Histological tumour type (Core)

All cervical carcinomas should be typed according to the 2014 World Health Organization (WHO) classification.[1] Carcinosarcoma is also included since, although it is included in the category of mixed epithelial and mesenchymal tumours, it is essentially a carcinoma which has undergone sarcomatous differentiation/metaplasia. The major subtypes of cervical carcinoma are squamous cell carcinoma (SCC), adenocarcinoma (with various subtypes), adenosquamous carcinoma and neuroendocrine tumours. While it is beyond the remit of this document to detail the morphological appearances of the different tumour types in detail, a few points should be noted.

SCCs are nearly all caused by high-risk human papillomavirus (HPV) with rare exception[2,3] and are subclassified by the WHO based on their histological growth pattern and the presence of keratinization. However, the subclassification of SCC seems to have little or no bearing on clinical behaviour and so it is not considered necessary to specify the subtype (keratinizing, papillary, basaloid, warty, verrucous etc). However, it may be useful to record unusual subtypes, for example lymphoepithelioma-like, since the behaviour of these is not well established.

There are several subtypes of cervical adenocarcinoma, the most common being the usual type which, in the majority of cases, is associated with high-risk HPV. The other, less common subtypes (gastric type, mesonephric, clear cell and others) are generally unassociated with HPV infection and have different and distinct histologic appearances. While there is limited information regarding the clinical behaviour of the adenocarcinoma subtypes, it is now well established that gastric type adenocarcinomas of the cervix (adenoma malignum or mucinous variant of minimal deviation adenocarcinoma is the morphologically well differentiated end of the spectrum of gastric type adenocarcinoma) have a particularly aggressive behaviour with poor prognosis, even in early stage disease.[4-6] Therefore, it is extremely important from both a prognostic stance as well as an aetiologic and epidemiologic perspective (in light of widespread HPV vaccination programs) to correctly identify these tumour subtypes. The ubiquitous use of and reliance on p16 immunohistochemistry to diagnose cervical adenocarcinoma may cause diagnostic problems for HPV negative tumours, since these do not exhibit the diffuse block-type immunoreactivity characteristic of HPV-related tumours (see **ANCILLARY STUDIES**).[7,8] In addition, in the era of molecular characterization and targeted therapy, correct identification of the tumour subtypes will be even more crucial for understanding tumour biology and discovery of potential therapeutic targets.

Adenosquamous carcinomas (defined in WHO 2014 blue book as a malignant epithelial tumour comprising both adenocarcinoma and squamous carcinoma[1]) are usually related to high-risk HPV. To make a diagnosis of adenosquamous carcinoma, malignant squamous and glandular components should be identifiable on routine haematoxylin and eosin stained sections. The demonstration of foci of intracytoplasmic mucin by mucin stains in an otherwise typical squamous carcinoma should not result in diagnosis of an adenosquamous carcinoma. Carcinomas which lack evidence of squamous differentiation (intercellular bridges, keratinisation) but have abundant mucin-producing cells should be diagnosed as poorly-differentiated adenocarcinomas. Adenosquamous carcinoma should also be distinguished from a spatially separate squamous carcinoma and adenocarcinoma, which occasionally occurs. While some studies have indicated a worse outcome than pure squamous or adenocarcinomas, there is not robust evidence to confirm these findings.[9,10]

Primary serous carcinoma of the cervix is exceedingly rare and some doubt its existence, although it is included in the 2014 WHO Classification. Most cases reported as primary cervical serous carcinoma are likely to represent a metastasis from the corpus or extrauterine sites or a usual HPV-related adenocarcinoma with marked nuclear atypia. Metastasis should be excluded before diagnosing a primary cervical serous carcinoma. Usual type cervical adenocarcinomas can have a papillary growth pattern and may show high-grade nuclear atypia, which can mimic serous carcinoma. Whether true p53 mutation-associated serous carcinoma of the cervix exists is unresolved at this time.

While endometrioid type adenocarcinoma of the cervix is a subtype listed in the 2014 WHO classification, in the past this has been an over-used diagnostic category and some even doubt its existence as a primary cervical neoplasm. Most adenocarcinomas classified as primary cervical endometrioid adenocarcinomas in the literature represent usual type cervical adenocarcinomas with mucin depletion. These are different from true endometrioid type adenocarcinomas of the uterine corpus or adnexa which are driven by hormones and not HPV-associated. If endometrioid

adenocarcinoma occurs as a primary neoplasm in the cervix, it is most likely in the setting of endometriosis and has the same histologic and immunohistochemical profiles as endometrioid adenocarcinomas of the uterine corpus or ovary. As with serous carcinoma, extreme caution should be exercised before diagnosing a primary cervical endometrioid adenocarcinoma.

Neuroendocrine carcinomas (NECs) (small cell and large cell neuroendocrine carcinoma) are uncommon but well described in the cervix and can occur in pure form or associated with another tumour type, typically adenocarcinoma, squamous carcinoma or adenosquamous carcinoma. These are referred to in the WHO 2014 blue book as high-grade neuroendocrine carcinomas. The term 'small cell neuroendocrine carcinoma' is preferred to 'small cell carcinoma' since a small cell variant of squamous carcinoma occurs and if the term "neuroendocrine" is not applied, this may result in confusion. When mixed with another tumour type, the percentage of the neuroendocrine component should be given. Regardless of the percentage of NEC, it is recommended that the tumour be reported as mixed since all tumours containing a component of NEC have a very poor prognosis and the NEC component may be underestimated in a limited sample.[11] Several studies of small cell neuroendocrine carcinomas of the cervix have shown that adjuvant chemotherapy after surgery for early stage disease provides significant clinical benefit compared to surgery alone and therefore, it is extremely important to correctly diagnose any component of NEC. Additionally, in many institutions surgical resection is not undertaken for a NEC even if early stage but instead chemotherapy treatment is given. Diagnosing NEC or a component of NEC can be difficult, especially in small samples, but a combination of synaptophysin, chromogranin, CD56, TTF1 and p63 has been shown to be helpful in making the distinction between NEC and poorly-differentiated non-NEC (see **ANCILLARY STUDIES**).[12,13]

WHO classification of tumours of the uterine cervix

Epithelial tumours	
Squamous tumours and precursors	
Squamous intraepithelial lesions	
High-grade squamous intraepithelial lesion	8077/2
Squamous cell carcinoma, not otherwise specified	8070/3
Keratinizing	8071/3
Non-keratinizing	8072/3
Papillary	8052/3
Basaloid	8083/3
Warty	8051/3
Verrucous	8051/3
Squamotransitional	8120/3
Lymphoepithelioma-like	8082/3
Glandular tumours and precursors	
Adenocarcinoma in situ	8140/2
Adenocarcinoma	8140/3
Endocervical adenocarcinoma, usual type	8140/3
Mucinous carcinoma, NOS	8480/3
Gastric type	8482/3
Intestinal type	8144/3
Signet-ring cell type	8490/3
Villoglandular carcinoma	8263/3
Endometrioid carcinoma	8380/3
Clear cell carcinoma	8310/3
Serous carcinoma	8441/3
Mesonephric carcinoma	9110/3
Adenocarcinoma admixed with neuroendocrine carcinoma	8574/3
Other epithelial tumours	
Adenosquamous carcinoma	8560/3
Glassy cell carcinoma	8015/3
Adenoid basal carcinoma	8098/3
Adenoid cystic carcinoma	8200/3
Undifferentiated carcinoma	8020/3
Neuroendocrine tumours	
Low-grade neuroendocrine tumour	
Carcinoid tumour	8240/3
Atypical carcinoid tumour	8249/3
High-grade neuroendocrine carcinoma	
Small cell neuroendocrine carcinoma	8041/3
Large cell neuroendocrine carcinoma	8013/3
Mixed epithelial and mesenchymal tumours	
Carcinosarcoma	8980/3

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.

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