

# Laparoscopic treatment of borderline ovarian tumours. A systematic review of the literature

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## ABSTRACT

**Background and purpose:** The laparoscopic management of borderline ovarian tumours (BOTs) is controversial. The aim of our study was to review the scientific literature on this approach.

**Methods:** The search strategies used included an online search of the MEDLINE database of relevant publications and reviews from 2003 to 2018 regarding laparoscopic treatment of BOTs. Additional reports were collected by systematically reviewing all the references from the retrieved papers.

**Results:** Recent articles have discussed the type of surgery (laparotomy or laparoscopy), the possibility of fertility-sparing surgery, and the need for restaging procedures and adjuvant therapy.

**Conclusions:** Over recent decades, the management of BOTs has shifted from radical surgery to more conservative therapy due to the need for fertility-sparing surgery and the increasing use of laparoscopy.

## KEYWORDS

Borderline ovarian tumour, borderline ovarian neoplasm, atypical proliferative tumour, surgery, laparoscopic treatment, laparoscopic management, minimal invasive surgery.

## Introduction

Borderline ovarian tumours (BOTs) are uncommon but not rare ovarian neoplasms. Their incidence is low, with around 4.8/100 000 new cases per year calculated in European series<sup>[1]</sup>; the incidence is even lower in American series: between 1.5 and 2.5/100 000 cases per year<sup>[2,3]</sup>.

BOTs occur in women at approximately 40 years of age (or at a younger age in 27–36% of cases), as opposed to an average age of 60 years in the case of invasive carcinoma<sup>[4]</sup>; BOTs are also defined as ovarian tumours with low malignant potential. These tumours account for 15% of all epithelial ovarian cancers and are not BRCA related. More than 80% of women with BOTs present with stage I disease. As indicated above BOTs, are neoplasms of epithelial origin, and constitute an intermediate category between benign and malignant forms<sup>[5]</sup>; they are characterised by upregulated cell proliferation and the presence of slight nuclear atypia, but without destructive stromal invasion<sup>[5]</sup>. The current 2014 World Health Organisation (WHO) Classification of Tumours of the Female Genital Organs uses the term “borderline tumour” interchangeably with “atypical proliferative tumour”<sup>[6]</sup>. The 5- and 10-year survival rates for early-stage BOT (stage I) are 99 and 97%, respectively, and thus, conservative treatment is an option. Nevertheless, survival rates are less favourable for advanced stages of BOT, especially in the presence of invasive implants, and alternative treatment options need to be explored to preserve fertility in these patients<sup>[7]</sup>.

Among BOTs, six histological subtypes can be classified. On the basis of the epithelial cell type, serous (50–55%), mu-

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cinous (35–45%), endometrioid (2–3%), clear cell (<1%), seromucinous (5–7%) and borderline Brenner tumour (3–5%) subtypes can be distinguished<sup>[8]</sup>. Mucinous BOTs are classified as intestinal (85%) or endocervical/Mullerian type (15%), depending on the nature of the epithelial lining. They can be associated with pseudomyxoma peritonei (10%), necessitating a thorough investigation of the gastrointestinal tract with special attention to the appendix, which can be the primary tumour origin. BOTs can show microinvasion, lymph node and peritoneal spread, critically influencing the disease prognosis<sup>[9,10]</sup>. Ovarian serous borderline tumours (SBTs) have been the subject of considerable controversy, especially with regard to terminology and behaviour.

It has been proposed that they constitute a heterogeneous group of tumours, mostly comprising typical SBTs that are benign and designated atypical proliferative serous tumours (APSTs) and a small subset of SBTs with a micropapillary architecture that have a poor outcome and are designated non-invasive low-grade serous carcinomas (niLGSCs). It has also been argued that the difference in behaviour between the two groups is not due to the primary tumour subtype, but rather to the presence of extra-ovarian disease, specifically invasive

implants <sup>[11]</sup>. Among patients with stage I disease, the risk of subsequent serous carcinoma was significantly higher in those with niLGSCs as opposed to APSTs. Nonetheless, all-cause mortality risk is not different between APSTs and niLGSCs, among either stage I or >I cases. In addition, although the presence of invasive implants is the single most adverse prognostic factor, sub-classification into APSTs and niLGSCs is important because it allows stratification of stage I cases in terms of risk of advanced stage disease and invasive implants and subsequent development of serous carcinoma. Finally, it is important to emphasise that, although invasive implants carry the highest risk of subsequent serous carcinoma and all-cause mortality, non-invasive implants are also associated with a statistically significantly increased risk - albeit not nearly as high as that recorded for invasive implants <sup>[12]</sup>.

This review aims to provide a comprehensive and systematic review on laparoscopic treatment of BOTs analysing reviews, observational, cohort and case-control studies on this surgical approach that offer great advantages both for patients and for the healthcare system <sup>[13,14]</sup>.

## Methods

We searched the PubMed and MEDLINE electronic databases to find relevant articles published in the period 2003 to 2018. The search strategy was based on the following terms: “borderline ovarian tumour”, “borderline ovarian neoplasm”, “atypical proliferative tumour”, “surgery”, “laparoscopic treatment”, “laparoscopic management” and “minimally invasive surgery”. This review covers both early and advanced stages of BOTs, as well as rare entities like endometrioid, Brenner and clear-cell BOTs. All case reports, original studies, meta-analyses and reviews published in English and French were considered. In the case of duplicate publications from the same team, the most recent study was included.

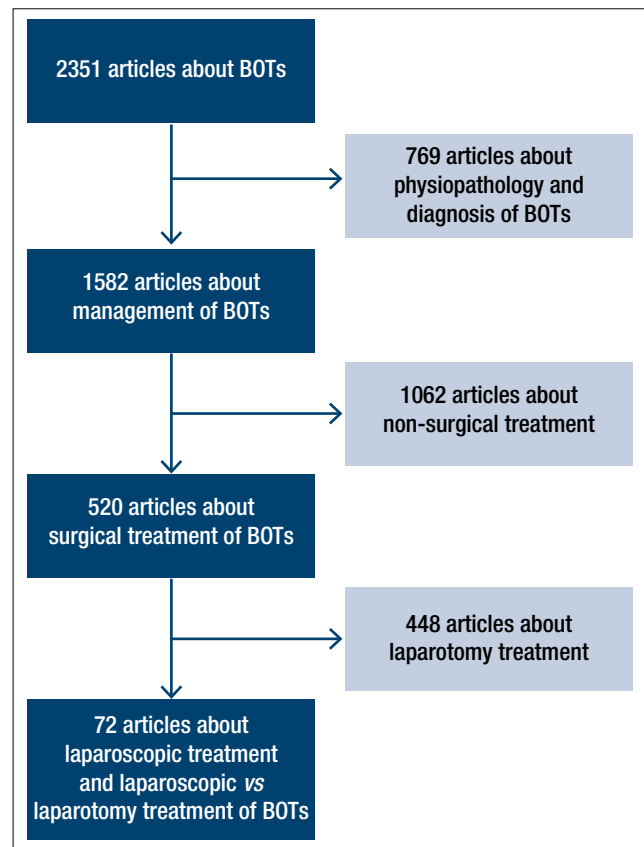
Relevant studies were evaluated by all the authors, and a consensus decision was made on their eligibility for inclusion in this review.

## Results

The electronic database literature identified 2351 articles about BOTs: 769 articles dealing with the physiopathology and diagnosis of BOTs and 1582 with BOT management. Of these, 1062 focused on non-surgical treatment and 520 on surgical treatment; of the latter, 448 articles dealt with laparotomy surgery, and just 72 with laparoscopic treatment of BOTs and laparoscopic versus laparotomy treatment; these 72 articles were included in this review (Figure 1).

Fertility is frequently an issue when discussing treatment options <sup>[15-18]</sup>. However, an equally important issue is whether we can reduce the morbidity caused by radical surgery and whether a more conservative approach is a safe alternative in terms of the cancer prognosis.

**Figure 1**



## Radical surgery

In postmenopausal women with BOTs, as well as in patients who have fulfilled their reproductive desire, radical surgery may be suggested. This generally involves bilateral salpingo-oophorectomy, total hysterectomy, inframesocolic omentectomy, peritoneal lavage to obtain samples for cytology, resection of macroscopically suspicious lesions and multiple peritoneal biopsies (including the omentum, intestinal serosa, mesentery, pelvic and abdominal peritoneum) <sup>[19]</sup>.

In the case of mucinous ovarian tumour identified on histological examination, especially in the context of pseudomyxoma peritonei, appendectomy should be performed to exclude a mucinous neoplasm of the appendix <sup>[19]</sup>. The role of retroperitoneal restaging remains unclear in the context of BOTs; it does not seem to be as crucial in these tumours as in their malignant counterparts, in which it may have both prognostic and therapeutic implications <sup>[20,21]</sup>. The results of a study conducted by Seidman and Kurman <sup>[9]</sup> suggested that systematic lymphadenectomy can be omitted from the initial treatment plan for BOTs; these researchers observed a survival rate of 98% among 43 women with nodal involvement, after a mean follow up of 6.5 years. Laparoscopy can be used successfully for performing a correct radical surgery in patients with BOTs. In two studies, the type of surgical approach (laparoscopic vs laparotomy) did not appear to influence the progression-free interval and the rate of recurrence <sup>[22,23]</sup>. Recent studies have also shown that laparoscopic surgical staging of ovarian cancer at an early stage is just as safe and adequate as laparotomy staging <sup>[24]</sup>.

## Conservative surgery

A conservative treatment may be proposed for women under the age of 40 years who have not completed childbearing<sup>[25]</sup>. In these cases, oophorectomy, unilateral salpingo-oophorectomy or cystectomy may be performed. Exploration of the cavity, omentectomy, peritoneal washing, resection of suspicious lesions, multiple peritoneal biopsies and adnexectomy are recommended, as for radical surgery, in the case of mucinous BOTs<sup>[26]</sup>. In a systematic review of the conservative management of BOTs, Darai *et al.*<sup>[7]</sup> showed that the rate of relapse after conservative treatment is 0–25%. This rate is higher than the rates reported for conventional radical surgery by bilateral salpingo-oophorectomy with or without hysterectomy, which vary between 0 and 5%. The rate of recurrence is correlated with the type of conservative treatment used (salpingo-oophorectomy or cystectomy), with a higher rate of 10–42% recorded in patients undergoing cystectomy. Moreover, in a randomised trial, Palomba *et al.*<sup>[27]</sup> reported a time to recurrence of 16 months in patients undergoing bilateral cystectomy versus 48 months in patients undergoing unilateral salpingo-oophorectomy and contralateral cystectomy. In this study, 32 patients with bilateral BOTs, treated laparoscopically, were randomised to bilateral cystectomy or unilateral salpingo-oophorectomy on the greater lesion and contralateral cystectomy. The cumulative pregnancy rate and cumulative probability of a first pregnancy were higher in patients treated with bilateral cystectomy. Nonetheless, patients undergoing bilateral cystectomy had a shorter time to first recurrence and a higher rate of radical treatment of the recurrence. These results suggest that bilateral cystectomy should be performed in the case of bilateral serous BOT if technically feasible in motivated patients to improve fertility but after informed consent on recurrences. Unilateral cystectomy is probably a better option for improving fertility in cases of unilateral tumour. According to du Bois *et al.*<sup>[28]</sup>, when conservative surgery was performed via laparotomy, the recurrence rate was about 7.7%, while it was as high as 14.9% after laparoscopy. However, in a multicentre study, there were no significant differences in recurrence rates after laparoscopy versus open surgery<sup>[23]</sup>. In their series of 687 patients with BOTs, Song *et al.* showed that laparoscopy and open surgery were both feasible in cases of small-volume disease and the absence of peritoneally disseminated disease. However, the laparoscopic approach was associated with more favourable surgical outcomes, including decreased operative time, operative blood loss and transfusion rates, as well as faster bowel movement recovery, shorter postoperative hospital stays and fewer perioperative complications, with no compromise in oncological outcomes<sup>[29]</sup>. The equivalent and much larger German study (ROBOT) showed that, compared with open surgery, initial laparotomy and laparoscopy converted to laparotomy showed hazard ratios of 1.176 (0.772–1.792) and 1.213 (0.582–2.527), respectively, indicating that laparoscopy is comparable to open surgery in terms of oncological outcomes, relapse rate and overall survival<sup>[30]</sup>. For these reasons, the proportion of early-stage gynaecological cancers managed with minimally invasive surgery has increased from 7% to 90%<sup>[31]</sup>. Although it is difficult to reach definitive conclusions on this matter due to the

lack of prospective studies, a skilled gynaecological oncologist with sufficient experience is best suited to perform laparoscopy surgery on BOT patients. In a retrospective French multicentre study of 358 patients, Fauvet *et al.*<sup>[22]</sup> confirmed that cyst rupture (33.9% vs 12.4%) and incomplete staging occurred significantly more frequently in the laparoscopy group. However, this had no influence on the relapse rate. The potentially higher risk of relapse and possible need for repeated surgery in this case, albeit commonly with no survival difference, should be discussed with the patient when balancing weighing up cosmesis and surgical burden. Routine biopsy on the contralateral ovary and multiple peritoneal biopsies are not considered necessary unless an abnormality appears macroscopically, since such procedures increase the risk of postoperative adhesions and are not of high value diagnostically because they may not produce a tumour sample<sup>[26]</sup>.

Cystectomy, which produces an increased risk of recurrence on the ipsilateral ovary<sup>[32]</sup>, should be carried out only in women with bilateral tumours or only one ovary, as well as extremely young patients. The increased relapse rate after cystectomy may be caused by the following: intraoperative cyst rupture, the presence of a multifocal BOT, or tumour margins affected after the cystectomy<sup>[33]</sup>. Nevertheless, most of these recurrences are borderline type, so they do not affect global survival rates<sup>[22,34]</sup>. From the analysis of the data in an Italian study<sup>[23]</sup>, it emerged that, considering the case series as a whole, the incidence of cyst rupture or spillage was effectively higher during laparoscopic surgery; nevertheless, on analysing the fertility-sparing surgery cases, no statistically significant difference in the incidence of spillage was found either when comparing laparoscopic versus laparotomy cystectomy, or laparoscopic versus laparotomy adnexectomy. Moreover, the relapse incidence did not depend on the type of surgical approach, even when considering only the group of cases where the spillage was caused by the surgeon. In addition, analysis of progression-free survival in these case series shows that only cystectomy has to be considered a risk factor. Invasive recurrent disease is a rare event after conservative treatment. Recurrent lesions of a non-invasive nature can be cured only by surgery, without affecting survival. It appears that the increased recurrence rate observed after conservative surgery does not influence survival<sup>[35]</sup>. One of the factors that increases the rate of recurrence after conservative treatment is the disease stage (especially in serous BOTs, where peritoneal implants can be found in 15–40% of cases). In a large series, Uzan *et al.*<sup>[36]</sup> demonstrated that conservative management may be an option for patients with peritoneal implants if the implants can be entirely removed. In mucinous BOTs, cystectomy is not recommended as a treatment for preserving fertility due to the high risk of recurrence in the form of carcinoma, as mucinous BOTs are globally associated with a higher mortality rate. For women under the age of 40 years who desire to have children and present with BOTs in stages II and III (with peritoneal implants), the surgical technique will vary according to the invasiveness of the implants: in patients with non-invasive implants, conservative surgery and total resectioning of the peritoneal implants may be carried out; in patients with invasive implants, radical surgery with complete resectioning of the implants is preferable<sup>[19]</sup>.

## Discussion

The surgical approach to BOTs is still under debate: while laparoscopy has become the standard approach for benign ovarian tumours, it has not been clearly proven to guarantee adequate staging or oncological safety in BOT patients [37-39]. The major concerns with laparoscopy are higher rates of cyst rupture, leading to a iatrogenic spread of tumour cells with a possible influence on patients' prognosis and clinical course [40]. Other disadvantages include a lack of tactile sensation, the development of port site metastases [41-43], and the problem of more difficult manipulation and removal of larger masses through the abdominal wall. The diameter of the cyst is a significant factor predicting laparoscopic failure, and it seems that laparoscopy should be reserved for ovarian masses of less than 5 cm [44]. In contrast, laparoscopy allows better illumination of the abdominal cavity, with better views of the peritoneal surface and diaphragm, lower risk of postoperative adhesions, better aesthetic results and quicker recovery times. In an original study by Delle Marchette et al., the surgical approach did not influence recurrence or fertility [45]. The main advantage of the mini-invasive approach is the reduced morbidity, especially the reduction of post-operative adhesions that could possibly impair fertility [46].

On the other hand, it is crucial that gynaecological oncologists have adequate laparoscopic experience in order to avoid cyst fluid spillage and limit healthy ovarian tissue ablation, thereby maximising the oncological and reproductive outcomes. The choice of surgical approach should be made taking into account on the size of the suspicious mass, the presence of adhesions, and the invasiveness of the surgery, while treating large cysts by laparoscopy should be avoided, as this enhances peritoneal tumour persistence and early relapse [45]. Most BOT patients are diagnosed in an early stage when the disease is still limited to the ovaries (78.5% in FIGO stage IA/B) [47].

Proper staging consists of a thorough exploration of the entire abdominal cavity with peritoneal washing, infracolic omentectomy, removal of all macroscopically suspicious peritoneal lesions and multiple peritoneal biopsies. Complete staging is performed in only 50% of patients or less, even though the pelvic peritoneum and abdominal peritoneum are involved in 58% and 48% of patients, respectively. Furthermore, invasive implants are present in the pelvic peritoneum and abdominal peritoneum in 9% and 14% of patients, respectively. The omentum is involved in 39% of patients, and in 9% of patients, these implants are invasive. Hence, a careful inspection of the peritoneum with resection of macroscopically suspicious lesions, multiple peritoneal biopsies and an infracolic omentectomy are necessary for a thorough staging [48]. The role of lymph node sampling is controversial due to the good global prognosis of this disease and the potential morbidity associated with the procedure [49,50]. Routine pelvic and para-aortic lymph node dissection is unnecessary for most women with BOTs [51]. Accordingly, a study conducted at the European Institute of Oncology (IEO), showed that the restaging procedure does not seem to have a significant effect on the management of patients diagnosed with BOTs [52]. Although staging is sometimes less extensive with laparoscopy, the difference versus laparotomy

falls short of statistical significance. In addition, laparoscopic surgery has not been associated with a deterioration in outcomes [29,53-56].

## Conclusion

Borderline tumours affect younger patients than invasive epithelial ovarian cancers do. Especially for young patients with early-stage borderline tumours who wish to preserve their fertility, the laparoscopic approach seems preferable [57-62]. Moreover, laparoscopic treatment can be practiced during pregnancy [63-65]. The risk of post-operative abdominal adhesions is considered to be lower after laparoscopy [46].

Unilateral oophorectomy and omentectomy is considered to be a safe conservative surgery option for patients with BOTs [66], provided the contralateral ovary is macroscopically normal. Ovarian resection or cystectomy should be avoided if the cyst looks suspicious on preoperative ultrasound examination, and the surgeon should try to avoid rupture of the cyst and intra-abdominal spillage [67,68]. Laparoscopic treatment of BOTs is feasible if the tumour is of moderate size, as this results in fewer complications and shorter hospital stays; furthermore, laparoscopic staging seems feasible if performed by experienced surgeons [7].

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