Management of borderline ovarian tumors – state of the art

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Borderline ovarian tumors (BOT) have invited controversy for decades. In the last couple of years research has showed a shift towards less aggressive treatment. This review summarizes the latest studies and therapeutic consequences thereof. Staging procedures are recommended in the setting of serous BOT, but controversial in the setting of mucinous BOT, where they may represent overtreatment. Surgical staging is limited to bilateral salpingo-oophorectomy, peritoneal cytology/biopsies and an omentectomy. Neither a hysterectomy nor lymphadenectomy should be undertaken. Conservative management should consist of a cystectomy or unilateral salpingo-oophrectomy in the setting of serous BOT and unilateral salpingo-oophrectomy in the case of mucinous BOT. Bilateral disease should be treated by bilateral cystectomy whenever possible. At present, there are no data to support the use of adjuvant treatment in any setting of BOT.


Introduction

Few tumors have invited contention and controversy so disproportionate to their incidence as borderline ovarian tumors (BOT), deriving from their enigmatic behavior, uncertain pathogenesis, and controversial management [1]. Indeed, few tumors have been marked by over-treatment as much as BOT have. Fortunately for BOT patients, but unfortunately to studies, BOT has an excellent prognosis, so that prospective studies with a significant number of events are unlikely to be established. By looking into other thoroughly studied cancers, it is tempting to expect BOT to be composed by different, unique orphan diseases and not one single entity called BOT.

BOT are a disease of younger, fertile women, with generally a benign course. Having an incidence of 1.8–4.8 out of 100 000 women per year, patients tend to be relatively youthful with a mean age of 38 years, but the highest frequency relative to invasive ovarian cancer of these tumors occurs in the 15 to 29 year-old age group [2]. Being mainly a disease of the young fertile patient, preserving fertility is often a concern. Recent reports have stirred the debate regarding the optimal conservative treatment for women with BOT [3-7]. While the corrected survival for patients with disease confined to the ovary is 100% at 15 years [8], over 30% of patients with ovarian serous BOT with invasive implants will develop persistent or recurrent tumor, most commonly low grade serous carcinoma [9]. For the group of patients with invasive implants, there is no consensus regarding standard therapy. Some oncologists would agree to warrant adjuvant treatment to these patients, based on their worse prognosis and tendency to recur not only as BOT but also as a low-grade ovarian neoplasm. However, the response of such tumors to systemic chemotherapy is generally suboptimal.

Surgical staging

Little is known about the prognostic impact of staging procedures in BOT, with conflicting data to this day. On the one hand, some studies show no major differences in
recurrence and survival rates between the unstaged and staged patients: in the largest retrospective series on recurrences after the conservative management of stage I serous BOT, including 119 patients, the risk of relapse was not related to the use of complete staging surgery [4]. Another large retrospective multicenter study including 539 patients from 14 institutions, concluded that comprehensive surgical staging, lymph node sampling or dissection and appendectomy were not beneficial in BOT [10]. A third retrospective multicenter study, enclosing 360 patients and evaluating the role of re-staging surgery, the rate of upstaging was 14.8% for serous tumors and the rate of upstaging was very low for patients with mucinous tumors. The study showed no difference in recurrence rates between the unstaged and staged patients, suggesting that most women derive little benefit from restaging surgery [11]. A further series of 27 patients reached the same conclusion: that the low yield of upstaging in patients with mucinous tumors (0%) does not warrant a second operation, while the higher yield of upstaging in patients with serous tumors (30.8%) suggests that the likelihood of upstaging the disease exceeds the potential morbidity, and the procedure may be warranted [12]. An additional retrospective study assessed the patient's clinical outcome following complete or incomplete surgical staging in cases treated for apparent stage I BOT. Although the absence of complete peritoneal staging in patients with an apparent "stage I" BOT increased the recurrence rate, the surgical restaging (in cases of incomplete initial surgery) did not modify the survival of patients with apparent "stage I" BOT [13]. Another large retrospective series including 247 BOT cases further showed no significant difference in recurrence and mortality between staged versus unstaged procedures[14]. Finally, a large meta-analysis of 42 studies including 4414 patients with serous BOT and 12 studies including 894 mucinous BOT pooled an incidence of 34.4% non-invasive implants and 7.3% of invasive implants in the case of serous BOT, while only 6 patients with mucinous BOT presented in non-invasive implants and none with invasive implants. The authors suggested (re-)staging procedures in mucinous BOT represent an overtreatment of these patients (Vasconcelos et al. Serous and mucinous borderline ovarian tumors: differences in clinical presentation, high-risk features and lethal recurrence rates, in press).

On the other hand there are some robust studies reporting staging quality as a prognostic factor: a recent retrospective study, including 950 patients confirmed by central pathology examination, reported that for patients with one missing staging procedure, the hazard ratio (HR) for recurrence was 1.25 (95%-CI 0.66–2.39; P=0.497). This risk increased with each additional procedure skipped, and concluded that the most crucial procedure was omentectomy, which retained a statistically significant impact on progression free survival analysis (HR 1.91; 95%-CI 1.15–3.19; P=0.013), adjusting for previously established prognostic factors as FIGO stage, tumour residuals, and fertility preservation [15]. A second retrospective study including 142 patients concluded that relapse incidence was significantly higher in non restaged, than in restaged patients (p=0.008) and that disease free survival was significantly longer among restaged than non-restaged patients, (p=0.072) [16]. Finally, retrospective single center study including 46 BOT patients with more than 10 years follow-up, reported an association between incomplete staging surgery and shorter time to BOT relapse [17].

In the setting of BOT, the tumor should be resected and the histologic diagnosis confirmed. Consultation with a gynecologic oncologist experienced in ovarian cancer surgery is crucial [18, 19]. Bilateral salpingo-oophorectomy is recommended for women beyond the fertile years or with advanced disease, but a hysterectomy is not required because the rate of uterine involvement in BOT is low and that hysterectomy does not favorably affect survival [20, 21]. The staging procedure includes an omentectomy, cytological washings and peritoneal biopsies, with an appendectomy being controversially indicated in the case of mucinous BOT (to exclude the extremely rare event of a GI metastatic tumor to the ovary with a macroscopically unremarkable appendix). Lymphadenectomy is not performed in BOT because a 98% survival at 6.5 years is found in women with lymph node involvement [22]. Endometrioid BOT represent an infrequent subset of tumors that can be associated with synchronous endometrioid adenocarcinoma of the uterine corpus. Although most tumors are stage I, and therefore surgical staging is not necessary in most of the cases, uterine curettage is required in cases of uterine preservation [21].

Although staging surgery in the setting of BOT probably does not correlate with survival advantage, the advantages of staging are to provide better information for prognostic counseling, to discover areas of occult invasion, and to obtain information about the biological behavior of these tumors. The presence of invasive implants is the single most important factor for lethal recurrence in serous BOT. For these reasons, most oncologists recommend a comprehensive staging procedure for most BOT patients. Because of a higher incidence of extra-ovarian disease, probably all patients presenting with serous BOT should be thoroughly staged (excluding systematic lymphadenectomy) and appropriately counseled. Regarding mucinous BOT the presence of peritoneal disease is extremely rare, and virtually non-existent in the form of invasive implants. The low incidence of peritoneal disease in mucinous BOT calls the
were mostly salvaged by surgery. The study therefore undergoing a simple cystectomy had more recurrences, they remained statistically significant. Although patients bilaterality). However in the multivariate analysis, only age difference in recurrence rate (albeit patients that underwent this topic and it includes a modest 32 patients with bilateral mechanical infertility in up to 14% of the cases.

There is only one randomized controlled trial approaching this topic and it includes a modest 32 patients with bilateral BOT followed for 132 months. It showed no cumulative difference in recurrence rate (albeit patients that underwent bilateral cystectomy showed a shorter disease free survival and higher rate of radical treatment for recurrence). This led a recent to the recommendation that bilateral BOT should be treated with bilateral cystectomy in women wishing to retain fertility. A retrospective study including 119 stage I BOT identified three prognostic factors for recurrence in univariate analysis (young age, type of conservative treatment (adnexectomy versus cystectomy) and tumor bilaterality). However in the multivariate analysis, only age remained statistically significant. Although patients undergoing a simple cystectomy had more recurrences, they were mostly salvaged by surgery. The study therefore advocates the use of a simple cystectomy in the treatment of unilateral serous BOT. A systematic review analyzing 39 studies that included 5105 patients, comparing the different fertility sparing approaches reported a pooled recurrence rate for patients undergoing cystectomy, bilateral cystectomy, unilateral salpingo-oophorectomy and unilateral salpingo-oophorectomy + contralateral cystectomy respectively of 25.3%, 25.6%, 12.5% and 26.1%. The odds ratio of recurrence reduction with 95% CI for cystectomy compared to unilateral salpingo-oophorectomy was 2.714, p=0.0001. The authors concluded that cystectomy in unilateral serous BOT is significantly associated with a higher recurrence rate, albeit no impact on survival can be demonstrated. Whether this is related to the duration of follow-up, remains to be proven. On the contrary, a more conservative approach (bilateral cystectomy) should be definitively favored in bilateral BOT, which is almost always

serous, because no significant difference is seen in terms of recurrence rate when compared to unilateral salpingo-oophorectomy and contralateral cystectomy.

Fertility sparing surgery

BOT is mainly a disease of the young fertile patient; therefore preserving fertility is often a concern. There is a lack of randomized controlled trials evaluating the outcome of fertility sparing surgery in BOT and consequently there is a lack of standardized treatment guidelines. Robust studies have strongly tended to a lesser aggressive surgical approach, advocating a simple cystectomy in the case of early stage serous BOT and unilateral salpingo-oophorectomy in the case of mucinous BOT. Contralateral ovarian biopsies are contraindicated because clinically occult bilateral ovarian involvement has been noted in only 2.5% of women undergoing staging for ovarian malignancy and ovarian surgery may impair future fertility, culminating in mechanical infertility in up to 14% of the cases.

Patients with established risk factors for recurrence such as residual disease after up-front surgery and the presence of invasive implants, should be particularly advised to undergo more aggressive surgical procedures, while patients with micropapillary pattern and stromal micro-invasion in serous BOT and intra-epithelial carcinoma in mucinous BOT should be made alert to these apparent, albeit indefinite, risk factors and counseled accordingly. Patients with bilateral disease

Mucinous BOT is believed to be less harmful than, and behave differently from, serous BOT. While classically virtually all mucinous BOT are mostly stage I with an excellent prognosis with 98% survival at 10 years, treated solely by unilateral salpingo-oophorectomy, two recent studies showed that these tumors tend to recur as invasive ovarian cancer in the presence of tumor stage ≥IC, IECA (intraepithelial carcinoma) ≥10% and microinvasion. The exclusion of IECA seems to be of prognostic relevance therefore it is important to optimally sample for pathological evaluation, for which an USO should be also advised. This was also concluded in a recent systematic review evaluating risk factors for disease recurrence. On the contrary, a recent large meta-analysis including 894 patients with mucinous BOT, including 311 patients with IECA, reported no difference in the lethal recurrence rate between early stage typical mucinous BOT and BOT with IECA (respectively: 3.6% and 3.7%). In this study both stromal microinvasion and IECA were not associated with a higher lethal recurrence rate in mucinous BOT. IECA appeared with a relatively high incidence, but no impact on lethal recurrence rates could be demonstrated (Vasconcelos et al. Serous and mucinous borderline ovarian tumors: differences in clinical presentation, high-risk features and lethal recurrence rates, in press).

Regarding fertility outcomes, although it seems logical to speculate that women undergoing cystectomy would have higher pregnancy rates than women undergoing unilateral salpingo-oophorectomy due to the higher loss of ovarian reserve in the latter, the data of the present published studies are inconclusive. The previously mentioned review reported a cumulative pregnancy rate for women with BOT of 55.7%. The cumulative pregnancy rate for women undergoing unilateral salpingo-oophorectomy and cystectomy was similar (45.4% and 40.3% respectively). The patients should be counseled about these facts, as well as about the fact that undergoing an USO doesn’t seem to compromise fertility outcomes, while achieving significantly lower recurrence rates.

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should be preferably treated with bilateral cystectomy, while the concept of maximal cytoreduction that implies a unilateral salpingo-oophorectomy and contralateral cystectomy should be abandoned. In the setting of unilateral serous BOT a simple cystectomy is significantly associated with a higher recurrence rate, albeit no impact on survival can be demonstrated. Therefore this procedure has been advocated by many gynecologic oncology centers. In the case of mucinous BOT data are more controversial, due to the uncertain significance of IECA, so that currently a unilateral salpingo-oophorectomy is indicated. The patients should be counseled about these facts, as well as about the fact that undergoing a unilateral salpingo-oophorectomy doesn’t seem to compromise fertility outcomes, while achieving significantly lower recurrence rates.

**Adjuvant treatment with cytotoxic agents**

While the corrected survival for patients with BOT confined to the ovary is 100% at 15 years, over 30% of patients with ovarian serous BOT with invasive implants will develop persistent or recurrent tumor, most commonly low-grade serous carcinoma. For the group of patients with invasive implants, there is no consensus regarding standard therapy. Some oncologists would agree to warrant adjuvant treatment to these patients, based on their worse prognosis and tendency to recur not only as BOT but also as a low-grade ovarian neoplasm. In the present, chemotherapy is mostly offered to patients with invasive implants, regardless of histological subtype.

A meta-analysis including 27 articles and 3124 patients, 181 with invasive implants, reported a pooled recurrence estimate for patients with BOT with invasive implants undergoing adjuvant treatment was 44.0% and for patients undergoing upfront surgical treatment was 21.3%. Considering only the studies including serous BOT with invasive implants, the pooled recurrence estimate for patients undergoing adjuvant treatment 44.3% and for those undergoing surgical treatment 23.1%. In both cases the recurrence reduction was not statistically significant (p=0.114 and p=0.181). Adjuvant chemotherapy is often reserved for patients with invasive implants or bulky unresectable residual tumors, therefore a bias in the selection of patients with higher risk of relapse could explain the worse outcome observed in these studies for those patients receiving chemotherapy. Nonetheless, according to this data, there is no benefit in adding adjuvant treatment to upfront surgery in patients with BOT with invasive implants presenting with primary disease. Another meta-analysis including 31 studies and 4965 BOT patients, 244 of which with invasive implants, favored surgical treatment only (OR=7.44; 95%CI=3.39–16.32; p<0.0005) albeit with moderate heterogeneity of the studies (I^2=35.0%). Likewise, the cumulative complete response rate reported in that analysis was low, at 48.1%.

Regarding the largest published cohorts on the topic, Bell included 31 patients with invasive implants, followed for a median of 53 months, 48.4% of whom received platinum-based treatment. Of those, 26.7% died, while none of the patients who did not receive chemotherapy died. In a seminal work by Gershenson including 39 patients with BOT with invasive implants followed by 111 months (making it the largest published series including solely BOT patients with invasive implants), 79.4% were treated with platinum-based chemotherapy. The results indicated no difference between those who received platinum-based chemotherapy and those who did not. In fact, patients who received post-operative platinum-based chemotherapy had a significantly worse progression-free survival than all other patients. Moreover, over 30% of the patients developed persistent or recurrent tumor, most commonly serous carcinoma. The recent work by Leary included 36 patients serous BOT with invasive implants treated with surgery and platinum-based adjuvant treatment, of which 13 (36.1%) of which relapsed at a median of 27.3 months, 8 (22%) with invasive disease. Their cohort compares favorably with the rate of relapse in the form of carcinoma (20–30%) described in the literature for BOTs with invasive implants, and the authors conclude that chemotherapy played a favorable role. As the findings of this study are inferential due to the methodology used, the robustness of the conclusions maybe overstated, requiring caution in interpretation. In the afore-mentioned meta-analysis, the pooled recurrence estimate for patients undergoing surgical treatment only was lower than that reported by Leary, at 23.1%.

At present, there is no evidence to support the use of adjuvant treatment in patients with invasive implants in the primary treatment setting, although the majority of BOT patients with invasive implants will be offered this treatment, particularly since BOT with invasive implants has been classified as low-grade serous carcinoma by FIGO. The use of first-line chemotherapy on patients presenting with primary BOT with invasive implants should be individually discussed with the patient, with the patient being informed about the lack of evidence to support this treatment form. Nonetheless, approximately 0.8% of BOT patients will suffer a high-grade invasive relapse. In this setting it is very likely that patients will profit from adjuvant treatment.

**Summary**

Recommendations are summarized in Table 1.
Surgical staging probably offers no survival benefit to BOT patients, but offers the possibility to detect high-risk features and extra-ovarian disease that help in counseling these patients. Due to virtually non-existent extra-ovarian disease in patients with mucinous BOT re-staging procedures in these patients should be avoided, as they represent an overtreatment of these patients. Surgical staging includes bilateral salpingo-oophorectomy with an omentectomy, peritoneal biopsies and peritoneal cytology. Lymph node dissection and hysterectomy are not part of the current staging procedure.

Patients wishing to preserve fertility should preferably be offered a unilateral salpingo-oophorectomy, although a simple cystectomy may be discussed with serous BOT patients. Patients with bilateral disease, which are almost always of serous histology, should be offered bilateral cystectomies.

Regarding adjuvant treatment, there is absolutely no indication to preform chemotherapy in the setting of primary BOT, even in the presence of invasive implants. Due to the re-classification of these patients as low-grade ovarian carcinomas, these patients will be advised to undergo adjuvant chemotherapy, although response rates will surely remain sub-optimal.

References


