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Pattern based classification of endocervical adenocarcinoma: a review

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Summary

While endocervical adenocarcinoma is comprised of several histological subtypes, the most common subtype is human papillomavirus-associated usual type, and management of these tumours is primarily determined by FIGO (International Federation of Gynecology and Obstetrics) stage, a clinically based staging system. Early stage cervical cancer is determined by the pathological evaluation of tumour microscopic measurement (depth of invasion), which can be particularly challenging because of the lack of a defined point of origin. Yet important treatment decisions, cone versus radical surgery, are based on this imperfect system, resulting in overtreatment and related morbidities in many patients for whom it may not be necessary. There is a growing consensus, however, for a more conservative approach, one that reduces morbidity and prevents loss of fertility in these (often young) patients. This movement has been supported, in part, by the development of a morphology based risk stratification system which was devised in order to recognise those tumours that, while invasive, could potentially be treated more conservatively. In this review, we provide the reader with the background and rationale for a more conservative approach in treating endocervical adenocarcinoma, summarise the risk stratification system, and review the system's utility and reproducibility. In addition, we comment on recent updates that attempt to further refine the system. The application of this morphology based classification could help identify a subset of patients with endocervical adenocarcinoma (who would otherwise undergo radical surgery based on FIGO staging alone) that have good clinical outcomes and could be treated more conservatively.

Key words: Endocervical adenocarcinoma; risk stratification; pattern based; review.

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CERVICAL CARCINOMA STAGING AND TREATMENT

Endocervical adenocarcinoma is a heterogeneous disease comprised of various histological subtypes that have different aetiologies and clinical outcomes.[1,2] The most common type is human papillomavirus (HPV)-associated usual endocervical adenocarcinoma, and despite the success of cervical cancer screening, the incidence of this adenocarcinoma appears to be increasing.[3] Management of cervical cancer is based primarily on the International Federation of Gynecology and Obstetrics (FIGO) Staging system, which relies on clinical parameters, meaning that clinicians determine tumour stage by the presence or absence of a grossly visible or palpable lesion.[4,5] When a mass is clinically identified, the tumour is stage FIGO IB, independent of the microscopic examination and its morphological features, including depth of invasion. Since patients beyond stage FIGO IB1 are usually not surgical candidates, pathologists infrequently encounter these types of cases.[6] In tumours that are not clinically visible, stage is determined by microscopic measurements.[7] Therefore, in early stage cervical carcinoma, accurate measurements are crucial for patient management. According to the FIGO staging system, tumours measuring $\leq$7 mm in horizontal extent and invading no greater than 5 mm are stage IA, while those with greater measurements but less than 4 cm in size are stage IB1. The difference in treatment based on microscopic measurements can be dramatic, such that a stage IA1 tumour with no lymphovascular invasion can be treated with cone biopsy alone, yet a tumour that is 1 mm greater in depth of invasion (stage IA2) could result in a radical hysterectomy with lymph node dissection.[8]

There are several problems with the current staging system as it applies to adenocarcinoma, as the staging parameters lack specific guidelines on how to measure invasive adenocarcinoma. Unlike the squamous epithelium which has a defined basement membrane, beyond which invasion is obvious, endocervical glands do not have such a landmark. Rather, the endocervical mucosa is a series of invaginations along the canal that form gland-like structures throughout the cervical wall, sometimes reaching deep into the wall or expanding with mucus to form deeply placed Nabothian cysts, making determination of the exact point of origin of invasive adenocarcinoma quite challenging.[9,10] This is especially challenging if adenocarcinoma *in situ* (AIS) is associated with an invasive carcinoma, since a clear distinction between the two may not be possible in up to 20% of cases.[10–12] Additionally, when the tumour is predominantly exophytic, it can be difficult to know how to measure the depth of invasion. Inconsistent measuring methods can greatly affect therapy since, as mentioned above, a difference of a millimetre can mean the difference between retaining or

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losing fertility, as well as undergoing a morbid procedure such as lymph node dissection.

RATIONALE FOR A MORE CONSERVATIVE TREATMENT APPROACH AND NEED FOR A NEW RISK STRATIFICATION SYSTEM IN ENDOCERVICAL ADENOCARCINOMA

Conservative management of invasive tumours has become common practice in oncology in an effort to preserve organ function and decrease morbidity without affecting patient outcomes. The uterus, though it does not serve a life sustaining role, does have the unique function of sustaining pregnancy; with many more women delaying child-bearing into their 30s and 40s, the diagnosis of an invasive cervical cancer may not allow that option, with radical hysterectomy as standard treatment in many cases. Not only does the patient lose the ability to become pregnant, but complications related to radical surgery and lymph node dissection have been well reported and are not inconsequential. These include voiding difficulties, urinary tract infection, incontinence, pyrexia, haemorrhage, nerve-site injury and lymphoedema.[13] Conservative management is becoming more accepted, with the increasing use of sentinel lymph node mapping in gynecological tumours[14–17] and trachelectomies and cone excisions being included in the treatment algorithms of the latest National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines).[8] However, these conservative practices are not widespread and most gynecological oncological surgeons will still perform full lymph node dissection for early stage (IA2–IB1) cervical carcinoma. Furthermore, the need for a more specific and tailored treatment algorithm is becoming apparent in this era of personalised medicine. Not much progress has been made in developing 'targeted therapy' in cervical cancer. In the head and neck region where the other significant proportion of HPV associated tumours occur, the presence of HPV is of critical importance in determining the prognosis and the treatment plan, since data have now shown that HPV related squamous cell carcinomas respond better to radiation therapy than HPV unrelated tumours.[18–20] In the cervix, the vast majority of cancers are HPV associated and, therefore, there is not the same opportunity to stratify patients based on HPV status. Hence, stratification based on other factors such as pattern of invasion may provide more information in determining therapy and prognosis.

PATTERN BASED CLASSIFICATION SYSTEM

A recently described morphology based classification system for endocervical adenocarcinoma has proposed a novel method of stratifying patients into risk categories based on the pattern of stromal invasion.[21–23] This new system has the potential to greatly reduce the number of unnecessary radical procedures in patients with early stage disease. The initial impetus to study the value of pattern classification in endocervical adenocarcinoma stemmed from the observation that radical surgeries were being performed on patients whose tumours showed histological features that pathologists typically associate with indolent behaviour. These included tumours without destructive stromal invasion or evidence of lymphovascular invasion. These types of cases were often the ones being sent for expert consultation to determine (1) the presence of invasion and/or (2) the depth of invasion. As mentioned previously, the lack of a defined basement membrane in endocervical glands presents unique challenges in the histological evaluation of true stromal invasion and the distinction between *in situ* and invasive disease.

Diaz De Vivar *et al.* initially described these three patterns of invasion in endocervical carcinomas in 2013[21] with subsequent expansion of their morphological details by Rutgers *et al.* in 2016 (Table 1).[24] It is important to note that the system only applies to usual type HPV-associated endocervical adenocarcinomas but not to any of the other variants (e.g., gastric-type, clear cell, mesonephric, etc.) and that the entire tumour must be examined histologically (if obvious destructive stromal invasion is absent) in order to classify the tumour into the appropriate group. Pattern A endocervical adenocarcinomas are characterised by well-formed glands frequently forming groups with relatively well preserved lobular architecture without destructive stromal invasion, single cells or detached clusters of tumour cells (Fig. 1A,B). There should be no solid growth but complex intraglandular proliferations are acceptable (cribriforming or papillae). Lymphovascular invasion should be absent as otherwise would disqualify the tumour from pattern A (all pattern A tumours initially studied lacked lymphovascular invasion). Pattern B tumours show localised (limited/early) destructive invasion arising in a background of pattern A glands (Fig. 1C,D). Individual cells or clusters of tumour cells are seen in desmoplastic or inflamed stroma, and these foci can be single, multiple or linear at the base of the tumour, but should not exceed 5 mm (total). Pattern C tumours show diffuse destructive invasion that usually elicits a desmoplastic/inflammatory response (Fig. 1E). The glands can be angulated, or have a canalicular/labyrinthine appearance, and incomplete/fragmented glands (as seen in MELF pattern of endometrioid carcinomas) are frequent, sometimes associated with mucin lakes (Fig. 1F). Solid growth can also be seen. Lymphovascular invasion can be present in either pattern B or C and should be documented separately. The geographic relationship of the tumour to large calibre vessels does not affect pattern classification; e.g., pattern A glands involving deep stroma, usually in the vicinity of medium calibre vessels, are still pattern A independent of the depth of invasion.

Examination of the entire tumour is required to differentiate between patterns A and B, as pattern B tumours by definition are composed of pattern A type glands but additionally have microscopic tumour cells involving the adjacent stroma with destructive features that might be less than 1 mm away. Thus, careful examination is necessary. It is usually recommended that when in doubt, obtaining deeper sections from pattern A tumours with areas that might represent pattern B, such as loose, desmoplastic, or inflamed stroma would be helpful. Careful examination for lymphovascular invasion is also crucial, as the presence of tumour in vascular spaces would by definition exclude a pattern A. Differentiating some pattern A tumours from AIS can be challenging but from results of studies discussed herein of inconsequential relevance. Differentiating pattern B from pattern C depends on both quantitative and qualitative features. Obvious pattern C adenocarcinomas are diagnostically straightforward such that most pathologists can confidently diagnose them as definitively malignant and invasive. However, when the entire tumour does not show pattern C features, quantitative criteria are required to determine the upper end of the