

Borderline ovarian tumours in a middle-income country setting: a 10-year retrospective review of cases in a tertiary hospital in South Africa

AK Ghunney,^{1,2}  T Adams,^{1,2,3}  L Rogers,^{1,2} 

¹Division of Gynaecological Oncology, Department of Obstetrics and Gynaecology, Groote Schuur Hospital, University of Cape Town, South Africa

²South African Medical Research Council Gynaecological Cancer Research Centre, University of Cape Town, South Africa

³Global Surgery, University of Cape Town, South Africa

Corresponding author, email: amaghunney@gmail.com

Background: The diagnosis and management of borderline ovarian tumours (BOT) remain controversial almost a century after their initial description. Little research has been done in Africa to provide answers on the prevalence and outcomes of these tumours. This study reviewed cases of BOTs at Groote Schuur Hospital over 10 years.

Methods: A retrospective review of women diagnosed with BOTs at Groote Schuur Hospital between January 2005 and December 2014 was undertaken. Women with multiple primary tumours, who were lost to follow-up or had inadequate clinical data, were excluded. Demographic characteristics, preoperative, operative, postoperative, oncological, and pathological data were retrieved and analysed.

Results: In the study period, 91 patients were diagnosed with BOTs. Of these, 19 were eliminated, and 72 were analysed. BOTs accounted for 22.3% of the 409 ovarian neoplasms. Fertility-sparing surgery was done in 31.9% ($n = 23$). Mucinous histology was the most common histological subtype (57%). Our overall recurrence rate was 13.9% ($n = 10$), with 40% being invasive ($n = 4$). The five-year overall survival (OS) rate was 91.7%, and the five-year relapse-free survival (RFS) rate was 89.9%. Despite small numbers, all patients with invasive recurrence died within five years of recurrence, while all patients who recurred with borderline histology were alive five years after recurrence.

Conclusion: Mucinous histology was the most common histological subtype (57%). Despite BOTs having a generally favourable prognosis, patients who recurred with invasive disease were all dead five years after recurrence. Patients who recurred with borderline histology were all alive five years after recurrence.

Keywords: borderline ovarian tumours, fertility-sparing surgery, recurrence, survival, stage

Introduction

Borderline ovarian tumours (BOTs) are characterised by increased epithelial proliferation, nuclear atypia, and mildly increased mitotic activity without stromal invasion.¹ They are intermediate in nature compared with benign cystadenomas and invasive carcinomas of the ovary.² BOTs account for approximately 10–20% of all ovarian neoplasms, with an incidence of 4.8/100 000 per year.³ Serous and mucinous histological subtypes account for over 95%.⁴ These frequently occur in younger women, with approximately one-third of patients diagnosed before 40 years.⁵ At diagnosis, 65–70% of serous and about 90% of mucinous BOTs are stage I.⁶ With a five-year survival rate of 99% at stage I, they have an excellent prognosis.⁷

For decades, the standard of care for managing BOTs was radical surgery, comprising hysterectomy and bilateral salpingo-oophorectomy. In recent years, owing to their favourable prognosis and early stage at diagnosis, there has been a trend towards fertility-sparing surgery (see Appendix), especially since many women are in their reproductive years at diagnosis. Fertility-sparing surgery is associated with an increased risk of recurrence but does not affect overall survival (OS).⁸

Almost a century after their initial description, much controversy still exists regarding the terminology, role of imaging and tumour markers in diagnosis, the role of complete surgical staging (see Appendix), the radicality of surgery, the necessity of restaging surgery (see Appendix), the role of adjuvant therapy, and prognostic factors that affect survival.^{1,9,10} Data on BOTs generated in middle-income countries is still sparse and non-existent in some countries. This study aimed to describe the demographic characteristics, occurrence, treatment, and outcomes of women diagnosed with BOTs at Groote Schuur Hospital, a tertiary hospital in South Africa, an upper-middle-income country.

Methods

This study is a quantitative, retrospective, descriptive review undertaken at Groote Schuur Hospital, a tertiary hospital in South Africa. All patients diagnosed with BOTs between January 2005 and December 2014 were identified using the gynaecological oncology database. All histology registered in the database had previously undergone central pathology review. Women with multiple primary tumours, lost to follow-up within five years of diagnosis, or for whom adequate clinical data could not be retrieved were excluded. Demographic characteristics,

preoperative, operative, postoperative, oncological, and pathological data were retrieved from patients' folders and the gynaecological oncology database (University of Cape Town Human Research Ethics Committee, number R016/2103).

All patients were restaged according to the 2014 International Federation of Gynaecology and Obstetrics (FIGO) staging of cancer of the ovary, fallopian tubes, and peritoneum. Patients were considered optimally debulked if < 1 cm of the tumour was left during surgery. Our institution does not routinely perform systematic lymphadenectomy during surgery for ovarian tumours. On follow-up reviews, recurrence was excluded based on patients' symptoms and examination findings. Patients suspected to have tumour recurrence had tumour markers and imaging done.

JMP software version 17.1.0 (SAS Institute Inc., Cary, United States) was used for data processing and analysis. Continuous data were presented as medians and interquartile ranges. Categorical data were presented as frequencies and percentages. A comparison of CA-125 levels and stage was performed using the Kruskal–Wallis test. The relationship between recurrence and pathological factors was analysed using the chi-square test, and significant variables were further analysed using binomial logistic regression. The Kaplan–Meier method was used for survival analysis. The association between survival and clinicopathological factors was analysed using multiple logistic regression.

Approval was granted by the University of Cape Town Human Research Ethics Committee (HREC REF 129/2023) and Groote Schuur Hospital. The study was conducted in compliance with the Declaration of Helsinki.¹¹

Results

Between 2005 and 2014, 91 patients with a histological diagnosis of BOTs were registered in the gynaecological oncology database of the Groote Schuur Hospital. Details are shown in Figure 1. This study included 72 women and excluded 19. Of the eight women excluded for a second malignancy, three had breast cancer, one had vulvar cancer and B-cell lymphoma of the thyroid, one BOT diagnosed after surgery for carcinosarcoma of the uterus, one synchronous cervical cancer, another synchronous serous endometrial cancer, and the last synchronous endometrioid carcinoma of the ovary.

Demographic characteristics

Table I presents the demographic characteristics of the patients. The median age was 48.5 years (range 16–82). Most patients were of mixed ancestry (77.8%, $n = 56$), and almost a third (31.9%, $n = 23$) were below 40 years old.

Surgery and staging

Most women (70.8%, $n = 51$) underwent complete surgical staging (Table II). Of the 21 patients not completely surgically staged, eight (38.1%) did not undergo peritoneal washings and omentectomy, five (23.8%) did not undergo omentectomy, seven (33.3%) did not undergo peritoneal washings for cytology, and one (4.8%) did not undergo an examination of the upper

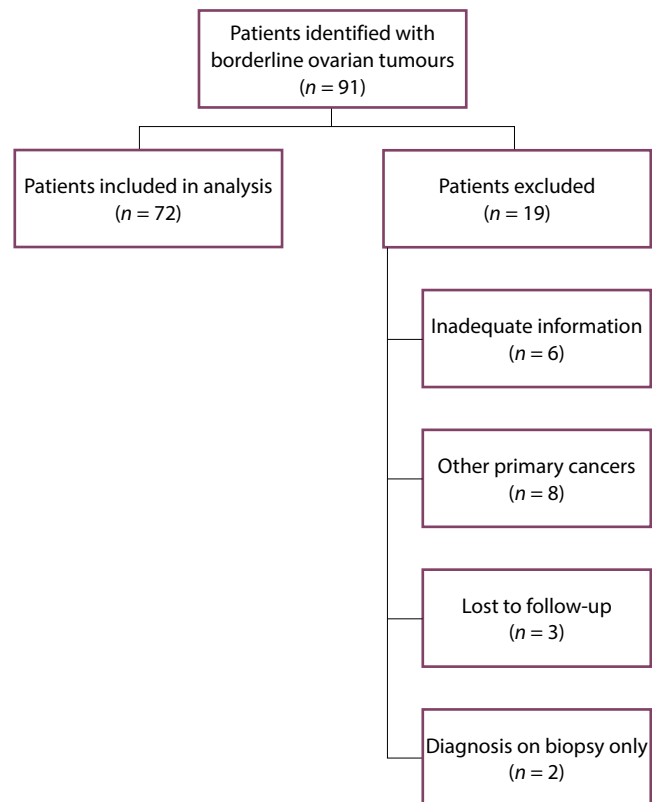


Figure 1: Flow chart of the study cohort

abdomen. None of these patients underwent restaging surgery. Four patients had completion surgery (see Appendix), two after recurrence as a borderline tumour, one after recurrence as an invasive disease, and one three months after primary surgery on histological confirmation of the involvement of the contralateral ovary and uterine implants.

Of the patients, 88.9% ($n = 64$) had stage I disease at diagnosis, 5.6% ($n = 4$) had stage II disease, and 5.6% ($n = 4$) had stage III disease. All patients with extraovarian disease (\geq stage II) had tumours of serous histology. Most patients (68.1%, $n = 49$) underwent radical surgery, and 80.6% of patients ($n = 58$) were optimally debulked.

Correlation between preoperative CA-125, surgical staging, and histology

There was no correlation between CA-125 levels and disease stage ($p = 0.055$). Even so, CA-125 levels $> 1\,000$ U/ml were found almost exclusively in patients with extraovarian disease ($n = 5$, four patients staged IIB–IIIB, one stage IA but not fully staged). However, there was a statistically significant difference in the distribution of CA-125 levels between serous and mucinous BOTs ($p < 0.001$), with CA-125 levels $> 1\,000$ U/ml occurring exclusively in serous BOTs ($n = 5$).

Histological subtypes

Mucinous histology was the most common subtype (56.9%, $n = 41$) (Table II). Of the 27 patients diagnosed with serous BOTs, one had a typical variant, three had micropapillary variants, and the variants were not assessed in 23 patients. Seven of the 27 serous BOTs were associated with implants. Six of these implants were non-invasive, and the seventh was not sub-classified. Two

Table I: Demographic characteristics

Age	
Median (range in years)	48.5 (16–82)
< 40, <i>n</i> (%)	23 (31.9)
> 40, <i>n</i> (%)	49 (68.1)
Parity	
Median (range in years)	2 (0–9)
Race	
Black, <i>n</i> (%)	11 (15.3)
White, <i>n</i> (%)	5 (6.9)
Mixed ancestry, <i>n</i> (%)	56 (77.8)
Complete surgical staging	
Yes, <i>n</i> (%)	51 (70.8)
No, <i>n</i> (%)	21 (29.2)
Stage at diagnosis, <i>n</i> (%)	
IA	45 (62.5)
IB	3 (4.2)
IC	16 (22.2)
IIA	1 (1.4)
IIB	3 (4.2)
IIIA	2 (2.8)
IIIB	1 (1.4)
IIIC	1 (1.4)
CA-125 value (U/ml)	
Median (range)	100 (5–2 944)
Elevated CA-125 > 35 U/ml, <i>n</i> (%)	
Yes	38 (52.8)
No	19 (26.4)
Not done	15 (20.8)
Venous Thromboembolic Events, <i>n</i> (%)	
Yes	0 (0)
No	66 (91.7)
Unknown	6 (8.3)

patients with implants recurred. One had non-invasive implants, and the type of implant was not stated in the other. Both recurrences were of borderline histology.

Adjuvant therapy

None of our patients received adjuvant therapy.

Follow-up and survival data

Patients were followed up for 13–169 months (median 98).

Recurrences and deaths

There were 10 patients (13.9%) with recurrences and 10 patients (13.9%) who died; however, not all patients who recurred died. There were 11 recurrences in 10 patients. Recurrence was of borderline histology in six patients and invasive disease in three. The last patient recurred twice: first as a borderline tumour and then as an invasive disease. Six of the 10 patients who passed away died of other comorbidities. The four tumour-related deaths were all due to invasive recurrence.

Table II: Surgical and pathological characteristics

Type of surgery, <i>n</i> (%)	
Fertility-sparing surgery	23 (31.9)
Radical surgery	49 (68.1)
Type of fertility-sparing surgery, <i>n</i> (%)	
Unilateral salpingo-oophorectomy	18 (78.3)
Unilateral salpingo-oophorectomy and contralateral cystectomy	3 (13.0)
Unilateral cystectomy	1 (4.3)
Unilateral cystectomy and contralateral ovarian biopsy	1 (4.3)
Route of surgery, <i>n</i> (%)	
Laparotomy	71 (98.6)
Laparoscopy	1 (1.4)
Optimal debulking	
Yes	58 (80.6)
No	3 (4.2)
Unknown	11 (15.3)
Complete surgical staging	
Yes	51 (70.8)
No	21 (29.2)
Restaging surgery	
Yes	0 (0)
No	21 (100)
Appendicectomy, <i>n</i> (%)	9 (12.5)
Frozen section, <i>n</i> (%)	0 (0)
Lymphadenectomy, <i>n</i> (%)	3 (4.2)
Completion surgery, <i>n</i> (%)	4 (17.4)
Histology	
Serous	27 (37.5)
Mucinous	41 (56.9)
Seromucinous	1 (1.4)
Other	3 (4.2)

The six patients who recurred with borderline histology were all alive at five-year follow-up, including one patient who had no intervention after recurrence was diagnosed (frozen pelvis at primary surgery). Five of these six patients are alive now, 10–14 years after their initial diagnosis of BOT (including the patient with a frozen pelvis who did not have repeat laparotomy on recurrence). The sixth patient was recently lost to follow-up.

Only two of the 10 patients who recurred had mucinous histology. One patient recurred as low-grade mucinous adenocarcinoma, and the other was reported as metastatic adenocarcinoma. Both malignant transformations in serous borderline tumours were to high-grade serous carcinoma.

Time to recurrence

The median time to recurrence was 42.9 months (range 1.0–108.0).

Five-year overall survival

The five-year OS rate was 91.7% (85.5% to 98.3% with a 95% confidence interval [CI]). The five-year OS was 90.6% for stage

Table III: Analysis of surgical and pathological factors and association with recurrence

Recurrence	Yes (n = 10)	No (n = 62)	Total (n = 72)	p-value
Stage				0.6281
I	8.0 (80.0%)	56.0 (90.3%)	64.0 (88.9%)	
II	1.0 (10.0%)	3.0 (4.8%)	4.0 (5.6%)	
III	1.0 (10.0%)	3.0 (4.8%)	4.0 (5.6%)	
Complete surgical staging				0.4171
Yes	6.0 (60.0%)	45.0 (72.6%)	51.0 (70.8%)	
No	4.0 (40.0%)	17.0 (27.4%)	21.0 (29.2%)	
Implants				0.0441
Yes	2.0 (20.0%)	5.0 (8.1%)	7.0 (9.7%)	
No	5.0 (50.0%)	52.0 (83.9%)	57.0 (79.2%)	
Unknown	3.0 (30.0%)	5.0 (8.1%)	8.0 (11.1%)	
Type of surgery				0.0051
FSS	7.0 (70.0%)	16.0 (25.8%)	23.0 (31.9%)	
Radical	3.0 (30.0%)	46.0 (74.2%)	49.0 (68.1%)	
Histology				0.0291
Serous	8.0 (80.0%)	19.0 (30.6%)	27.0 (37.5%)	
Mucinous	2.0 (20.0%)	39.0 (62.9%)	41.0 (56.9%)	
Seromucinous	0.0 (0.0%)	1.0 (1.6%)	1.0 (1.4%)	
Other	0.0 (0.0%)	3.0 (4.8%)	3.0 (4.2%)	
Optimally debulked				0.0211
Yes	6.0 (60.0%)	52.0 (83.9%)	58.0 (80.6%)	
No	2.0 (20.0%)	1.0 (1.6%)	3.0 (4.2%)	
Unknown	2.0 (20.0%)	9.0 (14.5%)	11.0 (15.3%)	

FSS – fertility-sparing surgery

I (83.8% to 98.1%, 95% CI) and 100% for both stage II and III disease (100% to 100%, 95% CI).

Five-year relapse-free survival

The five-year relapse-free survival (RFS) rate was 89.9% (80.0% to 95.1%, 95% CI). The five-year RFS was 90.1% for stage I (82.9% to 98.0%, 95% CI), 100% for stage II (100% to 100%, 95% CI), and 75% for stage III disease (42.6% to 100%, 95% CI). There was one case of recurrence in a patient with stage II disease, but this occurred after 75.9 months. Another recurrence was observed in a patient with stage III disease a month after optimal debulking.

Prognostic factors

Analysis of surgical and pathological factors and their association with recurrence showed that serous histology, fertility-sparing surgery, residual disease, and implants were significantly associated with recurrence (Table III). Binomial logistic regression analysis revealed serous histology and fertility-sparing surgery were independently associated with recurrence ($p = 0.016$ and $p = 0.026$, respectively).

Discussion

In this study, patients with BOTs ($n = 91$) comprised 22.3% of the 409 women with ovarian neoplasms registered in the gynaecological oncology database at Groote Schuur Hospital between 2005 and 2014. Consistent with previously published data, 32% of patients with BOTs at our hospital were under the

age of 40.^{5,12} Mucinous histology accounted for almost 57%, and serous 37.5%, compared to unpublished data from this same institution that reported 47.9% mucinous histology and 49.3% serous.¹³ Similar data was reported from Charlotte Maxeke Academic Hospital in Johannesburg, where 50% of BOTs were of mucinous histology and 40% serous.¹⁴ The suggestion of a higher proportion of BOTs being mucinous in South Africa needs further prospective studies. Our finding that 94.5% of tumours were either serous or mucinous is similar to previously published data.⁴

Contrary to a study by Messalli et al.,¹⁵ which found that up to 49% of patients were asymptomatic at diagnosis, 90.3% of our patients presented with one or more symptoms. These were most commonly pain/abdominal distension, comparable to a study by Paulsen, which reported that 75% of patients present with at least one symptom.¹⁶

CA-125 levels were higher in patients with serous than mucinous histology ($p < 0.001$). Similar results were obtained by Gotlieb et al.¹⁷ Although the highest CA-125 levels ($> 1\,000$ U/ml) were detected almost exclusively in patients with extraovarian disease, CA-125 levels were not significantly associated with disease stage ($p = 0.055$), likely due to the small number of patients with advanced-stage disease.

No known patient experienced a venous thromboembolic event. Bakhru obtained similar results.¹⁸ Fertility-sparing surgery was performed for 31.9% of patients ($n = 23$). Of these, 20 patients were younger than 40. The parities of the three patients below the age of 40 who underwent radical surgery were three, three, and two, respectively.

Incomplete surgical staging occurred in 29.2% of patients ($n = 21$), and none had restaging surgery. Of these patients, 19 (90.5%) were assigned stage I and may not have benefitted from restaging surgery, according to a study by Bendifallah et al.¹⁹ Their study reported no statistically significant difference in OS or five-year RFS between patients with presumed stage I disease who were completely surgically staged and those who were not.¹⁹ Our reported figure of 70.8% of patients completely surgically staged is significantly higher than reported in other studies.^{19,20} It is important to note that random peritoneal biopsies performed as part of full surgical staging in these studies are not routinely performed at our institution, likely accounting for our higher percentage of fully staged patients.

Nine patients underwent routine appendectomy. Eight of these had mucinous histology and one seromucinous. The appendix was histologically uninvolved in all nine cases. In mucinous BOTs, microscopic tumour involvement in a macroscopically normal-looking appendix is rare, and appendectomy can be omitted, according to a systematic review by Cosyns et al.²¹ In recent years, our institution has reviewed its protocols and now omits appendectomy in mucinous ovarian neoplasms with normal-looking appendices.

Our overall recurrence rate was 13.9%, and the rate of invasive relapse was 5.6%. In Europe, published overall recurrence rates are between 3% and 10%, lower than our calculated overall recurrence rate of 13.9%.^{12,24} Despite our low study numbers,

Table IV: Predictors of overall and relapse-free survival on univariate and multivariate analysis

Predictor		Number of patients (%)	Overall survival		Relapse-free survival	
			Univariate analysis, HR (95% CI, <i>p</i> -value)	Multivariate analysis, HR (95% CI, <i>p</i> -value)	Univariate analysis, HR (95% CI, <i>p</i> -value)	Multivariate analysis, HR (95% CI, <i>p</i> -value)
Age			1.05 (1.01 to 1.09, <i>p</i> = 0.014)	1.05 (1.00 to 1.10, <i>p</i> = 0.050)	1.01 (0.98 to 1.04, <i>p</i> = 0.378)	1.05 (1.01 to 1.09, <i>p</i> = 0.018)
Stage	I	64 (88.9)	-	-	-	-
	II	4 (5.6)	0.00	0.00	1.14 (0.15 to 8.70, <i>p</i> = 0.898)	0.85 (0.09 to 8.30, <i>p</i> = 0.887)
	III	4 (5.6)	0.00	0.00	1.65 (0.21 to 12.70, <i>p</i> = 0.630)	1.71 (0.18 to 16.27, <i>p</i> = 0.640)
Histology	Serous	27 (37.5)	-	-	-	-
	Mucinous	41 (56.9)	1.01 (0.29 to 3.59, <i>p</i> = 0.986)	0.91 (0.20 to 4.01, <i>p</i> = 0.897)	0.35 (0.13 to 0.95, <i>p</i> = 0.040)	0.28 (0.09 to 0.89, <i>p</i> = 0.031)
	Other	4 (5.6)	0.00	0.00	0.00	0.00
Complete surgical staging	Yes	51 (70.8)	-	-	-	-
	No	21 (29.2)	1.49 (0.42 to 5.29, <i>p</i> = 0.539)	1.55 (0.27 to 8.83, <i>p</i> = 0.621)	1.34 (0.49 to 3.70, <i>p</i> = 0.571)	0.54 (0.14 to 2.11, <i>p</i> = 0.377)
CA-125 level	Low	19 (33.3)				
	High	38 (66.7)	0.35 (0.08 to 1.56, <i>p</i> = 0.167)		3.55 (0.44 to 28.84, <i>p</i> = 0.236)	
Type of surgery	FSS	23 (31.9)	-	-	-	-
	Radical	49 (68.1)	2.04 (0.43 to 9.61, <i>p</i> = 0.367)	1.02 (0.12 to 8.90, <i>p</i> = 0.983)	0.60 (0.22 to 1.60, <i>p</i> = 0.305)	0.19 (0.04 to 0.91, <i>p</i> = 0.038)

CI – confidence interval, FSS – fertility-sparing surgery, HR – hazard ratio

40% of our recurrences ($n = 4$) were invasive, higher than the 20% reported in a previous study.⁴ A possible explanation is that microinvasion and the micropapillary pattern of serous borderline tumours, which may be associated with higher recurrence rates, were not assessed in most of our specimens.⁶

Higher recurrence rates were noted in patients who underwent fertility-sparing surgery ($p = 0.026$). It has long been established that fertility-sparing surgery, particularly cystectomy, is associated with higher recurrence rates than radical surgery (10–20% vs. 5%).²⁴ We established a recurrence rate of 30.4% in patients who underwent fertility-sparing surgery versus 6.1% in those who underwent radical surgery. Of the patients who underwent cystectomy, 60% (3/5) recurred compared with 22.2% (4/18) who underwent oophorectomy alone. Nonetheless, the type of surgery had no impact on OS ($p = 0.983$), but radical surgery was associated with better RFS on multivariate analysis (hazard ratio 0.19 [0.04–0.91, $p = 0.038$]) (Table IV). With a five-year OS of 91.7% and a five-year RFS of 89.9%, our survival outcomes were lower than those reported in the literature.⁷

Stage I disease was diagnosed in 88.9% of our patients ($n = 64$), slightly higher than the 78.9% published by du Bois et al.⁴ Also, 70.4% of serous and 100% of mucinous borderline tumours were stage I at diagnosis, compared to data published by Gershenson.⁶ Stage I disease has an excellent prognosis, with a five-year OS of up to 99%.⁷ We obtained a lower five-year OS of 90.6% and a five-year RFS of 90.1% in patients with stage I disease. This was possibly due to negative prognostic factors, such as microinvasion and the micropapillary pattern of serous borderline tumours, which were not assessed in our study.⁶

Though these prognostic factors do not impact the management of BOTs, and adjuvant therapy is still not offered in their presence, perhaps more intensive postoperative surveillance for the early detection and management of recurrence can be recommended in these cases.

Most patients were assigned stage I ($n = 64$) versus four patients each for stages II and III. There were more recurrences in stage I disease, which is unexpected. However, because patients who were incompletely staged were not restaged, a lingering question is whether patients with advanced-stage disease were incorrectly assigned stage I, resulting in seemingly poorer survival outcomes in our patients with stage I disease.

Four out of six patients who recurred as borderline tumours were managed successfully with surgical intervention (two completion surgeries, one partial oophorectomy, and one repeat cystectomy), as established by a study that found that most recurrences can be salvaged with surgery alone.²⁵ The two patients who had conservative surgery after recurrence were both in their twenties with no children. They both recurred in the remaining ovary following unilateral salpingo-oophorectomy and contralateral cystectomy at primary surgery. One patient underwent percutaneous drainage of a cyst, and the last was observed on account of a frozen pelvis. All patients who recurred histologically as borderline tumour only were alive five years after recurrence, similar to results obtained by Silva et al.,²⁶ and 10–14 years following the initial diagnosis of BOT. They include the one patient who was only observed upon diagnosis of recurrence.

All four patients who recurred as invasive disease died within five years of recurrence, reflecting the importance of identifying

prognostic factors for malignant transformation, which our study was unable to do given the small numbers. None of our patients received adjuvant therapy. This coincides with several studies that reported no survival benefit of adjuvant therapy in managing BOTs.^{22,23}

Despite most patients having mucinous histology, only two out of 10 recurrences (20%) were of mucinous histological subtype, both as invasive diseases (100%). Similar results were obtained by Uzan et al.,²⁷ who reported that the risk of recurrence is higher in serous histology, and the risk of invasive recurrence is higher in mucinous histology. However, the association between mucinous histology and malignant transformation did not reach statistical significance in our study ($p = 0.930$), most likely due to the small number of cases.

Strengths and weaknesses

This study is one of few studies on BOTs in Africa, and importantly, in a middle-income country, providing valuable insights into the occurrence, demographic characteristics, operative and postoperative management, and survival outcomes in women with BOTs managed in Africa. An interesting finding is that mucinous histology is the most common histologic subtype, in contrast to previous studies that quote serous histology as the most common.^{4,12} Another strength is that central pathology review was performed.

Limitations include the inherent bias posed by the retrospective nature of the study, the small number of study participants and events, the short follow-up period, especially because BOTs are known to recur later (32% five years after diagnosis), and the lack of subtyping of serous BOTs in most cases.⁴

Implications for practice and future research

In our study, all patients (100%) who recurred as BOT were alive five years after recurrence (including one patient who had no intervention following recurrence), in contrast to 100% mortality in patients who recurred as an invasive disease. All patients who recurred as invasive disease died within five years of recurrence, reflecting their importance. The number of recurrences and malignant transformations was small in our study. The identified (albeit controversial) risk factors for recurrence and malignant transformation, including the micropapillary pattern of serous BOTs and the presence of microinvasion, were not assessed in most of our patients.¹ A large multicentre study with long-term follow-up is required to confirm these findings. It is imperative that pathologists comprehensively report on BOT characteristics to answer these important questions.

Conclusion

BOTs accounted for 22.3% of ovarian neoplasms registered in our gynaecological oncology database during the study period. Mucinous histology was the most common histological subtype (57%). Despite BOTs having a favourable prognosis, all women who had invasive recurrence died within five years of recurrence.

Acknowledgements

We acknowledge Professors Lynette Denny and Nomonde Mbatani of the Gynaecological Oncology Unit, Groote Schuur

Hospital, Dr. Nazia Fakie of the Department of Radiation Oncology, Groote Schuur Hospital, for her work on the gynaecological oncology database, Dr. Rakiya Saidu, Groote Schuur Hospital for her work in analysing the data, and Dr. Jackie Chokoe Maluleke of the Department of Pathology, Groote Schuur Hospital.

Conflict of interest

The authors declare no conflict of interest.

Funding source

The statistician fee was paid by the South African Medical Research Council Gynaecological Cancer Research Centre.

Ethical approval

Approval was granted by the University of Cape Town Human Research Ethics Committee (HREC REF 129/2023) and Groote Schuur Hospital. The study was conducted in compliance with the Declaration of Helsinki.

ORCID

AK Ghunney  <https://orcid.org/0009-0003-1470-931X>

T Adams  <https://orcid.org/0000-0002-3686-3540>

L Rogers  <https://orcid.org/0009-0003-1759-5485>

References

1. Fischerova D, Zikan M, Dundr P, Cibula D. Diagnosis, treatment, and follow-up of borderline ovarian tumors. *Oncologist*. 2012;17(12):1515-33. <https://doi.org/10.1634/theoncologist.2012-0139>.
2. Patrono MG, Minig L, Diaz-Padilla I, et al. Borderline tumours of the ovary, current controversies regarding their diagnosis and treatment. *Ecantermedicalscience*. 2013;7:379. <https://doi.org/10.3332/ecancer.2013.379>.
3. Lenhard MS, Mitterer S, Kümper C, et al. Long-term follow-up after ovarian borderline tumor: relapse and survival in a large patient cohort. *Eur J Obstet Gynecol Reprod Biol*. 2009;145(2):189-94. <https://doi.org/10.1016/j.ejogrb.2009.04.031>.
4. Du Bois AD, Ewald-Riegler N, du Bois O, Harter P. Borderline tumours of the ovary - a systematic review. *Geburtshilfe Frauenheilkd*. 2009;69(9):807-33. German. <https://doi.org/10.1055/s-0029-1186007>.
5. Morice P. Borderline tumours of the ovary and fertility. *Eur J Cancer*. 2006;42(2):149-58. <https://doi.org/10.1016/j.ejca.2005.07.029>.
6. Gershenson DM. Management of borderline ovarian tumours. *Best Pract Res Clin Obstet Gynaecol*. 2017;41:49-59. <https://doi.org/10.1016/j.bpobgyn.2016.09.012>.
7. Trimble CL, Kosary C, Trimble EL. Long-term survival and patterns of care in women with ovarian tumors of low malignant potential. *Gynecol Oncol*. 2002;86(1):34-7. <https://doi.org/10.1006/gyno.2002.6711>.
8. Zanetta G, Rota S, Chiari S, et al. Behavior of borderline tumors with particular interest to persistence, recurrence, and progression to invasive carcinoma: a prospective study. *J Clin Oncol*. 2001;19(10):2658-64. <https://doi.org/10.1200/JCO.2001.19.10.2658>.
9. Colombo N, Sessa C, du Bois A, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. *Ann Oncol*. 2019;30(5):672-705. <https://doi.org/10.1093/annonc/mdz062>.
10. Gershenson DM. Clinical management potential tumours of low malignancy. *Best Pract Res Clin Obstet Gynaecol*. 2002;16(4):513-27. <https://doi.org/10.1053/beog.2002.0308>.
11. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-4. <https://doi.org/10.1001/jama.2013.281053>.
12. Trillsch F, Mahner S, Woelber L, et al. Age-dependent differences in borderline ovarian tumours (BOT) regarding clinical characteristics and outcome: results from a sub-analysis of the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) ROBOT study. *Ann Oncol*. 2014;25(7):1320-7. <https://doi.org/10.1093/annonc/mdu119>.
13. Hendricks A. An audit of the management of women with borderline ovarian tumours treated at Groote Schuur Hospital between 1984-2008 [thesis]

- [Internet]. University of Cape Town; 2017. Available from: <http://hdl.handle.net/11427/25292>. Accessed 14 September 2023.
14. Pillay L, Wade R. A retrospective study of the epidemiology and histological subtypes of ovarian epithelial neoplasms at Charlotte Maxeke Johannesburg Academic Hospital. *South Afr J Gynaecol Oncol*. 2021;13(1):26-35. <https://doi.org/10.1080/20742835.2021.1962084>.
 15. Messalli EM, Grauso F, Balbi G, et al. Borderline ovarian tumors: features and controversial aspects. *Eur J Obstet Gynecol Reprod Biol*. 2013;167(1):86-9. <https://doi.org/10.1016/j.ejogrb.2012.11.002>.
 16. Paulsen T. Epithelial ovarian cancer: a clinical epidemiological approach on diagnosis and treatment [Internet]. University of Oslo; 2007. Available from: <http://urn.nb.no/URN:NBN:no-16877>. Accessed 21 October 2023.
 17. Gotlieb WH, Soriano D, Achiron R, et al. CA 125 measurement and ultrasonography in borderline tumors of the ovary. *Am J Obstet Gynecol*. 2000;183(3):541-6. <https://doi.org/10.1067/mob.2000.105940>.
 18. Bakhr A. Effect of ovarian tumor characteristics on venous thromboembolic risk. *J Gynecol Oncol*. 2013;24(1):52-8. <https://doi.org/10.3802/jgo.2013.24.1.52>.
 19. Bendifallah S, Nikpayam M, Ballester M, et al. New pointers for surgical staging of borderline ovarian tumors. *Ann Surg Oncol*. 2016;23(2):443-9. <https://doi.org/10.1245/s10434-015-4784-9>.
 20. Morice P, Uzan C, Fauvet R, et al. Borderline ovarian tumour: pathological diagnostic dilemma and risk factors for invasive or lethal recurrence. *Lancet Oncol*. 2012;13(3):e103-15. [https://doi.org/10.1016/S1470-2045\(11\)70288-1](https://doi.org/10.1016/S1470-2045(11)70288-1).
 21. Cosyns S, De Sutter P, Tournaye, Polyzos NP. Necessity of appendectomy for mucinous borderline ovarian tumors. Systematic review. *Arch Gynecol Obstet*. 2016;294(6):1283-9. <https://doi.org/10.1007/s00404-016-4174-y>.
 22. Faluyi O, Mackean M, Gourley C, Bryant A, Dickinson HO. Interventions for the treatment of borderline ovarian tumours. *Cochrane Database Syst Rev*. 2010;2010(9):CD007696. <https://doi.org/10.1002/14651858.CD007696.pub2>.
 23. Vasconcelos I, Olschewski J, Braicu I, Sehouli J. Limited efficacy of platinum-based adjuvant treatment on the outcome of borderline ovarian tumors. *Eur J Obstet Gynecol Reprod Biol*. 2015;186:26-33. <https://doi.org/10.1016/j.ejogrb.2014.12.022>.
 24. Du Bois A, Trillsch F, Mahner S, Heitz F, Harter P. Management of borderline ovarian tumors. *Ann Oncol*. 2016;27 Suppl 1:i20-2. <https://doi.org/10.1093/annonc/mdw090>.
 25. Nayyar N, Lakhwani P, Goel A, Pande PK, Kumar K. Management of borderline ovarian tumors - still a gray zone. *Indian J Surg Oncol*. 2017;8(4):607-14. <https://doi.org/10.1007/s13193-017-0697-3>.
 26. Silva EG, Gershenson DM, Malpica A, Deavers M. The recurrence and the overall survival rates of ovarian serous borderline neoplasms with noninvasive implants is time dependent. *Am J Surg Pathol*. 2006;30(11):1367-71. <https://doi.org/10.1097/01.pas.0000213294.81154.95>.
 27. Uzan C, Nikpayam M, Ribassin-Majed L, et al. Influence of histological subtypes on the risk of an invasive recurrence in a large series of stage I borderline ovarian tumor including 191 conservative treatments. *Ann Oncol*. 2014;25(7):1312-9. <https://doi.org/10.1093/annonc/mdl139>.

Appendix

Complete surgical staging: Controversial. Historically includes hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node sampling, peritoneal washings and biopsies, omentectomy (plus appendectomy for mucinous BOT), extrapolated from surgery for invasive epithelial ovarian tumours. In this manuscript, complete surgical staging refers to exploratory laparotomy, hysterectomy, bilateral salpingo-oophorectomy (or fertility-sparing surgery), peritoneal washings, and omentectomy.

Completion surgery: Surgery performed in a patient who received fertility-sparing surgery at primary surgery to remove the rest of her reproductive organs (ovary, tube, uterus) after the patient has completed her family history or when the patient recurs.

Fertility-sparing surgery: Conservation of the uterus and salvage of at least a portion of one ovary (i.e. unilateral oophorectomy, unilateral oophorectomy with contralateral cystectomy, unilateral cystectomy, or bilateral cystectomies).

Re-staging surgery: Surgery performed to complete staging in a patient who was not adequately staged at primary surgery.