Carcinoma of the Renal Pelvis and Ureter Histopathology Reporting Guide
Nephroureterectomy and Ureterectomy Specimen

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

Elements in **black text** are REQUIRED. Elements in **grey text** are RECOMMENDED.

SCOPE OF THIS DATASET

CLINICAL INFORMATION (Note 1)

Previous history of urinary tract disease or distant metastasis (select all that apply)

- ○ Information not provided
- ○ No previous history
- ☐ Non-invasive papillary
- ☐ Carcinoma in situ, flat
- ☐ Invasion into lamina propria
- ☐ Muscle invasive disease
- ☐ Other, *specify*
- ☐ Distant metastasis

Previous therapy (select all that apply)

- ○ Information not provided
- ○ No previous therapy
- ☐ Bacillus Calmette-Guerin (BCG)
- ☐ Chemotherapy, intravesical, *specify*
- ☐ Chemotherapy, systemic
- ☐ Radiation therapy
- ☐ Other, *specify*

Other clinical information, *specify*

OPERATIVE PROCEDURE (Note 2)

- ○ Not specified
- ○ Nephroureterectomy
- ○ Ureterectomy, partial
- ○ Ureterectomy, complete
- ○ Ureterectomy with cystectomy
- ○ Ureterectomy with cystoprostatectomy
- ○ Other, *specify*

ADDITIONAL SPECIMENS SUBMITTED (Note 3)

- ○ Submitted, *specify*
- ○ Not submitted

TUMOUR FOCALITY (Note 4)

- ○ Unifocal
- ○ Multifocal
- ○ Cannot be assessed, *specify*

MAXIMUM TUMOUR DIMENSION (Note 5)

- ○ Cannot be assessed
- ○ No macroscopically visible tumour

Maximum tumour dimension (largest tumour)

mm

Additional dimensions (largest tumour)

mm X mm

MACROSCOPIC TUMOUR SITE (select all that apply) (Note 6)

- ○ Indeterminate
- ○ No macroscopically visible tumour
- ☐ Ureter
- ☐ Renal pelvis
- ☐ Other, *specify*

MACROSCOPIC EXTENT OF INVASION (select all that apply) (Note 7)

- ○ Cannot be assessed
- ○ No macroscopically visible tumour
- ○ Non-invasive tumour visible
- ☐ Invasion into wall
- ☐ Invasion into periureteral/peripelvic tissue
- ☐ Invasion into renal stroma
- ☐ Invasion into perinephric fat
- ☐ Involvement of other adjacent structures, *specify*

BLOCK IDENTIFICATION KEY (Note 8)

(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

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HISTOLOGICAL TUMOUR TYPE (Note 9)
(Value list from the WHO Classification of Tumours of the Urinary System and Male Genital Organs (2016))

- ○ Urothelial carcinoma
- ○ Squamous cell carcinoma
- ○ Adenocarcinoma
- ○ Tumours of Müllerian type
  - ○ Clear cell carcinoma
  - ○ Endometrioid carcinoma
- ○ Neuroendocrine tumour
  - ○ Small cell neuroendocrine carcinoma
  - ○ Large cell neuroendocrine carcinoma
- ○ Other, *specify*

Histological sub-type/variant (urothelial carcinoma)

- ○ Not identified
- ○ Present, *specify sub-type/variant and percentage*
  (select all that apply)

☐ Squamous ⇒	%	☐ Micropapillary ⇒	%
☐ Glandular ⇒	%	☐ Plasmacytoid ⇒	%
☐ Nested ⇒	%	☐ Sarcomatoid ⇒	%
☐ Other, *specify*	⇒		%

NON-INVASIVE CARCINOMA (select all that apply) (Note 10)

- ○ Not identified
- ○ Indeterminate
- ☐ Carcinoma in situ, flat
  - ○ Focal
  - ○ Multifocal
- ☐ Papillary carcinoma, non-invasive
- ☐ Other, *specify*

ASSOCIATED EPITHELIAL LESIONS (Note 11)

- ○ Present, *specify*
- ○ Not identified

HISTOLOGICAL TUMOUR GRADE (Note 12)

- ○ 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*

MICROSCOPIC EXTENT OF INVASION (select all that apply) (Note 13)

- ○ Cannot be assessed
- ☐ 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*

LYMPHOVASCULAR INVASION (Note 14)

- ○ Not identified
- ○ Present
- ○ Indeterminate

MARGIN STATUS (Note 15)

- ○ Cannot be assessed
- ○ Not involved
- ○ Involved
  - ○ Invasive carcinoma (select all that apply)
    - ☐ Distal
    - ☐ Proximal
    - ☐ Soft tissue
    - ☐ Other, *specify*
  - ○ Carcinoma in situ/non-invasive high-grade urothelial carcinoma (select all that apply)
    - ☐ Distal mucosal
    - ☐ Proximal mucosa
    - ☐ Other, *specify*

REGIONAL LYMPH NODE STATUS (Note 16)

- ○ No regional nodes submitted
- ○ Not involved
  - Number of lymph nodes examined
- ○ Involved
  - Number of lymph nodes examined
  - Number of positive lymph nodes
  - ○ Number cannot be determined

Extranodal spread

- ○ Present
- ○ Not identified

Size of largest metastasis mm

Location of involved lymph nodes, *specify*

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COEXISTENT PATHOLOGY (Note 17)

Non-neoplastic renal tissue

- ○ Not applicable
- ○ Insufficient tissue
- ○ No significant pathologic alterations
- ○ Significant pathologic alterations, *specify*

Other histopathological features

- ○ Present, *specify*
- ○ None identified

ANCILLARY STUDIES (Note 18)

- ○ Not performed
- ○ Performed, *specify*

HISTOLOGICALLY CONFIRMED DISTANT METASTASES (Note 19)

- ○ Not identified
- ○ Indeterminate
- ○ Present, *specify site(s)*

PATHOLOGICAL STAGING (AJCC TNM 8th edition)## (Note 20)

TNM Descriptors (only if applicable) (select all that apply)

- ☐ m - multiple primary tumours
- ☐ r - recurrent
- ☐ y - post-therapy

Primary tumour (pT)

- ○ 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

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

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* *Please note, use of terminology is incorrect. Stroma should be substituted for parenchyma.*

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Scope

The dataset has been developed for the reporting of resection specimens from patients with primary carcinoma of the ureter and renal pelvis. The protocol applies to carcinomas (non-invasive and invasive), with or without associated epithelial lesions. Urothelial tumours diagnosed as papilloma or papillary urothelial neoplasm of low malignant potential are not carcinomas and this dataset does not apply to those diagnoses. Biopsy and transurethral resection specimens are dealt with in a separate dataset. For bilateral tumours, complete a separate dataset for each.

Note 1 - Clinical information (Recommended)

Reason/Evidentiary Support

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]

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Note 2 - Operative procedure (Required)

Reason/Evidentiary Support

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.[6,7]

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.[6,8,9] Low-risk upper tract urothelial carcinoma is defined by the European Association of Urology (EAU) as those that are unifocal, <1 cm in size, with low-grade cytology, low-grade histology on ureteroscopic biopsy and are non-invasive on multidetector computed tomography urography.[6] 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.

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Note 3 - Additional specimens submitted (Required)

Reason/Evidentiary Support

If any additional tissues are resected documentation of these is a necessary part of the pathology report.

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Note 4 - Tumour focality (Required)

Reason/Evidentiary Support

A large meta-analysis found tumour multifocality to be a significant predictor of subsequent development of an intravesical tumour.[10] 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.[11]

In the most recent EAU guidelines,[6] 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 al[12] concluded that multifocality was an independent predictor of cancer specific survival. This reflected several large series in the literature.[13,14]

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Note 5 - Maximum tumour dimension (Required and Recommended)

Reason/Evidentiary Support

Tumour size is prognostic for upper tract tumours pre-surgical resection. In the current EAU guidelines they conclude that it is not prognostic post resection.[6] 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.[7,15,16] 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.

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Note 6 - Macroscopic tumour site (Required)

Reason/Evidentiary Support

Studies evaluating the significance of tumour location of upper tract urothelial carcinoma have had inconsistent results.[7,17-20] In the most recent analysis of the subject by the 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.[10,11] It has also been found that location in the lower ureter is associated with a higher risk than the upper ureter.[21]

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.

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Note 7 - Macroscopic extent of invasion (Required)

Reason/Evidentiary Support

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 re-evaluating 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 al[22] is quite compelling. This proposal was based on an earlier report that divided stromal invasion into microscopic (<5 mm in depth) and extensive (>5 mm in depth).[23] 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 al[24] 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.[25] None of these suggestions have however been adopted in the 8th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual.[26]

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Note 8 - Block identification key (Recommended)

Reason/Evidentiary Support

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).

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Note 9 - Histological tumour type (Required)

Reason/Evidentiary Support

Histological tumour type

The majority of primary carcinomas of the upper tracts are urothelial carcinoma with non-urothelial carcinomas accounting for approximately 2% of tumours.[27] 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.[27-29]

The 2016 World Health Organization (WHO) classification is utilized for assigning histological tumour type.[30] As in the 2004 WHO Classification,[31] a tumour is classified as a urothelial carcinoma if there is any identifiable urothelial component no matter how small and including urothelial 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.[32-36] For example the National Comprehensive Cancer Network (NCCN) includes tumours with "any small-cell component in the category of non-urothelial cell carcinoma.[36,37] 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.[38] TTF-1 is expressed in about 50% of cases.[39,40]

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. [30]

Histologic subtype/variant

The 2016 WHO classification includes a number of recognised morphologic variants as outlined in the table below.[30] Because urothelial carcinoma has a remarkable capacity for morphologic variation the number of histologic variants that have been described in the literature is extensive.[41,42] In the development of the 2016 WHO classification not all of these are included.[30] 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.[43] 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.[44]

Practically all of the described variants of urothelial carcinoma have been reported in the upper tracts.[45,46] 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.[47]

Reporting the percentage of variant histology when present is recommended (this is recommended in the WHO 2016 monograph).[30] 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 tract[a30]

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.

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Note 10 - Non-invasive carcinoma (Required)

Reason/Evidentiary Support

There is substantial data that the presence of concomitant urothelial CIS is associated with a worse recurrence-free and cancer-specific survival.[12,48-50] 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.

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Note 11 - Associated epithelial lesions (Recommended)

Reason/Evidentiary Support

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.

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Note 12 - Histological tumour grade (Required)

Reason/Evidentiary Support

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 WHO[30] remains the same as in the 2004 WHO[31] and continues to recommend the grading system first put forward by the International Society of Urological Pathology (ISUP) in 1997.[51] The system is now recommended by almost all major pathology and urology organizations as the preferred grading system.[2,4]

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.[52] This lesion represents up to one-third of newly diagnosed non-invasive 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.[12,53] 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.[6] Low grade tumours may also be managed endoscopically and not come to resection.[6,54,55] 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.[56-58] The nomograms both from Seisen et al[57] and from Cha et al[56] utilized the 1998 WHO/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,[59-61] while others suggest that the 1973 grade to be provided if based on institutional choice.[2,4,30] 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.[2,59,61,62] 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.[63] The International Collaboration on Cancer Reporting (ICCR) dataset follows the WHO 2016[30] approach with reporting of the WHO 2016 grade as a required element and the inclusion of other grading systems as optional.

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.[64-66] In studies using the 1998 ISUP/WHO 2004 grading system the vast majority of invasive tumours are high grade.[67,68] The conclusion of the International Consultation on Urologic Disease pathology group was that all invasive carcinomas should be considered high grade.[2,69] 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.[70-73] 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.[74] 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.[63,65,75,76] 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.[30] If invasive tumours are graded using an alternative grading system this should be indicated.

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Note 13 - Microscopic extent of invasion (Required)

Reason/Evidentiary Support

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.[56-58] 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).[22] Another group substaged these tumours on whether the invasion was limited to the medulla or into the renal cortex and/or pelvic fat.[25] Follow up reports have confirmed the applicability of both approaches.[24,77] None of these approaches have been adopted in the 8th edition of the AJCC Staging Manual.[26]

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.

Note 14 - Lymphovascular invasion (Required)

Reason/Evidentiary Support

Lymphovascular invasion has been repeatedly found to be an important prognostic indicator for urothelial carcinoma of the upper tracts. The most recent EAU guidelines conclude that it is an independent predictor of outcome in these tumours.[6] It is included in both the Cha et al and Seisen et al nomograms.[56,57] There are many other studies where it has been reported to be an independent predictor as well.[48,58,77-79]

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.

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Note 15 - Margin status (Required)

Reason/Evidentiary Support

Positive surgical margins (generally the bladder cuff in nephroureterectomy series) have been correlated with increased risk of subsequent development of an intravesical tumour.[80,81] In the meta-analysis by Seisen et al[10] 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.[82] This has not however been a consistent finding[24] and was not a significant predictor of cancer specific survival in the meta-analysis by Seisen et al (2015).[10] Of interest margin status was not tested in the development of the nomograms by Cha et al (2012)[56] or Seisen et al (2014).[57]

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.

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Note 16 - Regional lymph node status (Required and Recommended)

Reason/Evidentiary Support

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.[83] 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.[84,85] 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.[86] Similarly Fajkovic et al[87] 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.[88] 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.[89]

In the most recent EAU guidelines for upper tract carcinoma it is stated that "extranodal extension is a powerful predictor of clinical outcome in upper tract urothelial carcinomas and positive lymph node metastases".[6] This conclusion was based on a study by Fajkovic et al[87] in which the presence of extranodal extension was an independent predictor of tumour recurrence and cancer specific mortality. In another study the presence of extranodal extension was "marginally" associated with a worse prognosis.[90] Studies of metastatic carcinoma of the urinary bladder have also evaluated the significance of extranodal extension with similar findings in most[91-93] but not all.[94]

The topic of micrometastases has also been addressed. Abe et al[95] performed IHC for cytokeratin on 5 slides from negative lymph nodes in 51 patients with histologically negative nodes (on re-examination) and found micrometastases in 7 (14%). With a median follow up of 45 months there was no difference in cause-specific survival between the IHC+ and IHC- cases.

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Note 17 - Coexistent pathology (Required and Recommended)

Reason/Evidentiary Support

It is important to recognise that medical kidney diseases may be present in non-neoplastic renal tissue in nephrectomy specimens.[96-98] 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.

Note 18 - Ancillary studies (Recommended)

Reason/Evidentiary Support

In addition to specifying ancillary studies performed, results should be provided (if available).

The current EAU guidelines recommend evaluation for Hereditary Nonpolyposis Colorectal Cancer (HNPCC or Lynch syndrome) at the time of medical history taking.[99] They also recommend DNA sequencing to identify hereditary cancers misclassified as sporadic. In a recent comprehensive review,[100] the authors recommend tissue testing of upper tract urothelial carcinomas (IHC 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.[101] There is at least one report indicating that these tumours are more responsive to adjuvant chemotherapy.[102]

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Note 19 - Histologically confirmed distant metastases (Required)

Reason/Evidentiary Support

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.

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Note 20 - Pathological staging (Required)

Reason/Evidentiary Support

Pathologic stage is the single most important prognostic parameter for patients that have undergone nephroureterectomy or ureterectomy for upper tract carcinoma.[12] Pathologic stage is also a significant predictor of subsequent intravesical recurrence.[10] 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.[103] 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.[104] 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).[22] Another group substaged these tumours on whether the invasion was limited to the medulla or into the renal cortex and/or pelvic fat.[25] Follow up reports have confirmed the applicability of both approaches.[24,77] These have not been adopted in the 8th edition of the AJCC Cancer Staging Manual.[26]

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.[105]

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