| **Required/ Recommended** | **Element name** | **Values** | **Commentary** | **Implementation notes** |
| --- | --- | --- | --- | --- |
| Recommended | CLINICAL INFORMATION | **Previous history of urinary tract disease or distant metastasis**Single selection value list:• Information not provided • No previous history •Provide details, including site(s), if present**Previous therapy** Single selection value list:• Information not provided • No previous history •Provide details, including site(s), if present**Cytoscopic appearance** Multi selection value list (select all that apply):•Information not providedOR•Polypoid•Papillary•Red (erythematous) area•Normal•Other, specify**Other clinical information, specify**Text | Knowledge of any relevant history is critical in the accurate diagnosis of tumours throughout the urinary tract.1-4 This may be relevant to the specific diagnosis being entertained. This is a recommended rather than a required item as it is the responsibility of the clinician requesting the pathological examination of a specimen to provide information that will have an impact on the diagnostic process or affect its interpretation. Patients with a history of urothelial neoplasia are at risk for urothelial tumours throughout the urinary tract and this may inform the interpretation in subsequent specimens. Urothelial tumours in the urinary bladder and upper tract may have been treated with therapies such as Bacillus Calmette-Guerin (BCG), mitomycin C and others. These can be associated with morphologic changes that have the potential for misdiagnosis if the pathologist is unaware of the prior treatment.5,6 Radiation therapy (to the bladder or to adjacent organs) can be associated with pseudocarcinomatous hyperplasia that can be misdiagnosed as invasive carcinoma.7,8 Nephrogenic adenoma can be seen following biopsy or transurethral resection (TUR) and can mimic recurrent tumour clinically and pathologically.9,10 Knowledge of the cystoscopic appearance can also be helpful in some cases.1,3 For example, when evaluating a biopsy for the presence or absence of papillary neoplasia, knowledge of the cystoscopic finding of a papillary lesion can inform the interpretation. Finally knowledge of a history of carcinoma elsewhere such as prostatic adenocarcinoma, colorectal adenocarcinoma, cervical squamous cell carcinoma, and others can greatly assist in the interpretation of biopsy/TUR specimens in the right circumstances. References 1 Amin MB, Smith SC, Reuter VE, Epstein JI, Grignon DJ, Hansel DE, Lin O, McKenney JK, Montironi R, Paner GP, Al-Ahmadie HA, Algaba F, Ali S, Alvarado-Cabrero I, Bubendorf L, Cheng L, Cheville JC, Kristiansen G, Cote RJ, Delahunt B, Eble JN, Genega EM, Gulmann C, Hartmann A, Langner C, Lopez-Beltran A, Magi-Galluzzi C, Merce J, Netto GJ, Oliva E, Rao P, Ro JY, Srigley JR, Tickoo SK, Tsuzuki T, Umar SA, Van der Kwast T, Young RH and Soloway MS (2015). Update for the practicing pathologist: The International Consultation On Urologic Disease-European association of urology consultation on bladder cancer. Mod Pathol 28(5):612-630. 2 Hansel DE, Amin MB, Comperat E, Cote RJ, Knuchel R, Montironi R, Reuter VE, Soloway MS, Umar SA and Van der Kwast TH (2013). A contemporary update on pathology standards for bladder cancer: transurethral resection and radical cystectomy specimens. Eur Urol 63(2):321-332. 3 Chandra A, Griffiths D and McWilliam LJ (2010). Best practice: gross examination and sampling of surgical specimens from the urinary bladder. J Clin Pathol 63(6):475-479. 4 College of American Pathologists (CAP) (2017). Protocol for the Examination of Specimens from Patients with Carcinoma of the Urinary Bladder. Available at: http://www.cap.org/ShowProperty?nodePath=/UCMCon/Contribution Folders/WebContent/pdf/urinary-17protocol-3300.pdf (Accessed 1st March 2017). 5 Lopez-Beltran A, Luque RJ, Mazzucchelli R, Scarpelli M and Montironi R (2002). Changes produced in the urothelium by traditional and newer therapeutic procedures for bladder cancer. J Clin Pathol 55(9):641-647. 6 Oxley JD, Cottrell AM, Adams S and Gillatt D (2009). Ketamine cystitis as a mimic of carcinoma in situ. Histopathology 55(6):705-708. 7 Baker PM and Young RH (2000). Radiation-induced pseudocarcinomatous proliferations of the urinary bladder: a report of 4 cases. Hum Pathol 31(6):678-683. 8 Chan TY and Epstein JI (2004). Radiation or chemotherapy cystitis with "pseudocarcinomatous" features. Am J Surg Pathol 28(7):909-913. 9 Lopez JI, Schiavo-Lena M, Corominas-Cishek A, Yague A, Bauleth K, Guarch R, Hes O and Tardanico R (2013). Nephrogenic adenoma of the urinary tract: clinical, histological, and immunohistochemical characteristics. Virchows Arch 463(6):819-825. 10 Pina-Oviedo S, Shen SS, Truong LD, Ayala AG and Ro JY (2013). Flat pattern of nephrogenic adenoma: previously unrecognized pattern unveiled using PAX2 and PAX8 immunohistochemistry. Mod Pathol 26(6):792-798. |   |
| Required | SPECIMEN SITE | Single selection value list:• Renal pelvis• Ureter• Bladder, specify site(s)• Prostate/prostatic urethra• Urethra, specify site(s)• Other, specify | Since this dataset applies to the full breadth of the urinary tract the specific anatomic site is essential to the correct site identification and interpretation. The differential diagnostic considerations will have many site specific alternatives. Although the key staging landmarks have much overlap there are also several that will be site specific such as the renal stroma in renal pelvis tumours, prostatic stroma in the prostatic urethra and corporal bodies in the penile urethra. Location within individual sites can also be important to interpretation. In the urinary bladder specimens from the dome/anterior wall will include urachal lesions in the differential diagnosis. In the posterior wall/trigone/bladder neck secondary tumours from adjacent organs become important considerations in differential diagnosis. The distribution of muscularis mucosae fibres also vary by location in the urinary bladder and so knowledge of location can assist in evaluation of smooth muscle in the context of staging parameters.1 In males the urethra is divided into four regions, the preprostatic, prostatic, membranous and penile. Knowing the origin of a “urethral” biopsy or transurethral resection (TUR) is important as there are histologic differences between regions as well as different glandular elements that may be relevant to the interpretation of a given specimen. If biopsies are from different locations then a separate dataset should be completed for each specimen site. References 1 Paner GP, Ro JY, Wojcik EM, Venkataraman G, Datta MW and Amin MB (2007). 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. Am J Surg Pathol 31(9):1420-1429. | If biopsies are from different locations then a separate dataset should be completed for each specimen site. |
| Required | OPERATIVE PROCEDURE | Single selection value list• Not specified• Transurethral resection (TUR)• Biopsy• Other, specify | Documentation of the specific procedure performed should be a standard part of any pathology report. |  |
| Recommended | BLOCK IDENTIFICATION KEY | Text | The origin/designation of all tissue blocks should be recorded and it is preferable to document this information in the final pathology report. This is particularly important should the need for internal or external review arise. The reviewer needs to be clear about the origin of each block in order to provide an informed specialist opinion. If this information is not included in the final pathology report, it should be available on the laboratory computer system and relayed to the reviewing pathologist. Recording the origin/designation of tissue blocks also facilitates retrieval of blocks, for example for further immunohistochemical or molecular analysis, research studies or clinical trials. The block identification is not a required element within the synoptic report but we would consider it required within the report text (most often is included in the gross description section). | List overleaf or separately with an indication of the nature and origin of all tissue blocks. |
| Required | HISTOLOGICAL TUMOUR TYPE | Single selection value list:• Urothelial carcinoma• Squamous cell carcinoma• Adenocarcinoma• Tumours of Müllerian typeo Clear cell carcinomao Endometrioid carcinoma• Neuroendocrine tumouro Small cell neuroendocrine carcinomao Large cell neuroendocrine carcinoma• Other, specify**Histological sub-type/variant (urothelial carcinoma)**Single selection value list:• Not identifiedOR• Present, specify sub-type/variant and percentageMulti selection value list (select all that apply)/Numeric:o Squamous \_\_\_%o Glandular \_\_\_%o Nested \_\_\_%o Micropapillary \_\_\_%o Plasmacytoid \_\_\_%o Sarcomatoid \_\_\_%o Other, specify \_\_\_% | The 2016 World Health Organization (WHO) classification is utilized for assigning histological tumour type.1 As in the 2004 WHO Classification,2 a tumour is classified as a urothelial carcinoma if there is any identifiable urothelial component no matter how small and including urothelial carcinoma in situ (CIS). The one exception to this rule is for cases with a neuroendocrine component (small cell neuroendocrine carcinoma or large cell neuroendocrine carcinoma) where classification is in the neuroendocrine tumour category. For those cases that are mixed, the other elements should be reported with an estimated percentage. In the above scheme, this would be managed by placing the other component in the histological tumour type element. For example a mixed tumour with 70% small cell neuroendocrine carcinoma and 30% urothelial carcinoma would be reported under the histological tumour type as Neuroendocrine tumour (small cell neuroendocrine carcinoma) and then under histological tumour type – Other, specify - urothelial carcinoma (30%). For biopsies and transurethral resections (TURs) that contain pure adenocarcinoma or pure squamous cell carcinoma, they should be diagnosed as such. Without evaluation of the entire lesion it is not however possible to exclude the possibility of a urothelial carcinoma with squamous or glandular differentiation and consider a comment explaining that should always be included. The presence of keratinizing squamous metaplasia particularly when there is dysplasia would support the diagnosis of primary squamous cell carcinoma.3 Similarly the presence of intestinal metaplasia with dysplasia would support the diagnosis of primary adenocarcinoma. None the less a definitive diagnosis of either should be made with caution in biopsy or transurethral resection of bladder tumour (TURBT) material. There are no reliable immunohistochemical markers to distinguish these possibilities with certainty in the individual case. In urothelial carcinoma with glandular differentiation, the glandular component may retain its “urothelial” profile including expression of p63, GATA3 and high molecular weight cytokeratin but often these are lost with the tumour showing an enteric immuno-histochemical profile. Markers of squamous differentiation such as desmoglein 3, CK14 and MAC387 have not been proven to reliably separate pure squamous cell carcinoma from urothelial carcinoma with squamous differentiation.4 Further for both adenocarcinoma and squamous cell carcinoma the diagnosis of primary origin in the urinary bladder requires clinical correlation to exclude the possibility of origin at another site. The 2016 WHO classification now includes carcinomas arising in the urachus as a separate category.1 These are defined as carcinomas arising from urachal remnants. In general it is not possible to diagnose these in biopsy and TURBT material based on the morphologic findings alone. Criteria for the diagnosis of urachal carcinoma include location in the bladder dome or anterior wall, an epicentre in the bladder wall or perivesical tissue, the absence of diffuse cystitis glandularis/ intestinal metaplasia outside of the dome/anterior wall region and the absence of a known primary elsewhere.5 The majority (over 80%) of urachal carcinomas are adenocarcinoma followed by urothelial carcinoma, squamous cell carcinoma and small cell neuroendocrine carcinoma. If a diagnosis of urachal carcinoma is rendered the histologic type should be specified. Adenocarcinomas of the urachus are most often mucinous and can be either solid or cystic. Other variants of adenocarcinoma including enteric and signet ring-cell also occur. The WHO does include a category of “mucinous cystic tumour of low malignant potential” that could not be diagnosed with certainty in biopsy/TURBT material.1 There are no reliable immunohistochemical markers to distinguish adenocarcinomas of urachal origin from primary adenocarcinomas of the bladder proper or from secondary adenocarcinomas of gastrointestinal origin.4-6 Also new in the 2016 WHO classification is the category of Müllerian tumours.1 For the purposes of this dataset this consists primarily of clear cell adenocarcinoma and rare examples of endometrioid carcinoma. These tumours are morphologically the same as their counterparts in the female genital tract. They are rare tumours and most often when clear cell adenocarcinoma presents as a primary bladder tumour it represents secondary involvement most often originating in a urethral diverticulum.7 Diagnosis therefore requires clinical correlation to support diagnosis as a primary bladder tumour. Clear cell adenocarcinoma and endometrioid carcinoma may arise from endometriosis or rarely Müllerianosis.8-11 Clear cell adenocarcinoma must also be distinguished from urothelial carcinoma with divergent differentiation along Müllerian lines in which case it would be classified under urothelial carcinoma.12 Expression of markers such as p63, GATA3 and high molecular weight cytokeratin are not present in clear cell adenocarcinoma and in the absence of a recognisable urothelial component would suggest this possibility.13 Müllerian type clear cell adenocarcinoma has similar immunohistochemical profile to primary tumours of the female genital tract and cannot be used to distinguish a primary from a secondary origin.10,14-16 The neuroendocrine tumour category includes small cell neuroendocrine carcinoma, large cell neuroendocrine carcinoma, well-differentiated neuroendocrine tumour and paraganglioma. Small cell neuroendocrine carcinoma is by far the most common of these. By definition this is a malignant neoplasm with neuroendocrine differentiation. About one-half of cases are pure and one-half are mixed with another component with urothelial carcinoma being most frequent. Cases with mixed differentiation are included in this category. There does remain some controversy regarding the percentage of the neuroendocrine component required to classify a tumour as a neuroendocrine carcinoma. From a practical standpoint cases with a small cell neuroendocrine carcinoma component irrespective of the amount are managed as small cell neuroendocrine carcinoma with the larger series in the literature including cases with only a focal component of small cell carcinoma.17-21 For example the National Comprehensive Cancer Network (NCCN) includes tumours with “any small-cell component in the category of non-urothelial cell carcinoma.21,22 The diagnosis is defined by morphologic criteria but most cases do demonstrate evidence of neuroendocrine differentiation by immunohistochemistry. The most sensitive immunohistochemical markers are CD56 and synaptophysin.4 TTF-1 is expressed in about 50% of cases.23,24 In cases with pure small cell morphology the possibility of direct spread from an adjacent organ or metastasis must be excluded clinically. Lastly there are carcinomas arising in the urinary bladder that have no specific differentiation and based on exclusion of metastasis from another site are considered to be primary in the urinary tract. In the 2004 WHO classification these were included as a variant of urothelial carcinoma but given that by definition they have no urothelial differentiation these should be reported using the “carcinoma, type cannot be determined” category.2 **Histologic subtype/variant** The 2016 WHO classification includes a number of recognised morphologic variants as outlined in the table below.1 Because urothelial carcinoma has a remarkable capacity for morphologic variation the number of histologic variants that have been described in the literature is extensive.25,26 In the development of the 2016 WHO classification not all of these are included.1 In general the variants that have been specifically recognised fall into three broad categories. Variants that have a deceptively bland morphology, such as the nested variant, could be misdiagnosed as benign or considered low grade although their behaviour is the same as for high grade tumours. In the second category are tumours that have a morphology that mimics other tumours. Lastly are those tumours that have important prognostic or therapeutic implications. The importance of variant histology in clinical management decisions has been receiving increasing clinical attention.27,28 Some variants have been highlighted because of the high frequency of under staging when present in biopsy or TURBT specimens.29 There are an increasing number of therapeutic algorithms that incorporate variant histology as a significant factor.30 For T1 urothelial carcinoma, the presence of variant histology is one feature that is used in determining whether to consider immediate cystectomy.21,31 The level of evidence for specific variants having independent prognostic information varies from the variant having no clinical significance but being important diagnostically (e.g. nested, microcystic, etc), to no data, to data indicating the variant has prognostic significance (e.g. micropapillary, plasmacytoid, sarcomatoid). Rather than making reporting of specific subtypes that have some supporting data mandatory and others lacking data recommended it is considered best to make the entire category a required element. Reporting the percentage of variant histology when present is recommended (this is recommended in the WHO 2016 monograph).1 The data supporting this is very limited and only available for selected variants (micropapillary, sarcomatoid, lymphoepithelioma-like), with divergent differentiation (glandular, squamous). There is also insufficient data available for setting specific amounts of each specific variant in order for it to be clinically significant. Given the lack of data, if variant histology is identified, it should be reported and the estimated percentage of the tumour it makes up reported. For cases with more than one variant present, the percentage of each is recommended to be documented.**WHO classification of tumours of the urothelial tracta1**Descriptor / ICD-O codes**Urothelial tumours***Infiltrating urothelial* carcinoma 8120/3Nested, including large nestedMicrocysticMicropapillary 8131/3Lymphoepithelioma-like 8082/3Plasmacytoid / signet ring cell / diffuseSarcomatoid 8122/3Giant cell 8031/3Poorly differentiated 8020/3Lipid-richClear cell*Non-invasive urothelial lesions*Urothelial carcinoma in situ 8120/2Non-invasive papillary urothelial carcinoma, low-grade 8130/2Non-invasive papillary urothelial carcinoma, high-grade 8130/2Papillary urothelial neoplasm of low malignant potential 8130/1Urothelial papilloma 8120/0Inverted urothelial papilloma 8121/0Urothelial proliferation of uncertain malignant potentialUrothelial dysplasia**Squamous cell neoplasms**Pure squamous cell carcinoma 8070/3Verrucous carcinoma 8051/3Squamous cell papilloma 8052/0**Glandular neoplasms**Adenocarcinoma, NOS 8140/3Enteric 8144/3Mucinous 8480/3Mixed 8140/3Villous adenoma 8261/0**Urachal carcinoma** 8010/3**Tumours of Müllerian type**Clear cell carcinoma 8310/3Endometrioid carcinoma 8380/3**Neuroendocrine tumours**Small cell neuroendocrine carcinoma 8041/3Large call neuroendocrine carcinoma 8013/3Well-differentiated neuroendocrine tumour 8240/3Paraganglioma b 8693/1a The morphology codes are from the International Classification of Diseases for Oncology (ICD-O). Behaviouris coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situand grade III intraepithelial neoplasia; and /3 for malignant tumours.b Paraganglioma is not an epithelial derived tumour.© WHO/International Agency for Research on Cancer (IARC). Reproduced with permissionReferences 1 World Health Organization (2016). World Health Organization (WHO) Classification of tumours. Pathology and genetics of the urinary system and male genital organs. Moch H, Humphrey PA, Reuter VE, Ulbright TM. IARC Press, Lyon, France.2 WHO (World Health Organization) (2004). World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Urinary System and Male Genital Organ. Eble JN, Sauter G, Epstein JI and Sesterhenn IA. IARC Press, Lyon, France. 3 Lagwinski N, Thomas A, Stephenson AJ, Campbell S, Hoschar AP, El-Gabry E, Dreicer R and Hansel DE (2007). Squamous cell carcinoma of the bladder: a clinicopathologic analysis of 45 cases. Am J Surg Pathol 31(12):1777-1787. 4 Amin MB, Trpkov K, Lopez-Beltran A and Grignon D (2014). Best practices recommendations in the application of immunohistochemistry in the bladder lesions: report from the International Society of Urologic Pathology consensus conference. Am J Surg Pathol 38(8):e20-34. 5 Gopalan A, Sharp DS, Fine SW, Tickoo SK, Herr HW, Reuter VE and Olgac S (2009). Urachal carcinoma: a clinicopathologic analysis of 24 cases with outcome correlation. Am J Surg Pathol 33(5):659-668. 6 Paner GP, McKenney JK, Barkan GA, Yao JL, Frankel WL, Sebo TJ, Shen SS and Jimenez RE (2011). Immunohistochemical analysis in a morphologic spectrum of urachal epithelial neoplasms: diagnostic implications and pitfalls. Am J Surg Pathol 35(6):787-798. 7 Kosem M and Sengul E (2005). Clear cell adenocarcinoma of the urinary bladder. Scand J Urol Nephrol 39(1):89-92. 8 al-Izzi MS, Horton LW, Kelleher J and Fawcett D (1989). Malignant transformation in endometriosis of the urinary bladder. Histopathology 14(2):191-198. 9 Allen D, O'Brien T, Pingle P and Chandra A (2005). Endometrioid adenocarcinoma of the bladder. Histopathology 46(2):232-233. 10 Drew PA, Murphy WM, Civantos F and Speights VO (1996). The histogenesis of clear cell adenocarcinoma of the lower urinary tract. Case series and review of the literature. Hum Pathol 27(3):248-252. 11 Lah K, Desai D, Hadway P, Perry-Keene J and Coughlin G (2013). Primary vesical clear cell adenocarcinoma arising in endometriosis: a rare case of mullerian origin. Anticancer Res 33(2):615-617. 12 Sung MT, Zhang S, MacLennan GT, Lopez-Beltran A, Montironi R, Wang M, Tan PH and Cheng L (2008). Histogenesis of clear cell adenocarcinoma in the urinary tract: evidence of urothelial origin. Clin Cancer Res 14(7):1947-1955. 13 Gilcrease MZ, Delgado R, Vuitch F and Albores-Saavedra J (1998). Clear cell adenocarcinoma and nephrogenic adenoma of the urethra and urinary bladder: a histopathologic and immunohistochemical comparison. Hum Pathol 29(12):1451-1456. 14 Oliva E, Amin MB, Jimenez R and Young RH (2002). Clear cell carcinoma of the urinary bladder: a report and comparison of four tumors of mullerian origin and nine of probable urothelial origin with discussion of histogenesis and diagnostic problems. Am J Surg Pathol 26(2):190-197. 15 Tong GX, Weeden EM, Hamele-Bena D, Huan Y, Unger P, Memeo L and O'Toole K (2008). Expression of PAX8 in nephrogenic adenoma and clear cell adenocarcinoma of the lower urinary tract: evidence of related histogenesis? Am J Surg Pathol 32(9):1380-1387. 16 Vang R, Whitaker BP, Farhood AI, Silva EG, Ro JY and Deavers MT (2001). Immunohistochemical analysis of clear cell carcinoma of the gynecologic tract. Int J Gynecol Pathol 20(3):252-259. 17 Choong NW, Quevedo JF and Kaur JS (2005). Small cell carcinoma of the urinary bladder. The Mayo Clinic experience. Cancer 103(6):1172-1178. 18 Siefker-Radtke AO, Dinney CP, Abrahams NA, Moran C, Shen Y, Pisters LL, Grossman HB, Swanson DA and Millikan RE (2004). Evidence supporting preoperative chemotherapy for small cell carcinoma of the bladder: a retrospective review of the M. D. Anderson cancer experience. J Urol 172(2):481-484. 19 Mackey JR, Au HJ, Hugh J and Venner P (1998). Genitourinary small cell carcinoma: determination of clinical and therapeutic factors associated with survival. J Urol 159(5):1624- 1629. 20 Lynch SP, Shen Y, Kamat A, Grossman HB, Shah JB, Millikan RE, Dinney CP and Siefker-Radtke A (2013). Neoadjuvant chemotherapy in small cell urothelial cancer improves pathologic downstaging and long-term outcomes: results from a retrospective study at the MD Anderson Cancer Center. Eur Urol 64(2):307-313. 21 National Comprehensive Cancer Network (NCCN). NCCN Guidelines. Available at: https://www.nccn.org/professionals/physician\_gls/f\_guidelines.asp (Accessed 1st March 2017). 22 Clark PE, Agarwal N, Biagioli MC, Eisenberger MA, Greenberg RE, Herr HW, Inman BA, Kuban DA, Kuzel TM, Lele SM, Michalski J, Pagliaro LC, Pal SK, Patterson A, Plimack ER, Pohar KS, Porter MP, Richie JP, Sexton WJ, Shipley WU, Small EJ, Spiess PE, Trump DL, Wile G, Wilson TG, Dwyer M and Ho M (2013). Bladder cancer. J Natl Compr Canc Netw 11(4):446-475. 23 Agoff SN, Lamps LW, Philip AT, Amin MB, Schmidt RA, True LD and Folpe AL (2000). Thyroid transcription factor-1 is expressed in extrapulmonary small cell carcinomas but not in other extrapulmonary neuroendocrine tumors. Mod Pathol 13(3):238-242. 24 Jones TD, Kernek KM, Yang XJ, Lopez-Beltran A, MacLennan GT, Eble JN, Lin H, Pan CX, Tretiakova M, Baldridge LA and Cheng L (2005). Thyroid transcription factor 1 expression in small cell carcinoma of the urinary bladder: an immunohistochemical profile of 44 cases. Hum Pathol 36(7):718-723. 25 Amin MB (2009). Histological variants of urothelial carcinoma: diagnostic, therapeutic and prognostic implications. Mod Pathol 22 Suppl 2:S96-s118. 26 Lopez-Beltran A and Cheng L (2006). Histologic variants of urothelial carcinoma: differential diagnosis and clinical implications. Hum Pathol 37(11):1371-1388. 27 Xylinas E, Rink M, Robinson BD, Lotan Y, Babjuk M, Brisuda A, Green DA, Kluth LA, Pycha A, Fradet Y, Faison T, Lee RK, Karakiewicz PI, Zerbib M, Scherr DS and Shariat SF (2013). Impact of histological variants on oncological outcomes of patients with urothelial carcinoma of the bladder treated with radical cystectomy. Eur J Cancer 49(8):1889-1897. 28 Kim SP, Frank I, Cheville JC, Thompson RH, Weight CJ, Thapa P and Boorjian SA (2012). The impact of squamous and glandular differentiation on survival after radical cystectomy for urothelial carcinoma. J Urol 188(2):405-409. 29 Hansel DE, Amin MB, Comperat E, Cote RJ, Knuchel R, Montironi R, Reuter VE, Soloway MS, Umar SA and Van der Kwast TH (2013). A contemporary update on pathology standards for bladder cancer: transurethral resection and radical cystectomy specimens. Eur Urol 63(2):321-332. 30 Shah JB, McConkey DJ and Dinney CP (2011). New strategies in muscle-invasive bladder cancer: on the road to personalized medicine. Clin Cancer Res 17(9):2608-2612. 31 Babjuk M, Burger M, Zigeuner R, Shariat SF, van Rhijn BW, Comperat E, Sylvester RJ, Kaasinen E, Bohle A, Palou Redorta J and Roupret M (2013). EAU guidelines on non-muscleinvasive urothelial carcinoma of the bladder: update 2013. Eur Urol 64(4):639-653. | Value list from the WHO Classification of Tumours of the Urinary System and Male Genital Organs (2016).Note that permission to publish the WHO Classification of Tumours may be needed in your implementation. It is advisable to check with the International Agency for Research on Cancer (IARC). |
| Required | NON-INVASIVE CARCINOMA | Single selection value list:• Not identified• IndeterminateMulti selection value list (select all that apply): • Carcinoma in situ, flato Focal o Multifocal• Papillary carcinoma, non-invasive• Other, specify | The majority of patients with urothelial carcinoma present initially with non-invasive disease. Most of these have a non-invasive papillary tumour and much less frequently have urothelial any identifiable urothelial component no matter how small and including urothelial carcinoma (CIS) as the initial diagnosis. Non-invasive papillary tumours account for 70% to 75% of newly diagnosed cases with over one-half being in the lower grade categories (papillary urothelial neoplasm of low malignant potential, low grade papillary carcinoma).1,2 Urothelial CIS in its pure form counts for 1% to 3% of newly diagnosed urothelial tumours and is by definition high grade.3 Much more often it coexists with high grade papillary urothelial carcinoma and is found in association with invasive urothelial carcinoma in up to 65% of cases.3-5 Papillary tumours range from benign (papilloma, papillary urothelial neoplasm of low malignant potential) to low and high grade carcinomas. CIS and papillary carcinoma develop by different genetic pathways and have different biologic behaviour and so are considered as different entities within the non-invasive category.6 Classification of non-invasive urothelial tumours into the papillary and in situ categories has both prognostic and management implications. Further the identification of CIS coexisting with papillary carcinoma also has significance for prognosis and treatment. In biopsy and transurethral resection of bladder tumour (TURBT) specimens both diagnoses can be rendered when the papillary carcinoma and the CIS are present on different tissue fragments or in specimens submitted from different sites. When flat lesion is present adjacent to and in continuity with a papillary tumour the question becomes whether the flat part represents a “shoulder” of the papillary tumour or coexisting CIS. There are no generally accepted criteria for making this decision even though the diagnosis does have clinical significance. We would recommend making the diagnosis of associated CIS in this situation if (i) there is a gap of normal urothelium between the papillary tumour and the flat lesion or (ii) if the morphology of the flat lesion is different than that of the epithelium on the surface of papillary fronds. For patients presenting with invasive urothelial carcinoma the recognition and documentation of an associated non-invasive papillary carcinoma and/or CIS remains important. For patients with T1 disease the presence of CIS indicates a significantly increased risk of subsequent recurrence and of progression to muscle invasive disease. For patients with CIS of the bladder unresponsive to Bacillus Calmette-Guerin (BCG) therapy this is an indication for early cystectomy.7-9 The presence of associated CIS in newly diagnosed high grade T1 disease may also be used to support early cystectomy.7,10 For patients presenting with invasive urothelial carcinoma there are data that such cases arising through the “papillary” pathway have stage for stage a better prognosis that those developing via the “flat” pathway.11,12 There is also evidence that the extensiveness of the CIS is significant and so distinguishing between a single focus and diffuse (or multifocal) disease is important. For the purpose of this dataset, diffuse is defined as the presence of CIS in more than one site as indicated by biopsies submitted separately or involving more than one tissue fragment in a TURBT specimen. Lastly non-urothelial CIS can also occur in the urinary tract. Most frequently this is squamous cell CIS typically in association with keratinizing squamous metaplasia. This can be identified in patients with invasive squamous cell carcinoma but also can be diagnosed in the absence of invasive disease. Adenocarcinoma in situ is not a well-defined lesion in the urinary tract. In cases of intestinal metaplasia varying degrees of atypia can be seen up to high grade dysplasia, a term we would prefer rather than adenocarcinoma in situ. Urothelial CIS can show areas of squamous and glandular differentiation and these should not be diagnosed as squamous or adenocarcinoma in situ respectively. References 1 Gardmark T, Bladstrom A, Hellsten S and Malmstrom PU (2006). Analysis of clinical characteristics, management and survival of patients with Ta T1 bladder tumours in Sweden between 1997 and 2001. Scand J Urol Nephrol 40(4):276-282.2 Kirkali Z, Chan T, Manoharan M, Algaba F, Busch C, Cheng L, Kiemeney L, Kriegmair M, Montironi R, Murphy WM, Sesterhenn IA, Tachibana M and Weider J (2005). Bladder cancer: epidemiology, staging and grading, and diagnosis. Urology 66(6 Suppl 1):4-34. 3 Zincke H and Utz DC (1986). Review of Mayo Clinic experience with carcinoma in situ. Urology 27(3):288. 4 Wolf H, Olsen PR, Fischer A and Hojgaard K (1987). Urothelial atypia concomitant with primary bladder tumour. Incidence in a consecutive series of 500 unselected patients. Scand J Urol Nephrol 21(1):33-38. 5 Koss LG (1979). Mapping of the urinary bladder: its impact on the concepts of bladder cancer. Hum Pathol 10(5):533-548. 6 Zieger K, Marcussen N, Borre M, Orntoft TF and Dyrskjot L (2009). Consistent genomic alterations in carcinoma in situ of the urinary bladder confirm the presence of two major pathways in bladder cancer development. Int J Cancer 125(9):2095-2103. 7 Babjuk M, Burger M, Zigeuner R, Shariat SF, van Rhijn BW, Comperat E, Sylvester RJ, Kaasinen E, Bohle A, Palou Redorta J and Roupret M (2013). EAU guidelines on non-muscleinvasive urothelial carcinoma of the bladder: update 2013. Eur Urol 64(4):639-653. 8 Dalbagni G (2007). The management of superficial bladder cancer. Nat Clin Pract Urol 4(5):254-260. 9 Gofrit ON, Pode D, Pizov G, Zorn KC, Katz R, Duvdevani M and Shapiro A (2009). The natural history of bladder carcinoma in situ after initial response to bacillus Calmette-Guerin immunotherapy. Urol Oncol 27(3):258-262. 10 Kulkarni GS, Hakenberg OW, Gschwend JE, Thalmann G, Kassouf W, Kamat A and Zlotta A (2010). An updated critical analysis of the treatment strategy for newly diagnosed highgrade T1 (previously T1G3) bladder cancer. Eur Urol 57(1):60-70. 11 Dyrskjot L, Zieger K, Real FX, Malats N, Carrato A, Hurst C, Kotwal S, Knowles M, Malmstrom PU, de la Torre M, Wester K, Allory Y, Vordos D, Caillault A, Radvanyi F, Hein AM, Jensen JL, Jensen KM, Marcussen N and Orntoft TF (2007). Gene expression signatures predict outcome in non-muscle-invasive bladder carcinoma: a multicenter validation study. Clin Cancer Res 13(12):3545-3551. 12 Choi W, Porten S, Kim S, Willis D, Plimack ER, Hoffman-Censits J, Roth B, Cheng T, Tran M, Lee IL, Melquist J, Bondaruk J, Majewski T, Zhang S, Pretzsch S, Baggerly K, Siefker-Radtke A, Czerniak B, Dinney CP and McConkey DJ (2014). Identification of distinct basal and luminal subtypes of muscle-invasive bladder cancer with different sensitivities to frontline chemotherapy. Cancer Cell 25(2):152-165. |  |
| Recommended | ASSOCIATED EPITHELIAL LESIONS | Single selection value list:• Present, specify• Not identified | A variety of neoplastic lesions that fall short of carcinoma are recognised in the urinary tract. These include papillary lesions such as urothelial papilloma, papillary urothelial neoplasm of low malignant potential and inverted urothelial papilloma. Similarly flat lesions such as urothelial dysplasia, keratinizing squamous metaplasia with dysplasia and intestinal metaplasia with dysplasia can be seen. Identification of these may have diagnostic implications (e.g. the presence of keratinizing squamous metaplasia with dysplasia supporting the diagnosis of primary squamous cell carcinoma) but do not have known proven prognostic or clinical significance otherwise. While for completeness it may be useful to report such findings, it is not considered to be a required element in the context of a carcinoma diagnosis. |  |
| Required | HISTOLOGICAL TUMOUR GRADE | Single selection value list:• Not applicable• Cannot be determined**Urothelial carcinoma**• Low-grade • High-grade • Other, specify**Squamous cell carcinoma or adenocarcinoma**• GX: Cannot be assessed• G1: Well differentiated• G2: Moderately differentiated• G3: Poorly differentiated• Other, specify | Histologic grading of urothelial tumours is best considered in two categories, non-invasive papillary tumours and invasive carcinoma. For non-invasive papillary tumours the 2016 World Health Organization (WHO) remains the same as in the 2004 WHO and continues to recommend the grading system first put forward by the International Society of Urological Pathology (ISUP) in 1997.1 The system is now recommended by almost all major pathology and urology organizations as the preferred grading system.2,3 This is a 3-tiered system with the lowest category of papillary urothelial neoplasm of low malignant potential considered to represent a tumour without the capacity to invade or metastasize and as such is considered to be a benign neoplasm.4 This lesion represents 21% to 36% of newly diagnosed non-invasive (Ta) papillary tumours5,6 and overall between 11% and 21% of newly diagnosed noninvasive papillary bladder tumours.7,8 Papillary urothelial neoplasm of low malignant potential is not reported using this dataset. It is nonetheless a significant diagnosis and does indicate an increased risk for the development of other neoplasms in the urinary tract. In one large study that included 1,006 non-invasive papillary tumours (papillary urothelial neoplasm of low malignant potential, 212 [21%]; low grade papillary carcinoma, 603 [60%]; high grade papillary carcinoma, 191 [19%]), treated by transurethral resection (TUR) with or without intravesical therapy, recurrence occurred in 18%, 35% and 34% of each respectively and progression in 2%, 7% and 29% respectively.5 The majority of studies have had similar results with no or minimal risk of progression in grade or stage for papillary urothelial neoplasm of low malignant potential.5,7,9,10 There are significant differences in the risk of progression to invasive carcinoma and death from bladder cancer between low and high grade papillary urothelial carcinoma.5,11,12 The grade of noninvasive papillary carcinoma is the major variable in the choice of therapy in these patients.13 Other features of importance in predicting outcome of patients with Ta papillary tumours are number of tumours/multifocality, 12,14-16 tumour size,12,17-19 the presence of associated carcinoma in situ (CIS),12 and a history of prior recurrence. 12 It has also been suggested that for low grade papillary tumours the frequency of follow up cystoscopies can be reduced.20 Grade heterogeneity is not uncommon in papillary urothelial carcinoma being reported in up to 32% of cases.4,21 It is currently recommended that tumour grade be assigned based on the highest grade present. Some authors have recommended considering a tumour low grade if the high grade component accounts for less than 5% of the tumour volume.4,22 Using the 1999 WHO grading system, Billis et al found that pure grade 3 tumours were more often muscle invasive than tumours with mixed grade 2 and 3 cases.21 They also reported that pure grade 1 tumours were invasive in 25% of cases compared to 66% of predominantly grade 1 tumours with a grade 2 component.21 Specific percentages of the grades in the mixed grade cases were not provided. In another study Cheng et al studied grade heterogeneity in non-invasive papillary neoplasms using the 1998 ISUP grading system.4 Tumours were evaluated based on predominant and secondary grades but ignored secondary components if less than 5%.4 In their study worst, predominant and average grade all were significant predictors of progression.4 Progression was higher in pure high grade tumours (>95% high grade) than in mixed high/low grade tumours (5% to 95% high grade).4 In another study tumours with less than 10% of high grade histology (5% of the cases) were compared with low and high-grade tumours.23 The progression free and cancer specific survival of the mixed cases was similar to low grade tumours and significantly better that the high grade cases.23 The limited data does not allow for a definitive statement regarding reporting of cases with a small volume of high grade tumour or to determine what percentage of high grade tumour is necessary to indicate a significantly worse prognosis. The International Consultation on Urologic Disease (ICUD) recommended against the application of an arbitrary percentage of high grade tumour when assigning grade.24 The 2016 WHO recommends grading based on the highest grade component and acknowledges the uncertainty of how to approach cases with a small proportion of high grade tumour. It does indicate that “it may be prudent to state the proportion of high-grade disease.” The use of the 1973 WHO grading system for papillary tumours remains in use in many regions and some published guidelines specifically recommend the reporting of both the current WHO grade with the 1973 grade,13,25,26 while others provide for the 1973 to be provided by institutional choice.2,3,27 It is beyond the scope of this commentary to provide a detailed argument for or against the 1973 WHO. Interested readers can review those discussions elsewhere.24-26,28 There is an extensive literature based on the 1973 WHO system documenting its significance as a predictor of outcome for papillary urothelial carcinoma. These include many studies using material from phase III clinical trials. The current European Organisation for Treatment and Research of Cancer (EORTC) risk tables, developed from the data of 8 phase III clinical trials use the 1973 WHO grading system.12 The International Collaboration on Cancer Reporting (ICCR) dataset follows the WHO 2016 approach with reporting of the WHO 2016 grade as a required element and the inclusion of other grading systems as optional.27 The grading of invasive urothelial carcinoma is another area of controversy. In North America the vast majority of invasive urothelial carcinomas have been diagnosed as high grade in contrast to European studies where a substantial percentage of invasive tumours have been graded as 2 or even 1. Currently there is general agreement that grade 1 tumours (WHO 1973), largely corresponding to papillary urothelial neoplasm of low malignant potential, lack the capacity to invade.29-31 In studies using the 1998 ISUP/WHO 2004 grading system the vast majority of invasive tumours are high grade.32,33 The conclusion of the ICUD pathology group was that all invasive carcinomas should be considered high grade.24,34 It has been noted that there are variants of urothelial carcinoma that have low grade cytologic features such the nested variant, but that appear to behave stage for stage like usual high grade carcinoma.35-38 When variant histology such as this is present the tumours should be reported as high grade despite the bland cytology in order to reflect the biologic behaviour.39 Nonetheless it is equally apparent that many pathologists have graded invasive urothelial carcinomas using the 1973 WHO and other systems and have demonstrated its prognostic significance.12,30,40,41 The 2016 WHO recommends continuing to grade invasive carcinoma using the WHO 2004 system recognising that the vast majority of tumours will be high grade.27 If invasive tumours are graded using an alternative grading system this should be indicated. References 1 Epstein JI, Amin MB, Reuter VR and Mostofi FK (1998). The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. Bladder Consensus Conference Committee. Am J Surg Pathol 22(12):1435-1448. 2 College of American Pathologists (CAP) (2017). Protocol for the Examination of Specimens from Patients with Carcinoma of the Urinary Bladder. Available at: http://www.cap.org/ShowProperty?nodePath=/UCMCon/Contribution Folders/WebContent/pdf/urinary-17protocol-3300.pdf (Accessed 1st March 2017). 3 Hansel DE, Amin MB, Comperat E, Cote RJ, Knuchel R, Montironi R, Reuter VE, Soloway MS, Umar SA and Van der Kwast TH (2013). A contemporary update on pathology standards for bladder cancer: transurethral resection and radical cystectomy specimens. Eur Urol 63(2):321-332. 4 Cheng L, Neumann RM, Nehra A, Spotts BE, Weaver AL and Bostwick DG (2000). Cancer heterogeneity and its biologic implications in the grading of urothelial carcinoma. Cancer 88(7):1663-1670. 5 Pan CC, Chang YH, Chen KK, Yu HJ, Sun CH and Ho DM (2010). Prognostic significance of the 2004 WHO/ISUP classification for prediction of recurrence, progression, and cancer-specific mortality of non-muscle-invasive urothelial tumors of the urinary bladder: a clinicopathologic study of 1,515 cases. Am J Clin Pathol 133(5):788-795. 6 Oosterhuis JW, Schapers RF, Janssen-Heijnen ML, Pauwels RP, Newling DW and ten Kate F (2002). Histological grading of papillary urothelial carcinoma of the bladder: prognostic value of the 1998 WHO/ISUP classification system and comparison with conventional grading systems. J Clin Pathol 55(12):900-905. 7 Fujii Y, Kawakami S, Koga F, Nemoto T and Kihara K (2003). Long-term outcome of bladder papillary urothelial neoplasms of low malignant potential. BJU Int 92(6):559-562. 8 Holmang S and Johansson SL (2002). Stage Ta-T1 bladder cancer: the relationship between findings at first followup cystoscopy and subsequent recurrence and progression. J Urol 167(4):1634-1637. 9 Holmang S, Hedelin H, Anderstrom C, Holmberg E, Busch C and Johansson SL (1999). Recurrence and progression in low grade papillary urothelial tumors. J Urol 162(3 Pt 1):702- 707.10 Pich A, Chiusa L, Formiconi A, Galliano D, Bortolin P and Navone R (2001). Biologic differences between noninvasive papillary urothelial neoplasms of low malignant potential and low-grade (grade 1) papillary carcinomas of the bladder. Am J Surg Pathol 25(12):1528- 1533.11 Burger M, van der Aa MN, van Oers JM, Brinkmann A, van der Kwast TH, Steyerberg EC, Stoehr R, Kirkels WJ, Denzinger S, Wild PJ, Wieland WF, Hofstaedter F, Hartmann A and Zwarthoff EC (2008). Prediction of progression of non-muscle-invasive bladder cancer by WHO 1973 and 2004 grading and by FGFR3 mutation status: a prospective study. Eur Urol 54(4):835-843. 12 Sylvester RJ, van der Meijden AP, Oosterlinck W, Witjes JA, Bouffioux C, Denis L, Newling DW and Kurth K (2006). Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol 49(3):466-465. 13 Babjuk M, Burger M, Zigeuner R, Shariat SF, van Rhijn BW, Comperat E, Sylvester RJ, Kaasinen E, Bohle A, Palou Redorta J and Roupret M (2013). EAU guidelines on non-muscleinvasive urothelial carcinoma of the bladder: update 2013. Eur Urol 64(4):639-653. 14 Kiemeney LA, Witjes JA, Heijbroek RP, Verbeek AL and Debruyne FM (1993). Predictability of recurrent and progressive disease in individual patients with primary superficial bladder cancer. J Urol 150(1):60-64. 15 Lutzeyer W, Rubben H and Dahm H (1982). Prognostic parameters in superficial bladder cancer: an analysis of 315 cases. J Urol 127(2):250-252. 16 Parmar MK, Freedman LS, Hargreave TB and Tolley DA (1989). Prognostic factors for recurrence and followup policies in the treatment of superficial bladder cancer: report from the British Medical Research Council Subgroup on Superficial Bladder Cancer (Urological Cancer Working Party). J Urol 142(2 Pt 1):284-288. 17 Kilinc MF, Sonmez NC, Dalkilic A, Arisan S and Guney S (2014). Analysis of results of recurrence and progression rates of high-grade Ta bladder cancer and comparison with results of high-grade T1. Urologia 81(4):237-241. 18 Dalesio O, Schulman CC, Sylvester R, De Pauw M, Robinson M, Denis L, Smith P and Viggiano G (1983). Prognostic factors in superficial bladder tumors. A study of the European Organization for Research on Treatment of Cancer: Genitourinary Tract Cancer Cooperative Group. J Urol 129(4):730-733. 19 Millan-Rodriguez F, Chechile-Toniolo G, Salvador-Bayarri J, Palou J, Algaba F and VicenteRodriguez J (2000). Primary superficial bladder cancer risk groups according to progression, mortality and recurrence. J Urol 164(3 Pt 1):680-684. 20 Herr HW, Donat SM and Reuter VE (2007). Management of low grade papillary bladder tumors. J Urol 178(4 Pt 1):1201-1205; discussion 1205. 21 Billis A, Carvalho RB, Mattos AC, Negretti F, Nogueira CR, Oliveira MC, Valenca JT, Jr., Adam RL, Cotta AC, Nunes MS and Dinamarco PV (2001). Tumor grade heterogeneity in urothelial bladder carcinoma--proposal of a system using combined numbers. Scand J Urol Nephrol 35(4):275-279. 22 May M, Brookman-Amissah S, Roigas J, Hartmann A, Storkel S, Kristiansen G, Gilfrich C, Borchardt R, Hoschke B, Kaufmann O and Gunia S (2010). Prognostic accuracy of individual uropathologists in noninvasive urinary bladder carcinoma: a multicentre study comparing the 1973 and 2004 World Health Organisation classifications. Eur Urol 57(5):850-858. 23 Gofrit ON, Pizov G, Shapiro A, Duvdevani M, Yutkin V, Landau EH, Zorn KC, Hidas G and Pode D (2014). Mixed high and low grade bladder tumors--are they clinically high or low grade? J Urol 191(6):1693-1696. 24 Amin MB, Smith SC, Reuter VE, Epstein JI, Grignon DJ, Hansel DE, Lin O, McKenney JK, Montironi R, Paner GP, Al-Ahmadie HA, Algaba F, Ali S, Alvarado-Cabrero I, Bubendorf L, Cheng L, Cheville JC, Kristiansen G, Cote RJ, Delahunt B, Eble JN, Genega EM, Gulmann C, Hartmann A, Langner C, Lopez-Beltran A, Magi-Galluzzi C, Merce J, Netto GJ, Oliva E, Rao P, Ro JY, Srigley JR, Tickoo SK, Tsuzuki T, Umar SA, Van der Kwast T, Young RH and Soloway MS (2015). Update for the practicing pathologist: The International Consultation On Urologic Disease-European association of urology consultation on bladder cancer. Mod Pathol 28(5):612-630. 25 Lopez-Beltran A, Bassi PF, Pavone-Macaluso M and Montironi R (2004). Handling and pathology reporting of specimens with carcinoma of the urinary bladder, ureter, and renal pelvis. A joint proposal of the European Society of Uropathology and the Uropathology Working Group. Virchows Arch 445(2):103-110.26 The Royal College of Pathologists (RCPath) (2013). Dataset for tumours of the urinary collecting system (renal pelvis, ureter, urinary bladder and urethra). Available at: https://www.rcpath.org/resourceLibrary/dataset-for-tumours-of-the-urinary-collectingsystem--renal-pelvis--ureter--urinary-bladder-and-urethra.html (Accessed 16th February 2016). 27 World Health Organization (2016). World Health Organization (WHO) Classification of tumours. Pathology and genetics of the urinary system and male genital organs. Moch H, Humphrey PA, Reuter VE, Ulbright TM. IARC Press, Lyon, France. 28 Harnden P (2007). A critical appraisal of the classification of urothelial tumours: time for a review of the evidence and a radical change? BJU Int 99(4):723-725. 29 Mikulowski P and Hellsten S (2005). T1 G1 urinary bladder carcinoma: fact or fiction? Scand J Urol Nephrol 39(2):135-137. 30 van Rhijn BW, Musquera M, Liu L, Vis AN, Zuiverloon TC, van Leenders GJ, Kirkels WJ, Zwarthoff EC, Boeve ER, Jobsis AC, Bapat B, Jewett MA, Zlotta AR and van der Kwast TH (2015). Molecular and clinical support for a four-tiered grading system for bladder cancer based on the WHO 1973 and 2004 classifications. Mod Pathol 28(5):695-705. 31 Kruger S, Thorns C, Bohle A and Feller AC (2003). Prognostic significance of a grading system considering tumor heterogeneity in muscle-invasive urothelial carcinoma of the urinary bladder. Int Urol Nephrol 35(2):169-173. 32 Cao D, Vollmer RT, Luly J, Jain S, Roytman TM, Ferris CW and Hudson MA (2010). Comparison of 2004 and 1973 World Health Organization grading systems and their relationship to pathologic staging for predicting long-term prognosis in patients with urothelial carcinoma. Urology 76(3):593-599. 33 Otto W, Denzinger S, Fritsche HM, Burger M, Wieland WF, Hofstadter F, Hartmann A and Bertz S (2011). The WHO classification of 1973 is more suitable than the WHO classification of 2004 for predicting survival in pT1 urothelial bladder cancer. BJU Int 107(3):404-408. 34 Amin MB, McKenney JK, Paner GP, Hansel DE, Grignon DJ, Montironi R, Lin O, Jorda M, Jenkins LC, Soloway M, Epstein JI and Reuter VE (2013). ICUD-EAU International Consultation on Bladder Cancer 2012: Pathology. Eur Urol 63(1):16-35. 35 Linder BJ, Frank I, Cheville JC, Thompson RH, Thapa P, Tarrell RF and Boorjian SA (2013). Outcomes following radical cystectomy for nested variant of urothelial carcinoma: a matched cohort analysis. J Urol 189(5):1670-1675. 36 Lopez-Beltran A, Cheng L, Montironi R, Blanca A, Leva M, Roupret M, Fonseca J, Vidal A, Menendez CL, Pallares J, Bollito E, Reymundo C, Luque RJ and Comperat E (2014). Clinicopathological characteristics and outcome of nested carcinoma of the urinary bladder. Virchows Arch 465(2):199-205. 37 Wasco MJ, Daignault S, Bradley D and Shah RB (2010). Nested variant of urothelial carcinoma: a clinicopathologic and immunohistochemical study of 30 pure and mixed cases. Hum Pathol 41(2):163-171. 38 Cox R and Epstein JI (2011). Large nested variant of urothelial carcinoma: 23 cases mimicking von Brunn nests and inverted growth pattern of noninvasive papillary urothelial carcinoma. Am J Surg Pathol 35(9):1337-1342. 39 Amin MB et al (2012). Bladder Cancer. Pathology Consensus Guidelines by the Pathology of Bladder Cancer Work Group. Soloway S, Khoury A (Eds). ICUD-EAU, Paris, France. 40 Nishiyama N, Kitamura H, Maeda T, Takahashi S, Masumori N, Hasegawa T and Tsukamoto T (2013). Clinicopathological analysis of patients with non-muscle-invasive bladder cancer: prognostic value and clinical reliability of the 2004 WHO classification system. Jpn J Clin Oncol 43(11):1124-1131. 41 Patschan O, Sjodahl G, Chebil G, Lovgren K, Lauss M, Gudjonsson S, Kollberg P, Eriksson P, Aine M, Mansson W, Ferno M, Liedberg F and Hoglund M (2015). A Molecular Pathologic Framework for Risk Stratification of Stage T1 Urothelial Carcinoma. Eur Urol 68(5):824-832. |  |
| Required | STATUS OF MUSCULARIS PROPRIA | Single selection value list:• Present• Not present/submitted | The presence or absence of muscularis propria is a vital piece of information in determining the adequacy of a biopsy or transurethral resection (TUR) specimen that contains an invasive carcinoma.1-3 For such patients, the absence of muscularis propria in a transurethral resection of bladder tumour (TURBT) would be an indication for a repeat TUR to be performed if treatment is other than cystectomy. It is well documented that absence of muscularis propria in a TURBT specimen is associated with a significantly increased risk of residual disease and early recurrence.4 The current European Association of Urology (EAU) guidelines recommend repeat TUR (i) after an incomplete initial TUR, (ii) if there is no muscle in the specimen after initial resection with the exception of Ta, LG/G1 tumours and primary carcinoma in situ (CIS), (iii) in all T1 tumours and (iv) in all HG/G3 tumours except primary CIS.3 It generally is also considered appropriate to comment on the presence or absence of muscularis propria in a biopsy or TUR specimen, irrespective of the presence or absence of invasive carcinoma. References 1 Hansel DE, Amin MB, Comperat E, Cote RJ, Knuchel R, Montironi R, Reuter VE, Soloway MS, Umar SA and Van der Kwast TH (2013). A contemporary update on pathology standards for bladder cancer: transurethral resection and radical cystectomy specimens. Eur Urol 63(2):321-332. 2 Lopez-Beltran A, Bassi PF, Pavone-Macaluso M and Montironi R (2004). Handling and pathology reporting of specimens with carcinoma of the urinary bladder, ureter, and renal pelvis. A joint proposal of the European Society of Uropathology and the Uropathology Working Group. Virchows Arch 445(2):103-110. 3 Babjuk M, Burger M, Zigeuner R, Shariat SF, van Rhijn BW, Comperat E, Sylvester RJ, Kaasinen E, Bohle A, Palou Redorta J and Roupret M (2013). EAU guidelines on non-muscleinvasive urothelial carcinoma of the bladder: update 2013. Eur Urol 64(4):639-653. 4 Mariappan P, Finney SM, Head E, Somani BK, Zachou A, Smith G, Mishriki SF, N'Dow J and Grigor KM (2012). Good quality white-light transurethral resection of bladder tumours (GQWLTURBT) with experienced surgeons performing complete resections and obtaining detrusor muscle reduces early recurrence in new non-muscle-invasive bladder cancer: validation across time and place and recommendation for benchmarking. BJU Int 109(11):1666-1673. |  |
| Required | EXTENT OF INVASION | Cannot be assessedOR Multi selection value list (select all that apply):• Papillary carcinoma, non-invasive• Carcinoma in situ, flat• Tumour invades subepithelial connective tissue (lamina propria)• Tumour invades muscularis propria (detrusor muscle)• Tumour involving prostatic urethra• Tumour involving prostatic ducts and acini• Tumour invasive into prostatic stroma• Tumour invasive into renal stroma• Tumour invasive into periurethral muscle• Tumour invasive into corpus spongiosum• Tumour invasive into corpus cavernosum• Other, specify | Reporting the extent of invasion is a critical part of the assessment of carcinomas arising in the urinary tract. The elements included reflect the anatomic landmarks that are essential to the pathologic staging of each tumour and vary by site within the urinary tract.1 It is not appropriate to assign pathologic stage on biopsy or transurethral resection (TUR) specimens and pathologic stage is not an element within this dataset. It is however possible, based on the assessment of the extent of invasion to recognise the least pathological stage possible in a given case. The diagnosis of invasion can be challenging. Throughout the urothelial tract histologic features that are indicative of stromal invasion include individual tumour cells, irregular nests or cords of cells, retraction artefact around nests, increased cytoplasmic eosinophilia and a myxoid or desmoplastic stromal response.2,3 Several studies have documented the difficulty with the diagnosis of invasion.4-6 Two large studies based on central review of patients being entered on clinical trials have demonstrated the over diagnosis of invasion in 35% to 53% of cases.7,8 Studies have also demonstrated lack of agreement among pathologists with special interest in urologic pathology.9 In some cases immunohistochemistry with a pan cytokeratin marker is helpful in identifying individual cells particularly when there is a heavy inflammatory infiltrate present. Following the principles of the American Joint Committee on Cancer (AJCC) TNM staging system the diagnosis of invasion should be limited to cases with unequivocal invasion.1 Identification of invasion of smooth muscle fibres in specimens from the renal pelvis, ureter and urethra all indicate T2 disease. In the urinary bladder the presence of the muscularis mucosae complicates the interpretation as involvement of these fibres still represents a T1 tumour.10 Muscularis mucosae fibres can be present throughout the bladder.11 The trigone/bladder neck region least often has recognisable muscularis mucosae fibres and from a practical perspective involvement of smooth muscle in this location essentially always indicates muscularis propria invasion. Muscularis mucosae fibres are typically thin and wispy forming small bundles that taper at the ends and usually are only a few cells thick. They lack the dense eosinophilic cytoplasm characteristic of muscularis propria. Often the fibres are seen in association with a layer of thick walled blood vessels. The muscularis mucosae can however occasionally be thickened and better defined, more closely mimicking muscularis propria. Smoothelin, a cytoskeletal protein is differentially expressed in the muscularis propria and not the muscularis mucosae.12 Application in challenging cases can be helpful but for the most part the marker has not gained widespread application.13,14 Regarding the use of smoothelin for staging, the International Society of Urological Pathology (ISUP) states “limited experience and conflicting data preclude smoothelin or vimentin to be recommended routinely for subclassifying muscle type at this time.”15 In some cases it is not possible to be certain if the smooth muscle involvement represents muscularis mucosae or muscularis propria. In those cases this should be specifically commented upon. Repeat TUR on these cases is necessary to determine the true depth of involvement.14 Assessment of the presence or absence of muscularis propria invasion can also be hampered by cautery artefact. This can result in stromal changes that mimic smooth muscle leading to over staging or make muscularis propria unrecognisable leading to under staging.16 Pathologists have used histochemistry (trichrome stain) or immunohistochemistry (desmin) to help determine if muscle is represented in cauterized tissue but no controlled studies of the reliability of these approaches is available. Urothelial carcinoma can be primary in the prostatic urethra but in the majority of cases involvement is seen in association with a bladder tumour.17-19 Among all male patients with bladder cancer the prostate is involved in approximately 4% of cases.20 Prostatic involvement is found in 15% to 48% of patients undergoing cystoprostatectomy for urothelial carcinoma of the bladder.21-24 Involvement is usually by urothelial CIS but occasionally papillary tumours are seen. Extension into the prostatic ducts is frequently present in these cases and should not be mistaken for invasion. Inflammation can be present around the ducts in the absence of invasion. Usually invasion of the subepithelial connective tissue or the prostatic stroma elicits a desmoplastic response. Immunohistochemistry is frequently required to distinguish urothelial carcinoma from high grade prostatic carcinoma.15 Glandular and or squamous differentiation can be present as with urothelial carcinoma elsewhere. References 1 Edge SE, Byrd DR, Compton CC, Fritz AG, Greene FL and Trotti A (Eds) (2010). AJCC Cancer Staging Manual 7th ed., New York, NY.: Springer. 2 Amin MB, Gomez JA and Young RH (1997). Urothelial transitional cell carcinoma with endophytic growth patterns: a discussion of patterns of invasion and problems associated with assessment of invasion in 18 cases. Am J Surg Pathol 21(9):1057-1068. 3 McKenney JK, Gomez JA, Desai S, Lee MW and Amin MB (2001). Morphologic expressions of urothelial carcinoma in situ: a detailed evaluation of its histologic patterns with emphasis on carcinoma in situ with microinvasion. Am J Surg Pathol 25(3):356-362. 4 Tosoni I, Wagner U, Sauter G, Egloff M, Knonagel H, Alund G, Bannwart F, Mihatsch MJ, Gasser TC and Maurer R (2000). Clinical significance of interobserver differences in the staging and grading of superficial bladder cancer. BJU Int 85(1):48-53. 5 Bol MG, Baak JP, Buhr-Wildhagen S, Kruse AJ, Kjellevold KH, Janssen EA, Mestad O and Ogreid P (2003). Reproducibility and prognostic variability of grade and lamina propria invasion in stages Ta, T1 urothelial carcinoma of the bladder. J Urol 169(4):1291-1294. 6 van Rhijn BW, van der Kwast TH, Kakiashvili DM, Fleshner NE, van der Aa MN, Alkhateeb S, Bangma CH, Jewett MA and Zlotta AR (2010). Pathological stage review is indicated in primary pT1 bladder cancer. BJU Int 106(2):206-211.7 Van Der Meijden A, Sylvester R, Collette L, Bono A and Ten Kate F (2000). The role and impact of pathology review on stage and grade assessment of stages Ta and T1 bladder tumors: a combined analysis of 5 European Organization for Research and Treatment of Cancer Trials. J Urol 164(5):1533-1537.8 Witjes JA, Moonen PM and van der Heijden AG (2006). Review pathology in a diagnostic bladder cancer trial: effect of patient risk category. Urology 67(4):751-755. 9 Pathologists of the French Association of Urology Cancer Committee (1993). Lamina propria microinvasion of bladder tumors, incidence on stage allocation (pTa vs pT1): recommended approach. World J Urol 11(3):161-164. 10 Ro JY, Ayala AG and el-Naggar A (1987). Muscularis mucosa of urinary bladder. Importance for staging and treatment. Am J Surg Pathol 11(9):668-673. 11 Paner GP, Ro JY, Wojcik EM, Venkataraman G, Datta MW and Amin MB (2007). 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. Am J Surg Pathol 31(9):1420-1429. 12 Paner GP, Shen SS, Lapetino S, Venkataraman G, Barkan GA, Quek ML, Ro JY and Amin MB (2009). Diagnostic utility of antibody to smoothelin in the distinction of muscularis propria from muscularis mucosae of the urinary bladder: a potential ancillary tool in the pathologic staging of invasive urothelial carcinoma. Am J Surg Pathol 33(1):91-98. 13 Paner GP, Brown JG, Lapetino S, Nese N, Gupta R, Shen SS, Hansel DE and Amin MB (2010). Diagnostic use of antibody to smoothelin in the recognition of muscularis propria in transurethral resection of urinary bladder tumor (TURBT) specimens. Am J Surg Pathol 34(6):792-799. 14 Miyamoto H, Sharma RB, Illei PB and Epstein JI (2010). Pitfalls in the use of smoothelin to identify muscularis propria invasion by urothelial carcinoma. Am J Surg Pathol 34(3):418- 422. 15 Amin MB, Trpkov K, Lopez-Beltran A and Grignon D (2014). Best practices recommendations in the application of immunohistochemistry in the bladder lesions: report from the International Society of Urologic Pathology consensus conference. Am J Surg Pathol 38(8):e20-34. 16 Hansel DE, Amin MB, Comperat E, Cote RJ, Knuchel R, Montironi R, Reuter VE, Soloway MS, Umar SA and Van der Kwast TH (2013). A contemporary update on pathology standards for bladder cancer: transurethral resection and radical cystectomy specimens. Eur Urol 63(2):321-332. 17 Cheville JC, Dundore PA, Bostwick DG, Lieber MM, Batts KP, Sebo TJ and Farrow GM (1998). Transitional cell carcinoma of the prostate: clinicopathologic study of 50 cases. Cancer 82(4):703-707. 18 Oliai BR, Kahane H and Epstein JI (2001). A clinicopathologic analysis of urothelial carcinomas diagnosed on prostate needle biopsy. Am J Surg Pathol 25(6):794-801. 19 Shen SS, Lerner SP, Muezzinoglu B, Truong LD, Amiel G and Wheeler TM (2006). Prostatic involvement by transitional cell carcinoma in patients with bladder cancer and its prognostic significance. Hum Pathol 37(6):726-734. 20 Mungan MU, Canda AE, Tuzel E, Yorukoglu K and Kirkali Z (2005). Risk factors for mucosal prostatic urethral involvement in superficial transitional cell carcinoma of the bladder. Eur Urol 48(5):760-763. 21 Lerner SP and Shen S (2008). Pathologic assessment and clinical significance of prostatic involvement by transitional cell carcinoma and prostate cancer. Urol Oncol 26(5):481-485. 22 Revelo MP, Cookson MS, Chang SS, Shook MF, Smith JA, Jr. and Shappell SB (2004). Incidence and location of prostate and urothelial carcinoma in prostates from cystoprostatectomies: implications for possible apical sparing surgery. J Urol 171(2 Pt 1):646- 651. 23 Wood DP, Jr., Montie JE, Pontes JE and Levin HS (1989). Identification of transitional cell carcinoma of the prostate in bladder cancer patients: a prospective study. J Urol 142(1):83- 85. 24 Knoedler JJ, Boorjian SA, Tollefson MK, Cheville JC, Thapa P, Tarrell RF and Frank I (2014). Urothelial carcinoma involving the prostate: the association of revised tumour stage and coexistent bladder cancer with survival after radical cystectomy. BJU Int 114(6):832-836. |  |
| Recommended | SUBSTAGING T1 DISEASE | Numeric:Depth of invasion \_\_\_ mmAND/ORTotal maximum dimension of invasive tumour \_\_\_mmAND/ORSingle selection value list:• Invasion superficial to muscularis mucosae• Invasion involving and/or deep to muscularis mucosae | There have been many efforts to establish the optimum method of identifying T1 tumours with low and high risk for recurrence, progression and death from bladder cancer. One focus of many of these reports has been to “substage” T1 tumours. The two methods most used can be divided into quantitative and anatomical. The largest volume of literature has tried to use the muscularis mucosae (MM) as a landmark to subdivide T1 tumours into 2 or 3 subgroups. The first study of this type is the report of Younes et al who divided tumours into T1a (invasion superficial to MM), T1b (to the MM) and T1c (deep to the MM).1 They found that the T1b/T1c tumours were associated with a worse progression free and cancer specific survival. Since that report numerous groups have reported their experience with this approach.1 The largest study to date is that of Rouprȇt et al (2013) that evaluated 587 cases from multiple institutions in France.2 On multivariable analysis, pT1b (involving or deep to MM) tumours had a significantly worse recurrence-, progression and cancer specific survival.2 These authors also provide a comprehensive literature review that included 21 prior publications.2 Based on this review a few observations can be made: (i) the ability to assess MM ranged from 58% to 100% (ii) on univariate analysis use of MM was a significant predictor of recurrence free survival in 4/12 reports, progression free survival in 15/17 reports and of cancer specific survival in 4 of 7 reports and (iii) on multivariable analysis it was significant for recurrence free survival in 3/12, for progression free survival in 13/16 and for cancer specific survival in 3/6 publications.2 Additional studies have been published subsequently.3-5 The study by Orsolo et al (2015) is significant in that this is a prospective study that used substaging based on invasion superficial to the MM (T1a) versus involving or deep to MM (T1b) to stratify patient treatment.5 The publication reports on the first 200 patients entered into the protocol.5 Although the follow up is limited in this initial report, substage was a highly significant predictor of tumour progression on multivariable analysis.5 These authors concluded: “In HGT1 bladder cancer, the strategy of performing a second TUR only in T1b cases results in a global low progression rate of 15.5%. Tumours deeply invading the lamina propria (HGT1b) showed a three-fold increase in risk of progression. Substaging should be routinely evaluated, with HGT1b Recent guidelines have generally recommended that pathologists provide some indication of volume or depth of invasion without specifying a preferred method.12 In the International Consultation on Urologic Disease (ICUD) recommendations for quantitation, Amin et al stated “It is recommended that pathologists provide some form of estimate of the lamina propria invasion in pT1 tumours (e.g. focal, multifocal, extensive, etc)” and “Involvement of the MM may be included in a comment to provide information on the depth/extent of invasion.” The 2016 WHO follows this recommendation as do the recently released College of American Pathologists reporting guidelines. 12,13 Clinical guidelines have also noted the importance of depth of invasion. In the ICUD section on treatment of high grade Ta, carcinoma in situ (CIS) and T1 urothelial carcinoma, the author’s first recommendation is “The assessment of T1 urothelial carcinoma should be based on tumour grade, early recurrence, multiplicity, tumour size, concomitant CIS, urothelial carcinoma involving the prostatic mucosa or ducts, and depth of invasion.”14 Because of the potential for additional information in T1 tumours to directly impact clinical decision making the International Collaboration on Cancer Reporting (ICCR) guidelines have included substaging of TI disease as a non-required element. The dataset also provides for alternative methods for reporting as there is insufficient data to recommend one alternative over the others. References 1 Younes M, Sussman J and True LD (1990). The usefulness of the level of the muscularis mucosae in the staging of invasive transitional cell carcinoma of the urinary bladder. Cancer 66(3):543-548. 2 Roupret M, Seisen T, Comperat E, Larre S, Mazerolles C, Gobet F, Fetissof F, Fromont G, Safsaf A, d'Arcier BF, Celhay O, Validire P, Rozet F, Irani J, Soulie M and Pfister C (2013). Prognostic interest in discriminating muscularis mucosa invasion (T1a vs T1b) in nonmuscle invasive bladder carcinoma: French national multicenter study with central pathology review. J Urol 189(6):2069-2076. 3 Soukup V, Duskova J, Pesl M, Capoun O, Feherova Z, Zamecnik L, Hanus T and Babjuk M (2014). The prognostic value of T1 bladder cancer substaging: a single institution retrospective study. Urol Int 92(2):150-156. 4 De Marco V, Cerruto MA, D'Elia C, Brunelli M, Otte O, Minja A, Luchini C, Novella G, Cavalleri S, Martignoni G and Artibani W (2014). Prognostic role of substaging in T1G3 transitional cell carcinoma of the urinary bladder. Mol Clin Oncol 2(4):575-580. 5 Orsola A, Werner L, de Torres I, Martin-Doyle W, Raventos CX, Lozano F, Mullane SA, Leow JJ, Barletta JA, Bellmunt J and Morote J (2015). Reexamining treatment of high-grade T1 bladder cancer according to depth of lamina propria invasion: a prospective trial of 200 patients. Br J Cancer 112(3):468-474. 6 Cheng L, Weaver AL, Neumann RM, Scherer BG and Bostwick DG (1999). Substaging of T1 bladder carcinoma based on the depth of invasion as measured by micrometer: A new proposal. Cancer 86(6):1035-1043. 7 van der Aa MN, van Leenders GJ, Steyerberg EW, van Rhijn BW, Jobsis AC, Zwarthoff EC and van der Kwast TH (2005). A new system for substaging pT1 papillary bladder cancer: a prognostic evaluation. Hum Pathol 36(9):981-986. 8 Chang WC, Chang YH and Pan CC (2012). Prognostic significance in substaging ofT1 urinary bladder urothelial carcinoma on transurethral resection. Am J Surg Pathol 36(3):454-461. 9 van Rhijn BW, van der Kwast TH, Alkhateeb SS, Fleshner NE, van Leenders GJ, Bostrom PJ, van der Aa MN, Kakiashvili DM, Bangma CH, Jewett MA and Zlotta AR (2012). A new and highly prognostic system to discern T1 bladder cancer substage. Eur Urol 61(2):378-384. 10 Hu Z, Mudaliar K, Quek ML, Paner GP and Barkan GA (2014). Measuring the dimension of invasive component in pT1 urothelial carcinoma in transurethral resection specimens can predict time to recurrence. Ann Diagn Pathol 18(2):49-52. 11 Brimo F, Wu C, Zeizafoun N, Tanguay S, Aprikian A, Mansure JJ and Kassouf W (2013). Prognostic factors in T1 bladder urothelial carcinoma: the value of recording millimetric depth of invasion, diameter of invasive carcinoma, and muscularis mucosa invasion. Hum Pathol 44(1):95-102. 12 College of American Pathologists (CAP) (2017). Protocol for the Examination of Specimens from Patients with Carcinoma of the Urinary Bladder. Available at: http://www.cap.org/ShowProperty?nodePath=/UCMCon/Contribution Folders/WebContent/pdf/urinary-17protocol-3300.pdf (Accessed 1st March 2017). 13 World Health Organization (2016). World Health Organization (WHO) Classification of tumours. Pathology and genetics of the urinary system and male genital organs. Moch H, Humphrey PA, Reuter VE, Ulbright TM. IARC Press, Lyon, France. 14 Burger M, Witjes F, Babjuk M, Brausi M, Cheng C, Comperat E, Dinney C, Jager W, Otto W, Shah J, Thurof J (2012). Bladder Cancer. High grade Ta, CIS, and T1 urothelial carcinoma. Soloway S, Khoury A (Eds). EAU/ICUD, Paris, France. |  |
| Required | LYMPHOVASCULAR INVASION | Single selection value list:• Not identified • Present • Indeterminate | The data on lymphovascular invasion (LVI) in urothelial carcinoma in the urinary bladder has continued to grow with many large series now reported. 1-5 These have included very large multiinstitutional series (e.g. Kluth et al4 – 8102 patients), cases from phase 3 clinical trials (von Rundstedt et al5 – SWOG4B951/NCT00005047) and in the generation of prognostic scores (Eisenberg et al3 – SPARC Score) all of which have found LVI to be a highly significant predictor of outcome. Studies that have evaluated the significance of LVI on biopsy or transurethral resection of bladder tumour (TURBT) material specifically are much more limited.6-16 These have almost all been based on H&E evaluation with limited utilisation of immunohistochemistry. The frequency of identification of LVI has ranged from <10% to as high as 67%. Among the better studies are the paper by Olsson et al (2013) which is population based [all newly diagnosed T1 tumours (N=211)] in the Southeastern region of Sweden with relatively uniform treatment.16 These authors identified LVI in 8% of cases and also included an indeterminate category (22% of cases).16 The presence of LVI was an independent predictor of recurrence free-, progression free- and cancer specific survival.16 The prospective study by Orsola et al (2005) in contrast found no significant association with progression-free or cancer specific survival.17 This study is limited by the short follow up. Overall the majority of these studies have found LVI to be important but, as indicated, data is limited. Specific data on LVI determination in biopsy/ transurethral resection (TUR) specimens of upper tract and urethra are not available. There are several reports that have found LVI to be significant (various endpoints) in resection specimens for upper tract urothelial carcinoma. 18-21 These large, contemporary series have consistently identified LVI as a significant parameter in upper tract urinary cancer. For example, the study by Cha et al (2012) was a multi-institutional retrospective analysis of 2244 patients treated by radical nephroureterectomy.18 The cases were divided into a development and an external validation cohort. LVI (based on the pathology reports) was an independent predictor of recurrence free survival and cancer specific survival in both cohorts and was included in the 2-year and 5-year recurrence-free and cancer-specific survival nomograms.18 For urethral carcinoma there is no substantive literature available. In the 2013 Guidelines on Urethral Carcinoma by the European Association of Urology (EAU), LVI is not recognised as a prognostic indicator.22 The role of immunohistochemistry in determining the presence or absence of LVI has been limited. The problem with recognising LVI on H&E sections has been demonstrated for urothelial carcinoma. Algaba23 and Lopez-Beltran24 among others have pointed out the importance of utilising strict criteria and these should be followed. Criteria recommended by Algaba (2006) included tightly cohesive tumour cells with a smooth border and the cells at the periphery having a shell-like appearance, the tumour thrombus floating free in the lumen of a space with an unequivocal endothelial cell lining, the presence of fibrin and/or red blood cells around the thrombus, and the space preferably associated with an arteriole with the surrounding stroma appearing normal.23 The possibility of routinely performing immunohistochemistry on T1 cases is much discussed but with little data. In one report8 immunohistochemistry for D2-40 and CD34 was performed on 25 TUR specimens and the H&E evaluation of LVI was changed in only one case. This contrasts with the report by Larsen et al (1990) who found that only 14% of cases diagnosed as LVI by H&E were confirmed by immunohistochemistry. 6 It is likely that the Larsen study overstates the problem of overcalling of LVI in current practice. The International Consultation on Urologic Disease (ICUD) pathology committee noted that there is well documented value to using immunohistochemistry in other organs to maximize detection of LVI (e.g. breast, etc) but little for urothelial carcinoma. They concluded “The general use of immunohistochemistry in the routine setting cannot however be recommended since performing two immunohistochemical stains on even selected paraffin blocks with bladder cancer would be extremely time consuming and cost intensive.”25 Although the data on LVI in biopsy/TUR specimens is limited, the compelling evidence in large resection studies of urothelial carcinoma of the urinary bladder and upper tract support inclusion as a required element in this dataset. References 1 Fritsche HM, Burger M, Svatek RS, Jeldres C, Karakiewicz PI, Novara G, Skinner E, Denzinger S, Fradet Y, Isbarn H, Bastian PJ, Volkmer BG, Montorsi F, Kassouf W, Tilki D, Otto W, Capitanio U, Izawa JI, Ficarra V, Lerner S, Sagalowsky AI, Schoenberg M, Kamat A, Dinney CP, Lotan Y and Shariat SF (2010). Characteristics and outcomes of patients with clinical T1 grade 3 urothelial carcinoma treated with radical cystectomy: results from an international cohort. Eur Urol 57(2):300-309. 2 Shariat SF, Svatek RS, Tilki D, Skinner E, Karakiewicz PI, Capitanio U, Bastian PJ, Volkmer BG, Kassouf W, Novara G, Fritsche HM, Izawa JI, Ficarra V, Lerner SP, Sagalowsky AI, Schoenberg MP, Kamat AM, Dinney CP, Lotan Y, Marberger MJ and Fradet Y (2010). International validation of the prognostic value of lymphovascular invasion in patients treated with radical cystectomy. BJU Int 105(10):1402-1412. 3 Eisenberg MS, Boorjian SA, Cheville JC, Thompson RH, Thapa P, Kaushik D and Frank I (2013). The SPARC score: a multifactorial outcome prediction model for patients undergoing radical cystectomy for bladder cancer. J Urol 190(6):2005-2010. 4 Kluth LA, Rieken M, Xylinas E, Kent M, Rink M, Roupret M, Sharifi N, Jamzadeh A, Kassouf W, Kaushik D, Boorjian SA, Roghmann F, Noldus J, Masson-Lecomte A, Vordos D, Ikeda M, Matsumoto K, Hagiwara M, Kikuchi E, Fradet Y, Izawa J, Rendon R, Fairey A, Lotan Y, Bachmann A, Zerbib M, Fisch M, Scherr DS, Vickers A and Shariat SF (2014). Gender-specific differences in clinicopathologic outcomes following radical cystectomy: an international multi-institutional study of more than 8000 patients. Eur Urol 66(5):913-919. 5 von Rundstedt FC, Mata DA, Groshen S, Stein JP, Skinner DG, Stadler WM, Cote RJ, Kryvenko ON, Godoy G and Lerner SP (2015). Significance of lymphovascular invasion in organconfined, node-negative urothelial cancer of the bladder: data from the prospective p53- MVAC trial. BJU Int 116(1):44-49. 6 Larsen MP, Steinberg GD, Brendler CB and Epstein JI (1990). Use of Ulex europaeus agglutinin I (UEAI) to distinguish vascular and "pseudovascular" invasion in transitional cell carcinoma of bladder with lamina propria invasion. Mod Pathol 3(1):83-88. 7 Lopez JI and Angulo JC (1995). The prognostic significance of vascular invasion in stage T1 bladder cancer. Histopathology 27(1):27-33. 8 Kunju LP, You L, Zhang Y, Daignault S, Montie JE and Lee CT (2008). Lymphovascular invasion of urothelial cancer in matched transurethral bladder tumor resection and radical cystectomy specimens. J Urol 180(5):1928-1932. 9 Andius P, Johansson SL and Holmang S (2007). Prognostic factors in stage T1 bladder cancer: tumor pattern (solid or papillary) and vascular invasion more important than depth of invasion. Urology 70(4):758-762. 10 Streeper NM, Simons CM, Konety BR, Muirhead DM, Williams RD, O'Donnell MA and Joudi FN (2009). The significance of lymphovascular invasion in transurethral resection of bladder tumour and cystectomy specimens on the survival of patients with urothelial bladder cancer. BJU Int 103(4):475-479. 11 Cho KS, Seo HK, Joung JY, Park WS, Ro JY, Han KS, Chung J and Lee KH (2009). Lymphovascular invasion in transurethral resection specimens as predictor of progression and metastasis in patients with newly diagnosed T1 bladder urothelial cancer. J Urol 182(6):2625-2630. 12 Segal R, Yafi FA, Brimo F, Tanguay S, Aprikian A and Kassouf W (2012). Prognostic factors and outcome in patients with T1 high-grade bladder cancer: can we identify patients for early cystectomy? BJU Int 109(7):1026-1030. 13 Tilki D, Shariat SF, Lotan Y, Rink M, Karakiewicz PI, Schoenberg MP, Lerner SP, Sonpavde G, Sagalowsky AI and Gupta A (2013). Lymphovascular invasion is independently associated with bladder cancer recurrence and survival in patients with final stage T1 disease and negative lymph nodes after radical cystectomy. BJU Int 111(8):1215-1221. 14 Brimo F, Wu C, Zeizafoun N, Tanguay S, Aprikian A, Mansure JJ and Kassouf W (2013). Prognostic factors in T1 bladder urothelial carcinoma: the value of recording millimetric depth of invasion, diameter of invasive carcinoma, and muscularis mucosa invasion. Hum Pathol 44(1):95-102. 15 Branchereau J, Larue S, Vayleux B, Karam G, Bouchot O and Rigaud J (2013). Prognostic value of the lymphovascular invasion in high-grade stage pT1 bladder cancer. Clin Genitourin Cancer 11(2):182-188. 16 Olsson H, Hultman P, Rosell J and Jahnson S (2013). Population-based study on prognostic factors for recurrence and progression in primary stage T1 bladder tumours. Scand J Urol 47(3):188-195. 17 Orsola A, Trias I, Raventos CX, Espanol I, Cecchini L, Bucar S, Salinas D and Orsola I (2005). Initial high-grade T1 urothelial cell carcinoma: feasibility and prognostic significance of lamina propria invasion microstaging (T1a/b/c) in BCG-treated and BCG-non-treated patients. Eur Urol 48(2):231-238. 18 Cha EK, Shariat SF, Kormaksson M, Novara G, Chromecki TF, Scherr DS, Lotan Y, Raman JD, Kassouf W, Zigeuner R, Remzi M, Bensalah K, Weizer A, Kikuchi E, Bolenz C, Roscigno M, Koppie TM, Ng CK, Fritsche HM, Matsumoto K, Walton TJ, Ehdaie B, Tritschler S, Fajkovic H, Martinez-Salamanca JI, Pycha A, Langner C, Ficarra V, Patard JJ, Montorsi F, Wood CG, Karakiewicz PI and Margulis V (2012). Predicting clinical outcomes after radical nephroureterectomy for upper tract urothelial carcinoma. Eur Urol 61(4):818-825. 19 Godfrey MS, Badalato GM, Hruby GW, Razmjoo M and McKiernan JM (2012). Prognostic indicators for upper tract urothelial carcinoma after radical nephroureterectomy: the impact of lymphovascular invasion. BJU Int 110(6):798-803. 20 Hurel S, Roupret M, Ouzzane A, Rozet F, Xylinas E, Zerbib M, Berod AA, Ruffion A, Adam E, Cussenot O, Houlgatte A, Phe V, Nouhaud FX, Bensadoun H, Delage F, Guillotreau J, Guy L, Karsenty G, De La Taille A and Colin P (2013). Impact of lymphovascular invasion on oncological outcomes in patients with upper tract urothelial carcinoma after radical nephroureterectomy. BJU Int 111(8):1199-1207. 21 Lee SM, Russell A and Hellawell G (2015). Predictive value of pretreatment inflammationbased prognostic scores (neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio) for invasive bladder carcinoma. Korean J Urol 56(11):749- 755. 22 Gakis G, Witjes JA, Comperat E, Cowan NC, De Santis M, Lebret T, Ribal MJ and Sherif AM (2013). EAU guidelines on primary urethral carcinoma. Eur Urol 64(5):823-830. 23 Algaba F (2006). Lymphovascular invasion as a prognostic tool for advanced bladder cancer. Curr Opin Urol 16(5):367-371. 24 Lopez-Beltran A, Bassi PF, Pavone-Macaluso M and Montironi R (2004). Handling and pathology reporting of specimens with carcinoma of the urinary bladder, ureter, and renal pelvis. A joint proposal of the European Society of Uropathology and the Uropathology Working Group. Virchows Arch 445(2):103-110. 25 Amin MB et al (2012). Bladder Cancer. Pathology Consensus Guidelines by the Pathology of Bladder Cancer Work Group. Soloway S, Khoury A (Eds). ICUD-EAU, Paris, France. |  |
| Recommended | COEXISTENT PATHOLOGY | Single selection value list:• None identified• Present, specify | Biopsy and endoscopic resection specimens from throughout the urinary tract that are diagnosed with carcinoma can also show a number of non-neoplastic conditions. Although some findings such as keratinizing squamous metaplasia and diffuse intestinal metaplasia may be relevant in a specific case the reporting of these findings does not have sufficient significance to be considered a required element. |  |
| Recommended | ANCILLARY STUDIES | Single selection value list:• Not performed• Performed, specify | Currently there are no ancillary studies that are recommended for routine use in urothelial carcinoma of the urinary tract. If immunohistochemical studies are performed for differential diagnosis or to assist in staging or the detection of lymphovascular invasion they could be listed in this section. If ancillary studies are performed at the request of the clinician or in following an institutional policy or for any other reason, these should be included in the report. |  |