


# The Diagnosis, Treatment, Prognosis and Molecular Pathology of Borderline Ovarian Tumors: Current Status and Perspectives

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**Abstract:** Borderline ovarian tumors (BOTs) are a type of low malignant potential tumor that is typically associated with better outcomes than ovarian cancer. Indeed, its 10-year survival rate is as high as 95%. However, there is a small subset of patients who experience relapse and eventually die. It has been shown that the prognosis of BOTs was based on pathological diagnosis, the age at diagnosis, pre-operative carbohydrate antigen 125 level, invasive implants, and micropapillary patterns. Now the molecular-targeted therapy and molecular-genetic diagnosis have developed into a form of precision medicine. Recent studies on extensive molecular characterizations and molecular pathological mechanisms of BOTs have helped us understand the genomic landscapes of BOTs, and therefore BOTs could be reclassified into biologically and clinically more accurate and effective subtypes. The purpose of this review is to summarize current status for the diagnosis and treatment of BOTs and to describe the research progress on molecular pathologies, with a goal of providing a theoretical perspective for the diagnosis and treatment of BOTs.

**Keywords:** borderline ovarian tumor, diagnosis, prognosis, molecular characterization

## Introduction

In 1929, Taylor first proposed the concept of a borderline ovarian tumor, which was called a “semi-malignant ovarian tumor” at the time. In 1971, the International Federation of Obstetrics and Gynecology (FIGO) identified borderline ovarian tumors as a “low-grade malignant tumor” completely different from ovarian cancer. In the World Health Organization (WHO) classification of female genital tumors in 2014, the word “low-grade malignant tumor” was replaced by “borderline tumor” or “atypical proliferative tumor”.<sup>1</sup>

Borderline ovarian tumors (BOTs) account for 15% of epithelial ovarian tumors.<sup>2</sup> Depending on the type of tissue that is undergoing aberrant growth, BOTs can be divided into mucinous borderline ovarian tumors (MBOTs), serous borderline ovarian tumors (SBOTs), endometrial borderline tumors, clear cell borderline tumors, brenner borderline tumors, and others.<sup>3</sup> In a cohort study in Denmark, MBOTs accounted for 50% of BOTs, and SBOTs accounted for 44% of cases.<sup>4</sup> Of note, the relative portion of BOTs that are MBOTs in Asia is 75.2%, which is different from other continents.<sup>5</sup>

Compared with ovarian cancer, the vast majority of BOT is often limited to one or both sides of the ovary. Impressively, 75% of BOT is diagnosed at stage I,

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resulting in a good prognosis and a 10-year survival rate of about 95%.<sup>6</sup> However, a small fraction of patients still experience recurrence or transformation into low-grade serous ovarian carcinoma (LGSOC), and the transformation was concealed, and LGSOC have been shown to respond poorly to platinum chemotherapy.<sup>7</sup> Therefore, identifying the risk factors for invasive recurrence and clinical nonresponse are key to ensuring the successful treatment of BOT.<sup>8</sup> The primary method of treatment of BOTs is surgery. The choice of surgery should be evaluated according to patients' age, fertility requirements, pathological stage, and pathological types.<sup>9</sup> Because of the poor response of BOTs to chemotherapy, adjuvant chemotherapy is generally not recommended.<sup>10</sup>

In this work, we will discuss the diagnosis, treatment, prognosis, and current understandings of the molecular pathology of two common types of BOT.

## Diagnosis and Treatment

### Diagnosis

Whereas the preoperative diagnosis of BOTs is difficult, a speculative diagnosis can be made according to clinical manifestations, tumor markers, and imaging examination. However, the final diagnosis needs to be supported by a pathological diagnosis encompassing the unusual degree of epithelial cell proliferation, and the existence of microinvasion.<sup>11,12</sup>

Almost 30% of patients with BOTs have no prior symptoms prior to diagnosis, and about 50–60% of patients have non-specific symptoms such as abdominal pain, abdominal distention, nonspecific vaginal bleeding, and sexual discomfort.<sup>13</sup> In a study of 151 women with BOTs, 84% had these non-specific symptoms before diagnosis, and the average duration of symptoms in these patients was 6 months.<sup>14</sup>

Transvaginal ultrasound (TVUS), magnetic resonance imaging (MRI), and computed tomography (CT) are indispensable methods to assist in the presumptive diagnosis of BOTs. In a systematic review and meta-analysis of imaging tools for the diagnosis of BOTs, their sensitivities and specificities are 77.0% and 83.0% (TVUS), 85% and 74% (MRI), respectively.<sup>15</sup> Ultrasound imaging had a certain value for the preoperative diagnosis of BOTs.<sup>16–18</sup> However, recent reports have suggested that the preoperative diagnosis of BOTs is only with an accuracy of 69%.<sup>19</sup> Due to the absence of typical morphological features in BOTs, it is hard to distinguish BOTs from benign or malignant ovarian tumors.<sup>20,21</sup> The value of CT and MRI features in differentiating BOTs from malignant tumors was relatively limited because of solid components size and septations' thickness.<sup>22,23</sup>

In a study of 266 patients from South Korea, when compared with a single tumor marker, such as ultrasound, menopausal state, carbohydrate antigen 125 (CA125), human epididymis protein 4 (HE4) and carbohydrate antigen 19–9 (CA19-9), the risk algorithm for ovarian cancer (ROMA, combined CA125, HE4 and Menopausal state) was found to be the best way to distinguish malignant and borderline tumors from benign tumors.<sup>24</sup> While other studies indicated that the malignant tumor risk index (RMI, combined CA125, ultrasound and Menopausal state) is the best prediction method for distinguishing between borderline and benign ovarian tumors (Table 1).<sup>17</sup> When the cutoff value of RMI1, RMI2<sup>18</sup> and RMI3<sup>19</sup> is 200, the sensitivities are 80%, 90%, 80%, respectively, and the specificities are 86.4%, 82.6%, and 86.4%, respectively. At the cutoff value of 450, RMI 4 has a sensitivity of 86.8% and a specificity of 91.0%.<sup>20</sup>

### Treatment

Patients with any stage of BOT should undergo surgery. It is recommended that fertility-preserving patients should take

**Table 1** Different Algorithms of Malignant Tumor Risk Index (RMI)

	Formula	Ultra Sound Score (U)	Menopausal Status (M)	CA125	Tumor Size (S)
RMI1 <sup>79</sup>	$U \times M \times CA125$	Score=0,U=0; Score=1,U=1; Score≥2, U=3	Premenopause M=1; Postmenopause, M=3	Actual measured value	–
RMI2 <sup>80</sup>	$U \times M \times CA125$	Score=0 or 1, U=1; Score≥2, U=4	Premenopause M=1; Postmenopause, M=4		–
RMI3 <sup>81</sup>	$U \times M \times CA125$	Score=0 or 1, U=1; Score≥2, U=3	Premenopause M=1; Postmenopause M=3		–
RMI4 <sup>82</sup>	$U \times M \times S \times CA125$	Score=0 or 1, U=1; Score≥2, U=4	Premenopause M=1; Postmenopause M=4		<7 cm, S = 1; >7 cm, S = 2

unilateral or bilateral salpingo-oophorectomy.<sup>25</sup> For patients without fertility requirements, total hysterectomy and bilateral salpingo-oophorectomy are recommended.<sup>7</sup> Patients with metastases should be treated with maximal resection of the tumor. Laparoscopic surgery and open surgery showed similar recurrence rates and 10-year disease-free survival rate for BOTs.<sup>26</sup> The laparoscopic surgery showed more favorable surgical outcomes including shorter operative time, shorter hospital stays, less blood loss, less transfusion requirement, sooner recovery of bowel movement, and fewer perioperative complications.<sup>27,28</sup> The role of adjuvant chemotherapy for BOTs is still controversial. In early series, adjuvant chemotherapy showed beneficial effects in patients with advanced-stage,<sup>29</sup> but in a prospective Gynecologic Oncology Group Study, Sutton et al<sup>30</sup> noted that cisplatin-based chemotherapy had no effect on overall survival. And in a retrospective study of 80 patients with FIGO stage II–IV BOTs, Shih et al<sup>31</sup> reported that there are no difference in 3-year progression-free survival between patients who had received adjuvant chemotherapy or not.

It has been shown that the human cancer cell lines (extracted from “Cancer Cell Line Encyclopedia (CCLE)” database<sup>32</sup> and categorized based on their KRAS mutation status) with the KRAS G12V mutation was more sensitive to AZD6244 (selumetinib) than cells with wild-type KRAS.<sup>33</sup> A small-scale study showed that 2 SBOTs with the G12V mutation had development into LGSOC, and responded better to selumetinib.<sup>33</sup> This study confirmed that research on the molecular pathology of disease can critically inform the clinical management of BOT.

## Recurrence and Prognosis

Although the prognosis of most BOTs is good, there are still a few patients who will relapse and eventually die. According to a retrospective survey conducted by the Sloan Kettering Cancer Center in the United States, the age at the time of diagnosis, preoperative CA125 level, invasive implants, and micropapillary patterns are clinical factors that predict the risk of recurrence of BOTs.<sup>34</sup> Additionally, higher stage at diagnosis, the use of BOT surgical method, and a history of pelvic inflammation are also clinical factors for the recurrence of BOTs.<sup>35,36</sup>

## Peritoneal Implants

In the 1970s and 1980s, peritoneal implantation was widely used as a prognostic indicator. Implants were classified as invasive implants or non-invasive implants according to the morphology under the microscope.<sup>37</sup> At

that time, invasive implants and non-invasive implants were the most important prognostic indicators.<sup>38</sup> After 7.4 years of follow-up, the survival rate of patients with non-invasive peritoneal implants was 95.3%, while that of patients with invasive peritoneal implants was 66%. Invasive implantation was indicative of relatively poor outcomes.<sup>31,38</sup> It is generally believed that the mortality of SBOTs patients is typically attributable to death due to non-ovarian tumor diseases.<sup>39</sup> There is still a considerable controversy on how to treat SBOTs because of the difficulty in distinguishing non-invasive implants and invasive implants.<sup>39</sup> In one study, McKinney et al pathologists independently evaluated 8 morphological characteristics of peritoneal and/or lymph node implants in 181 patients with high-grade serous borderline tumors. These results showed that low-power destructive tissue invasion was the best predictor of poor prognosis.<sup>40</sup>

## Operation Methods

Based on a multivariate analysis of 127 BOTs, fertility-preserving surgery is an independent prognostic factor of decreased 5-year recurrence-free survival (RFS). Indeed, conservative surgery is closely related to recurrence.<sup>41</sup> Vasconcelos and de Sousa Mendes<sup>42</sup> analyzed 39 studies using the PubMed database and Cochrane Library, including a total of 5105 women that underwent conservative surgery (2624 serous, 2120 mucinous, and 361 other types of BOT). They found that unilateral SBOT had a higher recurrence rate after ovarian tumor resection, but that there was no significant difference in overall survival rate across tumor types.

## Micropapillary Pattern

A micropapillary pattern has often been reported to be associated with invasive implants, bilateral ovarian involvement, and lymph node metastasis.<sup>43–46</sup> However, the use of micropapillary pattern as an independent factor to predict BOTs is controversial in the field.<sup>46,47</sup> Park et al<sup>46</sup> and Chang et al<sup>47</sup> pointed out that the micropapillary pattern is a poor prognostic factor for BOTs because it is closely associated with microinvasion, lymph node metastasis, and peritoneal implants, but they did not report the micropapillary pattern as an independent risk factor for death. In contrast, Burks, Shih, Sozen et al suggested that the micropapillary pattern was an independent risk factor associated with recurrence of BOTs.<sup>34,43,48</sup>

In general, it seems likely that the micropapillary pattern, invasive peritoneal implants, and the method of

surgery can affect the prognosis of patients with BOT; however, follow-up studies are needed to confirm whether these factors independently or collectively affect BOT recurrence and prognosis.<sup>49</sup>

## Molecular Pathology

The development of molecular biology has greatly promoted our understanding of the occurrence, and progression of BOTs. As a low malignant potential ovarian epithelial tumor, peritoneal metastases are also observed in BOTs, but the peritoneal implantation in BOTs may subside by itself, which is totally different from malignant ovarian tumor, and responsible for the high survival rate of BOTs. However, the driver of metastatic tumor regression or malignant progression in BOTs is still unknown. Here, we summarized the research progress of the molecular characteristics of BOTs and compared the difference between BOTs and malignant ovarian tumors, with the aim to find the driver genes for the malignant transformation potential or metastatic tumor regression.

### Molecular Profiling of Borderline Ovarian Tumors

A variety of studies discussed the molecular characteristic of BOTs and their relationship with malignant ovarian tumor and benign ovarian tumor. As shown in Table 2, according to the molecular characteristics, some experts

believed that BOTs may close to benign ovarian tumors, while other experts suggested that BOTs may close to malignant ovarian tumors.

Waldemarson et al<sup>50</sup> carried out isobaric tags for relative and absolute quantitation (iTRAQ) technology to present a shotgun quantitative proteomic screen of 51 ovarian tissue samples (7 normal cases, 4 benign cases, 16 borderline cases and 24 malignant cases) and further confirmed selected candidate proteins from the shotgun screen using multiple reaction monitoring (MRM) analysis. Receiver Operating Characteristic (ROC)-area analysis using MRM profile showed that the malignant and benign tumors were perfectly separated with a ROC-area of 1 while the ROC analysis placed BOTs closer to the malignant than the benign tumors (ROC area = 0.97, benign vs borderline, ROC area = 0.85, borderline vs malignant). Further, Bengtsson et al<sup>51</sup> used two-dimension difference gel electrophoresis (2D-DIGE) analysis to study 64 epithelial ovarian tissues (8 normal tissues, 12 benign tumor tissues, 17 borderline tumor tissues, 27 malignant tumor tissues). ROC-area analysis based on statistical analysis of gel images also showed that BOTs were closer to the malignant tumors than the benign tumors (ROC area = 0.98, borderline vs benign, ROC area = 0.92, borderline vs malignant). However, in Alaiya et al study, 40 of ovarian tumor cases (including 10 BOTs) were classified by hierarchical cluster analysis based on the expression of proteins analyzed by 2D-DIGE, and it was found that BOTs were more closely related to benign tumors than to malignant tumors.<sup>52</sup> Curry et al<sup>53</sup> used Affymetrix HGU133 plus2 GeneChip microarrays to study the gene expression profile of 3 LGSOCs, 13 SBOTs and 8 serous ovarian cystadenomas. Unsupervised clustering revealed that the benign and malignant tumors were clearly separated, whereas BOTs showed two different molecular subtypes: benign-like group and malignant-like group.

### Gene Expression and Pathways Alteration in BOTs

Although only few studies have focused on the molecular mechanism of malignant transformation of BOTs, the limited studies still greatly promote our understanding of the biological pathology of BOTs and provide important information for the prognosis and recurrence risk prediction of BOTs (Table 3).

It has been reported that 88% of SBOTs contain BRAF or KRAS mutations and that 86% of cystadenoma epithelial cells adjacent to SBOTs harbor the same mutations, indicating that mutations in BRAF or KRAS are very early

**Table 2** Molecular Profiling of BOTs

Authors	Methods	Results
Waldemarson et al <sup>50</sup>	iTRAQ Screen MRM Analysis ROC-Curve Analysis	ROC area=1, benign vs malignant ROC area=0.97, benign vs borderline ROC area=0.85, borderline vs malignant
Bengtsson et al <sup>51</sup>	2D DIGE Analysis ROC-Curve Analysis	ROC area=1, benign vs malignant ROC area=0.98, benign vs borderline ROC area=0.92, borderline vs malignant
Alaiya et al <sup>52</sup>	Hierarchical cluster Analysis	BOTs close to benign tumors
Curry et al <sup>53</sup>	Gene Expression Microarrays Hierarchical cluster Analysis	Benign-like BOTs Malignant-like BOTs

**Table 3** The Mutation or Abnormal Expression Frequency of BOTs-Related Genes

	Gene	SBOTs	MBOTs
MAPK Pathway Activation <sup>56-58,63</sup>	BRAF mutation	23-48%	0.0%
	KRAS mutation	17-39.5%	92.3%
	ERBB2 mutation/Amplification	6%	3.8%/11.5%
	Claudin-1 overexpression	26.3%	NA
PI3K/AKT Pathway Activation <sup>57,64</sup>	p53 mutation/Overexpression	Overexpression	11.5%
	CDKNA2 mutation	NA	19.2%
	PTEN mutation	NA	3.8%
	PIK3CA mutation	NA	15.4%
Hedgehog Pathway Activation <sup>74</sup>	SHH positive expression	42.8%	0.0%
	IHH positive expression	14.3%	0.0%
	DHH positive expression	71.4%	12.5%
	PTCH positive expression	71.4%	62.5%
	SMO positive expression	42.8%	62.5%
	GLI1 positive expression	57.1%	37.5%
Clarification of Mucinous Subtype & Indicators for the Malignant Features	TFF3 strong expression <sup>66</sup>	0.0%	61.4%
	IMP3 strong expression <sup>68</sup>	8.3%	42.2%

events in the development of SBOTs.<sup>54,55</sup> In addition, the ERBB2 mutation was found in 6% of SBOTs.<sup>56</sup> In MBOTs, mutations of KRAS (92.3%), p53 (11.5%), CDKN2A (19.2%), PIK3CA (15.4%), PTEN (3.8%), ERBB2 (3.8%) and amplification of ERBB2 (11.5%) have been reported. Besides, 7.7% of MBOTs showed ERBB2 amplification and KRAS mutation at the same time.<sup>57</sup> The amplification region of ERBB2 contains KRAS mutations, indicating that these mutations occur in the same cell line and that the mutation frequency of the KRAS allele is consistent in the amplification and non-amplification region of ERBB2. This suggests that the mutation occurred before the amplification event.<sup>57</sup> Moreover, mutations in KRAS, BRAF, and ERBB2 are mutually exclusive; mutations in any one of these three genes will activate the mitogen-activated protein kinase (MAPK) signaling pathway, leading to uncontrolled cell proliferation.<sup>56</sup> The incidence of KRAS mutation in SBOTs (17-39.5%) was similar to that in LGSOC (19-54.5%). On the contrary, the incidence of BRAF mutation in SBOT and LGSOC was 23-48% and 0-33%, respectively.<sup>58</sup> Therefore, benign ovarian serous tumors may progress to SBOTs due to BRAF mutations, but such mutations rarely participate in the transformation to LGSOC.<sup>59</sup> SBOTs with BRAF mutations are associated with cell senescence and up-regulation of tumor suppressor genes.<sup>60</sup> KRAS mutations are common (>70%) in recurrent LGSOC, while BRAF mutations are rare,

which suggested that recurrent LGSOC could arise from SBOTs having KRAS mutations or other genetic changes but not BRAF mutations.<sup>33</sup>

The vast majority of peritoneal implants, both non-invasive and invasive, harbored the same KRAS or BRAF mutations, presented in the associated SBOT.<sup>61</sup> Compared with non-invasive implants, patients with invasive extra-ovarian peritoneal implants had a higher stage of disease, a higher recurrence rate and a shorter survival period.<sup>62</sup> KRAS mutations are common in SBOTs with invasive implants and recurrent low-grade serous ovarian cancer, but the BRAF V600E mutation is not common.<sup>33,62</sup> Therefore, regardless of the histological subtypes of implants, KRAS mutations are an important prognostic indicator of tumor recurrence and decreased disease-specific survival rate.<sup>62</sup> In addition, El-Balat et al found that Claudin-1 is related to predictors of poor prognosis (eg, peritoneal implantation and micropapillary pattern), and the authors hypothesized that the overexpression of Claudin-1 may be related to the activation of the mitogen-activated protein kinase (MAPK) signaling pathway.<sup>63</sup>

Different from inhibited p53 signaling in high-grade serous ovarian cancer (HGSOC), overexpressed p53 and changes in genes associated with the p53 pathway were observed in SBOTs.<sup>64</sup> Cheng et al<sup>65</sup> confirmed that SBOTs contained wild-type p53 by sequencing. Besides, they found that inhibition of p53 can significantly increase the invasiveness of SBOT cells. By activating the PI3K/AKT

pathway, p53 reduces the expression of E-cadherin and regulates the transformation of SBOT cells from non-invasive ovarian cancer to invasive ovarian cancer. This result not only indicated that the development of SBOTs to invasive LGSOC involves a reduction in of p53 signal transduction but also suggested that p53 can inhibit the epithelial–mesenchymal transformation (EMT) process in SBOTs cells and thus the transformation to invasive ovarian cancer.

El-Balat et al<sup>66</sup> further analyzed the expression of Trefoil factor-3 (TFF3) in 137 cases of BOT by immunohistochemistry and studied its relationship with histopathological characteristics. They found that the strong expression rate of TFF3 was 21.9% and there was no strong TFF3 expression in SBOTs and endometrial borderline tumors. On the other hand, TFF3 was highly expressed in 61.4% of MBOT ( $P < 0.001$ ), suggesting that TFF3 potentially plays a role in MBOTs.<sup>66</sup> In addition, insulin-like growth factor II mRNA binding protein 3 (IMP3) is considered a prognostic marker of ovarian clear cell carcinoma.<sup>67</sup> El-Balat et al<sup>68</sup> analyzed the expression of IMP3 in 140 cases of BOT in a cohort and found that the expression of IMP3 was not related to the age of patients, FIGO stage, microinvasion, or the presence of implants, but was related to the mucinous subtype of BOTs (mucinous vs other subtypes, 42.2% vs 9.5%,  $P < 0.001$ ). In MBOT, the expression of IMP3 was correlated with the presence of carcinoma in situ, but not with other subtypes ( $P = 0.021$ ). The expression of IMP3 in BOT is associated with mucinous subtype, which can be used as an early indicator of malignant feature. The high specific expression of TFF3 and IMP3 in MBOT may help elucidate the relationship between mucus subtypes and malignant transformation.

The hedgehog (Hh) signal pathway plays a critical role in ovarian tumorigenesis and most authors frequently examined the 6 components of the pathway: Sonic hedgehog (SHH), Indian hedgehog (IHH) and Desert hedgehog (DHH), the Hh-ligand receptor Patched 1 (PTCH1), the transmembrane protein Smoothed (SMO) and the glioma-associated oncogene homolog 1 (GLI1).<sup>69–72</sup> Recent data showed that the expression of GLI1 correlated with poor prognosis of advanced serous ovarian cancer.<sup>73</sup> Chen et al<sup>74</sup> used immunohistochemical staining to detect the immunoreactivity of Hh pathway proteins in 86 cases of primary ovarian epithelial tumors (14 benign tumors, 15 BOTs, 57 cancers) and 6 normal ovarian epithelial cells. The extent of immunoreactivity of Hh pathway proteins in BOTs was between benign and malignant tumors and the immunostaining score of GLI1 was

significantly increased in carcinomas compared to those in BOTs.<sup>74</sup> However, Ozretić et al<sup>75</sup> detected the expression of molecules related to Hh pathway in 41 samples (16 cases of malignant epithelial ovarian cancer, 7 cases of BOT, 9 cases of normal ovarian tissue and 9 cases of fallopian tube tissue) by real-time quantitative PCR. This study showed that GLI1 was highly expressed in BOTs than to ovarian cancer.<sup>75</sup> Song et al<sup>76</sup> using immunofluorescent staining to evaluate the expression of genes in Hh pathway in 193 cases of ovarian epithelial tumors (including 147 cases of malignant epithelial ovarian cancer, 30 cases of BOT, 16 cases of benign ovarian epithelial tumors) and 11 cases of normal ovarian epithelial tissues. Compared with benign ovarian epithelial tumor, GLI1 was highly expressed in BOT but there was no significant difference in expression of GLI1 in BOTs versus ovarian cancer.<sup>76</sup> Survivin has recently been described as a new target of this pathway.<sup>77</sup> In a study by Kanter et al,<sup>77</sup> the expression of Survivin in mucinous ovarian tumors was found in 88.1% of malignant tumors and 18.2% of borderline tumors, respectively, suggesting that Survivin was positively correlated with malignant mucinous tumors.

## Discussion

BOTs are typically diagnosed earlier in development and thus have a higher survival rate. However, they can spread to the peritoneum and eventually to lymph nodes, similar to cancer, so it is important to identify the risk factors that predict invasive recurrence or disease-related death. Pathologists play a key role in assessing the borderline character of ovarian tumors and in determining the likelihood of aggressive recurrence and potential death from disease. In addition, recent molecular research has proved to aid our understanding of the pathogenesis of disease and invasive recurrence of BOT; however, significant further work is required to clarify the relationship between ovarian tumors and extra-ovarian diseases, to determine prognosis indicators, and to develop methods for targeted treatment. Varying definitions of BOTs may arise due to a relatively small number of available tumor samples or the use of different analysis methods. Ideally, more BOTs samples should be characterized at the genetic level in order to potentially identify gene subtypes for further study. KRAS and BRAF mutations represent the early events in the development of SBOTs, but BRAF mutations seem to have a protective effect on the progression of LGSOC, and KRAS mutations usually occur in SBOTs with LGSOC recurrence. Further, p53-mediated inhibition of PI3K/AKT signaling may be a key factor

regulating the progression of SBOTs to an invasive phenotype. The Ras/MAPK and PI3K/AKT pathways regulate cell apoptosis, growth and expression of a diverse set of genes, critically impacting cell membrane receptor signal transmission. The interaction between the Ras/MAPK and PI3K/AKT pathway has been demonstrated in many cell types and experiments.<sup>78</sup> Therefore, the molecular implications of interactions between the Ras/MAPK pathway and PI3K/AKT pathway in the transformation of SBOT to invasive and recurrent LGSOC still needs to be explored. Various publications have come to differing results of the expression of components of the hedgehog signal pathway in BOTs. GLI1 has been shown to be a risk factor in the development of ovarian cancer.<sup>73</sup> Due to people using different methods to monitor GLI1 expression level, there is not a clear consensus on its gene expression level and protein expression level in BOTs and ovarian cancer. Hence, further studies are required to clarify the function of GLI1 in BOTs. The incidence of MBOT in Asia is higher than around the world,<sup>5</sup> and the molecular mechanisms influencing the occurrence, development, and recurrence of MBOT remain to be elucidated.

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## Disclosure

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