OUTCOME OF PATIENTS WITH CERVICAL CANCER REFERRED FOR TREATMENT AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL FROM FAR EAST RAND HOSPITAL.

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

Johannesburg 2021

DECLARATION

I, Sylvain M Kalonji declare that this Research Report is my own, unaided work. It is being submitted for the Degree of Masters in Medicine (MMed) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

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Sylvain M Kalonji

15th of February 2021 in Johannesburg

PRESENTATIONS ARISING FROM THIS STUDY

1) SASGO 2018 (August) Stellenbosch, Cape Town, Abstract and Poster
2) COGI 2018 (November) London, United Kingdom, Abstract and Poster

ABSTRACT

Introduction and Background

Cervical cancer is a common malignancy worldwide and in South Africa. It remains a burden in developing countries (where 80% of cases are diagnosed) in terms of adequate screening programs, diagnosis and appropriate treatment. Patients with cervical cancer are treated in specialized cancer centers; therefore referring patients from one center to another can present with various challenges that need to be looked at. In our study, we have described various aspects of patients with cervical cancer referred from Far East Rand Hospital (FERH) to Charlotte Maxeke Johannesburg Academic Hospital (CMJAH); we have described the stages of the disease, the time spent from presentation to histology diagnosis/referral/ and treatments; we have also looked at the treatment related complications and the overall outcomes at 1 year follow up post treatment.

Methods

This was a retrospective cross-sectional descriptive study. We selected patients with cervical cancer from January 2012 to December 2016; patients were initially seen at FERH then referred to CMJAH for continuation of care after histology confirmation of the disease. 40 patient's files were retrieved at FERH and only 33 files were found at CMJAH; 7 patient's file did not meet our inclusion criteria hence we excluded them from the study. One year follow up after treatment initiation was done.

Results

All our 33 patients (100%) had cervical squamous cell carcinoma. Two patients (6.1%) were at stage IB, 11 patients (33.3%) at stage IIB, 3 patients (9.1%) at stage IIIA, 11 patients (33.3%) at stage IIIB, 4 patients (12.1%) at stage IVA, and 2 patients (6.1%) at stage IVB.

The median time interval from Pap smear to treatment initiation (in days) was as follow: 17 days(IQR 5-138) from Pap smear to cervical biopsy, 42 days(IQR 33-65) from biopsy to histology results, 7 days(IQR 0-23) from biopsy results to CMJAH referral, 2 days(IQR 0-17) from referral to CMJAH to date seen at CMJAH, 7 days(IQR 0-22) from CMJAH visit to date seen at radiation oncology unit, 52 days(IQR 37-79) from radiation oncology to treatment initiation.

Two patients (6.06%) had surgery plus vault radiotherapy, 22 patients (66.67%) had radiotherapy, 7 patients (21.21%) had chemoradiation, and 4 patients (12.1%) had palliative treatment.

Overall, 2 patients (6.06%) died, 7 patients (21.21%) had palliative care, 1 patient (3.03%) had cancer recurrence, 12 patients (36.34%) had cancer remission in the 1st year of follow up, and 11 patients (33.33%) were lost to follow up after radiotherapy.

Discussion

We have noted that the vast majority of our patients (31 out of 33) presented with advanced disease at the initial visit; this is a similar finding with other studies done in South Africa but different in developed countries where there is adequate screening services. The median waiting times from final histology diagnosis to treatment were very long; this is also found in some studies done in other developing countries but very different to the turnaround time from diagnosis to treatment in developed countries where infrastructures and human resources are adequate.

Conclusion

When diagnosed at early stage, cervical cancer can be treated and cured. Most of our patients presented with advanced disease hence did not qualify for surgery as treatment modality. Our study also identified excessive delays from diagnosis to referral/treatment. The number of patients requiring chemo radiation, radiotherapy and palliative care was higher than those requiring surgery for treatment.

ACKNOWLEDGEMENTS

I would like to express my gratitude to the following people:

1. Dr L Mbodi & Dr L Likanza, my supervisors for their continuous support and patience through the process of the Mmed

2. Dr S Maswime for her mentorship role

3. Dr Pearl Makwiting & Dr Pretty Mapaila for their assistance with collection of data

4. And my lovely wife Nathalie Kalonji for her continuous support.

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List of Abbreviations

ACS: American Cancer Society

AIDS: Acquired Immune Deficiency Syndrome

ASCCP: American Society for Clinical Pathology

CCC: Comprehensive Cancer Care

CIN: Cervical Intraepithelial Neoplasia

CMJAH: Charlotte Maxeke Johannesburg Academic Hospital

COGI: Controversies in Obstetrics, Gynaecology and Infertility

DES: Diethylstilbestrol

EBRT: External Beam Radiation Therapy

FBC: Full Blood Count

FERH: Far East Rand Hospital

FIGO: Fédération Internationale de Gynécologie et Obstétrique

HIV: Human Immunodeficiency Virus

HPV: Human Papilloma Virus

HDR: High-Dose Radiotherapy

GOPD: Gynaecology Out Patients Department

MDT: Multi-Disciplinary Team

MMed: Master of medicine

NHRD: National Health Research Database

RS: Relative Survival

RT: Randomised Trials

SA: South Africa

SASGO: South African Society of Gynaecology Oncology

SASOG: South African Society of Obstetrics and Gynaecology

TB: Tuberculosis

USA: United State of America

UK: United Kingdom

WHO: World Health Organization

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Figure 2: Typical flow of cervical cancer patients within the healthcare system in Johannesburg district.

CHAPTER 1: INTRODUCTION AND OVERVIEW

1.1 Background

Cervical cancer remains the second most common cancer among women worldwide and the most common cancer amongst black African in South Africa.[1] There are 500.000 cases of cervical cancers worldwide every year; of which mortality is about 50%.[1] This is largely due to presentation at a late stage.[1] Lack of availability of treatment facilities may be another factor contributing to this high mortality.[1]

In the USA, nearly 13.000 new cases of cervical cancer are diagnosed annually; with an estimated 4120 disease-related deaths predicted for 2016.[2] The incidence for cervical cancer in the USA has decreased more than 50% in the last 30 year because of the widespread screening[3]. In 1975, the rate was 14.8 per 100.000 women. By 2011 it decreased to 6.7 per 100.000 women. Mortality from the disease had undergone similar decrease from 5.55per 100.000 women in 1975 to 2.3 per 100.000 women in 2011.[3]

In Europe, the first incidence peak age for cervical cancer is between 30 to 34 years and there is a second rise in incidence above the age of 70 years. [4, 5]

In 2015, it was estimated that the number of new cases of cervical cancer in South Africa was about 5743 new cases and 3027 deaths from the disease.[6]

Various factors can explain the reason why women present late to seek medical help; this can include an absence of a properly implemented cervical cancer screening program throughout the country[7]; also lack of awareness on the matter.

Cervical cancer treatment takes place in specialized centres. Patients have to be referred to those centres for treatment; in low and middle income countries, access to such centres can be very difficult[8] and this will result in treatment delay with poor prognosis.

1.2 Problem statement

Cervical cancer ranks as the fourth leading cause of death in women worldwide. [9] It is reported that more than 80% of cervical cancer cases are diagnosed in developing countries.[10] The lifetime risk of developing cervical cancer in South Africa (SA) is one in 31. Forty per cent of the country's malignancies are diagnosed in Gauteng Province, probably because of the highest number of cancers diagnosing laboratories in the province. Patient usually present to our health facilities with more advanced disease than the first world countries[7]. This may be due many factors including poor education, lack of awareness, inadequate screening programmes, poor access to health care facilities, lack of funding and staff shortage.[11, 12]

At Far East Rand Hospital (a regional hospital in Ekurhuleni district in Gauteng Province), we have seen a good number of patients with cervical cancer in recent years. Those patient presented to the facility being referred from the local clinics (mostly) at various clinical stage of the disease and having different symptoms or asymptomatic. And since Far East Rand is a secondary/regional hospital, those patients had to be worked up and once the histology diagnosis of cervical cancer is confirmed, they get referred to Charlotte Maxeke Johannesburg Academic Hospital (academic/tertiary centre) for appropriate cancer related care.

It has been observed that in some instances, stage of the disease at FERH was a bit different from the stage at CMJAH, probably because of the different skills set in these two institutions

In view of the increased prevalence of the disease in the community and high mortality that comes with it, we felt motivated to study the profile of patients coming to Far East Rand Hospital (FERH) for cervical cancer related services. We looked at the stage of the disease at presentation; time spent from presentation at FERH to diagnosis, from diagnosis to referral and from referral to treatment at CMJAH. We also looked at outcomes and complications.

At CMJAH gynaecology oncology department, here are few things needed before any referral:

- A referral letter (with relevant patient's clinical information and probable clinical staging of the disease);
- A hard copy of histology confirmation of the cancer;
- A copy of blood results for the full blood count and renal function test;

- A telephonic booking to be made by the referring doctor to get a specific date for a particular patient; and all referred patients are seen only on Thursdays.

The main purpose/aim of the study was to describe what has happened to patients during this entire referral process.

It may serve as a backbone to use for other analytic studies which might compare different variables to outcomes.

1.3 Objectives of the study

In this study, we were aiming to describe:

1. The profile of patients with cervical cancer seen at FERH (from January 2012 to December 2016).
2. The initial disease staging before referral to CMJAH
3. The histological types of cervical cancer seen at FERH (from January 2012 to December 2016).
4. The outcomes of patients referred to CMJAH (up to 12 month after definitive treatment).

CHAPTER 2: LITERATURE REVIEW

2.1 Aetiology of cervical cancer

Human Papilloma virus (HPV) is the most important aetiological factor, with most (99, 7%) tumours containing HPV DNA. HPV 16 and HPV 18 are the two most common high-risk types detected in more than 70% of cervical malignancies. Other high risk HPV sub-types include 31, 33, 35, 39, 45, 51 and 58.[13]

Peak HPV infection incidence is seen in the late teens and early 20s, but in 80% of patients, the infection resolves within 12 to 18 months with median duration of infection of roughly 8 months.[14] Infection with oncogenic (or high risk) HPV usually is necessary but not sufficient factor for development of squamous cervical neoplasia. Therefore, only a small fraction of women infected with high risk HPV will develop significant cervical abnormalities and cancer.[13]The persistence of these oncogenic HPV subtypes is necessary for progression and invasion as illustrated on figure below. [15]

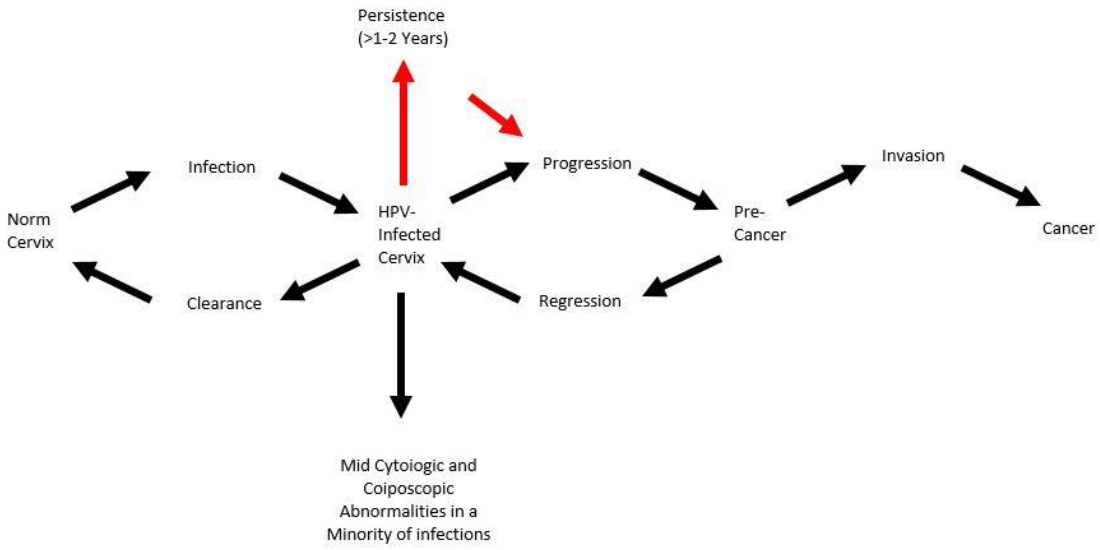

Figure 1: Flow diagram of the natural history of cervical carcinogenesis (adapted image)

2.2 Host Risk Factors

2.2.1HIV and AIDS

Much of the world is currently in the grip of the HIV epidemic and South Africa has an ever-increasing number of patients diagnosed with HIV infection.[15] The HIV infection leads to immune deficiency and the prevalence of HPV infection as well as premalignant cervical disease are much higher in HIV positive patients compared to their control. [15]

Several studies have found the prevalence of squamous intra-epithelial lesions among HIV positive women to be 30-63%.[15, 16] Further, the prevalence and degree of dysplasia increases with advancing level of immunosuppression.[15]About 61 % of adolescents and young people living with HIV are adolescent girls and young women, and about 78 % live in sub-Saharan Africa.[17]

In Johannesburg, a study done in 2000 demonstrated that HIV positive patients presented with invasive cervical carcinoma almost 10 years earlier than HIV negative patients; and patient with a low CD4 count (< 200) are significantly more likely to have advanced stage disease at initial diagnosis than HIV negative patients. [18]

2.2.2 Smoking and Cigarette.

The smoking of cigarette is associated with a two-fold increase in the risk of developing cervical cancer; the exposure to both passive and active smoking potentiate adverse role in cervical carcinogenesis.[19]

2.2.3 Coital factors.

Sexual intercourse is regarded as an important risk factor for development of cervical carcinoma; age at the first intercourse plays an important role.[20]Cervical cancer is caused by sexually transmitted carcinogenic human papillomaviruses.[21] Most of these infections will clear within 1 to 2 years, but only those that persist will progress rapidly to cervical intraepithelial neoplasia (CIN) grade 2 or worse.[22]

2.3 Commonest presenting symptoms

Common presenting symptoms in advanced cervical cancer include: abnormal vaginal bleeding, low abdominal pain, and malodorous vaginal discharge.[23]

2.4 Primary prevention: HPV vaccination

Three vaccines are shown to be effective at preventing HPV infection:

- A bivalent vaccine, which cover HPV 16 and HPV 18.
- A quadrivalent vaccine, which , in addition to HPV 16 and HPV 18, also covers HPV 6 and HPV 11; and
- A 9-valent vaccine approved in 2014, which covers an additional 5 high risk HPV genotypes.

The bivalent and quadrivalent vaccines offer limited cross protection against approximately 30 % of cases of cervical cancer caused by HPV genotypes other than HPV 16 and HPV 18.[24] The 9 valent vaccine covers approximately 20% of more high- risk HPV infection caused by 5 additional HPV genotypes. [25]

HPV vaccination is the optimal strategy for primary prevention of cervical cancer worldwide.[26] More than 70% of cervical cancer is caused by HPV infection.[21] Since 2014, the department of health in South Africa has rolled out HPV vaccination to girls aged 9-13 years.[27] This is to prevent the infection by HPV in girls and protects them against developing cancer-causing HPV in adulthood.[27]

Other methods of primary prevention include: education program on safer sex practices and the use of condoms during sexual intercourse.

2.5 Secondary prevention: Screening for cervical cancer

Research shows that well implemented and non-opportunistic National Cervical Screening Program can significantly reduce the morbidity and mortality rates attributed to cervical cancer. According to World Health Organization (WHO), successful screening program require more than 80% coverage, appropriate follow up and management of patients with positives tests, effective links between screening diagnosis and treatment services, high quality care and adequate resources. [28]

Opportunistic cervical cancer screening has been available to all South African women for the last five decades and is commonly practiced in private sector. In several regions partial screening takes place. However, currently there is still no effective population-wide screening program in South Africa. [29]

Screening in general takes place in patients without the disease in other to detect those at risk of developing that disease.

The South African Society of obstetrics and Gynaecology (SASOG) have adopted this type of screening program for cervical cancer among South African women; it might look non ethical to have two screening models for the same country, but the reality in South Africa is that the health system in low resource setting (public clinics/hospital) differ enormously from the one in high resource setting (private hospice/clinics).

Table 1: SASOG screening program for cancer of the cervix 2015 (Adapted from [30])

	LOW RESOURCE	**HIGH RESOURCE**
Initiate screen	Age 25 At diagnosis of HIV positive	Age 25 At diagnosis of HIV positive
End screen	Age 55 or Hysterectomy Only after previous negative tests Never end if HIV positive	Age 65 or Hysterectomy Only after previous negative tests Never end if HIV positive
Interval HPV test	10 years if HIV negative or unknown 5 years if HIV positive	5 years if HIV negative or unknown 3 years if HIV positive
Interval Cytology	5 years if HIV negative or unknown 3 years if HIV positive	3 years if HIV negative or unknown Yearly if HIV positive
Timing	Ten-yearly: At ages 25,35.45,55 Five yearly: Also at ages 30,40,50 Three yearly: At ages 25,28,30,33,36,	Five yearly: Also at age: 30,40,50 Three yearly: At ages 25,28,30,33,36 40, 43, 46 etc.

	40,43,46, etc.	Yearly: each year
Follow up	After single abnormal screening test or after treatment: • HIV negative and < 35 years: 5yearly until normal • HIV Positive or > 35 years: Yearly until normal BACK to screen when normal Treat after second abnormal test	After single abnormal screening test or after treatment: • HIV negative and < 35 years: 5yearly until normal • HIV Positive or > 35 years: Yearly until normal BACK to screen when normal Treat after second abnormal test

In the USA, the American Cancer Society (ACS), the American Society for Colposcopy and Cervical Pathology (ASCCP) and the American Society for Clinical Pathology (ASCP) updated their joint guidelines for cervical cancer screening. Below are their recommendations (Level A evidence) [3]:

1. Cervical cancer screening should begin at age of 21 years.
2. Women aged 21 to 29 years should be tested with cervical cytology alone, and screening should be performed every 3 years.
3. For women aged 30 – 65 years, co-testing with cytology and HPV testing every 5 years is preferred.
4. Screening by any modality should be discontinued after 65 years in women with evidence of adequate negative prior screening test results and no history of CIN2 or higher.
5. In women who have had hysterectomy with removal of the cervix (total hysterectomy) and have never had CIN 2 or higher, routine cytology screening and HPV testing should be discontinued.
6. Women with any of the following risk factors may require more frequent cervical cancer screening than recommended in the routine screening guidelines which were intended for average-risk women:

   Women who are infected with HIV

   Women who are immune compromised (such as those who have received solid organ transplants)

Women who were exposed to diethylstilbestrol (DES) in utero

Women who were previously treated for CIN2, CIN3 or cancer.

2.6 Cervical cancer histological classification

There are several histopathological subtypes of cervical cancer:

1. Squamous cell carcinoma (80%)
2. Adenocarcinoma (15%)
3. Adenosquamous (3% to 5%)
4. Rare: transitional cell, neuroendocrine, small cell, adenoid cystic, mesonephric, adenoma malignum, lymphoma, sarcoma.

2.7 Cervical Cancer Staging (FIGO 2015).

Currently staging remains clinical rather than surgical to allow for comparison with developing countries that do not have access to more advanced imaging and surgical services.

Table 2: The 2015 FIGO Staging for cervical cancer

Stage IA: Invasive carcinoma diagnosed by biopsy • Stage IA1: stromal invasion depth < 3mm and lateral extension < 7mm • Stage IA2: invasion depth > 3 and < 5 mm with lateral extension < 7mm.
Stage IB: visible lesion confined to the cervix • Stage IB1 : < 4 cm • Stage IB2 : > 4 cm
Stage II : Cancer invades beyond the cervix but not to the pelvic sidewall , or the distal third of the vagina • Stage IIA1 : vaginal involvement < 4 cm • Stage IIA2 : vaginal involvement > 4 cm

• Stage IIB: parametrium involvement.
Stage III: tumour affixed to pelvic sidewall, or involving the lower third of the vagina, or is associated with a non-functioning kidney or hydro nephrosis. • Stage IIIA : involves lower third of the vagina
• Stage IIIB : extension to the pelvic sidewall , non-functioning kidney, or hydro nephrosis
Stage IV : carcinoma has extended out of the pelvis, involving bladder , or rectum • Stage IVA: focally advanced disease. Stage IVB: extra-pelvic metastasis

2.8 Step by step treatment approach

The management of invasive cervical cancer is stage dependent; and it consists of surgery or radiation therapy, with chemotherapy.[31] Treatment plans are based on clinical practical guideline, local expertise and available resources (oncologists, adequate materials for radiation etc.); and individualised discussions between the patient and the physician.

In South Africa, cancer treatment takes place in tertiary hospital where radiation and oncology services with necessary skills and equipment can be found. Patients have to be referred to these centres for care.

At CMJAH cisplatin is used for chemotherapy in patient with cervical cancer; the dosage is 80mg/m2 three weekly.

Stage IA1: micro invasive disease

Conisation is the preferred method of diagnostic excision but loop electrosurgical excision procedure may be acceptable as long as adequate margins, proper orientation and a non-fragmented specimen can be obtained.

Lymphadenectomy is not required for stage IA1 disease in the absence of lymphovascular invasion as the risk of nodal metastasis is very small (1%).[31]

Stage IA2-IIA: early stage disease

Radical hysterectomy with lymphadenectomy is preferred to chemoradiation for patients with non-bulky tumours measuring < 4 cm without parametrial involvement (stage IA2, IB1, and IIA1). For those with tumours larger than 4 cm (stage IB2, and IIA2), chemo radiation is preferred given the high likelihood that post-operative chemoradiation will be required for adverse pathological findings. Adjuvant radiotherapy following radical hysterectomy has been shown to increase risk of treatment morbidity to the patient, even if it improves progression-free survival.[32]

In patients with stage IA2 to IB1 disease who desire to preserve fertility, radical trachelectomy with lymphadenectomy may be considered instead of radical hysterectomy for tumours smaller than 2 cm.[33]

Stage IIB-IVA: Locally advanced disease.

Chemoradiotherapy is the 1st line therapy for patients with bulky early stage and locally advanced disease.

Stage IVB: Metastatic disease

Combination of chemotherapy first line treatment for metastatic disease option include:

- Cisplatin or topotecan with paclitaxel and bevacizumab
- Cisplatin and paclitaxel
- Carboplatin and paclitaxel with or without bevacizumab
- Cisplatin and topotecan
- Topotecan and paclitaxel
- Cisplatin and gemcitabine

The practice and protocol of management at the Charlotte Maxeke Johannesburg academic hospital on early stage disease (stages 1A1 to 1B2) is similar to the

international guidelines/protocol. However, patients with stage 2A are manged as late stages disease with chemo-radiation. [34]

Radiotherapy is given as follow [34]:

- Post-operative radiation, 4 field technique to a dose of 48Gy in 24 daily fractions.
- StageIB2 and IIA, IIB cis-platinum 80mg/m2 with radiation 3 weekly.
- For inoperable stage IB1, IB2, IIA, IIB (proximal), pelvic radiation 46 GY in 23 daily fractions in 2 to 4 field. High-Dose Rate (HDR) intracavity radiation to a dose of 26GY four weekly.
- Stage IIB (distal), pelvic radiation with 50Gy in 25 daily fraction using2 to 4 fields HDR intracavitary radiation of 24 GY in 3 weekly fraction from week 3
- Stage III3B, 40 GY in 16 daily fractions using 2 or 4 fields.
- Palliative radiation is 20Gy in two monthly fraction using fields.

Successful radiation therapy depends on the following:

- Greater sensitivity of the cancer cell
- Greater ability of normal tissue to recuperate after irradiation
- Patient in good physical condition.

In early stage of the disease (IB2), evidence show that when comparing radiotherapy alone with radiotherapy plus cisplatin- based chemotherapy (post hysterectomy), chemo radiation was found to significantly improve long term PFS (progression free survival) and OS (overall survival)

Chemo radiation has some shortcomings related to access, efficacy, and tolerability. Neoadjuvant chemotherapy is most studied alternative treatment modality for FIGO stage IB2 to IVA.

2.9 Referral system of patients with cervical cancer

Worldwide, patients diagnosed with any malignancy including cervical cancer are usually treated in a designated cancer care centre according to the countries policies and standard protocols. Hence, moving patients from one facility of care to another for appropriate treatment is common even though these present challenges that may need to be addressed to improve patients' outcome.

Having a centralized system for cancer treatment has an advantage of access to highly specialized multidisciplinary services all in one place: radiation oncology, medical oncology, gynaecology oncology etc. The disadvantage of this system is that some patients have to travel long distance to access these services and some other patients can easily default due to transport challenges especially in poor communities.

A study in the USA looked at the cervical cancer survival of patients referred at a tertiary centre.[35]Several factors were analysed to establish their impact on the overall survival: patient demographic information, stage of the disease, patients comorbid factors (Hypertension, coronary artery disease and other cardiovascular disease, diabetes, collagen vascular disease, pulmonary disease, venous thromboembolism disease, and psychiatric disorders). It was found that only comorbid diseases were having a impact on the overall survival; and patients with 2 or more comorbidities and worse prognosis.[35]

Another study was conducted in the USA to evaluate the potential relationship between outcomes in cervical cancer patients based on distance from a Comprehensive Cancer Centre (CCC). It found that overall survival for patients living more than 100 miles from the CCC was worse when compared to patients in closer proximity. [2] They suggested that outreach efforts may help decrease the impact of geographic disparities on outcomes.

In developing countries, cancer services are not easily accessible especially in rural areas.[36] Patients have to travel long distances to access appropriate centres of care. Joint efforts from governments and different health partners can help assist vulnerable patients in resource constrained settings. A successful example of this kind of partnership was illustrated in Rwanda by the creation of Butaro Cancer Centre of excellence which helped to expand cancer services nationally and reduced the burdens on patients. [36] In 2011, driven by its strong equity agenda, and together with their health's partners, the Rwanda's ministry of health decided to expand cancer care nationally, targeting poor, rural-based patients. In July 2012, the Butaro Cancer Center of Excellence, a public rural-based facility, was inaugurated. Services available include: pathology-based diagnosis, imaging, chemotherapy, radiotherapy, surgery, palliative care and socioeconomic access support; this improved the care of patients with cancer in remote areas of Rwanda.[36]

Low income countries also face other various challenges in delivering cervical cancer health services including the lack of radiation therapy centres,[37] costs of service delivery involved at different level of care, difficulty in collecting proper data to conduct relevant research or surveys to improve cervical cancer service delivery. [38, 39]

In South Africa, cancer services are mostly available in tertiary hospitals. Patients get referred from primary and secondary health care centre. Patients are usually given a booking date based on the next available space (which can be 4 to 8 weeks from booking time) and not on the nature of their disease. At most times there are delays as a result of the huge number of people in need of these services and this is likely to have a negative impact on the outcome. Some patients use their own transport to get to tertiary centres, but in all centres, transport is organised and funded by the state. Follow up care at tertiary level will depend on the initial diagnosis and staging as well as the treatment plan and complications.

Below is our flow diagram showing the typical flow of patients from primary healthcare to tertiary centres.

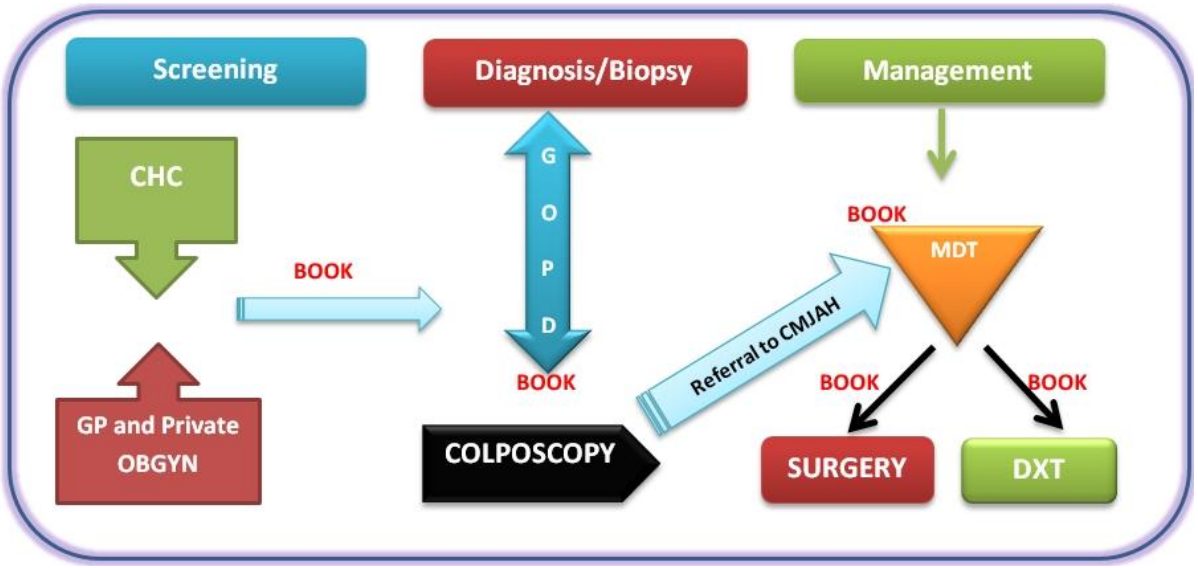

Figure 2: Typical flow of cervical cancer patients within the healthcare system in Johannesburg district.

This flow diagram explains what happens at different level of care in the management of patient with cervical cancer:

- The screening can be done either at a community health care center (CHC) or by a general practitioner and a gynaecologist.

- In the presence of abnormal screening result, the patient will have either a colposcopy and/or a biopsy to establish the final histological diagnosis; this can be done in a gynaecology outpatient department (GOPD).
- Once there is a histology confirmed diagnosis of cancer, the patient is then referred to CMJAH gynaecology oncology outpatient department; from here, the patient will be further worked up, staged and then presented to a multidisciplinary team meeting involving the gynaecologist oncologist, the radiation oncologist and the medical oncologist for a final decision. This final treatment decision can either be surgery, radiotherapy or chemoradiation, depending on the stage of the disease.

A study conducted at Chris Hani Baragwanath Academic Hospital between April 2003 to December 2006 showed that the average time from cervical cytology screening to the colposcopy was 113 days. [40]

In the cervical heath implementation project, the South African National Department of Health has identified several factors that are barriers for access to colposcopy services and pre-cancerous treatment as follow:

- Lack of guidelines and protocols
- Poor communication between screening facilities and colposcopy/treatment services (inadequate referral systems and lack of proper feedback to the referral centre)
- Colposcopy and treatment not available (especially in rural area) and lack of trained colposcopists to render services when needed. [41]

Snyman LC et al conducted a study in Pretoria to look at reasons why unscreened patients presented with advanced stage disease, as well as their presenting symptoms and behaviour following the onset of symptoms. Patients interviewed in the study reported that they presented to their nearest health facilities (local clinics, general practitioners or district hospitals) with gynaecological symptoms (per vaginal bleeding, per vaginal discharge and lower abdominal pain) within 4 weeks of the onset of these symptoms. It was found that, out of 85 patients interviewed, only 41% had a gynaecological exam done at the 1st visit and 15% appropriately referred, compared to 23% at the 2nd visit. The late presentation was therefore associated with no gynaecological examination and these factors have contributed to further delay in diagnosis, referral and treatment. [7]

At CMJAH, patients referred for cervical cancer are seen at the gynaecology oncology clinic and their management is stage dependant. Some of these patients with a much- advanced or non-operable disease will then be presented and discussed with the radiation-oncology team at a multi-disciplinary meeting and a treatment plan will be then decided upon.

Often the referring hospital do not know exactly all the requirements from CMJAH before referring patients; and there are no policies regarding the referral cases to be prioritised. Sometime patients referred get turned back to the referring institutions because they are not properly worked up or have incomplete records without documents that carry vital information necessary for finalizing the decision. This delays treatment and can impact negatively on the overall outcome.

2.10 Outcome of patients referred for cervical cancer care

2.10.1 Waiting times for referral to Oncology centres

A UK centre study reported that the average time from first visit at head and neck oncology clinic to starting radiotherapy was 40 days. Six centres had an average waiting period of less than 28 days. The findings of the study reported wide variations in the quality of care between centres and that failure to comply with guidelines had serious implications both for patient outcomes and for the success of the National Cancer Plan. [42]

The results from the national survey in the UK suggest that the tumours most likely to be adversely affected by long waiting times are those with shorter volume doubling times or a little chance of tumour control at the outset of treatment. They concluded that a system of patient triage and prioritization of patients was deemed most likely to benefit patients reducing waiting time and may be necessary in the current climate of limited radiotherapy resources. [43]

In their editorial, Coles et al highlighted that they certainly have to consider, as a professional group, what they might do to address the problem of prolonged waiting for radiotherapy. They suggest an average of 2 weeks with not more than 4 weeks would appear safer for those with new lung, cervix and head and neck cancers. Unfortunately, the tumour would not wait

for all system to be perfect, and undoubtedly, they would use more neoadjuvant chemotherapy with all the attendant financial and practical consequences, they concluded. [44]

Blanckenberg ND at all looked at the impact of the introduction of colposcopy service in a rural South African sub-district in Western Cape on uptake of colposcopy; they found that an establishment of a colposcopy service in a rural sub-district increased uptake of colposcopy and decreased the delay from cervical smear to colposcopy. The service removed 202 booked patients in one year from colposcopy load of the referral hospitals.[45]

In an editorial by Lotriet E, it was reported that by June 2017, there wasn't a single oncologist employed at any state hospital in Durban, and only two left in Kwazulu-Natal province in South Africa.[46] This makes us to understand that some of the delays might be due to the shortage of human capital.

2.10.2 The Impact of delay in initiating Radiotherapy on Oncology patients in general.

Chen et al looked at the relationship between waiting time for radiotherapy (RT) and clinical outcome. This was a systematic review of literature between 1975 and 2005 to identify clinical studies describing the relationship between waiting time and outcomes of radiotherapy. They identified 44 studies; a meta-analysis of 20 high quality studies demonstrated a significant increase in the risk of local recurrence with increased waiting time (more than 4 weeks). The study focus on post-operative radiotherapy for breast cancer, post-operative radiotherapy for head and neck cancer, definitive radiotherapy for head and neck cancer. The increase in local recurrence translated into decrease survival. [47]

A study was done By Anni RJ at all to assess tumor progression in waiting time for radiotherapy in head and neck cancer. Negative impact was found in waiting time for radiotherapy of more than 38 days. [48] From an average of 4 weeks, the majority of patients developed significant signs of tumor progression.[48]

2.10.3 Effects of treatment delay and associated factors on survival in cervical cancer patients

There are several factors which affect local recurrence, overall survival disease free survival in patients treated with cervical cancer; it has been well established that prolonged treatment times are associated with increased cancer recurrence, and decreased survival.[49]

In their study, Vitzthum et al wanted to identify the sources of delays in treatment completion for patients with cervical cancer; they found that prolonged treatment times beyond 56 days are associated with worse outcomes for cervical cancer treated with radiation therapy.[50]

In Taiwan, a national wide population-based study was done to look at factors involved in the delay of treatment initiation for cervical cancer patients. The study focused on cervical cancer patients who delayed treatment for at least 4 months, and examined the characteristics, related factors, and survival in these patients. It was found that delayed treatment was associated with age, comorbidity, cancer stage, diagnosing hospital level, and hospital ownership. Delaying treatment for 4 months or more substantially raised mortality risk in cervical cancer patients.[51]

Lohlun KN et al looked at the impact of waiting times for radiotherapy for cervical cancer in Johannesburg. Their objective was to evaluate the potential impact of radiotherapy delays. They concluded that a relationship between time waited and disease progression could not be proven; however the study does highlight unacceptable long delays for radiotherapy and a wait of less than 40 days is recommended. This study was underpowered.[12]

2.10.4 Cancer survival by stage

Stage at diagnosis, the anatomical extend of a disease, is a major determinant of patients outcomes.[52] It is crucial in predicting prognosis, and to inform treatment decision, as well as to assess the effect of public health intervention such as screening programmes and education or awareness campaigns, which aim to improve early stage diagnosis.[53]

A study was done in Germany looking at survival of cervical cancer patients by age, histology and stage. The aim of the study was to derive most up to date and detailed survival estimates for cervical cancer patients in Germany; 15.685 patients with cervical cancer diagnosed from 1997 to 2006 were included. Trends in survival between 2002- 2006 were examined; and among other results, it was found that 5 year relative survival was 84.6% for localized disease, 48.2% for reginal, and 17.9% for distance stage of the disease.[54]

A population based study on cancer survival by stage at diagnosis was done in Kuwait. One of the objectives of the study was to estimate stage-specific net survival at 1 and 5 years after diagnosis, and to assess differences in stage-specific survival between Kuwait and the United States. They looked at data of patients diagnosed with cancer between 2000 and 2013, with follow up to 31/December/2015. Summary stage of 12 malignancies was examined. It was

found that 1 and 5 year survival for colon, rectal, breast, cervical and prostate cancer was about 90% or higher for patients diagnosed at localized stage. Age standardized 5-year net survival for all stages combined was lower in Kuwait than in the USA for colon, breast, lung cancer but stage-specific survival was similar.[55]

CHAPTER 3: METHODOLOGY

3.1 Setting

FERH is a regional (secondary) hospital located in the district of Ekurhuleni in Gauteng Province in the Republic of South Africa. The hospital receives patients referred from surrounding community health clinics and midwives obstetric led units. The obstetrics and gynaecology department work load in the hospital is moderate, probably due to the urban location of the hospital.

The gynaecology ward at FERH is a 39 beds ward that caters for all patients with gynaecology related illnesses as well as all female patients having surgical related illnesses.

Patient with cervical cancer go to FERH as referral from local clinics (mainly) or self-referred if acutely ill and brought by paramedics from their homes. They are seen either from the outpatient section of the department of gynaecology (GOPD) or from the accident and emergency department (if acutely ill). If need be, they get admitted to the appropriate ward from these two areas.

Patients suspected with cervical cancer are fully assessed with history and clinical examination done by a medical officer in the gynaecology department; a cervical biopsy is taken and once there is a histology confirmation of the disease, an abdominal sonar a chest X ray, full blood count, and a renal function test (Urea and Electrolytes + Creatinine) are done. Sometimes a clinical staging is done by the medical officer but this is not so consistent and in some few cases specialist gynaecologists in the department do help with the staging.

After all the above are done, patients are sent to CMJAH for further treatment. At CMJAH, there is a once weekly gynaecology oncology clinic taking place. Prior booking by the referring institution telephonically is needed and patients are given a date to go to CMJAH. Some of the patients use the hospital transport to get to CMJAH if they can't afford transport costs. At the gynaecology oncology department, patients are thoroughly reassessed with history and clinical examination done by a registrar rotating in the department, supervised by the gynaecologist oncologist. A new clinical staging is done, results are accessed and all patients are discussed at a joint meeting at the Radiation Oncology department for individualised management decision. The meeting is call MDT meeting (multidisciplinary team meeting), it is done once a week and the following specialities do attend it: gynaecology oncology, medical oncology and radiation oncology.

3.2 Study design.

This was a cross sectional descriptive study. Data were collected retrospectively. We have studied all women who came at FERH for cervical cancer related health services from 1st January 2012 to 31st December 2016. Follow up of up to 12 months after arrival at CMJAH for continuation of care was done.

3.3 Study population.

Study population included women who were seen at FERH for cervical cancer related care from 1st January 2012 to 31st December 2016. There was no sample size calculation done, because this was a descriptive study.

Pap smears were done at the local clinics (by nurses or doctors) or by private general practitioners; all the biopsies were done at FERH. The specimen for both Pap smear and biopsies are all sent at the national health laboratory services (NHLS); at the NHLS level, there is a centralized service for all cytology and histology specimens for Gauteng province. Hence the turnaround time is very long (6 weeks or more). For the Pap smear specimen done by private doctors, the results were available in 48 hours through different private laboratory.

The simulation procedure done at radiation/oncology department prior to commencing radiotherapy entails explanation of the procedure to the patient, patient set-up and positioning or immobilization. CT scanning the patient, then contouring the volumes of the tumor that need to be treated and normal structures that need to be avoided. It also encompasses planning the dose that will be delivered to the target volume.

3.4 Radiotherapy at CMJAH

Details of protocol used at CMJAH radiation oncology department given above (under the section step by step treatment) and referenced accordingly [34]

The following factors dictate the dosage of radiotherapy:

- The stage of the disease
- The patient's performance/clinical status

- Oncologist discretion in view of patient clinical condition and clinical response to treatment.

3.5 Inclusion criteria.

Women with a histology confirmation of cervical cancer at FERH during the study period and referred to CMJAH MDT. The histology results considered were the initial results from FERH.

3.6 Exclusion criteria.

Women with other types of histological confirmed malignancies rather than cervical cancer as well as women whose files were no retrieved at CMJAH for outcomes evaluation were excluded.

3.7 Data collection.

Women seen at FERH for cervical cancer care from 1st January 2012 to 31st December 2016 were identified from the hospital cancer registry and. The medical records of these patients were retrieved and relevant data reviewed, captured and analysed.

The very same patients were traced and followed at CMJAH oncology clinic, their medical records were retrieved and relevant data regarding work up for treatment and the actual treatment was reviewed, and captured.

Each patient was given a study number to maintain anonymity. The final data sheet only reflects the study number and data pertaining to the study.

Details of the women were only available to the researcher, to the doctors who assisted with data collection and the supervisors. Data has been secured and will be kept safe for a period of 5 years.

3.8 Variable recorded.

Age

Parity and gravity

Citizenship

Marital status

Behaviour (smoking and alcohol consumption)

Blood test (FBC and U&E creatinine)

HIV status

Imaging: Chest X ray and abdominal sonar

Pap smear results

Presenting symptoms

Histology results

Treatment modality at CMJAH: surgery/chemo-radiation/other

3.9 Ethical considerations

This study commenced after the postgraduate committee and Human Research Ethics Committee (medical) of the University of Witwatersrand gave approval (Ethic clearance number M170939).The research project/proposal was submitted to the National Health Research Database (NHRD) and it was registered (Reference number GP 201712 013)

Permission to conduct the study has been obtained from the offices of the Chief Executive Officer at FERH and CMJAH.

The study has adhered to South African Good Clinical Practice Guidelines [56] and the declaration of Helsinki. [57]

3.10 Funding

All research related expenses were incurred by the primary investigator. There were no donation or funding received for this study.

CHAPTER 4: RESULTS

There were 40 patients who met the inclusion criteria for the study and were referred from FERH to CMJAH for treatment between January 2012 and December 2016. Seven patients were excluded from the study as their records at CMJAH were not found.

4.1 Demographic characteristics

The table below summarises a description of the demographic factors of our patients.

Table 4.1: A Description of the demographic factors

Variable	N=33
Age	49 (SD=11)
Parity	
0	1 (3.03%)
1-4	27 (81.82%)
>4	5 (15.15%)
Race	
Black	32 (96.97%)
Non-black(white)	1 (3.03%)
Nationality	
SA	31 (93.94%)
Non-SA	2 (6.06%)
Marital status	
Single	12 (36.36%)
Married	20 (60.61%)
Unknown	1 (3.03%)
HIV Positive	
yes	16 (48.48%)
no	17 (51.52%)
HIV treatment	
Yes	13 (81.25%)
No	3 (18.75%)
Smoking	
Yes	3 (9.09%)
No	30 (90.91%)

4.2 Presenting Symptoms

The commonest presentation on our study was pelvic pain. Of the 33 patients, 30 (90.91%) had pelvic pain; 29 patients (87.88%) had per vagina bleeding; 14 patients (42.42%) had per vaginal discharge; 4 patients (12.12%) and bowel symptoms and 3 patients (9.09%) had urinary symptoms.

4.3 Comorbid Diseases

There were 2 patients (6.06%) who had Diabetes Mellitus, 5 patients (15.1%) who had Hypertensive disease and 4 patients (12.1%) had previous history of Tuberculosis.

4.4 Stage of cancer at FERH

At FERH, patients were assessed and clinically staged before referral and 4 patients (12.4%) were said to be at stage IA, 3 patients (9.1%) were at stage IB, 2 patients (6.1%) were at stage IIA, 4 patients (12.4%) were at stage IIB, 4 patients (12.4%) were at stage IIIA, 10 patients (30.3%) were at stage IIIB, 4 patients (12.4%) were at stage IVA, and only 2 patients (6.1%) were at stage IVB. None of the patients were referred without a record of their clinical staging. Staging was done by a medical officer with no gynaecological oncology training.

4.5 Stage of the disease at MDT

At the MDT, no patients were found to be at stage IA, there were 2 patients (6.1%) who were at stage IB, no patient was at stage IIA, 11 patients (33.3%) were at stage IIB, 3 patients (9.1%) were at stage IIIA, 11 patients (33.3%) were at stage IIIB, 4 patients (12.1%) were at stage IVA and 2 patients (6.1%) were at IVB. Overall, staging at FERH was similar to what was found at CMJAH MDT.

Below is a table representing stages of the disease both at FERH and CMJAH

Table 4.2 stages at FERH and CMJAH

STAGE	FERH	CMJAH
Ia	4	0
Ib	3	2
IIa	2	0
IIb	4	11
IIIa	4	3
IIIb	10	11
Iva	4	4
IVb	2	2

4.6 The histological types of cervical cancer

All our patients had squamous cell carcinoma (100%). There were no cases of any other histological subtype noted according to the pathologist's report. There were 81.8% of patients who had a moderately differentiated disease, 18.2% with unknown differentiation and none of the patients had a poorly differentiated disease.

4.7 Outcomes of patients referred to CMJAH

It appears that most patients who were referred from FERH to CMJAH used their own transport and some of them used the hospital transport available. We are not able to give details on this regards because this information was not available in records/files from both FERH and CMJAH.

At CMJAH, patients were first seen at the gynaecology out patient's department, none of them were admitted. They were then given an appointment at the radiation oncology department where they were assessed by a multidisciplinary team (MDT) of gynaecologists

together with radiation oncologists. The final decision on the treatment option was taken during the MDT assessment.

Of the 33 patients who arrived at CMJAH, 31 of them (93.9%) were referred and managed at radiation Oncology in collaboration with the CMJAH Gynaecology-Oncology unit and medical oncology.

There were 2 patients (6.06%) who were treated with surgery and 22 patients (66.67%) had radiation therapy, 7 patients (21.21%) had chemo radiation and there were 4 patients (12.1%) treated with palliative care. The treatment modalities were as recorded at the CMJAH Radiation Oncology unit.

Table 4.3 the treatment modalities in these patients.

Treatment modality	N=33
Surgery	2 (6.06%)
Radiation	22 (66.67%)
Chemo radiation	7(21.21%)
Palliative	4 (12.12%)

Radiotherapy was given as External Beam Radiotherapy (EBRT) in 22 patients (66.67%) and 19 patients (57.6%) were also treated with brachytherapy. There were 2 patients (5.2%) who received radiation as haemostatic dose to stop the bleeding.

Table 4.4 EBRT: dosage and fraction

EBRT	66.67% (n=22)		
Dose -		**Fraction**	

20 Gy	4.6% (1)	9.1% (2)	4.6% (1)
40 Gy	31.8% (7)	16	31.8% (7)
42.5 Gy	4.6% (1)	17	4.6% (1)
46 Gy	9.1% (2)	23	13.6% (3)
48 Gy	9.1% (2)	24	9.1% (2)
50 Gy	27.3% (6)	25	22.7% (5)
60 Gy	4.6% (1)	Hypo	4.6% (1)

Table 4.5 Brachytherapy: dosage

Brachytherapy	57.6% (N=19)
Dose	
5 Gy	5.3% (1)
6.5 Gy	10.5% (2)
7 Gy	5.3% (1)
8 Gy	21.1% (4)
9 Gy	21.1% (4)
17 Gy	5.3% (1)
18 Gy	10.5% (2)
24 Gy	10.5% (2)
26 Gy	5.3% (1)

4.8 Complications during radiotherapy.

Few patients had early and late complications/side effects associated with radiotherapy as listed in the table below. The early complications were: burns, cystitis, urethritis and Proctitis. The late complication was vaginal fibrosis.

Table 4.6: Complications of radiotherapy

Complications	N=22
Burns	2 (9.09%)
Vaginal fibrosis	4 (18.18%)
Cystitis	2 (9.09%)
Urethritis	1 (4.85%)
Proctitis	1 (4.85%)

4.9 Average time from initial investigations at FERH to treatment initiation at CMJAH

The table below summarises the time internal from the abnormal Pap smear to the initiation of treatment at CMJAH/MDT.

Table 4.7: Average Time Interval.

Activity Interval	Median days (IQR)
Pap smear to cervical biopsy	17 [IQR 5 – 138]
Biopsy to Biopsy results	42 [IQR 33- 65]
Biopsy results to Referral to CMJAH	7 [IQR 0 – 23]
Referral to CMJAH to date seen at CMJAH	2 [IQR 0 – 17]
Date seen at CMJAH to date seen at MDT	7 [IQR 0 – 22]
MDT to treatment initiation	52 [IQR 37 – 79]

4.10 Overall survival in 1 year follow-up after treatment initiation.

In total, we had 2 patients (6.06%) who died, 11 patients (33.33%) were lost to follow up after radiotherapy at CMJAH, 1 patient (3.03%) had recurrence of the disease, 12 patients (36.34%) had cancer remission and 7 patients (21.21%) were referred for palliation care.

Our study followed up patients up to one year post treatment initiation. We had a high number of patients who were lost to follow up. It's unclear what happened to them. The 7 patients (21.21%) who qualified for palliation were in an advanced stage of the disease with poor prognosis, they were sent to various hospices and we did not follow them up further.

Regarding Pap smear results after treatment, it is important to note that 12 patients (36.34%) had a negative Pap smear at 1 year post treatment initiation; 1 patient had high grade cell on Pap smear and it was then found that she had disease recurrence on biopsy; for the 2 patients that died (6.06%), Pap smear was not done yet after their treatment. 11 patients (33.33%) were lost to follow up after completing radiotherapy, hence no Pap smear was recorded for

them; and 7 patients (21.21%) had an ongoing disease in advanced stage and were referred for palliative care and did not need a Pap smear.

CHAPTER 5: DISCUSSION

Cervical cancer diagnosed in early stage can successfully be treated with surgery. This leads to a complete cancer remission with a good 5 year survival rate. In our study, only 2 patients (6.06%) presented at early stage and were treated surgically. This finding confirms the impression that most of our patients present to the health facilities with advanced stages of the disease.[7] Kang Y-J at al. did a study to estimate the optimal uptake rate for surgery, radiotherapy, chemotherapy and chemo-radiation for cervical cancer treatment in Australia and Canada; it was found that the estimated optimal rates for surgery for early stage was 63% in Australia (95% CI: 61-64), and 38% in Canada (95% CI: 36-39%). [58] These figures imply that majority of patients in Australia and Canada presented earlier, hence the higher rate of surgery as treatment in these developed countries.

A prospective analysis of presentation, management, and outcomes of cervical cancer in Southern Malawi was done in 2017. This was a descriptive study. There was 300 patients recruited; 132 (44%) patients had stage 1 disease, and at 2 months from presentation, 31 patients in early stage (40.8%) had surgery completed. These figures are much better than ours, probably because of the nature of data collection (prospective) and also the high power of the study.[59]

In our study, some patients had to wait up to three months before getting their histology results. This was very long. The turnaround time from the South African National Health Laboratory Services (NHLS) to process a histology specimen is 6 to 8 weeks; if the request is fast tracked, it than take up to 2 weeks maximum to get the report. No specimen was fast tracked in our study. The long turnaround time at the NHLS is due to the high workload with very limited resources. The standard and good practice point for gynaecological tumour recommend that provisional or final pathology reports have to be communicated to the lead clinician within 10 working days of the specimen being taken.[60]

The above mentioned study in Malawi describing the presentation, management and short-term outcomes of patients with newly diagnosed cervical cancer at Queen Elizabeth Central Hospital found that biopsy specimen took 2 months to be reported.[59]These findings differ a bit from ours, but they are also not in conformity with the accepted standards.

The New Zealand clinical audit on gynaecological cancer pathway for faster cancer treatment done in 2016 noted that out of 72 gynaecological cancer cases identified, the ideal time from biopsy for tissue diagnosis to the time for the histology report (aiming for less than 14 days) was met in only 35% of cases.[10] The target time of histology report here was better than ours, although the 14 days target was not met in most cases. This is probably explained by adequate resources for histology diagnosis as compared to ours.

In terms of waiting time before radiation therapy for advanced cancers, 2 to 4 weeks seems to be acceptable.[43] In our study, there were delays at different levels of care before the patients were started on treatment (surgery/radiotherapy/chemotherapy). A median number of 52 days (37 to 79) of waiting time before radiotherapy/chemoradiation was noted at MDT. This is likely due to limited resources (staff shortage, less equipment etc.)

In 2011, a study was conducted in Johannesburg at CMJAH Radiation Oncology on the impact of waiting time for radiotherapy for cervical cancer; it was found that the median waiting time from first visit to simulation was 55 days; and from simulation to treatment initiation it was 19 days; a total of 74 days delay was therefore noted [12]. This study could not establish a link between long waiting time and poor outcome. There is no significant difference between these findings and ours; both studies however have showed a longer waiting time than the accepted average.

In 2015, Nascimento MI wanted to describe the waiting time for radiotherapy for patients with cervical cancer in Baixada Fluminense region in Brazil; 342 cervical cancer cases were enrolled, and it was found that 72.2% began their radiotherapy within 60 days from the diagnostic confirmation date. [61] This is still higher than the average accepted waiting time.

An audit on radiotherapy practice at the cancer centre of a tertiary hospital in Delhi (India) found that the median waiting time to start radiotherapy course was 41 days[62]. Haque N et al. reported a waiting of up to six months before receiving radiotherapy in Bangladesh, [63] this was more than the average time.

A study in the United Kingdom analysed the radiotherapy planning process at the London Regional, it was noted that 84.9% of patients were treated within 14 days.[64] The waiting time in developed countries seems to be within the average.

In some instances, delayed treatment influences the overall outcome. A study was done in Brazil looking at the effect of waiting time for radiotherapy on five year overall survival in women with cervical cancer between 1995 to 2010; a total of 342 patients with cervical cancer referred to radiotherapy in the Baixada Fluminense, in Greater Metropolitan Rio de Janeiro State, Brazil was recruited; it was found that delayed radiotherapy for more than 64 days was associated with increased mortality when evaluating the 5-year survival in these patients. [65] Our study did not evaluate the impact of a long waiting time for radiotherapy on the overall outcome.

The delays in cancer care can emotionally and physically affect women. In 2015, a qualitative study was done by Ntinga SN et al. to describe how women experienced the late effects of cervical cancer treatment in South Africa. It was found that the late effects deriving from cervical cancer treatment deprived women of the lives they lived before they were treated for cervical cancer. Women were burdened with physical changes which aggravated their already difficult financial situation, and they had to live with unattended health needs. Sexual dysfunction changed their intimate partner relationships, leading to anxiety about the possible loss of their life partners.[66]

It is important to mention that most of patients in our presented with advanced stage of the cancer: 11 patients (33.3%) were at stage IIB; 3 patients (9.1%) were at stage IIIA; 11 patients (33.3%) were at stage IIIB; 4 patients (12.1%) were at stage IVA and 2 patients (6.1%) were at stage IVB. This confirms that most patients in our setting present with advanced disease.[7] This is due to the absence of a good screening program, resulting in patients becoming symptomatic prior to diagnosis.[7]

In the study in Malawi done by Rudd P et al. (mentioned above), it was found that out of the 300 patients studied, 168 (56%) presented with more advanced disease (stage II to IV) as compared to 132 (44%) who were at stage I.[59] Reasons for the late presentation are not given in the study; but we can notice that more patients do present late in developing countries.

In their study, Kang Y-J at al. estimated the optimal uptake rate for surgery, radiotherapy, chemotherapy and chemo-radiation for cervical cancer treatment in Australia and Canada (mentioned above); they found that majority of patients presented in early stage of the disease (stage IA to IIA); 75% in Australia vs 54 % in Canada. These figures show that majority of patients in developed countries do present earlier.[58]

In our study, 22 patients (66.6%) with an advanced disease were treated with radiotherapy (EBRT and Brachytherapy HRD).Hata M. et al found that low dose radiotherapy given to patients with stage IV A disease prevent vesicovaginal and rectovaginal fistulas. [67]

Chemoradiation was used in 7 patients (21.2%). The targeted patients were those with stage IIB to IIIA mostly. Patients with pelvic side wall involvement were treated with radiotherapy only with no chemotherapy. Zuliani at all has found that cisplatin added to radiation, can offer small but significant benefit in disease-free interval with acceptable toxicity in the management of stage IIIB cancer. [68] It is not known why chemotherapy was given to the rest of the patients in our study.

About 12.1% of patients in our study did qualify for palliative care. Some had low dose palliative radiotherapy to improve the quality of life and for pain control. Few of them had to be sent to hospices for supportive care because of their advanced disease and the poor prognosis. Not much information could be retrieved from what happened to those patients once sent to hospices and hence we cannot comment about whether the radiotherapy helped at all in symptoms control. In their studies, Mishra at al found that the monthly palliative pelvic radiotherapy in advanced cervical cancer was associated with an improvement in symptoms control with acceptable complications and a median survival of 7 months. [69]

The age range of patients with cervical cancer in our study was 36 to 58 years with a mean age of 47 years. This shows that the disease does affect women at younger age as well. In 2009, Moodley M reported on the challenges of cervical cancer in Southern Africa; it was noted that cervical cancer usually affects women in the fifth and sixth decade of life, but the prevalence of cervical cancer is now found in the fourth decade of life for HIV infected women.[1] Human papillomavirus (HPV) is now known to be the main factor in the aetiology of cervical cancer with over 99.7% of cases being associated with previous high risk HPV infection.[70] In a study done in Nigeria by Okunade KL et al to look at the prevalence and risk factors for genital high risk HPV, it was noted that out of the 200 participants, the highest proportion of women with genital high risk HPV positive infection was in the 30-39 year age group (46.6%). No women in the 60-69 years age group had genital HPV. It was also demonstrated that early age of sexual debut and increasing number of lifetime sexual partners are the most important factors associated with genital high risk HPV infection.[70] These

findings might also explain why cervical cancer is found in the third and fourth decade of life.

In 2017, Ghazi Sharkas et al. conducted a study to look at the trends in the incidence of cervical cancer in Jordan from 2000 to 2013. They found that a total of 591 women were diagnosed with cervical cancer on that period in Jordan; the age at diagnosis ranged between 15 and 97 years, with a median of 50 years.[71] The findings in this study are slightly different from ours, with extreme age groups noted to be affected by cervical cancer. It is not clear why the cancer was found so early (at 15 years) in the study; but from these findings, we can see that cervical cancer can affect women across all age groups.

Plummer M et al studied the time since first intercourse and the risk of cervical cancer; data from the International Collaboration of Epidemiological Studies of Cervical Cancer were used; it was found that the risk for invasive cervical carcinoma is approximately proportional to the square of time since first intercourse up to age 45. They also noted that the age specific incidence rates of cervical cancer in unscreened populations remain fairly constant above age 45.[20] This is almost similar to our findings where the mean age of developing cervical cancer was 47 year.

In terms of parity and incidence of cervical cancer, our study found that 27 patients (81.82%) diagnosed with cervical cancer had 1 to 2 children; there was 1 patient (3.03%) who was nulliparous and 5 patients (15.15%) who had more than 4 children.

In their study, Muwonge R et al assessed the effect of socio-demographic and sexual reproductive factors on the prevalence of invasive cervical cancer and CIN diagnosed in seven sites of different sub-Saharan countries between January 2000 and August 2007; a total of 47.361 women screened and investigated for disease confirmation, it was found that 485 women had invasive cancer, 1.069 had CIN1, 517 had CIN2 and 175 had CIN3.It was also found that the risk for cervical cancer was 3 fold higher in women who had at least three pregnancies versus 0 or one pregnancy (95% CI 2.1-4.2). The authors therefore concluded that high parity probably explains the persistently high rates of cervical cancer in sub-Saharan Africa; this is probably due to the exposure of the exocervix and/or the increased levels of oestrogen and progesterone for more prolonged periods during pregnancy in multiparous women.[72] The findings in our study seem to attest to this theory.

Regarding the HIV status of participants in our study, we noted that 16 patients (48.48%) were HIV positive and 17 patients (51.52%) were HIV negative; out of the 16 HIV positive patients, 13 patients (81.25%) were on anti-retroviral therapy and 3 patients (18.75%) were not. In 2017, Harling G et al did a study to re-estimate the national HIV prevalence in SA; 26.710 participants were interviewed and invited for the test; it was found that the prevalence of HIV was 15.1% (95% CI 12.1 – 18.6) in male aged 15 to 49 years and 23.3% (95% CI 21.7-25.8) in female aged 15 to 49 years.[73]Many young women are therefore more at risk of HIV in SA then men. Women infected with HIV are thought to be 3-5 times more likely to develop cervical lesions that can become cancerous; [74] and both the disease progression and the recurrent disease after treatment are correlated with low CD4 cell count.[75] Our study noted that the incidence of cervical cancer was almost similar in both HIV positive and negative group (48.48% vs 51.52% respectively). Because of high prevalence of HIV in women aged 15 to 49 years compared to their male counterpart in SA, and because literature suggests that the risk of cervical cancer is 3 to 5 times higher in HIV women as compared to HIV negative women, one would have expected to find more incidence of cervical cancer in HIV positive women in our study. The reasons for the similarities in both groups are not clear.

A study on HIV infection and survival among women with cervical cancer was done in 2016 in Botswana. A total of 348 women with cervical cancer were enrolled; it was noted that 231 of them (66.4%) were HIV positive and 96 (27.6%) were HIV negative.[76] These findings differ a bit from ours. However we acknowledge that our study was less powered due to the small sample size.

Our study noted that only 3 patients (9.09%) reported active smoking and 30 patients (90.91%) denied cigarette smoking. We did not investigate the issue of passive smoking. These findings are not consistent with the association of cigarette smoking with cervical cancer. In 2005 the International Collaboration of Epidemiological Studies of cervical cancer looked at the association between carcinoma of the cervix and tobacco smoking; data on 13.541 women with carcinoma of the cervix and 23.017 women without carcinoma of the cervix from 23 epidemiological studies were analysed; it was noted that smokers are at an increased risk of squamous cell but not adenocarcinoma of the cervix.[77]

Louie K S et al evaluated the potential impact of passive smoking on cervical cancer for the International Agency for Research on cancer Multi center cervical cancer study group in

2011. A total of 1.919 couples were interviewed. Information on smoking and sexual behaviour was collected. Passive smoking could not be detected as an independent risk factor for invasive cervical carcinoma in the absence of active smoking. The combined effects of exposure to active and passive smoking suggest its potential adverse role in cervical carcinogenesis.[19]

Jiang J et al. did a study to see the effects of active, passive, and combined smoking on cervical cancer mortality in China; smoking habits of 1.865 women (aged 35+) who had died from cervical cancer were analysed; there was 51% excess risk of death from cervical cancer among smokers.[78]

With regards to presenting symptoms at the initial visit, our study noted that 30 patients (90.91%) presented with pelvic pain as initial symptom of the disease. Pelvic pain is a common presentation in advanced disease; therefore most of our patients presented late.

In 2014, a study was conducted in the UK to look at the reasons for delay in help-seeking for breast and cervical cancer symptoms among minority ethnic groups; a total of 54 heathy women from different ethnic group were interviewed; it was found that appraising a symptom as possibly linked to a cancer during a medical consultation was an important factor encouraging help-seeking. Open discussion about cancer among minorities could help raise awareness about the importance early detection and promote help-seeking.[64] In another study, an evaluation of gynaecological symptoms reported by young women to assess the potential of early diagnosis of cervical cancer was done; more than 30.000 women aged 15 to 29 years of age were involved, 1.6% of those women presented with intermenstrual bleeding as early symptom of cervical cancer; 0.5% had post coital bleeding, and 1.3% had vaginal discharge.[79]

Literature suggests that 80% of cervical cancer cases found in the general population are squamous cell carcinoma, 15% are adenocarcinoma and 5% constitute other histological subtypes. This was not the case in our findings. We had 100% of squamous cell carcinoma, confirmed by the histopathological report. A study done in Durban (SA) by Moodley M et al.[80] reported that in the public sector, 80% of patients had squamous cell carcinoma of the cervix. The same study found a slightly high proportion (38.8%) of women with cervical adenocarcinoma in private sector. Another study on cervical cancer in younger patients also

showed that 77% of the study population had squamous cell carcinoma and 25 % had adenocarcinoma. [81] Our findings differ from the general trend probably because this was a small study based in one institution.

CHAPTER 6: LIMITATIONS OF THE STUDY

Since this study was looking at the outcome of patients transferred from FERH to CMJAH, we had to collected data starting from FERH. It was very challenging and difficult to retrieve files at FERH.

There were a considerable number of patients who were lost to follow up after initial treatment at CMJAH. It is not clear whether they died, defaulted treatment, or changed the province.

CHAPTER 7: CONCLUSION

Cervical cancer disease still places a burden in our health care system. We have noted that most of patients in our study presented with late symptoms of the disease and this did not allow surgery as primary mode of treatment; most of patients received chemoradiation, radiation therapy or palliative care.

Delays were noted at each step of care within the health system: from diagnosis (at Far East Rand Hospital) to the time spent at Charlotte Maxeke Johannesburg Academic Hospital waiting for radiation therapy/chemoradiation.

CHAPTER 8: RECOMMANDATIONS

The referring hospital should fast track any cervical biopsy that appears suspicious in order to cut down on the waiting period before transfer.

We are also suggesting collaboration between CMJAH gynaecology oncology department and FERH gynaecology department for skill improvement required at a reginal hospital, with emphasis on diagnosis, clinical staging and appropriate work up of common gynaecological malignancies before transfer to CMJAH.

Record keeping at FERH should be improved to improve on patient care and facilitate future studies.

There is a need for population cancer awareness campaign to prevent late presentation on one hand; and on the other hand there is a need to capacitate the cancer specialized center with human resources and infrastructures to cut down on the long waiting period.

Further studies on the impact of treatment delays on disease progression, and various other aspects that affect survival are needed.

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APPENDIX

M (M) Dr S Kalonji

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M170938

NAME: Dr S Kalonji
(Principal Investigator)
DEPARTMENT: School of Clinical Medicine
Department of Obstetrics and Gynaecology
Chris Hani Baragwanath Academic Hospital

PROJECT TITLE: Outcome of patients with cervical cancer referred for treatment at Charlotte Maxeke Johannesburg Academic Hospital from Far East Rand Hospital

DATE CONSIDERED: 28/09/2017

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Dr L Mbodi

APPROVED BY: Professor PE Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 17/11/2017

This clearance certificate is valid for 3 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 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 be approved, I/we undertake to resubmit to the Committee. I agree to submit a yearly progress report. The data for annual re-certification will be one year after the date of approval (reading whilst the study was initially reviewed in September and will therefore be due in the month of September each year. Unexpected changes to the application must be reported to the clinical area given by the HREC (Medical).

Principal Investigator's Signature Date 12/10/2017

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

GAUTENG PROVINCE
REPUBLIC OF SOUTH AFRICA

FAR EAST RAND HOSPITAL
OFFICE OF THE: CHIEF EXECUTIVE OFFICER

Far East Rand Hospital
Private Bag x 50
SPRINGS
1560

Enquiries: Dr M M Lesia
Telephone: (011)812-4309
Fax: (011)813-1411
Cell: 082 418 6527
E-mail: Nkele.Lesia@gauteng.gov.za

PERMISSION TO CONDUCT RESEARCH

TITLE OF PROJECT:
Outcome of patients with Cervical Cancer Referred for Treatment at CMJAH From Far East Rand Hospital.
UNIVERSITY: University of the Witwatersrand

Principal Investigator: Dr. MS Kalonji

Institution: Far East Rand Hospital

Protocol Ref no: M170939

The CEO/Clinical Manager recommends that the said research be conducted at Far East Rand Hospital. The CEO/Clinical Manager of Far East Rand Hospital is accordingly informed and the study is subject to:-

- Permission having granted by the CEO/ Clinical Manager.
- The hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital.
- The research will not impose additional workload on our staff.
- The CEO/Clinical Manager will be informed of any serious adverse events as soon as they occur.
- Permission is granted for the duration of the Ethics Committee approval as well as Gauteng Department of Health Research Committee approval.
- The researcher will provide hospital management with feedback every six months and at the end of the study.

Approved/~~Not Approved~~
Hospital Acting CEO

Date: 1/11/2017

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Ms. N. Mathi
Office of the Clinical Director
Tell: (011) 488-4812
Email: Nohwen.Mathi@gauteng.gov.za
15 December 2017

GP_201712_013

Dear Dr. S. Kalonji

STUDY TITLE: Outcome of Patients with Cervical Cancer Referred for Treatment at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) from Far East Rand Hospital (FERH)

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

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

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

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

Supported/~~not supported~~

Dr. M.E Mofokeng
Clinical Director
DATE: 19/12/2017

Approved/~~not approved~~

M.G. Boqhabi
Chief Executive Officer
Date: 19/12/2017

APPENDIX

STUDY ALLOCATION NUMBER:

DEMOGRAPHIC DATA

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

CO MORBID DISEASES (If yes, specify below)

Diabetes/Endocrine	Yes		No		Treatment	Unknown	
Cardiovascular	Yes		No		Treatment	Unknown	
Respiratory	Yes		No		Treatment	Unknown	
Cardiac disease	Yes		No		Treatment	Unknown	
HIV	Yes		No		Treatment	Unknown	
Dermatology	Yes		No		Treatment	Unknown	
Infectious	Yes		No		Treatment	Unknown	
Others							

MALIGNANCY

Stage at referral		Stage at MDT		Stage at Therapy initiation			
Previous malignancy	Yes		No		If yes, which one?		
If yes, previous management	Chemo	Radiation	Both	Surgery alone	Surgery & Radiation	None	Unknown

Current histology							Unknown	
Differentiation	Poor		Moderate		Poor		Unknown	
Subtype (if applicable)								

WORKUP FROM ERH (Mark if done)

Cxix	Normal		Abnormal		Not done	
HB (g/dl)		WCC		Urea		
Creatine		V\		CD4		
Ultrasound						

RISK FACTORS

Smoking	Yes		No		Unknown					
Age at coitarche										
Sexual partners		Previous Pap smear		Yes	No	If yes, results				
HIV	Negative		Positive		If yes, Treatment		Yes		No	

PRESENTING SYMPTOMS

Abnormal bleeding	Post menopausal		Post coital		Intermenstrual	
PV discharge	Yes		No		Unknown	
Pains	Yes		No		Unknown	
Urinary symptoms	Yes		No		Unknown	
Bowel symptoms	Yes		No		Unknown	

REFERAL

Date of abnormal		Where was it done		Date referred to FERH		Date arrived at FERH

Pap							
Diagnosis at FERH	Booked OPD	Seen same day	Biopsy	LLETZ	Date of samplin g	Date of follow up results	
Referral for treatment	Date referred to CMIAH		Date arrived		Seen(date)	Booked (date booked for)	
Date seen at DMT		Diagnosis/Stage		Decision			
Decision to Treatment	Duration		Type of treatment planned				

COMPLICATIONS DURING SURGERY

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

COMPLICATIONS POST RADIOTHERAPY

Burns	Yes		No		Unknown	
Cystitis	Yes		No		Unknown	
Urethritis	Yes		No		Unknown	
Proctitis	Yes		No		Unknown	
Vaginal fibrosis	Yes		NO		Unknown	
Other						

Types of Radiations	EBRT	Brachytherapy	Full	Boost	Palliation	
Dose of Radiation						
Fraction						

READMISSION

Reason	Elective		Emergency		Other	
Period readmitted (days)						

Palliative Care Service Given	Psychological	Social Worker	Hospital	Unknown