

Review Article

Borderline Ovarian Tumours : An Update

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ABSTRACT

Borderline ovarian tumours are clinical entities less frequently encountered by obstetricians and gynecologists. Management options keep on changing with time and fertility sparing procedures and laparoscopy keep emerging. Surgical removal of all visible tumours still remains the most effective management. So far, non surgical treatment modalities have not been found to be beneficial. Pathologists are increasingly able to identify poor prognostic features in histology. Molecular biological studies are progressively being elucidated as prognostic features which might help us more in understanding the carcinogenic process and progression of the disease. This review outlines the recent literature regarding pathology, diagnosis, treatment, prognosis and recurrence. Oncologic concerns are discussed with emphasis on mode of surgery, fertility sparing surgery and the outcomes.

INTRODUCTION

Taylor, first in 1929 in his classic paper described border line ovarian tumours as 'semi-malignant' ovarian tumour. In the early 1970s, the WHO and FIGO proposed the term 'borderline malignancy' or tumours of 'low malignant potential.' In WHO classification (2003) 'borderline tumour' is the term used and seems to be the most popular among gynecologic

pathologists and oncologists. Borderline ovarian tumours (BOTs) represent 10% to 15% of ovarian cancers.² They present with unique characteristics: patients are usually younger than women with invasive cancer with a mean age of 38 years;³ diagnosis is at an early stage and consequently the long term prognosis and the progression-free survival are good.⁴

Risk Factors:

Like malignant tumours, nulliparous women have an increased risk of developing BOTs, and lactation is found to be protective. However, unlike invasive ovarian cancer, oral contraceptive use is not protective.⁵ Borderline tumours do not appear to be part of the phenotype of families with germline mutations in the BRCA genes, suggesting that they are not intermediates to ovarian cancer, at least not in families with BRCA associated ovarian cancer syndromes.^{6,7}

Histopathology:

According to the WHO definition, a borderline epithelial tumour lacks obvious invasion of the stroma and has mitotic activity and nuclear abnormalities intermediate between clearly benign and unquestionably malignant tumours of a similar cell. The absence of obvious stromal invasion is a principal diagnostic criterion. Borderline tumours of every surface epithelial cell type have been reported. A review of 1063 cases showed that 50% of BOTs were the serous 46% mucinous, and 3.9% were mixed, endometrioid, clear cell or Brenner tumours.⁸

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Serous BOT:

Serous BOTs are most common type, bilaterality is seen in 25-50% of serous histotype.¹⁰

Histological criteria for diagnosis include.¹¹

- Epithelial multi-layering of more than four cell layers
- Not more than four mitoses per 10 high-power fields
- Mild nuclear atypia (slight pleomorphism, sometimes prominent nucleoli)
- Increased nuclear/cytoplasmic ratio
- Slight to complex branching or bridging of epithelial papillae and pseudopapillae
- Epithelial budding and cell detachment into the lumen
- No destructive stromal invasion

Peritoneal implants:

About 20-46% of serous BOT have peritoneal implants.³ These have been classified into invasive and noninvasive categories with noninvasive implants sub classified as epithelial, desmoplastic or both. According to FIGO and WHO guidelines, the diagnosis of 'borderline' is based on the histological features of the ovarian tumour regardless of the appearance of the extraovarian disease. Approximately 15–20% of patients with 'advanced stage' BOTs have associated invasive serous carcinoma (invasive implants) involving the peritoneum; the remainders have non-invasive implants. Invasive implants display cytological atypia and infiltrate underlying tissue, and have the appearance of well-differentiated serous carcinoma. In contrast, non-invasive implants do not invade underlying normal tissue and have an appearance similar to that of the serous BOT.¹² There is now consensus that invasive implants are associated with a significantly worse prognosis than non-invasive implants. Seidman proposed that since serous BOT with invasive implants have a clinical course similar to a low grade invasive carcinoma with a 34% mortality rate, it is more reasonable to classify these tumours as carcinomas.¹³

Microinvasion:

A particular variant, of serous BOT 'micropapillary serous carcinoma' (MPSC) has a strong association with invasive implants, with a 10 year survival of approximately 60% in advanced stage.¹⁴ WHO recognizes MPSC as 'serous BOT with micropapillary pattern'. If the invasive implants and MPSCs are removed from the borderline category, virtually all remaining advanced stage serous BOT have a benign behaviour with a 10 year survival of 98–100%.¹⁴ Though BOTs are tumour without invasion, foci of stromal microinvasion (invasive foci smaller than 10 mm² and less than 3 mm in their longest linear dimension) have been described.

Lymph node involvement:

Para-aortic and pelvic lymph node involvement is present in 7–23% of cases on node sampling at the time of surgery, and a few patients develop postoperative distant disease in cervical and scalene lymph nodes.¹⁶⁻¹⁸

Mucinous BOT:

Borderline mucinous tumours are less common than serous BOT. Typically, they produce large multicystic masses and over 90% are unilateral. Two basic types of borderline mucinous tumours are the intestinal type (85%) and the endocervical-like (15%) type. Mucinous carcinomas that involve both ovaries and present as advanced stage disease may be primary, but are often metastatic, typically from the gastrointestinal tract. The preponderance of evidence indicates that pseudomyxoma peritonei almost always results from intraperitoneal spread of a nonovarian adenomatous mucinous neoplasm, especially appendiceal tumour.^{20, 21}

Symptoms:

Almost seventy-five percent of women with BOT have abdominal pain/abdominal discomfort/tense abdomen/bowel irregularity. Women with borderline ovarian tumours reported significantly longer duration of any symptom and distended or tense abdomen than women with invasive ovarian cancer.^{22,23} Other studies have reported similar findings,^{24,25}

Diagnosis:

The diagnosis of borderline ovarian tumours is usually made on pathologic specimens obtained at the time of surgery. Preoperative diagnostic criteria for borderline tumours have not been extensively studied; tumour markers, USG, Doppler, CT and MRI have got limited clinical utility.

Ultrasonography:

By transvaginal ultrasonography and Doppler, intramural blood flow is detected in both borderline and malignant ovarian tumours with decreased pulsatility and resistance index.²⁶ BOTs may appear complex or unilocular but the most frequent diagnostic feature on imaging BOT is the presence of papillae within the cyst.²⁷

Tumour markers:

Studies on smaller patient populations have reported elevated CA 125 levels in 15% to 50% of patients with BOT.^{28,30} Serum concentration of CA-125 do not correlate with tumour stage. Engelen and colleagues evaluated the role of CA 19-9 in BOTS and concluded that this marker might be more useful in diagnosing mucinous tumours.³¹ Other serum markers have also been analysed but none of those have clinical utility.³²

Staging:

The FIGO classification (International Federation of Gynecology and Obstetrics (1987) is used for staging. At diagnosis about 68% are in stage I, 11% stage II, 21% III and 1% in stage IV.

Surgery:

The exclusive treatment for BOT is surgery. Total abdominal hysterectomy and bilateral salpingo-oophorectomy with peritoneal cytology, omentectomy and multiple peritoneal biopsies is the gold standard treatment for women in peri or post-menopausal age group, patients who have completed childbearing or those who have no desire to preserve their fertility.¹⁰ Appendectomy should be classically added particularly in mucinous tumour. Debulking is indicated if large extra-ovarian disease is present.

Role of lymphadenectomy:

Pelvic and paraaortic lymphadenectomy is not required for disease staging.³⁴ Routine lymphadenectomy was not associated significant improvement in one study. Recent studies have suggested that lymphadenectomy can be omitted even for the advanced disease, because there is no difference in recurrence or survival rate.^{36,37} Thus, the role of lymphadenectomy is limited to research based settings.

Need for staging:

Recent studies have questioned the benefit of staging, especially in the absence of gross extraovarian disease, as there is no difference in prognosis among staged and unstaged patients.^{38,39} These results could be easily explained as most patients upstaged after staging or restaging surgery, are upstaged on the basis of isolated positive peritoneal cytology and/or the discovery of microscopic noninvasive implants on the omentum or random biopsies that have no impact on subsequent treatment.³⁶ However, conclusions taken from these data can only be reasonably applied to patients who have apparent early stage disease. Restaging surgery can be safely omitted,¹ if the BOT is of serous or mucinous subtype and without micropapillary patterns;² peritoneum explored and reported as normal on the surgical report of the initial surgery and;³ the patient is willing for a careful follow-up. If any of these criteria is not fulfilled, restaging surgery should be proposed.³⁶ Laparoscopy seems a safe and effective alternative in reducing the invasiveness of restaging.⁴⁰ A decision on repeat surgical procedure on those where BOT is diagnosed after cystectomy alone is controversial and need a thorough discussion with the patient.

Fertility sparing surgery:

Because BOTs are common during the childbearing years at an early stage and have an excellent long-term survival, fertility sparing treatment with uterine preservation and at least part of one ovary has become a pivotal and well-consolidated approach during the last decade. Data appear to confirm that, even though the risk of relapse is substantial after conservative

treatment of BOT, patient survival is not altered by the use of this approach. The decision to perform cystectomy versus oophorectomy will depend on factors e.g. patient age, patient's child-bearing wishes, presence of bilateral disease, and expectations preoperatively of both surgeon and patient. Often, the diagnosis is not known until after surgery. Therefore, recommendations as to whether to perform cystectomy versus oophorectomy is not always useful in practice.

Oophorectomy or Cystectomy?

Salpingo-oophorectomy has been widely used to reduce recurrence and to preserve good reproductive functions in patients with unilateral BOTs and oophorectomy with contralateral cystectomy has been used in bilateral BOTs. Routine ovarian biopsy of a normal looking ovary should be avoided due the risk of postoperative adhesions and infertility. Studies show that cystectomy is related to a higher recurrence rate compared with oophorectomy; 12-58% vs. 0-20%.⁴⁷⁻⁴⁹ In a recent study, bilateral cystectomy increased significantly the cumulative pregnancy rate without increasing significantly the cumulative recurrence rate.⁴⁹ But, this ultra-conservative surgery resulted in a statistically significant earlier time to relapse with the risk of developing a recurrence <2.5 years earlier after bilateral cystectomies than after standard fertility-sparing surgical treatment. The analysis of recurrences seems to demonstrate a non-significant increase in patients treated with bilateral cystectomy.⁵⁰⁻⁵² The drawback is that a longer follow up is needed as these tumours are known for very late recurrences.

Conservative surgery in advanced stage:

Although conservative surgery can be done for patients with early-stage disease, limited data exist relating to its applicability in advanced stage BOT with peritoneal implants three studies have shown that a conservative management could be safely proposed in selected group of young patients with carefully followed up.^{53,54, and 55} As the prognosis depends on invasiveness of the implant and the amount of residual disease, careful selection of cases is needed and a total resection of the implants

could minimize the possibility of 1) missing an invasive implant and 2) residual disease. The results observed in these studies over a period of 35-60 months follow up showed that the rate of borderline recurrence on contralateral ovary could appear high, but this rate remains acceptable as such recurrence had no impact on the survival and furthermore could be easily cured using a new (conservative) surgery. None of the patients developed an ovarian cancer on a spared ovary and none of the patients died. These results demonstrate that conservative surgery could be safely proposed in carefully selected patients with non-invasive implants. On the other hand, prognosis of patients with invasive implants is more pejorative.

Role of laparoscopy:

There is limited data on the laparoscopic management of BOT.^{56-59,49} Available studies demonstrate that laparoscopic treatment of BOT is feasible and safe in patients with early stage disease. Data is scanty on the laparoscopic management of advanced stage BOT.^{55,60} In the series by Queried et al 2 patients undergoing a laparoscopic restaging surgery had microscopic peritoneal implants removed during the laparoscopic procedure without any deleterious effect.⁴⁰

Fertility outcome:

The reproductive outcome of women who undergo conservative surgery for BOT is adequate, and spontaneous fertility rate varies between 32% and 65%.⁵⁸⁻⁶⁰ However, ovulation induction is often required for these patients to conceive.⁶¹

Is ovarian stimulation safe?

The link between ovarian stimulation and the risk of ovarian cancer is debatable. A multicenter retrospective study has reported the outcomes of 30 patients with a previous history of a BOT that underwent infertility therapy⁶² 4 recurrences (16%) were observed after a median follow-up of 93 months from treatment of the BOT and 42 months after infertility therapy. It seems that infertility drugs could be used safely in patients who are treated for early stage disease. In patients with more advanced stage disease, the number of patients is too limited to

draw conclusions regarding the effect of infertility drugs on outcomes.

Follow up:

For women who are treated conservatively, follow-up is important, for such patients transvaginal ultrasound⁶³ is best modality for follow up. The need for completion surgery as a routine procedure after conservative surgery remains controversial and discussion of this option depends on several factors (histologic subtype, stage, type of conservative surgery; and the patient's preferences). As the recurrences could be easily cured and survival rates are not changed, several studies suggest that systematic removal of the spared ovary is not mandatory provided that patients have regular follow-up. However, a number of patients will choose to have definitive treatment as soon as their family is complete because of psychological stress.

Frozen section:

The ability to diagnose borderline tumours accurately in the operating room gives surgeons the option to do fertility preserving surgery. Frozen section analysis of ovarian tumours differentiating between invasive and non-invasive specimens has sensitivity between 65% and 97% and specificity between 97% and 100%.⁶⁴ Frozen section analysis of BOT, however, is notoriously difficult with a significantly lower sensitivity and specificity compared to benign and malignant tumours of the ovary.⁶⁵ In a recent retrospective study of 317 women with BOT, it was found that intraoperative frozen section analysis has an overall sensitivity of 71.1% and an overall positive predictive value of 84.3%; over diagnosis and under diagnosis frequently occurred with 6.6% and 30.6%, respectively.⁶⁶ Other studies have also shown similar results.^{67,68} Mucinous tumours and tumour diameter >10cm are the predictors of under diagnosis of BOT during frozen section analysis. Large tumours should be grossly examined thoroughly and multiple sections may be appropriate to increase the sensitivity for focal borderline changes. A minimum of one section per cm of maximum tumour diameter (excluding cystic areas with

smooth walls) for tumours under 10 cm, and two sections per cm for larger tumours is recommended. Surgical interventions based on intraoperative frozen section analysis should be used with caution, especially in clinical settings without pathology units specialized in gynecologic pathology.

Role of Chemotherapy:

Early stage (stage I & II) and stage III BOTs with no residual tumour after surgery do not benefit with adjuvant chemotherapy. Many investigators have used chemotherapy for patients with advanced stage (III & IV) BOT with or without residual disease with mixed results.^{41,44} Regimens similar to epithelial ovarian carcinoma (EOC) have been used.^{45,46} Currently, this area remains investigational and all such patients should be enrolled in clinical trials.

Survival rate:

Long-term prognosis for patients with BOT is good with overall and disease free survival rates of 95% and 78%, respectively.⁶⁹ The survival rate for patients with Stage I tumours ranges from 95 to 100%.^{70,72} Subgroups such as those with micropapillary architecture and invasive implants have a higher risk of recurrence.⁷³ In a review of 467 patients from 25 studies (mean follow up) of 7.4 years, the survival for patients with non-invasive implants was 95%, compared to 66% for patients with invasive implants.⁷¹ In another study, for invasive form 10-year survival rate was 33%.⁷⁴ Similar to the serous tumours, mucinous BOT when confined to the ovary, have an excellent prognosis, with survival rates approaching 100%; the survival for advanced disease is 40–50%.⁷⁵

Recurrence:

In a report of 160 Stage I tumours, 11 patients (6.8%) developed recurrent tumour, often after prolonged postoperative intervals of 7–39 years (mean, 16 years), and eight were fatal.⁷⁶ Recurrent tumour may develop after latent intervals as long as 20–50 years. Some of these may be due to new tumours arising from the peritoneum or from endosalpingiosis. The overall risk of “malignant transformation”

among patients with borderline tumours is very low: Kurman and Trimble reviewed the literature and found a rate of 0.7% among serous BOT.⁷⁷ When recurrence occurs and fertility is still an issue, then repeat conservative procedure is performed. In the case of an extraovarian recurrence with invasive implants extensive cytoreductive surgery is the treatment option of choice.⁷⁸

Prognostic factors:

The most important prognostic factors of patients with advanced stage borderline tumour are (1) the histologic characteristic of the implants (non-invasive or invasive) and (2) the presence of residual disease at the end of surgical procedure.^{79-81, 41} Residual disease at the completion of secondary debulking is an important prognostic factor because 12% of patients with optimal debulking died of disease compared with 60% of patients whose tumour was suboptimally debulked.⁴⁶ Trope et al found that the main independent prognostic factor for disease-free survival and long-term survival was FIGO stage, followed by histologic type and patient age.⁸² Presence of micropapillary pattern alone is not considered an unfavourable prognostic factor.⁷² BRAF and KRAS mutations in serous and KRAS mutations in mucinous tumour have been associated with tumour progression. Yet, further analysis of SBT genomes is critical for the identification of potential molecular genetic alterations that play a key role in tumorigenesis and role as prognostic factors.⁸³ Borderline ovarian tumours with aneuploid DNA content have a worse prognosis for recurrence and survival.^{84,85}

Conclusion:

BOTs are rare epithelial ovarian tumours with excellent prognosis and varied treatment options. Surgery remains the cornerstone of treatment. Proper staging is always needed whenever surgery is attempted. Patients with early stage disease can safely undergo fertility sparing treatment. However, a few pathological entities in this group of tumours still present a challenge to the gynecologists.

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