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PATHOLOGY of urothelial carcinoma *in situ*

November 19, 2021

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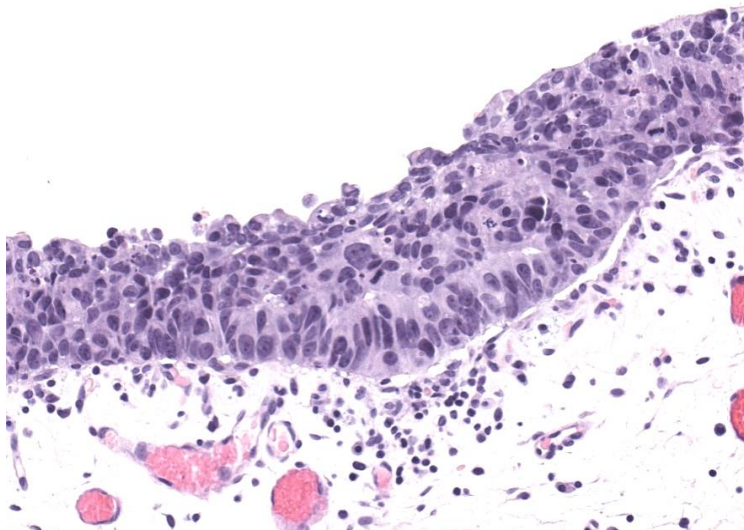


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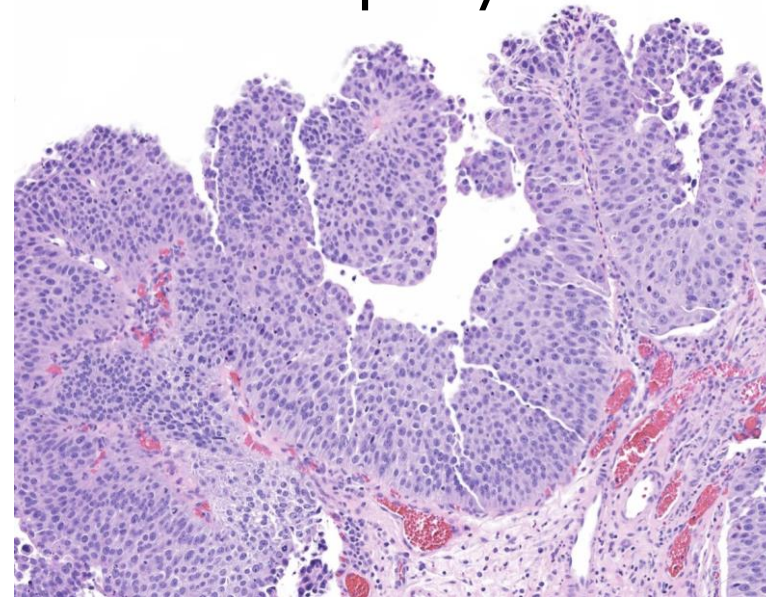
Urothelial Carcinoma *in situ* (UCIS)

- A flat urothelial lesion (non-papillary)
 - Surface urothelium contains cytologically malignant cells
 - Synonym: *High grade intraurothelial neoplasia*
- UCIS - high grade (by definition)
 - No low grade UCIS

Flat (in situ)



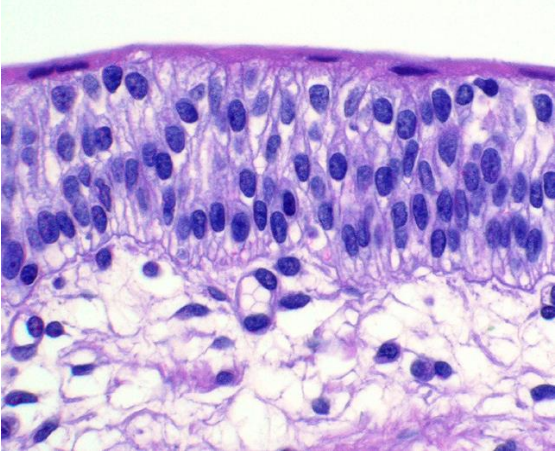
Papillary



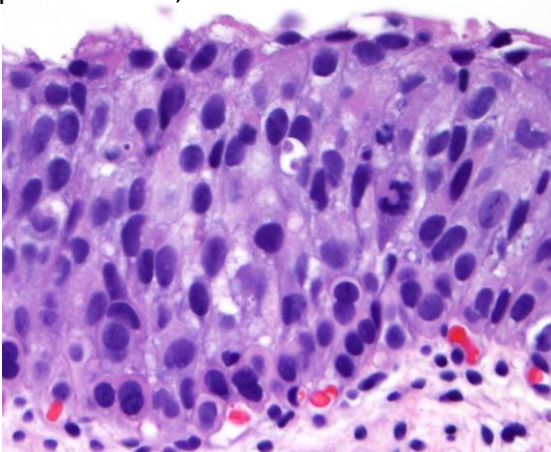
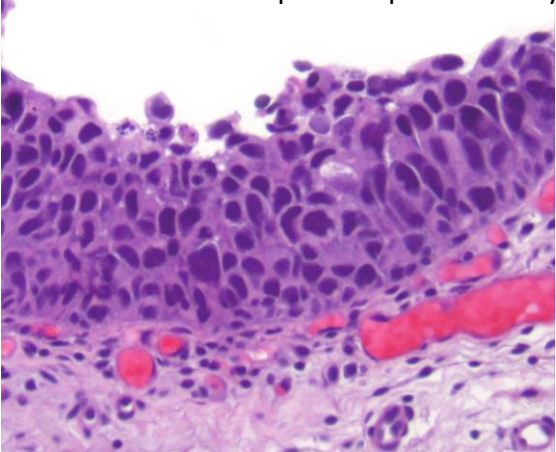
Flat Urothelial Carcinoma (*in situ*)

Histologic criteria and spectrum of morphology

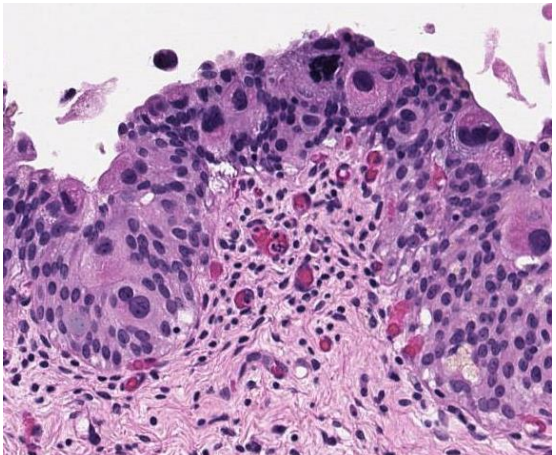
Normal urothelium



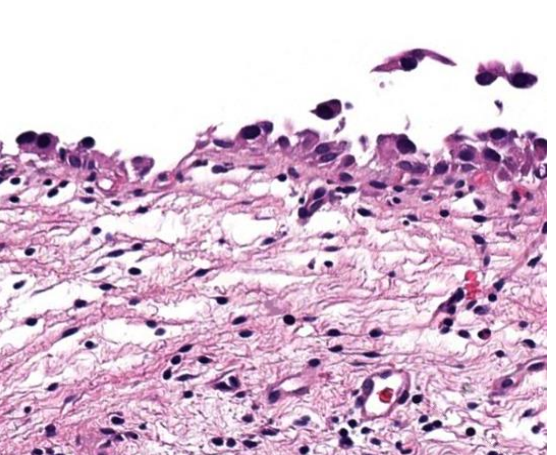
Nuclear pleomorphism and hyperchromasia, visible mitoses



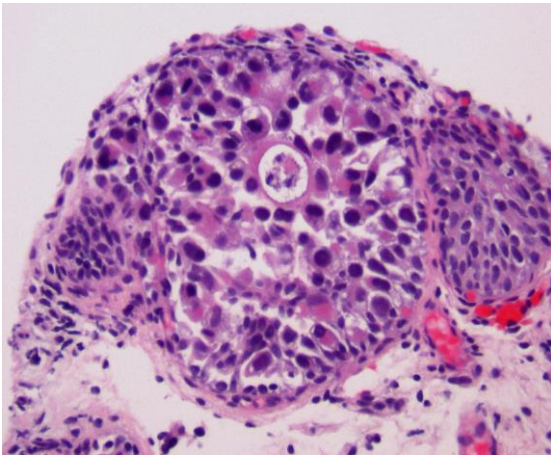
Pagetoid/undermining spread



Discohesive tumor cells



Involvement of Brunner's nests



Urothelial Carcinoma *in situ* (UCIS)

- Pure form is rare , 1-3% of newly diagnosed UC
 - *Carcinoma paradoxicum*
 - More common with/adjacent to, or subsequent to papillary UC
 - Primary CIS: high grade malignant flat lesion at initial TUR without any prior or concomitant papillary tumor
 - Secondary CIS: flat CIS concomitant with or after a prior papillary tumor

Table 3. Multivariate analysis of progression to cT1 or higher invasive disease and cT2 or higher muscle invasive disease adjusted for RC before progression

Variables*	cT1 or Higher, or RC		cT2 or Higher, or RC	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Primary vs secondary CIS	1.37(1.05–1.81)	0.020	1.72(1.27–2.33)	0.001
Age	1.01(0.99–1.02)	0.178	1.01(0.99–1.02)	0.568
Gender	1.18(0.86–1.63)	0.300	1.15(0.80–1.65)	0.455
BCG response	1.12(0.85–1.46)	0.421	1.03(0.76–1.39)	0.865

* Excluding 84 patients due to progression before BCG or missing data.

Chade DC et al. *J Urol.* 2010

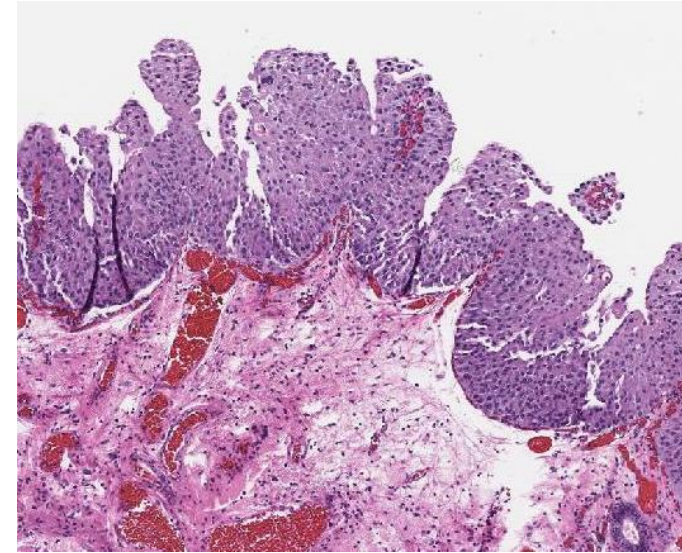


Urothelial Carcinoma *in situ*

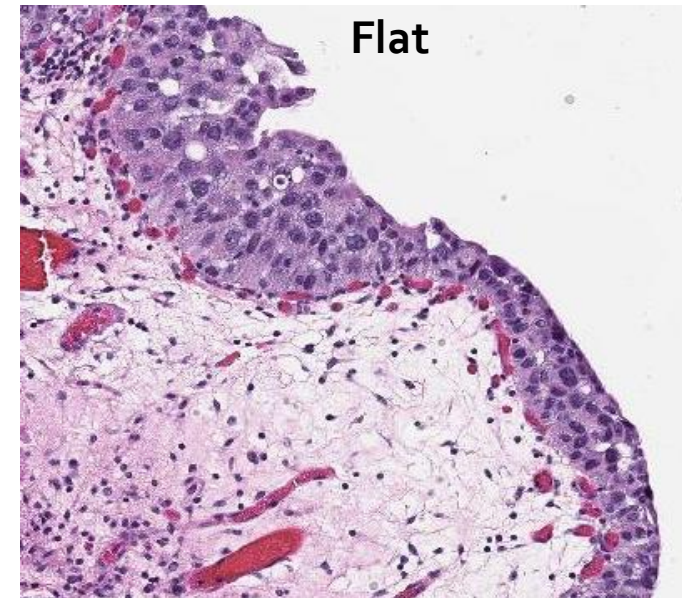
Flat and papillary



Papillary



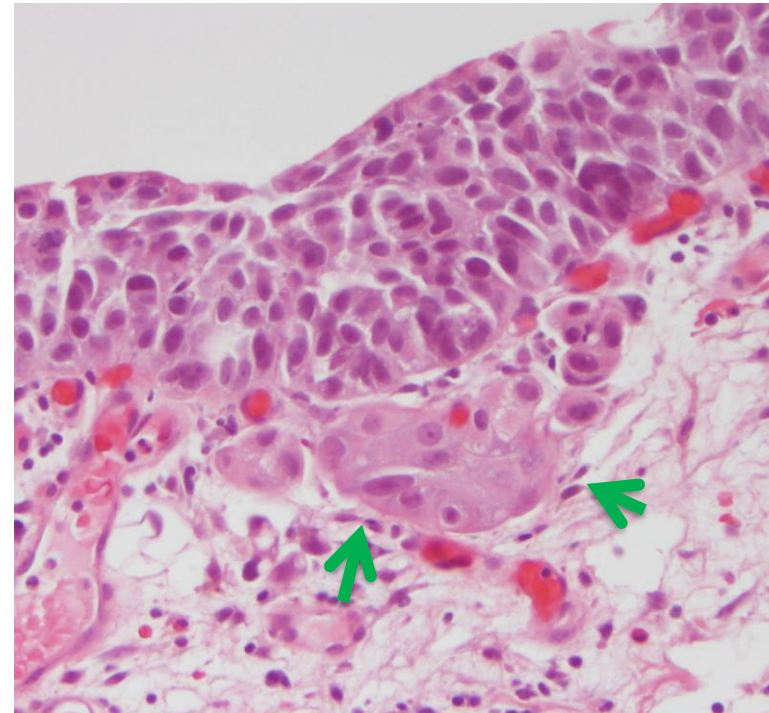
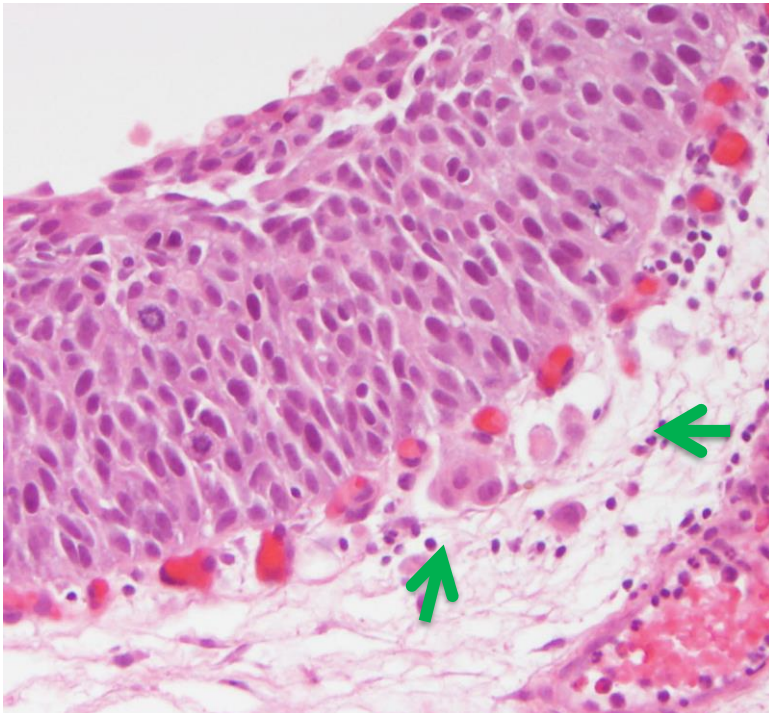
Flat



Flat Urothelial Carcinoma (*in situ*), with invasion

UCIS is a documented precursor of invasive cancer

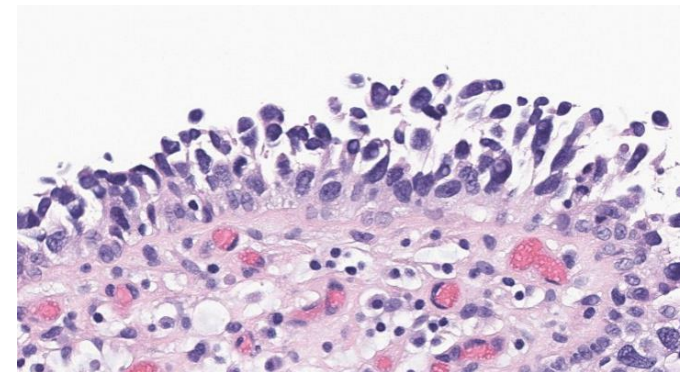
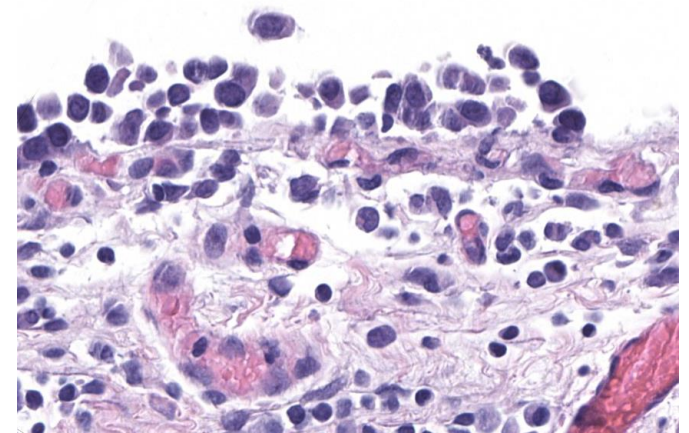
- Commonly in association with invasive disease (45%-65%)



Role of urine cytology (Paris System)

UCIS is associated with high rate of positive urine cytology (>80%)

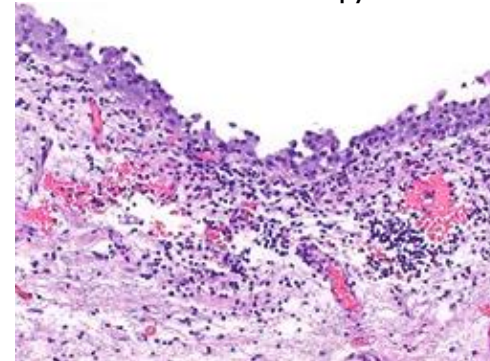
- I. Adequacy of urine specimen (non-diagnostic or unsatisfactory)
- II. Negative for high grade urothelial carcinoma (negative)
- III. Atypical urothelial cells
- IV. Suspicious for high grade urothelial carcinoma (suspicious) (<10 cells)**
- V. High grade urothelial carcinoma (HGUC)**
- VI. Low grade urothelial neoplasia (LGUN)
- VII. Other malignancies, primary and metastatic and miscellaneous lesions



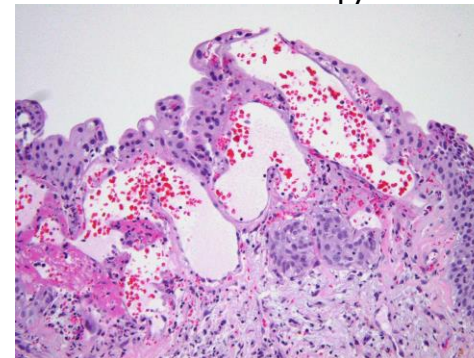
Flat Lesions with Atypia: Problems and Pitfalls

- Variability of normal urothelium
- Inflammatory atypia
- Post treatment atypia
- Extensive denudation

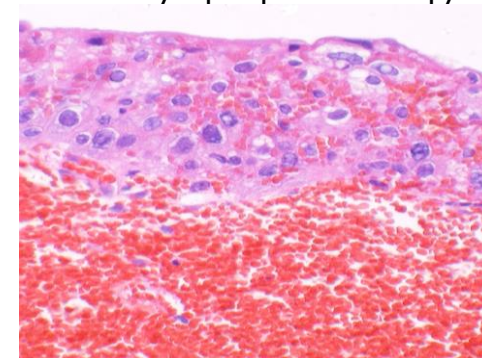
Post-BCG therapy



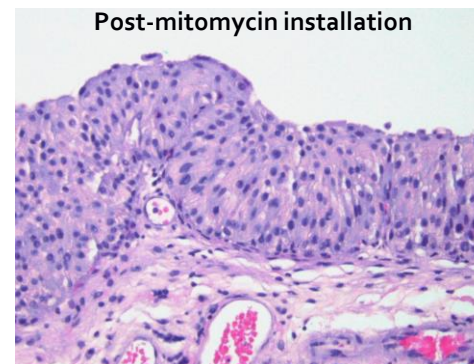
Post-radiation therapy



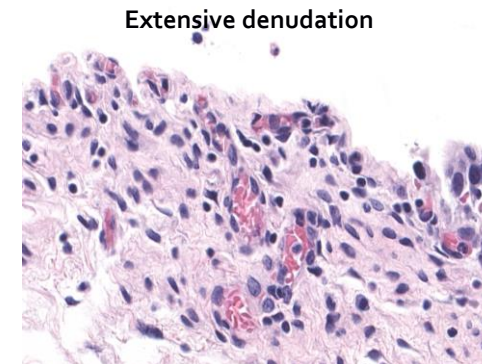
Post-cyclophosphamide therapy



Post-mitomycin installation



Extensive denudation



Flat Urothelial Lesions

Reproducibility

<u>Subset of interest</u>	<u>Kappa statistic</u>	<u>Degree of agreement</u>
• Normal	0.484	Good
• Reactive atypia	0.361	Fair
• Atypia ? dysplasia	0.317	Fair
• L.G. dysplasia	0.174	Poor
• HGD/CIS	0.653	Excellent
<hr/>		
• Non-H.G.D./CIS	0.653	Excellent
• H.G.D./CIS	0.653	Excellent

Amin, M.B., et al., *Intraepithelial lesions of the urothelium: an interobserver reproducibility study with proposed terminology and histologic criteria*. Mod Pathol, 1997. **10**: p. 69A.

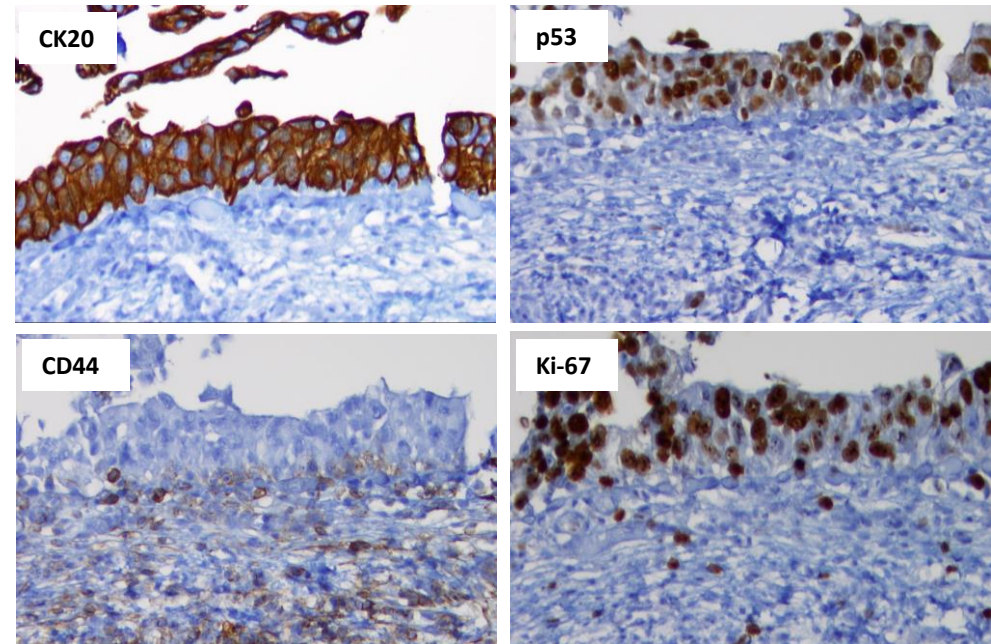
- Role for central pathology review
 - Facilitated by availability of digital pathology capabilities

- Challenging disease for molecular profiling

	n (%)		
	General Pathologists (N = 127)	GU Pathologist 1 (N = 127)	GU Pathologist 2 (N = 127)
Reactive atypia	35 (28)	62 (49)	34 (27)
Atypia of uncertain significance	35 (28)	15 (12)	18 (14)
Low-grade dysplasia	17 (13)	7 (5)	15 (12)
Carcinoma in situ	40 (31)	43 (34)	60 (47)

GU indicates genitourinary; H&E, haematoxylin and eosin.

Lawless ME et al. *Appl Immunohistochem Mol Morphol*. 2018



Conclusions

- Urothelial carcinoma in situ
 - There is a spectrum of morphologic features
 - Can be pure CIS or associated with papillary UC
 - Primary vs. secondary CIS
 - Not a strictly pathologic diagnosis
 - Implications for management and outcome
 - May be diagnostically challenging
 - Interobserver variability
 - Challenges for molecular studies



