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.[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 tract[a4]

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

Descriptor	ICD-O codes
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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