Borderline Ovarian Tumours in a Middle-Income Country Setting:

a Ten-Year Retrospective Review of Cases in a Tertiary Hospital in South Africa

Dissertation towards MPhil degree (Gynaecological Oncology) from the University of Cape Town

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DECLARATION

I, *Ama Kaki Ghunney*, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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FORMAT: Publication-ready format

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ABSTRACT

Introduction

The diagnosis and management of borderline ovarian tumours remain controversial almost a century after their initial description, and little research has been done in Africa to provide answers on the prevalence and outcomes of these tumours. This study is a review of cases of borderline ovarian tumours seen in Groote Schuur Hospital over a ten-year period.

Objective

To describe the demographic characteristics, occurrence, treatment, and outcomes of women diagnosed with borderline ovarian tumour at Groote Schuur Hospital, a tertiary hospital in South Africa.

Methods

A retrospective review of women diagnosed with borderline ovarian tumour in Groote Schuur Hospital between January 2005 and December 2014 was undertaken by reviewing our gynaecological oncology database and patients' folders. Women with multiple primary tumours, lost to follow-up, or with inadequate clinical data were excluded. Demographic characteristics, preoperative, operative, postoperative, oncologic, and pathologic data was retrieved and analyzed.

Results

Ninety-one patients were diagnosed with borderline ovarian tumour in the study period. Nineteen were eliminated and 72 analysed. Borderline ovarian tumours accounted for 22.3% of 409 ovarian neoplasms registered with our gynaecological oncology database in the study period. The median age was 48.5 years, (range, 16–82 years) with 31.9% (n=23) of women less than 40 years of age. Seventy-point eight percent (n=51) of patients were completely surgically staged and 80.6% (n=58) were optimally debulked. Thirty-one-point nine percent (n=23) underwent fertility-sparing surgery and of these 17.4% (n=4) had completion surgery. Mucinous histology was the most common histological subtype (57%). The median time to recurrence was 42.9 months (range 1.0 to 108.0 months).

Serous histology and fertility-sparing surgery were independently associated with recurrence (p=0.016, p=0.026 respectively). Our overall recurrence rate was 13.9% (n=10) with 40% of these being invasive (n=4). The 5-year overall survival rate was 91.7% and the 5-year relapse-free survival rate was 89.9%. Despite small numbers, all patients with invasive recurrence died within 5 years of recurrence, whiles all patients who recurred with borderline histology were alive 5 years after recurrence.

Conclusion

Mucinous histology was the most common histological subtype (57%). Regardless of a generally favourable prognosis, patients who recurred as invasive disease were all dead 5 years after recurrence, whiles patients who recurred with borderline histology were all alive 5 years after recurrence.

Figure 1: Flow Chart of Study Cohort

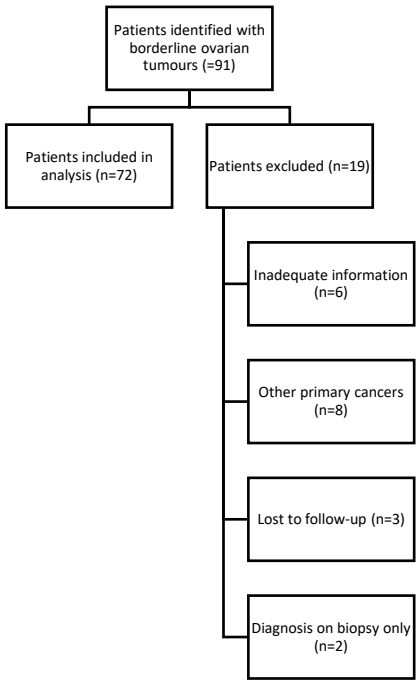

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Table 1: Demographic Characteristics

Age	
Median (range in years)	48.5 (16-82)
<40yrs n (%)	23 (31.9)
>40yrs n (%)	49 (68.1)
Parity	
Median (range in years)	2 (0-9)
Race	
Black n (%)	11 (15.3)
White n (%)	5 (6.9)
Mixed Ancestry n (%)	56 (77.8)
Complete surgical staging	
Yes n (%)	51 (70.8)
No n (%)	21 (29.2)
Stage at diagnosis n (%)	
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)
CA125 value (U/mL)	
Median (range)	100 (5 -2944)
Elevated CA125 (> 35U/mL), n (%)	
Yes	38 (52.8)
No	19 (26.4)
Not done	15 (20.8)
VTE n (%)	
Yes	0 (0)
No	66 (91.7)
Unknown	6 (8.3)

Table 2: Surgical and Pathological Characteristics

Type of surgery n (%)	
Fertility-sparing surgery	23 (31.9)
Radical Surgery	49 (68.1)
Type of fertility-sparing surgery n (%)	
Unilateral salpingo-oophorectomy	18 (78.3)
Unilateral salpingo-oophorectomy + contralateral cystectomy	3 (13.0)
Unilateral cystectomy	1 (4.3)
Unilateral cystectomy + contralateral ovarian biopsy	1 (4.3)
Route of Surgery n (%)	
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)
Re-staging Surgery	
Yes	0 (0)
No	21 (100)
Appendicectomy n (%)	9 (12.5)
Frozen Section n (%)	0 (0)
Lymphadenectomy n (%)	3 (4.2)
Completion Surgery n (%)	4 (17.4)
Histology	
Serous	27 (37.5)
Mucinous	41 (56.9)
Seromucinous	1 (1.4)
Other	3 (4.2)

Table 3: 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%)	

Table 4: Predictors of Overall and Relapse-Free Survival on Univariate and Multivariate Analysis

			Overall Survival		**Relapse-Free Survival**	
Predictor		**Number of Patients (%)**	**Univariate Analysis HR (95% CI, p-value)**	**Multivariate Analysis HR (95% CI, p-value)**	**Univariate Analysis HR (95% CI, p-value)**	**Multivariate Analysis HR (95% CI, p-value)**
Age			1.05 (1.01-1.09, p=0.014)	1.05 (1.00-1.10, p=0.050)	1.01 (0.98-1.04, p=0.378)	1.05 (1.01-1.09, p=0.018)
Stage	I	64 (88.9)	-	-	-	-
	II	4 (5.6)	0.00 (0.00-Inf, p=0.999)	0.00 (0.00-Inf, p=0.999)	1.14 (0.15-8.70, p=0.898)	0.85 (0.09-8.30, p=0.887)
	III	4 (5.6)	0.00 (0.00-Inf, p=0.999)	0.00 (0.00-Inf, p=0.999)	1.65 (0.21-12.70, p=0.630)	1.71 (0.18-16.27, p=0.640)
Histology	Serous	27 (37.5)	-	-	-	-
	Mucinous	41 (56.9)	1.01 (0.29-3.59, p=0.986)	0.91 (0.20-4.01, p=0.897)	0.35 (0.13-0.95, p=0.040)	0.28 (0.09-0.89, p=0.031)
	Other	4 (5.6)	0.00 (0.00-Inf, p=0.999)	0.00 (0.00-Inf, p=0.999)	0.00 (0.00-Inf, p=0.998)	0.00 (0.00-Inf, p=0.998)
Complete Surgical Staging	Yes	51 (70.8)	-	-	-	-
	No	21 (29.2)	1.49 (0.42-5.29, p=0.539)	1.55 (0.27-8.83, p=0.621)	1.34 (0.49-3.70, p=0.571)	0.54 (0.14-2.11, p=0.377)
Ca125 level	Low	19 (33.3)				
	High	38 (66.7)	0.35 (0.08-1.56, p=0.167)		3.55 (0.44-28.84, p=0.236)	
Type of Surgery	Fertility-Sparing Surgery	23 (31.9)	-	-	-	-
	Radical	49 (68.1)	2.04 (0.43-9.61, p=0.367)	1.02 (0.12-8.90, p=0.983)	0.60 (0.22-1.60, p=0.305)	0.19 (0.04-0.91, p=0.038)

LIST OF ABBREVIATIONS

BOT	Borderline ovarian tumour(s)
CA125	Cancer antigen 125
CI	Confidence interval
FIGO	International Federation of Gynaecology and Obstetrics
FSS	Fertility-sparing surgery
HR	Hazard ratio
OS	Overall survival
RFS	Relapse-free survival
VTE	Venous thromboembolism

CHAPTER 1: PUBLICATION-READY MANUSCRIPT

TITLE

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

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ABSTRACT

Objective

To describe the demographic characteristics, occurrence, treatment, and outcomes of women diagnosed with borderline ovarian tumour at Groote Schuur Hospital, a tertiary hospital in South Africa.

Methods

A retrospective review of women diagnosed with borderline ovarian tumour in Groote Schuur Hospital between January 2005 and December 2014 was undertaken by reviewing our gynaecological oncology database and patients' folders. Women with multiple primary tumours, lost to follow-up, or with inadequate clinical data were excluded. Demographic characteristics, preoperative, operative, postoperative, oncologic, and pathologic data was retrieved and analyzed.

Results

Ninety-one patients were diagnosed with borderline ovarian tumour in the study period. Nineteen were eliminated and 72 analysed. Borderline ovarian tumours accounted for 22.3% of 409 ovarian neoplasms registered with our gynaecological oncology database in the study period. The median age was 48.5 years, (range, 16–82 years) with 31.9% (n=23) of women less than 40 years of age. Seventy-point eight percent (n=51) of patients were completely surgically staged and 80.6% (n=58) were optimally debulked. Thirty-one-point nine percent (n=23) underwent fertility-sparing surgery and of these 17.4% (n=4) had completion surgery. Mucinous histology was the most common histological subtype (57%). The median time to recurrence was 42.9 months (range 1.0 to 108.0 months).

Serous histology and fertility-sparing surgery were independently associated with recurrence (p=0.016, p=0.026 respectively). Our overall recurrence rate was 13.9% (n=10) with 40% of these being invasive (n=4). The 5-year overall survival rate was 91.7% and the 5-year relapse-free survival rate was 89.9%. Despite small numbers, all patients with invasive recurrence died within 5 years of recurrence, whiles all patients who recurred with borderline histology were alive 5 years after recurrence.

Conclusion

Mucinous histology was the most common histological subtype (57%). Regardless of a generally favourable prognosis, patients who recurred as invasive disease were all dead 5 years after recurrence, whiles patients who recurred with borderline histology were all alive 5 years after recurrence.

- What is already known on this topic: The diagnosis and management of borderline ovarian tumours remain controversial almost a century after their initial description, and little research has been done in Africa to provide answers on the prevalence and outcomes of these tumours.
- What this study adds: mucinous histology was the commonest histological subtype of borderline ovarian tumours in the study period.
- How this study might affect research, practice or policy: It has been recommended that pathologists report comprehensively on features such as microinvasion and micropapillary pattern of borderline ovarian tumours, as these may influence recurrence and survival rates.

INTRODUCTION

Characterized by increased epithelial proliferation, nuclear atypia, and mildly increased mitotic activity in the absence of stromal invasion (1), borderline ovarian tumours are tumours intermediate in nature in comparison to benign cystadenomas and invasive carcinomas of the ovary (2).

They 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 > 95% (4) and they frequently occur in younger women, with approximately one-third of patients diagnosed before 40 years (5). Sixty-five percent to 70% of serous and about 90% of mucinous borderline ovarian tumours are stage I at diagnosis (6). With a 5-year survival rate of 99% at stage I, they have an excellent prognosis (7).

For decades, the standard of care for their management has been radical surgery, comprising hysterectomy and bilateral salpingo-oophorectomy. In recent years, owing to their favourable prognosis, coupled with early stage at diagnosis, there has been a trend towards fertility-sparing surgery, 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 (8).

Almost a century after their initial description, much controversy still exists regarding the terminology, role of imaging and tumour markers in diagnosis, role of complete surgical staging, radicality of surgery, necessity of restaging surgery, role of adjuvant therapy, and prognostic factors that affect survival (1,9,10).

Data on borderline ovarian tumours 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 borderline ovarian tumours 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 borderline ovarian tumours 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, or for whom adequate clinical data could not be retrieved were excluded.

Demographic characteristics, preoperative, operative, postoperative, oncologic, and pathologic data were retrieved from the patients' folders and gynaecological oncology database (University of Cape Town Human Research Ethics Committee Number R016/2103). All patients were re-staged according to the 2014 International Federation of Gynecology and Obstetrics staging of cancer of the ovary, fallopian tubes, and peritoneum.

Patients were said to be optimally debulked if <1cm of tumour (that is, no gross residual disease) was left during surgery. Our institution does not routinely perform systematic lymphadenectomy during surgery for ovarian tumours, so our patients did not have systematic lymphadenectomy done.

The JMP software version 17.1.0 (SAS Institute Inc., Cary, NC, USA) was used for data processing and analysis. Continuous data was presented as median and interquartile range [IQR]. Categorical data was presented as frequencies and percentages. Comparison of CA125 levels and stage was performed using the Kruskal–Wallis test. The relationship between recurrence and pathological factors was analysed using the chi-squared 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 clinicopathologic 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, and the study was conducted in compliance with the Declaration of Helsinki (11).
In accordance with the journal's guidelines, we will provide our data for independent analysis by a team selected by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centres if such is requested.

RESULTS

Between 2005-2014, 91 patients with a histological diagnosis of borderline ovarian tumour were registered in the Gynaecological Oncology Database of the Groote Schuur Hospital. Details are shown in Figure 1. Seventy-two women were included in this study and 19 excluded. Of the 8 women excluded for a second malignancy, 3 had breast cancer, 1 had vulvar cancer and B-cell lymphoma of the thyroid, 1 borderline ovarian tumour diagnosed after surgery for carcinosarcoma of the uterus, 1 synchronous cervical cancer, another synchronous serous endometrial cancer, and the last synchronous endometrioid carcinoma of the ovary.

Demographics Characteristics

The demographic characteristics of patients are presented in Table 1. The median age was 48.5 years, (range, 16–82 years). Most patients were of mixed ancestry (n=56, 77.8%), and almost a third of patients (n=23, 31.9%) were below 40 years.

Surgery and Staging

Most women (n=51, 70.8%) underwent complete surgical staging (see Table 2). Of the 21 patients not completely surgically staged, 8(38.1%) did not undergo peritoneal washings and omentectomy, 5(23.8%) did not undergo omentectomy, 7(33.3%) did not undergo peritoneal washings for cytology and 1(4.8%) did not undergo examination of the upper abdomen. None of these patients underwent restaging surgery. Four patients had completion surgery, 2 after recurrence as borderline tumour, 1 after recurrence as invasive disease, and 1 three months after primary surgery on histological confirmation of 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) stage III disease, respectively. All patients with extra-ovarian disease (stage 2 and above) had tumours of serous histology. The majority (n=49, 68.1%) of patients underwent radical surgery, and 80.6% of patients (n=58) were optimally debulked.

Correlation between Preoperative CA125, Surgical Staging and Histology

There was no correlation between CA125 levels and disease stage ($p = 0.055$) although CA125 levels > 1,000U/ml were found almost exclusively in patients with extra-ovarian disease (n=5, 4 patients stages IIB-IIIB, 1 patient stage IA, but not fully staged). However, there was a statistically significant difference in the distribution of CA125 levels between serous and mucinous borderline ovarian tumours ($p < 0.001$), with CA125 levels > 1,000U/mL occurring exclusively in serous borderline ovarian tumours (n=5).

Histological Subtypes

Mucinous histology was the most common subtype (n=41, 56.9%) (see Table 2). Of the 27 patients diagnosed with serous borderline ovarian tumour, 1 had typical variant, 3 micropapillary variant, and the variant was not assessed in 23 patients.

Adjuvant Therapy

None of our patients received adjuvant therapy.

Survival Data and Follow Up

Patients were followed up for 13–169 months (median, 98 months). Ten patients (13.9%) recurred and 10 (13.9%) died. Not all patients who recurred died. Six of the ten patients who passed away died of other comorbidities. The 4 tumour-related deaths were all due to invasive recurrence. Six patients who recurred with borderline histology were all alive at 5-year follow-up, including one patient who had no intervention after recurrence was diagnosed (frozen pelvis at primary surgery). Five of these 6 patients are alive now, 10 to 14 years after initial diagnosis of borderline ovarian tumour, (including the patient with frozen pelvis who did not have repeat laparotomy on recurrence). The sixth patient has recently been lost to follow up.

The 5-year overall survival rate (OS) was 91.7% (85.5% - 98.3%, 95% confidence interval (CI), and the 5-year relapse-free survival rate (RFS) was 89.9% (80.0% - 95.1%, 95% CI). Of the 10 patients who recurred, recurrence was of borderline histology in 6 patients and as invasive disease in 3. One patient recurred twice: first as borderline tumour and then as invasive disease. Of the 10 patients who recurred, only 2 had mucinous histology. Of these, one patient recurred as low-grade invasive disease and the other was reported as metastatic adenocarcinoma. Both malignant transformations in serous borderline tumours were to high-grade serous carcinoma.

The median time to recurrence was 42.9 months (range 1.0 to 108.0 months). The 5-year OS was 90.6% (83.8% - 98.1%, 95% CI) for stage I and 100% (100% - 100%, 95% CI) for both stage II and III disease. The 5-year RFS were 90.1% (82.9%–98.0%, 95% CI) for stage I, 100% (100%–100%, 95% CI) for stage II, and 75% (42.6%-100%, 95% CI) for stage III disease. 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 serous histology, fertility-sparing surgery, residual disease, and implants were significantly associated with recurrence (see Table 3). Binomial logistic regression analysis revealed serous histology and fertility-sparing surgery were independently associated with recurrence (p=0.016, p=0.026 respectively).

DISCUSSION

Summary of Main Results

In this study, patients with borderline ovarian tumour (n=91) comprised 22.3% of the 409 women with ovarian neoplasms registered with the gynaecological oncology database at the Groote Schuur Hospital between 2005 and 2014, with mucinous histology being the most common histological type (56.9%). The recurrence rate was 13.9% and the rate of invasive relapse was 5.6%. Thirty-point four percent of patients who received fertility-sparing surgery relapsed, compared to 6.1% of patients who received radical surgery. Nonetheless, the type of surgery had no impact on overall survival (p=0.983), but radical surgery was associated with better RFS on multivariate analysis, Hazard Ratio (HR) 0.19 (0.04-0.91, p=0.038) (Table 4).

Results in the Context of Published Literature

Thirty-two percent of patients with borderline ovarian tumours at our hospital were under the age of 40 years, consistent with previously published data (5,12). Mucinous histology accounted for almost 57%, and serous 37.5%, compared to unpublished data from this same institution which reported mucinous histology of 47.9% and serous, 49.3% (13), and data from the Charlotte Maxeke Academic Hospital in Johannesburg which reported 50% of borderline ovarian tumours were of mucinous histology and 40%, serous (14). The suggestion of a higher proportion of mucinous borderline ovarian tumours in South Africa needs further prospective studies. Our finding of 94.5% of tumours being either serous or mucinous is similar to previously published data (4).

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

CA125 levels were higher in patients with serous compared to mucinous histology (p<0.001) and similar results were obtained by Gotlieb et al (17). Although the highest CA125 levels (> 1,000U/mL) were detected almost exclusively in patients with extraovarian disease, CA125 levels were not significantly associated with disease stage (p=0.055), likely because of the small number of patients with advanced-stage disease.

No patient experienced a venous thromboembolic event; similar results were obtained by Bakhru (18).

There were 31.9% (n= 23) patients who underwent fertility -sparing surgery. Twenty of these patients were younger than 40 years. Three patients below the age of 40 years who underwent radical surgery were of parity 3,3 and 2 respectively.

Incomplete staging occurred in 29.2% (n=21) patients and none of these patients had restaging surgery. Nineteen (90.5%) of these patients were assigned stage I and may not have benefitted from re-staging surgery according to a study by Bendifallah et al which reported no statistically significant difference in OS or 5-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 that reported in other studies (19,20). It is important to note that random peritoneal biopsies which were performed as part of full surgical staging in these studies is not routinely performed in our institution, likely accounting for our higher percentage of fully staged patients.

Nine patients underwent routine appendicectomy. Eight of these had mucinous histology and one, seromucinous. The appendix was histologically uninvolved in all 9 cases. According to a systematic review by Cosyns et al, in mucinous borderline ovarian tumours, microscopic tumour involvement in a macroscopically normal-looking appendix is rare, and appendicectomy can be omitted (21). In recent years, our institution has reviewed its protocols and now omits appendicectomy in mucinous ovarian neoplasms with normal-looking appendices.

Stage I disease was diagnosed in 88.9% (n=64) of our patients, slightly higher than 78.9% published by du Bois et al (4). 70.4% of serous and 100% of mucinous borderline tumours were stage I at diagnosis compared to data published by Gershenson (6).

None of our patients received adjuvant therapy, in agreement with several studies which reported no survival benefit of adjuvant therapy in the management of borderline ovarian tumours (22,23).

In Europe, published overall recurrence rates are between 3% to 10% (12,24), lower than our calculated overall recurrence rate of 13.9%. Forty percent (n=4) of our recurrences were invasive, higher than the 20% reported in a previous study (4), despite our low study numbers. A possible explanation for this is that microinvasion and micropapillary pattern of serous borderline tumours, which may be associated with higher recurrence rates (6), were not assessed in the majority of our specimens.

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 rates of recurrence compared to radical surgery (10%-20% versus 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. Sixty percent (3 out of 5) of patients who underwent cystectomy recurred compared to 22.2% (4 out of 18) of patients who underwent oophorectomy alone.

With a 5-year OS of 91.7% and 5-year RFS of 89.9%, our survival outcomes were lower than those reported in the literature (7).

Stage I disease is known to have an excellent prognosis, with 5-year OS of up to 99% (7). We obtained a low 5-year OS of 90.6% and 5-year RFS of 90.1% in patients with stage I disease, possibly due to negative prognostic factors such as microinvasion and micropapillary pattern of serous borderline tumours (6), which were not assessed in our study. Though these prognostic factors do not impact on the management of BOT and adjuvant treatment is still not offered in their presence, perhaps, more intensive post-operative surveillance for early detection and management of recurrence can be recommended in these cases.

Again, most patients were assigned stage I (n=64), versus 4 patients each for stages II and III, with correspondingly more recurrences in stage I disease. However, because patients who

were incompletely staged were not re-staged, a lingering question is whether patients with advanced stage disease were incorrectly assigned stage I, thus resulting in seemingly poorer survival outcomes in our patients with stage I disease.
Four out of 6 patients who recurred as borderline tumour were managed successfully by surgical intervention (2 completion surgeries, 1 partial oophorectomy, 1 repeat cystectomy), as established by a study that found that most recurrences can be salvaged by 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. All patients who recurred as borderline tumour only were alive 5 years following initial diagnosis of borderline ovarian tumour, similar to results obtained by Silva et al (26). Five of these six patients are alive 10 to 14 years after initial diagnosis of borderline ovarian tumour, including one patient who was only observed on diagnosis of recurrence on account of a frozen pelvis. The last has recently been lost to follow up.
All 4 patients who recurred as invasive disease died within 5 years of recurrence, reflecting the importance of identifying prognostic factors for malignant transformation, which our study was unable to do, given the small numbers.
Despite the majority of patients having mucinous histology, only 2 out of 10 (20%) of recurrences were of mucinous histological subtype, both as invasive disease (100%). Similar results were obtained by Uzan et al., who reported that the risk of recurrence was higher in serous histology and the risk of invasive recurrence higher in mucinous histology (27). The association between mucinous histology and malignant transformation, however, 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 borderline ovarian tumours in Africa, and importantly, in a middle income country and provides useful insights into the occurrence, demographic characteristics, operative and postoperative management, and survival outcomes in women with borderline ovarian tumours 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 generally being 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 as borderline ovarian tumours are known to recur later (32% after 5 years after diagnosis) (4), and the lack of subtyping of serous borderline ovarian tumours in most cases.

Implications for Practice and Future Research

In our study, all (100%) patients who recurred as borderline ovarian tumour were alive 5 years after recurrence (including one patient who had no intervention following recurrence), in contrast to 100% mortality in patients who recurred as invasive disease. All patients who

recurred as invasive disease died within 5 years of recurrence, reflecting their importance. The number of recurrences and malignant transformations were small in our study and identified (albeit controversial) risk factors for recurrence and malignant transformation, including micropapillary pattern of serous borderline ovarian tumours and presence of microinvasion (1), were not assessed in most of our patients. A large multicentre study with long follow-up period is required to confirm these findings. It is imperative that pathologists comprehensively report on characteristics of borderline ovarian tumours to answer these important questions.

CONCLUSION

Borderline ovarian tumours accounted for 22.3% of ovarian neoplasms registered in our gynaecological oncology database in the study period. Mucinous histology was the most common histological subtype (57%). Despite borderline ovarian tumours having a favourable prognosis, all women who had invasive recurrence died within 5 years of recurrence.

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LIST of TABLES and FIGURES

Figure 1: Flow Chart of Study Cohort

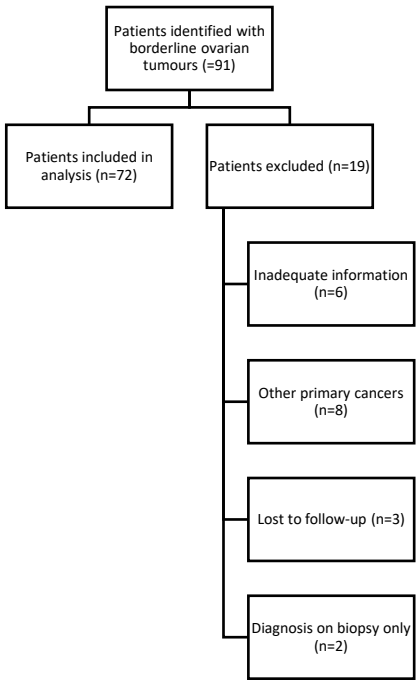

Table 1: Demographic Characteristics

Age	
Median (range in years)	48.5 (16-82)
<40yrs n (%)	23 (31.9)
>40yrs n (%)	49 (68.1)
Parity	
Median (range in years)	2 (0-9)
Race	
Black n (%)	11 (15.3)
White n (%)	5 (6.9)
Mixed Ancestry n (%)	56 (77.8)
Complete surgical staging	
Yes n (%)	51 (70.8)
No n (%)	21 (29.2)
Stage at diagnosis n (%)	
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)
CA125 value (U/mL)	
Median (range)	100 (5 -2944)
Elevated CA125 n (%)	
Yes	38 (52.8)
No	19 (26.4)
Not done	15 (20.8)
VTE n (%)	
Yes	0 (0)
No	66 (91.7)
Unknown	6 (8.3)

Table 2: Surgical and Pathological Characteristics

Type of surgery n (%)	
Fertility-sparing surgery	23 (31.9)
Radical Surgery	49 (68.1)
Type of fertility-sparing surgery n (%)	
Unilateral salpingo-oophorectomy	18 (78.3)
Unilateral salpingo-oophorectomy + contralateral cystectomy	3 (13.0)
Unilateral cystectomy	1 (4.3)
Unilateral cystectomy + contralateral ovarian biopsy	1 (4.3)
Route of Surgery n (%)	
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)
Re-staging Surgery	
Yes	0 (0)
No	21 (100)
Appendicectomy n (%)	9 (12.5)
Frozen Section n (%)	0 (0)
Lymphadenectomy n (%)	3 (4.2)
Completion Surgery n (%)	4 (17.4)
Histology	
Serous	27 (37.5)
Mucinous	41 (56.9)
Seromucinous	1 (1.4)
Other	3 (4.2)

Table 3: 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%)	

Table 4: Predictors of Overall and Relapse-Free Survival on Univariate and Multivariate Analysis

			Overall Survival		**Relapse-Free Survival**	
Predictor		**Number of Patients (%)**	**Univariate Analysis HR (95% CI, p-value)**	**Multivariate Analysis HR (95% CI, p-value)**	**Univariate Analysis HR (95% CI, p-value)**	**Multivariate Analysis HR (95% CI, p-value)**
Age			1.05 (1.01-1.09, p=0.014)	1.05 (1.00-1.10, p=0.050)	1.01 (0.98-1.04, p=0.378)	1.05 (1.01-1.09, p=0.018)
Stage	I	64 (88.9)	-	-	-	-
	II	4 (5.6)	0.00 (0.00-Inf, p=0.999)	0.00 (0.00-Inf, p=0.999)	1.14 (0.15-8.70, p=0.898)	0.85 (0.09-8.30, p=0.887)
	III	4 (5.6)	0.00 (0.00-Inf, p=0.999)	0.00 (0.00-Inf, p=0.999)	1.65 (0.21-12.70, p=0.630)	1.71 (0.18-16.27, p=0.640)
Histology	Serous	27 (37.5)	-	-	-	-
	Mucinous	41 (56.9)	1.01 (0.29-3.59, p=0.986)	0.91 (0.20-4.01, p=0.897)	0.35 (0.13-0.95, p=0.040)	0.28 (0.09-0.89, p=0.031)
	Other	4 (5.6)	0.00 (0.00-Inf, p=0.999)	0.00 (0.00-Inf, p=0.999)	0.00 (0.00-Inf, p=0.998)	0.00 (0.00-Inf, p=0.998)
Complete Surgical Staging	Yes	51 (70.8)	-	-	-	-
	No	21 (29.2)	1.49 (0.42-5.29, p=0.539)	1.55 (0.27-8.83, p=0.621)	1.34 (0.49-3.70, p=0.571)	0.54 (0.14-2.11, p=0.377)
Ca125 level	Low	19 (33.3)				
	High	38 (66.7)	0.35 (0.08-1.56, p=0.167)		3.55 (0.44-28.84, p=0.236)	
Type of Surgery	Fertility-Sparing Surgery	23 (31.9)	-	-	-	-
	Radical	49 (68.1)	2.04 (0.43-9.61, p=0.367)	1.02 (0.12-8.90, p=0.983)	0.60 (0.22-1.60, p=0.305)	0.19 (0.04-0.91, p=0.038)

FOOTNOTE

Contributors: AKG contributed to data collection and writing of the manuscript. LR and TA contributed to data interpretation and revision of the manuscript. All authors approved the final manuscript and agree to be accountable for all aspects of the final work.

Funding: None

Competing Interests: None to declare

Patient consent for Publication: Not required

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LIST OF APPENDICES

APPENDIX 1: DATA COLLECTION FORM

Study number	
Patient record number	
Patient folder number	
Patient rt number	

Age	
Race	
Parity	
Presenting complaint	Asymptomatic/incidental finding ○ Pain ○ Abdominal distension/mass ○ GI symptoms ○ AUB ○ Other ○ Not available ○
Co-morbidities	HIV/AIDS ○ Hypertension ○ Diabetes ○ Other ○
Ca125 performed	Yes ○ No ○
Ca125 level (iu/ml)	
Abdominopelvic imaging performed?	Yes ○

	No ○
Imaging modality	Ultrasound ○ CT scan ○ MRI ○
Size of mass on imaging (max diameter in cm)	
Mass diagnosed as ovarian on imaging?	Yes ○ No ○
Type of surgery	FSS ○ Radical surgery ○
FSS	USO only ○ USO + cystectomy ○ Unilateral cystectomy ○ Bilateral cystectomy ○
Optimally debulked	Yes ○ No ○ Not available ○
Route of surgery	Laparotomy ○ Laparoscopy ○ Laparoscopy converted to laparotomy ○
Complete surgical staging	Yes ○ No ○ Not available ○
Re-staging surgery	Yes ○ No ○ Not applicable ○ Not available ○
Completion surgery	Yes ○ No ○

	Not applicable ○ Not available ○
Lymphadectomy	Yes ○ No ○
Appendicectomy	Yes ○ No ○
Frozen section	Yes ○ No ○
Intra-operative findings/organs involved	Ascites ○ One ovary ○ Both ovaries ○ Fallopian tube(s) ○ Uterus ○ Peritoneum ○ Omentum ○ Bowel ○ Other viscera ○
Capsule rupture	Yes ○ No ○ Not available ○
Histology	sBOT ○ mBOT ○ Seromucinous ○ Other ○
sBOT	Typical variant ○ Micropapillary variant ○ Not applicable ○

	Not available ○
Implants	Yes ○ No ○ Not available ○ Not applicable ○
Type of implants	Invasive ○ Non-invasive ○ Not available ○ Not applicable ○
Microinvasion	Yes ○ No ○ Not available ○ Not applicable ○
Positive cytology	Yes ○ No ○ Not available ○
Histology (organs/tissue involved)	One ovary ○ Both ovaries ○ Fallopian tube(s) ○ Uterus ○ Omentum ○ Peritoneum ○ Lymph nodes ○ Other viscera ○
Stage	I ○ II ○

	III ○ IV ○
Adjuvant treatment	Yes ○ No ○
Type of adjuvant treatment	Chemotherapy ○ Radiotherapy ○ Hormonal therapy ○ Other ○
Specify adjuvant treatment	Drugs ○ Number of cycles ○ Duration of treatment ○
Response to adjuvant treatment	Complete response ○ Partial response ○ No response ○ Progression ○
Adjuvant-treatment related toxicity	Yes ○ No ○ Please specify, if yes
Recurrence	Yes ○ No ○ Not available ○
Time to recurrence	
Site of recurrence	
Management of recurrence	Surgery ○ Chemotherapy ○ Radiotherapy ○ Palliative Care ○ Other ○

Outcome	Discharged ○ Dead ○ Lost to follow-up ○
Date:	
Survival Time	
Cause of death	Tumour related ○ Not tumour related ○
Disease-free interval	
Progression-free interval	
Recurrence survival time	

APPENDIX 2: UCT FHS HREC APPROVAL LETTER

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: www.health.uct.ac.za/home/human-research-ethics

09 March 2023

HREC REF: 129/2023

Dr L Rogers
Department of Obstetrics & Gynaecology
H-Floor OMB
Email: Linda.rogers@uct.ac.za
Student: amaghunney@gmail.com

Dear Dr Rogers

PROJECT TITLE: BORDERLINE OVARIAN TUMOURS IN A LMIC SETTING: A TEN-YEAR RETROSPECTIVE AUDIT OF CASES IN A TERTIARY HOSPITAL IN SOUTH AFRICA- (MPHIL CANDIDATE-DR AMA GHUNNEY)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 March 2024.

Please submit a progress form, using the standardised Annual Report Form (FHS016) if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Ama Ghunney will also be involved in this study.

Please quote the HREC REF 129/2023 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

HREC/ref 129.2023

APPENDIX 3: GROOTE SCHUUR HOSPITAL APPROVAL LETTER

Western Cape Government

GROOTE SCHUUR HOSPITAL

Enquiries: Dr Bernadette Eick
E-mail: *GSHResearch.Request@westerncape.gov.za*

Dr L Rogers
Department of Obstetrics and Gynaecology

Email: Linda.Rogers@uct.ac.za

Dear Dr Rogers,

RESEARCH PROJECT: BORDERLINE OVARIAN TUMOURS IN A LMIC SETTING: A TEN-YEAR RETROSPECTIVE AUDIT OF CASES IN A TERTIARY HOSPITAL IN SOUTH AFRICA – (MPHIL CANDIDATE, DR AMA GHUNNEY)

Your recent communication to the hospital refers.

The extension of your research is approved in accordance with **UCT Ethics** clearance, until **30 March 2024.**

As previously mentioned,

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) No additional costs to the hospital should be incurred as indicated in your Annexure 2 i.e. Lab, consumables or stationery. **If access to TRACK Care/NHLS is required, kindly attach our letter of approval to the application form and approach Information Management to assist with data.**
d) **No patient folders may be removed from the premises or be inaccessible.**
e) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
f) Confidentiality must always be maintained.
g) Once the research is complete, please submit a copy of the publication or report.
h) **Please adhere to ALL COVID-19 regulations and Groote Schuur Hospital policies.**
i) **All Clinical Trials to be registered on Clinicom with Michelle Riley or Rowan James. michelle.riley@westerncape.gov.za / rowan.james@westerncape.gov.za**

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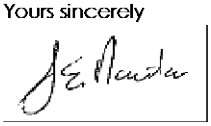
Observatory 7925

Private Bag X,
Observatory, 7935

Tel: +27 21 404 6288 fax: +27 21 404 6125
www.westerncape.gov.za/health

I would like to wish you every success with the project.

Yours sincerely



pp:
DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 6 April 2023

C.C. Prof Matjila, Dr Murray and Mr. A. Mohamed

APPENDIX 4: AUTHOR GUIDELINES FOR THE INTERNATIONAL JOURNAL OF GYNECOLOGICAL CANCER (ORIGINAL RESEARCH)

Available on: https://ijgc.bmj.com/pages/authors/#review

Motivation for Journal

The International Journal of Gynecological Cancer (IJGC) is co-owned by the International Gynecological Cancer Society (IGCS) and the European Society of Gynaecological Oncology (ESGO), two leading gynaecological cancer societies. With a high impact factor (journal citation reports) of 4.8, the IJGC remains very relevant in the dissemination of evidence-based literature on the prevention, detection, and treatment of gynaecological cancers. Considering the paucity of data on borderline ovarian tumours in Africa, publication of this manuscript in the IJGC will enable it reach a wide audience and contribute to literature on the subject in resource-limited settings.

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- Online only journal article: Dark P, Dunn G, Chadwick P, et alThe clinical diagnostic accuracy of rapid detection of healthcare-associated bloodstream infection in intensive care using multipathogen real-time PCR technology. BMJ Open 2011;1:e000181. doi: 10.1136/bmjopen-2011-000181
- Supplement article: Mugosa A, Cizmovic M, Lakovic T, et alAccelerating progress on effective tobacco tax policies in Montenegro. Tobacco Control 2020;29:s293-s299
- Abstract article: Bricca A, Swithenbank Z, Scott N, et al21 Predictors of recruitment in randomised controlled trials of smoking cessation: meta-regression analyses from the IC-SMOKE systematic review project. Abstract competing for the 'doug altman scholarship'. BMJ Evidence-Based Medicine 2019;24:A52-A53.
- Rapid response to an article: Krishnamoorthy KM, Dash PK. Novel approach to transseptal puncture. Heart Online [Rapid response] 18 September 2001. http://heart.bmj.com/cgi/eletters/86/5/e11#EL1

Databases and websites:

- Preprints: Rostami A, Sepidarkish M, Leeflang M, et al. First snap-shot meta-analysis to estimate the prevalence of serum antibodies to SARS-CoV-2 in humans. MedRxiv 20185017 [Preprint]. September 02, 2020 https://doi.org/10.1101/2020.08.31.20185017.
- Data citations: Wang G, Zhu Z, Cui S, at al. Glucocorticoid induces incoordination between glutamatergic and GABAergic neurons in the amygdala. Dryad Digital Repository [dataset]. August 11, 2017. https://doi.org/10.5061/dryad.k9q7h.
- Electronic citations: Moore A. Paracetamol: widely used and largely ineffective [online]. 2018. http://uk.cochrane.org/news/paracetamol-widely-used-and-largely-ineffective (accessed 23 May 2018).

Books and Legal:

- Book: Howland J. Preventing Automobile Injury: New Findings From Evaluative Research. Dover, MA: Auburn House Publishing Company 1988:163–96.
- Chapter in a book: Nagin D. General deterrence: a review of the empirical evidence. In: Blumstein A, Cohen J, Nagin D, eds. Deterrence and Incapacitation: Estimating the

Effects of Criminal Sanctions on Crime Rates. Washington, DC: National Academy of Sciences 1978:95–139.

- Legal material: Toxic substances Contro Act: Hearing on S776 Before the Subcommittee of the Environment of the Senate Comm. on Commerce, 94th Congress 1st September (1975).
- Law references: The two main series of law reports, Weekly Law Reports (WLR) and All England Law Reports (All ER) have three volumes a year e.g. Robertson v Post Office [1974] 1 WLR 1176

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