

Variants of bladder cancer

Dr Jonathan H Shanks

The Christie NHS
Foundation Trust,
Manchester, UK



Urothelial (transitional cell) and other bladder carcinoma variants

- With glandular differentiation/adenocarcinoma, if pure
- With squamous differentiation/squamous carcinoma, if pure
 - verrucous carcinoma
- With small cell differentiation
- With trophoblastic differentiation
- Clear cell
- Nested variant
 - microcystic/tubular variant
 - large cell nested variant
- With inverted growth pattern
- Cystic variant/resembling cystitis cystica
- Micropapillary variant
- Lymphoepithelioma-like differentiation
- Plasmacytoid variant
- Lipid variant
- With osteoclast-like giant cells
- Giant cell variant
- Sarcomatoid carcinoma/carcinosarcoma
- Undifferentiated
- Mixed differentiation



Adenocarcinoma (pure)

Classified by site:

- Urachal
- Non-urachal

Classified by type:

- NOS
- Enteric
- Mucinous
- Signet ring
- Clear cell
- Hepatoid
- Mixed

Always exclude metastasis/spread from elsewhere!



Most frequent sites for metastasis of tumour from elsewhere to bladder

Bates and Baithun 2000; Xiao et al 2012

- Stomach
- Lung
- Breast
- Hepatobiliary system/pancreas



Most frequent sites for direct extension of tumour from elsewhere to bladder

(Bates and Baithun, 2000)

- Colorectum
- Prostate
- Cervix



Spread/metastasis of tumour from other organs

- Colon (beta-catenin +/-)
- Cervix
- Prostate (PSA +/-; PRAP +/-; CK7-ve, CK20-ve, 34βE12-ve, CK6/5-ve)
- Lung (TTF-1 +/-)
- Others



Adenocarcinoma

- **Bladder adenocarcinoma, enteric type**
- CK20+, CK7-/+, PSA-, PrAP+/-, Uroplakin III-
- **Bowel adenocarcinoma**
- Beta-catenin (nuclear positivity)
- Almost never CK7+/CK20- or thrombomodulin + (unlike urothelial ca)
- CDX2 and villin do not differentiate bowel vs enteric type bladder adenoca



Immunohistochemical distinction between primary adenocarcinoma of the bladder and secondary colorectal adenocarcinoma

Wang HL *et al Am J Surg Pathol* 2001 25:1380-7

- 13/16 (81%) colorectal adenocarcinomas involving bladder showed nuclear β -catenin expression
- All 17 primary adenocarcinomas of bladder were negative



Remember

- For pure adenocarcinoma involving bladder, a primary elsewhere should be excluded clinically before accepting as a bladder primary, especially if there is no in-situ component
- Immunohistochemistry is morphology (differentiation) - specific rather than site-specific in this context e.g. primary bladder adenocarcinoma often shows enteric differentiation



Clear cell carcinoma of urinary bladder (Oliva *et al.* 2002)

- 4/13 cases were associated with conventional urothelial carcinoma
- 4/13 cases had associated endometriosis
- 9/13 were CK7+ve
- 5/13 were CK20+ve
- Metastasis from renal clear cell carcinoma is rare: usually alveolar growth, can be tubular/cystic; CK7 and CK20 typically negative; hobnail cells absent; delicate peritumoural vasculature present



Cytokeratin 14 as a marker of squamous differentiation in transitional cell carcinomas Harnden P *et al J Clin Pathol* 1997;50:1032-3

- 42 invasive tumours studied
- CK14 found in areas with squamous differentiation, including areas suggestive but not fully diagnostic of squamous differentiation by morphology (areas with more eosinophilic cytoplasm forming cohesive sheets)
- CK20 found in areas of transitional cell carcinoma
- All pure squamous cell carcinomas were CK14+ve/CK20 -ve



p63 is not useful in this context, since it stains both squamous and urothelial lesions!



p16 and HPV ISH expression in urothelial carcinoma with squamous differentiation and primary squamous carcinoma of the urinary bladder: an institutional review

[Stevens KA et al. USCAP abstract 1045, 2013]



The Christie NHS
Westwood Road, Manchester, M14 5RU

Calgranulin expression and association with the keratinocyte cytoskeleton Clark BR et al *J Pathol* 1990;160:25-30

The L1 antigen and squamous metaplasia in the bladder Tungekar MF et al *Histopathology* 1991;19:345-50

Squamous differentiation in primary urothelial carcinoma of the urinary tract as seen by Mac387 immunohistochemistry Lopez-Beltran A et al *J Clin Pathol* 2007;60:332-335

- Mac387 consistently demonstrated squamous differentiation in squamous metaplasia and squamous carcinoma of bladder
- -ve in normal & hyperplastic urothelium, urothelial carcinoma and adenocarcinoma
- Squamous differentiation tended to increase in extent with increasing grade and stage



No difference in survival when corrected for stage/grade compared with conventional urothelial carcinoma

Clinical importance of squamous metaplasia in invasive transitional cell carcinoma of the bladder

Martin JE et al *J Clin Pathol* 1989;42:250-250

Prediction of response to radiotherapy in invasive bladder cancer

Jenkins BJ et al *Br J Urol* 1990;65:345-348

- "Transitional cell carcinomas showing squamous metaplasia are mainly resistant to radiotherapy and alternative treatment methods should be sought"
- "Squamous metaplasia and/or beta hCG indicate resistance to radiotherapy"



The Christie NHS
Westwood Road, Manchester, M14 5RU

Predicting the outcome of radical radiotherapy for invasive bladder cancer

Vale JA et al *Eur Urol* 1993;24:48-51

Presence of "squamous metaplasia" was not predictive of either radiotherapy response or survival in multivariate analysis



The Christie NHS
Westwood Road, Manchester, M14 5RU

Key points

- Divergent squamous or glandular differentiation in urothelial carcinoma most often occurs in the setting of high grade (and often high stage) disease. Independent clinical relevance is doubtful.
- When stratified by stage, there no conclusive evidence of a difference in outcome



The Christie NHS
Westwood Road, Manchester, M14 5RU

Squamous cell carcinoma of bladder

Should be pure with no urothelial elements



The Christie NHS
Westwood Road, Manchester, M14 5RU

Clinical outcomes following radical cystectomy for primary nontransitional cell carcinoma of the bladder compared to transitional cell carcinoma of the bladder

Rogers CG *et al*
J Urol 2006;175:2048-2053

- 955 patients who underwent radical cystectomy + bilateral pelvic lymphadenectomy
- "Non-TCC" histology in 67 cases (7%)
 - Squamous carcinoma (pure) in 26
 - Adenocarcinoma (pure) in 13
 - Small cell carcinoma in 10
 - Other e.g. sarcomatoid carcinoma in 18



Rogers CG *et al* 2006

- Bladder cancer-specific progression and mortality did not differ between urothelial carcinoma (UC) and squamous carcinoma (SCC)
- Patients with non-UC, non-SCC histology (e.g. pure adenocarcinoma, small cell carcinoma, sarcomatoid carcinoma) were at a significantly higher risk of progression and death (differences held up in multivariate analysis)
- Patients with non UC subtypes were more likely to present at advanced stage (pT3 or pT4)



When pure small cell carcinoma is encountered, exclude a primary elsewhere clinically (e.g. lung), although it would be very unusual for a metastasis from lung to give a symptomatic bladder lesion as the first presentation



WHO (2004)

Neuroendocrine tumours

- Small cell carcinoma
- Carcinoid



Reactive von Brunn's nest proliferation vs nested urothelial carcinoma

Favouring reactive proliferation:

- Lack of deep infiltration and linear non-infiltrative base
- No detrusor involvement
- Lobular configuration
- Regular size, shape and spacing of nests
- Lack of cytological atypia (but areas of nested variant carcinoma also lack atypia)



Nested variant of urothelial carcinoma: a clinicopathologic and immunohistochemical study of 30 pure and mixed cases

Wasco M.J *et al. Hum Pathol* 2010;41:163-171

- Discrete small variably sized nests (90% cases)
- Areas of confluent growth (40% cases)
- Cystitis cystica-like areas in 33% cases
- Deep tumour-stroma interface jagged in 100% cases
- Scattered random cytological atypia seen in 90%
- Component of usual urothelial carcinoma in 63% cases



Nested variant of urothelial carcinoma: a clinicopathologic and immunohistochemical study of 30 pure and mixed cases Wasco MJ *et al. Hum Pathol* 2010;41:163-171 [see also Drew *et al.* 1996]

- 47% cases had only minimal stromal reaction to tumour
- 23% had a myxoid stroma
- 30% had a focal desmoplastic stroma
- Focal stromal retraction around nests seen in 30% cases
- Lymphovascular invasion in 73%
- 65% were stage pT3 at cystectomy and 57% had nodal metastases
- Associated with a significantly higher rate of detrusor invasion, pT3 disease and metastatic disease compared with usual UC of high grade
- Aggressive variant of urothelial carcinoma



Main differential diagnosis of nested variant urothelial carcinoma

- Florid reactive von Brunn's nest proliferation
- Inverted papilloma



Urothelial (transitional cell) and other bladder carcinoma variants

- With glandular differentiation
- With squamous differentiation
- With small cell differentiation
- With trophoblastic differentiation
- **Nested variant**
 - microcystic/tubular variant
 - large nested variant
- With inverted growth pattern
- Cystic variant/resembling cystitis cystica
- Micropapillary variant
- Lymphoepithelioma-like differentiation
- Plasmacytoid variant
- Lipoid variant
- Sarcomatoid carcinoma/carcinosarcoma
- Mixed differentiation



Microcystic/small tubular variant urothelial carcinoma versus cystitis glandularis/von Brunn's nest proliferation

Features favouring carcinoma:

- Haphazard growth/infiltrative pattern
- Cytological atypia
- Variation in size, shape and spacing of microcysts/tubules



Differential diagnosis with nephrogenic adenoma

- A peripheral layer of urothelial cells in tubules is not a feature of nephrogenic adenoma (NA is lined by single layer of cuboidal, flattened or hobnail cells) and can be a helpful feature in recognition of nephrogenic adenoma-like bladder carcinomas
- Lack of cytological atypia, infiltrative pattern and mitoses in nephrogenic adenoma
- NA is PAX2 and PAX8 positive



Large cell nested variant of urothelial carcinoma: 23 cases mimicking von Brunn nests and inverted growth pattern of noninvasive papillary urothelial carcinoma

Cox R, Epstein JI *Am J Surg Pathol* 2011;35:1337-42

- 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



Other potential differential diagnoses of nested variant urothelial carcinoma

- [Florid von Brunn's nests]
- [Inverted papilloma]
- Paraganglioma
- Carcinoid tumour



Urothelial transitional cell carcinoma with endophytic growth patterns. A discussion of patterns of invasion and problems associated with invasion in 18 cases (Amin *et al.*, 1997)

- 18 cases described
- 9 were stage Ta
- 8 were stage T1
- 1 was stage T2



Differential diagnosis = inverted papilloma



Inverted papilloma vs inverted urothelial carcinoma

Features supporting inverted papilloma:

- Usually dome shaped, usually solitary with absent to minimal exophytic component
- Well demarcated from surrounding tissue
- Absent atypia is usual (occasional cases may have some degenerate atypia)
- Relatively slender cords and trabeculae of even width and absence of solid areas
- Peripheral palisading and central spindling in trabeculae
- Destructive invasion absent
- Absence of large rounded nests



Carcinomas of the urinary bladder with deceptively benign-appearing foci (Talbert and Young, 1989)

- Three male patients aged 53-77 years
- In two cases deceptively benign appearance led to significant delay in diagnosis
- 2 cases resembled von Brunn's nests, cystitis glandularis, cystitis cystica and/or nephrogenic adenoma
- A third case closely resembled inverted papilloma
- Favouring carcinoma: irregular distribution +shape, closely packed nests, focal mild to moderate cytological atypia, detrusor invasion, blends with obvious carcinoma



Deceptively benign features which may be seen in urothelial carcinoma (Young and Oliva 1996)

Feature in carcinoma

- Nests
- Small tubules
- Medium-sized glands
- Cysts
- Inverted growth

Benign lesion mimicked

- von Brunn's nests
- Nephrogenic adenoma
- Cystitis glandularis
- Cystitis cystica
- Inverted papilloma



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 neo-adjuvant therapy 32% were alive at 5 years
- For group having immediate cystectomy 71% were alive at 5 years



Lymphoepithelioma-like carcinoma of urinary bladder

- Amin *et al.* 1994 (11 cases); Lopez-Beltran *et al.* 2001 (13 cases)
- Can mimic either lymphoma or chronic inflammatory infiltrate (large tumour cells in syncytial pattern may be subtle)
- Classified as pure, mixed with urothelial carcinoma (LELC>50%) and focal (LELC<50%)
- EBV (EBER/LMP) negative in all cases tested in these and other series
- Pure and predominant LELC cases showed better prognosis with response in some to chemotherapy



Lymphoepithelioma-like carcinoma of the urinary tract: a clinicopathological study of 30 pure and mixed cases.
Tamas EF Mod Pathol 2007;20:828-834

- 28 cases in bladder, 1 in renal pelvis, 1 in urethra
- 57% cases pure, remainder mixed
- For mixed cases, conventional urothelial ca in 10, focal gland differentiation in 3 and squamous elements in 2 (surface CIS seen in 6 cases; non-invasive papillary ca in 3)
- All -ve for EBV (ISH for EBER)
- Cases treated with cystectomy had similar prognosis to conventional urothelial carcinoma, whether cases were pure or mixed lymphoepithelioma-like carcinoma
- 3 had chemotherapy (2 disease free at 4 and 65 months, 1 recurrence at 17 months)



Plasmacytoid transitional cell carcinoma of urinary bladder. A clinicopathologic study of 9 cases.
Ro JY et al. Am J Surg Pathol 2008;32:752-757



Differential Diagnoses for discohesive variant urothelial carcinoma

- Malignant mesothelioma
- Metastatic carcinoma from breast (lobular)
- Metastatic gastric adenocarcinoma or signet ring adenocarcinoma from other primary sites
- Plasmacytoid variant urothelial carcinoma
- Histiocytic/inflammatory infiltrate



Transitional cell carcinoma of the bladder mimicking lobular carcinoma of the breast: a discohesive variant of urothelial carcinoma *Baldwin L et al. Histopathology 2005;46:50-56*

- 10 cases described (8M:2F)
- All presented with lower urinary tract symptoms
- Resembled lobular carcinoma from breast or diffuse ca from stomach
- 4 cases had typical urothelial carcinoma or CIS elements
- CK20 expressed in 7/10
- ER/PR expressed weakly/focally in 2 cases (others -ve)
- E-cadherin +ve in 3/10 cases



Features found in discohesive variant urothelial carcinoma but not in metastatic lobular carcinoma breast

- Uroplakin +ve (at least some cases)
- CK20 +ve (could be positive in GI primaries, including gastric)
- ER/PR –ve or rarely focal/weak +ve (typically positive in lobular carcinoma breast but less so in pleomorphic variant)



Urothelial carcinoma of the bladder, lipid cell variant: clinicopathologic findings and LOH analysis

Lopez-Beltran A *et al. Am J Surg Pathol* 2010;34:371-6

- 27 cases described
- Lipid cell component varied from 10% to 50% of the tumour
- In one third of cases it was >30% of tumour area
- Lipid found on EM
- All were mucin –ve
- Typical high grade conventional urothelial carcinoma was present in all cases, typically advanced stage
- LOH analysis using 4 microsatellite markers found similar abnormalities in the lipid and typical urothelial areas



Heterologous elements in sarcomatoid carcinoma:

- Osteosarcoma
- Chondrosarcoma
- Rhabdomyosarcoma
- Liposarcoma
- Angiosarcoma



Urothelial carcinoma with villoglandular differentiation: a study of 14 cases

Lim M *et al. Mod Pathol* 2009;22:1280-1286

- Filiform surface processes lined by epithelium that formed glandular lumens
- Most cases in elderly males
- Most were admixed with conventional papillary urothelial carcinoma that was high grade (both invasive and non-invasive)
- Several cases had other high grade forms of divergent differentiation (micropapillary, plasmacytoid, small cell or adenocarcinoma)
- Spread from a colorectal primary was excluded in all cases (need to be considered when this villoglandular pattern is encountered)



Invasive urothelial carcinoma with chordoid features: a report of 12 cases characterized by prominent myxoid matrix and cordlike epithelial architecture

Cox RM *et al. Am J Surg Pathol* 2009;33:1213-1218

- Pattern closely mimicked extraskeletal myxoid chondrosarcoma, mixed tumour/myoepithelioma of soft tissue and possibly yolk sac tumour
- Alcian blue +ve myxoid matrix
- Look for merging with typical urothelial carcinoma (present at least focally in all)
- Most cases were high stage at presentation and 75% had nodal metastases
- Lack of EWSR1 translocation (unlike extraskeletal myxoid chondrosarcoma)
- All were p63 and 34βE12 +ve; glypican-3 –ve; brachyury –ve; S100 –ve or only v focally +ve



Urothelial carcinoma with abundant myxoid stroma

Tavora F *et al. Hum Pathol* 2009

- 13 cases
- Cases with any component of adenocarcinoma were excluded
- Cords/individual cells but also small to medium sized nests and 'filiform areas'
- All were Alcian blue and D/PAS +ve in myxoid background
- All were CK7+ve, CDX2-ve; 5/13 were CK20 +ve
- 5 cases had bland cytology similar to nested variant urothelial carcinoma; the remainder were high grade
- Range of stages
- Behaviour uncertain in comparison to usual urothelial carcinoma
- Differential diagnosis = mucinous adenocarcinoma (from bladder, bowel or prostatic primary) but no glandular structures in cases described here

