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REVIEW ARTICLE

Borderline ovarian tumors: A contemporary review of clinicopathological characteristics, diagnostic methods and therapeutic options

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Summary

Borderline ovarian tumors (BOTs) differ from the epithelial ovarian malignancies with their excellent prognosis, curability with surgery, and being seen in relatively young ages. Thus, fertility sparing and conservative surgical approaches are currently recommended. Preoperative diagnosis of BOTs can be challenging because, clinical and ultrasonographic features might overlap with invasive carcinomas and sometimes with benign adnexal masses. Certain characteristics such as stage at diagnosis, age of the patient and histologic features are important while deciding the extensiveness and the type of surgery. Detailed evaluation of the entire abdominal cavity and sampling all suspected areas are imperative during operation. Frozen section is essential for the intraoperative diagnosis, despite the fact that the diagnostic value of frozen section is not as high as in invasive ovarian carcinomas. Routine appendectomy and/or contralateral ovarian biopsy in cases of isolated tumor with normal appearing appendix and/or contralateral ovary are not recommended. Conservative approach might improve the recurrence rate without worsening the overall survival. The exact role of laparoscopic surgery with its advantages and disadvantages in the treatment of BOTs needs to be confirmed with further studies.

Key words: *appendectomy, borderline ovarian tumors, conservative surgery, fertility-sparing surgery, recurrence, review*

Introduction

BOTs account for 5% of all epithelial ovarian tumors and 15% of all epithelial ovarian cancers [1]. In 1971, the International Federation of Gynaecology and Obstetrics (FIGO) described this group of ovarian tumors as 'low malignant potential' tumors [2], and since 1973 the World Health Organization (WHO) has called them BOTs [3].

The incidence of BOTs was reported to be increased from 2.6 to 5.5 per 100 000 women-years between 1978 and 2006, with an average annual percentage change of 2.6% [4]. The median age at diagnosis is 45 years with 34% of patients under the age of 40 being potential candidates for fertility-sparing surgery [5,6]. The relationship between BOTs and infertility drew attention in recent years. Infertility is frequently observed in patients with BOTs, with up to 35% of patients having a history of infertility before treatment [7]. The increased risk of BOTs is thought to be associated with infertility treatment [8].

There is no consensus on the diagnosis, staging, management and follow-up of BOTs. The aim of this review was to summarize the recent literature on BOTs and clarify the most controversial points of this disease like diagnostic methods, treatment options including

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fertility-sparing surgery and follow-up.

Histology

BOTs have been identified in all epithelial subtypes, including serous, mucinous, endometrioid, clear cell, Brenner (transitional cell) and mixed epithelial tumors. The majority of BOTs are serous (53.3%), followed by mucinous (42.5%) tumors and less common histotypes (4.2%) [9].

BOTs are histologically characterized by the presence of epithelial cells with nuclear atypia and mitotic activity in ≥10% of the tumor cells, and microscopic papillary projections [10], indicating the linkage of this disease to type I ovarian tumors (low-grade ovarian carcinomas) [9]. Ovarian stromal invasion is not common. BOTs with microinvasion are those with invasion of the stroma (foci <3mm in the longest dimension and ≤10 mm^2 in surface [6]. Although uncommon, metastatic noninvasive or invasive implants may occur in patients with BOTs. Microscopic characterstics of stromal invasion in implants could reduce 10-year survival from 95 to 60% [11]. In contrast to the serous BOTs, the mucinous subtype is less frequently associated with peritoneal implants.

Investigation of the genetic base of the ovarian primary BOTs and peritoneal implants revealed genetic heterogenity of serous BOTs and implants, as none of the markers examined showed constant reciprocity [12].

Clinical presentation

Almost 30% of patients with BOTs are asymptomatic. Approximately 50-60% of the patients present with complaints of abdominal distention and/or pelvic pain along with normal or slightly increased CA-125 levels. The positivity of CA-125 is likely in serous subtypes and positivity of CA 19-9 and CEA is likely in mucinous histology [13]. High preoperative values of CA-125 are related with advanced stage [14]. Fluid in the pelvic cavity is not common. Most BOTs are detected by pelvic ultrasound. BOTs are bilateral in 25–50% of patients with serous and in 5–10% of patients with mucinous subtypes [15].

Women who had given birth more than once and breastfeeding had a decreased risk of developing BOTs, while use of oral contraceptive agents were not a protective factor against the development of BOTs [16]. Key points in clinical presentation, diagnosis and management of BOT are summarized in Table 1.

Table 1. Key points in clinical presentation, diagnosis, and management of borderline ovarian tumors

Clinical presentation	30% of patients are asymptomatic.
	Most common presenting symptoms are abdominal distention and/or pelvic pain.
	High preoperative CA125 may indicate the possibility of advanced stage.
	Bilaterality is most common in serous subtypes.
Diagnosis	Presence of a cyst with internal papillae and septae or multiple septations on pelvic ultrasonography.
	Different ultrasonographic features for serous and mucinous subtypes exist.
	Frozen section is essential with a detection rate of 45 to 87%.
Therapeutic options	Aim of surgery: Removal of the macroscopically visible tumor tissue and staging.
	Radical surgery is recommended in patients who completed their reproductive wishes.
	Appendectomy is not routinely required.
	Conservative surgery is recommended in patients <40 year-old and with FIGO Stage 1a.
	Serous BOT: Uni- or bilateral cystectomy is recommended with close follow up.
	Mucinous BOT: Unilateral salpingo oophorectomy is recommended.
Follow up	Regular physical examination, pelvic ultrasonography, and serum tumor markers (especially CA125).
	Should be continued for 15 years.
Recurrence	Recurrence affects the prognosis if it is invasive.
	Optimal cytoreductive surgery is recommended in recurrence.

BOT: borderline ovarian tumor

Preoperative diagnosis

Preoperative diagnosis of BOTs can be challenging because clinical and ultrasonographic features might overlap with invasive carcinomas and sometimes with benign adnexal masses. Although the final diagnosis is based on histological examination [17], imaging techniques (mostly ultrasonography) are commonly used for preoperative diagnosis. Ultrasound can provide not only a detailed view of the pelvis but it can also detect the peritoneal implants on transvaginal and transabdominal scans with high accuracy (91-95%) and provide information for preoperative planning and staging [9]. The most characteristic finding on pelvic ultrasound is the presence of a cyst with internal papillae and septae, observed in 49-63% of the cases; around 18% of the cases show multiple septations. Internal solid parts or papillary pattern is seen in 78% of serous vs 40% of mucinous BOTs cases [15].

The various histological types of BOTs have different gross appearances together with different ultrasonographic features. Serous and endocervical-like mucinous BOTs display very similar ultrasonographic features and tend to have a smaller diameter, fewer locules, higher numbers of papillary projections, and higher color scores inside solid components than mucinous BOTs of intestinal type. Mucinous intestinal-type BOTs have different ultrasonographic features from other common borderline tumors. They are typically unilateral (>95%), large (20-22 cm), multilocular tumors with >10 locules, a smooth inner lining and outer surface and echogenic cyst fluid. ''Honeycomb nodule," defined as a multilocular nodule arising from the inner cyst wall, is present in nearly half of mucinous intestinal-type borderline tumors [18,19].

Magnetic resonance imaging (MRI) appearance of BOTs does not seem to allow an accurate preoperative diagnosis. A recent systematic review showed that MRI has sensitivity of 92% and specificity of 85% for the detection of borderline or invasive ovarian cancer [15].

Computerized tomography is used for detecting the intraabdominal presence of disease.

Intraoperative histological diagnosis of BOTs should be obtained by frozen section, even if it is known that frozen section has a potential sampling error. The reliability of frozen section is lower in BOTs compared to invasive tumors with a detection rate of 45 to 87% [15,20].

Therapeutic approaches

Surgery is the best treatment option for BOTs and the principle is the same as for invasive tumors; removal of the tumor tissue that is macroscopically visible. A careful inspection of the entire abdominal and pelvic cavity during operation is essential for surgical staging.

A-Radical surgery

In women who have completed their reproductive wishes, the standard radical surgery including exploration of the abdominal cavity, total hysterectomy with bilateral salpingooophorectomy, inframesocolic omentectomy, resection of macroscopically suspicious lesions, and peritoneal washing should performed. Pelvic and paraaortic lymphadenectomy is not considered necessary, because nodal involvement by borderline lesions did not significantly affect survival although it was associated with a higher rate of recurrence [15,20,21].

Gross appearance of appendix is crucial during abdominal inspection, particularly in cases with mucinous subtype. Appendectomy should be performed in cases with abnormal appearence. Routine appendectomy in cases of isolated tumor with normal appearing appendix is not recommended [21].

B-Conservative surgery

Since a significant number of patients with BOTs have reproductive wishes, fertility sparing surgery (preservation of the uterus and ovarian tissue in one or both adnexae) can be a viable treatment option in patients with non-invasive implants if the implants can be resected completely. Patients with FIGO stage 1 and age less than 40 years are good candidates for this type of surgery [22].

There are two types of conservative surgery; first, unilateral salpingo-oophorectomy (USO) and second, unilateral ovarian cystectomy with or without contralateral ovarian cystectomy (ultra-conservative surgery). The rate of relapse is higher after conservative treatment than after conventional radical surgery (0-25% vs 0-5%, respectively). And this rate increases with the type of conservative surgery with a higher rate of 10-42% in patients undergoing cystectomy compared with USO [23]. For serous tumors, several parameters could be used to decide for conservative surgery including age of the pa-

tient, persistence of normal ovarian tissue on ultrasonography or MRI, as well as the antral follicle count. Anti-Mullerian hormone (AMH) serum level determination has less relevance as it reflects the ovarian function of two ovaries and is thus only of use in cases of bilateral BOTs. For mucinous tumors, conservative treatment by cystectomy is not recommended due to the frequent association of BOT with frankly invasive lesions even though these lesions are often unilateral [23].

Macroscopic inspection and biopsy of the contralateral ovary in the presence of a macroscopically suspicious lesion is feasible in conservative surgery. The detection rate of a small focus of borderline disease in a macroscopically normal-appearing ovary with biopsy is very low and, in addition, post-operative ovarian adhesions were reported to be approximately 14% [15,24]. Bilateral salpingo-oophorectomy should only be performed in patients with bilateral massive BOT for which preservation of any part of an ovary is not feasible. The uterus could be preserved for oocyte donation or transfer of frozen embryos obtained before the bilateral salpingo-oophorectomy [23,25].

A complete resection of implants appears to be crucial in serous BOTs. Considering the aggressiveness and the poorer prognosis of BOTs with invasive peritoneal implants, conservative treatment should be used with caution in this setting [26]. In a recent review [27], the risk of progression to invasive carcinoma in BOTs and in the particular case of initial conservative management was reported to be 2-3%. Stage of disease is the most important factor which affect the risk of invasive recurrence in serous type BOTs. Mucinous tumors are more likely to recur as invasive carcinoma [27].

Yinon et al. [28] compared the clinical outcomes of 62 patients performing cystecomy vs USO as fertility sparing treatment. There was no statistically significant difference in mean tumor recurrence rates between patients who had undergone cystectomy only and those who had undergone USO (22.7% and 27.5%, respectively). In the cystectomy-treated group, the disease-free interval was shortened but, the difference was not significant. The authors concluded that conservative surgery is an acceptable option for women with BOTs who wish to preserve fertility. Palomba et al. [29] randomized 32 patients with a diagnosis of BOT as bilateral cystectomy vs USO on the greater lesion and contralateral cystectomy. The cumulative pregnancy rate and probability of a first pregnancy were reported as higher in patients treated with bilateral cystectomy compared to USO and contralateral cystectomy. However, for patients undergoing bilateral cystectomy it was reported to have a shorter time to first recurrence and a higher rate of radical treatment of the recurrence, although no impact on survival could be demonstrated [30]. Such major results suggest that unilateral or bilateral cystectomy is probably a good therapeutic option to improve fertility in serous BOTs with a close follow-up while USO is advisable in mucinous BOTs [31].

Advanced-stage BOTs with non-invasive implants can be safely treated with conservative surgery. For patients with invasive implants fertility-sparing surgery might be considered with an individualized approach [15].

Laparoscopy for BOTs

The role of laparoscopic surgery for BOTs is currently unclear. Advantages of laparoscopy are less adhesions and less morbidity. Disadvantages are port site metastasis and increased risk of rupture of the cyst capsule [22,32].

BOTs and reproductive outcomes

Patients with BOTs frequently (10-35%) present with a history of infertility, especially when BOT is serous, bilateral or with micropapillary pattern [33,34]. Moreover, surgery for BOT is also a cause of infertility due to adherences and the alteration of ovarian function and oocyte reserve.

The rate of spontaneous pregnancy in cases with BOTs treated with conservative surgery varies between 32 and 65% . Fertility rates are better if cystectomy was performed, the age of the patient was <40 years and the histologic type of BOT was non-serous (mainly mucinous) type [15,23].

Ovarian stimulation for in vitro fertilization has been reported to be possibly related with an increased risk of ovarian malignancies, especially BOT [7], although this relationship between hormonal agents and BOT cells was not confirmed in cell culture [35]. Additionally, usage of infertility drugs after fertility-sparing surgery of early-stage BOTs was reported to be safe in infertile patients in recent studies [36,37].

It was suggested to wait for least one or two

years after fertility-sparing surgery for BOTs before initializing treatment for infertility for two reasons: first, due to the possibility of achieving a spontaneous pregnancy and secondly because the risk of recurrence is higher during the first two years after the operation [15,38]. Pregnancy rate was reported as 40% in a series of 25 patients who were administered ovulation induction after being treated with conservative surgery for BOT [37].

Conservative management of early-stages BOTs results in a pooled estimate for spontaneous pregnancy rate of 54% with a low risk of lethal recurrence (pooled estimate: 0.5%). In patients with advanced-stage BOT, the spontaneous pregnancy rate is lower (34% in the single series reporting pregnancy rate in this context) and the risk of lethal recurrence increased (pooled estimate: 2%). Alternative treatment options need to be considered to preserve fertility in patients with advanged stage BOTs with invasive peritoneal implants [15].

Restaging surgery

If a simple cystectomy had been performed for a presumed benign cyst and the finding of an incidental discovery of a BOT, no further surgical procedure is generally needed if complete exploration of the abdominal cavity had been performed, no spillage occurred during surgery and the borderline lesion was on the inner side of the cyst without vegetation on the outer side of the cyst. Close follow-up should be enough to detect recurrent disease [15]. Second look surgery and lymph node dissection is essential in micropapillary serous BOTs [22].

Prognosis

The prognosis of BOTs is generally excellent. However, 11% of these tumors recur and 20-30% of the recurrences show malignant transformation [39].

Five and 10-year survival rates for early-stage BOT (stage I) are 99 and 97%, respectively and conservative treatment is thus an option in this setting. However, survival rates are less favorable for advanced stages of BOT, especially for BOT with invasive peritoneal implants [23,40].

Follow-up

The follow-up should include physical examination, ultrasonography and evaluation of tumor markers (especially CA-125). Follow-up must continue every 3 months for the first 2 years, every 6 months during the subsequent 3 years and every year up to 15 years after initial diagnosis [16].

Adjuvant chemotherapy (cisplatin-based) is not needed in stage 1 BOTs and debatable in advanced-stage BOTs. Although >90% of BOTs are estrogen receptor-positive, the role of hormonotherapy in the treatment of BOTs is controversial [22].

It was reported that any contraceptive methods including hormonal contraceptives and hormone replacement therapy could be used safely in the patients with a diagnosis of BOT [41,42].

Management of recurrence

Several authors have reported that the site of recurrence was generally in the remaining ovary. Initial stage (higher in advanced stage than stage 1), presence of invasive implants and micropapillary pattern and the type of the surgery performed (higher in the fertility-sparing surgery group than in the radical surgery group) were significant prognostic factors for recurrence [15,21].

Morice et al. estimated a mean time interval to progression to carcinoma of 75 months for serous BOTs and 33 months for mucinous BOTs, with a progression rate to invasive cancer of 2–3%. In cases of serous BOTs with microinvasion, the risk of recurrence was reported as 15%, of which 35% were invasive disease, with a death rate from the disease of 6% [27].

Du Bois et al. performed a multicenter study on 1236 patients, representing the largest series of BOTs about the analysis of prognostic factors [43]. The overall rate of invasive relapses was 2.3% and occurred in 30% of all relapses. Higher FIGO stages appear to be associated with higher recurrence rates. They reported no prognostic impact of microinvasion or micropapillary growth pattern on prognosis.

The only situation where recurrent disease could affect the prognosis is when the nature of the recurrent disease is invasive. Fertility-sparing surgery should be approached with caution in patients with invasive peritoneal implants because of this poor prognosis. The risk of progression to invasive carcinoma in the particular case of initial conservative surgery is 23%. The risk of lethal recurrence in early stage is 0.5%, while in patients with advanced stage is increased to 2%. It has been recently reported that mucinous BOTs recur in the form of invasive carcinoma more often than

serous BOTs [15].

When an extra-ovarian borderline or invasive relapse occurs, cytoreductive surgery should be performed [15]. The optimal cytoreductive surgery is an independent prognostic factor, and will determine the overall survival. Crispens et al. reported a mortality rate in patients with optimal debulking of 12%, compared to 60% of those who were suboptimally debulked [44].

BOT and its relationship with papillary tubal hyperplasia

Kurman et al. have recently identified a lesion in the tubal lumen, called 'papillary tubal hyperplasia', which is frequently associated with atypical proliferative serous tumors. Radical fimbriectomy, consists of removing all the tube and the fimbrio-ovarian junction, aimed to protect high-risk women from high-grade serous pelvic carcinoma, while preserving their ovarian function [15]. Combination of a radical fimbriectomy especially for patients with advanced stage BOT and peritoneal implants could be a possible alternative to salpingooophorectomy [45]. It is not necessary to resect the cornual portion of the fallopian tube since no cancer has ever been described to occur in this area. But, it is necessary to remove the portion of ovary tethered to the fimbria as this portion corresponds to the site of implantation of malignant cells (serous tubal intraepithelial carcinoma) from fallopian tubes.

Conclusion

BOTs are tumors of reproductive age with excellent prognosis with appropriate managemet and regular follow-up. Fertility-sparing surgery in the form of salpingo-oophorectomy or cystectomy could be a reasonable therapeutic option, especially in patients with early-stage and with good prognostic factors disease. Long-term regular follow-up is essential. Radical surgery should be considered in patients with advanced-stage disease and/or unwilling for fertility. Laparoscopic approach is a relatively new technique which needs to be studied in larger numbers of patiens with BOTs

Conflict of interests

The authors declare no confict of interests.

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