SELECTED AREAS OF DIFFICULTY IN STAGING OF ENDOMETRIAL CARCINOMAS.

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Accurate staging of cancer, including gynaecological cancer, is an important determinant of prognosis and guides optimal patient treatment. Accurate cancer staging also has wider implications for international benchmarking and the provision of robust information to healthcare providers and agencies involved in cancer registration. Staging data are also critical for research and provide an invaluable epidemiological resource. It is recommended by the International Collaboration on Cancer Reporting (ICCR) to stage endometrial cancers using the 2009 FIGO staging system (1,2); in this staging system, it is explicitly stated that carcinosarcomas be staged like other endometrial carcinomas. In this talk, problematic areas in the staging of endometrial cancer are discussed (3).

TUMOUR INVOLVEMENT OF INNER OR OUTER HALF OF MYOMETRIUM

Deep myometrial invasion by tumour has been shown to be a poor prognostic indicator in endometrial carcinoma and is an important determinant of adjuvant therapy. The tumour is FIGO Stage IA if myometrial invasion is absent or confined to less than one half (< 50% myoinvasion) and IB if it invades one half or more of the uterine wall (≥ 50% myoinvasion). Various methods of determining the extent of myometrial invasion have been evaluated in predicting regional lymph node metastasis. These have included the absolute depth of invasion from the endomyometrial junction to the deepest focus of invasive carcinoma, the distance from the uterine serosa to the deepest focus of invasive carcinoma and the percentage of myometrium involved, defined by the depth of myometrial invasion from the endomyometrial junction to the deepest focus of invasive carcinoma in comparison with the overall myometrial thickness (4).

In most cases, determining the depth of myometrial invasion is not difficult. However, in some instances, this may be problematic (5-7). The irregularity of the normal endomyometrial junction may make it difficult to determine the exact superficial reference point for measuring the depth of myometrial invasion. Tumour involvement of adenomyosis may also result in problems (see section on **Tumour Involvement of Adenomyosis**). Maximum depth of tumour invasion is best assessed in a well-orientated, full thickness block of the uterine wall from the site of deepest tumour infiltration. The uterine wall in the cornual region is thin and blocks from the cornual region should not be used for evaluation of depth of invasion. In cases where there is difficulty in ascertaining the depth of myometrial invasion, tumour that involves the arcuate vascular plexus of the uterus usually indicates > 50% myometrial invasion (5). Polypoid exophytic tumours may result in problems in assessing depth of myometrial invasion since smooth muscle metaplasia or incorporation of smooth muscle within these may result in misdiagnosis of myometrial invasion (6). Carcinomas confined to the endometrium can accentuate the normal irregular endometrial-myometrial junction which can result in overdiagnosis of superficial myometrial invasion. This was one reason for combining stages 1A (tumour confined to endometrium) and 1B (inner half of myometrium) in the 1988 FIGO staging system into stage 1A in the 2009 system. One study which involved interinstitutional review found that overdiagnosis of early myometrial invasion was very common (7).

TUMOUR INVOLVEMENT OF ADENOMYOSIS

Endometrial carcinomas of all morphological types may involve adenomyosis. In the absence of myometrial invasion outside the confines of the adenomyosis, the tumour is not considered myoinvasive. In other words, even with involvement of adenomyosis in the outer half of the myometrium, the tumour is still FIGO stage 1A. There is a relative paucity of studies examining the prognostic significance of involvement of adenomyosis, especially in the outer half of the myometrium, but the available evidence suggests that this is of little or no adverse prognostic significance in endometrioid adenocarcinomas (8,9). The published data supports the concept that tumour involvement of deeply located adenomyosis does not affect prognosis in an endometrioid adenocarcinoma which is otherwise confined to the inner half of the myometrium. One study also showed that even with small foci of myometrial invasion emanating from deeply located adenomyosis, there was no adverse outcome (9). However, this requires confirmation by further studies. Staging of such cases is also controversial but

when tumour invades the myometrium from adenomyosis in the outer half of the myometrium, this should be reported as FIGO stage IB.

Occasionally, it can be problematic to distinguish tumour involvement of adenomyosis from true myometrial invasion with a rounded contour or pushing edge and both may coexist. This problem is especially likely in postmenopausual women when the adenomyotic stroma is atrophic. Features suggesting involvement of pre-existing adenomyosis include a wholly rounded contour, the presence of accompanying benign glands, the presence of endometrioid type stroma which, as stated, may be atrophic, the absence of a desmoplastic response and the presence of adjacent uninvolved adenomyosis. In contrast, an irregular angulated contour, an absence of benign glands and the presence of a desmoplastic stromal response suggests true myometrial invasion. The difficulties may be further compounded when true myoinvasion emanates from adenomyosis or when an adenocarcinoma arises from adenomyosis without involvement of the overlying endometrium. Studies have assessed the value of CD10, a marker of endometrial stroma, in this scenario. However, this is of limited value since, although CD10 highlights residual endometrial stroma, there is also commonly immunoreactivity surrounding true myoinvasive glands (“fringe pattern”) (10,11). It can beconcluded that the presence of CD10 staining immediately surrounding neoplastic glands does not equate with involvement of adenomyosis. In contrast, absence of CD10 expression helps exclude involvement of adenomyosis by adenocarcinoma.

PATTERNS OF MYOMETRIAL INVASION

A number of morphologic patterns of myometrial invasion have been described, including diffusely infiltrating irregular glands (infiltrative pattern), "broad front" (or pushing border), adenoma malignum-like, adenomyosis-like, and microcystic, elongated and fragmented (MELF) (12,13). The adenoma malignum-like pattern is rare and consists of diffusely infiltrating “naked” glands without a stromal response. In 1 study, the infiltrative gland pattern was associated with higher stage, lymphovascular invasion and tumour recurrence, suggesting that this growth pattern may be associated with neoplasms having other histological features typically associated with more aggressive behaviour (12,13). In the following section, MELF type myometrial invasion is discussed in detail as there is evidence that this may be an independent predictor of the likelihood of lymph node metastasis (14,15).

Microcystic, Elongated and Fragmented (MELF) Pattern of Myometrial Invasion.

A not uncommon pattern of myometrial infiltration by low grade endometrioid adenocarcinomas has been referred to as MELF (microcystic, elongated and fragmented) (16). This pattern of myometrial invasion which is usually most conspicuous in the deeper aspects is characterised by a prominent fibromyxoid stromal reaction surrounding the myoinvasive glands with "outpouchings" from typical neoplastic glands that may become detached and lined by flattened epithelium, thus appearing as microcysts or slit-like spaces. The glands may become elongated or undergo fragmentation into small solid clusters or single cells which are surrounded by the fibromyxoid stroma. These cells may lie deeper within the myometrium than the well-formed glands and can be overlooked, resulting in an underestimation of the depth of myometrial infiltration. This pattern of infiltration may be mistaken for lymphovascular invasion because individual or small clusters of tumour cells may lie within glands which are lined by flattened epithelium (described as endothelial-like) which can be misconstrued as vascular channels. It is also not uncommon for lymphovascular invasion to be present in association with MELF-type myometrial invasion. Cytokeratin markers may be of value in distinguishing between glands lined by flattened cells and vascular spaces and also in identifying single invasive cells or small groups of cells deeper in the myometrium than appreciated on examination of haematoxylin and eosin stained sections.

It has been found that MELF type invasion is associated with an increased incidence of regional lymph node metastasis in stage I, low grade endometrioid adenocarcinomas (14,15). The lymph node involvement associated with MELF type invasion may be in the form of single or small groups of tumour cells with abundant eosinophilic cytoplasm mimicking histiocytes (17). Similar tumour cells may be seen in myometrial lymphovascular channels in association with MELF type invasion.

ASSESSMENT OF CERVICAL INVOLVEMENT

There are several problematic areas regarding the histological assessment of cervical involvement in endometrial carcinoma and one study revealed significant interobserver variation in the assessment of this amongst 6 specialist gynaecological pathologists (18).

One basic problem is that the junction between the lower uterine segment/isthmus and the endocervix is not clearly defined. There are no histological landmarks which define the junction and here there is an admixture of ciliated lower uterine segment endometrial glands and mucinous endocervical glands. In the interobserver variation study referred to, it was suggested that the uppermost mucinous gland might be taken as the junction between the cervix and the lower uterine segment (18) but another study suggested the lowermost ciliated gland was the most appropriate (19). There are no firm recommendations on this issue but it is suggested that the uppermost mucinous gland is taken as the junction between the lower uterine segment/isthmus and the endocervix.

Endocervical glandular involvement by endometrial carcinoma may be subtle and difficult to recognise, especially if it involves the surface and forms a monolayer and there is a risk of the pathologist missing subtle endocervical glandular involvement. Problems may also arise in the distinction between surface glandular involvement and so-called “floaters” or artefactual tumour incorporation (20). With “floaters” within the endocervical canal, it is usually relatively straightforward to ascertain that this does not represent true cervical involvement. However, problems arise when tumour is closely applied to the endocervical surface or embedded in granulation tissue secondary to implantation. Although cervical glandular involvement by endometrial carcinoma no longer denotes stage II disease, this being defined by cervical stromal involvement in the 2009 FIGO staging system (2), many oncologists still administer vault brachytherapy when there is cervical glandular involvement and so its recognition is still important.

There can also be issues in deciding whether tumour is confined to the cervical glandular epithelium or also involves the stroma. Normal endocervical epithelium as well as lining the surface invaginates to form crypts which lie within the superficial cervical stroma. Thus, tumour may be present within the cervical stroma but still confined to the glandular epithelium; it can be difficult in such cases to decide whether the neoplasm within the stroma is confined to pre-existing glandular elements, especially since endometrial adenocarcinomas invading the cervical stroma may not elicit a stromal reaction. Furthermore, some authors consider cervical glandular involvement to be confined to tumour involving the surface only while others allow for underlying crypt involvement. It is recommended that with crypt involvement the tumour should be clearly within the normal endocervical glandular field for it to be considered confined to the glandular epithelium.

A subtle “burrowing” pattern of cervical stromal involvement by endometrioid adenocarcinoma of the uterine corpus rarely occurs which can be misdiagnosed as cervical mesonephric remnants, tunnel clusters, tuboendometrial metaplasia or a coexistent premalignant or malignant endocervical glandular lesion (21,22). With this burrowing pattern, the tumour infiltrates as “naked” widely spaced, often cytologically bland, glands which lie beneath normal endocervical glands and do not elicit a stromal response. At low power, the infiltrating glands, given their location and morphological appearances, are especially likely to be misdiagnosed as mesonephric remnants, especially since they often have a somewhat linear arrangement and contain luminal eosinophilic “colloid-like” material, both features of cervical mesonephric remnants (ADD). As well as mesonephric remnants, this pattern of infiltration may be misdiagnosed as a primary cervical adenocarcinoma, either of usual or mesonephric type. In such cases, the primary neoplasm within the corpus may be small and exhibit minimal or even no myometrial invasion and often looks morphologically different to the tumour within the cervix. Immunohistochemistry may be useful in helping to confirm the cervical tumour represents spread from the primary within the corpus in that it is usually diffusely positive with ER and vimentin; mesonephric lesions, benign and malignant, are usually ER negative.

As discussed, there is a risk of missing focal microscopic endocervical surface involvement by endometrial carcinoma. The converse is that a common change may involve the endocervical surface epithelium, termed atypical reactive proliferation, which has the potential to be overdiagnosed as endocervical surface involvement by tumour, particularly when the changes are florid (23). This is a reactive phenomenon secondary to recent endometrial biopsy or curettage (23). The histological features, not all of which are present in every case, include nuclear stratification and multilayering with short micropapillary processes, squamoid change, hobnail cells and mild cytological atypia. Other features which may be present are surface erosion, clearing of the cytoplasm, fibrin deposition, an inflammatory cell infiltrate, fibrosis of the subepithelial tissue and extreme vascularity with a granulation tissue-like appearance (23); when benign glandular elements become entrapped within the fibrous stroma as the result of a repair process, the features may even mimic cervical stromal invasion by tumour. Tubal or tuboendometrial metaplasia of the endocervical glands or superficial endometriosis in a patient with an endometrial carcinoma may also be mistaken for tumour involvement.

SEROSAL INVOLVEMENT

The uterine serosa is considered involved when tumour is seen to penetrate through the serosal layer. This is sometimes associated with an inflammatory or desmoplastic stromal reaction. It most commonly occurs secondary to full thickness myometrial invasion but occasionally represents discontinuous tumour involvement, possibly secondary to transtubal spread; it may be useful to distinguish these two patterns of involvement. For staging purposes, serosal lymphovascular involvement, unaccompanied by tissue infiltration, is not considered as representing serosal involvement. Uterine serosal involvement with or without adnexal involvement has been shown to be an independent marker of high recurrence risk and signifies FIGO Stage IIIA disease (24).

ASSESSMENT OF LYMPHOVASCULAR INVASION

Although not related to staging, lymphovascular invasion is discussed here since there are multiple problems in its assessment and it has been shown in many studies to be an independent prognostic factor in endometrial adenocarcinomas (25-29); blood vascular invasion seems to be more important than lymphovascular invasion, although most pathologists do not routinely distinguish between the two (30). One large study (cases from PORTEC trials) found that substantial lymphovascular invasion (defined as three or more spaces involved by tumour outside the immediate invasive tumour border), in contrast to focal or no lymphovascular invasion, was the strongest independent prognostic factor for pelvic regional recurrence, distant metastasis and overall survival (29). They concluded that therapeutic decisions should be based on the presence of substantial and not any lymphovascular invasion (29). Of importance to the pathologist is that the presence or absence of lymphovascular invasion may be important in determining adjuvant therapy following hysterectomy. For example, with a low grade endometrioid adenocarcinoma involving the outer half of the myometrium, vault brachytherapy is usually given while if there is associated lymphovascular invasion, external beam radiotherapy is also likely to be administered. There are a number of problematic issues in the assessment of lymphovascular invasion and it is likely that there is significant interobserver variability amongst pathologists.

Lymphovascular invasion is typically most easily seen at the invasive front of the tumour and a perivascular lymphocytic infiltrate, including lymphoid aggregates, should raise the

possibility of vessel involvement (31). Lymphovascular invasion should be distinguished from retraction artifact which is not uncommon in endometrial carcinomas. This distinction may be difficult but retraction artifact is often more widespread than true lymphovascular invasion and is characterized by a smooth round contour; with true vascular invasion, the spaces typically have a more slit-like or angulated contour and are lined by endothelial cells. The identification of red blood cells and fibrin within the space may be useful in helping to confirm a true vascular channel. True lymphovascular invasion should also be distinguished from artifactual vascular involvement associated with tumour autolysis. Artifactual vascular involvement secondary to autolysis is characterised by “smearing artifact” or so-called “toothpaste” effect. The vascular invasion may be disproportionate in comparison with the low stage and grade of the tumour and often the vessels involved are predominantly in the outer myometrium where tumour may also be seen smeared on the serosa. Markers such as CD31 (stains all vascular channels) and D2-40 (specifically stains lymphatic channels) may assist in identifying vascular invasion, although these are not routinely used (30). Occasionally, small clusters of dyscohesive tumour cells with abundant eosinophilic cytoplasm which can mimic histiocytes are present within vessels and cytokeratins help in confirming their epithelial nature; these are especially common in association with MELF type myometrial invasion (17). The phenomenon of MELF type myometrial invasion mimicking lymphovascular invasion has already been discussed (section on **Microcystic, Elongated and Fragmented (MELF) Pattern of Myometrial Invasion).**

The occurrence of artifactual vascular pseudoinvasion in total laparoscopic hysterectomy (TLH) specimens using an intrauterine balloon manipulator has been reported (32-34). It has been suggested that this artifact, where both benign and malignant endometrial tissue may be displaced into vascular spaces, is the result of a closed positive pressure system created by the inflation of an intrauterine balloon following cautery occlusion of the fallopian tubes (32). Another suggestion is that the vascular pseudoinvasion is a grossing artifact secondary to mechanical disruption of friable polypoid tumour by the intrauterine balloon (33). Clues that this is an artifact include the contrast between the sometimes large amount of vascular involvement and the low tumour grade, the presence of stromal tissue accompanying the glands within vessels, preferential involvement of large thick-walled blood vessels in the outer myometrium and absence of tumour adherence to the vessel wall. Other features which may be seen in these specimens include disruption of the endometrial lining, endomyometrial clefts containing fragments of tumour, intratubal contaminants, nuclear crush artifact and

intravascular inflammatory debris. Although these studies are limited by short follow up such that the significance of vascular pseudoinvasion, if any, is not clear, it is important to be aware of this artifact as misinterpretation can result in unnecessary adjuvant treatment. An increased incidence of positive peritoneal washings has also been demonstrated with TLH and intrauterine balloon manipulators (34).

SYNCHRONOUS UTERINE AND TUBO-OVARIAN ADENOCARCINOMAS

A not uncommon scenario is the presence of an endometrioid adenocarcinoma in the uterine corpus and one or both ovaries, usually a single ovary (35-37). Most commonly, these are low grade (grade 1 or 2) and the question arises as to whether these represent synchronous independent neoplasms or a metastasis from one organ to the other, usually from the endometrium to the ovary. In this scenario, a variety of pathological features are of value. Most of these are traditionally considered to represent synchronous independent neoplasms and the overall prognosis is considered to be good, although there is a paucity of large studies with significant follow-up. Features favouring synchronous neoplasms include the low grade and low stage of both tumours. Adjacent atypical hyperplasia and lack of deep myometrial and lymphovascular invasion in the case of the endometrial tumour and association with endometriosis in the ovarian neoplasm are pointers in favour of synchronous neoplasms. Conversely high tumour grade, deep myometrial and lymphovascular invasion and bilateral ovarian involvement with a nodular pattern and surface deposits are suggestive of a uterine primary with ovarian metastasis.

Since uterine and ovarian endometrioid adenocarcinomas have an identical immunophenotype, there are no markers which are of assistance, although it has been suggested in one study that vimentin is of value; in that study, vimentin was negative in 97% of primary ovarian endometrioid adenocarcinomas and positive in 82% of primary uterine corpus endometrioid adenocarcinomas (38).

Molecular investigations may assist in problematic cases, although these are expensive, not available in most surgical pathology laboratories and the results must always be interpreted in light of the clinicopathological features. Loss of heterozygosity, PTEN or beta-catenin gene mutation analysis, microsatellite instability and more recently gene expression profiling have all been used (35,37,39,40). Recent studies using whole-exome massively parallel

sequencing have shown that many cases which are presumed synchronous independent endometrioid adenocarcinomas of the uterine corpus and ovary are clonally related and are likely to represent metastasis from one site to the other (most likely endometrium to ovary) (39,40). This creates a dilemma in management and since these are still considered to have a good prognosis, at present it is still recommended to call these synchronous independent primaries until more information becomes available.

Occasionally a patient with a uterine serous carcinoma (sometimes conforming to serous endometrial intraepithelial carcinoma (serous EIC)) has a serous proliferation in one or both ovaries or fallopian tubes. With serous neoplasms at more than one site, it is considered that these represent metastatic disease from one site to the other until proven otherwise since the theory of a "field-effect" in serous neoplasia has no firm evidence. Fallopian tube mucosal involvement by uterine serous carcinoma can occur and mimic serous tubal intraepithelial carcinoma (STIC) (41,42). A recent study which extensively examined the fallopian tubes in cases of uterine serous carcinoma found tubal involvement in 20% of cases (41). This was sometimes an incidental microscopic finding and upstaged the tumour in a significant minority of cases. Most cases with unilateral or bilateral high grade serous carcinoma (HGSC) in the ovary and/or STIC or HGSC in the tube but with an endometrial serous intraepithelial or invasive carcinoma will represent adnexal metastases from an endometrial primary (41). WT1 may be of value in these cases, although there is significant overlap. Most tubo-ovarian HGSCs (approximately 90-95%) exhibit nuclear positivity (usually, but not always, diffuse) with WT1 while most uterine serous carcinomas are negative. However, there is significant overlap in that a proportion of uterine serous carcinomas are WT1 positive (the percentage has varied between studies but may be up to 30%) and, as stated, a small percentage of tubal HGSCs are WT1 negative (43,44).

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