Borderline tumour - special features (Core and Non-core)

Terminology for ovarian borderline tumours has evolved over several years.[1,2] The preferred terminology is borderline tumour, for example serous or mucinous borderline tumour, and this has been endorsed in the 2020 World Health Organization (WHO) Classification.[3] Serous borderline tumours can be of typical or micropapillary subtypes, as per the latest WHO Classification.[3] For mucinous, endometrioid, clear cell, Brenner, and seromucinous tumours, the designation 'borderline tumour' is also used in the 2020 WHO Classification.[3] The terms 'low malignant potential' or 'atypical proliferative' are not recommended.[3] Synonyms formerly used for seromucinous borderline tumours include endocervical-type mucinous borderline tumour, Müllerian mucinous borderline tumour, and atypical proliferative (borderline) Müllerian tumour.[4]

Determining the lowest threshold for the diagnosis of a borderline tumour in the setting of a cystadenoma/cystadenofibroma with minimal epithelial proliferation can be subjective and quantitative criteria have been suggested: cystadenomas/cystadenofibromas with qualitatively sufficient epithelial stratification/complexity involving ≥10% of the epithelial volume are designated as borderline tumours arising within a cystadenoma/cystadenofibroma.[2] A borderline tumour in which the epithelial stratification/complexity involves <10% of the epithelial volume should be diagnosed as cystadenoma/cystadenofibroma with focal epithelial proliferation.

As serous borderline tumour can exhibit variable degrees of micropapillary or cribriform architecture, a diagnosis of micropapillary subtype of serous borderline tumour is based on the presence of ≥5 millimetres (mm) of confluent micropapillary (defined as micropapillae five times as long as they are wide) or cribriform growth.[3]

A standardised quantitative criterion for distinguishing microinvasion from frankly invasive carcinoma within a borderline tumour has not been established, with varying definitions used in different studies, including 1, 2, 3, 5 and 10 mm^2 as the upper limits of microinvasion.[1,2,5] The 2020 WHO Classification uses 5 mm^2 as a cut-off.[3] Some groups distinguish two patterns of stromal invasion in serous tumours which quantitatively falls short of frankly invasive carcinoma (<5 mm) - conventional 'microinvasion' (isolated and/or small clusters of eosinophilic cells and/ or small papillae cytologically similar to the non-invasive component within clear lacunar spaces) and 'microinvasive carcinoma' (glandular or micropapillary patterns qualitatively analogous to low grade serous carcinoma (LGSC)).[1,2] However, other investigators do not advocate this distinction. Due to insufficient numbers of cases in the literature, definitive conclusions regarding the clinical significance of this distinction cannot be drawn.[1,6] Analogous to the situation for serous tumours, some investigators advocate the separation of 'microinvasion' from 'microinvasive carcinoma' in mucinous borderline tumours while others use these two terms interchangeably.[5]

In mucinous borderline tumours, intraepithelial carcinoma is diagnosed in non-invasive foci with marked nuclear atypia, and is often associated with mitotic activity.[2,5] However, the reproducibility of this diagnosis has not been formally analysed. It has recently been suggested that p53 immunohistochemistry could be used instead or in support of a diagnosis of intraepithelial carcinoma but this remains to be proven.[7] Intraepithelial carcinoma for mucinous borderline tumours is a non-core item for reporting and the term intraepithelial carcinoma is not applied to other types of borderline tumour. Mucinous borderline tumours can be associated with mural nodules, which are classified as reactive sarcoma-like, anaplastic carcinoma, or sarcoma.

Sarcoma-like nodules are composed of a variable mixture of spindled/round mononucleated cells, often associated with marked inflammation.

Extra-ovarian implants occur in approximately 20% of serous borderline tumours and are more common with exophytic neoplasms. The most important adverse prognostic factor for ovarian serous borderline tumours in which there is extra-ovarian disease, is the presence of invasive implants, i.e., LGSC, in extra-ovarian tissues as this portends an adverse prognosis, with non-invasive implants having a favourable prognosis. Specifying the location and size of implants is important for determining the International Federation of Gynaecology and Obstetrics (FIGO) stage.[8] Non-invasive and invasive implants/LGSC may co-exist in the same specimen. Non-invasive implants are subclassified as epithelial or desmoplastic types.[2] Epithelial-type non-invasive implants resemble detached fragments of a serous borderline tumour involving extra-ovarian tissues. They do not exhibit infiltration of underlying tissue, and they are often present within mesothelial or epithelial-lined spaces although they may be adherent to the serosal surface. Desmoplastic non-invasive implants are composed of glands or papillary clusters within fibroblastic or granulation tissue-like stroma, but they do not exhibit infiltration of adjacent tissue. Often these are located on serosal surfaces or within septa in the omentum. Note that the presence of isolated individual or small clusters of eosinophilic epithelial cells within the stroma is generally considered to be within the spectrum of desmoplastic non-invasive implants rather than representing an invasive implant/LGSC.[1]

The most widely used criterion for diagnosing extra-ovarian LGSC/invasive implants in a patient with an ovarian serous borderline tumour is destructive invasion of underlying tissue.[9] Invasive implants often feature markedly crowded epithelial nests, glands or micropapillary clusters with a haphazard arrangement. The nests, glands and papillae are sometimes surrounded by clefts.[1,2]

In occasional cases, it may not be possible to definitively distinguish non-invasive from invasive implants/LGSC and the recommendation is to designate such implants as being of indeterminate type.[10] This terminology should only be used sparingly, and obtaining a specialist gynaecological pathology opinion and submitting additional sections for histological examination (if an omentectomy specimen), may be useful.

When invasive implants are present this should be diagnosed in the final pathology report as extra-ovarian LGSC;[1,2,11] this has been endorsed in the 2020 WHO Classification.[3] It is unclear whether invasive implants involving extra-ovarian sites in association with an ovarian serous borderline tumour represent metastases from the serous borderline tumour or an independent primary peritoneal tumour. A number of molecular studies analysing primary ovarian tumours with their associated implants have yielded varying results.[1] However, Ardighieri et al (2014) showed in a large population-based cohort has shown that the vast majority of implants are clonally related to the primary ovarian tumour.[12] Most of the cases from this study were non-invasive implants; however, all 10 invasive implants had the same mutational status (*KRAS* mutation, *BRAF* mutation, or wild-type *KRAS/BRAF*) as the corresponding serous borderline tumour, suggesting that invasive implants are clonally related to the primary ovarian tumour as opposed to representing independent primary peritoneal lesions.[12] Nevertheless, the number of invasive implants evaluated by molecular methods in the entire literature is limited. Carcinoma developing in patients with a previous diagnosis of serous borderline tumour are mostly LGSCs and most are clonally related to the serous borderline tumour i.e., represent tumour progression.[13] From a practical point of view, for cases of invasive implants in association with an ovarian tumour diagnosed as serous borderline tumour, it is recommended to consider additional sampling of ovarian tissue to demonstrate LGSC or micropapillary serous borderline tumour.[14]

Implants may also be encountered in the setting of seromucinous borderline tumours, and the same issues for serous tumours pertain. In general implants do not occur in the setting of mucinous, endometrioid, clear cell or Brenner borderline tumours.

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