



### III ЕЖЕГОДНЫЙ КОНГРЕСС РОССИЙСКОГО ОБЩЕСТВА ОНКОПАТОЛОГОВ

20–21 апреля 2018 года

13.00–14.00	<b>ПЕРЕРЫВ НА ОБЕД</b>
14.00–15.40	<b>Сессия – Онкоурология</b> (председатель – Ковылина М.В.)
14.00–14.25	<b>Antonio Lopez-Beltran</b> (Испания) CIS/Dysplasia of the urothelium
14.25–14.50	<b>Antonio Lopez-Beltran</b> (Испания) Pathologic assessment of invasion in TUR specimens
14.50–15.10	<b>Antonio Lopez-Beltran</b> (Испания) Urothelial tumors with inverted growth
15.10–15.30	<b>Antonio Lopez-Beltran</b> (Испания) Variants of urothelial carcinoma
15.30–15.40	<b>Дискуссия – все участники</b>

## Pathologic Assessment of Invasion in TUR Specimens

A. Lopez-Beltran

**T1 (cT1)**

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

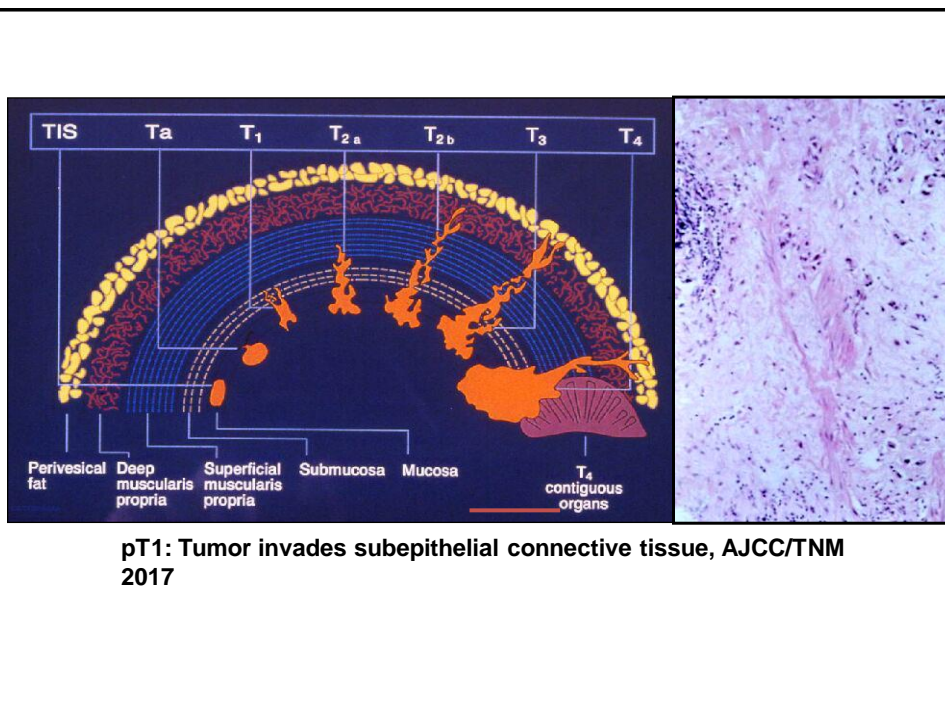
- ESSENTIAL:
- Grade
- T stage
- CIS
- Number of lesions
- Previous recurrences
- ADDITIONAL
- Recurrence at 3 month check
- Tumor size>> 3 cm

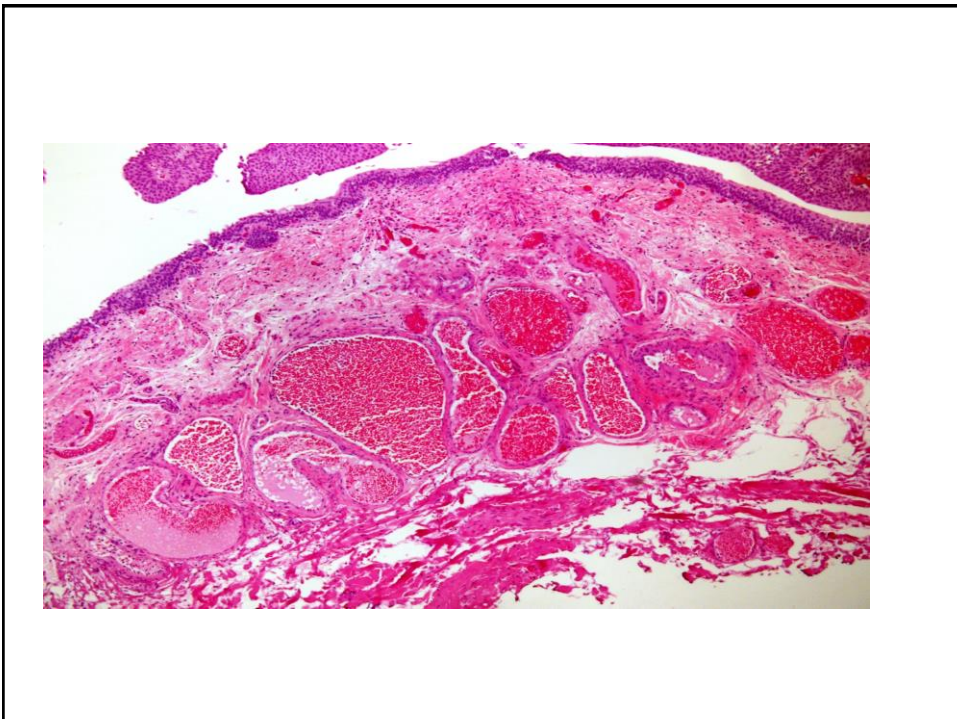
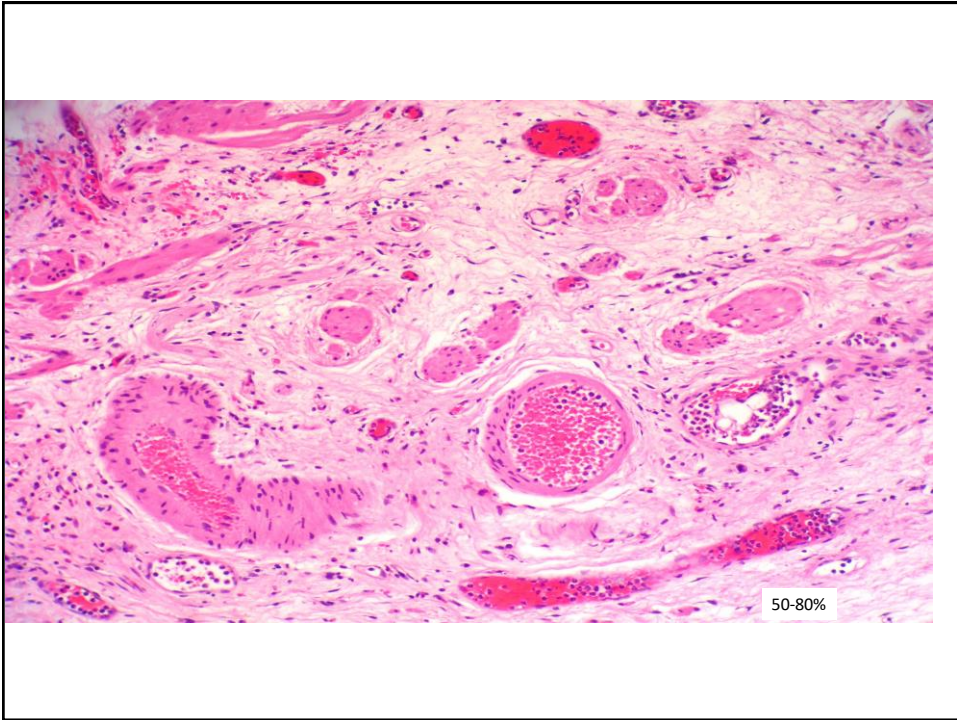
Prognostic factors metastasis risk/Survival MIBC T2-  
4No-1  
:TNM 2017

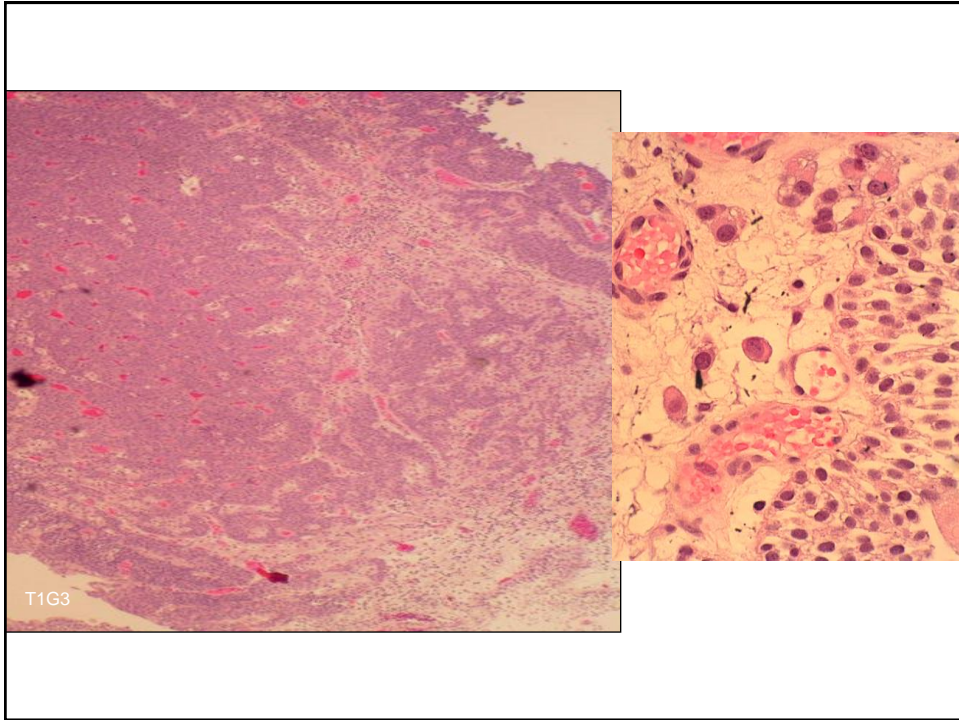
- ESSENTIAL:
- T category
- N category
- ADDITIONAL
- Grade
- Histological type
- LVI
- Concomitant CIS
- Tumor size
- Hydronephrosis

## Background

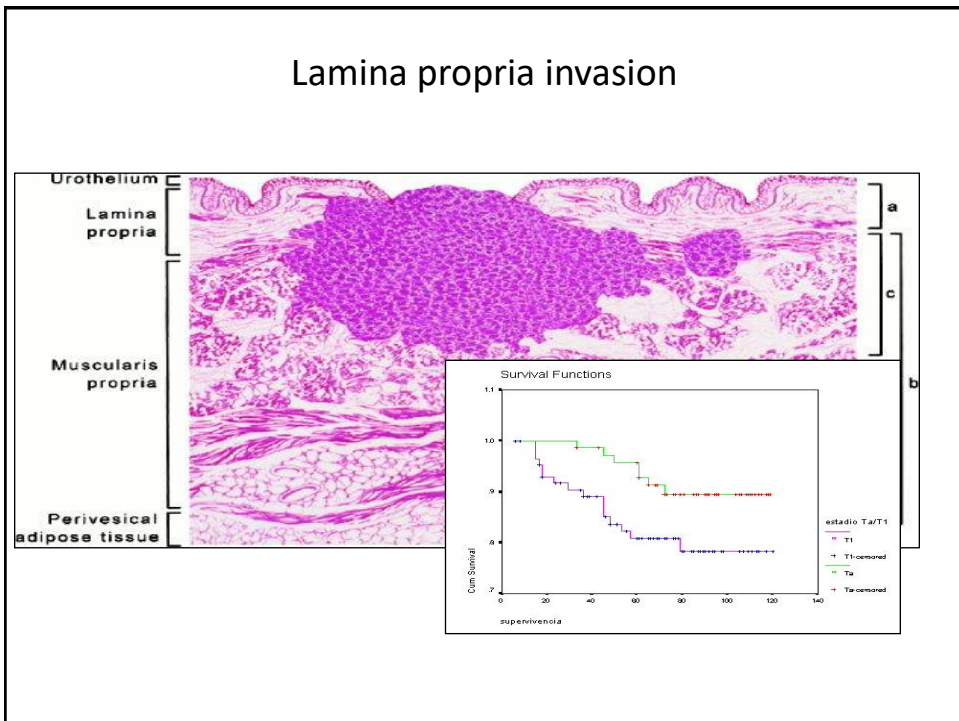
- T1 assessment and pitfalls
- T1 substaging-Proposals
- T2 assessment and pitfalls
- AJCC/TNM 2017







### Lamina propria invasion

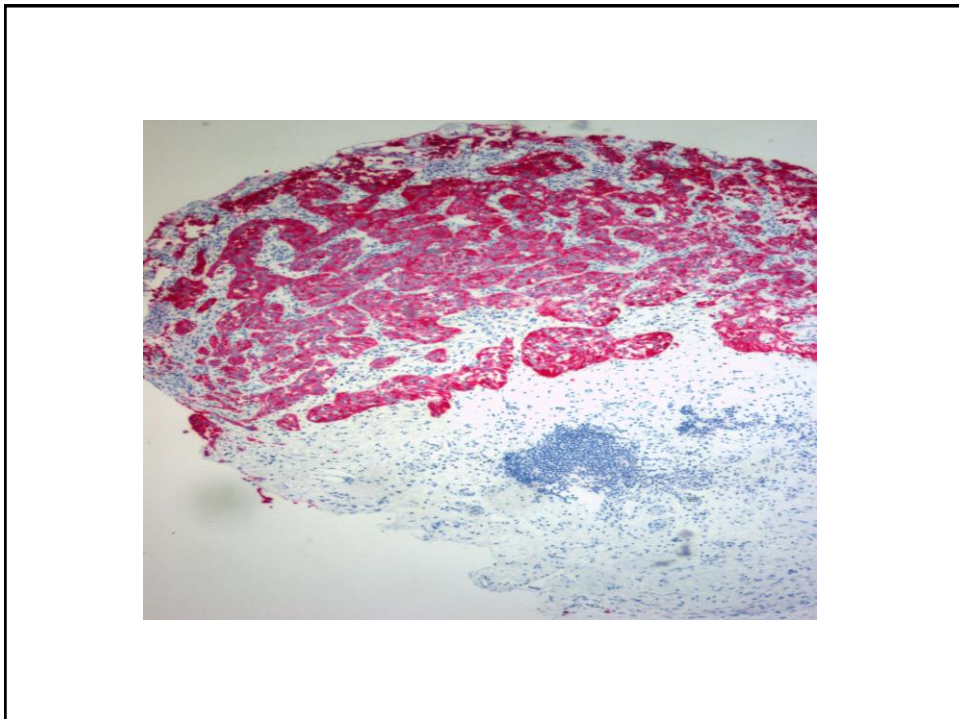
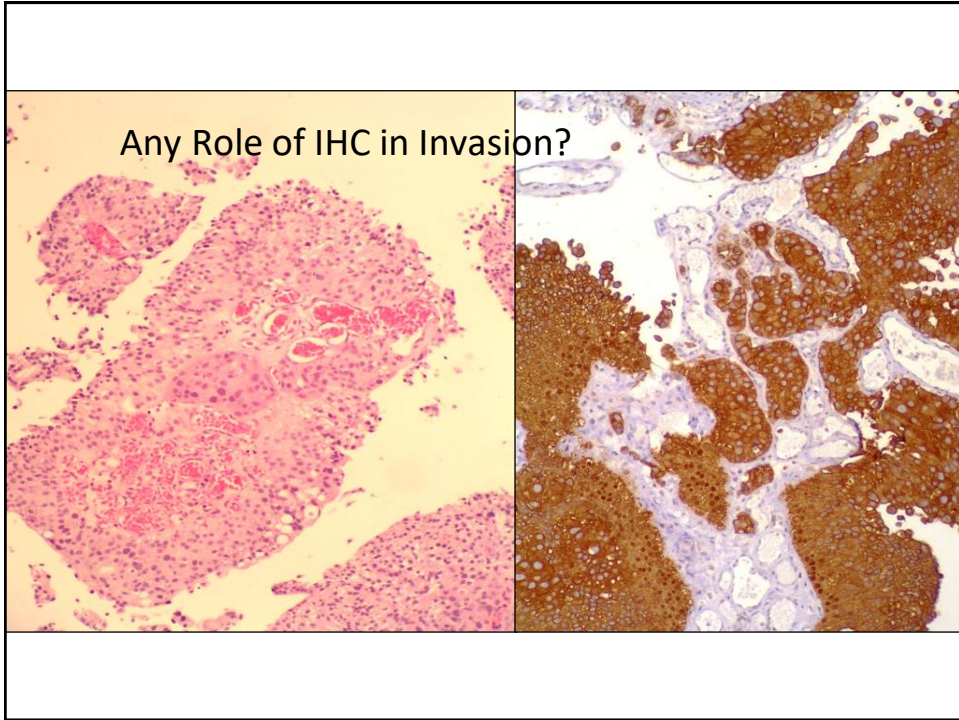


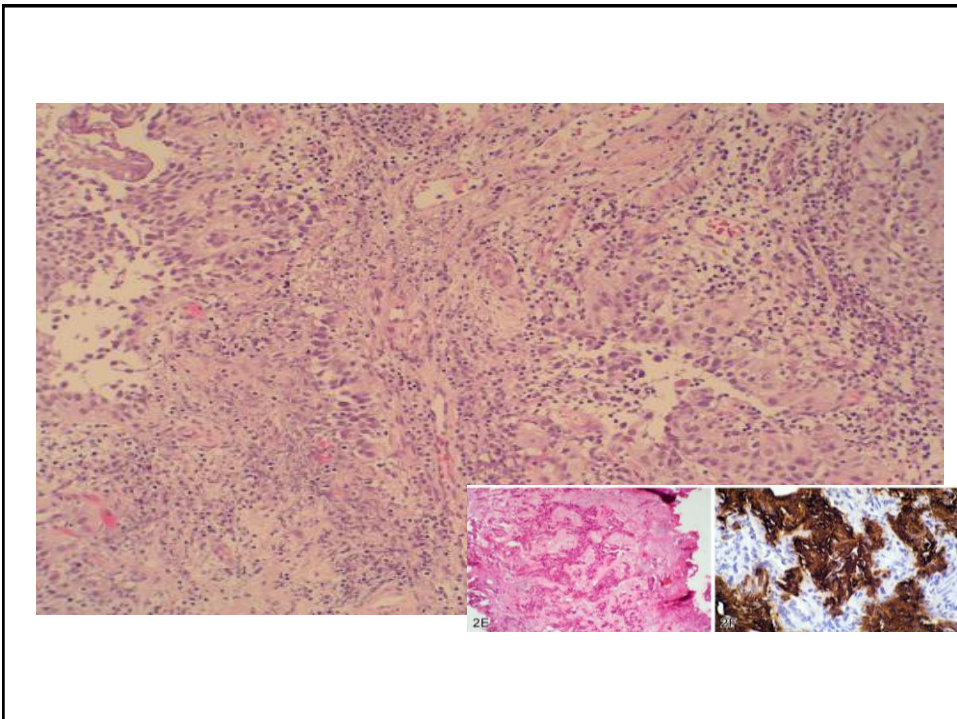
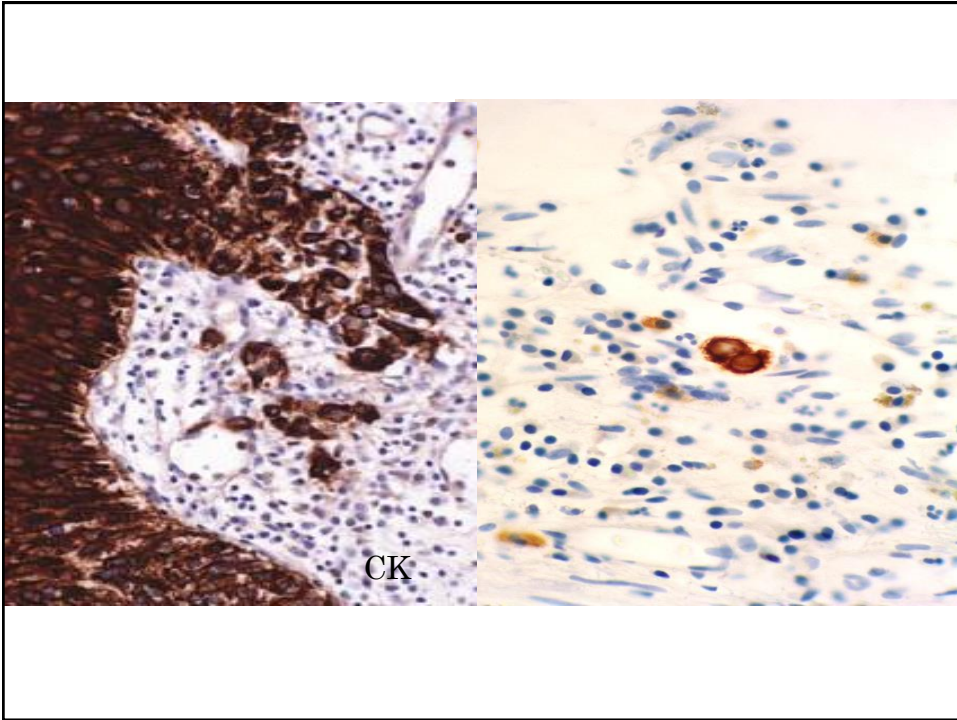
Important pathologic problem:  
Reproducibility in pT1

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%



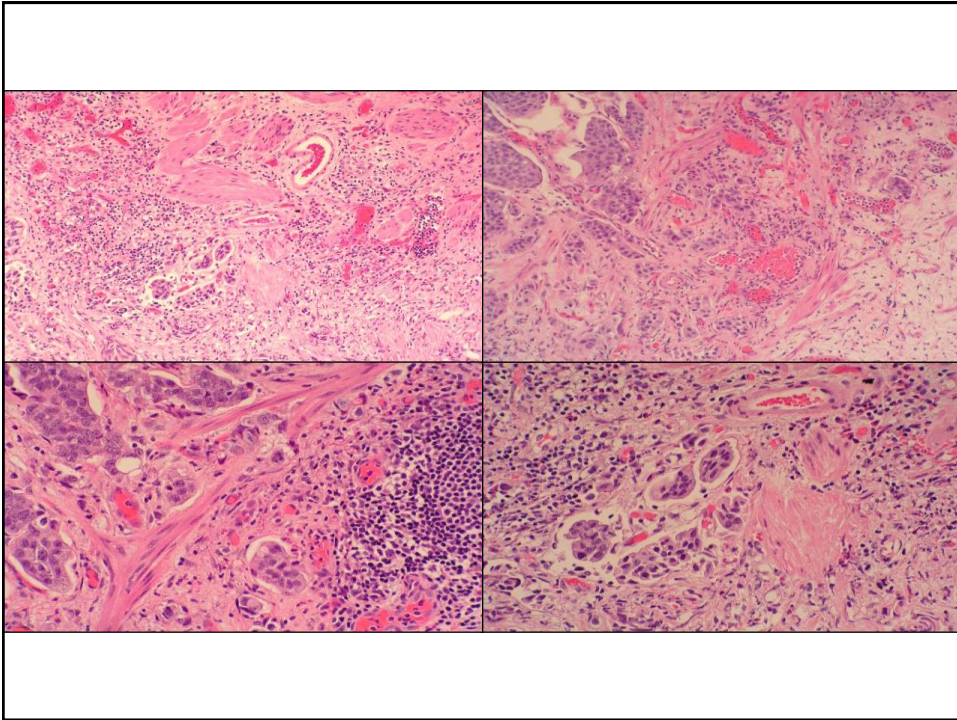




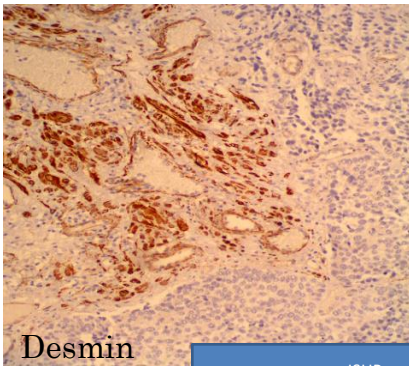
## T1 Substaging

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

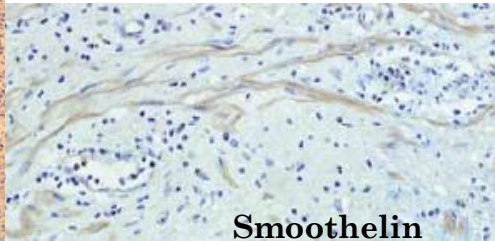
Year	Author	Staging system	Number of cases	Progression (%)	Survival (%)
1990	Younes et al. [6]	T1a (lamina propria)	15	NA	75
		T1b (into MM)	3		
		T1c (across MM)	14		11
1994	Hasui et al. [8]	T1a (Younes T1a)	60 <sup>a</sup>	6.7	95
		T1b (Younes T1b and c)	28 <sup>a</sup>	53.5	82
1995	Angulo et al. [21]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



### Muscularis Mucosae and invasion Role of IHC

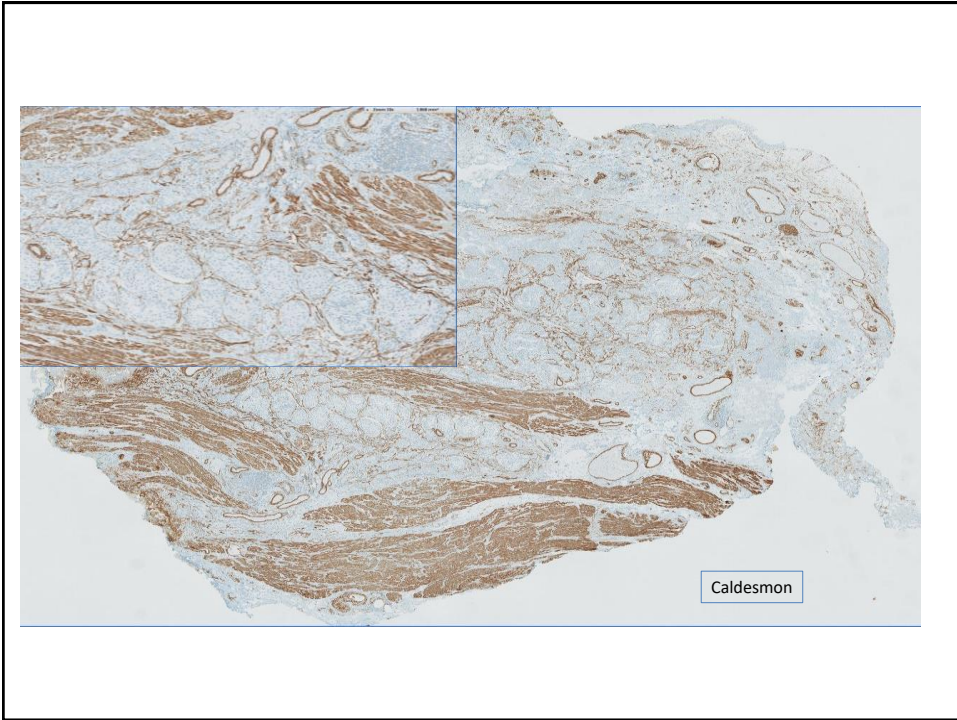


Desmin

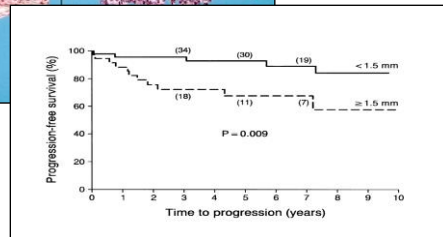
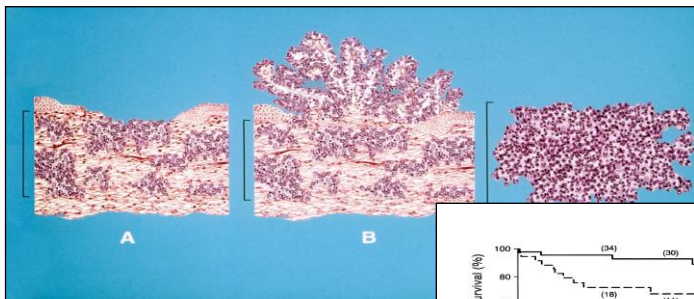


Smoothelin

ISUP consensus on IHC  
Amin, Trypkov, Lopez-Beltran et al 2014



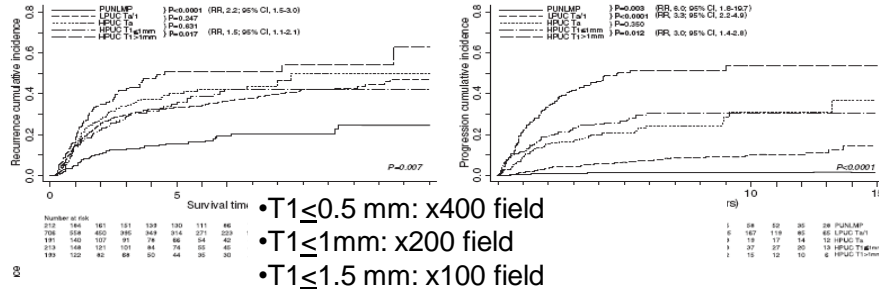
pT1 substaging is significant in patient survival?



## 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

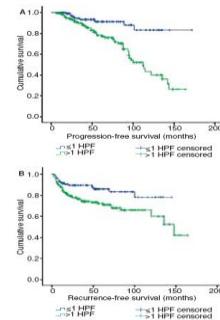


Histopathology 2011, 59, 722–732. DOI: 10.1111/j.1365-2559.2011.03989.x

## 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,<sup>1</sup> Wolfgang Otto,<sup>1</sup> Wolf F Wieland,<sup>1</sup> Robert Stoehr, Ferdinand Hofstaedter<sup>2</sup> & 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,<sup>1</sup> Roman Gulati<sup>2</sup> & Maria Tretiakova<sup>1</sup><sup>1</sup>Department of Pathology, University of Washington School of Medicine, Seattle, WA, USA, and <sup>2</sup>Fred Hutchinson Cancer Research Center, Seattle, WA, USA

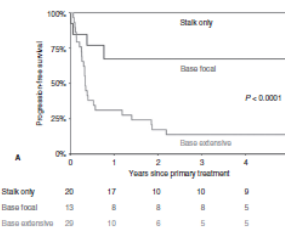
**Aim:** Pathological stage pT1 bladder cancers constitute a clinically heterogeneous group. However, current staging guidelines for superficially invasive cancers do not acknowledge the variability in type and extent of lamina propria invasion in papillary urothelial carcinomas (PUC), and historically 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 PUC diagnosed during 1999–2015 were retrospectively reviewed and characterized 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 ( $P = 0.21$ ).

**Conclusion:** 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



## Analysis of T1 Bladder Cancer on Biopsy and Transurethral Resection Specimens

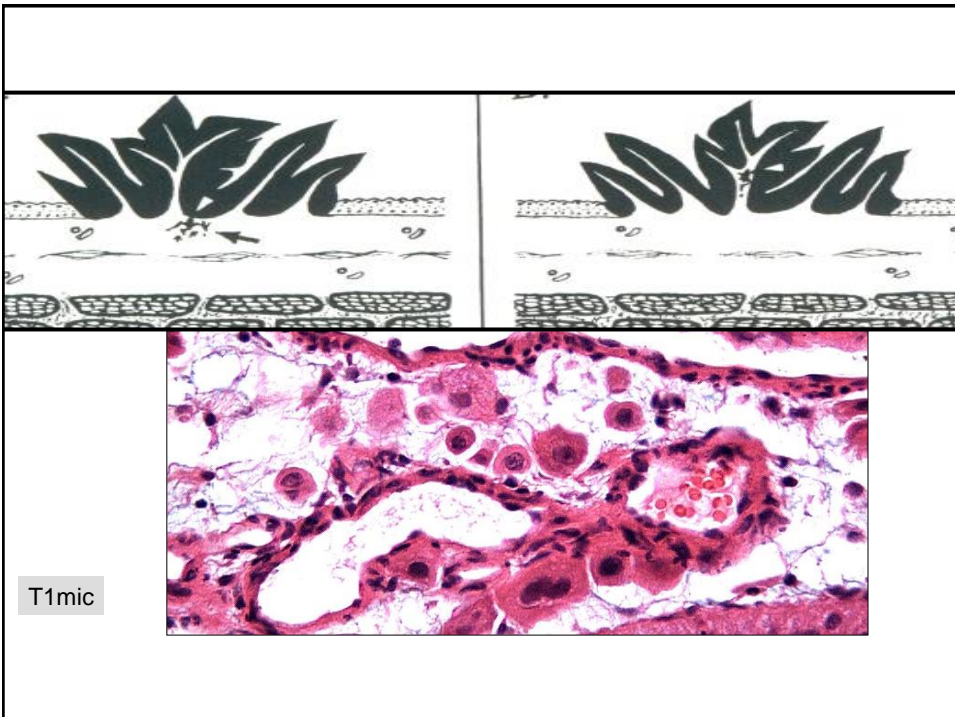
## Comparison and Ranking of T1 Quantification Approaches to Predict Progression to Muscularis Propria Invasion

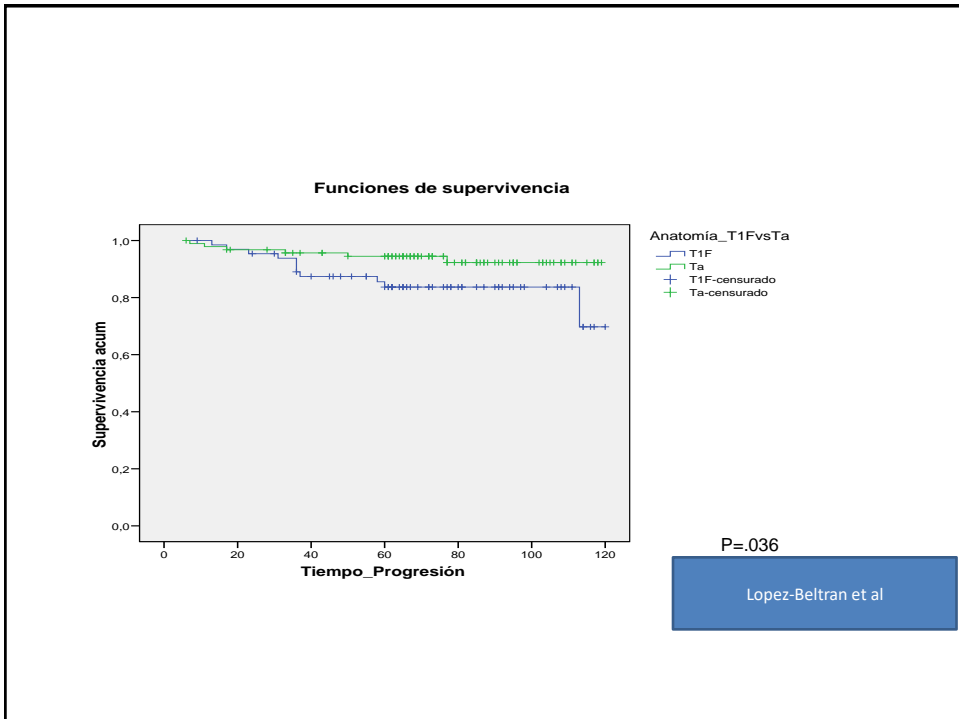
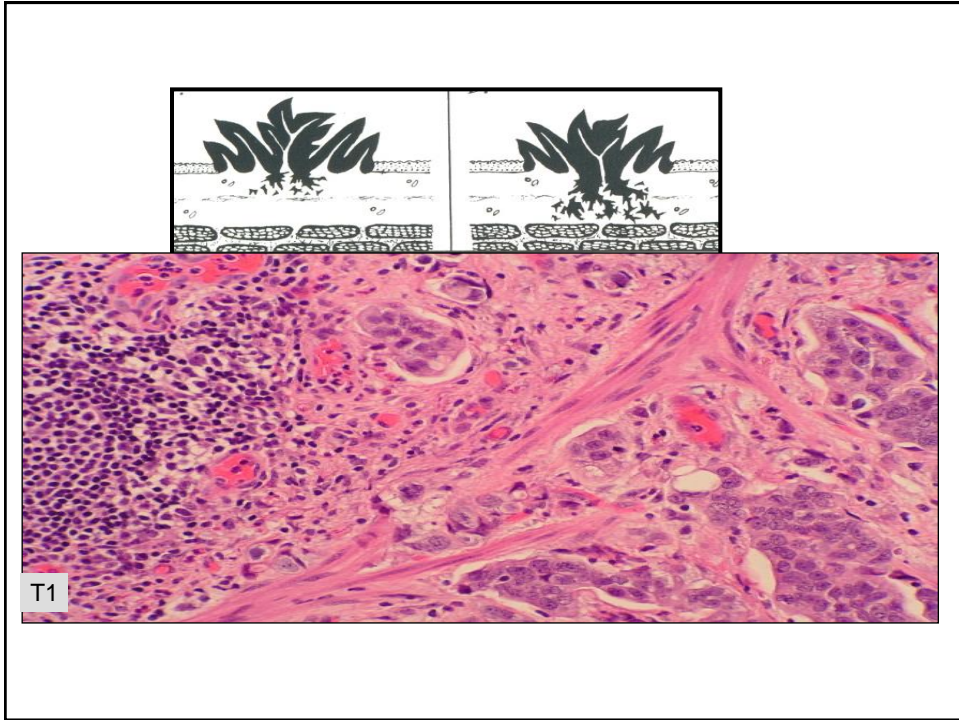
Mariah Z. Leivo, MD,\* Debashis Sahoo, PhD,† Zachary Hamilton, MD,‡ Leili Mirsadraei, MD, Ahmed Shabaik, MD,\* John K. Parsons, MD, PhD,‡ Andrew K. Kader, MD,‡ Ithaa Derveeshi, MD,‡ Christopher Kane, MD,‡ and Donna E. Hansel, MD, PhD\*†

## Recent proposals for T1 substaging

**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 subclassify 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 ( $P = 3.067 \times 10^{-76}$ ) 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 2.5 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  $\geq 2.3$  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  
Microinvasion vs. established invasion





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

LEYSHAM OXFORD  
healthsciences

## GENITOURINARY PATHOLOGY

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

ANTONIO LOPEZ-BELTRAN\* AND LIANG CHENG†

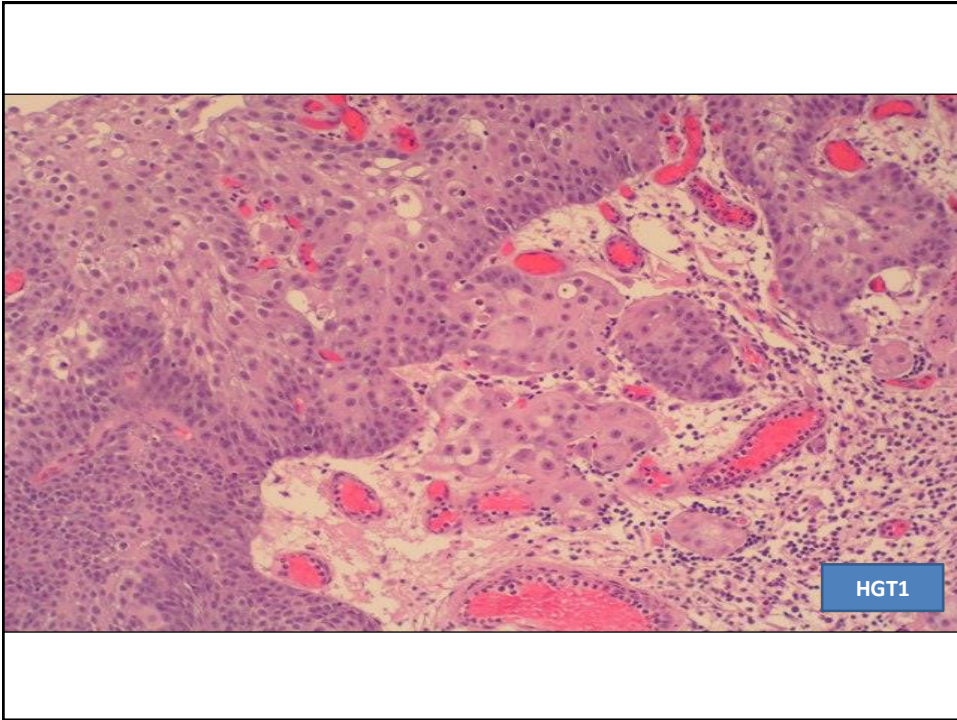
## Can we improve Invasion assessment?

### PATHOLOGIC ISSUES IN DIAGNOSIS OF LAMINA PROPRIA MICROINVASION

#### How we do identify invasion?

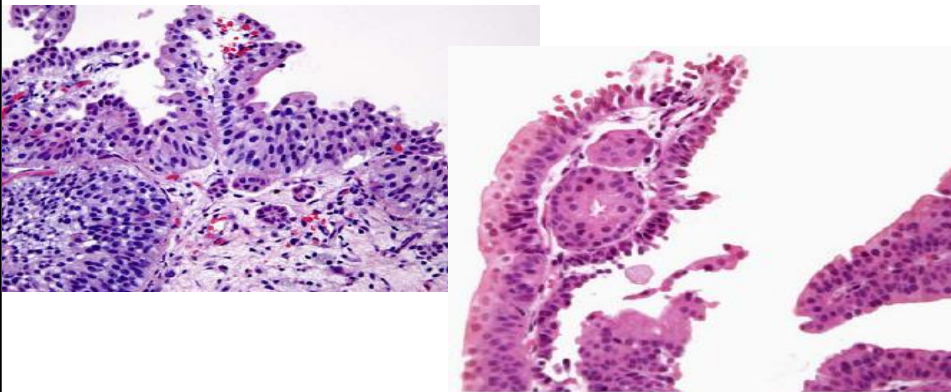
- **HOW:** General Features
  - Histologic grade
  - Stroma-epithelial interface (basement membrane)
  - Invading epithelium
  - Stromal response
- **WHERE:** Bladder Tumors with MICROINVASION
  - CIS with microinvasion
  - Papillary urothelial carcinoma with microinvasion
  - Papillary urothelial carcinoma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





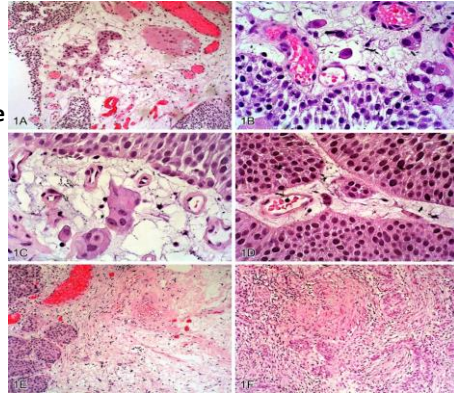
## Invasive Low-grade Papillary Urothelial Carcinoma: A Clinicopathologic Analysis of 41 Cases

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



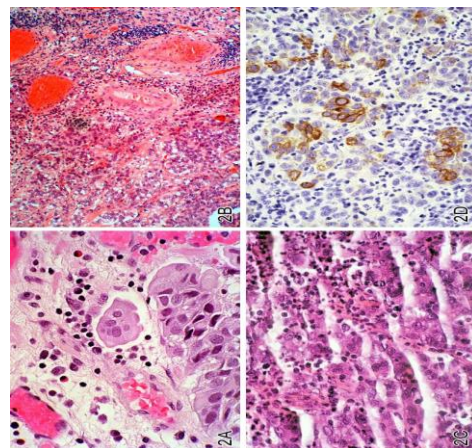
## Lamina propria invasion Main Issues to identify

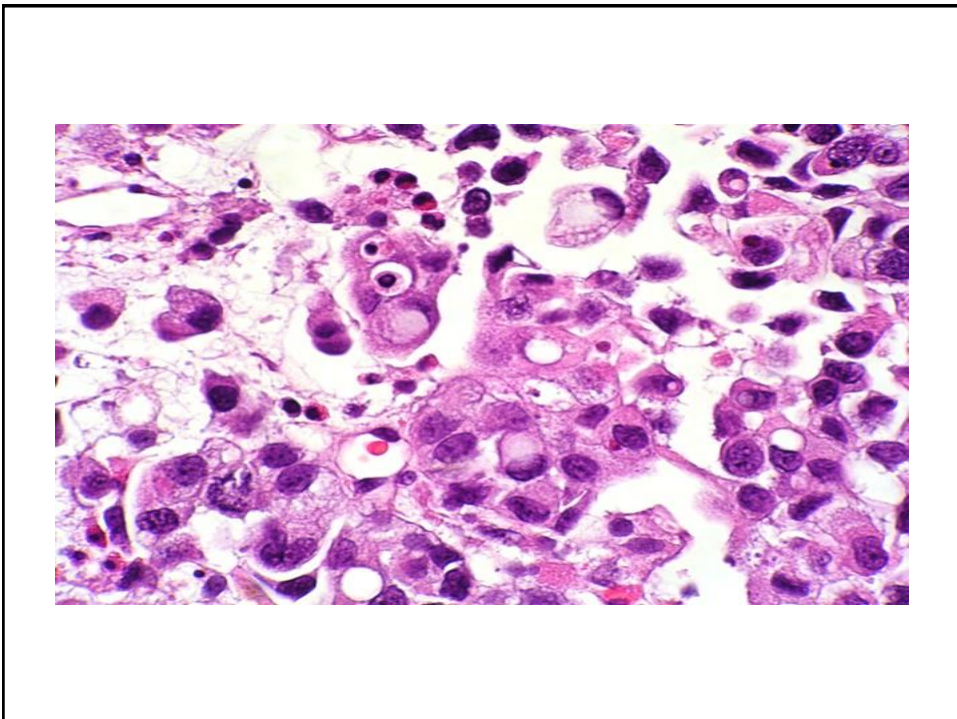
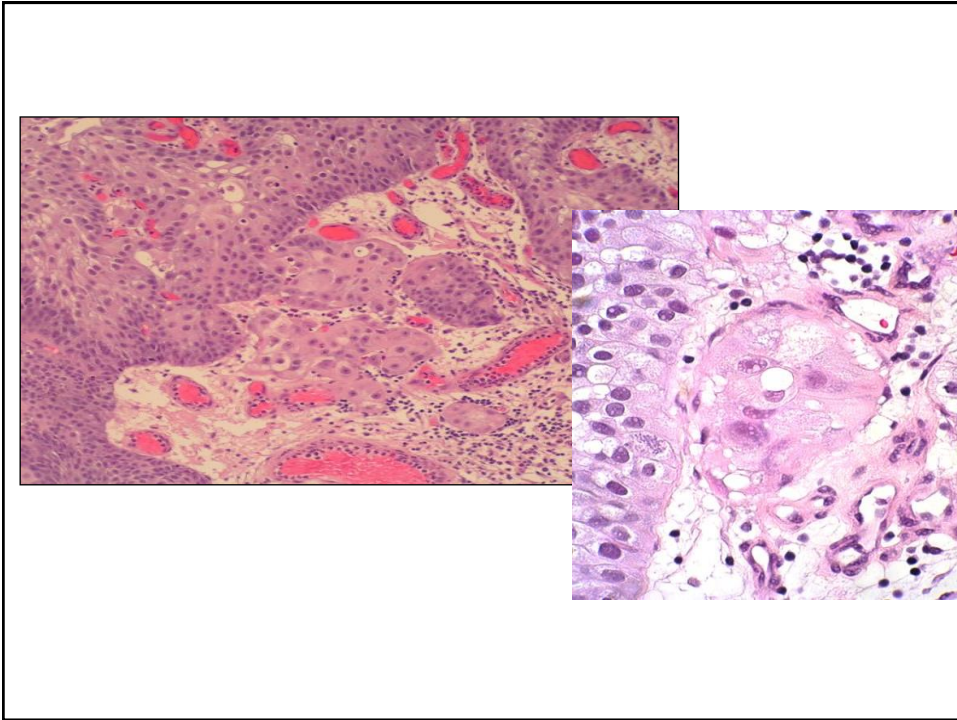
- **Invading epithelium**
  - Irregularly shaped nests
  - Single cell infiltration
  - Irregular or absent basement membrane
  - Tentacular finger-like processes
  - Invasive component with higher nuclear grade or more cytoplasm: paradoxical differentiation
  - Vascular invasion

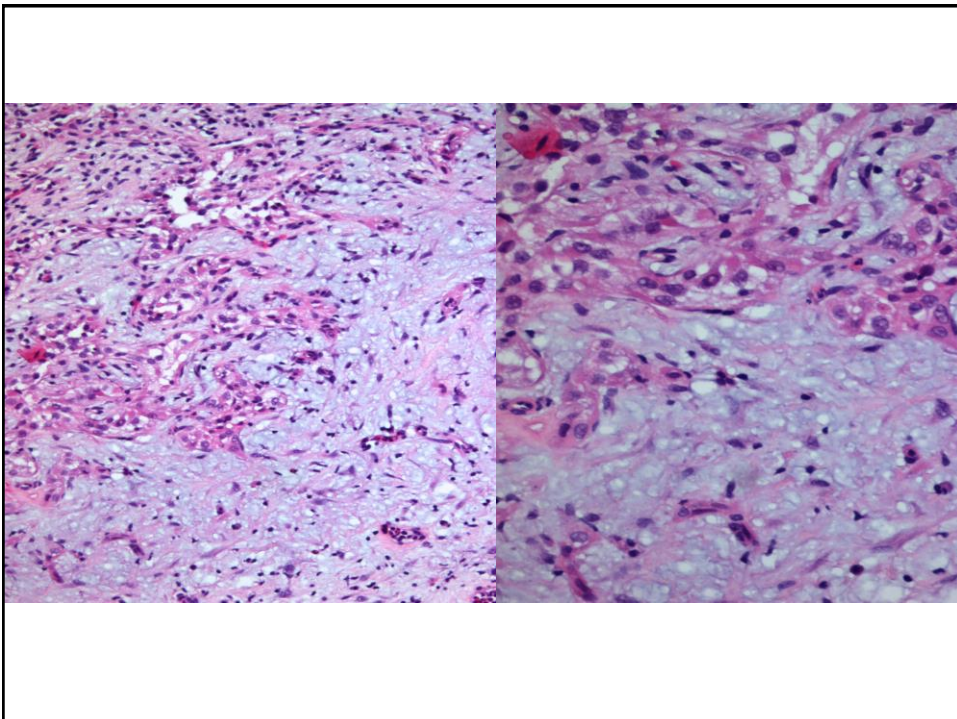
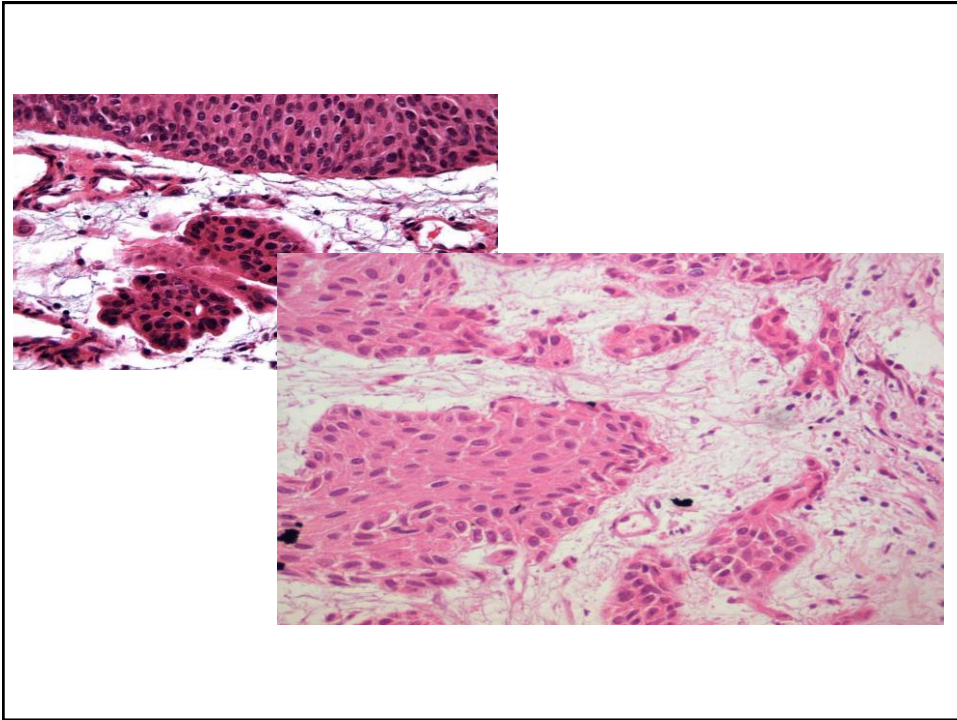


## Lamina propria microinvasion Main Issues to identify

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



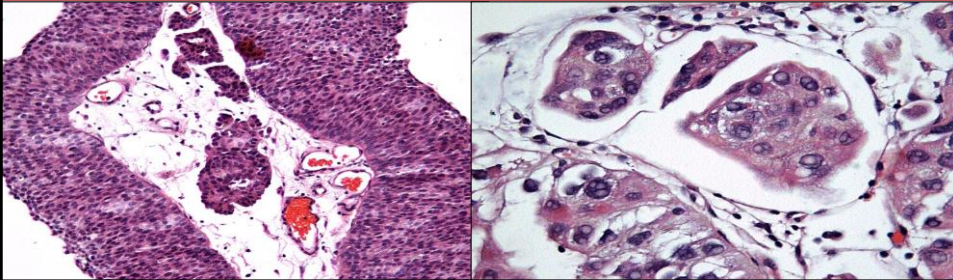




There are always difficult cases>>  
|inform the urologist|

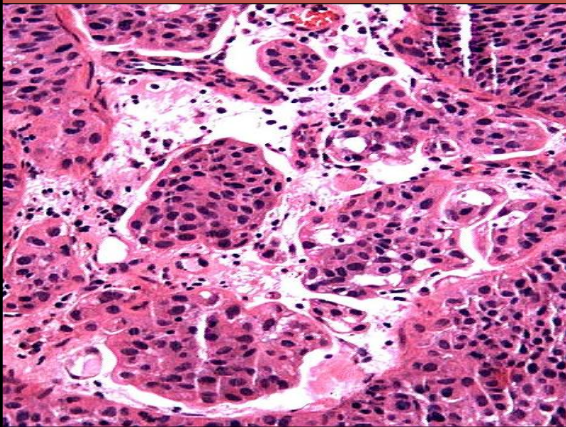
Microinvasion  
Examples

T1 bladder cancer



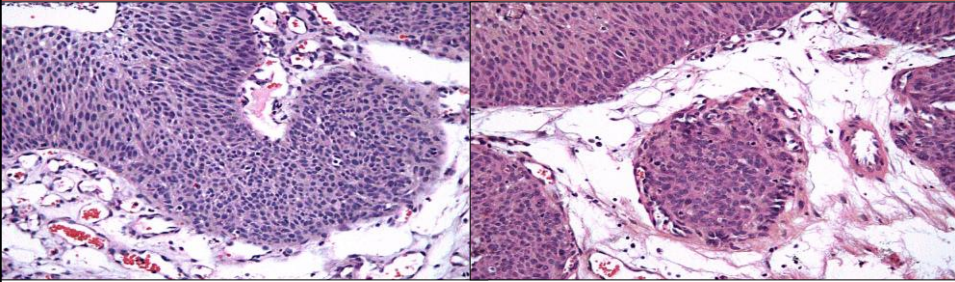
Nests without capillary net  
Nests retraction

T1 bladder cancer



Small and  
big nests

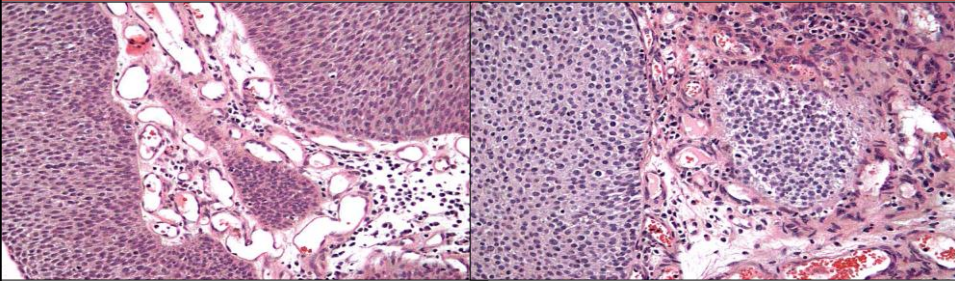
No Microinvasion



Pushing growth  
Big regular nests

This block contains two histological images side-by-side. The left image shows a large, well-defined nest of cells with a pushing border against the surrounding stroma. The right image shows a similar nest with a more irregular border, but still without microinvasion. The text 'No Microinvasion' is centered above the images, and 'Pushing growth' and 'Big regular nests' are centered below them.

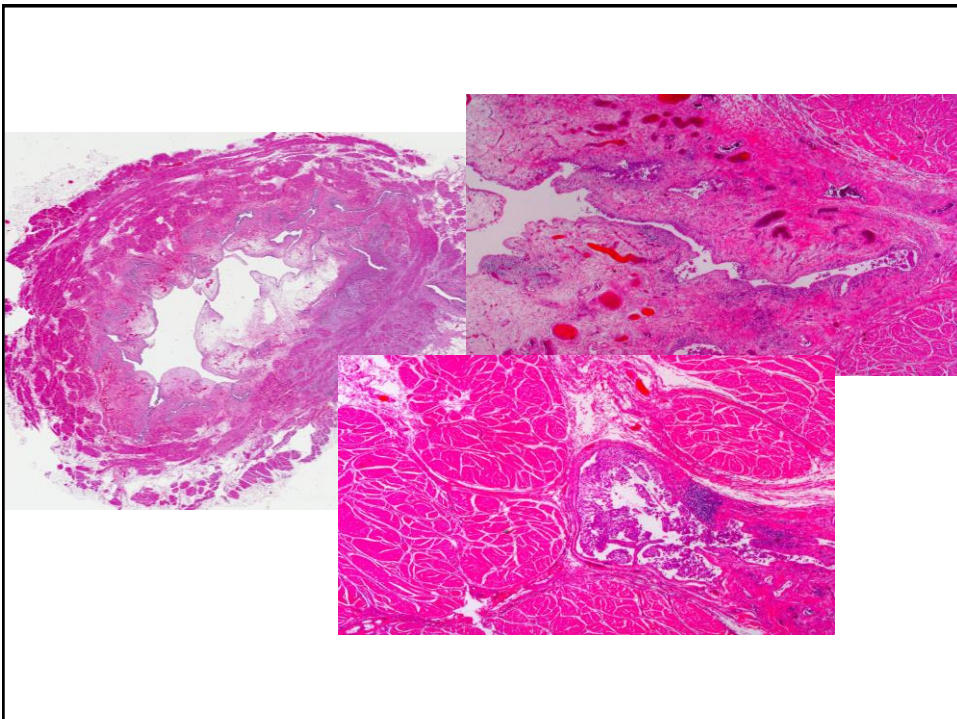
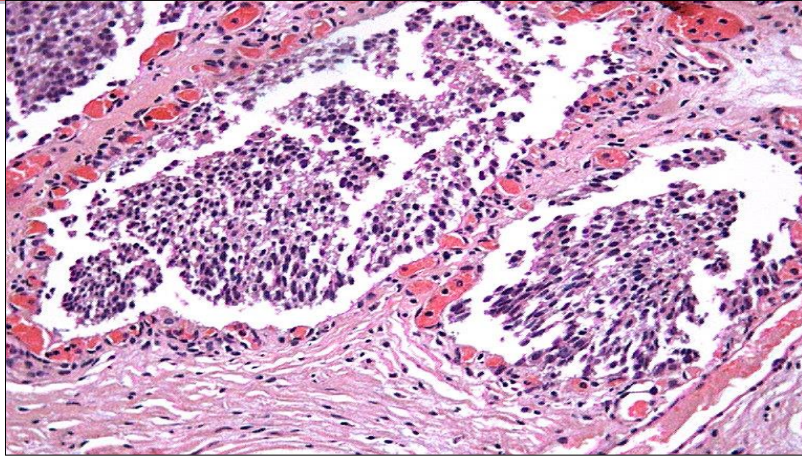
No Microinvasion



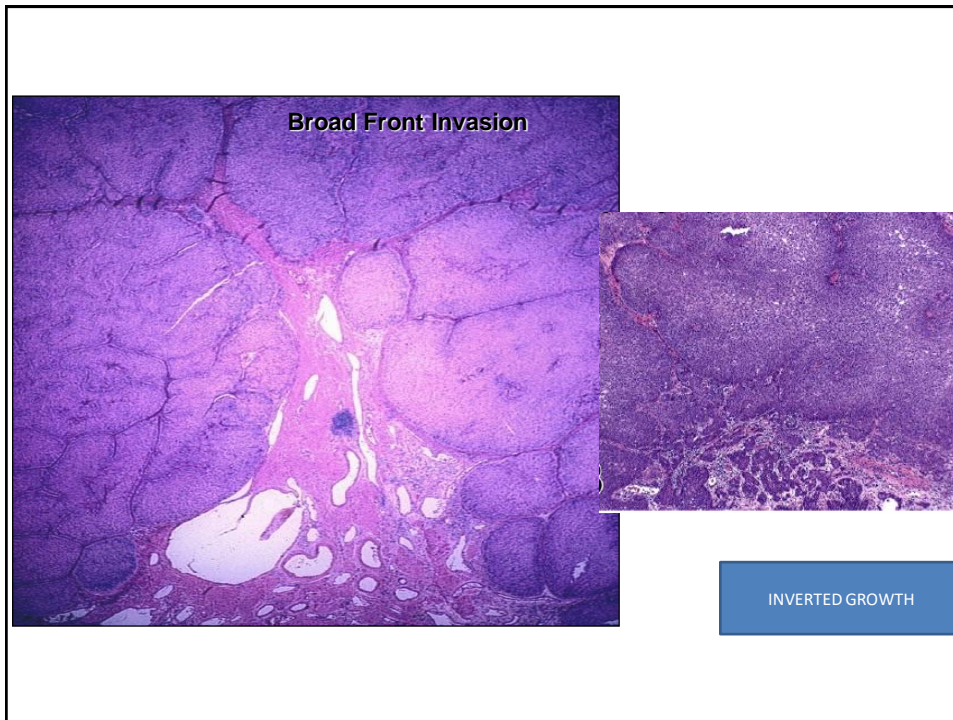
Regular nests  
Peripheral b.m and capillary net

This block contains two histological images side-by-side. The left image shows a regular nest with a clear peripheral basement membrane and a capillary net. The right image shows a similar nest with a more irregular border, but still without microinvasion. The text 'No Microinvasion' is centered above the images, and 'Regular nests' and 'Peripheral b.m and capillary net' are centered below them.

## No Microinvasion



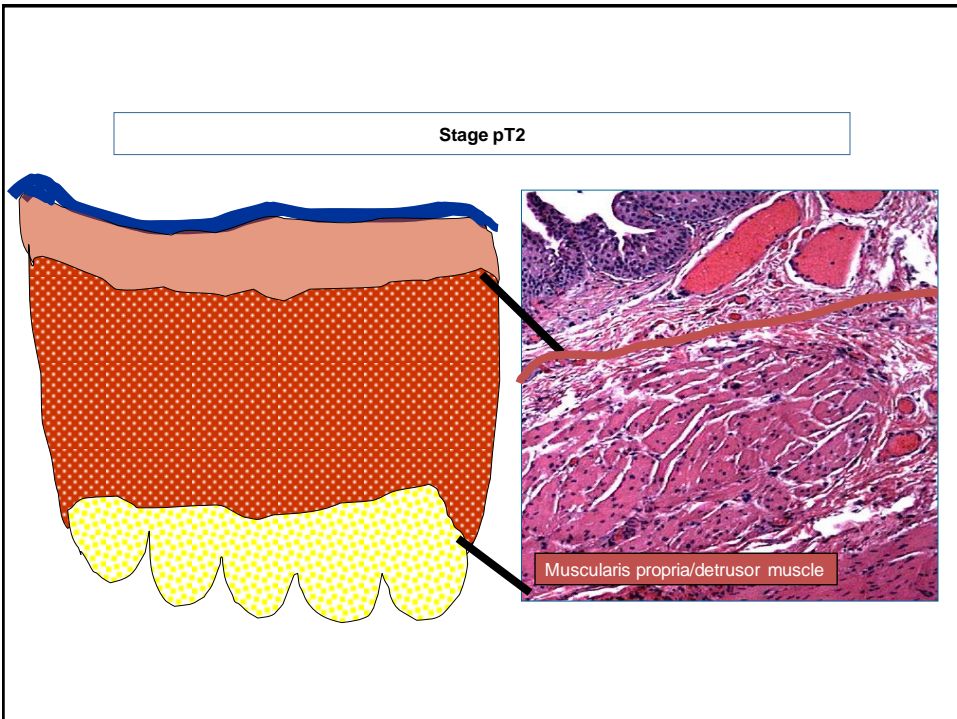




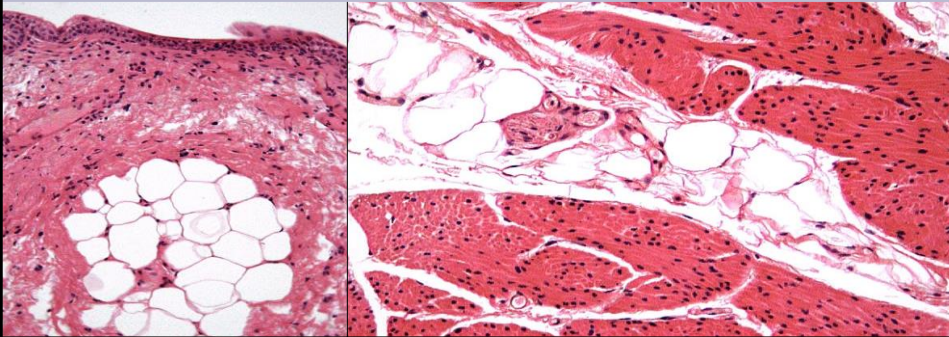
## Invasive Growth Patterns of Cancer

- 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



## T3 bladder cancer????



53%

100%

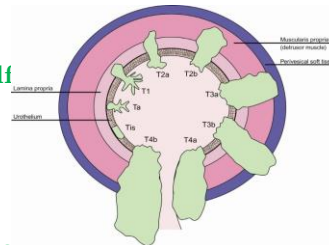
Am.J.Surg. Pathol. 2000, 24: 1286

¡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 propria 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%

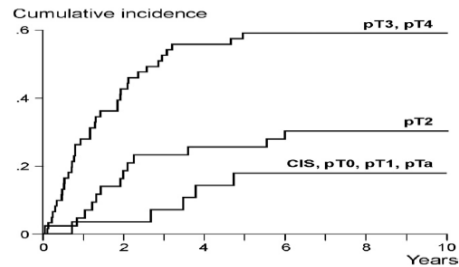
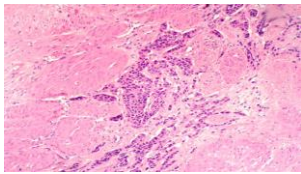
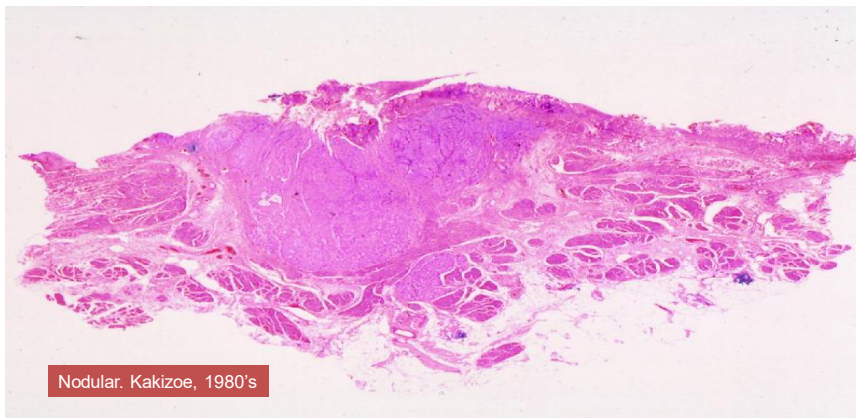
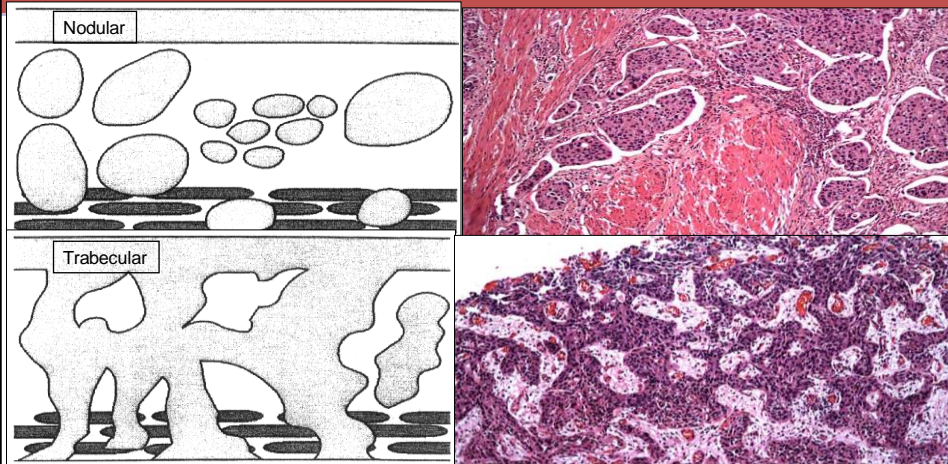


Fig. 1. Cumulative incidence of bladder cancer death by pathologic stage groups.

## Bladder Cancer: Pattern of Invasion

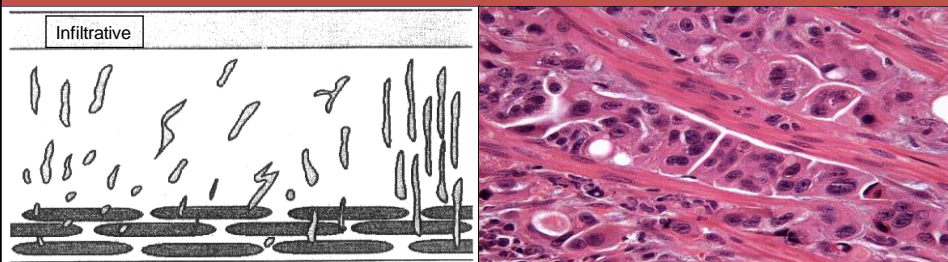


## Bladder Cancer: Pattern of Invasion



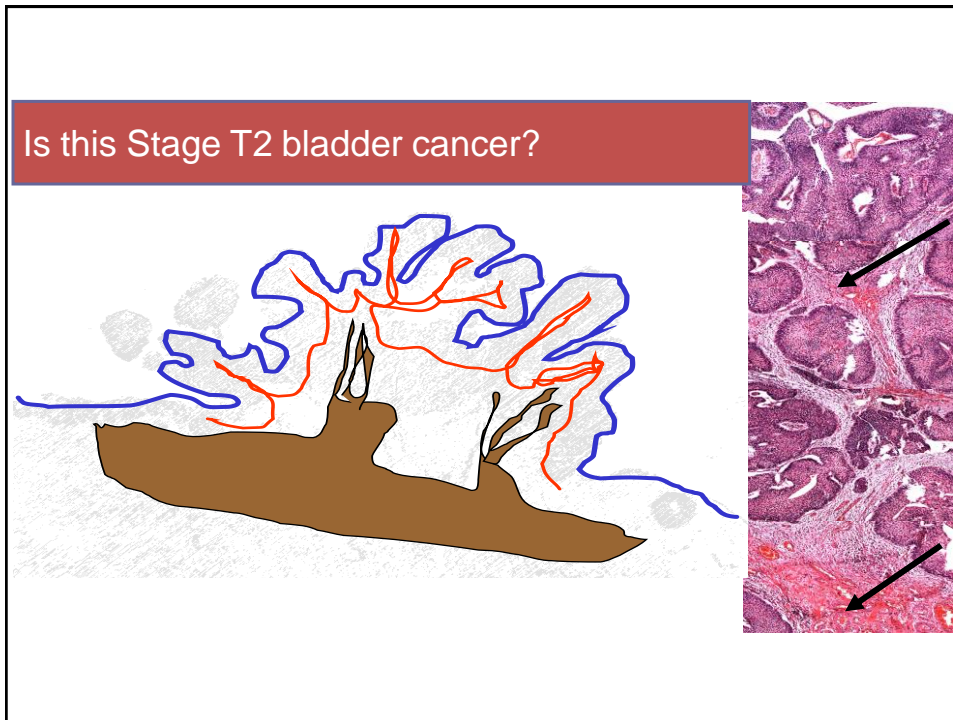
Biblioteca Universitaria de CórdobaBiblioteca  
Universitaria de Córdoba

## T2 bladder cancer



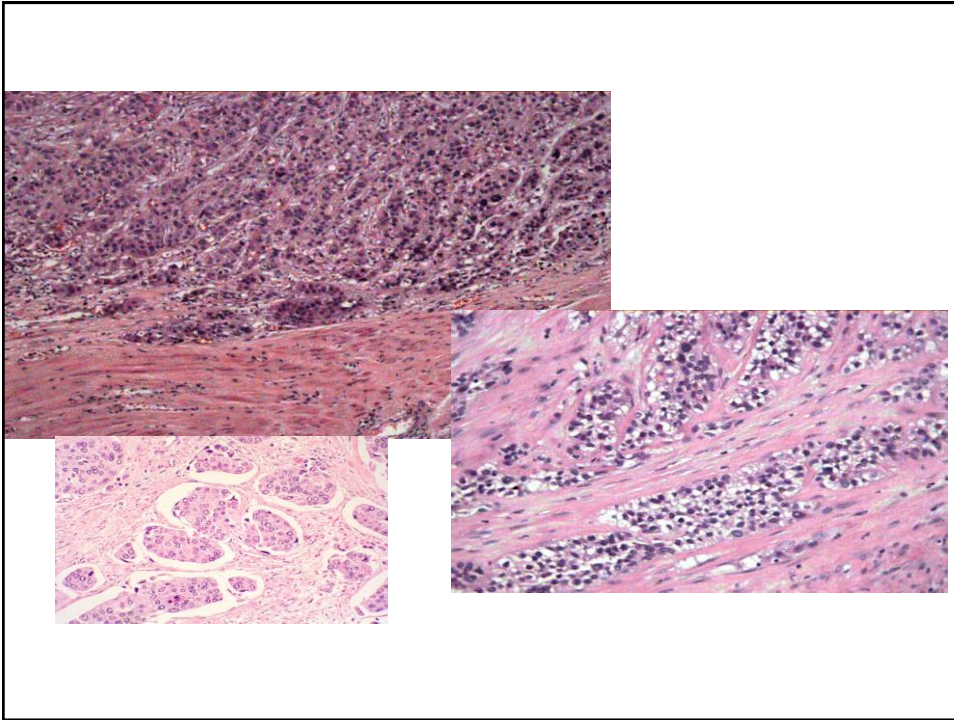
**MEDIAN SURVIVAL 5 Years**  
Infiltrative pattern      29 months  
Non infiltrative pattern    85 months

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



### Defining invasion of *muscularis propria*?

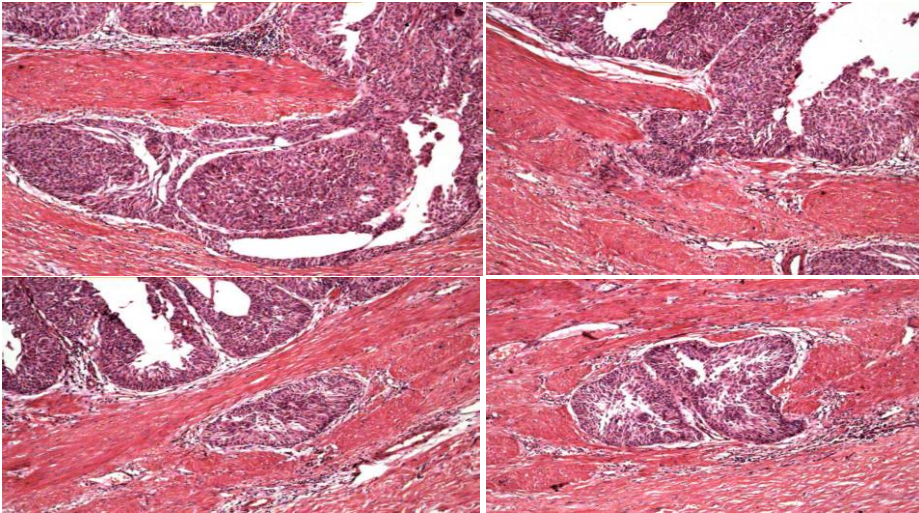
- Confusing terms that should be avoided:
- Superficial muscle invasion
- Deep muscle invasion
- Muscle invasion NOS
- Distinction between muscularis mucosae and muscularis propria is critical>>therapy
- Numerous blood vessels admixed with small bundles of smooth muscle>> MM
- Dense bundles of smooth 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 muscle>>R-Resection is mandatory
- Do not attempt to substage MP invasion (Turb)
- Presence/absence of MP should be included always in the final report >>> feedback to the urologist
- Caution 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



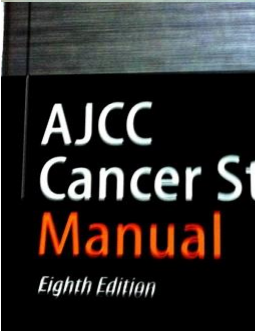
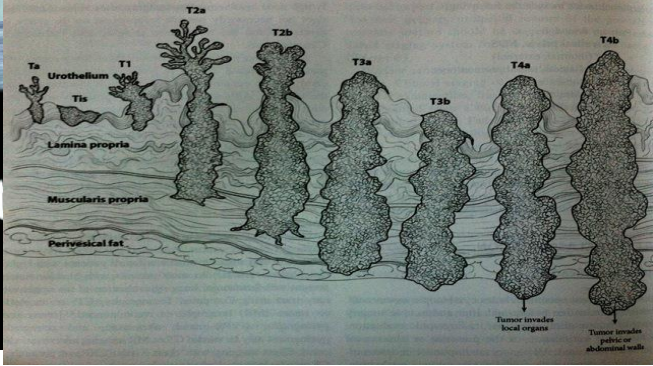
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**Urinary Bladder** 62

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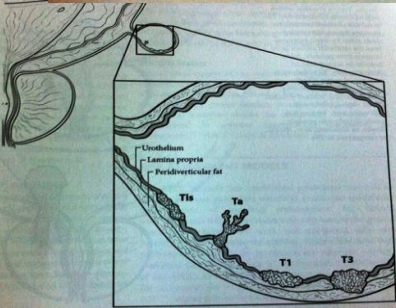
2017

The diagram illustrates the progression of urinary bladder cancer stages. It shows a cross-section of the bladder wall with layers: Urothelium, Lamina propria, Muscularis propria, and Perivesical fat. Stages shown include T0 (carcinoma in situ), T1 (invasion of lamina propria), T2a (invasion of superficial muscle), T2b (invasion of deep muscle), T3a (invasion of perivesical fat), T3b (invasion of adjacent organs), T4a (invasion of pelvic/abdominal wall), and T4b (invasion of distant organs).

**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.<sup>24–26</sup> 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 <i>in situ</i> : "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