# **Myometrial invasion** (Core and Non-core)

The extent of myometrial invasion has long been recognised to be an important risk factor for regional lymph node metastasis, and in some studies, for overall survival in Stage I endometrioid cancer patients.[1,2] Accordingly, the extent of myometrial invasion is a central component of most contemporary systems for prognostication, staging, intra- and post-operative risk stratification, and decision-making models for adjuvant therapy.[3-5]

Various methods of determining the extent of myometrial invasion have previously been evaluated. These have included the absolute depth of invasion (DOI) from the endomyometrial junction to the deepest focus of invasive carcinoma, the tumour free distance (TFD) to serosa, and the percentage of myometrium involved, expressed either as the percentage of the overall myometrial thickness that is infiltrated by carcinoma, or as one of three categories: none, <50%, or ≥50%.[6-16]

The widely used TNM and International Federation of Gynaecology and Obstetrics (FIGO) Staging Systems take the latter approach, with tumours limited to endometrium or invading less than half of myometrium categorised as Stage IA (pT1a), and tumours invading 50% or more categorised as Stage IB (pT1b).[5,17,18]

For cancer reporting, the absence or presence and depth of myometrial invasion should be recorded as none, <50%, or ≥50%; this is a core element. In addition, the absolute percentage of myometrial wall thickness that is invaded by carcinoma can be recorded as a non-core element.[19]

Depth of invasion (DOI) as an individual variable has received less investigation. Nevertheless, higher depths of invasion have been associated with an increased risk of lymphovascular invasion (LVI), lymph node involvement, high stage, recurrence and death of disease in some studies,[10,11,13,14] but not others.[8,9,12,15,16]

Tumour free distance (TFD) is the distance between the deepest point of myometrial invasion of the cancer and the nearest serosal surface.[8-16] TFD theoretically eliminates some of the difficulties that are inherent to determining the depth of myometrial invasion,[6,7] and is reportedly more reproducibly diagnosed by pathologists.[20] However, much like DOI, the prognostic significance of TFD is unclear, since the reported findings have been conflicting.[6,8-16] Most studies have found a statistically significant association, on univariate analyses, between shorter TFD and adverse clinicopathologic factors, including higher tumour grade, cervical involvement, LVI, and advanced patient age.[9,10,13,14] An association between TFD and lymph node involvement, adnexal involvement and/or larger tumour size has also been reported in some studies[9,10,12,13] but not others.[11,14,15] On multivariate analyses, TFD has been found to be an independent predictor of overall survival and recurrence free survival in only 50% and 33% of the studies that have evaluated these questions, respectively.[8-10,12,13,15] In two of the aforementioned studies, a TFD cut off of 10 millimetres was found to maximize sensitivity and specificity in predicting recurrences.[9,10] Both DOI and TFD are non-core elements. Additional studies are needed to clarify the prognostic roles of DOI and TFD.

Assessment of tumour invasion from adenomyosis is a controversial issue without strong scientific evidence. International Society of Gynecological Pathologists (ISGyP) guidelines state that “it is preferable to use the standard method for determining DOI, based on the location of the deepest focus of invasive carcinoma in relation to the total myometrial thickness in this area, irrespective of its relationship to adenomyosis.”[19] Thus, a tumour in which the only invasion arises from adenomyotic foci in the outer half of the myometrium, should be staged as FIGO Stage IB and accompanied by a comment that the clinical significance is unknown, and that this may be an overestimate of true DOI.[19,21]

Several patterns of myometrial invasion are recognised, and more than one pattern may be present within the same case.[22-25] The conventional *infiltrative* pattern is the most commonly encountered pattern, and has no specific prognostic significance.[22,23] This pattern is characterised by irregularly shaped glands that haphazardly infiltrate the myometrium, and are generally associated with a stromal response that may be granulation tissue-like, desmoplastic or inflammatory.[22,23,25] The *adenoma malignum-like pattern* is characterised by typically round, isolated glands that are unequivocally myoinvasive but are not associated with any significant stromal response. The glandular epithelium is generally less columnar than the non-myoinvasive component, and indeed may appear flattened.[25] Eosinophilic luminal secretions may be prominent, especially when the tumour involves the lower uterine segment or burrows into the cervix, potentially leading an endometrial carcinoma to be mistaken for mesonephric remnants or mesonephric proliferations. The *pushing or expansile pattern* is present in 9.4% to 21% of endometrioid carcinomas, and shows a broad, non-infiltrative myoinvasive front, generally without a significant stromal reaction.[22,23] The adenomyosis-like pattern is reminiscent of adenomyosis involved by cancer at scanning magnification, but tumour nests are smaller, overtly infiltrative and lack true endometrial stromal cells at the peripheries of myoinvasive nests.[22,23] The adenomyosis-like, adenoma-malignum, and expansile myoinvasive patterns are devoid of any specific prognostic significance.[22,23] The *microcystic, elongated and fragmented* (MELF) pattern is characterised by discrete foci of single cell clusters, cellular cords, or microcystic glands that are lined by variably flattened epithelium with eosinophilic or squamoid cytoplasm, and which are typically associated with a surrounding fibromyxoid stromal change with an interspersed, neutrophil-rich mixed inflammatory infiltrate.[24] In one meta-analysis comprising 14 studies and 588 patients, the MELF pattern was associated with larger tumour size, higher grade, lymph node metastasis, LVI and >50% myometrial invasion, but was not significantly associated with disease free survival, disease specific survival, or vaginal recurrence rates.[26] Nonetheless, the *diagnostic* significance of the MELF pattern of invasion is multi-fold: 1) the depth of myoinvasion may be underestimated if subtle epithelial cells within foci of MELF-associated fibromyxoid stroma in the myometrium are not recognised as such; 2) foci of MELF myoinvasion may be mistaken for LVI, or vice versa; and 3) lymph node metastases associated with the MELF pattern may be difficult to recognise, as they are frequently of small volume and a small subset of metastases may acquire a distinct histiocyte-like morphology.[27-30] Among the other potentially encountered myoinvasive patterns, single cell infiltration has been associated with an increased likelihood of extrauterine extension on multivariate analyses.[31] Tumour budding, which is probably a different iteration of the same biologic phenomenon, has also been associated with adverse clinicopathologic features and patient outcomes.[22,30,32,33] The pattern of myometrial invasion may be documented in the pathology report to facilitate future study, but is not a core item.

In most cases, determining the depth of myometrial invasion does not pose a challenge. However, a variety of circumstances may be encountered that may potentially render making this determination problematic.[34] The International Collaboration on Cancer Reporting Endometrial Cancer Dataset Authoring Committee endorses the ISGyP recommendations for handling these diagnostic scenarios as summarised below:[19]

1. Exophytic tumours and endometrial polyps: Exophytic carcinomas not uncommonly have an ‘incorporated’ myomatous stroma that should not be mistaken for true myometrium for the purposes of measuring the depth of myometrial invasion. Tumour thickness, which encompasses the exophytic component of a myoinvasive tumour, is not synonymous with the depth of myometrial invasion, where measurement begins at the endomyometrial junction. The location of the true endomyometrial junction may be inferred by comparing the area in question with an adjacent section that is uninvolved by myoinvasive carcinoma. For tumours that infiltrate an endometrial polyp, the same approaches are applicable. In endometrial carcinomas in general, every attempt should be made to submit at least one section that depicts any exophytic component, the most myoinvasive component, and an adjacent non-involved endomyometrial junction.

2. Uterine cornu and lower uterine segment: Given that the uterine wall thickness is thinnest at the cornu, the ISGyP recommendations are that the depth of myometrial invasion should not be measured at this focus, unless the tumour is entirely localised to the cornu, and/or extends to the serosa at that point. In contrast, for tumours whose maximal depth of myometrial invasion is in the lower uterine segment, measurements should be taken as they would be at other non-cornual areas of the uterine corpus.
3. Leiomyoma: For tumours that infiltrate a leiomyoma, measurements should be taken as if the leiomyoma represents non-leiomyomatous myometrium. Specifically, the thickness of the myometrial wall at the focus of myoinvasion should include the thickness of the leiomyoma, and the measurements of the depth of myometrial invasion should include the portion of the tumour that is invasive of the leiomyoma.
4. Lymphovascular invasion (LVI): Consistent with staging principles at other anatomic sites, LVI is not used, in and of itself, to upstage. Accordingly, in endometrial carcinoma, foci of LVI should not be used to determine the depth of myometrial invasion. For example, a Stage I tumour with <50% invasion of the myometrial wall but which shows LVI in the outer myometrium should be classified as Stage IA, rather than IB.

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