Uroplakin III
Invasive micropapillary carcinoma
Invasive micropapillary carcinoma
Micropapillary area of urothelial carcinoma in situ
International consultation on urologic disease [ICUD]: micropapillary urothelial carcinoma  Amin MB et al. Mod Pathol 2015;28:612-630

- Clinical implications: controversy over role of early cystectomy
  - recommended to document the percentage of micropapillary component
- Distinctive molecular features: ERBB2 mutation/amplification
Micropapillary bladder cancer: a review of the MD Anderson Cancer Center experience of 100 consecutive patients  Kamat AM et al. Cancer 2007;110:62-7

- Range of stages encountered
- Bladder-preserving therapy attempted with BCG in patients with low stage disease (<T2)
- 67% progressed and 22% developed metastases
- For 55 patients with >pT2 and <pT4 tumours who had cystectomy, 23 had intravesical therapy with delayed cystectomy and 32 had immediate cystectomy
- Stage distribution similar in the 2 cystectomy groups
- For group that had delayed cystectomy following neoadjuvant therapy 32% were alive at 5 years
- For group having immediate cystectomy 71% were alive at 5 years
**HER2** gene amplification occurs frequently in the micropapillary variant of urothelial carcinoma: analysis by dual color *in situ* hybridisation

Ching CB *et al.* *Mod Pathol* 2011;24:1111-19

- 68% of 19 cases of micropapillary urothelial carcinoma had 2+ or 3+ immunohistochemistry for HER2 protein
- Gene amplification was present in 42% of 19 cases with 100% correlation with 2+ or 3+ protein expression
- 53% of samples had aneusomy of chromosome 17 (*HER2* is at 17q11-21)
- Previous investigations on conventional urothelial carcinoma found an inconsistent and often low frequency of *HER2* gene amplification with no strong correlation between protein expression and gene amplification
International consultation on urologic disease [ICUD]: variants not reviewed in WHO 2004  Amin MB et al. Mod Pathol 2015;28:612-630

- Large nested variant
- Urothelial carcinoma with small tubules
- Undifferentiated carcinoma with rhabdoid cells
- Urothelial carcinoma with chordoid features
Nested variant urothelial carcinoma
Large cell nested variant of urothelial carcinoma: 23 cases mimicking von Brunn nests and inverted growth pattern of noninvasive papillary urothelial carcinoma


- Large irregular but cytologically bland infiltrative nests
- 19/23 cases had a surface papillary component; 17 had a low grade and 2 had a high grade surface component
- 20/23 cases invaded muscularis propria
- 4 cases had no stromal reaction
- 3/17 with follow up developed metastases
- Distinguished from inverted growth pattern Ta urothelial carcinoma by (1) muscularis propria invasion and/or (2) irregularly infiltrating nests and/or (3) a stromal reaction to the nests
TURBT in 44 year old man
Aspects of the NICE guidance pertinent to diagnosis [from NICE guidelines NG2. Feb 2015 http://www.nice.org.uk/guidance/ng2]

- “Do not substitute urinary biomarkers for cystoscopy to investigate suspected bladder cancer or for follow-up after treatment for bladder cancer, except in the context of a clinical research study”

- “Offer white-light-guided TURBT with one of photodynamic diagnosis, narrow-band imaging, cytology or a urinary biomarker test (such as UroVysion using fluorescence in-situ hybridization [FISH], ImmunoCyt or a nuclear matrix protein 22 [NMP22] test) to people with suspected bladder cancer. This should be carried out or supervised by a urologist experienced in TURBT”
FISH

- Useful in selected groups of patients as adjunct to improve sensitivity of cytology
- Follow up after intravesical therapy to increase the interval between surveillance cystoscopies
- Supportive evidence for equivocal or suspicious cytology
- Improved detection of low-grade upper tract lesions in instrumented samples

[Slide courtesy of Dr Ash Chandra]
UroVysion FISH

- Multicolour FISH developed in 2001
- Uses chromosome enumeration (centromeric) probes for chromosomes 3, 7 and 17 to look for polysomy
- Also uses a locus-specific probe to look for deletion of 9p21(p16)
- Mostly used in cytology especially in follow-up of patients with known bladder cancer
Multi-probe fluorescence in situ hybridisation: prognostic perspectives in superficial bladder cancer.

- 75 patients urine cytology f/u for bladder cancer
- Low risk group: FISH –ve or 9p21 loss and/or CEP3+ve
- High risk group: chromosome 7 or 17 aneuploidy
- 33% low risk cases recurred after mean 30 months; 11% progressed
- 67% high risk cases recurred after mean 17.6 months; 50% progressed
Considerations on the use of urine markers in the management of patients with high-grade non-muscle-invasive bladder cancer. Kamat AM et al. Urol Oncol. 2014;32:1069-77

Value of multicolor fluorescence in situ hybridisation (UroVysion) in the differential diagnosis of flat urothelial lesions


- Study of paraffin-embedded biopsies
- 29 normal biopsies and 86 flat urothelial lesions studied
- Dysplasia had polysomy for at least 1 marker in >50% of cells in 93% of cases
- CIS or invasive carcinoma had polysomy in >90% cells in 91% cases
- Polysomy of at least 1 polysomic marker found in 14% of normal and reactive and 17% of hyperplasia cases
- FISH positive histologically ‘normal’ biopsies were associated with simultaneous high grade urothelial lesions
GATA3 in invasive urothelial carcinoma
GATA3: a multispecific but potentially useful marker in surgical pathology.


- High sensitivity for urothelial and breast (ductal and lobular) confirmed
- High sensitivity for paraganglioma/phaeochromocytoma confirmed with neuroendocrine carcinoma negative
- Renal tumours negative, except for chromophobe carcinoma (51% +ve and oncocytoma (17% +ve)
- Prostate tumours extremely rarely +ve (2%)
- Most cutaneous squamous, basal and skin adnexal tumours +ve; much lower % positivity in non-cutaneous squamous carcinoma e.g. cervix 33%, larynx, 16%, lung 12%.
- Trophoblastic and yolk sac elements of germ cell tumours +ve but not other elements
- Malignant mesothelioma often +ve (58%)
- Some salivary gland carcinomas and pancreatic ductal carcinomas +ve
GATA3 is therefore useful for poorly differentiated tumours in the following situations

- Urothelial versus prostatic adenocarcinoma
- Urothelial versus renal cell carcinoma (other than chromophobe renal carcinoma)
- Paraganglioma/phaeochromocytoma versus neuroendocrine carcinoma
GATA3 expression in paragangliomas: a pitfall potentially leading to misdiagnosis of urothelial carcinoma

So JS and Epstein JI, *Mod Pathol* 2013;26:1365-70

- 12 paragangliomas of bladder and 20 paragangliomas of other sites examined
- At least 2+ positivity in 85% bladder cases and 65% of extravesical paragangliomas
Immunohistochemical evaluation of novel and traditional markers associated with urothelial differentiation in a spectrum of variants of urothelial carcinoma of the urinary bladder  

Paner GP et al.  
*Hum Pathol* 2014;45:1473-82

- In urothelial carcinoma variants (micropapillary, plasmacytoid, clear cell, microcystic), GATA-3 was expressed in 88% cases overall.
- GATA3 expression was lower in cases with squamous differentiation and was negative when >75% squamous differentiation present.
- GATA-3 expressed in 25% -30% lymphoepithelioma-like carcinoma, small cell carcinoma and sarcomatoid carcinoma in this study.
- Data presented on expression of other markers e.g. CK7, CK20 in variant patterns.

- 93% of pure urothelial carcinomas of bladder were GATA3 +ve
- All pure squamous carcinomas of bladder were GATA3 negative
- GATA3 was amongst several markers (CK14, uroplakin III desmoglein 3) that could be of some help in distinguishing squamous from urothelial differentiation in mixed tumours, though correlation of expression was not perfect
Urothelial carcinoma - immunophenotype

- Uroplakin III -/+  
- Uroplakin II +/-  
- GATA3 +  
- CK20 -/+  
- S100P +  
- Thrombomodulin +/-  
- p63 +/-  
- CK7 +/-  
- 34ßE12 +/-  
- CK5/6 +/-  
- [PAX8 -/+]
A newly developed uroplakin II antibody with increased sensitivity in urothelial carcinoma of the bladder Hoang LL, Arch Pathol Lab Med. 2014;138:943-9

- 78% urothelial carcinoma cases +ve across all grades (compared with 56% +ve for uroplakin III)
- Specific when compared with various tissues, incl. prostate and renal carcinoma, 63 colonic carcinoma; 20 lung squamous or adenocarcinoma
Uroplakin II outperforms uroplakin III in diagnostically challenging settings  
Smith SC et al. *Histopathology* 2014;65:132-8

- TMA study
- Similar specificity to uroplakin III with greater sensitivity
- None of the 88 non-urothelial tumours tested were positive for either uroplakin
Uroplakin II

Female 71 years: biopsy of left lung mass. History of cystectomy 10 years ago for urothelial carcinoma. Both tumours thought to be separate primaries radiologically but worth noting that she is a non-smoker. Sent as “probable primary lung cancer”
CK20
CK7
GATA3
Uroplakin 2 [uroplakin 3, PAX8, TTF1 –ve]

- All squamous carcinomas and adenocarcinomas of lung were negative for uroplakin II
Evidence on pT1 substaging since RCPath dataset


Forthcoming publications

• International Collaboration on Cancer Reporting (ICCR) Dataset (in preparation for bladder cancer)
• New WHO (due for publication March 2016)
  Dr VE Reuter will present an update on this at BAUP in November for bladder cancer
• TNM 8th edition (due summer 2016)