

Borderline ovarian tumours: management in the era of fertility-sparing surgery

Mattia Maramai^{1,2}, Fabio Barra^{1,2}, Mario Valenzano Menada^{1,2}, Sara Stigliani^{1,2}, Melita Moioli², Sergio Costantini^{1,2} and Simone Ferrero^{1,2}

¹Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DiNOGMI), University of Genova, Italy

²Academic Unit of Obstetrics and Gynaecology, IRCCS Ospedale Policlinico San Martino, Genova, Italy

Abstract

Borderline ovarian tumours (BOTs) are ovarian neoplasms characterised by epithelial proliferation, variable nuclear atypia and no evidence of destructive stromal invasion. BOTs account for approximately 15% of all epithelial ovarian cancers. Due to the fact that the majority of BOTs occur in women under 40 years of age, their surgical management often has to consider fertility-sparing approaches. The aim of this mini-review is to discuss the state of the art of fertility-sparing surgery for BOTs with a specific focus on the extent of surgery, post-operative management and fertility.

Keywords: *ovarian neoplasms, ovarian cysts, fertility preservation, salpingo-oophorectomy*

Introduction

Borderline ovarian tumours (BOTs) are a group of ovarian neoplasms described as 'semi-malignant disease' for the first time by Taylor [1] in 1929. BOTs are characterised by higher epithelial proliferation and more variable nuclear atypia than benign lesions; however, they have not stromal invasion, in contrast to carcinomas [2]. The vast majority of BOTs have serous or mucinous histotypes; other rare types are clear-cell, endometrioid and Brenner (transitional-cell) tumours. Despite the lack of stromal invasion, serous BOTs may present implants on peritoneal surfaces, which in a small percentage of cases, invade underlying tissue. In the presence of invasive implants, according to the 2014 WHO (World Health Organization) Classification of Tumours of Female Reproductive Organs, BOTs should be considered as low-grade serous carcinoma [2, 3].

BOTs account for approximately 15% of all epithelial ovarian cancers, with an annual prevalence of 1.8–4.8/100,000 [4, 5]. Overall, being characterised by a less aggressive biological behaviour, BOTs have a better prognosis than malignant epithelial ovarian cancers; in fact, studies with long term follow-up describe 5-year survival rates over 90% [6–8]. Additionally, compared to malignant ovarian cancers, these tumours tend to more

Correspondence to: Fabio Barra
Email: fabio.barra@icloud.com

ecancer 2020, 14:1031
<https://doi.org/10.3332/ecancer.2020.1031>

Published: 06/05/2020

Received: 27/12/2019

Publication costs for this article were supported by ecancer (UK Charity number 1176307).

Copyright: © the authors; licensee ecancermedicalscience. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

frequently occur in younger patients and at an earlier stage: more than a third of BOTs occur in women younger than 40 years of age, in contrast to malignant epithelial ovarian cancers, whose incidence is about 6% in the same age group. In two large series by Trillsch and du Bois, the diagnosis of BOTs was done at stage I in 78%–82% of cases [9, 10]. Several studies reported increasing in BOTs survival rates from 60's to present, probably due to the common misclassification with carcinomas; in fact, BOTs had a first specific definition by WHO in 1973; the same studies reported an increase in their incidence in the same period as well [4]; these reports could be partly attributed to a rising awareness of the distinctive pathologic features of BOTs [2, 11].

Surgery is the primary treatment for BOTs. Similarly to the management of malignant ovarian cancers, the extent of surgery depends on stage: for stage I disease, the therapeutic approach should include a surgical staging with total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, peritoneal washing and multiple biopsies; appendix should be removed in case of mucinous histology [12, 13]. In patients with evidence of advanced stage, all visible disease should be surgically removed [12, 14]. The use of minimally invasive or traditional open techniques has been evaluated in the current literature: a series of 105 patients treated by Trillsch *et al* [15] demonstrated no statistically significant differences in achieving a complete surgical cytoreduction by laparoscopy or laparotomy; moreover, the authors found an advantage in performing a complete surgical staging during primary surgery by laparotomy although these data equalised after re-staging procedures. Another series by Desfeux *et al* [16] reported no difference in recurrence rates and similar survival curves across these surgical approaches. For this reason, minimally invasive surgery is considered feasible and safe in the management of patients affected by BOTs. Casarin *et al* [17] analysed the impact of adnexal size on the risk of surgical spillage: in their retrospective analysis, adnexa larger than 10 cm in maximum diameter were associated with a 4-fold risk of surgical spillage with laparoscopic approach (54.5% versus 12.1%) compared to open surgery. In the sub-analysis of patients treated by laparoscopy, they found a positive correlation between the adnexa size and surgical conversion rates ($p = 0.003$), need for mini laparotomy for retrieving the specimens ($p = 0.006$) and global operative time ($p < 0.001$). Nevertheless, laparoscopy obtained less intraoperative blood loss ($p = 0.007$) and shorter operative time ($p < 0.001$).

The increasing use of robotic surgery in gynaecology was focalised also on the management of early-stage ovarian cancer and BOTs. In fact, the robotic-assisted approach is useful and safe in patients with presumed early stage disease [18]. In a retrospective analysis of 39 patients treated by minimally invasive surgery for presumed early-stage ovarian cancer, Bellia *et al* [19] showed no significant difference between laparoscopic versus robotic management in terms of operating time, needs for blood transfusion, intra- and post-operative complications and number of lymph nodes detected. Similar results were found by Nehzat *et al* [20] in a retrospective analysis of 63 patients with a presumed stage I ovarian cancer who underwent minimally invasive surgery. No difference was found in terms of estimated blood loss, length of stay and operative time.

Overall, the choice of surgical approach for BOTs should consider size of ovarian masses, presence and localisation of peritoneal implants, presence of bulky nodes, surgeon's skills and patient's individual characteristics [21, 22]. Another topic for debate on surgical management of early-stage BOTs is represented by the need for systematic lymphadenectomy: in a retrospective analysis by Matsuo *et al* [23], no difference was found in survival rates in patient undergoing lymphadenectomy. Despite extreme variability among the various series, up to 40%–50% of lymph node involvement has been reported in BOTs [24, 25]. However, the presence of positive lymph nodes does not seem to affect global recurrence and patient's overall survival [23, 25]. For this reason, the vast majority of investigators do not recommend routine pelvic and para-aortic lymphadenectomy for managing these tumours; otherwise, the removal of bulky suspicious nodes is suggested [24, 26]. The role of intra-operative frozen section (FS) during surgical management of BOTs is under debate: a retrospective analysis by Ureyen *et al* [27] reported a significant difference in concordance between FS and definitive diagnosis in serous and mucinous histologies (92% versus 62%); a wide decrease in concordance were found also in ovarian masses larger than 100 mm (90% versus 68%). Another paper from a tertiary referral centre highlighted that in older patients, under-diagnosis of borderline histology after FS rises from 33.3% to 53.3% [28]. In a retrospective study Shah *et al* [29] analysed concordance between FS diagnosis and final pathologic diagnosis of BOTs when performed in an academic hospital with a gynaecologic pathologist, an academic hospital with a nongynaecological pathologist and a community hospital with a nongynaecological pathologist; no significant differences were shown regardless of hospital type [29]. Globally considering the evidence from the literature, the use of FS in suspicious ovarian masses appears to reliably distinguish benign from malignant lesions. However, as reported above, its use in BOTs needs more caution, especially in cases of mucinous histology, large masses and older patients [30]. In cases of incomplete surgical staging at primary surgery, re-intervention for achieving complete staging does not likely affect survival rates related to BOTs [31].

Because many patients are still fertile at the time of diagnosis, not having completed the desire of childbearing, fertility-sparing surgery is considered as a relevant option in the management of BOTs. In many series published, the overall survival for patients undergoing a fertility-sparing surgery is close to 100% [10, 32–34].

Fertility-sparing approach

In woman with unilateral/bilateral ovarian involvement, fertility-sparing options include surgical procedures, such as unilateral cystectomy (US), unilateral salpingo-oophorectomy (USO), bilateral cystectomy (BC) or unilateral salpingo-oophorectomy plus contra-lateral cystectomy (USO+CC). In a French multi-centre study, including 313 patients with stage I BOTs, the recurrence rates after cystectomy, USO or BSO were 30.3%, 11% and 1.7%, respectively [35]. In a retrospective series, De Iaco *et al* [36] analysed the surgical outcome of 168 patient with affected by BOTs treated with conservative surgery between 1985 and 2006: 35 underwent US, 50 underwent USO and 83 radical surgery; recurrence rate was 34.3% in US group, 20% in USO group and 6% in radical surgery group; moreover, patients who experienced tumour relapse did not die of this disease [36]. The authors definitively suggested cystectomy as a suitable option in younger patients or women with bilateral BOT or previous history of unilateral adnexectomy, after appropriate counselling about the risk of local relapse. Vasconcelos *et al* [37] published a meta-analysis on studies, including 5,105 women, 2,725 of who underwent conservative surgery for BOTs. Among patients undergoing US, BC, USO and USO+CC, the pooled recurrence estimates were, respectively, 25.3%, 25.6%, 12.5%, and 26.1%. In sub-analysis on patients with unilateral BOTs, USO performed significantly better than US with an OR for recurrence reduction of 2.2 (95% CI = 0.793–2.841, $p < 0.0001$). Overall, in cases of bilateral BOTs, USO+CC did not obtain an advantage compared to BC in terms of recurrence (26.1% versus 25.6); therefore, less destructive approaches in this setting may be considered in order to preserve patients' fertility. Although no differences were found between conservative and radical surgery in terms of overall survival, the authors concluded that the low mortality rate precludes pooling estimation for death in relation to the different types of fertility sparing surgery; moreover, the short-term follow-up times tend to limit the interpretation of survival analysis. In this meta-analysis, the only prospective randomised controlled trial was an Italian paper published by Palomba *et al* [38], which compared BC and USO+CC, obtaining a significant shorter time to first recurrence in the BC group ($p < 0.01$); however, performing a regression analysis, the difference did not reach a statistical significance ($p = 0.14$); additionally, disease recurrence (1.23 [95% CI, 0.62–3.17; $p = 0.41$]) was not different between these groups.

Obtaining a biopsy from a normal appearing contra-lateral ovary is not recommended in patients undergoing surgical management for BOTs because the risk of under-diagnosis of an occult malignancy tends to be very low [33]. Furthermore, this procedure may cause adhesions that may impact negatively on fertility in 10%–20% of the cases; in fact, in cases of extensive biopsies, the risk of favouring the onset of iatrogenic menopause has been described [39].

The management of relapse of BOTs mostly depends on tumour location and histotype. In case of a relapse in remnant ovarian tissue, a second conservative surgery could represent a suitable treatment option in patients desiring to preserve fertility [40]; otherwise, in case of extra-ovarian relapse the surgical approach should be based on a complete cytoreductive surgery, associated with platinum/taxane-based chemotherapy in case of progression to low-grade serous carcinoma [14, 41]. Trans-vaginal ultrasonography seems to be the most effective technique in follow-up of patients treated conservatively for BOTs [42].

Pregnancy rates and infertility after fertility-sparing approach

It is difficult to exactly assess the impact of fertility-sparing treatments for BOTs on ovarian function and fertility. It has been reported that approximately 81% of women retain normal menstrual cycles after conservative surgery for BOTs [43]. As in benign diseases like endometriosis, the aim of fertility preservation after fertility-sparing surgery on the ovaries is debated [44]. In a meta-analysis by Raffi *et al* [45] the serum anti-Müllerian hormone (AMH) decreased by 38% after US or BC for ovarian endometriomas. Chang *et al* [46] also found a decrease in AMH serum levels after laparoscopic ovarian cystectomy; However, they observed a restore in AMH level after 3 months of follow-up, with no statistically difference with preoperative AMH levels. The same result was showed by Vignali *et al* [47] among patients underwent

US or BC for ovarian endometriomas: no differences was shown between preoperative and 12-months postoperative AMH levels ($p > 0.05$); moreover, no differences in antral follicle count (AFC) were shown [48].

Pregnancy rates in women attempting to conceive after fertility-sparing surgery are very heterogeneous [49]. In the current literature, the main published series report pregnancy rates after treatment for early stage BOTs ranging from 30% to 80% [50, 51]. A retrospective analysis by Delle Marchette *et al* [52] did not show differences in terms of pregnancy rates with regard to surgical approach (open versus laparoscopy) or type of surgery (UC versus USO). However, the need for additional surgical procedures reduced the probability of getting pregnant by about 40% [52].

Another controversial topic is the need to use assisted reproductive techniques for improving fertility outcomes. In selected patients, induction of ovulation and *in vitro* fertilisation may be required after fertility-sparing surgery in order to enhance the chance of conceiving. Potential associations between ovulation-inductor drugs and BOTs have been proposed by several authors: in 1994, Rossing *et al* [53] highlighted the relation between the use of clomiphene and the increased risk to develop BOTs or even invasive ovarian cancer. Subsequent studies reduced the emphasis on this association, which at the moment is characterised by low evidence [54–56]. A meta-analysis by Siristatidis *et al* [57] showed a statistically significant correlation between controlled ovarian hyper-stimulation and ovarian cancer (RR = 1.50, 95% CI: 1.17–1.9); however, when the analysis was based only on infertile women, no significant associations were noted (RR = 1.26, 95% CI: 0.62–2.55); with regard to BOTs, no conclusions have been drawn due to not negligible study limitations, such as short follow-up period, low statistical power and absence of control groups [41].

As general rule, fertility counselling should be mandatory in the management of BOTs among women aiming to spare fertility. Patients with diagnosis of BOTs should be referred to an oncofertility centre before surgery in order to assess their reproductive status and to plan subsequent operative management [58, 59].

Surveillance after fertility-sparing approach

Currently, there is no universally accepted standard-of-care regarding follow-up after surgery for BOTs. In a cohort of 39 women, Uzan *et al* [60] reported that the vast majority of non-invasive relapse of BOTs were diagnosed by ultrasound (16/23; 69%); CA125 elevation occurred in case of progression to invasive ovarian cancers (6/13; 46%) [60]. Same evidence was found by Zanetta *et al* [42] in a cohort of 28 women experiencing a relapse of BOTs. Frequency of post-operative visits and chose of exams are mainly dependent to the institutional or physician expertise; the performance of clinical examination, ultrasonography and serum tumour markers is widely accepted. Staging Classifications and Clinical Practice Guidelines for Gynaecological Cancers, edited by the Fédération Internationale de Gynécologie et d'Obstétrique in 2000 suggest that a control visit should be carried out every three months during the first year after surgery for invasive ovarian cancer, with an increase to every four to six months and every year after the fifth year. For BOTs, this frequency can be annual [61]. As in the case of fertility-sparing surgery, the majority of relapses occur in the remnant ovary, a routinely ovarian scan by ultrasound in the hands of a skilled operator should be done; computed tomography or magnetic resonance are second-line options, although their use appears pivotal in the case of elevation of serum CA125. In a multicentre prospective study, Fisherova *et al* [62] analysed the outcomes of 20 patients with a previous diagnosis of BOT and a recurrent ovarian mass: in this population a subjective transvaginal ultrasonographic assessment of the recurrent ovarian mass by a skilled operator obtained a sensitivity of 94% with a false-positive rate of 33%.

Disease relapse after fertility-sparing approach

The main clinical factors associated with disease relapse are advanced age at diagnosis, preoperative elevation of serum levels of CA125, presence of invasive implants and micropapillary histology [63].

Rates of relapse described after fertility sparing surgery for BOTs greatly differ in the current literature. The evidence shows that serous BOTs recurred more frequently than mucinous BOTs, despite progressing to an invasive carcinoma only in a smaller percentage of cases. In a retrospective analysis by Uzan *et al*. [64], 191 of 254 women (75.2%) underwent conservative management for BOTs; the authors found 43 cases of recurrence (26 serous BOT, 17 mucinous BOT; $p = 0.01$); among the women with initial diagnosis of serous BOT, only 3 (11.5%) developed an invasive carcinoma; in contrast, among those with initial diagnosis of mucinous BOT, invasive carcinoma occurred in 9 women (52.9%).

Recurrence of serous BOT in residual ovary almost always has a non-invasive histology; for this reason, it should be considered as a new primary BOT and could be potentially treated by a second fertility-sparing surgery; conversely, the vast majority of invasive recurrences are characterised by extra-ovarian involvement [14,65]. For mucinous BOT the relapse on residual ovary is related to disease persistence after an incomplete primary surgery, while extra-ovarian relapse is associated with higher risk of invasive histology and poor prognosis [66-67].

In a prospective observational study, Franchi *et al* [68] used transvaginal ultrasonography to assess the growth of recurrent ovarian cyst. They followed up patients with previous conservatively treated BOT and new ovarian cyst until the clinical setting recommended proceeding with surgery (no evidence of metastasis, no ascites, maximum diameter of the suspected recurrent lesion <40 mm, presence of 'ovarian crescent sign' and negative tumor marker). The median time prior to surgery was 9.8 months; the final histological report confirmed the previous histotype in all the patients [68].

Surgery completion after fertility-sparing approach

Recurrence rates in fertility-sparing surgery for BOTs are higher than after radical surgery; however, after the completion of desire of conception the surgical second look with removal of uterus and contra-lateral ovary remains debated. In fact, the published data does not report differences in terms of survival rates after completion of surgery for BOTs. For serous BOTs many authors suggest expectant management and performance of radical surgery only in cases of disease recurrence [13, 69]. For mucinous BOTs several authors suggest the completion of surgery, in fact, many mucinous tumours relapsed as invasive ovarian cancers [70]. In these young patients, psychological impact of disease should not be neglected; thus, an accurate and comprehensive preoperative fertility counselling has to be done [71].

Conclusion

Fertility sparing surgery for BOTs is feasible and does not seem to negatively influence patients' long-term survival, although higher disease recurrence rates have been reported. The extent of surgery should be individualised based on patient characteristics, tumour stage and histology. Women with a diagnosis of BOT should be referred to an oncofertility centre prior to performing fertility-sparing surgery in order to assess reproductive status and to plan future post treatment pregnancies. In these patients, a routine follow-up evaluation should be done, including clinical examination, ultrasound and dosage of serum tumour markers. Surgical management of relapse depends on disease localisation and histology.

Conflicts of interest

The authors have not conflict of interest to declare.

Authors' contributions

MMA	literature review, manuscript writing
FB	manuscript revision
MVM	literature review
SS	data analysis
MMO	data analysis
SF	manuscript revision
SC	supervision

Funding statement

This paper has not been funded.

References

1. Taylor HC (1929) **Malignant and semimalignant tumors of the ovary** *Surg Gynecol Obstet* **48** 204–230
2. Prat J (2017) **Pathology of borderline and invasive cancers** *Best Pract Res Clin Obstet Gynaecol* **41** 15–30 <https://doi.org/10.1016/j.bpobgyn.2016.08.007> PMID: [28277307](https://pubmed.ncbi.nlm.nih.gov/28277307/)
3. Kurman RJ, Carcangiu ML, and Herrington CS, *et al* (2014) *WHO Classification of Tumours of Female Reproductive Organs* (Lyon: IARC Press).
4. Skírnisdóttir I, Garmo H, and Wilander E, *et al* (2008) **Borderline ovarian tumors in Sweden 1960–2005: trends in incidence and age at diagnosis compared to ovarian cancer** *Int J Cancer* **123**(8) 1897–1901 <https://doi.org/10.1002/ijc.23724> PMID: [18661518](https://pubmed.ncbi.nlm.nih.gov/18661518/)
5. Akeson M, Zetterqvist BM, and Dahllöf K, *et al* (2008) **Population-based cohort follow-up study of all patients operated for borderline ovarian tumor in western Sweden during an 11-year period** *Int J Gynecol Cancer* **18**(3) 453–459 <https://doi.org/10.1111/j.1525-1438.2007.01051.x> PMID: [18476948](https://pubmed.ncbi.nlm.nih.gov/18476948/)
6. Karlsen NMS, Karlsen MA, and Høgdall E, *et al* (2016) **Relapse and disease specific survival in 1143 Danish women diagnosed with borderline ovarian tumours (BOT)** *Gynecol Oncol* **142**(1) 50–53 <https://doi.org/10.1016/j.ygyno.2016.05.005> PMID: [27168006](https://pubmed.ncbi.nlm.nih.gov/27168006/)
7. May J, Skorupskaite K, and Congiu M, *et al.* (2018) **Borderline ovarian tumors: fifteen years' experience at a Scottish Tertiary Cancer Center** *Int J Gynecol Cancer* **28**(9) 1683–1691 <https://doi.org/10.1097/IGC.0000000000001364> PMID: [30365457](https://pubmed.ncbi.nlm.nih.gov/30365457/)
8. Lenhard MS, Mitterer S, and Kümper C, *et al* (2009) **Long-term follow-up after ovarian borderline tumor: relapse and survival in a large patient cohort** *Eur J Obstet Gynecol Reprod Biol* **145**(2) 189–194 <https://doi.org/10.1016/j.ejogrb.2009.04.031> PMID: [19477060](https://pubmed.ncbi.nlm.nih.gov/19477060/)
9. Trillsch F, Mahner S, and Ruetzel J, *et al* (2010) **Clinical management of borderline ovarian tumors** *Expert Rev Anticancer Ther* **10**(7) 1115–1124 <https://doi.org/10.1586/era.10.90> PMID: [20645700](https://pubmed.ncbi.nlm.nih.gov/20645700/)
10. du Bois A, Ewald-Riegler N, and de Gregorio N, *et al* (2013) **Borderline tumours of the ovary: a cohort study of the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Study Group** *Eur J Cancer* **49**(8) 1905–1914 <https://doi.org/10.1016/j.ejca.2013.01.035> PMID: [23490647](https://pubmed.ncbi.nlm.nih.gov/23490647/)
11. Kalapotharakos G, Högberg T, and Bergfeldt K, *et al* (2016) **Long-term survival in women with borderline ovarian tumors: a population-based survey of borderline ovarian tumors in Sweden 1960–2007** *Acta Obstet Gynecol Scand* **95**(4) 473–479 <https://doi.org/10.1111/aogs.12846>
12. Colombo N, Sessa C, and du Bois A, *et al* (2019) **ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease** *Ann Oncol* **30**(5) 672–705 <https://doi.org/10.1093/annonc/mdz062> PMID: [31046081](https://pubmed.ncbi.nlm.nih.gov/31046081/)
13. Cadron I, Leunen K, and Van Gorp T, *et al* (2007) **Management of borderline ovarian neoplasms** *J Clin Oncol* **25**(20) 2928–2937 <https://doi.org/10.1200/JCO.2007.10.8076> PMID: [17617524](https://pubmed.ncbi.nlm.nih.gov/17617524/)
14. Gershenson DM (2017) **Management of borderline ovarian tumours** *Best Pract Res Clin Obstet Gynaecol* **41** 49–59 <https://doi.org/10.1016/j.bpobgyn.2016.09.012>
15. Trillsch F, Ruetzel JD, and Herwig U, *et al* (2013) **Surgical management and perioperative morbidity of patients with primary borderline ovarian tumor (BOT)** *J Ovarian Res* **6**(1) 48 <https://doi.org/10.1186/1757-2215-6-48> PMID: [23837881](https://pubmed.ncbi.nlm.nih.gov/23837881/) PMID: [3708757](https://pubmed.ncbi.nlm.nih.gov/3708757/)

16. Desfeux P, Camatte S, and Chatellier G, *et al* (2005) **Impact of surgical approach on the management of macroscopic early ovarian borderline tumors** *Gynecol Oncol* **98**(3) 390–395 <https://doi.org/10.1016/j.ygyno.2005.04.043> PMID: [16043215](https://pubmed.ncbi.nlm.nih.gov/16043215/)
17. Casarin J, Laganà AS, and Uccella S, *et al* (2019) **Surgical treatment of large adnexal masses: a retrospective analysis of 330 consecutive cases** *Minim Invasive Ther Allied Technol* 1–9 <https://doi.org/10.1080/13645706.2019.1649700> PMID: [31375049](https://pubmed.ncbi.nlm.nih.gov/31375049/)
18. Minig L, Padilla Iserte P, and Zorrero C, *et al*. (2016) **Robotic surgery in women with ovarian cancer: surgical technique and evidence of clinical outcomes** *J Minim Invasive Gynecol* **23**(3) 309–316 <https://doi.org/10.1016/j.jmig.2015.10.014>
19. Bellia A, Vitale SG, and Laganà AS, *et al* (2016) **Feasibility and surgical outcomes of conventional and robot-assisted laparoscopy for early-stage ovarian cancer: a retrospective, multicenter analysis** *Arch Gynecol Obstet* **294**(3) 615–622 <https://doi.org/10.1007/s00404-016-4087-9> PMID: [27040423](https://pubmed.ncbi.nlm.nih.gov/27040423/)
20. Nezhat FR, Finger TN, Vetere P, *et al* (2014) **Comparison of perioperative outcomes and complication rates between conventional versus robotic-assisted laparoscopy in the evaluation and management of early, advanced, and recurrent stage ovarian, fallopian tube, and primary peritoneal cancer** *Int J Gynecol Cancer* **24**(3) 600–607 <https://doi.org/10.1097/IGC.000000000000096> PMID: [24557439](https://pubmed.ncbi.nlm.nih.gov/24557439/)
21. Maneo A, Vignali M, and Chiari S, *et al* (2004) **Are borderline tumors of the ovary safely treated by laparoscopy?** *Gynecol Oncol* **94**(2) 387–392 <https://doi.org/10.1016/j.ygyno.2004.05.003> PMID: [15297177](https://pubmed.ncbi.nlm.nih.gov/15297177/)
22. Kane A, Uzan C, and Gouy S, *et al* (2010) **Fertility results and outcomes after pure laparoscopic management of advanced-stage serous borderline tumors of the ovary** *Fertil Steril* **94**(7) 2891–2894 <https://doi.org/10.1016/j.fertnstert.2010.04.045> PMID: [20537629](https://pubmed.ncbi.nlm.nih.gov/20537629/)
23. Matsuo K, Machida H, and Takiuchi T, *et al* (2017) **Role of hysterectomy and lymphadenectomy in the management of early-stage borderline ovarian tumors** *Gynecol Oncol* **144**(3) 496–502 <https://doi.org/10.1016/j.ygyno.2017.01.019> PMID: [28131526](https://pubmed.ncbi.nlm.nih.gov/28131526/)
24. Qian XQ, Hua XP, and Wu JH, *et al* (2018) **Clinical predictors of recurrence and prognostic value of lymph node involvement in the serous borderline ovarian tumor** *Int J Gynecol Cancer* **28**(2) 279–284 <https://doi.org/10.1097/IGC.0000000000001154>
25. McKenney JK, Balzer BL, and Longacre TA (2006) **Lymph node involvement in ovarian serous tumors of low malignant potential (borderline tumors): pathology, prognosis, and proposed classification** *Am J Surg Pathol* **30**(5) 614–624 <https://doi.org/10.1097/01.pas.0000194743.33540.e6> PMID: [16699316](https://pubmed.ncbi.nlm.nih.gov/16699316/)
26. Lesieur B, Kane A, and Duvillard P, *et al* (2011) **Prognostic value of lymph node involvement in ovarian serous borderline tumors** *Am J Obstet Gynecol* **204**(5) 438.e1–438.e4387 <https://doi.org/10.1016/j.ajog.2010.12.055>
27. Ureyen I, Turan T, and Cirik DA, *et al* (2014) **Frozen section in borderline ovarian tumors: is it reliable?** *Eur J Obstet Gynecol Reprod Biol* **181** 115–118 <https://doi.org/10.1016/j.ejogrb.2014.07.039> PMID: [25145763](https://pubmed.ncbi.nlm.nih.gov/25145763/)
28. Morton R, Anderson L, and Carter J, *et al* (2017) **Intraoperative frozen section of ovarian tumors: a 6-year review of performance and potential pitfalls in an Australian Tertiary Referral Center** *Int J Gynecol Cancer* **27**(1) 17–21 <https://doi.org/10.1097/IGC.0000000000000851>
29. Shah JS, Mackelvie M, and Gershenson DM, *et al* (2019) **Accuracy of intraoperative frozen section diagnosis of borderline ovarian tumors by hospital type** *J Minim Invasive Gynecol* **26**(1) 87–93 <https://doi.org/10.1016/j.jmig.2018.04.005>
30. Ratnavelu ND, Brown AP, and Mallett S, *et al* (2016) **Intraoperative frozen section analysis for the diagnosis of early stage ovarian cancer in suspicious pelvic masses** *Cochrane Database Syst Rev* **3**(3) PMID: [26930463](https://pubmed.ncbi.nlm.nih.gov/26930463/) PMCID: [6457848](https://pubmed.ncbi.nlm.nih.gov/6457848/)
31. Shim SH, Kim SN, and Jung PS, *et al* (2016) **Impact of surgical staging on prognosis in patients with borderline ovarian tumours: a meta-analysis** *Eur J Cancer* **54** 84–95 <https://doi.org/10.1016/j.ejca.2015.11.005> PMID: [26735354](https://pubmed.ncbi.nlm.nih.gov/26735354/)
32. Zanetta G, Rota S, and Chiari S, *et al* (2001) **Behavior of borderline tumors with particular interest to persistence, recurrence, and progression to invasive carcinoma: a prospective study** *J Clin Oncol* **19**(10) 2658–2664 <https://doi.org/10.1200/JCO.2001.19.10.2658> PMID: [11352957](https://pubmed.ncbi.nlm.nih.gov/11352957/)

33. Morice P, Camatte S, and El Hassan J, *et al* (2001) **Clinical outcomes and fertility after conservative treatment of ovarian borderline tumors** *Fertil Steril* **75**(1) 92–96 [https://doi.org/10.1016/S0015-0282\(00\)01633-2](https://doi.org/10.1016/S0015-0282(00)01633-2) PMID: [11163822](#)
34. Mandelbaum RS, Blake EA, and Machida H, *et al* (2019) **Utero-ovarian preservation and overall survival of young women with early-stage borderline ovarian tumors** *Arch Gynecol Obstet* **299**(6) 1651–1658 <https://doi.org/10.1007/s00404-019-05121-z> PMID: [30923905](#)
35. Poncelet C, Fauvet R, and Boccara J, *et al* (2006) **Recurrence after cystectomy for borderline ovarian tumors: results of a French multi-center study** *Ann Surg Oncol* **13**(4) 565–571 <https://doi.org/10.1245/ASO.2006.12.024> PMID: [16491337](#)
36. De Iaco P, Ferrero A, and Rosati F, *et al* (2009) **Behaviour of ovarian tumors of low malignant potential treated with conservative surgery** *Eur J Surg Oncol* **35**(6) 643–648 <https://doi.org/10.1016/j.ejso.2008.09.011>
37. Vasconcelos I and de Sousa Mendes M (2015) **Conservative surgery in ovarian borderline tumours: a meta-analysis with emphasis on recurrence risk** *Eur J Cancer* **51**(5) 620–631 <https://doi.org/10.1016/j.ejca.2015.01.004> PMID: [25661104](#)
38. Palomba S, Falbo A, and Del Negro S, *et al* (2010) **Ultra-conservative fertility-sparing strategy for bilateral borderline ovarian tumours: an 11-year follow-up** *Hum Reprod* **25**(8) 1966–1972 <https://doi.org/10.1093/humrep/deq159> PMID: [20573679](#)
39. Weinstein D and Polishuk WZ (1975) **The role of wedge resection of the ovary as a cause for mechanical sterility** *Surg Gynecol Obstet* **141**(3) 417–418 PMID: [1162571](#)
40. Fischerova D, Zikan M, and Dunder P, *et al* (2012) **Diagnosis, treatment, and follow-up of borderline ovarian tumors** *Oncologist* **17**(12) 1515–1533 <https://doi.org/10.1634/theoncologist.2012-0139> PMID: [23024155](#) PMCID: [3528384](#)
41. Seong SJ, Kim DH, and Kim MK, *et al* (2015) **Controversies in borderline ovarian tumors** *J Gynecol Oncol* **26**(4) 343–349 <https://doi.org/10.3802/jgo.2015.26.4.343> PMID: [26404125](#) PMCID: [4620372](#)
42. Zanetta G, Rota S, and Lissoni A, *et al* (2001) **Ultrasound, physical examination, and CA 125 measurement for the detection of recurrence after conservative surgery for early borderline ovarian tumors** *Gynecol Oncol* **81**(1) 63–66 <https://doi.org/10.1006/gyno.2000.6099> PMID: [11277651](#)
43. Morris RT, Gershenson DM, and Silva EG, *et al* (2000) **Outcome and reproductive function after conservative surgery for borderline ovarian tumors** *Obstet Gynecol* **95**(4) 541–547 PMID: [10725486](#)
44. Sleiman Z, Karaman E, and Terzic M, *et al* (2019) **Fertility preservation in benign gynecological diseases: current approaches and future perspectives** *J Reprod Infertil* **20**(4) 201–208
45. Raffi F, Metwally M, and Amer S (2012) **The impact of excision of ovarian endometrioma on ovarian reserve: a systematic review and meta-analysis** *J Clin Endocrinol Metab* **97**(9) 3146–3154 <https://doi.org/10.1210/jc.2012-1558> PMID: [22723324](#)
46. Chang HJ, Han SH, and Lee JR, *et al* (2010) **Impact of laparoscopic cystectomy on ovarian reserve: serial changes of serum anti-Müllerian hormone levels** *Fertil Steril* **94**(1) 343–349 <https://doi.org/10.1016/j.fertnstert.2009.02.022>
47. Vignali M, Mabrouk M, and Ciocca E, *et al* (2015) **Surgical excision of ovarian endometriomas: does it truly impair ovarian reserve? Long term anti-Müllerian hormone (AMH) changes after surgery** *J Obstet Gynaecol Res* **41**(11) 1773–1778 <https://doi.org/10.1111/jog.12830> PMID: [26420658](#)
48. Muzii L, Di Tucci C, and Di Felicianantonio M, *et al* (2014) **The effect of surgery for endometrioma on ovarian reserve evaluated by antral follicle count: a systematic review and meta-analysis** *Hum Reprod* **29**(10) 2190–2198 <https://doi.org/10.1093/humrep/deu199> PMID: [25085800](#)
49. Daraï E, Fauvet R, and Uzan C, *et al* (2013) **Fertility and borderline ovarian tumor: a systematic review of conservative management, risk of recurrence and alternative options** *Hum Reprod Update* **19**(2) 151–166 <https://doi.org/10.1093/humupd/dms047>
50. Song T, Hun Choi C, and Lee YY, *et al* (2011) **Oncologic and reproductive outcomes of cystectomy compared with oophorectomy as a treatment for borderline ovarian tumours** *Hum Reprod* **26**(8) 2008–2014 <https://doi.org/10.1093/humrep/der119> PMID: [21511712](#)

51. Fauvet R, Poncelet C, and Boccarda J, *et al* (2005) **Fertility after conservative treatment for borderline ovarian tumors: a French multi-center study** *Fertil Steril* **83**(2) 284–526 <https://doi.org/10.1016/j.fertnstert.2004.10.009> PMID: [15705364](https://pubmed.ncbi.nlm.nih.gov/15705364/)
52. Delle Marchette M, Ceppi L, and Andreano A, *et al* (2019) **Oncologic and fertility impact of surgical approach for borderline ovarian tumours treated with fertility sparing surgery** *Eur J Cancer* **111** 61–68 <https://doi.org/10.1016/j.ejca.2019.01.021> PMID: [30826658](https://pubmed.ncbi.nlm.nih.gov/30826658/)
53. Rossing MA, Daling JR, and Weiss NS, *et al* (1994) **Ovarian tumors in a cohort of infertile women** *N Engl J Med* **331**(12) 771–776 <https://doi.org/10.1056/NEJM199409223311204> PMID: [8065405](https://pubmed.ncbi.nlm.nih.gov/8065405/)
54. Lundberg FE, Johansson ALV, and Rodriguez-Wallberg K, *et al* (2019) **Assisted reproductive technology and risk of ovarian cancer and borderline tumors in parous women: a population-based cohort study** *Eur J Epidemiol* **34**(11) 1093–1101 <https://doi.org/10.1007/s10654-019-00540-3> PMID: [31377935](https://pubmed.ncbi.nlm.nih.gov/31377935/) PMCID: [6861355](https://pubmed.ncbi.nlm.nih.gov/6861355/)
55. Lerner-Geva L, Rabinovici J, and Olmer L, *et al* (2013) **Are infertility treatments a potential risk factor for cancer development? Perspective of 30 years of follow-up** *Gynecol Endocrinol* **29**(4) 400.
56. van Leeuwen FE, Klip H, and Mooij TM, *et al* (2011) **Risk of borderline and invasive ovarian tumours after ovarian stimulation for in vitro fertilization in a large Dutch cohort** *Hum Reprod* **26**(12) 3456–3465 <https://doi.org/10.1093/humrep/der322> PMID: [22031719](https://pubmed.ncbi.nlm.nih.gov/22031719/) PMCID: [3212878](https://pubmed.ncbi.nlm.nih.gov/3212878/)
57. Siristatidis C, Sergentanis TN, and Kanavidis P, *et al* (2013) **Controlled ovarian hyperstimulation for IVF: impact on ovarian, endometrial and cervical cancer - a systematic review and meta-analysis** *Hum Reprod Update* **19**(2) 105–123 <https://doi.org/10.1093/humupd/dms051>
58. Mangili G, Somigliana E, and Giorgione V, *et al* (2016) **Fertility preservation in women with borderline ovarian tumours** *Cancer Treat Rev* **49** 13–24 <https://doi.org/10.1016/j.ctrv.2016.06.010> PMID: [27428850](https://pubmed.ncbi.nlm.nih.gov/27428850/)
59. Del Pup L, Peccatori FA, and Levi-Setti PE, *et al* (2018) **Risk of cancer after assisted reproduction: a review of the available evidences and guidance to fertility counselors** *Eur Rev Med Pharmacol Sci* **22**(22) 8042–8059 PMID: [30536354](https://pubmed.ncbi.nlm.nih.gov/30536354/)
60. Uzan C, Kane A, and Rey A, *et al* (2011) **How to follow up advanced-stage borderline tumours? Mode of diagnosis of recurrence in a large series stage II-III serous borderline tumours of the ovary** *Ann Oncol* **22**(3) 631–635 <https://doi.org/10.1093/annonc/mdq414>
61. Benedet JL, Bender H, and Jones H 3rd, *et al* (2000) **FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers—FIGO Committee on Gynecologic Oncology** *Int J Gynaecol Obstet* **70**(2) 209–262 [https://doi.org/10.1016/S0020-7292\(00\)90001-8](https://doi.org/10.1016/S0020-7292(00)90001-8) PMID: [11041682](https://pubmed.ncbi.nlm.nih.gov/11041682/)
62. Fischerova D, Franchi D, and Testa A, *et al* (2010) **Ultrasound in diagnosis of new and borderline ovarian tumors** *Ultrasound Obstet Gynecol* **36**(suppl. 1) <https://doi.org/10.1002/uog.7771>
63. Shih KK, Zhou Q, and Huh J, *et al* (2011) **Risk factors for recurrence of ovarian borderline tumors** *Gynecol Oncol* **120**(3) 480–484 <https://doi.org/10.1016/j.ygyno.2010.11.016>
64. Uzan C, Nikpayam M, and Ribassin-Majed L, *et al* (2014) **Influence of histological subtypes on the risk of an invasive recurrence in a large series of stage I borderline ovarian tumor including 191 conservative treatments** *Ann Oncol* **25**(7) 1312–1319 <https://doi.org/10.1093/annonc/mdu139> PMID: [24713312](https://pubmed.ncbi.nlm.nih.gov/24713312/)
65. Sobiczewski P, Kupryjanczyk J, and Michalski W, *et al* (2016) **The evaluation of risk factors associated with relapse and recurrence of borderline ovarian tumors with long-term follow-up** *Int J Gynecol Cancer* **26**(6) 1053–1061 <https://doi.org/10.1097/IGC.0000000000000722> PMID: [27177283](https://pubmed.ncbi.nlm.nih.gov/27177283/)
66. Khunamornpong S, Settakorn J, and Sukpan K, *et al* (2011) **Mucinous tumor of low malignant potential (“borderline” or “atypical proliferative” tumor) of the ovary: a study of 171 cases with the assessment of intraepithelial carcinoma and microinvasion** *Int J Gynecol Pathol* **30**(3) 218–230 <https://doi.org/10.1097/PGP.0b013e3181fcf01a> PMID: [21464732](https://pubmed.ncbi.nlm.nih.gov/21464732/)

67. Trillsch F, Mahner S, and Woelber L, *et al* (2014) **Age-dependent differences in borderline ovarian tumours (BOT) regarding clinical characteristics and outcome: results from a sub-analysis of the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) ROBOT study** *Ann Oncol* **25**(7) 1320–1327 <https://doi.org/10.1093/annonc/mdu119> PMID: [24618151](https://pubmed.ncbi.nlm.nih.gov/24618151/)
68. Franchi D, Boveri S, and Radice D, *et al* (2016) **Ultrasonographic diagnosis and longitudinal follow-up of recurrences after conservative surgery for borderline ovarian tumors** *Am J Obstet Gynecol* **215**(6) 756.e1–756.e9 <https://doi.org/10.1016/j.ajog.2016.07.024>
69. Tinelli R, Tinelli A, and Tinelli FG, *et al* (2006) **Conservative surgery for borderline ovarian tumors: a review** *Gynecol Oncol* **100**(1) 185–191 <https://doi.org/10.1016/j.ygyno.2005.09.021>
70. Prat J (2014) **The results of conservative (fertility-sparing) treatment in borderline ovarian tumors vary depending on age and histological type** *Ann Oncol* **25**(7) 1255–1258 <https://doi.org/10.1093/annonc/mdu160> PMID: [24782452](https://pubmed.ncbi.nlm.nih.gov/24782452/)
71. Uzan C, Muller E, and Kane A, *et al* (2013) **Fertility sparing treatment of recurrent stage I serous borderline ovarian tumours** *Hum Reprod* **28**(12) 3222–3226 <https://doi.org/10.1093/humrep/det371> PMID: [24067602](https://pubmed.ncbi.nlm.nih.gov/24067602/)