# **Histological tumour type** (Required)

**Reason/Evidentiary Support**

The 2016 World Health Organization (WHO) classification is used for assigning histological tumour type.[1] As in the 2004 WHO Classification,[2] a tumour is classified as a urothelial carcinoma if there is any identifiable urothelial component no matter how small and including urothelial carcinoma in situ (CIS). The one exception to this rule is for cases with a neuroendocrine component (small cell neuroendocrine carcinoma or large cell neuroendocrine carcinoma) where classification is now 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%)*.

Also new in the 2016 WHO classification is the category of Müllerian tumours. For the purposes of this dataset this consists primarily of clear cell adenocarcinoma. Clear cell adenocarcinoma must also be distinguished from urothelial carcinoma with divergent differentiation along Müllerian lines in which case it would be classified under urothelial carcinoma.[3] Expression of markers such as p63, GATA3 and high molecular weight cytokeratin are not present in clear cell adenocarcinoma and in the absence of a recognisable urothelial component would suggest this possibility.[4] Müllerian type clear cell adenocarcinoma has a similar immunohistochemical profile to primary tumours of the female genital tract and cannot be used to distinguish a primary from a secondary origin.[5-8]

Primary adenocarcinomas of the urethra have some unique features to the other datasets in this series. Most primary adenocarcinomas of the urethra are considered to be of a not otherwise specified type. This group would include enteric type adenocarcinomas,[9,10] mucinous (colloid) adenocarcinomas[11,12] and signet ring cell carcinomas[13] Clear cell adenocarcinoma (discussed above) is relatively common in the urethra in contrast to elsewhere in the urinary tract.[9,14-16] Primary adenocarcinoma and adenoid cystic carcinoma arising in the accessory glands are also included in this dataset.[17-19]

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. 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.[20-23] For example the National Comprehensive Cancer Network (NCCN) includes tumours with “any small-cell component in the category of non-urothelial cell carcinoma.[24,25] Primary neuroendocrine tumours are exceedingly rare in the urethra and essentially are limited to case reports.[26,27]

There is a significant relationship between tumour location and histologic type. In females squamous cell carcinoma is the predominant type in the distal and meatal region with urothelial carcinoma and adenocarcinoma being found in the more proximal portion.[9,28,29] Urethral diverticula in particular are

a typical location for clear cell adenocarcinomas in females although other histologic types may arise from these structures.[9,14,30] In males squamous cell carcinoma accounts for the majority of tumours arising in the penile and bulbomembranous urethra[31,32] with urothelial carcinoma predominating in the prostatic urethra.[33,34] Adenocarcinomas in males occur predominantly in the bulbomembranous segment. The very rare adenocarcinomas of the accessory glands (Skene glands in females; Littre or Cowper glands in males) localize to the sites of those glands.

**Histologic subtype/variant**

The 2016 WHO classification includes a number of recognised morphologic variants as outlined in the table below.[1] Because urothelial carcinoma has a remarkable capacity for morphologic variation the number of histologic variants that have been described in the literature is extensive.[35,36] In the development of the 2016 WHO classification not all of these are included. In general the variants that have been specifically recognised fall into three broad categories. Variants that have a deceptively bland morphology, such as the nested variant, could be misdiagnosed as benign or considered low grade although their behaviour is the same as for high grade tumours. In the second category are tumours that have a morphology that mimics other tumours. Lastly are those tumours that have important prognostic or therapeutic implications.

The importance of variant histology in clinical management decisions has been receiving increasing clinical attention.[37,38] Some variants have been highlighted because of the high frequency of under staging when present in biopsy or transurethral resection of bladder tumour (TURBT) specimens, as discussed in the Urinary tract carcinoma – Biopsy and transurethral resection specimen dataset.[39,40] There are an increasing number of therapeutic algorithms that incorporate variant histology as a significant factor.[41]

The level of evidence for specific variants having independent prognostic information varies from the variant having no clinical significance but being important diagnostically (e.g. nested, microcystic, etc), to no data, to data indicating the variant has prognostic significance (e.g. micropapillary, plasmacytoid, sarcomatoid). Rather than making reporting of specific subtypes that have some supporting data mandatory and others lacking data recommended it is considered best to make the entire category a required element.

Reporting the percentage of variant histology when present is required (this is recommended in the WHO 2016 monograph). The data supporting this is very limited and only available for selected variants (micropapillary, sarcomatoid, lymphoepithelioma-like), with divergent differentiation (glandular, squamous) largely from tumours arising in 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 together with the estimated percentage of this component. For cases with more than one variant present, the percentage of each is required to be documented.

# WHO classification of tumours of the urothelial tract[a1]

| 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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