

Staging of bladder cancer

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Normal histology

- Urothelium: superficial umbrella cells, intermediate cells, parabasal and basal cells
- Lamina propria (submucosa): connective tissue, blood vessels and irregularly distributed smooth muscle (muscularis mucosae)
- Muscularis propria: detrusor muscle with irregularly arranged thick muscle bundles which condense into an inner longitudinal and outer circular layer at the bladder neck
- Serosa: peritoneum covers part of postero-superior surface



Further characterization of the muscle layers and lamina propria of the urinary bladder by systematic histologic mapping. Implications for pathologic staging of invasive urothelial carcinoma

Paner GP *et al. Am J Surg Pathol* 2007;31:1420-1429

- Discernable muscularis mucosae (MM) layer (continuous or discontinuous) seen in only 41% of sections
- Vascular plexus usually associated with MM but not always
- Haphazardly arranged smooth muscle fibres and an irregular outer border are features of MM rather than detrusor
- Adipose tissue can be seen in all layers of bladder wall and seen in lamina propria in 49% cases (but rare in the trigone)
- Hyperplasia of MM most common in bladder dome (can resemble detrusor)
- In the trigone the detrusor is relatively superficial in location and the MM is rarely present
- The authors comment that pT1 substaging remains problematic



Serosal fat

- With advancing age, serosal fat permeates between fibres of the muscularis propria and sometimes the lamina propria
- The presence of adipose tissue must be interpreted with caution as it does not imply perforation of bladder even if thin-walled
- In resected tissue, invasion of tumour into fat does not necessarily mean perivesical invasion



Bladder TNM staging

- Stage is the most powerful prognostic indicator and is a major defining parameter in disease management
- TNM is a dual staging system that includes a clinical (pretreatment) and postsurgical (histopathological) classification
- Clinical system is cTNM or simply TNM; pathological system is pTNM
- Microscopic (histological) staging of biopsy material does *not* in itself *necessarily* justify the use of pTNM
- Pathological assessment of the primary tumour (pT) entails a resection or biopsy adequate to evaluate the highest pT category of that tumour.



TNM Staging of bladder cancer (7th edition 2009)/AJCC 7th edition

pT Primary tumour

- pTX Primary tumour cannot be assessed
- pT0 No evidence of primary tumour
- pTa Non-invasive papillary carcinoma
- pTis Carcinoma *in situ*
- pT1 Tumour invades subepithelial connective tissue



T1 tumours

- T1 may be more appropriate than pT1 in a biopsy/TUR when margins/excision adequacy uncertain (or pT1 with qualifying remark, such as 'at least', where appropriate)
- Apparent T1 tumours in sampled (i.e. not all submitted) TURBT specimens should prompt submission of further tissue (RCPath dataset recommends that ideally all tissue should be submitted for TURBT specimens, particularly for re-resections. If not all embedded, then as a minimum, the first 20 g or 10 cassettes should be processed + at least 1 cassette for every additional 5 g. Further tissue should always be processed if no muscularis propria (detrusor muscle) is identified, until the entire specimen has been processed)
- Many advocate repeat/restaging TURBT when apparent T1 tumour in initial biopsy/TUR



Bladder staging on TUR/biopsy specimens

"There is a problem in staging of bladder tumours after TUR. The precondition for pT can only be met in cases of complete tumour resection i.e resection of all grossly visible tumour tissue from the remaining grossly tumour-free bladder wall (deep and laterally). If these additionally and separately submitted tissues are histologically negative, a complete tumour resection can be assumed"

(TNM supplement, A commentary on Uniform Use, 2nd Edition, 2001)



TNM Staging of bladder cancer (7th edition 2009)/AJCC 7th edition

- T2 Tumour invades muscle [this means muscularis propria/detrusor muscle, not muscularis mucosae]
 - T2a – Tumour invades superficial muscle (inner half)
 - T2b – Tumour invades deep muscle (outer half)
- T3 Tumour invades perivesical tissue
 - T3a – microscopically
 - T3b – macroscopically



Validation of the AJCC substaging of pT2 bladder cancer: deep muscle invasion is associated with significantly worse outcome Tilki D et al. Eur Urol 2010;58:112-7

- Multicentre international study of 565 pT2 cystectomy cases
- No neo-adjuvant chemotherapy or radiotherapy
- Median follow-up = 50 months
- 44% were pT2a and 66% were pT2b (NB assessment only possible in cystectomy, not in TURBT or biopsy)
- Recurrence free survival and cancer specific survival significantly better for pT2a compared with pT2b, even when adjusted for other pathological factors, including lymph node status
- Presence of lymphovascular invasion was also of independent prognostic significance



TNM Staging of bladder cancer (7th edition 2009)/AJCC 7th edition

- pT4 Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
 - pT4a Tumour invades prostate stroma, seminal vesicles, uterus or vagina
 - pT4b Tumour invades pelvic wall or abdominal wall

[underlined text denotes a change from the previous 6th edition TNM]



Possible sources of error/pitfalls in staging

- Sampling
 - surgical sampling
 - non-representative tissue
 - no detrusor muscle in biopsy
 - histological sampling
- Histological interpretation
 - biopsy artefacts (thermal damage/crush/tangential sectioning/fragmentation)
 - obscuring inflammation
 - CIS involving von Brunn's nests
 - difficult/uncommon lesions e.g. deceptively bland variants
 - broad front (inverted) growth pattern
 - ambiguity/wrong conclusion re: 'muscle' invasion



“Muscle invasion”

The term should not be used without further qualification

- muscularis mucosae invasion
- muscularis propria (detrusor muscle) invasion
- invasion of smooth muscle, indeterminate (impossible to determine whether muscularis propria/detrusor or muscularis mucosae)



Recommendation

- Presence/absence of muscularis propria (detrusor muscle) should be stated for all biopsy/TUR specimens, when this can be determined
- If only smooth muscle fibres of indeterminate type are present, this should be stated as an indication to the surgeon that muscularis propria may not be represented and further TURBT should be performed



Transurethral resection specimens of the bladder: outcome of invasive urothelial cancer involving muscle bundles indeterminate between muscularis mucosae and muscularis propria. Miyamoto H, Epstein JI *Urology* 2010;76:600-2

- 94 TURBTs studied where uncertainty remained over type of muscle (MM vs MP) involved
- Restaging TURBT within 3 months done in 61% cases
- 56% of the repeat TURBTs showed at least pT2
- Restaging TURBT is critical for all such cases, yet 39% did not have restaging TURBT within 3 months



“Accurate pathological staging of urothelial neoplasms requires better cystoscopic sampling” Maruniak NA, Takezawa and Murphy WM *J Urol* 2002;167:2404-7

- 217 consecutive biopsy/TUR cases studied from community practice setting in USA
- Muscularis propria was absent in 51% cases for low grade papillary tumours
- Muscularis propria absent in 24% cases for high grade carcinomas or CIS
- Incidence of interpretive discrepancies amongst pathologists required to assess status of muscularis propria was significant (24% cases)
- Commonest problem with interpretation was artifact, most frequently due to tissue thermocoagulation



Clinical understaging of high risk nonmuscle invasive urothelial carcinoma treated with radical cystectomy Dutta SC *et al J Urol* 2001;166:490-3

- 78 patients had cystectomy for high-risk clinical stage T1 (or less) cancer
 - refractory to intravesical therapy
 - pathological high grade
 - multifocal disease
 - radiographic suspicion of 'invasion'
 - severe symptoms
- pT2 or greater was found in 40% cases
- Understaging most pronounced if:
 - (1) suspicious radiography
 - or (2) absent detrusor muscle in biopsy



“Correlation between biopsy and radical cystectomy in assessing grade and depth of invasion in bladder urothelial carcinoma” Chang BS *et al., Urology* 2001;57:1063-6

- 169 biopsy cases of urothelial carcinoma examined
- 27% of 55 T1 cases on biopsy were found to be at least stage T3a at cystectomy
- 49% of 96 cases which were invading detrusor muscle in the biopsy were at least stage T3a at cystectomy; 23% had nodal metastases
- Pre-operative biopsy understaged the true extent of disease in 46% cases



“Staging error in the bladder tumor: the correlation between stage of TUR and cystectomy”

Bayraktar et al. *Int Urol Nephrol* 2001;33:627-9

- TUR and cystectomy stage compared in 80 cases
- All had 'complete TUR' with no residual macroscopic tumour followed by radical cystectomy
- Complete agreement in stage in only 20 cases (25%)
- All 60 cases with 'discordant staging' were upstaged in the cystectomy
- Half of 10 T1 tumours on TUR were stage T3a in the cystectomy
- For "T2 tumours" on TUR, 21% were pT2 at cystectomy; 36% were pT3a and 43% were pT3b



The role and impact of pathology review on stage and grade assessment of stages Ta and T1 bladder tumors: a combined analysis of 5 EORTC cancer trials. A Van Der Meijden et al *J Urol* 2000;164:1533-1537

- Local pathology compared with central pathology review compared for 1400 cases
- 90% Ta cases were confirmed as such on review
- Only 43% T1 cases classified as T1 at review
- Review downstaged 53% cases from T1 to Ta
- Review upstaged 3% T1 cases to \geq T2
- For T1G3 cases, 50% were downstaged to Ta; 10% were upstaged to \geq T2 and 39% were downgraded to G2
- In the T1G3 cases, stage or grade is often changed, so that review remains essential in this group. It is also justifiable to repeat TUR.



Pathological stage review is indicated in primary pT1 bladder cancer

van Rhijn BWG et al *BJU Int* 2010;106:206-11

- 144 reviewed pT1 cases studied
- 15% were downstaged at review
- 4% were upstaged at review
- In remainder, stage pT1 was agreed at review



Recognition of invasion may be hampered by:

- Tangential sectioning
- Thermal/crush artefact
- Inflammatory infiltrate obscuring tumour
- Inverted/broad front growth



Cystectomy cut-up

- Careful handling to avoid detachment of friable epithelial lesions e.g. CIS
- Take blocks to show deepest invasion of bladder wall etc.
- Careful macroscopic examination and description of depth of invasion of any tumour (subdivision of pT3 depends on macroscopic determination of whether or not there is invasion of perivesical fat beyond the muscularis propria)



'Apparent' stage T0 in cystectomy specimens post-TUR/radiotherapy

- Real pT category should be a composite of all available histology specimens e.g. if TURBT was T2 and cystectomy performed soon afterwards contains no tumour, the pT category for that case should be pT2 rather than pT0
- 'y' denoted post-treatment stage assignment e.g. ypT1
- 'y' stage takes into account scars, granulation tissue, mucin lakes etc which may represent regressed tumour
- 'y' stage may not be an accurate reflection of true pT stage



Stage assignment for multiple tumours

- Highest stage of any single tumour given followed by '(m)' or number of tumours e.g. pT2(m) or pT2(5)
- '(is)' added for tumours associated with CIS e.g. pT3 (is)
- Or, for multiple tumours associated with CIS e.g. pT3 (m, is)



The usefulness of the level of the muscularis mucosae in the staging of invasive transitional cell carcinoma of the urinary bladder

Younes M *et al* 1990 *Cancer* 66:543-548

- 50 cases of T1 cancer examined
- 3 substages assigned:
 - T1a = invasion of tissue superficial to muscularis mucosae
 - T1b = invasion of muscularis mucosae
 - T1c = invasion deep to muscularis mucosae
- T1a and T1b had 75% 5 year survival
- T1c had 11% 5 year survival



T1 substaging

- According to Mhawech *et al.* (*Eur Urol* 2002;42:459-63), immunohistochemistry for cytokeratin and desmin was a useful tool in substaging T1 bladder cancer.
- ICH downstaged 7/93 cases from T1b to T1a; upstaged 4 cases from T1a to T1b
- Only 3/93 tumours could not be subclassified into T1a/T1b



"Microstaging of pT1 transitional cell carcinoma of the bladder. Does it really differentiate two populations with different prognoses?"

Sozen S *et al.* *Urol Int* 2002;69:200-6

- 90 T1 tumours diagnosed by TUR re-examined histologically
- Muscularis mucosae only identifiable in 40 (55%) cases (cf 39% cases by Angulo *et al* and 33% cases by Platz *et al*)
- 34 were T1a; 16 were T1b
- Substaging differences were significant in multivariate analysis for recurrence and progression rates. Grade and multiplicity were not significant



Substaging of T1 bladder carcinoma based on the depth of invasion as measured by micrometer: a new proposal

Cheng L *et al.* *Cancer* 1999;86:908-12

- 55 T1 bladder cancers examined (TURBTs)
- All had cystectomy within 10 days
- Final stage was T1 (10 cases); T2a (9 cases); T2b (13 cases); T3 (11 cases); T4 (10 cases)
- Significant correlation found between depth of invasion at TURB and final stage
- >1.5mm depth and tumour grade predicted advanced stage disease (sensitivity, specificity, ppv and npv =81%, 83%, 95% and 56% respectively)
- Invasion above or below MM was not a predictor of final stage



Effect of tumour depth in T1 TUR cases on outcome

- 83 cases with T1 bladder cancer on TUR
- 93% 5 year progression-free survival if invasion <1.5mm depth
- 67% 5 year progression-free if invasion >1.5mm



A new system for substaging pT1 papillary bladder cancer: a prognostic evaluation van der Aa *et al. Hum Pathol* 2005;36:981-986

- Current study proposed a cutoff of <0.5mm for pT1 (mic) and >0.5mm for pT1 (ext). Refers to length of invasive front measured parallel to surface (approx 1HPF diameter)
- FGFR3 mutation found in 63% pT1(mic) and 7% of pT1 (ext), thus defined in 53 cases
- Presence of pT1 (ext) at initial diagnosis was the most important predictor of progression-free survival, clearly surpassing FGFR3 status
- Necessary to confirm findings in a larger, preferably prospective series



A new and highly prognostic system to discern T1 bladder cancer substage.

van Rhijn BW *et al. Eur Urol* 2012;61:378-384

- Substage according to the new system (T1m and T1e) was user-friendly, possible in 100% of cases, and very predictive of T1 BCa behavior, according to the authors
- "Future studies may ultimately lead to the incorporation of this new substaging system in the TNM classification system for urinary BCa"



T1 substaging: summary and conclusion

- A variety of different methods have been advocated by different authors
- May be difficult to apply in individual cases due to tangential sectioning etc.
- Whilst each method appears to have some bearing on outcome, there is no consensus on the optimum method
- Routine T1 substaging cannot be recommended as standard practice at this time



The spectrum of histopathologic findings in vesical diverticulum: implications for pathogenesis and staging.

Idrees MT *et al. Hum Pathol.* 2013;44:1223-32.

- Recommendation that pT2 category should not be used for bladder tumours arising in a diverticulum
- Due to absent/attenuated muscularis propria in the diverticular wall



Nodal classification of bladder carcinoma (TNM/AJCC, 7th Edition, 2009)

pN Regional lymph nodes [defined in 7th edition TNM as "the nodes of the true pelvis which essentially are the pelvic nodes below the bifurcation of the common iliac arteries but include the lymph nodes along the common iliac artery too" – see also node groups specified below]

- pNX Regional lymph nodes cannot be assessed
- pN0 No regional lymph node metastasis
- pN1 Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac or presacral)
- pN2 Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac or presacral)
- pN3 Metastasis in a common iliac lymph node(s)

[metastasis to non-regional lymph nodes is classified as pM1. Underlined text above signifies change from 6th edition TNM, 2002]



Carcinoma of urethra/prostatic ducts

- NB Urothelial carcinoma arising in urethra or prostatic ducts +/- stromal invasion of prostate is not regarded as pT4 bladder cancer in TNM/AJCC 7th edition, but rather is staged separately as a primary urethral carcinoma
- *Direct* invasion of the prostate by a bladder cancer arising in the bladder and *invading through the wall of the bladder and into the prostate* is considered pT4a bladder cancer



Cancer dataset for tumours of the urinary collecting system (renal pelvis, ureter, bladder and urethra), 2nd edition

Shanks JH, Chandra A, McWilliam M, Varma M [RCPath website, April 2013]

www.rcpath.org/publications-media/publications/datasets/urinary-collecting-system.htm

Tissue Pathways for Urological Pathology

O'Rourke D, Turner G, Allen D [RCPath website, May 2010]

Best practice: gross examination and sampling of surgical specimens from the urinary bladder

Chandra A, Griffiths D, McWilliam LJ *J Clin Pathol* 2010;63:475-479

