

**An audit of the management of women with Borderline
Ovarian Tumours treated at Groote Schuur Hospital
between 1984-2008**

By

Student: Aneeqah Hendricks

Student number: HNDANE002

SUBMITTED TO THE UNIVERSITY OF CAPE TOWN

In fulfilment of the requirements for the degree MMED in
Obstetrics and Gynaecology

Faculty of Health Sciences

UNIVERSITY OF CAPE TOWN

November 2016

Supervisor: Professor Lynette Denny
Department of Obstetrics and
Gynaecology

Co-supervisor: Dr Leon van Wijk
Department of Radiation Oncology

The copyright of this thesis vests in the author. No quotation from it or information derived from it is to be published without full acknowledgement of the source. The thesis is to be used for private study or non-commercial research purposes only.

Published by the University of Cape Town (UCT) in terms of the non-exclusive license granted to UCT by the author.

TABLE OF CONTENTS

DECLARATION	2
ABSTRACT	3
LIST OF TABLES AND FIGURES	4
LIST OF ABBREVIATIONS	5
CHAPTER ONE: INTRODUCTION AND LITERATURE REVIEW	6
CHAPTER TWO: METHODS	21
CHAPTER THREE: RESULTS	24
CHAPTER FOUR: DISCUSSION AND CONCLUSIONS	38,44
REFERENCES	45
APPENDICES	50

DECLARATIONS

I, ANEEQAH HENDRICKS, hereby declare that the work on which this dissertation 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.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

SIGNATURE: Aneeqah Hendricks.....

Signed by candidate

DATE: 15 December 2016.....

ABSTRACT

Background:

Borderline ovarian tumours (BOT) are an intermediate form of neoplasia, between benign and malignant and have been classified as epithelial tumours of low malignant potential. These particular tumours affect a younger age group than their invasive counterparts with an overall survival of 90 - 100%. The present study aims to document the experience of a single centre on the management of women with borderline ovarian tumours (BOT).

Methods:

Two hundred and thirteen patients diagnosed and treated with BOT between 1984 and 2008 were identified through the Gynaecology Oncology database that has been in existence since 1984. Details of management, outcome and survival were retrieved and data were analysed descriptively and for survival.

Results:

The median age at diagnosis was 45 years old, with 34 % of patients > 40 years old. The incidence of serous BOT (SBOT) was 47.9% (102/213) and 49.3 % (105/213) were mucinous BOT (MBOT). Most of the patients were diagnosed in Stage I 83.6% (178/213), 6.1%(13/213) were in stage II and 10.0% (22/213) were stage III. There were no patients in stage IV. At the end of the study period 73% (156/213) of the women were alive with no evidence of disease. Univariate analysis, indicated that the histological subtype of tumour, the type of surgery, the presence of residual disease, advanced stage disease, the presence of ascites were all statistically significant in affecting survival. Multivariate analysis, however, revealed that only the presence of residual disease was statistically significant as a prognostic predictor of poor outcome.

LIST OF TABLES AND FIGURES

1. Figure 1: Age distribution among 213 women
2. Figure 2 – Kaplan Meier Curve; Survival probability by age
3. Figure 3: Graph illustrating deaths by age group and causes
4. Figure 4: Kaplan – Meier Curve; survival probability by histological subtype of BOT
5. Figure 5. Kaplan Meier curve according to stage
6. Figure 6. Kaplan Meier Curve by Treatment type
7. Figure 7. Kaplan Meier curve of survival by residual disease post surgery
8. Figure 8. Kaplan Meier survival curve by whether an elevated CA 125 was detected or not
9. Figure 9. Kaplan Meier curve – survival probability by presence of ascites
10. Table 1. The association between key variables and disease specific survival estimated by Cox's proportional hazards ratios (crude and adjusted) and their 95%CI's among 213 women

ABBREVIATIONS

BOT	- Borderline Ovarian Tumour
FIGO	- International Federation of Gynaecologists and Obstetricians
SBOT	- Serous Borderline Ovarian Tumour
MBOT	- Mucinous Borderline Ovarian Tumour
OC	- Oral Contraception
RR	- Relative Risk
IOT	- Invasive Ovarian Tumour
ART	- Assisted Reproductive Techniques
WHO	- World Health Organisation
EBOT	- Endometrial Borderline Ovarian Tumour
NICE	- National Institute for Clinical Excellence
RMI	- Risk of Malignancy Index
GSH	- Groote Schuur Hospital
CR	- Complete Response
NE	- Not Evaluable
NR	- No Response
Bx	- Biopsy
TAH	- Total Abdominal Hysterectomy
BSO	- Bilateral Salpingo oophorectomy
O	- Omentectomy
USO	- Unilateral Salpingo oophorectomy
OOPH	- Oophorectomy

CHAPTER ONE: INTRODUCTION AND LITERATURE REVIEW

1.1 INTRODUCTION

1.2 EPIDEMIOLOGY

1.3 PATHOLOGY

1.3.1 SEROUS BOT

1.3.2 MUCINOUS BOT

1.3.3 UNCOMMON BOT

1.4 DIAGNOSIS

1.5 PROGNOSTIC PARAMETERS

1.6 MANAGEMENT OF BOT

1.6.1 CONSERVATIVE SURGERY

1.6.2 RADICAL SURGERY

1.6.3 IMTRAOPERATIVE DIAGNONSIS AND STAGING (LARAROSCOPY/LAPAROTOMY)

1.6.4 SURGICAL APPROACH (LAPAROSCOPY/LAPAROTPMY}

1.7 POSTOPERATIVE TREATMENT

1.7.1 ADJUVANT TRETAMENT (CHEMOTHERAPY, RADIOOTHERAPY, HORMONOTHERAPY AND TARGETED THERAPY)

1.7.2 TREATMENT OF RECURRENCES

1.7.3 TREATMENT OF INFERTILITY

1.7.4 TREATMENT OF HORMONE DEPRIVATION

1.8 FOLLOW UP

1.1 INTRODUCTION

Borderline ovarian tumours (BOT) are an intermediate form of neoplasia, between benign and malignant (1). They form a separate entity within the group of epithelial ovarian tumours, as recognised by the International Federation of Gynaecology and Obstetrics (FIGO) in 1961 and the World Health Organisation (WHO) in 1973 (2). They have been qualified as tumours of low malignant potential and they constitute 10-20% within the malignant epithelial ovarian group (3). These particular tumours affect a younger age group than their invasive counterparts with an overall survival of 90 -100%(4,5).

BOT's are defined by the presence of cellular proliferation and nuclear atypia without stromal invasion or an infiltrative pattern. Histologically they are divided into serous (50%), mucinous (45%) and other rare subtypes (endometrioid, clear cell and Brenner)(6).

The primary treatment is surgery, which includes a hysterectomy and at least a unilateral salpingo-oophorectomy or cystectomy, depending on extent of disease and fertility desires of the patient. Given that a third of the women diagnosed with BOT are under the age of 40, fertility may often be an issue (7). The low incidence and low recurrence or death rates makes it difficult to analyse prognostic factors and nearly impossible to perform prospectively randomised trials large enough to evaluate therapeutic strategies.

However very useful information can be obtained from existing databases, which can be compared to other centres, at which BOT's are treated. Consequently our aim was to review the available evidence from a database spanning 24 years, thereby auditing

the effectiveness of management of women with BOT at our institution. This audit could also assist in formulating guidelines for future management of BOT.

1.2 EPIDEMIOLOGY

BOTs were first described by Taylor in 1929 and frequently occur in younger females who want to preserve fertility (8). The incidence of BOT, as quoted by European literature, is 1.8 – 4.8 per 100,000 women per year (2). There has been an increased incidence of BOTs worldwide with a slightly decreasing incidence in ovarian carcinoma. For example, in Sweden they have seen an increase in incidence from 1.0 to 5.3 per 100,000 women between 1960 and 2005. This trend may reflect more accurate diagnosis of BOT (2).

BOTs differ from ovarian carcinomas with regard to percentile distribution of the different histological subtypes, their lower FIGO stage at diagnosis, excellent overall prognosis and higher infertility rates (2). However, from an epidemiological point of view, BOT and carcinoma share very close characteristics, therefore to distinguish a high risk group associated with BOT is challenging (2).

The average age of onset is between 20 and 46 years of age and about 25 % of the patients are younger than 35 at the time of diagnosis. BOT's account for 10-15 % of ovarian epithelial tumours with a ten year survival rate higher than 95 % and an 80 % twenty year survival rate, although 10-15 % will have recurrences and die of the disease (8,9). The risk and protective factors are similar to those of ovarian carcinoma, except for the association with BRCA genes as BOT is rarely seen in women with these mutations (2,3).

A possible positive influence of Oral Contraception (OC) on the risk of ovarian cancer has been discussed since the 1970's and a number of epidemiological

retrospective analyses assessing the risk and protective factors of OC on ovarian cancer, as well as large-scale prospective trials have been conducted. The broadest review to date was published in 2010 by Cibula et al. and endorsed the findings of previous meta-analyses (10). The findings were that the use of OC has a significant protective effect on the risk of ovarian cancer and the risk reduction is dependent on the duration of use. The exact mechanism of action has not been elucidated.

The ‘incessant ovulation’ hypothesis proposed by Fataly in 1971 (10) suggests that the development of ovarian cancer is a consequence of repeated micro trauma to the ovarian surface epithelium during ovulation. He proposed that the repeated DNA damage that occurs during ovulation and dysfunction of its recognition and repair are crucial for ovarian cancer-oncogenesis. Therefore the inhibition of ovulation seems to be the most important factor although suppression of gonadotrophin levels and the direct effect of progestin compounds may also play a role. The reduction in relative risk (RR) is maintained for several decades but diminishes in postmenopausal women and the risk reduction applies to all histological subtypes, including BOT with the exception of mucinous tumours (10). The inhibition of ovulation could therefore explain the protective influence of hormonal contraception as well as pregnancy and breast-feeding in ovarian cancer development (10,11).

There are studies that have shown an increase in serous BOTs in women undergoing assisted reproduction techniques (ART) which seems to correlate with hormonal levels achieved during ovarian stimulation and the damage caused by repeated gonadal punctures (3).

A number of oncogenes are under investigation to determine their role in the pathogenesis of BOT. One study found mutations in the K-ras proto-oncogene to be present more commonly in advanced stage presentations (12).

1.3 PATHOLOGY

The gross pathology of BOT tumours usually consists of unilocular or multilocular tumours with or without epithelial proliferations on the outer tumour surface (13,14). The World Health Organisation (WHO) defines a BOT as an epithelial ovarian tumour exhibiting an atypical epithelial proliferation without destructive stromal invasion (6).

Histologically they can be divided into serous (50%), mucinous (45%) and other rarer subtypes (namely endometrioid, Brenner and clear cell tumours). The staging system for BOT is the same one used for invasive ovarian tumours (IOTs), which is the FIGO classification (15). BOT's are bilateral in approximately 50% of serous BOT's and in 20% of cases with mucinous BOT. Endometrioid, clear cell and transitional cell tumours are almost always Stage 1 and predominantly unilateral (8).

Fifteen to 40 % of BOTs are associated with peritoneal implants, some of which can be invasive and these are thought to have a direct influence on relapse and survival. However, non – invasive implants can also result in relapse or progressive disease (16). Despite lack of destructive stromal invasion, BOT can also be associated with micro invasion, lymph node implants and the peritoneal implants mentioned above (15). A diagnosis of micro invasion in BOT is restricted to cases with one or more foci of early stromal invasion none of which should exceed 10mm (14).

A cyst adenoma or cystadenofibroma qualifies as a BOT once it contains more than 10 % borderline histology (15).

1.3.1 SEROUS BOT

Serous BOT's are often associated with implants (13). Implants can be classified as invasive or non-invasive, depending on their histological appearance. Extra-ovarian spread rarely presents as bulky metastatic disease. In most cases the so-called implants are either microscopic or small macroscopic (<1-2cm) (17). These tumours are bilateral in one third of the cases (3).

In one series, the authors report that 30 % of their patients with serous BOT and implants had recurrences, most commonly in the form of serous carcinoma (18).

The most important prognostic factor seems to be whether peritoneal implants are invasive or not (19). The prognosis of patients with noninvasive implants remains good if all the peritoneal implants are removed (19). Serous BOTs can be divided into two subtypes: typical pattern (90%) and micro – papillary pattern (10%). Serous BOT's with the typical pattern often present with a unilocular cystic mass with fine septa in its interior (3).

Specific histological features need to be present in order to classify a Serous BOT (SBOT) as having a micropapillary pattern, namely: micro papillary pattern must be contiguous over > 5 mm or in more than 10% of the tumour. This pattern has a worse prognosis, a higher rate of recurrence in the invasive form and greater percentage of bilaterality (2, 3).

1.3.2 MUCINOUS BOT

A study done by Ji et al. that evaluated the surgical management and outcome of Stage I BOT confirmed that Mucinous BOT (MBOT) tends to be significantly larger than serous BOT (20). They can have either a unilocular or multilocular cystic

structure with fine septa in their interior and intramural nodules (3). Peritoneal implants are very uncommon, occurring only in 15 % of these tumours. They are divided into two subtypes: intestinal (85 – 90%) and endocervical or mullerian (10 – 15%). The majority of intestinal types are unilateral and if they are bilateral then a primary intestinal cancer should be ruled out.

Endocervical or mullerian are bilateral in at least 40 % of the cases and 20 – 30% are associated with ipsilateral endometriomas or pelvic endometriosis (3).

1.3.3 UNCOMMON BOT

Uncommon subtypes encompass 3 – 4 % of BOTs. They include endometrioid, clear cell, transitional (Brenner) or mixed epithelial tumours (2). Endometrioid BOT (EBOT) either have an adenofibromatous appearance or a glandular / papillary appearance. They arise either from the surface ovarian epithelium or from endometriosis and have the potential to progress to low- grade endometrioid carcinoma (2). According to the WHO, EBOT can be defined as having atypical or histologically malignant endometrioid type glands or cysts often set in a dense fibrous stroma without stromal invasion (21). A review done on the management and prognosis of EBOT states that staging surgery is not required as most patients present with stage I disease but besides that, EBOT carries a good prognosis whether treated radically or conservatively. However, with conservative management uterine curettage is recommended as EBOT can be associated with synchronous endometrial endometrioid adenocarcinoma (21).

Clear – cell BOTs are characterised by atypical or histologically malignant glands or cysts lined by clear or hobnail cells set in a dense fibrous stroma with an absence of stromal invasion (2).

Borderline Brenner tumours have atypical or malignant features of the epithelium but lack stromal invasion. They resemble low – grade papillary urothelial carcinoma of the genital tract (2).

1.4 DIAGNOSIS

BOT's present in the same manner as other adnexal masses. Patients may complain of pelvic pain, dyspareunia and abdominal distension but can also be asymptomatic (2). Adnexal masses may be found incidentally at the time of pelvic examination and may occasionally also be detected incidentally during routine obstetric ultrasound (2).

One study showed that out of 811 women only 7% showed no symptoms and the most common symptoms were abdominal pain or pressure (44%) and general abdominal swelling (39%). There was little variation in symptoms across the different histologic subtypes of BOT although mucinous tumours were more likely to be associated with generalised abdominal swelling than the other tumour types (22).

In contrast to the above study regarding the frequency of symptoms, a study done by Messali et al. showed that 49% of patients did not report any symptoms and the diagnosis was usually made when an ultrasound that was done for another reason showed a suspicious cyst (1).

There are no pathognomonic ultrasonic features of BOT; however it is a priority in the diagnostic work-up often confirming the presence of a complex adnexal mass (8). CA 125 is elevated in 40-50% of patients with Stage 1 disease and in more than 90% of patients with advanced stage BOT (8). However, there are no data available to support the relevance of serum tumour markers in BOT, for identification of a high-risk group of BOT, with the exception of advanced- stage disease (12). Tumour

markers such as CA125 are most useful for assessing response to chemotherapy, where used (9).

The National Institute for Clinical Excellence (NICE) recommends an ultrasound for patients presenting with symptoms suggestive of a malignant ovarian neoplasm and a CA125 level more than or equal to 35 IU/ml (2). There was a lot of criticism following this guidance as CA125 is often negative in patients with BOT (2). There is also a high risk of false positives due to a variety of clinical variables such as menstruation, ovulation, endometriosis and liver disease.

The Risk of Malignancy Index (RMI), developed by Jacobs et al in 1990 is a scoring system that is derived from a logistic regression formula that combines menopausal status with the CA125 level and ultrasound variables (23).

In one study that evaluated the diagnosis, treatment and follow up of BOT, the RMI missed 73% of the patients with BOT as the performance is poor when applied to younger women and with pathology that is difficult to characterise with ultrasound (2).

Macroscopically, it is not possible to differentiate BOT from other tumours. The definitive diagnosis is histological. The criteria for diagnosis are: epithelial cell proliferation, stratified epithelium, microscopic papillary projections, cellular pleomorphism, nuclear atypia and mitotic activity (3). There can be no stromal invasion and this is what differentiates BOT from invasive carcinomas. However, in 10 % of BOT, there are areas of micro invasion, defined by foci of < 5 mm or that do not invade the stroma > 10 mm (3).

1.5 PROGNOSTIC PARAMETERS

The prognosis of BOT is generally excellent, however 11 % may recur and 20 – 30 % of those recurrences may show malignant transformation. To date, there is no agreement on the definition of prognostic factors in terms of recurrence as invasive disease (2). Different study series have found different variables to be significant prognostic indicators in terms of recurrence.

Morice et al. in 2009 did a retrospective review of 80 patients with SBOT and peritoneal implants. The aim of the study was to determine prognostic factors for patients with advanced stage disease. They found that the only prognostic factor for patients with advanced stage BOT was the type of peritoneal implant (17). They also found that the patients' prognosis with non – invasive implants was excellent, even with advanced stage BOT. They concluded that conservative management could be discussed in younger patients (18).

Another group from Turkey agreed with the group mentioned above. They looked at estimating the survival times and clinico – pathological variables in patients treated for BOT. It was a retrospective audit evaluating 100 patients. Their conclusion was that BOT has an overall excellent survival and that patients can be treated safely with conservative surgery (24).

Du Bois et al were part of the AGO Study Group evaluated BOTs over a twenty-year period, across 24 German centres found that a higher stage, incomplete staging, high residual tumour and organ preservation were independent prognostic factors for disease recurrence. Neither micro-invasion, nor a micropapillary growth pattern showed any significant impact on outcome in their study (15).

1.6 MANAGEMENT OF BOT

The standard treatment for BOT is surgical. This includes complete comprehensive staging by exploration of the entire abdominal cavity, bilateral oophorectomy, hysterectomy, infracolic omentectomy, peritoneal biopsies, peritoneal washings and removal of all macroscopic suspicious peritoneal lesions. Mucinous tumours also require an appendectomy (9) to exclude the appendix as the primary. Non-optimal staging in patients with BOT has a poor prognosis because without a deep peritoneal exploration there could be invasive implants (20).

The role of hysterectomy is to exclude intra-uterine disease, albeit rare, it does occur. In one study by Menczer et al, removal of the uterus did not improve survival (25). The purpose of this study was to assess the frequency of uterine involvement in patients with BOT and the effect of hysterectomy on survival. The study group comprised 225 patients and a hysterectomy was performed in 65.3% of patients. Uterine involvement was found in only 2%. The 13-year survival rate of the total group of patients was 85.8% and 88.5% for those with apparent Stage 1 disease. There was no survival difference between the overall staged and unstaged patients and between patients in stages II-III who did and did not undergo hysterectomy. This study therefore concluded the rate of uterine involvement in BOT is low and that hysterectomy does not favourably affect survival. The authors, who feel that the extension of any procedure without a clear indication seems unnecessary, thus question the necessity of hysterectomy in BOT (25).

1.6.1 CONSERVATIVE SURGERY

Conservative surgery can be defined as preservation of the uterus and at least part of the ovary in order to preserve fertility. Data from recent literature are reassuring

regarding the safety of conservative surgery. When conservative management is not feasible, due to bilateral massive ovarian tumour involvement then at least the uterus can be preserved for eventual transfer of frozen embryos, before radical surgery (2). However, assisted reproduction does come at a cost, and these patients should be counseled thoroughly and extensively prior to surgery and if the options of oocyte or embryo cryopreservation are acceptable and affordable then the uterus can be preserved.

1.6.2 RADICAL SURGERY

As mentioned above, radical treatment is defined as hysterectomy with BSO and conservative treatment is defined as a surgical procedure with conservation of the uterus and salvage of at least a portion of one ovary. Four types of conservative surgical procedure are performed: unilateral adnexectomy (UA), UA with contralateral cystectomy (UA+CC), unilateral cystectomy (UC) and bilateral cystectomy (BC)(26).

1.6.3 INTRAOPERATIVE DIAGNOSIS AND STAGING

In order to achieve complete FIGO staging a combination of intra operative exploration of the entire abdominal cavity should be conducted with peritoneal washings, omentectomy and complete resection of all macroscopic suspected lesions. Lymphadenectomy is not indicated because the recurrence and survival rates for patients with positive and negative lymph nodes are similar. This optimal staging allows a correct pathological diagnosis to be obtained and to define a group with a higher risk of recurrence (2). General obstetrician- gynaecologists are more likely to encounter BOT because of the imprecise clinical findings, than gynaecological

oncologists. A patient undergoing surgery for an adnexal mass may have either a laparoscopy or a laparotomy depending on several factors including the skill of the surgeon (17).

A study done by Lin et al focused on the adequacy of surgical staging. In this study the majority (78%) of BOT were encountered and staged primarily by general obstetrician – gynaecologists. Only 12 % of the patients had comprehensive surgical staging. General surgeons performed complete staging in 0% of patients, obstetrician – gynaecologists in 9% and gynaecological – oncologists in 50 % (27). Surgical staging of patients found to have BOT remains controversial (17). Some believe that the prognosis of these patients is excellent regardless of stage.

1.6.4 SURGICAL APPROACH (LAPAROSCOPY/LAPAROTOMY)

Laparoscopy is more frequently used to manage patients conservatively and is associated with a higher rate of cyst rupture and incomplete staging (28). A study done by Fauvet et al. showed that the type of surgical approach (laparoscopy vs. laparotomy) did not seem to influence the progression-free interval or rate of relapse (28). In this study, 149 of the 358 (41.6%) women underwent laparoscopy, 28.2% underwent conversion to laparotomy, mainly for suspected ovarian cancer or large tumour volume. Conservative treatment and cyst rupture were more frequent in the laparoscopy group and the rate of complete staging was lower in this group as well. No difference in the recurrence rate was noted between the groups but a higher rate of recurrence was noted after conservative treatment. Laparoscopic surgery is known to have lower morbidity and fewer adhesions, which are important for fertility (19). One study found laparotomy to be the standard of care in BOT as laparoscopy often results in rupture and improper staging (4). All laparoscopic procedures should

nevertheless be performed by oncologic surgeons who are trained in extensive laparoscopic procedures in order to obtain optimal surgical staging and debulking (29).

1.7 POSTOPERATIVE TREATMENT

1.7.1 ADJUVANT TRETAMENT

To date, there is no clear evidence that chemotherapy can decrease relapse rates or improve survival in any subset of patients with diagnosed BOT's. Poor response rates to traditional cytotoxic agents may be explained by the low proliferation rate of BOT's in general (2).

1.7.2 TREATMENT OF RECURRENCES

When an extra ovarian borderline or invasive relapse occurs then cytoreductive surgery as with the primary ovarian cancer should be carried out. Death will occur in 12 % of those who were correctly treated and in 60 % of those who received insufficient treatment (2). Hence, the optimum performance of this surgery is an independent prognostic factor that will determine the patient's survival.

1.7.3 TREATMENT OF INFERTILITY

Couples in developed countries are increasingly delaying childbearing, and preservation of the uterus and the contralateral ovary is routinely practiced in young women or those desiring further fertility in their clinical setting (9).

Spontaneous conception is reported after conservative surgery in 50% of patients without deterioration in the survival rate (26). Morice et al did this study and the objective was to assess the clinical outcome and fertility in patients treated

conservatively for BOT. There were 44 patients of whom 33 had UA and 11 had cystectomy (bilateral in 1 and along with contralateral adnexectomy in 5 patients). The main outcome of the study was tumour recurrence and pregnancy rates. Tumour recurrence rates were 15.1% after adnexectomy and 36.3 % after cystectomy. The five patients who had recurrence were alive and free of disease at the time of print of this journal. They underwent repeated conservative management. Seventeen pregnancies (15 spontaneous) occurred in 14 patients; 13 in patients with stage I and 4 in patients with stage III. The authors concluded that conservative management of BOT significantly increases the risk of recurrence but does not affect overall survival and that such management offers even patients with advanced disease the chance to have a spontaneous pregnancy (26).

1.7.4 TREATMENT OF HORMONE DEPRIVATION

Hormone Replacement therapy (HRT) should be offered to selected patients to prevent cardiovascular disease and osteoporosis after surgery. Quality of life is an important issue as many of the patients with BOT are young (2).

1.8 FOLLOW - UP

Regular follow-up is essential for early detection of recurrence in women with BOT and is usually a combination of clinical examination and CA 125 levels if indicated. Imaging is performed if required based on symptoms and clinical findings. Follow up should also occur for a long time as relapses may occur 15 years after surgery. Close monitoring is advised for women who were treated with conservative surgery because of the high rate of relapse (3).

CHAPTER TWO: METHODS

The Gynae Oncology Database at GSH was used to extract data to perform the audit. All patients with cancer that are treated at GSH are registered prior to, during and after treatment and have a unique registration number (RT number). An adult is defined as a female patient above the age of 13 years. This is the cut off age for referral to tertiary hospitals.

A study protocol was drafted and sent to the Departmental Ethics Committee for approval. Once this was obtained the protocol was approved by the Human Research Ethics Committee of the University of Cape Town and the Bioethics Committee of Groote Schuur Hospital and the Department of Radiation Oncology. (See Appendix B and C, respectively).

The specific aims and objectives of this retrospective study were:

- 1) To describe the demographic profile of women diagnosed with BOT treated at GSH between 1984 and 2008.
- 2) To define the surgical and pathological findings of women with BOT seen between 1984 and 2008.
- 3) To describe the surgical treatment of women with BOT.
- 4) To determine the survival probability in relation to different variables
- 5) To evaluate prognostic factors in this group of patients using Cox regression analysis

Access to the database was gained and it revealed that between 1984 and 2008, 213 Women with BOT were treated at GSH. A data capture sheet was designed using Microsoft Excel with drop down lists with the aim to obtain and record data only Relevant to this study (See Appendix A).

We then retrospectively evaluated all patients treated at GSH with BOT during 198 2008 taking into account the following categories: age, date of treatment (i.e. surgery), type of surgery, alive or dead, disease free survival, cause of death (if known), period of follow up, response to treatment defined as complete, partial, stable or progressive. Site of relapse was recorded as well as intervention or treatment administered.

If patients had died, then the date of death and cause were recorded.

The different surgical modalities were: unilateral oophorectomy; total abdominal Hysterectomy, bilateral salping oophorectomy and omentectomy (TAH+BSO+O); TAH, oophorectomy; bilateral oophorectomy or biopsy only.

A family history was recorded (yes or no) as well as the stage of BOT, using the old FIGO staging classification, which has since changed in 2014 (30).

The plan was to include race, as it is recorded on the database and could contribute toward the descriptive statistics of our patient population; however, the HREC felt that it would not benefit our study to include this variable, so race was excluded.

The last few categories on the data capture sheet was whether the patient had ascites or not, and whether the Ca125 was elevated or not.

The inclusion criteria included women over the age of 13 treated with BOT at GSH between 1984-2008 and who were registered on the gynae-oncology database.

The exclusion criteria would be women with any other malignancy and the need for Previous chemotherapy or radiotherapy.

For data analysis, the data was imported from Excel into Stata 12.

Descriptive and survival statistics were calculated. Kaplan – Meier curves were generated and illustrated survival probability for the univariate categories of survival probability by: age, histological subtype, stage, treatment type, residual disease,

treatment sequence, by the presence or absence of ascites and by whether Ca125 was raised or not. Univariate and multivariate Cox Regression models with backward variable selection procedures as well as Kaplan – Meier estimates to explore the different covariates on overall survival (OS). The chi – square test was used to compare categorical variables.

Ethical considerations

This retrospective observational study should be deemed minimal risk as it poses minimal risk to subjects and confidentiality is not breached.

According to the Health Act No. 61 and the WMA Declaration of Helsinki 2013, ethics approval must still be sought for a retrospective clinical audit but it is not necessary to get individual patient consent to use non-identifiable private information in research (31,32).

Patients were not identified therefore their consent was not required. The database is located in the Department of Radiation Oncology and is registered with the Human Research Ethics Committee (HREC) (R016/2013).

CHAPTER THREE: RESULTS

Descriptive statistics

Between 1984 and 2008, 213 women with Borderline Ovarian Tumours (BOT) were entered into the Gynae-Oncology Database at Groote Schuur Hospital (GSH). The median age was 45 years of age (range 17.3– 83.1 years). Figure 1 shows the age distribution of the women, with 34% (73/213) diagnosed under 40 years of age.

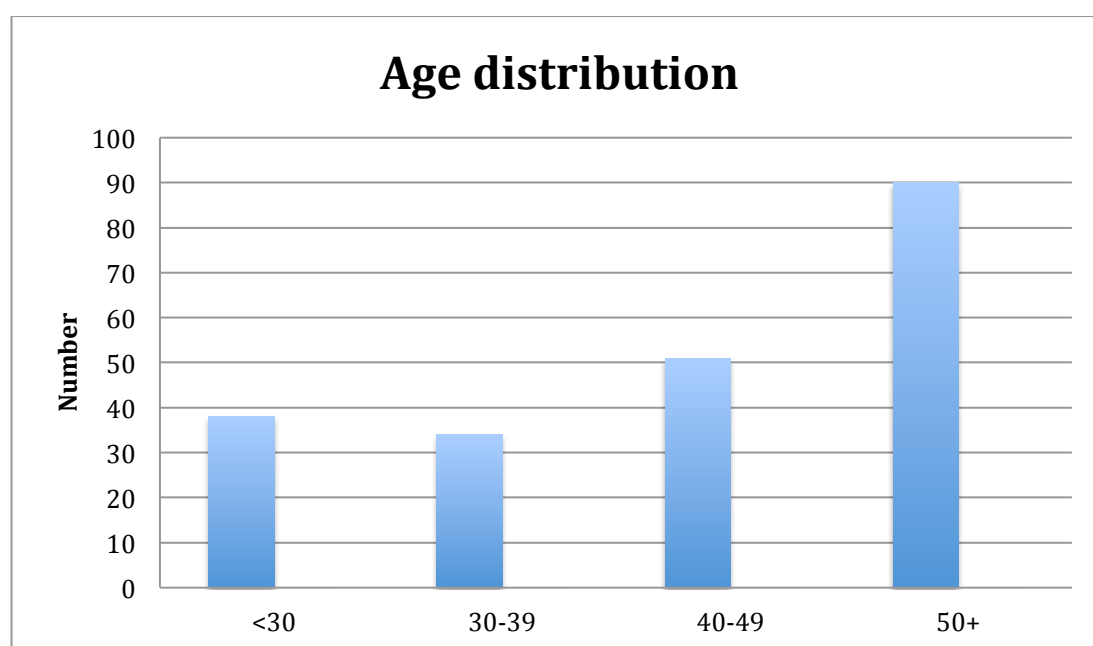


Figure 1: Age distribution among 213 women

At the end of the study period 73% (156/213) of the women were alive with no evidence of disease, 1.4% (3/213) were alive with disease, 5.6 % (12/213) had died of cancer and 15.0% (32/213) died of other co-morbidities. There was no information on 10 patients.

In terms of response to treatment, 93.4% (199/213) had a complete response (CR) to treatment. In 1 case response to treatment was not evaluable (NE). In 2 patients there was no response (NR). There was progressive disease in 5 patients (PD) and 6

patients showed partial response (PR). Seven women relapsed, two at distant sites and 5 loco-regional recurrences.

Survival statistics

Death by age

With univariate analysis there was no difference in survival by age ($p = 0.3$)

Figure 2 shows the Kaplan Meier curve for survival probability by age.

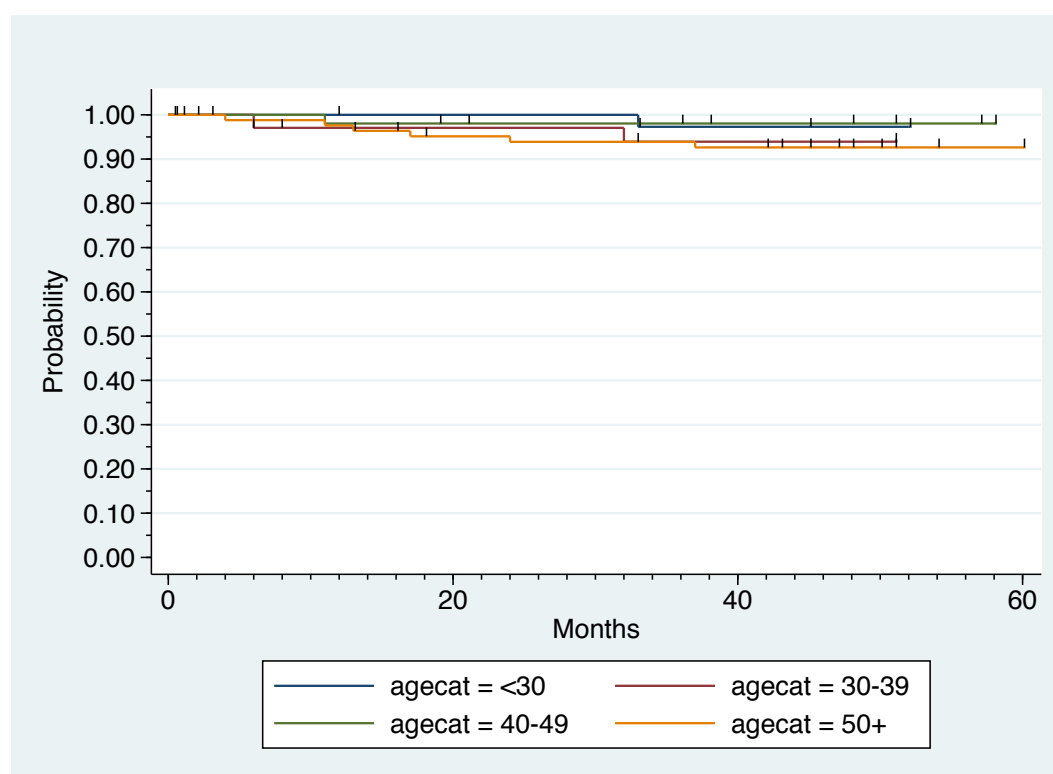


Figure 2 – Kaplan Meier Curve; Survival probability by age

There were 44 deaths in total; 12 cancer related and 32 women died from other non-cancer related causes. The majority of women who died were over the age of fifty i.e. 64% (28/44) of whom 75% (21/28) died from non-cancer related causes and 7 women died from cancer-related deaths.

Three women under the age of 30 died - 1 from cancer and 2 from other causes.

There were 13 deaths in the 30-49 age group of whom 4 were cancer related.

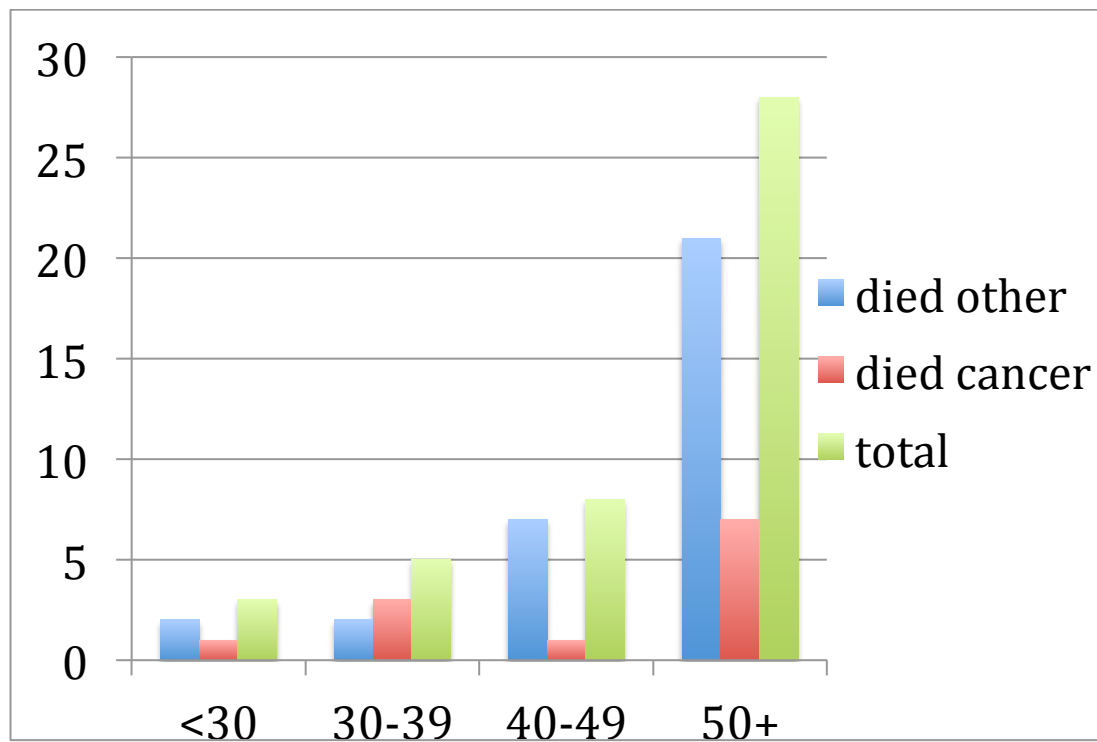
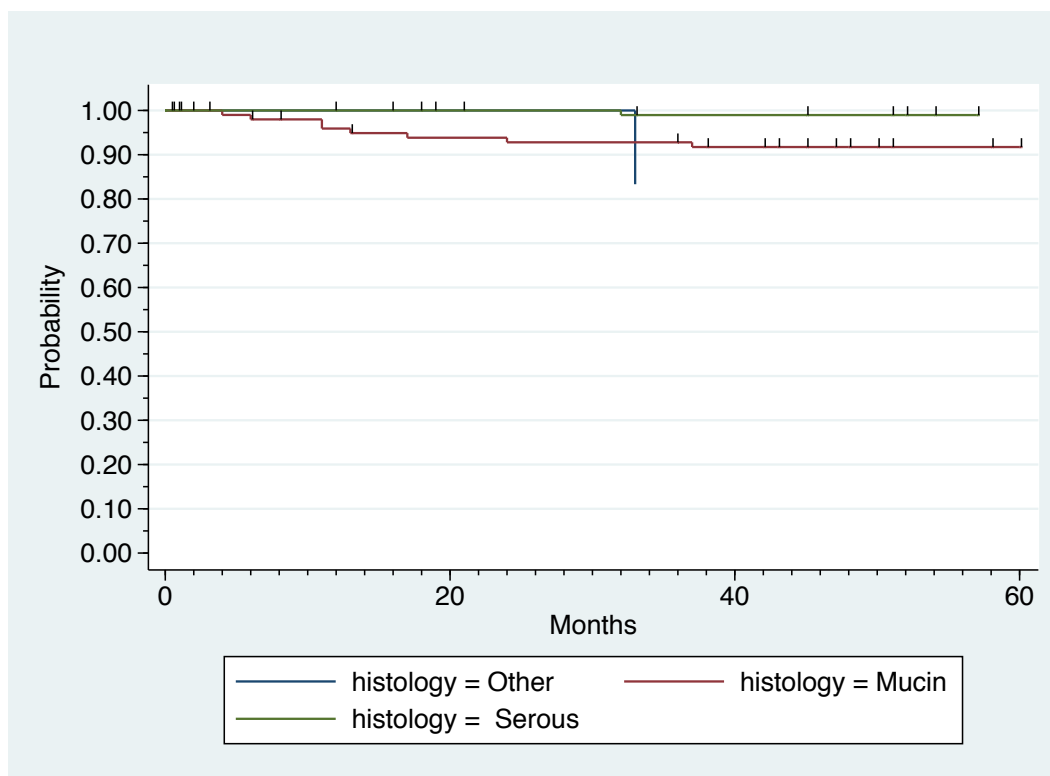


Figure 3: Graph illustrating deaths by age group and causes

Survival probability by Histologic subtype

In terms of histology 47.9 % (102/213) had a mucinous BOT, 49.3%(105/213) were serous papillary and 6 patients had other histology (4 endometrioid, 1 Brenner and 1 mixed). Of the 44 deaths, 23 were in women with mucinous tumours of which 47.8 % (11/23) died of cancer related causes. Outcome in women with mucinous tumours was significantly worse compared to women with serous tumours ($p = 0.01$).

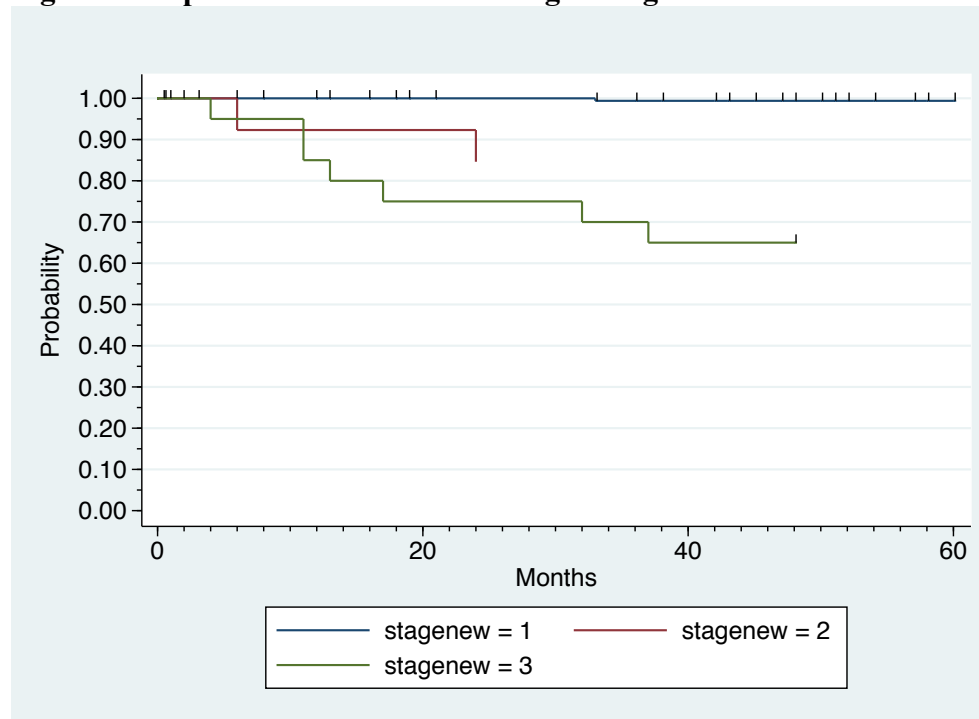
Figure 4. Kaplan – Meier Curve: survival probability by histological subtype of BOT



Survival probability by Stage

In terms of stage, 83.6% (178/213) of the patents were in Stage I, 6.1% (13/213) were in stage II and 10.0% (22/213) were stage III. There were no patients in stage IV. Of those in Stage I, 65.2% (116/178) were stage Ia, 0.6% (7/178) were in stage Ib and 30.3% (54/178) were stage Ic. Of those in stage III, 2.7 % (6/22) were IIIc. Of those in stage I, only two women died of cancer. In stage II, 3 women died (two were cancer related) and in stage III 9 women died, 8 from cancer related causes (p=0.0000 which is highly statistically significant in univariate analysis).

Figure 5. Kaplan Meier curve according to stage

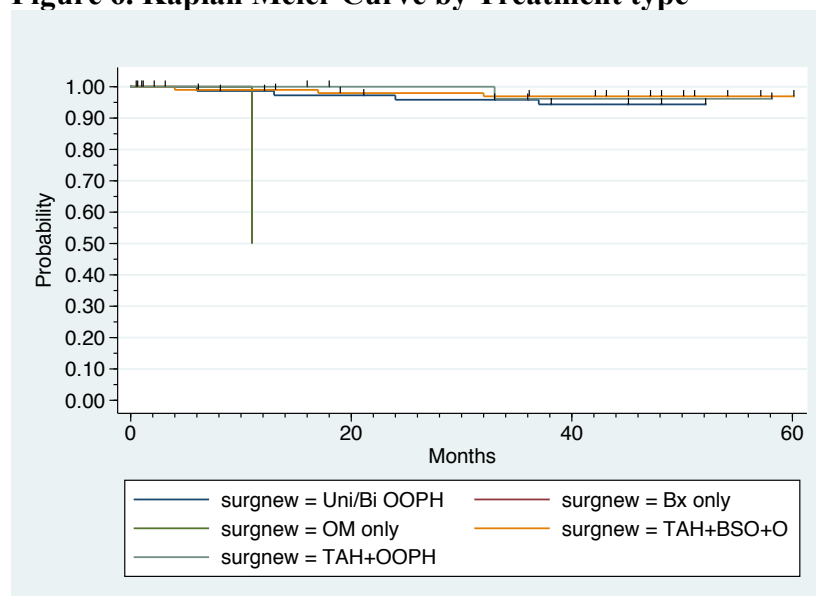


Survival probability by Treatment type

All 213 women underwent surgical procedures, of whom 48.4% (103/213) had standard surgery which was a total abdominal hysterectomy plus bilateral salpingo-oophorectomy with omentectomy (TAH, BSO, O). A further 13.6 % (29/213) underwent TAH and BSO without omentectomy.

A unilateral oophorectomy was performed in 26.8 % (57/213) and BSO was performed in 8.9% (19/213). Five women had either biopsy only (Bx) or omentectomy only (O). There were 17 deaths in women who underwent TAH+BSO+O, only three were cancer related. There were five deaths recorded in women who underwent BSO only and there were no deaths in women who underwent USO only. For purpose of this analysis, USO and BSO were grouped together and the differences in survival by different surgical interventions were highly statistically significant ($p = 0.0000$) with more radical surgery being associated with the best outcome.

Figure 6. Kaplan Meier Curve by Treatment type



Survival probability by Residual disease

The amount of residual disease post surgery was recorded in 212 women. There was no residual disease (RD) in 86.3% (183/212). In 9 women there was < 2 cm of RD and in 20 women there were > 2cm of RD. Of the 7 women with RD of >2cm that died, all deaths were cancer related. Among women with <2cm of RD, there were 5 deaths; 3 due to cancer. There were 2 cancer related deaths in females with no RD ($p = 0.00$), which is highly statistically significant.

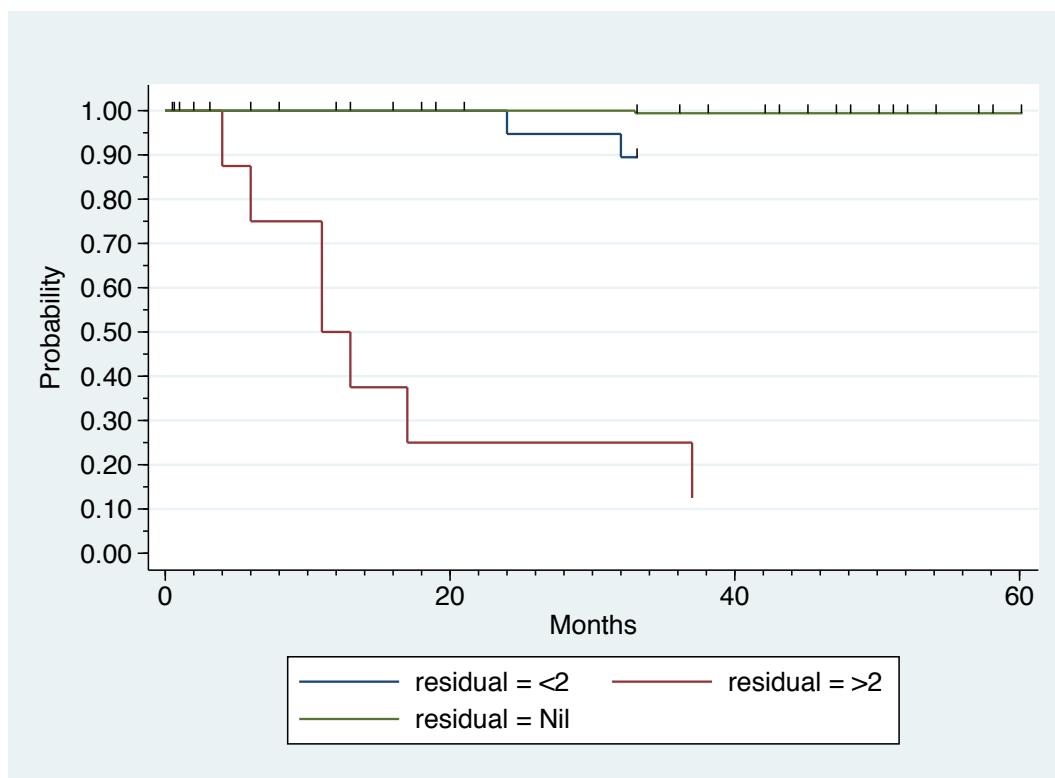


Figure 7. Kaplan Meier curve of survival by residual disease post surgery

Survival probability if CA125 was elevated or not

A Ca125 was available in 205 of patients in the database. The tumour marker was increased in 42.4% (87/205) of patients and was normal in 57.6% (118/205). 12 women with increased Ca125 died; of which 5 were cancer related 41.7 % (5/205).

Of the women with normal Ca125 levels there were 31 deaths of which 22.6% (7/31) were cancer related deaths. The difference in survival is not statistically significant with $p = 0.94$.

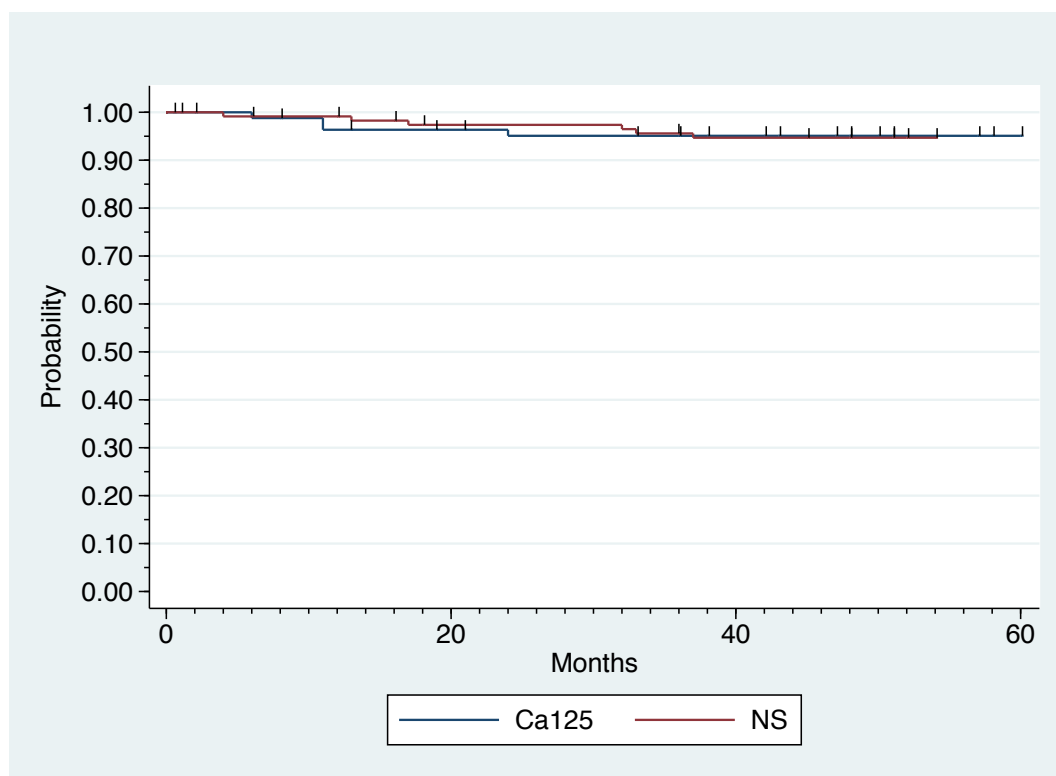


Figure 8. Kaplan Meier survival curve by whether an elevated CA 125 was detected or not

Treatment sequence

Of the 213 patients, the vast majority were treated with surgery only; 98% (209/213). 3 patients received adjuvant chemotherapy and 1 patient received adjuvant radiation. All 3 patients who received chemotherapy died of cancer, as did the one patient who received radiotherapy ($p = 0.0000$) which is highly statistically significant.

Survival probability by presence or absence of Ascites

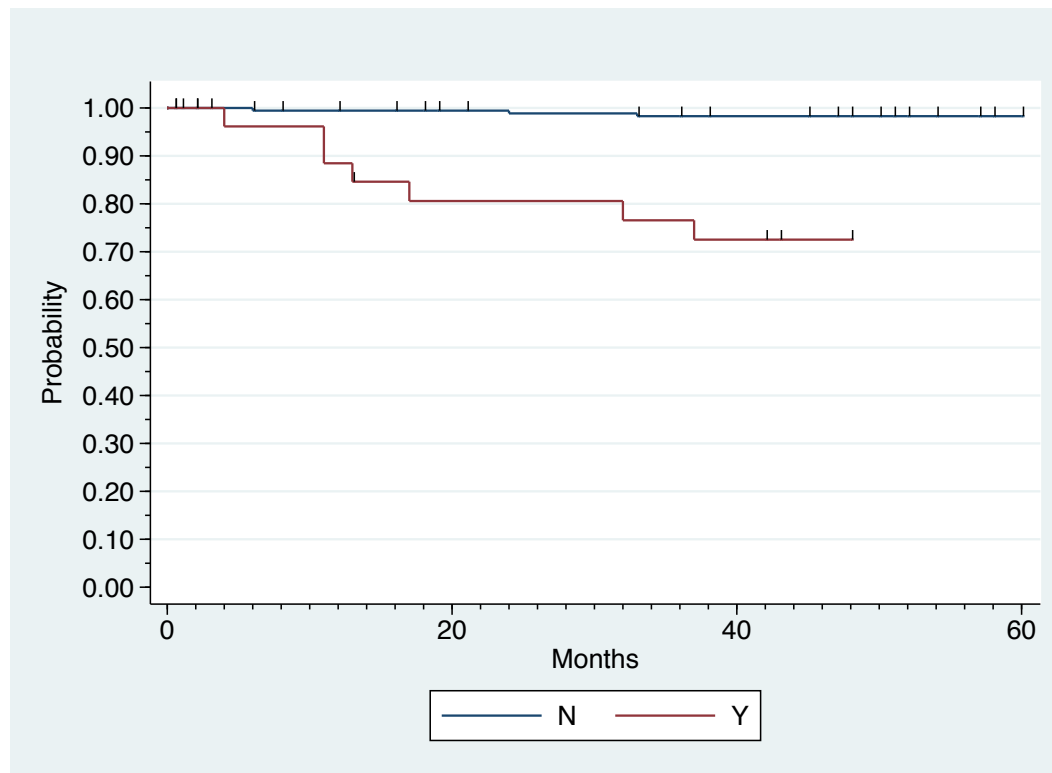


Figure 9. Kaplan Meier curve – survival probability by presence of ascites

The presence of ascites was noted in 3.6% (29/213). Of the women who had ascites, there were 11 deaths; 8 of them cancer related. The difference in survival in women with or without ascites is highly significant with $p = 0.0000$.

Table one shows the crude and adjusted Hazard Ratios of different variables. On univariate analysis histology, stage, type of surgery performed, residual disease and ascites were all associated with survival. However, using Cox proportional (Hazard

Ratios) HRs the only variable that remained statistically significant was the amount of residual disease after surgery, but with wide confidence intervals most likely related to small numbers of patients.

Table 1. The association between key variables and disease specific survival estimated by Cox's proportional hazards ratios (crude and adjusted) and their 95%CI's among 213 women

Variable	N	Person time (months)	Failure s	Rate (95%CI) /1000 person- months	Crude HR	Adjusted HR*
Age group (years)						
<40	72	10229.5	3	0.2(0.09-0.9)	1.0(reference)	
40-49	51	6803.0	1	0.1(0.02-1.0)	0.5(0.05-4.4)	
50+	90	8753.5	8	0.9(0.5-1.8)	2.3(0.6-8.7)	
Histology						
Serous	105	14084.5	1	0.07(0.01-0.5)	1.0(reference)	
Other	6	697.0	1	1.4(0.2-10.1)	16.9(1.1-270.7)	
Mucinous	102	11004.5	10	0.9(0.5-1.7)	10.8(1.4-84.5)	
Stage						

Variable	N	Person time (months)	Failure s	Rate (95%CI) /1000 person- months	Crude HR	Adjusted HR*
1	178	21916.5	2	0.02-0.4)	1.0(reference)	1.0(reference)
2	13	1824.0	2	1.1(0.3-4.4)	13.9(2.0-98.6)	3.0(0.1-100.1)
3	22	2045.5	8	3.9(2.0-7.8)	41.4(8.7-195.3)	1.5(0.03-67.4)
4	0	0	0	-	-	-
Surgery						
TAH+BSO+ O	103	12402.5	3	0.2(0.08-0.8)	1.0(reference)	1.0(reference)
Uni/bi OOPH	76	9175.0	5	0.5(0.2-1.3)	2.3(0.5-9.6)	1.2(0.2-6.3)
Bx only	3	284.5	1	3.5(0.5-25.0)	23.9(2.4-231.3)	2.0(0.2-24.9)
OM only	2	111.0	1	9.0(1.3-64.0)	23.9(2.4-231.3)	1.9(0.1-28.2)
TAH+OOP H	29	3813.0	2	0.5(0.1-2.1)	2.4(0.4-14.2)	0.6(0.1-4.7)
Residual						

Variable	N	Person time (months)	Failure s	Rate (95%CI) /1000 person- months	Crude HR	Adjusted HR*
Nil	183	22839.5	2	0.09(0.02-0.4)	1.0(reference)	1.0(reference)
<2	20	2664.0	3	1.1(0.4-3.5)	14.0(2.3-83.8)	8.3(0.3-251.7)
>2	9	218.5	7	32.0(15.3-67.2)	206.7(41.3-1033.8)	117.5(1.9-7322.1)
Marker						
Ca125	87	8893.0	5	0.6(0.2-1.4)	1.0(reference)	
NS	118	15757.0	7	0.4(0.2-0.9)	1.0(0.3-3.0)	
Rx seq						
1 or 11	209	25623.0	9	0.4(0.2-0.7)	1.0	
14	3	131.0	2	15.3(3.8-61.0)	23.3(4.9-109.7)	
142	1	32.0	1	31.3(4.4-221.8)	35.6(4.2-297.5)	
Ascites						

Variable	N	Person time (months)	Failures	Rate (95%CI) /1000 person- months	Crude HR	Adjusted HR*
N	184	23695.5	4	0.2(0.06-0.4)	1.0	1.0
Y	29	2090.5	8	3.8(1.9-7.6)	16.6(5.0-55.3)	1.1(0.1-11.0)

*Adjusted for age (single years) and other factors for which estimates appear

Statistically significant findings are shown in bold; HR: Hazard Ratio

CHAPTER FOUR: DISCUSSION AND CONCLUSION

In our study, the median age of patients with BOT was 45 years with 34% being diagnosed under age of 40, supporting the literature that BOTs occur more frequently in young adults. In a retrospective study done by Gungor et al., the mean age at diagnosis was 40.6 (5). Our study correlates with international data regarding age distribution of patients (see Figure 1: Age distribution among 213 women).

The youngest patient was 17 years old when she was diagnosed, had Stage I a MBOT and had a unilateral oophorectomy and then a second surgery (restaging surgery) in which an omentectomy was done. This patient had a complete response and last follow up was in 2010. In contrast, a study done by Uzan et al., the median age was 29 (7) .

Morice et al. did a review looking at the results of epithelial malignant and borderline ovarian tumours and proposed that conservative management could be performed in patients with BOT in order to preserve fertility potential (33). He concluded that this management would not affect survival in these patients. There is a place for conservative management in younger women who have not completed their childbearing, and it appears safe to carry out conservative surgery as long as they do not have invasive implant as well. These patients must also agree to remain under very close monitoring to ensure early diagnosis and treatment, should they have any recurrences.

In terms of current status, at the end of the study period, 73% were alive with no evidence of disease, 1.4% were alive with disease and 5.6% (12/213) had died of cancer. There was no information on 10 patients. One patient that died was treated at the age of 39, had stage I a, had TAH and oophorectomy but relapsed 5 years after initial surgery with metastases to lungs. This illustrates that even patients with early

stage disease can relapse. Another patient that died of cancer was diagnosed at age 34, had TAH, BSO and O, had progressive disease and still had relapse 2 years later and died. She had surgery with chemotherapy and radiation therapy and was stage III b. BOTs can be aggressive at times and is unresponsive to chemotherapy (3). In terms of response to treatment, 93.4% had complete response to treatment, 5 patients had progressive disease and 7 women relapsed. Two at distant sites and 5 loco – regional.

With univariate analysis there was no difference in survival by age ($p = 0.3$) Figure 2 shows the Kaplan Meier curve for survival probability by age.

In terms of histology 47.9 % (102/213) had a mucinous BOT, 49.3%(105/213) were serous papillary. This differs from most international data where SBOT occur more frequently (2,3). Six patients had other histology (4 endometrioid, 1 Brenner and 1 mixed). Of the 44 deaths, 23 were in women with mucinous tumours of which 47.8 % (11/23) died of cancer related causes. Outcome in women with mucinous tumours was significantly worse compared to women with serous tumours ($p = 0.01$)(see Figure 4. Kaplan – Meier Curve; survival probability by histological subtype of BOT). This is not in keeping with a recent study done by Avril et al., looking at the histopathologic features of ovarian BOT. They found that histopathologic parameters were not predictive of BOT recurrence (14).

In terms of stage, 83.6% (178/213) of the patents were in Stage I. Our findings are in keeping with the literature in that most BOT are diagnosed in the early stages, which is one of the reasons why they have a better outcome and no patients were diagnosed with stage IV disease.

Of those in stage I, only two women died of cancer. In stage II, 3 women died (two were cancer related) and in stage III 9 women died, 8 from cancer related causes ($p=0.0000$ which is highly statistically significant in univariate analysis)(see Figure 5. Kaplan Meier curve according to stage). This illustrates that the higher the stage, the potentially worse the outcome, as many authors have reported that staging is important as it has been shown to be a significant prognostic factor (24).

All 213 women underwent surgical procedures, of whom 48.4% (103/213) had standard surgery which was a total abdominal hysterectomy plus bilateral salpingo-oophorectomy with omentectomy (TAH, BSO, O). A further 13.6 % (29/213) underwent TAH and BSO without omentectomy. Laparoscopy was not performed on any of these patients.

A unilateral oophorectomy was performed in 26.8 % (57/213) and BSO was performed in 8.9% (19/213). Five women had either biopsy only (Bx) or omentectomy only (O). There were 17 deaths in women who underwent TAH+BSO+O, only three were cancer related. There were five deaths recorded in women who underwent BSO only and there were no deaths in women who underwent USO only. For purpose of this analysis, USO and BSO were grouped together and the difference in survival by different surgical interventions were highly statistically significant ($p = 0.0000$) with more radical surgery being associated with the best outcome (Figure 6. Kaplan Meier Curve by Treatment type).

As it is known, persistence or recurrence rates are higher with more conservative surgery, and our data confirms this. A study done by du Bois et al. showed that a

higher stage, incomplete staging, tumour residuals and organ preservation were all independent prognostic factors for disease recurrence (15).

The amount of residual disease post surgery was recorded in 212 women. There was no residual disease (RD) in 86.3% (183/212). In 9 women there was < 2 cm of RD and in 20 women there were > 2cm of RD. Of the 7 women with RD of >2cm that died, all deaths were cancer related. Among women with <2cm of RD, there were 5 deaths; 3 due to cancer. There were 2 cancer related deaths in females with no RD. The $p = 0.00$ which is highly statistically significant (see Figure 7. Kaplan Meier curve of survival by residual disease post surgery). The study done by du Bois et al is one, if not the largest and was also a retrospective – prospective study. Their findings regarding prognostic factors are mentioned above. They also claim their findings on staging quality and residual disease to be provocative (15). Residual tumour has rarely been analysed and where it has, has been shown to be a negative prognostic indicator, as is the case with our data. Hence, again this proves that the more radical the surgery, the better the outcome.

A Ca125 was available in 205 of patients in the database. The tumour marker was increased in 42.4% (87/205) of patients and was normal in 57.6%(118/205).

Of the women with normal Ca125 levels there were 31 deaths of which 22.6%|(7/31) were cancer related deaths. The difference in survival is not statistically significant with $p = 0.94$. A serum CA125 levels have been widely used to differentiate between benign and malignant ovarian neoplasms. Overall sensitivity and specificity range between 50 % - 100% but the positive predictive value remains < 10 % in most studies (24).

The presence of ascites was noted in 3.6% (29/213). Of the women who had ascites, there 11 deaths; 8 of them cancer related. The difference in survival in women with or without ascites is highly significant with $p = 0.0000$.

Of the univariate analysis, in our study, we found the presence of ascites, histological subtype (MBOT), the presence of residual disease; the type of surgery performed and advanced FIGO stage to be statically significant in affecting survival probability. Age and elevated CA125 were not statistically significant.

Using Cox proportional (Hazard Ratios) HRs the only variable that remained statistically significant was the amount of residual disease after surgery (see Table 1. The association between key variables and disease specific survival estimated by Cox's proportional hazards ratios (crude and adjusted) and their 95%CI's among 213 women).

Clear guidelines exist for the management of ovarian cancer, while less clear guidelines exist for the management of the more rare, less lethal and less researched BOT.

At GSH we have at our disposal a database, spanning twenty-four years that documents the clinical staging, treatment and outcomes of women with gynaecological cancer. BOTs may have a very long natural history and can recur up to twenty years after initial diagnosis; therefore long-term evaluation is required to better elucidate the natural history of these tumours. This study was done as an audit, using information available to us to determine whether our management differs from other centres locally and internationally.

We have found however, that our patients with BOT have a good overall survival and were able to predict that having residual disease is associated with poor outcome.

The limitations of this study is that it is a retrospective study, using the existing database only with the information currently recorded and there was no information on ten patients. We could not investigate clinical parameters such as disease symptoms, history of gravidity, history of contraception, accompanying medical illnesses or suggested risk factors like obesity or smoking. There exists the potential to further this current study by adding a prospective cohort study component to it, by active follow up and pathology review. Analysis of prognostic factors and clinical course may also help in the design of future prospective studies, as most of the current studies on BOT have been done retrospectively.

CONCLUSION

Younger women are more likely to be diagnosed with BOT than with ovarian carcinoma, and choosing the best treatment for these patients can be a challenge.

Further investigations are encouraged in order to better clarify the specific roles of the different predictive factors for relapse. BOT represents a wide spectrum of tumours with different biological potential and uncertain malignant potential. There are no precise prognostic or predictive markers to clearly distinguish between tumours of purely benign behaviour and those with risk of malignant transformation therefore oncologic safety must always be balanced against less radical fertility-sparing treatment.

In conclusion, this study stresses the importance of complete staging of BOT in order to prevent peritoneal relapse, some of which may be invasive. Complete staging enables clinicians to discover the presence of invasive implants. Based on the findings of this study, we suggest performing complete comprehensive staging surgery in patients diagnosed with BOT. the more radical the surgery, the better the outcome, particularly if debulking successfully achieves no residual disease.

The prognosis of BOT correlates with tumour related factors. The balance between recurrence risk and organ preservation and fertility – sparing surgery is an important issue deserving further research.

REFERENCES

1. Messalli, E., Grauso, F., Balbi, G., Napolitano, A., Seguino, E., Torella, M. Borderline Ovarian Tumors: features and controversial aspects. *European Journal of Obstetrics and Gynecology and Reproductive Biology*, 2013; 167:86-89.

Journal homepage: www.elsevier.com/locate/ejogrb
2. Fischerova, D., Zikan, M., Dundr, P., Cibul, D. Diagnosis, treatment, and follow-up of Borderline Ovarian Tumours .*The Oncologist*, 2012; 17:1515 - 1533.

www.TheOncologist.com
3. Abascal-Saiz, A., Sotillo-Mallo, L., de Santiago, J., Zapardiel, I. Management of borderline ovarian tumours: a comprehensive review of the literature. *Ecancer*, 2014; 8(403): 1-8

www.ecancer.org
4. Cadron, I., Amant, F., Van Gorp, T., Neven, P., Leunen, K., Vergote, I. The management of borderline tumours of the ovary. *Current opinion in Oncology*, 2006; 18: 488 – 493.
5. Gungor, T., Cetinkaya, N., Yalcin, H., Ozdal, B., Ozgu, E., Baser, E., Uygur, D., Caglar, M., Sirvan, L., Eryaka, S. Retrospective evaluation of borderline ovarian tumors: single centre experience of 183 cases. *Archives of Gynecology and Obstetrics*, July 2014.

6. Romeo, M., Pons, F., Barretina, P., Radua, J. Incomplete staging surgery as a major predictor of relapse of borderline ovarian tumour. *World Journal of Surgical Oncology*, 2013. 11; 13: 1-7.
7. Uzan, C., Muller, E., Kane, A., Rey, A., Gouy, S., Bendiffallah, S., Dullivard, P., Fauvet, R., Darai, E., Morice, P. Prognostic factors for recurrence after conservative treatment in a series of 119 patients with Stage I serous borderline tumours of the ovary. *Annals of Oncology*, January 2014. 25; 1: 166-171.
8. Guidozi, F. Management of Borderline Ovarian Tumours (n.d.)
www.aortic-africa.org/images/.../
9. Seracchioli, R., Venturoli, S., Maria Colombo, F., Govon, F., Missiroli, S., Bagnoli, A. Fertility and tumour recurrence rate after conservative laparoscopic management of young women with early stage borderline ovarian tumours. *Fertility and Sterility*, November 2001; 76(5): 999-1004.
10. Beral, V., Cibula, D., Gompel, A., Mueck, A.O., La Vecchia C., Hannaford, P.C., Skouby, S.O., Zikan, M. and Dusek, L. Hormonal contraception and risk of cancer. *Human Reproduction Update*, 2010; 16(6): 631-650.
11. Riman, T., Dickman P.W., Nilsson, S., et al. Risk factors for epithelial borderline ovarian tumours: results of a Swedish case-control study. *Gynecologic Oncology* 2001; 83: 575-585.
12. Morice, P., Uzan, C., Fauvet, R., Gouy, S., Dullivard, S., Davas, E. Borderline ovarian tumour: pathological diagnostic dilemma and risk factors for invasive or lethal recurrence (Review). *The Lancet oncol*, March 2012; 13:103-105.

13. Link, C., Reed, E., Sarosy, G., Kohn, E. Borderline Ovarian Tumours (Review). *American Journal of Medicine*; August 1996; 101: 217- 225.
14. Avril, S., Hahn, E., Specht, K., Hauptmann, S., Hoss, C., Kiechle, M., Hofler, H., Schmalfeldt, B. Histopathologic features of ovarian borderline tumours are not predictive of clinical outcome. *Gynecologic Oncology* (2012); 127: 516- 524.
15. Du Bois, A., Ewald-Riegler, N., de Gregorio, N., Ruess, A., Mahner, S., Fotopoulou, C., Kommoss, F., Schmalfeldt, B., Hilpert, F., Fehm, T., Burges, A., Meier, W., Hillemans, P., Hanka, L., Hasenburg, A., Strauss, H., Hellriegel, M., Wimberger, P., Keyver – Paik, M., Baumann, K., Canzler, U., Wollschlaeger, K., Forner, D., Pfisterer, J., Schroder, W., Munstedt, K., Richter, B., Kommoss, S., Hauptmann, S. Borderline tumours of the ovary: a cohort study of the Arbeitsgemeinschaft Gynakologische Onkologie (AGO) Study Group. *European Journal of Cancer* (2013); 49: 1905 – 1914.
16. Wu, T., Lee, C., Wu, M., Hsueh, S., Huang, K., Yeh, C., Lai, C. Prognostic factors predicting recurrence in borderline ovarian tumours. *Gynecologic Oncology* (2009); 114: 237 – 241.
17. Gershenson, D.M. Clinical management potential tumours of low malignancy. *Best practice and research on Obstetrics and Gynecology*, 2002; 16(4): 513-527.
18. Morice, P., Camatte, S., Rey, A., Atallah, D., Lhomme, C., Pautier, P., Pomel, C., Cote, J-F, Haie – Meder, C., Dullivard, P., Castaigne, D.

- Prognostic factors for patients with advanced stage serous borderline tumours of the ovary. *Annals of Oncology*, 2003; 14: 592 – 598.
19. Deffieux, X., Morice, P., Camatte, S., et al. Results after laparoscopic management of serous borderline tumour of the ovary with peritoneal implants. *Gynecologic Oncology* 2005; 97:84-89.
 20. Ji, H., Yliskoski, M., Antilla, M., Syrjänen, K., Saarikoski, Management of Stage 1 borderline ovarian tumours. *International journal of obstetrics and gynecology*, 1996; 54: 137-144.
 21. Uzan, C., Berretta, R., Rolla, M., Gouy, S., Fauvet, R., Darai, E., Dullivard, P., Morice, P. Management and prognosis of endometrioid borderline tumours of the ovary. *Surgical Oncology*, 2012; 21: 178 – 184.
 22. Webb, P.M., Purdie, D.M., Grover, S., Jordan, S., Dick, M.L., Greene, A.C. Symptoms and diagnosis of borderline, early and advanced epithelial ovarian cancer. *Gynecologic oncology*, 2004; 92:232-239.
 23. Jacobs, I., Oram, D., Fairbanks, J., et al. A risk of Malignancy Index incorporating CA125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. *British journal of obstetrics and gynaecology*, 1990; 97: 922-929.
 24. Ayhan, A., Guven, E., Guven, S., Kukukali. Recurrence and prognostic factors in borderline ovarian tumours. *Gynecologic Oncology*, 2005; 98: 439 – 445.
 25. Menczer, J., Chetrit, A., Sadetzki, S. The effect of hysterectomy on survival of patients with borderline ovarian tumours. *Gynecologic oncology*, 2012; 125: 372-375.
 26. Morice, P., Camatte, S., El Hassan, J., Pautier, P., Dullivard, P., Castaigne, D. Clinical outcomes and fertility after conservative treatment of ovarian borderline tumours. *Fertility and Sterility*, 2001; 75 (1): 92-96.

27. Lin, P.S., Gershenson, D.M., Bevers, M.W. The current status of surgical staging of ovarian serous borderline tumours. *Cancer* 1999; 85: 905 – 911.
28. Fauvet, R., Boccaro J., Dufournet, C. Laparoscopic management of borderline ovarian tumours: Results of a French Multicentre study. *Annals of Oncology* 2005; 16: 403 – 410.
29. Romagnolo, C., Gadducci, A., Sartori, E., et al. Management of Borderline Ovarian tumours: Results of an Italian multicenter study. *Gynecologic Oncology* 2006; 101:255-260.
30. Prat, J. Classification for Cancer of the ovary, fallopian tube and peritoneum. *International Journal of Gynecology and Obstetrics* 2014; 124: 1-5.
31. Health Act No. 61 2003. South Africa.
<http://www.info.gov.za/gazette/acts/2003/a61-03.pdf>
32. WMA Declaration of Helsinki 2013
<http://www.wma.net/e/policy/b3.html>
33. Morice, P., Camatte, S., Wicart-Poque, F., Atallah, D., Rouzier, R., Pautier, P., Pomel, C., Lhommé, C., Dullivard, P., Castaigne, D. Results of conservative management of epithelial malignant and borderline ovarian tumours. *Human Reproduction Update* 2003; 9(2): 185-192.

APPENDICES

Appendix A

The data capture sheet was done using Microsoft Excel and is separately attached, as it could not be formatted into this document. However the various categories included in the data capture sheet, as well as the drop down list of options can be found below.

The different categories are:

- **AGE**, options are $< 30 = 1$
 $30 - 39 = 2$
 $40 - 49 = 3$
 $50 + = 4$
- **RTN** = Unique registration number on the gynae-oncology database
- **ENTRY** = DATE OF SURGERY
- **CS** = CURRENT STATUS, OPTIONS ARE: **A-NED** = Alive, no evidence of disease; **Lost** = cannot track patient; **D-oth** = dead from other cause, not cancer related; **A- dis** = alive with disease
- **LFU** = last follow up date
- **Resp** = response to treatment. Different options are:
CR = complete response
PR = partial response
SD = stable disease
PD = progressive disease

- **NE** = non evaluable
- **CRDATE** = date of complete response
- **RELDATE** – date when relapse noted
- **RELSITE** - site of relapse: distal, local or regional.
- **RXREL** - treatment related, type of treatment

Namely1. Surgery

2. External beam radiation

3. Brachy therapy

4. Chemotherapy

5. Hormonal treatment

6. TLC

- **DATE DEAD**= date of death
- **RXSTART**- usually date of surgery
- **RXEND**- usually the date of surgery unless other modalities were used
- **RXSEQ**= treatment sequence. Type of therapy in code (see no 10 above)
- **SURG** – type of surgery performed

1. Uni OOPH (unilateral oophorectomy)

2. TAH+BSO+O (total abdominal hysterectomy, bilateral salpingo oophorectomy and omentectomy)

3. TAH+OOPH (total abdominal hysterectomy and oophorectomy)

4. Bil OOPH (bilateral oophorectomy)

5. Biopsy only (biopsy only)

5.

- **FAMHIST** =family history. Options are YES (Y) OR NO (N)
- **STAGE** – STAGE OF OVARIAN CANCER USING THE **OLD FIGO CLASSIFICATION**

STAGE I

Ia

I b

Ic

STAGE 2

IIa

IIb

IIc

STAGE 3

IIIa

IIIb

IIIc

STAGE 4

IV a

IV b

- **Ruptured**= cyst ruptured, Yes (y) or no (n)
- **CYTOL**= cytology positive, Yes (Y) OR NO (N).
- **ASCITES** = Ascites present, yes (Y) or No (N).
- **MARKER** = Tumour marker

- Options are: NS = not specified,

CA125

OTHER

Appendix B



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



Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492 • Facsimile [021] 406 6411
Email: Sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

23 September 2014

HREC/REF: 669/2014

Prof L Denny
Obstetrics & Gynaecology
H-floor
OMB

Dear Prof Denny

Project Title: AN AUDIT OF THE MANAGEMENT OF WOMEN WITH BORDERLINE OVARIAN TUMOUR TREATED AT GROOTE SCHUUR BETWEEN 1984-2008 (Mmed candidate- Dr A Hendricks)

Thank you for your response letter dated 19 September 2014, addressing the issues raised by the Human Research Ethics Committee (HREC).

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 September 2015.

Please submit a progress form, using the standardised Annual Report Form, if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

We acknowledge that the following student:-Dr Aneeqah Hendricks is also involved in this project.

Please note that the on-going ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC REF in all your correspondence.

Yours sincerely

Signed by candidate

PP

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938

Hrec/ref:669/2014

Appendix c



GROOTE SCHUUR HOSPITAL

Enquiries: Dr Bernadette Eick
E-mail : Bernadette.Schmitz@westerncape.gov.za

Professor L. Denny
Obstetrics & Gynaecology
H-Floor – Old Main Building

E-mail: aneegahhendricks@gmail.com / Lynette.Denny@uct.ac.za

Dear Professor Denny

RESEARCH PROJECT: An Audit of the Management of Women with Borderline Ovarian Tumour Treated at Groote Schuur Hospital Between 1984-2008 (Mmed Candidate – Dr A. Hendricks)

Your recent letter to the hospital refers.

You are hereby granted permission to proceed with your research.

Please note the following:

- a) Your research may not interfere with normal patient care
- b) Hospital staff may not be asked to assist with the research.
- c) No hospital consumables and stationary may be used.
- d) **No patient folders may be removed from the premises or be inaccessible.**
- e) Please introduce yourself to the person in charge of an area before commencing.
- f) Please discuss the study with the Head of Department before commencing.
- g) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
- h) Confidentiality must be maintained at all times.

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

Yours sincerely

Signed by candidate

DR BERNADETTE EICK
CHIEF EXECUTIVE OFFICER
Date: 8th October 2014

C.C. Mr L. Naidoo, Professor L. Denny, Dr L. van Wijk and Dr H. Aziz

G46 Management Suite, Old Main Building,
Observatory 7925

Tel: +27 21 404 6288 fax: +27 21 404 6125

Private Bag X,
Observatory, 7935

www.capegateway.gov.za

