Histological tumour type (Required)

Reason/Evidentiary Support

The 2016 World Health Organization (WHO) classification is utilized for assigning histological tumour type.[1] As in the 2004 WHO Classification,[2] a tumour is classified as a urothelial carcinoma if there is any identifiable urothelial component no matter how small and including urothelial carcinoma in situ (CIS). The one exception to this rule is for cases with a neuroendocrine component (small cell neuroendocrine carcinoma or large cell neuroendocrine carcinoma) where classification is in the neuroendocrine tumour category. For those cases that are mixed, the other elements should be reported with an estimated percentage. In the above scheme, this would be managed by placing the other component in the histological tumour type element. For example a mixed tumour with 70% small cell neuroendocrine carcinoma and 30% urothelial carcinoma would be reported under the histological tumour type as *Neuroendocrine tumour (small cell neuroendocrine carcinoma)* and then under histological tumour type – Other, specify - *urothelial carcinoma (30%)*.

For biopsies and transurethral resections (TURs) that contain pure adenocarcinoma or pure squamous cell carcinoma, they should be diagnosed as such. Without evaluation of the entire lesion it is not however possible to exclude the possibility of a urothelial carcinoma with squamous or glandular differentiation and consider a comment explaining that should always be included. The presence of keratinizing squamous metaplasia particularly when there is dysplasia would support the diagnosis of primary squamous cell carcinoma.[3] Similarly the presence of intestinal metaplasia with dysplasia would support the diagnosis of primary adenocarcinoma. None the less a definitive diagnosis of either should be made with caution in biopsy or transurethral resection of bladder tumour (TURBT) material. There are no reliable immunohistochemical markers to distinguish these possibilities with certainty in the individual case. In urothelial carcinoma with glandular differentiation, the glandular component may retain its “urothelial” profile including expression of p63, GATA3 and high molecular weight cytokeratin but often these are lost with the tumour showing an enteric immuno-histochemical profile. Markers of squamous differentiation such as desmoglein 3, CK14 and MAC387 have not been proven to reliably separate pure squamous cell carcinoma from urothelial carcinoma with squamous differentiation.[4] Further for both adenocarcinoma and squamous cell carcinoma the diagnosis of primary origin in the urinary bladder requires clinical correlation to exclude the possibility of origin at another site.

The 2016 WHO classification now includes carcinomas arising in the urachus as a separate category.[1] These are defined as carcinomas arising from urachal remnants. In general it is not possible to diagnose these in biopsy and TURBT material based on the morphologic findings alone. Criteria for the diagnosis of urachal carcinoma include location in the bladder dome or anterior wall, an epicentre in the bladder wall or perivesical tissue, the absence of diffuse cystitis glandularis/ intestinal metaplasia outside of the dome/anterior wall region and the absence of a known primary elsewhere.[5] The majority (over 80%) of urachal carcinomas are adenocarcinoma followed by urothelial carcinoma, squamous cell carcinoma and small cell neuroendocrine carcinoma. If a diagnosis of urachal carcinoma is rendered the histologic type should be specified. Adenocarcinomas of the urachus are most often mucinous and can be either solid or cystic. Other variants of adenocarcinoma including enteric and signet ring-cell also occur. The WHO does include a category of “mucinous cystic tumour of low malignant potential” that could not be diagnosed with certainty

in biopsy/TURBT material.[1] There are no reliable immunohistochemical markers to distinguish adenocarcinomas of urachal origin from primary adenocarcinomas of the bladder proper or from secondary adenocarcinomas of gastrointestinal origin.[4-6]

Also new in the 2016 WHO classification is the category of Müllerian tumours.[1] For the purposes of this dataset this consists primarily of clear cell adenocarcinoma and rare examples of endometrioid carcinoma. These tumours are morphologically the same as their counterparts in the female genital tract. They are rare tumours and most often when clear cell adenocarcinoma presents as a primary bladder tumour it represents secondary involvement most often originating in a urethral diverticulum.[7] Diagnosis therefore requires clinical correlation to support diagnosis as a primary bladder tumour. Clear cell adenocarcinoma and endometrioid carcinoma may arise from endometriosis or rarely Müllerianosis.[8-11] Clear cell adenocarcinoma must also be distinguished from urothelial carcinoma with divergent differentiation along Müllerian lines in which case it would be classified under urothelial carcinoma.[12] Expression of markers such as p63, GATA3 and high molecular weight cytokeratin are not present in clear cell adenocarcinoma and in the absence of a recognisable urothelial component would suggest this possibility.[13] Müllerian type clear cell adenocarcinoma has similar immunohistochemical profile to primary tumours of the female genital tract and cannot be used to distinguish a primary from a secondary origin.[10,14-16]

The neuroendocrine tumour category includes small cell neuroendocrine carcinoma, large cell neuroendocrine carcinoma, well-differentiated neuroendocrine tumour and paraganglioma. Small cell neuroendocrine carcinoma is by far the most common of these. By definition this is a malignant neoplasm with neuroendocrine differentiation. About one-half of cases are pure and one-half are mixed with another component with urothelial carcinoma being most frequent. Cases with mixed differentiation are included in this category. There does remain some controversy regarding the percentage of the neuroendocrine component required to classify a tumour as a neuroendocrine carcinoma. From a practical standpoint cases with a small cell neuroendocrine carcinoma component irrespective of the amount are managed as small cell neuroendocrine carcinoma with the larger series in the literature including cases with only a focal component of small cell carcinoma.[17-21] For example the National Comprehensive Cancer Network (NCCN) includes tumours with “any small-cell component in the category of non-urothelial cell carcinoma.[21,22] The diagnosis is defined by morphologic criteria but most cases do demonstrate evidence of neuroendocrine differentiation by immunohistochemistry. The most sensitive immunohistochemical markers are CD56 and synaptophysin.[4] TTF-1 is expressed in about 50% of cases.[23,24] In cases with pure small cell morphology the possibility of direct spread from an adjacent organ or metastasis must be excluded clinically.

Lastly there are carcinomas arising in the urinary bladder that have no specific differentiation and based on exclusion of metastasis from another site are considered to be primary in the urinary tract. In the 2004 WHO classification these were included as a variant of urothelial carcinoma but given that by definition they have no urothelial differentiation these should be reported using the “carcinoma, type cannot be determined” category.[2]

Histologic subtype/variant

The 2016 WHO classification includes a number of recognised morphologic variants as outlined in the table below.[1] Because urothelial carcinoma has a remarkable capacity for morphologic variation

the number of histologic variants that have been described in the literature is extensive.[25,26] In the development of the 2016 WHO classification not all of these are included.[1] In general the variants that have been specifically recognised fall into three broad categories. Variants that have a deceptively bland morphology, such as the nested variant, could be misdiagnosed as benign or considered low grade although their behaviour is the same as for high grade tumours. In the second category are tumours that have a morphology that mimics other tumours. Lastly are those tumours that have important prognostic or therapeutic implications.

The importance of variant histology in clinical management decisions has been receiving increasing clinical attention.[27,28] Some variants have been highlighted because of the high frequency of under staging when present in biopsy or TURBT specimens.[29] There are an increasing number of therapeutic algorithms that incorporate variant histology as a significant factor.[30] For T1 urothelial carcinoma, the presence of variant histology is one feature that is used in determining whether to consider immediate cystectomy.[21,31]

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

Reporting the percentage of variant histology when present is recommended (this is recommended in the WHO 2016 monograph).[1] The data supporting this is very limited and only available for selected variants (micropapillary, sarcomatoid, lymphoepithelioma-like), with divergent differentiation (glandular, squamous). There is also insufficient data available for setting specific amounts of each specific variant in order for it to be clinically significant. Given the lack of data, if variant histology is identified, it should be reported and the estimated percentage of the tumour it makes up reported. For cases with more than one variant present, the percentage of each is recommended to be documented.

WHO classification of tumours of the urothelial 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	

Descriptor	ICD-O codes
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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