Borderline Ovarian Tumor—An Overview and Evidence Based Management

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INTRODUCTION

Borderline ovarian tumors (BOTs) were first described as ‘semimalignant’ovarian tumor by Taylor in 1929. Later on in 1970, World Health Organization (WHO) and International Federation of Gynecology and Obstetrics (FIGO) gave following terminologies to indicate their indolent course:

- Borderline tumor
- Tumors of low malignant potential (LMP)
- Atypical proliferative tumors

Although College of American Pathologist (CAP) cancer protocols (2016-17) for ovarian cancer used term borderline but deferred using low malignant potential. These are epithelial neoplasms that are histologically distinguished from ovarian carcinomas by the absence of stromal invasion.

They share 10-15% of cases of all the ovarian epithelial malignancies. Most of the etiological and protective factors of BOT are similar to ovarian carcinoma. Use of hormonal contraceptives does not confer protective effect for BOTs. Excessive use of ovulation inducing drugs is also associated with increased risk of BOTs.

The distinguishing features of BOT from ovarian cancer are:

- The median age is 40 years, approximately 20 years younger than epithelial ovarian cancer.
- Association with infertility is more as compared to ovarian carcinoma.
- There is lesser frequency of BRCA mutation.
- Most of these patients present with early stage disease as compared to ovarian carcinoma where presentation is usually in late stages.
- Overall prognosis and 10 years survival rate is good due to the early stage presentation.
HISTOPATHOLOGY

FIGO classification for BOTs is similar to other ovarian tumors.12 Most of BOTs (60-70%) are diagnosed at stage 1 as compared to ovarian carcinoma where only 25% of the patients present in stage 1.13 It is very rare to find BOTs in stage 4.14 It is important to distinguish BOTs from benign cystadenomas histopathologically. Important features which favor the diagnosis of BOT are:

• Presence of epithelial budding
• Multilayering of the epithelium
• Increased mitotic activity
• Presence of nuclear atypia.

The feature that distinguishes BOT from ovarian carcinomas is the absence of stromal invasion.11 Borderline epithelial tumors are typically serous (53-65%) or mucinous (30-40%) but other histologic subtypes can also occur i.e. endometrial tumors, clear-cell tumors, Brenner’s tumors.15,16

Serous BOT

One-third of serous BOTs are bilateral and are the most common variety (35%) to give peritoneal implants. These implants are invasive in 15–25% of the cases and most commonly affect the omentum. In advanced stages, almost 25% involve the lymphatics with descending order of frequency: pelvic, omental, mesenteric, para-aortic and supradiaphragmatic regions.

There are two sub types:

• Typical pattern: Found in 90% of cases and have unilocular cyst with fine interior septa.

• Micropapillary pattern: These are found in 10% of the cases and have micropapillary appearance contiguous over >5 mm or more on histopathological examination.17 These have poor prognosis as compared to typical pattern serous BOTs because of higher prevalence of bilaterality, invasive implants, a high recurrence rate and upstaging after restaging surgery.

Expected 10 years survival rate differs in serous BOTS with and without invasive implants i.e. 60-70% and >95% respectively.18

Mucinous BOT

These are larger in size than serous BOTs. On gross examination, they demonstrate unilocular/multilocular cysts, with fine interior septa and intramural nodules.19

Peritoneal implants are uncommon (only 15% of cases).

There are two sub types:

• Intestinal: These are most common (85-90%) and are mainly unilateral. Primary intestinal cancer must be ruled out in presence of bilaterality.

• Endocervical or müllerian: These are found in 10-15% of the cases. Bilaterality is found in 40% of the cases and 20-30% are associated with pelvic endometriosis/ipsilateral endometriomas or BOT of mixed histology (seromucinous).

CLINICAL FEATURES AND DIAGNOSIS

Clinical presentation20 can be

• Asymptomatic in one third of cases
• Nonspecific symptoms: abdominal pain or distension in 50–60% of patients
• Vaginal bleeding in 10% of cases

Women with BOTs have significantly longer duration of any symptom as compared to any other ovarian malignancy.21

INVESTIGATIONS

Imaging: Ultrasound is an accurate method to discriminate between benign and malignant adnexal masses.22 Papillary projections are more commonly found in the BOTs as compared to invasive cancer.23 The newer imaging modalities i.e the three-dimensional (3D) ultrasound24/color Doppler25/computed tomography/magnetic resonance imaging/positron emission tomography have little or no additional advantage in making the diagnosis and only lead to extra costs/discomfort to the patient. As imaging does not help much in making the diagnosis, accurate preoperative staging of BOTs is possible only in 29-69% of cases.26

Tumor markers: CA 125 levels is raised in only 15 to 50% of patients with BOT.27 Engelen et al reported that the estimation of CA 19-9 levels might be more useful in diagnosing mucinous tumors.28 Many other serum markers have also been evaluated but in vain.29

PROGNOSTIC FACTORS

BOTs have generally excellent prognosis; although 10% cases may recur and 20-30% among them show malignant transformation. The features associated with poor prognosis are:
• Transformation of borderline tumors to invasive disease which is dependent on
  • Cell type
  • Stage
  • Implant type (for serous BOTs)
  • Micropapillary architecture (for serous BOTs)
    and is associated with invasive implants in 45% of patients.\(^{31}\)
  • Microinvasion.
• Postoperative macroscopic residual disease
• Pathologically advanced stage
• Extraovarian invasive implants: This along with pathologically advanced stage are major predictor for both recurrence as well as poorer survival.\(^{30}\)
• Histological type: Serous tumors have poor prognosis whereas nonserous tumors have excellent prognosis irrespective of the presence or, absence of intraepithelial carcinoma and/or microinvasion.\(^{32}\)
• Genetic factors: Presence of aneuploid DNA content have a worse prognosis for recurrence and survival.\(^{33}\)
  Both BRAF and KRAS mutations in serous and only KRAS mutations in mucinous tumor have been associated with tumor progression and poor prognosis.
• Type of surgery and surgical approach affect the prognosis by having an impact on residual disease and in presence of residual tumor load have poor impact on recurrence rate.\(^{34}\)
  Conservative treatment in form of preservation of uterus and one ovary, is associated with increased disease recurrence in the remaining ovary, although it does not lead to poorer survival as most of the recurrences in the remaining ovary are noninvasive type especially for early stages.\(^{35}\)
  Unilateral oophorectomy instead of cystectomy is preferred when the contralateral ovary is normal in younger age group where fertility is desired so as to avoid recurrence. Conservative laparoscopic approach is associated with twice more recurrence rate than laparotomy but overall survival rate is not reduced.\(^{36}\)
• Lymph node involvement does not affect the prognosis therefore, systematic lymphadenectomy can be omitted. Incomplete pathological staging in comparison to optimal surgical staging is associated with a higher recurrence rate.
• Postoperative adjuvant treatment (chemotherapy, radiotherapy) is not recommended as it leads to increased treatment related morbidity and mortality rather than the disease itself.\(^{37}\)

**MANAGEMENT OF BORDERLINE OVARIAN TUMORS**

BOTs are mainly diagnosed during younger age group when the factors like fertility desire, premature menopause, perioperative morbidity, and role of adjuvant treatments govern the therapeutic decisions.\(^{38}\)
In absence of any prospective randomized trials, recommendations regarding treatment are mainly based on retrospective analysis. The mainstay of treatment is surgery.

*Surgery:* In absence of fertility desire, total abdominal hysterectomy with bilateral salpingo-oophorectomy along with peritoneal cytology, omentectomy and multiple peritoneal biopsies is the gold standard.\(^{39}\)
Appendectomy may be added particularly in mucinous tumor. In cases of large extra-ovarian disease, optimum debulking is indicated.

**Role of Conservative Surgery**

Conservative surgery involves comprehensive surgical staging, uterine preservation, removal of involved ovary. In the background of convincing results of conservative surgery in all stages of BOTs, it is the preferred choice wherever the fertility is desired.\(^{40}\)
Those who have been treated with fertility sparing surgery should be monitored with regular sonography and when the family is complete, completion surgery is recommended. Uterine preservation keeps the hope alive for frozen embryo transfer in patients where bilateral oophorectomy is performed. As the recurrence rate for cystectomy is quite high, It is recommended to do extensive sampling of the resection margins of the removed ovarian cyst.\(^{41}\)
Cystectomy is contraindicated in mucinous subtype and should be reserved for patients with bilateral tumors or having only one ovary.\(^{42}\)

A wedge biopsy from the contralateral ovary to rule out any concurrent occult lesion is not recommended (except in cases of suspicious macroscopic lesions) as postoperative adhesions around remaining ovary may lead to infertility. In cases of serous BOTs which are often bilateral, the best noninvasive technique to rule out any concurrent contralateral intraovarian tumor is a preoperative transvaginal scan which may be done intraoperatively to achieve macroscopic negative margin.
In cases of relapse in the remaining ovary, conservative surgery is reserved only for young patients desirous of fertility, having noninvasive implants and are compliant for long-term follow-up. Contrarily if the relapse is of invasive nature and family is completed, complete debulking is recommended. As solitary recurrences in the uterus is extremely rare, only salpingo-oophorectomy can be done without doing concurrent hysterectomy. It is associated with added advantage of decrease morbidity.

In BOT patients where the primary surgery was either incomplete or incompletely staged, further management depends on the presence of invasive implant and fertility desire. Those who want fertility preservation can undergo fertility sparing surgery with resection of residual disease.

**Intraoperative Diagnosis and Staging**

In ovarian tumor, FIGO staging is mainly surgical staging. This surgical staging involves systematic abdominal cavity inspection along with peritoneal washings, hysterectomy with bilateral salpingo-oophorectomy, omentectomy and multiple peritoneal biopsies. One must try to do complete resection of all macroscopic suspected lesions. Routine lymphadenectomy is not recommended as recurrence and survival rates with positive or negative lymph nodes are similar but it may lead to upstaging of disease.

Surgical staging can be done at the time of primary surgical removal of the ovarian tumor after a positive frozen section confirms the diagnosis of BOT. It can also be done as a restaging surgery after the permanent histological report of primary surgery confirms the diagnosis of borderline tumor. Final diagnosis should be made using permanent sections as frozen section gives false negative results in at least one third of cases. 20-30% of BOT diagnosis on frozen section changes to carcinomas in final reporting whereas only 5% of BOT diagnosis on frozen section changes to benign tumor.

Complete staging with omentectomy is recommended for bilateral tumors only and should not be performed in unilateral tumors as the incidence of extraovarian lesion is 56% in former as compared to 15% in later. Complete staging is recommended for unilateral tumors with suspicious peritoneal lesions or micropapillary patterns.

Role of hysterectomy is debatable especially in absence of any peritoneal implants on the uterine serosa. Appendectomy should be reserved for mucinous ovarian tumor as there are meagre chances of appendiceal involvement in early-stage ovarian malignancy including BOTs.

**Surgical Approach (Laparoscopy/Laparotomy)**

Few studies have been done on the laparoscopic management of BOT. For early stage disease, laparoscopic approach is feasible and safe. Data is scanty in cases of advanced stage BOT. Conservative surgeries like cystectomies are preferred through laparoscopy because of lower morbidity and fewer adhesions, which are important for fertility. Many retrospective studies have shown mixed results with laparoscopic approach. Some studies have shown that laparoscopic management is associated with a higher rate of cyst rupture, incomplete staging and higher recurrence rate. On the other hand two studies, an Italian and a French study have shown that the type of surgical approach does not influence the progression-free interval and relapse rate.

**POSTOPERATIVE TREATMENT**

**Adjuvant Treatment (Chemotherapy, Radiotherapy, Hormone therapy, and Targeted Therapy)**

Aggressive treatment after surgery is not recommended and the need for any adjuvant treatment is dependent on presence or absence of any invasive component. Postoperatively patient can be kept on observation if there is no sign of any invasive disease. No randomized data has shown any advantage in relation to relapse rates or survival with adjuvant chemotherapy in patients with diagnosed BOTs especially with non invasive implants. Many studies have shown high rate of residual or recurrent disease, even after addition of adjuvant chemotherapy or radiotherapy in BOTs. Low proliferation rate may be one reason for poor response rates of BOTs to traditional cytotoxic agents. There is no benefit of chemotherapy in absence of any microscopic invasion. Although the significance of invasive implant remains investigational, but in cases of presence of invasive implants on peritoneal surface,
adjuvant chemotherapy may be considered with the same regimen used for low grade serous epithelial ovarian cancer namely intravenous carboplatin with paclitaxel or, docetaxel. Estrogen-receptor positivity is seen in majority (90%) of serous BOTs, but only few case reports have shown responses to tamoxifen, leuprolide, and anastrazole. Cytostatic effect of medroxyprogesterone acetate has also been studied. Since serous BOTs are associated with KRAS and BRAF mutations, future clinical trials may target MEK inhibitors or other anticancer agents acting on RAS/RAF/MEK/MAPK pathway, which may give good results in terms of prolonged disease-free interval and overall survival especially in advanced stage disease. Similarly alternative treatment strategies may be tried in endometrioid or clear-cell BOTs which are associated with PI3K/PTEN signalling pathway defects.

**TREATMENT OF INFERTILITY**

As already discussed above that the ovulation inducing drugs doubles the risk of BOTs. The reason of infertility in these patients are
- They were infertile before developing BOT in one third of cases
- Formation of postoperative adhesions
- Decrease in ovarian reserve due to ovarian resection.

Fifty percent of these patient may conceive spontaneously after fertility sparing surgery. In young patients with advanced disease where fertility sparing surgeries are not possible, germ cells preservation should be considered.

**TREATMENT OF HORMONE DEPRIVATION**

Hormone replacement therapy (HRT) can be offered to young women after oophorectomy to prevent cardiovascular disease and osteoporosis which may improve the quality of life.

**FOLLOW-UP**

The estimated overall recurrence rate is approximately 10%. Longer period of follow-up is needed for these patients in view of late relapses and deaths in treated patients of BOTs.

Late recurrences are considered as a recurrence from the initial tumor but if this recurrent tumor is invasive in nature, one should suspect a malignant transformation as well. As the period of follow-up is prolonged, chances of recurrent disease of invasive nature are increased, although actual rate for malignant transformation is very low (2-4%). Close follow-up for adequate period of time is recommended for patients having one or more negative prognostic factors.

- Advanced stage disease
- Invasive implants
- Residual tumor
- Micropapillary borderline
- Conservative surgery
- Incomplete staging.

Follow-up is done with a combination of clinical examination, ultrasound, CA125 and CA19–9 (for mucinous tumors) levels. Follow-up is done every 3 monthly for initial 2 years, every 6 monthly for 3 to 5 years and then yearly thereafter.

Postoperative surveillance in these patients is best done with transvaginal and transabdominal ultrasound which have a sensitivity of 95% and false-positive rate of 33%. Serum CA125 level estimation and clinical assessment (symptoms and gynecologic examination) are of limited value in follow-up as CA 125 is negative in majority of cases and recurrent tumors tend to be significantly smaller to give any symptomatic presentation.

**TREATMENT OF RECURRENCES**

The non invasive relapse in the remaining ovary can be managed by conservative surgery (cystectomy) if fertility is desired. If there is no desire to preserve fertility, panhysterectomy is recommended. On the other hand if the recurrence is outside ovary whether non invasive or invasive, the treatment option is extensive cytoreductive surgery with intention of no or, minimal residual disease, as suboptimal debulking is associated with significantly poor outcome. Further after second surgery, non invasive cases are observed and invasive cases are managed as per the grading of tumor. Low grade invasive implants are treated similar to low grade serous epithelial carcinoma and high grade as epithelial ovarian cancer.

**CONCLUSION**

Borderline ovarian tumors is not a single entity but a wide spectrum of tumor biological behavior and presentation associated with uncertain malignant
potential. Till date, because of paucity of randomized studies and meta analysis, there is lack of any clear cut prognostic or predictive markers which may differentiate between purely benign tumors and those with a tendency to progress to frank carcinomas. Hence while making any treatment decision, it is important to weigh the oncologic safety against the advantages of less radical treatment.

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Nil

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There are no conflict of interest.

**REFERENCES**