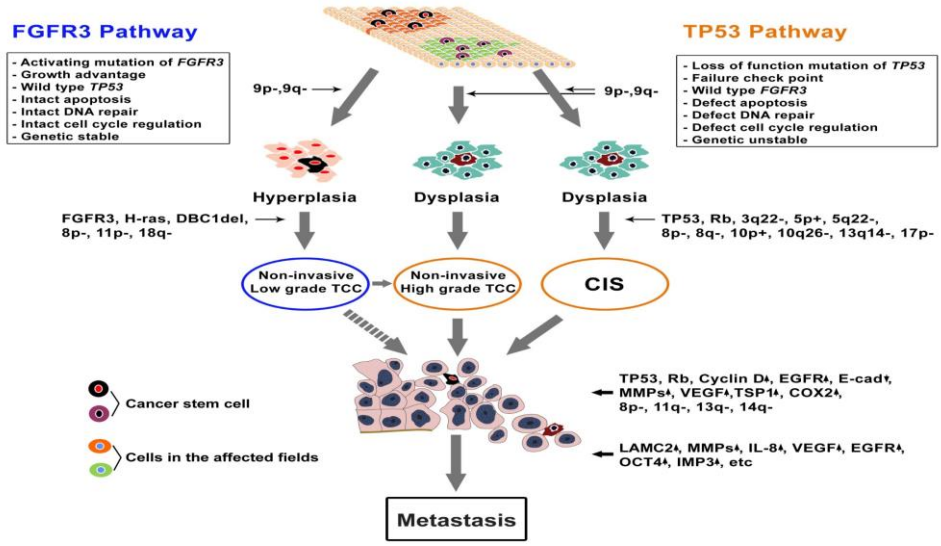
III ЕЖЕГОДНЫЙ КОНГРЕСС
РОССИЙСКОГО ОБЩЕСТВА ОНКОПАТОЛОГОВ

20–21 апреля 2018 года

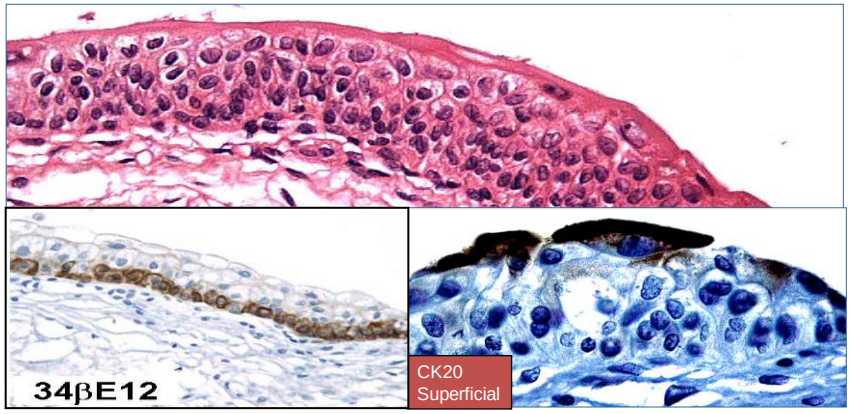
13.00–14.00	**ПЕРЕРЫВ НА ОБЕД**
14.00–15.40	**Сессия – Онкоурология** (председатель – Ковылина М.В.)
14.00–14.25	**Antonio Lopez-Beltran** (Испания) CIS/Dysplasia of the urothelium
14.25–14.50	**Antonio Lopez-Beltran** (Испания) Pathologic assessment of invasion in TUR specimens
14.50–15.10	**Antonio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

CIS/Dysplasia of the Urothelium

A. Lopez-Beltran



The Urothelium



Urothelial Dysplasia

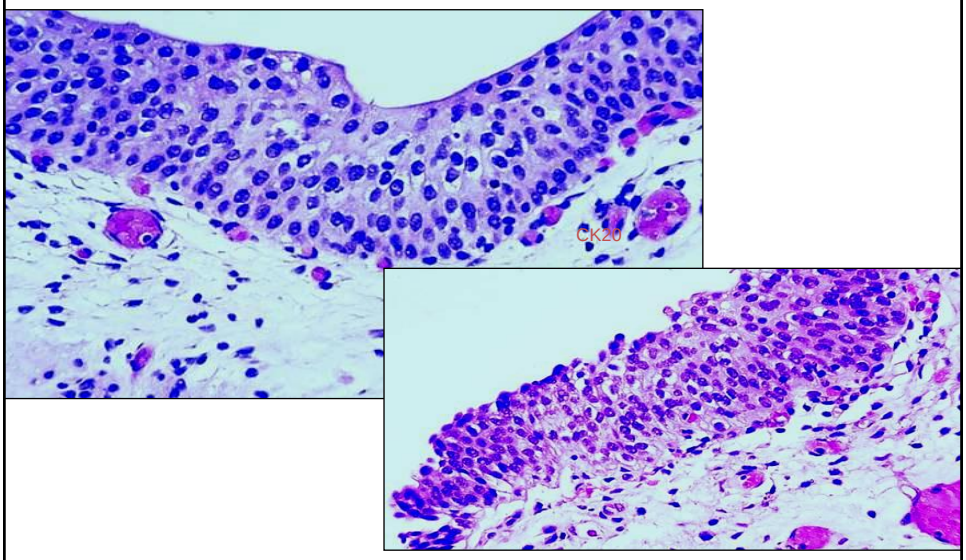
UROTHELIAL DYSPLASIA
(Low grade intraurothelial neoplasia)

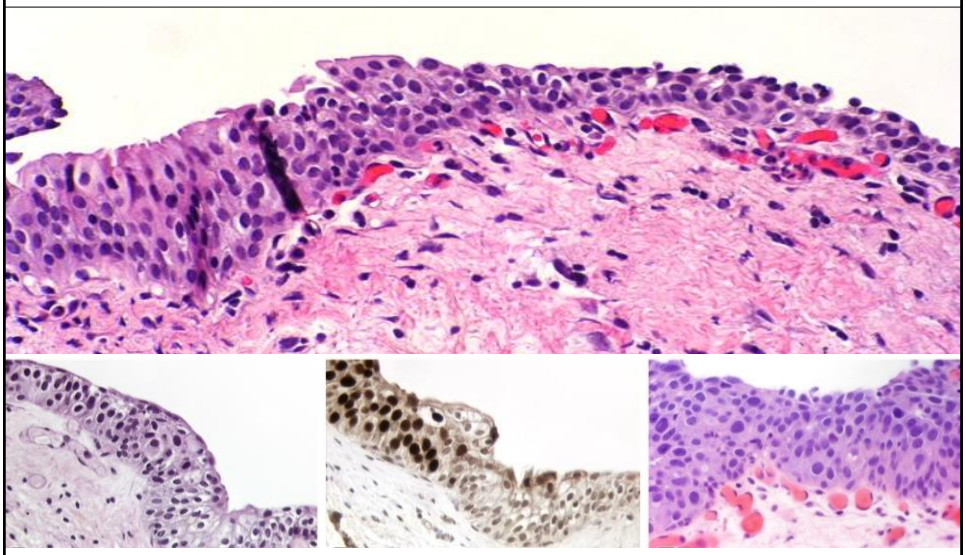
- Definition:
  - Presence of some but not all features of CIS.
- Primary/secondary (22-86%)
- Low>> interobserver reproducibility
- Appearance of urothelium at histology:
  - G1/LG (WHO, 1973/2004)
- Markers' alteration: CK20, HMWCK, Ki-67, p53¡¡¡
- Alterations in chromosome 9 and p53

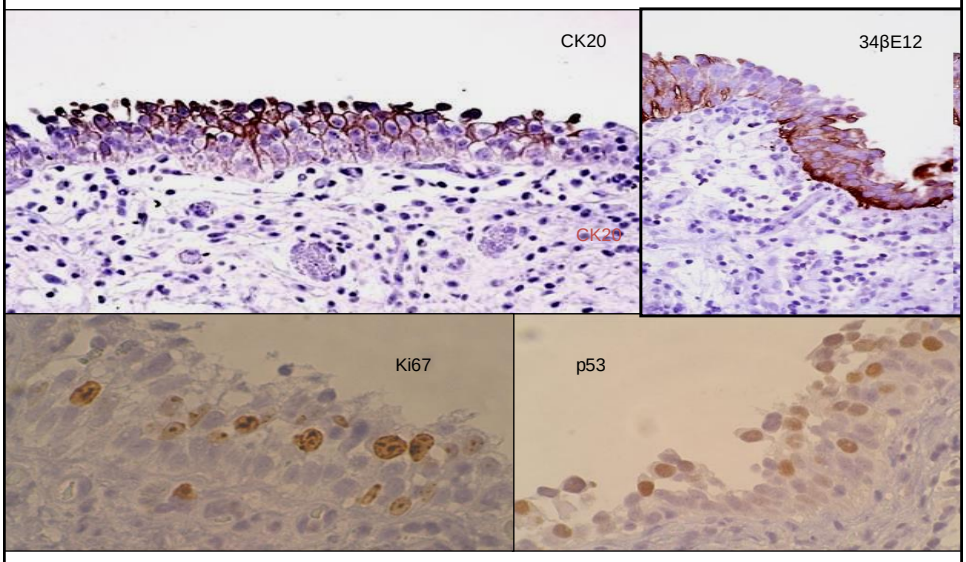
	Reactive atypia	Flat hyperplasia	Dysplasia
Recurrence	No	Unknown	Unknown* 73% versus 43% in cases without dysplasia†
Progression	No	Unknown	13–19%‡,* 30–36%§,†

*Primary.
†Secondary.
‡Progression to carcinoma *in situ*.
§Progression to muscle-invasive carcinoma.

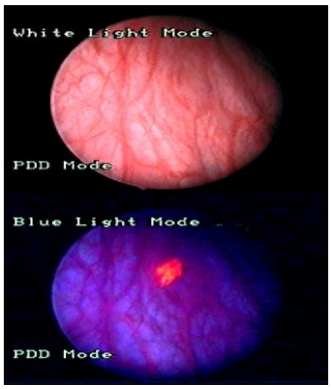
Montironi, Lopez-Beltran, et al 2008


CK20





Urothelial Carcinoma In Situ



Urothelial Carcinoma In situ
(High-grade intraurothelial neoplasia)

- **Definition: N**on-papillary, flat, lesion in which the epithelium contains cells that are identical to high grade Ca.
- CIS >>may not involve the entire thickness of the epithelial layer
- Umbrella cells>> may be present.
- Interobserver agreement >>high
- De novo (primary):
  - 1%-3% of urothel.Ca; 10% of CIS
  - Less likely to progress to invasive disease than secondary CIS after BCG.

Urothelial Carcinoma In situ
(High-grade intraurothelial neoplasia)

- Secondary (concomitant) CIS:
  - 90%
  - 45%-65% of invasive Uca and 7-15% of papillary Uca.
  - **Grade: G1, 2%; G2, 13% ; G3, 60%**
- CIS multifocal or extensive is more likely to progress.
- Cancer –specific survival after Cyp
  - 80% or higher at 10 years
- Most commonly seen in UB, but also ureters

(6-60%), renal pelvis and urethra(20-67%, involving prostate ducts/acini, in up to 40%).

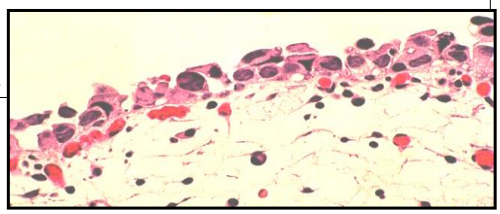
Primary Versus Secondary Carcinoma in Situ

Definitions of primary and secondary CIS vary somewhat in the pathologic and urologic literature. Takenaka et al.[16] separate lesions into the following categories: (1) primary CIS, occurring without associated previous urothelial tumor; (2) concomitant CIS, occurring in conjunction with a newly diagnosed bladder tumor; and (3) secondary CIS, diagnosed during follow-up of a known bladder tumor, with or without a concomitant tumor at the time of CIS diagnosis. This convention is used by some other authors, and may be gaining in usage.[15,46–49]

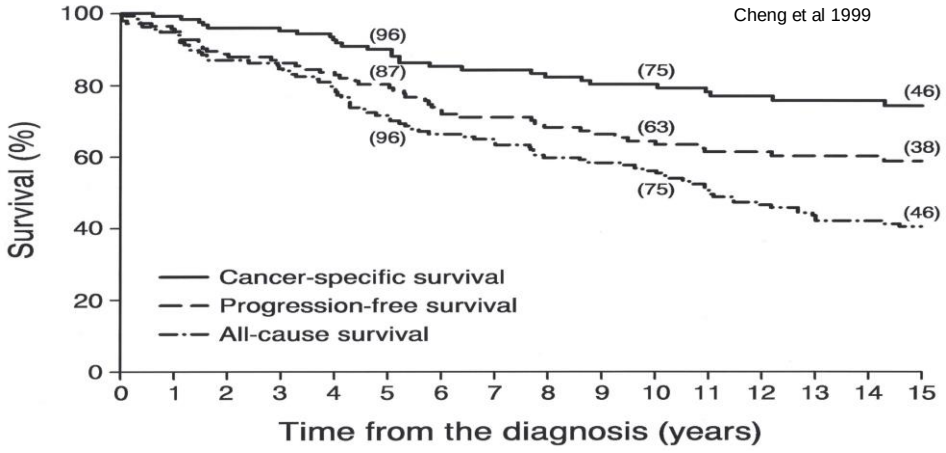
Carcinoma In situ

	Reactive atypia	Flat hyperplasia	Dysplasia	Carcinoma *in situ*
Recurrence	No	Unknown	Unknown* 73% versus 43% in cases without dysplasia†	Unknown* Unknown†
Progression	No	Unknown	13–19%‡,* 30–36%§,†	28%§,* 42–83%§,†

*Primary.
†Secondary.
‡Progression to carcinoma *in situ*.
§Progression to muscle-invasive carcinoma.

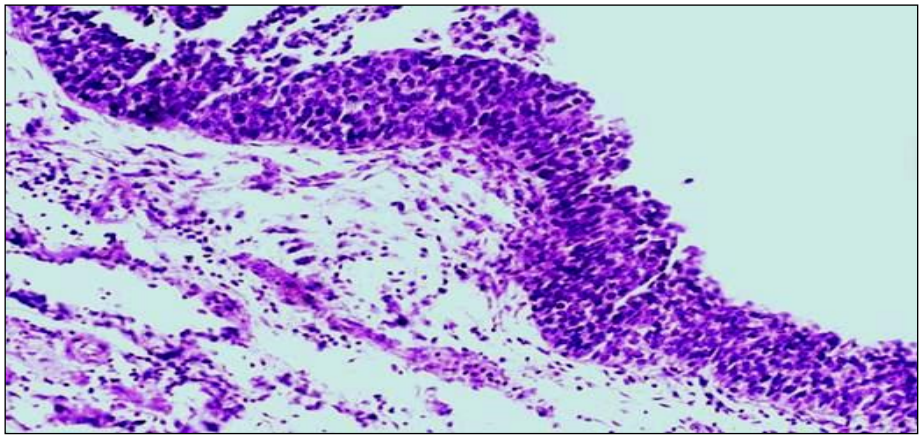


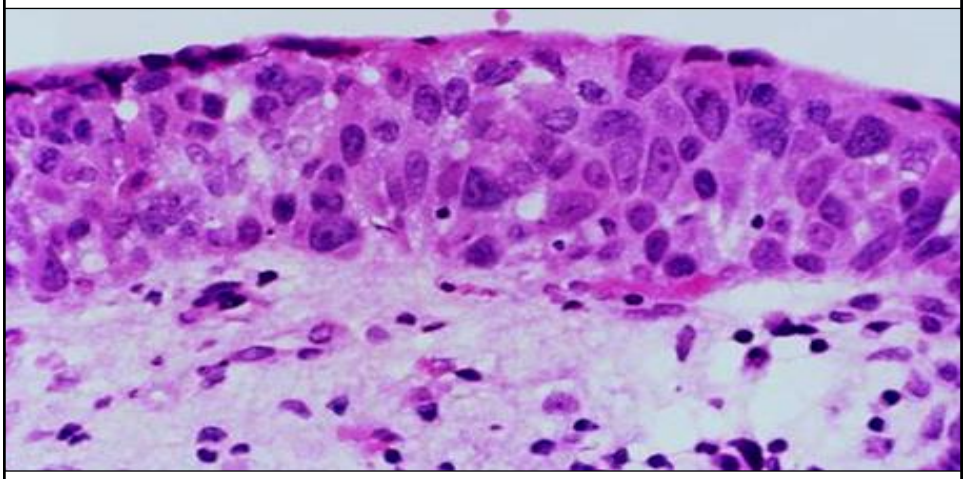
Primary CIS

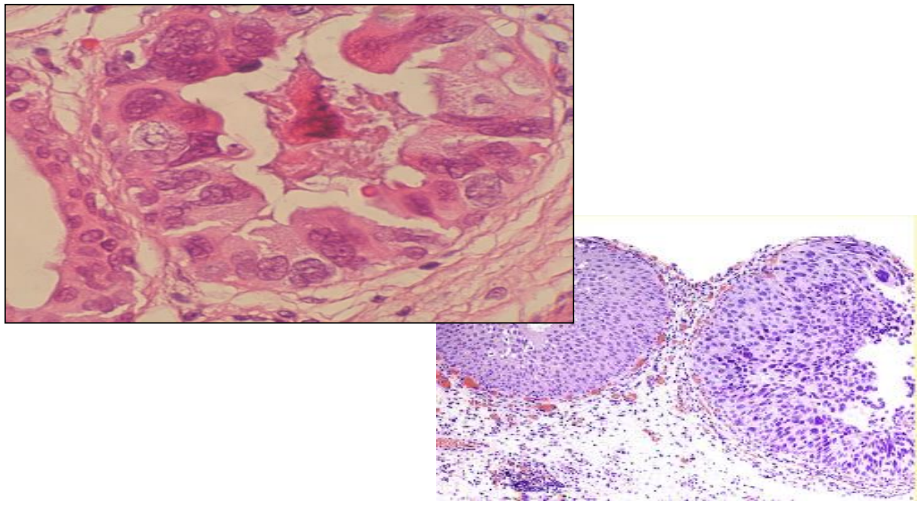


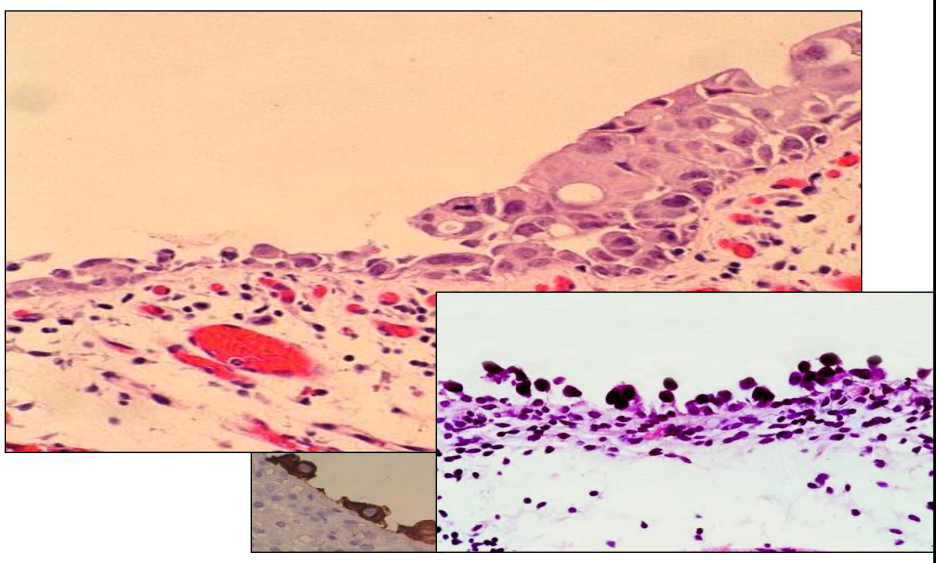
Carcinoma In situ
Morphologic expressions

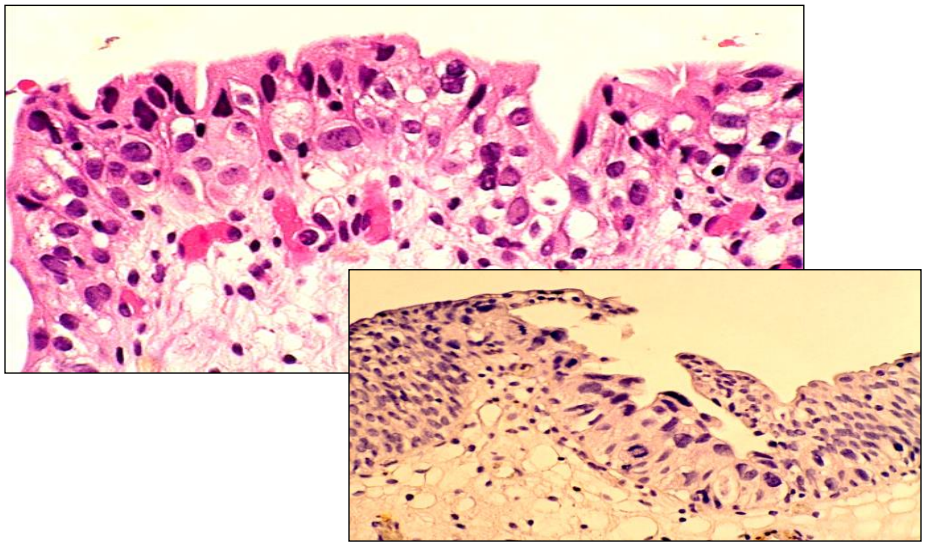
- Small cell CIS
- Large cell CIS (Giant cells CIS)
- “Denuding cystitis”and “clinging CIS”
- Undermining (lepidic) growth
- Pagetoid CIS
- CIS involving von Brunn’s nests/Cystitis cystica
- CIS with microinvasion
- CIS with squamous or glandular diff.

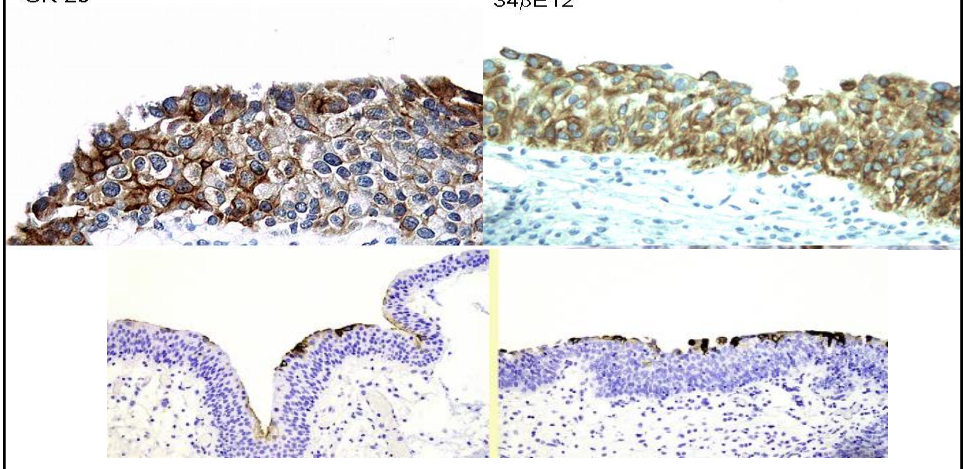


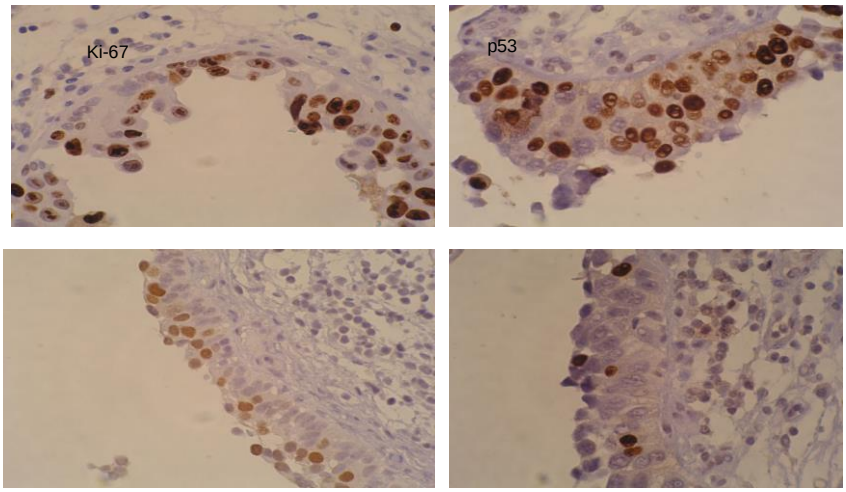








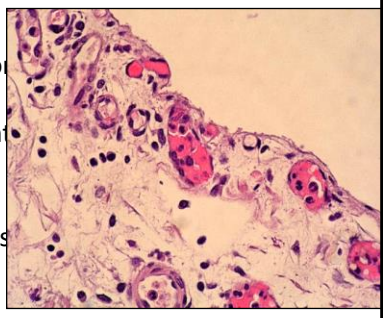

CK 20
34βE12

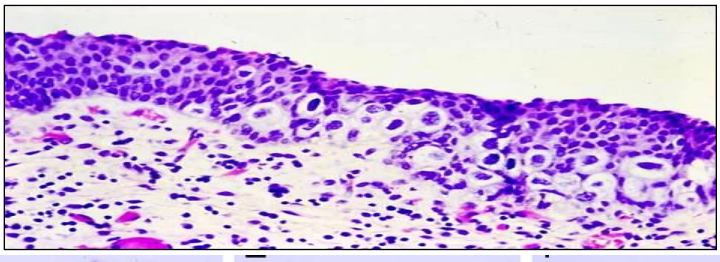


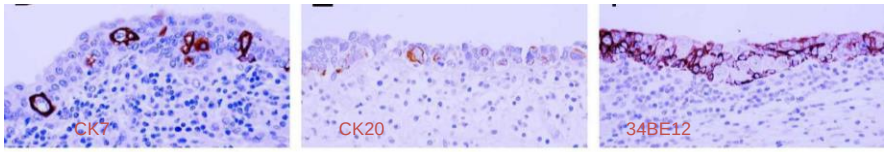
CIS: Clinical Significance of Morphologic Variations

DENUDING CYSTITIS

- False negative bx?
- Recommend Cytology, deeper sectioning>>vo
  Brunn Nests?
- Of patients with a denuded biopsy subsequen
  CIS was diagnosed in:
- 19% of patients with no history of CIS
- 31% of patients with known urothelial neoplas
- 54% of patients who had a previous diagnosis
  CIS

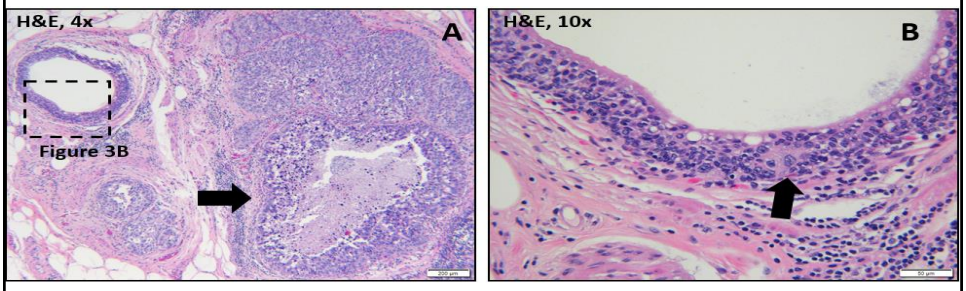


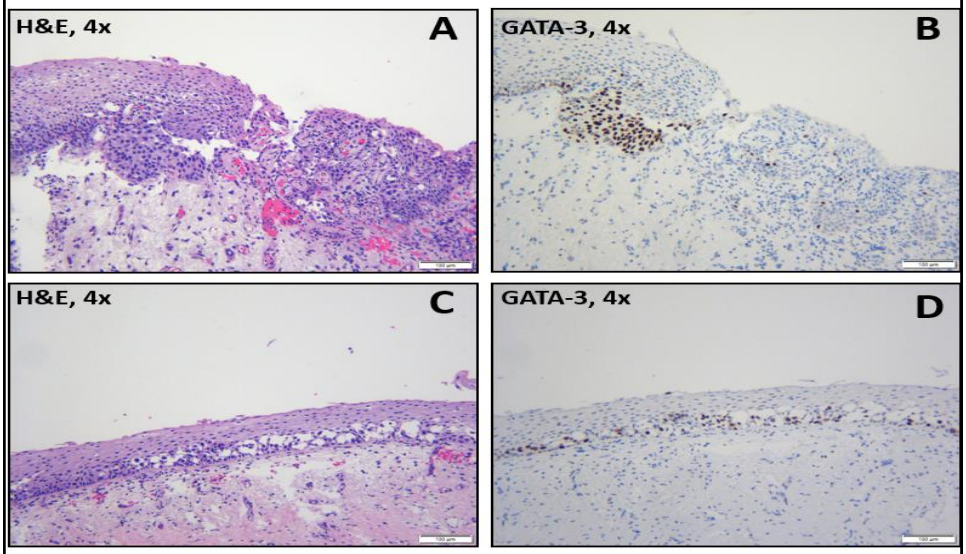




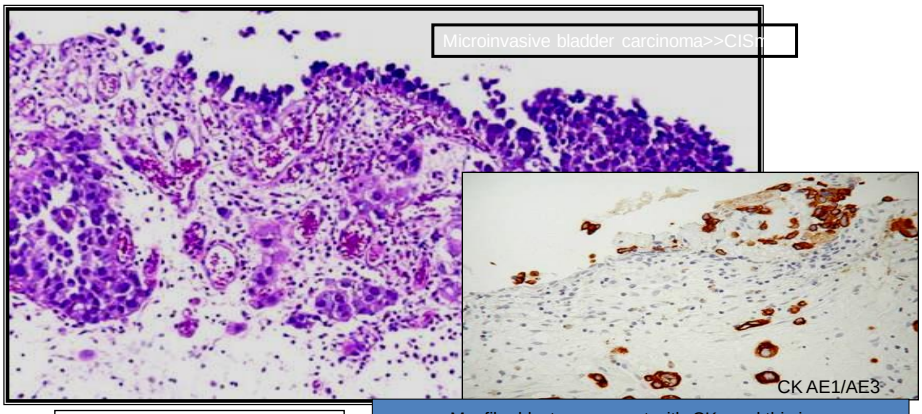
Pagetoid CIS
Clinical Significance (N=11)

- 14% cases of pagetoid CIS
- Mostpatients were male (*n*=10) 31 to 78 years
- The lesion can be present with primary (isolated) (*n*=2) or secondary (concomitant) (*n*=9) CIS.
- 64% NED 2-5 years
- Pagetoid CIS is usually a focal lesion occurring in a *clinical and histological setting of conventional CIS*
- Treated in the same way as cCIS
- Same progression and survival rates as cCIS
- A panel of immunostains including CK7+/CK20+/TM+ may assist in differentiating urothelial pagetoid CIS from extramammary Paget disease >>CK7+/CK20–.





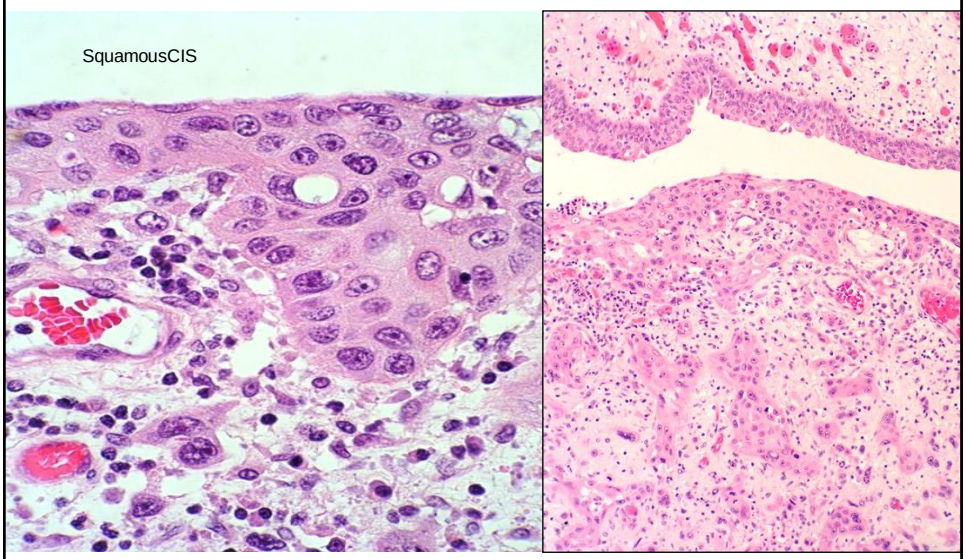
- PAGETOID TUMORS
- Paget disease-Vulva
  - CK7+, CK20-, MUC5AC+, GCDFP-15+, CEA+, EMA+
- Pagetoid prostate adenocarcinoma
  - PSA+. PSMA+, PAP+
- Pagetoid urothelial carcinoma
  - CK7+, CK20+, Uroplakin+
- Pagetoid melanoma
  - HMB45+, Melan A+



- <5mm
- <2mm
- Less 20 invading cells from stroma-epithelial interface

Myofibroblasts may react with CKs and this is a potential diagnostic pitfall

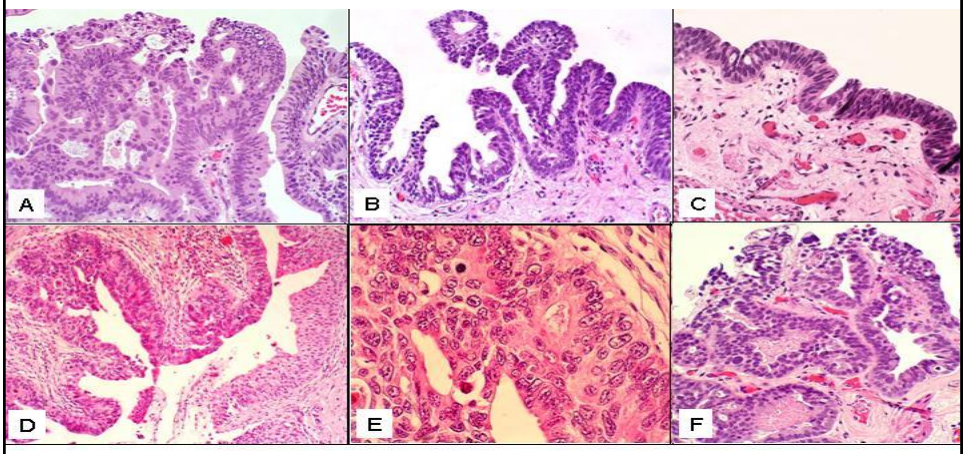
*FARROW: **34%** CISmic (5.8% LN metastases)*

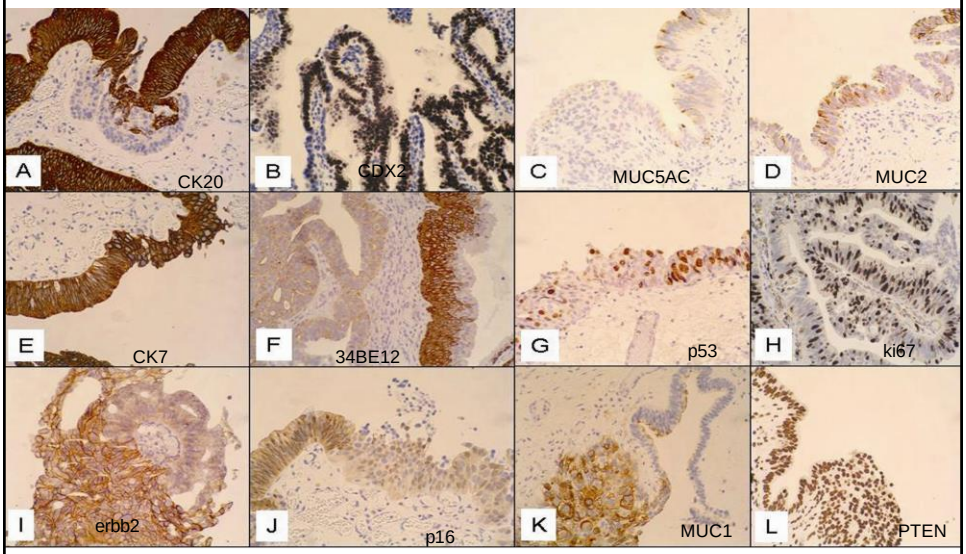


Squamous cell carcinoma in situ

- A recent report on 11 patients:
- 3 patients with *invasive squamous cell carcinoma at intervals of 2, 3, and 4 months*
- 1 had invasive *UC with squamous* features in cyp at 12 months
- 1 had squamous cell CIS at 10 months
- 1 had high-grade urothelial carcinoma (not otherwise specified) at re-biopsy at an interval of 6 months
- 1 had no evidence of disease at 8 month. *Guo&Epstein*

- HPV DNA was detected in 1 case of squamous cell CIS. [*Lagwinski*]
- Enhanced expression of EGFR>>therapeutic target. [*Lagwinski*].





Flat urothelial carcinoma in situ of the bladder with glandular differentiation☆,☆☆

Antonio Lopez-Beltran MD, PhD[a,*], Rafael E. Jimenez[b], Rodolfo Montironi[c], Carlo Patriarca[d], Ana Blanca[a], Carmen L. Menendez[e], Ferran Algaba[f], Liang Cheng[g]

MUC1core was negative in all cases. We concluded that urothelial carcinoma in situ with glandular differentiation is a variant of carcinoma in situ that follows the natural history of conventional urothelial carcinoma in situ. The immunophenotype suggests urothelial origin with the expression of MUC5A and CDX2 as signature for glandular differentiation.

Hum Pathol, 2011

None developed pure infiltrating Adca

Carcinoma In situ

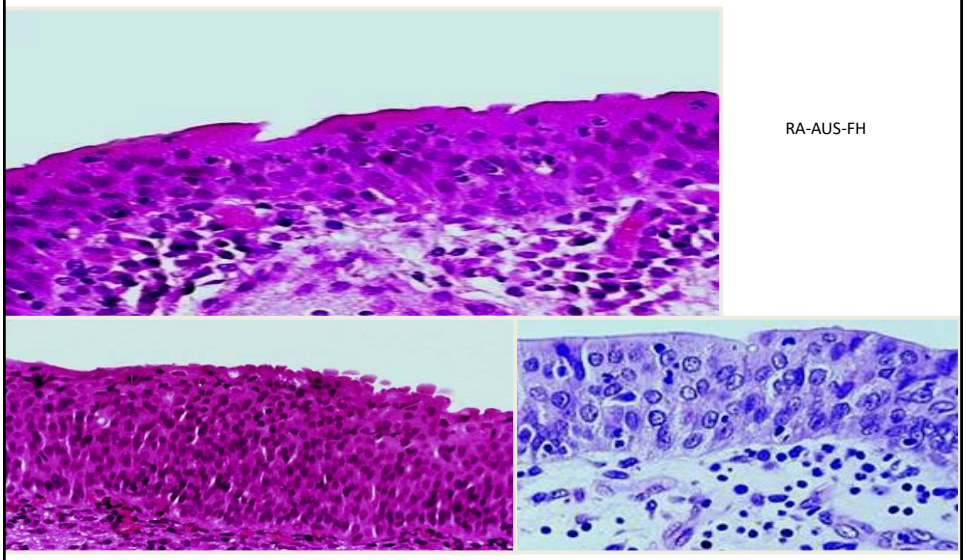
MORPHOLOGICAL EXPRESSIONS OF CIS:

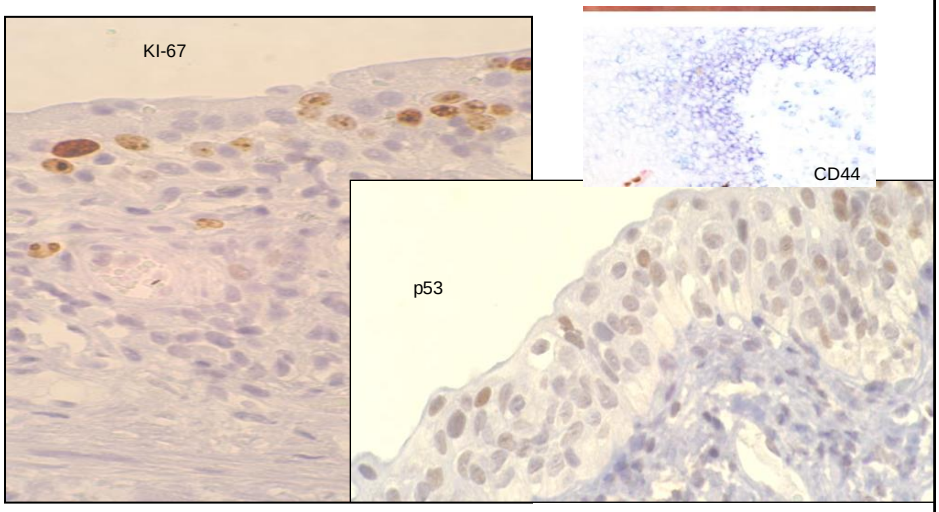
DO THEY HAVE ANY CLINICAL VALUE?

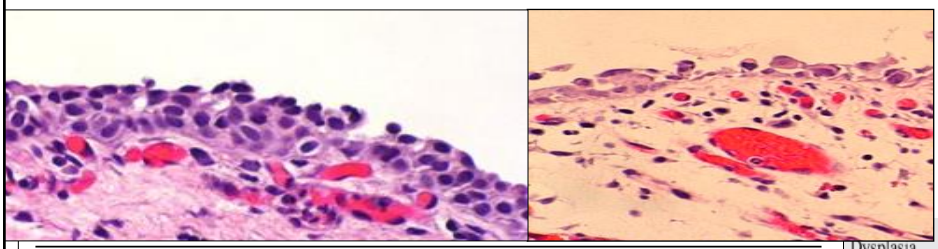
NO¡¡¡

- Awareness of the histologic diversity by pathologist will facilitate the diagnosis of *CIS avoiding unnecessary work up* for patients.
- **Pathology report: urothelial CIS with no specific mention of the morphologic pattern**

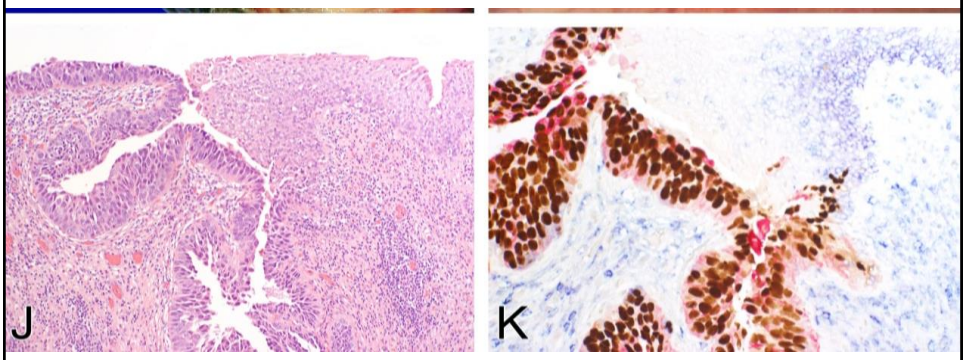
CIS: Pathologic Differential Diagnosis


RA-AUS-FH


KI-67
CD44
p53



	Normal urothelium	Reactive atypia	Carcinoma *in situ*	Dysplasia
Cytokeratin 20	Umbrella cells	Umbrella cells	Full thickness	Deep layers
CD44	Basal and parabasal cells	All cell layers	Residual normal basal cells of the normal urothelium	Absent
p53	Negative	Negative	Full thickness	Positive



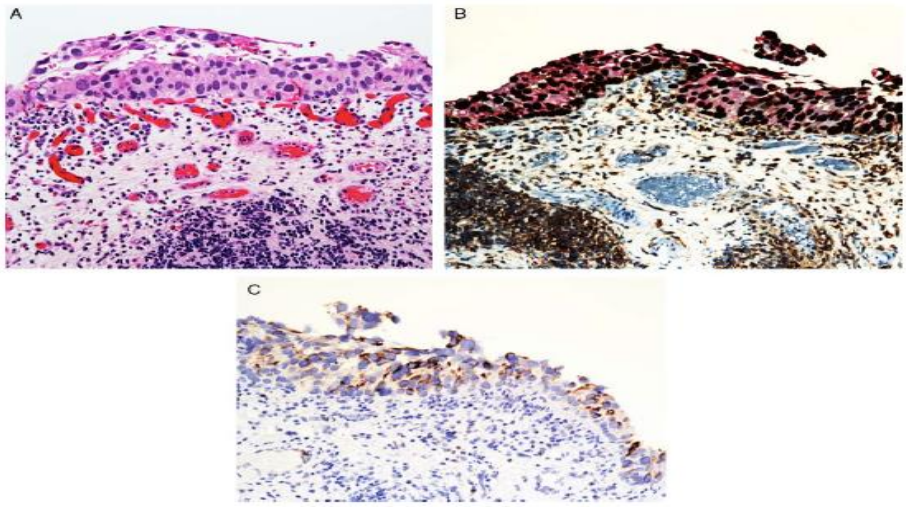
Uro-3/Urothelial CIS

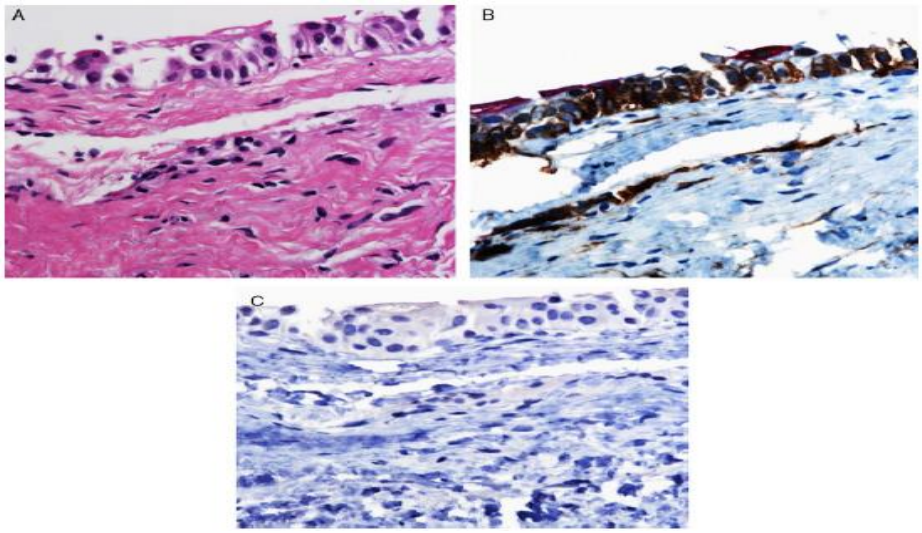
Utility of a Triple Antibody Cocktail Intraurothelial Neoplasm-3 (IUN-3-CK20/CD44s/p53) and α-Methylacyl-CoA Racemase (AMACR) in the Distinction of Urothelial Carcinoma In Situ (CIS) and Reactive Urothelial Atypia

AJSP, 2013

TABLE 2. Summary of the Immunohistochemistry Results Using the IUN-3 Cocktail

Diagnosis	No. Cases	IUN-3 Malignant (n [%])	IUN-3 Indeterminate (n [%])	IUN-3 Reactive (n [%])	AMACR (n [%])
CIS nontreated	43	36 (84)	7 (16)	0	14/18 (78)
CIS posttherapy	24	17 (71)	7 (29)	0	4/8 (50)
Reactive/benign	35	0	0	35 (100)	0/19 (0)
Reactive posttherapy	33	0	6	25 (81)	0/5 (0)

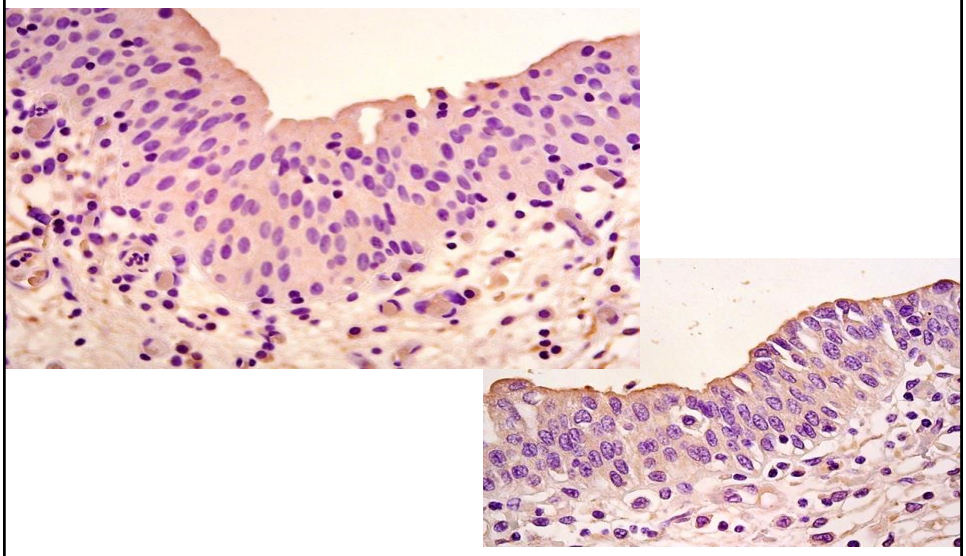


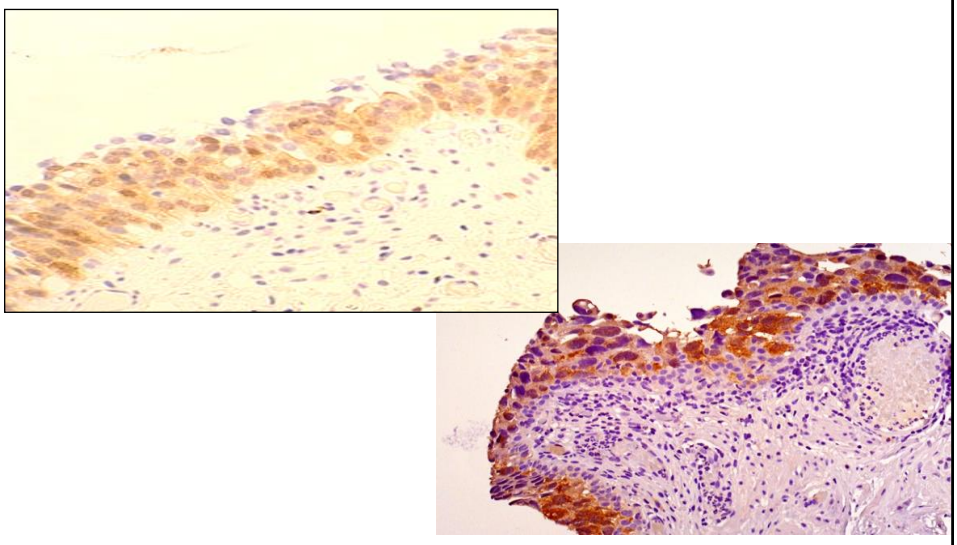


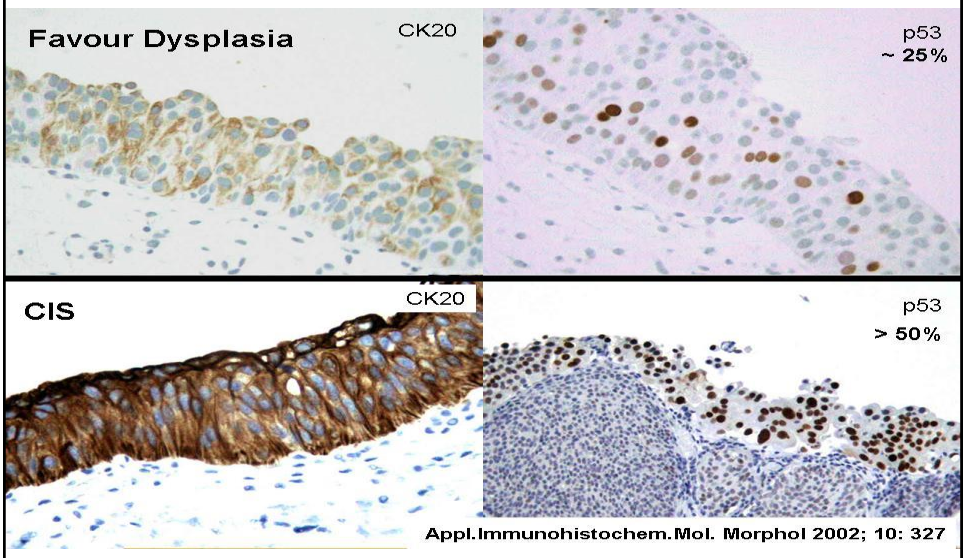
Immunohistochemical features of selected flat intraepithelial lesions of the urinary bladder

	Normal	Simple hyperplasia	Reactive atypia	Atypia of unknown significance	Dysplasia	Urothelial carcinoma in situ
CK20	Limited to umbrella cells	Limited to umbrella cells	Limited to umbrella cells	Limited to umbrella cells	Deep layers	Full-thickness expression
CD44	Limited to basal cells	Limited to basal cells	Increased reactivity in all cell layers	Increased reactivity in all cell layers	Absent	Absent
p53	Often negative	Maybe positive	Maybe positive	Maybe positive	Often positive	Positive
p16	Absent	Unknown	Absent	Unknown	Often positive	Positive

Cheng, Lopez-Beltran et al







Marker	Reactive urothelium	Urothelial carcinoma in situ
CD44	Increased reactivity in all cell layers	Absent to rare basal cells
P53	Absent	Positive, frequently all cell layers
CK20	Limited to umbrella cells	Aberrant expression through all cell layers

Best Practices Recommendations in the Application of Immunohistochemistry in Diagnostic Urologic Pathology Report from the International Society of Urologic Pathology Consensus Conference

Mahul B. Amin, Kiril Trpkov, Antonio Lopez-Beltran et al

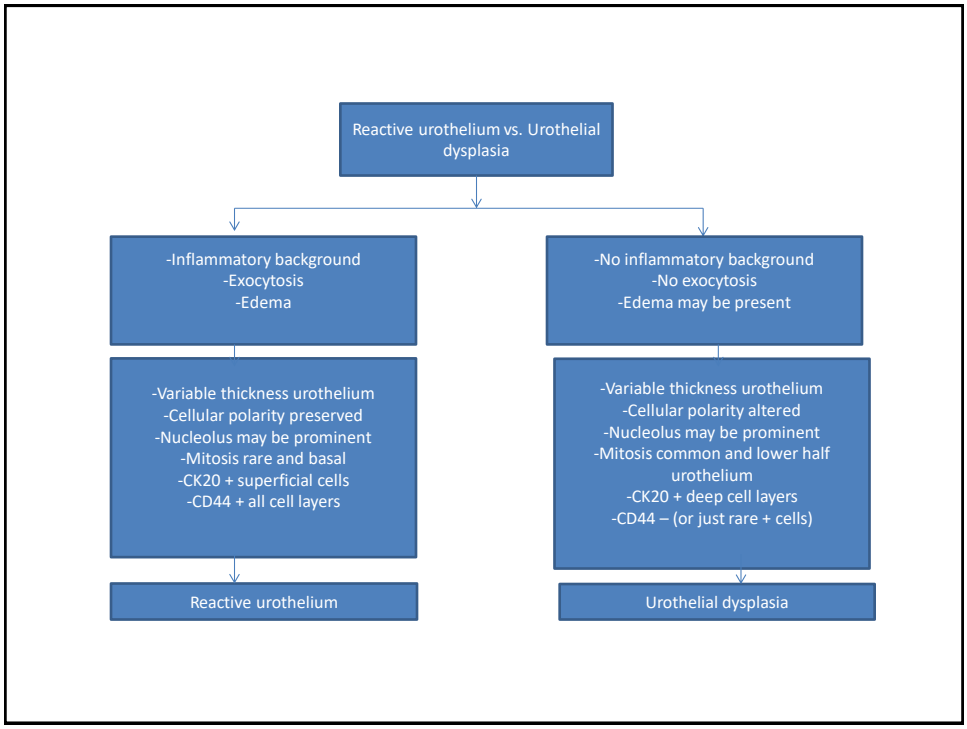
AJSP 2014

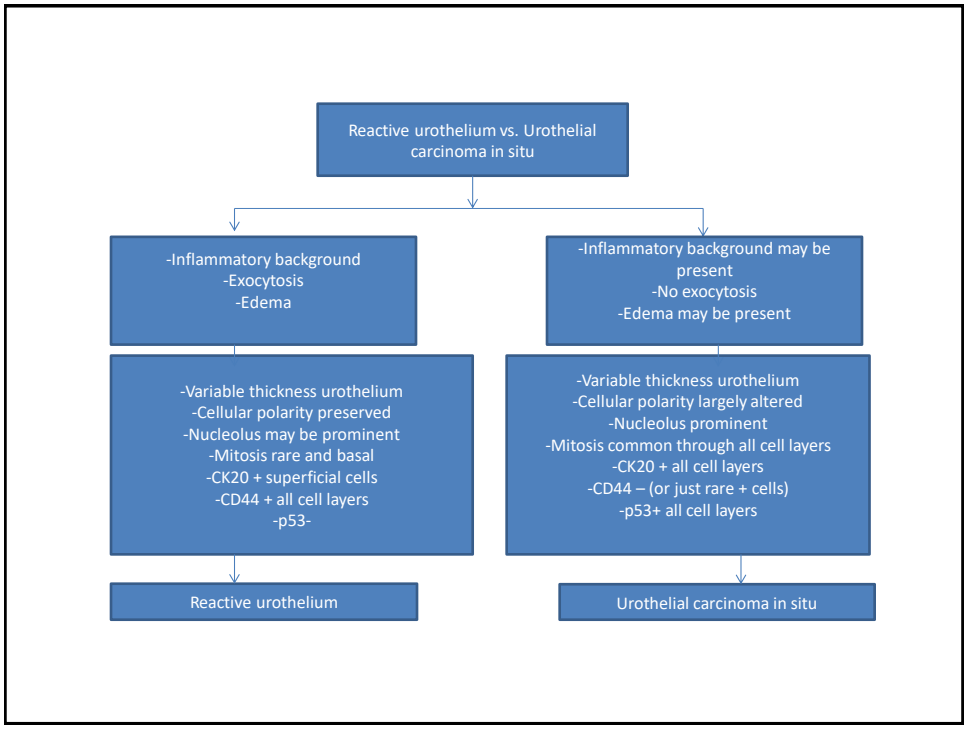
ISUP Recommendations (consensus**):**

- Morphology remains the gold standard in this differential diagnosis
- At best, the IHC panel of CK20/p53/CD44(s) has potential utility
- Is variably used and has limitations

- The immunostaining pattern must be interpreted with strict morphologic correlation
- Overreliance on IHC may be misleading, particularly in the post-treatment setting.
- IHC has no role in the distinction of dysplasia versus CIS

Limited data on FISH UroVysion, p16,HER2, Racemase and others.
Ki67 is not recommended since it may be present in both CIS and reactive atypia.


Reactive urothelium vs. Urothelial dysplasia
-Inflammatory background
-Exocytosis
-Edema
-No inflammatory background
-No exocytosis
-Edema may be present
-Variable thickness urothelium
-Cellular polarity preserved
-Nucleolus may be prominent
-Mitosis rare and basal
-CK20 + superficial cells
-CD44 + all cell layers
-Variable thickness urothelium
-Cellular polarity altered
-Nucleolus may be prominent
-Mitosis common and lower half urothelium
-CK20 + deep cell layers
-CD44 – (or just rare + cells)
Reactive urothelium
Urothelial dysplasia


Reactive urothelium vs. Urothelial carcinoma in situ
-Inflammatory background
-Exocytosis
-Edema
-Inflammatory background may be present
-No exocytosis
-Edema may be present
-Variable thickness urothelium
-Cellular polarity preserved
-Nucleolus may be prominent
-Mitosis rare and basal
-CK20 + superficial cells
-CD44 + all cell layers
-p53-
-Variable thickness urothelium
-Cellular polarity largely altered
-Nucleolus prominent
-Mitosis common through all cell layers
-CK20 + all cell layers
-CD44 – (or just rare + cells)
-p53+ all cell layers
Reactive urothelium
Urothelial carcinoma in situ

MIMICS OF UROTHELIAL FLAT NEOPLASIA

Therapies causing "cellular atypia" in the urothelium

Systemic cyclophosphamide

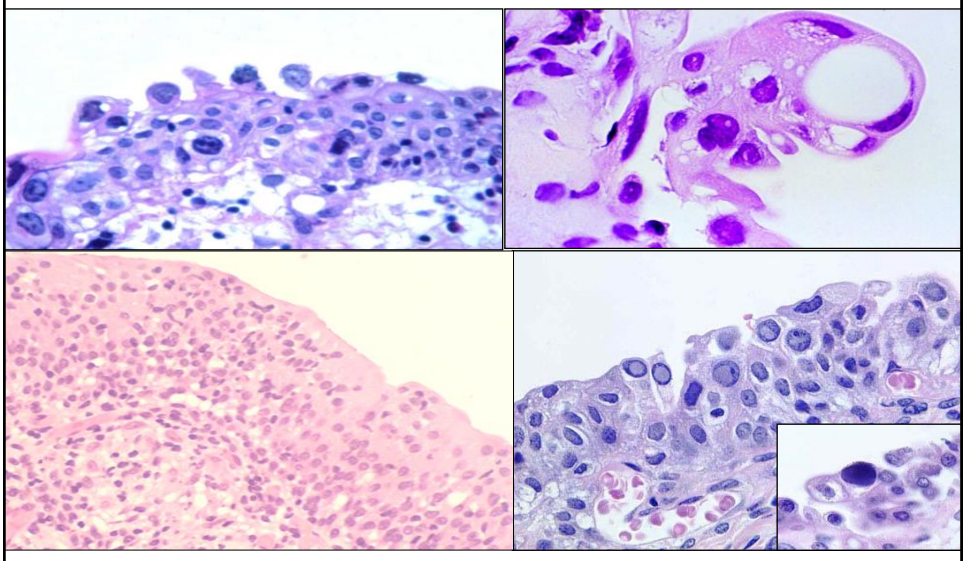
- Necrosis of the urothelium
- Large, bizarre nuclei with coarse chromatin
- Atypical form of regeneration
- Small-to-medium-sized nucleoli

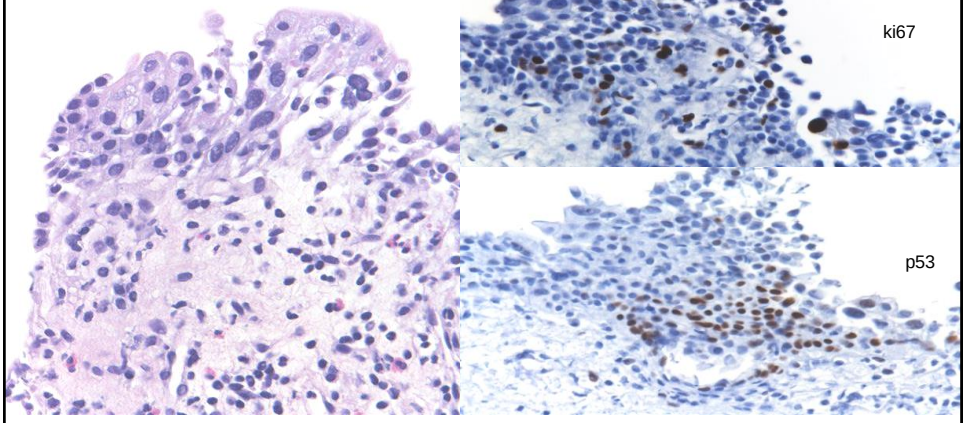
Reactivation of polyomavirus infection
owing to systemic cyclophosphamide therapy
External beam radiotherapy
Intravesical therapy
-Immunotherapy: bacillus Calmette-Guering, interferon-α, others
-Chemotherapy: thiotepa, mitomycin C

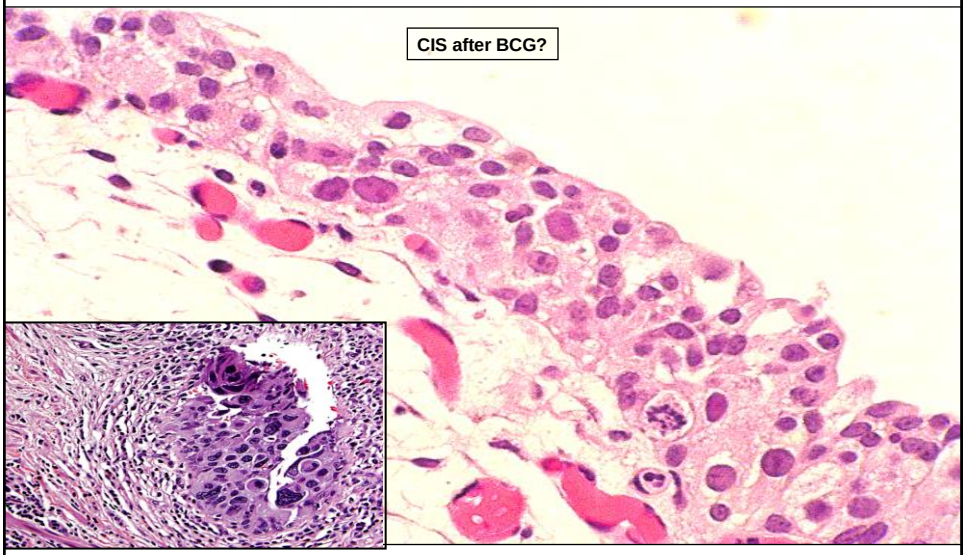
- Denudation of the surface epithelium
- Profound effects on the surface umbrella urothelial cells
- Less significant abnormalities in the deeper layers of the urothelium
- Nuclear and cytoplasmic vacuolization
- Low nuclear-to-cytoplasmic ratio

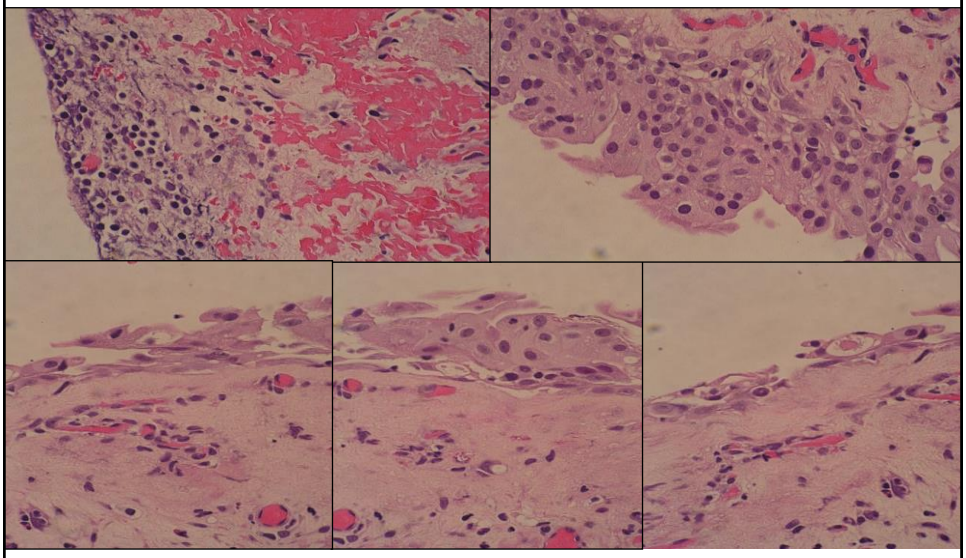
Other chemotherapeutic agents

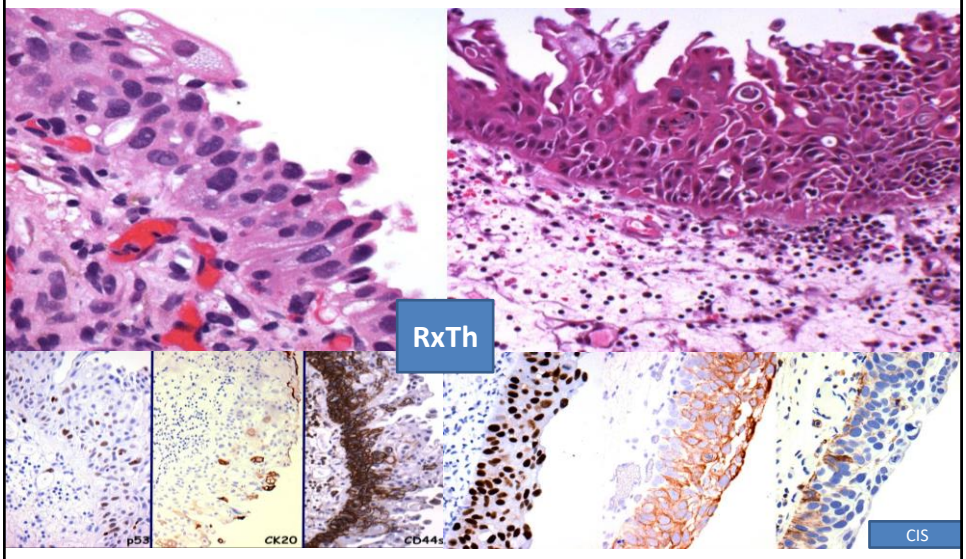
Lopez-Beltran et al Histopathology, 20017




ki67
p53


CIS after BCG?



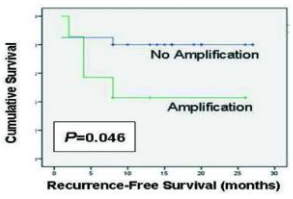

RxTh
p53
CK20
CD44s
CIS

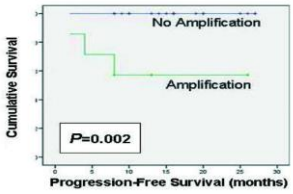
Summary

Histologic parameters useful in the evaluation of flat lesions with atypia

- Thickness of urothelium
- Polarity
- Cytoplasmic clearing
- Nuclear size
- Nuclear crowding
- Nuclear borders including notches
- Nuclear chromatin distribution
- Nucleoli
- Mitoses
- Number of cells/intraurothelial background
- Intercellular cohesion
- Accompanying inflammation
- Neovascularity and inflammation at the base
- of the lesion

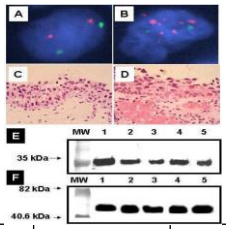
Other predictive/pronostic biomarkers





Cyclin D3 (CCND3) gene amplification

Lopez-Beltran et al 2011



Variable	RR	95% CI	*P*-value
Recurrence-free survival			
Cyclin D3 gene amplification	3.159	0.785-12.704	0.105
Type of CIS (primary vs. secondary)	24.535	0.4-154.062	0.057
Progression-free survival			
Cyclin D3 gene amplification	**61.503**	1.1-274.710	0.041
Type of CIS (primary vs. secondary)	23.945	0.9-240.458	0.065

Take-Home Points

- Morphology remains as the clinical gold standard for flat lesions.
- An IHC panel of CK20/CD44/p53 has clinical potential in selected cases
- Ki67 is not recommended in differential diagnosis
- Amon others, p16 and/or Racemase IHC have potential as “single marker” to separate reactive changes (-) from CIS (+), but need further validation.
- Cyclin D3 gene amplification has potential as predictive biomarker in CIS.
- Genomic studies should define prognostic subgroups within CIS.

¡THANKS !