The morbidity and mortality associated with surgery for Radical Hysterectomy and Pelvic Lymph Node Dissection done at Charlotte Maxeke Johannesburg Academic Hospital for cervical cancer

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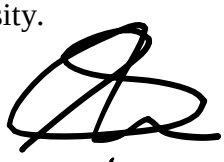
DECLARATION

I, Godfrey Thabo Mmalekutu, declare that the research reported in this work is completely my own. It is submitted to the Faculty of Health Sciences for the degree of Masters of Medicine in Obstetrics and Gynaecology, at the University of Witwatersrand, Johannesburg.

This work has not been submitted before for any other degree or examination at this, or any other university.



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ABSTRACT

Background

Cancer of the cervix was ranked fourth in 2018 worldwide for both incidence (6%) and mortality (7.5%), with 570 000 estimated new cases and 311 000 deaths.[1] In South Africa following breast cancer, it is the second most commonly diagnosed cancer among women. Its incidence rate increases with increasing age and was found to be 20.42 and 82.02 per 100 000 among women of ages 30-34 and 65-69 years respectively.[1] It is the leading cancer among black South African women and the fifth common cancer among South African white women, and it is estimated to kill approximately 8 women every day in South Africa.[64] However, early cervical cancer (IA-IB2) has a relatively favourable prognosis, with a greater than 80% survival rate.[2] For early stage disease, treatment with either radical surgery or radiation appears equally effective, with 5-year survival rates of approximately 70-80%. However, radiation therapy as primary treatment for early-stage cervical cancer is usually reserved for women who are not candidates for surgery due to medical comorbidities or poor functional status. [2]

Surgical approach remains the main curative intent treatment for solid tumors. Its benefit includes better access and visualisation of tumor, and the opportunity to surgically remove any grossly positive lymph nodes while maintaining the functioning of the ovaries.[3] The extensive parametrectomy involved with this procedure has been associated with pelvic organs dysfunction. The main advancement in the surgical treatment of early cervical cancer has been the de-escalation of radical surgical approach, with less parametrectomy in tumors ≤ 2cm, however maintaining same oncologic outcomes.[49,71]

Today, the proficient performance of the RH is the bench-mark of the gynaecologic oncology surgeon. The management of early-stage disease (IA1-IB2) at the CMJAH one of the tertiary hospitals in Johannesburg South Africa, is similar to the international guidelines. However, patients with stage IIA are managed as late-stage disease with chemo-radiation.[28] There exist a lot of controversies on the outcome of RH whether performed by open, laparoscopic, or robotic methods regarding the surgical outcome and histological subtypes. No available documented data exists in CMJAH, on the outcomes of cervical cancer patients treated with this procedure. This study describes the morbidity and mortality associated with RH and PLND performed on early-stage cervical cancer patients at CMJAH.

Methods and Materials

We retrospectively reviewed medical records of women who underwent Radical Hysterectomy and Pelvic Lymph Node Dissection (RH and PLND) for early-stage cervical cancer at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) from 1 January 2015 to 31 December 2016. Descriptive analysis of data was performed, including means and standard deviations (SD) for normally distributed data and medians and interquartile ranges (IQR) for non-normally distributed continuous data.

The crude and unadjusted intraoperative and post-operative complications of surgery rates were calculated. Chi squared test was used to assess the relationships between groups of radical hysterectomy subtypes, demographic and clinical characteristics, staging, morphological appearance of tumors, and other histological subtypes. Fisher's exact test was used where the requirements for the Chi squared test were not met.

Results

Twenty-three women met the study criteria, eighteen blacks and five whites with a mean age of 45.65years (SD±13.23). Twenty-Three Radical Hysterectomy and Pelvic Lymph Node Dissection (RH and PLND) were performed to completion, twelve were done by a gynaecology oncologist and eleven by a training fellow gynaecologist in the unit. The commonest type of procedure performed was Q-M class B (82.61%) with level II lymph node dissection done in 52.17% of the cases. RH and PLND was performed in 86.96% (20/23) of patients with stage 1B1 disease, 8.70% (2/23) 1A2, and 4.35% (1/23) HGSIL. The histological subtypes before surgery, were Squamous cell carcinoma (69.57%), Adeno-carcinoma (17.39%), and Adeno-Squamous carcinoma (13.04%).

Lymph node involvement was found in 67.00% (4/6) patients with stage IB1, 17.00% (1/6) IB2 with a basaloid variant of squamous cell carcinoma and one patient (17.00%) with advanced disease IIA2, and 5 of 6 patients received adjuvant chemo-radiation treatment, one patient with stage IB2 did not receive chemo-radiation as she got lost to follow up. The overall complications rate was 21.74% (5/23), these included post-operative ileus (8.70%), blood vessel injury (4.35%), post-operative wound infection (4.35%), and pulmonary embolism (4.35%).

Pre-operative use of broad-spectrum antibiotics (cefazolin or augmentin®) was associated with lower rates of post-operative infections (4.35%) requiring admission and the use of intravenous antibiotics. Prophylactic use of low molecular weight heparin (clexane®) at a dose of 1milligram per kilogram daily was associated with 95.65% prevention of venous thrombo-embolic disease. No patient in our study required admission to the intensive care unit. There were no deaths reported during the study period.

Conclusion

For early-stage disease, treatment with either radical surgery or radiation appears equally effective, with 5-year survival rates of approximately 70-80%. However, radiation therapy as primary treatment for early-stage cervical cancer is usually reserved for women who are not candidates for surgery due to medical comorbidities or poor functional status. Pelvic radiation therapy (with or without chemotherapy) uniformly results in ovarian failure due to the doses required for curative-intent therapy and if ovarian preservation is necessary, consideration of transposition out of the radiation field should be considered.

Open Radical Hysterectomy and Pelvic Lymph Node Dissection remains the treatment of choice for early cervical cancer, with a favourable prognosis and oncological outcomes. We have shown that when done under standardized practices, Radical Hysterectomy was associated with less morbidity and yielded lower rates of early and late complications (21.4%) with favourable oncological outcomes. The shorter turnaround time between diagnosis of disease and surgery has resulted in early intervention, before disease progression. However, more prospective studies are needed to establish this association.

The retrospective nature of our study failed to show any association between some risk factors (eg BMI) known to affect surgical outcomes as they were not recorded. Our study was limited as it had a low number of participants and did not look at other known complications of RH like sexual and lower urinary tract dysfunction. A well-structured and powered, multicentre prospective study is needed to look at the broader picture regarding the morbidity and mortality associated with RH and PLND performed for early cervical cancer.

ACKNOWLEDGEMENTS

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List of Abbreviations

AJCC	American Joint Committee on Cancer
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
DFS	Disease-Free Survival
DNA	Deoxy Nucleic Acid
FIGO	The Féderation Internationale de Gynécologie et d'Obstétrique
GOG	Gynecologic Oncology Group
GY	Gray
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
LLETZ	Large Loop Excision of Transformation Zone
LUT	Lower Urinary Tract
LVSI	Lympho Vascular Space Invasion
NHLS	National Health Laboratory Services
PFS	Progression-Free Survival
PLND	Pelvic Lymphadenectomy
PNI	Perineural Invasion
RH	Radical Hysterectomy

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CHAPTER 1: INTRODUCTION

Cancer of the cervix remains a major public health burden. However, its related mortality and incidence has dramatically declined in developed countries, due to screening programs, with a diagnosis at an early stage. It was ranked fourth in 2018 worldwide for both incidence (6%) and mortality (7,5%), with 570 000 estimated new cases and 311 000 deaths.[1] In South Africa following breast cancer, it is the second most commonly diagnosed cancer among women. Its incidence rate increases with increasing age and was found to be 20.42 and 82.02 per 100 000 among women of ages 30-34 and 65-69 years respectively. Black South African women are the most affected by cervical cancer ranking 1st in this population, while ranking 5th among South African white women.[1] The treatment of early-stage cervical cancer with either radical hysterectomy (RH) and pelvic lymph node dissection (PLND) or primary radiotherapy is equally effective, with a 5-year overall survival of 85-90% in patients with stage IB and 65-75% in patients with stage IIA disease. [2] Surgical approach remains the main curative intent treatment for solid tumors. Its benefit includes better access and visualisation of tumor, and the opportunity to surgically remove any grossly positive lymph nodes while maintaining the functioning of the ovaries.[3] Despite the oncologic benefits of the procedure, RH and PLND are associated with significant morbidity including blood loss, lower urinary tract injuries, sexual and pelvic organs dysfunction. [4,5]

Radical hysterectomy involves the removal of the uterus in conjunction with resection of the upper vaginal cuff, the parametrium, the utero-sacral ligaments, and mobilisation of the distal end of the ureter.[6] Some of the women treated with this surgical procedure will require adjuvant chemo-radiotherapy therapy due to the presence, of residual disease or high-risk factors for recurrence. The involvement of the parametrium, lymph nodes, and positive resection margins are associated with a high-risk of disease recurrence. [6,7]

Less radical surgical approaches, with similar oncological outcomes, have been introduced in order to reduce the rates of pelvic organ dysfunction associated with the extent of damage during parametrectomy.[6,8] The minimally invasive surgery (robotic or laparoscopic) is less time consuming as compared to open RH when done for early cervical cancer, however, they have been found to yield the same oncological outcomes. It also has added advantages of shorter

hospital stay, less febrile morbidity, lower estimated blood loss and less wound-related complications.[9,10]

1.2 BACKGROUND AND LITERATURE REVIEW

1.2.1 Cervical cancer

The persistent infection with carcinogenic human papillomavirus (HPV) types is the main cause in triggering the development of cervical cancer. These are sexually transmitted DNA viruses that infect the epithelium. They are found in majority of the pre-invasive and malignant lesions of the cervix. Low-risk HPV types include types 6, 11, 42, 43, and 44. High-risk HPV types include types 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 70.[11] Included in the high-risk group are some HPV types that are less frequently found in cancers and are considered intermediate risk subtypes for the development of cervical cancer. HPV 16 & 18 are the most common subtypes associated with about 70-75% of all cervical cancers and 40-60% of its precursors.[11,12,13] HPV 6&11 are low risk subtypes associated with benign lesions (plantar warts, common warts, flat warts).[12] The two most common histologic subtypes are squamous cell carcinoma (75%) and adenocarcinoma (20-25%). The other cell types are rare. HPV 16 is more commonly associated with squamous cell carcinoma of the cervix, whereas HPV 18 is a risk factor for cervical adenocarcinoma.

The implementation of both primary and secondary prevention methods can make cervical cancer occurrence and death largely avoidable.[14] WHO recommends 3-5 yearly cytology screening Papanicolaou smear in low resource setting beginning at age 30-49yrs and a Visual Inspection with Acetic acid (VIA) or HPV testing every 5years. Consistent evidence indicates that the licensed bivalent (Cervarix, GlaxoSmithKline) and quadrivalent (Gardasil, Merck) HPV vaccines containing HPV16 and HPV18 antigens protect with high efficacy against infection and precancerous cervical lesions associated with these types when individuals are not yet exposed.[15] In South Africa Gardasil vaccine is incorporated into school immunisation program and is given to grade 4 school girls between ages of nine to thirteen years in two separate doses given six months apart.

In the past few years, a nonavalent vaccine (Gardasil-9) has also been licenced, which protects against seven carcinogenic HPV (16,18,31,33,45,52,58) that, together, cause approximately

90% of cervical cancers. Papanicolaou testing has been extensively utilised to screen for cervical cancer worldwide, and has undoubtedly led to a major decline in cervical cancer burden in several resource-rich countries, however, the method might have reached its limits, with reports from several countries with longstanding high-quality Pap smear-based programmes indicating that trends have either stabilised or began to rise.[16]

Meta-analyses and pooled analyses of randomised trials have shown that screening with HPV tests protects better against future cervical precancerous lesions and invasive cancers than screening by cytology[17] and, therefore, virological screening programmes are becoming increasingly recommended.[18] Histologic evaluation of cervical biopsy remains the primary tool to diagnose cervical cancer. A well planned and implemented National Cervical Screening Program that fit the target populations within the limits of cost-effectiveness, can reduce the mortality and morbidity rates attributed to cervical cancer. The proposed South African Screening guidelines are shown in table 1.1 and 1.2 below

Table 1.1 Primary Screening Test

SETTING	LOW RESOURCE		HIGH RESOURCE	
HIV status	**HIV unknown or negative**	**HIV positive**	**HIV unknown or negative**	**HIV positive**
Initiate screening	Age 25	At diagnosis of HIV	Age 25	At diagnosis of HIV
Exit screening (only after negative test)	Age 55 or hysterectomy	Never end	Age 65 or hysterectomy	Never end
Interval if HPV screening	10-yearly	5-yearly	5-yearly	3-yearly
Interval if cytology screening	5-yearly	3-yearly	3-yearly	1-yearly
Timing	3-yearly: 25,28,30,33,35,38,40,43,45,48,50,53,55,58,60, etc. 5-yearly: 25,30,35,40,45,50,55,60,65, etc. 10-yearly: 25,35,45,55, etc.			
Follow-up	HIV negative or < 35 years: 5-yearly until normal	HIV positive or > 35 years: yearly until normal	HIV negative or < 35 years: yearly until normal	HIV positive or > 35 years: yearly until normal
	Back to screen when normal. Retreat after second abnormal test.			

Table 1.2 Triage or secondary screening tests

TRIAGE TEST	INDICATIONS	RESULTS	MANAGEMENT
VILI or VIA visual inspection using Lugol's iodine or acetic acid	Low resource settings	Possible invasive lesion	Biopsy
	Medium risk result on cytology or HPV test	No lesion	Do not treat
		Small lesion	Cryotreatment or LLETZ
		Large lesion	LLETZ
CYTOLOGY conventional or liquid based cytology	Low or high resource settings	Normal	Do not treat
	Medium risk result on HPV test	Positive = ASCUS or worse	Cryotreatment or LLETZ
CYTO-STAIN or similar biomarker	High resource settings	Normal	Do not treat
	Medium risk result on cytology or HPV test	Positive	Colposcopy and biopsy
HPV TEST with or without partial genotyping	High resource settings	Normal	Do not treat
	Medium risk result on cytology	Positive	Colposcopy and biopsy

1.2.3 Cervical Cancer Staging (FIGO system)

Cervical cancers are staged clinically. The Féderation Internationale de Gynécologie et d'Obstétrique (FIGO) classification is generally based on clinical examination of the anatomical extent of disease for all cancers except cervical cancer. The American Joint Committee on cancer (AJCC) staging, bases staging on premises that cancers of the same anatomic site and histology share similar patterns of growth and similar outcome.[19,20] Staging is an ongoing process informed by data on outcomes and survival.

While treatment may broadly be dictated by stage, it has to be tailored according to the individual case, provider preferences, and resources. Table 2.3 describes the stage and 5-year survival as per FIGO 2009. Cervical cancer staging is based on clinical assessment. Staging is important in estimating the extent of the disease for prognostic and treatment purposes.[19, 21, 22,23] FIGO in 2018 revised its classification on cervical cancer staging (Annexure E). One of the major changes from the prior FIGO staging is the inclusion of three subgroups for stage IB disease rather than two.

Table 1.3: FIGO staging (2009) and 5-year Survival estimates.[24]

Stage	Description	5-year survival (%)
IA1	Confined to the cervix, diagnosed only by microscopy with invasion of < 3 mm in depth and lateral spread < 7 mm	94.6
IA2	Confined to the cervix, diagnosed with microscopy with invasion of > 3 mm and < 5 mm with lateral spread < 7mm	92.6
IB1	Clinically visible lesion or greater than A2, < 4 cm in greatest dimension	80.7
IB2	Clinically visible lesion, > 4 cm in greatest dimension	79.8
IIA1	Involvement of the upper two-thirds of the vagina, without parametrial invasion, < 4cm in greatest dimension	76.0
IIA2	> 4 cm in greatest dimension	74.2
IIB	With parametrial involvement	73.3
IIIA	Involvement of the lower third of the vagina. No extension to the pelvic sidewall.	50.5
IIIB	Extension into the pelvic sidewall or hydronephrosis or non-functioning kidney.	46.4
IVA	Spread of the tumor into adjacent pelvic organs.	29.6
IVB	Spread to distant organs	22.0

1.3 Surgical Management of Early Stages Cervical Cancer

Early stages cervical cancer is defined as the disease (≤4cm in greatest dimension) limited to the cervix: Stage 1A-1B1, according to Féderation Internationale de Gynécologie et d'Obstétrique (FIGO) 2009 classification, and Stage 1A-1B2 according to the 2018 revised FIGO classification.

Pre-invasive cervical lesions may regress spontaneously and if they persist, Large Loop Excision of the Transformation Zone (LLETZ) or cone biopsy may be used to treat them. Invasive diseases, however, are managed differently according to the stage, functional status and fertility desires.[25]

1.3.1 StageIA1: micro invasive disease

Stage IA1 disease is managed by a conservative surgery with excellent survival outcome.[26] In patients with stage IA1 without LVSI, conisation with negative margins is the preferred treatment of choice, but LLETZ may be acceptable as long as adequate margins, proper orientation, and a non-fragmented specimen can be obtained.[25] Lymphadenectomy is not required for stage IA1 in the absence of LVSI as the risk of nodal metastasis is lower <1%. Patients with cervical cancer IA1 with LVSI are treated with Radical Hysterectomy and Pelvic Lymph Node Dissection (RH and PLND).

1.3.2 Stage IA2- IIA: early-stage disease

Most patients with these stages of the disease are treated by RH and PLND (Wertheim's procedure). However, up to 15% of the early-stage disease may have positive pelvic nodes and will require adjuvant treatment.[13] Stage IB1 cervical cancers are defined by a broad range of tumor characteristics such as tumor size, depth of invasion, lymph node metastasis, and parametrial invasion. Lymph node metastasis, parametrial involvement and tumor size ≥2cm are classified as high-risk factors for recurrence and indicate the need for adjuvant chemo-radiotherapy. Less radical surgery such as modified radical hysterectomy or simple hysterectomy with pelvic lymphadenectomy can be considered in patients with a tumor depth of invasion of ≤10mm, no LVSI and aged ≤50 years.[26]

Radical trachelectomy is a generally accepted fertility sparing procedure. It has oncological outcomes comparable with radical hysterectomy. However less radical fertility sparing surgery without parametrectomy is associated with a high-risk of disease recurrence.[27]

The management of early-stage disease (IA1-IB2) at the CMJAH is similar to the international guidelines. However, patients with stage IIA are managed as late-stage disease with chemo-radiation.[28]

1.4 Radical Hysterectomy (RH)

Radical hysterectomy and Pelvic Lymph Node Dissection is widely used for the treatment of patients with early cervical cancer. Radical hysterectomy involves the removal of the uterus in conjunction with resection of the upper vaginal cuff, the parametrium, the utero-sacral ligaments, and mobilisation of the distal end of the ureter.[6] The first true RH was performed by John Clark at the Johns Hopkins hospital in 1895. However, the procedure is linked to Wertheim of Vienna, who reported his series of 500 cases of radical extended abdominal hysterectomy and partial lymphadenectomy performed from1898 until 1911.[29]

The most frequent site of the local spread of cervical cancer is the parametrium. The parametrial spread occurs through direct microscopic extension or by lymphatic channels. Therefore, the removal of the parametrial tissue has been considered to be of paramount importance in the treatment of early-stage cervical cancer.[30] However, the wide excision of the parametrium is associated with a wide range of postoperative pelvic organs dysfunction. This is attributed to denervation of the autonomic nerve supply to these organs during the parametrectomy.[6, 31]

Postoperative bladder dysfunction, sexual dissatisfaction, and anorectal mobility disorders are some of the reported complications associated with parametrectomy. Studies have observed that the procedure (RH and PLND) is done on patients with mean age of 42 years.[32,33] It is a preferred procedure and was performed in 72% of patients who had FIGO Stage IB1, 24% Stage IB2, and 4% with either Stage IA2 or IAI (LVSI) cervical cancer. The common histologic subtypes following RH, in order of descending frequency were, squamous carcinoma,

adenocarcinoma and adenosquamous.[32,33] Bilateral salpingo-oophorectomy and para-aortic lymph node dissection were reported to have been done in 59% and 47% of patients respectively, during RH and PLND.[33] McCann et al. and Rutledge reported that 77% and 82%, respectively, of patients who underwent RH were of the white race. However, both studies were done in United States of America.[33,32]

1.4.1 The types of Radical Hysterectomies

There are three classifications of RH which are used for the simplification of surgical protocols. Table 2.4.1.1 shows similarities in the surgical approach of different classes.

1. Piver-Rutledge-Smith[34] – Is the oldest classification with five classes (5). It only applies to open surgery and was developed at a time when minimally invasive and fertility-sparing operations did not exist. It ignored the vaginal approach and did not take into account the concept of nerve preservation. Its use has become absolute.
2. Gynaecologic Cancer Group of the European Organization of Research and Treatment of Cancer (GCG-EORTC) – Its purpose was to simplify and clarify some technique details, and in particular, to standardise the procedure in oncologic departments in Europe, that were taking part in the trials of this organization.
3. Querlow and Morrow[6] – This is the most evolved and recent classification, its techniques can be adapted for conservative operations and for different types of surgical approaches: abdominal, vaginal, laparoscopic or robotic.

Table 1.4.1.1: Surgical approach in Piver-Rutledge and Querleu-Morrow classes

	Simple extrafascial hysterectomy	Modified radical hysterectomy	Radical hysterectomy
Piver and Rutledge Classification	Type I	Type II	Type III
Querleu and Morrow classification	Type A	Type B	Type C
Indication	Stage IA1	Type IA1 with LVSI. IA2	Stage IB1 and IB2, selected Stage IIA
Uterus and cervix	Removed	Removed	Removed
Ovaries	Optional removal	Optional removal	Optional removal
Vaginal margin	None	1–2 cm	Upper one-quarter to one-third
Ureters	Not mobilized	Tunnel through broad ligament	Tunnel through broad ligament
Cardinal ligaments	Divided at uterine and cervical border	Divided where ureter transits broad ligaments	Divided at pelvic side wall
Uterosacral ligaments	Divided at cervical border	Partially removed	Divided near sacral origin
Urinary bladder	Mobilized to base of bladder	Mobilized to upper vagina	Mobilized to middle vagina
Rectum	Not mobilized	Mobilized below cervix	Mobilized below cervix
Surgical approach	Laparotomy or laparoscopy or robotic surgery	Laparotomy or laparoscopy or robotic surgery	Laparotomy or laparoscopy or robotic surgery

The 2017 updated Queleu-Morrow classification of Radical Hysterectomy has been widely accepted and used. It describes four types of radical hysterectomy, including a limited number of subtypes (Class A-D). It is based on the lateral extent of the resection.[6]

Class A: Limited Radical Hysterectomy

This involves the removal of the cervix in its entirety down to the vaginal fornix, together with a paracervical margin. The paracervical margin is transected halfway between the ureter and the cervix, medially to the ureter but lateral to the cervix. It can be used for the management of selected low-risk IB1 invasive cervical cancers less than 2cm with negative pelvic nodes, no deep stromal invasion and no lymph-vascular space invasion.

Class B: Resection of the paracervix at the ureter

Class B1: Modified Radical Hysterectomy

This involves the partial resection of the dorsal and ventral parametria, unroofing, and mobilization of the ureter laterally permitting the transection of the paracervix at the level of the ureteral tunnel.

Class B2: Modified Radical Hysterectomy and Pelvic Lymphadenectomy (PLND)

This follows the same steps taken in class B1 combined with the resection of pelvic nodes. The procedure may be redefined by the use of indocyanine green navigation, which allows the surgeon to identify the lymph vessel and lymph node component of the paracervix more clearly.

Class C: Classical Radical hysterectomy.

This corresponds to the classical RH. Rectovaginal and rectouterine ligaments transection is performed at the rectum, while transection of the ventral perimetrium is performed at the bladder. The ureter is then identified, mobilized and lateralized completely.

Class C1: Nerve Preserving Radical Hysterectomy.

The ventral parametrium is transected only after the systemic identification of the inferior hypogastric plexus together with its bladder branches.

Class C2: No preservation of autonomic nerves.

Both ventral and dorsal parametria are transected without identification and preservation of the inferior hypogastric plexus and sacral splanchnic nerves. The ureter is completely dissected from the ventral parametrium, prior to the transection of the parametrium at the level of the bladder.

Class D: Laterally extended resection.

This involves extended resection of structures lateral to the paracervix.

Class D1: Palfalvi-Ungar laterally extended parametrectomy

This involves the resection of the entire paracervix at the pelvic sidewall together with the hypogastric and obturator vessels, exposing the roots of the sciatic nerve. It may be used for stage IIB disease.

Class D2: D1 plus resection of the adjacent fascial/muscular structures.

It involves the steps in D1 plus resection, when necessary, of the obturator fascia and obturator muscle ventrally, the coccygeous muscle and pelvic part of the piriformis muscle dorsally, and sacrospinous ligament and acetabulum laterally. This procedure is usually performed for laterally recurrent tumours.

1.4.2 Radical Vaginal Hysterectomy

The use of radical vaginal hysterectomy in the treatment of uterine neoplasm was first proposed by Schuchardt at the end of the nineteenth century.[35] The procedure was further developed and improved in the 1920s by Schauta[36] and Amreich.[37] The procedure never gained popularity because it omitted lymph node dissection. However, following the recent spread of endoscopic surgery with the development of laparoscopic lymphadenectomy technique, and the re-proposal of an extraperitoneal lymphadenectomy, has brought a new interest to the use of radical vaginal hysterectomy in gynaecologic oncology.[38]

During radical vaginal hysterectomy, same steps are carried out as in the extended abdominal radical hysterectomy, although in reverse order. There have been three classes of radical vaginal hysterectomy reported in the literature, for the treatment of endometrial and cervical cancers.[38]

1.4.3 Minimally invasive surgery versus Open radical hysterectomy approach

Women with early–stage cervical cancer are most frequently treated with RH by an open or minimally invasive approach (laparoscopic or robotic). Patients receiving a minimally invasive approach are found to be younger with fewer comorbidities and more likely to have stage 1A disease.[39] Before 2018, most of retrospective cohort studies have shown that laparoscopic approach for early-stage cervical cancer was an acceptable alternative to laparotomy with reduced perioperative morbidity, shorter hospital stays and faster recovery, and no significant survival differences for patients undergoing minimally invasive approach versus open. However, in October 2018, an international, multicentre, randomized clinical trial showed that patients with stageIA1 (LVSI) – IB1 cervical cancer who underwent laparoscopic RH had lower overall survival and disease-free survival rates than those who underwent open surgery [40]

The minimally invasive approach in patients with pathologic stage 1B disease has been associated with a 2-fold higher rate of death and recurrence compared to open radical hysterectomy.[41] The Laparoscopy Approach to Cervical Cancer (LACC) trial showed that minimally invasive approach was associated with a 4-fold higher rate of recurrence and a 6-

fold higher rate of all-cause death compared to open approach in women with stage 1A1-1B1 cervical cancer.[40] The association between minimal invasive approach and shorter overall survival has been reinforced by epidemiologic studies using the Surveillance, Epidemiology, and End Results (SEER) database and the National Cancer Database (NCDB).[30]

In patients with cervical adenocarcinoma with tumor size ≤2cm in the RWS, the 5 years survival and disease-free survival rates of the laparascopy group were lower than those of the abdominal group. However, in patients with stage IB1 cervical cancer with tumor size ≤2cm and squamous cervical cancer subtype, the laparoscopic and abdominal groups had similar survival outcomes.[42] It has been reported in some studies that, in patients with squamous cell carcinoma IB1 ≤2cm they might be suitable candidates for laparoscopic surgery, while patients with adenosquamous and adenocarcinoma with tumors ≤2cm are not suitable candidates for laparoscopic surgery.[42]

1.5 Surgical Outcome of RH and PLND

Most of the procedures are performed to completion. Heidi et al. in their study reported that during surgery for early-stage cervical cancers (IA2-IIA), 93% hysterectomies were completed and 7% were abandoned for finding grossly positive nodes (84%) and pelvic spread (16%).[43] About 8.4%-10.7% of patients with stage IB1 had involvement of the parametrium, and the presence of positive pelvic nodes was a strong predictor for parametrial spread.[44] These findings were unrelated to comorbid diseases, age, and histological subtypes.

There was no statistical difference found in the study by McCann[33] et al. when comparing patients with close margins to those without regarding race, stage, grade, or histology. However, robotic surgery was more associated (90%) with positive close surgical margins as compared to open radical laparotomy (58%) (p=0.005).[33]Mahawerawat[45] et al. reported that the median number of pelvic lymph nodes removed in RH and PLND was 23 lymph nodes (range 4-49) in stage IA2 cervical cancer.

1.6 Disease recurrence and survival after RH and PLND

The rate of local and distant recurrence in patients with stage IB1, as reported by Rutledge[33] et al. were 80% (8/10) and 20% (2/10) respectively. While patients in stage IB2 group had 45% (9/20) distant and 55% (11/20) local recurrences respectively.[32] Adenocarcinoma histologic subtype and pelvic lymph node metastasis, accompanied by high lymph node ratio were the most prognosticators associated with disease recurrence and poor survival of patients after RH and PLND for early-stage cervical cancer with high-risk factors, while parametrial invasion and resection margin involvement alone were not. [46]

UP to 50% of recurrences occur during the 1st year. Following a curative-intent procedure (RH), cervical cancer survivors can be followed up by physical examination and Papanicolaou smear quarterly for the 1st two years and then 6 monthly for the next 3 years.[47] Following 5-years Disease-Free-Survival, the patient may be safely returned to annual assessment with history, general physical and pelvic examination, with yearly vault smears.[47]

In a comparison study between stage 1B1 and 1B2 disease, the 2-year Disease-Free Survival (DFS) was found to be 92.1% for node negative stage IB1 tumors vs. 81.4% for node negative stage IB2 tumors (P = 0.1917). A multivariate analysis showed lymph vascular space invasion (LVSI) (RR 7.75, CI 2–27, P = 0.0001) and outer 2/3 depth of invasion (RR 5.8, CI 2–20, P = 0.0029) as independent predictors of DFS.[48]

The 5-year DFS of patients with tumors that expressed two and three high-risk factors were 50.3% and 30% respectively.[49] While there was no difference in the risk of loco-regional recurrence after treatment, irrespective of the number of high-risk factors present, there was a significantly increased risk of distant recurrence in cervical cancer with multiple high-risk factors. Univariate analysis of surgical margin status using ≤10 mm, ≤5 mm, and ≤2 mm showed that closer margins were associated with a higher hazard of recurrence with the hazard ratios of 1.51 (95% CI: 0.45–5.12, p=0.506), 2.83 (95% CI: 0.96–8.38, p=0.061), and 3.22 (95% CI: 1.37–7.55, p=0.007) for ≤10 mm, ≤5 mm, and ≤2 mm, respectively.[33]

1.7 Complications associated with RH and PLND

In 1905 Ernest Wertheim reported outcomes of the first 270 patients treated by RH which included an operative mortality rate of 18% and morbidity rate of 31%. Bladder dysfunction and lymphocysts formation are the most common complications occurring in 5-15% of cases. The operative complication rate for patients who had stage 1B1 disease was found to be 11.0% and 12.8% in IB2. These include hemorrhage requiring intraoperative transfusion, hollow visceral injuries, and ureteral injuries.[50] The disease stage comparative overall postoperative complication rate is 45.9% (IB1) vs. 43.0% (IB2). These include thromboembolic event, fistula formation, bowel obstruction, infection requiring intravenous antibiotics, presence of lymphoedema and readmission.[50]

Nerve-sparing Radical Hysterectomy is associated with fewer complications and faster recovery of pelvic function compared to conventional RH. It yields lower rates of sexual dysfunction. Improvement in surgical technique, administration of prophylactic antibiotics, thromboembolic prophylaxis, and advances in critical care medicine have resulted in lower operative morbidity associated with RH and PLND. However, clinical tumor size, stage of disease (1B1 vs 1B2), age at surgery, tobacco use, BMI, race, para-aortic lymphadenectomy, nodal positivity, and parametrial extension were not associated with treatment (surgery) related morbidity in a univariate analysis.[33]

1.7.1 Acute Haemorrhage

The most frequent site of troublesome intra-op bleeding during RH occurs from the pelvic floor veins in the dissection of the cardinal ligaments and the hypogastric vessels. Preparation and planning for massive haemorrhage is essential for all surgeons and gynaecologic operating team.[51] Rutledge et al., on their study, reported the average blood loss to be 664 ml in the IB1 group and 676 ml in the IB2 group ($P = 0.873$).[32]

1.7.2 Ureteric injuries and Lower Urinary Tract (LUT) dysfunction

Bladder dysfunction is common and results from extensive dissection of the ureters at the bladder base and transection of the utero-sacral ligaments, which interrupts autonomic nerve supply to the bladder. Ureteric injuries are uncommon <1%. During a hysterectomy the injuries occur mostly at the lower third of the ureter. The most common mechanism in descending order of frequency include: ligation, kinking by suture, transection, partial transection, crush and devascularisation of the ureter.[52,53] Kiran et al. reported an increase in the rate of ureteric injuries during abdominal RH for cervical cancer from 1.47% (2001-2005) to 2.48% (2006-2010).[50]

Radical surgery may be complicated by early or late LUT dysfunction (8-80%). Early LUT dysfunction presents with voiding difficulties, which may require prolonged urethral catheterisation. Late LUT dysfunction may present with bladder dysfunction affecting storage and compliance, resulting in urinary incontinence that can resolve within 6 to 12 months or persist for longer.[54] Although the survival outcomes of women undergoing standard radical hysterectomy with pelvic lymphadenectomy for stage Ia2 to IIa cervical cancer are generally good, bladder dysfunction following standard radical hysterectomy can affect the quality of life significantly. Nerve-sparing radical hysterectomy may offer improved quality of life. However, there is the potential that a nerve-sparing approach may compromise oncological outcomes and increase the risk of disease recurrence.

1.7.3. Pararectal and Paravescical Space Lymphocysts

About 1% of patients develop lymphocysts in the pararectal and paracervical spaces, following RH and PLND. These develop due to the interruption of efferent pelvic lymphatics. They present with pelvic pain which may radiate down to the hip, fever, pressure symptoms, and lymphoedema of the legs in the weeks after the surgery. Variation in the incidence of lymphocysts formation depends on the extent of lymphadenectomy, retroperitoneal drain placement, and differences in the surgical technique used for ligating lymphatic channels. Large lymphocysts can be managed with guided –percutaneous drainage or laparoscopic surgical resection.[55]

1.7.4. Post-operative Infections

Radical Hysterectomy involves the bridge into the genital tract which may predispose the patient to both an ascending aerobic and anaerobic infections. Rutledge et al. reported 62 out of 195 cases of post-operative infection that required intravenous antibiotics.[32] Prophylactic broad-spectrum antibiotics with both aerobic and anaerobic cover has shown to reduce the febrile morbidity and decrease rates of serious infections in women undergoing RH.[56]

1.7.5 Sexual dysfunction

The most common sexual dysfunction symptoms reported by cervical cancer survivors following RH are decrease in sexual interest, vaginal dryness, and dyspareunia. [56] Juntana et al. reported in their study, that radical hysterectomy alone for stage IB cervical cancer had minor negative short-term effects on sexual function. In this study, 93% of women who underwent radical hysterectomy resumed sexual intercourse in six months after surgery.[56]

1.7.6 Pulmonary embolism

Malignancy is associated with the risk of thrombosis. Radical abdominopelvic cancer surgery fulfils the components of Virchow's triad (stasis of blood, hypercoagulability, and endothelial damage) and therefore increasing the risk of post-operative venous thromboembolism.[57] Patients undergoing surgery with an active malignancy have at least twice the risk of postoperative deep vein thrombosis and non-fatal pulmonary embolism and more than three times the risk of fatal pulmonary embolism compared with patients undergoing surgery for inflammatory benign conditions.[58, 59] The incidence of thromboembolic disease after RH has decreased over time, as a result of widespread implementation of thrombo-prophylaxis. Nevertheless, it remains the leading cause of mortality in the immediate postoperative period.

1.8. Adjuvant Therapy

After surgery, adjuvant radiotherapy or concurrent chemoradiation is recommended based on the presence of risk factors on histopathologic examination. Intermediate risk factors include large tumor size, LVSI, and deep stromal invasion and high-risk factors include lymph node metastasis, parametrial involvement and resection margin involvement. About 25% of patients with stage IB cervical cancer have intermediate risk factors (30% risk of recurrence in 3 years) for recurrence, suggesting the need for adjuvant treatment. Adjuvant radiotherapy reduces the risk of recurrence and the risk of progression or death in patients with early-stage cervical cancer with intermediate-risk factors.[13,60, 61]

Concurrent administration of Cisplatin-based chemotherapy during radiotherapy is a standard practice for postoperative adjuvant therapy in the high-risk group.[49] The role of consolidation with systematic chemotherapy after postoperative adjuvant therapy, has been proposed by Hakyoung Kim in his study for cases with multiple high-risk factors for early-stage cervical cancer.[62] However, Rutledge et al. found that adjuvant radiation did not significantly influence disease-free survival in stage 1B1 and 1B2 RH.[32] The overall success of radiotherapy depends on the sensitivity of the cancer cells, the ability of normal tissue to recuperate after irradiation and the general physical condition of the patient.

1.8.1 RADIATION THERAPY IN EARLY-STAGE CERVICAL CANCER

Radiation therapy as primary treatment for early-stage cervical cancer is usually reserved for women who are not candidates for surgery due to medical comorbidities or poor functional status. Pelvic radiation therapy (with or without chemotherapy) uniformly results in ovarian failure due to the doses required for curative-intent therapy and if ovarian preservation is necessary, consideration of transposition out of the radiation field should be considered.

When indicated, computed tomography-based planning should be used to adequately visualize the cervix, rectum, bladder, small bowel, and nodal stations. Typically, the whole pelvis is treated to 45 Gy in 25 once-daily fractions of 1.8 Gy. Brachytherapy is used to give the final

dose to the cervical primary, to a total of 80 Gy (small-volume cervical tumors) to 87 Gy or higher (larger-volume cervical tumors)

Sexual dysfunction is commonly reported by cervical cancer survivors. Compared to women who had surgery only, women treated with radiation therapy had more symptoms of vaginal dryness, difficulty achieving orgasm and dyspareunia.[63] Some studies suggest that Quality Of Life may be worse among women who are also treated with radiation therapy (RT) or chemotherapy [64]. Women treated with surgery alone or surgery followed by adjuvant chemotherapy reported better quality of life scores compared to women treated with surgery followed by adjuvant radiation therapy.[64]

The combined chemotherapy and radiation therapy as the primary treatment for early stage cervical cancer has been associated with a higher incidence of bowel dysfunction and a non-significant trends towards higher incidence of urinary incontinence, sexual dysfunction and pelvic pain.[65]

1.9 RADICAL TRACHELECTOMY

Radical trachelectomy is a generally accepted fertility sparing procedure for women with early cervical cancer. It is a curative conservative procedure in which the cervix, upper 1-2 cm of the vagina, parametria (tissue adjacent to the cervix), and paracolpos are resected while preserving the uterine corpus and fundus. This can be approached vaginally, abdominally, laparoscopically, or robotically. The fertility rates are however significantly reduced in comparison with the general population. Approximately 15% of women who undergo trachelectomy may be infertile and may require some form of assisted reproductive technology.

The eligibility criteria for fertility-sparing surgery were initially proposed by Roy and Plante in 1998. [67] These criteria include the following:

- Desire to preserve fertility
- Lesion size of 2 cm or smaller
- FIGO stage 1A1 with presence of vascular space invasion or FIGO stage 1A2 and 1B1

- No involvement of the upper endocervical canal as determined with MRI
- No lymph node metastasis

It has oncological outcomes comparable with radical hysterectomy. However less radical fertility sparing surgery without parametrectomy is associated with a high-risk of disease recurrence.[27] Major concern of obstetrical care in women following simple or radical trachelectomy is the higher rate of preterm delivery (varying between 12% and 28%) before the 37th week.

Patient selection is critical to decrease the risk of recurrence. Risk factors for recurrence include lesions greater than 2 cm, presence of lymph-vascular space invasion, unfavourable histology, and close (defined as < 5 mm) surgical margins.

1.10 PROBLEM STATEMENT

It is currently estimated that there are about 5743 new cases of cervical cancer and 3027 deaths from the disease globally.[1] In South Africa, it is estimated that one out of 41 South African women are affected by cervical cancer. It is estimated to kill approximately 8 women every day in South Africa.[63] Radical hysterectomy is the standard procedure for stages IA2 to IB2, and yet is associated with morbidity. Today, the proficient performance of the RH is the bench-mark of the gynaecologic oncology surgeon. Extensive training and knowledge of the pelvic anatomy form a useful armamentarium for the execution of this complex procedure.

The management of early-stage disease (IA1-IB2) at the CMJAH one of the tertiary hospitals in Johannesburg South Africa, is similar to the international guidelines. However, patients with stage IIA are managed as of late-stage disease with chemo-radiation.[28] There exist a lot of controversies on the outcome of RH whether performed by open, laparoscopic, or robotic methods regarding the surgical outcome and histological subtypes. No available documented data exists in CMJAH, on the outcomes of cervical cancer patients treated with this procedure. This study describes the morbidity and mortality associated with RH and PLND performed on early-stage cervical cancer patients at CMJAH.

CHAPTER 2: METHODS AND MATERIALS

2.1 Specific Objectives

i. To describe the demographics of patients who were treated with Radical Hysterectomy and PLND for early-stage cervical cancer at CMJAH.
ii. To describe the types of Radical Hysterectomy and level of Pelvic Lymphadenectomy performed at CMJAH, and to document the intra-operative practices recorded.
iii. To describe the complications (immediate, intermediate, and late) associated with the type of surgery being performed.

2.2 Study Design and Setting

A descriptive retrospective review of women who underwent Radical Hysterectomy and Pelvic Lymph Node Dissection for early-stage cervical cancer at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) from 1 January 2015 to 31 December 2016 was performed. CMJAH is a tertiary hospital in Johannesburg, South Africa. It is a training institution for undergraduate medical professionals, post-graduate medical specialists, and super-specialists in different medical departments, attached to the Faculty of Health Sciences at the University of Witwatersrand. It is one of the cancer referrals centres for patients around Gauteng province.

2.3 Ethical Considerations

Ethical approval was obtained from the University of Witwatersrand Human Research Ethics Committee and formally approved on the 15/02/2019. Permission to perform the study and access to medical records was obtained from the office of the CMJAH Chief Executive Officer and the head of Obstetrics and Gynaecologic department at the hospital as well as the Gauteng provincial health department on the 27/09/2018 and 20/09/2018 respectively (Annexure F). The clearance certificate number is M181082. (Appendix B).

2.4 Data Collection and Analysis

All women who underwent Radical Hysterectomy in the period of the study were identified from the operating theatre register and gynaecology ward admission books. Participants were assigned study numbers. Their medical records were retrieved and for those who met the inclusion criteria, their data was captured onto a standardised collection sheet (annexure1), reviewed and analysed. Study participant's demographics, identity, or passport numbers other than their hospital numbers were used to search for any missing data, from the hospital's records, archives and from the online NHLS Labtrack® results view system.

Table 2.1 The inclusion and exclusion criteria for study participation.

Inclusion	**Exclusion**
Women with histologically confirmed cervical cancer and underwent Radical Hysterectomy for clinically stages 1A2-1B2	Women with other types of histologically confirmed malignancies other than cervical cancer Women who had hysterectomy for benign gynaecological pathologies and other malignancies and the diagnosis of cervical cancer made on hysterectomy histopathological report Women whose primary surgery was a simple hysterectomy and were re-operated to complete parametria and lymph node resection Women with incomplete records or missing files

Descriptive analysis of data was performed, including means and standard deviations (SD) for normally distributed data and medians and interquartile ranges (IQR) for non-normally distributed continuous data. Descriptive statistics and graphical presentations were carried out

using STATA program with a 5% significance level. Precision was managed using 95% confidence intervals.

Radical hysterectomy procedure was used as the denominator for all the analysis and repeat or relook surgery for complications were not reanalyzed. The crude and unadjusted intraoperative and post-operative complications of surgery rates were calculated. Chi squared test was used to assess the relationships between groups of radical hysterectomy subtypes, demographic and clinical characteristics, staging, morphological appearance of tumors, and other histological subtypes. Fisher's exact test was used where the requirements for the Chi squared test were not achieved.

CHAPTER 3: RESULTS

3.1 Patients Demographics

Twenty-eight patients met the study criteria. Twenty-three medical records were found and met the eligibility criteria for the study. Five patients were excluded due to missing records. The mean age of the participants in our study was 45.65years (SD± 13.23). 78% (18/23) of patients in the study were blacks and 21.74 % (5/23) were whites. The mean parity among the group was 2.86 (SD± 1.73). Of the twenty-three participants, eight (34.78%) had no Astern-Operative-Oncology-Group (ECOG) status documented.

Fourteen (60.87%) patients were assessed as ECOG 1 and one (4.35) patient was assessed as ECOG 2. Six (26.09%) patients were HIV positive and seventeen (73.91%) were HIV negative. 65% (15/23) of patients did not have any co-morbidities, 26% (6/23) had hypertension and 8.70% (2/23) had both hypertension and diabetes mellitus. None of the patients had diabetes mellitus alone. The patient's body mass index (BMI) was not calculated and recorded in their folders. Table 1 below shows the clinical characteristics of the participants.

Table 3.1 Clinical characteristics of patients

Characteristics	**Variable**	**(n)= 23**
Age (years)	Mean	45,65 (SD±13.23)
Ethnicity	Black	18(78.26%)
	White	5(21.74%)
Co-morbidities:	HIV-positive	6 (26.09%)
	Hypertension	6 (26.09%)
	Hypertension & Diabetes Mellitus	2 (8.70%)
	No co-morbidities	15 (65.00%)
Parity	Mean parity	2.86 (range 0-7)
Smoking	Unknown	1 (4.35%)
	Yes	6 (26.09%)
	No	16 (69.57%)
ECOG Score	0	8(34.78%)
	1	14(60.87%)
	2	1(4.35%)

3.2 Pre-operative histopathological staging of the disease

Thirteen (56.52%) biopsies and ten (43.48%) Large Loop Excision of Transformation Zone (LLETZ) were done for diagnosis. Two (8.70%) patients had stage 1A2 cancer of the cervix, twenty (86.96%) had a stage 1B1 disease and one patient's (4.35%) staging was unknown.

Lympho Vascular Space Invasion (LVSI) was unknown in 39.13% (9/23) of patients, 13.04% (3/23) had LVSI while 47.83% (11/23) did not have LVSI on their histology reports. Below are the graphic representations of patient's pre-operative state.

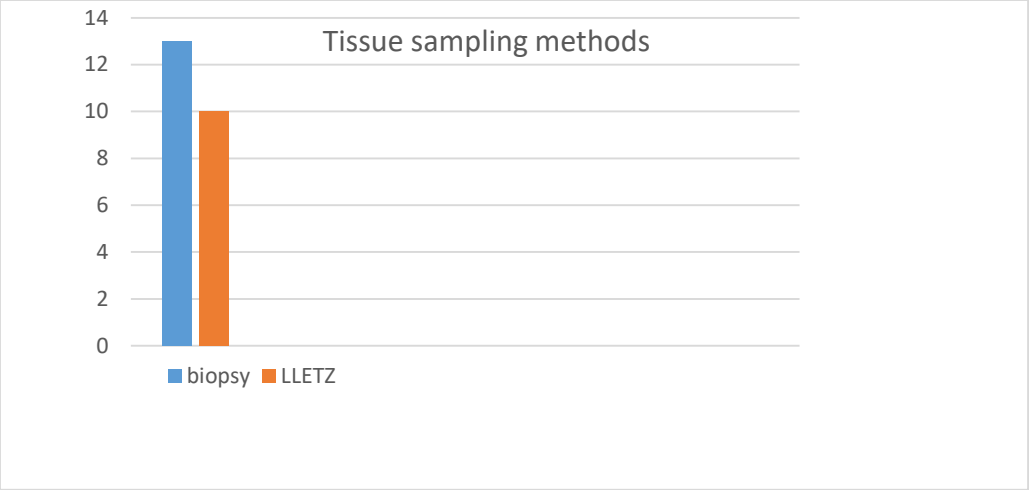

Figure 3.2.1 The methods used for tissue sampling in diagnosing cancer of the cervix

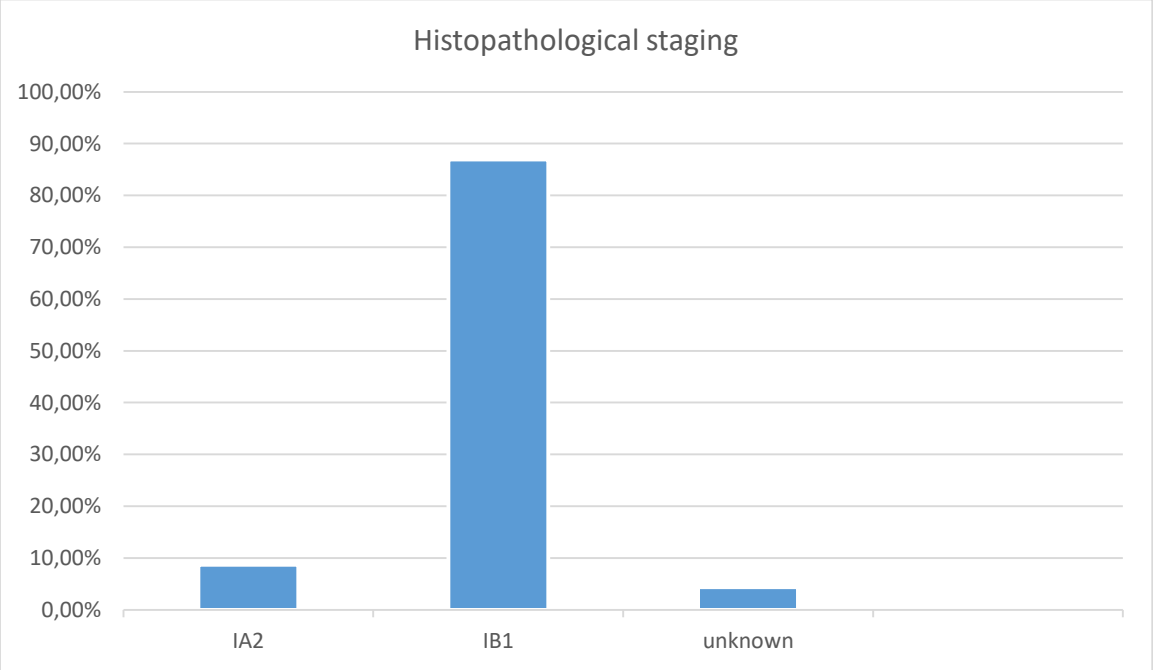

Figure 3.2.2 The pre-operative histological staging of patients.

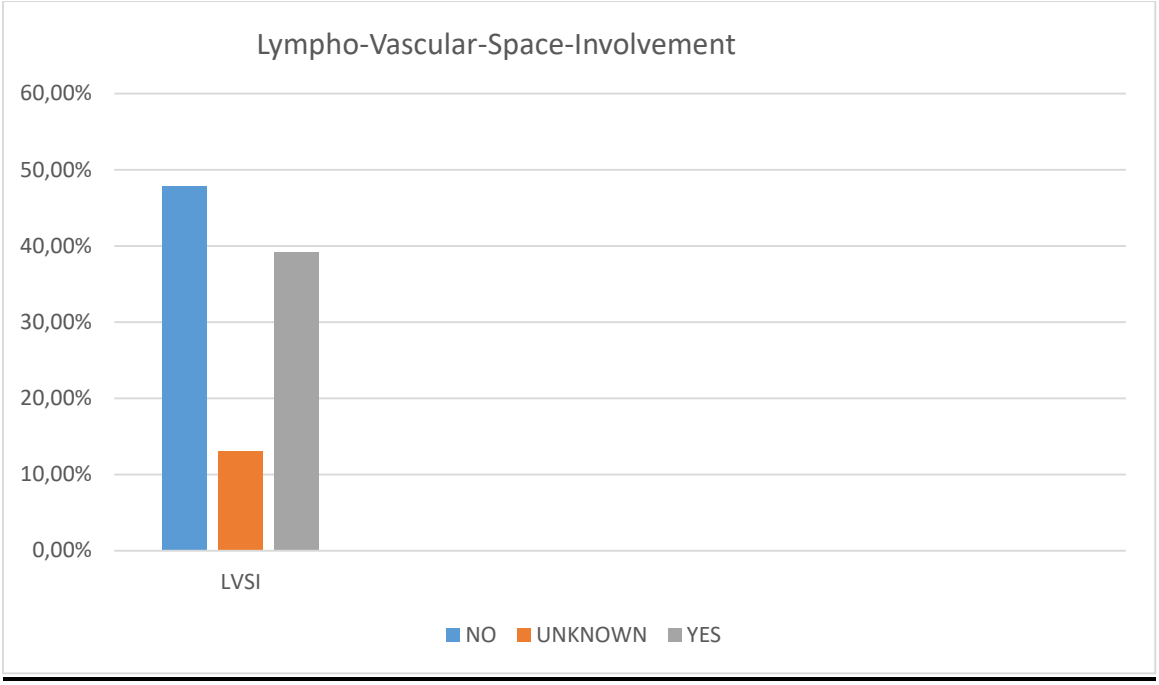

Figure 3.2.3 The percentage of patients who had LVSI.

3.3 Histological sub-types

Sixteen (69.57%) patients had squamous cell carcinoma of the cervix, four (17.39%) had adeno-carcinoma and three (13.04%) had adeno-squamous carcinoma. Figure 4.3.1 below illustrates different histological subtypes before radical hysterectomy surgery.

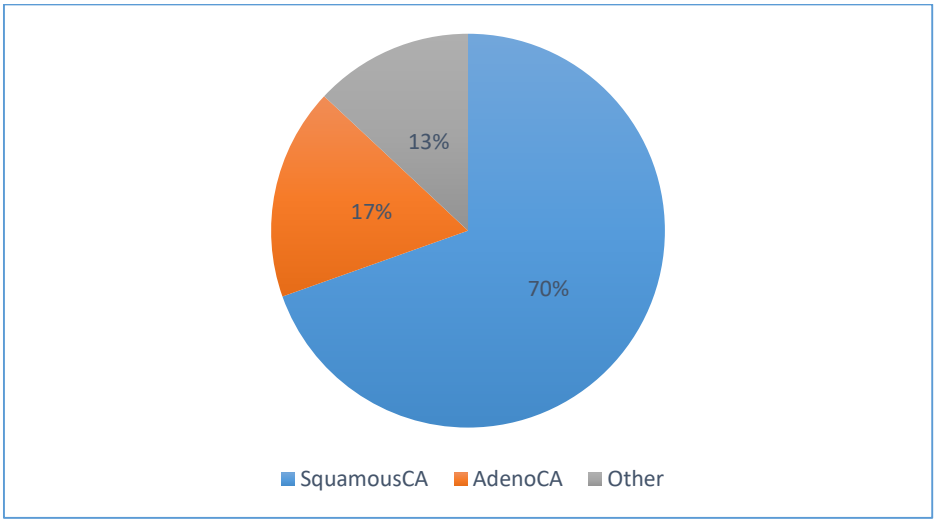

Figure 3.3.1 The histological subtype of the cancer before surgery

3.4 Surgical practices and outcomes

A total of twenty-three operations were performed to completion. Twelve (52.17%) were performed by a certified gynaecology oncologist and eleven (47.83%) were done by a training fellow in the unit. Three (13.04%) operations were completed using Q-M class A type of abdominal hysterectomy, nineteen (82.61%), and one (4.35) other hysterectomies were completed by Q-M class B and C respectively. The involvement of the bladder, parametrium, and ovaries was not documented at surgery. Ovaries were removed in ten (43.48%) of the operations and retained in thirteen (56.52%). The mean number of lymph nodes removed was 28.26 (±10.58 SD).

The level of Lymph node dissection was, level 2 in 12 (52.17%) of the operations, level 3 in (8) 34.78%, and it was not documented in 3 (13.04%) operations. The average duration of surgery was 127.87 minutes (±24.62SD). Nylon suturing material was used for skin closure in seven (30.43%) of the operations and surgical clips were used in sixteen (69.57%). Suturing material used for the peritoneum and subcutaneous tissue were not documented. Nineteen (82.16%) patients received Cephalosporin (Cefazolin), and three (13.04%) received Penicillin (Augmentin) as prophylaxis prior to the operation. It was not documented in one (4.35%) of the patient's records if they received any antibiotic prophylaxis. Postoperatively seven (30.43%) patients stayed for less than three days, eleven (47.83%) stayed between three and five days, and five (21.74%) remained admitted for more than five days. Figure 4.4.1 below illustrates the length of stay after an operation.

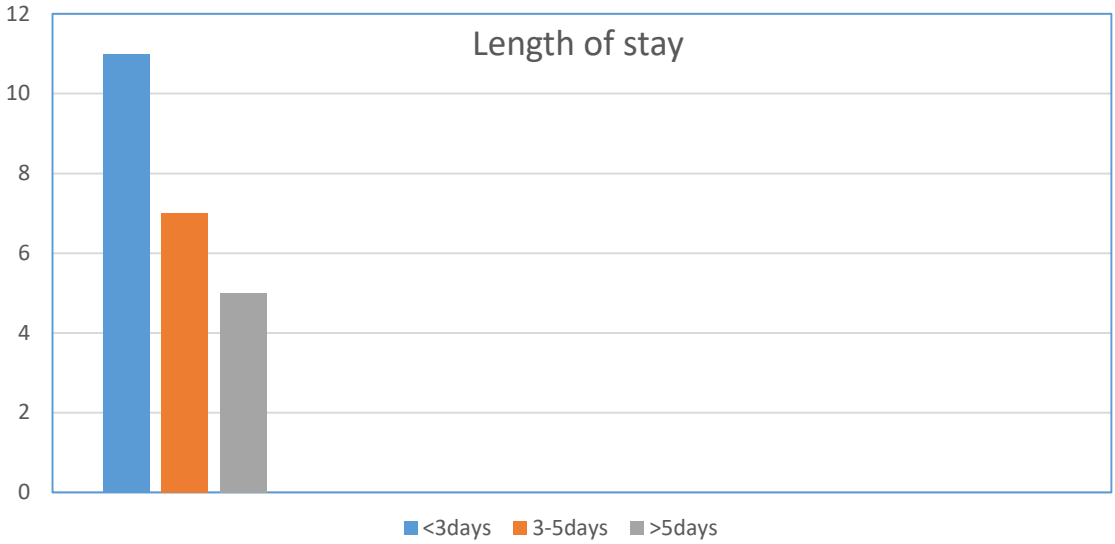

Figure 3.4.1 The patient's length of stay post-surgery

3.5 Early complications

The mean blood loss at surgery was 615.22 ml (SD±471.56). Blood vessel injuries were reported in 1 (4.35%) of the operations. No other injuries were reported in twenty-two other operations. Postoperatively, two (8.70%) patients developed an ileus, one (4.35%) had sepsis and one (4.35%) had a pulmonary embolus.

3.6 Late complications

Two patients (8.70%) experienced early complications following their surgery and needed readmission to hospital. Majority of patient's wounds 91.30% (21/23) were healed at follow up, while 4.35% (1/23) was dehisced and another 4.35% (1/23) was septic.

3.7 Post-operative pathological outcomes

The summary of histological findings of the specimens submitted after the operations are shown in table 3.7.1 below.

Table 3.7.1 The histo-pathological findings post RH and PLND

Histological category	**Findings**	**N=23**
Tumour size	<2cm	19 (82,61%)
	>2cm	4 (17,39%)
	Unknown	2 (8,70%)
Staging	1A2	3 (13,04)
	1B1	14 (60,87%)
	1B2	2 (8,70%)
	Other	2 (8,70%)
LVSI	Yes	4 (17,39%)
	No	15 (65,22%)
	Unknown	4 (17,39%)
Number of lymph node involved	0	17(73,91%)
	1	3 (13,04%)
	2	2 (8,70%)
	6	1 (4,35%)

3.8 Follow up

Twenty-three RH and PLND operations were performed and completed, with an average duration of 127.87 (±24.62 SD) minutes.

All operations were done to completion and no operation was abandoned due to intra-op findings of an advanced disease, this may be due to the fact that at CMJAH only stages IA2-IB1 are treated with RH and PLND, 53.17% of operations were performed by a gynaecology oncologist and 46.83% done by a fellow gynaecologist. Fellow gynaecologists performed operations under the supervision of a gynaecology oncologist. This ensured standardisation and uniformity in the execution of these operation and prevented deviation from protocol.

CHAPTER 4: DISCUSSION

The treatment of early-stage cervical cancer with either radical hysterectomy (RH) and pelvic lymph node dissection (PLND) or primary radiotherapy is equally effective, with a 5-year overall survival of 85-90% in patients with stage IB and 65-75% in patients with stage IIA disease.[3] For early-stage disease, treatment with either radical surgery or radiation appears equally effective, with 5-year survival rates of approximately 70-80%. However, radiation therapy as primary treatment for early-stage cervical cancer is usually reserved for women who are not candidates for surgery due to medical comorbidities or poor functional status. [2] Surgical approach remains the main curative intent treatment for solid tumors. Its benefit includes better access and visualisation of tumor, and the opportunity to surgically remove any grossly positive lymph nodes while maintaining the functioning of the ovaries.[3] In our institution due to limited resources we do not offer primary radiation therapy for early cervical cancer, it is reserved for patients with advanced disease and as an adjuvant therapy post-surgery in patients with high risk factors of recurrence.

In most studies, the reported mean age of patients treated with radical hysterectomy is 42 years at the time of surgery.[32,33] These were larger studies with over a hundred participants. In our study, the mean age of 46 years was comparable to the one found by Juntana[56] of 45.3 years (28-59 range) in his study of thirty participants and in keeping with most literature.

Studies in the United States done by Mc'Cann[33] et al and Rutledge[32] et al respectively showed that 72% and 82% of women who underwent RH were of the white race. However, in our study done in South Africa with a population of predominantly blacks, 78% of women who underwent RH were blacks and only 22% whites. It will be difficult to conclude that a radical hysterectomy procedure is likely to be performed in a certain racial grouping as this may be associated with a percentage of such a racial group in that population.

The median parity of 2.86 (0-7 range) was in keeping with the fertility rate of 2.43 in South Africa as reported in The World Bank Collection of Development Indicators of 2017.[64]

Hypertension was found to be the commonest comorbid disease (26.09%), followed by diabetes mellitus (8.70%). These findings were not associated with adverse oncological outcomes in our

study as was also reported in the study by Frumovitz M[44] and Mahawerawat S[45]. The two medical conditions are also not risk factors for pathogenesis of cervical cancer.

The prevalence of HIV in this study was 26.09% slightly higher than the one of 21,8% which was found in 2005 amongst women with invasive cervical cancer in Kwazulu-Natal (South Africa).[65] Perhaps this is because the number of people who test for HIV and declare the results has drastically increased with less stigmatisation of the disease since 2005. The presence of HIV infection was associated with a 20% risk of developing a complication post RH and PLND. HIV is associated with a high rate of malignancies such as vulvar and cervical cancer in young patients.

Tissue sampling for diagnosis of cervical cancer was done with either a punch biopsy (52.52%) or LLETZ (43.48%). Both sampling methods yielded adequate specimen for analysis and none was found to be superior to the other in yielding the results. This was also reported in a study by Andrea et al.[66]

Our finding of the commonest histological subtype being squamous cell carcinoma (69.57%), was expected and in keeping with both local and international literature.[32,65,67] There is an increase in adeno-carcinoma globally and researchers also believe that this histologic subtype is underreported. Our findings of (17.39%) adeno-carcinoma and 13.04% Adeno-Squamous carcinoma were slightly less than that reported by Wang et al of 20%.[68] However our study had a small population and was conducted in one centre. Cervical cancer stage IB1 (FIGO 2009) remain the commonest reason for radical hysterectomy in many centres.[45] This was also the reason in our study. The findings by Rutledge and McCann et al. also support these findings.[32,33]

Q-M type B RH yields a higher OS and DFS compared to C2 RH, when used for the treatment of stage IA1 (LVSI)-IIA2 cervical cancer.[69] Most surgeons, including those in our centre (82.61% of hysterectomies) prefer Q-M type B RH irrespective of age. Guidelines from major societies and the FIGO does not include routine oophorectomy. There were 43.48% oophorectomies done together with the radical hysterectomy but the reasons for such were not recorded or specified.

The closure of the skin post-surgery was done either with nylon monofilament suture or with surgical clips. Nylon suturing material was used in 69.57% (16/23) of patients while surgical skin clips were used in 30.43% (7/23) of patients. This did not show any increased risk in the development of post-operative wound infection or wound dehiscence.

Level II (Obturator, Internal iliac, External iliac, Common iliac) lymph node dissection was the commonest approach (52.17%) used to cultivate the lymph nodes in this cohort. Even though there was an adequate yield of total number lymph nodes (28.26, SD±10.58) per FIGO and other societies' criteria, this is not a recommended level of lymphadenectomy. The recommended is a level III (para-aortic) lymphadenectomy but this is rarely performed in this centre although recommended by FIGO. Lymph node involvement was not a common finding. However, in cases where lymph nodes were positive, there was an association with LVSI as well as stage 1B1 of the disease. (67%). Perhaps this because most cases of RH were done for stage IB1 cervical cancer than any other stage. The presence of lymph node involvement is associated with a high-risk of recurrence rate (≤40%) in postoperative cervical cancer.[70] Five of the six patients in our study with lymph node involvement received adjuvant chemo-radiation for this reason. The one patient with stage IIA2 disease, who by protocol, was supposed to receive adjuvant chemo-radiation but did not receive adjuvant therapy because she was lost to follow up.

Chemoradiation is associated with significant haematological and gastro-intestinal toxicities and other complications. However, in our study, these side effects were not recorded in the accessed patient's records except on one patient who received radiotherapy and suffered avascular necrosis of the right hip. This adverse event required treatment by orthopaedic surgeons. It is known that postoperative adjuvant treatment significantly increases recurrence-free survival (RFS) in cervical cancer patients with intermediate risk-factors such as tumor size ≥ 2cm, stromal invasion and LVSI.[7] In our study four (4) patients had tumors ≥2cm, three (3/4) had lymph node involvement, and two (2/4) had LVSI. They received adjuvant therapy as per protocol.

Lymph node involvement was the best predictor for adjuvant chemo-radiation treatment in our study. Patients with tumor size ≥ 2cm were more likely (75%) to receive adjuvant chemo-radiation treatment as they have increased likelihood lymph node involvement by the tumour (nodal metastasis). This association of larger tumors size and high rate of nodal involvement, parametrial involvement and decreased survival has been previously reported in the literature.[32,69] However, some authors argue that there are other tumour characteristics (depth of invasion, LVSI, parametrial involvement and nodal involvement) other than tumor size alone, which may influence prognosis of the disease.[49] Rutledge et al, found that stage of disease did not independently predict nodal involvement.[32]

The surgical complication rate of 21.74% which includes blood vessels injury (4.35%), post-operative ileus (8.70%), post-operative infection (4.35%) and pulmonary embolism (4.35%), was comparable to that reported by Chirag et al, in United States of America (23.4%) in his study comparing surgical and oncologic outcomes after robotic radical hysterectomy or open radical hysterectomy for early cervical cancer.[71] For an academic centre with high patient volume, it was an expected finding because attending surgeons would be experienced and would have acquired skills and expertise to reduce the complications rate.

Antibiotic prophylaxis consists of administration of antibiotics to reduce the rate of postoperative infection, which could affect 40%-50% of women after vaginal hysterectomy, and more than 20% after abdominal hysterectomy. Pre-operative use of broad-spectrum antibiotics (cephalosporin or penicillin) was associated with lower rates of post-operative infections (4.35%) requiring admission and the use of intravenous antibiotics. In our centre, prophylactic antibiotics are routinely given before surgery. However, the choice of antibiotics varies depending on the surgeon's, anaesthetist's preferred choice, or drug availability. Prophylactic use of low molecular weight heparin (clexane) at a dose of 1milligram per kilogram daily was associated with 95.65% prevention of venous thrombo- embolic disease. (Reference this). In our institution, patients with malignancy who are post-surgery receive low molecular weight heparin for six (6) by protocol.

It has been reported that gynaecology patients with malignancies are at high-risk for intensive care unit admissions following surgery when compared to those with benign disease (Odds

Ratio 5.46).[72] However, in our study, no patient required admission to the intensive care unit. This might be because RH and PLND was only performed in stages IA2- IB1 and most of the patients had a favourable ECOG score or that only patients who were well were selected for this procedure due to poor availability of Critical Care unit beds in our institution.

It is reported that up to 50% of recurrences occur during the first year after therapy.[47] When comparing robotic versus open radical hysterectomy in the treatment of early cervical cancer, distant recurrences were found to occur more frequently in the robotic surgery group (4.6% vs 3.4%) than in the open radical hysterectomy group. [17] In this study, the recurrence rate was not associated with the type or approach used for RH. Therefore, even though our institution does not perform laparoscopic RH, or robotic RH, we expected the recurrence rate to be similar or less. However, in our study, we did not find any reported or documented cases of disease recurrence.

Some studies reported that women who had an open radical hysterectomy for cervical cancer had reduced risk of death when compared to women who underwent nerve-sparing radical hysterectomy.[73,74] No women assigned to standard radical hysterectomy in either of the included studies died from any cause.[74] We could not establish if there were any deaths in our study due to the retrospective nature of the study, and lack of data because of the lost to follow up of some participants.

CHAPTER 5: CONCLUSION

For early-stage disease, treatment with either radical surgery or radiation appears equally effective, with 5-year survival rates of approximately 70-80%. However, radiation therapy as primary treatment for early-stage cervical cancer is usually reserved for women who are not candidates for surgery due to medical comorbidities or poor functional status. Pelvic radiation therapy (with or without chemotherapy) uniformly results in ovarian failure due to the doses required for curative-intent therapy and if ovarian preservation is necessary, consideration of transposition out of the radiation field should be considered.[3]

Surgery remains the cornerstone of curative-intent treatment of majority of solid tumours. Primary surgical approach offers many advantages including the following: depth of invasion, lymph vascular space invasion (LVSI), identification of occult extra uterine disease such as nodal involvement or parametrial extension or intra- peritoneal spread, debulking of lymphatic disease and improved preservation of ovarian function when compared to primary radiation therapy.[2] In view of the fact that 5-year survival rates for early cervical cancer range from 88-97% and that more than 50% of the woman are younger than 50years of age, the surgical procedure should be adapted to achieve the best possible oncologic outcome while ensuring minimal short term and long-term morbidity.

We have shown that when done under standardized practices; a Radical Hysterectomy and Pelvic Lymph Node Dissection done for early cervical cancer is associated with less morbidity and yielded lower rates of early and late complications in five of the twenty-three patients (21.74%), with favourable oncological outcomes. The shorter turnaround time between diagnosis of disease and surgery has resulted in early intervention, before disease progression. However, more prospective studies are needed to establish this association.

5.1 Strengths and Limitations

Our study was the first to look at the practices and outcomes related to radical hysterectomy and pelvic lymph node dissection in CMJAH. The retrospective nature of our study failed to look at the impact of some risk factors (eg BMI) known to affect surgical outcomes following an RH and PLND because they were not recorded in patients' records. Our study had a low

number of participants and did not look at other known long-term complications of RH like sexual dysfunction and lower urinary tract dysfunction. The study looked at data from only one centre in the Wits academic circuit, with three other centres providing oncology treatment.

5.2 Implications for future research

This was just a snapshot looking at the surgical practices and outcomes associated with the radical hysterectomies done at CMJAH for early cervical cancer. A well-structured and powered multicentre prospective study is needed to look at the broader picture regarding the morbidity and mortality associated with RH and PLND done for early cervical cancer in our setting.

CHAPTER 6: REFERENCES

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Annexure A: Data Collection Sheet

Study number:

Demographic data

Age				
Race	A	W	C	Other
Origin	Gauteng	Outside Gauteng	Other countries	Unknown
Parity				
BMI	Unit ($Kg/m^{2)}$		Unknown	

Co-morbid diseases

Hypertension	Yes		no		unknown	
Diabetes	Yes		no		unknown	
HIV	Positive		Negative		Rx (if positive)	
Others	Yes		no		unknown	
Other malignancies	Which				Unknown	
Smoking	Yes			No		Unknown

ECOG status

0	1	2	3

Pre-operative state

Tissue sampling	Biopsy	LLETZ	Incidental	Unknown		
Stage of disease	1A2	1B1	1B2	Unknown	Other	
Histological subtype	Squamous	Adeno	Adenosquamous	Other		Unknown
LVSI	Negative	Positive	No report			

Time from diagnosis to surgery (days):

Time from surgery to death (days):

Pre-operative antibiotics received

Yes	no	Not stated
If yes, which drugs?		

Intra-operative findings

Involvement	Parametria	Bladder	Ovaries	Unknown
Anatomy	Distorted	Normal	Unknown	
Type of Hysterectomy (Q-M)	1	2	3	4
Level of Lymphadenectomy	1	2	3	Unknown
Ovaries	Removed	Retained	Hitched	No report
Surgery	Completed	Abandoned	Biopsy	No report
Surgeon	Gynaecological oncologist	Fellow gynae oncologist	Gynaecologist	Other
Ancillary surgeons involved	Urology	Colorectal	Gen Surgeon	Vascular
	None	Unknown		
Wound closure material	Peritoneum	Sheath	Subcutaneous	Skin

Duration of surgery (min):

Injuries	Ureter(s)	Bowel	Vessels	Others	Unknown	none
YES (tick)						

Estimated Blood loss (mls):

	Unknown	

Post op state

Anaelgesia (I=Inpatient, O= On DC)	Drug name	Dose	Duration	Unknown	Not given	
Antibiotics (I=Inpatient, O= On DC)	Drug name	Dose	Duration	Unknown	Not given	

Thromoprophylaxis (I=Inpatient, O= On DC)	Drug name	Dose	Duration	Unknown	Not given	
Other drugs	Drug name	Dose	Duration	Unknown	Not given	
Admission to ICU/HCA	Yes	No	If yes # days			
Duration of hospital stay	≤3 days	3-5 days	≥ 5days			
Immediate complications	Bleeding	Ileus	Sepsis	Source	Culture R	
Readmission	Yes	No	Unknown			

Follow up

Wound	Healed	Unhealed	Dehisced	Unknown
	Septic			

Post-Surgery Histology

Histological subtype			No residual disease	
Tumour size	≤2cm		≥2cm	
Stage				
Lymph nodes yield		Number of involved nodes		Unknown
Parametria	Free	Involved	Unknown	
LVSI	Involved	Uninvolved	Unknown	
Depth of invasion				

Adjuvant therapy

Radiotherapy		Chemotherapy		Chemo-Radiation	Unknown	
		None				

Demised

Yes		No		Unknown	
Date of demise					
Surgery to demise					

Last time seen: _ _ _ _/ _ _/ _ _

Annexure B: Wits HREC Clearance letter and Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

TO: Dr GT Mmalekutu
School of Clinical Medicine
Department of Obstetrics and Gynaecology
Gynaelogical Oncology Unit
Chris Hani Baragwanath Academic Hospital

E-mail: mmalekutugodfrey@gmail.com

CC: Supervisor: Dr L Mbodi <mlangi2005@yahoo.co.uk>
and <HREC-Medical.ResearchOffice@wits.ac.za>

FROM: Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 15/02/2019

REF: *R14/49*

PROTOCOL NO: **M181082** *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

PROJECT TITLE: *The morbidity and mortality associated with surgery of radical hysterectomy and pelvic lymph node dissection done at at Charlotte Maxeke Johannesburg Academic Hospital*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

R14/49 Dr GT Mmalekutu

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M181082

NAME: (Principal Investigator)	Dr GT Mmalekutu
DEPARTMENT:	School of Clinical Medicine Department of Obstetrics and Gynaecology Gynaelogical Oncology Unit Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	The morbidity and mortality associated with surgery of radical hysterectomy and pelvic lymph node dissection done at at Charlotte Maxeke Johannesburg Academic Hospital
DATE CONSIDERED:	26/10/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr L Mbodi
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	15/02/2019

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date of the meeting when the study was initially reviewed. In this case, the study was initially reviewed in **October** and will therefore reports and re-certification will be due early in the month of **October** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Annexure C: FIGO 2009 cervical cancer staging

Stage I	The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded)
IA	Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤5 mm and largest extension ≥7 mm
IA1	Measured stromal invasion of ≤3.0 mm in depth and 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 the cervix uteri 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 the uterus, but not to the pelvic wall or to the lower third of the vagina
IIA	Without parametrial invasion
IIA1	Clinically visible lesion ≤4.0 cm in greatest dimension
IIA2	Clinically visible lesion >4 cm in greatest dimension
IIB	With obvious parametrial invasion
Stage III	The tumor extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney **
IIIA	Tumor 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 edema, 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 5.00 mm and a horizontal extension of not >7.00 mm. Depth of invasion should not be >5.00 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 mm).

The involvement of vascular/lymphatic spaces should not change the stage allotment.

**On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. All cases with hydronephrosis or non-functioning kidney are included, unless they are known to be due to another cause.

Annexure D: FIGO 2018 cervical cancer staging

Stage	Description
I	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm[a]
IA1	Measured stromal invasion <3 mm in depth
IA2	Measured stromal invasion ≥3 mm and <5 mm in depth
IB	Invasive carcinoma with measured deepest invasion ≥5 mm (greater than Stage IA), lesion limited to the cervix uteri[b]
IB1	Invasive carcinoma ≥5 mm depth of stromal invasion, and <2 cm in greatest dimension
IB2	Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
IB3	Invasive carcinoma ≥4 cm in greatest dimension
II	The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Involvement limited to the upper two-thirds of the vagina without parametrial involvement
IIA1	Invasive carcinoma <4 cm in greatest dimension
IIA2	Invasive carcinoma ≥4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes[c]
IIIA	The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent (with r and p notations)[c]
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. (A bullous edema, as such, does not permit a case to be allotted to Stage IV)
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

When in doubt, the lower staging should be assigned.

[a] Imaging and pathology can be used, where available, to supplement clinical findings with respect to tumor size and extent, in all stages.

[b] The involvement of vascular/lymphatic spaces does not change the staging. The lateral extent of the lesion is no longer considered.

[c] Adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to Stage IIIC. Example: If imaging indicates pelvic lymph node metastasis, the stage allocation would be Stage IIIC1r, and if confirmed by pathologic findings, it would be Stage IIIC1p. The type of imaging modality or pathology technique used should always be documented.

Annexure E: Permission letter from the CEO to conduct research

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Ms. N. Mzila
Office of the Clinical Director
Email:Nolwazi.Mzila@gauteng.gov.za
Tell: (011): 488-4812
27 September 2018

Dear Dr. G. T. Mmalekutu

STUDY TITTLE: The Morbidity and Mortality Associated with Surgery for Radical Hysterectomy and Pelvic Lymph Node Dissection Done at Charlotte Maxeke Johannesburg Academic Hospital for Cervical Cancer.

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

Supported / not supported

PP

Dr. M.I. Mofokeng
Clinical Director
DATE: 27/09/2018

Approved / ~~not approved~~

Ms. G. Bogoshi
Chief Executive Officer
DATE: 28/09/2018

Annexure F: Permission letter from the clinical manager

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Office of the Head of Department: Obstetrics and Gynaecology
Enquiries: Dr L. Chauke

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

20 September 2018

Ms G. Bogoshi
CEO
Charlotte Maxeke Johannesburg Academic Hospital
Parktown
Johannesburg

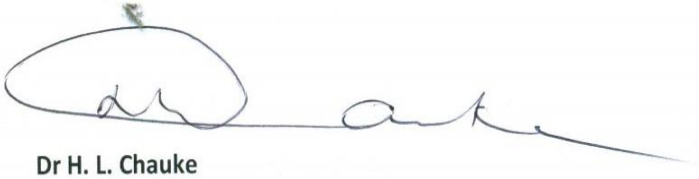
Dear CEO

Re: Request to conduct research titled:

Permission to obtain: The morbidity and mortality associated with surgery for Radical Hysterectomy and Pelvic Lymph Node Dissection done at Charlotte Makeke Johannesburg Academic Hospital for cervical cancer: Dr G T Mmalekutu

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

Thank you



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

Annexure G: Turn-It-In Report

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5	Christina E. Boutsicaris, Gary S. Phillips et al. "The impact of close surgical margins after radical hysterectomy for early-stage cervical cancer", Gynecologic Oncology, 2013 Publication	
	Rutledge, T.L.. "A comparison of stages IB1 and	

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IB2 cervical cancers treated with radical hysterectomy. Is size the real difference?", Gynecologic Oncology, 200410 — 1 %

Publication

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Maria C. Cusimano, Nancy N. Baxter, Lilian T. Gien, Rahim Moineddin, Ning Liu, Fahima Dossa, Karla Willows, Sarah E. Ferguson. "Impact of surgical approach on oncologic outcomes in women undergoing radical hysterectomy for cervical cancer", American Journal of Obstetrics and Gynecology, 2019 — 1%

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Chunlin Chen, Ping Liu, Yan Ni, Lian Tang, Yan Xu, Xiaonong Bin, Jinghe Lang. "Laparoscopic versus abdominal radical hysterectomy for stage IB1 cervical cancer patients with tumor size ≤ 2 cm: a case-matched control study", International Journal of Clinical Oncology, 2020 — 1%

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&NA;, . "Abstract :", International Journal of Gynecological Cancer, 2012. — 1%

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Stefano Greggi, Gennaro Casella, Felice Scala, Francesca Falcone, Serena Visconti, Cono Scaffa. "Surgical Management of Early Cervical Cancer: When Is Laparoscopic Appropriate?", Current Oncology Reports, 2020 — 1%

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11 Junichi Kodama, Tomoyuki Kusumoto, Keiichiro Nakamura, Noriko Seki, Atsushi Hongo, Yuji Hiramatsu. "Factors associated with parametrial involvement in stage IB1 cervical cancer and identification of patients suitable for less radical surgery", Gynecologic Oncology, 2011

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