Outcomes of patients with Stage IB1 and IB2 Cervical Cancer who have had Wertheim's Hysterectomies with or without adjuvant chemo-radiotherapy as primary treatment at Charlotte Maxeke Johannesburg Academic Hospital

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Dr Sandra Marques Nascimento Fonseca

Research report submitted to the University of the Witwatersrand in partial fulfilment for the degree of Master of Medicine

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DECLARATION

I, Dr Sandra Marques Nascimento Fonseca declare that this dissertation is my own work.

It is being submitted as partial fulfilment for Masters in Medicine degree in Obstetrics and Gynaecology.

It has not been previously submitted for any degree or examination to the Faculty of Health Sciences of the Witwatersrand University or any other institution.

Dr SM Nascimento Fonseca

Date 30 July 2016

DEDICATION

I dedicate this work to my mother Maria Jose da Silva who died of cervical cancer. She and my sons Gabriel and Zavier will always be my inspiration and the reason I will keep striving to do great things in the field of Obstetrics and Gynaecology.

ACKNOWLEDGEMENTS

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3. Dr Jeffrey Kotzen, who gave me valuable insight into the existing radiation oncology post-operative protocols for study patients with regards to further management, side effects and future follow up.

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ABSTRACT

Background

Cervical cancer is the 3rd most common female malignancy worldwide. It is classified and managed according to stage as defined by the FIGO Committee on Gynaecology Oncology classification of 2009. Stage specific treatment is tailored according to prognosis and risk of recurrence as determined by tumour type, tumour size, tumour grade, lymph node metastases, lymphovascular space involvement (LVSI), parametrial spread and presence of any other metastatic deposits at presentation. This study only concentrated on patients who presented with Stage IB1 and 1B2 tumours managed by Class III / Meig's Radical / Wertheim's hysterectomy and bilateral pelvic lymphadenectomy.

Aims

Primary Outcome

1. Assess disease free interval and overall survival 2 years post-operatively.

Secondary Outcomes

1. Assess adequacy of patient selection
2. Assess risk factors for recurrence
3. Compare recurrence risk of HIV positive patients versus HIV negative patients.
4. Determine surgical and post-surgical complication rate.

Materials and Methods

This was a retrospective institutional cohort study conducted at the Charlotte Maxeke Johannesburg Academic Hospital. All patients with Stage IB1 or IB2 cervical cancer treated with Wertheim hysterectomies between 2002 and 2012 were included.

Surgical records, histology records, further postoperative management records and gynaecological outpatient follow up records were used to collect data for the patients.

Histological findings post-operatively determined further management. Surgical margins had to be 10mm clear of tumour with no positive lymph nodes otherwise external beam radiotherapy and brachytherapy or chemo-radiotherapy were recommended in addition to primary surgical management.

Results

Of the 72 patients initially identified, 69 patients were suitable for study inclusion. The mean age of the study population was 45 years. Study population racial distribution: 68.12% were Black, 26.09% were White, 2.9% were Coloured and 2.9% were Indian. Average parity and gravidity of patients alive at the end of the study was 2.86 and 3.56; while average parity and gravidity of patients deceased at the end of the study was 2.5 and 2.8 respectively. Study population ECOG status: 16% were ECOG 0, 83% were ECOG 1 and 1% were ECOG 2. Overall survival at the end of the study was 86% and patients were disease free postoperatively for an average of 5 years. Thirty three percent of the patients were disease free for more than 5 years. Preoperative clinical staging and postoperative histological staging correlated only in 61% of cases. Correct management by Wertheim's hysterectomy was rendered to 75% of patients whereas the remainder were incorrectly managed and should have had either a simple hysterectomy with no pelvic lymphadenectomy or radiotherapy only as primary therapy. More advanced stages, tumours ≥ 4cm, adenomatous cell type, > 5mm depth of invasion, >7mm lateral spread, higher number of nodes positive for metastatic disease, surgical margins ≤ 10mm, positive lympohovascular space, parametrial and pouch of Douglas (POD) involvement were factors that had a poorer prognosis with regards overall survival, disease-free interval or both. Poorly differentiated tumours were

more likely to recur but did not have a poorer prognosis compared with regards to overall survival or disease free interval at 2 or more years compared to well and moderately differentiated tumours. Mortality of HIV reactive patients was 16.7% compared to 12.5% for HIV non-reactive patients. This difference was not statistically significant at the 95% confidence level. HIV status also did not increase risk of recurrence. Lower CD4 counts were shown to have a lower disease-free period and overall survival. Intra-operative surgical complication rate was 6%. Immediate post-operative complication rate was 16%. Of the patients who required DXT or DXT and chemotherapy 33% had side-effects or complications from adjuvant therapy. Patients treated with DXT and chemotherapy had had more side-effects than those treated with DXT only.

Conclusion

The mean age of the study population was 45 years. This was lower compared to other larger studies possibly due to younger presentation related to HIV disease. HIV positive patients with lower CD4 counts were shown to have poorer prognosis with regards to survival. HIV status was not shown to be a risk factor for recurrence. The overall survival and disease-free period at 5 years was similar to that of other international studies. Only two thirds of the patients were adequately selected for surgery according to the institution's criteria for a Wertheim's hysterectomy and therefore it may be necessary to reconsider the pre-operative assessment of these patients. More advanced stages, tumours ≥ 4cm, adenomatous cell type, poor differentiation, > 5mm depth of invasion, >7mm lateral spread, higher number of nodes positive for metastatic disease, surgical margins ≤ 10mm, positive lympohovascular space, parametrial and pouch of Douglas involvement were factors that had a poorer prognosis with regards to recurrence, overall survival and disease-free interval. However, the rates of recurrence were not statistically significant at a 95% confidence level.

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1. INTRODUCTION

Cervical cancer is the 3rd most common female malignancy globally but it is commonest cancer in the developing world. The worldwide burden of disease (85%) and mortality from disease (88%) is therefore primarily in developing countries. In 2008 the global mortality:incidence ratio of cervical cancer was 52%, accounting for 270000 deaths. [1]

Cancer of the uterine cervix is classified according to the internationally recognised FIGO Committee on Gynaecology Oncology classification of 2009. [2]

Table 1: FIGO classification of Carcinoma of the Cervix Uteri 2009

Stage I	Carcinoma confined to cervix
IA	Invasive carcinoma diagnosed microscopically, with depth ≤5.0 mm and extension ≤7.0 mm
IA1	Measured stromal invasion of ≤3.0 mm in depth and horizontal extension of ≤7.0 mm
IA2	Measured stromal invasion of >3.0 mm and not >5.0 mm with an extension of not >7.0 mm
IB	Clinically visible lesions limited to cervix or pre-clinical cancers greater than stage IA*
IB1	Clinically visible lesion ≤4.0 cm in greatest dimension
IB2	Clinically visible lesion >4.0 cm in greatest dimension
Stage II	Cervical carcinoma invades beyond uterus, but not to pelvic wall or to lower third of the vagina
IIA	Without parametrial invasion
IIAl	Clinically visible lesion ≤4.0 cm in greatest dimension
IIA2	Clinically visible lesion >4.0 cm in greatest dimension
IIB	With obvious parametrial invasion
Stage III	The tumour extends to pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or non-functioning kidney**
IIIA	Tumour involves lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney
Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous oedema, as such, does not permit a case to be allotted to Stage IV
IVA	Spread of the growth to adjacent organs
IVB	Spread to distant organs

* All macroscopically visible lesions–even with superficial Invasion–are allotted to stage IB carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.0 mm and a horizontal extension of not >7.0 mm. Depth of invasion should not be >5.0 mm taken from the base of the epithelium of the original tissue–superficial or glandular. The depth of invasion should always be reported in mm, even in those

cases with "early (minimal) stromal invasion" (~1.0 mm). The involvement of vascular/lymphatic spaces should not change the stage allotment.
** On rectal examination, no cancer-free space between the tumour and the pelvic wall. All cases with hydronephrosis or non-functioning kidney are included, unless they are known to be due to another cause. [2]

Stage specific treatment of the above-mentioned stages is tailored according to prognosis and risk of recurrence as determined by tumour type, tumour size, tumour grade, lymph node metastases, lymphovascular space involvement (LVSI), parametrial spread and presence of any other distant metastatic deposits which correlate with outcomes in numerous studies.[3]

Within our institution only the following treatment options are practised:

- Stage IA1 is treated with simple hysterectomy if childbearing is complete or by cervical conisation if childbearing is incomplete. Stage IA1 with LVSI is managed by modified radical hysterectomy and pelvic lymphadenectomy.
- Stage IA2 is managed by a simple hysterectomy and pelvic lymphadenectomy.
- Stage IB1 and some Stage IB2 are managed with radical hysterectomy and pelvic lymphadenectomy.
- Bulky Stage IB2 and Stage IIA2 treatment is chemo radiation only.
- Stages IIB to IVA are managed with chemo radiation only. Patients with IVA lesions and a fistula are candidates for pelvic exenteration.
- Stage IVB management is palliative chemotherapy and or palliative radiotherapy or supportive care i.e. pain control and hospice. [4, 5] Even though radical trachelectomy and pelvic lymphadenectomy is recommended for select patients with Stage IA1 with LVSI, Stage IA2 and even Stage IB1 who desire to maintain fertility, this modality has not been practised in our institution.

2. LITERATURE REVIEW

For Stage IB squamous carcinoma lesions of the cervix, early studies done between 1970 and 1990 indicated that the 5 year survival rates were 80 to 90% if either radical hysterectomy with pelvic lymph-adenectomy or if radical radiation therapy were used as primary therapy. In these studies rates of major complications were low with either of these therapeutic techniques. [6, 7] Later studies done in 2009 showed that risk of death was 59% lower in patients treated primarily with surgery versus radiotherapy (RT). [8] Therefore primary surgery was then recommended over primary RT for the management of these lesions.

Recurrence rates however were higher and survival rates were lower in patients treated surgically if lymph nodes, parametria and surgical margins were involved and if patients had large or deeply invasive lesions. In these cases, adjuvant radiotherapy or chemo-radiotherapy (CRT) was required to reduce recurrences and improve survival. CRT decreases recurrences and improves survival more than RT alone (80% versus 63%). [9]

Hysterectomies are classified into: Class I, Class II, Class III and Class IV. [10]

Class I hysterectomy is aimed at removal of all cervical tissue only.

Class II, is aimed at removal of more para cervical tissue, but preserves distal ureteric and bladder blood supply. The upper third of the vagina and medial half of the cardinal ligaments are removed.

Class III hysterectomy entails radical excision of parametrial and paravaginal tissues, as well as pelvic lymphadenectomy. Uterine arteries are ligated at their origin from the internal iliac arteries. Uterosacral ligaments are resected at their sacral attachments and cardinal ligaments are excised at

the pelvic wall. Half of the vagina is excised. The ureter is dissected from the pubo-cervical ligament almost completely but the superior vesicle artery is spared thereby preserving some of the distal ureteric blood supply.

Class IV hysterectomy is aimed at complete removal of all peri-urethral tissue, more extensive excision of the peri-vaginal tissue and internal iliac vessel excision at the pelvic wall if necessary. The superior vesicle artery blood supply is lost as the ureter is completely excised off the pubo-vesicle ligament and three quarters of the vagina is removed. A more extensive lateral dissection is done if metastases occupy the parametrium. [10]

At our institution, Class III or Meig's Radical hysterectomy/Wertheim's hysterectomy and bilateral pelvic lymphadenectomy is recommended for patients with Stage IB1 and most patients with IB2 tumours. These patients must have a good functional status as defined by the WHO / European Cooperative Oncology Group (ECOG) Performance Status Scoring System, they must be medically fit for surgery, under 65 years of age and should weigh ≤ 85kgs. Ovaries are conserved in pre-menopausal patients younger than 45 years of age. [11] Pre-operatively patients with clinically significant lymphadenopathy do not qualify for Wertheim's hysterectomy, but if intra-operatively enlarged or clinically suspicious nodes detected, surgery should be completed. [11]

Histological findings post-operatively play a significant role in determining further management. Surgical margins must be 10mm clear of tumour with no positive lymph nodes or tumour deposits in parametria or POD, otherwise external beam radiotherapy and vaginal vault intra-cavitary brachytherapy with or without adjuvant chemotherapy is recommended in addition to primary surgical management.

Patients' with a poor functional status, clinically significant lymph nodes and or significant vaginal involvement do not qualify for surgical intervention but are treated with CRT only. Post-operative external beam radiation uses a 4 field pelvic box technique administering 48Gy of high energy photons in 24 daily fractions. Four separate fields are used (opposed anterior-posterior beams and opposed lateral fields). Each field is shaped shielding as much of the surrounding normal tissues as possible especially the small intestines and rectum. Concurrent chemotherapy is used in our institution if the patient has 2 or more risk factors. Risk factors include LVSI, multiple positive pelvic nodes, positive margins or tumour deposits seen in parametria or POD. Cis-platinum is given once weekly for three weeks. Positive or close margins are boosted with 15Gy vaginal ovoid brachytherapy in 3 divided doses 4 to 6 weeks after external beam radiotherapy or reduced external beam field ports to a dose of 60-65Gy are used. [11] In our institution brachytherapy is administered by a tandem and ovoid applicator inserted intra-vaginally under anaesthesia.

Internationally Stage IB disease is managed surgically in the same way as it is in our institution. Patients with significant lymphadenopathy are also excluded from surgery. Post-operative management however is then decided by classifying patients as intermediate risk or high risk. Sedlis' criteria are used to classify women as intermediate risk and Peters' criteria are used to classify women as high risk.

INTERMEDIATE RISK (Sedlis' Criteria) [12]

1. LVSI plus deep 1/3 cervical stromal invasion in any size tumour.
2. LVSI plus middle 1/3 cervical stromal invasion in ≥ 2cm tumour.
3. LVSI plus superficial 1/3 cervical stromal invasion ≥ 5cm tumour.
4. No LVSI but middle or deep 1/3 cervical in ≥ 4cm tumour.

Recurrence risk and death if the above risk factors are present is about 30% after surgery. [12] In these patients only adjuvant RT is recommended as although adjuvant CRT improves recurrence risk, no difference was shown in overall survival. [13]

HIGH RISK (Peters' Criteria) [9, 14]

1. Positive surgical margins
2. Pathological parametrial involvement
3. Positive pelvic nodes

Recurrence risk is 40% and risk of death 50% with the above risk factors. [9, 14] Adjuvant CRT is therefore advocated internationally for these high-risk patients.

Aside from the controversy of whether patients with Stage IB should be treated with RT alone or with CRT post-operatively, a study by Rose PG et al also looked at outcomes when two chemotherapeutic agents were used as opposed to one. Hydroxyurea, 5- Fluorouracil and Cisplatin alone or in combination were assessed in advanced cervical cancer. Cisplatin alone or in combination was superior to the other agents. [3]

Peters et al. compared outcomes of high risk patients treated postoperatively with RT alone to CRT (Cisplatin and 5-Fluorouracil). Results showed that CRT was more effective for progression free survival at 4 years (80% versus 63%) and overall survival at 4 years (81% versus 71%) but caused more serious toxicity, namely: Neutropenia (35 versus 3 cases), Leukopenia (40 versus 1 case), Nausea (17 versus 2), Vomiting (15 versus 2) compared to RT alone.

In light of the toxicity risk, single-agent platinum based CRT is more often recommended internationally because it still significantly increases overall survival, and reduces progression and

recurrence rates compared to RT alone, even in high risk patients. [3] In our institution we offer only single agent cisplatin chemotherapy with the irradiation.

Anecdotal evidence suggests that patients in our institution should have good outcomes as we are highly selective by only managing Stage IB1 patients surgically and then with adjuvant RT or CRT whereas internationally Stage IB1, some IB2 and some IIA are managed in this way. Since tumour size and depth of invasion are independent risk factors for higher rates of recurrence and lower disease-free survival time it would seem that we should have good outcomes if patients were adequately selected.

A study by Landoni et al assessed intra-operative, early and late complications associated with Class III hysterectomies. Four percent of the patients developed intra-operative and early adverse outcomes and complications including obturator nerve resection, ureteric resection, uterine artery haemorrhage, haematomas, uterovaginal fistulae, pulmonary emboli, deep vein thromboses and wound abscess. Late complications occurred in 38% of cases and complications included abdominal hernia, wound infection, ileus, lower limb oedema, lymphocysts, hydroureteronephrosis, stress incontinence, atonic bladder and low compliance bladder. Patients who then received RT post operatively had a cumulative complication rate of 45%. [15]

HIV positive women have a five to eight-fold higher risk of cervical cancer compared to HIV negative women. [16] HIV positive women with invasive cervical cancer also tend to have lower CD4 counts and higher viral loads than those without cervical cancer and present about 10 years earlier with more advanced disease. [17, 18] Patho-physiologically the HIV-encoded Tat protein enhances the expression of HPV associated oncogenesis. [19] Radical hysterectomy is also used for tumours up to and including stage IIA in HIV positive asymptomatic patients without any significant increase in overall morbidity relative to HIV positive women. [20] Postoperative CRT is also used for women at

increased risk of recurrent or persistent disease but recovery from myelosuppression may be slower than in HIV-negative women. [16]

A cervical carcinoma cohort of stages IB1-IB2 followed up over 9 years following radical surgery with or without radiotherapy showed that 5-year progression-free survival rates for surgery-alone and surgery with RT groups were 93% and 90% and overall survival rates were 96% and 91% respectively. [21]

Problem Statement

The type and frequency of complications after Wertheim's hysterectomy with or without adjuvant therapy had never been assessed at our institution and this study attempted to quantify and assess our complications. In addition, the recurrence risk differences between HIV positive and negative women was also analysed. Our study assessed disease free interval and overall survival in our institution at a minimum of 2 years post-operatively depending on the date of surgery.

3. AIM

The primary aim of this study was to assess disease free interval and overall survival of those patients who presented with Stage IB1 cervical cancer and had a radical hysterectomy and pelvic lymphadenectomy as their primary modality of treatment irrespective of whether they received adjuvant CRT or not. Secondary aims were to assess the adequacy of selection, recurrence rate, prognostic factors causing high rates of recurrence, morbidity, mortality and complications in patients with Stage IB1 post Wertheim's hysterectomy alone or with further management namely adjuvant radiotherapy or chemo-radiotherapy.

4. OBJECTIVES

The purpose of this study was to:

4.1. Primary

1. Assess the disease-free interval and overall survival in our institution at 2 years post-operatively.

4.2. Secondary

1. Assess the adequacy of patient selection for Wertheim hysterectomy in view of correlation between pre-operative clinical staging and post-operative histological staging.
2. Determine risk factors for recurrence.
3. Quantify increases in recurrence risk of HIV positive patients versus HIV negative patients.
4. Determine surgical and post-surgical complication rate.

5. METHODS

5.1. Setting

Charlotte Maxeke Johannesburg Academic Hospital is a tertiary/quaternary hospital associated with the University of the Witwatersrand, Faculty of Health Sciences. The hospital offers a full range of secondary, tertiary and quaternary (highly specialised) services. The hospital offers services to the population of Gauteng province and neighbouring provinces. Patients are also referred from other clinics, primary, secondary and tertiary hospitals that may not provide all the services available at Charlotte Maxeke Johannesburg Academic Hospital. Costs of patient treatment are funded by a National Tertiary Services Grant, as well as Provincial allocation. The hospital also serves many patients from other African countries that are usually self-referrals and who feel the health service in their countries is inadequate.

5.2. Study population

At our institution, all patients with cervical cancer are presented at a combined gynaecology/oncology clinic once every week. Clinical findings in conjunction with histological findings are used to determine management strategy. At this meeting, potential candidates for Wertheim's hysterectomy are assessed by a senior gynaecologist or subspecialist. Patients included in the study were clinically staged as either IB1 or IB2 and fulfilled all pre-operative requirements for management by Wertheim's hysterectomy with regards to age, ECOG status, tumour size, tumour type and confinement to cervix.

The ECOG Performance Status Scoring System of criteria is used by doctors & researchers to assess patients' disease progression, how disease affects daily living abilities, and to determine appropriate treatment and prognosis. (See Table 2)

Table 2: ECOG Performance Status Scoring System

Score	Description
0	Asymptomatic (Fully active, able to carry on all pre-disease activities without restriction)
1	Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work)
2	Symptomatic, <50% in bed during the day (Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours)
3	Symptomatic, >50% in bed, but not bed bound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours)
4	Bed bound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair)
5	Death

Positive Margins = tumour present at or within 1mm of the inked margin of resection.

Negative Margins = no tumour within 1 cm of the inked margin.

5.2.1. Inclusion criteria

All the patients who had a Wertheim's hysterectomy at Charlotte Maxeke Johannesburg Academic Hospital for Stage IB1 and 1B2 cervical cancer were included.

5.2.2. Exclusion criteria

Patients with any stage not managed by Wertheim's hysterectomy

5.3. Study design

This was a retrospective cohort record review of all Wertheim Hysterectomies for cervical cancer Stages IB1 or IB2 done between the 1st of January 2002 and the 31st of December 2012.

5.4. Data collection

Names and hospital numbers of the patients and dates of their surgeries were collected from the gynaecology theatre record books. All cases treated between 2002 and 2012 were included. Names and hospital numbers were then used to access patients' admission and surgical records. From these records, we noted the following variables:

- duration of surgery,
- intra-operative complications,
- number of blood products required, as well as
- immediate post-operative recovery and complications.

The National Health Laboratory Services (NHLS) database post-operative histology reports were accessed and all histological parameters documented. These included the:

- tumour cell type,
- grade, depth of invasion, and lateral spread,
- LVSI, and
- POD and parametrial involvement.
- Positive margins were noted if tumour was present at or within 1mm of the inked margin of resection.
- Negative margins were noted if no tumour was present within 1 cm of the inked margin of resection.

Histological stage and number of positive pelvic lymph nodes removed were also noted.

We accessed radiation-oncology clinic files for further management post-operatively as determined by histology findings. Patients either received no further management, or radiation or chemo-radiotherapy depending on the risk category within the stage of disease.

We then accessed these patients' gynaecology outpatient files. Both these and the radiation oncology files were used to note post-operative follow up and cervical smears, as well as to determine disease free interval, overall survival and recurrence rates. Where patients had not followed up within the last 3 months of data collection – they were contacted telephonically or at home addresses supplied in these files. For patients who had not followed up within the last 3 months of data collection and could not be contacted telephonically or at home addresses we requested that the department of home affairs check if their deaths had been registered.

5.5. Data analysis

This was a retrospective institutional cohort study. Relevant patient information was collected on a patient information sheet. These details were then entered into a Microsoft Excel datasheet, and analysed statistically. Categorical data was summarized using frequencies, percentages and cross-tabulations, while continuous data was summarized using means, standard deviation and ranges.

For the primary objective, disease free interval and overall survival were expressed as means with 95% confidence intervals using the Kaplan Meyer test.

For the secondary objectives, Fischer's exact test was employed. Statistical significance was set at $p < 0.05$.

5.6. Ethics Approval

Application for ethics was granted by the Wits Ethics Committee. Informed consent was not required since the study was based on record reviews and did not interfere with patient management. Each patient's data was entered under a subject number and no names or hospital numbers were used in the final statistical analysis to ensure confidentiality of individual patients.

All data was represented as aggregates thereby guaranteeing the confidentiality of individual patients.

5.7. Timing

The study included data from the files of all Wertheim's hysterectomies done at Charlotte Maxeke Johannesburg Academic Hospital for Stage IB1 cervical cancer from the 1ST January 2002 to 31st December 2012. The study also included data from the same patients' files of subsequent postoperative visits, both gynaecological, radiation oncology and medical oncology.

5.8. Funding

The primary costs in the study were stationery and telephone calls for patient follow up which the researcher funded herself.

5.9. Permission from institution

Permission to do the study and to access patient's files with surgical, cytological and histological data was requested and granted from the superintendent Ms Bogoshi as well as clinical heads of departments of Obstetrics and Gynaecology, Prof F. Guidozzi, Radiation Oncology, Prof V. Sharma and Anatomical Pathology / NHLS, Prof MJ Hale. Copies of the approval letters are included in the appendix. Access to patient files with follow up information post-surgery, radiotherapy or radio/chemotherapy was also requested.

6. RESULTS

Initially 72 patients were identified for the study from the theatre case records as having had either radical hysterectomy or Wertheim's hysterectomy with pelvic lymphadenectomy. These were all Class III Meigs hysterectomies according to the Piver-Rutledge-Smith classification. Two were excluded as they were endometrial carcinomas and not cervical carcinomas. One was excluded because the procedure was abandoned when a lymph node removed intra-operatively showed metastatic disease on frozen section and therefore 69 patients were therefore included in the study.

6.1. Demographic profile of patients

6.1.1. Age distribution

The mean age of the study population was 45 years of age. The distribution of cases performed per age group is shown in Figure 1 below.

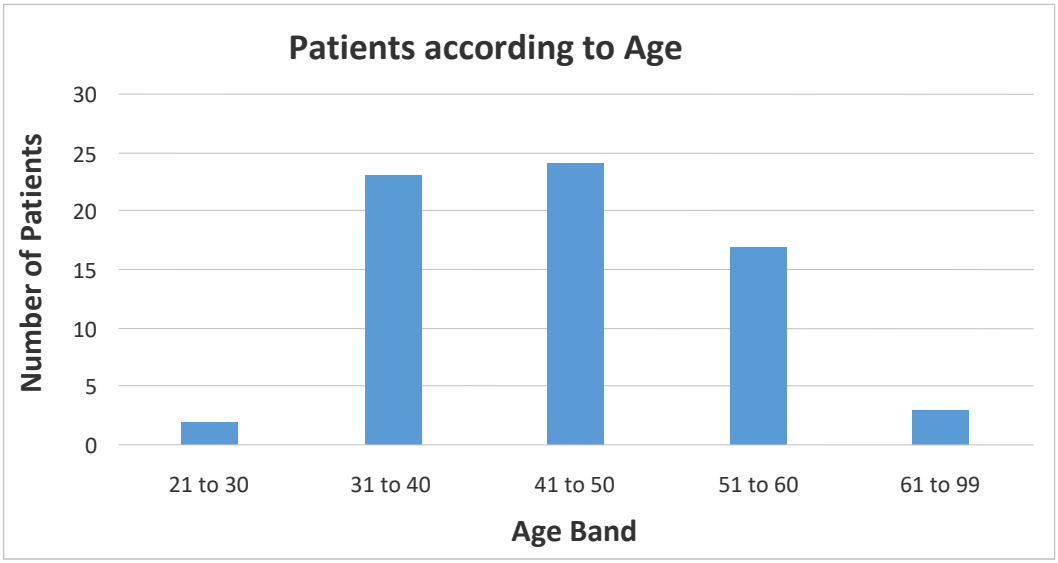

Figure 1: Distribution of cases performed per age group

6.1.2. Race profile

The racial distribution of patients is represented in the pie chart below. The majority of the patients were Black 47 (68.12%), followed by White 18 (26.09%), then Coloured 2 (2.9%) and Indian 2 (2.9%). (See Figure 2)

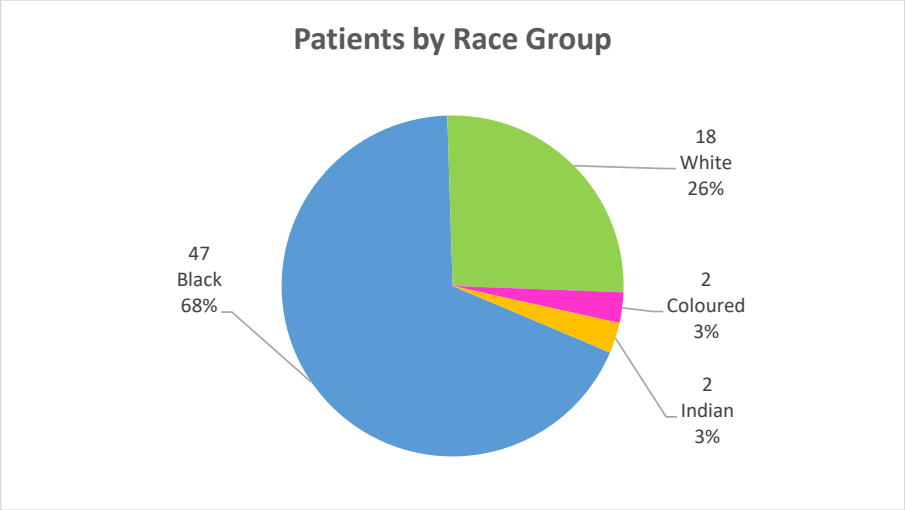

Figure 2: Race distribution of Patients

6.1.3. Parity and Gravidity

The average parity for the patients included in the study who were alive was 2.86 and that of those who were deceased at the end of the study was 2.5. At the end of the study, the average gravidity was 3.56 for patients who were alive and 2.8 for those who had died.

6.1.4. HIV status and CD4 count

Forty (58%) of the patients in the study were HIV seronegative, 24 (35%) were HIV seropositive and the status of 5 (7%) of the patients was unknown. (See Figure 3)

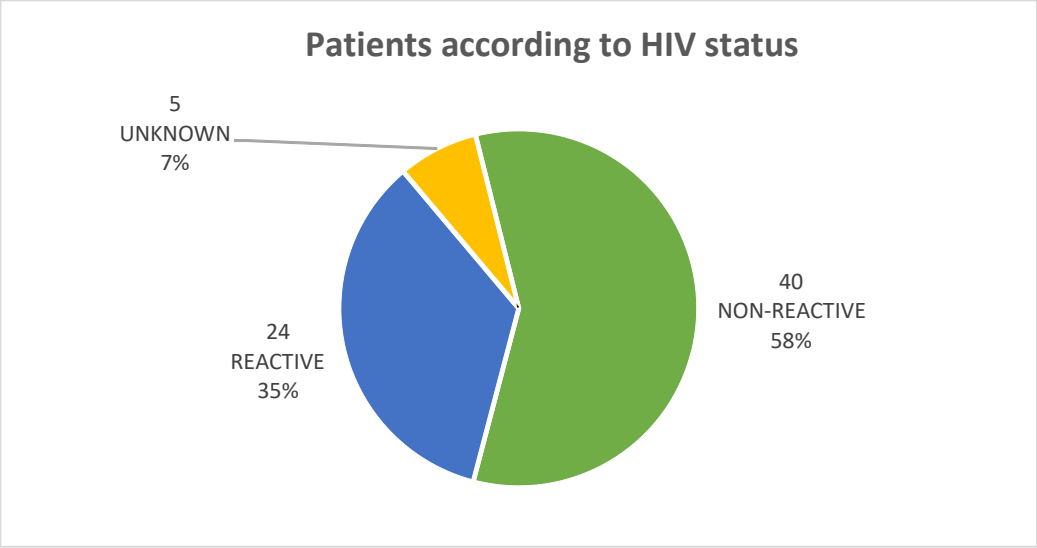

Figure 3: Distribution of Patients by HIV status

The distribution of the CD4 counts of the HIV reactive is shown in Figure 4.

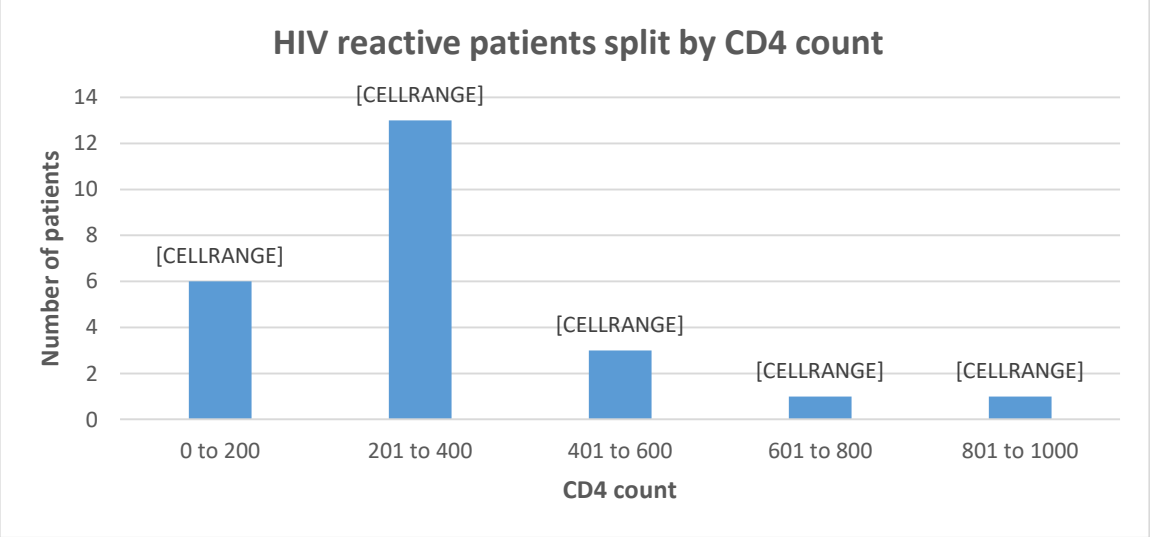

Figure 4: The distribution of the CD4 counts of the HIV reactive patients

6.1.5. ECOG Performance Status

The majority of patients in the study were ECOG performance status 1 i.e. symptomatic and 100% ambulatory 57 (83%). 11 (16%) were ECOG performance status 0 i.e. Asymptomatic and 1 (1%) was ECOG performance status 2 i.e. Symptomatic > 50%ambulatory. The most common symptom that patients presented with was a foul-smelling vaginal discharge. (See Table 3)

Table 3: Distribution of Patients by ECOG Performance Status

ECOG Performance Status	No. of patients
Asymptomatic	11
Symptomatic and 100% ambulatory	57
Symptomatic > 50% ambulatory	1
Symptomatic < 50% ambulatory	0
Bed bound	0
Death	0
Total	69

6.2. Disease free interval

The primary objective of the study was to assess disease free interval and overall survival 2 years post operatively. The figure below summarises the post-operative disease free periods experienced by patients in the study and the proportion of patients who experienced them. (See Figure 5)

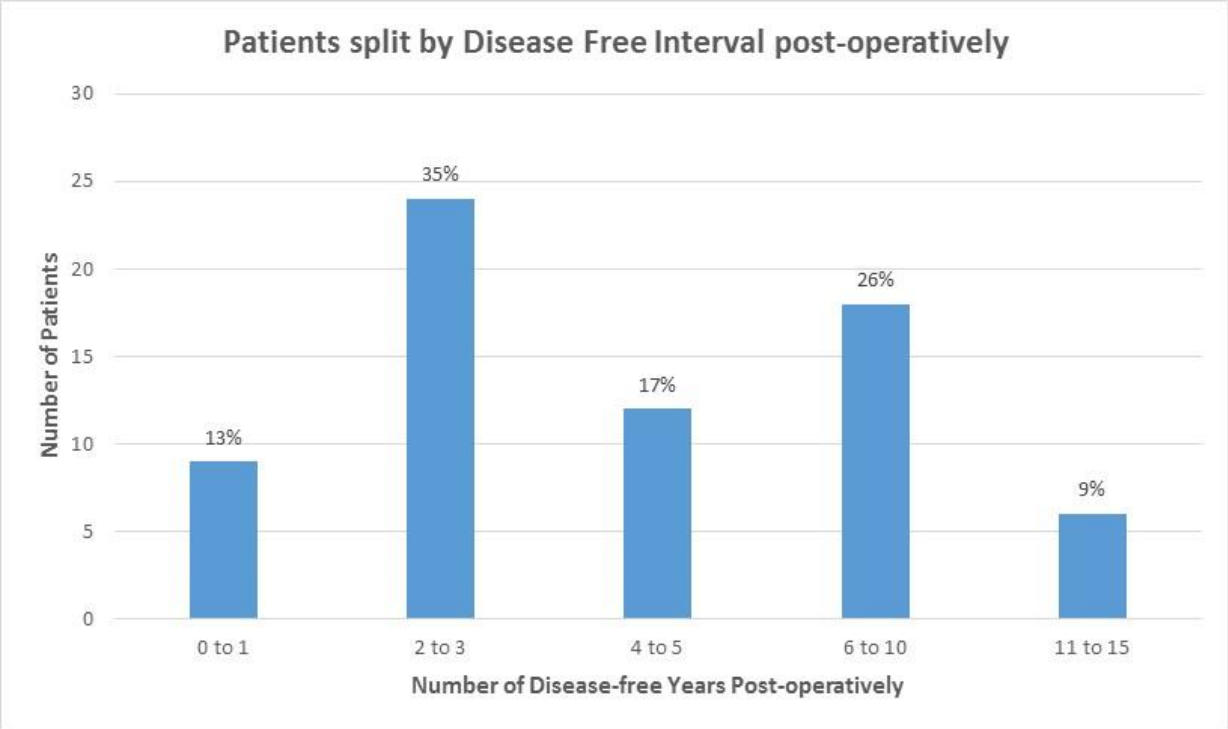

Figure 5: Proportion of patients split by number of Disease-free years post-operatively

The average number of years disease free postoperatively was 5 years for patients included in the study, although 24 (35%) of the patients were disease free for more than five years. Analysing only the patients which were in the study for more than 5 years increases the average number of disease free years to six years.

6.3. Survival Analysis

The overall survival at 30 June 2015 showed that 59 (86%) of the patients were alive and 10 (14%) were deceased. Of the 10 cases that demised:

- Five were due to local recurrence and cause of death was renal failure;
- One was due to metastatic disease initially identified in the liver.
- Two of the patients who died had squamous cell tumours of the oesophagus. One of these initially had an adenoid basaloid cervical carcinoma and the other one initially had a squamous cell cervical carcinoma.
- One was due to an HIV-associated illness according to a family member
- One cause of death was unknown as all available contact details were no longer in service and the patient's family no longer lived at given address. The department of home affairs was only willing to furnish us with this patient's date of death but not the cause of death. (See Figure 6)

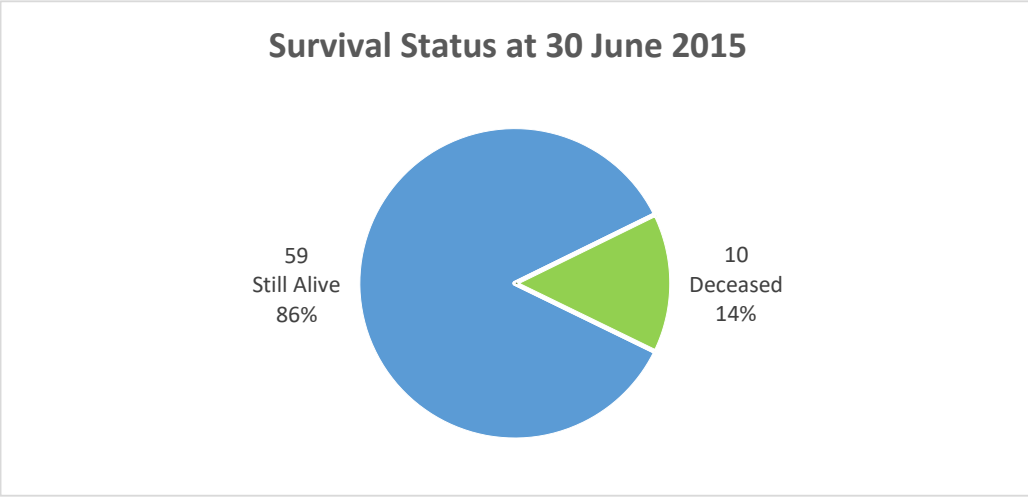

Figure 6: Survival status of patients as at 30 June 2015

Survival analysis of patients by HIV status is covered in detail in Section 6.8 of this report.

6.4. Kaplan Meier Analysis

A brief synopsis of when patients died in the months following surgery and treatment clearly shows that death is unlikely up to 3 years postoperatively with or without adjuvant CRT. Approximately 30% of the study population was only followed up for less than 3 years beyond the cut-off point of the study and therefore their survival beyond 3 years is not included in this Kaplan Meier plot. (See Figure 7)

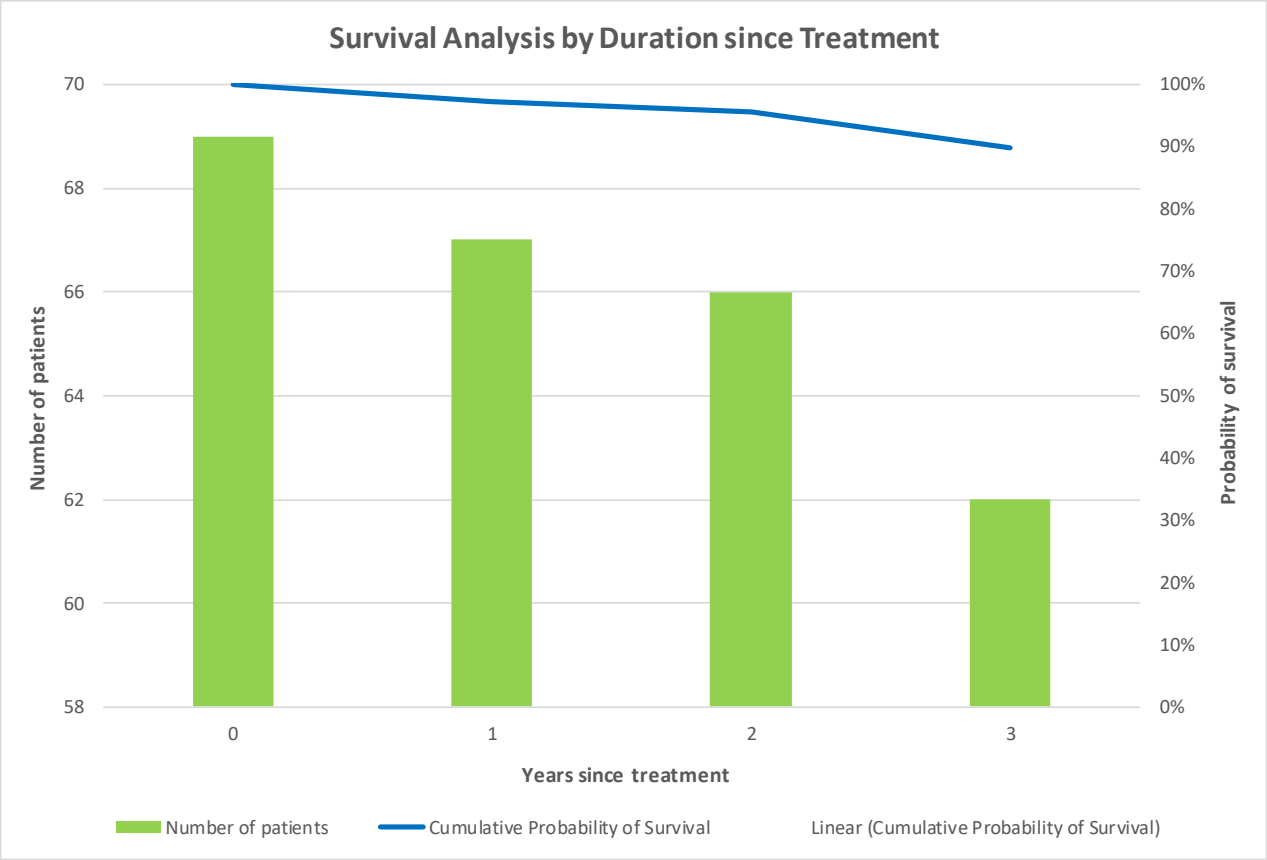

Figure 7: Survival Analysis by Duration since Treatment

Table 4: Survival probabilities by Duration

Years since treatment	Probability of survival	Cumulative Probability of Survival
0	100%	100%
1	97%	97%
2	99%	96%
3	94%	90%
4	68%	61%
5	86%	52%
6	81%	42%
7	86%	36%
8	72%	26%
9	89%	23%
10	69%	16%
11	64%	10%
12	71%	7%
13	60%	4%
14	33%	1%

Table 5: Patients entering study by Year

Year	Number of patients	Number of years in study
2002	5	13
2003	1	12
2004	3	11
2005	3	10
2006	6	9
2007	1	8
2008	9	7
2009	7	6
2010	7	5
2011	6	4
2012	21	3
2013	0	2
2014	0	1

The number of patients entering the study each year is shown in Table 5. A much larger number of patients (21) entered the study in 2012 compared to previous years. An oncology fellow joined the group of surgeons in 2012. It is possible that the detection rate of resectable early stage cervical cancer increased for surgical teaching purposes in that year. Nineteen surgeries were performed by the team in 2012 which was significantly higher than the average of 2.6 surgeries per surgeon in the preceding years. This caused a distortion in the numbers as patient follow up for the study ended in 30/06/2015 with a resultant drop in the numbers of patients after Year 3.

6.5. Co-morbidities

Survival was then assessed relative to co-morbidities to assess any trends or commonalities.

Table 6: Co-morbidities by survival status

Co-morbidities and Survival Status	Still Alive	Deceased
Diabetes mellitus	2	1
Epilepsy	2	0
Asthma	1	0
COPD	2	0
Heart disease	0	1
Hypertension	15	4
Other	6	2
Nil	38	5
	28	**8**

Table 7: Number of co-morbidities and survival status

Number of co-morbidities	Still Alive	Deceased
0	38	5
1	16	2
2	3	3
3	2	0
Total	**59**	**10**
Average	**0.47**	**0.80**

Of those who died 1 in 2 lived with co-morbidities compared to those alive, where about 1 in 3 had co-morbidities. This may suggest an association of improved survival status for those without co-morbidities. Chi-squared testing at the 95% confidence level does not show definitive correlation between the existence of, and numbers of, co-morbidities, with survival status. This is partly due to the low number of deaths in the study as well as some co-morbidities impacting mortality more than others, e.g. hypertension was the most common co-morbidity amongst the patients and can be medicinally controlled.

With regards to duration of disease free interval on overall survival, the Fisher exact test for significance at 95% confidence yielded a p-value of 0.00012 for overall survival at 2 years post-operatively indicating a strong statistically significant relationship at 2 years post-operatively between the disease free interval and overall survival.

6.6. Adequacy of Patient Selection

A secondary objective of the study was to assess the adequacy of patient selection for Wertheim Hysterectomy. To determine this, we compared the preoperative clinical staging based on either initial clinical assessment of patients referred from other hospitals with histology results or from postoperative diagnostic histology in cases where abnormal cytology was used to initially investigate patients or from diagnostic histology where clinically suspicious IB1 lesions were suspected. Eight patients had less significant disease on postoperative histological assessment.

These included:

- Two patients had HGSIL on pap smears and squamous cell carcinomas on LLETZ biopsy
- One patient had HGSIL on pap smear and adenoid basal cell carcinoma on LLETZ biopsy
- One patient had HGSIL on pap smear and squamous cell carcinoma on cone biopsy
- One patient had HGSIL suspicious for invasion on pap smear and squamous cell carcinoma on LLETZ biopsy
- One patient had squamous carcinoma on pap smear and on cervical punch biopsy
- One patient had squamous carcinoma on pap smear and on LLETZ biopsy
- One patient had no pap smear results and adeno-squamous carcinoma on cervical punch biopsy

If patients were adequately selected the clinical staging and histological staging should have been the same. However in 6 of the above-mentioned 8 cases, poor correlation between clinical and histological stage was probably due to the bulk of the tumour having been resected with the

initial histological diagnostic procedure i.e. LLETZ or cone biopsy. In 2 of the 8 cases, where diagnosis was based only on cervical punch biopsies, it is likely that incorrect clinical staging explains the discrepancy. The correct management in these 2 cases would then have been a simple hysterectomy.

We found that the preoperative and postoperative stages correlated in 42 (61%) of the patients and these were therefore treated correctly. Overall preoperative and postoperative stages did not correlate in 27 (39%) of the patients.

Four (6%) of the patients which were incorrectly assessed as IB1 preoperatively but were IB2 postoperatively and therefore were also managed correctly since Wertheim's Hysterectomy is the correct management for IB1 and IB2.

Eight (12%) of the patients were staged as IB1 preoperatively but postoperatively had Stage IA1 or Stage IA2 disease – these cases were therefore over treated based on postoperative histology but correctly treated based on preoperative histology and or clinical assessment. This brings the overall total of correctly managed patients to 52 (75%).

Two (3%) of the above-mentioned 8 (12%) who were staged based on clinical assessment were not staged correctly and should have had a simple hysterectomy.

Fifteen patients (22%) were staged as IB1/IB2 preoperatively but postoperatively 6 (9%) were IIA, 2 (3%) were IIB and 7 (10%) were IIIB.

This means a total of 17 (25 %) were incorrectly managed, as they should have either had a simple hysterectomy or not have been managed surgically but with radiation alone or chemo-radiation as per our and international protocols.

A summary of the results of the analysis is shown in the table below. (See Table 8)

Table 8: Correlation between Pre-Operative Clinical stage & Post-Operative Histological Stage

Count of patients by staging	Preoperative Clinical Staging		Preoperative Clinical Staging	
Postoperative Stage	Stage IB1	Stage IB2	Stage IB1	Stage IB2
NIL	2	0	12%	0%
Stage IA1	3	0		
Stage IA2	3	0		
Stage IB1	42	0	61%	
Stage IB2	4	0	25%	0%
Stage IIA	5	1		2%
Stage II B	2	0		
Stage IIIA	0	0		
Stage IIIB	6	1		
Stage IVA	0	0		
Stage IVB	0	0		
Total	67	2		

Key to colour coding

	Over-treatment
	Correct treatment
	Incorrect treatment

Chi-squared testing was performed on the overall adequacy of patient selection compared against expectations of 80% correct management. This showed statistically significant difference with expectation (p-value of 0.000005803) – i.e. inadequate patient selection. However, it cannot be definitively stated whether patient selection is more adequate for pre-operative staging for Stage IB1 or for Stage IB2 - given the low number of patients identified as IB2 at preoperative staging.

6.7. Risk Factor Analysis

Another secondary objective was to assess risk factors for recurrence. Due to the low number of patients with recurrence (only 12 out of the total 69) the Fisher tests for recurrence by individual prognostic factors did not yield differences that are statistically significant. There are however some strong trends observable from the prognostic factors for these patients.

Each of these factors are analysed in turn in the sections below.

6.7.1. Post-Operative Histology Cell Type

Seventy percent of the cohort had squamous cell carcinomas, 15% had adenomatous cell carcinomas and 1% had other cell carcinomas. The latter was one patient that had a basal cell carcinoma (Figure 8). Probability of patients with adenomatous carcinoma who had either adenocarcinoma, adenoid basal or adeno-squamous carcinoma subtype had lower survival 90% versus squamous carcinoma subtype 96% at 2 years but had a higher disease-free period 90% compared to those with a squamous carcinoma subtype 83%. (Table 9) and (Table 11) respectively. (See Figure 8)

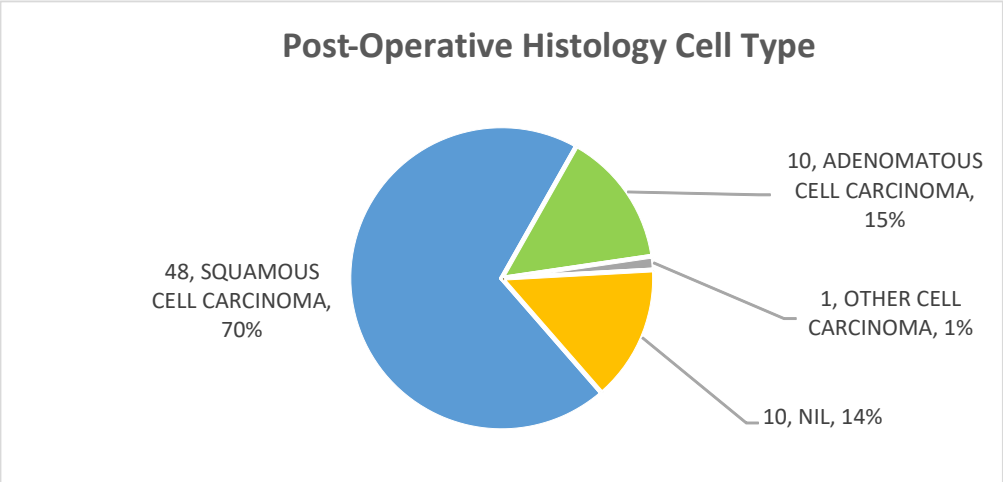

Figure 8: Distribution of Post-Operative Histology Cell Type

Table 9: Survival Period according to Post-Operative Histology Cell Type

Post-Operative Histology Cell Type	Number of patients surviving < 2 years	Number of patients surviving ≥ 2 years	Total number of patients	Probability of survival period ≥ 2 years
Adenomatous cell carcinoma	1	9	10	90%
Nil	0	10	10	100%
Other cell carcinoma	0	1	1	100%
Squamous cell carcinoma	2	46	48	96%
Aggregate	**3**	**66**	**69**	**96%**

Survival periods by Postoperative Histology Cell Type do not differ significantly at the 95% level confidence level. (See Table 9)

Table 10: Recurrence rates according to Post-Operative Histology Cell Type

Postoperative Histology Cell Type	Non-Recur	Recur	**Total**
Adenomatous Cell Carcinoma	10	0	10
Nil	10	0	10
Other Cell Carcinoma	1	0	1
Squamous Cell Carcinoma	36	12	48

Recurrence rates by Postoperative Histology Cell Type do not differ significantly at the 95% level confidence level. However, it is worth noting that all patients who had recurrence also had squamous cell carcinoma. (See Table 10)

Table 11: Disease Free Period according to Post-operative Histology Cell Type

Post-Operative Histology Cell Type	Number of patients with disease free period < 2 years	Number of patients with disease free period ≥ 2 years	Total number of patients	Probability of disease free period ≥ 2 years
Adenomatous Cell Carcinoma	1	9	10	90%
Nil	0	10	10	100%
Other Cell Carcinoma	0	1	1	100%
Squamous Cell Carcinoma	8	40	48	83%
Grand Total	**9**	**60**	**69**	**87%**

6.7.2. Postoperative stages

Three of the 5 patients who died of recurrence had more advanced postoperative stages than Stage IB1/IB2 – 1 was Stage IIA and 2 were Stage IIIB. All 5 had positive margins and 3 had nodes which were positive for metastatic disease.

As expected our study data shows that the probability of surviving and being disease free for more than 2 years is highest for no residual tumour present after initial diagnostic procedure for histology 100% and 100% respectively.

Probability of survival at 2 years was higher for stage I at 96% and Stage II at 100% compared to Stage III at 86%. Probability of being disease free for more than 2 years was highest for Stage I at 94%, followed by Stage II at 63%, and lowest for Stage III at 57%. We can infer from these results that patients with Stage I and II disease are more likely to be alive and disease free at 2 years or more compared to those with Stage III disease. (See Figure 9)

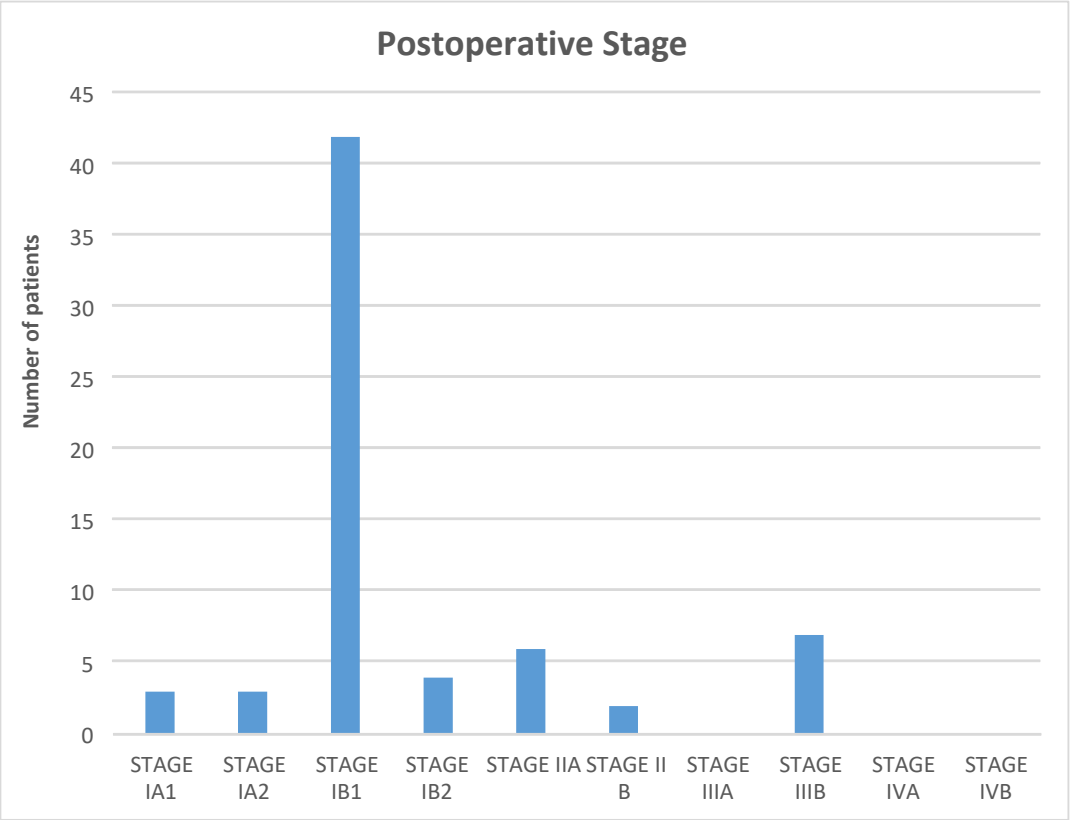

Figure 9: Distribution of patients according to Stage

The influence of the Stage on the survival period is shown below in Table 12.

Table 12: Survival Period according to Post-operative Stage

Postoperative stage	Number of patients surviving < 2 years	Number of patients surviving ≥ 2 years	Total number of patients	Probability of survival period ≥ 2 years
Nil	0	2	2	100%
Stage I	2	50	52	96%
Stage II	0	8	8	100%
Stage III	1	6	7	86%
Grand total	**3**	**66**	**69**	**96%**

The influence of the Stage on the disease-free period is shown in Table 13.

Table 13: Disease Free Period according to Stage

Postoperative stage	Number of patients with disease free period < 2 years	Number of patients with disease free period ≥ 2 years	Total number of patients	Probability of disease free period ≥ 2 years
Nil	0	2	2	100%
Stage I	3	49	52	94%
Stage II	3	5	8	63%
Stage III	3	4	7	57%
Grand total	**9**	**60**	**69**	**87%**

Postoperative stage did not have a statistically significant impact on the 2 year Disease Free Period or 2 year Survival Period at 95% confidence level.

6.7.3. Tumour Grade

With regards to tumour grade as a risk factor for recurrence, 80% of the patients included in the study had moderately differentiated tumors' on histology. The patients' with poorly differentiated tumours had the highest probability of surviving (100%) and second highest probability (86%) of being disease free at 2 years or more. This is not in keeping with the fact that poorly differentiated tumours are more aggressive but is likely due to a relatively smaller number of patients in this category and the short follow up period of the study. Well differentiated tumours are the least aggressive but this has not been shown in this study since there was only a 50% probability of patients with this grade surviving and being disease free at 2 years or more, this can however be explained by the fact that results may be skewed owing to the small number of patients which fell into the well differentiated category.

Patients with moderately differentiated tumours (88%) were more likely to be disease free at 2 years or more compared to those with well differentiated tumours (50%). Patients with

moderately differentiated tumours were also more likely to survive at 2 years or more (97%) compared to patients with well differentiated tumours (50%).

The influence of the tumour grade on the survival and disease free period is shown in the tables below. (See Tables 14 and 15)

Table 14: Survival Period according to Tumour Grade

Tumour Grade	Number of patients surviving < 2 years	Number of patients surviving ≥ 2 years	Total number of patients	Probability of survival period ≥ 2 years
Moderately Differentiated	2	58	60	97%
Poorly Differentiated	0	7	7	100%
Well Differentiated	1	1	2	50%
Grand Total	**3**	**66**	**69**	**96%**

Table 15: Disease Free Period according to Tumour Grade

Tumour Grade	Number of patients with disease free period < 2 years	Number of patients with disease free period ≥ 2 years	Total number of patients	Probability of disease free period ≥ 2 years
Moderately Differentiated	7	53	60	88%
Poorly Differentiated	1	6	7	86%
Well Differentiated	1	1	2	50%
Grand Total	**9**	**60**	**69**	**87%**

Recurrence rates over the entire study period by tumour grade do not differ significantly at the 95% confidence level.

Ten out of the 12 patients that had recurrence had moderately differentiated tumours – (20%) recurrence for this tumour grade. Two of the 5 poorly differentiated tumours recurred – (40%) for this tumour grade. Neither of the 2 well differentiated recurred. This suggests in this study that tumour grade is more likely to give an indication of recurrence but not survival and disease free period with the disease. (See Table 16)

Table 16: Recurrence rates by Tumour Grade

Tumour Grade	Non-Recur	Recur	**Total**
Moderately Differentiated	50	10	60
Poorly Differentiated	5	2	7
Well Differentiated	2	0	2
Total	57	12	69

6.7.4. Tumour size

Six percent of the patients in the study had tumours more than 4cm in size and 94% had tumours less than or equal to 4cm in size. The influence of tumour size on survival period and disease-free period can be seen in the tables below. (See Tables 17 and 18)

Table 17: Survival Period according to Tumour Size

Tumour Size	**Number of patients surviving < 2 years**	**Number of patients surviving ≥ 2 years**	**Total number of patients**	**Probability of survival period ≥ 2 years**
> 4CM	1	3	4	75%
≤ 4CM	2	63	65	97%
Grand Total	**3**	**66**	**69**	**96%**

Table 18: Disease Free Period according to Tumour Size

Tumour Size	Number of patients with disease free period < 2 years	Number of patients with disease free period ≥ 2 years	Total number of patients	Probability of disease free period ≥ 2 years
> 4CM	1	3	4	75%
≤ 4CM	8	57	65	88%
Grand Total	**9**	**60**	**69**	**87%**

The patients in our study who had tumours more than 4cm in size had a lower probability of survival (75%) and of being disease free (75%) at 2 or more years compared to those who had tumours 4cm and less in size who had a 97% probability of survival and an 88% probability of being disease free at 2 years or more.

The table below shows the recurrence rates by size of the tumour.

Table 19: Recurrence rates by Tumour Size

Tumour Size	Non-Recur	Recur	Total
> 4CM	4	0	4
≤ 4CM	53	12	65
Total	57	12	69

Recurrence rates by tumour size do not differ significantly at the 95% level confidence level. However, worth noting is that all patients that had recurrence had tumour size ≤ 4cm.

6.7.5. Tumour Depth of Invasion

Patients who had tumours with a depth of invasion less than or equal to 3 mm, as well as those with tumours more than 3mm but less than 5 mm of depth had the highest probability (100%) of surviving and of being disease free (100%) at 2 years or more. Those who had tumours of more than 5mm in depth had a lower probability of survival 93% and a lower probability of being disease free 80% at 2 years or more.

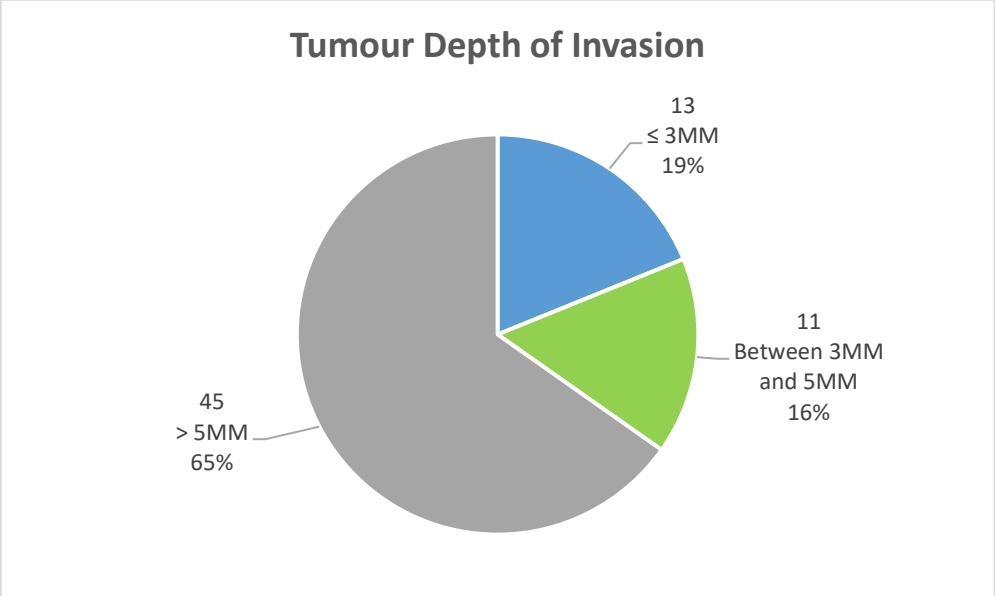

Figure 10: Distribution of Tumour Depth of Invasion

The influence of tumour depth of invasion on survival period and disease-free period can be seen in the tables below. (See Tables 20 and 21)

Table 20: Survival Period according to Tumour Depth of Invasion

Tumour Depth of Invasion	Number of patients surviving < 2 years	Number of patients surviving ≥ 2 years	Total number of patients	Probability of survival period ≥ 2 years
≤ 3MM	0	13	13	100%
>3MM and < 5MM	0	11	11	100%
> 5MM	3	42	45	93%
Grand Total	**3**	**66**	**69**	**96%**

Table 21: Disease Free Period according to Tumour Depth of Invasion

Tumour Depth of Invasion	Number of patients with disease free period < 2 years	Number of patients with disease free period ≥ 2 years	Total number of patients	Probability of disease free period ≥ 5 years
≤ 3MM	0	13	13	100%
>3MM and < 5MM	0	11	11	100%
> 5MM	9	36	45	80%
Grand Total	**9**	**60**	**69**	**87%**

Recurrence rates by tumour depth of invasion do not differ significantly at the 95% level confidence level. The majority of the patients with recurrence (10 out of 12) had tumour depth of invasion >5mm. None of the patients with tumours 3mm or less in depth had recurrence. (See Table 22)

Table 22: Recurrence rates according to Tumour Depth of Invasion

Tumour Depth Of Invasion	Non-Recur	Recur	Total
≤ 3MM	13	0	13
> 3MM and < 5MM	9	2	11
> 5MM	35	10	45
Total	**57**	**12**	**69**

6.7.6. Tumour Lateral Spread

Seventy percent of the patients had tumours that had lateral spread more than 7mm and 30% had tumours with lateral spread less than or equal to 7mm.

Tumours that had spread laterally to less than or equal to 7mm had a 100% probability of survival and a 95% probability of being disease free at 2 years or more postoperatively and this was as expected much higher than tumours that had spread laterally more than 7mm where

probability of survival was 94% and probability of being disease free was 83% at 2 years or more post operatively.

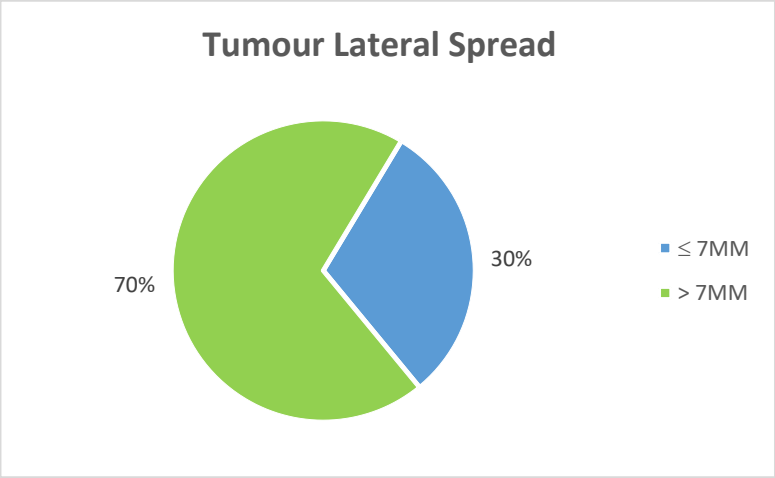

Figure 11: Distribution of Tumour Lateral Spread

The influence of tumour lateral spread on survival period and disease-free period can be seen in the tables below. (See Tables 23 and 24)

Table 23: Survival Period according to Tumour Lateral Spread

Tumour Lateral Spread	Number of patients surviving < 2 years	Number of patients surviving ≥ 2 years	Total number of patients	Probability of survival period ≥ 2 years
> 7MM	3	45	48	94%
≤ 7MM	0	21	21	100%
Grand Total	**3**	**66**	**69**	**96%**

Table 24: Disease Free Period according to Tumour Lateral Spread

Tumour Lateral Spread	Number of patients with disease free period < 2 years	Number of patients with disease free period ≥ 2 years	Total number of patients	Probability of disease free period ≥ 2 years
> 7MM	8	40	48	83%
≤ 7MM	1	20	21	95%
Grand Total	**9**	**60**	**69**	**87%**

Recurrence rates by tumour lateral spread do not differ significantly at the 95% confidence level The majority of patients with recurrence (11 out of 12) had tumour lateral spread > 7MM. (See Table 25)

Table 25: Recurrence rates by Tumour Lateral Spread

Tumour Lateral Spread	Non-Recur	Recur	**Total**
> 7MM	37	11	48
≤ 7MM	20	1	21
Total	**57**	**12**	**69**

6.7.7. Lymphovascular space involvement

Seventy two percent of the patients had no lymphovascular space involvement. Twenty eight percent did have lymphovascular space invasion histologically.

Patients with histology that showed presence of lymphovascular space invasion had lower probabilities of survival and being disease free 2 years postoperatively compared to those without lymphovascular space invasion 96% and 92% respectively as opposed to 95% and 74% respectively. (See Figure 12)

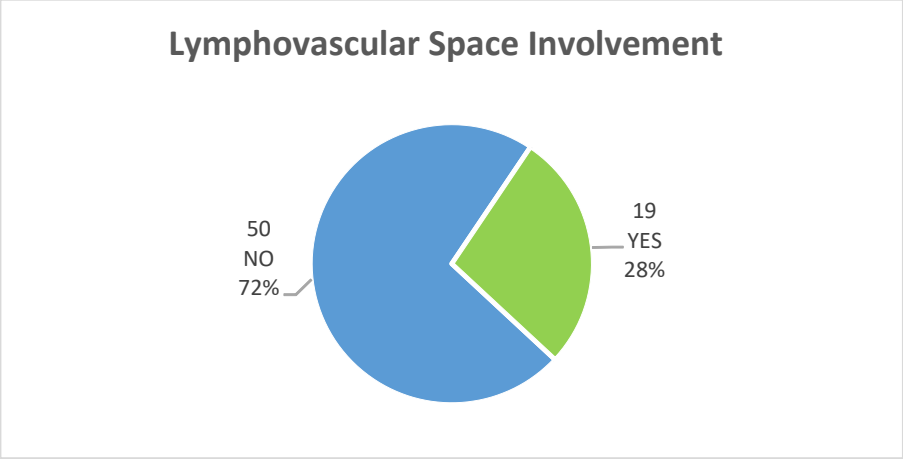

Figure 12: Distribution of Lymphovascular Space Involvement

The influence of Lymphovascular Space Involvement on survival period and disease free period can be seen in tables 26 and 27 below.

Table 26: Survival Period according to Lymphovascular Space Involvement

Lymphovascular Space Involvement	Number of patients surviving < 2 years	Number of patients surviving ≥ 2 years	Total number of patients	Probability of survival period ≥ 2 years
No	2	48	50	96%
Yes	1	18	19	95%
Grand Total	**3**	**66**	**69**	**96%**

Table 27: Disease Free Period according to Lymphovascular Space Involvement

Lymphovascular Space Involvement	Number of patients with disease free period < 2 years	Number of patients with disease free period ≥ 2 years	Total number of patients	Probability of disease free period ≥ 2 years
No	4	46	50	92%
Yes	5	14	19	74%
Grand Total	**9**	**60**	**69**	**87%**

Fisher tests performed on recurrence rates by Lymphovascular Space Involvement do not differ significantly at the 95% level of confidence. However at 2 or more years postoperatively relative to numbers in each group, 36% of the patients with lymphovascular space involvement had a recurrence as opposed 16% recurrence for those who did not have lymphovascular space involvement. (See Table 28)

Table 28: Recurrence rates by Lymphovascular Space Involvement

Lymphovascular Space Involvement	Non-Recur	Recur	**Total**
NO	43	7	50
YES	14	5	19
Total	**57**	**12**	**69**

6.7.8. Number of positive lymph nodes

Fifty-nine patients had no positive lymph nodes, three had 1 positive lymph node, four had 2, one had 3, one had 6 and one had 8 positive lymph nodes.

The study generally showed very high probability rates of survival at 2 or more years postoperatively but the greater the number of positive nodes removed at radical hysterectomy the lower the probability of being disease free at 2 or more years postoperatively. Survival was 97% where there were no positive nodes, 67% where there was 1 positive node and 100% for 2 to 8 positive nodes. Probability of being disease free was 93% for no positive nodes, 67% for 1, 50% for 2 and 0% for 3 and 8 positive nodes. The only result not in keeping with this trend was shown for one patient where 6 positive nodes were removed but the patient survived and was disease free for longer than 2 or more years post-operatively. Since this was only the case for one patient it cannot be deemed to be significant.

The influence of Positive Lymph Nodes on survival period and disease-free period can be seen in the tables 29, 30 and 31.

Table 29: Survival Period according to Number of Positive Lymph Nodes

Number Of Positive Lymph Nodes	Number of patients surviving < 2 years	Number of patients surviving ≥ 2 years	Total number of patients	Probability of survival period ≥ 2 years
0	2	57	59	97%
1	1	2	3	67%
2	0	4	4	100%
3	0	1	1	100%
6	0	1	1	100%
8	0	1	1	100%
Grand Total	**3**	**66**	**69**	**96%**

Table 30: Disease Free Period according to Number of Positive Lymph Nodes

Number of Positive Lymph Nodes	Number of patients with disease free period < 2 years	Number of patients with disease free period ≥ 2 years	Total number of patients	Probability of disease free period ≥ 2 years
0	4	55	59	93%
1	1	2	3	67%
2	2	2	4	50%
3	1	0	1	0%
6	0	1	1	100%
8	1	0	1	0%
Grand Total	**9**	**60**	**69**	**87%**

Table 31: Recurrence rates by Number of Positive Lymph Nodes

Number Of Positive Lymph Nodes	Non-Recur	Recur	**Total**
0	51	8	59
1	3	0	3
2	2	2	4
3	0	1	1
6	1	0	1
8	0	1	1
Total	57	12	69

Recurrence rates by number of positive lymph nodes do not differ significantly at the 95% level of confidence. The majority of the patients with recurrence had no positive lymph nodes (8 out of 12 patients).

6.7.9. Parametrial Involvement

Ninety four percent of the patients had no parametrial involvement and 6% did have parametrial involvement. In patients with parametrial involvement the survival probability was 100% as opposed to 95% in those without involvement at 2 years or more. However the inverse was noted with regards to probability of remaining disease free at 2 years or more. Only 50%

of those with parametrial involvement were disease free compared to 89% of those without parametrial involvement.

The influence of Parametrial Involvement on survival and disease-free period is shown below. (See Tables 32, 33 and 34)

Table 32: Survival Period according to Parametrial Involvement

Parametrial Involvement	Number of patients surviving < 2 years	Number of patients surviving ≥ 2years	Total number of patients	Probability of survival period ≥ 2 years
No	3	62	65	95%
Yes	0	4	4	100%
Grand total	3	66	69	96%

Table 33: Disease Free Period according to Parametrial Involvement

Parametrial Involvement	Number of patients with disease free period < 2 years	Number of patients with disease free period ≥ 2 years	Total number of patients	Probability of disease free period ≥ 2 years
No	7	58	65	89%
Yes	2	2	4	50%
Grand Total	**9**	**60**	**69**	**87%**

Table 34: Recurrence rates by Parametrial Involvement

Parametrial Involvement	Non-Recur	Recur	**Total**
No	55	10	65
Yes	2	2	4
Total	57	12	69

Recurrence rates by parametrial involvement do not differ significantly at the 95% confidence level. However, worth noting was that 10 out of the 12 patients with recurrence did not have parametrial involvement.

6.7.10. Pouch of Douglas Involvement

Seven percent (5) of the patients had Pouch of Douglas involvement and 93% (64) had no Pouch of Douglas involvement.

In patients where the pouch of Douglas was involved probability of survival at 2 years or more was slightly higher at 100% as opposed to 95% when there was no involvement which has been shown in previous studies but a relatively very small number of patients fell into the category where there was involvement and this is also therefore unlikely to be significant. Patients with pouch of Douglas involvement did have a marginally lower probability of being disease free after 2 years compared with those that did not have involvement – 80% as opposed to 88%.

The influence of Pouch of Douglas Involvement on survival period and disease-free period can be seen in the tables below. (See Tables 35, 36 and 37)

Table 35: Survival Period according to Pouch of Douglas Involvement

Pouch of Douglas Involvement	Number of patients surviving < 2 years	Number of patients surviving ≥ 2 years	Total number of patients	Probability of survival period ≥ 2 years
No	3	61	64	95%
Yes	0	5	5	100%
Grand total	**3**	**66**	**69**	**96%**

Table 36: Disease Free Period according to Pouch of Douglas Involvement

Pouch Of Douglas Involvement	Number of patients with disease free period < 2 years	Number of patients with disease free period ≥ 2 years	Total number of patients	Probability of disease free period ≥ 2 years
No	8	56	64	88%
Yes	1	4	5	80%
Grand Total	**9**	**60**	**69**	**87%**

Table 37: Recurrence rates by Pouch of Douglas Involvement

Pouch Of Douglas Involvement	Non-Recur	Recur	**Total**
No	54	10	64
Yes	3	2	5
Total	57	12	69

Ten out of the 12 patients with recurrence did not have Pouch of Douglas Involvement.

Pouch of Douglas Involvement however was not statistically significant at the 95% confidence level for survival, disease free period or recurrence.

6.7.11. Surgical Margins

Fifty eight percent had surgical margins that were inadequate at less than or equal to 10mm. Forty two percent had adequate surgical margins where tumour was histologically more than 10mm from the nearest resection margin.

As shown in previous studies if surgical margins were less than or equal to 10mm probability of survival was 93% and probability of being disease free was 78% at 2 years or more which is lower compared to that of margins more than 10mm where survival probability was 100% and disease-free probability was 100% for the same time period.

The influence of Surgical Margins on survival period and disease-free period can be seen in the tables below. (See Tables 38, 39 and 40)

Table 38: Survival Period according to Surgical Margins

Surgical Margins	**Number of patients surviving < 2 years**	**Number of patients surviving ≥ 2 years**	**Total number of patients**	**Probability of survival period ≥ 2 years**
> 10MM	0	29	29	100%
≤ 10MM	3	37	40	93%
Grand Total	**3**	**66**	**69**	**96%**

Table 39: Disease Free Period according to Surgical Margins

Surgical Margins	Number of patients with disease free period < 2 years	Number of patients with disease free period ≥ 2 years	Total number of patients	Probability of disease free period ≥ 2 years
> 10MM	0	29	29	100%
≤ 10MM	9	31	40	78%
Grand Total	**9**	**60**	**69**	**87%**

Table 40: Recurrence rates by Surgical Margins

Surgical Margins	Non-Recur	Recur	**Total**
> 10MM	27	2	29
≤ 10MM	30	10	40
Total	**57**	**12**	**69**

Recurrence rates by Surgical Margins Involvement do not differ significantly at the 95% confidence level. However, worth noting was that 10 out of the 12 patients with recurrence had surgical margins ≤10mm.

6.7.12. Post-Operative Cytology

Average disease-free years (5.35) and average survival years (6.25) were highest for patients' who had post-operative cytology negative for intraepithelial neoplasia and malignancy as expected. However, unexpectedly disease-free years and average survival was higher for those with HGSIL c.f. those with LGSIL on postoperative cytology. Patients with cytology showing radiation reaction postoperatively had the lowest average disease free years (3) and lowest average survival years. (See Table 41)

Table 41: Average Disease Free and Survival Periods by Post-Operative Cytology Results

Post-operative Cytology Results	Average Disease free years	Average Survival years
Negative for Intra-Epithelial Lesion / Malignancy	5.35	6.25
HGSIL	4.80	5.60
LGSIL	4.23	4.23
ASCUS	5.00	5.40
AGCUS	n/a	n/a
Carcinoma-In-Situ	n/a	n/a
Radiation Reaction	3.00	3.00
Other	4.50	4.50
Not Done	4.09	4.73

6.8. Survival analysis by HIV status

Quantify survival differences at end of study between HIV positive patients versus HIV negative patients. (See Table 42)

Table 42: Comparative rates of mortality by HIV status

HIV status	Deceased at end study	Still Alive at end of study	Total patients by HIV status
Non-Reactive	5	35	40
Reactive	4	20	24
Unknown	1	4	5
Total number of patients	**10**	**59**	**69**

Mortality rates	HIV Non-reactive	12.5%
	HIV Reactive	16.7%
	Unknown	20.0%

Survival differences between HIV positive versus HIV negative patients over the full period of analysis do not appear to be very different. (See Tables 43 and 44)

Table 43: Survival figures 2 years after treatment according to HIV Status

HIV status	Not alive at end of 2 years	Alive at end of 2 years	**Total**
HIV positive	1	23	24
HIV negative	2	38	40
Unknown	0	5	5
Total	3	66	69

Table 44: Survival figures 5 years after treatment according to HIV Status

HIV status	Not alive at end of 5 years	Alive at end of 5 years	**Total**
HIV positive	3	8	11
HIV negative	3	23	26
Unknown	1	4	5
Total	7	35	42

Fisher Tests performed at the 5% level show that survival differences between HIV positive patients versus HIV negative patients are not statistically significant over 2 years or 5 years post treatment.

6.9. Recurrence risk of HIV positive patients versus HIV negative patients

Recurrence risk of HIV positive versus HIV negative patients was also compared as a secondary objective. Mortality rates for reactive patients (16.7%) were higher than for non-reactive patients (12.5%). (See Table 45)

Table 45: Recurrence rates by HIV Status

	Number of patients			**Proportion**		
Recurrence rate	**Non Reactive**	**Reactive**	**Unknown**	**Non Reactive**	**Reactive**	**Unknown**
Recurrence	10	1	1	25%	4%	20%
Non-recurrence	30	23	4	75%	96%	80%
Total	40	24	5			
Recurrence rate	25%	4%				

The recurrence rate however was higher in the HIV non-reactive group 25% compared to 4% in the HIV reactive group. Fisher Tests performed at the 95% confidence level show that recurrence differences between HIV reactive versus HIV non-reactive patients was statistically significant over 2 years post treatment. (See Figure 13)

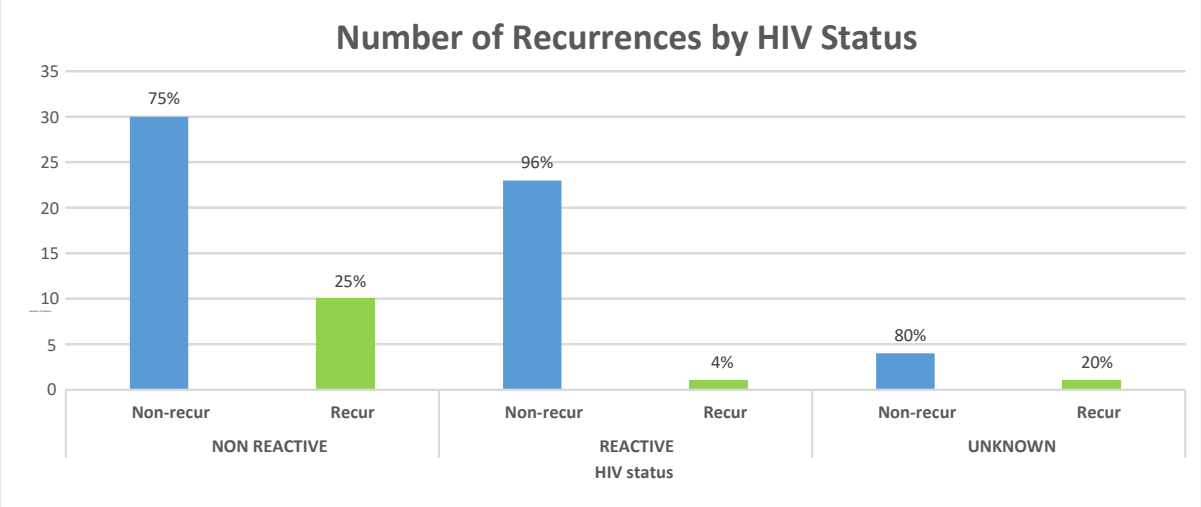

Figure 13: Distribution of Recurrences by HIV Status

Disease free years and overall survival distributed by CD4 count bands generally suggests the lower the count at diagnosis and management the lower the disease-free period and overall survival. (See Figure 14)

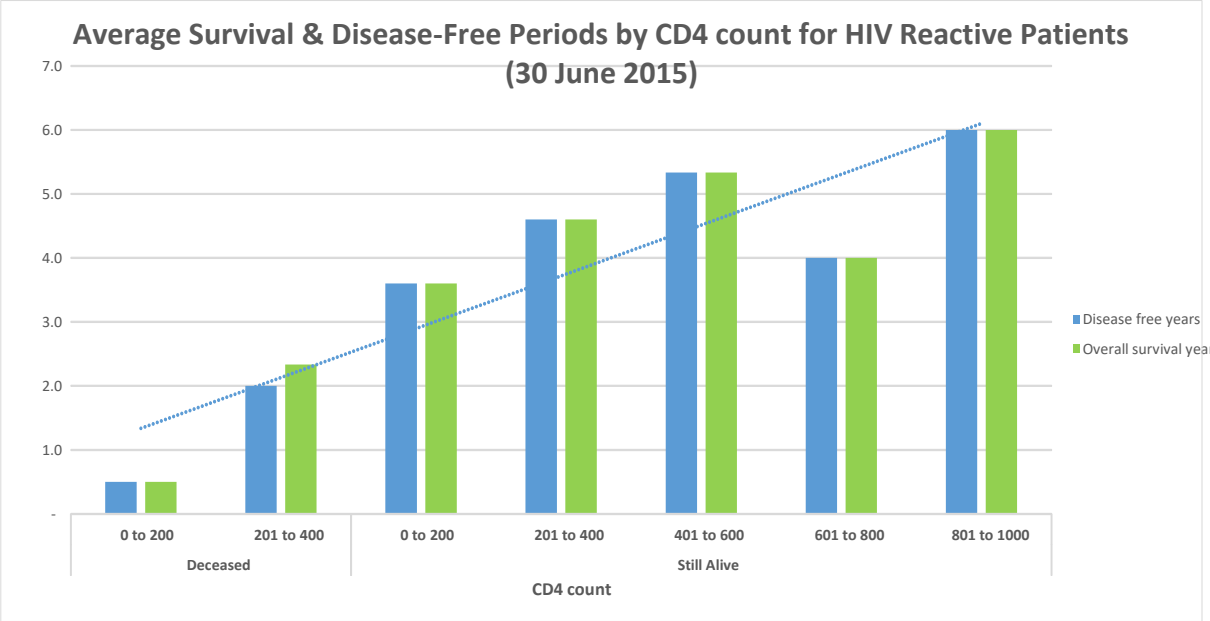

Figure 14: Disease free years and overall survival distributed by CD4 count

6.10. Surgical and post-surgical complication rate

Surgical and post-surgical complication rates were also assessed as part of the secondary objectives. Intra-operative surgical complication rate was 6% and complications did not include any of the common surgical complications that had been identified in previous studies. Complications were entered under the group "other" and included unilateral oophorectomy due to bleeding in 2 cases and generalized bleeding or difficult haemostasis requiring transfusion due to intra-operative anaemia in 2 cases. (See Table 46)

Table 46: Patients by type of Surgical Complication

Surgical Complications	No. Of Patients
Obturator Nerve Resection	0
Ureteric Resection	0
Uterine Artery Haemorrhage	0
Bladder Injury	0
Other	4
Nil	65
Total	69

Surgical Complication Rate	6%

The immediate post-surgical complication rate was also low at 16%. The most common complications were in the category other 4 (6%) and were also complications not identified in previous studies – these included: - immediate post-operative anaemia in 1 case requiring transfusion, stress incontinence which resolved in 1 case, chylous ascites which resolved in 1 case and a piece of drain broke off on removal of the drain postoperatively and patient required a re-look to remove this piece in 1 case. The next most common complication was wound sepsis (4%), followed equally by abdominal hernia (3%) and ileus (3%). (See Figure 15 and Table 47)

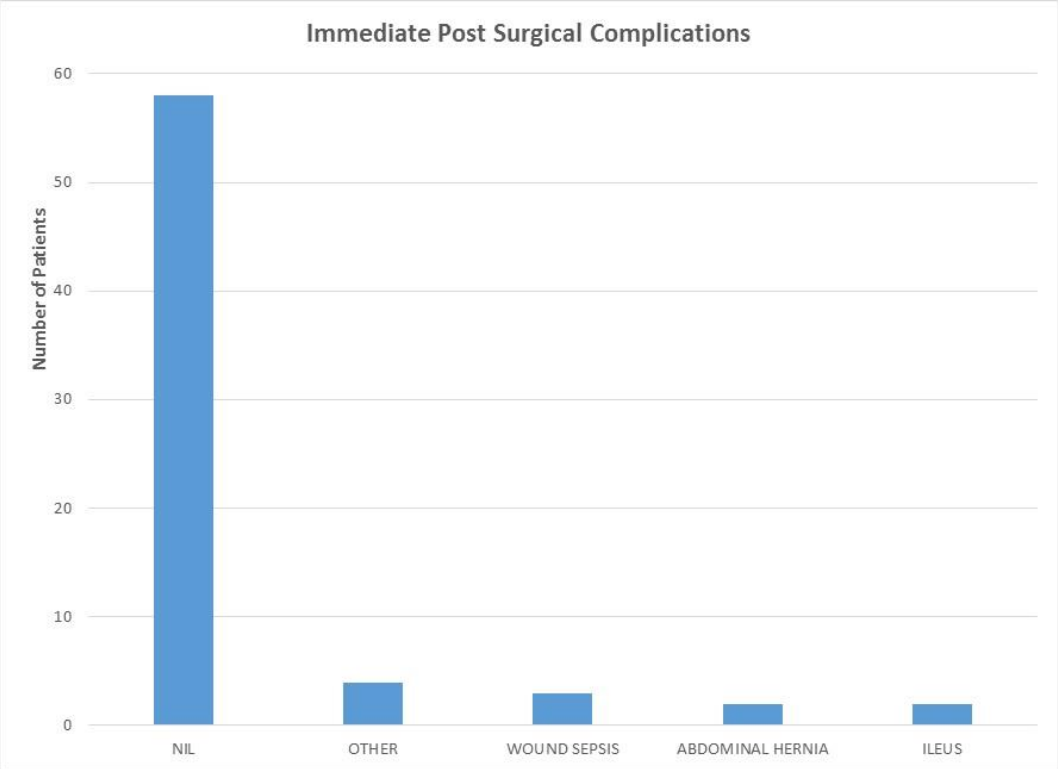

Figure 15: Number of patients by type of Immediate Post-Surgical Complication

Table 47: Patients split by Immediate Post-Surgical Complications

Immediate Post-Surgical Complications	No. of patients
Nil	58
Other	4
Wound Sepsis	3
Abdominal Hernia	2
Ileus	2
Haematoma	0
Uterovaginal Fistula	0
Pulmonary Embolism	0
Deep Vein Thrombosis	0
Lower Limb Oedema	0
Lymphocyst	0
Hydro-Ureter	0
Stress Incontinence	0
Atonic Bladder	0
Low Compliance Bladder	0
Total	69

Immediate post-surgical complication rate	16%

6.11. Post-Surgical Management Complications

We also assessed the most common complications associated with post-surgical management which included either no further management, DXT alone or combined chemotherapy and DXT. The patients who did receive post-surgical management complained of one or more complications as follows: 46 (67%) had no complications, 12 (17%) had 1 complication, 5 (7%) had 2 complications and 6 (9%) had 3 complications. (See Table 48)

Table 48: Post-Surgical Management Complications Rate

Number of Post-Surgical Management Complications	No. of patients
0	46
1	12
2	5
3	6
	69
Average number of complications per patient (overall)	0.58
Average number of complications for patients who had them	1.74

Thirty-six (52%) of the patients received no further management, 25 (36%) received DXT only and 8 (12%) received combined chemotherapy with DXT. The complication rate for combined chemotherapy with DXT was highest at 75% compared to DXT alone which was 64%. The lowest complication rate was in patients who received no further post-operative management at 3%. (See Table 49)

Table 49: Complication rates by post-surgical management type

Number of complications per patient	DXT	Chemo-Radiation	NIL
0	9	2	35
1	9	2	1
2	2	3	0
3	5	1	0
Total	25	8	36

Complication rate by Post - surgical management type	**64%**	**75%**	**3%**

The most common complication was diarrhoea / proctitis in 13 patients, skin irritation / rash in 12, cystitis in 10, nausea and vomiting in 1, hepatotoxicity in 1 and postmenopausal symptoms in 1. Other complications, not identified for the protocol data collection sheet, were noted in 2 patients and included a DVT in 1 patient had a mucositis of the introitus. (See Table 50)

Table 50: Number of patients split by Post-Surgical Management Complications

Post -Surgical Management Complications	No. of patients affected
Nil	46
Proctitis/Diarrhoea	13
Skin Irritation/Rash	12
Cystitis/Frequency	10
Nausea and Vomiting	1
Hepatotoxicity	1
Postmenopausal symptoms	1
Other	2
Lyphoedema	0
Alopecia	0
Mucositis	0
Electrolyte Disturbances	0
Anaphylactic Reaction	0
Fatigue	0

Upon review of patient histories it was found that preoperative cytology results were as follows - 29 (42.03%) were HGSIL, 14 (20.29%) were squamous carcinoma, 5 (7.25%) were HGSIL suspicious for invasion. 4 (5.80%) were endocervical adenocarcinoma, 4 (5.8%) were ASCUS, 9 (13.04%) were negative for intraepithelial lesion/malignancy, 3 (4.35%) did not have preoperative cytology and 1 (1.45%) had a LGSIL.

The postoperative histology results were grouped into squamous carcinoma, adenomatous carcinoma and other cell carcinoma. As the total number of patients included in the study is relatively small adenosquamous carcinomas were grouped into the adenomatous carcinoma group. Squamous cell carcinomas were the majority 54 (78.26%) followed by the Adenomatous type cell carcinoma 14 (20.29%) and then other cell carcinomas 1 (1.45%). (See Table 51)

Table 51: Patients by Preoperative Histology Results

Preoperative Histology Results	No. of patients
Squamous Cell Carcinoma	54
Adenomatous Cell Carcinoma	14
Other Cell Carcinoma	1
Total	69

6.12. Surgery analyses

6.12.1. Surgeries by year by Surgeon

Over the study period 2002 to 2012 only 3 surgeons performed the operations at Charlotte Maxeke Johannesburg Academic Hospital. Two were senior gynaecological oncology specialists, surgeons 1 and 2 and one was a sub-speciality fellow training in gynaecological oncology, surgeon 3.

Over the study period the first surgeon performed 21 operations, the second 27 operations and the third 21 operations. The table shows the number of surgeries per surgeon in each year of the study. (See Table 52)

Table 52: Surgeries by year by Surgeon

Year	Surgeon 1	Surgeon 2	Surgeon 3	Total
2002	3	2	-	5
2003	-	1	-	1
2004	1	2	-	3
2005	-	3	-	3
2006	2	4	-	6
2007	1	-	-	1
2008	3	6	-	9
2009	4	3	-	7
2010	5	2	-	7
2011	2	2	2	6
2012	-	2	19	21
Grand Total	**21**	**27**	**21**	**69**

6.12.2. Total Lymph Nodes Removed per Surgery by Surgeon

The average number of lymph nodes removed by each surgeon per operation was calculated and was as follows – surgeon 1 (11.43), surgeon 2 (12.93), surgeon 3 (10.43). (See Table 53)

Table 53: Total Lymph Nodes Removed per Surgery by Surgeon

Total Lymph Nodes removed per surgery	Surgeon 1	Surgeon 2	Surgeon 3
0 to 5	2	6	3
6 to 10	7	4	8
11 to 15	8	10	6
16 to 20	4	4	4
21 to 25	0	1	0
26 to 30	0	0	0
31 to 35	0	1	0
36 to 40	0	1	0
Average per surgery	**11.43**	**12.93**	**10.43**

6.12.3. Surgical Complications according to Surgeon

Surgeon 2 had the lowest complication rate at 4%, followed by surgeon 1 with 5%. Complications were highest for surgeon 3 at 10%. Average intra-operative complication rate was 6%. (See Table 54)

Table 54: Surgical complication rate by Surgeon

Number of Surgical Complications	Surgeon 1	Surgeon 2	Surgeon 3	Total
No complications	20	26	19	65
Complications	1	1	2	4
Surgical Complication rate	5%	4%	10%	6%

7. DISCUSSION

The mean age of our study population was 45 years which is slightly lower than that found in a large study from Ethiopia where over 1000 women were followed up after surgery and or radiotherapy for early stage disease where the mean age was 49 years. [22] This may be explained by the high incidence of HIV in South Africa where immune compromise causes invasive disease to be more aggressive and occur earlier.

According to the South African census of 2011, 48.7% of the population was male and 51.3% was female. This almost equal distribution of sex helps us compare the races included in our study. Black people are the majority at 79.2 % and this may explain the 68.12% of black patients in our study. The census showed that Coloured and White people both formed 8.9% of the total population whereas in our study White patients formed 26.09%, and Coloured patients were 2.9% but this may be explained by the fact that there are a much higher number of White people living in Gauteng province where our hospital is based relative to Coloured people and the opposite is true for the Western Province explaining this difference relative to the national race demographic. The census showed that 2.5% of the population were Indian, which is close to the 2.9% of Indian patients included in our study. [23] This indicates that our study was representative of the racial demographic in South Africa but that future studies should probably include patients from different hospitals in all provinces to improve accuracy of outcomes being assessed.

Since the average parity for patients who were alive and dead at the end of the study was 2.86 and 2.5 respectively and the average gravidity for patients who were alive and dead at the end of the study was 3.56 and 2.8 respectively. It would suggest from this study that patients with higher numbers of pregnancies and children have a better prognosis if they develop an early stage cervical cancer.

In 2013 the United Nations Aids Gap Report estimated that 25% of the total 24.7 million HIV positive people living in Sub-Saharan Africa were South African. Fifty eight percent of the 24.7 million were female. [24] According to the South African 2011 census there are 26.68 million females in the country. [23] This implies then that approximately 3.58 million (13.6%) of women in South Africa of all age groups are currently HIV positive. In this study 35% of the patients were HIV positive – this much higher number relative to the general population may be explained by the fact that HIV newly acquired infections are lower in younger populations due to education and prevention programs and that most patients in the study and who acquire cervical cancer are of middle age. Cervical cancer is also more prevalent in HIV positive patients especially in those with low CD4 counts. Our study period was from 2002 to 2012 and anti-retrovirals were only made freely available to the population from 2004 and only to patients with CD4 counts below 200. This would imply that a large proportion of the HIV positive cohort who had pre-malignant lesions that may have regressed on ARV therapy had progressed due to late initiation of therapy. The percentage of early stage cervical cancers requiring Wertheim hysterectomies may therefore decrease over the next few years with the advent of ARV initiation now occurring at CD4 counts of 350 and below. We can assume this since the majority (79%) of HIV positive patients included in this study had CD4 counts less than 400. 25% had CD4 counts of 0 to 200 and 54% had CD4 counts of 201 to 400. Only 8% had CD4 counts of 601 to 1000.

In view of the fact that a Wertheim's hysterectomy is considered a major surgical procedure and that post-surgical recovery an important consideration in overall prognosis. Only patients who are relatively healthy and well are selected for the procedure. The majority 83% of patients selected for surgery in this study were ECOG performance status 1, i.e. symptomatic but 100% ambulatory.

Only 16% were ECOG performance status 0, i.e. asymptomatic. This implies that in this group of cervical tumours evaluated as clinically respectable the majority presented with symptomatic disease but were otherwise still relatively well.

The study showed that overall survival on 30 June 2015 was 86% which is in keeping with previous studies that showed 5 year survival to be between 82 to 90%. [25] Overall average disease free period was 5 years in our study. Thirty three percent of the patients were disease free for more than five years. 85.51% were disease free for 2 years or more also in keeping with a study that showed recurrence free rate at 2 years between 79 to 88%. [12] The study results also proved statistically at 95% confidence that the disease-free interval was highly significant to overall survival both at 2 years and 5 years postoperatively. We also showed that survival status was higher for patients without co-morbidities. A much larger number of patients (21) entered the study in 2012 compared to previous years because an oncology fellow joined the group of surgeons that year. It is likely that the detection rate of early stage resectable cervical cancer increased for surgical teaching purposes in that year.

Adequacy of patient selection for surgery was only 75% and overall 30% of patients were incorrectly staged pre-operatively. This led to 25% receiving the incorrect management according to our institutions protocols. This suggests that a preoperative MRI scan should be used in addition to clinical assessment to correctly identify patients suitable for management by Wertheim's Hysterectomy. A recent prospective study showed MRI scans to be superior to clinical assessment with regards to tumour size, internal os and parametrial involvement and that when combined with clinical assessment accuracy of correct clinical stage improved significantly. [26]

Previous studies have shown that number of positive nodes, tumour cell type, grade, size, depth of invasion and lateral spread as well as presence of lymphovascular space, parametrial and Pouch of Douglas involvement on histological specimens all impact recurrence risk and rates of patient survival and duration of remaining disease free. [9, 12, 27] Although similar patterns were observed in this study, applying Fisher's Exact tests for these risk factors did not show statistical significance at the 95% confidence level due to the small sample size of this study.

Regarding risk factors for recurrence our study showed that an adenomatous subtype was more aggressive than a squamous subtype since the overall disease-free period and survival was lower for the adenomatous subtype. This is in keeping with other studies which have assessed recurrence risk and overall survival relative to tumour histological subtype. [28, 29]

Pelvic lymph node metastasis, parametrial invasion and positive surgical margins have been shown to be high risk for recurrence as opposed to lymphovascular space invasion, deeper tumour invasion and increased tumour size which are relatively considered intermediate risk factors for recurrence. [9, 12, 27]

In this study tumour size did predict outcome differences. Patients with tumours more than 4cm in size had a 75% probability of surviving and a 75% probability of being disease free at 2 or more years compared to those who had tumours of 4cm and less in size who had a 97% probability of survival and an 88% probability of being disease free at 2 years or more.

This was also the case with depth of invasion where both the 2 year or more probability of survival and being disease free was 100% for tumours less than or equal to 3mm and for tumours with depth 3mm and more but less than 5mm - this decreased to 93% and 80% for tumours more than 5mm in depth.

Patients with tumours that had spread laterally less than or equal to 7mm had 100% probability of survival and 95% probability of being disease free at 2 years or more compared to those with

tumours more than 7mm where survival probability decreased to 94% and disease-free probability decreased to 83%.

Patients with lymphovascular space invasion had lower probabilities of survival and being disease free 2 years postoperatively relative to those without lymphovascular space invasion 96% and 92% as opposed to 95% and 74%. These differences were not very high showing then that indeed lymphovascular space involvement is more of an intermediate risk factor for recurrence.

With regards to pelvic lymph node involvement patients' probability of surviving 2 or more years postoperatively irrespective of the number of positive lymph nodes was high. However, generally the probability rate of being disease free 2 or more years postoperatively decreased exponentially with increasing number of positive nodes harvested at surgery. One patient with 6 positive nodes was disease free at 2 or more years postoperatively indicating that a good 2 year outcome may still be achieved if bimodal adjuvant therapy is used to decrease recurrence and that it definitely increases patient survival in the 2 or more years postoperative time period.

Interestingly, patients with parametrial and or pouch of Douglas involvement had a reduced 2 year probability of being disease free but their survival probability was marginally higher compared to those patients who had no involvement. These differences may be attributed to the smaller sample size of patients who did have involvement of either the parametria or pouch of Douglas or it may indicate that these risk factors are less predictive of short term survival compared to other risk factors assessed by the study.

Positive margins are considered margins where tumour was found less than 10mm from the resection borders histologically. Our study showed an 7% decrease in the 2 year probability of survival and a 22% decrease in the 2 year probability of being disease free if tumour was not more than or equal to 10mm from the resection borders. Eighty three percent of patients with positive

margins in this study had recurrence which is therefore in keeping with what other studies have shown that positive margins are a high risk factor for recurrence.

Survival and disease free intervals were highest for patients with post-operative cytology showing negative for intra-epithelial lesion or malignancy and lowest for patients with cytology showing radiation reaction. This is likely due to the latter patients having had more risk factors for recurrence which necessitated the use of adjuvant radiotherapy compared to the others who had complete resection and no risk factors for recurrence.

In general the results showed that HIV non reactive patients had longer survival and disease free periods than those who were HIV reactive. Reactive patients tended to have a similar number of disease free years to overall survival – implying that patients demised soon after recurrence. Non reactive patients lived with recurrence for longer. Although the statistics for patients with unknown HIV status appear higher than those with known HIV status – there were only 5 patients in the unknown category and hence the results were not statistically significant.

The study also showed that for HIV reactive patients the lower the CD4 count at diagnosis and management, the lower the disease-free period and overall survival. This suggests that all HIV positive women with confirmed malignancies should be on antiretroviral therapy or initiated immediately if already not on treatment. Furthermore, patients should be counselled on increased risk of cervical cancer recurrence if they default treatment at a later stage if tumour is successfully excised with no risk factors requiring adjuvant therapy.

Both the intra-operative surgical complication rate (6%) and the immediate post-surgical complication rate (16%) was low this may be due to the fact that only 3 senior surgeons performed all the surgeries – 2 of which were experienced gynaecological oncology surgeons and 1 a

gynaecological oncology fellow. The numbers of lymph nodes harvested by all 3 surgeons was similar and the complication rate for the 2 more experienced surgeons was similar 5% and 4% and lower compared for that of the fellow which was 10%. The cumulative complication rate for our institution was therefore 22% with no mortalities but is slightly higher than the 16, 5% found in a very similar study done over 5 years that followed up 115 patients. [30]

A high percentage of patients 47.83% required adjuvant therapy either radiation only or chemo-radiation. The most common early complications of the adjuvant therapy were proctitis or diarrhoea, then skin irritation and rashes followed by cystitis and frequency.

8. LIMITATIONS

Due to the small sample size, some results need to be interpreted with care especially where a category was represented by a small number of patients. A larger sample size would be preferable to draw conclusions with statistical significance.

Another limitation of the study was that 10 patients could not be reached telephonically or at their home addresses at the cut-off date for data collection. Their survival status was confirmed by the Department of Home Affairs but their disease-free interval was assumed to be at their last follow up date at our hospital. If these patients relocated and continued follow up at different hospitals the assumed disease-free interval and survival without recurrence for these 10 patients would be incorrect.

Patients included in the study were representative of the racial group demographic in the country except for white and coloured patients. White patients had a higher representation and Coloured patients a lower presentation as compared to that in the country but were correctly represented for the province of Gauteng. Future similar studies need to be done in hospitals in more than one province to better represent the racial demographic of the country.

The patients in our study also only represent those of middle and low socio-economic groups since most South Africans who are affluent have self-funded medical aids and are not treated at government institutions but at private hospitals. We can thus not comment on what differences socio-economic status might have on survival and disease-free periods with this disease.

This study relied on retrospective data and missing data was anticipated. Where information was missing patients were asked when contacted telephonically regarding their follow up and well-being.

Patients with complications may not have necessarily returned to CMJAH – these unknown losses to follow-up may have given biased complication rates.

ABBREVIATIONS

CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CRT	Chemo-radiotherapy
DXT	Deep X Ray Therapy (adjuvant radiotherapy)
ECOG	European Cooperative Oncology Group
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique (International Federation of Gynaecology and Obstetrics)
HIV	Human Immunodeficiency Virus
LVSI	Lympho-Vascular Space Invasion
NHLS	National Health Laboratory Services
POD	Pouch of Douglas
RT	Radiotherapy
WHO	World Health Organisation

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APPENDICES

APPENDIX 1: DATA COLLECTION SHEET

1. NAME OF SURGEON

2. PATIENT ID

3. AGE

4. RACE

5. PARITY

6. CO-MORBIDITIES
   - □ DIABETES MELLITUS
   - □ EPILEPSY
   - □ ASTHMA
   - □ COPD
   - □ HEART DISEASE
   - □ HYPERTENSION
   - □ OTHER

7. HIV STATUS
   - □ REACTIVE CD4 COUNT ……
   - □ NON-REACTIVE
   - □ UNKNOWN

8. ECOG PERFORMANCE STATUS
   - □ 0 ASYMPTOMATIC
   - □ 1 SYMPTOMATIC 100% AMBULATORY
   - □ 2 SYMPTOMATIC > 50% AMBULATORY
   - □ 3 SYMPTOMATIC < 50% AMBULATORY
   - □ 4 BED-BOUND
   - □ 5 DEATH

9. PREOPERATIVE CYTOLOGY RESULTS
   - □ HGSIL
   - □ LGSIL
   - □ ASCUS
   - □ AGCUS
   - □ HGSIL SUSPICIOUS FOR INVASION
   - □ SQUAMOUS CARCINOMA
   - □ ENDOCERVICAL ADENOCARCINOMA
   - □ NIL

10. PREOPERATIVE HISTOLOGY RESULTS
   - □ SQUAMOUS CELL CARCINOMA
   - □ ADENOMATOUS CELL CARCINOMA
   - □ OTHER CELL CARCINOMA

11. PREOPERATIVE CLINICAL STAGING
   - □ STAGE IB1
   - □ STAGE IB2

12. DATE OF SURGERY

13. POST-OPERATIVE HISTOLOGY CELL TYPE
   - □ SQUAMOUS CELL CARCINOMA
   - □ ADENOMATOUS CELL CARCINOMA
   - □ OTHER CELL CARCINOMA

14. POSTOPERATIVE HISTOLOGY STAGE
   - □ STAGE IA1
   - □ STAGE IA2
   - □ STAGE IB1
   - □ STAGE IB2
   - □ STAGE IIA
   - □ STAGE II B
   - □ STAGE IIIA
   - □ STAGE IIIB
   - □ STAGE IVA
   - □ STAGE IVB

15. TUMOUR GRADE
   - □ POORLY DIFFERENTIATED
   - □ MODERATELY DIFFERENTIATED
   - □ WELL DIFFERENTIATED

16. TUMOUR SIZE
    - □ ≤ 4CM
    - □ > 4CM

17. TUMOUR DEPTH OF INVASION
    - □ < 3MM
    - □ > 3MM
    - □ < 5MM
    - □ > 5MM

18. TUMOUR LATERAL SPREAD
    - □ < 7MM
    - □ > 7MM

19. LYMPHOVASCULAR SPACE INVOLVEMENT
    - □ YES
    - □ NO

20. NUMBER OF POSITIVE LYMPH NODES

21. TOTAL LYMPH NODES REMOVED

22. PARAMETRIAL INVOLVEMENT
    - □ YES
    - □ NO

23. POUCH OF DOUGLAS INVOLVEMENT
    - □ YES
    - □ NO

24. SURGICAL MARGINS
    - □ ≥ 10MM
    - □ < 10MM

25. SURGICAL COMPLICATIONS
    - □ OBTURATOR NERVE RESECTION
    - □ URETERIC RESECTION
    - □ UTERINE ARTERY HAEMORRHAGE
    - □ BLADDER INJURY
    - □ OTHER
    - □ NIL

26. IMMEDIATE POST SURGICAL COMPLICATIONS
    - □ HAEMATOMA
    - □ UTEROVAGINAL FISTULA
    - □ PULMONARY EMBOLISM
    - □ DEEP VEIN THROMBOSIS
    - □ WOUND SEPSIS
    - □ ABDOMINAL HERNIA
    - □ ILEUS
    - □ LOWER LIMB OEDEMA
    - □ LYMPHOCYST
    - □ HYDRO-URETER
    - □ STRESS INCONTINENCE
    - □ ATONIC BLADDER
    - □ LOW COMPLIANCE BLADDER
    - □ OTHER
    - □ NIL

27. POST SURGICAL MANAGEMENT
    - □ DXT
    - □ CHEMOTHERAPY
    - □ CHEMO-RADIATION

28. POST SURGICAL MANAGEMENT COMPLICATIONS
    - □ PROCTITIS/DIARRHOEA
    - □ CYSTITIS/FREQUENCY
    - □ NAUSEA AND VOMITING
    - □ SKIN IRRITATION/RASH
    - □ LYPHOEDEMA
    - □ ALOPECIA
    - □ OTOTOXICITY
    - □ OCULAR TOXICITY
    - □ HEPATOTOXICITY
    - □ NEUROTOXICITY
    - □ NEPHROTOXICITY
    - □ MYELOSUPRESSION
    - □ ELECTROLYTE DISTURBANCES
    - □ ANAPHYLACTIC REACTION
    - □ FATIGUE
    - □ OTHER
    - □ NIL

29. POST-OPERATIVE CYTOLOGY RESULTS
    - □ NEGATIVE FOR INTRA-EPITHELIAL LESION / MALIGNANCY
    - □ HGSIL
    - □ LGSIL
    - □ ASCUS
    - □ AGCUS
    - □ CARCINOMA-IN-SITU
    - □ NOT DONE

30. NUMBER OF YEARS FOLLOWED UP POST-OPERATIVELY

31. NUMBER OF YEARS DISEASE FREE POST-OPERATIVELY

32. NUMBER OF YEARS OVERALL SURVIVAL

33. SURVIVAL STATUS AT 30/06/2015

34. DATE OF DEATH

APPENDIX 2: PERMISSION LETTERS

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries: Mrs. L. Mapaisa
Office of the Director: Clinical Services
Tell: (011)488-3365
Fax: (011)488-3753
07 November 2014

Ms. Sandra Marques Nascimento Fonseca
Registrar
Obstetrics and Gynaecology
University of the Witwatersrand

Dear Ms. Fonseca

RE: Outcomes of patients with Stage IB1 and IB2 Cervical Cancer who have had Wertheim's Hysterectomies with or without Adjuvant Chemo-Radiotherapy as Primary Treatment at Charlotte Maxeke Johannesburg Academic Hospital

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 in anyway incur or inherit costs as a 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 Head of Department 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.

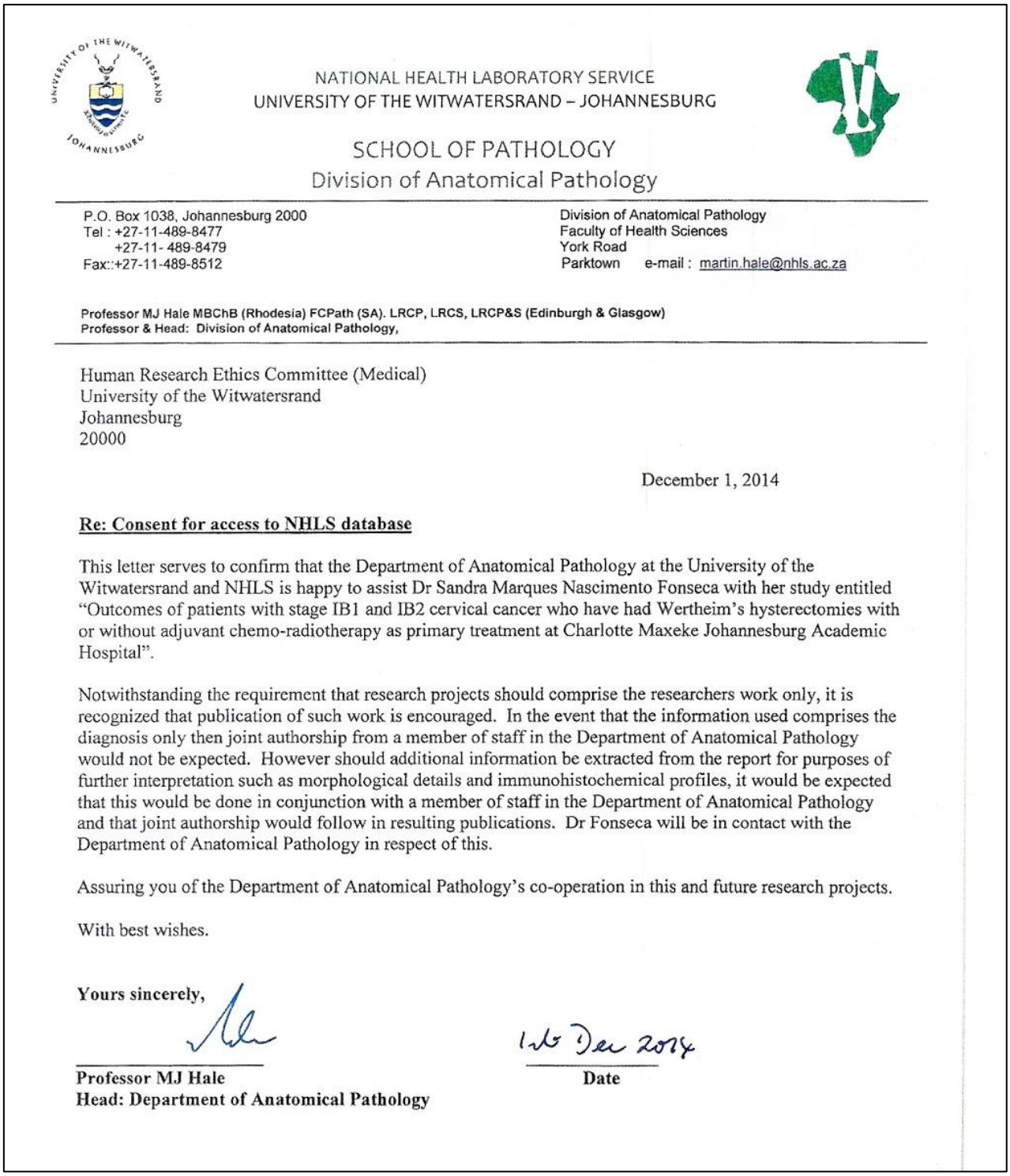
Supported / ~~not supported~~

Dr. M.I. Mofokeng
Director: Clinical Services
DATE: 12/11/2014

Approved / not approved

Ms. G. Bogoshi
Chief Executive Officer
DATE: 13/11/2014

Figure 16: Permission from CMJAH CEO



NATIONAL HEALTH LABORATORY SERVICE
UNIVERSITY OF THE WITWATERSRAND – JOHANNESBURG

SCHOOL OF PATHOLOGY
Division of Anatomical Pathology

P.O. Box 1038, Johannesburg 2000
Tel : +27-11-489-8477
+27-11- 489-8479
Fax::+27-11-489-8512

Division of Anatomical Pathology
Faculty of Health Sciences
York Road
Parktown e-mail : martin.hale@nhls.ac.za

Professor MJ Hale MBChB (Rhodesia) FCPath (SA). LRCP, LRCS, LRCP&S (Edinburgh & Glasgow)
Professor & Head: Division of Anatomical Pathology,

Human Research Ethics Committee (Medical)
University of the Witwatersrand
Johannesburg
20000

December 1, 2014

Re: Consent for access to NHLS database

This letter serves to confirm that the Department of Anatomical Pathology at the University of the Witwatersrand and NHLS is happy to assist Dr Sandra Marques Nascimento Fonseca with her study entitled "Outcomes of patients with stage IB1 and IB2 cervical cancer who have had Wertheim's hysterectomies with or without adjuvant chemo-radiotherapy as primary treatment at Charlotte Maxeke Johannesburg Academic Hospital".

Notwithstanding the requirement that research projects should comprise the researchers work only, it is recognized that publication of such work is encouraged. In the event that the information used comprises the diagnosis only then joint authorship from a member of staff in the Department of Anatomical Pathology would not be expected. However should additional information be extracted from the report for purposes of further interpretation such as morphological details and immunohistochemical profiles, it would be expected that this would be done in conjunction with a member of staff in the Department of Anatomical Pathology and that joint authorship would follow in resulting publications. Dr Fonseca will be in contact with the Department of Anatomical Pathology in respect of this.

Assuring you of the Department of Anatomical Pathology's co-operation in this and future research projects.

With best wishes.

Yours sincerely,

Professor MJ Hale
Head: Department of Anatomical Pathology

1st Dec 2014
Date

Figure 17: Permission from Head of Anatomical Pathology

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Obstetrics and Gynaecology Department
Tel: 011 488 4178
Fax: 011 643 2522

9th January 2015

Human Research Ethics Committee (Medical)
University of the Witwatersrand
Johannesburg
2000

To whom it may concern

Re: Dr Sandra Nascimento Fonseca. Proposed research dissertation: Outcomes of patients with Stage IB1 and IB2 Cervical Cancer who have had Wertheim's Hysterectomies with or without adjuvant chemo radiotherapy as primary treatment at Charlotte Maxeke Johannesburg Academic Hospital

This is to certify that I fully support the above mentioned study taking place at the Charlotte Maxeke Johannesburg Academic Hospital.

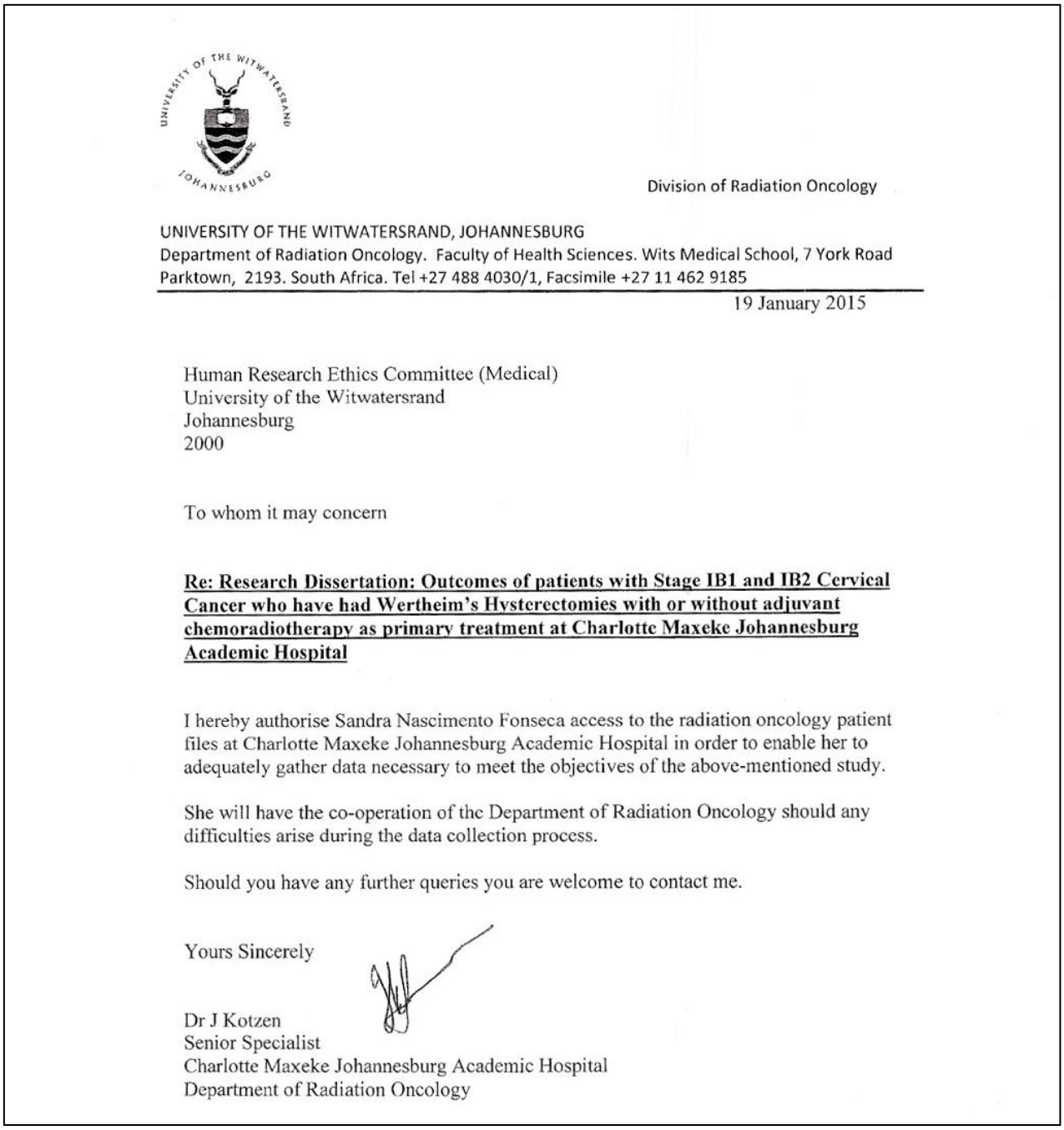
I will be one of the co supervisors and will assist further if any other need arises.

Should you require any other information I will gladly oblige.

Kind regards,

Prof F Guidozzi
Academic Head and Chief Specialist
Charlotte Maxeke Johannesburg Academic Hospital
and the University of the Witwatersrand

Figure 18: Permission from Head of Obstetrics and Gynaecology



Division of Radiation Oncology

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Department of Radiation Oncology. Faculty of Health Sciences. Wits Medical School, 7 York Road
Parktown, 2193. South Africa. Tel +27 488 4030/1, Facsimile +27 11 462 9185

19 January 2015

Human Research Ethics Committee (Medical)
University of the Witwatersrand
Johannesburg
2000

To whom it may concern

Re: Research Dissertation: Outcomes of patients with Stage IB1 and IB2 Cervical Cancer who have had Wertheim's Hysterectomies with or without adjuvant chemoradiotherapy as primary treatment at Charlotte Maxeke Johannesburg Academic Hospital

I hereby authorise Sandra Nascimento Fonseca access to the radiation oncology patient files at Charlotte Maxeke Johannesburg Academic Hospital in order to enable her to adequately gather data necessary to meet the objectives of the above-mentioned study.

She will have the co-operation of the Department of Radiation Oncology should any difficulties arise during the data collection process.

Should you have any further queries you are welcome to contact me.

Yours Sincerely

Dr J Kotzen
Senior Specialist
Charlotte Maxeke Johannesburg Academic Hospital
Department of Radiation Oncology

Figure 19: Permission from Senior Specialist of Radiation Oncology

Human Research Ethics Committee (Medical)

Research Office Secretariat: Senate House Room SH 10005, 10th floor. Tel +27 (0)11-717-1252
Medical School Secretariat: Phillip Tobias Building, 2nd Floor, Tel +27 (0)11-717-2700
Private Bag 3, Wits 2050, www.wits.ac.za.

19 September 2014

Dr M Mofokeng
Clinical Director
Charlotte Maxeke Johannesburg Academic Hospital (CMJAH)
Parktown
Johannesburg

Dear Dr Mofokeng

SUBJECT: **CONFIRMATION OF STUDY APPROVAL**
Protocol Ref no: M140814
Protocol Title: Outcomes of Patients with Stage IB1 and IB2 Cervical Cancer who have had Wertheim's Hysterectomies with or without Adjuvant Chemo-Radiotherapy as Primary Treatment at Charlotte Maxeke Johannesburg Academic Hospital
Principal Investigator: Dr SMN Fonseca
Department of Obstetrics and Gynaecology

This letter serves to confirm that the Human Research Ethics Committee (Medical) has approved the above mentioned study. In order for a clearance certificate to be issued, the researcher is required to submit written approval to conduct the study in your hospital.

Yours Sincerely,

Ms Zanele Ndlovu
Administrative Officer
Human Research Ethics Committee (Medical)

UNIVERSITY OF THE WITWATERSRAND
OFFICE OF THE DEPUTY VICE CHANCELLOR RESEARCH
19 SEP 2014
RESEARCH OFFICE HREC (Medical)
JOHANNESBURG

Figure 20: Confirmation of Study Approval from Human Research Ethics Committee

R14/49 Dr Sandra Margues Nascimento Fonseca

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140814

NAME: (Principal Investigator)	Dr Sandra Marques Nascimento Fonseca
DEPARTMENT:	Obstetrics and Gynaecology Charlotte Maxeke Johannesburg Academic Hospital Klerksdorp Hospital
PROJECT TITLE:	Outcomes of Patients with Stage IB1 and IB2 Cervical Cancer Who Have Had Wertheim's Hysterectomies With or Without Adjuvant Chemo-Radiotherapy as Primary Treatment at Charlotte Maxeke Johannesburg Academic Hospital
DATE CONSIDERED:	29/08/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Franco Guidozzi
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	23/01/2015

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 Secretary in Room 10004, 10th floor, Senate House, University.

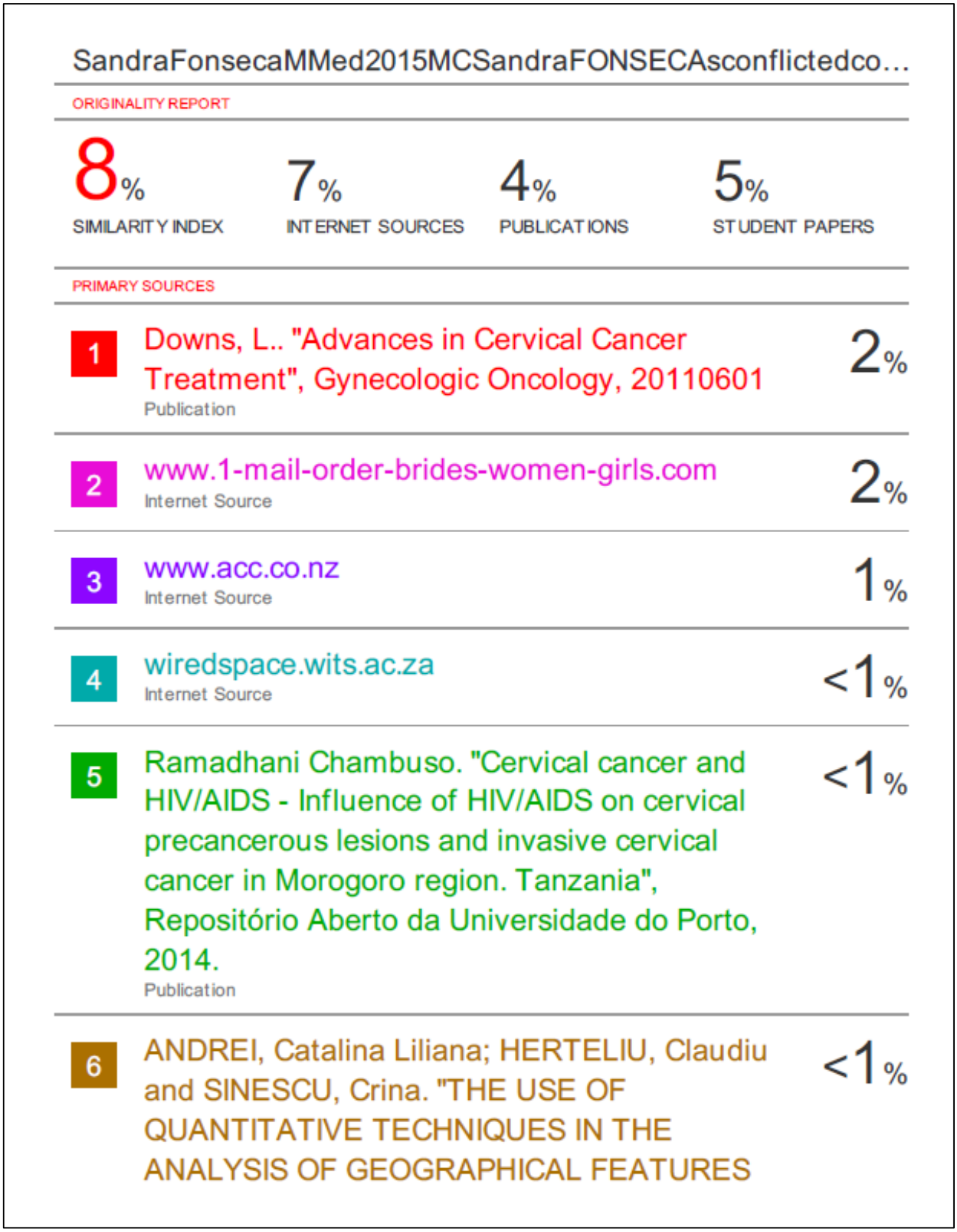
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.**

Principal Investigator Signature Date 28/1/2015

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Figure 21: Clearance Certificate from Human Research Ethics Committee

APPENDIX 3: TURNITIN REPORT



SandraFonsecaMMed2015MCSandraFONSECAsconflictedco…

ORIGINALITY REPORT

8%	7%	4%	5%
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