Management of borderline ovarian tumors

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Background: Borderline ovarian tumors (BOT) are epithelial tumors of the ovaries with both malignant and non-malignant aspects. On the one hand, they are characterized by cellular proliferation and nuclear atypia but, on the other hand, they usually do not show infiltrative growth pattern. Balancing radicality between oncologic safety and treatment burden has already led to remarkable changes in the management pattern over the last decades and is still a challenging task.

Design: This review is based on both a systematic review published by the authors and added with evidence gained from actually published literature.

Results: As they frequently affect younger patients, the clinical management of BOT is complicated by aspects as preserving fertility and reducing postoperative morbidity. Over the past decades, the surgical therapy shifted from a radical approach to more conservative treatment. Today, fertility-sparing surgery is first-choice treatment in younger patients. In addition, minimal-invasive surgery has become the preferred surgical approach in these patients. Even recurrences are curable in most patients because only a minority of relapses transform to invasive cancer.

Conclusion: More studies on BOT are needed and longer follow-up and better characterization of high-risk subtypes are crucial to better understand long-term risk of BOT and avoid the rare but the fatal outcome in those few patients being undertreated by the current management strategies.

Key words: borderline tumour, fertility sparing surgery, malignant transformation

Since the 1970s, the World Health Organization (WHO) and the International Federation of Gynecology and Obstetrics (FIGO) classify borderline ovarian tumors (BOT) as a stand-alone group of ovarian epithelial tumors [1, 2]. They are characterized by nuclear abnormalities, increased mitotic activity but in contrast to ovarian cancer, they do not exert infiltrative destructive growth or stromal invasion [3]. BOT represent 10% to 20% of all ovarian epithelial tumors [4] and epidemiologic data indicate that one-third of patients with BOT are younger than 40 years [5, 6]. Therefore, preservation of the childbearing potential plays a very important role and is a central issue of counseling patients with BOT. Fortunately, BOT present more frequently as a disease limited to the ovaries compared with invasive carcinoma, as was recently shown by Du Bois et al. [7] who reported in a systematic review of 6362 cases that 78.9% of the patients with BOT are diagnosed at FIGO stage I. Disease spread within the pelvis or beyond (FIGO stages II–III) is rarely seen at the time of diagnosis, disease beyond the abdomen (FIGO stage IV) is an exception [3]. As is the case for epithelial ovarian cancer, every surface epithelial cell type (serous, mucinous, endometrioid, clear cell, transitional cell and mixed epithelial cell) has been reported to be the origin for BOT [8]. However, serous (S-BOT, 53.3%) and mucinous (M-BOT, 42.5%) BOT are by far the most common [7].

As a consequence of the epidemiologic data with many patients still in the reproductive age, there is considerable interest in conservative management with preservation of the childbearing ability. For this reason, gynecologists require objective and reliable prognostic parameters for a thorough consultation. To establish informed consent, patients not opting for radical surgery need to be able to understand their risk for relapse. However, most of the relapses are BOT again and thus a second chance for cure exists—in contrast to invasive ovarian carcinoma.

Similar to epithelial ovarian cancer, the FIGO stage at the time of diagnosis is one of the strongest prognostic factors [4, 9, 10]. While only 5% of patients initially diagnosed in FIGO stage I are confronted with relapse of the disease, patients with extended disease are faced with recurrence in up to 25% of cases [4, 7, 10].

A histopathological feature that is possibly linked to a worse prognosis is the presence of microinvasion [10–12]. However, this has not been confirmed in large meta-analyses [13, 14] and therefore needs further investigation. For peritoneal implants, especially invasive implants, prognostic significance has been reported in several studies [4, 12–18]. It has been postulated that the presence of invasive implants represents the most important risk factor besides the initial FIGO stage [13]. Therefore, these patients have to be followed very closely. Invasive implants share many features with cancer and they may already mark the transformation to invasive carcinoma. Consequently, they are recognized as low-grade ovarian cancer in the latest WHO classification of tumors of the reproductive tract [19].

A comprehensive surgical treatment of BOT includes both the complete removal of all macroscopic tumor lesions within the abdomen and a complete staging [20]. Surgical procedures that are used for epithelial ovarian cancer are usually also applied to BOT. However, this might cause
over-treatment in some patients. According to the FIGO requirements, staging includes hysterectomy, bilateral salpingo-oophorectomy, omentectomy, peritoneal washing with cytology, resection of peritoneal lesions, systematic peritoneal biopsies in all areas of the abdomen as well as pelvic and paraaortic lymphadenectomy [21, 22]. The requirement of systematic lymph node dissection has been a controversy in the past years. Despite lymph node involvement in 21% to 29% of cases, occasionally leading to an upgrade in FIGO stage [23–26], recurrence and survival rates for patients with affected or not affected lymph nodes remain similar [13, 26, 27]. Different investigators concluded from these results that systematic lymphadenectomy can be omitted as part of the initial treatment of BOT [7, 9, 28, 29].

Appendectomy should be carried out in M-BOT to exclude the possibility of ovarian metastasis of mucinous tumors of the appendix [28, 30].

As mentioned earlier, fertility-preserving surgery in BOT is a very important topic in consideration of the significantly younger age of these patients compared with those suffering from epithelial ovarian cancer. Therefore, preservation of the uterus and at least one ovary has to be discussed with the patients and should be regarded as an acceptable standard of care, despite the fact that available data suggest that in general the rate of recurrence is higher after conservative management (10% to 20% versus ~5% for radical surgery) [4, 18, 28, 31–33]. However, this higher recurrence rate did not result in a higher mortality rate in the so far largest series, the German ROBOT study [34].

Laparoscopy seems to be the most attractive surgical approach to BOT. The ROBOT study did not show any disadvantage for laparoscopy compared with laparotomy as initial or final surgical approach with respect to both relapse rate and overall survival [34]. In a retrospective French multicenter study of 358 patients, Fauvet et al. [35] confirmed that cyst rupture (33.9% versus 12.4%) and incomplete staging occurred significantly more frequent in the laparoscopy group. However, this had also no influence on the relapse rate. The potentially higher risk for relapse and the possible need for repeated surgery in this case, but commonly without survival difference, have to be discussed with the patient when balancing cosmesis and surgical burden.

To date, there is no proven benefit from any adjuvant therapy (chemotherapy or radiotherapy), even in advanced disease stages or when there is presence of invasive implants [18, 36]. In 1993, Trope et al. carried out a meta-analysis of four prospective studies conducted in Norway on BOT in FIGO stage I/II. This analysis revealed that survival rates were even higher in patients without adjuvant therapy (99%) than in patients who received adjuvant therapy (radio-/chemotherapy, 94%) [36]. In 2005, Longacre et al. [15] published a survey of 276 patients with BOT treated at Stanford University Hospital between 1958 and 1998. All patients had a follow-up of more than 5 years. Of 113 patients with advanced S-BOT, 52 received adjuvant therapy (34 chemotherapy, 8 radiotherapy, 10 both chemotherapy and radiation), while 61 patients did not receive any further treatment. Seventy-one percent of the patients in the adjuvant group were still alive after a median follow-up of 126.5 months. In contrast, 87% of the patients without adjuvant therapy survived after 93 months of median follow-up [15]. Therefore, current guidelines do not recommend adjuvant treatment of patients even with advanced BOT [28, 30].

For patients who received fertility-preserving surgery, the question will arise whether the remaining ovary and uterus should be resected once the family planning is completed. As discussed before, the risk for recurrence is significantly higher, although most recurrences remain BOT. For this reason, it appears acceptable to wait until recurrence develops [9, 28]. Nevertheless, for some patients, the psychological impact of waiting for relapse may be considerable, and removal of the remaining ovary might be an option because the majority of relapses occurs in the remaining ovary. In any case, the low (but not nil) risk for the development of invasive ovarian cancer should be discussed speaking against a general recommendation toward completion surgery.

Overall, recurrence rates are estimated between 3% and 10% [4, 9, 37, 38]. A systematic review [7] showed that 37% of recurrences are diagnosed during the first 2 years, 31% in year 2–5, and 32% of patients experience relapse later than 5 years after diagnosis, including 10% occurring after more than 10 years [7]. With such long intervals, the question then arises whether these tumors possibly developed ‘de novo’ instead of really being relapses [39, 40].

Malignant transformation describes the situation in which patients with BOT develop recurrent disease in the form of invasive ovarian cancer. Usually, these malignant tumors represent as low-grade carcinoma and this can even occur after several years [15]. Twenty percent of patients diagnosed with recurrence will have invasive ovarian cancer [7], so that several investigators tried to identify the molecular changes being responsible for this transformation [41–43]. It has been reported that the expression profile of BOT and low-grade carcinoma is quite similar. Both frequently present with K-ras, B-raf mutations and high expression levels of c-Fos in contrast to high-grade carcinoma [44–46]. They are slowly developing from benign lesions and are characterized by a relative chemoresistance [47].

In clinical surveys, the rates of recurrence and malignant transformation are seemingly biased and underestimated due to lack of long-term follow-up. This has to be considered when probability of relapse and death are discussed with the patients. Future studies will have to account for this large time frame.

disclosure

The authors do not have relevant affiliation or financial involvement with any organization for or entity with a financial interest. There is no financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript. This manuscript was based on and contains parts of prior own work: [34, 48, 49].

references


