

# Lymph node involvement in ovarian serous tumors of low malignant potential (borderline tumors): Pathogenesis and clinical significance

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Back in 1929, Taylor first described borderline ovarian tumors (BOTs) as “semi-malignant ovarian tumors”, since an ovarian hyperplastic cyst could mimic malignancy with relatively favorable outcome even when associated with widespread peritoneal dissemination [1].

In 1973, the World Health Organization (WHO) proposed the term of “borderline tumor” and added the synonym ‘carcinoma with low malignant potential’ (LMP) in their classification of ovarian tumors [2, 3].

According to the WHO definition, an ovarian borderline epithelial tumor histologically lacks obvious invasion of the stroma, while its mitotic activity and nuclear abnormalities intermediate between clearly benign and unquestionably malignant tumors.

In 1999, combined classification of the International Society of Gynecologic Pathologists and the WHO, the term ‘LMP Tumor’ replaced ‘LMP carcinoma’ as a synonym of BOT [3].

Serous BOTs are the most common type, bilaterality is seen in 25–50% of histotypes [4].

Histologically, typical borderline serous tumors are noninvasive proliferative neoplasms characterized by multiple fibrous papillae with extensive and complex hierarchical branching. Moreover, the epithelium of papillae shows multi-layering of more than four cell layers. Neoplastic cells show mild nuclear atypia (slight pleomorphism, sometimes prominent nucleoli).

Detachment and exfoliation of cells from the papillae is another feature of neoplasm. Mitotic figures may be absent or found in very small numbers, and are not abnormal [5].

Although BOTs are tumors without invasion, foci of stromal micro-invasion (invasive foci smaller than 10 mm<sup>2</sup> and less than 3 mm in their longest linear dimension) have been observed.

Recognition of lymph node involvement in BOT has engendered discussion about its pathogenesis and prognostic significance in the international literature

## Pathogenesis of lymph node involvement in ovarian serous tumors of low malignant potential (borderline tumors)

To explain the occurrence of lymph node involvement in the lymph nodes of patients with ovarian serous borderline tumors (SBTs), two theories have been suggested, designated respectively “endosalpingiosis” and “metastatic”.

According to the “Endosalpingiosis Theory”, nodal SBTs could develop from nodal endosalpingiotic glands, which are non-neoplastic inclusions of the Müllerian type that possess neoplastic potential. In support of this theory, there are cases in which some authors have observed morphologic transitions between endosalpingiotic deposits and borderline tumors within the same node [6, 7]. Moreover, this ectopic Müllerian epithelium could be susceptible to the same hormonal and genetic alterations as their native counterparts.

In fact, Emerson et al. observed that the same X chromosome inactivation patterns were identical among ovarian and nodal lesions in many cases [8].

In addition, Alvarez et al. found an identical mutation in the K-ras gene in ovarian SBTs and their synchronous endosalpingiotic deposits in 2 out of the 3 cases that they evaluated [9].

The metastatic theory suggests that nodal SBT-type lesions might originate from synchronous ovarian SBTs. In these instances, lymph node metastases might be occurring as the result of micro-invasion, which would provide the tumor cells with access to the lymphovascular system of the subjacent stroma. Thus, in these cases,

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neoplastic elements could produce mediators such as Type IV collagenase and plasminogen activators, which facilitate the destruction of the basement membrane and the extracellular matrix with resultant invasion of the subjacent stroma, and invasion of the lymphovascular system [10–13]. However, many studies have found remarkably low frequency of nodal involvement in micro-invasive SBT types [14–18].

Other authors have suggested that ovarian SBTs might be transported to the lymph nodes only after exiting the ovary, most likely via the lymphatics of the peritoneal surfaces [19, 20].

This hypothesis might be supported by the observations of Camatte et al., who found nodal involvement in all serous BOT with peritoneal implants [21].

### Clinical significance of lymph node involvement in ovarian serous tumors of low malignant potential

The behavior of ovarian serous borderline tumors (SBTs) and the significance of various prognostic factors are unclear and difficult to evaluate.

Many studies have suggested that the most important prognostic indicators for SBTs are the surgical pathological stage and the sub-classification of extra-ovarian disease into invasive and noninvasive implants [22].

In addition, the clinical outcomes of lymph node involvement in patients treated for borderline ovarian tumor have engendered discussion about its prognostic significance.

Several investigators have suggested that lymph node involvement in SBTs has no impact on overall survival [21–25]. Instead, other authors have demonstrated that lymph node involvement in SBTs can increase the incidence of disease recurrence [26].

More recently, some studies have suggested that the histologic diversity of lymph node involvement patterns is very important for overall survival.

Indeed, these studies observed a decrease in disease-free survival for cases of SBTs that featured lymph node involvement as discrete nodular aggregates of epithelium greater than 1 mm in linear dimension [27].

The role of lymphadenectomy in SBOTs as a therapeutic procedure remains unclear. Some authors have suggested that routine lymphadenectomy should not be performed in patients with early-stage disease, but could be useful in cases with enlarged lymph nodes [21].

Since lymph node involvement is the only indication of extra-ovarian disease, and since the neoplasm can recur exclusively in the lymph nodes as low-grade serous carcinoma, some researchers underline the importance of lymphadenectomy as a necessary part of a staging procedure and for the purposes of tumor reduction in all cases of SBOT [26, 27]. Moreover, since pelvic lymph nodes are most commonly involved, these could be

removed when complete lymph node sampling cannot be carried out because of technical reasons or concerns over morbidity [26, 27].

All hypothesis about pathogenesis and the clinical and pathologic features of lymph node involvement in SBOT cannot explain the prognostic significance of this neoplasm. Thus, further studies are necessary, using large series and molecular investigations.

**Keywords:** Borderline tumor, Lymph node, Ovarian tumor, Serous tumor

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#### Guarantor

The corresponding author is the guarantor of submission.

#### Conflict of Interest

Authors declare no conflict of interest.

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