| **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  Multi selection value list (select all that apply):  • Non-invasive papillary  • Invasion into lamina propria  • Carcinoma in situ, flat  • Muscle invasive disease  • Distant metastasis  • Other, specify  **Previous therapy**  Single selection value list:  • Information not provided  • No previous history  Multi selection value list (select all that apply):  • Bacillus Calmette-Guerin (BCG)  • Chemotherapy, intravesical, specify  • Chemotherapy, systemic  • Radiation therapy  • Other, specify  **Other clinical information, specify**  Text | In addition to demographic information about the patient and details of destination of the report, several items of clinical information can help the pathologist in the handling and reporting of specimens of the upper urinary tract. 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. Specific observations on the upper tract epithelium are not available and may or may not be similar to those described in the urinary bladder. The application of Bacillus Calmette-Guerin (BCG) and other “intravesical” agents is used in upper tract tumours however.5  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 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.  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 ureter and renal pelvis. Available from: http://www.cap.org/ShowProperty?nodePath=/UCMCon/Contribution Folders/WebContent/pdf/renalpelvureter-17protocol-1000.pdf (Accessed 1st March 2017).  5 Shapiro EY, Lipsky MJ, Cha DY, McKiernan JM, Benson MC and Gupta M (2012). Outcomes of intrarenal Bacillus Calmette-Guerin/interferon-alpha2B for biopsy-proven upper-tract carcinoma in situ. J Endourol 26(12):1645-1650. |  |
| Required | OPERATIVE PROCEDURE | Single selection value list:  • Not specified  • Nephroureterectomy  • Ureterectomy, partial  • Ureterectomy, complete  • Ureterectomy with cystectomy  • Ureterectomy with cystoprostatectomy  • Other, specify | Documentation of the specific procedure performed should be a standard part of any pathology report. The term ‘partial’ refers to cases where the entire ureter is not removed. A complete (radical) nephroureterectomy assumes that the bladder cuff is present. This is the standard operation for high risk urothelial carcinoma irrespective of location.1,2 In the past the role for segmental ureterectomy in urothelial carcinoma has been largely limited to patients with specific indication, in particular patients with an absent or non-functioning kidney on the opposite side. More recently, this approach has also been used in patients with a normal functioning contralateral kidney, particularly those patients with low risk disease.1,3,4 Low-risk upper tract urothelial carcinoma is defined by the European Association of Urology (EAU) as those that are unifocal, <1 cmin size, with low-grade cytology, low-grade histology on ureteroscopic biopsy and are non-invasive on multidetector computed tomography urography.1 When segmental ureterectomy specimens are submitted for pathological examination it is crucial that the tissue be oriented as to lower and upper ends should a margin prove to be positive.  References  1 Roupret M, Babjuk M, Comperat E, Zigeuner R, Sylvester RJ, Burger M, Cowan NC, Bohle A, Van Rhijn BW, Kaasinen E, Palou J and Shariat SF (2015). European Association of Urology Guidelines on Upper Urinary Tract Urothelial Cell Carcinoma: 2015 Update. Eur Urol 68(5):868-879.  2 Leow JJ, Orsola A, Chang SL and Bellmunt J (2015). A contemporary review of management and prognostic factors of upper tract urothelial carcinoma. Cancer Treat Rev 41(4):310-319.  3 Seisen T, Colin P and Roupret M (2015). Risk-adapted strategy for the kidney-sparing management of upper tract tumours. Nat Rev Urol 12(3):155-166.  4 Lucca I, Klatte T, Roupret M and Shariat SF (2015). Kidney-sparing surgery for upper tract urothelial cancer. Curr Opin Urol 25(2):100-104. |  |
| Required | ADDITIONAL SPECIMENS SUBMITTED | Single selection value list:  • Submitted, specify  • Not submitted | If any additional tissues are resected documentation of these is a necessary part of the pathology report. |  |
| Recommended | TUMOUR FOCALITY | Single selection value list:  • Unifocal  • Multifocal  • Cannot be assessed, specify | A large meta-analysis found tumour multifocality to be a significant predictor of subsequent development of an intravesical tumour.1 In this study other significant pathologic predictors of an increased risk for intravesical recurrence were tumour location (ureter), pT stage, and tumour necrosis; features that were not significant were tumour size, tumour grade, concomitant carcinoma in situ (CIS) and lymphovascular invasion. In a different meta-analysis predictors of intravesical recurrence were location (ureter higher), pT stage (lower=higher risk), and tumour size (higher with tumour >3 cm); features that were not significant were concomitant CIS, multifocality and tumour grade.2 In the most recent European Association of Urology (EAU) guidelines,3 multifocality is not listed as a significant prognostic indicator postoperatively. It is listed as significant preoperatively. In contrast, in a comprehensive literature review, Lughezzani et al4 concluded that multifocality was an independent predictor of cancer specific survival. This reflected several large series in the literature.5,6  References  1 Seisen T, Granger B, Colin P, Leon P, Utard G, Renard-Penna R, Comperat E, Mozer P, Cussenot O, Shariat SF and Roupret M (2015). A Systematic Review and Meta-analysis of Clinicopathologic Factors Linked to Intravesical Recurrence After Radical Nephroureterectomy to Treat Upper Tract Urothelial Carcinoma. Eur Urol 67(6):1122-1133.  2 Yuan H, Chen X, Liu L, Yang L, Pu C, Li J, Bai Y, Han P and Wei Q (2014). Risk factors for intravesical recurrence after radical nephroureterectomy for upper tract urothelial carcinoma: a meta-analysis. Urol Oncol 32(7):989-1002.  3 Roupret M, Babjuk M, Comperat E, Zigeuner R, Sylvester RJ, Burger M, Cowan NC, Bohle A, Van Rhijn BW, Kaasinen E, Palou J and Shariat SF (2015). European Association of Urology Guidelines on Upper Urinary Tract Urothelial Cell Carcinoma: 2015 Update. Eur Urol 68(5):868-879.  4 Lughezzani G, Burger M, Margulis V, Matin SF, Novara G, Roupret M, Shariat SF, Wood CG and Zigeuner R (2012). Prognostic factors in upper urinary tract urothelial carcinomas: a comprehensive review of the current literature. Eur Urol 62(1):100-114.  5 Kamihira O, Hattori R, Yamaguchi A, Kawa G, Ogawa O, Habuchi T, Kawauchi A, Uozumi J, Yokoi S, Tsujihata M, Hasui Y, Miyakoda K, Tada H, Ono Y and Naito S (2009). Laparoscopic radical nephroureterectomy: a multicenter analysis in Japan. Eur Urol 55(6):1397-1407.  6 Ouzzane A, Colin P, Xylinas E, Pignot G, Ariane MM, Saint F, Hoarau N, Adam E, Azemar MD, Bensadoun H, Cormier L, Cussenot O, Houlgatte A, Karsenty G, Bruyere F, Maurin C, Nouhaud FX, Phe V, Polguer T, Roumiguie M, Ruffion A and Roupret M (2011). Ureteral and multifocal tumours have worse prognosis than renal pelvic tumours in urothelial carcinoma of the upper urinary tract treated by nephroureterectomy. Eur Urol 60(6):1258-1265. |  |
| Required and  Recommended | MAXIMUM TUMOUR DIMENSION | Single selection value list:  • Cannot be assessed  • No macroscopically visible tumour  Numeric:  Maximum tumour dimension (largest tumour)  • \_\_\_ mm  Recommended:  Additional dimensions (largest tumour)  • \_\_\_ mm x \_\_\_ mm | Tumour size is prognostic for upper tract tumours pre-surgical resection. In the current European Association of Urology (EAU) guidelines they conclude that it is not prognostic post resection.1 Small (<1 cm) is considered in these guidelines to be part of the definition of low-risk disease. A recent comprehensive review did however conclude that size was a significant predictor of progression-free and recurrence free survival.2-4 Given the limited size of the referenced studies this parameter requires additional larger studies to confirm its independent significance. Nonetheless tumour size remains an integral part of the gross description of a tumour and documentation of at least the largest dimension of a tumour is considered to be a required element of this dataset.  References  1 Roupret M, Babjuk M, Comperat E, Zigeuner R, Sylvester RJ, Burger M, Cowan NC, Bohle A, Van Rhijn BW, Kaasinen E, Palou J and Shariat SF (2015). European Association of Urology Guidelines on Upper Urinary Tract Urothelial Cell Carcinoma: 2015 Update. Eur Urol 68(5):868-879.  2 Leow JJ, Orsola A, Chang SL and Bellmunt J (2015). A contemporary review of management and prognostic factors of upper tract urothelial carcinoma. Cancer Treat Rev 41(4):310-319.  3 Pieras E, Frontera G, Ruiz X, Vicens A, Ozonas M and Piza P (2010). Concomitant carcinoma in situ and tumour size are prognostic factors for bladder recurrence after nephroureterectomy for upper tract transitional cell carcinoma. BJU Int 106(9):1319-1323.  4 Simone G, Papalia R, Loreto A, Leonardo C, Sentinelli S and Gallucci M (2009). Independent prognostic value of tumour diameter and tumour necrosis in upper urinary tract urothelial carcinoma. BJU Int 103(8):1052-1057. |  |
| Required | MACROSCOPIC TUMOUR SITE | Single selection value list:  • Indeterminate  • No macroscopically visible tumour  Multi selection value list (select all that apply):  • Ureter  • Renal pelvis  • Other, specify | Studies evaluating the significance of tumour location of upper tract urothelial carcinoma have had inconsistent results.1-5 In the most recent analysis of the subject by the European Association of Urology (EAU), it was concluded that ureteral location was associated with a worse prognosis than renal pelvic location.6 Several reports have also demonstrated that tumour location is a significant predictor of subsequent development of intravesical disease. These reports have consistently noted an increased risk to be associated with ureteral rather than renal pelvic origin.7,8 It has also been found that location in the lower ureter is associated with a higher risk than the upper ureter.9 Further knowledge of the gross location of the tumour is important in the evaluation of histologic sections. In cases where examination of the sections does not show the relationship of the tumour to renal stroma, a gross description describing location as renal pelvis should prompt re-examination of the specimen and submission of additional sections as appropriate.  References  1 Leow JJ, Orsola A, Chang SL and Bellmunt J (2015). A contemporary review of management and prognostic factors of upper tract urothelial carcinoma. Cancer Treat Rev 41(4):310-319.  2 Milojevic B, Djokic M, Sipetic-Grujicic S, Milenkovic-Petronic D, Vuksanovic A, Bumbasirevic U, Vukovic I, Dragicevic D and Tulic C (2012). Upper urinary tract transitional cell carcinoma: location is not correlated with prognosis. BJU Int 109(7):1037-1042.  3 Favaretto RL, Shariat SF, Chade DC, Godoy G, Adamy A, Kaag M, Bochner BH, Coleman J and Dalbagni G (2010). The effect of tumor location on prognosis in patients treated with radical nephroureterectomy at Memorial Sloan-Kettering Cancer Center. Eur Urol 58(4):574-580.  4 Raman JD, Ng CK, Scherr DS, Margulis V, Lotan Y, Bensalah K, Patard JJ, Kikuchi E, Montorsi F, Zigeuner R, Weizer A, Bolenz C, Koppie TM, Isbarn H, Jeldres C, Kabbani W, Remzi M, Waldert M, Wood CG, Roscigno M, Oya M, Langner C, Wolf JS, Strobel P, Fernandez M, Karakiewcz P and Shariat SF (2010). Impact of tumor location on prognosis for patients with upper tract urothelial carcinoma managed by radical nephroureterectomy. Eur Urol 57(6):1072-1079.  5 Yafi FA, Novara G, Shariat SF, Gupta A, Matsumoto K, Walton TJ, Fritsche HM, El-Hakim A, Trischler S, Martinez-Salamanca JI, Seitz C, Ficarra V, Zattoni F, Karakiewicz PI and Kassouf W (2012). Impact of tumour location versus multifocality in patients with upper tract urothelial carcinoma treated with nephroureterectomy and bladder cuff excision: a homogeneous series without perioperative chemotherapy. BJU Int 110(2 Pt 2):E7-13.  6 Roupret M, Babjuk M, Comperat E, Zigeuner R, Sylvester RJ, Burger M, Cowan NC, Bohle A, Van Rhijn BW, Kaasinen E, Palou J and Shariat SF (2015). European Association of Urology Guidelines on Upper Urinary Tract Urothelial Cell Carcinoma: 2015 Update. Eur Urol 68(5):868-879.  7 Seisen T, Granger B, Colin P, Leon P, Utard G, Renard-Penna R, Comperat E, Mozer P, Cussenot O, Shariat SF and Roupret M (2015). A Systematic Review and Meta-analysis of Clinicopathologic Factors Linked to Intravesical Recurrence After Radical Nephroureterectomy to Treat Upper Tract Urothelial Carcinoma. Eur Urol 67(6):1122-1133.  8 Yuan H, Chen X, Liu L, Yang L, Pu C, Li J, Bai Y, Han P and Wei Q (2014). Risk factors for intravesical recurrence after radical nephroureterectomy for upper tract urothelial carcinoma: a meta-analysis. Urol Oncol 32(7):989-1002.  9 Otsuka M, Taguchi S, Nakagawa T, Kawai T, Morikawa T, Miyazaki H, Fujimura T, Fukuhara H, Kume H and Homma Y (2016). Lower ureteral lesion is an independent predictor of intravesical recurrence after radical nephroureterectomy for upper tract urothelial carcinoma. Urol Oncol 34(2):59.e59-59.e13. |  |
| Required | MACROSCOPIC EXTENT OF INVASION | Single selection value list:  • Cannot be assessed  • No macroscopically visible tumour  • Non-invasive tumour visible  Multi selection value list (select all that apply):  • Invasion into wall  • Invasion into periureteral/peripelvic tissue  • Invasion into renal stroma  • Invasion into perinephric fat  • Involvement of other adjacent structures, specify | In contrast to the urinary bladder the gross evaluation of tumour extent is not an element of the pathologic staging system. Nonetheless, estimating the gross extent of disease can help in block selection and reporting cases if there is a discrepancy between the gross evaluation and the microscopic findings. When a discrepancy is found between the two, this should be resolved by reevaluating the gross appearance and submitting additional blocks if appropriate. It is recognised that the gross estimation may both over and under estimate the microscopic extent of disease and assignment of pathologic stage is based on the latter. For tumours of the renal pelvis there has been a proposed modification of pT3 to distinguish microscopic “pT3a” from macroscopic “pT3b” invasion of the renal stroma. The data from Shariat et al1 is quite compelling. This proposal was based on an earlier report that divided stromal invasion into microscopic (5 mm in depth).2 Those authors commented that extensive invasion was most often apparent grossly and microscopic was not. In a follow up study to the Shariat proposal, Park et al3 confirmed the significance and lent support to the proposed change in pT3. Finally, another group divided the pT3 tumours into those that invaded the medulla only and those that invaded the cortex and found the latter to be significantly worse.4 None of these suggestions have however been adopted in the 8th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual.5  References  1 Shariat SF, Zigeuner R, Rink M, Margulis V, Hansen J, Kikuchi E, Kassouf W, Raman JD, Remzi M, Koppie TM, Bensalah K, Guo CC, Mikami S, Sircar K, Ng CK, Haitel A, Kabbani W, Chun FK, Wood CG, Scherr DS, Karakiewicz PI and Langner C (2012). Subclassification of pT3 urothelial carcinoma of the renal pelvicalyceal system is associated with recurrence-free and cancerspecific survival: proposal for a revision of the current TNM classification. Eur Urol 62(2):224- 231.  2 Yoshimura K, Arai Y, Fujimoto H, Nishiyama H, Ogura K, Okino T and Ogawa O (2002). Prognostic impact of extensive parenchymal invasion pattern in pT3 renal pelvic transitional cell carcinoma. Cancer 94(12):3150-3156.  3 Park J, Habuchi T, Arai Y, Ohyama C, Inoue T, Hatakeyama S, Jeon SS, Kwon GY, Kwak C, Moon KC, Kim CS and Ahn H (2014). Reassessment of prognostic heterogeneity of pT3 renal pelvic urothelial carcinoma: analysis in terms of proposed pT3 subclassification systems. J Urol 192(4):1064-1071.  4 Sassa N, Tsuzuki T, Fukatsu A, Majima T, Kimura T, Nishikimi T, Yoshino Y, Hattori R and Gotoh M (2012). Is pT3 urothelial carcinoma of the renal pelvis a homogeneous disease entity? Proposal for a new subcategory of the pT3 classification. Histopathology 61(4):620- 628.  5 Amin M.B., Edge, S., Greene, F.L., Byrd, D.R., Brookland, R.K., Washington, M.K., Gershenwald, J.E., Compton, C.C., Hess, K.R., Sullivan, D.C., Jessup, J.M., Brierley, J.D., Gaspar, L.E., Schilsky, R.L., Balch, C.M., Winchester, D.P., Asare, E.A., Madera, M., Gress, D.M., Meyer, L.R. (Eds.) (2017). AJCC Cancer Staging Manual 8th ed. Springer, New York. |  |
| 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 type  o Clear cell carcinoma  o Endometrioid carcinoma  • Neuroendocrine tumour  o Small cell neuroendocrine carcinoma  o Large cell neuroendocrine carcinoma  • Other, specify  **Histological sub-type/variant (urothelial carcinoma)**  Single selection value list:  • Not identified  OR  • Present, specify sub-type/variant and percentage  Multi selection value list (select all that apply) / Numeric:  o Squamous \_\_\_%  o Glandular \_\_\_%  o Nested \_\_\_%  o Micropapillary \_\_\_%  o Plasmacytoid \_\_\_%  o Sarcomatoid \_\_\_%  o Other, specify \_\_\_% | The majority of primary carcinomas of the upper tracts are urothelial carcinoma with non-urothelial carcinomas accounting for approximately 2% of tumours.1 Primary squamous cell carcinoma, adenocarcinoma and small cell neuroendocrine carcinoma account for almost all other types and generally exist in the literature as small institutional case series.1-3 The 2016 World Health Organization (WHO) classification is utilized for assigning histological tumour type.4 As in the 2004 WHO Classification,5 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%). 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. As in the urinary bladder, in the upper tract 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.6-10 For example the National Comprehensive Cancer Network (NCCN) includes tumours with “any small-cell component in the category of non-urothelial cell carcinoma.10,11 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.12 TTF-1 is expressed in about 50% of cases.13,14 Lastly there are carcinomas arising in the urinary tract 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. 4 Histologic subtype/variant The 2016 WHO classification includes a number of recognised morphologic variants as outlined in the table below.4 Because urothelial carcinoma has a remarkable capacity for morphologic variation the number of histologic variants that have been described in the literature is extensive.15,16 In the development of the 2016 WHO classification not all of these are included.4 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. There are therefore data on histologic variants in upper tract tumours though not as robust as for primary bladder urothelial carcinoma. One large series of 1648 patients reported variant histology in 24% of cases with squamous (9.9%) and glandular (4%) differentiation being most common.17 Patients with variant histology had worse recurrence-free and cancer-specific survival although it was not independent for either. An additional study of 417 cases found variant histology in 22% (also with squamous and glandular being most common) and found variant histology to be an independent predictor of cancer specific survival.18 Practically all of the described variants of urothelial carcinoma have been reported in the upper tracts.19,20 These are mostly isolated case reports or small case series. One report of 39 upper tract micropapillary urinary carcinoma (out of 519 cases) found the micropapillary variant to be associated with advanced stage and reduced cancer specific survival.21 Reporting the percentage of variant histology when present is recommended (this is recommended in the WHO 2016 monograph). 4 The data supporting this is very limited and only available for selected variants (micropapillary, sarcomatoid, lymphoepithelioma-like), and those with divergent differentiation (glandular, squamous) in series from the urinary bladder. 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 as well as the estimated percentage of this component. For cases with more than one variant present, the percentage of each is recommended to be documented.  **WHO classification of tumours of the urothelial tracta4**  Descriptor / ICD-O codes  **Urothelial tumours**  *Infiltrating urothelial carcinoma 8120/3*  Nested, including large nested  Microcystic  Micropapillary 8131/3  Lymphoepithelioma-like 8082/3  Plasmacytoid / signet ring cell / diffuse  Sarcomatoid 8122/3  Giant cell 8031/3  Poorly differentiated 8020/3  Lipid-rich  Clear cell  *Non-invasive urothelial lesions*  Urothelial carcinoma in situ 8120/2  Non-invasive papillary urothelial carcinoma, low-grade 8130/2  Non-invasive papillary urothelial carcinoma, high-grade 8130/2  Papillary urothelial neoplasm of low malignant potential 8130/1  Urothelial papilloma 8120/0  Inverted urothelial papilloma 8121/0  Urothelial proliferation of uncertain malignant potential  Urothelial dysplasia  **Squamous cell neoplasms**  Pure squamous cell carcinoma 8070/3  Verrucous carcinoma 8051/3  Squamous cell papilloma 8052/0  **Glandular neoplasms**  Adenocarcinoma, NOS 8140/3  Enteric 8144/3  Mucinous 8480/3  Mixed 8140/3  Villous adenoma 8261/0  **Urachal carcinoma 8010/3**  **Tumours of Müllerian type**  Clear cell carcinoma 8310/3  Endometrioid carcinoma 8380/3  **Neuroendocrine tumours**  Small cell neuroendocrine carcinoma 8041/3  Large call neuroendocrine carcinoma 8013/3  Well-differentiated neuroendocrine tumour 8240/3  Paraganglioma b 8693/1  a The morphology codes are from the International Classification of Diseases for Oncology (ICD-O). Behaviour  is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ  and 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 permission.  References  1 Busby JE, Brown GA, Tamboli P, Kamat AM, Dinney CP, Grossman HB and Matin SF (2006). Upper urinary tract tumors with nontransitional histology: a single-center experience. Urology 67(3):518-523.  2 Holmang S, Lele SM and Johansson SL (2007). Squamous cell carcinoma of the renal pelvis and ureter: incidence, symptoms, treatment and outcome. J Urol 178(1):51-56.  3 Miller RJ, Holmang S, Johansson SL and Lele SM (2011). Small cell carcinoma of the renal pelvis and ureter: clinicopathologic and immunohistochemical features. Arch Pathol Lab Med 135(12):1565-1569.  4 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.  5 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.  6 Choong NW, Quevedo JF and Kaur JS (2005). Small cell carcinoma of the urinary bladder. The Mayo Clinic experience. Cancer 103(6):1172-1178.  7 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.  8 Mackey JR, Au HJ, Hugh J and Venner P (1998). 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It is advisable to check with the International Agency for Research on Cancer (IARC). |
| Required | NON-INVASIVE CARCINOMA | Single selection value list:  • Not identified  • Indeterminate  Multi selection value list (select all that apply):  • Carcinoma in situ, flat  o Focal  o Multifocal  • Papillary carcinoma, non-invasive  • Other, specify | There is substantial data that the presence of concomitant urothelial carcinoma in situ (CIS) is associated with a worse recurrence-free and cancer-specific survival.1-4 It is therefore important in these specimens to sample grossly normal portions of the resected ureter and renal pelvis for evaluation. These studies have not specifically recorded the extent of the associated CIS. For the purposes of this dataset we have divided CIS into focal and multifocal and arbitrarily defined these as involvement of a single versus multiple blocks.  References  1 Novara G, Matsumoto K, Kassouf W, Walton TJ, Fritsche HM, Bastian PJ, Martinez-Salamanca JI, Seitz C, Lemberger RJ, Burger M, El-Hakim A, Baba S, Martignoni G, Gupta A, Karakiewicz PI, Ficarra V and Shariat SF (2010). Prognostic role of lymphovascular invasion in patients with urothelial carcinoma of the upper urinary tract: an international validation study. Eur Urol 57(6):1064-1071.  2 Wheat JC, Weizer AZ, Wolf JS, Jr., Lotan Y, Remzi M, Margulis V, Wood CG, Montorsi F, Roscigno M, Kikuchi E, Zigeuner R, Langner C, Bolenz C, Koppie TM, Raman JD, Fernandez M, Karakiewizc P, Capitanio U, Bensalah K, Patard JJ and Shariat SF (2012). Concomitant carcinoma in situ is a feature of aggressive disease in patients with organ confined urothelial carcinoma following radical nephroureterectomy. Urol Oncol 30(3):252-258.  3 Lughezzani G, Burger M, Margulis V, Matin SF, Novara G, Roupret M, Shariat SF, Wood CG and Zigeuner R (2012). Prognostic factors in upper urinary tract urothelial carcinomas: a comprehensive review of the current literature. Eur Urol 62(1):100-114.  4 Otto W, Shariat SF, Fritsche HM, Gupta A, Matsumoto K, Kassouf W, Martignoni G, Walton TJ, Tritschler S, Baba S, Bastian PJ, Martinez-Salamanca JI, Seitz C, Pycha A, Burger M, Karakiewicz PI, Ficarra V and Novara G (2011). Concomitant carcinoma in situ as an independent prognostic parameter for recurrence and survival in upper tract urothelial carcinoma: a multicenter analysis of 772 patients. World J Urol 29(4):487-494. |  |
| 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)1 remains the same as in the 2004 WHO2 and continues to recommend the grading system first put forward by the International Society of Urological Pathology (ISUP) in 1997.3 The system is now recommended by almost all major pathology and urology organizations as the preferred grading system.4,5 This is a 3-tiered system with the lowest category of papillary urothelial neoplasm of low malignant potential representing a tumour without the capacity to invade or metastasize and as such is considered to be a benign neoplasm.6 This lesion represents up to one-third of newly diagnosed noninvasive papillary tumours in the urinary bladder. No good data exists regarding the proportion in upper tract tumours but as upper tract tumours are more often high grade it is presumed to be less. 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. Histologic grade is a significant predictor of cancer specific survival in urothelial carcinoma of the upper urinary tract.7,8 In contrast to the urinary bladder where relatively few patients with low grade non-invasive papillary tumours are managed by cystectomy, many such patients do undergo nephroureterectomy or segmental ureterectomy. Histologic grade is one suggested determining factor in selecting patients for segmental ureterectomy versus nephroureterectomy.9 Low grade tumours may also be managed endoscopically and not come to resection.9-11 For those patients undergoing surgical resection for papillary tumours, grade is a significant prognostic indicator. It is included as a variable in the nomograms based on the largest series in the literature.12-14 The nomograms both from Seisen et al13 and from Cha et al12 utilized the 1998 WHO/International Society of Urological Pathology (ISUP) grading system (equivalent to the 2004 and 2016 WHO grading systems). 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,15-17 while others suggest that the 1973 grade to be provided if based on institutional choice.1,4,5 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.5,15,17,18 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 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. 20-22 In studies using the 1998 ISUP/WHO 2004 grading system the vast majority of invasive tumours are high grade.23,24 The conclusion of the International Consultation on Urologic Disease pathology group was that all invasive carcinomas should be considered high grade.5,25 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.26-29 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.30 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.19,21,31,32 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.1 If invasive tumours are graded using an alternative grading system this should be indicated.  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| Required | MICROSCOPIC EXTENT OF INVASION | • Cannot be assessed  OR  Multi selection value list (select all that apply):  • No evidence of primary tumour  • Papillary carcinoma, non-invasive  • Carcinoma in situ, flat  • Tumour invades subepithelial connective tissue (lamina propria)  • Tumour invades muscularis propria  • Tumour invades beyond muscularis propria into periureteric or peripelvic (renal sinus) fat  • Tumour invades into the renal stroma  • Tumour invades through the kidney into the perinephric fat  • Tumour invades adjacent structures, specify | Pathologic stage is a major prognostic indicator postoperatively. It is included in all three of the published nomograms based on the largest datasets available in the literature. 1-3 The diagnosis of invasion in upper tract tumours can be complicated by the distortion induced by the expansile mass growing in a confined space. This can result in thinning of the wall in the ureter or renal pelvis. Tumours with inverted architecture can compress the muscularis propria with near complete absence of this layer in tissue sections and diagnosis of invasion requires identification of a clearly infiltrative component. Given the very thin layer of subepithelial connective tissue in the ureter and renal pelvis, there is essentially no identifiable muscularis mucosae and invasion of any smooth muscle should be considered to represent T2 disease. For tumours arising in the renal pelvis involvement of the renal stroma is an important element in the staging system. Invasion of the renal stroma is included in the definition of pT3 disease. This must be distinguished from in situ spread of the tumour into the collecting ducts of the kidney which does not impact stage assignment. There have been proposals to substage pT3a tumours with renal stromal involvement. In one study a significant survival difference was found between tumour with microscopic renal stromal invasion (defined as 5 mm or less from the basement membrane) compared with gross invasion (greater than 5 mm).4 Another group substaged these tumours on whether the invasion was limited to the medulla or into the renal cortex and/or pelvic fat.5 Follow up reports have confirmed the applicability of both approaches.6,7 None of these approaches have been adopted in the 8th edition of the American Joint Committee on Cancer (AJCC) Staging Manual.8 Invasive carcinomas can also extend through the renal stroma and extend into the perinephric fat. Those tumours are staged as pT4. This needs to be distinguished from involvement of sinus fat in cases with renal stroma invasion that would still be considered pT3. Direct invasion of an adjacent organ, including the adrenal gland, is also staged as pT4.  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| Required | LYMPHOVASCULAR INVASION | Single selection value list:  • Not identified  • Present  • Indeterminate | Lymphovascular invasion has been repeatedly found to be an important prognostic indicator for urothelial carcinoma of the upper tracts. The most recent European Association of Urology (EAU) guidelines conclude that it is an independent predictor of outcome in these tumours.1 It is included in both the Cha et al and Seisen et al nomograms.2,3 There are many other studies where it has been reported to be an independent predictor as well.4-8 As in other datasets the use of immunohistochemistry (IHC) to determine the presence or absence of lymphovascular invasion is considered optional. It should be noted that none of the major studies referenced above used IHC as a routine part of the evaluation.  References  1 Roupret M, Babjuk M, Comperat E, Zigeuner R, Sylvester RJ, Burger M, Cowan NC, Bohle A, Van Rhijn BW, Kaasinen E, Palou J and Shariat SF (2015). European Association of Urology Guidelines on Upper Urinary Tract Urothelial Cell Carcinoma: 2015 Update. Eur Urol 68(5):868-879.  2 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.  3 Seisen T, Colin P, Hupertan V, Yates DR, Xylinas E, Nison L, Cussenot O, Neuzillet Y, Bensalah K, Novara G, Montorsi F, Zigeuner R, Remzi M, Shariat SF and Roupret M (2014). Postoperative nomogram to predict cancer-specific survival after radical nephroureterectomy in patients with localised and/or locally advanced upper tract urothelial carcinoma without metastasis. BJU Int 114(5):733-740.  4 Kikuchi E, Margulis V, Karakiewicz PI, Roscigno M, Mikami S, Lotan Y, Remzi M, Bolenz C, Langner C, Weizer A, Montorsi F, Bensalah K, Koppie TM, Fernandez MI, Raman JD, Kassouf W, Wood CG, Suardi N, Oya M and Shariat SF (2009). Lymphovascular invasion predicts clinical outcomes in patients with node-negative upper tract urothelial carcinoma. J Clin Oncol 27(4):612-618.  5 Novara G, Matsumoto K, Kassouf W, Walton TJ, Fritsche HM, Bastian PJ, Martinez-Salamanca JI, Seitz C, Lemberger RJ, Burger M, El-Hakim A, Baba S, Martignoni G, Gupta A, Karakiewicz PI, Ficarra V and Shariat SF (2010). Prognostic role of lymphovascular invasion in patients with urothelial carcinoma of the upper urinary tract: an international validation study. Eur Urol 57(6):1064-1071.  6 Roscigno M, Cha EK, Rink M, Seitz C, Novara G, Chromecki TF, Fritsche HM, Matsumoto K, Walton TJ, Carballido J, Filippo Da Pozzo L, Bertini R, Ficarra V, Otto W, Karakiewicz PI, Pycha A, Fajkovic H, Naspro R, Scherr DS, Montorsi F and Shariat SF (2012). International validation of the prognostic value of subclassification for AJCC stage pT3 upper tract urothelial carcinoma of the renal pelvis. BJU Int 110(5):674-681.  7 Lee HY, Li CC, Huang CN, Ke HL, Li WM, Liang PI, Yang SF, Tu HP, Wu WJ and Yeh HC (2015). Prognostic significance of lymphovascular invasion in upper urinary tract urothelial carcinoma is influenced by tumor location. Ann Surg Oncol 22(4):1392-1400.  8 Roupret M, Hupertan V, Seisen T, Colin P, Xylinas E, Yates DR, Fajkovic H, Lotan Y, Raman JD, Zigeuner R, Remzi M, Bolenz C, Novara G, Kassouf W, Ouzzane A, Rozet F, Cussenot O, Martinez-Salamanca JI, Fritsche HM, Walton TJ, Wood CG, Bensalah K, Karakiewicz PI, Montorsi F, Margulis V and Shariat SF (2013). Prediction of cancer specific survival after radical nephroureterectomy for upper tract urothelial carcinoma: development of an optimized postoperative nomogram using decision curve analysis. J Urol 189(5):1662-1669. |  |
| Required | MARGIN STATUS | Single selection value list:  • Cannot be assessed  • Not involved  • Involved  • Invasive carcinoma  Multi selection value list (select all that apply):  o Distal  o Proximal  o Soft tissue  o Other, specify  • Carcinoma in situ/non-invasive high-grade urothelial carcinoma Multi selection value list (select all that apply):  o Distal mucosal  o Proximal mucosa  o Other, specify | Positive surgical margins (generally the bladder cuff in nephroureterectomy series) have been correlated with increased risk of subsequent development of an intravesical tumour. 1,2 In the metaanalysis by Seisen et al3 this was a statistically significant indicator of an increased risk of bladder recurrence. Positive surgical margins (generally the bladder cuff in nephroureterectomy series) have also been correlated with increased risk of distant metastases and cancer specific survival.4 This has not however been a consistent finding5 and was not a significant predictor of cancer specific survival in the meta-analysis by Seisen et al (2015).3 Of interest margin status was not tested in the development of the nomograms by Cha et al (2012)6 or Seisen et al (2014).7 In choosing microscopic margin status, if both invasive carcinoma and carcinoma in situ are present, then invasive carcinoma should be selected. If low grade tumour or carcinoma in situ is present at the margin, this should be noted.  References  1 Abouassaly R, Alibhai SM, Shah N, Timilshina N, Fleshner N and Finelli A (2010). Troubling outcomes from population-level analysis of surgery for upper tract urothelial carcinoma. Urology 76(4):895-901.  2 Bolenz C, Fernandez MI, Trojan L, Herrmann E, Becker A, Weiss C, Alken P, Strobel P and Michel MS (2008). Lymphovascular invasion and pathologic tumor stage are significant outcome predictors for patients with upper tract urothelial carcinoma. Urology 72(2):364- 369.  3 Seisen T, Granger B, Colin P, Leon P, Utard G, Renard-Penna R, Comperat E, Mozer P, Cussenot O, Shariat SF and Roupret M (2015). A Systematic Review and Meta-analysis of Clinicopathologic Factors Linked to Intravesical Recurrence After Radical Nephroureterectomy to Treat Upper Tract Urothelial Carcinoma. Eur Urol 67(6):1122-1133.  4 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.  5 Park J, Habuchi T, Arai Y, Ohyama C, Inoue T, Hatakeyama S, Jeon SS, Kwon GY, Kwak C, Moon KC, Kim CS and Ahn H (2014). Reassessment of prognostic heterogeneity of pT3 renal pelvic urothelial carcinoma: analysis in terms of proposed pT3 subclassification systems. J Urol 192(4):1064-1071.  6 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.  7 Seisen T, Colin P, Hupertan V, Yates DR, Xylinas E, Nison L, Cussenot O, Neuzillet Y, Bensalah K, Novara G, Montorsi F, Zigeuner R, Remzi M, Shariat SF and Roupret M (2014). Postoperative nomogram to predict cancer-specific survival after radical nephroureterectomy in patients with localised and/or locally advanced upper tract urothelial carcinoma without metastasis. BJU Int 114(5):733-740. |  |
| Required and  Recommended | REGIONAL LYMPH NODE STATUS | Single selection value list/ Numeric:  • No regional nodes submitted  • Not involved  o Number of lymph nodes examined \_\_\_  • Involved  o Number of lymph nodes examined \_\_\_  o Number of positive lymph nodes \_\_\_  o Number cannot be determined  o Size of largest metastasis \_\_\_mm  o Location of involved lymph nodes, specify  Recommended:  Extranodal spread  o Present  o Not identified | The staging system for tumours of the renal pelvis and ureter differs from the urinary bladder in that it includes both the number of lymph nodes involved and the size of the metastases in assigning the pN category.1 It is therefore necessary to both determine the number of lymph nodes involved by tumour (one or greater than one) and the greatest dimension of the metastasis (cutpoint is at 2 cm). By definition for tumours of the renal pelvis, the renal hilar, paracaval, aortic and retroperitoneal lymph nodes not otherwise specified are considered regional. For carcinomas of the ureter the regional lymph nodes are the renal hilar, Iliac (common, internal/hypogastric, external), paracaval, periureteral, and pelvic not otherwise specified. Involvement of lymph nodes other than as defined is considered to represent pM1 disease. There are limited published data indicating that the number of lymph nodes removed, the number of positive nodes and the lymph node density (% positive nodes) are significant prognostic indicators in patients with upper tract carcinoma and lymph node positive disease.2,3 In contrast, another study did not find the number of nodes removed or the number of positive nodes to correlate with outcome; lymph node density was however significant. 4 Similarly Fajkovic et al5 did not find either the number of nodes removed or the number of positive nodes to correlate with outcome. For patients with node-negative disease it has been reported that the number of nodes resected correlates with the likelihood that the patient is a true pN0.6 This study used a statistical modelling method and was based on 814 lymph node dissections. To reach >95% confidence that a pN0 result was “true” a minimum of 15 nodes needed to be examined. With only 1 lymph node they estimated that 44% of true pN+ cases would be misclassified as pN0. Another study reported that removal of 8 lymph nodes had a >75% probability of finding a positive lymph node and with 13 lymph nodes a >90% probability was achieved.7 In the most recent EAU guidelines for upper tract carcinoma it is stated that “extranodal extension is  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 Bolenz C, Shariat SF, Fernandez MI, Margulis V, Lotan Y, Karakiewicz P, Remzi M, Kikuchi E, Zigeuner R, Weizer A, Montorsi F, Bensalah K, Wood CG, Roscigno M, Langner C, Koppie TM, Raman JD, Mikami S, Michel MS and Strobel P (2009). Risk stratification of patients with nodal involvement in upper tract urothelial carcinoma: value of lymph-node density. 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Urology 79(4):840-845.  5 Fajkovic H, Cha EK, Jeldres C, Donner G, Chromecki TF, Margulis V, Novara G, Lotan Y, Raman JD, Kassouf W, Seitz C, Bensalah K, Weizer A, Kikuchi E, Roscigno M, Remzi M, Matsumoto K, Breinl E, Pycha A, Ficarra V, Montorsi F, Karakiewicz PI, Scherr DS and Shariat SF (2012). Prognostic value of extranodal extension and other lymph node parameters in patients with upper tract urothelial carcinoma. J Urol 187(3):845-851.  6 Xylinas E, Rink M, Margulis V, Faison T, Comploj E, Novara G, Raman JD, Lotan Y, Guillonneau B, Weizer A, Pycha A, Scherr DS, Seitz C, Sun M, Trinh QD, Karakiewicz PI, Montorsi F, Zerbib M, Gonen M and Shariat SF (2013). Prediction of true nodal status in patients with pathological lymph node negative upper tract urothelial carcinoma at radical nephroureterectomy. 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Eur Urol 68(5):868-879.  9 Ouzzane A, Colin P, Ghoneim TP, Zerbib M, De La Taille A, Audenet F, Saint F, Hoarau N, Adam E, Azemar MD, Bensadoun H, Cormier L, Cussenot O, Houlgatte A, Karsenty G, Maurin C, Nouhaud FX, Phe V, Polguer T, Roumiguie M, Ruffion A and Roupret M (2013). The impact of lymph node status and features on oncological outcomes in urothelial carcinoma of the upper urinary tract (UTUC) treated by nephroureterectomy. World J Urol 31(1):189-197.  10 Fleischmann A, Thalmann GN, Markwalder R and Studer UE (2005). Extracapsular extension of pelvic lymph node metastases from urothelial carcinoma of the bladder is an independent prognostic factor. J Clin Oncol 23(10):2358-2365. 11 Seiler R, von Gunten M, Thalmann GN and Fleischmann A (2011). Extracapsular extension but not the tumour burden of lymph node metastases is an independent adverse risk factor in lymph node-positive bladder cancer. Histopathology 58(4):571-578.  12 Masson-Lecomte A, Vordos D, Hoznek A, Yiou R, Allory Y, Abbou CC, de la Taille A and Salomon L (2013). External validation of extranodal extension and lymph node density as predictors of survival in node-positive bladder cancer after radical cystectomy. Ann Surg Oncol 20(4):1389-1394.  13 Fritsche HM, May M, Denzinger S, Otto W, Siegert S, Giedl C, Giedl J, Eder F, Agaimy A, Novotny V, Wirth M, Stief C, Brookman-May S, Hofstadter F, Gierth M, Aziz A, Kocot A, Riedmiller H, Bastian PJ, Toma M, Wieland WF, Hartmann A and Burger M (2013). Prognostic value of perinodal lymphovascular invasion following radical cystectomy for lymph nodepositive urothelial carcinoma. Eur Urol 63(4):739-744.  14 Abe T, Shinohara N, Muranaka M, Sazawa A, Maruyama S, Osawa T, Harabayashi T, Kubota K, Matsuno Y, Shibata T, Toyada Y, Shinno Y, Minami K, Sakashita S, Kumagai A, Takada N, Togashi M, Sano H, Mori T and Nonomura K (2010). Role of lymph node dissection in the treatment of urothelial carcinoma of the upper urinary tract: multi-institutional relapse analysis and immunohistochemical re-evaluation of negative lymph nodes. Eur J Surg Oncol 36(11):1085-1091. |  |
| Required and Recommended | COEXISTENT PATHOLOGY | **Non-neoplastic renal tissue**  Single selection value list:  • Not applicable  • Insufficient tissue  • No significant pathologic alterations  • Significant pathologic alterations, specify  Recommended:  **Other histopathological features**  Single selection value list:  • Present, specify  • None identified | It is important to recognise that medical kidney diseases may be present in non-neoplastic renal tissue in nephrectomy specimens. 1-3 It is presumed that similar findings may be present in nephroureterectomy specimens and likely would have similar clinical significance although specific studies are not yet available. Assessment of the non-neoplastic kidney may be complicated by changes related to urinary tract obstruction with hydronephrosis and other sequelae. No formal definition exists for insufficient renal stromal tissue. In nephroureterectomy specimens this is generally not relevant as the entire kidney is removed.  References  1 Bijol V, Mendez GP, Hurwitz S, Rennke HG and Nose V (2006). Evaluation of the nonneoplastic pathology in tumor nephrectomy specimens: predicting the risk of progressive failure. Am J Surg Pathol 30(5):575-584.  2 Henriksen KJ, Meehan SM and Chang A (2007). Non-neoplastic renal diseases are often unrecognized in adult tumor nephrectomy specimens: a review of 246 cases. Am J Surg Pathol. 31(11):1703-1708.  3 Bonsib SM and Pei Y (2010). The non-neoplastic kidney in tumor nephrectomy specimens: what can it show and what is important? Adv Anat Pathol 17(4):235-250. |  |
| Recommended | ANCILLARY STUDIES | Single selection value list:  • Not performed  • Performed, specify | In addition to specifying ancillary studies performed, results should be provided (if available). The current European Association of Urology (EAU) guidelines recommend evaluation for Hereditary Nonpolyposis Colorectal Cancer (HNPCC or Lynch syndrome) at the time of medical history taking. 1 They also recommend DNA sequencing to identify hereditary cancers misclassified as sporadic. In a recent comprehensive review, 2 the authors recommend tissue testing of upper tract urothelial carcinomas (immunohistochemistry and/or molecular) similar to gastrointestinal tract guidelines in any one of the following situations: (i) the patient is <60 years of age or (ii) there is a family history of an upper tract urothelial carcinoma, endometrial carcinoma, or a colon cancer diagnosis in a relative <60 years of age, or (iii) if there is a personal history of colon or endometrial cancer. It has been shown that upper tract tumours associated with microsatellite instability frequently have an inverted growth pattern.3 There is at least one report indicating that these tumours are more responsive to adjuvant chemotherapy. 4  References  1 Roupret M (2016). Reply to Yan Shibing and Wei Qiang's Letter to the Editor re: Morgan Roupret, Marko Babjuk, Eva Comperat, et al. European Association of Urology Guidelines on Upper Urinary Tract Urothelial Cell Carcinoma: 2015 Update. Eur Urol 2015;68:868-79. Eur Urol 69(3):e51-52.  2 Mork M, Hubosky SG, Roupret M, Margulis V, Raman J, Lotan Y, O'Brien T, You N, Shariat SF and Matin SF (2015). Lynch Syndrome: A Primer for Urologists and Panel Recommendations. J Urol 194(1):21-29.  3 Hartmann A, Dietmaier W, Hofstadter F, Burgart LJ, Cheville JC and Blaszyk H (2003). Urothelial carcinoma of the upper urinary tract: inverted growth pattern is predictive of microsatellite instability. Hum Pathol 34(3):222-227.  4 Hollande C, Colin P, de La Motte Rouge T, Audenet F, Yates DR, Phe V, Ouzzane A, Droupy S, Ruffion A, de La Taille A, Guy L, Cussenot O, Rozet F, Xylinas E, Zerbib M, Spano JP, Khayat D, Bitker MO and Roupret M (2014). Hereditary-like urothelial carcinomas of the upper urinary tract benefit more from adjuvant cisplatin-based chemotherapy after radical nephroureterectomy than do sporadic tumours. BJU Int 113(4):574-580. |  |
| Required | HISTOLOGICALLY CONFIRMED DISTANT METASTASES | Single selection value list:  • Not identified  • Indeterminate  • Present, specify site(s) | Documentation of known metastatic disease is an important part of the pathology report. Such information, if available, should be recorded with as much detail as is available including the site and reference to any relevant prior surgical pathology or cytopathology specimens. |  |
| Required | PATHOLOGICAL STAGING (TNM 8th edition)  TNM descriptors | Choose if applicable:  • m - multiple primary tumours  • r - recurrent  • y - post-therapy | Pathologic stage is the single most important prognostic parameter for patients that have undergone nephroureterectomy or ureterectomy for upper tract carcinoma.1 Pathologic stage is also a significant predictor of subsequent intravesical recurrence.2 Stage may also be an important parameter in the consideration of the use of adjuvant chemotherapy. Accurate assignment of pathologic stage is therefore of considerable clinical significance. A careful gross examination with appropriate submission of sections is integral to the determination of pathologic stage. Knowledge of the anatomical origin of the sections can also be important to interpretation of the microscopic findings given the complex anatomy, particularly in the renal hilar region. Understanding the anatomy and histology of the various parts of the upper tract are important to the subsequent interpretation of the specimen.3 As discussed earlier, throughout the upper tract the subepithelial connective tissue tends to be very thin and is often distorted by the intraluminal tumour. The muscularis propria can be similarly attenuated. Further in the region of the renal sinus and calyces there may be no visible muscle fibres and the distinction of subepithelial connective tissue invasion (pT1) from the renal sinus connective tissue (pT3) may be quite arbitrary. In such cases identification of a convincing focus of invasion can change the stage assignment from pTa to pT2 or even pT3.4 In the area of the renal papillae the urothelium sits on the renal stroma with an essentially invisible zone of subepithelial connective tissue such that virtually any invasion will result in designation as pT3a tumour. For tumours in the renal sinus and calyces the relationship of the tumour with the renal stroma can be complex. Non-invasive tumour extending into the renal collecting ducts does not constitute renal stromal invasion and over staging as pT3 must be avoided. Fortunately when urothelial carcinoma invades renal stroma it almost always elicits a stroma response and this can be helpful in difficult cases. As discussed earlier, there have been proposals to substage pT3a tumours with renal stromal involvement. In one study a significant survival difference was found between tumour with microscopic renal stromal invasion (defined as 5 mm or less from the basement membrane) compared with gross invasion (greater than 5 mm).5 Another group substaged these tumours on whether the invasion was limited to the medulla or into the renal cortex and/or pelvic fat.6 Follow up reports have confirmed the applicability of both approaches.7,8 These have not been adopted in the 8 th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual.9 Invasive carcinomas can also invade through the full width of the renal stroma and extend into the perinephric fat. Those tumours are staged as pT4. This needs to be distinguished from involvement of sinus fat in cases with renal stroma invasion that would still be considered pT3. Assessment of pathological stage can also be challenging in tumours with an inverted architecture. In the urinary bladder it is distinctly unusual to see non-invasive tumours with inverted architecture grow into the muscularis propria and so finding large pushing tumour fronts there suggests the diagnosis of invasion, perhaps related to a large nested pattern. In the renal pelvis and calyces this becomes more problematic given the histological anatomy of that location. Non-invasive tumours with inverted architecture can push on renal sinus fat. Problematic cases should be extensively sampled in an effort to document unequivocal invasion. Note, in regards to terminology parenchyma should be substituted with stroma. 10  References  1 Lughezzani G, Burger M, Margulis V, Matin SF, Novara G, Roupret M, Shariat SF, Wood CG and Zigeuner R (2012). Prognostic factors in upper urinary tract urothelial carcinomas: a comprehensive review of the current literature. Eur Urol 62(1):100-114.  2 Seisen T, Granger B, Colin P, Leon P, Utard G, Renard-Penna R, Comperat E, Mozer P, Cussenot O, Shariat SF and Roupret M (2015). A Systematic Review and Meta-analysis of Clinicopathologic Factors Linked to Intravesical Recurrence After Radical Nephroureterectomy to Treat Upper Tract Urothelial Carcinoma. Eur Urol 67(6):1122-1133.  3 Reuter VE (2007). Urinary bladder, ureter and renal pelvis. Histology for Pathologists. Mills SE. Wolters Kluwer Lippincott Williams & Wilkins, Philadelphia, PA.  4 Gupta R, Paner GP and Amin MB (2008). Neoplasms of the upper urinary tract: a review with focus on urothelial carcinoma of the pelvicalyceal system and aspects related to its diagnosis and reporting. Adv Anat Pathol 15(3):127-139.  5 Shariat SF, Zigeuner R, Rink M, Margulis V, Hansen J, Kikuchi E, Kassouf W, Raman JD, Remzi M, Koppie TM, Bensalah K, Guo CC, Mikami S, Sircar K, Ng CK, Haitel A, Kabbani W, Chun FK, Wood CG, Scherr DS, Karakiewicz PI and Langner C (2012). Subclassification of pT3 urothelial carcinoma of the renal pelvicalyceal system is associated with recurrence-free and cancerspecific survival: proposal for a revision of the current TNM classification. Eur Urol 62(2):224- 231.  6 Sassa N, Tsuzuki T, Fukatsu A, Majima T, Kimura T, Nishikimi T, Yoshino Y, Hattori R and Gotoh M (2012). Is pT3 urothelial carcinoma of the renal pelvis a homogeneous disease entity? Proposal for a new subcategory of the pT3 classification. Histopathology 61(4):620- 628.  7 Park J, Habuchi T, Arai Y, Ohyama C, Inoue T, Hatakeyama S, Jeon SS, Kwon GY, Kwak C, Moon KC, Kim CS and Ahn H (2014). Reassessment of prognostic heterogeneity of pT3 renal pelvic urothelial carcinoma: analysis in terms of proposed pT3 subclassification systems. J Urol 192(4):1064-1071.  8 Roscigno M, Cha EK, Rink M, Seitz C, Novara G, Chromecki TF, Fritsche HM, Matsumoto K, Walton TJ, Carballido J, Filippo Da Pozzo L, Bertini R, Ficarra V, Otto W, Karakiewicz PI, Pycha A, Fajkovic H, Naspro R, Scherr DS, Montorsi F and Shariat SF (2012). International validation of the prognostic value of subclassification for AJCC stage pT3 upper tract urothelial carcinoma of the renal pelvis. BJU Int 110(5):674-681.  9 Amin M.B., Edge, S., Greene, F.L., Byrd, D.R., Brookland, R.K., Washington, M.K., Gershenwald, J.E., Compton, C.C., Hess, K.R., Sullivan, D.C., Jessup, J.M., Brierley, J.D., Gaspar, L.E., Schilsky, R.L., Balch, C.M., Winchester, D.P., Asare, E.A., Madera, M., Gress, D.M., Meyer, L.R. (Eds.) (2017). AJCC Cancer Staging Manual 8th ed. Springer, New York.  10 Delahunt B, Egevad L, Samaratunga H, Varma M, Verrill C, Cheville J, Kristiansen G, Corbishley C and Berney DM (2017). UICC drops the ball in the 8th edition TNM staging of urological cancers. Histopathology 71(1):5-11. | Note that permission to publish the TNM cancer staging tables may be needed in your implementation. It is advisable to check. |
| Required | Primary tumour (pT) | Single selection value list:  • TX Primary tumour cannot be assessed  • T0 No evidence of primary tumour  • Ta Papillary non-invasive carcinoma  • Tis Carcinoma in situ  • T1 Tumour invades subepithelial connective tissue  • T2 Tumour invades the muscularis  • T3 *For renal pelvis only*: Tumour invades beyond muscularis into peripelvic fat or into the renal  parenchyma\*  *For ureter only:* Tumour invades beyond muscularis into perinephric fat  • T4 Tumour invades adjacent organs, or through the kidney into the perinephric fat |  | Please note, use of terminology is incorrect. Stroma should be substituted for parenchyma. |
| Required | Regional lymph nodes (pN) | • NX Regional lymph nodes cannot be assessed  • N0 No lymph node metastasis  • N1 Metastasis in a single lymph node, ≤2 cm in greatest dimension  • N2 Metastasis in a single lymph node, >2 cm; or multiple lymph nodes |  |  |