

Controversies in borderline ovarian tumors

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Borderline ovarian tumors (BOTs) represent about 15% to 20% of all ovarian malignancies and differ from invasive ovarian cancers (IOCs) by many characters. Historically, standard management of BOT is peritoneal washing cytology, hysterectomy, bilateral salpingo-oophorectomy, omentectomy, complete peritoneal resection of macroscopic lesions; in case of mucinous BOTs, appendectomy should be performed. Because BOTs are often diagnosed at earlier stage, in younger age women and have better prognosis, higher survival rate than IOCs, fertility-sparing surgery is one of the option to preserve childbearing capacity. The study of such conservative surgery is being released, and still controversial. After surgery, pregnancy and ovarian induction followed by *in vitro* fertilization are also significant issues. In surgery, laparoscopic technique can be used by a gynecologic oncology surgeon. So far postoperative chemotherapy, radiotherapy and hormone therapy are not recommended. We will discuss controversial issues of BOTs on this review and present the outline of the management of BOTs.

Keywords: Borderline Ovarian Tumors; Data Collection; Fertility; Management

INTRODUCTION

Borderline ovarian tumors (BOTs) represent an independent disease entity among epithelial ovarian cancers (EOCs), officially classified by the International Federation of Gynecology and Obstetrics (FIGO) in 1961 and by the World Health Organization in 1973. Currently, three terminologies are used to describe these tumors: borderline tumor, tumor of low malignant potential, and atypical proliferative tumor [1]. BOTs are characteristically difficult to diagnose using preoperative radiological methods, exhibit inconsistencies in expression of tumor markers, and are often inaccurately identified using frozen sections.

Although it is agreed that complete surgical resection of the tumor is the best curative method for BOTs, there are no clear-cut answers and much debate regarding the extent of surgery, the need for fertility preservation in the treatment of young women, the use of laparoscopic surgery, and the use of

postoperative chemotherapy and infertility treatments.

As such, our objective is to help readers by summarizing data drawn from recent literature and drawing conclusions based on our evaluation of these data.

EPIDEMIOLOGY

BOTs account for approximately 15% to 20% of all EOCs and occur in approximately 1.8 to 4.8 of 100,000 women each year [2-5]. Although there has been a recent decreasing trend in ovarian malignancies worldwide, the percentage of BOTs among ovarian malignancies is actually increasing [6]. This is believed to be the result of improved accuracy in the pathological diagnosis of BOTs and of changes in risk factors associated with BOT, in comparison to previous years.

HISTOLOGY

More than 96% of BOTs are serous or mucinous type. Other rare types are endometrioid, clear cell, or Brenner (transitional cell) tumors. Histological distribution of the BOT types may

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depend on the geographic region. In Western countries such as USA, France, and Italy, the serous type is most common, while in Korea and Japan, mucinous type is more common [7].

Serous borderline ovarian tumor (sBOT) is characterized by hierarchical arborizing edematous papillae, focally covered by stratified epithelium with variable nuclear atypia with few mitoses and absence of destructive stromal invasion. Bilateral tumors represent about 30%, and about 70% are confined to one or both ovaries (stage I) at the time of diagnosis. Micropapillary sBOT (non-invasive, low-grade serous carcinoma) contains complex nonhierarchical micropapillae and only mild nuclear atypia with marked epithelial cell proliferation. Micropapillary sBOT is associated with higher frequencies of bilaterality, surface ovarian involvement, advanced stage at diagnosis, stromal microinvasive foci, invasive implants, and lymph node involvement [8,9]. Microinvasion is diagnosed when a focus of stromal invasion is limited to an area of no more than 10 mm.

Mucinous borderline ovarian tumor (mBOT) accounts for about 30% to 50% of all BOTs and are less likely to be bilateral (7%) [10]. There are two histological subtypes: the intestinal type (85% to 90%) and the endocervical type (10% to 15%), they have different clinicopathologic features. The intestinal type occurs at an older age, is frequently unilateral, exhibits large multilocular cyst, is associated with pseudomyxoma peritonei, and has a good prognosis. The endocervical type occurs in younger women and is more bilateral (20% to 30%), presents a unilocular cystic tumor, and has a more advanced stage, is correlated with implants or lymph node metastasis, and its mortality rate may increase up to 50% depending on the stage [11,12].

WHAT IS THE DIFFERENCE BETWEEN BOTs AND INVASIVE OVARIAN CANCERS?

The distribution of tumor stages differs between these tumor types. At the time of diagnosis, about 75% of BOT patients present with FIGO stage I tumors, compared to 20% of invasive ovarian cancer (IOC) patients; 60% of IOC patients are diagnosed with stage III disease [13].

Additionally, age at tumor occurrence is different. Generally, the average age of IOC patients is 55 years, whereas that of BOT patients is 45 years, with tumor presentation generally occurring 10 years earlier in the latter [14,15].

The prognosis of BOTs differs from that of IOCs. Unlike IOC patients, most BOT patients exhibit excellent survival rates. The 5-year survival rate for stage I BOTs is approximately 95% to 97%, and even patients presenting with stage II to III BOTs have 5-year survival rates of 65% to 87% [16]. On comparing

survival rates according to histological subtypes, the 10-year survival rates for serous and mBOTs are approximately 96.9% and 94%, respectively, with even sBOTs in advanced stages showing good prognosis with a 10-year survival rate up to 89.9%.

The accuracy of BOT identification using frozen sections is low. The concordance rate between the emergency frozen section biopsy conducted during IOC surgery and the final biopsy results varies greatly depending on the malignancy status of the tumor. Diagnostic concordance rates for benign and malignant tumors are 94% and 98%, respectively, whereas the diagnostic concordance rate for BOTs is only 70%. About 20% to 30% of the cases that are diagnosed as BOT using frozen sections are ultimately determined to be IOC, and although uncommon, approximately 5% of the cases diagnosed as BOT via frozen section analysis are ultimately determined to be benign tumors [15,17]. Among the cases that are ultimately identified as BOT, approximately 6.6% to 9.9% and 24.1% to 30.6% of the cases are misdiagnosed as IOC or benign tumors, respectively [18,19]. As such, it is difficult to decide on the extent of surgery or the treatment direction based only on the results of frozen section tests.

BRCA mutation is rarely observed in BOTs. According to Gotlieb et al. [20], BRCA mutation occurs in only 4.3% of patients with early stage BOT, compared to approximately 24.2% of patients with early stage IOC.

HOW IS SURGICAL STAGING PERFORMED DURING BOT SURGERY?

In order to define the FIGO stages, the entire abdominal cavity must be thoroughly examined; peritoneal washing, hysterectomy, bilateral salpingo-oophorectomy, and omentectomy must be performed; and all suspicious lesions must be excised during surgery. For mBOT, appendectomy is recommended. Lymphadenectomy is the most controversial issue of the surgery. Micropapillary sBOT, for which lymphadenectomy is recommended, is associated with lymph node involvement and high recurrence rate [8,21,22]. Because metastasis to the lymph nodes is not known to affect survival or recurrence, lymphadenectomy is not necessary when clinically early stage [18,23].

IS RESTAGING NECESSARY WHEN THE FINAL BIOPSY RESULTS INDICATE BOT?

When only cystectomy is performed, relapse rates can be as high as 31% [18]. According to histological subtypes, cystecto-

my in unilateral sBOT shows a significantly higher recurrence rate (43.2%) than unilateral salpingo-oophorectomy (USO), although this has no impact on survival. Similarly, recurrence rate for cystectomy (29%) was higher than USO (7.9%) in unilateral mBOT [24]. Therefore, it is ideal to perform cystectomy only when the tumor is present bilaterally or when one ovary has already been removed. In addition, some authors have suggested that more conservative bilateral cystectomy may be favored in bilateral sBOT for patients who want to preserve childbearing capacity, because no significant difference is seen in recurrence rate compared to USO with contralateral cystectomy [24]. However, Koskas et al. [25] stated that cystectomy is not recommended due to the high likelihood of mBOT developing into an invasive cancer. The presence of tumor cells in the margins or tumor rupture during surgery are factors that can predict relapse after cystectomy [26]. Therefore, it is important to perform thorough pathological tests on the margins around the resected tumor [27], and efforts should be taken not to rupture the tumor during surgery.

There is much debate over the need for a second surgery to restage those tumors that were diagnosed as benign during surgery, but as BOT in the final biopsy. According to the studies by Camatte et al. [23] and Fauvet et al. [21], surgical restaging does not impact the survival rate of patients. Increase in tumor stage after restaging is generally due to positive biopsy results from peritoneal lavage or to the presence of noninvasive implants. Because approximately 39% of BOTs metastasize to the omentum and about 9% are accompanied by invasive implants, restaging is recommended if the abdominal cavity and the peritoneal surfaces were not thoroughly examined during the first surgery [28]. In particular, unstaged micropapillary sBOT is associated with extra-ovarian disease, invasive implants, and lymph node involvement, so restaging procedure may be needed [8,22].

FERTILITY-SPARING SURGERY AND INFERTILITY AFTER FERTILITY SPARING SURGERY

Fertility-sparing surgery refers to the sparing of the uterus, along with one or both ovaries, during surgical staging. Because BOTs are relatively prevalent among young women and have an excellent prognosis, preserving fertility is often an issue. However, since the patient's survival and safety are just as important as fertility, fertility-sparing surgery requires a careful approach. Recently published literature describes fertility-sparing surgery as relatively safe and effective for BOT patients [29,30]. According to Trillsch et al. [31], the recurrence rate following radical surgery was approximately 5%, whereas

that following fertility-sparing surgery was higher at 10% to 20%. Recurrence generally occurs not in the form of invasive cancer, but as BOTs, and often occurs in the ovary that was spared during surgery [32]. Recurrence outside of the ovaries occurs in 20% of advanced stage BOTs (FIGO stage II, III), compared to 2% of FIGO stage I cases [18].

There is a consensus that tumor recurrence occurs more frequently following fertility-sparing surgery. However, higher recurrence rates do not necessarily lower the survival rate. Recurrence of BOT has a relatively good prognosis, but recurrence of IOC has a poor prognosis. Survival rates of patients experiencing an IOC relapse varies from 8% to 73%, with higher recurrence rates seen when the tumor is in an advanced stage initially or is accompanied by an invasive implant [29,33-41].

It was reported that 50% of BOT patients went on to have natural pregnancies after fertility-sparing surgery [14]. However, 35% of BOT patients had a history of infertility prior to surgery [16], and postoperative infertility can occur due to adhesion during surgery or reduced ovarian tissues. Infertility treatments are given in these cases, but there are concerns that ovarian stimulation induced by these treatments may increase the probability of BOT relapse.

Although some existing reports have indicated that using infertility drugs may increase the risk of BOT, no conclusions were drawn due to study limitations, such as short follow-up period, low statistical power, and the absence of control groups. According to a recently published study by van Leeuwen et al. [42], which followed-up on patients in the Netherlands for over 15 years, occurrence of BOT was twice as high in people who had undergone *in vitro* fertilization (IVF) when compared to those who had not. Moreover, recurrence of EOC was also increased in patients who had undergone IVF. Therefore, until a future large-scale prospective study is published, attempting pregnancy without IVF, if possible, is recommended. In cases where IVF is absolutely needed, extremely careful follow-up will be necessary.

Fertility-sparing surgery is typically performed to preserve the possibility of future pregnancies, but according to Fauvet et al. [43], no successful pregnancies occurred among BOT patients who received fertility-sparing surgery after the age of 40. Based on the findings above, fertility-sparing surgery should be considered only for women who are under the age of 40 and present with FIGO stage I tumors.

LAPAROSCOPY/LAPAROTOMY

Traditionally, just as in IOC, laparotomy has been frequently used in BOT. Although laparoscopy has been used widely in

recent years, there have been recent studies on its safety for use in BOT patients. Concerns over implementing laparoscopy for BOTs include tumor rupture during surgery, port site metastasis, and a decreased survival rate due to failure to thoroughly define the surgical stage. According to Fauvet et al. [21] and Oh et al. [44], tumor rupture and incomplete staging were more common when using laparoscopy to resect BOT. Furthermore, according to du Bois et al. [18], when fertility-sparing surgery was performed via laparotomy, the relapse rate was approximately 7.7%, compared to laparoscopy, which was as high as 14.9%. However, according to multicenter studies conducted in Italy and France, there are no significant differences in relapse rates following laparoscopy versus laparotomy [37,45]. Additionally, the morbidity rate was lower and adhesion, which is important for infertility, occurred less frequently when surgery was performed via laparoscopy [46]. Although the frequency of port site metastasis in IOC has been reported to be as high as 17%, there are almost no related studies for BOT [47]. Camatte et al. [48] performed laparoscopic surgery on 34 BOT patients, among whom two were reported to have port site metastasis, while Gotlieb et al. [38] reported port site metastasis in one patient after IVF. Although it is difficult to make definitive conclusions on this matter due to the lack of prospective studies, it is believed that a skilled oncology specialist with sufficient experience would be most desirable when performing laparoscopic surgery on BOT patients.

IS POSTOPERATIVE ADJUVANT CHEMOTHERAPY NECESSARY?

Recently first-line adjuvant treatment of BOTs is platinum-based adjuvant chemotherapy regardless of histological subtypes. However, postoperative adjuvant chemotherapy or radiotherapy fails to lower the relapse rate or improve the survival rate in both the early and advanced stages of BOT. There were no additional benefits from postoperative adjuvant therapy for cases involving non-invasive or invasive implants [15,45,49-51]. Because BOT generally shows a low proliferation rate, traditional cytotoxic drugs are thought to be ineffective. However, adverse effects or toxicity still occurs. Although $\geq 90\%$ of serous BOTs are estrogen receptor-positive [52,53], there are no detailed studies, only case reports, testing the effect of tamoxifen, leuprolide, or anastrozole on these tumors [54].

Based on the findings above, the adverse effects of postoperative chemotherapy, radiotherapy, and hormone therapy outweigh their benefits, and they are not recommended for

BOT patients.

TREATMENT FOR RELAPSE

When BOT recurs in the spared ovary after fertility-sparing surgery and the patient desires to preserve fertility, a second fertility-sparing surgery, identical to the first, can be considered. If the patient does not desire to preserve fertility, bilateral salpingo-oophorectomy can be performed [55].

If BOT or IOC recurs in areas outside of the ovaries, the best possible treatment is to perform cytoreductive surgery. The presence of residual tumor is the most important predicting factor for prognosis, and it was reported that successfully cytoreductive surgery resulted in approximately 12% patient mortality, compared to 60% mortality following unsuccessful cytoreductive surgery. Because the complete and partial response rates in relapsed BOT patients who received chemotherapy were 15.1% and 11.3%, respectively, it is important to surgically remove as much of the tumor as possible [18].

CONCLUSIONS

Table 1 summarizes the controversial issues of BOTs. Standard management of BOTs is hysterectomy, bilateral salpingo-oophorectomy and peritoneal staging. BOTs is diagnosed at young reproductive women, and have good prognosis than IOCs, recently fertility sparing surgery is a good option in young patients who desire preservation of fertility with early stage disease. Although long-term survival does not seem to be negatively influenced by fertility-sparing surgery, the recurrence rate following fertility-sparing surgery was higher at 10% to 20%. Patients with advanced stage or needed postoperative IVF, extremely careful follow-up will be required. When BOT recurs in the spared ovary after fertility-sparing surgery and if patient do not want to preserve the fertility, bilateral salpingo-oophorectomy can be performed. But, if BOT or IOC recurs in other areas, cytoreductive surgery is the best treatment. Certain risks such as the possibility of ruptured tumors, incomplete staging, and port site metastasis follow laparoscopic surgeries but when performed by a professional gynecologic oncology surgeon, the surgery should be safe. Postoperative adjuvant therapy is not recommended.

Upon taking all of these risks and factors into account, if the patients' age and desire to conceive as well as their clinical stage are taken into consideration and treatments are made by a professional oncology specialist, it will aid in the prognosis and lives of BOT patients.

Table 1. Summarize the controversial issues of borderline ovarian tumors (BOTs)

Issue	Comment
Surgical staging	Hysterectomy, bilateral salpingo-oophorectomy, omentectomy, peritoneal cytology and multiple biopsies; in case of mucinous BOTs, appendectomy should be performed. Lymphadenectomy is not performed routinely.
Restaging	Restaging is recommended if the abdominal cavity and the peritoneal surfaces were not thoroughly examined during the first surgery.
Oophorectomy vs. Cystectomy	Oophorectomy is more preferred than cystectomy.
Fertility-sparing surgery and infertility treatment	Fertility-sparing surgery is used in young patients who want to preserve the fertility with early stage disease. If possible, attempting pregnancy without <i>in vitro</i> fertilization (IVF) is recommended. In cases where IVF is absolutely needed, extremely careful follow-up will be necessary.
Laparoscopy vs. Laparotomy	Laparoscopic technique can replace the laparotomy when performed by skilled oncologic surgeons.
Adjuvant treatment	Adjuvant chemotherapy, radiotherapy and hormone therapy are not recommended.
Treatment of recurrence	If patient want to preserve fertility, a second fertility-sparing surgery, if not, bilateral salpingo-oophorectomy or cytoreductive surgery should be performed.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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