

Early and Intermediate Outcomes of Patients who underwent
Gynaecological Oncology Surgery at Charlotte Maxeke Johannesburg
Academic Hospital.



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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Masters in Medicine (MMed)

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DECLARATION

I, **Madithame Rachel Nchabeleng-Shibambu**, declare that this research report is my own, unaided work. It is being submitted for the Degree of Masters in Medicine (MMed) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other university.

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13 October 2020 in Johannesburg

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ABSTRACT

Aim

To investigate the immediate and intermediate outcomes of patients who underwent gynaecological oncology surgery at Charlotte Maxeke Johannesburg Academic Hospital in 2015 and 2016. The study focused on patients who experienced sustained complications during the open abdominal surgery.

Objectives

To investigate the comorbidities associated with the complications in the women who underwent open abdominal surgery for confirmed gynaecological cancers.

Method

This was a retrospective study. We checked the patients' files to investigate the health status during operation and up to the 6 weeks postoperatively. The study was approved by the University of Witwatersrand Ethics Committee on Human Research.

Results and Discussion

Two hundred and six (206) patients were operated for suspected gynaecological malignancies during the period. Ninety patients were confirmed to have malignancies. Thirty-one (31) patients had various complications while one died from haemorrhage.

Conclusion

The finding that haemorrhage was the most common complication in open abdominal gynaecological oncology surgery was expected due to the extensiveness of the surgical procedure, the likelihood of neo-vascularization, and tumour infiltration into vessels.

ABBREVIATIONS

BMI	Body Mass Index
BSO	Bilateral Salpingo-Oophorectomy
CD4	Cluster of Differentiation 4 (T lymphocyte cell)
CONSORT	Consolidated Standards of Reporting Trials
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CT	Computerized Tomography
DM	Diabetes Mellitus
DVT	Deep Vein Thrombosis
EBL	Estimated Blood Loss
ECOG	Eastern Cooperative Oncology Group
ETP	Extended Thromboprophylaxis
HAART	Highly active antiretroviral therapy
HIV	Human Immunodeficiency Virus
LMWH	Low Molecular Weight Heparin
MMMT	Malignant Mixed Mullerian Tumour
MS	Metabolic Syndrome
NG tube	Nasogastric tube
NLHS	National Health Laboratory Services
PE	Pulmonary Embolism
RCT	Randomized Clinical Trials

SCC	Squamous Cell Carcinoma
SSI	Surgical site infections
TAH	Total Abdominal Hysterectomy
US	United States
UTI	Urinary Tract Infection
VTE	Venous Thromboembolism

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CHAPTER 1: INTRODUCTION AND OVERVIEW

1.1 Background

Cancer accounts for a considerable portion of deaths around the world. In the United States of America, cancer accounted for 584,881 deaths in 2013, after heart disease at 611,105.¹ Surgery has been used as a curative-intent treatment for most of the solid tumours (sarcomas, carcinosarcomas, and lymphomas). Surgery can be offered together with neo-adjuvant or adjuvant treatment such as hormonal therapy, chemotherapy, external radiation therapy, and brachytherapy.² Any surgical procedure carries the risk of an adverse outcome. Age, functional status and medical comorbidities are individual characteristics that are associated with various degrees of risk in terms of postoperative complications.³

According to the Consolidated Standards of Reporting Trials recommendations, adverse effects from surgery were poorly reported in cancer trials. This reporting has not improved over time. A recommendation was made for the development of specific surgical adverse effects reporting.⁴

1.2 Problem Statement

There are limited data on the complications following gynaecological oncology surgery in South Africa and abroad. The incidence of mortality and morbidity following gynaecological oncology surgery is ordinarily not reported along with preoperative risk adjustments for these individual characteristics.

1.3 Justification for the Study

Surgery is the foundation of treatment for gynaecologic malignancies. Reduction of surgical complications cannot be overstated in modern day healthcare. There are two main aspects to the goal of minimizing surgical complications. Firstly, it is to reduce the surgery associated morbidity, and secondly, it involves a reduction in the costs of healthcare, which can be achieved

by means of a reduction in hospital stay and readmission rates. Morbidity and mortality due to surgical complications in gynaecologic oncology patients should be prevented to avoid imposing additional suffering on an individual who already carries a morbid diagnosis.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction and Background

Any surgical procedure carries risks of adverse outcomes. Age, functional status, and medical comorbidities are individual characteristics that are associated with the risk of postoperative complications.³ Global cancer statistics show that cervical cancer is the first most common gynaecologic cancer in Sub-Saharan African and the third most common gynaecological cancer worldwide.⁵ Uterine cancer is the second most common female reproductive cancer in low-middle income countries and the most common female reproductive cancer in high income countries.⁵ The factors associated with risk for endometrial cancer include metabolic problems and pre-existing medical conditions, including advanced age, obesity, and diabetes mellitus. These risk factors may predispose women with endometrial cancer to an increased risk of postoperative wound complications. Wound complications not only increase health cost but also affect a patient's recovery from illness, in addition to causing anxiety and discomfort.⁶

In assessing time and productivity costs, we found that case-patients (64%) were more likely than controls (42%) to have spent at least half a day in bed and missing planned regular activities ($p=0.04$). Differences between case-patients and controls in other areas of lost productivity, such as missed days of work and an inability to complete regular activities, were however not significant⁷

2.2 Wound Infection and Other Wound Complications

Obesity is one major issue that affects wound healing. Patients with increased body mass index (BMI) are more likely to have delayed and incomplete wound healing. Increased wound tension, trauma, and necrosis of the abdominal wall, secondary to more forceful retraction during operation, are factors associated with delayed wound healing in obese patients. These patients may harbour micro-organisms in their skin folds, resulting in wound infection and separation.

Relative hypo-perfusion, and ischemia occurring in subcutaneous adipose tissue, and resulting in decreased delivery of optimal tissue level of prophylactic antibiotics, may contribute to frequent wound complications in obese patients.⁸ In comparison to patient with normal weight, wound complications were 5.6-times more likely among gynaecologic cancer patients with BMI ≥ 30 kg/m².⁸ The Nhokaew et al.⁶ study found an incidence rate of 7.84% for wound complications in patients who underwent laparotomy for endometrial cancer. Patients experiencing wound complication tended to have underlying DM, a previous history of major abdominal surgery, and a high BMI compared to patients who did not have wound complications.⁶ Women with BMI ≥ 30 kg/m² and endometrial cancer were found to have significantly more postoperative surgical complications, including antibiotics use and wound complications. These complications occurred in open surgery and risk increased along with an increase in obesity. However, there was no observed impact on 30-day mortality.⁶ In contrast, findings on ovarian cancer patients by Fotopoulou et al.⁹ showed no significant difference between obese and normal weight patients with regard to the morbidity associated with operative procedures.

Surgical site infections (SSIs) in obese patients may prolong hospital stays, introduce antimicrobial resistant bacteria, expose patients to medication reactions or errors and, more importantly, even lead to decreased overall survival. This is evidenced in a retrospective review of 888 gynaecologic oncology patients who underwent primary surgery for ovarian cancer. In the study, increased BMI, operative time, and advanced stage disease were independently associated with SSIs.¹⁰ With the goal of reducing SSIs in mind, there has been an interest in implementing new strategies for the elimination of SSIs. One such strategy has been the introduction of “bundled interventions” in the perioperative time frame. Johnson et al.¹¹ proposed the use of “bundled interventions” in gynaecologic oncology patients undergoing laparotomies for surgical staging.

Using bundled interventions to reduce surgical site infection after major gynecologic cancer surgery, the investigators paired commonly used pre-interventions (patient education regarding infections, use of a chlorhexidine gluconate shower prior to surgery, chlorhexidine gluconate, isopropyl alcohol skin preparation in the operating room, prophylactic use of cefazolin) with newly proposed intraoperative and postoperative interventions (sterile closing trays, and a

shower with 4% chlorhexidine gluconate following dressing removal 24 hours post operatively). The authors showed a statistically significant decrease of overall SSI from 5.9% to 1.5% in patients with the newly proposed intraoperative and postoperative interventions, in continuing with the bundled care for reduction of SSIs in gynaecologic oncologic patients.¹¹ Al-Niaimi et al. and Chapman et al.^{12,13} have identified perioperative glycaemic control as an important aspect of the “bundle intervention”. Al-Niaimi et al.¹² initiated intensive glycaemic control for 24 hours after surgery in 372 patients with diabetes mellitus and postoperative hyperglycaemia.

The study found that intensive glycaemic control significantly lowers SSI rates. Similarly, Chapman et al.¹³ used perioperative immune modulating diets (IMDs) to control blood glucose levels in patients undergoing laparotomies.

Consumption of IMDs remained protective against wound complications with an OR of 0.45 [CI 0.25-0.84]. Although helpful and important in reducing SSI, these “bundled interventions” are not likely to be the silver bullet in SSI prevention. Gynaecological oncologists therefore need to consider how improving and advancing current surgical techniques could reduce SSI. In the current era of medicine where preventing perioperative adverse events like SSIs has become the focus of quality improvement efforts, gynaecologic oncologists are in search of less morbid procedures to achieve superior surgical and oncological outcomes for their patients¹⁰

Wound complications were found in 34% of the patients in a retrospective study on high-risk women undergoing abdominal gynaecologic surgery in a tertiary referral centre. A multivariate analysis on this study found wound that complications were correlated with an increased BMI of 30–39.9 kg/m² (OR = 5.62, 95% CI 2.08–15.19, $p < 0.0001$) and BMI ≥ 40 kg/m² (OR = 10.27, 95% CI 3.66–28.88, $p < 0.0001$), prior abdominal surgery (OR 3.28, 95% CI 1.89–5.70, $p < 0.0001$), serum albumin ≤ 3.5 g/dl (OR 4.24, 95%CI 1.87–9.61, $p = 0.0005$), pulmonary disease (OR 2.22, 95% CI 1.09–4.51, $p = 0.03$), lysis of adhesions (OR 3.57, 95% CI 1.04–12.26, $p = 0.04$), and length of surgery (OR 2.42, 95% CI 1.35–4.35, $p = 0.003$). Risk for wound complication was lower with pelvic drain placement (OR 0.26, 95% CI 0.11–0.64, $p = 0.003$).¹⁴

2.3 Thromboembolism after surgery (Venous and Pulmonary)

There is an increased risk of postoperative venous thromboembolism (VTE) in patients who underwent abdominopelvic cancer surgery.¹⁵ The National Comprehensive Cancer Network (NCCN) has published guidelines regarding VTE prevention in cancer patients.¹⁶ The guidelines divide surgical patients into four groups according to their VTE risk, namely low risk (minor surgery in patients aged <40 years without any additional risk factors); moderate risk (minor surgery in patients with additional risk factors, or surgery in patients aged 40–60 years without additional risk factors); high risk (surgery in patients aged >60 years, or surgery in patients aged 40–60 years who have additional risk factors); and highest risk (surgery in patients with multiple risk factors, or surgery in patients undergoing hip or knee arthroplasty, or major trauma).¹⁶

Therefore, Low-molecular-weight heparin (LMWH) thromboprophylaxis has been recommended for use in the patients undergoing abdominopelvic cancer surgery to prevent the risk of postoperative venous thromboembolism (VTE). There is twice the risk of postoperative deep vein thrombosis (DVT) and non-fatal pulmonary embolism (PE), and more than three times the risk of fatal PE in patients undergoing major surgery with the active neoplastic disease as compared with patients undergoing surgery for non-inflammatory benign conditions. Postoperative activation of the coagulation system persists beyond the first 7–10 days following surgery, with the VTE incidence remaining as high as 25 % even 4–6 weeks after the surgical intervention.^{15, 16}

A study by Fagarasanu et al.¹⁵ demonstrated the benefit of the administration of low-molecular-weight heparin for extended duration thromboprophylaxis after abdominal or pelvic surgery for cancer. This has shown a significant reduction in the incidence of venous thromboembolism and postoperative DVT without increasing the risk of major bleeding. The total incidence of major bleeding events at 3 months was 1.4 %.¹⁵ There was a twofold increase in the rate of major bleeding complications associated with increase the higher dose of dalteparin.¹⁶ The routine use, and consideration of extended thromboprophylaxis (ETP) in the setting of abdominal and pelvic surgery for cancer patients was recommended. The ETP regimen significantly reduced the incidence of all VTEs compared with the conventional thromboprophylaxis (CTP) regimen [2.6 %

(59/2292) vs. 5.6 % (124/ 2209); RR 0.44, 95 % CI 0.28–0.70, number needed to treat (NNT) = 39].¹⁵

A Cochrane review of 4 randomized controlled trials examining extended prophylaxis has shown a decrease in VTE and a decrease in symptomatic VTE.¹⁶ Khorana et al.¹⁷ attributed the death in ambulatory patients receiving active therapy to cancer-associated thrombosis. The study looked into the relative contribution of thromboembolism to death in cancer patients with active disease and who are on chemotherapy.¹⁷

Thrombo-embolism as a co-morbidity with other haematological conditions were found to have an impact on patients with ovarian cancer.¹⁸ For women with ovarian cancer, all comorbidity diagnoses increased mortality significantly, except hypertension when diagnosed within one year after cancer diagnosis. Ståhlberg et al.¹⁸ found that thromboembolism was the most hazardous (HR = 7.83 if diagnosed 1–5 years after cancer and HR = 1.95 within one year after cancer), followed by hematologic complications (HR = 7.11 and 1.84 respectively). When analyzing the separate diagnoses included in hematologic complications, thrombocytopenia was most hazardous the first year after cancer diagnosis (HR = 5.50) and anaemia after 1–5 years (HR=7.54). This was mainly observed among those with a more prosperous prognosis, including younger age, longer time since cancer diagnosis, and less aggressive tumours.¹⁸

Pneumatic compression stockings reduce the rate of VTE when compared to observation within the first 5 days postoperatively. Their efficacy is equivalent to heparin and improved when combined with heparin in gynaecologic oncology patients.¹⁶

2.4 Infection after surgery

A one-year single institute experience study in Rome, Italy by Fagotti et al.¹⁹ reported that infections occurred in 9.7% of the patients and 7.8% of those had severe events. Severe events requiring re-hospitalization and surgical intervention included abdominal abscesses, sepsis and wound infections with dehiscence. Mild wound infections were noted in 1.9% and these were managed in an outpatient manner.

Large-spectrum antibiotics proved to be effective in 57.1% of infections, CT-guided transcutaneous drainage was used in 14.3% patients, and laparotomic drainage was required in 28.8% of the patients.¹² The median time of occurrence of the abscess was 17 days (range 9–30). All patients with intra-abdominal infected collection underwent large-spectrum intravenous antibiotic treatment (metronidazole, cefazoline, meropenem, and teicoplanin for bacterial infections, and Diflucan for mycotic infections). It proved to be effective in 8 women (57.1%), whereas 2 patients (14.3%) required CT-guided transcutaneous drainage and 4 cases (28.6%) laparotomic drainage. The distribution of the germs isolated in these patients was as follows: *Staphylococcus* (4 cases; 21.4%), *Enterococcus* and/or *Escherichia coli* (4 cases; 21.4%), *Candida* (2 cases; 14.3%), *Bacterioides fragilis*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia* and *Prevotella bivia*.¹⁹ The study by Inagaki et al.²⁰ reported the most frequent cause of death in patients with cancer to be Gram-negative infections. The complications were controlled by means of vigorous antibiotic and better antineoplastic therapy.²⁰ Bacterial infection is a common cause of morbidity and mortality in patients with cancer, while viral infection can cause disease in patients with lymphoma.²¹

Antibiotics are administered intravenously within 1 hour before skin incision (usually at the time of anaesthesia induction). The dose should be increased in obese patients (BMI > 35 or >100 kg) and repeated after 1–2 times the half-life of the chosen medication in prolonged operations (So for example 3 hours for cefazolin, which has a half-life of 1.8 hours) and in case of blood loss >1500 ml.²² For patients who are allergic to penicillin or cephalosporin, a combination of clindamycin and gentamycin intravenous (IV) or a quinolone (eg. ciprofloxacin) can be used.²²

2.5 Impact of Anaemia on Surgical morbidities

Preoperative anaemia is associated with postoperative poor prognostic outcome and it is therefore important to correct it before elective surgery. Treating anaemia pre-operatively helps avoid the adverse effects of anaemia, transfusion or both. Severe anaemia is associated with a high risk of surgical complications.²¹

The recent guideline from the British Committee for Haematology showed no evidence of any benefit from pre-operative transfusion to improve surgical outcomes (in cardiac surgery patients) in the absence of other blood management measures. There was no reduction in total transfusion requirements.^{22, 23}

After adjusting for confounders by means of multivariate logistic regression, Richards et al.²⁴ found that there were increased odds of 30-day mortality, morbidity, respiratory, renal, wound sepsis, venous thrombosis, and other systems complications which are independently and significantly associated with preoperative anaemia. They also reported that the risk did not correct despite the use of perioperative transfusion. The findings by Prescott et al.²⁵ supported this. The study by Prescott et al.²⁵ found transfusion to be associated with higher composite morbidity, mortality, surgical site infections, and length of hospital stays.

Allogeneic blood transfusions have reportedly been associated with poor outcomes, including increased mortality, and wound, pulmonary and renal complications, and this has been attributed to transfusion-induced immune modulation (TRIM), a transient depression of the immune system following transfusion with blood products. TRIM has also been implicated in the higher rates of cancer recurrence and shorter times to recurrence associated with the transfusion of allogeneic blood, both of which have been widely reported over the last 25 years.

2.6 Urological Injuries

Urologic complications included bladder injury, ureteral injury, ureterovaginal fistula, vesicovaginal fistula, and ureter fistula (fistula formation in the ureter but not in the vaginal stump). Urologic complications were defined as a new diagnosis of urologic complications or injury or medical repair of urologic complications (ureteral repair, bladder repair, ureteral indwelling stent, ureteroureterostomy, ureterovesical implantation, or fistula repair).²⁷

An investigation on urologic injuries during gynaecologic surgery by Satitniramai et al.²³ found urinary bladder injuries to be the most common urinary tract injuries during gynaecologic surgery.²³ The incidence of intra-operative ureteric and bladder injury and postoperative bladder complications was highest for cervical cancer surgery when compared with other gynaecological

cancers. This is likely to be related to the higher proportion of radical hysterectomies undertaken for cervical cancer.²³ The presence of adhesions and previous pelvic surgery were significant risk factors associated with these injuries. The overall 10-year incidence was 0.30% and the incidence of bladder injury was 0.18%, (0.083% for ureteric and 0.014% for combined ureter and bladder injury).²³

Liu et al.²⁷ showed that the ureteral and bladder injuries after radical hysterectomy accounted for 31.2% of urologic complications, and postoperative genitourinary fistulas accounted for 68.8% (223/324). The incidence of any urologic complications was 1.54%: 83 (0.39%) for ureteral injuries, 17 (0.08%) for bladder injuries, 1 (0.005%) for ureteral injury combined with bladder injury, and 223 (1.05%) for genitourinary fistulas. Iatrogenic ureteral injuries, more than half of which occur during gynaecologic surgery, may have devastating consequences for both patients and physicians. Gynaecologists have employed various techniques such as cystoscopy, ureteral stents, and lighted ureteral stents to prevent ureteral injuries.²⁸ Lee et al.²⁸ suggests the use of intraurethral indocyanine green and subsequent visualization under near-infrared fluorescence appears to be a promising technique for primary and secondary prevention of ureteral injuries.

2.7 Haemorrhage during Gynaecologic Oncologic Surgery

Yu et al.²⁹ defined intraoperative haemorrhage as any blood loss that requires a blood transfusion and surgical blood loss of more than 1000 millilitres. The loss of 30% to 40% of the patient's blood volume leads to cardiovascular instability and hypotension. Blood loss greater than 40% is considered life-threatening. It is important for all surgeons and gynaecologic operating room teams to plan, prepare, and practice for a massive haemorrhage.²⁹

Galaal et al.²⁶ investigated the use of intraoperative cell salvage. Intraoperative cell salvage is such a measure that would potentially reduce the dependence on allogeneic transfusion. It was initially contraindicated in cancer, partly because of the theoretical risk of disseminating malignant tumour cells into patients' bloodstream. However, in patients undergoing surgery for a gynaecological malignancy, leucocyte depletion filters were shown to be effective in eliminating viable nucleated malignant cells from the returned blood.

Circulating tumour cells are prevalent in cancer surgery but are not associated with survival, and it has been suggested that circulating tumour cells with the potential to form metastatic lesions are rare. Emerging evidence suggests that, far from compromising outcomes, intraoperative autologous transfusion is associated with improved outcomes in surgery for other gynaecological cancers such as cervical cancer. Several studies in early stage (I-IIA) cervical cancer patients report that intraoperative autologous transfusion significantly reduces the need for allogeneic blood transfusion, without compromising survival or post-operative complication rates.²⁶

Lack of availability of blood products can be a challenge in a very low income setting as in Africa, where blood products are notoriously scarce. Malawian has high HIV prevalence among its adult population and the majority of blood donors in Malawi are high school students. To accommodate students, blood donations are usually conducted in schools. As a consequence, blood product availability is at its nadir during school holidays.³⁰ The system was developed to address this problem. Patients who were booked for major surgical gynaecologic procedures were asked to mobilize potential blood donors among their families, friends, and relatives. The hospital then exchanged the blood that was donated on their behalf by family members for hospital-banked blood that was required for the surgical procedures. The hospital would also track down any unused blood donated to other patients who had already undergone surgical procedures and re-allocate it to cancer patients who could not find any potential donors. This requires concerted effort and time investment from both the blood bank staff as well as clinicians.³⁰

2.8 Obesity and Surgical outcome

2.8.1 Cervical Cancer

Papadia et al.³¹ has reported an estimated blood loss of 800 to 1391 millilitres in obese patients. There was an increase in EBL with increasing weight. There was 10% intraoperative complication rate in obese patients which mainly related to haemorrhage. The most common postoperative complications were fever, ileus, infections, urinary tract infections (UTIs), and dehiscence of the

wound and thromboembolic events. The postoperative complications rate ranged from 20% to 90%.²²

2.8.2 Endometrial Cancer

Obese and morbidly obese patients with endometrial cancer were found to have a higher mean operation time (212 minutes) compared to non-obese patients (184 minutes).³¹ There was also a high mean EBL of 441 to 819 mL for obese and morbidly obese patients compared to 324 to 464 mL for non-obese patients. Obese patients had a 10% intraoperative complication rate related to haemorrhage. Obese patients had a higher probability of having only total abdominal hysterectomy and bilateral Salpingo-oophorectomy performed. Papadia et al.³¹ reported more blood loss for obese patients. Obese and morbidly obese patients recorded a higher rate of wound infections and dehiscence compared to non-obese patients.³¹ BMI was not associated with other postoperative complications such as postoperative ileus, pneumonia, fever, deep venous thrombosis (DVT), pulmonary embolism (PE), lymphedema, and UTIs.³¹ There was no relation between BMI and length of hospital stay.³¹

CHAPTER 3: RESEARCH METHODS

3.1 Aim of the Study

The aim of the study was to investigate early and intermediate complications following gynaecological oncology surgery at Charlotte Maxeke Johannesburg Academic Hospital.

3.2 Specific Objectives

1. To describe the socio-demographic factors of the patients who had complications during surgical treatment for gynaecological oncology at Charlotte Maxeke Johannesburg Academic Hospital.
2. To describe the types of gynaecological malignancies in these patients.
3. To describe comorbid diseases in these patients.
4. To describe complications of the disease, surgery, chemotherapy, and radiotherapy.

3.3 Methodology

3.3.1 Study Setting

Charlotte Maxeke Johannesburg Academic Hospital is a tertiary hospital, serving as a referral hospital for the surrounding academic hospitals such as Chris Hani Baragwanath Academic Hospital, Rahima Moosa Mother and Child Hospital, Helen Joseph Hospital, and regional and district hospitals in the surrounding greater Johannesburg region.

3.3.2 Study Sample

All women who had recorded complications during and after pelvic gynaecological surgery for suspected gynaecological malignancy from January 2015 to December 2016 at CMJAH.

3.3.3 Sample Size

Gynaecological oncology patients who under-went laparotomy for a confirmed gynaecological malignancy or a suspected malignancy which was subsequently confirmed by histology, from January 2015 to December 2016. Patients who had complications intraoperatively, within 24 hours or from 24 hours to 6 weeks postoperatively, were included in the study.

3.3.4 Study Design

The study is retrospective, using medical records of patients at Charlotte Maxeke Johannesburg Academic hospital.

3.3.5 Inclusion Criteria

Gynaecological oncology patients who under-went laparotomy for a confirmed gynaecological malignancy or a suspected malignancy which was subsequently confirmed by histology, from January 2015 to December 2016.

Patients who received postoperative care at CMJAH.

Patients who had complications during surgery or up to 6 weeks post operatively.

3.3.6 Exclusion Criteria

A patient who had surgery prior to the study period.

Patients who had vaginal and vulvar surgeries.

Patients without histological or histopathological confirmation of malignancy.

Patients who had no complications during surgery or up to 6 weeks post operatively.

3.3.7 Data Collection

The study was conducted at the Charlotte Maxeke Johannesburg Academic Hospital. Admission ward hospital records were used to trace the patients who had surgery, and the early and

intermediate outcome of, as well as patients' performance until discharge. Gynaecology theatre record books were retrieved to check the operations done during the study period. Files from the elective gynaecology ward were retrieved to obtain a further history and track the treatments that were done.

The electronic records of the patients who had oncology were obtained from hospital records. Permission to collect and interpret the data was sought from the clinical head of the medical oncology unit, radiation oncology, and the other wards involved.

Records of cytology, histology, and haematological studies as well as other biochemistry were retrieved from the NHLS system using patient's hospital numbers as well as barcodes. Information was then entered onto the data collection sheet and National Health Laboratory Services online database.

3.3.8 Data Analysis

The study employed quantitative techniques. Descriptive data analysis was used for most of the data collected, using means $\pm$ 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 means of 95% confidence intervals.

Surgery was used as the denominator for all the analysis and repeat surgery for complications were not reanalysed. The crude and unadjusted intraoperative and postoperative complication rates were calculated.

Hospital reported postoperative complications were calculated. Statistical analysis was performed using STATA and multivariate regression was used to determine significant predictors of intra-operative and post-operative complications.

3.4 Ethical Requirements and Permission to Conduct Study

Permission to perform the study was obtained from the Charlotte Maxeke Hospital Chief Executive Officer and the head of the Medical Oncology unit at the hospital. Approval from the University of Witwatersrand Human Research Ethics Committee was sought before the study was conducted (M170974).

CHAPTER 4: RESULTS

4.1 Study Population, Exclusion and Inclusion Criteria

A total of 206 women had an elective laparotomy for confirmed and suspected gynaecological malignancy at CMJAH between January 2015 and December 2016. Figure 4.1 below summarises the study population. Ninety (90) of the patients had a confirmed malignancy on post-operative histology and of these, 32 had recorded complications. The 32 women met the inclusion criteria for our study.

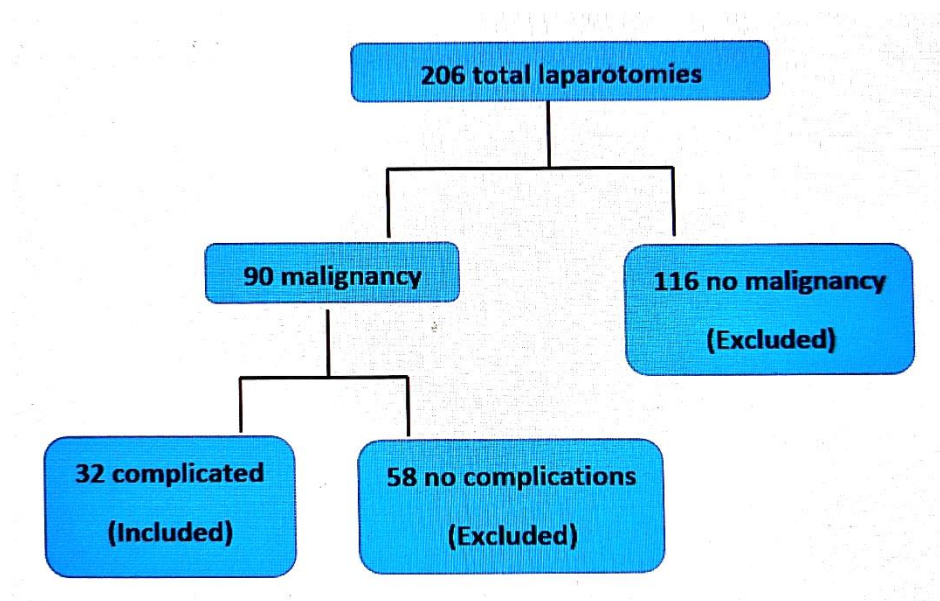


Figure 4.1 Study population and exclusions

4.2 Demographics

The mean age on our population was 56 years ($SD \pm 13.26$) with ages between 26 years and 76 years. Their mean parity was 2.78 ($SD \pm 1.75$) with a range 0 to 5 and more. Twenty-four (24, 75.00%) patients were Africans, 2 (6.25%) patients were Caucasians and 6 (18.75%) patients' race was not documented. All the women (32, 100%) in our study were South African citizens.

4.3 Risk Factors for Poor Morbidity

Pre-operative work-up was abnormal in 1 (3.13%) out of 32 patients. The patient exhibited bilateral pleural effusion on chest radiography.

There were 20 (62.50%) patients who had co-morbid diseases. Of the women who had co-morbid diseases, 6 (18.75%) patients had both hypertension and diabetes mellitus and 14 (43.75%) patients had only hypertension. All the women (100%) who had co-morbid diseases were on treatment. There were 8 (25%) patients who were HIV positive on treatment and 24 (75%) patients were HIV negative. The CD4 count and viral load on those who were positive were unknown or undocumented.

All women had a functional status assessment done on admission. The ECOG (Eastern Cooperative Oncology Group) functional status was used. There was 1 (3.13%) patient with an ECOG score of 0, twenty-five (75.1%) patients with an ECOG score of 1, and 6 (18.75%) patients with an ECOG score of 2. Ten complications occurred during surgery in these patients. Patients with an ECOG score of 0 had no complications while complications were recorded in 8 (80.00%) patients with an ECOG score of 1, and 2 (20.00%) patients had an ECOG score of 2. Ten (10) patients were readmitted due to surgery and disease complications, one (10.00%) patient had an ECOG score of 0, eight (80.00%) patients had an ECOG score of 1, and 1 (10.00%) patient had an ECOG score of 2.

4.4 Organ Systems Affected

The majority (15 of 32, 46.88%) of women in our study had malignancy of the endometrium. There were 10 (31.25%) patients with malignancy of the cervix, 5 (15.63%) patients with malignancy of the ovary, 1 (3.13%) patient with malignancy of the fallopian tube, and 1 (3.13%) patient had undocumented organ system affectation. Figure 4.2 below shows the distribution of organ systems affected. Twenty-eight (87.50%) had a primary gynaecological malignancy and 4 (12.50%) patients had malignancies secondary to the spread to the gynaecological organs.

There was a history of previous malignancy in 2 (12.50%) of the 32 women.

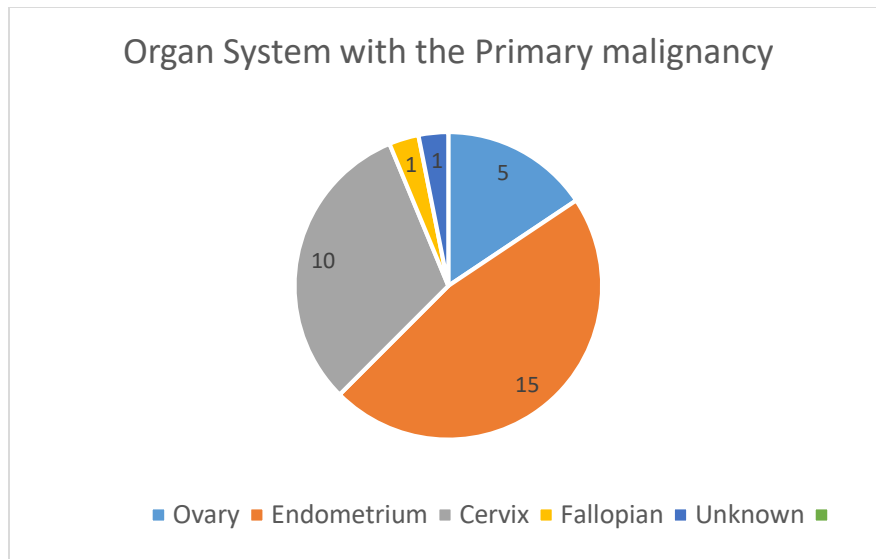


Figure 4.2 Organ system with malignancy and complications rate

4.5 Gynaecological Surgery Performed

The duration of operation was between 65 to 435 minutes with a mean of 141.59 (SD±77.69) minutes. The blood loss was estimated to be 200 to 1500 millilitres with a mean of 615.62 (SD±315.31) millilitres.

Seven (7) types of surgical procedures were done on these patients. TAH and BSO were the most common surgical procedures done in 16 (50.01%) patients, followed by TAH, BSO & Omentectomy in 5 (15.63%) patients, and radical hysterectomy and lymphadenectomy in 5 (15.63%) patients, TAH & BSO & Omentectomy & lymphadenectomy in 2 (6.25%) patients, TAH, BSO, Omentectomy & bowel resection in 2 (6.25%) patients, and TAH, BSO & lymphadenectomy in 2 (6.25%) patients. Table 4.1 below shows the types of surgical procedures performed.

Table 4.1 Types of open abdomen surgical procedures performed.

Type of surgery	Frequency	Percentage
TAH & BSO	16	50.01
TAH & BSO and Omentectomy	5	15.63
Radical Hysterectomy and lymphadenectomy	5	15.63
TAH, BSO, Omentectomy and lymphadenectomy	2	6.25
TAH, BSO, Omentectomy, and bowel resection	2	6.25
TAH, BSO, and lymphadenectomy	2	6.25

4.6 Histopathological Results

Seventeen (17) different types of cancer histology's were reported. The top 5 were invasive squamous cell carcinoma 8 (25.00%), invasive endometroid endometrial carcinoma 4 (12.50%), carcinosarcoma 4 (12.50%), invasive adenocarcinoma of the ovary 2 (6.25%) and serous carcinoma of the ovary 2 (6.25%). Histological differentiation was unknown or unreported in 28 (87.50%) and reported as moderately differentiated in 3 (9.38%) and poorly differentiated in 1 (3.13%).

4.7 Surgical Complications

There were 10 (31.25%) complications reported during surgery. The complications during surgery were bleeding 5 (50.00%), bladder injury 3 (30.00%), bowel injury 1 (10.00%), and ureter injury 1 (10.00%). There were 2 cases of complications that occurred within 24 hours of surgery (6.25%).

Table 4.2 Complications characteristics

Complication period	Number	Percentages
Intra-operative		
Bleeding	5	50
Bladder	3	30
Bowel injury	1	10
Ureteric injury	1	10
24 hrs to 6 weeks		
Sepsis	9	42.86
Bowel obstruction	2	9.52
Others	2	9.52
Reason for Readmission		
Wound sepsis	5	55.56
Sepsis (unspecified)	1	11.11
Bowel obstruction	2	22.22
Acute gastroenteritis with electrolyte imbalance	1	11.11

The patients who were discharged and then readmitted due to complications had mean hospital stays of 12.12 (SD±6.70) days upon readmission. *Klebsiella pneumoniae* was cultured in 1 (11.11%) patient as the source of infection while 8 (88.89%) of those who were readmitted had no report of specific infective microorganisms cultured on blood or wound swab.

One patient had pulmonary emboli confirmed on ventilation or perfusion scan. One patient from the 32 died of hypovolemic shock in theatre within 24 hours of surgery.

CHAPTER 5: DISCUSSION

Nhokaew et al.⁶ reported that the mean age associated with complications following endometrial cancer was 56.9 years. In our study, the mean age was 56 years and even though this is an inclusive study and not limited to endometrial cancer, our findings were in keeping with the age reported in the literature as associated with complications of gynaecological oncology surgery. In the study done in Malawi by Chunula et al.³⁰, the median age was reported as 46 years, however, their study was specific to patients' early stages of invasive carcinoma of the cervix. A United Kingdom study by Iyer et al.³² looked into surgical outcomes in gynaecological outcomes and reported a median age of 62 years. However, it is noted that women who are above 50 years of age are generally at increased risk for gynaecological malignancies and by default, associated complications in surgery.

Our findings of 75% of women being of the African race in this study was expected as this public healthcare institution mostly serves African patients. We do not think the increased number of patients of African race with complications is a true reflection of the association between race and complications for open surgery in gynaecological malignancy but biased due to population distribution. Ereckson et al.³ in the United States reported that 60.3% of white patients had complications. Their race population distribution is not similar to ours.

The finding of complications in association with comorbidity of diabetes mellitus and hypertension in 62.50% of patients was expected. The two chronic conditions are associated with an increased body mass index (BMI) and metabolic syndrome (MS). Both increased BMI as well as MS are associated with cancer risk, intra-operative difficulty, and complications as well as operative wound complications. Nhokaew et al.⁶ also reported that the patients experiencing wound complication tended to have underlying DM, a previous history of major abdominal surgery, and high BMI.

There was no statistical association between a Human Immunodeficiency Virus (HIV) positive status and surgical complications. Instead, complications were seen in 75% of patients who were HIV negative as compared to 25% who were HIV positive. These findings trigger further explorations of what was previously known regarding HIV disease and infections or complications

especially in this era of availability of the highly active antiretroviral therapy (HAART). However, these findings should be interpreted with caution as this was a retrospective study with a small study sample as well as incomplete data regarding HIV status on a significantly large population of the study.

We have found no statistical association between ECOG functional status and surgical complications. A functional status ECOG score of 1 was found in 80% of the surgical complications. This functional status is expected to lead to a good outcome as these patients' health status is reasonably good. It is unknown why these patients had a high rate of surgical complications. Perhaps the reasons are that patients with a good ECOG functional status are likely to be managed surgically as they are medically fit for surgery than in the case of patients with an ECOG of 3 who may be referred directly to chemotherapy or radiotherapy.

The rate of complications was higher in endometrial cancer compared with cervical cancer. This is contrary to findings by Iyer et al.³² who reported more complications in ovarian cancer, followed by cervical cancer. However, in our study, almost half of the study population had endometrial cancer. The complication rate in this group can be attributed to associated co morbidities such as MS and high BMI.

Our study found sepsis to be the most common complication occurring in forty per cent (40%) of the patients between 24 hours and 6 weeks after surgery, and fifty-five per cent (55%) of the patients were readmitted with wound sepsis. This could be attributed to high BMI on our study population, DM, and prior surgery. This is corroborated by Nhokaew et al. and Erekson et al.^{6, 3} in their research findings. Iyer et al.³² reported a lower rate of 30.1% and 27.8% for wound breakdown and infection, respectively. However, this study was based on overall oncology surgeries including those for cancer of the vulva.

Our operation times were reasonable and there was lower estimated blood loss as opposed to findings by Papadia et al.³¹ TAH and BSO was the most common procedure performed and the increased rate of complications in this group with comorbid diseases was expected. An earlier study at the same institution by Guidozzi and Ball³³ reported longer operating times and higher blood loss of 318 minutes and 2900 ml respectively in gynaecological surgery for combined malignant and non-malignant cases. Not surprisingly, they found increased postoperative

complications in patients where the surgical procedure was performed for gynaecologic cancer (procedures including radical dissection, lymphadenectomy, or debulking). These procedures are more difficult and the operative times are longer.

Our study has found haemorrhage to be the most common intra-operative complication followed by bladder injury. The study by Iyer et al.³² corroborated with our study whilst Satitniramai et al.²³ found contrary results, with bladder injuries being the most common complications in their study. Chinula et al.³⁰ reported transfusion in a high number of patients postoperatively. However, our population and gynaecological surgeons' experience may not be similar. It is also not known how blood loss was calculated or estimated in all these studies. It is not known if the estimation by the anaesthetists in all these studies was based on a universal tool or strategy.

There was one (3.12%) mortality in our study. The patient had choriocarcinoma with metastasis to the lung and an ECOG score of 2. She demised due to haemorrhage in theatre. This is attributed to the stage of the disease. Chinula et al.³⁰ also reported a similar rate with 3.57% mortality due to haemorrhage. Ereckson et al. and Iyer et al.^{3, 32} reported lower mortality rates of 0.17% and 0.13% respectively. Guidozzi and Bale³³ reported a 60% mortality in those patients with advanced ovarian cancer. This was attributed to the stage of the disease and the extent of the operations, which involved extensive primary cytoreductive surgery with multiple organ resection.³³ However, the mortality rate on our study needs to be interpreted with caution as this study was low powered and was also a retrospective study.

CHAPTER 6: CONCLUSION

Gynaecological oncology surgery is associated with considerable mortality and morbidity and our study provides much needed estimates of complication risk associated with open abdominal surgeries (exploratory laparotomy, hysterectomy with or without bilateral Salpingo-oophorectomy, lymphadenectomy and omentectomy) and procedures for specific cancers to counsel patients and benchmark surgical performance. It is expected that haemorrhage will be the commonest complication in open abdominal gynaecological oncology surgery due to the extensiveness of the procedure, likelihood of neo-vascularization and infiltration of the tumour to vessels.

General sepsis and wound sepsis were other common complications that needed to be considered. The prevention of surgical wound complications are important topics of inquiry. However, before interventions can be designed and implemented, specific risk factors associated with wound complication must be identified.

There are two reasons for the goal to reduce SSIs: one, to limit the patient's morbidity and two, to reduce the costs of healthcare by decreasing readmission rates and limiting prolonged hospital stays. In the former, SSIs can result in significant morbidity and mortality.

CHAPTER 7: LIMITATIONS

This was a retrospective study which naturally has limitations. The study was also conducted in one centre over a period of two years. The study sample was small. There is limited data on gynaecological oncology surgeries in South Africa which made it difficult to find a study to compare it with.

There was missing information on the patient's records regarding many variables. The intraoperative haemorrhage was difficult to define or determine due to the lack of a standard tool to estimate blood loss. The need for intraoperative or postoperative blood transfusion was used as a marker of significant intraoperative haemorrhage.

CHAPTER 8: STRENGTH OF THE STUDY

The study highlighted complications to look out for in open abdominal surgery and may help reduce patient's morbidity as well as reduce the costs of healthcare by decreasing readmission rates and limiting prolonged hospital stays.

CHAPTER 9: RECOMMENDATIONS FOR FUTURE RESEARCH AND CLINICAL PRACTICE

There is a need for further and larger studies, preferably in the form of prospective and multi-centred studies to validate our findings. Perhaps future studies should also compare surgeon's experiences and the level of specialization in evaluating complication rates. There is also a need to assess quality of life and late complications in these patients.

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ANNEXURE 1:**Data Collection Sheet****DEMOGRAPHIC DATA**

Age at diagnosis (in years)												
Parity	0	1	2	3	4	5	>5	Unknown				
Race	African		Indian		Asian		Coloured		Caucasian		Unknown	
Education	None		Primary		Prematric		Matric		Tertiary		Post Grad	Unknown
Nationality	SA		Southern Afr (Country)					Other Countries			Unknown	
Smoking	Previous		Current		Weight(kg)				Height(m)			

CO MORBID DISEASES (if yes, specify below)

Diabetes/Endocrine	Yes		No		Treatment		Yes	No
Cardiovascular	Yes		No		Treatment		Yes	No
Respiratory	Yes		No		Treatment		Yes	No
Cardiac disease	Yes		No		Treatment		Yes	No
HIV	Yes		No		Treatment		Yes	No
Dermatology	Yes		No		Treatment		Yes	No
Thrombosis	Yes		No		Treatment		Yes	No
Neurology	Yes		No		Treatment		Yes	No
Autoimmune	Yes		No		Treatment		Yes	No
Infectious	Yes		No		Treatment		Yes	No

FUNCTIONAL STATUS AT DIAGNOSIS

ECOG	1		2		3		4	
------	---	--	---	--	---	--	---	--

MALIGNANCY

Ovary		Endometrium		Cervix		Fallopian tube		Unknown	
Primary		Secondary		Recurrence		Persistent			
Previous malignancy		Yes		No		If yes, which one?			
If yes, previous management		Chemo		Radiation		Both		Surgery alone	Surgery & Radiation
Current histology								Unknown	
Differentiation		well		moderate		poor		unknown	

PREOPERATIVE WORKUP

White Cell Count		Haemoglobin		Albumin	
Platelets		Urea		Total Protein	
Creatinine		Glucose		ECG	
ECG		Normal		Abnormal	Unknown
CXR		Normal		Abnormal	Unknown
Others					

SURGICAL PROCEDURE DONE (Tick all applicable single or combinations)

Total Abdominal Hysterectomy		Bilateral Salpingo-Oophorectomy	
Omentectomy		Unilateral Salpingo-Oophorectomy	
Radical Hysterectomy		Lymphadenectomy	
Bowel Resection		Upper Abdomen Surgery	
Total Laparoscopic Hysterectomy		Laparoscopic Assisted Vaginal Hysterectomy	
Duration of surgery(minutes)		Estimated blood loss (ml)	

COMPLICATIONS DURING SURGERY

Bleeding	Yes		No		Unknown					
Cardiorespiratory	Yes		No		Unknown					
Drug reaction	Yes		No		Unknown					
Visceral injury	Bladder		Rectum		Bowel		Vessels		Ureters	
Other(s)										
Unknown										

COMPLICATIONS 24 hrs. POST SURGERY UNTIL 6 WEEKS

Bleeding	Primary		Secondary		Unknown		Hematoma	
Sepsis	Yes		No		Unknown			
Abscess	Yes		No		Unknown			
Hematoma	Yes		No		Unknown			
Urological	Retention		Incontinence		Fistula			
Respiratory	LRTI		Effusion		Collapse		Oedema	
Wound	Sepsis		Dehiscence		Burst abdomen			
Neurological	Depression		Confusion		Psychosis			
Lymphatic	Lymph Edema		Lympho Cyst					
Cardiac	AF		MI		Failure			
Thromboembolism	DVT		PE		Unknown			
Other(s)								

COMPLICATIONS AT 6 WEEKS OR MORE POST SURGERY

Bleeding	Primary		Secondary		Unknown		Hematoma	
Sepsis	Yes		No		Unknown			
Abscess	Yes		No		Unknown			
Hematoma	Yes		No		Unknown			
Urological	Retention		Incontinence		Fistula			
Respiratory	LRTI		Effusion		Collapse		Oedema	
Wound	Sepsis		Dehiscence		Burst abdomen			
Neurological	Depression		Confusion		Psychosis			
Lymphatic	Lymph Edema		Lympho Cyst					
Cardiac	AF		MI		Failure			
Thromboembolism	DVT		PE		Unknown			
Other(s)								

READMISSION

Reasons	Elective		Emergency		Other	
Period readmitted (days)						

IF SEPSIS,

Source	Wound		Urine		Malignant lesion		Chest		CSF	
Organism(s)										

IF THROMBOSIS, REGION

Peripheral Veins	Yes		No	
Pulmonary	Yes		No	
Unspecified				

RECORDED CAUSE OF DEATH (IF DEMISED)

--

Time of death	Within 24hrs		Within 6 weeks		After 6 weeks	
Place of death	ward		ICU		Theatre	

ANNEXURE 2: University of Witwatersrand Human Research Ethics Committee Permission



R14/49 Dr MR Nchabeleng-Shibambu

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL) CLEARANCE CERTIFICATE NO. M170974

NAME:
(Principal Investigator)
DEPARTMENT:

Dr MR Nchabeleng-Shibambu
School of Clinical Medicine
Department of Obstetrics and Gynaecology
Chris Hani Baragwanath Academic Hospital

PROJECT TITLE:

Early and intermediate outcomes of patients who
underwent gynaecological oncology surgery at
Charlotte Maxeke Johannesburg Academic Hospital

DATE CONSIDERED:

29/09/2017

DECISION:

Approved unconditionally

CONDITIONS:

SUPERVISOR:

Dr L Mbodi

APPROVED BY:


Professor PE Cleaton-Jones, Chairperson, HREC (Medical)
15/11/2017

DATE OF APPROVAL:

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and ONE COPY returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/We fully understand the conditions under which I am/we are authorised to carry out the above mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. I agree to submit a yearly progress report. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed, in this case, the study was initially reviewed in September and will therefore be due in the month of September each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

ANNEXURE 3: Permission to Conduct Research: Charlotte Maxeke Johannesburg Academic Hospital, CEO



GAUTENG PROVINCE

HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

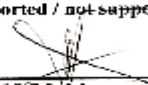
Enquiries:
Ms. N. Mzila
Office of the Clinical Director
Email: Nelwazi.Mzila@gauteng.gov.za
Tell: (011) 488-4812
16 October 2017

Dear Dr. M R. Nchabeleng – Shibambu

STUDY TITLE: Early and Intermediate outcomes of patients who underwent Gynaecological Oncology Surgery at Charlotte Maxeke Johannesburg Academic Hospital

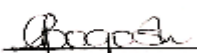
Permission to conduct the above mentioned study is provisional approved. Your study can only commence once Ethics approval is obtained. Please forward a copy of your Ethics Clearance Certificate as soon as the study is approved by the Ethics Committee for the CEO's office to give you the final approval to conduct the study.

Supported / not supported


Dr. M.I. Motokeng
Clinical Director

DATE: 17/10/2017

Approved / not approved


Ms. G. Bogoshi

Chief Executive Officer

DATE: 19.10.2017

ANNEXURE 4: Permission to Conduct Research: Department of Obstetrics and Gynaecology, Charlotte Maxeke Johannesburg Academic Hospital, Clinical HOD



GAUTENG PROVINCE
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries: Dr L. Chauke

12 October 2017

Tel: 011 488-3179
Fax: 011 643-2522

Ms Bogoshi
CEO
Charlotte Maxeke Johannesburg Academic Hospital
Parktown
Johannesburg

Dear CEO

Re: Request for permission to conduct research titled:

Permission to obtain:
Early and intermediate outcomes of patients who underwent Gynaecological Oncology surgery at Charlotte Maxeke Johannesburg Academic Hospital :-
Dr M R Nchabeleng-Shibambu

The above matter refers. I have looked at the protocol and **satisfied to recommend** that she be granted permission to conduct study as proposed. The candidate has also satisfied the requirements of the Wits Human Research Committee.

Thank you

Dr H. L. Chauke
Chief Specialist and Clinical Head
Department of Obstetrics and Gynaecology
Charlotte Maxeke Johannesburg Hospital
and the University of the Witwatersrand