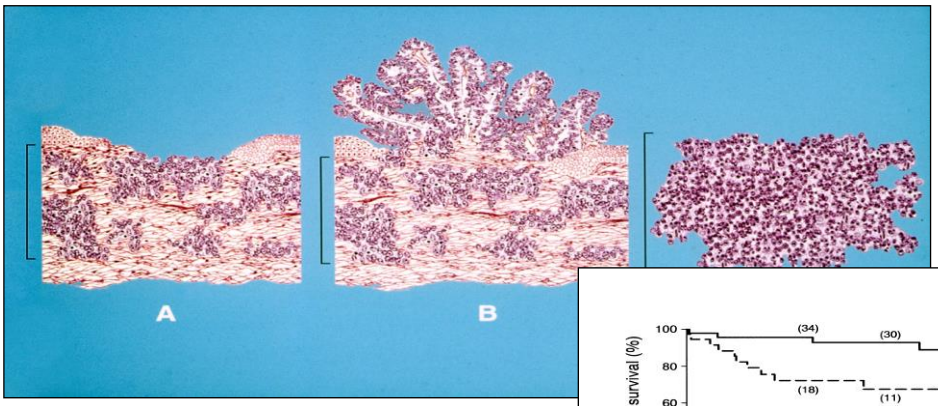


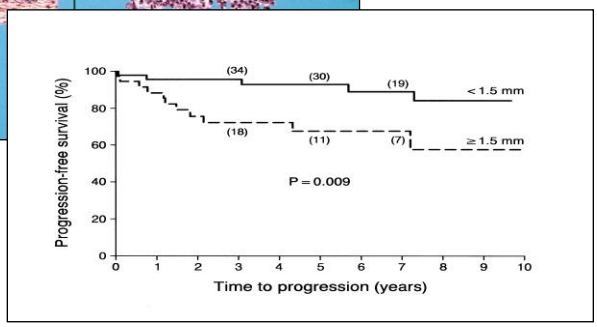


ISUP consensus on IHC bladder
Amin, Trypkov, Lopez-Beltran et al 2014
Not recommended



pT1 substaging is significant in patient survival?

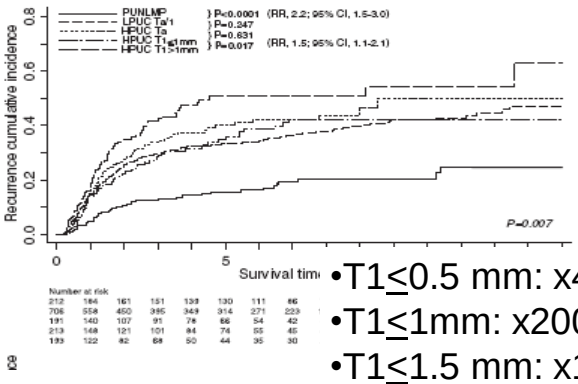


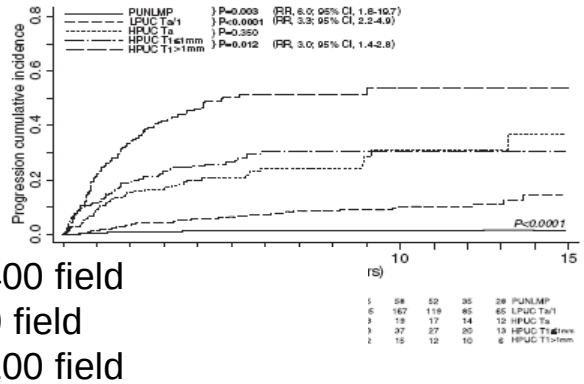


Prognostic Significance in Substaging of T1 Urinary Bladder Urothelial Carcinoma on Transurethral Resection

Wei-Chin Chang, MD, Yen-Hwa Chang, MD, PhD,† and Chin-Chen Pan, MD*‡*

tumors treated by transurethral resection were studied. Substaging was performed using 0.5, 1.0, and 1.5 mm as thresholds to distinguish extensive from focal invasion. Correlations to





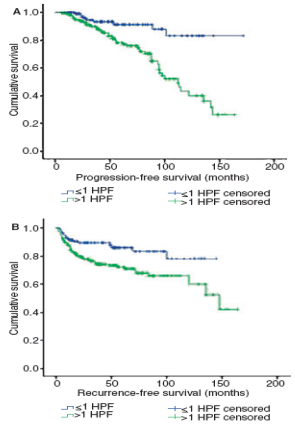
- T1≤0.5 mm: x400 field
- T1≤1mm: x200 field
- T1≤1.5 mm: x100 field

Histopathology 2011, **59**, 722–732. DOI: 10.1111/j.1365-2559.2011.03989.x

Substaging by estimating the size of invasive tumour can improve risk stratification in pT1 urothelial bladder cancer—evaluation of a large hospital-based single-centre series

Simone Bertz, Stefan Denzinger,[1] Wolfgang Otto,[1] Wolf F Wieland,[1] Robert Stoehr, Ferdinand Hofstaedter[2] & Arndt Hartmann

Methods and results: Specimens of 309 patients with pT1 urothelial carcinoma were re-evaluated histologically, including size of infiltrating tumour area estimated as equal to or smaller than one high-power field (HPF) or larger than one HPF, and tumour infiltration in relation to the muscularis mucosae (pT1a/b). Results were correlated with clinical follow-



Histopathology

Histopathology 2017, 71, 406–414. DOI: 10.1111/his.13247

Stalk versus base invasion in pT1 papillary cancers of the bladder: improved substaging system predicting the risk of progression

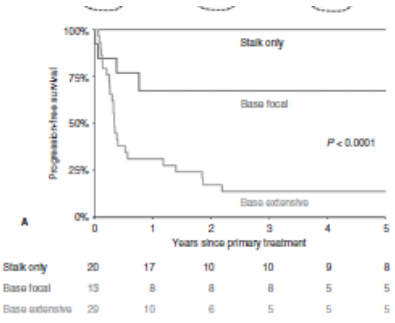
Margaret Lawless,[1] Roman Gulati[2] & Maria Tretiakova[1]
[1]*Department of Pathology, University of Washington School of Medicine, Seattle, WA, USA, and* [2]*Fred Hutchinson Cancer Research Center, Seattle, WA, USA*

Aims: Pathological stage pT1 bladder cancers constitute a clinically heterogeneous group. However, current staging guidelines for superficially invasive cancers do not acknowledge the variability in type and extent of lamina propria invasion in papillary urothelial carcinomas (PUCs), and historically proposed substaging systems showed either high interobserver variation or limited value in predicting patient outcomes. The aim of this study was to reappraise pT1 PUC substaging, with the objective of identifying a novel scheme that is reproducible and prognostically meaningful.

Methods and results: pT1 PUCs diagnosed during 1999–2015 were retrospectively reviewed and characterised as focal invasion confined to the papillary stalk, focal invasion of the tumour base, or extensive invasion of the tumour base. Cases with concurrent flat carcinoma *in situ*, angiolymphatic invasion, absent muscularis propria or clinically advanced disease were excluded. We calculated cumulative incidence rates of recurrence, progression and death by tumour subtype, and evaluated differential risks by using log-rank tests and Kaplan–Meier curves stratified by type and extent of invasion. Among 62 patients satisfying the inclusion criteria, 22 of 29 patients with base-extensive invasion progressed, whereas four of 13 with base-focal and none of 20 with stalk-only invasion progressed. There was strong evidence that base-extensive patients had a higher risk of progression and death resulting from bladder cancer than base-focal or stalk-only patients ($P < 0.0001$). However, tumour subtype was not significantly associated with risk of recurrence ($P = 0.21$).

Conclusions: We propose an innovative substaging approach for reporting the site and extent of lamina propria invasion in patients with pT1 PUC, allowing patient stratification for risk of progression.

Recent proposals for T1 substaging



Recent proposals for T1 substaging

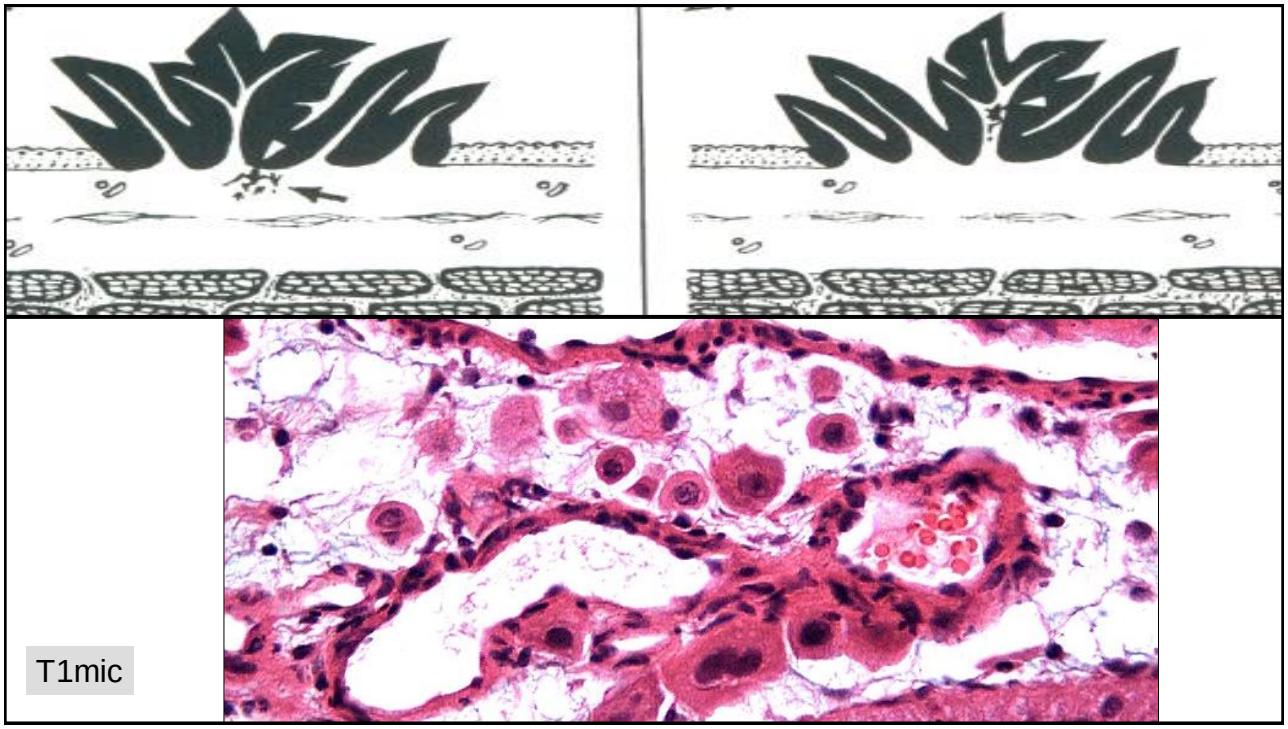
Analysis of T1 Bladder Cancer on Biopsy and Transurethral Resection Specimens

Comparison and Ranking of T1 Quantification Approaches to Predict Progression to Muscularis Propria Invasion

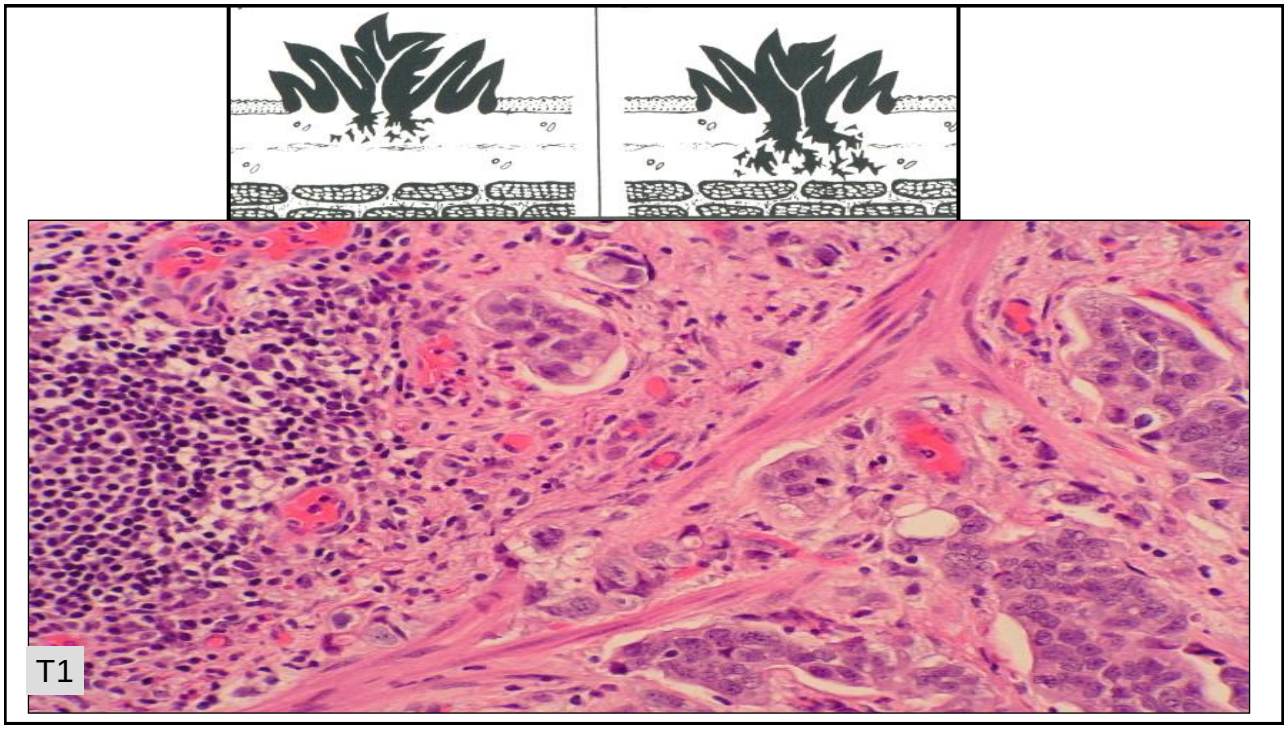
Mariah Z. Leivo, MD, Debashis Sahoo, PhD,† Zachary Hamilton, MD,‡ Leili Mirsadraei, MD, Ahmed Shabaik, MD,* John K. Parsons, MD, PhD,‡ Andrew K. Kader, MD,‡ Ithaar Derweesh, MD, Christopher Kane, MD,‡ and Donna E. Hansel, MD, PhD*‡*

Abstract: Urothelial carcinoma of the bladder invasive into lamina propria on biopsy or transurethral resection of bladder tumor, termed "T1" disease, progresses to muscularis propria invasion in a subset of patients. Prior studies have proposed histopathologic metrics to predict progression, although methods vary widely and it is unclear which method is most robust. This poses a challenge since recent World Health Organization and American Joint Commission on Cancer editions encourage some attempt to substratify T1 disease. To address this critical problem, we analyzed T1 specimens to test which T1 quantification method is best to predict progression and to then establish the optimal cut-off. Progression was analyzed for all patients or for patients with definitive muscularis propria only. Multivariate analysis and outcomes modeling controlled for additional histopathologic features. Our results suggest that aggregate linear length of invasive carcinoma (ALLICA) measured by optical micrometer is far superior to other methods ($P = 3.067 \times 10^{-6}$) and could be applied to 100% of specimens. ALLICA retained significance in multivariate analysis and eliminated contribution of other histopathologic features to progression. The best cut-off for ALLICA using a 30% false-positive threshold was 2.3 mm and using a 10% false-positive threshold at 25 mm, although the latter severely limited patients who could achieve this threshold. After comparison of all proposed methods of T1 quantification, we recommend the adoption of the ALLICA measurement and a cut-off of ≥ 2.3 mm as the best predictor of progression, acknowledging that additional nonhistopathologic methods may be required to increase broad applicability and further reduce the false-positive threshold.

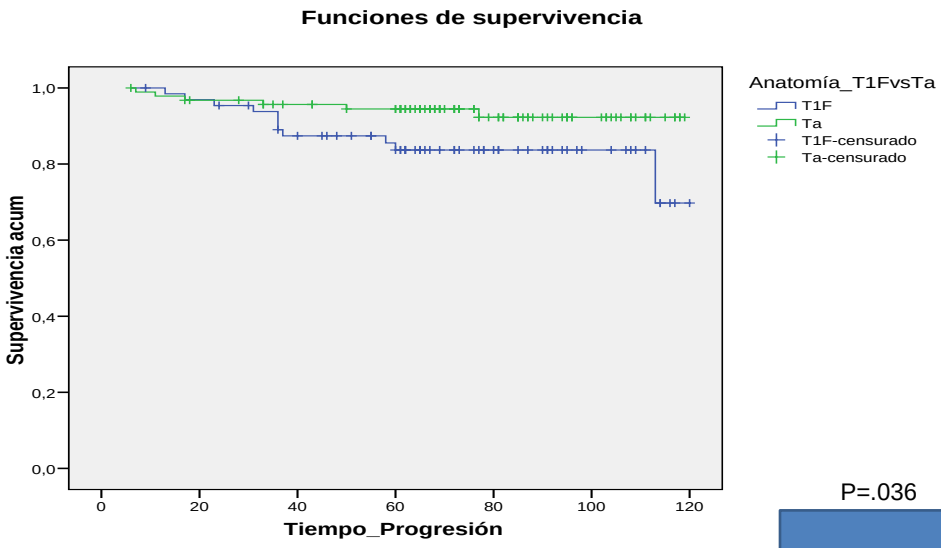
Another important issue in pT1
is the level of invasion
<u>Microinvasion vs. established invasion</u>



T1mic



T1



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Lopez-Beltran et al

Pathology (December 2003) 35(6), pp. 484–491

Taylor & Francis
healthsciences

GENITOURINARY PATHOLOGY

Stage pT1 bladder carcinoma: diagnostic criteria, pitfalls and prognostic significance

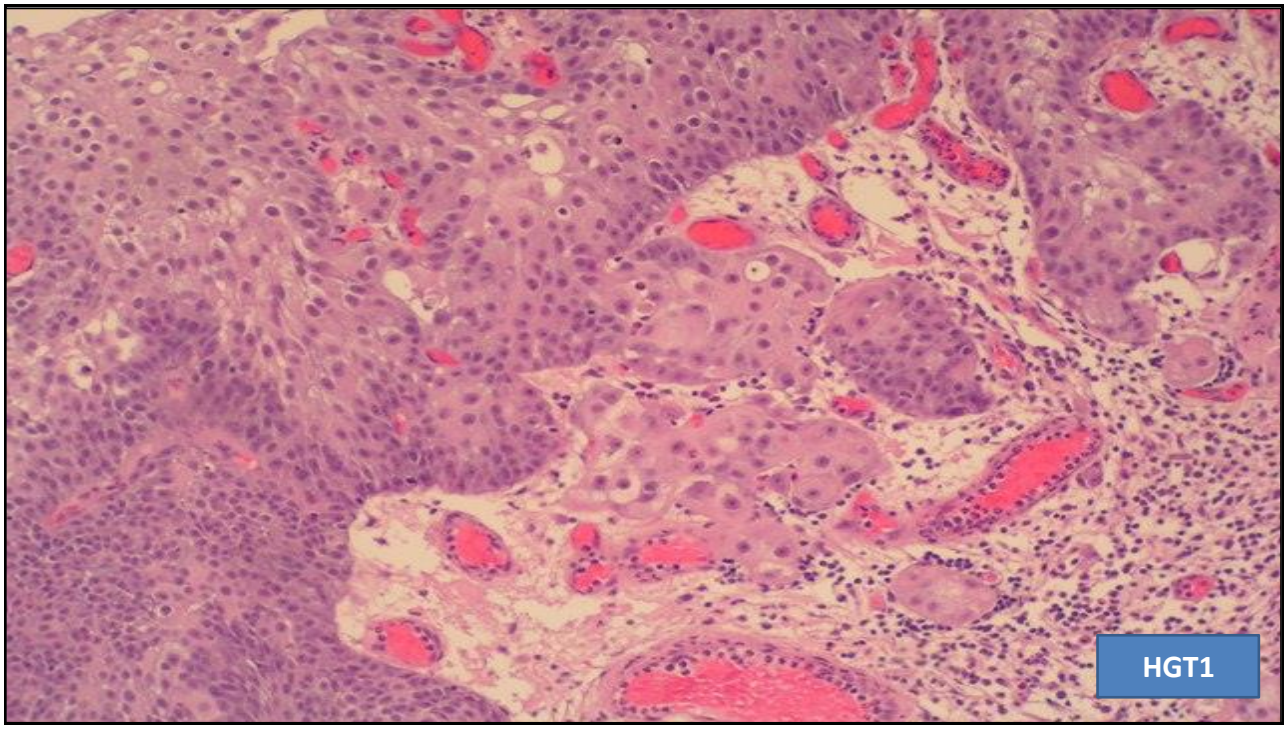
ANTONIO LOPEZ-BELTRAN* AND LIANG CHENG†

Can we improve
Invasion assessment?

PATHOLOGIC ISSUES IN DIAGNOSIS OF LAMINA PROPRIA MICROINVASION

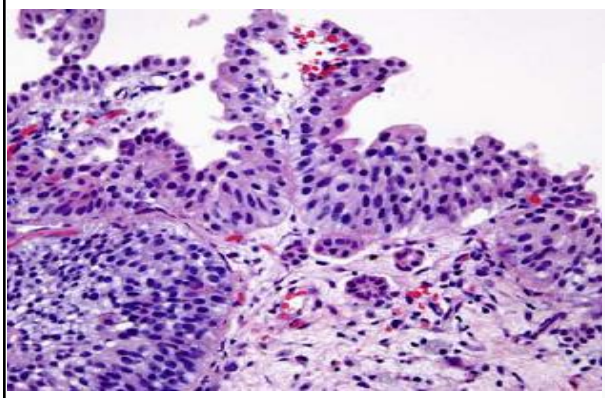
How we do identify invasion?

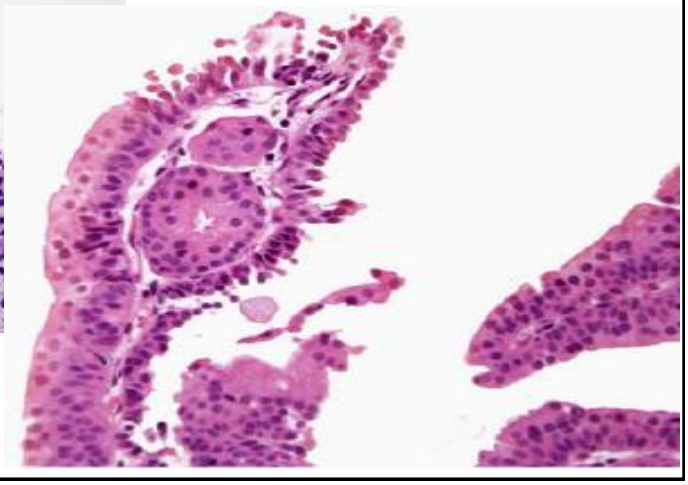
- **HOW: General Features**
- **Histologic grade**
- **Stroma-epithelial interface (basement membrane)**
- **Invading epithelium**
- **Stromal response**
- **WHERE: Bladder Tumors with MICROINVASION**
- **CIS with microinvasion**
- **Papillary urothelial carcinoma with microinvasion**
- **Papillary urothelial carcinoma with invasion into stalk**
- **Well-established invasion into underlying lamina propria**
- **Urothelial carcinoma with endophytic/broad front growth pattern**



Invasive Low-grade Papillary Urothelial Carcinoma: A Clinicopathologic Analysis of 41 Cases

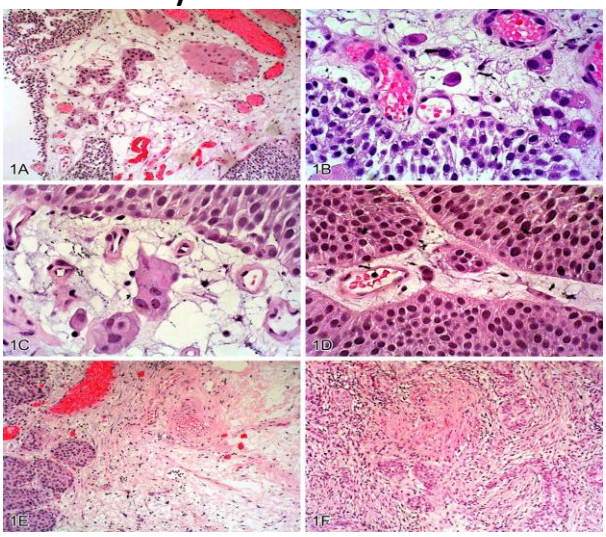
Adam D. Toll, MD and Jonathan I. Epstein, MD*†‡*





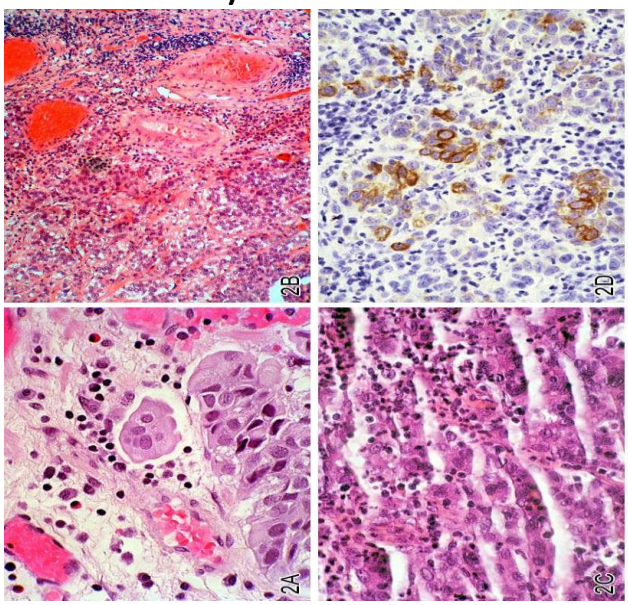
Lamina propria invasion
Main Issues to identify

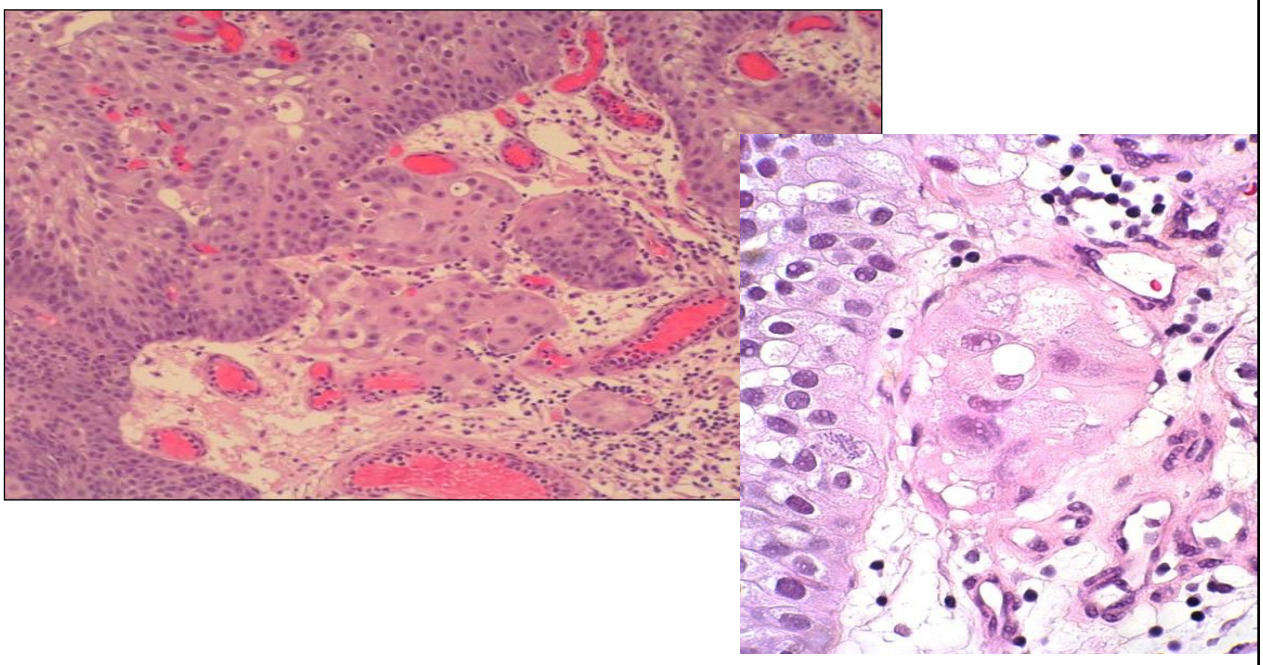
- **Invading epithelium**
  - **Irregularly shaped nests**
  - **Single cell infiltration**
  - **Irregular or absent basement membrane**
  - **Tentacular finger-like processes**
  - **Invasive component with higher nuclear grade or more cytoplasm: paradoxical differentiation**
  - **Vascular invasion**

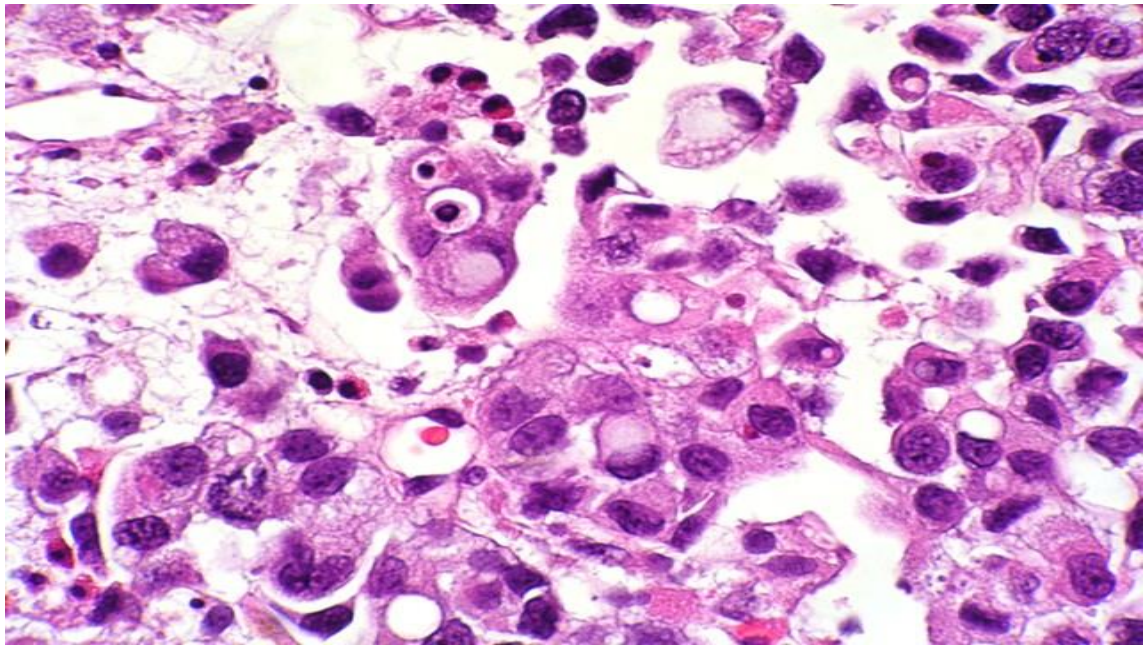


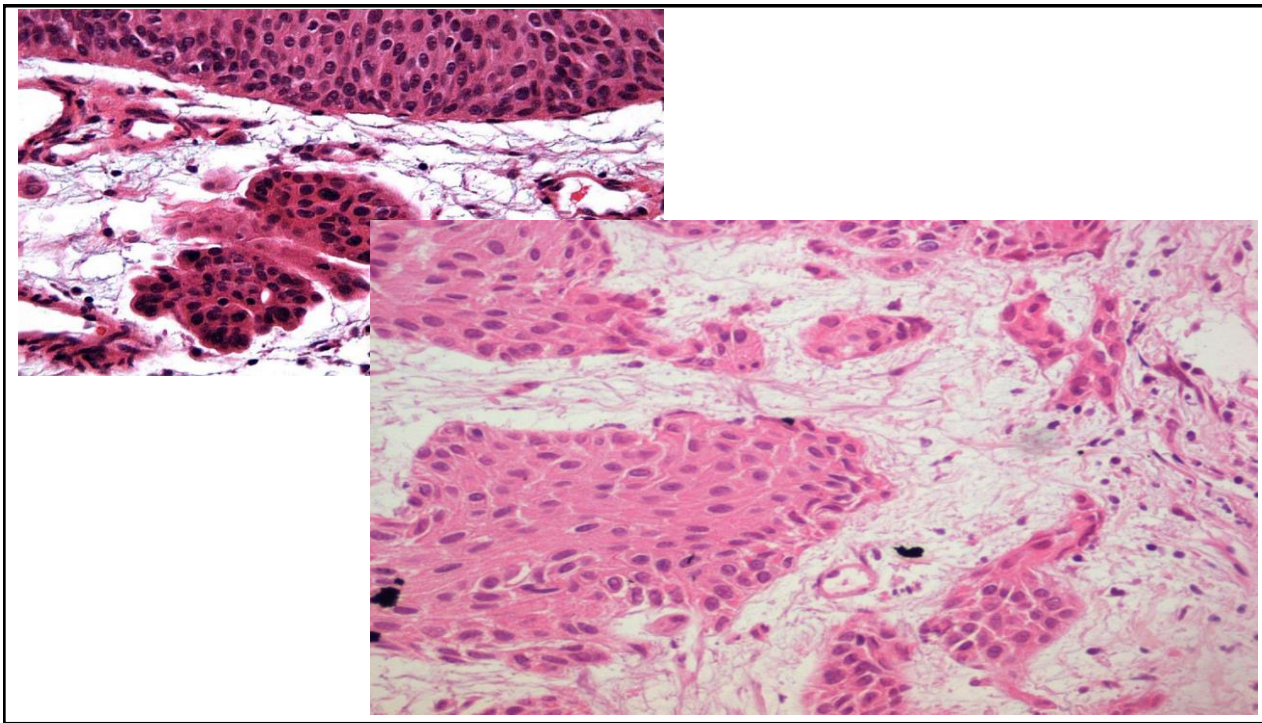
Lamina propria microinvasion
Main Issues to identify

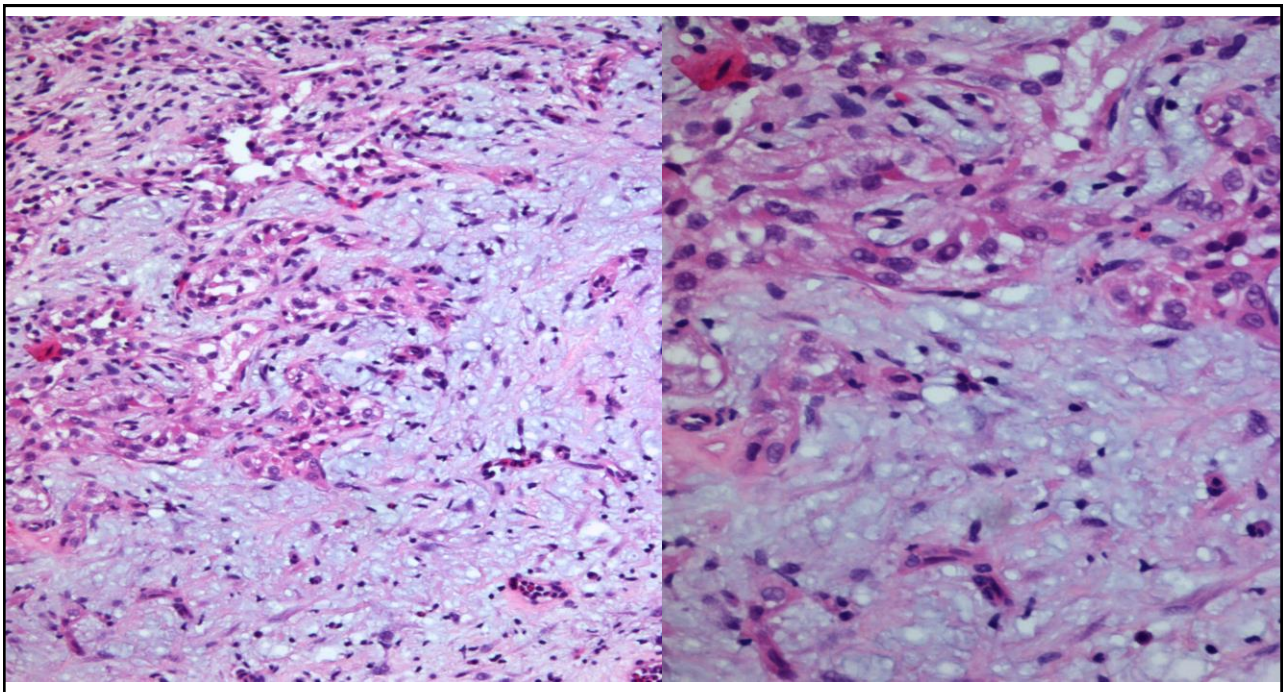
- **Stromal response**
  - **Desmoplasia**
  - **Retraction artifact**
  - **Inflammation**
  - **Myxoid stroma**
  - **Pseudosarcomatous stroma**
  - **Absent stroma response**







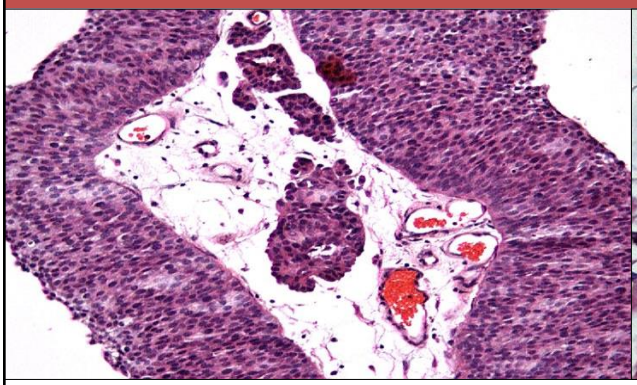


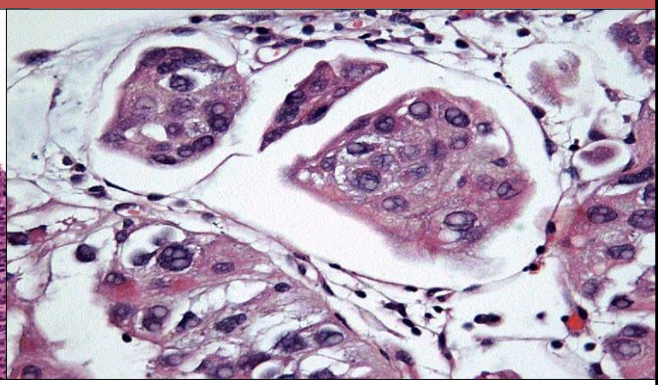


There are always difficult cases>>
¡inform the urologist¡

Microinvasion
Examples

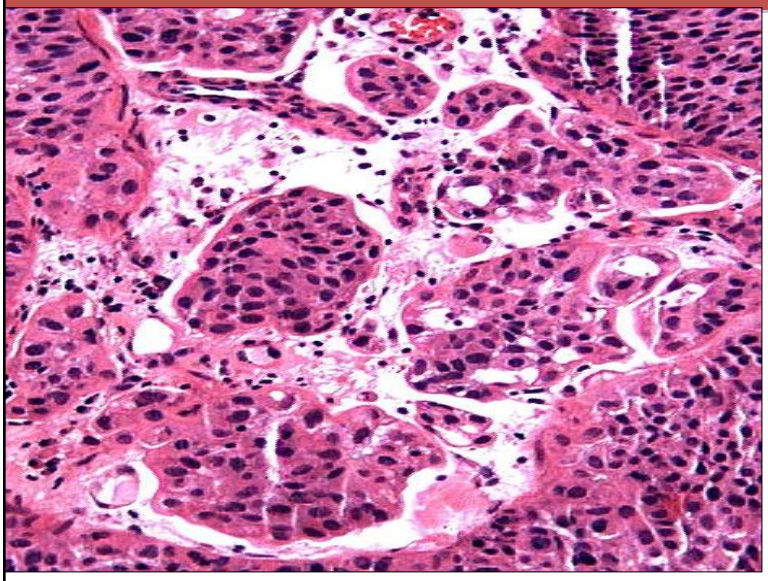
T1 bladder cancer





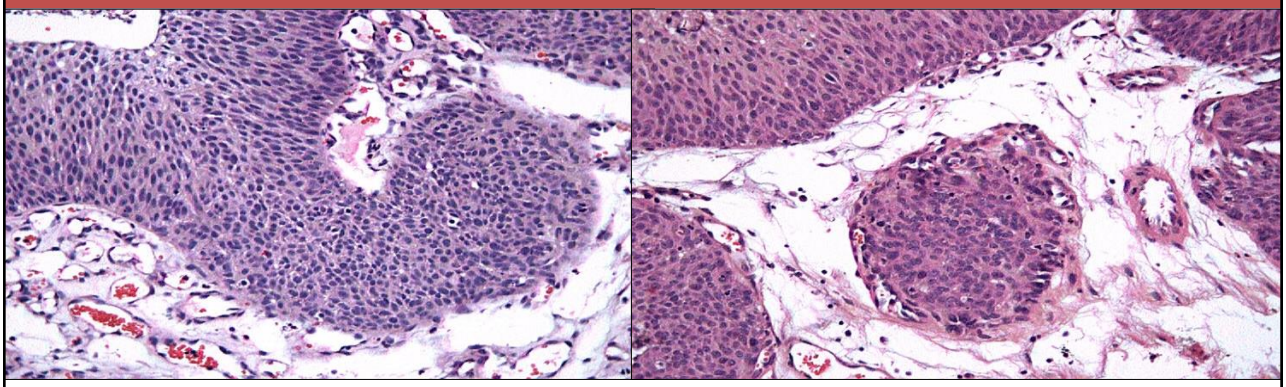
Nests without capillary net
Nests retraction

T1 bladder cancer



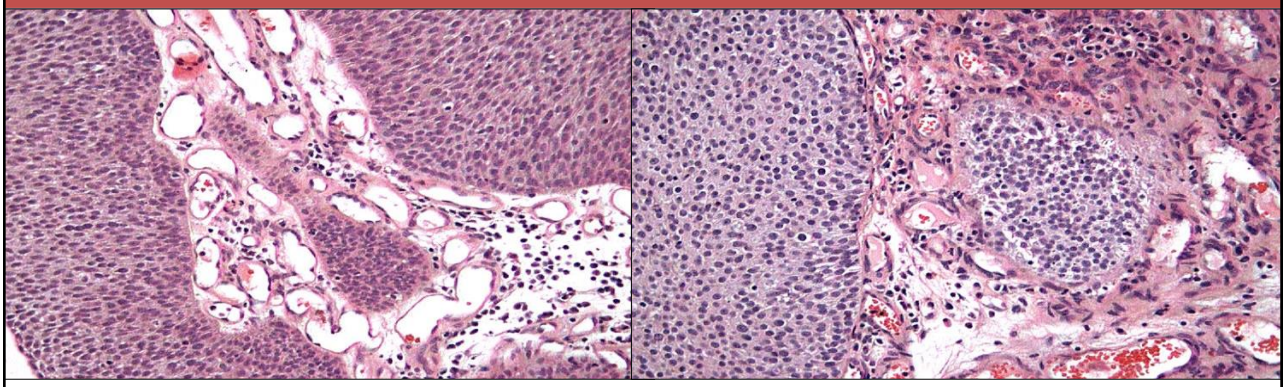
Small and
big nests

No Microinvasion



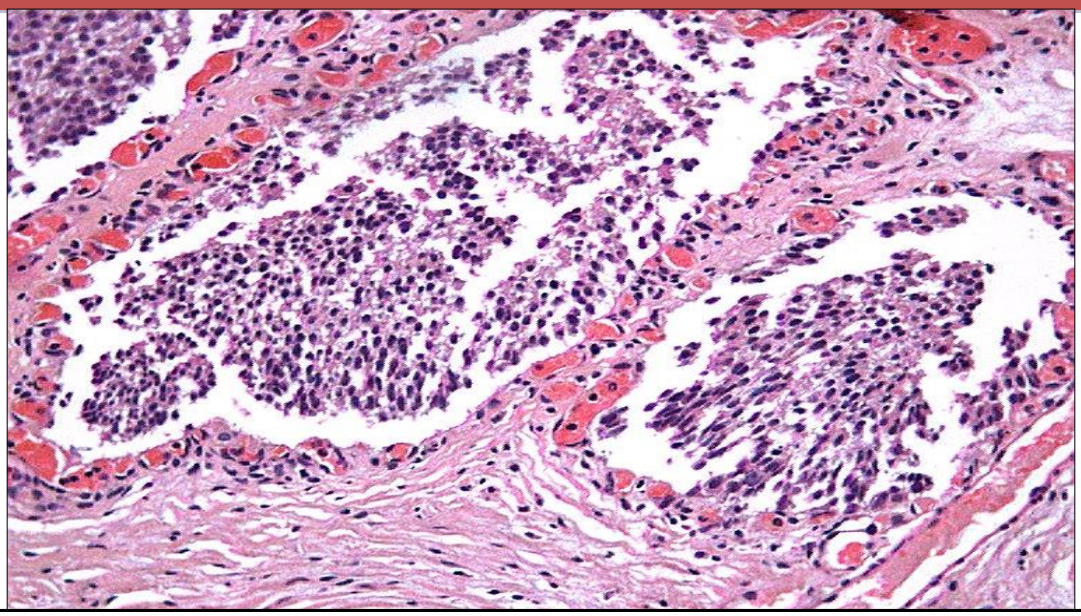
Pushing growth
Big regular nests

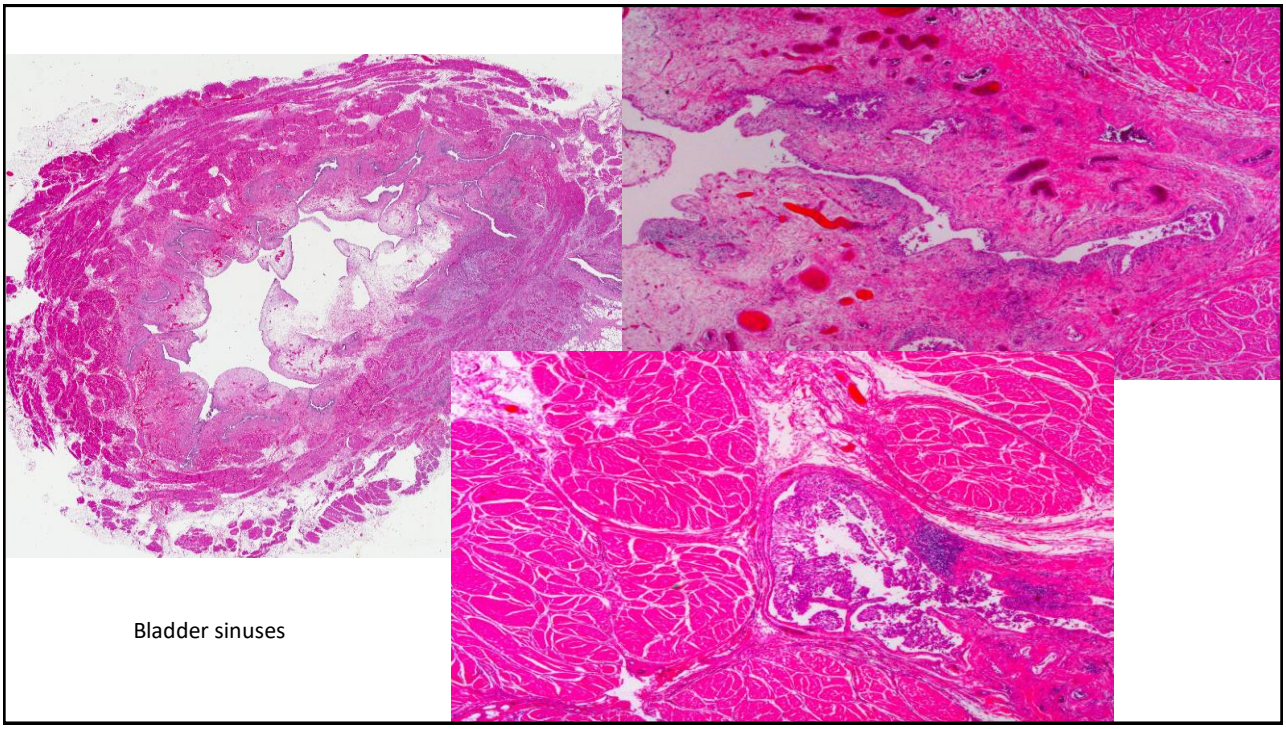
No Microinvasion



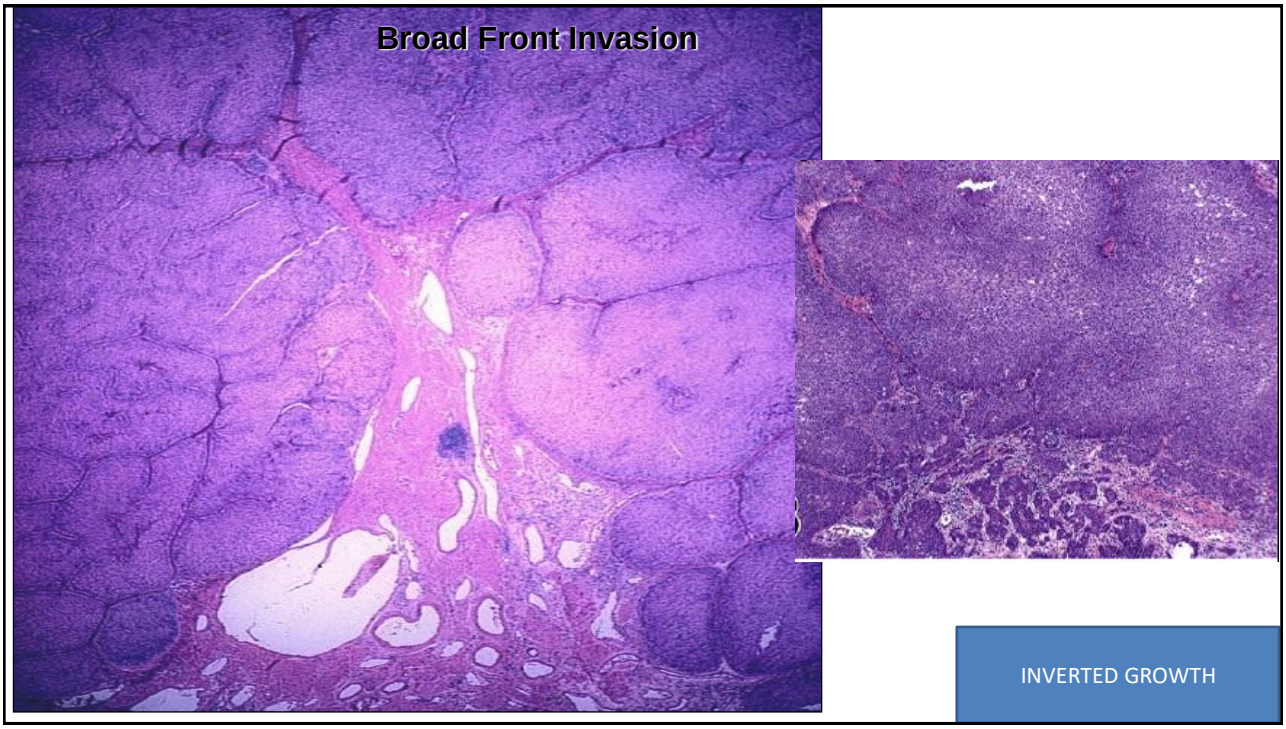
Regular nests
Peripheral b.m and capillary net

No Microinvasion





Bladder sinuses



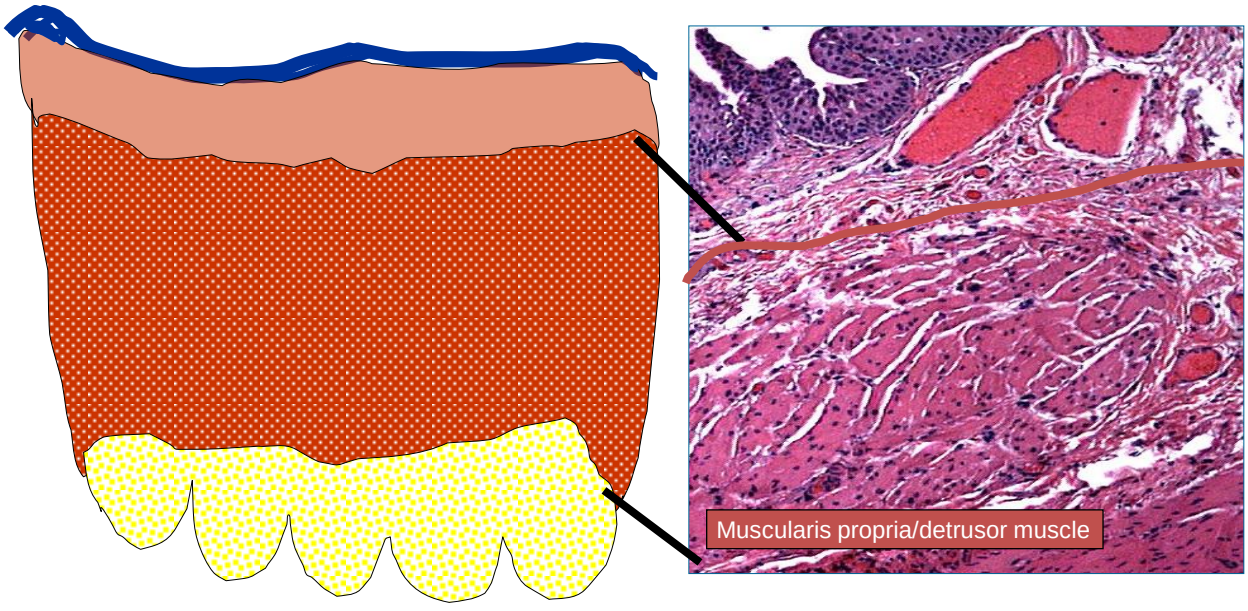
INVERTED GROWTH

Invasive Growth Patterns of Cancer

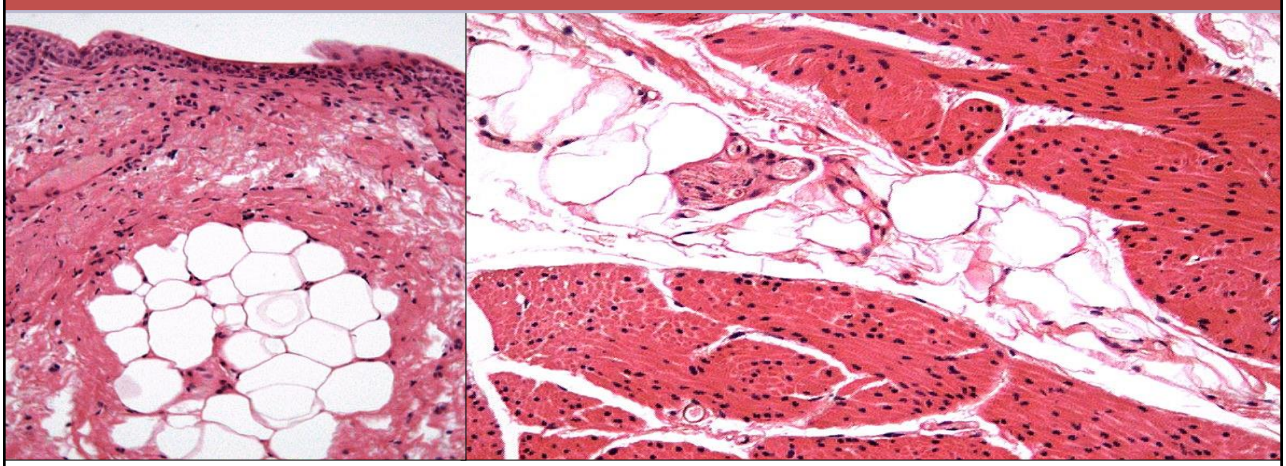
- **The diagnosis of invasion should be made when there are:**
- **Irregularities of the contours of the neoplastic nests**
- **Jagged edges**
- **Desmoplastic or inflammatory stroma surrounding these nests.**

Invasive Bladder Cancer
Stage pT2 at least

Stage pT2



T3 bladder cancer????



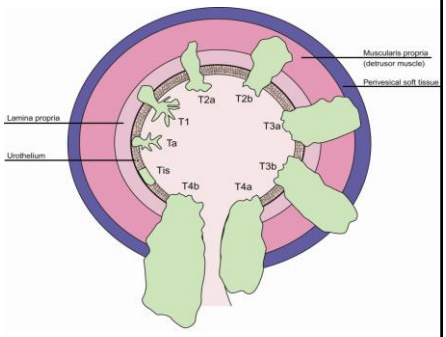
53% **100%** Am.J.Surg. Pathol. 2000, 24: 1286

¡BE CAREFUL WITH FAT TISSUE¡

Bladder Cancer Staging

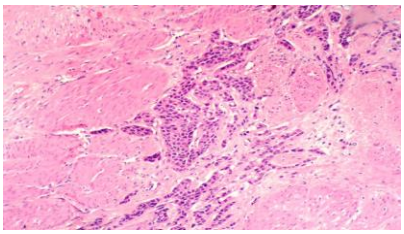
AJCC/TNM 2016. Category T

T0... No evidence of primary tumor
Tis... Urothelial Carcinoma "In Situ" (Flat Tumor)
Ta... Papillary tumor without invasion
T1... Subepithelial connective tissue invasion (invades lamina propria)
T2... Muscularis propia invasion
a.- Superficial invasion (inner half)
b.- Deep (outer half)
T3... Perivesical fat tissue invasion
a.- Microscopically
b.- Macroscopically
T4...Extravesical invasions
a.-Prostatic stroma, uterus, vagina
b.-Pelvic wall, abdominal wall



Invasive urothelial carcinoma
Depth of invasion

- pT system of staging has an excellent correlation with prognosis
- 5-year survival
  - pT1 75%
  - pT2 40%
  - pT3-pT4 20%



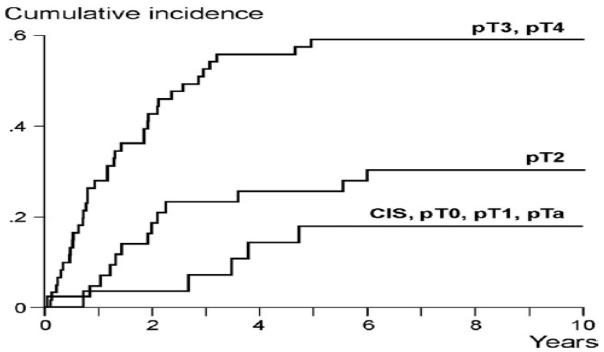
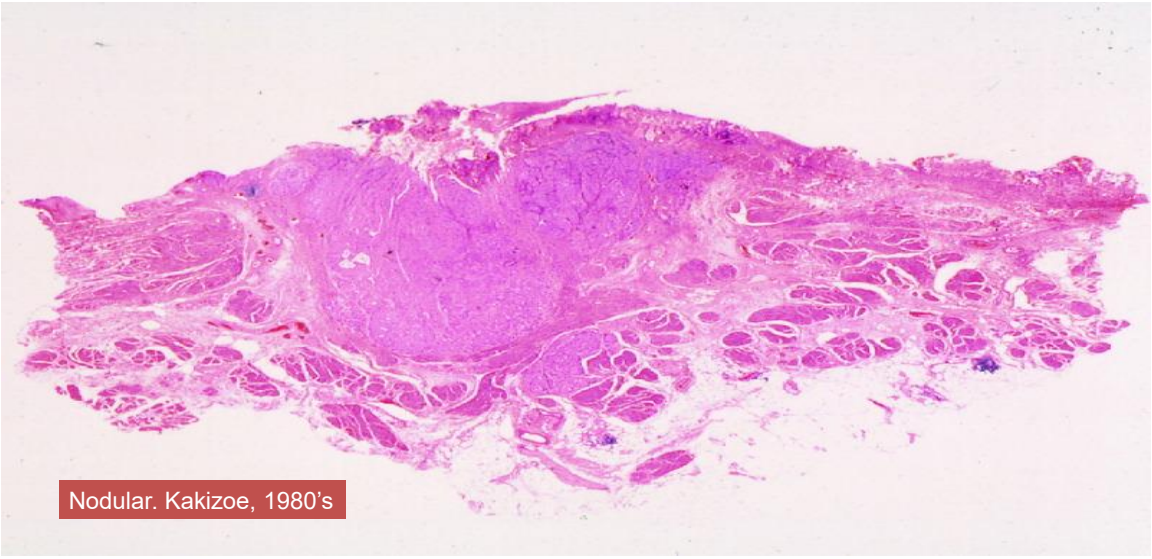


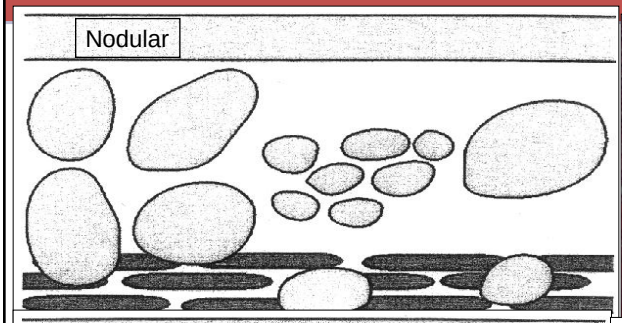
Fig. 1. Cumulative incidence of bladder cancer death by pathologic stage groups.

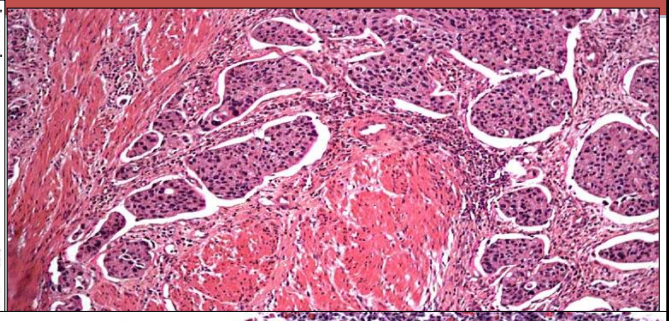
Bladder Cancer: Pattern of Invasion

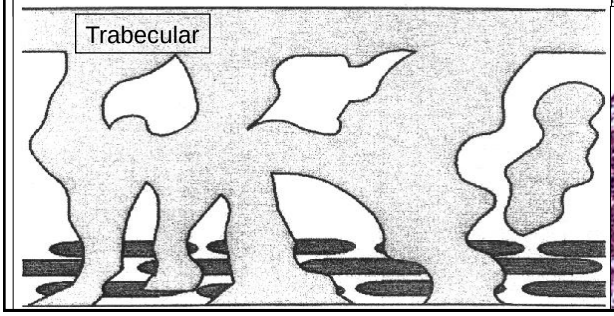


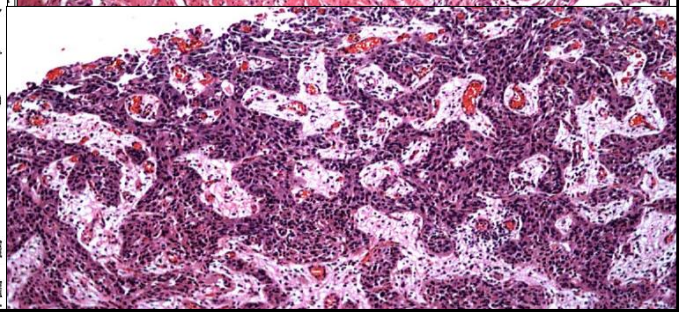
Nodular. Kakizoe, 1980's

Bladder Cancer: Pattern of Invasion

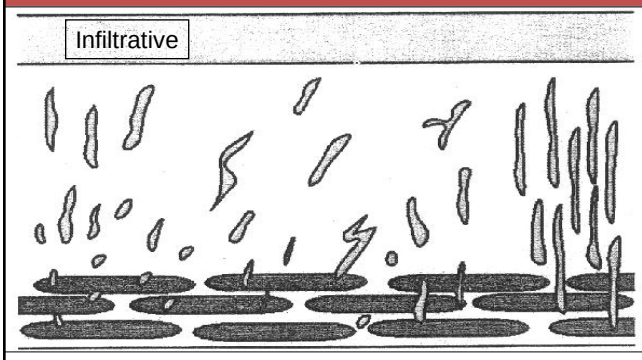


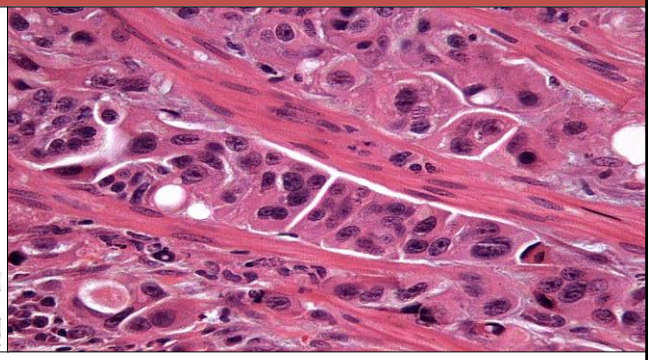






T2 bladder cancer

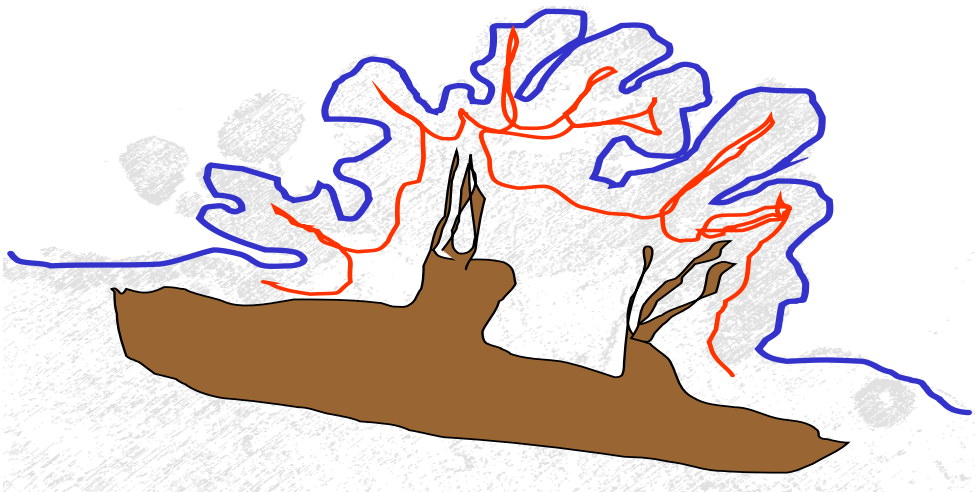


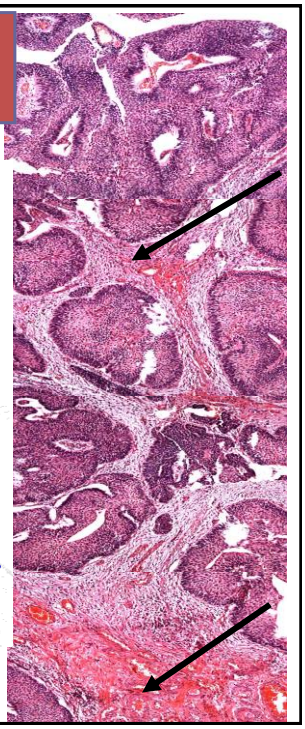


MEDIAN SURVIVAL 5 Years
Infiltrative pattern 29 months
Non infiltrative pattern 85 months

Jimenez R, Am. J. Surg. Pathol. 2000; 24: 980

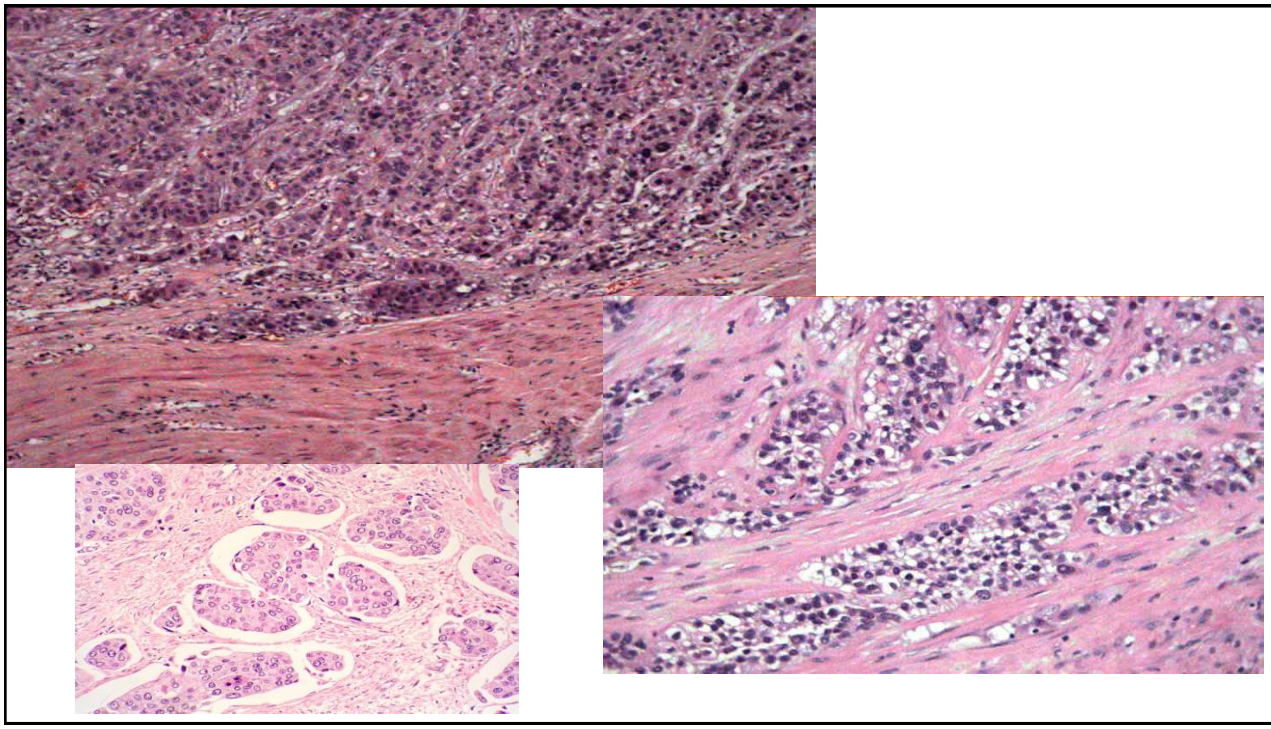
Is this Stage T2 bladder cancer?





Defining invasion of *muscularis propria*?

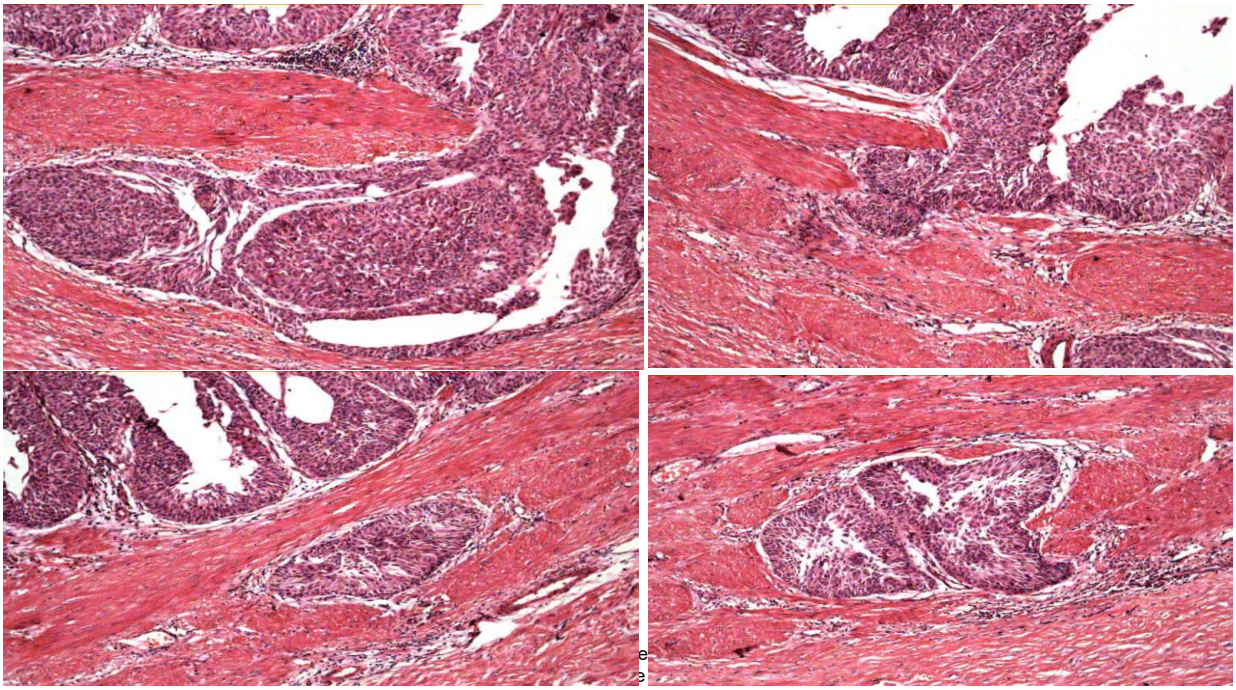
- Confusing terms that should be avoided:
- Superficial muscle invasion
- Deep muscle invasion
- Muscle invasion NOS
- Distinction between muscularis mucosae and muscularis propria is critical>>therapy
- Numerous blood vessels admixed with small bundles of smooth mucle>> MM
- Dense bundles of smooth muscle>> MP



Are there situations in which it is difficult to define MP?

- Difficult cases?
- Inform the urologist?
- In selected cases (rare)>>diagnosis of undeterminate for type of mucle>>R-Resection is mandatory
- Do not atempt to substage MP invasion (Turb)
- Presence/absence of MP should be included always in the final report >>> feedback to the urologist
- Cauthery artefact>>difficult to differentiate in some cases MM vs. MP
  - IHC with anti-smooth muscle actin/desmin/smoothelin/vimentin>>helpful in selected cases

Difficult cases?
Example



Urinary Bladder

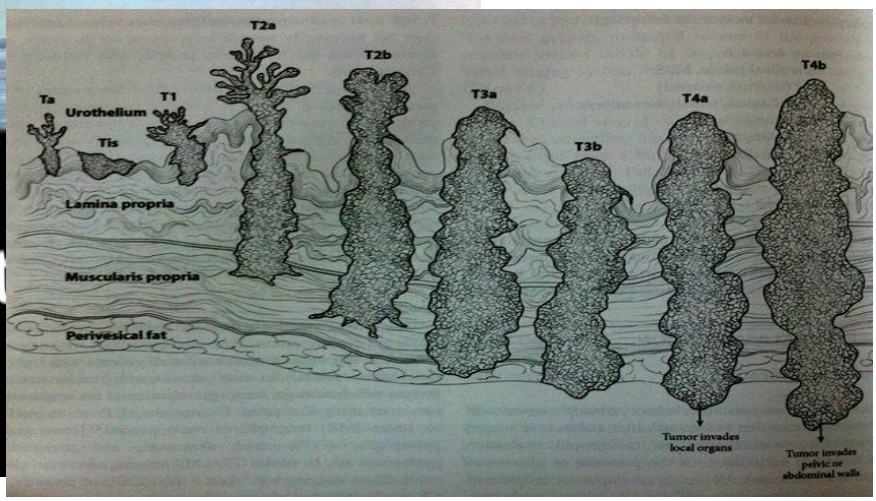
62

Bernard H. Bochner, Donna E. Hansel, Jason A. Efstathiou, Badrinath Konety, Cheryl T. Lee, James M. McKiernan, Elizabeth R. Plimack, Victor E. Reuter, Srikala Sridhar, Raghunandan Vikram, and Walter M. Stadler

2017

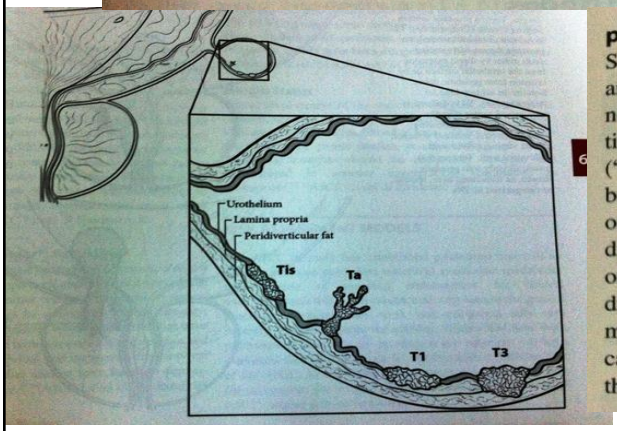
AJCC Cancer St Manual

Eighth Edition



Summary of Changes

Change	Details of Change
Definition of Regional Lymph Node (N)	Perivesical lymph node involvement is classified as N1.
Definition of Distant Metastasis (M)	M1 is subdivided into M1a and M1b. M1a refers to a non-regional lymph node only. M1b refers to non-lymph-node distant metastases.
AJCC Prognostic Stage Groups	Stage III is subdivided into IIIA and IIIB. Stage IV is subdivided into IVA and IVB.



pT1 Categorization

Several experts have recommended substaging of pT1 disease, and numerous subcategories have been proposed. Although not formally endorsed in this staging system, pT1 categorization appears to have prognostic value, with early invasion ("microinvasive disease") into the lamina propria showing better outcomes than more advanced pT1 disease. The method of pT1 substaging has not been optimized, but microinvasive disease has been defined by different groups as invasive tumor of <1 high power field in content, greatest invasive tumor diameter of 1 mm, or invasive tumor above the muscularis mucosae extending to a depth of 2 mm or less. An attempt to categorize pT1 disease is strongly recommended using one of the above methods.[24–26] AJCC Level of Evidence: II

DEFINITIONS OF AJCC TNM

Definition of Primary Tumor (T)

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Non-invasive papillary carcinoma
Tis	Urothelial carcinoma *in situ*: "flat tumor"
T1	Tumor invades lamina propria (subepithelial connective tissue)
T2	Tumor invades muscularis propria
pT2a	Tumor invades superficial muscularis propria (inner half)
pT2b	Tumor invades deep muscularis propria (outer half)
T3	Tumor invades perivesical soft tissue
pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4	Extravesical tumor directly invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Extravesical tumor invades directly into prostatic stroma, uterus, vagina
T4b	Extravesical tumor invades pelvic wall, abdominal wall

Take-Home Messages

- There is a need to define T1 sub-staging with criteria and methods to be applied
- When detrusor muscle is positive sign out as stage T2 at least
- When not clear if positive muscle is MM or MP talk to urologist
- A R-TUR will solve the problem in most cases
- IHC has potential value in selected cases.
- Follow AJCC 2017 in practice

THANKS