Principles of Treatment for Borderline, Micropapillary Serous, and Low-Grade Ovarian Cancer

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Abstract

Borderline ovarian tumors (BOTs) are less common than epithelial ovarian cancers (EOCs). Low-grade EOCs (LG-EOCs) occur even less frequently than BOTs. After primary therapy, recurrence rates of BOTs and LG-EOCs are significantly lower and the stage-adjusted survival is higher than for high-grade EOCs. Thus, determining the best management in terms of traditional ovarian cancer staging and debulking procedures is more challenging and has been recently brought to question. This article reviews the particulars of BOTs and LG-EOCs, their similarities and differences, and how they are best managed and treated, and emphasizes the major role of surgery and the controversial role of chemotherapy. Because these tumors disproportionately affect younger women, this review addresses ovarian preservation in circumstances when fertility or hormonal preservation is desired.

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Describe and discuss the similarities and differences between borderline ovarian tumors (BOTs) and low-grade epithelial ovarian carcinomas (LG-EOCs)
- Assess the role of surgery, chemotherapy and fertility/hormonal preservation in the management of BOTs and LG-EOCs

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The International Federation of Gynecology and Obstetrics and the WHO introduced borderline ovarian tumors (BOTs) into their classification of ovarian cancer in 1971 and 1973, respectively.^{1,2} BOTs are 4.5 to 5.9 times less common than epithelial ovarian cancer (EOC).^{3–5} They constitute 10% to 20% of EOCs, and more than 95% of BOTs are of serous (sBOT) or mucinous (mBOT) histologies. BOTs have also been described less frequently in endometrioid, clear cell, and other histologies.^{5–7} Cancer registries in the United States stopped mandated recording of BOTs in 2001; therefore, contemporary data derives from retrospective assessments and large series in Scandinavian National Registries and Europe. BOTs usually occur in women at a mean age of 45 to 52 years, approximately 10 years younger than that of EOCs.^{5,8–10} Population-based data suggest that BOT and low-grade EOCs (LG-EOCs) are most common in white women. LG-EOC, with one-third the incidence, is more likely than BOT to occur in patients older than 45 years.^{3,11} Furthermore, the patient profile of low-grade serous EOC (LG-sEOC) is more comparable to that of sBOT than high-grade serous EOC (HG-sEOC).¹² Three-quarters of sBOTs occur at an early stage and overall 5-year survival is greater than 95%.^{3,7,13–16} Their recurrence rates vary depending on stage at diagnosis, degree of surgical aggressiveness, and BOT histology, but in large contemporary series these rates range between 5% and 12%.^{17–19} Among patients with BOT, 1% to 2% recur as invasive carcinomas.^{7,18,19} Recurrences are more common after fertility-sparing surgery.⁷

mBOTs are more frequently early stage than are sBOTs, with more than 90% of contemporary cases diagnosed at stage I; survival is close to 100%.^{3,20} It is important to note that mucinous tumors of the ovary that are associated with pseudomyxoma peritonei are almost always of appendiceal origin.²¹ Borderline tumors displaying clear cell, endometrioid, and Brenner tumor histologies are much less common than mBOTs and sBOTs, and are usually stage I and unilateral.¹³ Endometrioid BOTs constitute approximately 1% of BOTs in multiple series, and their patient demographic profile is similar to that of mBOT and sBOT.²² Clear cell BOTs are rare with fewer than 50 cases reported in the literature. These patients are older than other patients with BOT, usually 60 to 70 years old.²⁰

Most risk factors for sBOTs are similar to those for EOC except for the use of oral contraceptives, which

may not yield the same level of risk reduction; the lack of association with the protective effect of tubal ligation; familial predilection; and *BRCA* carrier status.^{6,8,23,24} Endometrioid and clear cell BOTs have been associated with estrogen excess and/or endometriosis, thus these are considered potential risk factors.²⁰

This article reviews the spectrum from BOT (low malignant potential tumors) to low-grade carcinoma with a discussion of micropapillary features, which warrant differential consideration.

Terminology and Pathology

The most recent WHO Classification of the Tumors of the Female Genital Tract provides comprehensive diagnostic criteria, pathologic features, and associated genetic alterations in an effort to increase consistency in pathologic diagnosis of these rare tumors.²⁵ Borderline components should comprise at least 10% of the cyst and may contain areas of invasion less than 3 to 5 mm in greatest linear dimension.²⁶ Adequate sampling of the primary tumor is one section per centimeter for tumors less than 10 cm and 2 sections per cm for larger tumors. Inadequate sampling can miss an invasive cancer.²⁷

Serous Histology

sBOTs contain epithelial cells exhibiting an unusual degree of proliferation.²⁵ The fundamental difference between sBOTs and LG-sEOC is stromal invasion.²⁶ If the area of invasion is small, the tumor is called an *sBOT with microinvasion*; these constitute 10% to 15% of sBOTs and carry a good prognosis.²⁸ Micropapillary serous borderline tumors (MPSCs) or noninvasive micropapillary serous carcinomas are sBOTs without invasion but with micropapillary architecture.^{28–30} One population-based study suggested that MPSCs constitute 26% of sBOTs, but that the micropapillary characteristic itself did not confer a worse prognosis³¹; this, however, remains a debated topic. Detailed gene expression analysis supports an association between MPSCs and LG-sEOC.³²

Mutations in *KRAS* and *BRAF* are common in sBOTs and MPSCs, with frequencies exceeding 60%, but rare in HG-EOCs.^{33,34} *p53* mutations are more likely to occur in HG-EOC, as commonly as 95.9% of the time.^{34–38} The presence of *KRAS* and *BRAF* mutations and expression of p21/WAF1 in LG-sEOC lends further support to their association

with sBOT.^{34,37} A continuum likely exists from sBOT to LG-sEOC. The aforementioned genetic differences and histologic associations between sBOT and LG-EOC suggest that the pathogenesis of LG-EOCs and HG-EOCs is different. Wild-type *p53* and activating *KRAS/BRAF* mutations can be useful clinically to distinguish LG-EOC and HG-EOC.

Mucinous Histology

The BOT Workshop held in Bethesda in August 2003 was instrumental in clarifying terminology for mucinous tumors, including borderline types.³⁹ There are 2 types of histologically distinct mBOTs: gastrointestinal and endocervical or seromucinous type. mBOTs are primarily gastrointestinal type, stage I at presentation, unilateral (95%), and rarely fatal (1% disease-related mortality).³⁹ Endocervical-type mBOTs are less common, more frequently bilateral (30%–40%), confined to the ovaries, and likely to exhibit benign behavior even at higher stages.^{39,40} Updated genetic assessments suggest that seromucinous BOTs do not have a serous component despite some papillary architecture, and that they are often associated with endometriosis.⁴¹

Gastrointestinal and seromucinous mBOTs are immunophenotypically distinct.⁴² The immunohistochemical profile of seromucinous mBOTs shows frequent expression of estrogen receptors (ERs; 100%), progesterone receptors (PRs; 67%), CA 125 (92%), and CK7 (100%).⁴² They do not express CDX2 or CK20, differentiating them from the gastrointestinal-type mBOTs, which express CK7 (93%), CK20 (86%), and CDX2 (39%), but not ER or PR, and infrequently express CA 125 (11%).⁴² These receptor patterns might be therapeutically useful.

In contrast to sBOTs, mBOTs are often associated with their invasive counterparts with mucinous carcinomas, frequently displaying areas of normal and borderline components.⁴³ Specific gene mutations that support the progression from benign to borderline to invasive tumors are *KRAS*-activating mutations in exons 12 and 13.⁴⁴

Other Histologies

Endometrioid BOTs display endometrioid-type epithelium with proliferative, crowded glands and nuclear atypia.²⁶ These areas may resemble atypical endometrial hyperplasia or endometrioid carcinoma. They frequently arise in endometriotic cysts or are

associated with either benign adenofibromas or endometrioid carcinomas.^{22,26} β -catenin and *PTEN* mutations are found in endometrioid BOTs and their invasive counterparts.⁴³ Clear cell BOTs resemble clear cell adenofibromas but display crowded glands with epithelial proliferation.²⁶ Although an association of clear cell BOTs with invasive clear cell carcinoma exists, the gene mutation association appears to be less frequent.⁴³ Brenner BOTs resemble transitional cell tumors of the urinary tract and display nuclear atypia and epithelial proliferation beyond that seen in a benign Brenner tumor.²⁶ Endometrioid, clear cell, and Brenner BOTs are usually unilateral, do not have extraovarian disease or peritoneal implants, and are confined within a benign tumor of the same histology.²⁰

Micropapillary sBOTs

Burks et al⁴⁵ identified a subset of well-differentiated, noninvasive serous tumors that may be associated with malignant behavior. These are characterized by a filigree pattern of highly complex micropapillae covered by cells with a high nuclear-to-cytoplasmic ratio.^{28,45} A total of 75% to 92% of MPSCs are associated with sBOTs and 62% of invasive MPSCs were associated with noninvasive MPSCs, sBOTs, and/or adenofibromas, leading to the conclusion that they are related.^{45,46} An MPSC must have at least a 5-mm continuous length of micropapillary or cribriform ar-

Figure 1. Serous ovarian carcinomas are divided into 2 types. All ovarian neoplasms have increased cellular proliferation. Type 2 tumors are high-grade carcinomas that typically present at advanced stage and have *p53* mutations. Type 1 tumors comprise low-grade carcinomas that frequently have mitogen activated protein kinase (MAPK) pathway-activating mutations. Serous borderline ovarian tumors and micropapillary serous borderline tumors commonly have MAPK-activating mutations similar to type 1 carcinomas; these tumors are not frankly invasive but may present with invasive implants. Although less common than high-grade and low-grade carcinomas, they may have metastatic implants in the peritoneal cavity.

chitecture and can display focal invasion.²⁸ Across reviews, MPSCs are more likely than sBOTs to be bilateral and have surface involvement or peritoneal implants.^{28,46,47} In a series of MPSC from The University of Texas MD Anderson Cancer Center, Bristow et al⁴⁸ reported that nearly 75% of MPSCs present at an advanced stage. Patients with MPSC confined to the ovary do well and deaths due to tumor are rare, whereas patients with advanced-stage MPSC have a disease-related mortality of 32.4%⁴⁸; of note, almost all had invasive tumor implants. Invasive implants consist of a proliferation of epithelium which effaces the underlying tissue.²⁸ Evidence has accumulated to suggest that the poor prognosis associated with MPSCs is due to the increased presence of invasive implants.^{14,49–51} Typical sBOTs with invasive implants also have inferior survival. Other studies have not confirmed the association of MPSC and more frequent invasive implants, and argue that conservative surgery is a bigger factor.^{47,52} This apparent contradiction may be a function of sample size and of the denominator in each series, especially when it consists mostly of typically less straightforward consultative cases, thereby potentially creating an overinterpretation of the prognostic attribution of invasive implants in MPSC.^{49,52} Although controversy remains, we agree that both patients with sBOT and those with MPSC are more likely to do poorly if invasive implants are present, especially if they are not surgically debulked (Figure 1).

Management

Borderline Tumors

BOTs are frequently diagnosed in women of child-bearing age who desire fertility preservation. In studies assessing the recurrence risk and survival of patients undergoing conservative treatment with unilateral salpingo-oophorectomy or cystectomy, ovarian preservation is consistently associated with an increased risk of recurrence but has no apparent effect on long-term survival, and most patients can be salvaged with completion surgery and debulking.^{7,17–19,53–56} The utility of fertility preservation has been investigated and multiple studies have cited conception rates of 40% to 60%.^{54,57,58}

Several studies have investigated the role of complete surgical staging in patients with BOTs, including peritoneal washings, peritoneal biopsies,

and at least omental biopsies; many also included appendectomy and retroperitoneal lymph node sampling.^{10,17–19,53} They all revealed that omitting staging procedures might increase recurrence rates but does not adversely affect survival.^{10,17,18} Residual disease after surgery is a risk factor for recurrence, thus every effort should be made to remove all visible tumor.⁵⁹ Lymph node metastases occur in sBOTs with reported incidences of 0% to 20%, but are infrequent in mBOTs.^{7,53,60–62} Furthermore, true lymph node involvement must be distinguished from endosalpingiosis, a common benign finding of müllerian glandular inclusions. Lymph node metastases occur more commonly in patients with obvious peritoneal implants or grossly enlarged nodes at the time of surgical staging; hence it may be prudent to perform lymphadenectomy in these unique patients.⁶³ The presence of BOT cells in retroperitoneal lymph nodes does not appear to alter prognosis,^{51,62,64} and because retroperitoneal lymph node sampling increases surgical complexity and risk, multiple groups have advocated omitting this procedure except in cases of obvious advanced disease.^{64,65}

Minimally invasive surgery, as performed by gynecologic oncologists, is adequate treatment for BOTs. In early studies, there were more cyst ruptures with laparoscopy; however, its safety has been confirmed with no difference in rates of recurrence or survival.^{55,66}

It is now established that conservative therapy with removal of all visible disease but without comprehensive surgical staging is an acceptable treatment for BOT. Patients may undergo unilateral salpingo-oophorectomy with preservation of the uterus and contralateral ovary for fertility preservation. For prognostic and staging reasons, it is still recommended that peritoneal and omental sampling be performed in patients without evidence of extraovarian disease; however, retroperitoneal lymph node sampling can be avoided. In patients with macroscopic disease outside of the ovary, debulking with possible lymphadenectomy is advisable, because patients with residual disease have increased rates of recurrence.^{59,60,67} Recurrence rates are higher in patients who have ovarian cystectomies, thus preservation of the ipsilateral ovary is not advised except under special circumstances.^{18,19} Proponents of comprehensive staging argue that frozen pathology may show BOT in cases in which the final pathology reveals invasive

carcinoma. There is credibility to these claims, with studies showing frozen pathology sensitivities of 65% to 86%^{53,61,68}; however, there was no difference in survival when patients with pathology upgraded to carcinoma were included in analyses.⁵³ Finally, some gynecologic oncologists recommend completion of surgery after childbearing, because most recurrences are in the contralateral ovary.⁵⁶

Adjuvant therapy is difficult to recommend in the treatment of BOTs because these tumors infrequently lead to death even with postoperative residual disease.⁶⁹ Additionally, adjuvant chemotherapy and/or radiation therapy does not offer a survival benefit to patients with BOT.^{55,69–73} In some studies, patients who received adjuvant chemotherapy had worse outcomes, with lower overall survival, than those managed expectantly.^{60,69,74} Chemotherapy complications and secondary malignancies are valid concerns.^{27,65,73} For heavy disease burden or residual disease, targeted and hormonal therapies could be considered as for LG-sEOC.

When a patient has tumor recurrence, a repeat surgical procedure with complete debulking is advised because BOTs are not sensitive to chemotherapy, and because it will allow for pathologic evaluation for “malignant transformation.”^{67,71}

Micropapillary Tumors

As with other BOTs, surgery is the mainstay of treatment for MPSCs. Stage I MPSC has a 1% to 2% recurrence risk after surgical treatment.^{14,45–47,49,50} Seidman and Kurman²⁷ found that MPSCs have an 11-fold higher risk of recurrent invasive carcinoma compared with sBOTs without invasive implants. However, they recommended subsequent treatment only for those with invasive implants, noting that survival is otherwise excellent with surgery alone.

Analysis of clinical management in MPSC reveals that the amount of residual disease is the only significant factor influencing progression-free and overall survival in advanced-stage disease.⁴⁸ This finding led to the conclusion that optimal surgical debulking to no visible residual disease is paramount in the management of MPSC. In a series of conservatively treated MPSCs, the biggest risk for recurrence was conservative treatment itself.⁵²

The role for chemotherapy in the treatment of MPSC is undefined. Response rates of 75% have been cited, similar to the 57% response rate to che-

motherapy in patients with sBOTs with invasive implants.^{48,60} Despite uncertain long-term results, many institutions still recommend chemotherapy for patients with MPSC with residual disease and for sBOTs with invasive implants or residual disease.

Low-Grade Ovarian Carcinomas

Initial Surgical Therapy: The cornerstone of management of LG-sEOC is surgical debulking. Similar to high-grade carcinoma, more than two-thirds of patients are diagnosed with stage III disease.⁷⁵ Surgical debulking of LG-sEOC to no visible disease at surgery confers maximal survival benefit. In a subset analysis of LG-sEOCs from GOG 182, patients with greater than 1 cm and with 0.1 to 1 cm of residual disease had significantly higher odds of recurrence compared with patients debulked to no visible disease.⁷⁶ The median progression-free survival in patients with no visible disease was 33.2 months compared with 14.7 and 14.1 months for the optimally and suboptimally debulked patients, respectively. In one of the largest retrospective analysis of patients with LG-EOC, residual disease at the completion of primary surgery was associated with a significant increased risk of dying.⁷⁵ Optimal surgery includes at least hysterectomy, bilateral salpingo-oophorectomy, omentectomy, lymph node assessment, and resection of all visible disease. Optimal debulking surgery is ideally performed by a high-volume provider.⁷⁷

Adjuvant and Recurrence Therapy: The role of chemotherapy in the treatment of LG-EOC is currently unclear. Data from recent studies support relative chemoresistance in LG-EOC at all phases of treatment, including in the neoadjuvant setting with a 4% complete response and an 88% stable disease rate, the adjuvant setting with a 5% negative second-look rate, and the setting of recurrent disease in which an overall response rate to various regimens is reported to be only 3.7%.^{78–80}

Studies quantifying the overall response rates to hormonal therapy in LG-sEOC are limited. In patients with recurrent LG-sEOC receiving various hormonal agents, the overall response and stable disease rate are 9% and 62%, respectively.⁸¹ Tumors with higher ER and PR expression appear to have better response rates.⁸¹

Acting on the knowledge that most LG-sEOCs have mutations in the MAPK pathway, a recent phase II trial found promising results, similar to those

seen with aromatase inhibitor therapy, with the use of the oral MEK1/2 inhibitor selumetinib, such that 15% and 65% of patients had an objective clinical response and stable disease, respectively.⁸²

Several questions remain, including which subgroup, if any, benefit from adjuvant therapy. Hindered by the lack of measurable disease and overall low response rates to therapies, there is a concern that most women might have limited benefit from adjuvant therapy while having to endure the side effects of treatment.

Conclusions

BOTs, MPSCs, and LG-sEOCs are a less common group of ovarian tumors with distinctly different epidemiology and biologic behavior than HG-EOC. They display an indolent presentation and recurrence pattern, making them challenging to study. Furthermore, studies have generally consisted of variably staged and treated patients, causing a consensus statement on the best treatment to be challenging to substantiate. We agree with the Gynecologic Cancer InterGroup guidelines that BOTs should be treated exclusively with surgery and LG-sEOCs should be debulked with consideration of hormonal or targeted molecular therapies for residual or recurrent disease.^{83,84} Attempts to treat these patients identically to those with HG-EOCs should cease outside of the role for surgical debulking. Other support for differential management comes from mutational analyses that suggest sBOTs and LG-EOC are related, whereas HG-EOCs are a separate entity.²⁹ Clinical trials examining the use of novel agents and hormonal therapy need to be conducted with an observational control arm. We also need better clarification of which histologic and immunologic factors, if any, identify truly high-risk patients who may benefit from more aggressive staging, adjuvant therapy, or closer surveillance.

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Posttest Questions

1. Which of following statements regarding BOTs and LG-EOCs are true?
 - a. The fundamental difference between sBOTs and sLG-EOC is stromal invasion
 - b. MPSCs are sBOTs without invasion but with micropapillary architecture
 - c. Detailed gene expression analysis supports an association between MPSCs and LG-sEOCs
 - d. All of the above
2. Which of the following statements regarding BOTs is FALSE?
 - a. BOTs are frequently diagnosed in women of childbearing age who desire fertility preservation
 - b. Residual disease after surgery is a risk factor for recurrence thus every effort should be made to remove all visible tumor
 - c. Adjuvant therapy is no longer recommended because these tumors infrequently lead to death even with postoperative residual disease
 - d. Repeat surgery with complete debulking is not advised in the case of tumor recurrence
3. True or False: The utility of fertility preservation in patients with BOTs has been investigated and multiple studies have cited conception rates of 40% to 60%.