# Outcomes of women treated with chemotherapy for Ovarian Cancer at CMJAH

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# Declaration

I Justin Boitumelo I. Molebatsi declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Medicine at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree at this or any other university.

Signed _____

Date _____

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# Abstract

## Background

Ovarian cancer remains an important cause of mortality in women worldwide. It is the leading cause of death from gynaecological cancers. Worldwide, it is diagnosed in more than 200 000 women annually and is responsible for over 125 000 deaths. In Southern Africa, it is estimated to contribute 3.3% of the total cancer mortality figures in women. The aim of this study was to review the 2 year recurrence free survival for women treated with chemotherapy for ovarian cancer in a South African tertiary care hospital.

## Methods

This was a retrospective cohort of women with primary ovarian cancer treated with chemotherapy at the Charlotte Maxeke Johannesburg academic hospital between 2010 and 2014. Data were extracted from patient records using a standardized data extraction tool.

Data was analysed using the STATA Software (StataCorp LP, USA). Precision was managed by using 95% confidence intervals.

## Results

This study showed a 33.78% overall recurrence-free survival at 2 years. The association between surgical stage at presentation with recurrence status at 2 years showed no statistical significance (Pearson chi2(18) = 26.6848 P = 0.085). The difference in outcomes between patients treated with adjuvant chemotherapy and neo-adjuvant chemotherapy did not reach statistical significance (Pr = 0.157)

## Conclusion

Despite extensive surgery and platinum based chemotherapy, this study demonstrates that prognosis for patients with advanced ovarian cancer remains poor with only a third of patients surviving recurrence-free at 2 years follow up.

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## Abbreviations

ASA: American Society of Anaesthesiologists

BRCA: Breast Cancer gene

CASH Study: Cancer and Steroid Hormone Study

CA 125: Cancer antigen 125

CMJAH: Charlotte Maxeke Johannesburg Academic Hospital

CT: Computerized Tomography

ECOG: Eastern Cooperative Oncology Group

EORTC: European Organization for Research and Treatment of Cancer

FIGO: The International Federation of Gynaecologists and Obstetricians

FSH: Follicle Stimulating Hormone

GOG: Gynecology Oncology Group

HNPCC: Hereditary Non-Polyposis Colorectal Cancer

HREC: Human Ethics Research Committee

LH: Luteinizing Hormone

U.S: United States

USA: United States of America

# Chapter 1: Protocol and Extended Literature review.

## Introduction

Ovarian cancer still remains a significant cause of mortality to women worldwide.[1] It is recorded as the leading cause of death from gynaecologic cancers.[2] Worldwide, it is diagnosed in more than 200 000 women yearly and is responsible for over 125 000 deaths.[1] Every woman has a lifetime risk of developing ovarian cancer of 1 in 75, with a 1 in 100 chance of dying from the disease.[3] It predominantly affects postmenopausal women in their sixth decade of life[4], with fewer than 1% of epithelial ovarian cancers occurring in women younger than 20 years of age.[3] Two thirds of those cancers diagnosed in women in their twenties are germ-cell tumors.[3] If the cancer is diagnosed early, while the disease is only confined to the ovaries, it is highly curable, with an expected 80-95% 5 year survival.[4] However, early diagnosis is difficult due to its presentation with vague and non-specific symptomatology.[2] Nearly 75% of ovarian cancer patients present with already advanced stage disease and the overall survival rate in this group of patients ranges between 20 – 30%.[4]

## Pathophysiology

The pathogenesis of ovarian cancer is not well understood; however, some hypotheses have been described in attempt to explain the mechanisms of its origin. The first is the "Incessant Ovulation Hypothesis" which describes repeated trauma and damage to the ovarian epithelium during each ovulatory cycle. This increases the rate of cellular divisions associated with the repair of the epithelium and results in increased potential for genetic mutation and therefore ovarian neoplasm.[5,6]

The second theory is the "Gonadotrophin Hypothesis" which attributes the risk of ovarian cancer to the impact of gonadotrophins LH and FSH.[6]

## Risk factors

A family history of ovarian cancer remains the most important risk factor for the disease.[3] The risk is associated with the number of first- and second-degree (maternal or paternal) relatives previously diagnosed with either ovarian or breast cancer and their age at diagnosis.[3,6] Mutations on both BRCA1 and BRCA2 genes are both associated with a risk or predisposition for breast and ovarian cancer. A majority of the hereditary ovarian cancers appear to be associated with mutations in these genes.[3] About two thirds of those BRCA gene mutation associated ovarian cancers are linked to a BRCA 1 mutation on chromosome 17q and the remaining third are associated with a BRCA 2 gene mutation on chromosome 13q.[3,6] The average lifetime risk for ovarian cancer is estimated at about 30% in carriers of the BRCA1 mutation, and this was reported in three U.S based population studies.

Hereditary nonpolyposis colorectal cancer syndrome (HNPCC / Lynch syndrome) associates colon cancer with an increased risk of certain gynaecology malignancies such as ovarian and endometrial cancers.[3] Ovarian cancer is noted in about 10% of patients with HNPCC.[3] Certain reproductive factors have also been associated with an increased risk for ovarian cancer development. Late menopause may be an associated risk, with an increased ovarian cancer risk also consistently reported among nulliparous women.[3] The use of ovulation inducing drugs has also been described in a series of publications to raise concern about risk of ovarian cancer.[3] Prolonged treatment with fertility drugs has been associated with an increased risk for the development of borderline and invasive epithelial ovarian cancers.[3]

## Protective factors

Increased parity has been found in numerous epidemiological studies to be associated with a protective benefit against ovarian cancer.[3] Multiparous women have a risk reduction of up to 40 – 60% when compared to nulliparous women.[3] An estimated 16-22% risk reduction has been associated with each delivery, however pregnancies that resulted in spontaneous or induced abortions conferred only minimal or no significant change in ovarian cancer risk.[3,6]

Epidemiological studies over the past several decades have consistently reported a protective association between the use of oral contraceptives and risk reduction for ovarian cancer.[3,6] Continuous use of oral contraceptives for four, eight and twelve years is associated with a reduction for ovarian cancer risk of 40%, 53% and 60% respectively.[3] The Cancer and

Steroid Hormone study (CASH) suggested that, ten year use of the oral contraceptive pill by women with a known family history, reduced the risk of developing ovarian cancer to below that of the general population. Even high risk patients, with a known BRCA1 and BRCA2 mutation carrier status, have up to a 60% risk reduction of ovarian cancer with continuous use of the oral contraceptive pill for six years or more.[3]

**Screening for ovarian cancer**

Screening for this disease is at present not possible owing to its vague presentation, however, it is noted that up to 89% of patients diagnosed with early stage disease (stage 1/2) had some symptoms,[2] This has prompted ongoing research to define ovarian cancer symptom indices that can be used to encourage early presentation and diagnosis by educating women and healthcare professionals.[2]

**Staging and classification of ovarian cancer**

Ovarian cancer is staged surgically.[7] Findings at the primary surgery, prior to formal cytoreduction, determine the initial stage which can be modified by histopathology and radiological imaging.[7]All suspicious sites should be biopsied and ascietic fluid collected for cytological evaluation.[7]

The table below represents the FIGO staging for ovarian cancer

Table 1: FIGO Staging of ovarian cancer and 5-year survival per stage

| Stage | Description | 5-year survival |
|---|---|---|
| I | Growth limited to the ovaries | |
| Ia | Growth limited to one ovary, no ascites present containing malignant cells, no tumour on the external surfaces, capsule intact | 86.9% |
| Ib | Growth limited to both ovaries, no ascites present containing malignant cells. No tumor on external surfaces, capsule intact. | 71.3% |
| Ic | Tumor either stage 1a or 1b, but with tumor on surface of one or both ovaries, or with capsule ruptured, or with ascites present containing malignant cells, or with positive peritoneal washings | 79.3% |
| 2 | Growth involves one or both ovaries with pelvic extension | |
| 2a | Extension and/or metastases to the uterus and/or tubes | 66.6% |
| 2b | Extension to pelvic tissues | 55.1% |
| 2c | Tumor either stage 2a or 2b, but with tumor on surface of one or both ovaries, or with capsule(s) ruptured, or with ascites present containing malignant cells, or with positive peritoneal washings | 57% |
| 3 | Tumor involving one or both ovaries with histologically confirmed peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastasis equals stage 3. Tumor limited to true pelvis but with histologically proven malignant extension to small bowel or omentum | |
| 3a | Tumor grossly limited to true pelvis, with negative nodes, but with histologically proven microscopic seeding of abdominal peritoneal surfaces, or histologically proven extension to small bowel or mesentery | 41.1% |
| 3b | Tumor of one or both ovaries with histologically confirmed implants, peritoneal metastasis of abdominal peritoneal surfaces none exceeding 2cm in diameter, nodes are negative | 24.9% |

| | | |
|---|---|---|
| 3c | Peritoneal metastasis beyond the pelvis >2cm in diameter and/or positive retroperitoneal or inguinal nodes | 23.4% |
| 4 | Growth involving one or both ovaries with distant metastases. If pleural effusion is present, there must be positive cytology to allot the case to stage4. Parenchymal liver metastasis equals stage 4. | 11.1% |

## Treatment of ovarian cancer.

### Chemotherapy

The management of ovarian cancer involves extensive surgery and chemotherapy.[2]

Patients with early stage cancer (FIGO stage 1a/1b) can be cured by surgery alone, without the addition of adjuvant chemotherapy and have an expected 5 year survival rate of about 90%.[2,4] The standard of care for women with advanced ovarian cancer involves a combination of extensive surgery with a platinum/taxane chemotherapy regimen.[2,4,8] The Society of Gynecologic Oncology and American Society of Clinical Oncology recommend that all women with suspected advanced epithelial ovarian cancer should be evaluated first by a gynaecologic oncologist, prior to onset of therapy to determine whether they would be suitable for primary cytoreductive surgery.[9]

The current use of chemotherapy as an adjunct to extensive surgery in the management of advanced ovarian cancer follows decades of clinical trials, which have seen the evolution from single agent chemotherapy to combination chemotherapy regimens.[4] Single agent alkylating agents where some of the first drugs used in ovarian cancer treatment.[4] In 1979, clinical trials by Rossof et al demonstrated that Cisplatin was an active chemotherapeutic agent in advanced or recurrent ovarian cancer with a response rate ranging 13-30%.[10] The majority of patients are diagnosed with serous carcinomas, which have shown a high response rate to platinum-based chemotherapy.[2] In the late 1980s and early 1990, the standard combination chemotherapy was Cisplatin and cyclophosphamide.[4] This followed

research that showed that the time to progression and the duration of survival were markedly improved with combination chemotherapy compared to single agents.[4] A meta-analyses of multiple randomized studies by Aarbo et al in 1991 introduced carboplatin as a substitute to Cisplatin as it demonstrated similar efficacy but with a better side effect profile.[11] The introduction of Paclitaxel in the 1990s further changed the standard of care in ovarian cancer.[4] Two randomized clinical trials demonstrated an improved outcome for Paclitaxel and Cisplatin compared to Cisplatin and cyclophosphamide. In 2003, similar results were duplicated by du Bois et al. supporting the combination of a platinum based agent with paclitaxel as the standard of care for patients with advanced ovarian cancer.[4]

**Role of surgery in ovarian cancer**

The standard of care for advanced ovarian cancer consists of a combination of extensive debulking surgery with a platinum-based chemotherapy regimen.[2,12] Even in advanced and widely disseminated disease, surgery remains crucial in attaining optimum outcome.[2] Certain factors remain important in the prognosis of ovarian cancer patients undergoing surgery and they include, the amount of residual disease remaining following the initial surgery, and that the surgery should be performed by an expert in gynaecologic cancer surgery.[13,14] A study by the European Organisation for Research and Treatment of Cancer (EORTC) emphasized the important role of surgery in the treatment of ovarian cancer.[2] In this study, patients who had had suboptimal primary cytoreductive surgery during chemo were randomised into 2 groups. The first group received secondary debulking surgery versus the second group which received no further surgery. An improvement in median survival was clearly demonstrated in the group that underwent secondary surgery.[2]

The amount of residual disease following the primary surgery is an independent risk factor to overall survival.[2,8] It is not always possible to achieve maximal debulking at the primary surgery, this secondary to advanced stage disease.[2] Other factors such as CA-125 >500, age older than 60 years and a American Society of Anaestheologists (ASA) physical status score of 3 / 4 were also associated with suboptimal primary debulking surgery.[8] The EORTC-NCIC conducted a trial in which they compared primary cytoreductive surgery with adjuvant chemotherapy and neoadjuvant-chemotherapy with interval cytoreduction.[2] No statistically significant difference in overall survival between the two treatment options was demonstrated.[2,8] The choice of treatment between the two still remains controversial, with a

preference for primary chemotherapy in patients with advanced stage disease 3C/4 to provide an environment for achieving optimal debulking at time of surgery.[2,8]

Interval debulking surgery was also associated with a lower post-operative mortality[2] and complications such as haemorrhage, post-operative infections and fistulae formation.[2,8]

Another subject of great controversy is the comparison of intra-peritoneal chemotherapy with intravenous chemotherapy.[2,4] The rationale to support the use of intra-peritoneal chemotherapy arises from the fact that the majority of clinical recurrences are intra-peritoneal.[2] The delivery of chemotherapy into the peritoneal cavity would therefore increase the intensity of the chemotherapy on any residual tumor, while minimizing the systemic side effects of these cytotoxic drugs.[2,4]

There is concern that locally delivered chemotherapy (i.e. intra-peritoneal) has poor tissue penetrance and therefore should only be used in patients with minimal residual tumor following the cytoreductive surgery.[2,4]

Three studies conducted in 1996, 2001 (GOG 114 [2]) and 2006 (GOG 172[2]) showed an improvement in survival outcome in patients treated with intra-peritoneal versus intravenous chemotherapy.[2,4] Despite this, the use of intra-peritoneal (IP) chemotherapy is still uncommon, perhaps owing to the lack of familiarity with IP chemotherapy, and the need for surgically placed catheters, which is not without its complications.[4] Complications, may include, infection, catheter leakage or blockage.[4]

The use of molecular-targeted agents has been explored in the treatment of ovarian cancer. However, more research is still needed in that field.[2,4]

**Outcomes and Survival**

Uzan et al looked at recurrence of lymph nodes on patients with epithelial ovarian cancer and found that the median overall survival from the date of the first surgical procedure was 114 (range, 43–172) months.[9] The 5-year overall survival from treatment of recurrent disease was 71% (CI, 41–90). Median survival without a second relapse was 44 (range, 8–158) months.[9]

Their overall median duration of follow-up after the diagnosis of the nodal recurrence(s) was 50 (range, 13– 158) months.[9] The new recurrences were located on the peritoneum (2),

pleural cavity (1), spleen (1), and lymph nodes in 4 (iliac nodes in 2 patients, para-aortic nodes in 1, and lymph node metastasis to the splenic hilus in 1).[9]

**Progression free survival**

The Australian Ovarian Cancer Study Group found that in comparison with advanced serous ovarian cancer, primary peritoneal cancer patients were older (mean age 65.5 vs. 60.2 years, $p < 0.001$), more often treated with neoadjuvant chemotherapy (38.4% vs. 11.4%, $p < 0.001$).[15]

The women with primary peritoneal cancer had significantly shorter progression-free (11.6 vs. 13.6 months, $p = 0.007$) and overall survival (31.7 vs. 39.8 months, $p = 0.012$).[15] The presence of residual disease and use of neoadjuvant chemotherapy were both independently associated with increased risk of progression and death in multivariate analysis.[15]

### Justification of the Study

Ovarian cancer contributes significantly to morbidity and mortality of women worldwide and as such, emphasis should be made on the management protocol of this malignancy.

This study aimed to explore the standard treatment protocols for ovarian cancer (both operable and non-operable stages of disease) at Charlotte Maxeke Johannesburg academic hospital compared to international standards and furthermore to determine survival outcome in the patient population treated at this center.

### Primary Objectives

1. To describe the 2 (two) year outcome of patients who received chemotherapy for ovarian cancer at Charlotte Maxeke academic hospital

### Secondary Objectives

1. To describe the treatment regimen employed for ovarian cancer at Charlotte Maxeke Johannesburg Academic Hospital
2. To compare outcomes of primary cytoreduction followed by adjuvant chemotherapy with neo-adjuvant chemotherapy and interval cytoreduction

## Methods

### Study Setting

The study was conducted at the Charlotte Maxeke Johannesburg Academic hospital medical oncology unit. Most of the ovarian cancer patients who presented to this unit were referred from the referral hospitals. A few patients were referred directly from the gynaecological oncology department within the hospital.

Charlotte Maxeke Johannesburg Academic hospital is a tertiary centre, serving as a referral hospital for the surrounding academic hospitals such as Chris Hani Baragwanath Academic Hospital, Rahima Moosa Mother and Child Hospital and Helen Joseph Hospital, and regional as well as district hospitals in the surrounding greater Johannesburg region. The Charlotte Maxeke Johannesburg Academic hospital medical oncology service is offered at Area 395. Patients with ovarian cancer treated with chemotherapy are followed up 3 months after their last dose of chemotherapy, then at 6 months, then annually thereafter.

**Inclusion Criteria**

- Women with primary ovarian cancer treated with chemotherapy at Charlotte Maxeke Johannesburg Academic Hospital between 2010 and 2014.
- Women who continued their follow up at the medical oncology unit and/or the gynaecological oncology unit.

**Exclusion Criteria**

- Women with no available documented post chemotherapy follow up.
- Women who did not receive chemotherapeutic agents.
- Any woman with secondary ovarian cancer.

**Study Sample**

The study sample was a period based retrospective sample, with no sampling strategy. All women who received chemotherapy for the treatment of ovarian cancer were included, as described above. The sample comprised of all patients with ovarian cancer over a 4 year period.

**Study Design**

The study was a retrospective cohort, using medical records of patients who started treatment for ovarian cancer at Charlotte Maxeke Johannesburg Academic Hospital between the years of 2010 to 2014.

## Data Collection

Data was collected from records at the medical oncology unit and files retrieved from the departmental filing rooms. Permission to collect and interpret the data was obtained from the clinical head of the medical oncology unit. All the demographic data, disease characteristics including stage and ECOG functional status, presenting symptoms, risk and protective factors for ovarian cancer, management of ovarian cancer and disease recurrence were all obtained from the files. All missing information was recorded as unknown and patients or attending doctors were not further interviewed to augment the available data. The type of chemotherapy and side effects experienced were recorded as appearing on the patient's files. The Ca 125 for monitoring the patients was checked at 3 months, 6 months and 1-year interval as either available on the file or the NHLS Labtrak online system. Data on histology, cytology and biochemical results were retrieved from the files and NHLS online database.

Time to recurrence was calculated as the period from completion of treatment to period where the diseases recurrence was diagnosed at follow up. This was recorded in months. In the medical oncology unit, the recurrence was confirmed with both the rise in Ca125 and radiological (CT scan) evidence of either ovarian masses, ascites/effusion or metastasis.

All patients at CMJAH were required to have a CT scan done either before receiving neo-adjuvant chemotherapy of adjuvant chemotherapy post-surgery. The definition of optimum cytoreduction was based on either written report from the surgeon of estimated size of malignant tumor left or as per report of the post-surgery CT scan done in preparations for chemotherapy.

Recurrence-free survival was defined as no evidence (serological or radiological) of disease at follow up, after completion of treatment.

## Data Analysis

The study employed quantitative techniques. Descriptive data analysis was used for most of the data collected, using means ± standard deviations (for normally distributed continuous data, medians and ranges (for non-normally distributed continuous data), and proportions with percentages (for categorical data). Precision was managed by using 95% confidence intervals. No specific hypotheses were set, but where necessary, hypothesis testing employed tests such

as Chi-squared, Fisher's exact, Student's t and Mann-Whitney to explore associations between various predictors and outcomes. Data was analysed using the STATA Software (StataCorp LP, USA).

## Ethics

Permission to perform the study was obtained from the Charlotte Maxeke hospital Chief Executive Officer and the head of Medical Oncology unit at the hospital. Approval from the University of Witwatersrand Human Research Ethics Committee was sought before the study was conducted (HREC approval number M161172).

## Funding

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## Chapter 2: Submissible Article

Outcomes of women treated with chemotherapy for Ovarian Cancer at CMJAH

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# Abstract

## Background

Ovarian cancer remains an important cause of mortality in women worldwide. It is the leading cause of death from gynaecological cancers. Worldwide, it is diagnosed in more than 200 000 women annually and is responsible for over 125 000 deaths. In southern Africa, it is estimated to contribute 3.3% to the total cancer mortality figures in women. The aim of this study was to review the 2 year recurrence free survival for women treated with chemotherapy for ovarian cancer in a South African tertiary care hospital.

## Methods

This was a retrospective cohort of women with primary ovarian cancer treated with chemotherapy at the Charlotte Maxeke Johannesburg academic Hospital between 2010 and 2014. Data were extracted from patient records using a standardized data extraction tool.

Data was analysed using the STATA Software (StataCorp LP, USA). Precision was managed by using 95% confidence intervals.

## Results

This study showed a 33.78% overall recurrence-free survival at 2 years. The association between surgical stage at presentation with recurrence status at 2 years showed no statistical significance (Pearson chi2(18) = 26.6848 P = 0.085). The difference between patients treated with adjuvant chemotherapy and those treated with neo-adjuvant chemotherapy did not reach statistical significance (P = 0.157)

## Conclusion

Despite extensive surgery and platinum based chemotherapy, this study demonstrates that prognosis for patients with advanced ovarian cancer remains poor with only a third of patients surviving recurrence-free at a 2 years follow up.

## Introduction

Ovarian cancer remains an important cause of mortality in women worldwide.[1] It is recorded as the leading cause of death from gynaecological cancers.[2] Worldwide, it is diagnosed in more than 200 000 women annually and is responsible for over 125 000 deaths[1] It predominantly affects postmenopausal women in the sixth decade of life.[4] If diagnosed early, while the disease is confined to the ovaries, it is highly curable, with an expected 80-95% 5 year survival.[4] However, early diagnosis is difficult due to its presentation with vague and non-specific symptoms[2]. Nearly 75% of ovarian cancer patients present with advanced stage disease and the overall survival rate in this group of patients ranges from 20 - 30%.[4] The standard of care for women with advanced ovarian cancer involves a combination of extensive surgery with a platinum/taxane chemotherapy regimen.[2,4,8] Even in advanced and widely disseminated disease, surgery remains crucial in attaining optimum outcome[2]

Owing to its vague presentation, there are presently no definite screening tools for ovarian cancer however, it is noted that up to 89% of patients presenting with early stage disease present with some symptomatology.[2] This has prompted ongoing research to define ovarian cancer symptom indices that can be used for early patient identification.[2]

It is estimated that in southern Africa, ovarian cancer contributes 3.3% to the total cancer mortality in women. The aim of this study was to review the 2 year recurrence free survival for women treated with chemotherapy for ovarian cancer in a South African tertiary care hospital.

## Methods

The study was conducted at the Charlotte Maxeke Johannesburg Academic Hospital Medical Oncology Unit. Charlotte Maxeke Johannesburg Academic hospital is a tertiary centre, and has the only public sector medical oncology unit in the Johannesburg metropolitan area. The majority of ovarian cancer patients treated at this centre are patients referred from surrounding regional and academic hospitals and some are patients referred from the gynaecological oncology unit within the hospital. Charlotte Maxeke is the only hospital in the southern part of Gauteng that offers both medical and radiation oncology services. The hospital's Radiation Oncology Unit is the largest in the country and treats about 3 500 patients a year. It is also the main teaching hospital for the University of the Witwatersrand. Patients in the medical oncology unit with ovarian cancer treated with chemotherapy are

followed up 3 months after their last dose of chemotherapy, then at 6 months, then annually lifelong thereafter.

This was a retrospective audit of women with ovarian cancer who started treatment at the unit between 2010 and 2014. All women with primary ovarian cancer who received chemotherapy were included. Patients also needed to have attended their follow up at the unit for inclusion. Patients who were excluded were those who had no available documented post chemotherapy follow up, those who did not receive chemotherapy and those with a secondary ovarian cancer.

Data were collected from records at the medical oncology unit and files retrieved from the medical records department. Data on histology, cytology and biochemical results was retrieved from the files and the National Health Laboratory Services database.

Primary surgery which was often performed at the referring institutions included total abdominal hysterectomy and bilateral salpingo-ophorectomy and in some patients, omental biopsy and peritoneal washings.

Data were extracted from patient records using a standardized data extraction tool. Permission to collect and interpret data was obtained from the clinical head of the medical oncology unit. Further permission to perform the study was obtained from the Charlotte Maxeke Hospital chief executive officer. Ethical approval was also obtained from the University of the Witwatersrand Human Research Ethics Committee (M161172).

All data collected were analyzed using the Stata software. Chi-squared independence test was used for hypothesis testing between all nominal categorical data. Precision was managed by using 95% confidence intervals

## Results

A total of 104 women were evaluated and treated for ovarian cancer at the CMJAH Medical Oncology centre between January 2010 and December 2014. Records for 28 (27.4%) of the women could not be found and were excluded from the study. 76 women were included in the analysis. Two files were excluded because the women had secondary ovarian disease, with the primary malignancy elsewhere. Seventy-four women were included in the final analysis. Fifty-nine(79.7%) of those who were included for analysis received either neo-

adjuvant or adjuvant chemotherapy and 15(19.7%) were not treated with chemotherapy. (Figure 2.1)

The 74 women were aged between 20 years and 83 years with a mean age of 55.8 years. There were 23(30.2%) who were 50 years of age or younger and 51(69.8%) who were older than 50 years of age. The women were mainly South African 72(97%) with 2(2.6%) from Lesotho. The racial distribution of the study population was 51 (68.9%) black, 16 (21%) white, 6 (7.89%) Indian and 1(1.3%) coloured.

At two years, there were 25 (33.78%) women who had no evidence of disease persistence (recurrence-free) and 13(17.57%) who had positive evidence of recurrence. There were 36(48.65%) whose recurrence status was unknown due to loss to follow up.

Furthermore, at two years 3(13.04%) women who had had evidence of recurrence at 1 year had no recurrence at the 2-year assessment. They had a second cycle of chemotherapy when there was recurrence at 1 year. Twelve women (52.17%) who had recurrence at one year still had evidence of disease persistence at two years. There were 8 women with initial recurrence at one year who were lost to follow-up and their recurrence status at two years was unknown.

Table 2.1. Disease recurrence at 2 years compared to the cycle of chemotherapy received.

| Recurrence at 2 years | Chemotherapy Cycle | | | Total |
|---|---|---|---|---|
| | No Chemo | Neo-adjuvant | Adjuvant | |
| NO | 6<br>40.00 | 4<br>16.67 | 15<br>42.86 | 25<br>33.78 |
| YES | 1<br>6.67 | 7<br>29.17 | 5<br>14.29 | 13<br>17.57 |
| Unknown | 8<br>53.33 | 13<br>54.17 | 15<br>42.86 | 36<br>48.65 |
| TOTAL | 15<br>100.00 | 24<br>100.00 | 35<br>100.00 | 74<br>100.00 |

Pearson chi2(4) = 6.6323 P = 0.157

There were 17(32.69%) women whose disease stage was pre-determined, who were recurrence free at 2 years. Of those who were recurrence-free at the 2 years review, 3(17.6%) were stage 1a, 5(29.4%) were stage 1b, 4(23.5%) stage 1c. There were no women with surgical stage 2a and 2c disease and (5.88%) 1 woman had stage 2b (refer tables 2.2 and 2.3).

There were 11 (21.15%) women with confirmed recurrence at 2 years. No women with stage 1 disease who had recurrence and only 1(9%) with surgical stages 2a and 2b (Refer table 2). Four (36.4%) women with recurrence at 2 years had stage 3c disease and there were 5(45.5%) with stage 4 cancer. The surgical stage for 24(46.15%) women was unknown (Refer tables 2.2 and 2.3).

Table 2.2. Disease recurrence at 2 years compared to surgical stage at presentation.

| Recurrence at 2 years | Surgical stage | | | | | | Total |
|---|---|---|---|---|---|---|---|
| | 1a | 1b | 1c | 2a | 2b | | |
| No | 3<br>60.00 | 5<br>100.00 | 4<br>40.00 | 0<br>0.00 | 1<br>33.33 | | 17<br>32.69 |
| Yes | 0<br>0.00 | 0<br>0.00 | 0<br>0.00 | 1<br>50.00 | 1<br>33.33 | | 11<br>21.15 |
| Unknown | 2<br>40.00 | 0<br>0.00 | 6<br>60.00 | 1<br>50.00 | 1<br>33.33 | | 24<br>46.15 |
| TOTAL | 5<br>100.00 | 5<br>100.00 | 10<br>100.00 | 2<br>100.00 | 3<br>100.00 | | 52<br>100.00 |

Table 2.3. Disease recurrence at 2 years compared to surgical stage at presentation.

| Recurrence at 2 years | Surgical stage | | | | | Total |
|---|---|---|---|---|---|---|
| | 2c | 3a | 3b | 3c | 4 | |
| No | 0<br>0.00 | 1<br>50.00 | 0<br>0.00 | 2<br>20.00 | 1<br>7.69 | 17<br>32.69 |
| Yes | 0<br>0.00 | 0<br>0.00 | 0<br>0.00 | 4<br>40.00 | 5<br>38.46 | 11<br>21.15 |
| Unknown | 1<br>100.00 | 1<br>50.00 | 1<br>100.00 | 4<br>40.00 | 7<br>53.85 | 24<br>46.15 |
| TOTAL | 1<br>100.00 | 2<br>100.00 | 1<br>100.00 | 10<br>100.00 | 13<br>100.00 | 52<br>100.00 |

Pearson chi2(18) = 26.6848 P = 0.085

Twenty-six (34.2%) women had early stage disease (i.e. Stage 1 and 2 disease) and an equal number (34.2%) had advanced disease (stage 3 and 4 disease) at time of presentation.

Table 2.4 (Surgical stage at presentation)

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Stages | 1A | 1B | 1C | 2A | 2B | 2C | 3A | 3B | 3C | 4 |
| Number | 5 | 5 | 10 | 2 | 3 | 1 | 2 | 1 | 10 | 13 |
| Percentage | 6.5% | 6.5% | 13.1% | 2.6% | 3.9% | 1.3% | 2.6% | 1.3% | 13.1% | 17.1% |
| Unknown | | 22 (29.7%) | | | | | | | | |

Women with early stage disease (FIGO stage 1 to 2b) represented on the Kaplan-Meier graph as Stg = 1, who had early evidence of disease recurrence/ progression were identified as early as 12 weeks. This was achieved through serial monitoring of the tumour marker Ca-125, with a 10% increase in the result considered as significant. Those with late stage disease (FIGO 2c to 4) presented as stg = 2, who completed their treatment course, and lived beyond the first year of follow up, showed no evidence (biochemical or radiological) of disease recurrence during that period. This difference in early recurrence status between these two groups based

on disease stage at presentation was statistically significant (P >Chi2 = 0.0420). (Refer Figure 2.1)

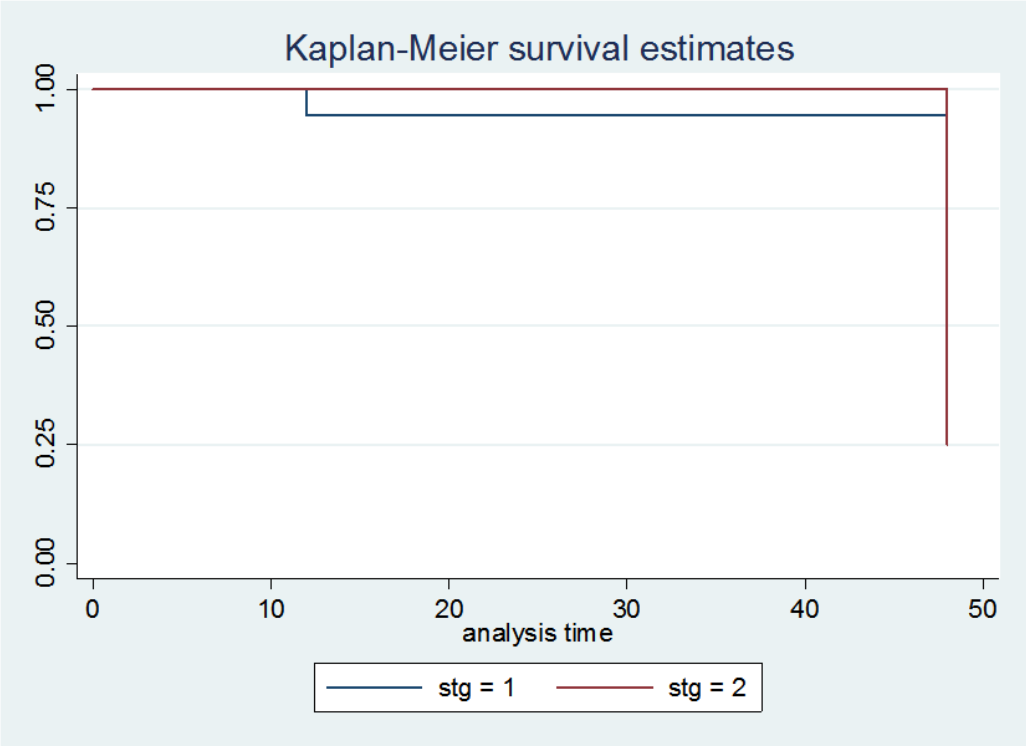


Figure 2.1 Illustration of evidence of early disease recurrence compared with stage of disease.

A total 46(62.1%) women had primary cytoreductive surgery and only 6 (8.1%) had interval cytoreduction following a cycle of neo-adjuvant chemotherapy. The majority of women had their primary surgery performed at their referring hospital, this surgery being performed by general gynaecologists. The surgical outcomes for women that had primary surgery showed that 8(10.5%) had no residual tumor, 9(11.8%) had optimal surgery, 23(30.2%) were classified as having had sub-optimal surgery and the surgical outcome of 36(47.3%) was unknown. All the 20(27%) with stage 1 disease had primary cytoreductive surgery. Seven (35%) of those with stage 1 Ovarian Cancer, were reported to have optimal surgical outcome, 3(15%) had sub-optimal surgery, 6(30%) had no residual tumor and the surgical outcome of 4(20%) was not documented. Six (8.1%) women with stage 2 disease had primary surgery, and 1(16.6%) was reported optimal surgical outcome, 3(50%) reported as suboptimal, and the surgical outcome for the remaining 2 women was not documented. Eight (61.5%) of the 13 women with stage 3 disease had primary cytoreduction, and 2(15.3%) had interval

cytoreduction. Surgical records for the remaining 3 women with stage 3 disease were not found. Only 1(7.69%) woman with stage 3 cancer who had primary cytoreduction was considered to have had optimal surgery, 7(53.8%) had sub-optimal surgery, and surgical outcomes for 5 women were not found on record. There were a total 13 women with stage 4 disease, and of these, 6(46.1%) had primary surgery and 1(7.7%) had interval cytoreduction. All the 6 women with primary surgery where reported as sub-optimal, and the surgical outcome for the woman with interval cytoreduction was not recorded. Seven women reported to have primary cytoreduction, and 3 interval cytoreduction had no clearly documented surgical stage.

Sixty-one (82.4%) of study population received either neo-adjuvant or adjuvant chemotherapy and 13(17.6%) were not treated with chemotherapy. Twenty-four (39.3%) received neo-adjuvant chemotherapy and 37(60.6%) received adjuvant chemotherapy. Forty-seven (77%) of those who were treated with chemotherapy received a combination of Carboplatin and Paclitaxel. This chemotherapy regimen was first-line and generally well tolerated with 80.2% of women completing their prescribed cycle without any adverse side effects.

There were 19.7% women who had severe side effects necessitating an interruption in their chemotherapy cycle. Some of the side effects experienced included low platelet counts 3(4.91%), low white cell count 3(4.91%), constipation 2(3.27%) vomiting 1(1.63%) and low blood pressure 1(1.63%). There were 25(33.78%) women who had no evidence of disease recurrence (biochemical or radiological) at 2 years. Of the 25 women with no recurrence, 6(25%) were treated with surgery only owing to early stage disease, 4(16.67%) received neo-adjuvant chemotherapy and 15(60%) received adjuvant chemotherapy following primary debulking surgery. Thirteen (17.57%) women had disease recurrence at 2 years. This disease persistence was evidenced by rising levels of the tumour marker CA125 and confirmed radiologically by either ultrasound or by a computerized tomography (CT) scan. In the women with recurrence at 2 years, only 1 (7.6%) had not received chemotherapy, 7(53.8%) were treated with neo-adjuvant chemotherapy and 5(38.46%) had adjuvant chemotherapy. The recurrence status of 36(48.65%) women was unknown. Eight (21%) of the women whose recurrence was unknown did not receive any chemotherapy, 13(36.1%) were treated with neo-adjuvant chemotherapy and 15(41.66%) received adjuvant chemotherapy.

Fifteen (24.5%) women required second-line chemotherapy and this was given in varying regimens illustrated in (Table1.2).

Table 2.5 Second-line Chemotherapy drugs

| Drug/Combination | Number | Percentage | Commonest side effects |
|---|---|---|---|
| Paclitaxel/ carboplatin | 2 | 13.3% | Nausea/vomiting<br>Neutropenia |
| Gemzar/ Cisplatin | 5 | 33.3% | Constipation |
| Gemzar | 3 | 20% | Nil |
| Carboplatin/ Gemzar | 3 | 20% | Thrombocytopenia |
| Carboplatin/ Docetaxel | 1 | 6.6% | Nil |
| Xeloda | 1 | 6.6% | Thrombocytopenia |

The most common presenting symptom was abdominal distension in 52 (70.2%) women. There were 43(58.1%) women who presented with abdominal pain, 11(14.9%) with early satiety and only 1(1.4%) with intractable heartburn. Thirty-one women (41.9%) presented with a combination of pain and abdominal distention and 4(5.4%) with the triad of abdominal pain, abdominal distention and early satiety.

The mean Ca125 level before therapy (whether surgical or chemotherapy) was 543.7U/ml (range 2.7 – 11184U/ml). There were 30 (40.5%) women who had Ca125 within normal ranges. Of these women, 15(20.2%) had stage 1 disease. The mean Ca125 in women with disease greater than stage 1 was 1844.2U/ml. Those who had primary surgery had a mean Ca125 of 243.3U/ml at 3 months reassessment.

Sixty-five women (85.5%) had no documented history of contraceptive use, with only one (1.3%) with confirmed use of the combined oral contraceptive for a duration of 3 years. There were 5(6.5%) women who had a first-degree relative with breast cancer, and a further 2(3.6%) who had first and second-degree relatives with colon and stomach cancer respectively. Thirty-eight (50%) women had comorbid Hypertension and only 5(6.5%) had

Diabetes Mellitus. Eight (10.8%) women were nulliparous, 13(17.5%) had only 1 child, 25(33.8%) had between 2 to 4 children and 5(6.8%) had 5 or more children. Twenty-three women (31.1%) had no record of their parity.

Eleven (14.86%) of women were smokers, 22(29.7%) non-smokers, and 41(55.4%) had unknown smoking status. Only 5(6.75%) women were HIV positive and on anti-retroviral therapy, 64(86.5%) were HIV negative and the HIV status of 5 (6.7%) was unknown.

The figure below illustrates patients' ECOG functional status at presentation.

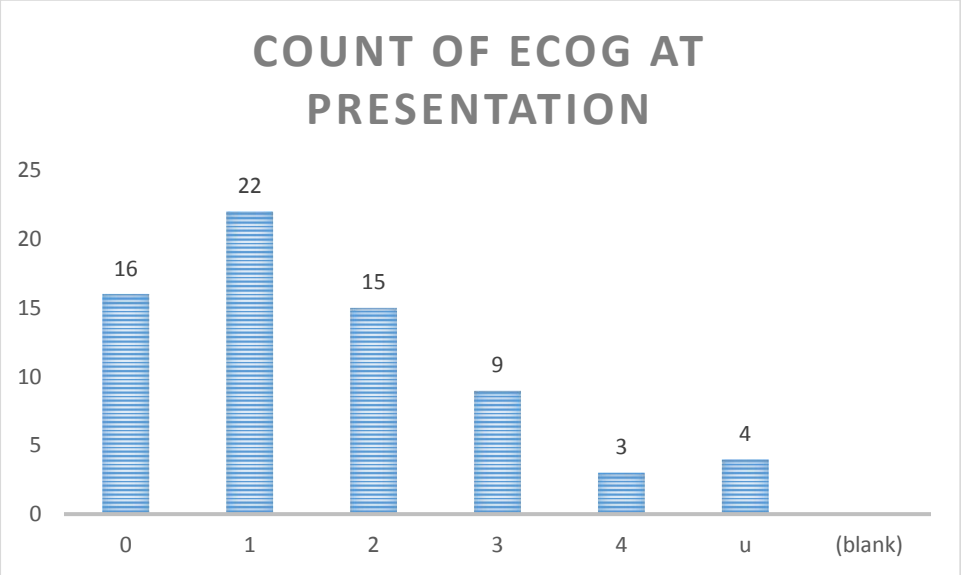


**Figure 2.2** The above chart represents the ECOG staging of women at presentation.

## Discussion

This study showed a 33.78% (25) recurrence free survival at 2 years, with nearly (13) 18% participants showing evidence of disease recurrence. There is a paucity of published literature describing survival status at 2 years with most data including that of the American Cancer Society describing survival status at 5 years. The lack of earlier data on 2 years follow up following ovarian cancer treatment therefore justifies our analysis. Only 13% of the study population had early evidence of disease persistence were recurrence-free at 2 years, a

finding which was not statistically significant. Von Georgi et.al in 2003 also stated that early follow up of patients with ovarian cancer did not seem to influence the natural course of disease and patient survival.[19]The benefit of early follow up is that it affords the opportunity to offer patients psychological support and counselling in order to improve their overall quality of life.[19]

When the recurrence status at 2 years was analysed with reference to their cancer surgical stage at presentation, the difference was not statistically significant (P= 0.085). Those with advanced stage disease (described as stages 2c to 4) who survived death by the end of the first year of follow up, had similar recurrence free status at 2 years as those participants who were enrolled into the study with early stage disease (stages 1 to 2b).

Because Ovarian Cancer tends to spread peritoneally, it is difficult to completely resect all the tumor with surgery alone.[20] More than 80% of women in this study were treated with chemotherapy. The remaining 19.8% who were not treated with chemotherapy were either diagnosed early and therefore adequately treated with surgery only or diagnosed with advanced disease and demised before their scheduled chemotherapy. The choice of chemotherapeutic drugs was made by the attending clinicians at the oncology unit based on their protocols and these were guided by international recommendations. Those who did not receive chemotherapy either had early stage disease and were adequately treated with surgery only or, had advanced disease, and although initially scheduled for chemotherapy, died before onset of treatment. Over 80% of the women in this study were treated with either neo-adjuvant or adjuvant chemotherapy. Of the women treated with chemotherapy, 77% received a combination of Carboplatin and Paclitaxel. All women in the study who received adjuvant chemotherapy were treated with 6 cycles of a combination of Carboplatin and Paclitaxel. Those who received neo-adjuvant chemotherapy were treated with an initial 3 cycles of chemotherapy before their reassessment for operability. The current use of chemotherapy as an adjunct to surgery in treating patients with advanced cancer of the ovary followed years of clinical trials.[4] In current practice, it is believed that treatment of patients with advanced ovarian cancer with six or more courses of chemotherapy significantly improves their prognosis.[20] Despite the positive correlation of the chemotherapy course to the overall prognosis, our study showed no statistically significant association between the cycle of

chemotherapy received by study patients and their recurrence status at 2 years. ((Chi2(4) = 6.6323 P = 0.157)). Although not shown to be statistically significant, the small sample size could have been a limitation.

Because of the location of the ovary deep into the pelvis, the lack of adequate screening tools and the vague presentation of ovarian cancer, most patients present with already advanced disease at time of diagnosis and onset of treatment. This finding was also demonstrated in our study population. The standard of care for ovarian cancer involves a combination of extensive surgery with a platinum/Taxane chemotherapy regimen[2,4,8], a consistent therapy regimen used in our study population. The majority of women treated at our study centre were referrals from other centres, at which they had already had primary cytoreductive surgery. This is a significant finding as certain factors remain important in the prognosis of ovarian cancer patients undergoing surgery, including the amount of residual disease remaining following the initial surgery, and that the surgery should be performed by an expert in gynaecologic cancer surgery.[13,14] The Society of Gynaecologic Oncology and the American Society of Clinical Oncology recommend that all women with suspected ovarian cancer should be evaluated first by a gynaecologic oncologist, prior to onset of therapy to determine whether they would be suitable for primary cytoreductive surgery.[9]

Disease persistence, or early disease recurrence was measured using serial serum measurements of the tumor marker CA 125 and then confirmed radiologically using either ultrasound or computerized tomography (CT) scanning. The use of the marker Cancer antigen125 (CA 125) is not specific for all histological subtypes of ovarian cancer and has been shown to be elevated in almost all patients with late stage ovarian cancer.[5]

CA 125 is an important component in the management of ovarian cancer.[18]Following the combination therapy of surgery and chemotherapy, a majority of patients maintain small amounts of residual tumor deposits throughout the peritoneum which are difficult to evaluate by physical examination or radiological studies, hence the important role of this tumor marker. This tumor marker has the ability to show changes in tumor mass during treatment and at follow-up following completion of the chemotherapy cycle.[21]There is no consensus on how to interpret serial Ca125 results to demonstrate disease progression or recurrence. The medical oncology center uses a 10% increase in serial ca125 results to indicate a possibility of disease progression, perhaps a threshold too low. According to previous studies,

progressive disease was indicated by a 50% increase in serial Ca125 levels.[18] Other interpretations of Ca 125 were that, there was a 50% increase in level over 3 occasions, or if there was a persistent elevation in Ca 125 above a level of 100U/ml for more than 2 months without a decrease by 50%.[18] The use of a lower threshold for Ca125 in our study may be associated with a higher false positive rate

The mean age of the women on our study was 55 years with 69.8% of women older than 50 years. Ovarian cancer is predominantly a disease of post-menopausal women, common in the 5th and 6th decade of life.[4] This finding of a higher incidence of ovarian cancer in older patients supports the "Incessant Ovulation" theory in the pathophysiology of ovarian cancer, which describes a higher risk for genetic mutation and ovarian neoplasm during the process of repair, following the damage and trauma to the ovarian epithelium during each ovulatory cycle.[5] The association between prognosis in ovarian cancer and age is inconclusive, however some reports have suggested that younger women tend to have a better outcome compared to older women.[16]

Globally, the risk of ovarian cancer is higher in white women, intermediate for Hispanics, and lowest amongst black populations and Asians. This was a contrast finding in our study population where 68% of women with ovarian cancer were of the black race, with only 21% of patients being white. Though the Charlotte Maxeke Johannesburg Academic Hospital treats a majority of black patients, this study suggests that there are more Africans with ovarian cancer than previously thought. This is also supported by the fact that more women presented in the late stage of disease. It may be a condition that is under reported and under-diagnosed.

It was surprising to find that 85.5% of the women had no documented history of contraceptive use. It is well documented that the use of oral contraceptive confers a protective benefit against ovarian cancer. There is an inverse association with the use of the combined oral contraceptive pill and the risk of ovarian cancer[3,6], with a reduction in risk of 40%, 53% and 60% with continuous contraceptive use for four, eight and twelve years respectively.[3] This protective benefit of the use of the combined oral contraceptive pills persists even after pill use has been discontinued.[3] The protective benefit of oral contraceptive use described by years of epidemiological data report about a 20% reduction in ovarian cancer risk with every

5 years of contraceptive use, and this protective benefit persisting for decades even after the cessation of pill use.[6] There is also no difference in the protective benefit of the different contraceptive pill formulations.[20] The Cancer and Steroid hormone study (CASH) suggested that, ten year use of the oral contraceptive pill by women with a known family history, reduced the risk of developing ovarian cancer to below that of the general population. High risk patients, with a known BRCA 1 and BRCA2 mutation carrier status, have up to a 60% risk reduction of ovarian cancer with continuous use of the oral contraceptive pill for six years or more.[3]

It was found that 56.5% of the women had co-morbid Diabetes and Hypertension. Metabolic syndrome is a known risk factor for gynecological Malignancy. A raised BMI is a significant component of the metabolic syndrome and, a meta-analysis in 2007 inclusive of 28 population studies reported an increase in the risk of ovarian cancer in women with a Body Mass Index of 25-29.9kg/$m^2$ and obese women (BMI $\geq$30 kg/$m^2$) compared to women with a normal Body Mass Index (18.5 -24.9 kg/$m^2$).[6]

Nulliparity is a known risk factor for ovarian malignancy. However, in our study there were only 10.8% of women who were nulliparous. The majority (40.6%) had a parity of 2 and greater. This is not expected of a study population that has no other protective factors from ovarian malignancy.

A proportion of women (27.4%) were excluded due to the absence of records. Poor record keeping also proved another limitation as there were many unknown variables which may have contributed to study outcomes. Patients were not all operated by a gynaecologic oncologist. This was an important factor as patient prognosis may be affected by the surgeon's level of expertise. The major strength of this study was that it was the first review of Ovarian Cancer in the Johannesburg population and the first 2 year follow up of women who have been treated for ovarian cancer. This provides an opportunity for future studies. Furthermore, this study creates opportunities for future research.

## Conclusion

This study demonstrated that a majority of women with ovarian cancer present with advanced stage disease. In those patients with advanced ovarian cancer, recurrence free survival was similar between women treated with primary cytoreductive surgery followed by platinum–based chemotherapy and those patients treated with neo-adjuvant chemotherapy. Despite extensive surgery and platinum based chemotherapy, our study demonstrates that prognosis for patients with advanced ovarian cancer remains poor with only a third of patients remaining recurrence-free at a 2 years follow up.

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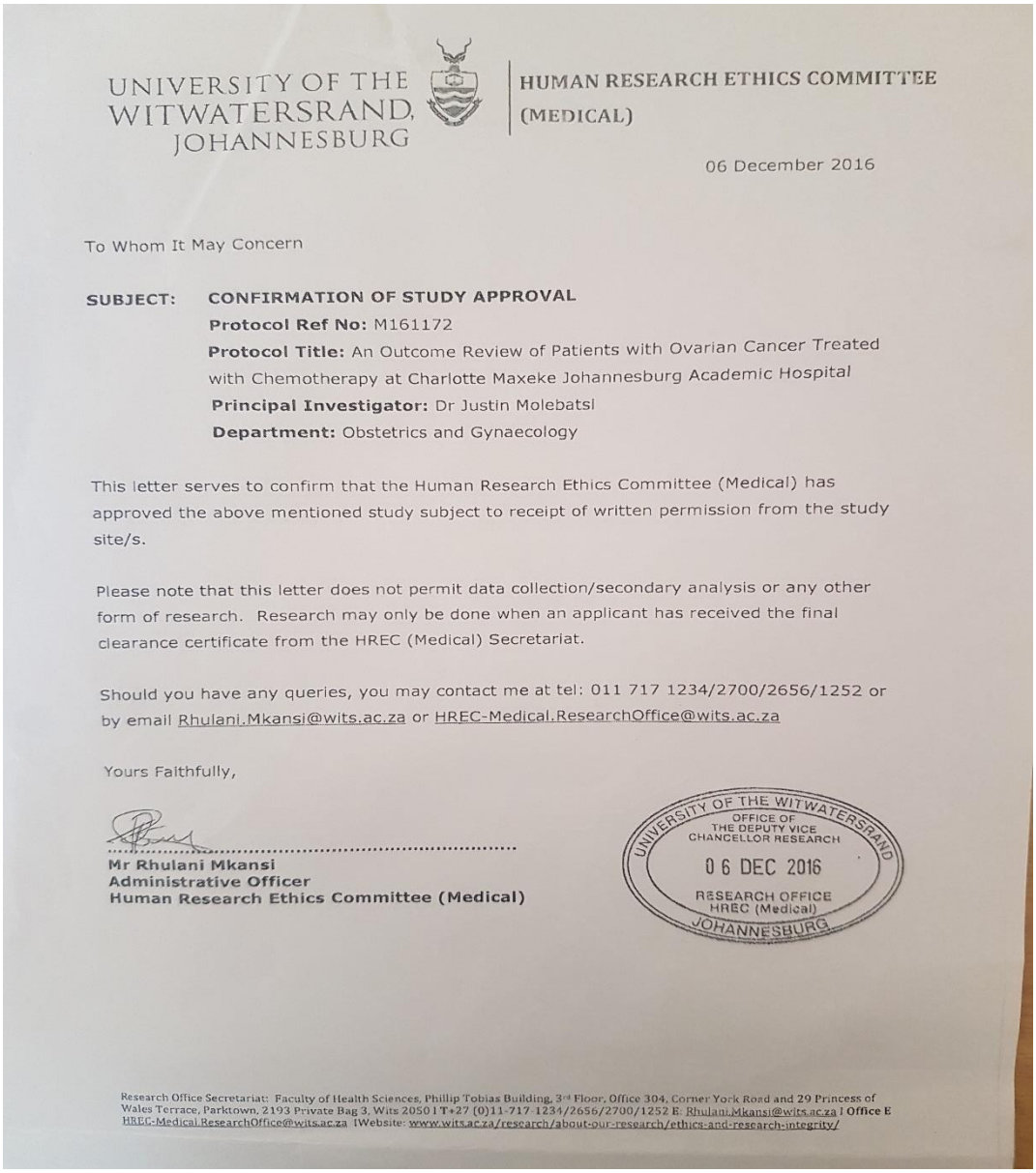
# Chapter 3: Appendices

APPENDIX A: Ethics Approval



UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

06 December 2016

To Whom It May Concern

**SUBJECT:** **CONFIRMATION OF STUDY APPROVAL**
**Protocol Ref No:** M161172
**Protocol Title:** An Outcome Review of Patients with Ovarian Cancer Treated with Chemotherapy at Charlotte Maxeke Johannesburg Academic Hospital
**Principal Investigator:** Dr Justin Molebatsi
**Department:** Obstetrics and Gynaecology

This letter serves to confirm that the Human Research Ethics Committee (Medical) has approved the above mentioned study subject to receipt of written permission from the study site/s.

Please note that this letter does not permit data collection/secondary analysis or any other form of research. Research may only be done when an applicant has received the final clearance certificate from the HREC (Medical) Secretariat.

Should you have any queries, you may contact me at tel: 011 717 1234/2700/2656/1252 or by email Rhulani.Mkansi@wits.ac.za or HREC-Medical.ResearchOffice@wits.ac.za

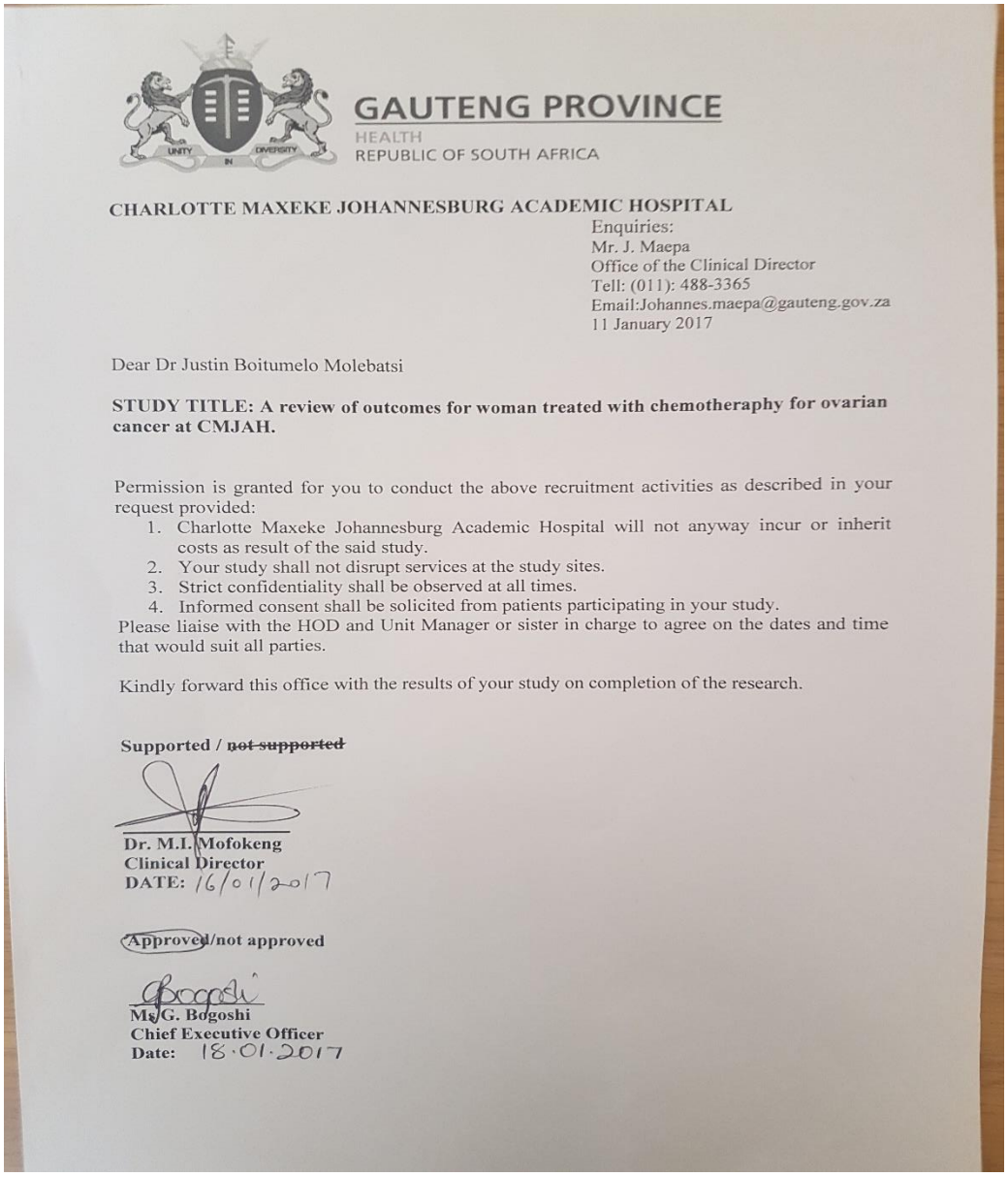
Yours Faithfully,

**Mr Rhulani Mkansi**
**Administrative Officer**
**Human Research Ethics Committee (Medical)**

UNIVERSITY OF THE WITWATERSRAND
OFFICE OF THE DEPUTY VICE CHANCELLOR RESEARCH
06 DEC 2016
RESEARCH OFFICE HREC (Medical)
JOHANNESBURG

Research Office Secretariat: Faculty of Health Sciences, Phillip Tobias Building, 3rd Floor, Office 304, Corner York Road and 29 Princess of Wales Terrace, Parktown, 2193 Private Bag 3, Wits 2050 | T+27 (0)11-717-1234/2656/2700/1252 E: Rhulani.Mkansi@wits.ac.za | Office E HREC-Medical.ResearchOffice@wits.ac.za |Website: www.wits.ac.za/research/about-our-research/ethics-and-research-integrity/

# APPENDIX B: CEO Approval letter



GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

**CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL**

Enquiries:
Mr. J. Maepa
Office of the Clinical Director
Tell: (011): 488-3365
Email:Johannes.maepa@gauteng.gov.za
11 January 2017

Dear Dr Justin Boitumelo Molebatsi

**STUDY TITLE: A review of outcomes for woman treated with chemotheraphy for ovarian cancer at CMJAH.**

Permission is granted for you to conduct the above recruitment activities as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic Hospital will not anyway incur or inherit costs as result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall be observed at all times.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the HOD and Unit Manager or sister in charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

**Supported / ~~not supported~~**

**Dr. M.I. Mofokeng**
**Clinical Director**
**DATE:** 16/01/2017

**Approved/not approved**

**Ms G. Bogoshi**
**Chief Executive Officer**
**Date:** 18.01.2017

APPENDIX C: Plagiarism certificate

APPENDIX D:Data Collection Sheet

| STUDY NUMBER: |
|---|

DEMOGRAPHIC DATA

| Age(years) | At diagnosis | Onset of treatment | | Race | |
|---|---|---|---|---|---|
| | | | | Nationality | |
| Parity | | | | | |

| **Presenting symptom** | Distention | Pain | Early Satiety | Intractable heartburn | Other | Unknown |
|---|---|---|---|---|---|---|
| | | | | | | |

RISK & PROTECTIVE FACTORS

| COC USE | Yes | | No | | Unknown | |
|---|---|---|---|---|---|---|
| If yes, duration of use | <5 years | | 5-10 years | | >10 years | |
| Smoking | Yes | | No | | Unknown | |
| Family history of cancer? | Yes | | No | | Unknown | |
| If yes, which? | Breast | Ovary | Colon | Prostate | Other | Unknown |
| | | | | | | |
| **ECOG at presentation** | 0 | 1 | 2 | 3 | 4 | Unknown |
| | | | | | | |
| **Co-morbid disease** | HPT | | DM | | HIV | Other |
| **If HIV positive** | CD4 | | VL | | ARVs (Y/N) | Duration |
| **Type of Surgery** | Primary Cytoreduction | | | Interval cytoreduction | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Surgical Staging** | 1b | 1c | 2a | 2b | 2c | 3a | 3b | 3c | 4 |
| | | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Surgical Outcome** | No residual tumor | | Optimal | | Suboptimal | | Unknown | |
| **Chemo drug(s) used** | | | | | | | | |
| **Cycles of chemo** | Neoadjuvant | | Adjuvant | | Unknown | | | |
| **Side effects** | | | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **ECOG after cycle completion** | 0 | 1 | 2 | 3 | 4 | Unknown |
| | | | | | | |

FOLLOW UP EVALUATION

| | Ca125 | Physical Exam | Ultrasound | Symptoms recurrence | | |
|---|---|---|---|---|---|---|
| **3 months** | | | | | Unknown | |
| **6 months** | | | | | Unknown | |
| **12 months** | | | | | Unknown | |

LONG TERM FOLLOW UP AND OUTCOME (At 2 years)

| Year | Recurrence free | Metastasis | ECOG | Additional treatment (chemo/surgical) |
|---|---|---|---|---|
| Year 1 | | | | |
| Year 2 | | | | |

| | | | | |
|---|---|---|---|---|
| Date of first encounter | | | | |
| Date of last encounter | | | | |
| Lost to follow up? | Yes | | No | |
| Did patient die in the 2 years | Yes | | No | |
| If yes, period of death from chemo initiation(months) | | | | |