

Memorial Sloan Kettering Cancer Center

### PATHOLOGY of urothelial carcinoma in situ

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#### WHO classification of tumours of the urothelial tract

Urothelial tumours Infiltrating urothelial carcino Nested, including large Microcystic Micropapillary Lymphoepithelioma-like	ma 8120/3 nested 8131/3 8082/3	Neuroendocrine tumours Small cell neuroendocrine carcinoma Large cell neuroendocrine carcinoma Well-differentiated neuroendocrine tumour Paraganglioma	8041/3 8013/3 8240/3 8693/1
Sarcomatoid Giant cell Poorly differentiated Lipid-rich	<i>Non-invasive urot</i> Urothelial carcino	<i>helial neoplasms</i> ma in situ	8720/3 8720/0
Clear cell Non-invasive urothelial Urothelial carcinoma in Non-invasive papillary u	Non-invasive pap carcinoma, lov	illary urothelial w-grade illary urothelial	8900/3 8890/3 9120/3 8825/1
carcinoma, low-grac Non-invasive papillary u carcinoma, high-gra Papillary urothelial neor low malignant poten Urothelial papilloma Inverted urothelial papil Urothelial proliferation c malignant potential Urothelial dysplasia	carcinoma, hig Papillary urothelia	gh-grade Il neoplasm of	8714/0 8714/3 8815/1 8890/0
	Urothelial papillor Inverted urothelia	potential na I papilloma	9120/0 9580/0 9540/0
Squamous cell neopla Pure squamous cell car Verrucous carcinoma Squamous cell papillor	Urothelial prolifera malignant pote	ation of uncertain ential	8140/3
Glandular neoplasms Adenocarcinoma, NOS	Urothelial dysplas		
Enteric Mucinous Mixed	8144/3 8480/3 8140/3	Urothelial tumours of the urethra	
Villous adenoma Urachal carcinoma	8261/0 8010/3	The morphology codes are from the International Classifica for Oncology (ICD-O) [917A]. Behaviour is coded /0 for be /1 for unspecified, borderline, or uncertain behaviour; /2 for situ and grade III intrapitibilial population and /2 for mailed	ation of Diseases nign tumours; carcinoma in
Tumours of Müllerian type Clear cell carcinoma Endometrioid carcinoma	8310/3 8380/3	The classification is modified from the previous WHO class taking into account changes in our understanding of these	ification {756A}, lesions.



#### Eur Urol. 2016 Jul;70(1):106-119

# **Urothelial Carcinoma** *in situ* (UCIS)

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



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### **Flat Urothelial Carcinoma (in situ)** Histologic criteria and spectrum of morphology

Normal urothelium



Pagetoid/undermining spread

Nuclear pleomorphism and hyperchromasia, visible mitoses



Discohesive tumor cells



Involving von Brunn 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
    - <u>Primary CIS</u>: high grade malignant flat lesion at initial TUR without any prior or concomitant papillary tumor
    - <u>Secondary CIS</u>: flat CIS concomitant with or after a prior papillary tumor

Table 3. Multiv	rariate analysis of progression to cT1 or higher invasive disease
and cT2 or hig	her muscle invasive disease adjusted for RC before progression

Variables*	cT1 or Higher, or RC		cT2 or Higher, or RC	
Valiables	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

Chade DC et al. J Urol. 2010

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





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### 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)</li>
- 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



#### Flat Urothelial Lesions <u>Reproducibility</u>

	Карра	Degree of
<u>Subset of interest</u>	<u>statistic</u>	<u>agreement</u>
Normal	0.484	Good
<ul> <li>Reactive atypia</li> </ul>	0.361	Fair
• Atypia ? dysplasia	0.317	Fair
<ul> <li>L.G. dysplasia</li> </ul>	0.174	Poor
• HGD/CIS	0.653	Excellent
Non-H.G.D./CIS	0.653	Excellent
11.0.0./CI3	0.053	LACENEIIL

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



