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Borderline ovarian tumours: A comprehensive review of published evidence

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ABSTRACT

Borderline Ovarian Tumours (BOTs) comprise 15–20 % of all epithelial ovarian tumours. BOTs are characterised by increased mitotic activity but lack infiltrative destructive growth and stromal invasion. Several dilemmas and controversies have been discussed in the literature regarding BOT management including surgical approach (radical versus fertility-sparing surgery), surgical route (open versus laparoscopic surgery) and impact on disease recurrence, follow-up protocols/modalities (imaging, serum biomarkers), role of completion surgery, lymph node dissection during staging, adjuvant chemotherapy, as well as use of Hormone-Replacement Therapy (HRT) post-surgery. We performed a structured narrative review on Medline and Cochrane Library Databases to identify studies pertaining to the management of BOTs. Identifying areas of agreement and outstanding uncertainty are integral to optimise robust treatment regimens for BOT management and improve the Quality of Life (QoL) and clinical outcomes for patients. We discuss a framework of recommendations to counsel, manage and follow-up women diagnosed with BOT.

1. Introduction

Borderline ovarian tumours (BOTs) comprise 15–20 % of epithelial ovarian tumours and are characterised by increased proliferative activity but devoid of stromal invasion [1]. The annual incidence of BOTs is 1.8–4.8 in 100,000, with one third affecting premenopausal women <40 years old [2].

Overall, 53.3 % of BOTs are demarcated as serous and 42.5 % as mucinous histological epithelial subtypes, commonly implanting in

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mesothelial or peritoneal surfaces Du Bois [3,4] (Fig. 1). The remaining 4.2 % are endometrioid, clear cell, transitional cell or mixed types. Evidence regarding BOT pathogenesis is still slim, however, infertility, nulliparity and ovarian microtrauma through ovarian stimulation in assisted reproduction methods such as IVF have been reported to have a role [1,4] Conversely, parity, contraceptive use and breastfeeding are associated with low BOT incidence [4,5].

BOTs were initially described as a 'semi-malignant' disease [6], and later characterised by the International Federation of Gynaecology and Obstetrics (FIGO) as tumours exhibiting 'low malignant potential' [7] before the World Health Organisation coined the term 'borderline tumours' in 1973 [8]. These terms are often used interchangeably with BOTs.

1.1. Micro-invasion

"Micro-invasion" occurs when clusters of BOT cells <5 mm in greatest dimension are seen in the ovarian stroma, typically surrounded by a clear space [4]. Micro-invasion as a histological feature has predominantly been described in the serous epithelial BOT subgroup. It is more commonly found in pregnant women with BOTs but does not significantly alter their management. In women with Stage I BOTs micro-invasion does not alter the prognostic outcome [9].

1.2. Implants

BOT cells can migrate to peritoneal or mesothelial surfaces forming lesions which are defined as "implants". Implants are mostly associated with serous BOTs and spontaneous resolution has been reported in the literature [10]. There have been no reports of implants or micro-invasion in mucinous tumours, though these tumours are often large, unilateral and adherent to the ovarian surface [11].

Implants with no invasion of the underlying tissues are defined as non-invasive implants. In contrast, "invasive implants" commonly invade fat and muscle [11]. The term "invasive implants" was coined by the WHO and has now been re-classified as low-grade serous ovarian cancer (LGSOC) in 2014. In rarer cases, during histological examination, a clearly invasive pattern of implants may not be proven, nevertheless cells may display cytological features consistent with low-grade ovarian cancer. Invasive implants displaying micropapillary and micro acinar architecture have been shown to have a close correlation with invasive implant formation and subsequent LGSOC progression.

1.3. Molecular profile

Recent advances in understanding of the molecular profile of epithelial tumours have illustrated two main development pathways: Type I or Low-Grade Tumours and Type II or High-Grade Tumours. Type I tumours following the low-grade pathway are typically slow growing with progression from benign to borderline, and eventually undergo malignant transformation [12]. Conversely, Type II tumours are fast growing, devoid of precursors and associated with a poor prognosis [12] (Fig. 2).

BOTs originate from the low-grade pathway and their precursor lesions are mostly cystadenomas for serous or mucinous BOTs

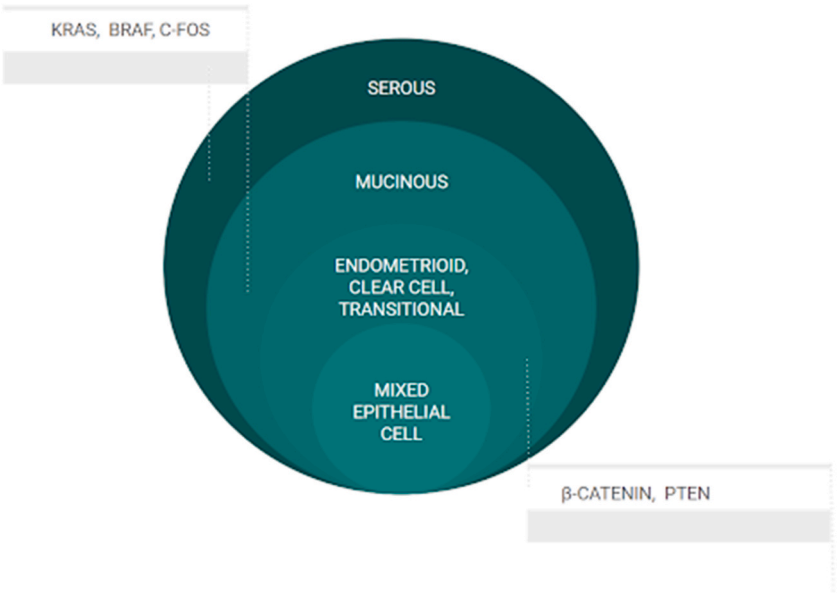

Fig. 1. Borderline Ovarian Tumour (BOT) types, with associated mutational pathways. Original Diagram. Colour to be used in print. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

(Fig. 2). Their molecular profile is characterised by mutations in the BRAF and KRAS gene pathways in addition to increased c-fos transcription [13–15]. Serous BOTs are characterised by KRAS and BRAF mutations making them more susceptible to progressing into LGSOC [14,16]. Specifically, KRAS mutations have been linked to greater risk of recurrence and worse disease specific survival [17]. In contrast, mucinous BOTs are more strongly characterised by KRAS mutations and can progress into intraepithelial or mucinous carcinomas. Endometriotic cysts or adenofibromas are the precursor lesions of the Mullerian subtype of mucinous BOTs. Endometrioid and Clear cell BOT subtypes are associated with aberrations in beta-catenin and PTEN genes, whilst the molecular profile of transitional (Brenner) neoplasms has yet to be fully elucidated due to their rarity [16].

1.4. Stage at diagnosis

The majority (~70 %) of BOTs are diagnosed at FIGO stage I (disease confined to the ovary) whilst ~20 % are diagnosed as stage II or III (disease spread in the pelvis and beyond) [18]. Stage IV BOTs (disseminated disease beyond the abdomen) are exceptionally rare and make up 0.6 % of diagnoses [19]. The majority of patients with BOTs have an excellent prognosis with a 5-year survival rate of 95–97 % for stage I and 65–87 % for stage II or III tumours [1].

1.5. Aims

We performed a comprehensive review of the literature to summarise all the published evidence on current treatment approaches for BOTs, discuss ongoing debates and controversies and form recommendations for treatment stratification and follow up.

2. Methods

We conducted a comprehensive review to address ongoing dilemmas and controversies surrounding BOTS. We defined a search strategy (appendix A) and searched MEDLINE and the Cochrane Library from inception till April 17, 2023 (Fig. 3). Published practice guidelines (Table 1), original studies and high-impact reviews were screened by two reviewers (KBP/MS) (Tables 2 and 3). We summarised the findings from the relevant published evidence under the following eight themes:

- Surgical approach
- Recurrence and prognosis
- Follow up protocols & role of surveillance imaging and biomarkers
- Completion surgery
- Role of lymphadenectomy in the staging of BOTs
- Role of chemotherapy in the treatment of advanced stage BOTs
- HRT Use
- Future directions in BOT management

3. Results

Published guidelines are summarised on Table 1. Key impact papers are summarised on Table 3, and key studies on follow-up recommendations on Table 2.

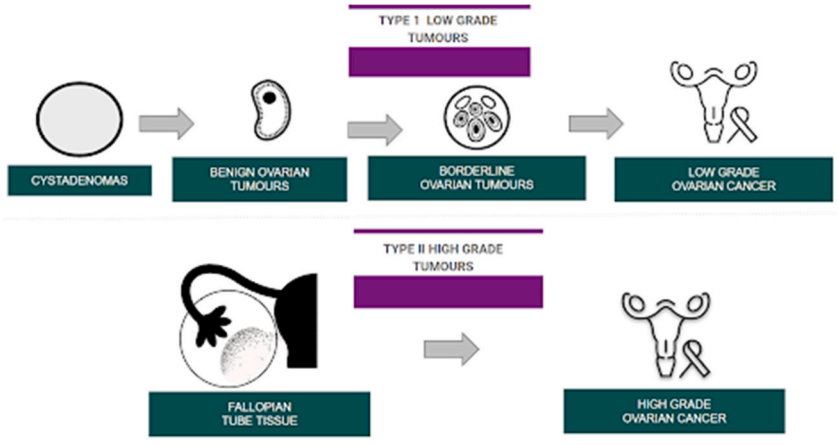

Fig. 2. Type I and Type II Ovarian Tumour Progression. Original Diagram. Colour to be used in print. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

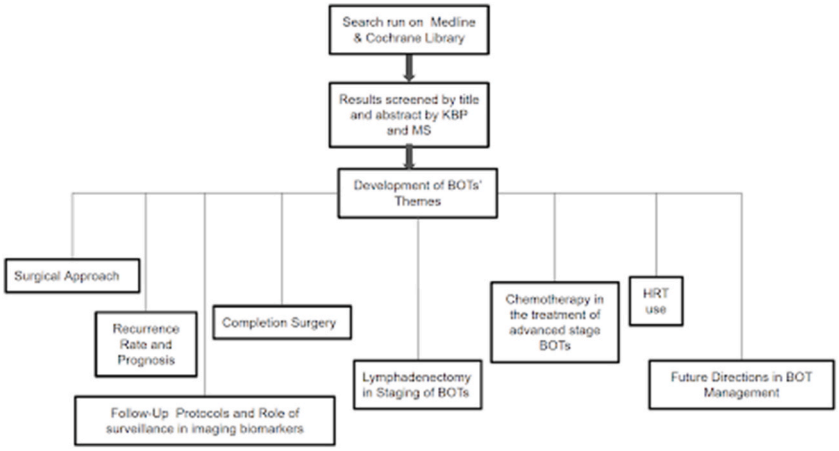

Fig. 3. Results articulated within eight themes covering key topics in BOT management. Original diagram. Colour to be used in print.

3.1. Surgical approach

The mainstay of treatment for BOTs is surgery. The surgical approach and route should be discussed in detail during preoperative consultation, and counselling should be focused on the individual needs and expectations of each patient, including their fertility aspirations along with oncological safety. The two main approaches are Radical Surgery or Fertility Sparing Surgery (FSS) (Fig. 4).

3.1.1. Radical surgery

The term 'Radical Surgery' refers to pelvic clearance in the form of complete removal of the tumour through bilateral salpingo-oophorectomy (BSO), hysterectomy along with complete surgical staging and removal of visible disease (cytoreduction). Surgical staging involves omentectomy, peritoneal lavage for cytology and multiple peritoneal biopsies [20]. This approach is typically offered to postmenopausal women, women >40years old, or women who have completed their family and are willing to endure potential side-effects from early menopause following surgery. Hysterectomy has been associated with decreased risk of recurrence in post-menopausal women and improved disease-free survival albeit not significantly associated with risk of death due to the disease [21]. Less commonly, radical surgery is appropriate for women who may not wish to undergo long periods of follow-up. These indications require careful counselling by experienced professionals as decisions can often be complex and multifaceted. The gold standard approach would be to involve a multidisciplinary team of expert radiologists, gynae oncologists and fertility specialists. Radical surgery is associated with 0–5 % recurrence of disease, with good prognosis and patient outcomes [22].

3.1.2. Guidelines on radical surgery for BOTs

Guidelines from the British Gynaecological Cancer Society (BGCS), FIGO and European Society of Gynaecological Oncology (ESGO) support surgical resection as the gold standard management for BOTs; this includes cytoreduction with adequate staging via peritoneal biopsies, cytology and omentectomy [10,23–25]. Previously, in the case of mucinous BOTs an appendectomy was also performed to rule out potential metastatic deposit however, the 2019 European Society of Medical Oncology (ESMO)-ESGO consensus does not recommend this [24]. Most guidelines conclude that there is no benefit from lymph node dissection in the management of BOTs and no proven survival benefit [26]. Therefore, lymph node dissection or sampling is not recommended as part of staging during radical or fertility sparing surgery, and only clinically enlarged lymph nodes should be removed [27,28].

3.1.3. Fertility sparing surgery

Fertility sparing surgery (FSS), otherwise known as 'conservative surgery' involves resection of BOTs through unilateral salpingo-oophorectomy (USO) or cystectomy (as opposed to BSO). As outlined by FIGO this is only performed after close inspection of the contralateral ovary to rule out involvement [10]. Ultra-conservative surgery may be offered in the form of a cystectomy if a patient has one ovary [29]. A combination of USO and cystectomy may be used if patients have bilateral tumours. Similarly to radical surgery, adequate surgical staging is a necessity in the form of omentectomy, peritoneal biopsies and resection of any visible abnormal cells. FSS may be offered as an alternative to pre-menopausal women (usually <40years old), women who are yet to complete their family, women diagnosed with stage I BOTs with no peritoneal implants and women willing to comply with extensive follow-up regimens. At initial counselling or during follow-up, patients are counselled for 'completion surgery', a second-stage procedure after completing their family [29]. Completion surgery includes contralateral oophorectomy ± hysterectomy, although the role of the latter is still equivocal. FSS is associated with a 10–30 % recurrence rate; the most common site of recurrence is the intact contralateral ovary. This recurrence rate depends primarily on the nature of the procedure; with cystectomy resulting in the highest rates (up to 31 %) [4]. Recurrence rates also depend on the initial stage at presentation, route of surgery, age of the patient and other factors discussed below [18,30]. There is consensus that FSS can be an independent prognostic factor for recurrence, therefore extensive counselling is needed

Table 1
Guidelines & Scientific Impact Papers on BOT management.
NR= Not reported, Bold = Guideline and Level of evidence scale, Non-Bold = Recommendations discussed.

	Route of Surgery	Recurrence	Follow-Up	Completion Surgery	Lymphadenectomy	Chemotherapy	Hormone-Replacement Therapy
International Federation of Gynaecology & Obstetrics (FIGO) 2018 Report [53]	- Mainstay treatment is cytoreductive surgery and surgical staging. - Radical surgery involves hysterectomy, BSO and surgical staging. - FSS may be offered in the form of USO or cystectomy with surgical staging. - In patients with late recurrence secondary staging may be conducted.	**NR**	- Follow-up post BOT management should be the same as those with malignant epithelial ovarian cancer albeit at more sparse time intervals. - If FSS is performed the contralateral ovary should be followed up with transvaginal ultrasound annually.	**NR**	**NR**	- Hormonal Adjuvant Therapy has shown to have some benefit in late recurrent invasive disease.	**NR**
European Society of Gynaecological Oncology (ESGO)2021 Guidelines [25] 2021 Guidelines [25]	- **Open or Laparoscopic surgery may be performed.** - **In Stage I BOT with a wish for fertility preservation USO or cystectomy may be performed if indicated. A combination of the two methods may be used in cases of bilateral BOTS. If there is no wish for fertility preservation a BSO will be performed and routinely offered if women who are menopausal** - **Extensive surgical staging of disease is recommended in all BOT surgical management through inspection of the abdominal cavity, omentectomy, peritoneal biopsies and washings for cytology are required.** - **Removal of the appendix is not**	- **In cases of recurrence secondary cytoreductive surgery is recommended. If the surgery is successful, patients may return to routine follow-up.** - **In select cases of relapse adjuvant endocrine therapy may be used in the form of aromatase inhibitors.**	- **1-year post surgery physical examination is recommended every 3–6 months in addition to as ultrasound in Fertility Sparring Surgery. Optional use of tumour biomarkers such as Ca-125, CEA or Ca-19–9 may be used as well as CT scans for Stage III or residual disease.** - **At 2–5 years post-surgery physical examination is recommended every 6–12 months in addition to as ultrasound in FSS. Optional use of tumour biomarkers such as Ca-125, CEA or Ca-19–9 may be used as well as CT scans for Stage III or residual disease.** – **5 years post-surgery physical examination is recommended every 12 months in**	NR	- **Lymphadenectomy in surgical staging is not performed is not indicated.**	**NR**	**NR**

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Table 1 (*continued*)

	Route of Surgery	Recurrence	Follow-Up	Completion Surgery	Lymphadenectomy	Chemotherapy	Hormone-Replacement Therapy
	indicated unless in mucinous BOT cases. - **In FIGO Stage II/III disease a BSO with complete cytoreductive surgery is recommended with fertility preservation offered in selected patients.**		**addition to as ultrasound in FSS.**				
British Gynaecological Cancer Society (BGCS)2017 Report [23] 2017 Report [23]	- **Complete tumour reaction and surgical staging is associated with improved patient survival (Grade B).** - **FSS is a viable option for young patient albeit regular monitoring through sonography is recommended (Grade B).**	**NR**	**NR**	**NR**	- **Pelvic and Para-aortic lymphadenectomy is not recommended unless 'bulky' lymph nodes are present (Grade B).**	- **There is currently no evidence to support the use of chemotherapy in the management of BOTs (Grade B).**	**NR**
French College of Gynecologists and Obstetricians (CNGOF) 2021 Guidelines [77] 2021 Guidelines [77]	- **FSS is an option is recommended for women of childbearing age diagnosed with BOTs, although they should be counselled on the risks of potential infertility following surgical intervention (Grade C).** - **In Stage I BOTs laparoscopy is preferred over laparotomy if the risk of tumour rupture is low (Grade C).** - **In bilateral BOTs cystectomy is recommended to preserve fertility (Grade B).** - **In mucinous BOTs unilateral adnexectomy may be performed (Grade C).**	NR	- **Following BOT treatment, follow- up regimens are recommended past five years due to the median time taken seen in BOT (Grade B).** - **Clinical examination and use of Ca-125 should routinely be conducted and measured respectively (Grade B).** - **Transvaginal or abdominal ultrasound should be used for women who underwent FSS for BOT (Grade C).**	- **Completion surgery following FSS is not recommended or after family completion (Grade B).**	- **Lymphadenectomy is not recommended in early-stage BOT management (Grade C).** - **Lymphadenectomy is not recommended in advanced BOT stages (Grade C).**	**NR**	- **HRT is not a contraindication for women who have been diagnosed and treated for serous and mucinous BOTs (Grade C).** - **HRT is recommended for women <45 years old with mucinous BOTs due to the benefits on the cardiovascular system and bone health as well as resistance of mucinous BOTs to hormones (Grade C).** - **For women >45y old following management of BOTs HRT is not contraindicated and should be considered. HRT benefits and risks should be discussed with the patient and**

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Table 1 (*continued*)

	Route of Surgery	Recurrence	Follow-Up	Completion Surgery	Lymphadenectomy	Chemotherapy	Hormone-Replacement Therapy
	- **An appendectomy may be performed if there is evidence of invasive macroscopic disease (Grade C).** - **Hysterectomy is not routinely recommended for the treatment of serous or mucinous BOTs unless the uterus is macroscopically involved or fertility is not a concern. In this case, FSS may be offered. (Grade C).** - **Surgical restaging includes omentectomy (Grade B), peritoneal lavage/ cytology and peritoneal biopsies need to be performed (Grade C).** - Secondary surgical intervention is indicated in advanced BOTs or previous sub-optimal resection (Grade C).						**multidisciplinary team (Grade C).**
European Society of Medical Oncology – European Society of Gynaecological Oncology (ESMO-ESGO) 2019 Consensus [24]	- **Preservation of ovarian tissue and the uterus is recommended for women of childbearing age diagnosed with BOTs at Stage I (Level of evidence III, Strength of recommendation A). FSS could also be considered in selected patients with Stage II/ III serous BOT (Level of evidence V, Strength of recommendation B).** - **USO is recommended for patients with**	**NR**	**NR**	**NR**	- **Lymphadenectomy is not recommended in stage II/III serous BOTs (Level of evidence IV, Strength of evidence B).**	- **The use of chemotherapy as first-line for treatment of advanced stage BOTs is not recommended (Level of evidence III, Strength of evidence B).**	**NR**

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Table 1 (*continued*)

	Route of Surgery	Recurrence	Follow-Up	Completion Surgery	Lymphadenectomy	Chemotherapy	Hormone-Replacement Therapy
	mucinous BOT subtypes to decrease the risk of invasive recurrence after cystectomy (Level of evidence IV, Strength of recommendation A). - **A cystectomy is a viable alternative in the management of serous BOTs in women of reproductive age (Level of evidence IV, Strength of recommendation B).** - **Peritoneal staging surgery is recommended in the management of serous BOTs (Level of evidence III, Strength of recommendation B).** - **FSS may be considered in select causes of advanced BOT stages (Level of evidence V, Strength B).** - **Restaging surgery should be considered in serous BOTs which exhibit a micropapillary pattern and where incomplete abdominal inspection was not possible (Level of evidence III and IV, Strength of recommendation B).** - **Removal of the appendix should not be performed in BOT management (Level of evidence V, Strength of recommendation A).**						

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Table 1 (*continued*)

	Route of Surgery	Recurrence	Follow-Up	Completion Surgery	Lymphadenectomy	Chemotherapy	Hormone-Replacement Therapy
	- **All peritoneal implants should be removed at the time of surgery (Level of evidence IV, Strength A).**						
National Comprehensive Cancer Network (NCCN) 2020 Ovarian Borderline Epithelial Tumour Guidelines [39]	- **If the patient has had previous radical surgery and (suspected) BOT recurrence occurs surveillance is advised (Category 2A).** - **If the patient has had previous radical surgery and recurrence with LGSOC occurs adjuvant treatment is advised (Category 2A).**	- **If recurrence occurs evaluation should be conducted by a specialist and debulking should be carried out if appropriate (Category 2A).** - **Non-invasive disease should be observed.** - **LGSOC should be treated as specified in the LGSOC pathway.** - **Invasive disease should be treated as epithelial ovarian cancer.**	- **Follow-up is recommended 3–6 months for the first 5 years and annually thereafter (Category 2A).** - **Examination includes a pelvic examination as well as tumour marker measurements if they are initially elevated. (Category 2A).** - **Imaging can be either CT, MRI or PET scan if indicated (Category 2A).** - **Patients undergoing FSS can be followed up with ultrasound (Category 2A).**	- **For patient that previously underwent FSS completion surgery may be offered in the form of hysterectomy contralateral USO following completion of the patient's family (Category 2B).**	- **The need for lymphadenectomy may be considered on a case-by-case basis (Category 2A).**	- **Chemotherapy has shown to be of no benefit in BOT management (Category 2A).**	**NR**
British Gynaecological Cancer Society (BGCS) ovarian, tubal and primary peritoneal cancer guidelines: Recomm endations for practice update 2024(38)	- **For early stage, bilateral serous BOTs, if fertility and endocrine function preservation is desired a cystectomy is indicated (Grade C).** - **A conservative surgical strategy is preferred for women of childbearing age to preserve fertility. Laparoscopic surgery is preferred if BOTs can be removed without risk of rupture (Grade C). Risk of rupture should be mitigated to prevent BOT rupture, such as converting to laparotomy and using**	**NR**	- **Follow-up is recommended to last beyond 5-yers due to the long median time to recurrence. At initial assessment if Ca-125 or CA19–9 are elevated they may be useful biomarkers to monitor (Grade D).** - **Fertility Sparring surgery is safe for young patient albeit due to the increased risk of recurrence – regular follow up with sonography is recommended (Grade C).** - **For patient aged 18–24 years they should be managed under gynae**	**NR**	**There is no evidence of lymph node dissection in BOT treatment (Grade B).**	**There is no evidence of chemotherapy for BOT treatment (Grade B) .**	- **For women <45 years who are diagnosed with mucinous BOTs, and develop menopausal symptoms following treatment, HRT should be recommended in the absence of contraindications (Grade C).** - **For Serous BOTs, the benefits and risks to HRT should be discussed in detail as the BOTs may be hormone sensitive (Grade D).**

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Table 1 (*continued*)

	Route of Surgery	Recurrence	Follow-Up	Completion Surgery	Lymphadenectomy	Chemotherapy	Hormone-Replacement Therapy
	endoscopic bags to remove the tumour specimen and prevent tumour spillage (Grade D). **Complete macroscopic tumour resection should be the surgical aim of recurrent or advanced stage BOT (Grade B).** **Frozen section may be used to aid intra-operative management, albeit it's use is more established in invasive malignancy (Grade B).** - **Hysterectomy is not routinely indicated, except in cases where the uterus is affected by disease or fertility is not a concern for the patient (Grade C).** - **Appendicectomy is indicated in cases where the appendix is found to be macroscopically pathological (Grade D).** - **In serous BOT diagnosed after cystectomy, restaging surgery for adnexal removal should not be performed in the absence of pathological features, residual disease, post-operative imaging or endocrine/fertility concerns (Grade C).** - **Restaging surgery is indicated for BOTs with micropapillary features as well as no satisfactory inspection of the abdominal cavity during initial surgery (Grade C).**		**and teenage/young adult multidisciplinary teams (Grade D)**				

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Table 1 (*continued*)

	Route of Surgery	Recurrence	Follow-Up	Completion Surgery	Lymphadenectomy	Chemotherapy	Hormone-Replacement Therapy
	In mucinous BOTs, if cystectomy has been performed previously adnexectomy is recommended. Restaging surgery may be considered if a patient has previously undergone a cystectomy and the appendix was not inspected in the first surgery (Grade C).						
British Gynaecological Cancer Society and British Menopause Society guidelines: cancer 2024 (76) Management of menopausal symptoms following treatment of gynaecological cancer 2024 (76) cancer 2024 (76)	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**	- **Following treatment of BOTs, HRT should be offered to women if they have menopausal symptoms (Grade C).** - **HRT should be actively recommended for those with surgical menopause resulting from treatment of early-stage disease (Grade C).**

Table 2
Key impact papers on BOT Follow-Up.

Author/ Year	Location	Design	Scope	Key Findings	Recommendation		
					Follow-Up	Recurrence	Other
Engelen et al 2000 (67)	Netherlands	Retrospective cohort study	Study assessing preoperative levels of serum biomarkers Ca-125, CEA and CA19-9 as well as the use of biomarkers in follow-up to detect disease recurrence earlier (median follow up 84 months).	- CA-125, CEA and Ca19-9 were elevated pre-operatively in some patients (34 %,9 % and 46 % respectively). Ca19-9 was more commonly elevated in mucinous tumours. – 5 % (2 of 43) of patients had recurrent disease, one patient has a high Ca-125 coinciding with recurrence and the other patient a persistently high.	- Ca19-9 should be used in the follow-up of mucinous BOTs. - The use of serum biomarkers in BOT follow may detect recurrence early in a small minority of patients albeit more studies are needed to establish the routine use of biomarkers in clinical practice.	- The use of biomarkers in follow-up may detect recurrence in a small number of patients.	NR
Zanetta et al 2001 (66)	Italy	Prospective Cohort Study	Study assessing the use of physical examination, ultrasound and use of the serum biomarker Ca-125 in the follow- up of patients treated with FSS for BOT (median follow-up 71 months). Follow-up included physical examination and ultrasound every 3 months for the first two years and every 6 months thereafter. Serum Ca-125 was measured every 6 months post-surgery.	– 17 % (23/164) of women who underwent FSS had recurrent disease either of BOT or invasive disease. - The sensitivity of ultrasound to detect recurrent BOTs or invasive disease was 100 %. – 18/19 cases (94.7 %) of recurrent BOT were identified by ultrasound. - Women with invasive disease had an abnormal adnexal mass (5/23 cases). - Ca-125 was able to correctly identify the majority of recurrences.	- The use of transvaginal ultrasound is the most reliable methods to use in the follow-up of young patients following BOT surgery.	NR	NR
Morice et al 2001 (45)	France	Retrospective Cohort Study	To identify tumour recurrence and rate of pregnancies in women that underwent surgical intervention following BOT diagnosis. 44 patients were diagnosed with BOTs, 32 with Stage I, and 12 with Stage II/III. Follow-up included clinical examination	- Recurrence rates were 5.7 %, 15.1 % and 36.3 % for radical, USO and cystectomy surgery respectively. - BOT recurrences were diagnosed during routine follow-up.	- Conservative treatment with routine follow-up may be offered to young women diagnosed with low malignant potential tumours if patients are adherent and complaint with the follow-up regimen.	- Recurrence rates were higher in patients treated with USO and cystectomy.	NR

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Table 2 (*continued*)

Author/ Year	Location	Design	Scope	Key Findings	Recommendation		
					Follow-Up	Recurrence	Other
			in addition to measurement of tumour markers Ca-125 and Ca19-9 and ultrasound every 3 months in the first year, every 6 months for a further two years followed by annually thereafter (Median follow up 109 months).				
Uzan et al 2010 (68)	France	Prospective cohort study	To assess the rate of recurrence in 162 patients that underwent radical or conservative surgery for stage II/III BOTs (Median follow-up 8.2 years range 19–286 months). Follow-up included a triad of clinical examination, ultrasound and serum biomarker measurements of Ca-125 and Ca19-9 every 3 months in the first years and every 6 months the following 6 years and annually thereafter.	– 28 % (45 of 162 patients) showed relapsed disease. - Ca-125 was useful in diagnosing invasive recurrent tumours e.g. LGSOC (6 of 13). - Ultrasound was useful in identifying non-invasive cancers (16/23).	- Ultrasound is the most effective follow-up procedure.	- Ca-125 is useful for detecting invasive cancer recurrence.	- CT was used to follow up in some patients albeit more data is needed to identify the use of this modality in BOT follow-up.
Fischerova et al 2010 (64)	Czech Republic	Prospective Cohort study	To assess the value of early ultrasound to detect recurrence in 113 patients with newly diagnosed or recurrent BOTs.	- The use of early ultrasound permitted early conservative intervention for 56 % of recurrent BOTs.	- Ultrasound is a reliable method to detect recurrent BOTs and may be used in follow-up.	NR	NR
Romeo et al 2013 (60)	Spain	Retrospective Cohort Study	To analyse the risk of BOT recurrence using standardised surgical definitions and follow- up parameters (follow up 5.4 years).	– 10.9 % (5 of 46) of patients in the sample had recurrent BOTs – 25 % of recurrences occur after five years.	- Long term follow-up is needed to diagnose BOT relapse.	NR	Relapses may occur 10–15 years post-surgery, therefore long-term follow up may be beneficial
Song et al 2011 (40)	Korea	Retrospective Cohort Study	To identify oncological outcomes in patients who underwent USO or cystectomy for BOTs. Follow-up included physical examination, ultrasonography, and tumour markers every 3 months for the first 2 years and every 6 months the following 3 years and then annually thereafter.	– 7.7 % of patients (12/155) showed recurrence. - Recurrence rate was 6 % lower in the USO compared to the cystectomy group.	- Recurrent disease was diagnosed through multimodality of clinical examination, ultrasound and use of biomarkers Ca-125 and Ca19-9. - Transvaginal ultrasound is recommended as the optimal form of follow-up.	- Recurrence free survival in the USO group was 93.3 % and 90.7 in the cystectomy group.	NR

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Table 2 (*continued*)

Author/ Year	Location	Design	Scope	Key Findings	Recommendation		
					Follow-Up	Recurrence	Other
Sharma et al 2012 (65)	UK	Prospective Cohort Study	To identify the rates of epithelial ovarian cancer and BOTs in postmenopausal women with abnormal adnexa on ultrasound. Follow- up included ultrasound scans. Median follow up was 7.09 years.	– 4367 patients were identified with abnormal adnexal masses on ultrasound. – 23 cases were identified as BOTs. The absolute risk of developing epithelial ovarian cancer from BOTs was estimated at 0.73 % - BOTs may be followed up with ultrasound and Ca-125 may be elevated in more invasive cancers.	The modality of ultrasound is useful in identifying slow growing BOTs and Type I epithelial ovarian cancers.	NR	NR
Lazarou et al 2014 (70)	Germany	Retrospective Cohort Study	To better characterise BOTs and identify rate of recurrence. - Follow-up was available for 113 patients (median follow up 86 months) with 63 %, 43 % and 17 % followed up in five,10 and 15 years respectively.	- From 151 patients in the study 16.8 % of patient's experiences relapse and 52.6 % of relapses were invasive.	- Long term follow-up is recommended due to recurrence.	NR	NR
Froyman et al 2019 (63)	Belgium	Prospective Cohort Study	2-year interim analysis from the IOTA 5 study to identify the rate of adverse events in ovarian tumour diagnosed with ultrasound. - Follow-up included transvaginal clinical examination for 24 months.	- For the 1919 patients who were diagnosed with a new tumour on ultrasound examination 0.4 % had a confirmed BOT diagnosis. - Further follow- up after 24 months with transvaginal ultrasound five cases of BOT were observed.	- For ovarian lesions treated with conservative management at 2-years follow up transvaginal ultrasound is an effective modality to use at intervals of 3 months, 6 months and 12 months.		- The merit of long-term follow up must be determined by the completion of the IOTA-5 study.

for patients to fully appreciate implications regarding fertility, follow-up surveillance and risk of recurrence [31–34].

3.1.4. The role of frozen section in intraoperative decision making

Where there is uncertainty, the use of intraoperative frozen section analysis (FSA) of specimens is valuable to distinguish BOTs from OC or other benign tumours, stratify treatment approach intraoperatively and avoid a two-stage procedure [11,35]. Around 50–80 % of BOT cases are correctly diagnosed through intra-operative FSA [35,36]. This is commonly used when there is radiological suspicion of malignant potential to avoid a second stage procedure, and patients must be preoperatively counselled about the different surgical approaches following each result.

3.1.5. Guidelines on FSS for BOTs

BGCS guidelines recommend that FSS can be a safe option for younger patients, albeit with regular sonography to monitor for recurrent disease [23,37,38]. Furthermore, patients aged 18–24 should be discussed in gynaecological oncology as well as teenage/young persons multidisciplinary teams [38]. The 2019 ESMO/ESGO Consensus supports partial-oophorectomy, USO or cystectomy as a FSS approach, supplemented by adequate surgical staging [24] (Table 1). FIGO and ESGO guidance are in agreement that FSS with surgical staging should be the standard of care in women who wish to preserve fertility and are diagnosed with early-stage

Table 3
High impact papers.

Author/ Year	Location	Design	Scope	Key Findings	Recommendation		
					Follow-Up	Recurrence	Other
Engelen et al 2000 (67)	NR	Prospective Cohort Study	To investigate the use of tumour markers in the follow-up of patients who previously underwent surgery for BOT management.	Mucinous BOT recurrence may be associated with increased levels of Ca19-9 in follow-up. The use of Ca-125 detected recurrence in a small proportion of patients.	The use tumour markers may be able to detect recurrence in certain BOT subtypes.	The clinical value of serum biomarkers to detect recurrence required further investigation.	NR
Zanetta et al 2001 (66)	NR	Prospective Cohort Study	To better elucidate the optimal follow-up regimen for BOT surveillance in women who previously underwent FSS.	Recurrence and less commonly invasive disease is possible following FSS. Transvaginal ultrasounds is the recommended modality for follow-up.	Transvaginal ultrasound is the recommended methods to detect BOT recurrence.	FSS has been identified as a risk factor for recurrence.	The use of blood markers such as Ca-125 was not associated with increased incidence of recurrence.
Morice et al 2001 (45)	France	Retrospective Cohort Study	To study the clinical outcomes and impact on fertility for individuals undergoing conservative management for BOTs.	Recurrence rates of BOTs were more common in individuals who underwent cystectomy and adnexal excision of the tumour compared to those who underwent radical surgery. Early stage BOT diagnosis was associated with more favourable rates in pregnancy.	NR	Recurrence was more common in FSS compared to radical.	Earlier stage of BOT diagnosis was associated with better fertility outcomes compared to advanced disease.
Fauvet et al 2005 (54)	France	Retrospective Multicentre Study	To evaluate the efficacy of laparoscopic BOT staging compared to laparotomy.	Laparoscopic approaches to BOT staging result in higher incidences of recurrence.	NR	The increased incidence of cyst rupture and incomplete staging may contribute to higher incidences of recurrent disease.	Laparoscopic staging of BOTs is associated with increased risk of cyst rupture and incomplete disease staging.
Longacre et al 2005 (73)	United States of America	Prospective Cohort Study	To determine the outcomes of individuals with low malignant potential tumours and identify factors which demarcate them as benign or malignant with 5- years follow-up.	Tumours deemed surgically unresectable and those with invasive implants, micropapillary architecture and microinvasion were linked to decreased survival and or recurrence. Adjuvant treatment for advanced stage BOTs did not show any survival benefit.	Follow-up is necessary to detect recurrence and better characterise recurrent BOTs.	Factors such as micropapillary architecture, microinvasion, advanced stage of disease and incomplete staging were associated with recurrence.	Lymphadenectomy and adjuvant treatment for advanced BOTs has not shown to have any survival benefit.
du Bois et al 2009 (34)	Germany	Explorative Analysis of three randomised controlled trials	Identify factors associated with survival and recurrence rate of BOTs.	The aim of all BOT initial management should be complete resection of the tumour. 37 % of BOT recurrences occur in the first two years following surgery, 31 % between years 2–5, 32 % after 5 years and 10 % after 10 years.	Long-term follow-up is required to identify BOT recurrence.	Recurrence of BOTs	NR

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Table 3 (*continued*)

Author/ Year	Location	Design	Scope	Key Findings	Recommendation		
					Follow-Up	Recurrence	Other
Uzan et al 2010 (68)	France	Prospective Cohort Studies	To investigate the methods of follow-up and detection of recurrence in advanced stage BOT disease.	Ultrasound is a reliable method detect BOT recurrence and Ca-125 may be useful to detect invasive recurrent disease.	Non-invasive cancers may be best diagnosed with ultrasound whereas Ca-125 may be useful in detecting recurrent disease.	The follow-up regimen may include ultrasound imaging and potentially the use of serum tumour biomarkers.	NR
du Bois et al 2013 (33)	Germany	Retrospective-Prospective Cohort Study	To evaluate independent factors for BOT prognosis and recurrence and the oncological outcomes of laparotomy vs laparoscopic procedures.	The study identified that advanced Stage BOTs, FSS, incomplete staging and sub-optimal resection of the tumour was associated with worse BOT prognosis.	NR	Several factors were identified consistent with worse BOT prognosis and recurrence. Laparoscopy is a safe method for early-stage BOT management.	Hysterectomy is not recommended following FSS, when a patient experiences recurrence or wishes to undergo completion surgery. It should only be considered if the patients wishes and there is evidence of invasive implants in the uterus
Trillsch et al 2013 (52)	Germany	Retrospective Cohort Study	To investigate the patient outcomes of survival in recurrence when treating BOTs through laparotomy vs laparoscopic procedures.	There was no difference between laparoscopy or laparotomy in treating BOTs regarding disease recurrence or survival.	NR	Recurrence rates were similar in both arms.	NR
Hannibal et al 2017 (32)	Denmark	Retrospective/ Prospective population cohort study	To identify risk factors for BOT recurrence.	Women with LGSC were more likely to develop serous carcinoma, and invasive implants were also linked as a prognostic factor.	NR	Invasive implants, incomplete staging and FSS were linked with increase BOT recurrence.	NR

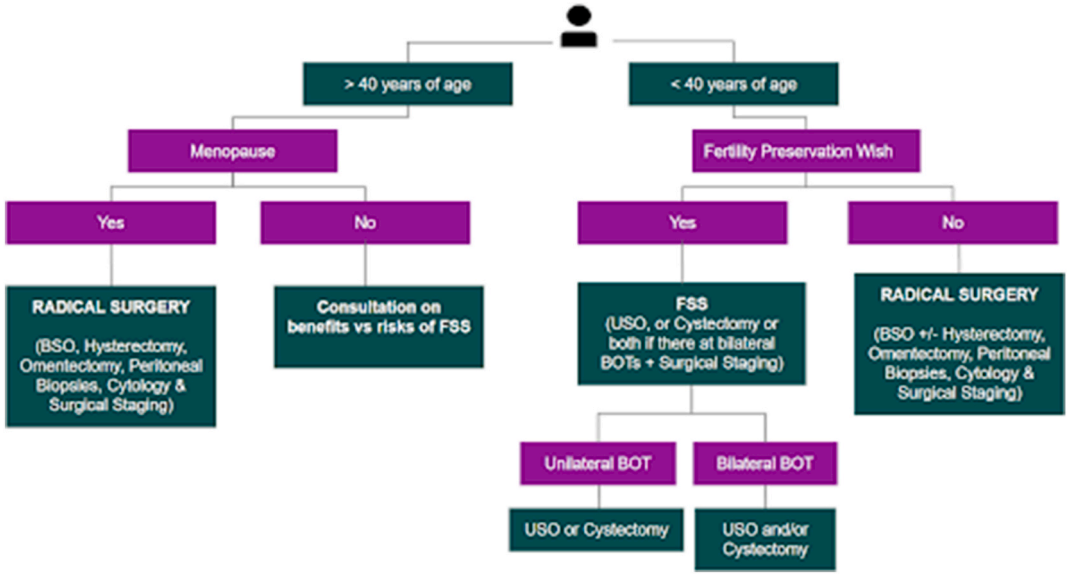

Fig. 4. Management Pathways for BOTs. Original Diagram. Abbreviations: FSS (Fertility Sparing Surgery), Unilateral Salpingo-Oopherectomy (USO), Bilateral Salpingo-Oopherectomy (BSO). Colour to be used in print. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

BOTs, although it is not contraindicated in advanced disease provided there is histological confirmation that the implants are non-invasive [10,24,25]. The National Comprehensive Cancer Network (NCCN) also states that FSS is an option for women wishing to preserve fertility provided they are counselled for recurrence or incomplete surgical staging during the first surgery [39].

In rarer cases where the patient has one ovary and FSS for BOT management is indicated FIGO recommends that a cystectomy or a partial oophorectomy should be performed [10,40]. Cystectomy in mucinous BOTs is a prognostic factor for recurrence and salpingo-oophorectomy has been suggested as an alternative for conservative management. [10,41]. In more advanced stages, FSS may only be considered if peritoneal involvement is resectable and there is no evidence of invasive implants, either radiologically or on post-operative final histology [42,43].

Patients who undergo FSS may decide to undergo completion surgery at a later stage with appropriate counselling on the risk of recurrence, benefits and risks as well as family completion [44]. ESGO highlights that FSS should ideally be conducted in a gynaecological oncology centre with access to specialist fertility services for extensive counselling [24].

3.1.6. Pregnancy outcomes and fertility considerations in FSS for BOTs

Successful pregnancies following FSS for BOTs have been reported [45], however, there are concerns that women should be counselled regarding the possibility of reduced fertility due to loss of ovarian tissue as well as potential formation of adhesions [46,47] depending on their surgical route [48]. Higher rates of spontaneous pregnancy occurs in patients treated with FSS for early-stage (54 %) compared to advanced stage (III/IV) (34 %) BOTs [49]. Therefore, women with advanced stage BOT may benefit from direct referral for assisted reproduction technologies (ARTs)such as IVF. Retrospective studies have been conducted to assess the adverse outcome following IVF. Fasouliotis et al., 2004 reported that of five women who previously underwent FSS for serous BOT, six pregnancies were achieved following IVF, with one patient suffering three recurrences of serous BOT at 13,27 and 43 months. [50]. In 2019, Li et al. conducted a retrospective case series of seventeen patients, whereby a clinical pregnancy rate of 58.2 % was observed after IVF resulting in nine live births [51]. Furthermore, six BOT recurrences at a median of 29 months of follow-up were noted in four patients in the case series. A pooled literature review of twenty-seven clinical studies by the same group estimated a projected pregnancy rate of 63.5 % following ARTs and a recurrence rate of 21.7 % for patients with the same condition [51]. More studies should be conducted to investigate the safety profile of ARTs in women who have FSS for BOT management. Women may undergo egg retrieval and cryopreservation prior to FSS [1].

3.1.7. Surgical route and quality of life considerations

3.1.7.1. Laparoscopy vs laparotomy. The ROBOT study identified no differences in overall patient survival and clinical outcomes between laparotomy and laparoscopic surgical approaches [52,53]. However, there have been concerns about sub-optimal staging and potential cyst rupture during laparoscopy which may lead to tumour spillage [54,55]. Tumour spillage was shown to be more common in tumours >10 cm in diameter, however, cyst rupture could be mitigated by using an endobag and by conducting surgery at specialised centres [1,56].

Postoperative complications (haematoma, viscera injury) and outcomes (length of stay) have been reported as better in patients

managed laparoscopically, however these cases were less complicated and extensive compared to those managed using an open approach [56]. Laparoscopy is a safe approach frequently used for younger patients with early-stage BOTs. However, it should be used with caution in the presence of peritoneal implants, and only in selected cases. Kane et al. proposed that BOTs with non-invasive implants could be treated laparoscopically [57]. They reported no cases of invasive cancer despite a 44.4 % recurrence rate (8/18) (14 of which were treated conservatively). However, the authors suggest that laparoscopy should not be used for invasive or 'bulky' implants <5 mm or for BOTs exhibiting sinister features such as micropapillary architecture on final pathology [57].

The BGCS has released a statement based on findings from du Bois et al., that when technically feasible (small volume disease with no extensive peritoneal disease) the laparoscopic approach is the preferred route, with fewer post-operative complications, improved quality of life, as well as better fertility outcomes due to lower adhesion formation, provided this does not compromise adequate surgical staging [23,33,34]. In the UK it is common practice to have a lower threshold to adopt open route in the case where there is radiologic evidence of extraovarian disease i.e. suspicion of any implants [23,33,34,58].

3.1.8. Quality of life and patient reported outcome measures

There has been increasing awareness and research into patient reported outcome measures (PROMs) and quality of life (QoL) parameters following surgery for epithelial ovarian tumours including BOTs in recent years. At 1 year post laparotomy, women with ovarian cancer reported worse QoL outcomes including financial difficulties compared to women who were diagnosed with benign or borderline disease [59]. Using validated questionnaires, patients with BOTs had lower reported physical and emotional symptom scores than patients with ovarian cancer, but higher scores than patients with benign tumours [59]. More studies are needed to explore QoL measures in different types of surgery.

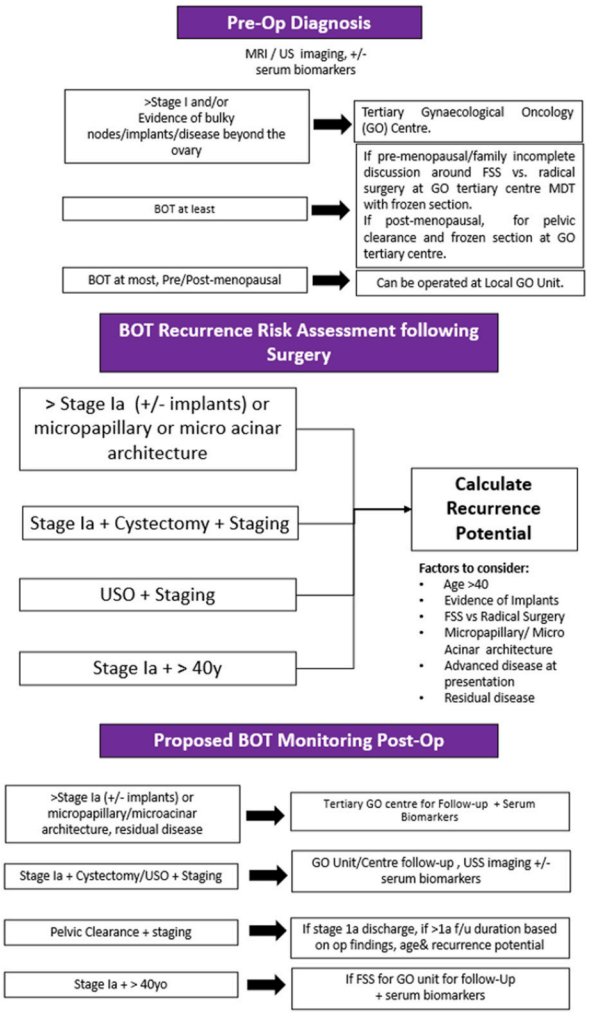

Fig. 5. Proposed Treatment/Follow Up Pathway. Abbreviations: FSS (Fertility Sparing Surgery), Unilateral Salpingo-Oopherectomy (USO), MDT (Multidisciplinary Team). Original Diagram. Colour to be used in print. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3.2. Recurrence rates & prognosis

Overall recurrence rates for BOTs are estimated at 3–10 %; in cases with more extensive disease (stage II and above) this is over 25 % [18]. The predominant factor influencing recurrence rates remains surgical modality at initial treatment.

FSS as previously stated is associated with higher recurrence at 10–30 % compared to radical surgery (0–5 %) [22]. Over a third (37 %) of BOT recurrences are diagnosed in the first two years, 31 % between years 2–5, 32 % within 5–10 years and 10 % over 10 years after diagnosis and treatment [3]. However, the higher recurrence rate following FSS may not translate to increased mortality [22]. Although most recurrent cases manifest histologically as BOT subtypes, approximately 20 % may undergo malignant transformation and progress to LGSOC (Low Grade Serous Ovarian Cancer) [52]; 2/3 of cases of malignant transformation are in women >40years old [52]. Serous BOTs with micropapillary and microacinar architecture have a greater association with extra-ovarian disease and a higher incidence of recurrence and death from disease than typical serous BOT (52). Other risk-factors for recurrence include incomplete staging, sub-optimal resection of the tumour, higher BOT stages and the presence of invasive peritoneal implants [60,61].

Several key clinical and molecular features of recurrent serous BOT subtypes have been described including micropapillary tumour patterns, microinvasion, lymph node involvement, increased patient age at diagnosis, and use of FSS(62). A personalised prediction tool integrating these factors has the potential to better characterise the risk of recurrence in serous BOTs and guide discussions around management accordingly.

3.3. Follow-up protocols & role of surveillance imaging and biomarkers

The main purposes of follow-up after BOT surgery are the timely diagnosis and appropriate management of recurrent disease, detection of malignant transformation, and optimisation of fertility outcomes for women who have not completed their family. These aims depend on stage at diagnosis as well as fertility aspirations, and hence follow-up modality can differ. Surveillance generally involves clinical examination, blood markers, ultrasound and/or MRI scanning if indicated, at least twice per year for the first two years and annually thereafter according to ESGO guidelines [24,45,63–65]. Observational studies have commonly set the timeframe of follow-up visits every 3-months in the first year, every 6-months from years 2–5 and annual follow-up thereafter, although the definitive time-frame for surveillance differs (Table 2) (Fig. 5).

3.3.1. Stage I disease follow-up frameworks

The primary aim of stage I BOT follow-up is to detect recurrence and offer additional treatment if indicated [26]. ESGO recommends follow-up should be twice a year for the first 2–3 years followed by yearly surveillance thereafter [24]. The current follow-up modality consists of clinical examination, with ultrasound reserved for women who underwent FSS; if the ultrasound identifies an abnormality then MRI is recommended for further characterisation. Transvaginal ultrasound has reported 100 % specificity in detecting disease for women who were previously treated with FSS(66). The value of biomarkers in BOT follow-up remains to be fully elucidated; whilst one study found the use of biomarkers did not help detect early recurrence for stage I disease [66], another found that serum biomarkers including Ca-125, CEA and Ca19-9 can identify recurrence in 5 % of patients [67]. This can be further complicated by the fact that not all BOT have raised serum biomarkers preoperatively, making their post-op interpretation challenging.

3.3.2. Stage II/III disease follow-up guidelines

Follow-up in stages II or III BOT primarily focuses on identifying and promptly acting on progression to invasive disease (LGSOC). Morice et al. proposed follow-up three times a year for the first three years, twice in years 3–5 and annually thereafter, albeit there is no robust evidence regarding the total length of follow up [26]. Based on this, ESGO recommends clinical examination combined with ultrasound and Ca-125. Ca125 can be particularly useful to monitor for progression to invasive disease [68]. ESGO still recommends ultrasound for patients who previously underwent FSS, whilst MRI and CT imaging may be considered [24].

BOT recurrence has been shown to occur up to four decades after initial presentation, with 77 % and 34 % of recurrences occurring within 5 and 10 years after the initial tumour, respectively, suggesting that follow-up may be required for at least 10 years [69,70].

3.4. Completion surgery

As many women affected by BOTs are of reproductive age, many elect to undergo FSS. During follow-up, discussions should be initiated regarding further surgery including removal of the contralateral ovary and uterus, following completion of their family. The term “completion surgery” refers to removal of the contralateral or both ovaries with or without hysterectomy. BGCS and ESGO guidelines state that the additional value of performing a hysterectomy is equivocal, associated with no disease-free survival or recurrence benefit [23,24]. However, a hysterectomy may be performed if the patient wishes or if there is evidence of disease involving the uterus and it is necessary for complete cytoreduction [33,34]. Generally, the risk of malignant transformation is low overall (~2 %), but considerable (about 30 % of those with relapsed disease). Nevertheless, malignant transformation is less frequent in women under 40 years of age at original diagnosis, compared to those aged over 40 years (12.0 % versus 66.7 %, $P < 0.001$); this should be taken into account prior to counselling for completion surgery [52]. Considerations which may inform decision-making for completion surgery include the stage and histological subtype of BOT, the type of FSS previously undertaken and the patient’s own personal views [1]. Completion surgery should be offered after a patient completes their family, often aiming to mitigate the psychological burden of follow-up [71].

3.5. Role of lymphadenectomy in the staging of BOTs

Currently, the NCCN, BGCS, ESGO and FIGO guidelines agree that lymphadenectomy in staging surgery for BOT has no clinical value [10,23,24,39]. However, in cases where implants are detected on nodes or nodes appear 'bulky' or enlarged, lymphadenectomy may be performed at the time of surgery with the aim to further examine histologically or debulk the abnormal disease volume [27,28] (Table 1).

3.6. Role of chemotherapy in the treatment of advanced stage BOTs

Current practice guidelines highlight that there is currently no definitive indication for chemotherapy for BOT management [23]. A meta-analysis comprising four prospective studies reported that adjuvant chemotherapy in stage I and II BOTs did not improve patient corrected overall survival and highlighted a high incidence of adverse side-effects such as organ toxicity [72]. A 2005 trial of patients with serous BOTs at early or advanced stages randomised to receive chemotherapy, radiotherapy, both or no treatment demonstrated no difference in survival [73], which has also been shown by several other trials [74,75]. ESGO and FIGO have suggested that endocrine therapy and adjuvant hormonal therapy may have some benefit in late recurrent invasive disease, however these treatment modalities are not routinely offered in the BOT management pathways [10,24,53].

3.7. HRT use

The evidence on hormone replacement therapy (HRT) use following BOT surgery is very limited. The BGCS/British Menopause Society (BMS) have highlighted the need for high quality studies to formulate robust evidence which will be the basis for solid counselling. For women undergoing radical surgery, or women who previously underwent FSS and are undergoing completion surgery, menopausal symptoms could be mitigated through HRT(23, 76). Generally, HRT can be safely offered if the tumour is found to be non-hormone sensitive, according to guidelines from the BGCS/BMS [23] and ESGO, with an acceptable adverse effects' profile [24]. According to the BGCS/BMS, cation should be exercised in the context of serous BOTs and residual disease, whilst for mucinous tumours HRT seems to be a safe option [76].

The Collège National des Gynécologues et Obstétriciens Français (CNGOF) advocate for the use of HRT in cases with no high-grade histological criteria (micropapillary pattern, stromal microinvasion, and peritoneal implants), however patients with BOTs with at least one high-risk criteria should be assessed on a case-by-case basis [77]. Based on current available evidence combined oestrogen ± progesterone administration is recommended unless there is any contraindication. The decision to start HRT should be discussed in detail with patients prior to and following surgery, with support offered by their healthcare team to address concerns. Although decisions about HRT are often straightforward and can be made in by the treating clinician, some patients have complex needs and access to specialist multidisciplinary menopause clinics is necessary. In such cases, robust counselling based on patients' individual symptoms and needs with regular re-assessment is essential.

3.8. Future directions in BOT management

The role of biomarker panels to identify early BOT transformations and potentially inform treatment merits further investigation [67,78]. Improved understanding of the molecular profile of BOTs has the potential to personalise management and integrate pharmacological approaches to treatment [78] such as targeting the BRAF/KRAS pathway implicated in serous and mucinous BOTs [79].

4. Discussion

BOTs are a heterogeneous group of neoplasms, the majority of which are diagnosed at stage I with an excellent prognosis. FSS is safe and clinically indicated in women who are yet to complete their family, however, is associated with higher risk of recurrence compared to radical surgery. Lymph node dissection and use of adjuvant chemotherapy are not supported by current evidence and guidelines.

4.1. Areas that require consensus

Length and modality of follow-up differs significantly across centres. An important question remains whether BOTs should be operated and/or followed up in units or tertiary specialist centres. Additionally, there is a clear need for high quality studies on the use of HRT, as well as quality of life post treatment. We discuss an approach to tackle those "grey areas" and propose recommendations for the local treatment pathway (Fig. 5).

4.2. Follow up – moving to a personalised approach?

The nature and length of follow-up can have a profound impact on a patient's perception of their condition as well as their mental health [12,59]. Several studies emphasise that the aim of follow up may vary between identifying a recurrent lesion or progression to invasive disease, or achieving reassurance whilst the patient completes their family. Repeated clinical visits may translate to anxiety and health-related worry, as well as service capacity strain and financial cost for each healthcare system [80,81].

To-date, there is no published health economic modelling on the impact of various follow-up regimes, taking into account QoL

parameters such as cancer-worry or anxiety related to hospital visits and multiple blood tests, their costs and impact on recurrence. Such a cost-utility analysis could examine the cost-effectiveness for different stages, histology, and primary treatment modalities of BOTs.

A simple calculation of post-operative overall predicted risk of recurrence or malignant transformation can act as the basis to further tailor follow up. A rough estimate of this can be easily obtained by considering well-established recurrence factors. However, the scientific basis of a robust prediction model should be the outcome of an individual participant data (IPD) meta-analysis of cohorts from several centres. Initial efforts to produce recurrence prediction models are available in the literature, however these are not validated, and it remains uncertain if these are clinically helpful [62].

Women should be given all the essential information and ultimately be able to choose between a conventional lengthy and intense follow-up pattern versus a more personalised one. Although the evidence is slim, this personalised follow-up approach has the potential to be more cost-effective, provided it does not result in significant additional morbidity, mortality, or treatment.

Several alternative strategies for personalised follow-up may be considered [82]. The BGCS have formulated the basis for patient-initiated follow-up (PIFU) and defined safety criteria across different diseases. PIFU should be integrated into local policy as an alternative approach, as long as there is clarity and consensus on entry-criteria to ensure oncological safety. Consideration should be given to the likelihood of recurrence. For instance, if the patient opts for cystectomy follow-up should be more frequent especially within the first few years [83]. In such cases clear counselling and recurrence risk stratification have a pivotal role in identifying high risk cases. A more personalised approach or PIFU may well improve compliance as it could be better tolerated by patients.

4.3. Where should patients with BOT be operated and followed up?

Diagnostic challenges (primarily radiological and interpretation of serum biomarkers) and pre-op differentiation between BOT and invasive cancer [62,84] push a significant proportion of these cases into the operating diary of tertiary oncology centres.

Where there is uncertainty regarding extraovarian or invasive disease, there is strong evidence that such cases should be performed in a tertiary centre [23]. This is to ensure facilities for frozen section pathology are available, as well as surgical expertise to perform lymph node dissection if this is required to achieve complete surgical staging and cytoreduction. However, in cases where there is radiological certainty that the tumour is BOT at most with no extraovarian disease, there is minimal or no role for a tertiary centre to be involved beyond the multidisciplinary consensus on the diagnosis and proposed staging route.

Regarding post-operative follow-up of BOTs, there is no current contraindication to divert cases back to the referring oncology unit, as long as there is an open referral route for re-discussion to the gynaecological oncology MDT if further concerns arise. Advanced stage disease (>Stage I) is a minority, and these cases should perhaps stay under the umbrella of a tertiary centre as the risk of malignant transformation is greater; especially cases that did not receive treatment in the form of radical surgery.

4.4. Approach to patient counselling

It is essential to reassure women that BOT's norm is not to "behave" as invasive disease, and the goal of any treatment approach is to maximise oncological safety with minimal radicality, preserving future fertility where possible. Counselling should be individualised; in the pre-op phase any uncertainty around radiological impression of BOT vs. invasive disease should be discussed. Family plans, radicality of proposed surgery, potential menopause effect and morbidity as well as QoL post laparoscopic or open surgery should be clearly explained. Following confirmation of BOT histology, a re-discussion around individualising follow up can develop confidence and reduce patients' cancer worry or anxiety.

4.4.1. Quality of life (QoL) post-surgery and use of HRT

Several studies discuss superiority of morbidity outcomes in laparoscopic vs. open surgery for BOTs. However, there is paucity of evidence on QoL post-surgery (open/laparoscopic), purely focused on BOT. Currently recommendations support use of HRT with premature menopause in BOT following surgery with no residual disease, but caution is advised if there is residual disease following surgery, microinvasive disease, recurrence, or peritoneal implants [76]. There is need for further high-quality studies for the use of HRT in BOTs and OC in general [23,76].

4.5. Recommendations regarding treatment pathway (Fig. 5)

1. All cases should be discussed and management planned within a Gynaecological Oncology (GO) MDT.
2. Any suspicion of >stage I disease including radiological evidence of bulky lymph nodes, peritoneal implants or disease beyond the pelvis should be discussed in gynaecology oncology MDT to decide on surgical management and offer surgery within a Gynaecological Oncology (GO) cancer centre (tertiary). Similarly, if radiology and serum biomarkers indicate at least presence of BOT ± malignancy then the case should be solely managed in the tertiary GO centre setting; if on the contrary they indicate BOT at most then the case can be managed in the local GO unit.
3. Follow up of advanced (>stage I) BOT, or BOT with distinct features of microacinar or micropapillary architecture should happen in a GO centre with regular more frequent (3 monthly) serum biomarker surveillance for the first 2 years, followed by 4–6 monthly for the next 3 years. Follow up of stage I disease depends on the treatment modality: if cystectomy was performed, then a more frequent follow up (3 monthly) for 2–5 years is advocated in the form of USS ± serum biomarker if secreting tumour. If USO (unruptured tumour) is performed, then a less frequent follow up (1–2 yearly) or PIFU can be advocated. In the case of cystectomy

Practice points

- Fertility Sparing surgery is safe for women who are yet to complete their family, however consideration should be given to communicate higher recurrence rate compared to radical surgery.
- Laparoscopic surgery where technically feasible is a safe option.
- Adjuvant chemotherapy and lymphadenectomy have not been shown to influence patient survival and have no role.
- Completion surgery can be offered as a second stage procedure; however hysterectomy has no established prognostic benefit.
- There is still no consensus regarding length and modality of follow-up. Risk stratification of recurrence can play a pivotal role in personalising follow up approaches.
- Prospective trials on assessing safety of HRT post BOT are essential to formulate robust evidence.

Research agenda

- Develop risk prediction models to stratify recurrence post treatment.
- Identify molecular biomarkers that predispose to extraovarian disease including implants and risk of malignant conversion.
- Identify histological and molecular profile of tumours with high tendency to recur.
- Prospective trials measuring QoL outcomes post BOT surgery including oncological safety of BOT.
- Standardise follow up intensity and modality including imaging and biomarkers. PIFU should be offered especially in low-risk stage I cases.

or USO, a mutual decision for completion BSO should take place throughout follow up in the GO centre or unit. In the case of radical surgery PIFU or discharge can be advocated if no other concerning factors. In women >40 years of age, the addition of serum biomarkers should be considered; this is to cover for a small though higher chance of malignant transformation. Follow-up following surgery for recurrent BOT should happen in a tertiary GO centre (Fig. 5).

4. GO tertiary MDT should lead decision-making pre and post operatively. Standardisation of follow-up modality (imaging ± biomarkers), frequency (first 5 years & total length) and location (centre vs. unit) should be agreed for each setting until strong evidence to formulate national guidance is available.

4.6. Future directions

Optimisation of preoperative diagnosis with the use of biomarker panels is essential. Personalising follow-up has the potential to improve patients' experience and provide cost efficiencies for each healthcare system. Developing better, accurate recurrence prediction model(s) would be a catalyst to stratify low vs intermediate or high-risk women. This would also allow further optimisation of resource re-allocation with less workload for tertiary centres. Advances in genomics and proteomics with better understanding of the molecular profile of tumours and their association with clinical outcomes may further help improve diagnostic and treatment pathways in the future.

5. Summary

BOTs are a heterogenous group of neoplasms with increased proliferative activity but no stromal invasion. Mostly (>90 %) BOTs are serous and mucinous tumours and often affect women over 40years. The mainstay of treatment is either radical surgery or FSS in pre-menopausal women. Consensus currently exists regarding the lack of evidence to support lymphadenectomy and adjuvant therapy. FSS has a higher risk of recurrence compared to radical surgery. 'Grey areas' regarding BOT management still exist regarding the modality and length of follow up for patients as well as the applicability of serum biomarkers for disease prognostication. Furthermore, HRT use, and quality of life outcomes of patients post BOT treatment would benefit from further research. The length and the modality of follow-up should be guided by the extent of disease (preoperatively), the type of surgical intervention (radical vs. FSS) as well as patients' preference. A gynaecological oncology MDT should review pre- and post-operative management; this should take place in a tertiary centre. Further research on the use of biomarkers (serum and potentially molecular profiling) may have the potential to improve treatment and follow-up regimens to optimise patient outcomes and allocation of health resources.

CRediT authorship contribution statement

Kyriaki-Barbara Papalois: Methodology, Visualization, Writing – original draft, Writing – review & editing. **Michail Sideris:** Conceptualization, Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Samuel George Oxley:** Writing – review & editing. **Arjun Jeyarajah:** Writing – review & editing. **Alexandra Lawrence:** Writing – review & editing. **Elly Brockbank:** Writing – review & editing. **Saurabh Phadnis:** Writing – review & editing. **James Dilley:** Writing – review & editing. **Ranjit Manchanda:** Conceptualization, Supervision, Writing – review & editing.

Ethics approval

N/A.

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Declaration of competing interest

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List of abbreviations

BGCS	British Gynaecological Cancer Society
BOTs	Borderline Ovarian Tumours
CNGOF	Collège National des Gynécologues et Obstétriciens Français
ESGO	European Society of Gynaecological Oncology
FIGO	International Federation of Gynaecology and Obstetrics
NCCN	National Comprehensive Cancer Network
FSS	Fertility Sparring Surgery
USO	Unilateral Salpingo-Oophorectomy
BSO	Bilateral Salpingo-Oophorectomy
GO	Gynecological Oncology Centre
WHO	World Health Organisation

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bpobgyn.2025.102688.

APPENDIX. A Search Strategy

("Ovarian Neoplasms" [Mesh] OR "ovarian neoplasms*" [Title/Abstract] OR "borderline ovarian tumour**" [Title/Abstract] OR "BOT* *" [Title/Abstract] OR "Tumours of Low Malignant Potential" [Title/Abstract])

AND.

("Disease Management" [Mesh] OR "Disease Management" [Title/Abstract] OR "Surgical Procedures, Operative" [Mesh] OR "Surgical Procedures, Operative" [Title/Abstract] OR "Radical Surgery" [Title/Abstract] OR "Hysterectomy" [Mesh] OR "Ovariectomy" [Mesh] OR "Salpingectomy" [Mesh] OR ″ Fertility Sparring Surgery" [Title/Abstract] OR " FSS" [Title/Abstract] OR "Organ Sparing Treatments" [Mesh] OR "Laparoscopy" [Mesh] OR "Laparotomy" [Mesh] OR "Follow-up" [Title/Abstract] OR "Follow up" [Title/Abstract] OR "Follow up" [Title/Abstract] OR "Case Management" [Mesh]) OR "Hormone Replacement Therapy" [Mesh] OR "HRT" [Title/Abstract] OR "Chemoradiotherapy, Adjuvant" [Mesh] OR "Chemoradiotherapy, Adjuvant" [Title/Abstract] OR "Recurrence" [Mesh] OR "Neoplasm Recurrence, Local" [Mesh] OR "Prognosis" [Mesh] OR "Quality of Life" [Mesh] OR "Quality of Life" [Title/Abstract] OR "QoL" [Title/Abstract])

Data availability

Available upon request.

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