

## BLADDER CANCER – WHAT IS NEW AND CLINICALLY RELEVANT



Canadian Geese - Geist Reservoir (my backyard), Indianapolis, USA

## BLADDER CANCER EPIDEMIOLOGY

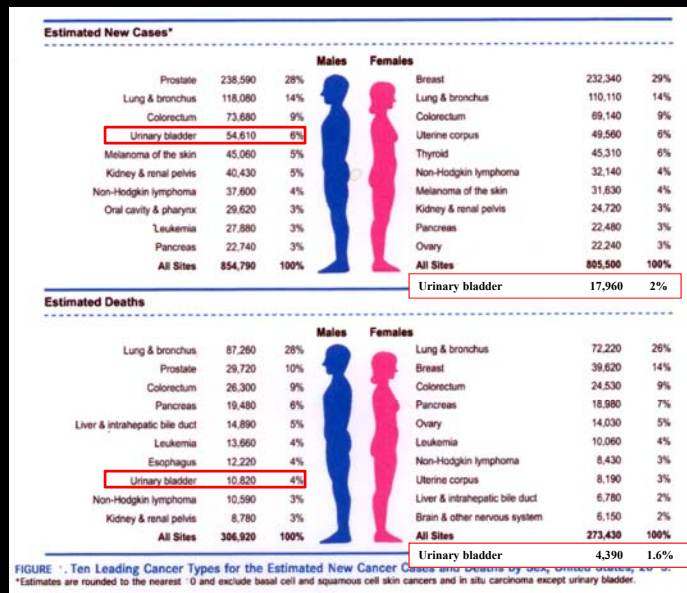
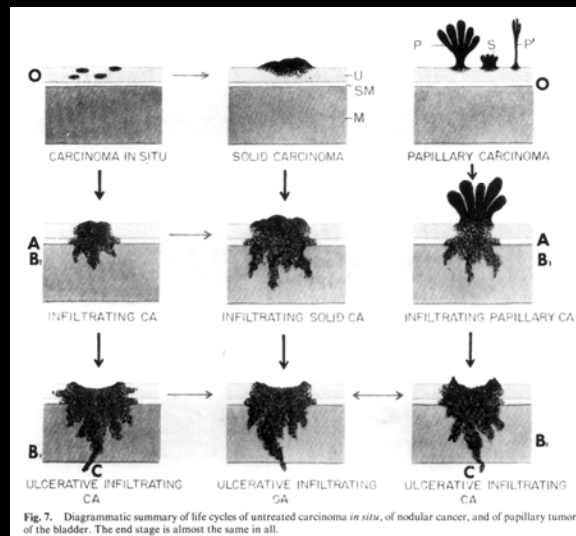


FIGURE 1. Ten Leading Cancer Types for the Estimated New Cancer Cases and Deaths by Sex, United States, 2013. \*Estimates are rounded to the nearest 10 and exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

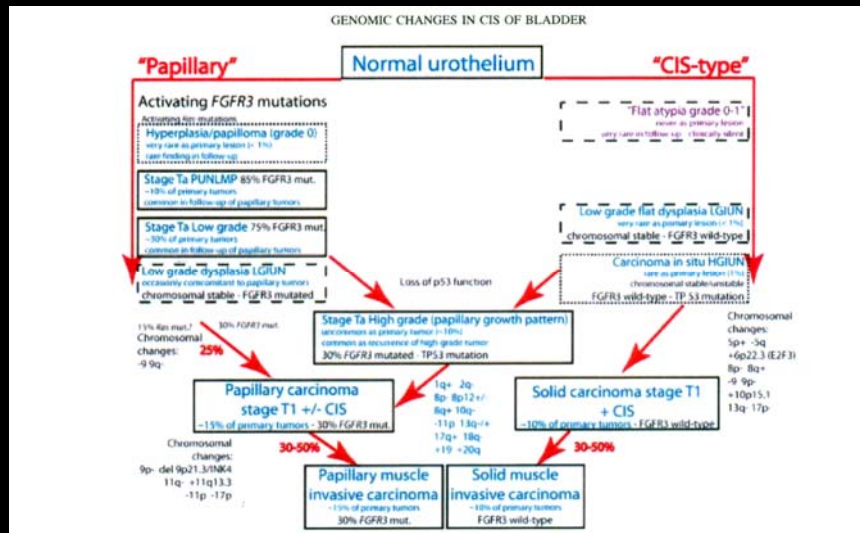
Siegel et al. *CaA Cancer J Clin* 63:11-30, 2013

# BLADDER CANCER MODEL



*Meyer M. Melicow, 1975*

# BLADDER CANCER GENETICS

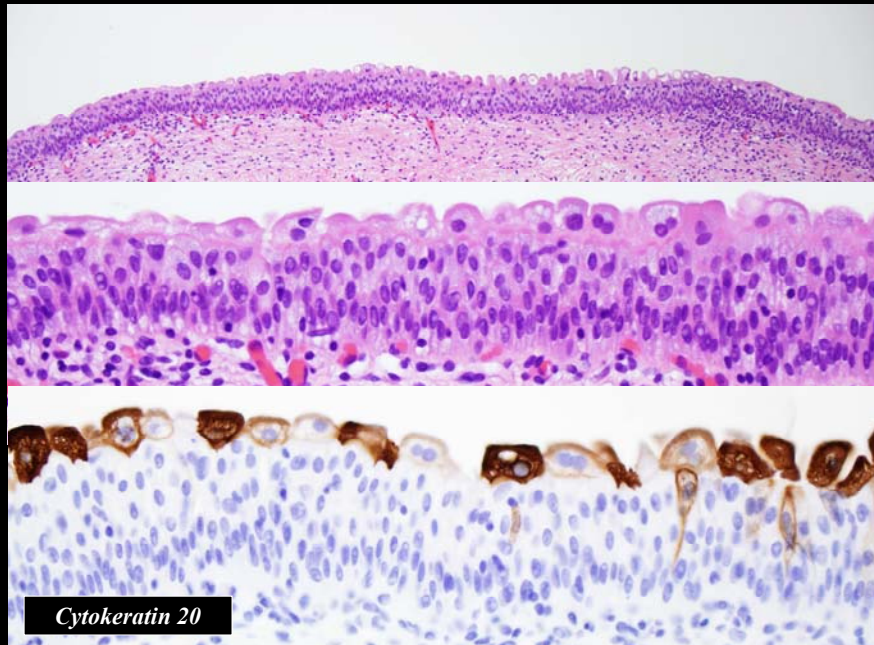


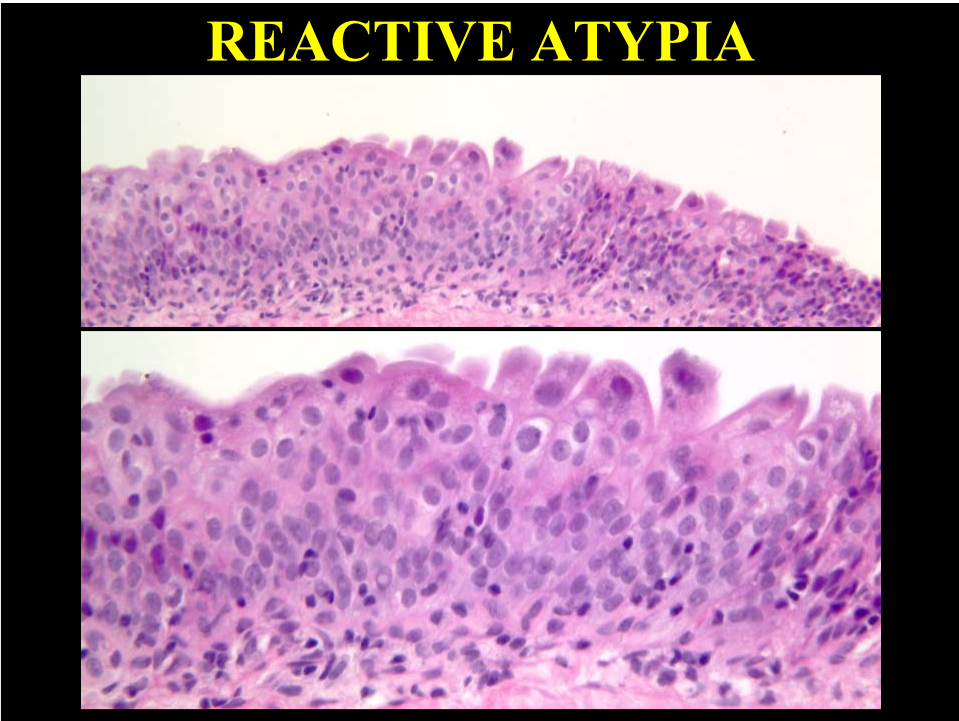
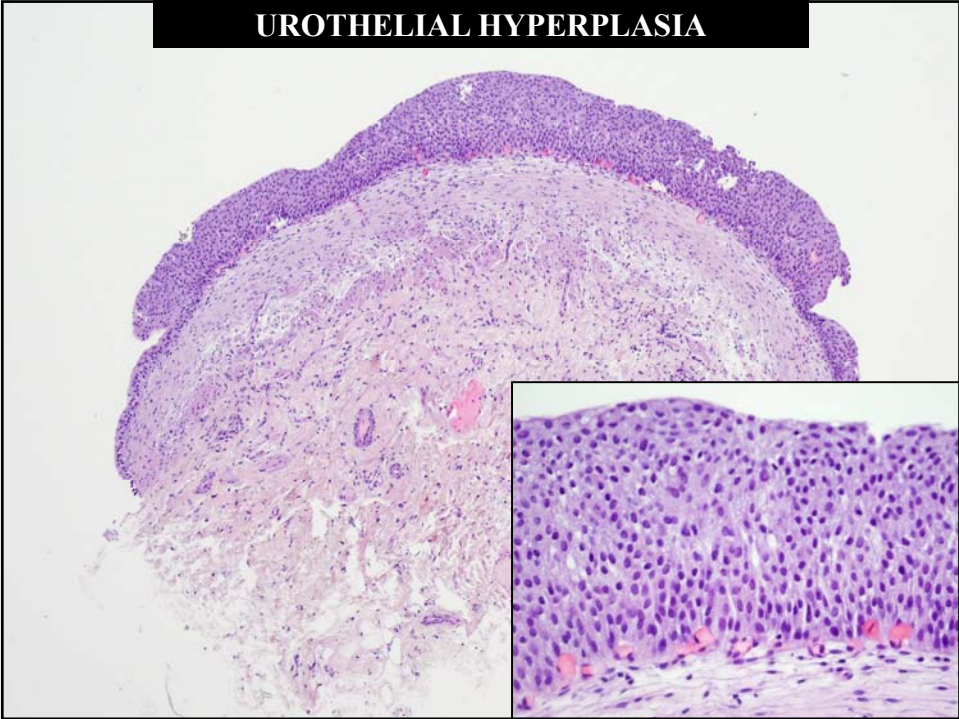
*Zieger et al. Int J Cancer 125;2095, 2009*

## WHO/ISUP 2004 CLASSIFICATION

- **NORMAL**
- **HYPERPLASIA**
- **FLAT LESIONS WITH ATYPIA**
  - Reactive (inflammatory) atypia
  - Atypia of unknown significance
  - Dysplasia (low grade intraurothelial neoplasia)
  - Carcinoma in situ (high grade intraurothelial neoplasia)
- **PAPILLARY NEOPLASMS**
  - Papilloma
  - Inverted papilloma
  - Papillary neoplasm of low malignant potential
  - Papillary carcinoma, low grade
  - Papillary carcinoma, high grade
- **INVASIVE NEOPLASMS**

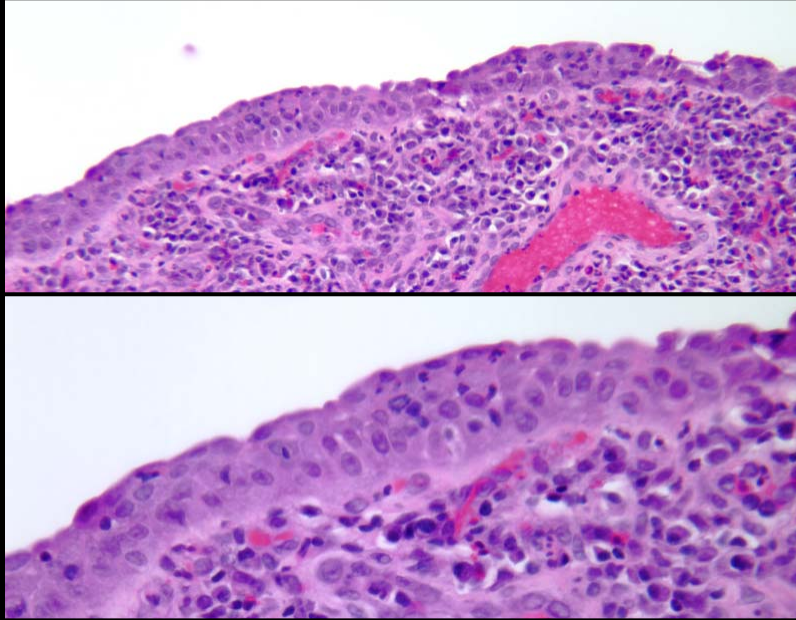
## NORMAL UROTHELIUM



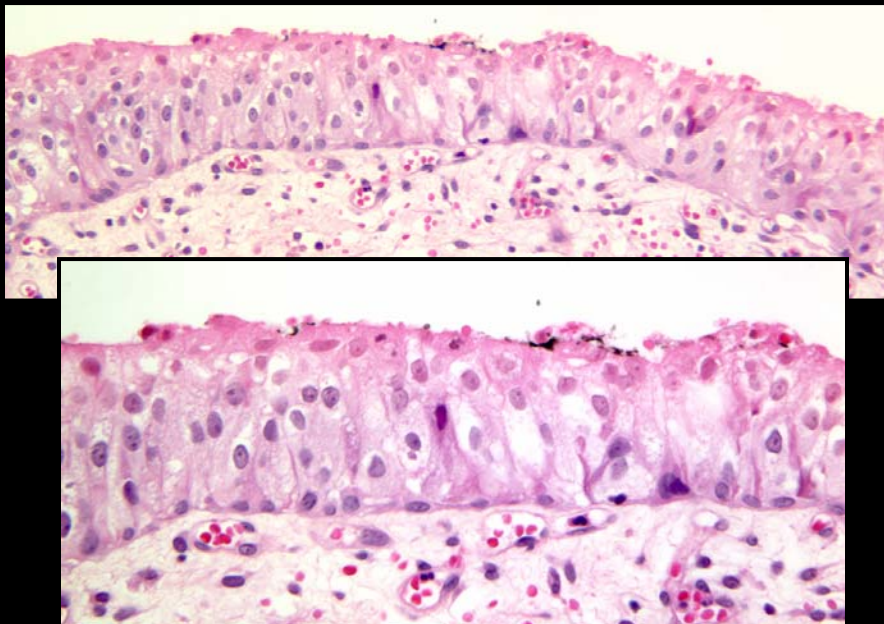




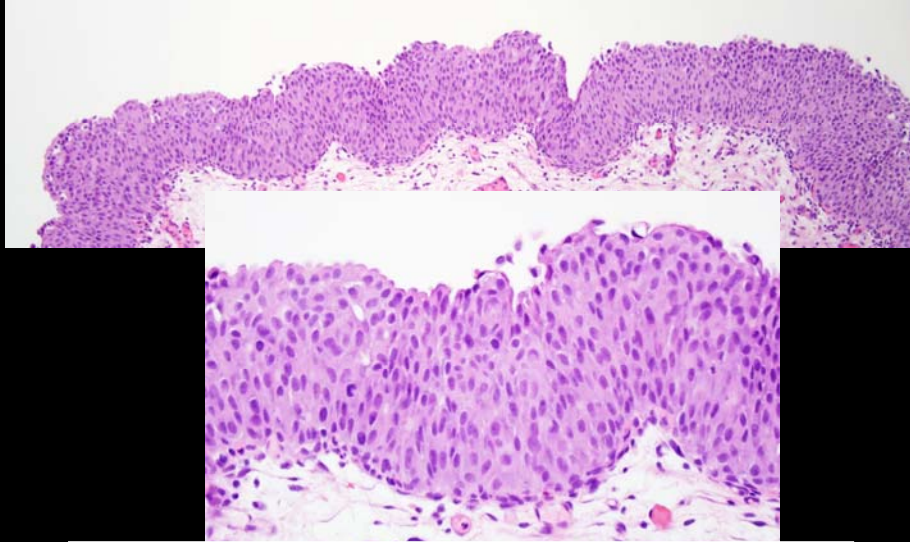
## REACTIVE ATYPIA



## DYSPLASIA

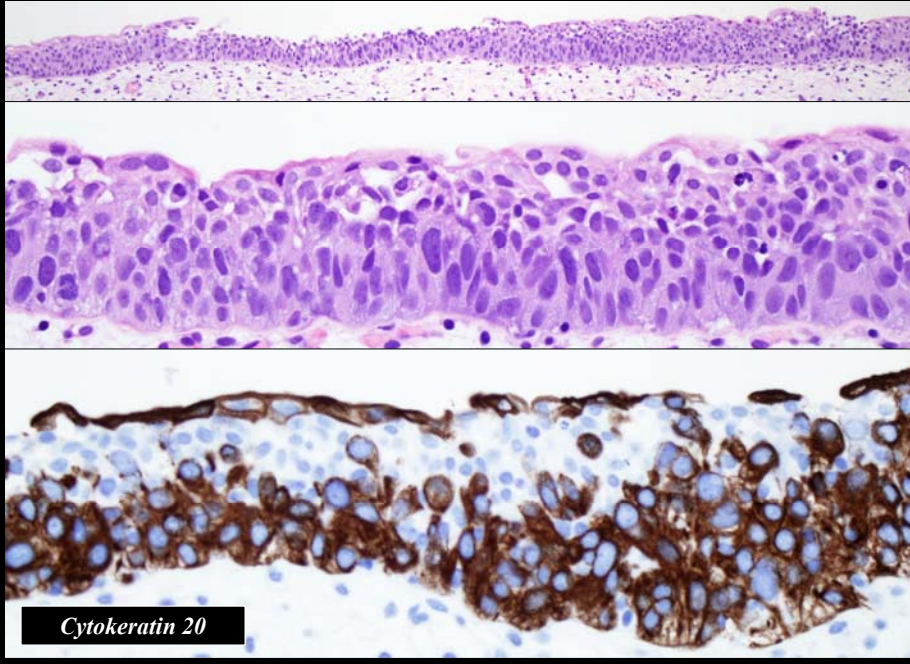


## DYSPLASIA



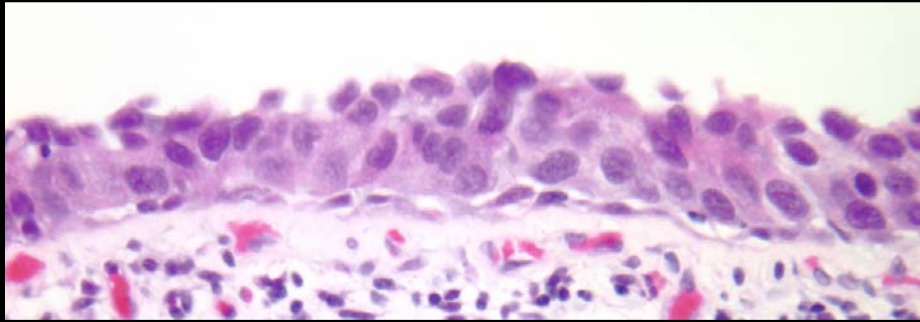
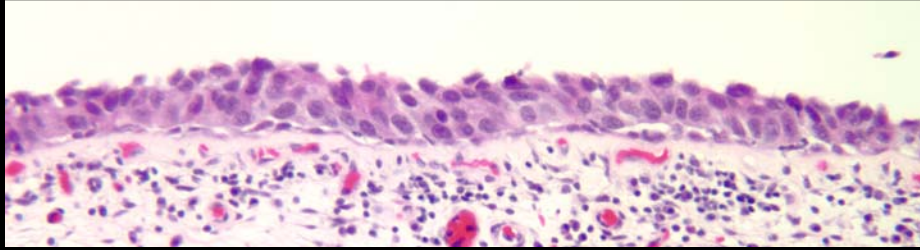
*Or Incipient Papillary Neoplasia?*

## CIS WITH UMBRELLA CELLS

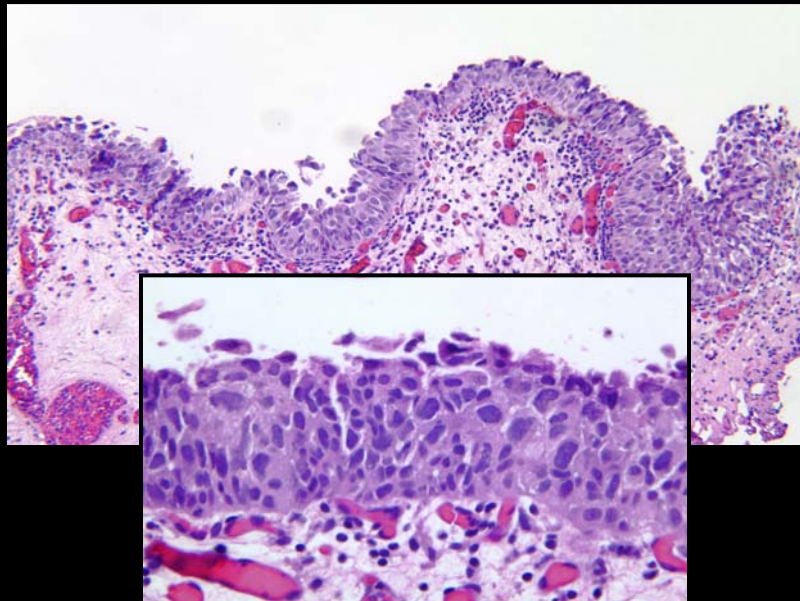


*Cytokeratin 20*

**CIS - LARGE CELL**

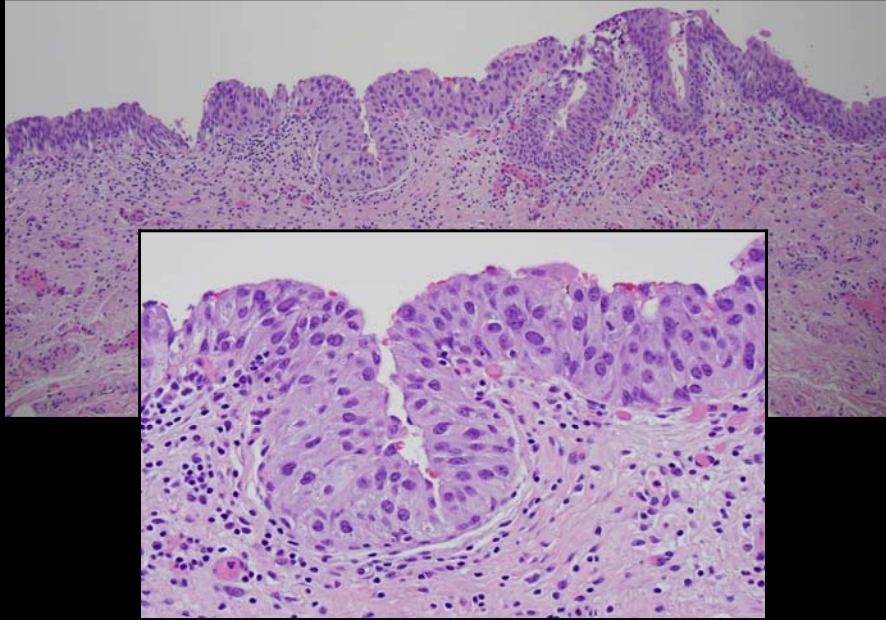


**CIS - LARGE CELL**

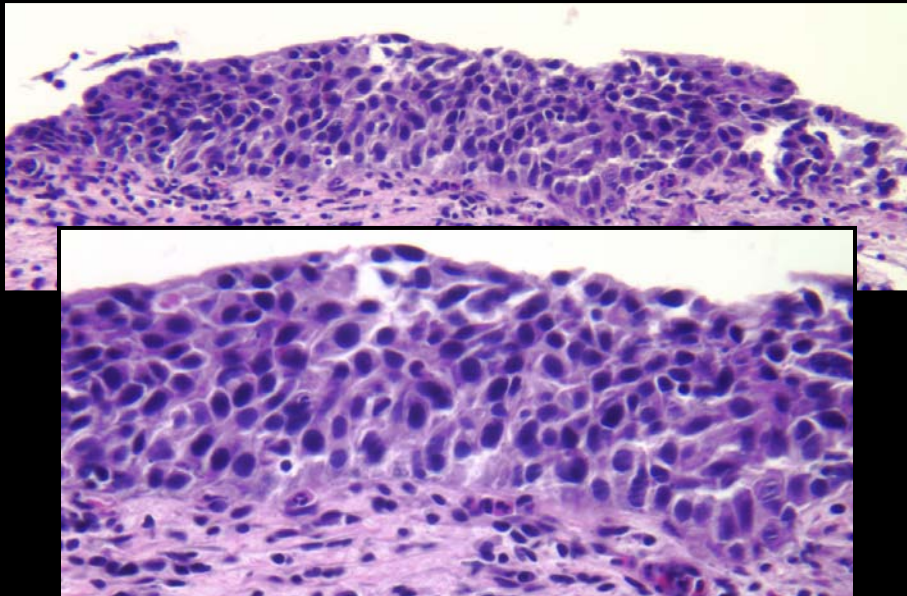




## CIS - LARGE CELL

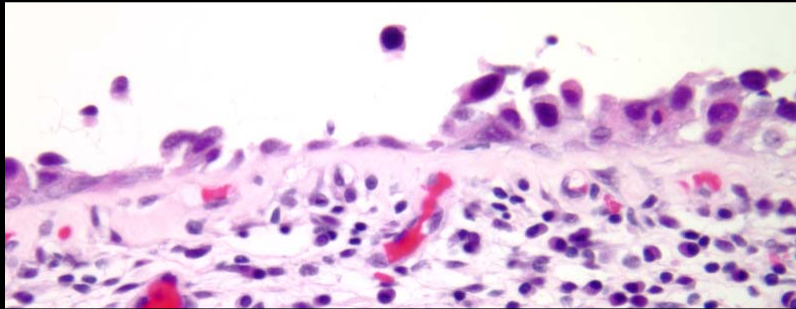
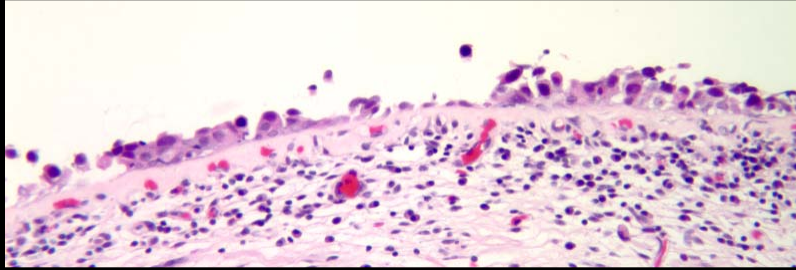


## CIS - "SMALL CELL"

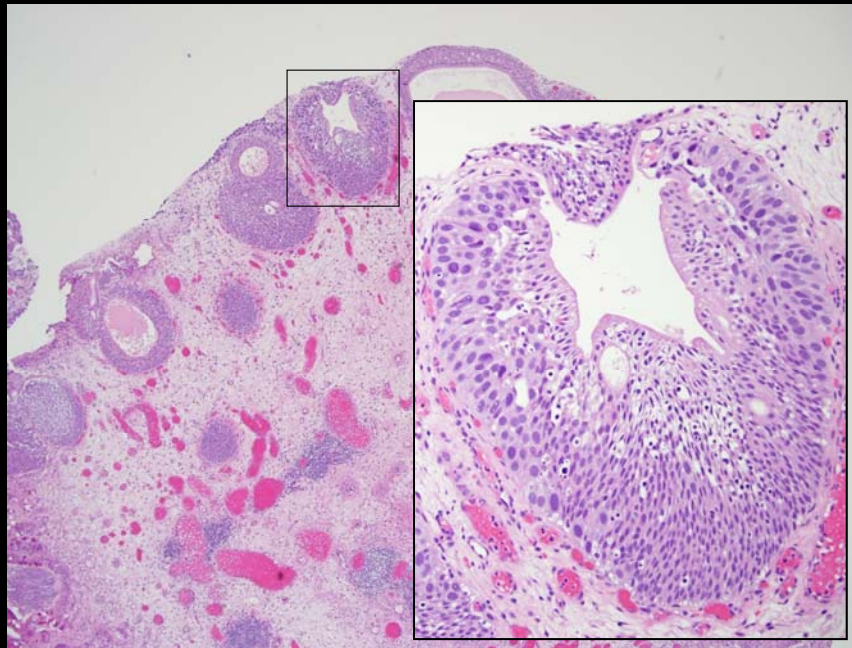




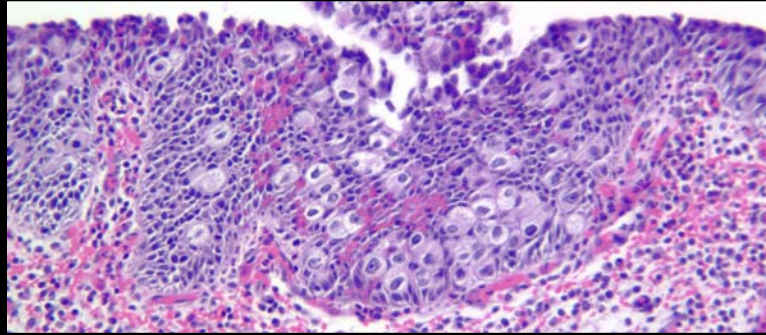
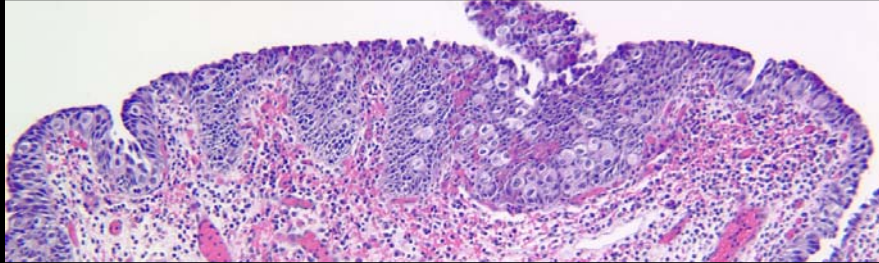
## CIS - DENUDING



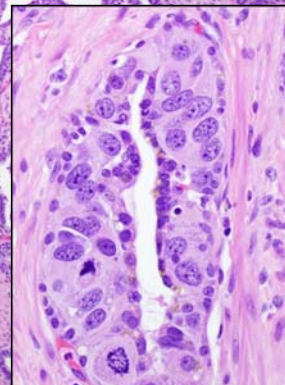
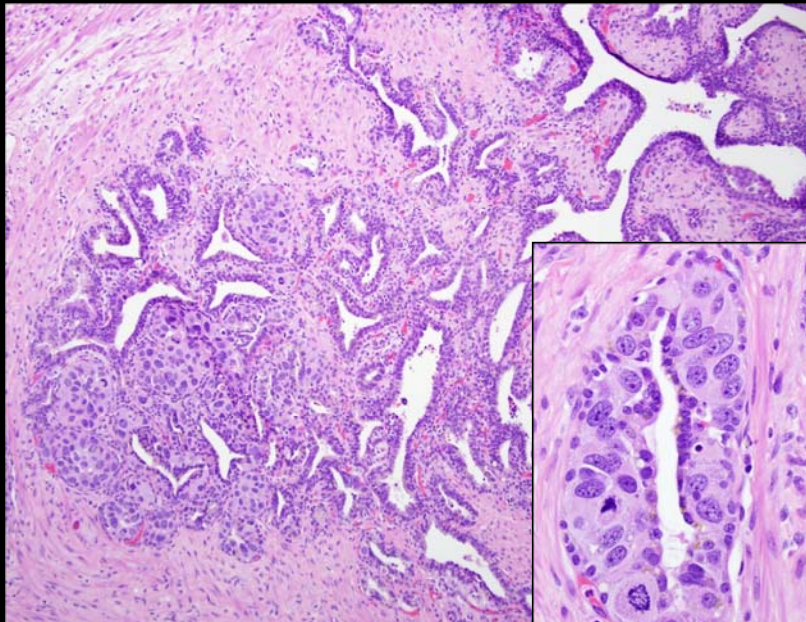
## CIS - DENUDING - VON BRUNN'S NESTS



## CIS - PAGETOID



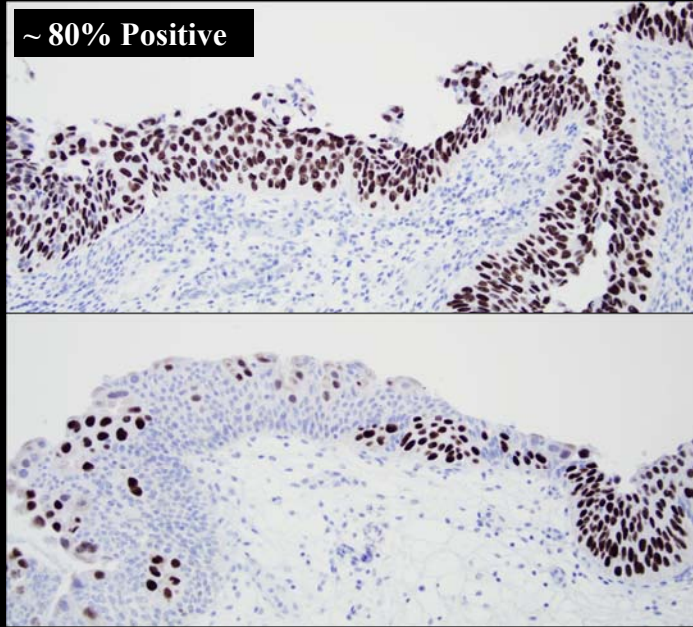
## SV: CIS - PAGETOID



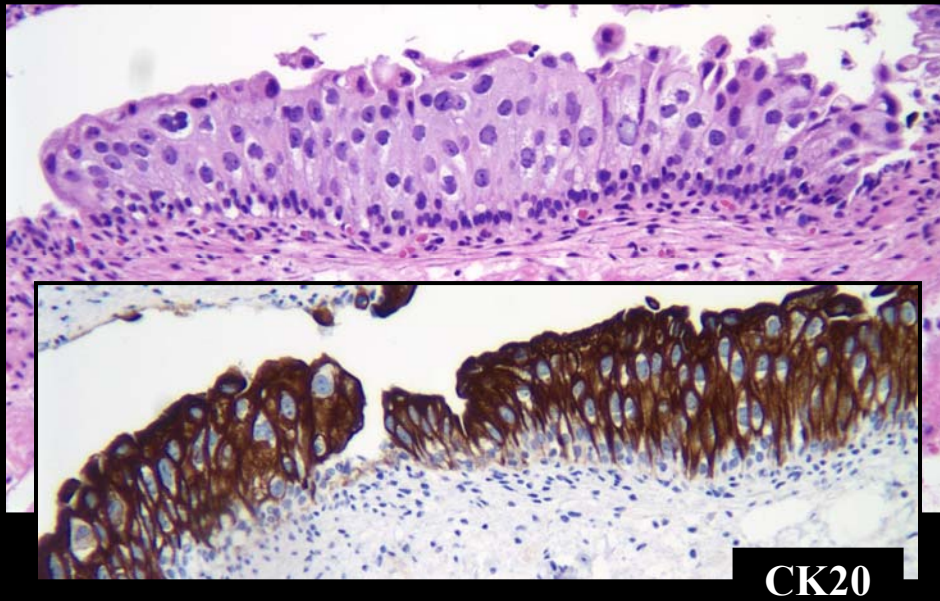


## CARCINOMA IN SITU – p53 IHC

~ 80% Positive



## CARCINOMA IN SITU

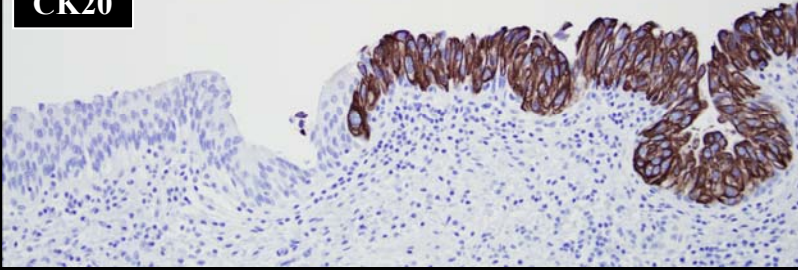


CK20

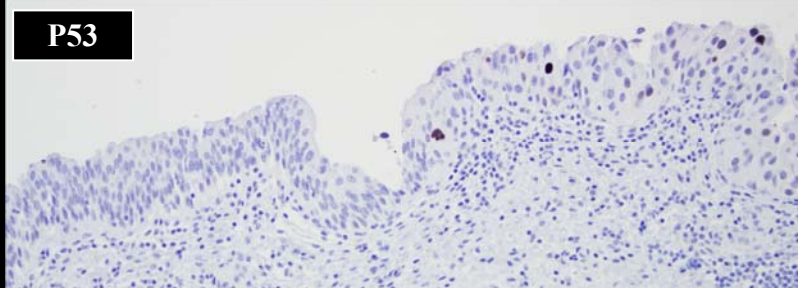


# CARCINOMA IN SITU

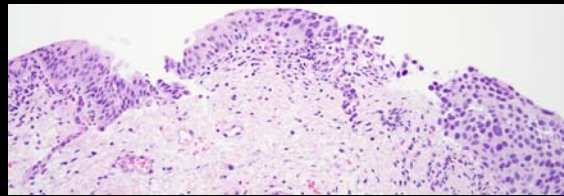
CK20



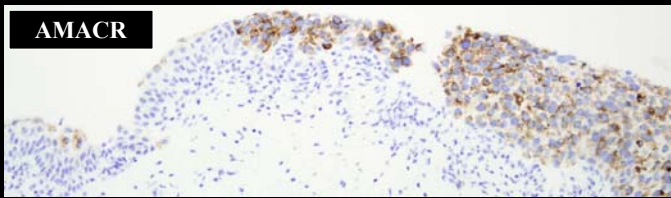
P53



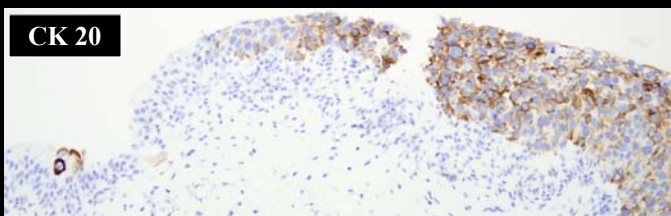
# CARCINOMA IN SITU

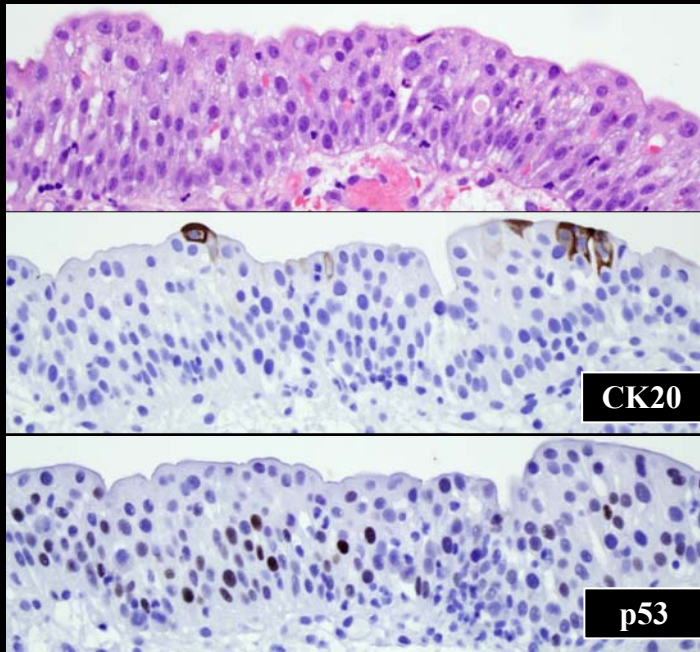


AMACR



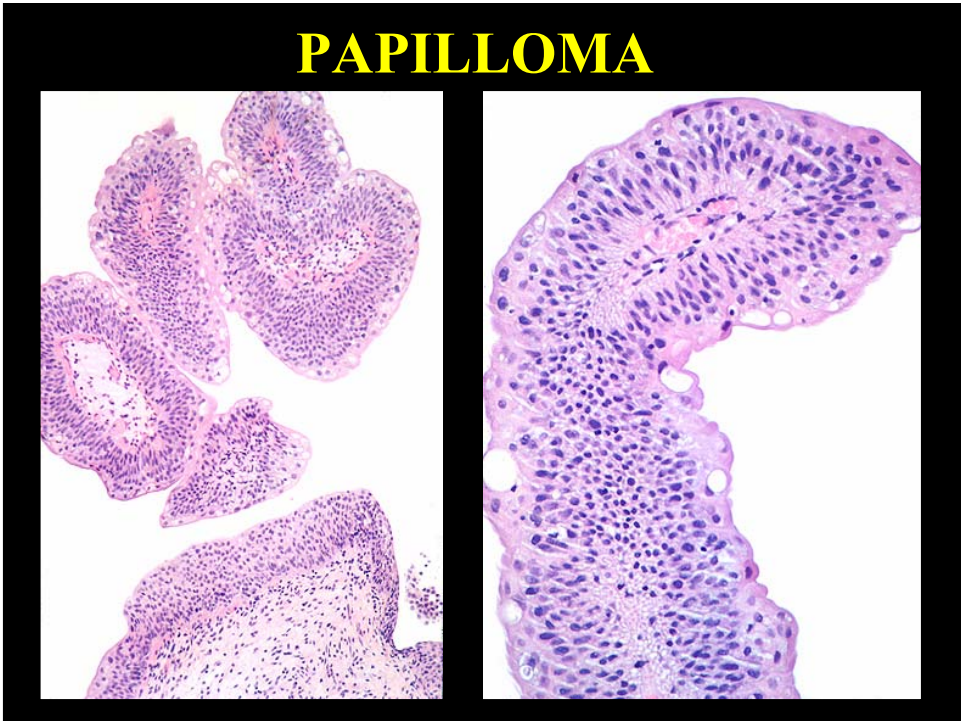
CK 20



**REACTIVE ATYPIA****UROTHELIAL CARCINOMA IN SITU - LONG TERM OUTCOME**

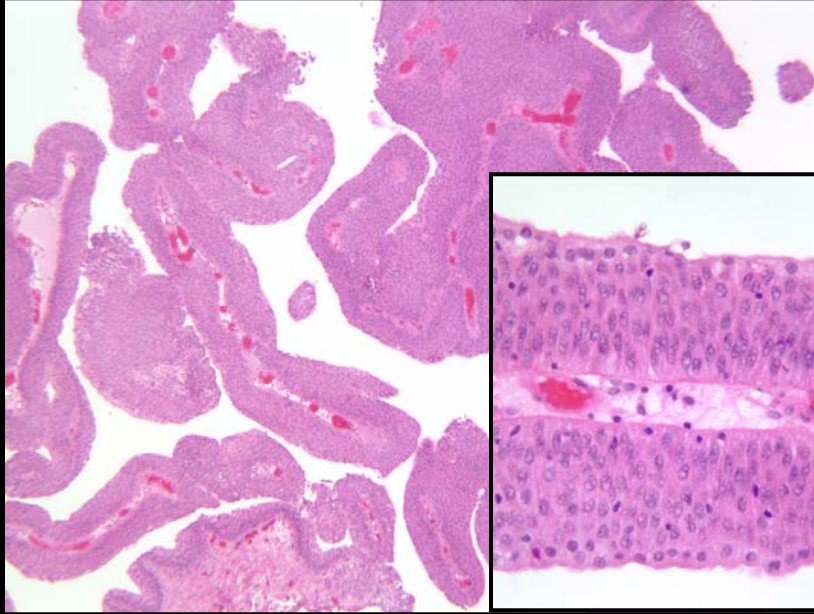
<b>SURVIVAL-TYPE</b>	<b>10-Year</b>	<b>15-Year</b>
<b>Progression-free</b>	<b>63%</b>	<b>59%</b>
<b>Cancer-specific</b>	<b>79%</b>	<b>74%</b>
<b>All-cause</b>	<b>55%</b>	<b>40%</b>

*Cheng et al, Cancer 85:2469, 2000*

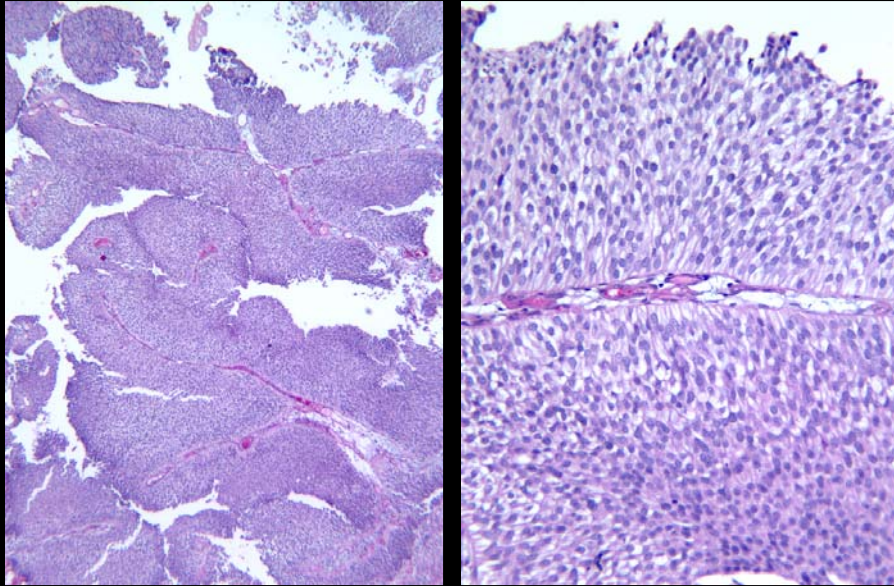




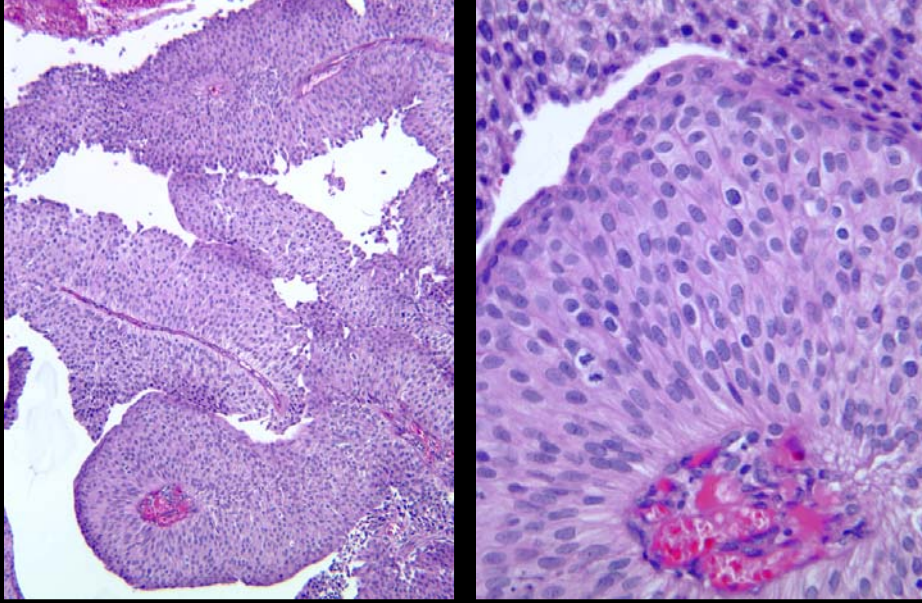
# PUNLMP



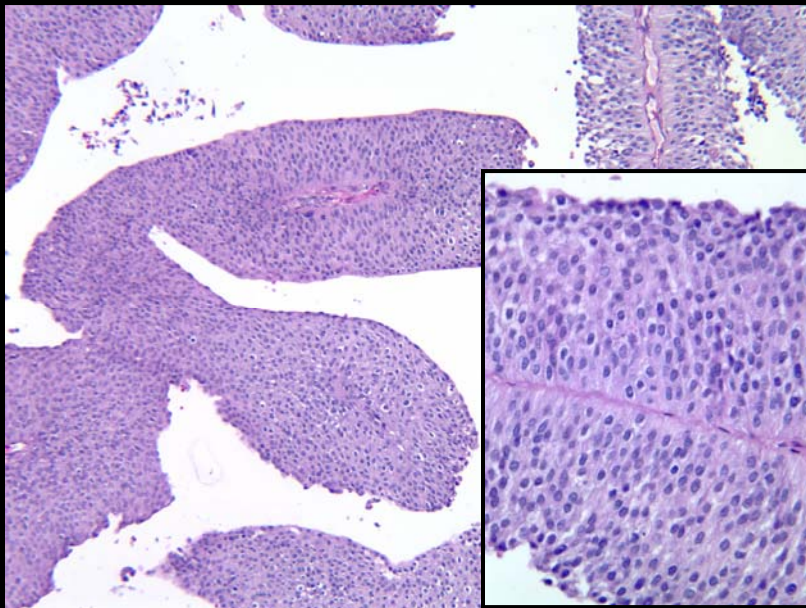
# PUNLMP



**LOW GRADE**

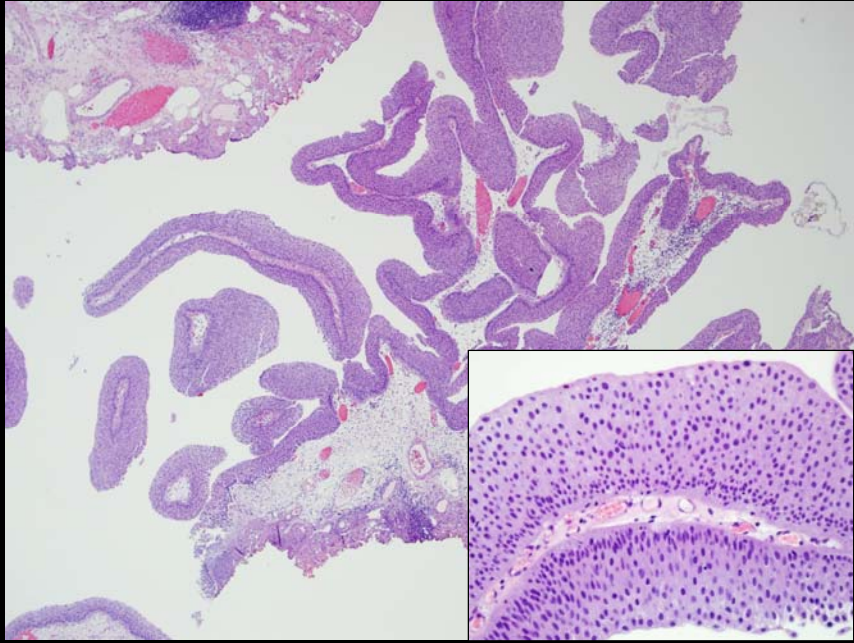


**LOW GRADE**

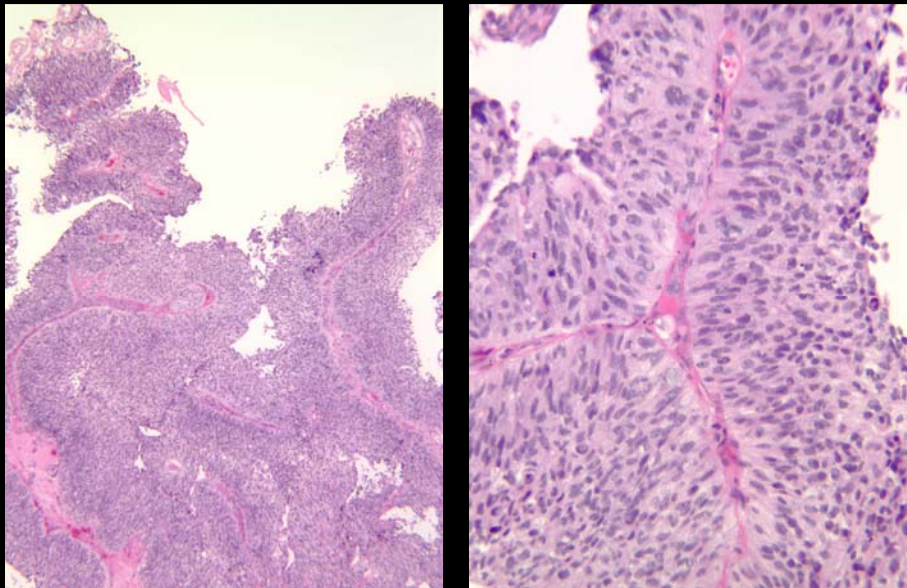




**LOW GRADE**

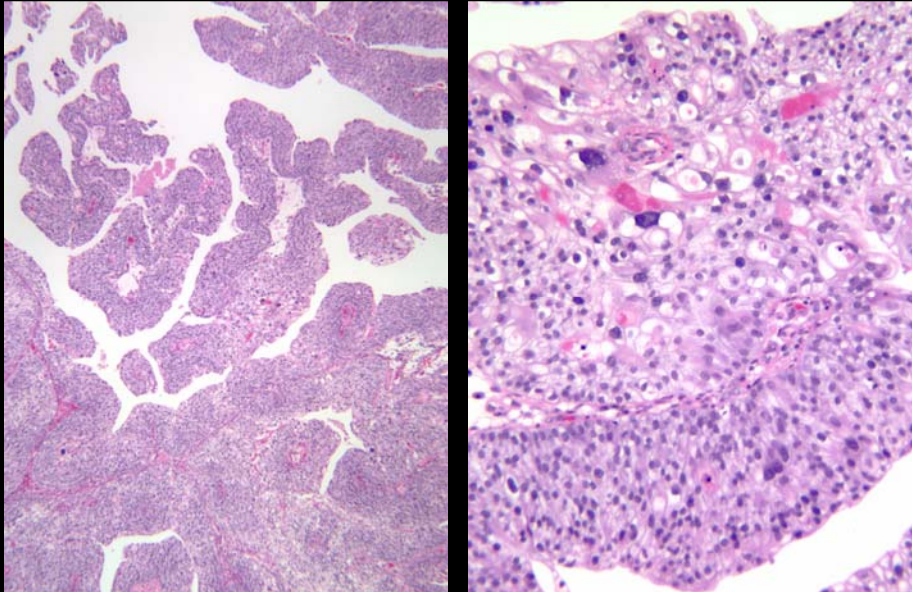


**HIGH GRADE**

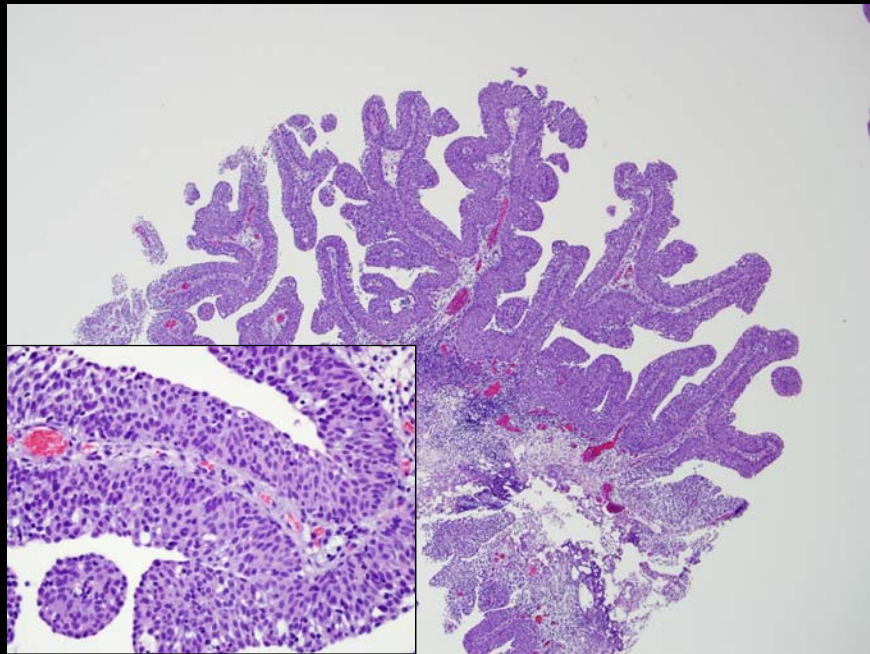




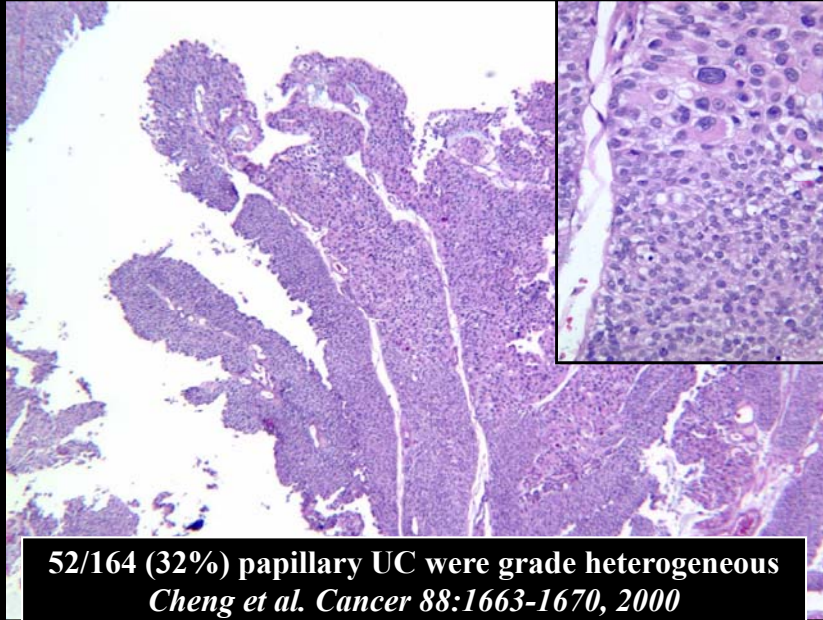
**HIGH GRADE**



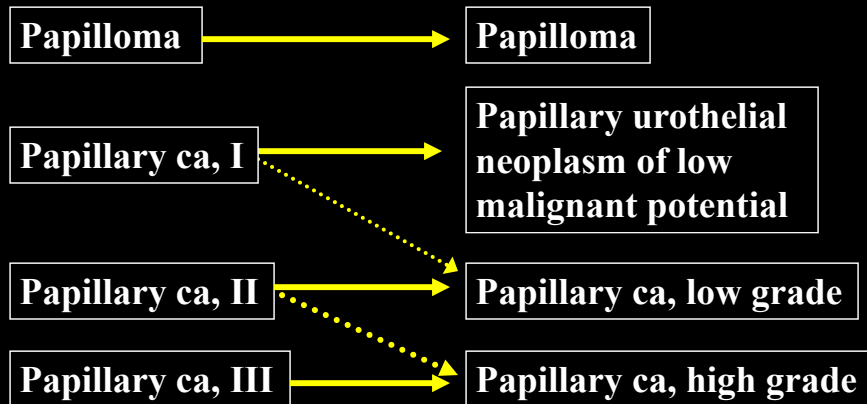
**HIGH GRADE**



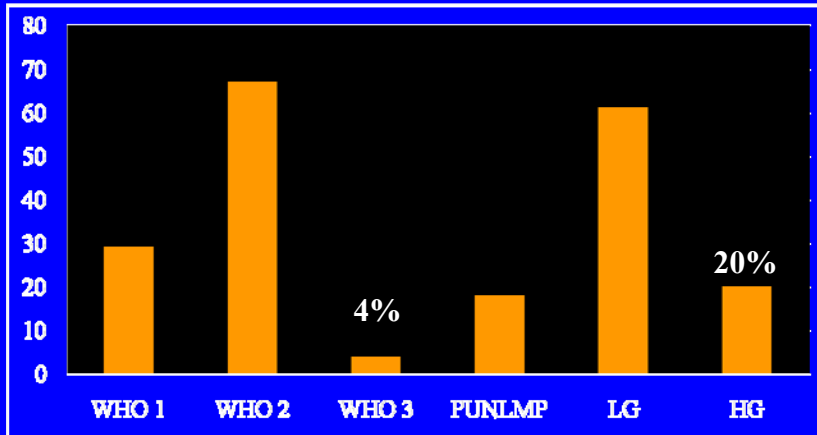
## BLADDER – PAPILLARY UC



## WHO 1973 vs WHO 2004

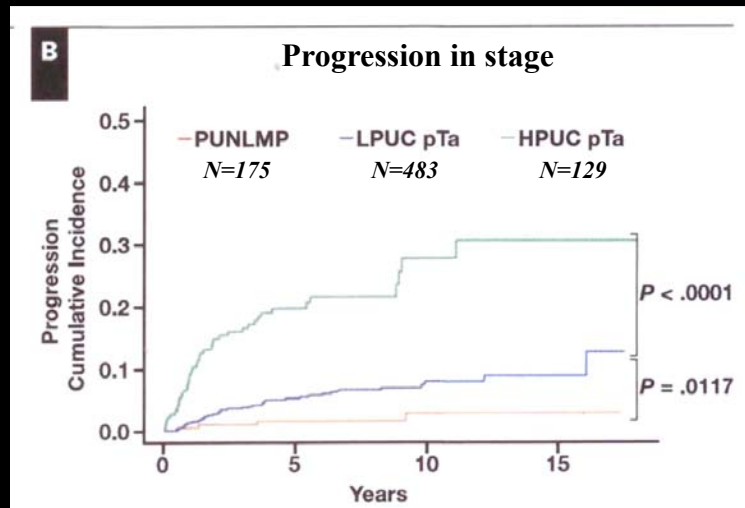


## GRADE DISTRIBUTION WHO 1973 vs WHO 2004



*Samaratunga et al. Urology 60:315, 2002*

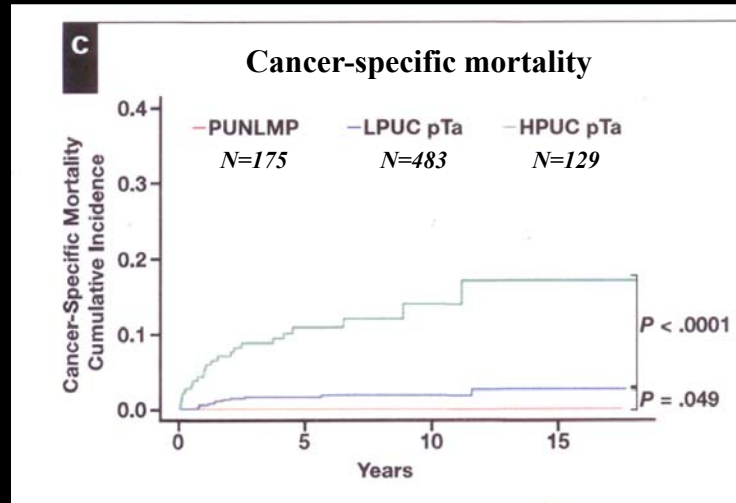
## pTa BLADDER CA LONG TERM OUTCOME



*Pan et al, AJCP 133:788, 2010*



## pTa BLADDER CA LONG TERM OUTCOME



*Pan et al, AJCP 133:788, 2010*

## STAGING OF BLADDER CANCER (2010 TNM)

- **pTa** Non-invasive, papillary
- **pTis** Non-invasive, flat
- **pT1** Invasion of subepithelial connective tissue (lamina propria)
- **pT2** Invasion of muscularis propria
  - pT2a inner one-half
  - pT2b outer one-half
- **pT3** Invasion of perivesical tissue
  - pT3a microscopically
  - pT3b macroscopically
- **pT4** Invasion of adjacent structures

## BLADDER CANCER: OUTCOME AFTER CYSTECTOMY

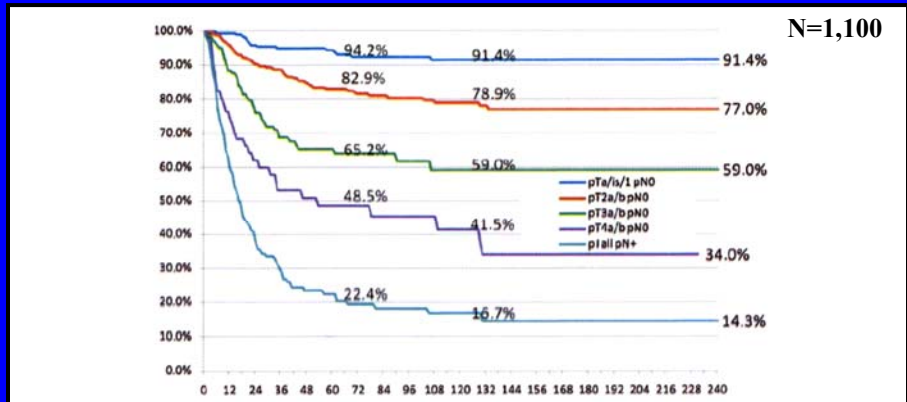


Fig. 8 – Disease-specific survival according to the maximum tumor stage (transurethral resection of bladder tumor and cystectomy specimens).

*Hautmann et al. Eur Urol 61:1039, 2012*

## TREATMENT OF T1 DISEASE

### Understanding Bladder Cancer Death

Tumor Biology Versus Physician Practice

David S. Morris, MD, Alon Z. Weizer, MD, Zaojun Ye, MS, Rodney L. Dunn, MS, James E. Montie, MD, and Brent K. Hollenbeck, MD, MS

**“ On the basis of clinical and administrative data, we estimate that between 31.2% and 46.8% of deaths potentially were avoidable.”**

*Cancer 115:1011, 2009*

## TREATMENT OF T1 DISEASE

 ELSEVIER

Urologic Oncology: Seminars and Original Investigations 27 (2009) 329–331


UROLOGIC ONCOLOGY

Seminar article

**Optimal timing of radical cystectomy for patients with T1 bladder cancer**

Bernard H. Bochner, M.D., FACS\*

Urology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY 10021, USA

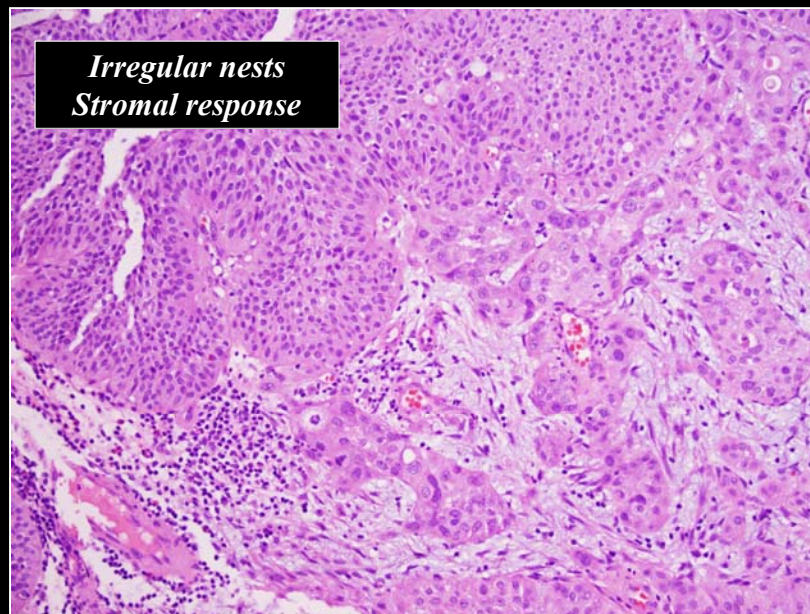
 **BJUI** Invasive T1 bladder cancer: indications and rationale for radical cystectomy

John P. Stein\* and David F. Penson

Department of Urology, University of Southern California Keck School of Medicine, Norris Comprehensive Cancer Center, Los Angeles, CA, USA

Accepted for publication 22 February 2008

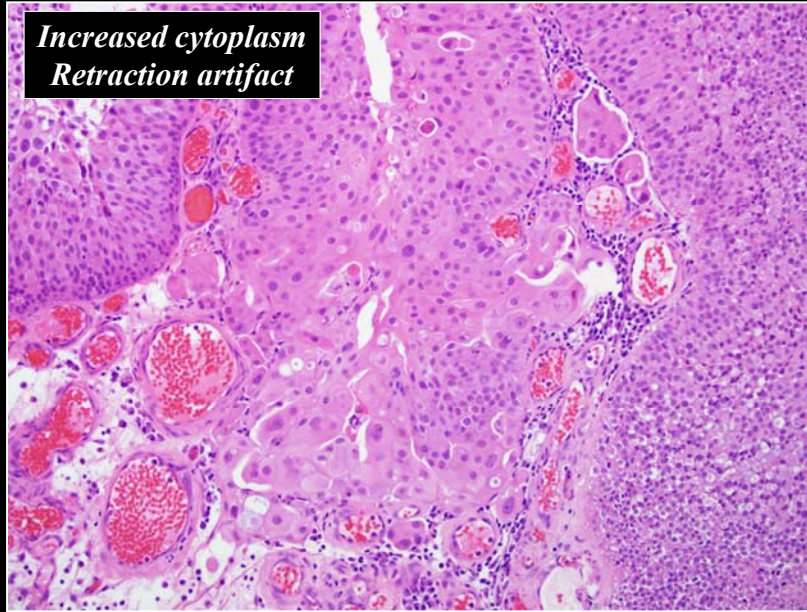
## DIAGNOSIS OF INVASION





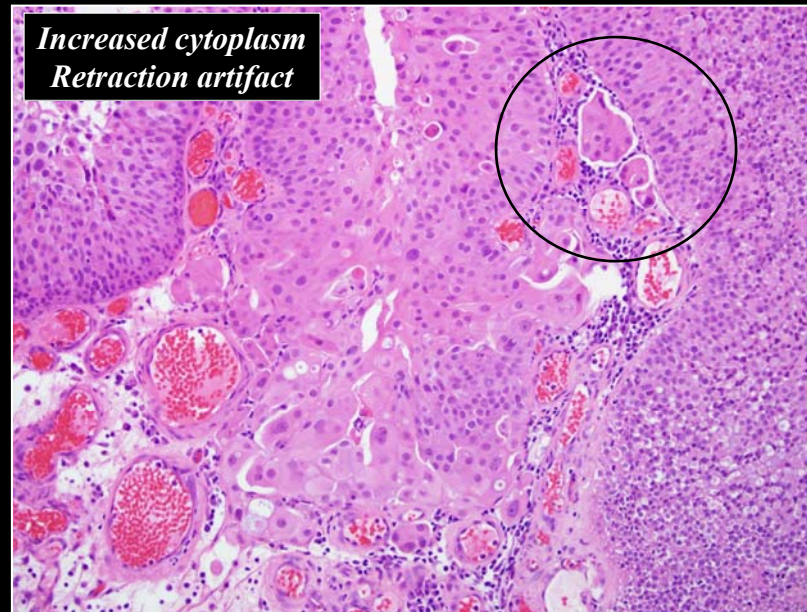
## DIAGNOSIS OF INVASION

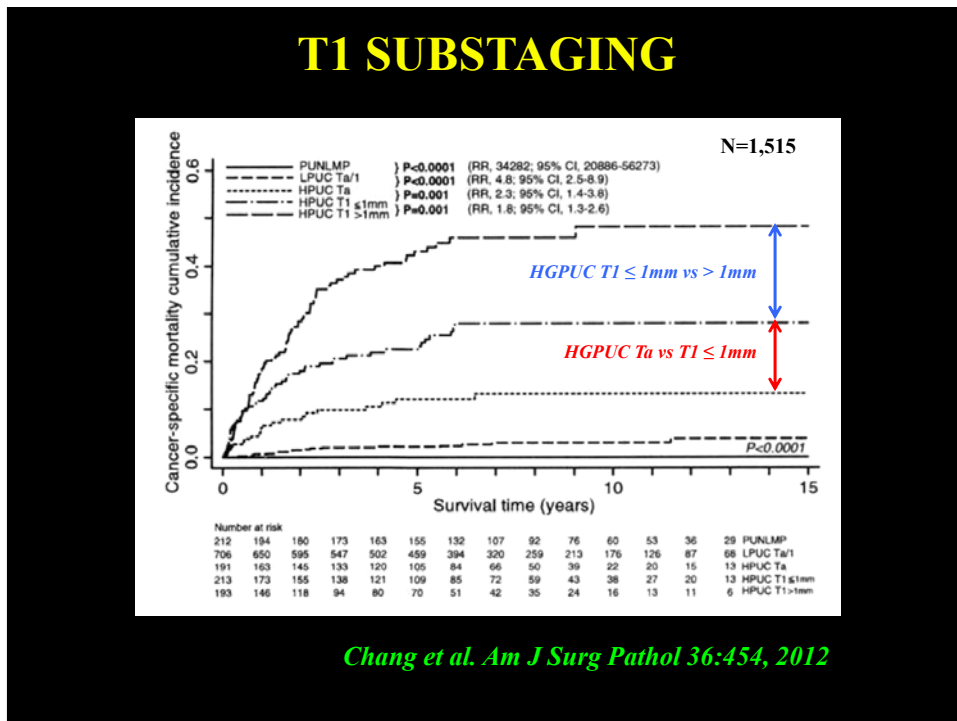
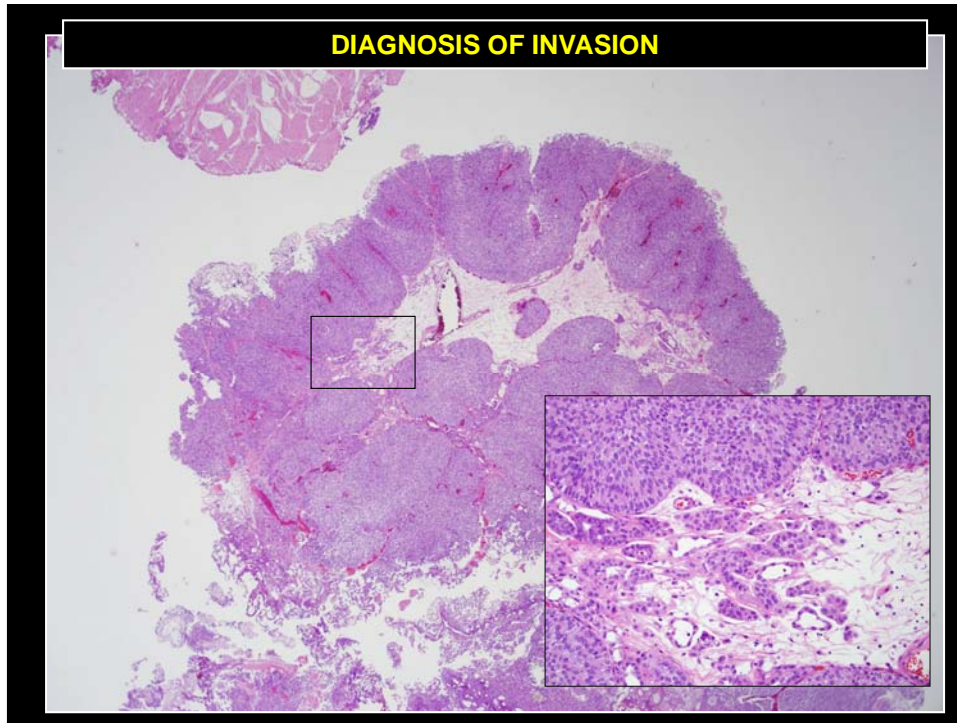
*Increased cytoplasm*  
*Retraction artifact*



## DIAGNOSIS OF INVASION

*Increased cytoplasm*  
*Retraction artifact*

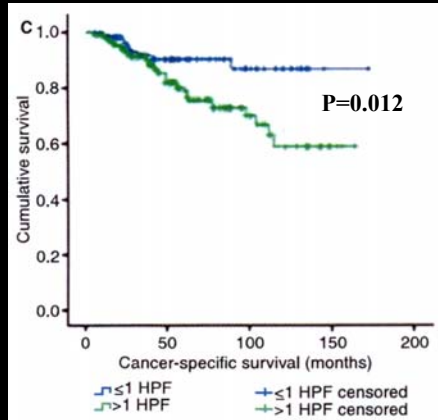
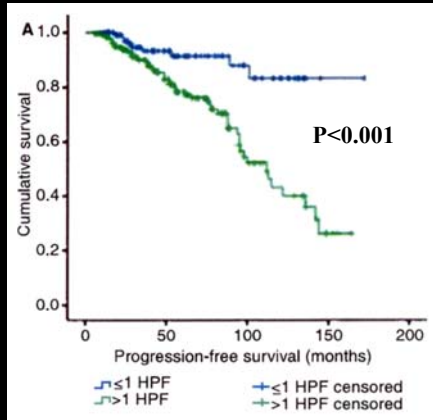




# T1 SUBSTAGING ( $\leq 1$ HPF vs $> 1$ HPF)

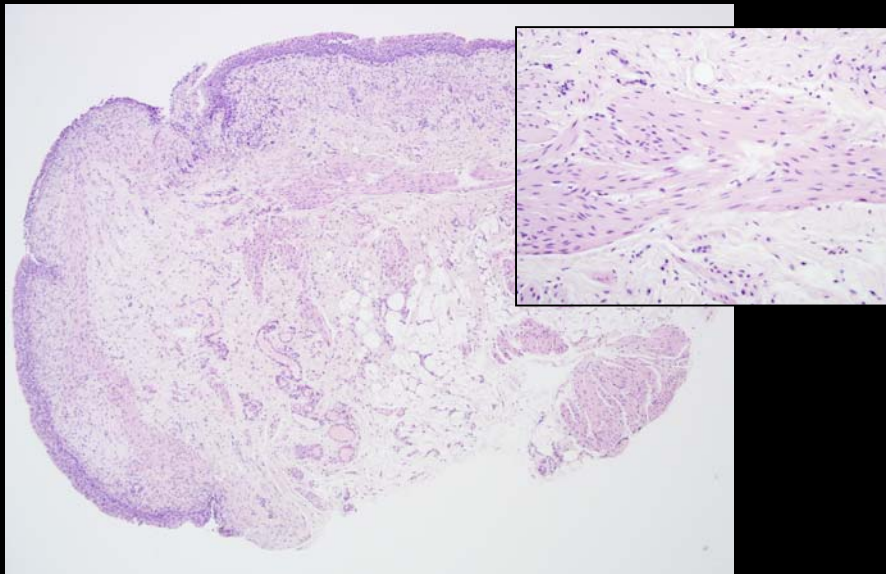
Progression-free survival

Cancer-specific survival



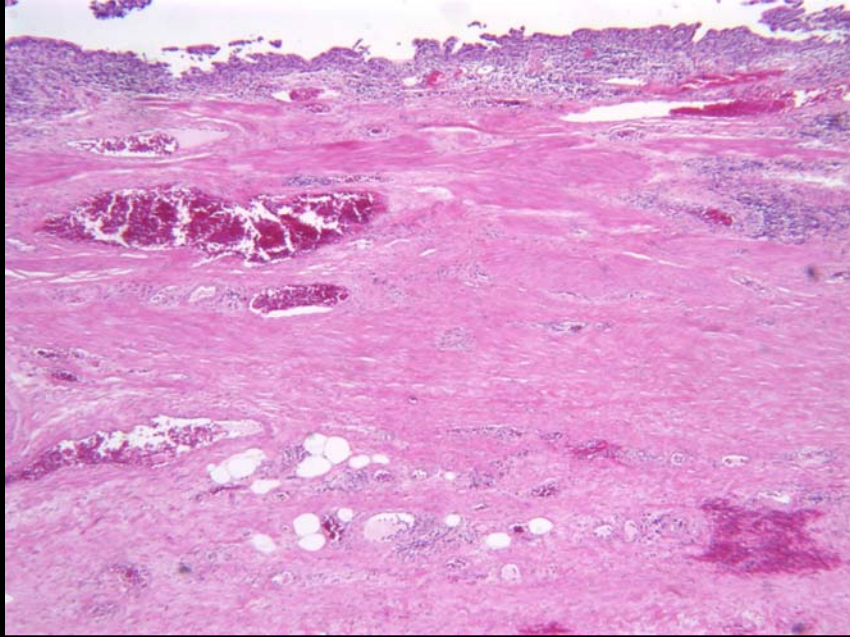
*Bertz et al. Histopathology 59:722, 2011.*

# MUSCULARIS MUCOSAE

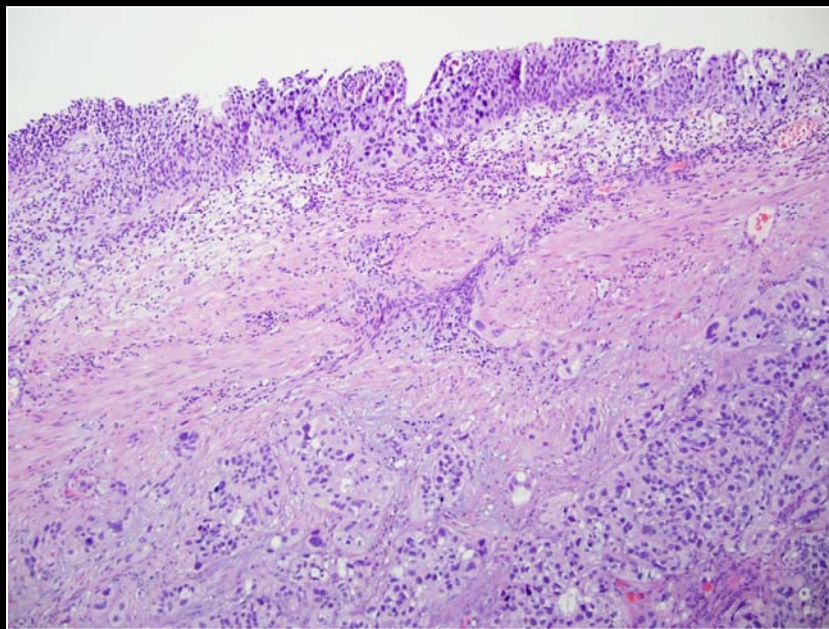




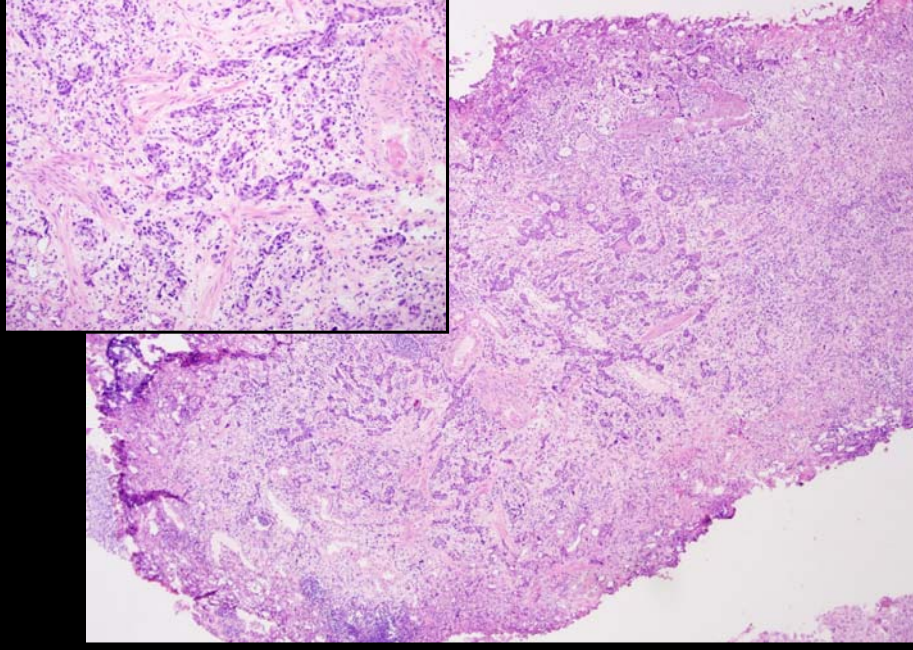
**TRIGONE REGION**



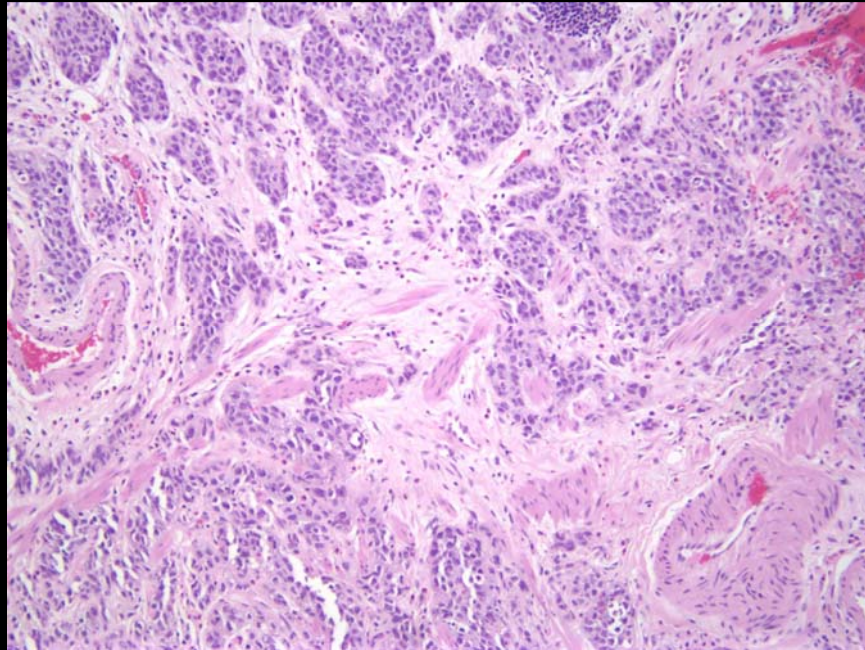
**TRIGONE REGION**



**MUSCULARIS MUCOSAE INVASION**

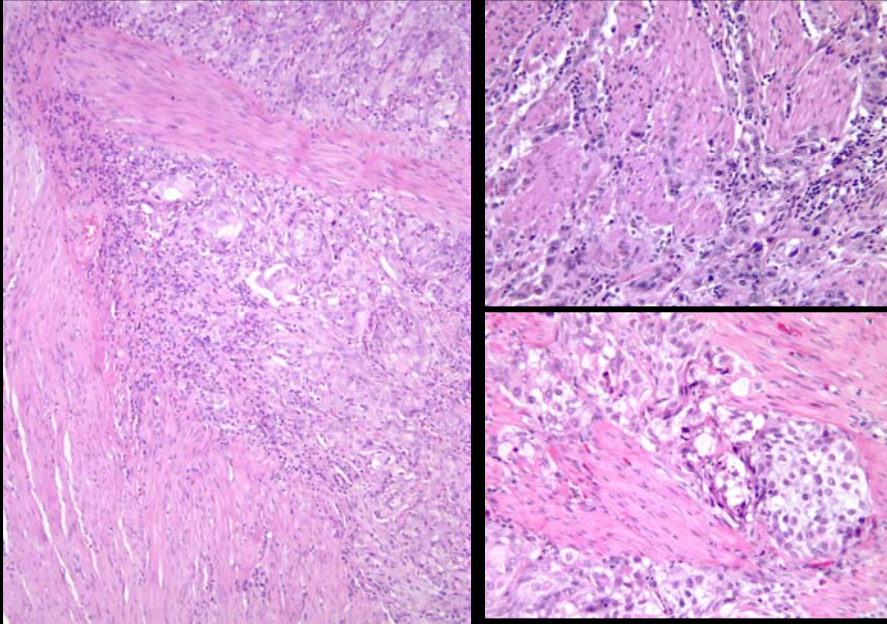


**MUSCULARIS MUCOSAE INVASION**

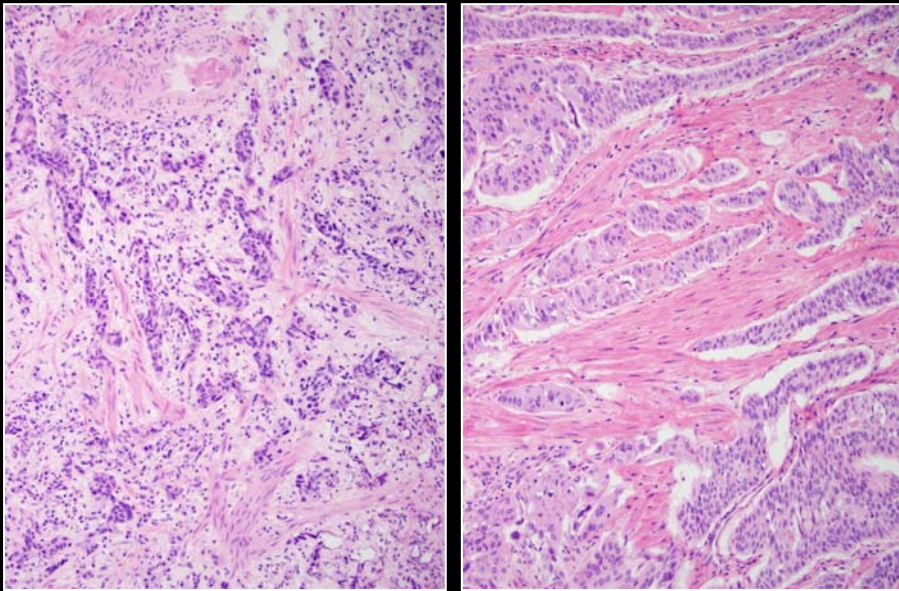




### MUSCULARIS PROPRIA INVASION

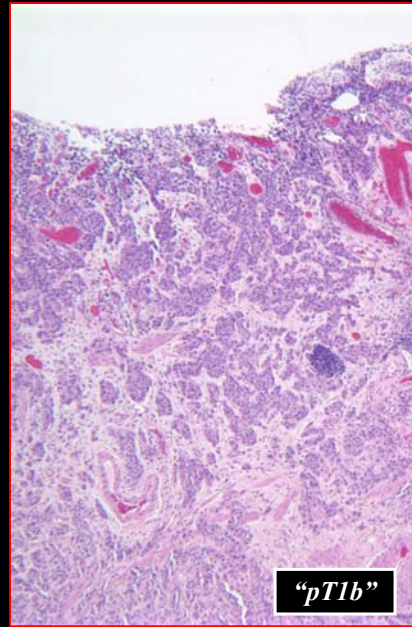
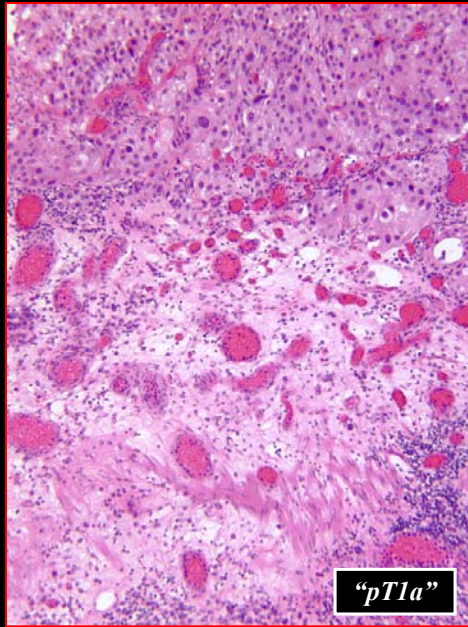


### MM vs MP INVASION



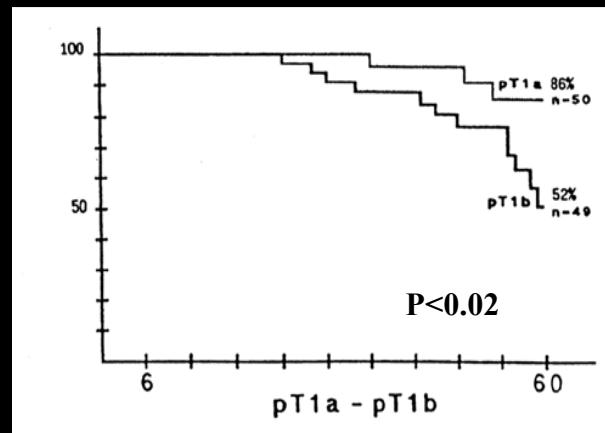


**pT1 – SUBSTAGING: MUSCULARIS MUCOSAE**



**SURVIVAL ACCORDING TO MUSCULARIS MUCOSAE INVASION**

- 343 patients - initial treatment
  - 170 pT1
- Cases centrally reviewed
- **Substaging possible in 99 (58%)**
- Treated by:
  - TURBT with intravesical tx



*Angulo et al, J Cancer Res Clin Oncol 119:578, 1993*

## T1 UC WITH LYMPHVASCULAR INVASION

- 118 newly diagnosed T1; all with TURBT +/- intra-vesical tx (85%)
- LVI diagnosis based on H&E alone
- LVI diagnosed in 33 cases (28%)

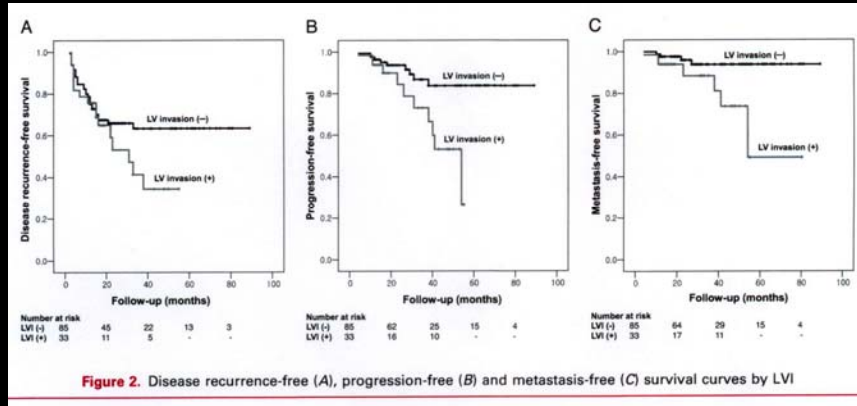
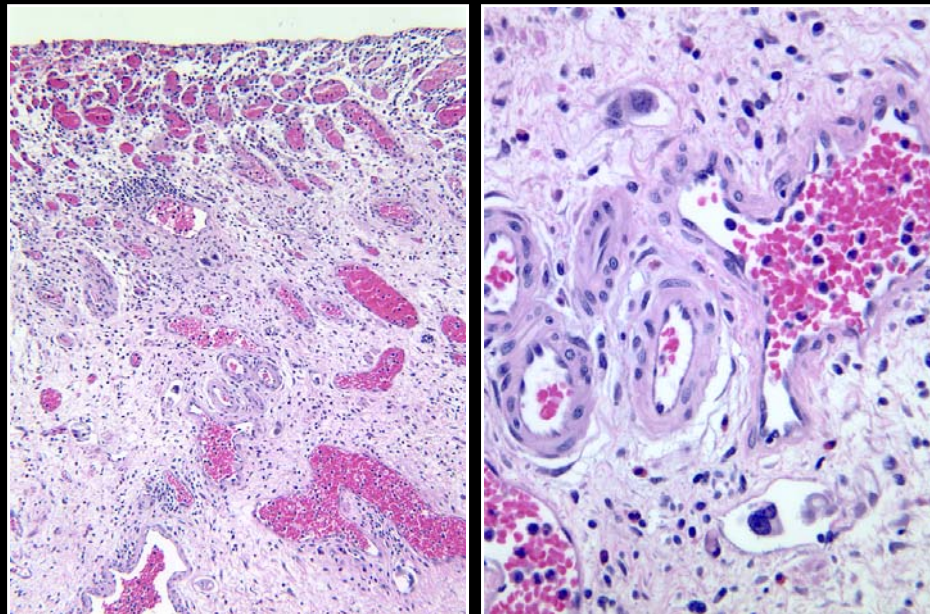


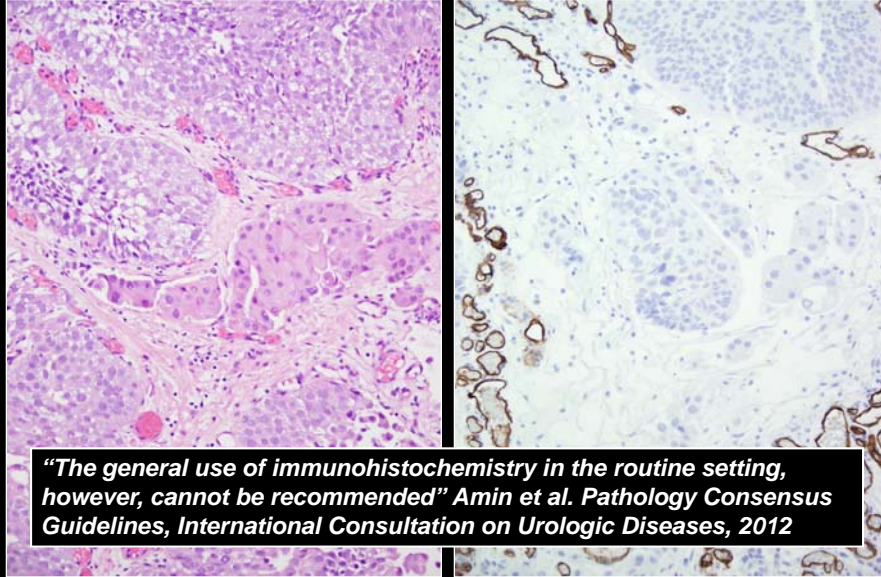
Figure 2. Disease recurrence-free (A), progression-free (B) and metastasis-free (C) survival curves by LVI

Cho et al. J Urol 182:2625-2631, 2009

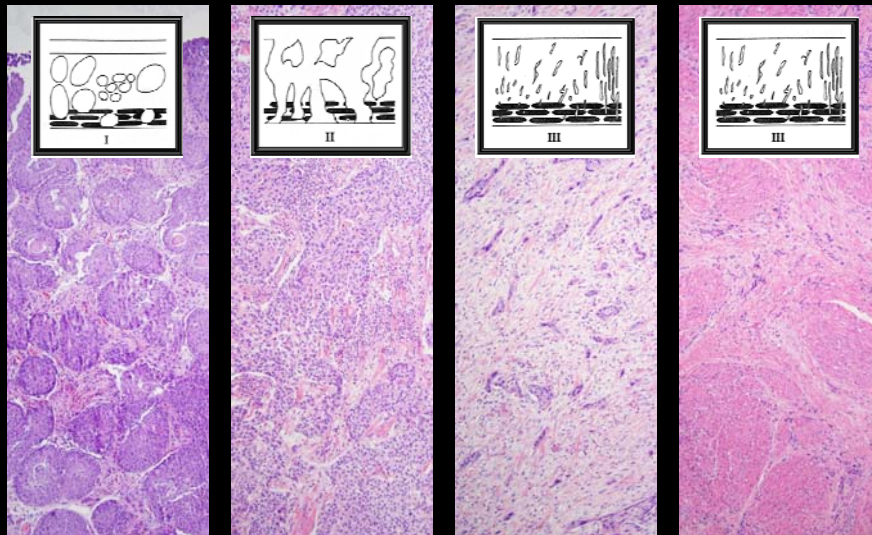
## CIS WITH LYMPHVASCULAR INVASION



## PROBLEMS WITH IDENTIFICATION OF LYMPHVASCULAR INVASION



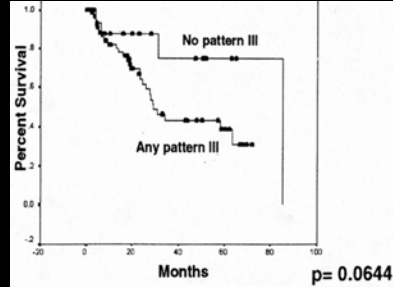
## UROTHELIAL CARCINOMA - PATTERN OF INVASION



*Jimenez et al, Am J Surg Pathol 24:980, 2000*



## UROTHELIAL CARCINOMA SURVIVAL BY PATTERN OF INVASION



*Jimenez et al, Am J Surg Pathol 24:980, 2000*

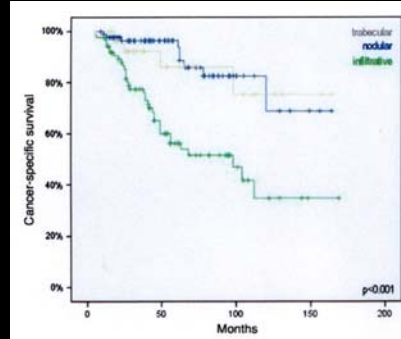


Figure 3. Comparison of cancer-specific survival in pT1G3 bladder carcinoma patients with different tumour growth patterns. Top line (dark) = nodular; middle line (pale) = trabecular; lower line = infiltrative.

*Denzinger et al. Scand J Urol 43:282, 2009*



*American Coots and a couple of mallards, Geist Reservoir, Indianapolis, IN*

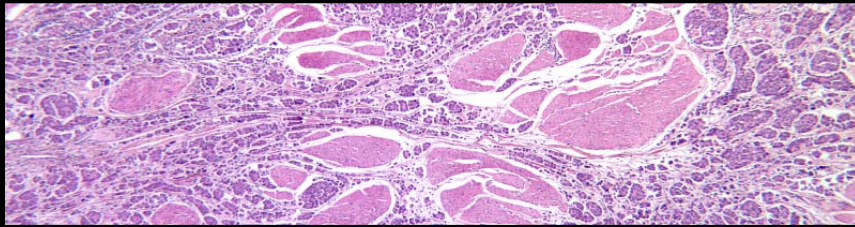
## UROTHELIAL CARCINOMA HISTOLOGIC VARIANTS

- Mixed differentiation
  - Nested variant
  - Microcystic variant
  - **Micropapillary variant**
  - **Plasmacytoid variant**
- Inverted growth pattern
  - Clear cell type
  - Lipid-rich
- Lymphoepithelioma-like variant
  - Lymphoma-like tumors
- Villoglandular architecture
- Tumors with HCG production
  - Sarcomatoid carcinoma

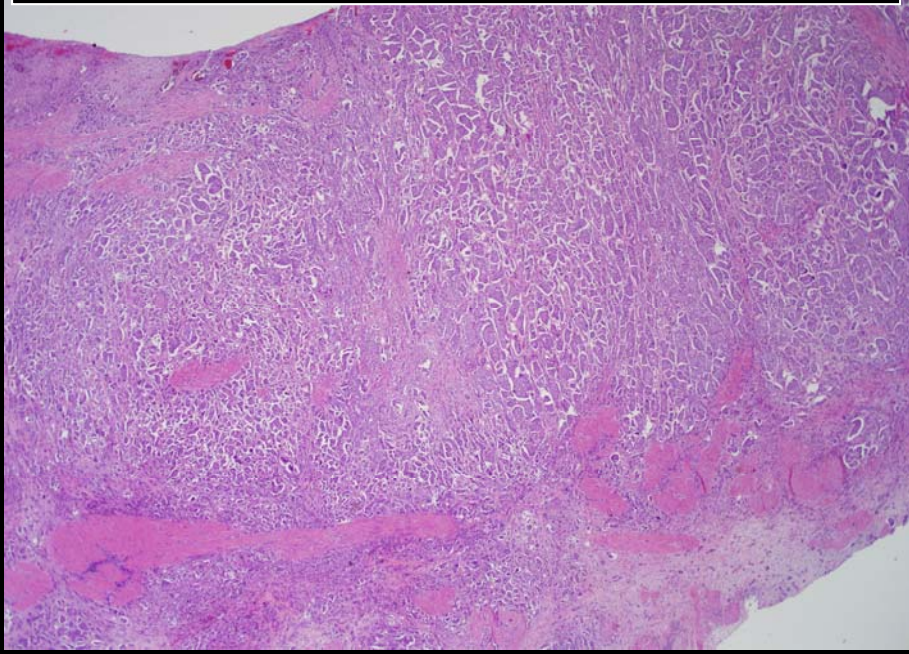
## UROTHELIAL CARCINOMA MICROPAPILLARY TYPE

- **CLINICAL**
  - Similar epidemiology to usual TCC
  - High stage, 50% with + LN at diagnosis
  - Worse prognosis with high % MP
- **PATHOLOGY**
  - Small, tight clusters of cells
  - Open spaces simulating lymphatic invasion
  - Deeply invasive
  - Suggested to be a form of glandular differentiation
  - Inversion of MUC1 staining to stromal aspect

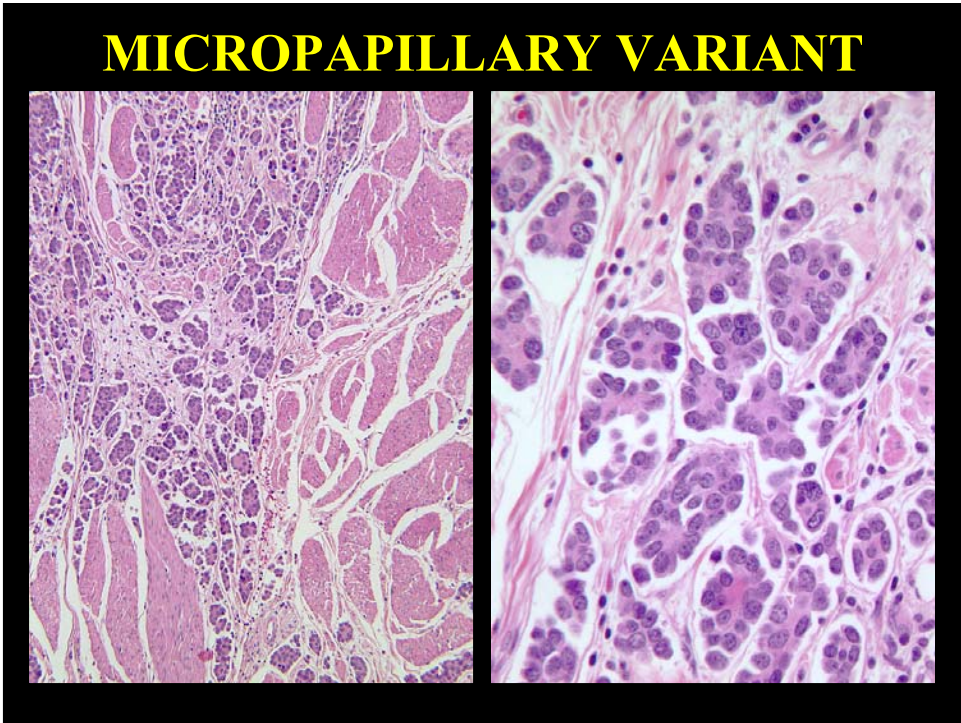
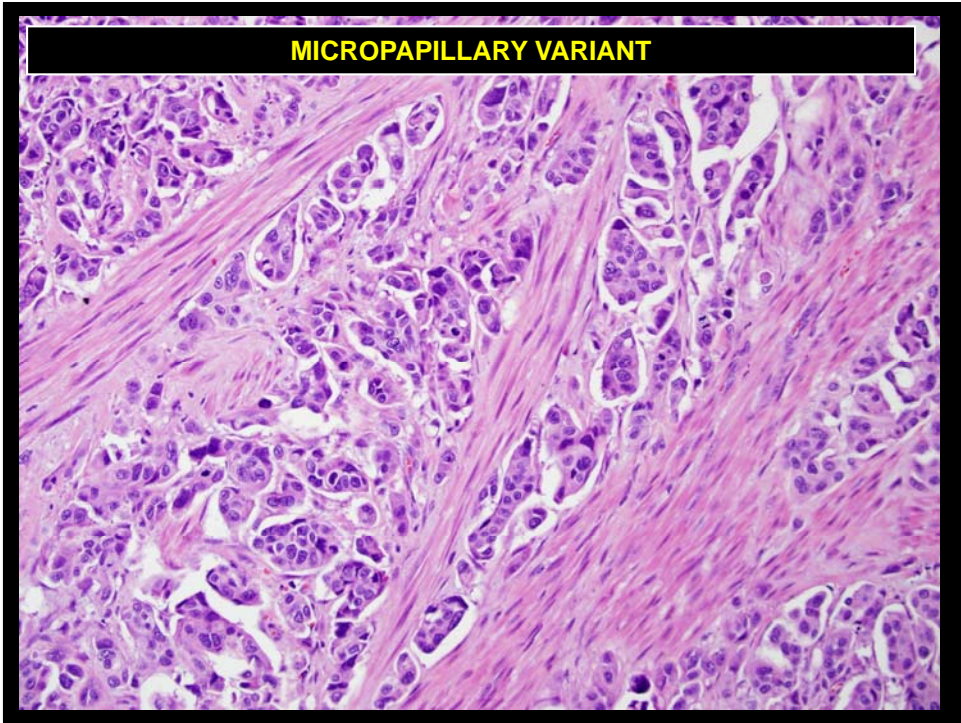
# MICROPAPILLARY VARIANT



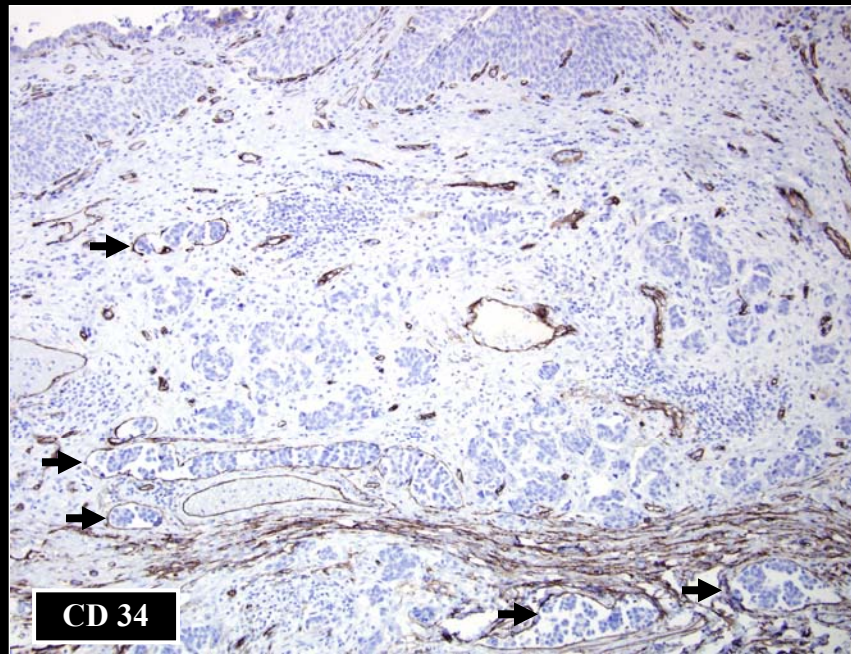
# MICROPAPILLARY VARIANT







## UC - MICROPAPILLARY VARIANT



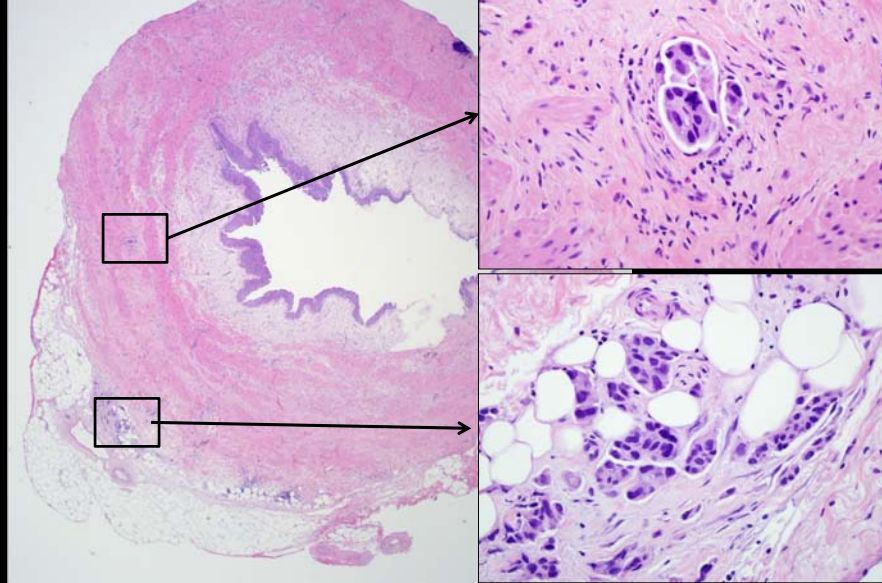
### UC - MICROPAPILLARY VARIANT: DIAGNOSTIC CRITERIA

- High degree of agreement with “classical cases” (Kappa value 0.79)
- Less agreement for equivocal cases
- Key features for diagnosis included:
  - Extensive retraction artifact
  - Multiple nests within the same lacunar space
  - Epithelial ring forms
  - Peripheral nuclear orientation

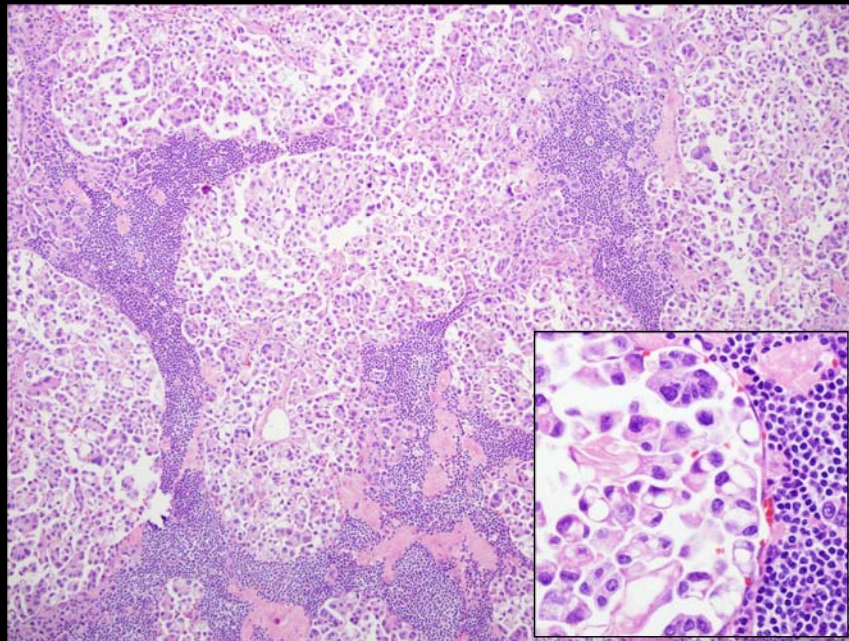
*Sangoi et al. Am J Surg Pathol 34:1367, 2010*



**UC - MICROPAPILLARY VARIANT  
URETER FROZEN SECTION**



**UC - MICROPAPILLARY VARIANT**





## UC – MICROPAPILLARY VARIANT: OUTCOME

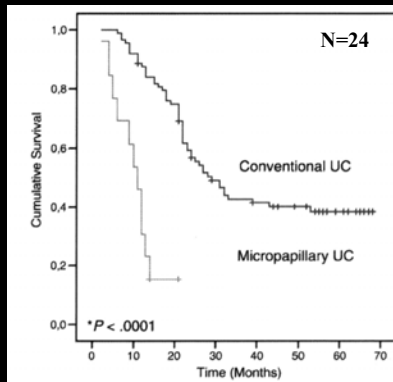


Fig. 2 Kaplan-Meier plots showing bladder cancer-specific mortality probability for conventional urothelial carcinoma compared with invasive micropapillary carcinoma. \**P* value based on log-rank test.

*Lopez-Beltran et al. Hum Pathol*  
42:1159-1164, 2010

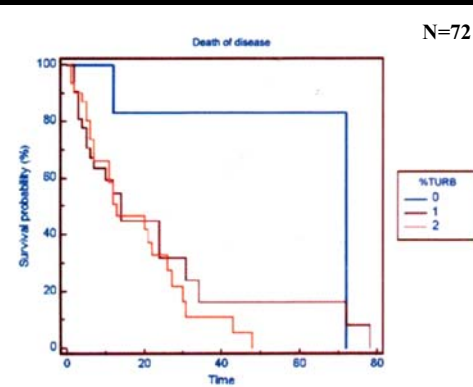
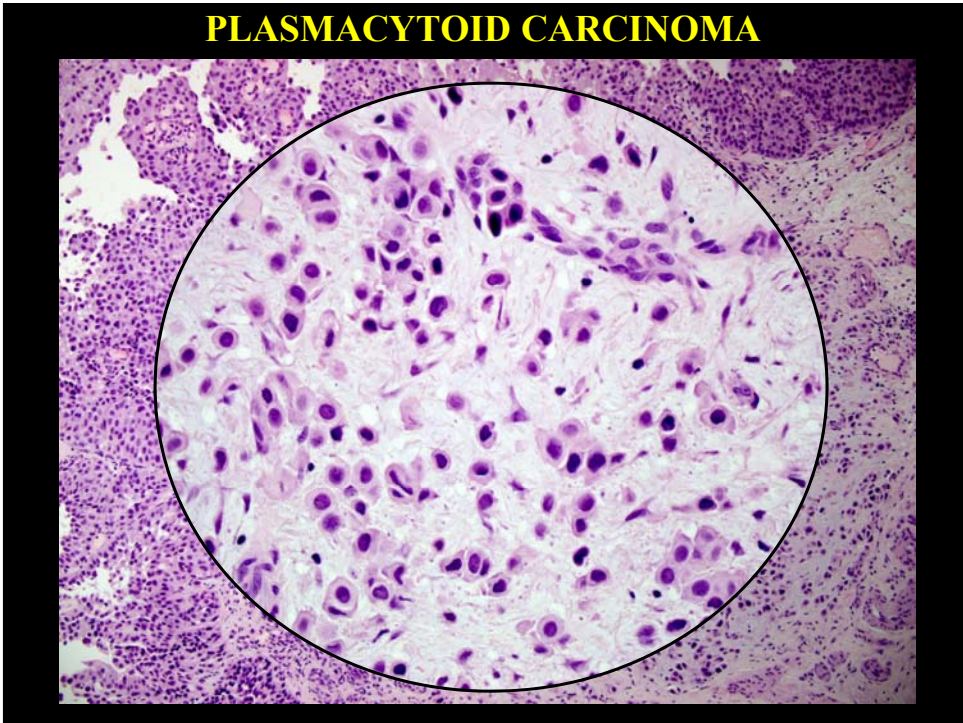
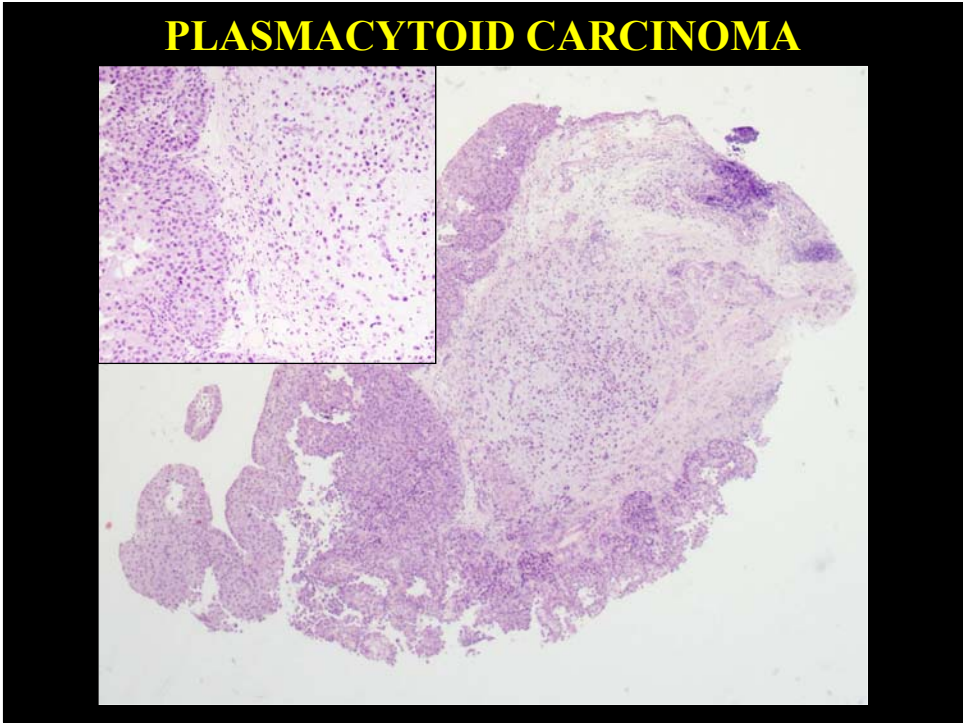


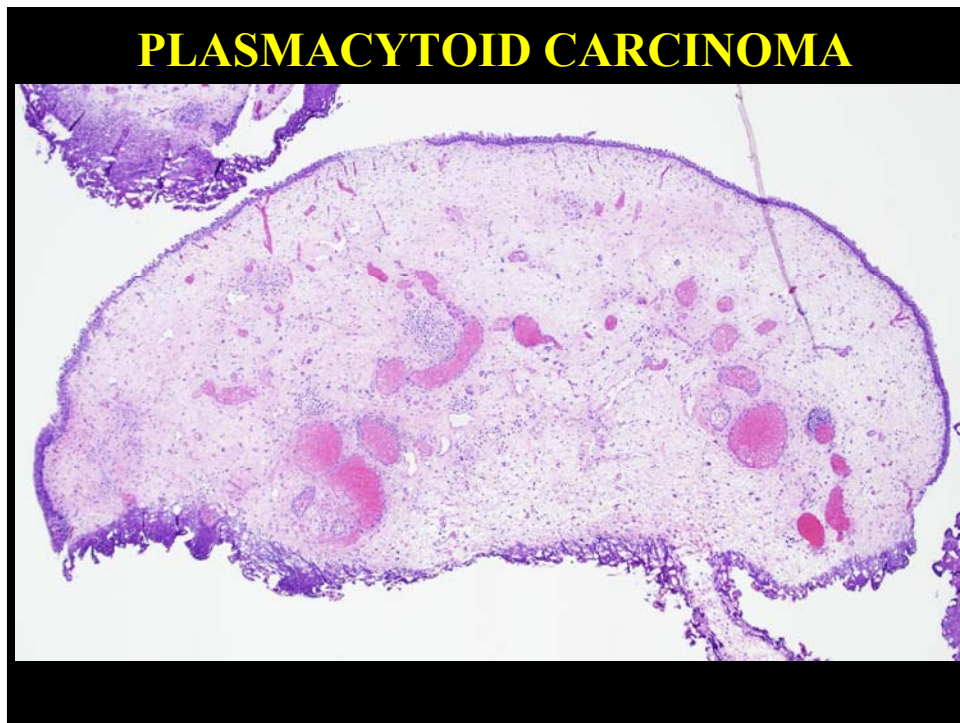
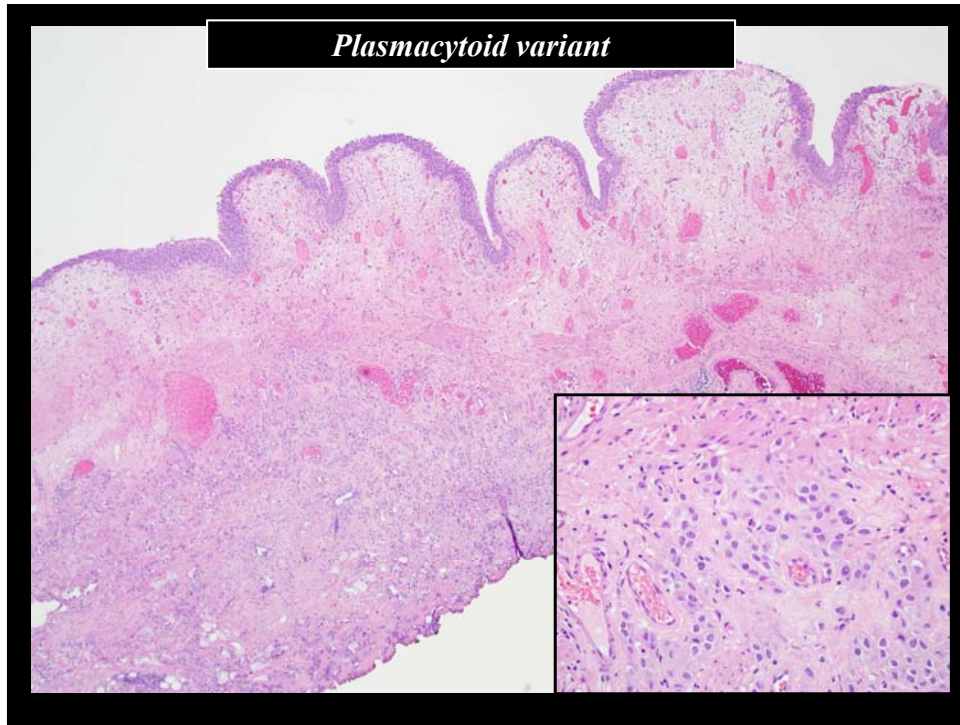
Fig. 5 Percentage of micropapillary carcinoma in the transurethral resections of bladder tumour and disease specific survival (0, < 10%; 1, 10-49%; 2, 50-100% MPC). Time in months.

*Comperat et al. Pathology 42:650-654,*  
2010

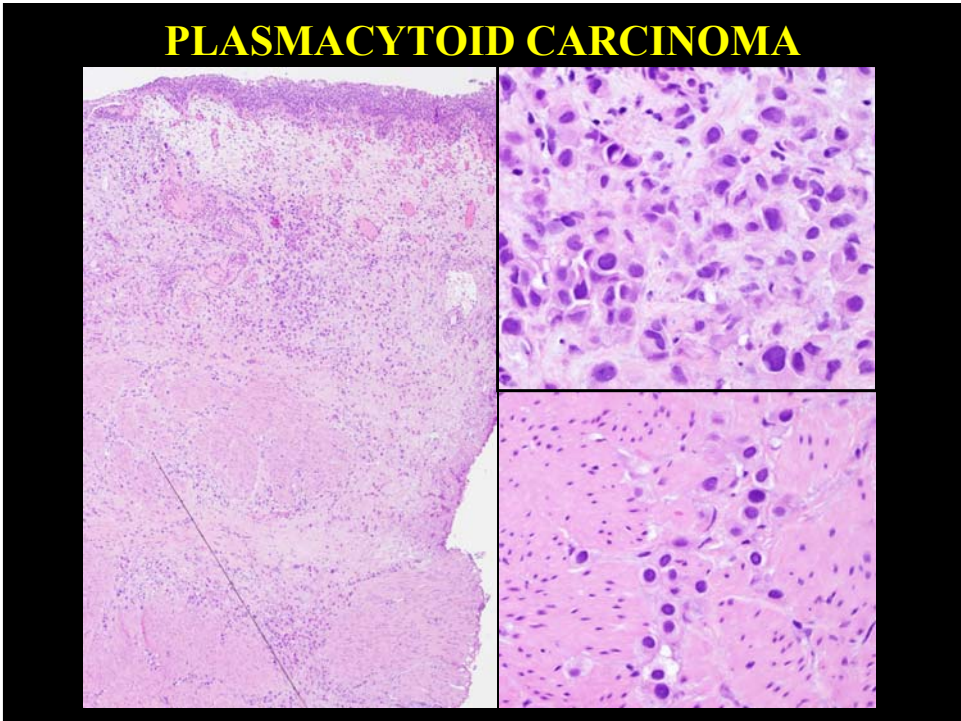
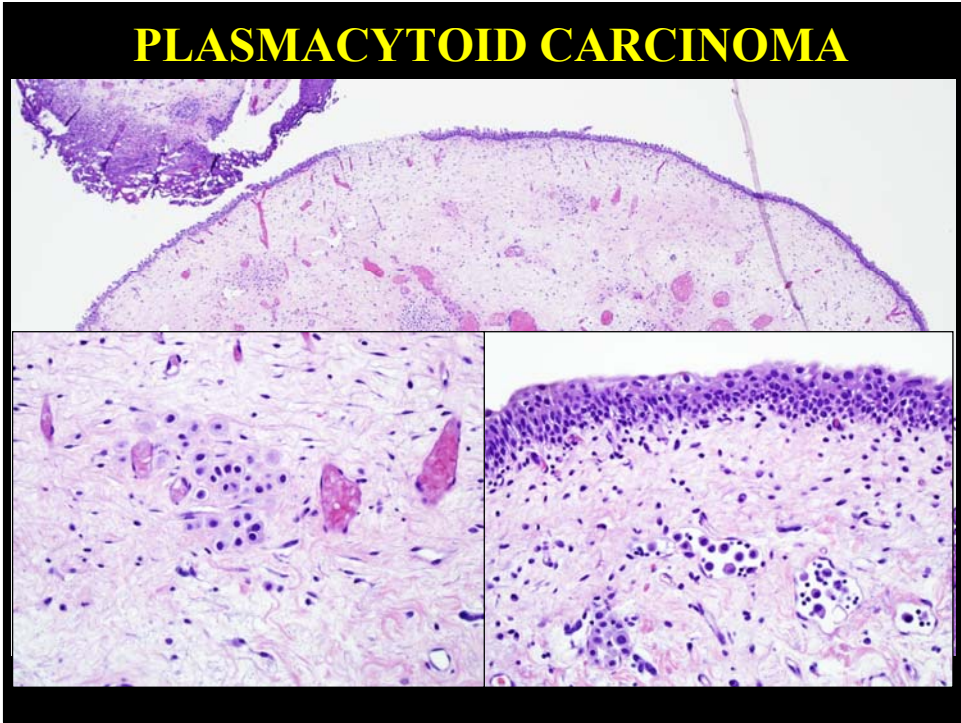
## UROTHELIAL CARCINOMA PLASMACYTOID CELL TYPE

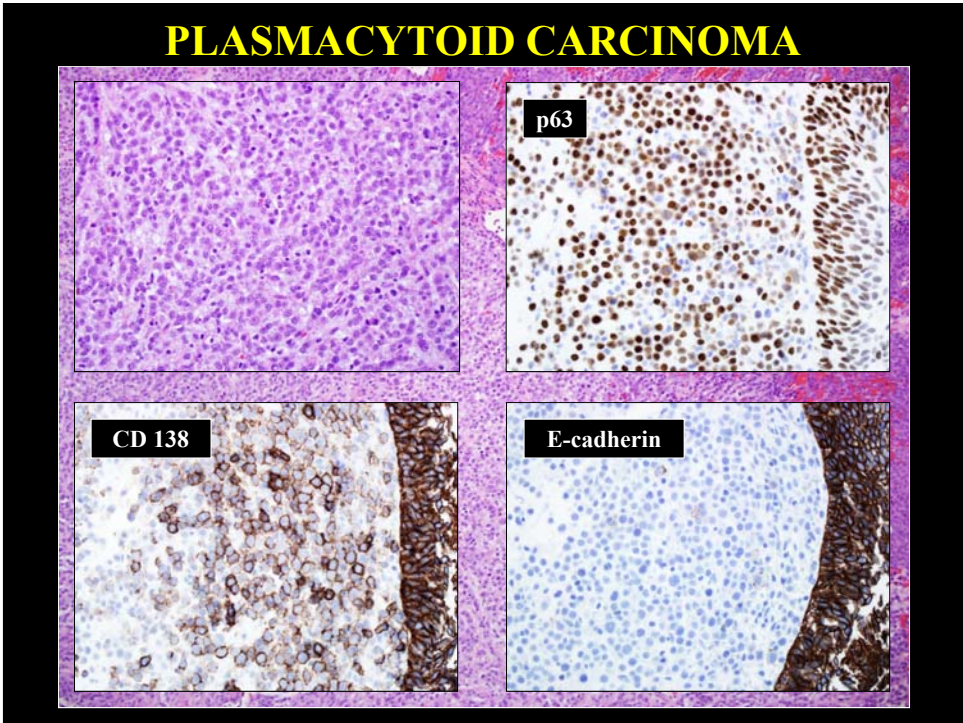
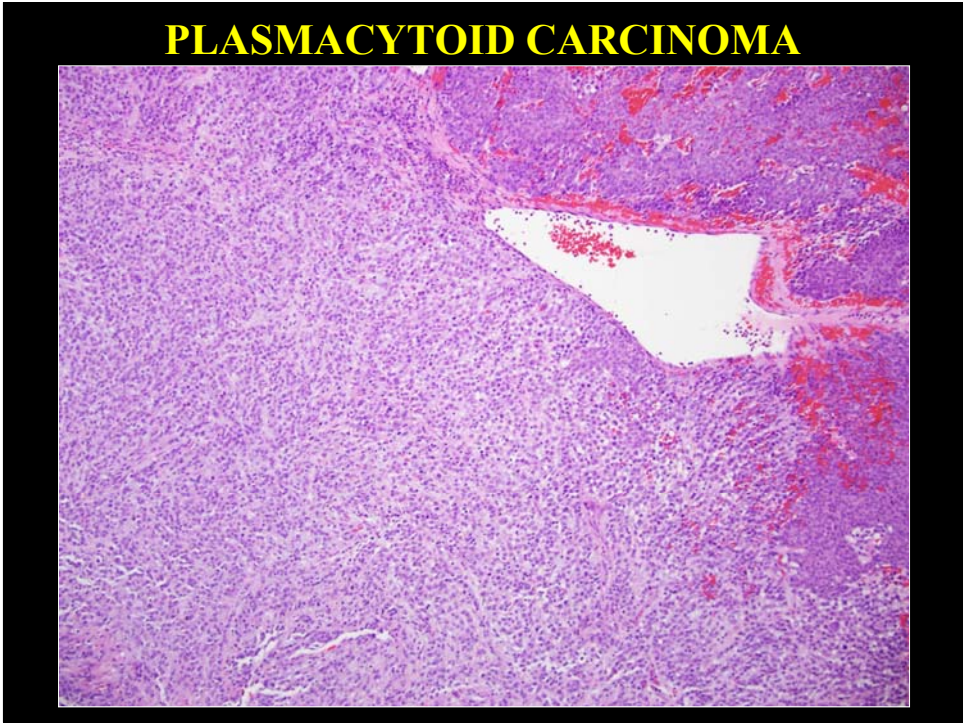
- **CLINICAL**
  - Described by Saphir in 1955 (“monocytoid SRC”)
  - Highly aggressive tumor
  - Linitis plastica-like; often no discrete mass but edematous mucosa in many
- **PATHOLOGY**
  - Sheets of poorly cohesive cells
  - Distinct monocytoid/plasmacytoid morphology with variable numbers of true signet-ring cells
  - +/- typical UC component
  - CK ++ (variable CK7/CK20), p63+, LCA -



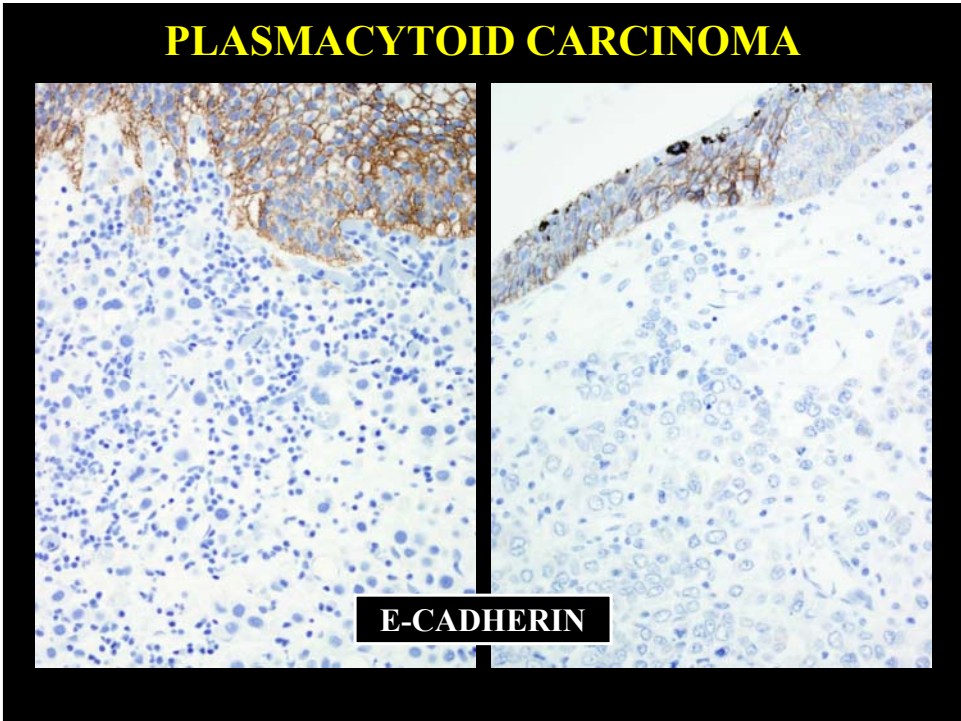
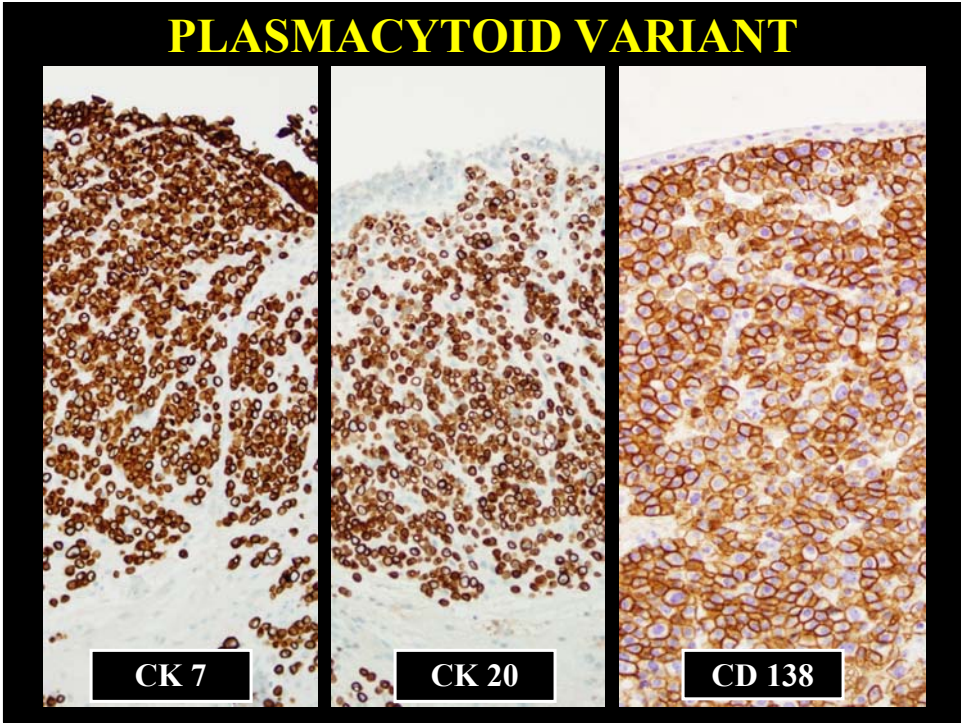






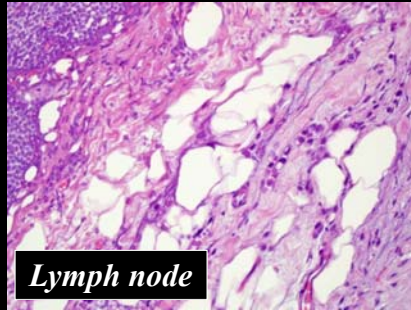
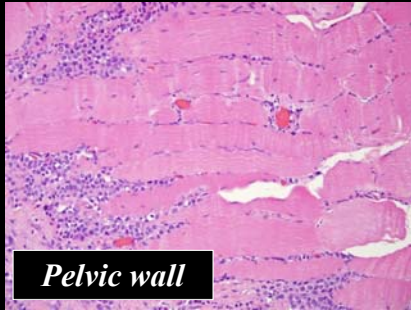
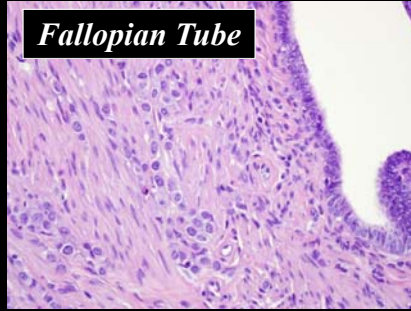
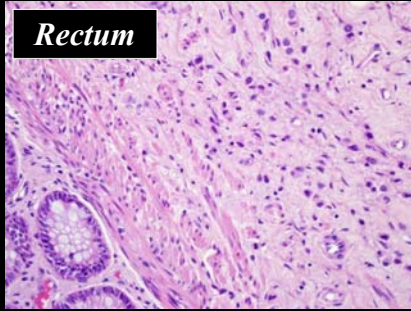




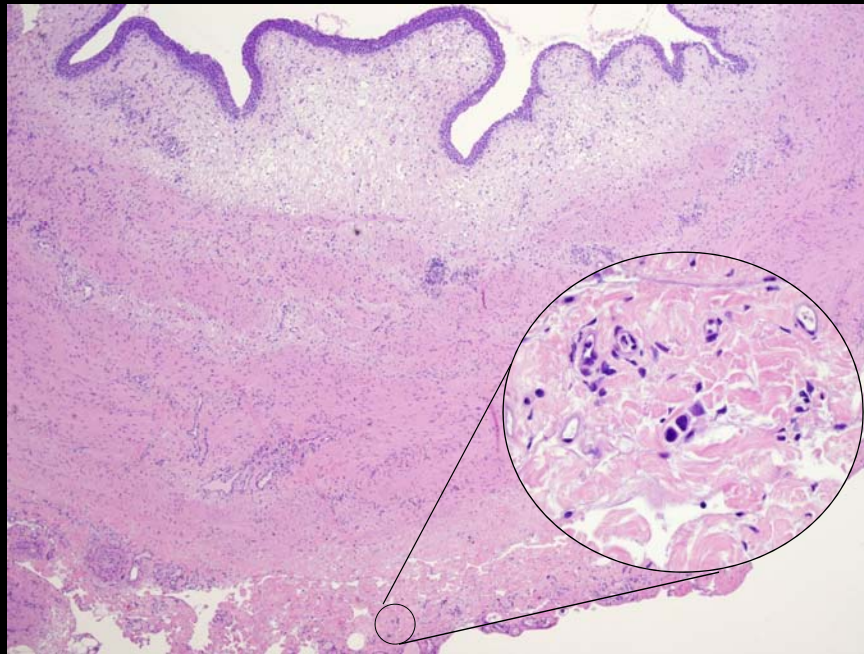


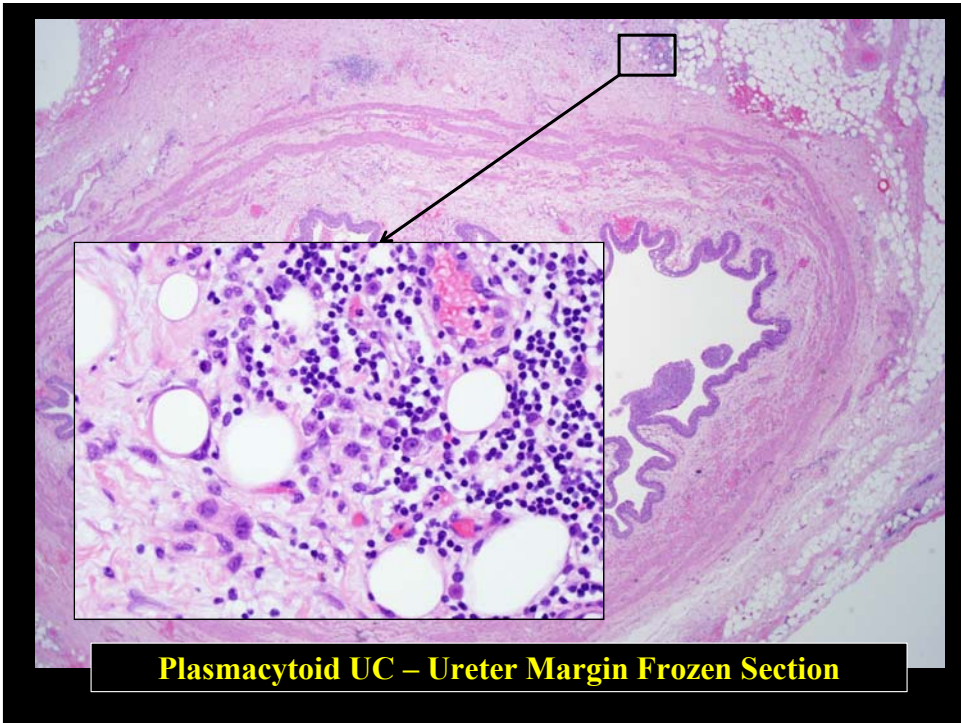
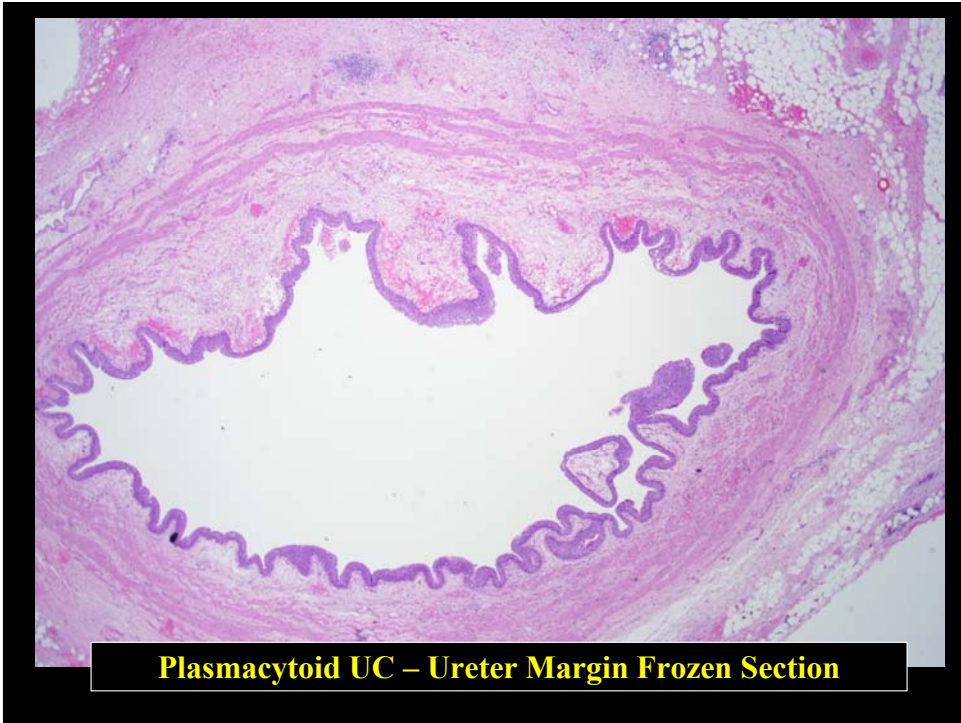


# PATTERN OF SPREAD

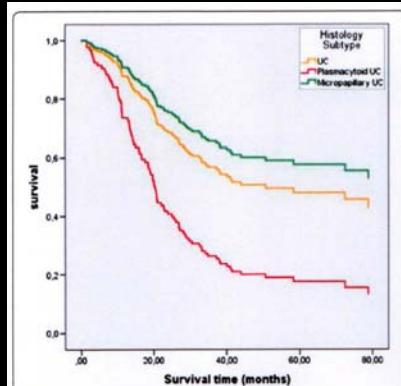


# URETER MARGIN





# PLASMACYTOID CARCINOMA



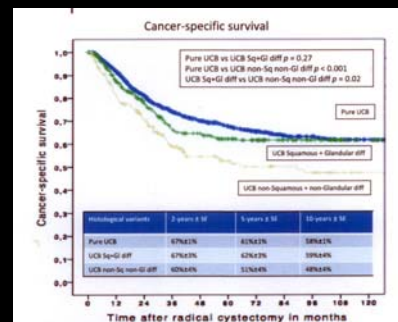
**Figure 4** Multivariate Cox's regression hazard analysis (adjusted to age, sex, tumor grade, tumor stage, lymph node and metastases status, type of chemotherapy): Correlation of histology subtype with overall survival. Patients with a plasmacytoid urothelial cancer (lower curve; N=18) have a 3.2-fold (95% CI: 1.0-9.9; P=0.045) increased risk of death while patients with conventional UC (middle curve; N=178) have a 1.3-fold (95% CI: 0.5-3.7; P=0.558) but not significant increased risk of death compared with patients with a micropapillary urothelial cancer (upper curve; N=9).

*Keck et al. BMC Cancer 13:71, 2013*

# PROGNOSTIC SIGNIFICANCE OF VARIANT HISTOLOGY

**Table 1**  
Frequency of histological variants of urothelial carcinoma in 1983 patients treated with radical cystectomy.

Histological variant	Number of patients (%)
Pure urothelial carcinoma	1495 (75.4)
Urothelial carcinoma variant	488 (24.6)
Squamous cell differentiation	227 (11.4)
Glandular differentiation	75 (3.8)
Sarcomatoid differentiation	40 (2.0)
Micropapillary differentiation	34 (1.7)
Small cell differentiation	40 (2.0)
Plasmacytoid differentiation	7 (0.4)
Multiple variant differentiation	65 (3.3)



- Multi-institutional (5)
- Radical cystectomy 2000 – 2008
- No neoadjuvant treatment

*Xylinas et al. Eur J Cancer 49:1889-1897, 2013*



# IMPORTANCE OF PATHOLOGY

## New Strategies in Muscle-Invasive Bladder Cancer: On the Road to Personalized Medicine

Jay B. Shah, David J. McConkey and Colin P.N. Dinney

*Clin Cancer Res* 2011;17:2608-2612. Published OnlineFirst March 17, 2011.

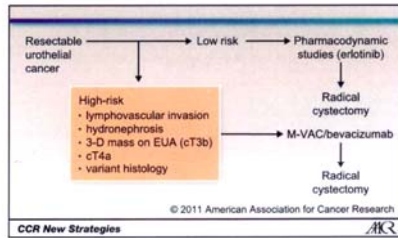


Figure 1. MD Anderson Cancer Center neoadjuvant paradigm for patients with invasive bladder cancer. All patients with invasive urothelial cancer are clinically stratified as either low risk or high risk for locoregionally advanced disease. Patients in the low-risk category (to whom chemotherapy is not typically administered) are offered enrollment in a single-agent study with a medication such as erlotinib. Erlotinib is given for 5 days prior to cystectomy. Pre-treatment tissue (obtained at TURBT) and post-treatment tissue (obtained at cystectomy) are then used for pharmacodynamic and molecular profiling studies. Patients in the high-risk category are offered enrollment in clinical trials that call for the addition of a novel agent (e.g., bevacizumab) to conventional chemotherapy. For all patients with resectable invasive bladder cancer, the neoadjuvant paradigm allows for the testing of novel agents as well as the acquisition of pre- and post-treatment tissue without compromising patient care.

## UROTHELIAL LESIONS II: BENIGN MIMICS OF BLADDER CANCER

