

# Borderline ovarian tumors: a review of its biology, molecular profile, and management

Tumores borderline de ovário: uma revisão de sua biologia, perfil molecular e manejo

Renata Colombo Bonadio<sup>1,2</sup>, Ana Gabriela de Siqueira Santos<sup>2</sup>, Maria Del Pilar Estevez-Diz<sup>1,2</sup>

## ABSTRACT

Borderline ovarian tumors typically exhibit indolent behavior and boast a favorable prognosis; however, a subset of patients experiences disease recurrence and progression to low-grade ovarian carcinoma. The complex biology underlying these phenomena has been illuminated through molecular analyses. KRAS and BRAF mutations have emerged as recurrent findings in borderline ovarian tumors. Specifically, KRAS mutations have been linked to a higher risk of recurrence and progression to low-grade ovarian carcinoma, while BRAF mutations seem to confer a protective effect, inducing a senescent state that mitigates the likelihood of progression. In this comprehensive review, we explore the biology and the molecular profile of borderline ovarian tumors, shedding light on recent discoveries that have enriched our comprehension. Additionally, we discuss the current state of borderline ovarian tumors management. Surgery remains the cornerstone of treatment. While cytotoxic therapies role is limited so far, molecular characterization emphasizes the imminent potential for personalized therapeutic approaches.

**Keywords:** Ovarian neoplasms; Rare diseases; Molecular biology.

1. Instituto D'Or de Ensino e Pesquisa (IDOR), São Paulo, Brazil.

2. Instituto do Câncer do Estado de São Paulo, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

**Financial support:** none to declare.

**Conflicts of interest:** RCB: Speaker fees and/or honoraria for consulting or advisory functions: Daiichi-Sankyo, Nestle Health Science, Zodiac, Gilead, MSD, BMS, AstraZeneca, Pfizer, Adium. Financial support for educational programs and symposia: AstraZeneca, Daiichi-Sankyo, MSD. Institutional Research grant: Novartis, AstraZeneca. MPED: Advisory board: AstraZeneca.

**Correspondence author:** Renata Colombo Bonadio.

E-mail: renata.colombo@hc.fm.usp.br

**Received on:** July 30, 2023 | **Accepted on:** January 8, 2024 | **Published on:** March 25, 2024

**DOI:** <https://doi.org/10.5935/2526-8732.20230437>



This is an open-access article distributed under the terms of the Creative Commons Attribution License.

## RESUMO

Os tumores borderline de ovário geralmente exibem comportamento indolente e apresentam prognóstico favorável; no entanto, um subconjunto de pacientes apresenta recorrência da doença e progressão para carcinoma de ovário de baixo grau. A biologia complexa subjacente a estes fenômenos foi iluminada através de análises moleculares. Mutações KRAS e BRAF surgiram como achados recorrentes em tumores borderline de ovário. Especificamente, as mutações KRAS têm sido associadas a um maior risco de recorrência e progressão para carcinoma de ovário de baixo grau, enquanto as mutações BRAF parecem conferir um efeito protetor, induzindo um estado senescente que mitiga a probabilidade de progressão. Nesta revisão abrangente, exploramos a biologia e o perfil molecular dos tumores borderline de ovário, lançando luz sobre descobertas recentes que enriqueceram nossa compreensão. Além disso, discutimos o estado atual do manejo de tumores borderline de ovário. A cirurgia continua sendo o pilar de tratamento. Embora o papel das terapias citotóxicas seja limitado até o momento, a caracterização molecular enfatiza o potencial iminente para abordagens terapêuticas personalizadas.

**Palavras-chave:** Neoplasias ovarianas; Doenças raras; Biologia molecular.

## INTRODUCTION

Borderline ovarian tumors (BOT) are a heterogeneous group defined by FIGO committee as “low malignant potential tumor”. They receive this nomenclature due to its behavior, which is in a spectrum between benign ovarian tumors and invasive carcinomas. ‘Borderline’ refers to its ambiguous biologic characteristic.<sup>[1]</sup> Given the rarity of this entity and the challenges encountered in clinical practice, we conducted a non-systematic literature review on PubMed and EMBASE to consolidate key information related to the diagnosis, molecular profile, and management of BOTs.

The diagnosis of BOTs is histologic. BOTs are defined by the presence of epithelial cell proliferation, with cellular atypia, and mitotic activity, but importantly no stromal invasion is present. The absence of stromal invasion is what differs BOTs from invasive ovarian carcinomas.<sup>[2]</sup> However, some BOTs might present microinvasive disease that is defined by the 2014 WHO (World Health Organization) classification as an upper limit of invasion of 5mm<sup>2</sup>.<sup>[1]</sup> Nonetheless, this definition remains controversial.<sup>[3]</sup>

An important epidemiologic particularity of BOTs is that it usually occurs in younger ages than invasive ovarian carcinomas, with a median age of 40 years at presentation. This characteristic has implications to the treatment, since fertility-sparing surgeries should often be considered, as we will discuss forward.

BOTs incidence is 1.8-4.8 per 100,000 women per year and represent around 15 to 20% of the cases of epithelial ovarian neoplasms.<sup>[4]</sup> BOTs typically manifest as cystic lesions with thin walls. Unlike invasive ovarian carcinomas, which often present with symptoms like ascites, peritoneal lesions, or

lymph node involvement, BOTs usually lack such features.<sup>[5]</sup> In rare cases, following cystic rupture, ovarian tissue containing BOTs may be discovered in the pelvic or peritoneal region, potentially leading to misdiagnosis as peritoneal implants. To accurately evaluate ovarian masses, both pelvic ultrasound and magnetic resonance imaging (MRI) should be employed, with MRI demonstrating higher diagnostic accuracy.<sup>[5]</sup> The serum CA125 level, which lack specificity for malignancies, can be elevated in some BOTs cases as well as in benign conditions.

Although different histologies might occur, the main BOTs histologic subtypes are serous (52-65%) and mucinous (32-42%).<sup>[2]</sup> Other types are found in 4.2% of the cases of BOT, represented by endometrioid, clear-cell, and Brenner tumors.<sup>[6]</sup>

Serous borderline tumors are characterized by intricate hierarchical branching papillae, featuring irregular papillae that extend from larger to progressively smaller structures. They also demonstrate extensive epithelial stratification, tufting, and detachment of individual cells. In terms of immunohistochemistry, serous borderline tumors typically exhibit positive staining for CK7 and negative staining for CK20.<sup>[4]</sup> Moreover, these tumors often exhibit elevated levels of both estrogen and progesterone. In contrast, they lack p53 positivity, which is a distinguishing feature compared to strongly positive p53 staining seen in serous carcinoma. Numerous studies have reported varying Ki-67 proliferation indices, with malignant tumors having the highest, followed by borderline tumors, and benign tumors displaying lower levels of Ki-67 expression.<sup>[4]</sup>

Mucinous borderline tumor on histological examination presents as cysts lined by stratified,

proliferative gastrointestinal-type mucinous epithelium with papillary infoldings and tufting. The cells show mild to moderate nuclear atypia and proliferative areas must comprise more than 10% of the epithelial volume of the tumor to qualify as mucinous BOT. They are classified into intestinal type (85%) and endocervical type (15%), based on their histological pattern and type of tumor cells. Immunohistochemically, is diffusely and strongly positive for CK7, whereas CK 20 displays variable positivity, only in a focal pattern. Nuclear staining for CDX2 is also common but is typically less diffuse and intense compared with intestinal tumors. Estrogen and progesterone expression are almost always negative. Some authors suggest that peritoneal implants are extremely rare or do not occur in association with mucinous borderline ovarian tumors, which is a main difference from mucinous gastrointestinal tumors. Thus, in the presence of peritoneal implants, other conditions should be considered in the diagnosis.<sup>[7,8]</sup>

As other ovarian tumors, BOTs are staged I-IV, according to FIGO stage. Although the majority of the tumors are stage I at diagnosis and present an excellent prognosis, more advanced stages present considerably lower disease specific survival (65%).<sup>[9]</sup>

Extra-ovarian implants are a particularity that should be carefully evaluated. The implants can be non-invasive or invasive. Epithelial cellular clusters that are often located at serosal surfaces, but do not infiltrate the underlying tissue represent the non-invasive implants.<sup>[1,3,10]</sup> Invasive implants, otherwise, cause invasive destruction of the adjacent tissue and has prognostic implications. In a cohort of 276 patients with serous BOTs, among those with invasive implants, the 10-year disease specific mortality rate was 45%.<sup>[11]</sup> Considering this singular behavior, the latest WHO classification considered that the invasive implants should actually be classified as low-grade ovarian carcinoma (LGOC).<sup>[1]</sup> An evaluation by a gynaecological pathology specialist might be important for the differentiation. Molecular profiling suggests that these invasive implants are clonally related to the primary borderline tumor.<sup>[12]</sup> This subject will be further discussed in detail in the following section.

Finally, although most cases of BOTs have an indolent behavior, a progression to low grade ovarian carcinoma can occur in up to 6.8% of the cases.<sup>[11]</sup> The main clinical factors identified as adverse prognostic factors associated with BOTs are advanced FIGO stages, presence of invasive implants, and incomplete surgical resection.<sup>[9,13]</sup> In addition, a comprehensive analysis of the molecular characteristics of BOTs is of utmost importance for a better understanding of who are the patients with a higher risk of progression to LGOC. Hopefully, this knowledge will help in the development of personalized treatment strategies in the future.

## MOLECULAR PROFILE

Two gene mutations that have been consistently reported in BOTs are the *KRAS* and the *BRAF*. *KRAS* mutations have been identified in 17%-39% of BOTs case, while *BRAF* mutations have been reported in 23-71%.<sup>[14-25]</sup> Considering these high frequencies, hypotheses were made that these genes participate in the pathogenesis of BOTs.

Interestingly, serous BOTs are often associated with serous cystadenomas and could possibly occur as an evolution from the latter. In a small cohort of 8 patients with BOTs related to serous cystadenomas, in six cases the *KRAS* or *BRAF* mutations identified in the BOTs were also present in the serous cystadenoma component.<sup>[26]</sup> Similarly, the majority of extra-ovarian implants share the same *KRAS/BRAF* mutation of the primary serous BOTs, also suggesting a clonal evolution in this situation.<sup>[12,27]</sup> In an analysis of 57 serous BOTs with peritoneal implants, the concordance of *KRAS* and *BRAF* mutations between the primary BOTs and its implant pairs was 95% ( $p < .001$ ).<sup>[12]</sup>

However, the implications of *KRAS* and *BRAF* mutations in the progression of BOT to LGOC are distinct. *KRAS* mutations are frequently present in LGOC as in BOTs, while *BRAF* mutations are more common in BOTs than LGOC (Table 1).

In a small cohort of 23 patients with primary BOTs who presented recurrent LGOC, a *KRAS* mutation was found in most of the patients (78%). In this cohort, a *BRAF* mutation was identified in only one patient, in a sample of the primary BOT. These findings led the authors to conclude that in serous BOTs, *KRAS* (but no *BRAF*) mutations are associated with recurrent LGOC.<sup>[28]</sup>

A recent study evaluated the presence of *KRAS* and *BRAF* mutations in extra-ovarian implants of 39 patients with serous BOT. Among invasive implants (low-grade serous carcinoma), 60% presented *KRAS* mutation, while none had *BRAF* mutation. In non-invasive implants, otherwise, a lower frequency of *KRAS* mutations (14%) and a higher frequency of *BRAF* mutations (5%) were found ( $p = .001$ ). Additionally, *KRAS* mutation was associated with higher recurrence rates (71% vs. 21%, HR 4.15,  $p = .002$ ) and inferior disease-specific survival ( $p = .010$ ). These results reinforce a role of *KRAS* mutation as a prognostic factor and as a possibly implied pathway in the evolution of BOTs to LGOC.<sup>[29]</sup>

The specific *KRAS* mutation might also have a prognostic implication. In the cohort of 23 patients with serous BOTs and recurrent LGOC, the *KRAS* G12V mutation was associated with a shorter survival. The five patients with *KRAS* G12V mutations had a median overall survival of 125 months in comparison with 189 and 168 months in patients with *KRAS* G12D mutations (N=8) and *KRAS* wild-type/rare *KRAS* mutations (N=10), respectively (HR 4.77,  $p = 0.023$ ).<sup>[28]</sup> In the study conducted by Zuo

**Table 1.** Frequency of KRAS and BRAF mutation in borderline ovarian tumors and low-grade ovarian carcinoma.

	N		KRAS		BRAF	
	BOT	LGOC	BOT	LGOC	BOT	LGOC
Mok et al. <sup>[13]</sup>	25	-	36%	-	-	-
Haas et al. <sup>[14]</sup>	20	6	35%	33%	-	-
Singer et al. <sup>[15]</sup>	51	21	33%	35%	28%	33%
Mayr et al. <sup>[16]</sup>	18	-	22%	-	31.2%	-
Anglesio et al. <sup>[17]</sup>	30	-	18%	-	48%	-
Verbruggen et al. <sup>[18]</sup>	30	-	-	-	41%	-
Wong et al. <sup>[19]</sup>	30	43	17%	19%	30%	2%
Vereczkey et al. <sup>[20]</sup>	27	17	39%	23%	23%	0%
Schlosshauer et al. <sup>[21]</sup>	29	4	-	-	41%	0%
Bösmüller et al. <sup>[22]</sup>	31	7	-	-	71%	14%
Grisham et al. <sup>[23]</sup>	56	19	25%	15%	44%	5%
Showeil et al. <sup>[24]</sup>	61	10	20%	40%	25%	40%

et al. (2018),<sup>[29]</sup> two patients with serous BOTs and peritoneal implants presented *KRAS* G12V mutation and both of them died of the disease. Despite of the small sample sizes, these observations contribute to generate the hypothesis that *KRAS* G12V mutation is a negative prognostic factor in serous BOT.

*BRAF* mutations, otherwise, have been implied as a protective factor against the progression to LGOC. In a study that evaluated the immunohistochemical phenotype of BOTs, *BRAF* mutations were associated with the expression of senescence markers (SA- $\beta$ -gal, p16 and p21) and reduction in DNA synthesis.<sup>[30]</sup> In the same way, another study showed that serous BOTs with *BRAF* mutation overexpressed genes with known cell growth inhibitory effects.<sup>[20]</sup> A retrospective study of 75 patients with BOTs/LGOC also showed that *BRAF* V600E mutation is associated with serous BOT ( $p=.002$ ), early stage disease ( $p<.001$ ), and improved prognosis.<sup>[24]</sup>

Additionally, the majority of the studies evaluating *KRAS/BRAF* mutations in ovarian tumors showed that the frequency of *BRAF* mutation in LGOC is lower than that of BOTs.<sup>[20]</sup> These studies also showed that *BRAF* and *KRAS* mutations are mutually exclusive. Table 1 summarizes the results of studies that evaluated the frequency of *KRAS* or *BRAF* mutations in BOTs and LGOC. Besides *KRAS* and *BRAF*, *HER2* mutations have also been reported in BOTs in lower frequencies.<sup>[18]</sup>

Although fewer studies evaluated gene mutations in mucinous BOTs, *KRAS* mutations also seem to occur early and frequently in this histology. *KRAS* mutations have been shown in 39-92% of the mucinous BOTs.<sup>[14,21,31-34]</sup> *HER2* amplification/overexpression has been identified in 6% of the cases in an analysis of 176 patients with mucinous BOTs.<sup>[34]</sup>

Finally, the molecular differences between BOTs and high-grade ovarian carcinoma (HGOC) have been consistently shown.<sup>[35]</sup> *KRAS/BRAF* mutations are rare in HGOC. More characteristic of these ovarian tumors

are the p53 mutations, which are present in 50-80% of the cases.<sup>[21,35,36]</sup> In addition, *BRCA* mutations occur in a high frequency in HGOC and are unusual in BOTs/LGOC. In a cohort of Jewish women with early-stage ovarian tumors, *BRCA* mutation was present in 24% of the women with HGOC and 4% of those with BOTs ( $p=.001$ ).<sup>[37]</sup> In another study of 478 ovarian tumor patients, 19 presented *BRCA1* mutations, none among the 190 patients with borderline tumors.<sup>[38]</sup>

## Management

The standard treatment for BOTs is surgery.<sup>[39]</sup> The principles of radical surgery in BOTs are the same as for epithelial ovarian carcinoma, but there is no need for lymphadenectomy, because recurrence and survival are not influenced by the lymph node status.<sup>[6]</sup> The recommended procedure includes total abdominal hysterectomy, bilateral salpingo-oophorectomy, resection of all suspicious lesions, inframesocolic omentectomy, and peritoneal washing. A thorough peritoneal exploration is important to identify the presence of peritoneal implants. Lymph node involvement is not a prognostic factor in BOTs and lymphadenectomy is not required.<sup>[9,40]</sup> In mucinous BOTs, appendectomy is also indicated to exclude primary gastrointestinal tumors.<sup>[6]</sup> Importantly, a complete resection should always be pursued since incomplete resections are associated with higher recurrence rates.<sup>[41]</sup>

However, since many patients are diagnosed during childbearing ages, fertility-sparing surgery should be considered in stage I disease. Unilateral salpingo-oophorectomy (complemented by abdominal exploration, resection of suspicious lesions, omentectomy, and peritoneal washing) is an alternative in these cases. Cystectomy, with removal only of the tumor lesion, with preservation of the ovary, is associated with higher risk of recurrence.<sup>[42,43]</sup> In a retrospective analysis of 313 women with stage I BOT, cystectomy, unilateral salpingo-

oophorectomy and bilateral salpingo-oophorectomy were associated with recurrence rates of 30.3%, 11%, and 1.7% ( $p < .001$ ).<sup>[43]</sup> In mucinous BOTs, a Chinese retrospective analysis showed recurrence rates of 17%, 13%, and 4%, respectively.<sup>[44]</sup> Cystectomy should be then reserved for selected cases, such as in young patients with bilateral tumors or who have a single ovary. Importantly, despite of the higher recurrence, conservative surgery does not affect survival.

Fertility-sparing surgery can also be considered in cases of advanced stage BOTs without invasive implants.<sup>[45,46]</sup> However, a meta-analysis showed that the risk of lethal recurrence increases compared to early stage BOTs (pooled estimate: 2% and 0.5%).<sup>[46]</sup> After conservative treatment of BOTs, a systematic review found a pregnancy rate of 48%.<sup>[47]</sup>

In cases where patients have undergone fertility-preserving surgery, a common dilemma arises regarding whether to remove the remaining ovary and uterus once they have completed their family planning. As previously discussed, there is a considerable risk of recurrence, although the majority of these recurrences are still classified as BOT. Consequently, it seems reasonable to consider delaying surgery until the actual recurrence manifests. However, it's worth noting that waiting for relapse may impose a significant psychological burden on some patients. In such instances, the option of removing the remaining ovary becomes an acceptable option, given that a majority of relapses tend to occur within this organ.<sup>[6]</sup>

There are concerns on the safety for laparoscopy use in BOTs patients, which consist in the risk of tumor rupture during surgery, higher risk of positive margins in case of cystectomy, failure to perform a correct surgical staging, and port site metastases. According to Fauvet et al. (2005),<sup>[48]</sup> incomplete staging and tumor rupture during surgery were more frequent during laparoscopic surgery. In case of BOTs treated by fertility-sparing surgery, the risk of recurrence was 7.7% in case of laparotomy and 14.9% in case of laparoscopy.<sup>[49]</sup>

However, the results of two multicenter studies were completely different.<sup>[50,51]</sup> Both the Italian and the French study found no significant differences in the recurrence rate, following laparotomy compared with laparoscopy. The ROBOT study did not show any disadvantage for laparoscopy compared with laparotomy with respect to both relapse rate and overall survival.<sup>[52]</sup> While literature results may vary and there remains some controversy regarding the potential for an increased risk of relapse with laparoscopy, it is unlikely to yield a significant difference in survival outcomes. Considering its advantages in terms of improved cosmetic results and reduced surgical impact, the option of laparoscopy can be explored and discussed with the patient.<sup>[6]</sup>

Chemotherapy has no role for typical BOTs. These tumors have low proliferative rates and do not benefit from cytotoxic treatments. Even when invasive implants are identified, the use of adjuvant chemotherapy is questionable due to the low response expected and the lack of evidence showing its benefit.<sup>[39,53,54]</sup>

Although BOTs, as well as LGOC, might express estrogen receptor, the use of endocrine therapy so far is limited to situations in which LGOC is present.

## Perspectives

As presented above, the molecular profile is potentially useful as a tool to identify patients with higher risk of recurrence and progression to LGOC. So far, however, this knowledge has not translated in changes in clinical practice for BOTs.

Considering the gene mutations identified in BOTs and LGOC, MAPK pathway was suggested as a potential target. Therefore, MEK inhibitors such as selumetinib and trametinib were evaluated for patients with recurrent LGOC.

Tsang et al. (201)<sup>[28]</sup> investigated cancer cell lines sensitivity to selumetinib according to KRAS status and confirmed that cell lines with KRAS G12V mutation are more sensitive to selumetinib than cell lines with KRAS wild-type (OR 4,13,  $p = 0.005$ ). In their study of patients with BOTs with recurrent LGOC, two patients had KRAS G12V mutation and both were responders when treated with selumetinib.<sup>[28]</sup>

Among 52 patients enrolled in a single-arm phase II trial evaluating selumetinib, 15% had an objective response and 65% had stable disease.<sup>[55]</sup> More recently, a phase II/III trial (GOG 281) compared trametinib with treatment of physicians' choice (paclitaxel, pegylated liposomal doxorubicin, topotecan, letrozole, or tamoxifen) for patients with LGOC previously treated with at least one platinum-based regimen. Trametinib was associated with a superior objective response rate (26% vs. 6%) and progression-free survival (median, 13 months vs. 7.2 months; HR 0.48, 95%CI=0.36-0.64,  $p < 0.001$ ).<sup>[56]</sup> On the other hand, another randomized trial evaluating the MEK inhibitor binimetinib was closed early for futility, despite some activity of the drug (objective response rate 16%).<sup>[57]</sup>

Finally, considering the frequency of BRAF mutations in BOTs/LGOC, it is interesting to mention the agnostic approval of the combination of dabrafenib (BRAF inhibitor) plus trametinib for patients with metastatic cancers harboring a BRAF V600E mutation.<sup>[58]</sup> Some impressive responses to this combination have been described in case reports of patients with LGOC with a BRAF V600E mutation.<sup>[59,60]</sup>

In face of these results, further studies directed to this pathway, including studies for patients with BOTs, are warranted.

## CONCLUSION

BOTs are indolent tumors and present an overall favorable prognosis. However, some patients might present recurrence and progression to LGOC. BOTs with *KRAS* mutations have higher risk of recurrence and progression to LGOC, while *BRAF* mutations have been shown to be a protective factor, associated with senescence. Although radical surgery remains the mainstay of the treatment of BOTs, the cumulative knowledge about its biology may allow the future development of personalized therapies. Studying rare tumors such as BOTs, however, remains a challenge. Global efforts are warranted to allow advances in the scientific knowledge and the management of these patients.

## AUTHORS' CONTRIBUTIONS

RCB	Collection and assembly of data, Conception and design, Data analysis and interpretation, Final approval of manuscript, Manuscript writing.
AGSS	Data analysis and interpretation, Final approval of manuscript, Manuscript writing.
MDPED	Conception and design, Data analysis and interpretation, Final approval of manuscript.

## REFERENCES

- World Health Organization (WHO). WHO classification of tumours of female reproductive organs. 4th ed. Lyon: WHO; 2014.
- Abascal-Saiz A, Sotillo-Mallo L, Santiago J, Zapardiel I. Management of borderline ovarian tumours: a comprehensive review of the literature. *Ecanermedicalscience*. 2014;8:403.
- McCluggage WG, Judge MJ, Clarke BA, Davidson B, Gilks CB, Hollema H, et al. Data set for reporting of ovary, fallopian tube and primary peritoneal carcinoma: recommendations from the International Collaboration on Cancer Reporting (ICCR). *Mod Pathol*. 2015 Aug;28(8):1101-22.
- Gica N, Mustata L, Botezatu R, et al. Management of borderline ovarian tumors: series of case report and review of the literature. *Indian J Surg*. 2021;12:617-24.
- Carbonnel M, Layoun L, Poulain M, Tourne M, Murtada R, Grynberg M, et al. Serous borderline ovarian tumor diagnosis, management and fertility preservation in young women. *J Clin Med*. 2021 Sep;10(18):4233.
- Du Bois A, Trillsch F, Mahner S, Heitz F, Harter P. Management of borderline ovarian tumors. *Ann Oncol*. 2016 Apr;27(Suppl 1):i20-i2.
- Fischerova D, Zikan M, Dundr P, Cibula D. Diagnosis, treatment, and follow-up of borderline ovarian tumors. *Oncologist*. 2012;17(12):1515-33.
- De Decker K, Speth S, Ter Brugge HG, Bart J, Massuger LFAG, Kleppe M, et al. Staging procedures in patients with mucinous borderline tumors of the ovary do not reveal peritoneal or omental disease. *Gynecol Oncol*. 2017 Feb;144(2):285-9.
- Seidman JD, Kurman RJ. Ovarian serous borderline tumors: a critical review of the literature with emphasis on prognostic indicators. *Hum Pathol*. 2000;31(5):539-57.
- Bell DA, Longacre TA, Prat J, Kohn EC, Soslow RA, Ellenson LH, et al. Serous borderline (low malignant potential, atypical proliferative) ovarian tumors: workshop perspectives. *Hum Pathol*. 2004 Aug;35(8):934-48.
- Longacre TA, McKenney JK, Tazelaar HD, Kempson RL, Hendrickson MR. Ovarian serous tumors of low malignant potential (borderline tumors): outcome-based study of 276 patients with long-term (> or =5-year) follow-up. *Am J Surg Pathol*. 2005 Jun;29(6):707-23.
- Ardighieri L, Zeppernick F, Hannibal CG, Vang R, Cope L, Junge J, et al. Mutational analysis of BRAF and KRAS in ovarian serous borderline (atypical proliferative) tumours and associated peritoneal implants. *J Pathol*. 2014 Jan;232(1):16-22.
- Malpica A, Longacre TA. Prognostic indicators in ovarian serous borderline tumours. *Pathology*. 2018 Feb;50(2):205-13.
- Mok SC, Bell DA, Knapp RC, Fishbaugh PM, Welch WR, Muto MG, et al. Mutation of K-ras protooncogene in human ovarian epithelial tumors of borderline malignancy. *Cancer Res*. 1993 Apr;53(7):1489-92.
- Haas CJ, Diebold J, Hirschmann A, Rohrbach H, Löhrs U. In serous ovarian neoplasms the frequency of Ki-ras mutations correlates with their malignant potential. *Virchows Arch*. 1999 Feb;434(2):117-20.
- Singer G, Oldt R, Cohen Y, Wang BG, Sidransky D, Kurman RJ, et al. Mutations in BRAF and KRAS characterize the development of low-grade ovarian serous carcinoma. *J Natl Cancer Inst*. 2003 Mar;95(6):484-6.
- Mayr D, Hirschmann A, Löhrs U, Diebold J. KRAS and BRAF mutations in ovarian tumors: a comprehensive study of invasive carcinomas, borderline tumors and extraovarian implants. *Gynecol Oncol*. 2006 Dec;103(3):883-7.
- Anglesio MS, Arnold JM, George J, Tinker AV, Tothill R, Waddell N, et al. Mutation of ERBB2 provides a novel alternative mechanism for the ubiquitous activation of RAS-MAPK in ovarian serous low malignant potential tumors. *Mol Cancer Res*. 2008 Nov;6(11):1678-90.
- Verbruggen MB, Sieben NL, Roemen GM, Rockx DA, van Diest PJ, Verheijen RH, et al. v-Raf murine sarcoma viral oncogene mutation status in serous borderline ovarian tumors and the effect on clinical behavior. *Int J Gynecol Cancer*. 2009 Dec;19(9):1560-3.

20. Wong KK, Tsang YT, Deavers MT, Mok SC, Zu Z, Sun C, et al. BRAF mutation is rare in advanced-stage low-grade ovarian serous carcinomas. *Am J Pathol*. 2010 Oct;177(4):1611-7.
21. Vereczkey I, Serester O, Dobos J, Gallai M, Szakács O, Szentirmay Z, et al. Molecular characterization of 103 ovarian serous and mucinous tumors. *Pathol Oncol Res*. 2011 Sep;17(3):551-9.
22. Schlosshauer PW, Deligdisch L, Penault-Llorca F, Fatemi D, Qiao R, Yao S, et al. Loss of p16INK4A expression in low-grade ovarian serous carcinomas. *Int J Gynecol Pathol*. 2011 Jan;30(1):22-9.
23. Bösmüller H, Fischer A, Pham DL, Fehm T, Capper D, von Deimling A, et al. Detection of the BRAF V600E mutation in serous ovarian tumors: a comparative analysis of immunohistochemistry with a mutation-specific monoclonal antibody and allele-specific PCR. *Hum Pathol*. 2013 Mar;44(3):329-35.
24. Grisham RN, Iyer G, Garg K, Delair D, Hyman DM, Zhou Q, et al. BRAF mutation is associated with early stage disease and improved outcome in patients with low-grade serous ovarian cancer. *Cancer*. 2013 Feb;119(3):548-54.
25. Showeil R, Romano C, Valganon M, Lambros M, Trivedi P, Van Noorden S, et al. The status of epidermal growth factor receptor in borderline ovarian tumours. *Oncotarget*. 2016 Mar;7(9):10568-77.
26. Ho CL, Kurman RJ, Dehari R, Wang TL, Shih IM. Mutations of BRAF and KRAS precede the development of ovarian serous borderline tumors. *Cancer Res*. 2004 Oct;64(19):6915-8.
27. Diebold J, Seemüller F, Löhns U. K-RAS mutations in ovarian and extraovarian lesions of serous tumors of borderline malignancy. *Lab Invest*. 2003 Feb;83(2):251-8.
28. Tsang YT, Deavers MT, Sun CC, Kwan SY, Kuo E, Malpica A, et al. KRAS (but not BRAF) mutations in ovarian serous borderline tumour are associated with recurrent low-grade serous carcinoma. *J Pathol*. 2013 Dec;231(4):449-56.
29. Zuo T, Wong S, Buza N, Hui P. KRAS mutation of extraovarian implants of serous borderline tumor: prognostic indicator for adverse clinical outcome. *Mod Pathol*. 2018 Feb;31(2):350-7.
30. Zeppernick F, Ardighieri L, Hannibal CG, Vang R, Junge J, Kjaer SK, et al. BRAF mutation is associated with a specific cell type with features suggestive of senescence in ovarian serous borderline (atypical proliferative) tumors. *Am J Surg Pathol*. 2014 Dec;38(12):1603-11.
31. Cuatrecasas M, Villanueva A, Matias-Guiu X, Prat J. K-ras mutations in mucinous ovarian tumors: a clinicopathologic and molecular study of 95 cases. *Cancer*. 1997 Apr;79(8):1581-6.
32. Li XS, Sun J, He XL. Expression of c-myc and mutation of the KRAS gene in patients with ovarian mucinous tumors. *Genet Mol Res*. 2015 Sep;14(3):10752-9.
33. Mackenzie R, Kommos S, Winterhoff BJ, Kipp BR, Garcia JJ, Voss J, et al. Targeted deep sequencing of mucinous ovarian tumors reveals multiple overlapping RAS-pathway activating mutations in borderline and cancerous neoplasms. *BMC Cancer*. 2015 May;15:415.
34. Anglesio MS, Kommos S, Tolcher MC, Clarke B, Galletta L, Porter H, et al. Molecular characterization of mucinous ovarian tumours supports a stratified treatment approach with HER2 targeting in 19% of carcinomas. *J Pathol*. 2013 Jan;229(1):111-20.
35. Singer G, Stöhr R, Cope L, Dehari R, Hartmann A, Cao DF, et al. Patterns of p53 mutations separate ovarian serous borderline tumors and low- and high-grade carcinomas and provide support for a new model of ovarian carcinogenesis: a mutational analysis with immunohistochemical correlation. *Am J Surg Pathol*. 2005 Feb;29(2):218-24.
36. Sundov D, Caric A, Mrklic I, Gugic D, Capkun V, Hofman ID, et al. P53, MAPK, topoisomerase II alpha and Ki67 immunohistochemical expression and KRAS/BRAF mutation in ovarian serous carcinomas. *Diagn Pathol*. 2013;8:21.
37. Gotlieb WH, Chetrit A, Menczer J, Hirsh-Yechezkel G, Lubin F, Friedman E, et al. Demographic and genetic characteristics of patients with borderline ovarian tumors as compared to early stage invasive ovarian cancer. *Gynecol Oncol*. 2005 Jun;97(3):780-3.
38. Bjørge T, Lie AK, Hovig E, Gislefoss RE, Hansen S, Jellum E, et al. BRCA1 mutations in ovarian cancer and borderline tumours in Norway: a nested case-control study. *Br J Cancer*. 2004 Nov;91(10):1829-34.
39. Berek JS, Kehoe ST, Kumar L, Friedlander M. Cancer of the ovary, fallopian tube, and peritoneum. *Int J Gynaecol Obstet*. 2018 Oct;143(Suppl 2):61-85.
40. Lesieur B, Kane A, Duvillard P, Gouy S, Pautier P, Lhommé C, et al. Prognostic value of lymph node involvement in ovarian serous borderline tumors. *Am J Obstet Gynecol*. 2011 May;204(5):438.e1-7.
41. Romeo M, Pons F, Barretina P, Radua J. Incomplete staging surgery as a major predictor of relapse of borderline ovarian tumor. *World J Surg Oncol*. 2013;11:13.
42. Suh-Burgmann E. Long-term outcomes following conservative surgery for borderline tumor of the ovary: a large population-based study. *Gynecol Oncol*. 2006 Dec;103(3):841-7.
43. Poncelet C, Fauvet R, Boccara J, Daraï E. Recurrence after cystectomy for borderline ovarian tumors: results of a French multicenter study. *Ann Surg Oncol*. 2006 Apr;13(4):565-71.
44. Cao DY, Shen K, Tao T, Yang JX, Xiang Y, Huang HF, et al. Clinicopathologic analysis of 130 cases of mucinous borderline ovarian tumors. *Zhonghua Fu Chan Ke Za Zhi*. 2011 Jan;46(1):15-8.
45. Huang Y, Zhang W, Wang Y. The feasibility of fertility-sparing surgery in treating advanced-stage borderline ovarian tumors: a meta-analysis. *Taiwan J Obstet Gynecol*. 2016 Jun;55(3):319-25.

46. Darai E, Fauvet R, Uzan C, Gouy S, Duvillard P, Morice P. Fertility and borderline ovarian tumor: a systematic review of conservative management, risk of recurrence and alternative options. *Hum Reprod Update*. 2013 Mar/Apr;19(2):151-66.
47. Swanton A, Bankhead CR, Kehoe S. Pregnancy rates after conservative treatment for borderline ovarian tumours: a systematic review. *Eur J Obstet Gynecol Reprod Biol*. 2007 Nov;135(1):3-7.
48. Fauvet R, Boccarda J, Dufournet C, Poncelet C, Darai E. Laparoscopic management of borderline ovarian tumors: results of a French multicenter study. *Ann Oncol*. 2005 Mar;16(3):403-10.
49. Du Bois A, Ewald-Riegler N, Du Bois O, Harter P. Borderline tumors of the ovary. A systematic review. *Geburstsh Frauenheilk*. 2009;69:807-33.
50. Romagnolo C, Gadducci A, Sartori E, Zola P, Maggino T. Management of borderline ovarian tumors: results of an Italian multicenter study. *Gynecol Oncol*. 2006 May;101(2):255-60.
51. Fauvet R, Boccarda J, Dufournet C, David-Montefiore E, Poncelet C, Darai E. Restaging surgery for women with borderline ovarian tumors: results of a French multicenter study. *Cancer*. 2004 Mar;100(6):1145-51.
52. Du Bois A, Ewald-Riegler N, Gregorio N, Reuss A, Mahner S, Fotopoulou C, et al. Borderline tumours of the ovary: a cohort study of the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Study Group. *Eur J Cancer*. 2013 May;49(8):1905-14.
53. Shih KK, Zhou QC, Aghajanian C, Huh J, Soslow RA, Morgan JC, et al. Patterns of recurrence and role of adjuvant chemotherapy in stage II-IV serous ovarian borderline tumors. *Gynecol Oncol*. 2010 Nov;119(2):270-3.
54. Vasconcelos I, Olschewski J, Braicu I, Sehouli J. Limited efficacy of platinum-based adjuvant treatment on the outcome of borderline ovarian tumors. *Eur J Obstet Gynecol Reprod Biol*. 2015 Mar;186:26-33.
55. Farley J, Brady WE, Vathipadiekal V, Lankes HA, Coleman R, Morgan MA, et al. Selumetinib in women with recurrent low-grade serous carcinoma of the ovary or peritoneum: an open-label, single-arm, phase 2 study. *Lancet Oncol*. 2013 Feb;14(2):134-40.
56. Gershenson DM, Miller A, Brady WE, Paul J, Carty K, Rodgers W, et al. Trametinib versus standard of care in patients with recurrent low-grade serous ovarian cancer (GOG 281/LOGS): an international, randomised, open-label, multicentre, phase 2/3 trial. *Lancet*. 2022 Feb;399(10324):541-53.
57. Monk BJ, Grisham RN, Banerjee S, Kalbacher E, Mirza MR, Romero I, et al. MILO/ENGOT-ov11: binimetinib versus physician's choice chemotherapy in recurrent or persistent low-grade serous carcinomas of the ovary, fallopian tube, or primary peritoneum. *J Clin Oncol*. 2020 Nov;38(32):3753-62.
58. Vranic S, Basu GD, Hall DW, Gatalica Z. Tumor-type agnostic, targeted therapies: braf inhibitors join the group. *Acta Med Acad*. 2022 Dec;51(3):217-31.
59. Tholander B, Koliadi A, Botling J, Dahlstrand H, Von Heideman A, Ahlström H, et al. Complete response with combined BRAF and MEK inhibition in BRAF mutated advanced low-grade serous ovarian carcinoma. *Ups J Med Sci*. 2020 Nov;125(4):325-9.
60. Lima B, Abreu MH, Sousa S, Bartosch C, Pereira D. Impressive and durable clinical responses obtained with dabrafenib and trametinib in low-grade serous ovarian cancer harbouring a BRAF V600E mutation. *Gynecol Oncol Rep*. 2022 Feb;40:100942.