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Treatment outcomes for patients receiving radiation therapy for stage iiib cervical cancer with lower third vaginal involvement in the department of radiation oncology, Charlotte Maxeke Johannesburg academic hospital

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TREATMENT OUTCOMES FOR PATIENTS RECEIVING RADIATION THERAPY FOR STAGE IIIB CERVICAL CANCER WITH LOWER THIRD VAGINAL INVOLVEMENT IN THE DEPARTMENT OF RADIATION ONCOLOGY, CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

"A DISSERTATION SUBMITTED TO THE FACULTY OF HEALTH SCIENCES IN THE PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE IN RADIATION ONCOLOGY AT THE UNIVERSITY OF WITWATERSRAND, JOHANNESBURG"

BY

DR DANIEL CLARENCE SCHNEEBERGER

BSC(Hons), MBChB, FC RAD ONC (SA)

SUPERVISORS

DR FAIZA MAHOMED: MBChB, FCFP(SA), FC RAD ONC (SA), MMED (RAD ONC)

DR UZMA MAJEED: MBBS, FC RAD ONC(SA), MRAD(T)(WITS), CCST(UK)

PROF PAUL RUFF: MBBCH, MMED (INT MED), FCP(SA)

DECLARATION

I, Daniel Clarence Schneeberger declare that this dissertation is my own work. It is submitted for the degree of Master of Medicine in Radiation Oncology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

Signed…D. Schneeberger……

28th Day of February 2024

DEDICATION

To my partner and my family.

ABSTRACT

Background and Objective

Cervical cancer remains a major healthcare problem in sub–Saharan Africa. Morbidity and mortality rates are disproportionately high compared to high income countries (HICs). This, in part, is due to late clinical presentation and diagnosis. Only two previous studies have evaluated treatment outcomes for patients with FIGO 2018 stage IIIB cervical cancer with lower third vaginal involvement. Both of these studies evaluated Asian populations (Thailand, China). All patients in these studies were treated with standard fractionated external beam radiation therapy. This single institution, retrospective study aims to report on local control and survival rates in an African group of patients with stage IIIB cervical cancer with lower third vaginal involvement, where a large portion were treated with hypofractionated external beam radiation therapy.

Methods

A retrospective review of treatment outcomes was conducted of patients with stage IIIB cervical cancer with lower third vaginal involvement who completed radiation therapy with curative intent at the Department of Radiation Oncology, Charlotte Maxeke Johannesburg Academic Hospital in Johannesburg, South Africa and whose first presentation was between 01 January 2016 and 31 December 2019. Local control was evaluated based on clinical examination at 6 months post completion of radiation therapy and survival data was recorded for patients at 2 years post completion of radiotherapy. Association analysis was performed between treatment outcomes and radiation fractionation and brachytherapy applicator choice.

Results

Of the 179 patients available, 22 received standard fractionated external beam radiotherapy (50Gy/25#) and 157 patients received hypofractionated external beam radiotherapy with 42.5Gy in 17 fractions. 118 patients were available at 6 months for analysis of local response of which 77% (n=91) had a clinical complete response and 23% (n=27) had treatment failure. At 2 years post completion of radiotherapy, 99 patients (55%) were lost to follow up. Of the patients with documented 2-year survival data, 65% (n=52) of patients were alive and 35% (n=28) of patients were dead. Median overall survival for the whole group was 9 months. External beam fractionation schedule had no association with local control (p=0.391) or overall survival (p=0.59). Choice of brachytherapy applicator also had no effect on local control (p=0.395) or overall survival (p=0.41).

Conclusion

The analysis was compromised by poor patient follow up, but local control rates and overall survival rates were comparable to the other two published studies on this group of patients, despite the use of a hypofractionated external beam protocol in this study. The use of a hypofractionated versus standard fractionated external beam radiation schedule had no correlation with either local control rates or survival. This should prompt prospective studies evaluating the efficacy of hypofractionated radiation therapy in the treatment of locally advanced cervical cancer. This study has managed to demonstrate meaningful local control and survival rates for patients with this advanced stage of disease.

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LIST OF ABBREVIATIONS

AC: Adenocarcinoma

ASC: Adenosquamous carcinoma

BT: Brachytherapy

CDC: Centre for Disease Control

DNA: Deoxyribonucleic acid

CMJAH: Charlotte Maxeke Johannesburg Academic Hospital

COVID-19: Coronavirus disease of 2019

EBRT: External Beam Radiation Therapy

ESA: Erythropoiesis Stimulating Agent

EQD2: Equivalent dose in 2Gy per fraction

FIGO: The International Federation of Gynaecology and Obstetrics

Hb: Haemoglobin

HICs: High Income Countries

HIV: Human Immunodeficiency Virus

HPV: Human Papilloma Virus

IGABT: Image Guided Adaptive Brachytherapy

LC: Local Control

LMICs: Low to middle income countries

LTVI: Lower third vaginal involvement

NCCN: National Cancer Comprehensive Network

OS: Overall survival

PFS: Progression free survival

RT: Radiation Therapy

SCC: Squamous Cell Carcinoma

SEER: Surveillance, Epidemiology, and End Results

UNICEF: United Nations International Children’s Emergency Fund

WHO: World Health Organizati

1 Background and Literature Review

1.1 Epidemiology

Cervical cancer remains a global health concern as it is the most common gynaecological cancer and is the fourth leading cause of cancer deaths in women globally (1). Although it has become a largely preventable and treatable disease, it is a disease that disproportionately affects women from low to middle countries (LMICs) largely in part due to inequalities in access to vaccination and screening. GLOBOCAN 2020 statistics report that worldwide, the age standardized cervical cancer incidence and mortality are 13.3 and 7.3 per 100 000 respectively. By comparison, Southern Africa has a cervical cancer incidence and mortality of about 36.4 and 20.6 per 100,000 women respectively (1). According to the South African National Cancer Report for 2020 cervical cancer was the second most common cancer amongst women overall but was the most common cancer diagnosed in black women (2). There are many reasons for this disparity. In LMICs, where fewer resources are available, access to medical care may be limited, women may lack knowledge of human papillomavirus (HPV), cervical cancer, and the value of regular screening. In addition, language and cultural barriers may limit women's access to screening and treatment. There is also a large disparity between high income countries and low-middle income countries in terms of human immunodeficiency virus (HIV) incidence (3,4). As Sub-Saharan Africa has a high burden of both HIV and HPV, the prevalence of cervical cancer is higher than that seen in more developed parts of the world. Not only is the incidence higher but so is the mortality to incidence ratio. The reason for this is that women in Sub Saharan Africa tend to present with more advanced disease, usually only once disease has become symptomatic. Population risk

factors related to presentation and incidence include HIV prevalence, high parity, no formal education, no condom use with non-regular partners, no formal education, young age at sexual debut and a high percentage rural population, all of which are well-documented problems in this region (4). In addition, women in Sub-Saharan Africa may be prone to presentation and diagnosis at advanced stage as Tekalign and Teshome (Nigeria) identified low education and residence in African or Asian countries as factors associated with late presentation in their meta-analysis (5).

1.2 Cervical cancer pathogenesis and risk factors

The central aetiological factor associated with the development of cervical cancer is infection with high-risk strains of the HPV virus especially serotypes 16 and 18. Sexual practices associated with the acquisition of HPV are seen as major risk factors for cervical cancer. These include early sexual debut, multiple sexual partners, and exposure to other sexually transmitted diseases (6). Other risk factors associated with the development of cervical cancer include immuno-suppression, especially HIV, smoking, and social factors such as poverty, limited education and limited access to screening and vaccination programs (7,8).

1.2.1 HPV and cervical cancer

HPVs are a large family of small non-enveloped DNA viruses consisting of over 150 serotypes. They are classified into high and low-risk types based on their ability to cause oncogenic transformation. Within the South African context, the most prevalent strains of oncogenic HPV (listed in order of prevalence) are 16, 18, 35, 45, 33 and 52, with strains 16 and 18 being responsible for most squamous cell cancers of the cervix (6).

The 6.8-8kb viral genome consists of 3 regions. The early region encodes molecules that are necessary for viral replication and regulation of the cell cycle. These are numbered E1, E2, E4, E5, E6, E7. The late area consists of the L1 and L2 genes that are necessary for capsid formation and the long control area contains regulatory elements to control viral replication and transcription (9). This DNA structure is wrapped around nucleosomes and organised into a covalent circle and wrapped in a 60nm capsid (6)

Within the life cycle of HPV, the virus invades in the basal layer of cervical epithelial cells which are the only mitotically active cells in the epithelium. Exposure to the basal layer occurs as a result of microtrauma caused during sexual intercourse, especially in adolescents. Cell entry then occurs after the virus first binds to the basement membrane and then to the cell surface through interactions with the viral L1 protein and heparin sulphate proteoglycans (10). Upon cell entry, complex mechanisms mediated by E1 and E2 result in viral replication by subversion of normal cellular machinery. E6 and E7 are the proteins that are responsible for oncologic

transformation. They become overexpressed because of deletions that occur in E2 at the time of integration into the host genome which does not occur in all HPV-positive cells but rather occurs in some hosts as a result of incompletely elucidated mechanisms involving various epigenetic changes and DNA methylation processes (9). The products of the E6 and E7 oncogenes promote viral replication through disruption of regulators of the cell cycle due to stimulation of the ubiquitin proteosome pathway and destruction of proteins which promote entry into the S phase of the cell cycle. At the same time, E6 damages p53 and prevents apoptosis. This ultimately results in genomic instability and mediates oncogenesis (9).

This progression to carcinogenesis is not part of the normal HPV life cycle but rather represents a non-productive finale that is associated with only a few HPV types and occurs after years to decades of persistent infection. The vast majority of infections however are benign and self-limiting (6).

1.2.2 Cervical cancer and the immunocompromised patient

Persistent infection by high-risk HPV increases the risk of progression to CIN (cervical intraepithelial neoplasia) and invasive cervical cancer. The majority of immunocompetent individuals are able to remain asymptomatic, though whether infection is truly cleared or suppressed to subclinical levels remains controversial (6). There is some evidence to suggest that infection with HPV triggers a primarily cell-mediated response and it has been demonstrated that T cell (T-helper and cytotoxic T cell) involvement is necessary for regression of pre-invasive lesions (11).

Research on the association between immune deficiency and cervical cancer has focused mainly on HIV but patients with other causes for their compromised immune response such as those with primary immune deficiency syndromes, or those on immunosuppressive therapy following solid organ transplant or for auto-immune conditions also have a higher incidence of cervical cancer than in the immunocompetent population (6,11,12).

HIV and HPV infections share common socio-behavioural risk factors such as early age at onset of sexual intercourse, multiple sexual partners, and smoking, thus making co-infection relatively common. HPV prevalence amongst HIV positive women varies according to factors such as age, region, social and sexual behaviours but studies have demonstrated prevalence rates of 89-98% (78-85% for high-risk types) amongst women living in Gauteng, South Africa (13). South Africa has one of the highest incidences of HIV infection in the world, with over 6 million people living with the virus and up to 1000 new infections occurring each day among individuals aged 15 to 45 (14). Observational data has suggested that existing or new HPV infection increases the risk of transmission of HIV through disruption of mucosal integrity and recruitment of immune cells despite the lack of clinically observable inflammation (15). HPV infection not only causes increased transmission of HIV, but HIV induced immunosuppression in turn causes inadequate clearance of HPV, resulting in persistent infection, and increased risk of progression to pre-invasive disease and then cervical cancer (16). Due to this association between

advanced immunodeficiency and CIN / cervical cancer, the United States Centre for Disease Control and Prevention added cervical cancer to its list of acquired immune deficiency syndrome (AIDS) defining illnesses. Bowers et al (2006) have suggested that this designation as an AIDS defining illness be removed. This is because, although the association between HIV and cervical cancer has been demonstrated, there has been a failure to clearly demonstrate an association between the risk of cervical cancer and either CD4 count or progression to AIDS. In addition, since the advent and widespread distribution of HAART, the incidence of cervical cancer has not shown a decline like other AIDS-defining malignancies such as Kaposi's Sarcoma or large B cell non-Hodgkin's lymphoma (17).

1.2.3 Smoking and cervical cancer

The association between smoking and squamous cell carcinoma of the cervix has been known since 2003 when a publication by Plummer et al. demonstrated in his pooled analysis of 8 other studies that this increased risk of cancer persists after controlling for factors such as HPV and other potential factors that affect the progression of infection with HPV to cancer (18). This correlation between increased risk of cancer and smoking exists only for squamous cell carcinomas. Adenocarcinoma of the cervix does not appear to have the same associations (18,19).

The association between smoking and HPV infection is complicated with data being conflicting. One study pooling data from 11 countries worldwide suggested that current smoking was associated with statistically significant

increased risk of HPV infection with risk increasing with number of cigarettes smoked per day, after allowing for other sexual covariates (20). A later study concluded that there is no evidence to suggest an increased risk of HPV infection with smoking but did suggest that smoking increased the risk of high-grade cervical intraepithelial neoplasia (CIN) after controlling for HPV status (21).

1.3 Staging of cervical cancer

Cervical cancer was the first malignancy to utilize a staging system, which dates back to 1928 when cervical cancer for the first time was grouped into different stages according to the extent of tumour growth (22). Since then, staging for cervical cancer has undergone several adaptations. Two major staging systems are currently in use, these being those issued by the International Federation of Gynaecology and Oncology (FIGO) as well as the staging recommendations provided by the American Joint Committee on Cancer (AJCC). The major difference between the two staging systems prior to the 2018 FIGO version is that the TNM staging system, developed by the AJCC, included information from surgical staging of patients. The FIGO committee on the other hand acknowledged that surgical staging was not universally available, particularly for patients from low-resource countries and that staging was based primarily on clinical and limited radiological studies. Even when surgical findings were available FIGO recommended that these findings be reported but should not be included in the stage determination of patients (22). FIGO 2009 allowed only limited radiological / clinical investigations to stage patients, with investigations being limited to chest

radiography, intravenous urography, barium enema, cystoscopy, proctoscopy and sigmoidoscopy. The 2018 update however allows for the use of cross sectional and metabolic imaging and does not strictly mandate the use of any given modality but rather allows the clinician options to assist in accurate staging based on available resources (23).

The differences between the 2009 and 2018 stage designations are presented in table 1 below but the major differences are in the subdivision of stage IA and B and the introduction of stage IIIC to the newest update. The currently accepted staging can be summarised as follows: stage I disease is limited to the cervix while stage II represents disease that has extended to involve the parametria or upper two thirds of the vagina. Stage III extends to the lower third of the vagina (IIIA) or parametrial involvement that extends to the pelvic side wall or where there is hydronephrosis or a non-functioning kidney related to the primary tumour (IIIB) or any sized tumour with involved pelvic or para-aortic lymph nodes (IIIC). Stage IV disease is disease that involves the bladder or rectum (IVA) or disease that has metastasized to any other organ (24).

Table 1 Comparison of FIGO staging systems of 2009 and 2018 (23).

Stage	2009 FIGO staging	2018 (current) FIGO update
I	The carcinoma is strictly confined to the cervix uteri (extension to the corpus should be disregarded)	The carcinoma is strictly confined to the cervix uteri (extension to the corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5mm and no wider than 7mm	No width requirement in update
IA1	Measured stromal invasion ≤3mm in depth and ≤7mm width	Measured stromal invasion ≤3mm in depth
IA2	Measured stromal invasion >3mm and <5mm in depth and ≤7mm width	Measured stromal invasion >3mm and <5mm in depth.
IB	Invasive carcinoma with measured deepest invasion >5mm, lesion limited to the cervix uteri, independent of lateral extension.	Invasive carcinoma with measured deepest invasion >5mm, lesion limited to the cervix uteri, independent of lateral extension
IB1	≤4cm	Invasive carcinoma >5mm depth stromal invasion and ≤2cm in greatest dimension
IB2	>4cm	Invasive carcinoma >2cm and ≤4cm in greatest dimension
IB3	-	Invasive carcinoma >4cm in greatest dimension
II	The carcinoma invades beyond the	No change

	uterus but has not extended onto the lower third of the vagina or to the pelvic side wall	
IIA	Involvement limited to the upper two-thirds of the vagina without parametrial involvement. IIA1 invasive carcinoma ≤ 4cm in greatest dimension. IIA2 invasive carcinoma >4cm in greatest dimension.	No change
IIB	With parametrial involvement but not up to the pelvic side wall.	No change
III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic side wall and/or causes hydronephrosis or non-functioning kidney.	The carcinoma involves the lower third of the vagina and/or extends to the pelvic side wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or paraaortic lymph nodes.
IIIA	Carcinoma involves the lower third of the vagina, with no extension to the pelvic side wall.	No Change
IIIB	Extension to the pelvic side wall and/or hydronephrosis or non-functioning kidney (unless known to be due to another cause)	No Change

IIIC	-	Involvement of pelvic and/or paraaortic lymph nodes, irrespective of tumour size and extent (with r and p notation for radiographically or pathologically detected).
IIIC1	-	Pelvic lymph node metastases only
IIIC2	-	Paraaortic lymph node metastases
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proved) the mucosa of the bladder or rectum. A bullous oedema, as such, does not permit a case to be allotted to stage IV.	No Change
IVA	Spread of the growth to adjacent organs.	No Change
IVB	Spread to distant organs	No Change

1.4 Prognostic factors

Prognosis is affected by stage as well as other patient-related, tumour-related and treatment-related factors.

1.4.1 Patient related prognostic factors

1.4.1.1 Age

The effect of age as a prognostic factor in cervical cancer has been studied by various authors, resulting in conflicting outcomes. Some authors have commented that age under 35 is a poor prognostic factor (25). Disputing this effect of young age on prognosis was a population-based study using the SEER database. These authors reviewed outcomes for younger patients stratified by clinical stage, histological type, race, and grade and found that age under 35 years had no effect on cancer-specific mortality (26). On the other hand, some authors have suggested that age over 70 is a poor prognostic factor. Quinn et al. used the Surveillance, Epidemiology and End Results (SEER) database, to analyse outcomes from 46 350 patients and found that advancing age was a negative prognostic factor when stratified by stage, race, histology and treatment. This was particularly true for women aged above 70 years old but women older than 50 years also experienced an increased risk of death (27). Mancebo et al. (2021)(Spain), in their retrospective analysis of 124 patients found that patients older than 65 years were more likely to be diagnosed at a more advanced stage and were less likely to receive treatment with curative intent, but that age over 65 did not predict for worse disease-

free survival or overall survival if treated with curative intent (28). Another single centre retrospective study from China found that although overall survival was lower amongst older women, age was not predictive for either disease free survival for cancer specific survival. This same study also showed that elderly women had significantly more grade 3 and above chronic toxicities which could be contributory to the lower overall survival (29). African data provided by the meta-regression by Drokow et al (2022) which analysed data from 16,122 women from various African countries showed that age had no impact on survival times when corrected for other factors (30). Overall, the effect of age on prognosis is confounded by several related issues including the risk of competing death from comorbid conditions, method of treatment and treatment side effects and thus, the prognostic effect of age has not been conclusively demonstrated.

1.4.1.2 Race

Disparities in incidence, treatment outcomes and mortality have been demonstrated by several authors with black and other non-white race groups presenting with more advanced stage disease and having worse treatment outcomes when compared to white women (30–32). These differences have been attributed to differences in access to screening programs, later stage at presentation in black women and differences in access to treatment or treatment received(33). It appears, however, that once these variables have been corrected, that cancer survival is comparable between different race groups (34,35).

1.4.1.3 Haemoglobin levels

Cervical cancer tumours have been shown in experimental and clinical studies to be characterised by a highly hypoxic metabolism. This is postulated to lead to radiation and chemo resistance. Squamous cell carcinomas have maximum oxygenation when haemoglobin (Hb) levels are around 12g/dL and become hypoxic when levels drop below 11g/dL (36). The effect of anaemia on the prognosis of cervical cancer patients is controversial. Barkati et al. (2013) showed that low pre-treatment Hb levels correlated with increased likelihood of having a more invasive phenotype of cancer with an increased chance of having positive nodes, and that on multivariate analysis Hb nadir was an independent prognostic factor for overall survival but pre-treatment Hb was not (37). These findings were similar to that of Thomas (2001) who also noted that on-treatment Hb negatively affected prognosis but not pre-treatment levels(38) Other authors have demonstrated that either baseline anaemia or mid therapy anaemia is a negative prognostic factor for decreased local control and overall survival (39,40). In dispute of this, Bishop et al. (2014) questioned whether anaemia was the cause of the poor prognosis or whether the strong correlation between anaemia and poor local control following radiotherapy was due to confounding risk factors such as tumour size. On his retrospective review of 2454 patients, it was found that low Hb levels before or during RT correlated with decreased freedom from distant metastasis, freedom from central recurrence and disease specific survival. On multivariate analysis however, there was only a correlation

between Hb less than 10 and freedom from distant metastasis and disease specific survival but not with freedom from central recurrence when other confounding variables were corrected for (41).

Whether or not correcting for anaemia with blood transfusion counteracts the negative prognostic influence of low Hb is also controversial. Both Bishop and Thomas noted in their aforementioned papers that correcting Hb levels with transfusion did not improve treatment outcomes (38,41). Grogan et al. (2009) sought to define the role of blood transfusions in 605 patients treated with radiotherapy for cervical cancer and found that maintaining Hb levels above 12g/dL through blood transfusions overcame the negative prognostic influence of anaemia (42). Kapp et al. (2002) also showed a therapeutic benefit in terms of improved pelvic control with the use of transfused pack cells (43). Despite this lack of consensus in the literature, an international Delphi consensus study of recommendations by 39 expert gynaecological radiation oncologists published in 2001, showed 89% consensus that a Hb target of 9g/dL should be maintained via blood transfusions for patients undergoing external beam radiation therapy or brachytherapy (43).

The erythropoiesis stimulating agents (ESAs) such as epoietin alpha and darbepoietin alpha can increase serum Hb levels and their use is recommended by organizations such as the European Society of Medical Oncology (ESMO) and the National Comprehensive Cancer

Network® (NCCN®) for treating certain cancer patients with anemia (45,46) . NCCN® notably recommends the use of ESAs for patients with cancer and chronic kidney disease or for some patients undergoing anticancer therapy with palliative intent. ESAs are also recommended for patients who refuse blood transfusions. For patients receiving curative intent treatment, blood transfusions are preferred to the use of ESAs due to a possible detrimental effect on survival (46). Multiple meta-analyses have reported decreased survival with the use of ESA's. though data is conflicting on whether this is true for all subgroups of patients (47–50). In a subgroup analysis of the Cochrane review by Tonia et al (2012), survival was decreased only when baseline Hb was above 12g/dL (49). These meta-analyses included a wide range of different cancer types and data regarding the use of ESAs specifically in cervical cancer is limited. Gupta et al (2009) investigated the role of epoietin alpha in anaemic patients with cervical cancer and found that the use of epoietin reduced the need for blood transfusion and improved patient reported energy levels and quality of life scores with no deleterious effect on overall survival (51). Conversely, Temkin et al (2005) showed in a retrospective review that the use of recombinant erythropoietin to treat anaemia in patients receiving concurrent chemoradiation therapy resulted in decreased disease-free survival and overall survival (52). Thomas et al (2008) attempted to investigate the use of erythropoietin in maintaining Hb levels in cervical cancer patients receiving concurrent chemoradiation with cisplatin in a phase III clinical trial setting. Due to insufficient

patient accrual no conclusions were able to be made about the effect on progression free survival or overall survival (38). The use of recombinant erythropoietin for treating anaemia in patients receiving curative intent radiation therapy for patients with cervical cancer therefore remains controversial and its use must be individualized based on the clinical scenario.

1.4.1.4 HIV Status

The effect of HIV seropositivity on treatment outcomes in patients with cervical cancer has not been evaluated by randomized prospective trials (53). In a retrospective study of 1362 Thai patients with cervical cancer, survival was not affected by HIV status (54). A similar retrospective study of Zambian women with stage I or II cervical cancer showed that while women with HIV were more likely to receive lower total doses of external beam radiotherapy than their HIV negative counterparts (median doses of 46Gy versus 50Gy respectively), HIV positivity did not lead to increased tumour progression (55). Another retrospective study conducted on women in Botswana enrolled a total of 348 women and found that HIV infection resulted in poorer 3-year survival rates when compared to HIV negative patients even when treated as per protocol and matched per stage. This adverse effect on prognosis was greatest for women with earlier stage of cancer, those treated with curative intent and those with lower CD4 count (56). In the South African context, Simonds et al. (2011) showed that HIV positive women were more likely to present at a more advanced stage and

were less likely to complete radiation or receive all the necessary cycles of concurrent chemotherapy which would negatively impact on their treatment outcomes (57).

1.4.2 Tumour related prognostic factors

1.4.2.1 Tumour size

Increasing tumour size has been shown to correlate with poorer prognosis by several authors and hence tumour size has been incorporated into the AJCC 8th and 9th edition as well as the FIGO staging systems (24,58).

1.4.2.2 Lower third vaginal involvement

Involvement of lower the lower third of the vagina has been shown in two separate retrospective studies to result in inferior local control and survival in patients with stage IIIB cervical cancer (59,60). It has been postulated that these inferior outcomes are due to tumour escape via inguinal drainage of lymphatics in the lower third of the vagina and insufficient coverage of tumour at time of brachytherapy (60).

1.4.2.3 Histology type

In a retrospective study looking at the effect of chemoradiation on the outcomes of different histological types, Rose et al. (2014) reviewed the Gynecologic Oncology Group (GOG) chemoradiation trials and found that when patients with adenocarcinoma (AC) were treated with radiation alone, they experienced inferior overall survival compared to

their squamous cell carcinoma (SCC) counterparts. When treated with chemoradiation however, survival was similar between the two groups (61).

In an updated review of the SEER database including more patients treated with concurrent chemoradiation rather than radiation therapy alone, Meng et. al (2021) attempted to determine the effects of histology on prognosis of 36310 cervical cancer patients. These results showed no difference in outcomes between SCC histology and AC or adenosquamous carcinoma (ASC) in stage I and IV cervical cancer patients but for patients with stage II or stage III disease, AC or ASC histology predicted for inferior cancer specific and overall survival (62).

1.4.3 Treatment Related Prognostic Factors

1.4.3.1 Treatment Duration

For patients treated with radiation therapy alone, extended treatment duration appears to have a negative impact on local control and survival as evidenced by several retrospective studies (63–65). Petereit et al. (1995) (USA) found that pelvic control decreased by 0.7% per day and 5-year survival decreased by 0.6% per day for each additional day of treatment beyond 55 days (55). Perez et al. (1995)(USA) similarly found decreased pelvic control (0.85% per day) with overall treatment times extended beyond 9 weeks or if brachytherapy was initiated greater than 4.5 weeks from the start of EBRT (64). These results combined have led to recommendations in major guidelines

such as FIGO or NCCN that treatment should be completed with 8 weeks of initiation (66,67). The proposed explanation for these inferior local control and survival outcomes is accelerated tumour repopulation during radiation therapy following which occurs following a delay in radiation delivery after its initiation (68,69).

These publications showing inferior oncological outcomes were published prior to the widespread concurrent use of chemotherapy. Tergas et al. (2016)(USA) published a review of outcomes of 7209 women from the National Cancer Database, treated with radiation and chemotherapy and found no difference in outcomes between those who completed treatment within or after 8 weeks but rather that inferior survival is only seen when treatment is extended beyond 10-12 weeks (69). It therefore remains uncertain whether chemotherapy partially negates the poor prognostic effects of delays in delivery of radiation therapy.

1.4.3.2 Chemotherapy

When given with radiation therapy, cisplatin-based chemotherapy has the potential to improve outcomes by eradicating micro metastases and acting as a radiation sensitizer (70). In 1999 the National Cancer Institute issued a recommendation that concomitant cisplatin based chemoradiation be given rather than radiotherapy alone in women with cervical cancer. This was based on evidence from 5 major trials which showed improved locoregional control, progression free survival and

overall survival with the addition of chemotherapy to radiation (71–75). In a meta-analysis of 13 trials that compar1ed chemoradiation versus radiation therapy alone, it was noted that chemotherapy (platinum and non-platinum based) resulted in a 6% absolute benefit in 5-year survival regardless of dose or schedule of chemotherapy. This meta-analysis also suggested that the benefit of chemotherapy was mostly seen for earlier stages of cancer and that the benefit declined with stage progression, but this information was only hypothesis generating and hasn't subsequently been confirmed in any prospective trials (76).

1.5 Treatment of Cervical Cancer

1.5.1 Prevention Strategies

1.5.1.1 Primary Prevention Strategies

Virtually all cervical cancers are a result of the persistent infection of highly oncologic HPV strains and strain 16 and 18 are responsible for around 70% of cases of cervical cancers (77). Elimination of these persistent strains thus has the potential to prevent invasive cervical cancer (78). Current vaccines available for the prevention of HPV mediated cervical cancers include the bivalent vaccine Cervarix® (GlaxoSmithKline, United Kingdom), which is protective against strains 16 and 18, Gardasil® (Merck Sharp & Dohme, United Kingdom) which in addition to these 2 strains also protects against strains 6 and 11 and finally there is the nonavalent Gardasil-9® which also protects against infection by strains 31, 33, 45, 52 and 58. The large phase III clinical trials conducted to establish the efficacy of the vaccine were designed

to demonstrate effectiveness in preventing pre-invasive conditions of the cervix such as CIN 2-3 lesions and adenocarcinoma in situ or persistent infection with an oncogenic strain (77,79,80). These end points were chosen because of the long lag time between HPV infection, progression to dysplasia and finally malignancy (78). Effectiveness in preventing invasive cancer has also been demonstrated in published reports using real-world data (78,81). HPV vaccination has also demonstrated benefit in the therapeutic management of CIN2 and 3 lesions. In a meta-analysis by Khalil et al (2023), 414 out of 713 vaccinated women with CIN 2 or 3 regressed to normal or CIN1 lesion, demonstrating an overall proportion of regression of 0.54 (95% CI 0.39 to 0.69). This is in comparison to an overall proportion regression of 0.27 (95% CI 0.20 to 0.34) for the unvaccinated group. No additional safety issues were identified in this study. The authors concluded that HPV vaccination in the therapeutic management of CIN2/3 lesions demonstrated modest efficacy and that additional issues related to implementation should be further evaluated (82).

The CDC recommends that all pre-teen boys and girls should begin vaccination from age 9 and for any persons aged 13-26 who have not previously been vaccinated. Although the recommended age is up until 26, those up to the age of 45 may also be eligible for the vaccine but this does not prevent progression to malignancy in individuals with an already acquired persistent infection. Two doses, 5 months apart are

recommended for 9-13 age group and 3 doses are recommended for older individuals and those who are HIV positive (83). Single dose vaccination may also be effective in preventing invasive cervical cancer. Basu et al (2021) reported results of a multicentric cohort study designed to investigate the difference in efficacy between a two-dose versus three dose schedule of Gardasil-4®. Following completion of recruitment, patients were allocated to one of four cohorts based on the number and timing of vaccine doses received. At 10 years post vaccination, adjusted vaccine effectiveness for persistent HPV 16/18 infection was 95.4% (85.0-99,9) for the one dose cohort which was comparable to the two- and three-dose cohorts (93.1% and 93.3% respectively) (84). The KEN SHE (NCT03675256) study is a randomised controlled trial investigating one dose HPV vaccination between Gardasil-9® and Cervarix® in adolescent and young women in Kenya. At 18 months post vaccination both vaccines were effective in preventing the incidence of persistent HPV 16/18 infections with a vaccine effectiveness of 97.5% (81.6-99.7%). The Gardasil-9® had a vaccine effectiveness of 88.9% (65.8-96.1) in preventing the incidence of HPV 16/ 18/ 31 33/ 45 /52 /58 infections. Similarly, the Dose Reduction Immunobridging & Safety Study (DoRIS) demonstrated that single dose vaccination with either Cervarix® or Gardasil-9® resulted in non-inferior HPV16 seroconversion compared to two or three doses but was unable to demonstrate non-inferiority for single dose vaccination for protection against HPV18 compared to the two- or three-dose schedules. Results from the Human Papillomavirus One

and Two-Dose Population Effectiveness (HOPE) (The University of Witwatersrand, HREC #181005) study, are awaited to provide insight into the impact of single dose vaccination in South African adolescent girls (85).

The HPV vaccine has been available in South Africa since 2008 for privately funded patients but in 2014, the South African government-initiated a school-based vaccination program with the bivalent HPV vaccine (Cervarix). At the start of the vaccination program in 2014, 85% of eligible girls in public schools received the first dose but 6 months later only 65% received the second dose. Since then, coverage rates have been encouraging but have been compromised by COVID 19. The WHO UNICEF cumulative data collected by 2020 shows that 65% of girls aged between 9 and 14 have not completed the full vaccination schedule, while coverage in some districts may be as low as 40% (86,87). Factors relating to logistics and the COVID-19 pandemic have been blamed for this low coverage (87).

1.5.1.2 Secondary Prevention Strategies

Screening for cervical cancer aims to identify and treat women with pre-invasive conditions of the cervix and therefore prevent the progression to invasive malignancy or to identify women with early disease in an effort to increase treatment options and reduce morbidity and mortality (88).

Screening for cervical cancer can be accomplished with visual inspection with acetic acid (VIA), cytology (Pap or liquid based), and HPV DNA testing (89). Since cervical cancer is caused by persistent infection with HPV, testing for high-risk strains of HPV is the most sensitive method of screening but its cost and lack of willingness to change prevents widespread adoption by LMICs, although the WHO recommends HPV testing wherever possible, it also accepts screening with VIA and Pap smear (89,90). In a meta-analysis by Mustafa et al. (2015), HPV testing had a pooled sensitivity of 95% (95% CI: 84%-98%) and a pooled specificity of 84% (95% CI: 72%-91%) when compared to VIA, which in comparison had a pooled sensitivity of 69% (95% CI: 54%-81%) and a pooled specificity of 87% (85% CI: 79%-92%) for identifying high grade intra epithelial lesions. When studies comparing VIA to cytology were analysed, VIA had a sensitivity and specificity of 77% (95% CI: 65-85%) and 82% (95% CI: 67-91%) respectively whereas Pap smear had a sensitivity of 84% (95% CI: 76-90%) and a specificity of 88% (95% CI: 79%-93%)(91)The majority of evidence for VIA based population screening have come from studies conducted in India.

In 2021 the WHO published recommendations on the screening and treating of cervical precancer lesions as part of their global effort to eliminate cervical cancer. In this article, the WHO recommended HPV DNA testing over VIA or cytology where available. They stated that samples may be collected either by a healthcare worker or may be self-

collected from the patient (92). Self-collected HPV testing has been demonstrated to result in improved participation in screening programs and is efficacious in terms of detecting high grade cervical lesions (93). Meta-analysis data has shown sensitivity of detecting CIN3+ lesions of 75-86% and specificity of 79.5% (94). The WHO guidelines recommended that screening begins at the age of 30 for women without HIV and from the age of 25 in women living with HIV regardless of when they were diagnosed with HIV. After the age of 50, women with and without HIV could stop screening, provided they had two consecutive negative results. Although the guideline recommended that women under the age of 50 should be prioritized, a caveat was that where resources were available, women aged up to the age of 65 should also be screened if they had never been screened previously. When HPV DNA testing is used, the WHO recommended screening every 5-10 years except for women living with HIV where screening was recommended every 3-5 years. In places where HPV testing is not available, the WHO recommended VIA or cytology testing every 3 years for all women, regardless of their HIV status. For screening programs that use HPV DNA testing, the WHO recommended either a “screen and treat approach” or a “screen, triage and treat approach” for women in the general population. For women living with HIV, the WHO recommended only the “screen, triage and treat approach”. The Who explained that in the “screen and treat approach”, women who test positive for a high-risk HPV strain should be treated immediately with ablative therapies or excisional treatment without confirmatory testing

or histopathological diagnosis. In the “screen, triage and treat” approach, the WHO recommended that a positive test should prompt a triage test which could include high-risk HPV DNA partial genotyping, VIA, cytology or colposcopy with or without histological confirmation, and the decision to treat should be based on the result of the triage test (92).

The South African National Department of Health Policy endorses screening with cytology and timing of initiation and interval screening is determined by risk. For general/low risk groups, defined as asymptomatic HIV negative women, three pap smears are offered per lifetime, starting at age 30 and spaced 10 years apart. High risk patients are defined as those with immunosuppression (of any aetiology). These patients should start screening from the time of diagnosis of HIV and be screened every 3 years provided the previous test was negative, or annually if any abnormality was detected on the previous screening test (8).

Unfortunately, cervical cancer screening uptake in sub-Saharan Africa has remained poor at around 12% owing to factors such as lack of knowledge of screening, low levels of education, lack of knowledge of HIV status, and lack of awareness of screening locations (95).

1.5.2 Surgery

Surgery with curative intent is the preferred approach for patients with up to and including stage IIA disease. Options include colposcopy with loop electrosurgical excision procedure (LEEP), conization, trachelectomy and hysterectomy (simple or radical) depending on the clinical context, stage and desire for future fertility (24,66,70).

Landoni et al. (1997)(Italy) compared radiation therapy (without concurrent chemotherapy) versus surgery for patients with stage IA to IIA disease and found equal 5-year overall survival and disease-free survival for both modalities. Adjuvant radiation therapy was administered to patients with close or positive margins, positive lymph nodes or tumours larger than 4cm. Toxicity was found to be worst for the surgical group though this was largely driven by the patients who received the adjuvant radiation therapy which represented 64% of the surgical group (96). For this reason, surgery is generally reserved for patients that are unlikely to require adjuvant radiation, those being small (<4cm) and confined to the cervix so that dual modality therapy is avoided along with the increased toxicity. For tumours clinically staged as IB3 and IIA2 or larger, definitive management with chemoradiation is preferred based on meta-analysis data showing superiority of chemoradiation over radiation therapy (24,66,76). No phase III clinical trials have compared surgery to chemoradiation in the definitive setting (24).

Surgery following neoadjuvant chemotherapy for locally advanced cervical cancer is listed as a treatment option by FIGO in their 2018 guidelines for settings that do not have routine access to radiation therapy (24). Benedetti Panici et al. (2002) (Italy) compared definitive radiation therapy versus neoadjuvant chemotherapy followed by surgery in patients with stage I to III squamous cell carcinoma of the cervix. Progression free survival and overall survival were both superior in the neoadjuvant chemotherapy arm for stage I and II disease but not in patients with stage III disease (83). Patients in this study did not receive concurrent chemotherapy with radiation which would be considered standard of care today. In a phase III trial investigating the role of neoadjuvant chemotherapy followed by radical hysterectomy versus definitive chemoradiation for patients with stage Ib2-II cervical cancer, the EORTC-5594 trial found no significant difference in the 5-year overall survival between the two groups though subgroup analysis showed a trend towards worse survival for patients with stage II disease. In the group that received chemotherapy followed by surgery, 48% required additional radiation while 8% of patients randomised to the chemoradiation arm required additional surgery (84). It therefore remains that chemoradiation therapy is the treatment of choice for patients with locally advanced cervical cancer and neoadjuvant chemotherapy followed by surgery should be reserved for instances where radiation services are not available.

1.5.3 Radiation Therapy

Radiation therapy is used in the adjuvant setting based on intermediate or high-risk features noted at time of surgery. Such intermediate factors are now known as the Sedlis criteria and are based on the results of the GOG92 trial which showed adjuvant pelvic directed EBRT post hysterectomy improved local control in patients if 2 of the following were present on the pathological specimen; >1/3 stromal invasion, LVSI or tumour diameter greater than 4cm (97). High risk features warrant adjuvant concurrent chemoradiation and these risk factors are positive surgical margins, positive parametrial invasion or positive lymph nodes and are based on the outcomes of the GOG 109 trial which showed improved PFS and OS with the addition of concurrent chemoradiation for patients with these factors (98).

For patients with tumours that have significant extra-cervical extension, or for tumours that are larger than 4cm, upfront treatment with chemoradiation is the treatment of choice owing to results of the Landoni trial, GOG92 and GOG 109 trials that showed equivalence of surgery and radiation therapy for early disease but increased toxicity when radiation therapy is added for adverse pathological features (96–98).

Modern radiation therapy for the definitive management of cervical cancer uses a combination of EBRT and BT to deliver an accumulative EQD2 of 80-90Gy to at least 90% of the high-risk clinical target volume (66,99). In usual situations a dose of 45-50Gy is delivered via EBRT and the

remainder by BT in an effort to spare the normal surrounding tissues including the bladder and rectum and thus prevent treatment related toxicity (99).

1.5.3.1 External Beam Radiation Therapy

External beam radiation therapy involves the delivery of radiation to tissues within the body from a source that is locate at a distance from the body. While doses have remained relatively constant over time, the radiation technique used for delivery of the dose has evolved over time in the treatment of cervical cancer.

Doses to the tumour in the range of 80-90Gy result in improved tumour control and survival. This is usually achieved by 45-50Gy being delivered by EBRT in 1.8-2Gy fractions and the remainder by BT and these are in the prescribed recommendations by all major gynaecology oncology groups (24,66,100,101).

The use of hypofractionated EBRT for cervical cancer is under active investigation but is not yet regarded as standard of care. Treating with doses larger that 2Gy per fraction, but to an equivalent BED, is an attractive option for treating cancer patients, especially in LMIC where shorter treatment times are more convenient to the patient, more cost effective to the health care system and allow larger numbers of patients to be treated in a shorter amount of time (102). One retrospective study from the University of Witwatersrand, South Africa, used an EBRT

dose of 40Gy in 16 fractions without concurrent chemotherapy for patients with stage IIIB cervical cancer. A complete response rate of 70% and DFS at 20 months of 59% were reported with no late genitourinary toxicities and one patient out of 104 experiencing grade 3 gastrointestinal toxicity (103). Prospective phase II trials are underway to evaluate the role of hypofractionated radiotherapy with or without concurrent chemotherapy (102).

Radiation technique has evolved considerably from 2D planning with Xray films to 3D conformal radiation therapy. The current standard of care is intensity modulated radiation therapy owing to its superior ability to conform to target volumes and spare normal organ toxicity (104). Typical radiation fields have been adapted based on tumour location with wider fields being necessary to cover inguinal nodal basins in the case of lower third vaginal involvement (70).

1.5.3.2 Brachytherapy

Brachytherapy allows for delivery of dose to a target with a steep gradient of dose fall-off. Different dose schedules for high dose rate BT have been recommended by the American Brachytherapy Society (105). 18Gy in 2 fractions is not one of these recommended regimens though there is some retrospective evidence and one prospective trial conducted at this academic centre that have shown good local control rates with acceptable toxicity with this dose prescription (106,107).

Like EBRT, BT has undergone an evolution from 2D, point based planning to 3D based volume planning with CT or MRI. The RetroEMBRACE trial was a retrospective, multi-institutional study that showed Image Guided Adaptive Brachytherapy (IGABT) results in excellent tumour control with acceptable toxicity. It also showed a trend towards improved OS compared to older studies using 2D techniques (108). This trial was followed up by the EMBRACE-I trial which was prospective in nature and confirmed excellent 5-year actuarial local control in the range of 92% for all stages of locally advanced cervical cancer with low toxicity rates (109).

Multiple high dose rate intracavitary BT applicators are commercially available. The most commonly used applicators are the tandem and ovoid (TO), the tandem and ring (TR) and the tandem and cylinder (TC). The TR and TO systems are often used interchangeably and deliver a similar dose distribution though the TO delivers a more lateral dose distribution to cover involved parametrial tissue, however dose distribution is not low enough to cover the entire vagina. The TC system is used for patients with narrow vaginas or for patients with lower vaginal involvement where dose can be extended inferiorly along the length of the vagina. For patients with extensive parametrial involvement or those with lower third vaginal involvement, dose distribution can also be optimised using interstitial techniques (110).

1.5.4 Chemotherapy

Chemotherapy given concurrently with radiation has proven to increase overall survival. The benefit of increased survival is seen mostly for patients with earlier disease where data has shown a 10% absolute benefit in survival. For patients with stage III and IVA disease, the survival benefit is only 3% (111).

In the meta-analysis by Vale et al. (2008) the benefit of concurrent chemotherapy was greatest with concurrent cisplatin-based chemotherapy, but benefit was seen also for non-platinum containing regimens though these are not widely used any longer (76). The most widely used regimen is 40mg/m^2 weekly cisplatin owing to its reported improved haematological toxicity over triweekly administration in two separate meta-analyses (112,113). An updated meta-analysis however has suggested that triweekly cisplatin resulted in improved local control rates when compared with weekly administration (114). The population served by CMJAH, Gauteng, may not tolerate standard dose cisplatin with concurrent radiation therapy as Nyongesa et al. (2006) demonstrated in a phase I clinical trial, that the maximum tolerated weekly dose of cisplatin was 25mg/m^2 when given concurrently with pelvic radiation in HIV negative patients (115).

For patients who have persistent or recurrent disease that is not amenable to local therapies, or those who have metastatic disease, chemotherapy is recommended to slow disease progression and improve survival. Platinum

based doublet chemotherapy resulted in improved response rates and survival compared to single agent platinum in a 2012 meta-analysis (116). The GOG 204 trial was designed to compare the efficacy of different platinum combinations. Patients were randomised to receive cisplatin with either paclitaxel, vinorelbine, topotecan or gemcitabine. No difference was found in response rate or risk of death among any of the groups. Combination with gemcitabine resulted in less risk of febrile neutropenia, while paclitaxel results in less risk of serious thrombocytopenia (117). Carboplatin may also be a reasonable alternative to cisplatin based on outcomes of the Japanese Clinical Oncology Group 0505 trial which showed no statistical difference in objective response rate or overall survival when either platinum was combined with paclitaxel. Side effects differed amongst the two arms, with cisplatin use resulting in increased rates of nausea and vomiting, serious neutropenia and renal insufficiency while carboplatin use resulted in increased rates of thrombocytopenia and sensory neuropathy (118). In the first line metastatic setting, the addition of bevacizumab to cisplatin and paclitaxel-based chemotherapy was evaluated by Krishnansu et al (2014). The addition of bevacizumab resulted in increased relative probability of response (1.45; 95%CI, 1.08 to 1.68; P=0.08) and median overall survival was increased from 13.3 months to 16.8 months (HR 0.7; 95% CI, 0.62 to 0.95; P=0.07). Toxicity was increased in the bevacizumab arm in terms of increased rates of hypertension, gastrointestinal or genitourinary fistulas and thromboembolic events (119). Patients receiving therapy in the first line recurrent / metastatic setting may also be considered for immune checkpoint

inhibition with pembrolizumab with or without bevacizumab, provided the tumour has a programmed death ligand 1 (PD-L1) expression combined positive score (CPS) of greater than or equal to one. The KEYNOTE-826 trial was a randomised phase III clinical trial that evaluated the addition of pembrolizumab versus placebo to standard first line therapy which was stated as platinum-based chemotherapy with the addition of bevacizumab at the investigator's discretion. Overall survival at 24 months was 53% in the pembrolizumab group and 41.7% in the placebo group (HR for death, 0.64; 95%CI, 0.50 to 0.81; P <0.001) (120).

1.6 Treatment Outcomes and Prognosis

The prognosis of patients withs stage IIIB cervical cancer with lower third vaginal involvement has only ever been evaluated in 2 retrospective studies. Fang et al. (2021) reported 2- and 5-year overall survival rates of 68.9% and 38.8% respectively in Chinese patients treated with standard fractionated radiation therapy with concurrent chemotherapy (60). Katanyoo (2017) had previously reported complete response rates of 81.9% following conventional chemoradiation with 2- and 5-year overall survival of 43.1% and 28.9% respectively in their study conducted in Thailand (59).

Both studies reported significantly worse survival for patients with stage IIIB disease with lower third vaginal involvement compared to those without lower third vaginal involvement.

1.7 Rationale for study

Charlotte Maxeke Johannesburg Academic Hospital is a tertiary/quaternary level hospital managed by the Gauteng department of health, that offers state funded radiation and medical oncology services. Although based in urban Johannesburg, the majority of the patients treated represent the “typical” sub-Saharan pattern of high level of poverty, low levels of overall education, high levels of co-infection with HIV and late presentations of cervical cancer. As such, a significant number of patients present with advanced disease. Among patients presenting with stage III disease, there are several patients presenting to this oncology clinic with FIGO stage IIIB disease with lower third vaginal involvement.

Only two papers have been identified that attempted to describe local control rates and survival outcomes for patients treated with curative intent radiation therapy in stage IIIB patients with lower third vaginal involvement. Both of these studies used standard fractionation and concurrent chemotherapy. One study was conducted on a Chinese population and the other was conducted on a Thai population. To date, there have been no papers published on treatment outcomes for patients with stage IIIB cervical cancer with lower third vaginal involvement in a South African population and no study has looked at the effect of hypofractionated external beam radiation therapy in this specific group. This study aims to be the first to report on treatment outcomes for this group of cervical cancer patients treated in Southern Africa, of which a substantial portion were treated with hypofractionated radiation therapy.

CMJAH is an academic centre, and all brachytherapy cases are performed by radiation oncology registrars using 2D imaging. While the vast majority of patients with cervical cancer extending to the lower third of the vagina should be treated with a tandem and cylinder, many were treated with either the Joss-Flynn applicator or the ring and tandem based on selection of brachytherapy applicator by a training radiation oncologist. This situation has allowed a unique opportunity to analyse local control outcomes for patients with lower third vaginal extension based on different brachytherapy applicators used.

1.8 Objectives of Study

The primary study objective:

- To analyse local control rates of cervical cancer, FIGO stage IIIB with lower third vaginal involvement after definitive radiation therapy.

The secondary study objectives:

- To analyse the survival of this group of patients at 2 years post completion of treatment.
- To determine the effect of radiation fractionation used and brachytherapy applicators used on treatment outcome.

2 Methodology

2.1 Study location

The Division of Radiation Oncology at the Charlotte Maxeke Johannesburg Academic Hospital. This is a tertiary / quaternary level hospital for Johannesburg in the southern part of the Gauteng Province, South Africa. It is a teaching hospital affiliated with The University of the Witwatersrand Faculty of Health Sciences.

2.2 Study subjects

Patients with FIGO stage IIIB cervical cancer with lower third vaginal involvement, treated with radiation therapy with curative intent as per departmental protocol between 2016 and 2019.

2.3 Study design

This was a retrospective, single centre mixed methods study. The total study period was 6 years. Patients were treated from 01 January 2016 to 31 December 2019 and 2 years follow up period was given for survival data up until 31 December 2021.

2.4 Sample size

Of the only two published studies looking at patients with stage IIIB cervical cancer with lower third vaginal involvement, one study had 72 patients who met these criteria and the other had 74 (59,60). In order to obtain a similar sample size with adequate follow up period, assuming 50% of patients were lost to follow up, 4 years of records were analysed. No patients after 2019

were included as there would have been insufficient follow up time for 2-year survival data. Between 2016 and 2019, 2030 patients were treated for cervical cancer in the department. Based on literature stating an 11% incidence at presentation of patients with lower third vaginal involvement 223 patients would have been available for analysis (121).

2.5 Inclusion criteria

1. All women treated with FIGO Stage IIIB Cervical Cancer with lower third vaginal involvement treated with radiation therapy between 01 January 2016 and 31 December 2019.
2. Patients above the age of 18 were included.
3. Patients with any histological subtype were included. This included patients with squamous cell, adenocarcinoma, adenosquamous, neuroendocrine and undifferentiated carcinomas.
4. HIV positive and negative patients were included.
5. Patients treated with hypofractionated or standard fractionated EBRT were included.
6. Patients receiving standard fractionated EBRT were allowed concurrent chemotherapy at the prescriber's discretion.

2.6 Exclusion Criteria

1. Patients who did not meet the FIGO 2018 criteria for stage IIIB with lower third vaginal involvement.
2. Patients who were treated with palliative doses of radiation (
3. Patients who did not complete the prescribed course of EBRT or BT

4. Patients being treated for recurrent disease after treatment for previously documented cervical cancer.
5. Patients with metastatic disease

2.7 Study Materials

Hospital department records were reviewed retrospectively for patients treated with radiation therapy. Records analysed include:

- Patient files
- Laboratory records
- Death notifications obtained from the Department of Home Affairs.

2.8 Study procedures

2.8.1 Obtaining patient records

Patients treated for cervical cancer in the department were identified through the MOSAIQ ® record and verify software system used in the department. Patients who were treated with palliative prescriptions were eliminated. The remaining files were physically obtained from the department filing office and were reviewed to determine if patients met inclusion criteria.

2.8.2 Ascertainment /authentication of records

To avoid missing patient files and records, the lead investigator of this study liaised with the records officers. For patients who were lost to follow-up, survival data was obtained using identification numbers provided from patient records and referencing these on the Lexis Windeed Website

(search.windeed.co.za) which provides survival data based on death notification information updated by the National Department of Home Affairs.

2.8.3 Radiation therapy

All patients were treated according to departmental protocol. Patients were treated with 2D based radiation. A fluoroscopic simulator was used, and patients were simulated supine, arms on chest with a knee and ankle rest. Radiation therapy portals were based on bony landmarks. The superior limit of the field was placed at the L4/L5 intervertebral space. The inferior limit of the field was set 2cm inferior to the vaginal introitus. The lateral borders of the field were extended to be in line with anterior superior iliac spine so as to cover the entire inguinal basin and soft tissue shielding over the superior portion of the iliac blades was used to allow for sparing of normal tissue. Patients were treated with EBRT at a dose of 50Gy in 25 fractions or 42.5Gy in 17 fractions at the discretion of the prescribing physician. Parallel opposed AP-PA beams were used, and dose was prescribed to the mid-plane.

Table2: Comparison of EBRT dose schedules used in terms of biological effective dose (BED) and equivalent dose per 2Gy fraction (EQD2)

	BED10	BED3	EQD2
42.5Gy in 2.5Gy per fraction	53.13Gy	77.92Gy	46.75
50Gy in 2Gy per fraction	60Gy	83Gy	50Gy

Brachytherapy was prescribed at 18Gy in 2 fractions and the prescription point was adjusted based on the brachytherapy applicator. For Joss-Flynn applicators, ovoid and tandem (OT) or ring and tandem (RT), dose was prescribed to point A. When cylinder and tandem was used, the dose was prescribed to 0.5cm from the cylinder surface.

2.8.4 Chemotherapy

Concurrent chemotherapy was not required as per departmental protocol over concerns of increased toxicity when combined with hypofractionated radiation therapy. Patients who received standard fractionated EBRT were permitted to have concurrent cisplatin. As per departmental protocol, cisplatin was given at a dose of 75mg/m^2 via intravenous infusion every 21 days concurrently with radiation therapy.

2.9 Ethics and Permission.

Ethical clearance was obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical) with certificate number M220761.

Permission from the Head of Department of Radiation Oncology as well as the CEO of the CMJAH were obtained before starting the study, as per university and hospital requirements.

2.9.1 Study record confidentiality

Patient information was recorded with respect to confidentiality. No identifying data was removed from patient files and all care was taken to ensure that only the principal investigator had access to the raw patient data through creation of a password protected Microsoft Excel data flow sheet. The data shall be used for the sole purpose of writing this dissertation and for any scientific publications associated with it.

2.10 Statistical analysis

Descriptive statistics were used to describe study data. Frequencies and proportions were used to describe categorical variables. The Pearson's Chi-square test was used to test for associations in bivariate analysis. Kaplan Meier curves were used to describe overall survival, time to treatment failure and metastasis free survival in the study. For incomplete data, patients were censored based on the last date of follow up and patients were considered at-risk for the event analysed at this time (122).

A logistic regression model was used to determine factors associated with lack of disease control 6 months post treatment with radiation in the study sample. A log rank test was used to compare survival between different external beam schedules. Covariates were included *a priori* in the adjusted analyses. Results were considered statistically significant if the 'p' value was less than 0.05 based on a two tailed test. Statistical analyses were performed in STATA 15.

2.11 Study variables

The following data were reported for all cases reviewed:

- Demographic data including age and self-reported race
- Tumour histological type
- Pre-treatment/ Baseline haemoglobin
- HIV status.
- For HIV positive patients, CD4 count was recorded.
- Baseline estimated glomerular filtration rate
- Qualifying criteria for stage IIIB: whether pelvic side wall involvement was present or if patients had unilateral or bilateral hydronephrosis.
- Number of cycles concurrent cisplatin given
- EBRT dose prescribed (50Gy/25# or 42.5Gy/17#)
- Brachytherapy applicator used
- Duration of follow up
- Local control assessment as based on physical exam at 6 months post completion date of treatment
- Survival at 2 years post completion date of radiation therapy
- Metastatic status and sites of metastases

2.12 Record review during follow up

Patients were followed up according to the departmental protocol where they were assessed at 6 weeks post treatment and then again 3 to 4 monthly for the first 2 years post treatment. During follow-up, history was taken, and a physical examination was done, including a bimanual pelvic and rectal exam. Routine Papanicolaou test was not required as per departmental protocol.

Biopsy was used to confirm the presence of disease if clinical examination revealed persistent pelvic disease after 6 months of treatment or if progressive disease was evident on examination as per departmental protocol. Additional investigations such as chest X-ray or CT scan were performed only if directed by findings on history or physical examination to evaluate for metastatic disease. Biopsy confirmation of metastatic disease was not required if imaging was suggestive.

Survival data was determined based on information available from the patient file or from death notification records at the Department of Home Affairs for patients who had identification numbers supplied in the patient file. If patients had laboratory results recorded on the NHLS following treatment, they were recorded as being alive at this date. In the event of loss to follow up and where survival information was not available, patients were censored based on date of last follow up visit. It was not possible to contact patients telephonically due to ethics limitations based on original protocol design.

2.13 Study collection instruments

All primary data extracted from raw patient records were entered into a Windows Excel based data flow sheet. Data was cleaned and verified and all patient identifying data was removed prior to data being transcribed to STATA,

2.14 Study limitations

This study was retrospective in design. Unfortunately, not all the data was adequately recorded in the patient files and information is missing. Follow up of patients was poor with large dropout rates occurring early into the follow up period.

3 Results

3.1 Baseline characteristics of stage IIIB cervical patients

3.1.1 Age at diagnosis

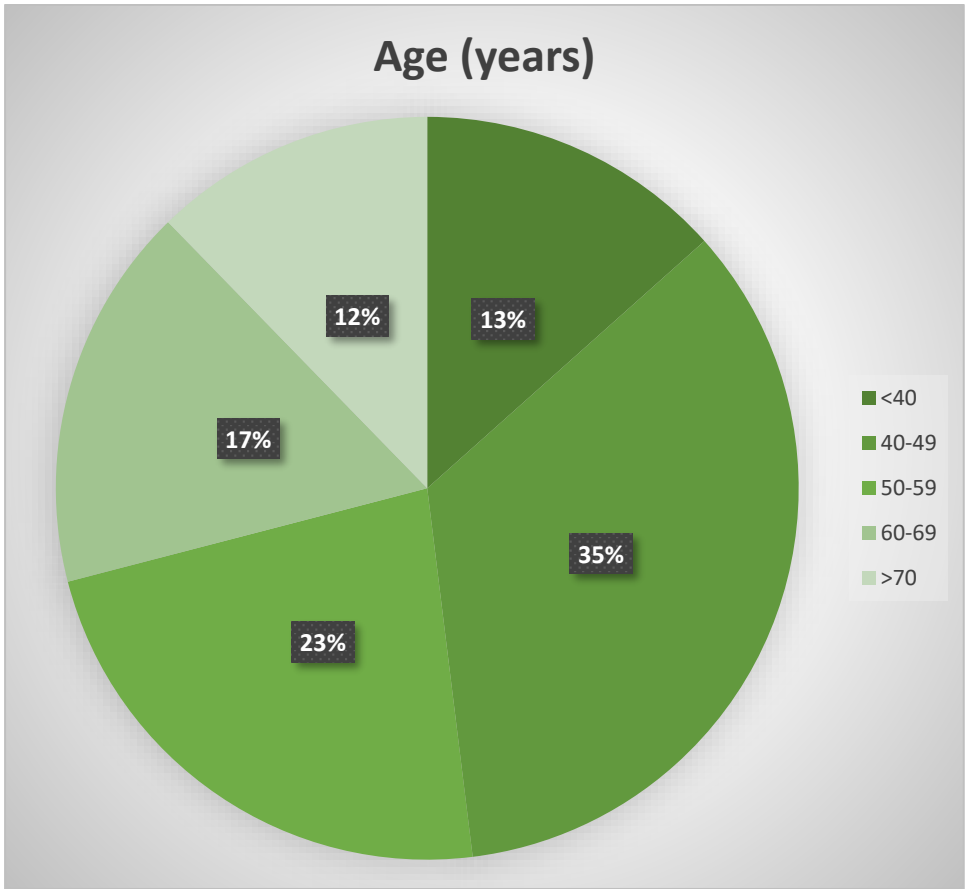


Figure 1: Breakdown of age of study participants

The mean age of patients in this study was 52 years old (range 30 to 86).

3.1.2 Self-Reported Race

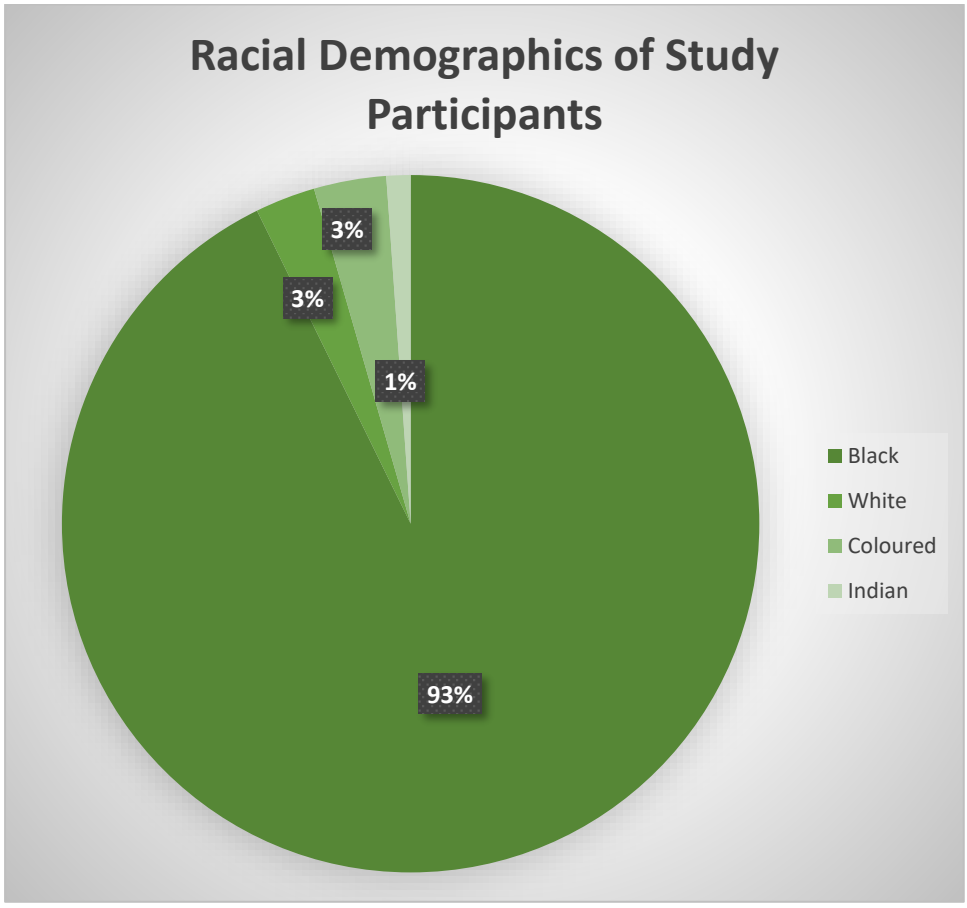


Figure 2: Breakdown of race group among patients

3.1.3 Histological subtype

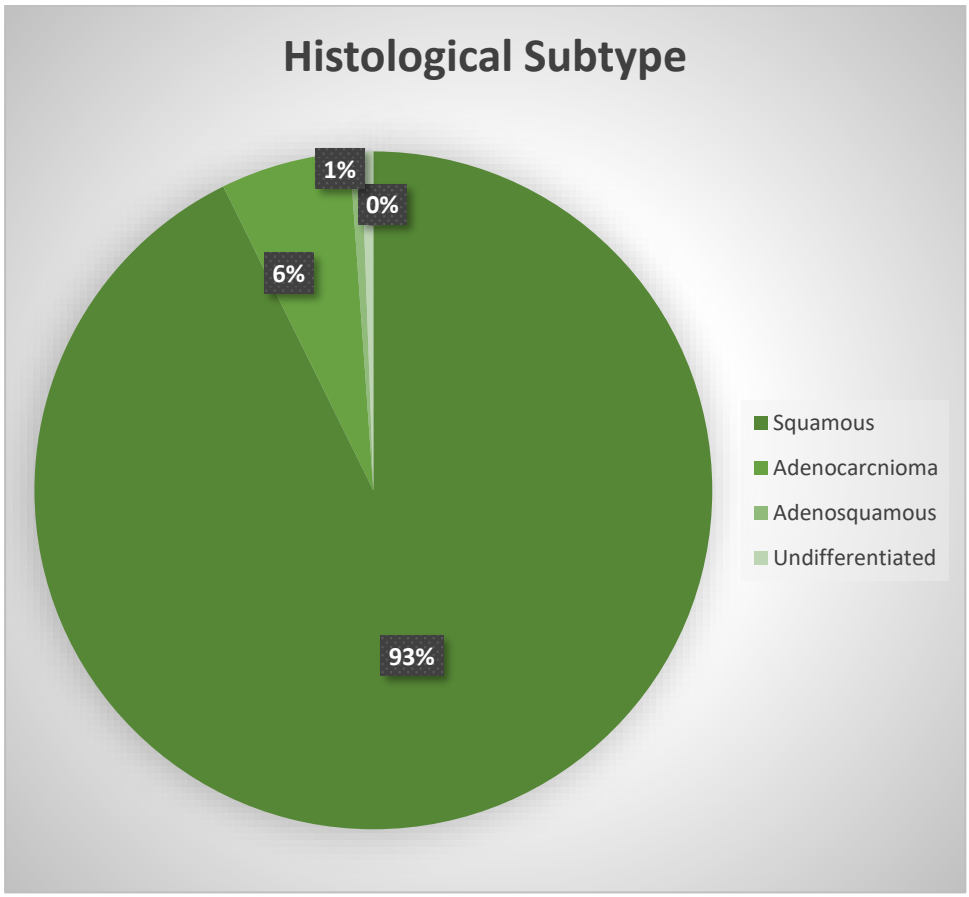


Figure 3: Breakdown of histological subtype among study participants

3.1.4 HIV status

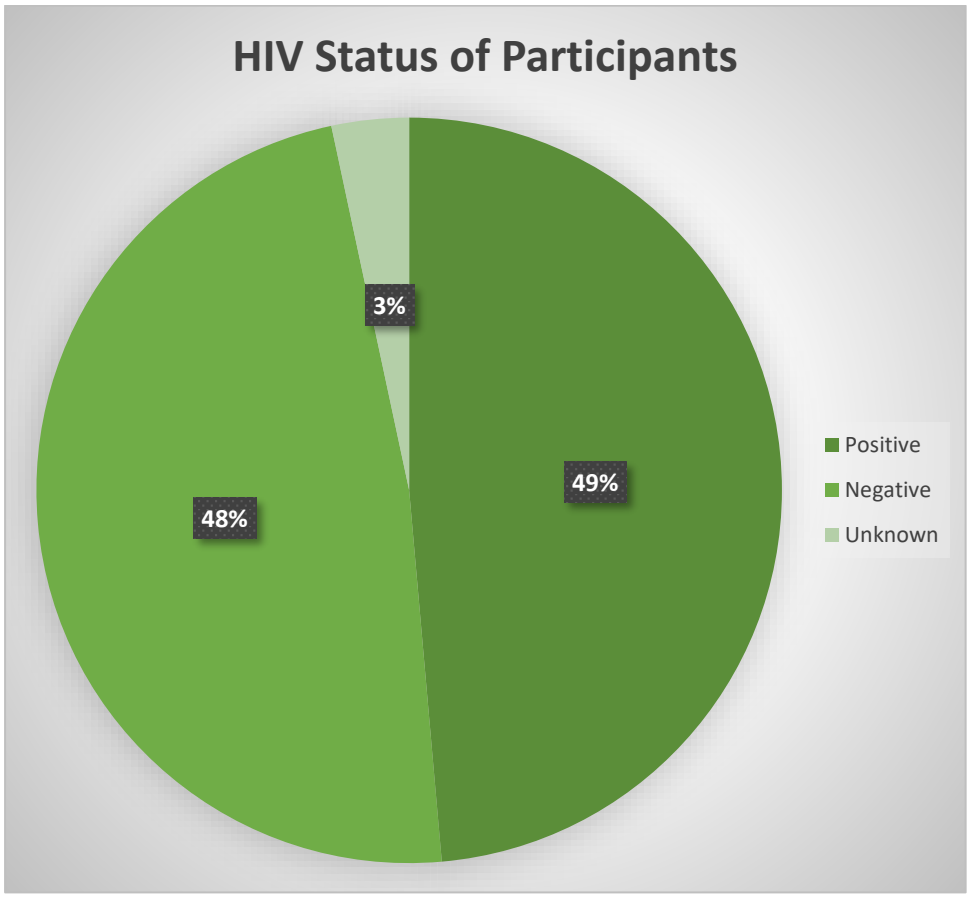


Figure 4: Breakdown of HIV status among study participants

3.1.5 CD4 Count

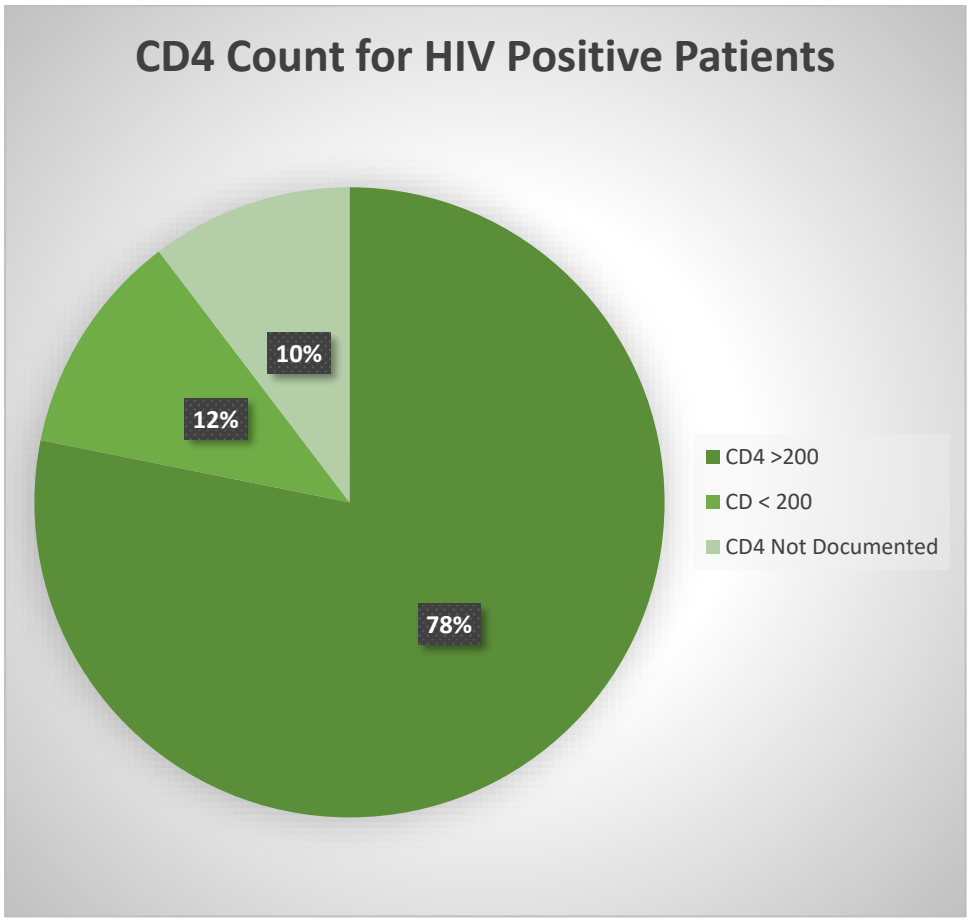


Figure 5: Breakdown of CD4 count in patients who were HIV positive

3.1.6 Baseline eGFR

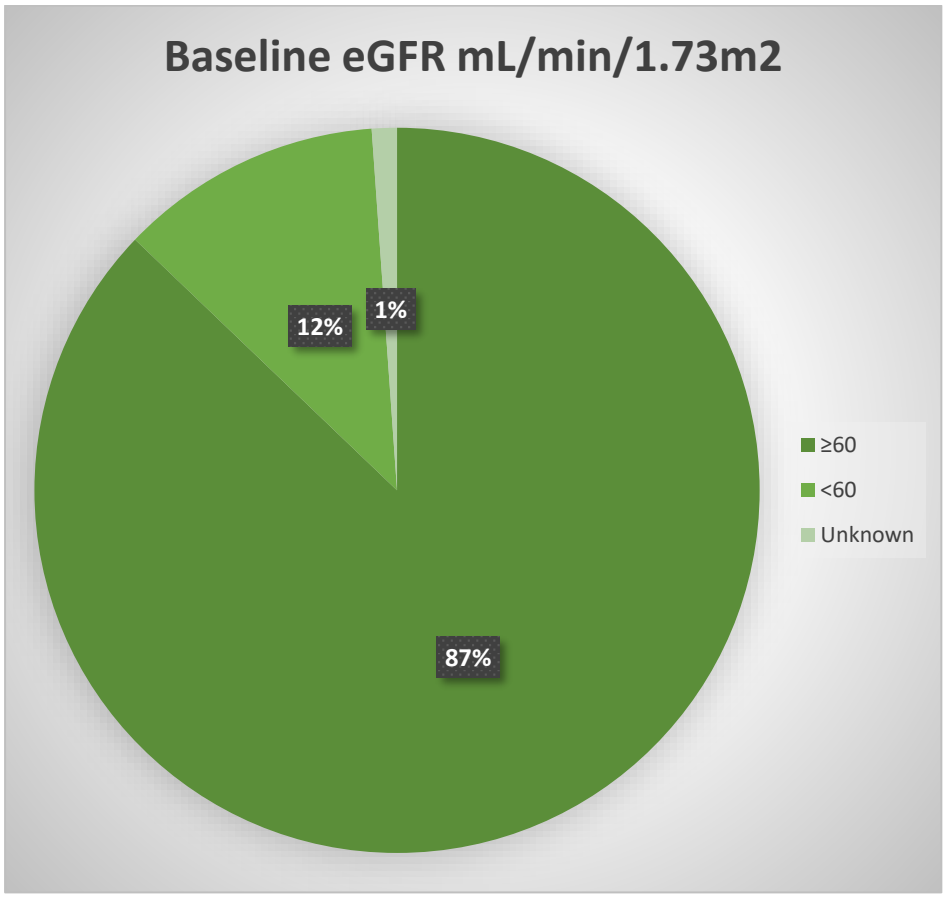


Figure 6: Baseline renal function of study participants expressed as eGFR

3.1.7 Baseline Hb

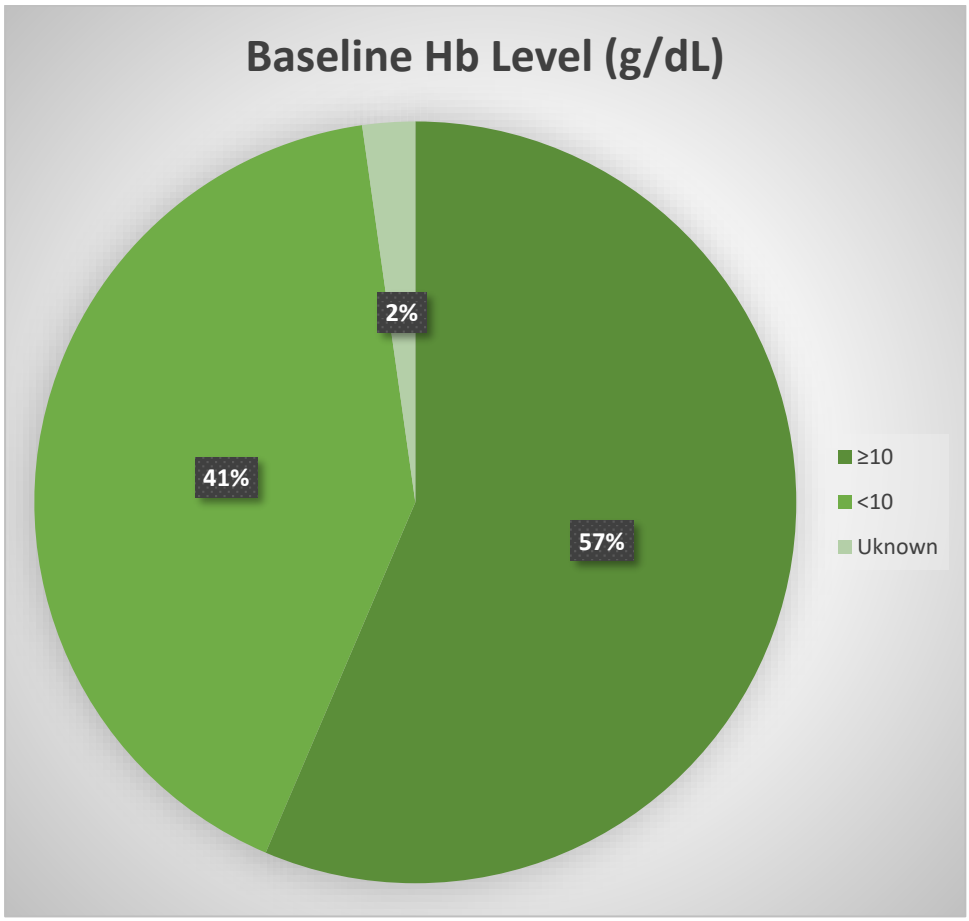


Figure 7: Baseline Haemoglobin levels of study participants

3.1.8 Pelvic side wall involvement

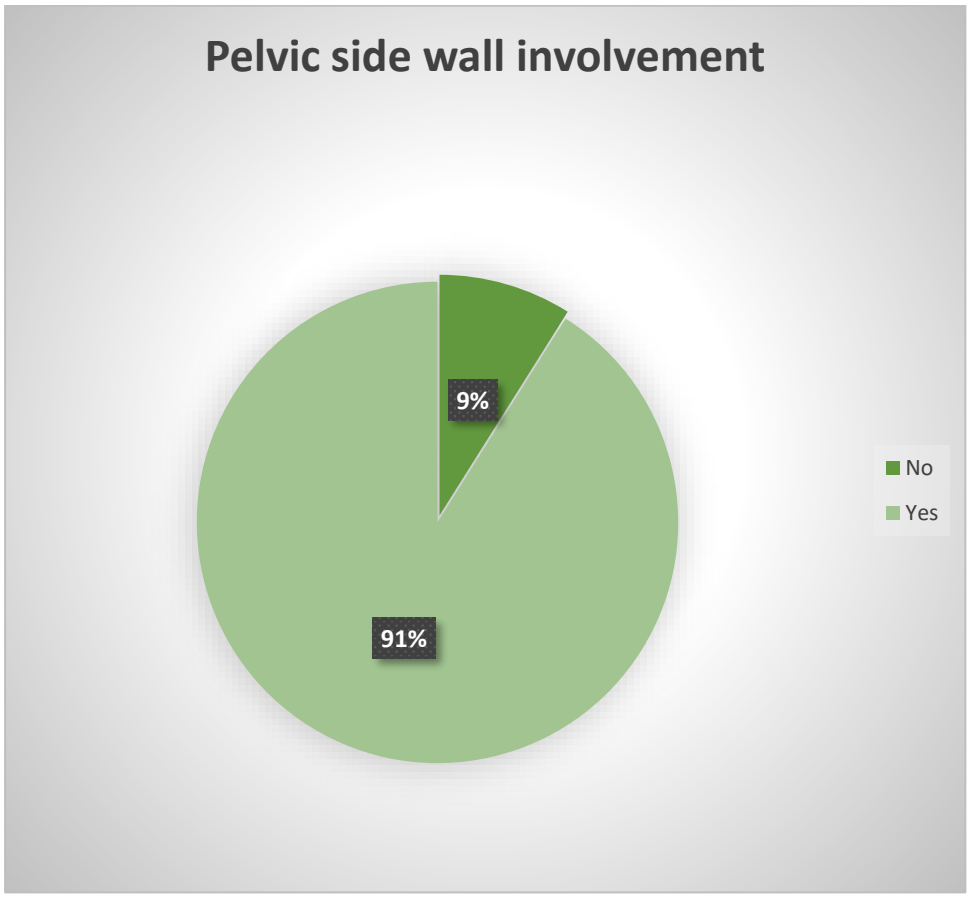


Figure 8: Fraction of patients presenting with stage IIIB cervical cancer defined by presence of pelvic side wall involvement.

3.1.9 Hydronephrosis

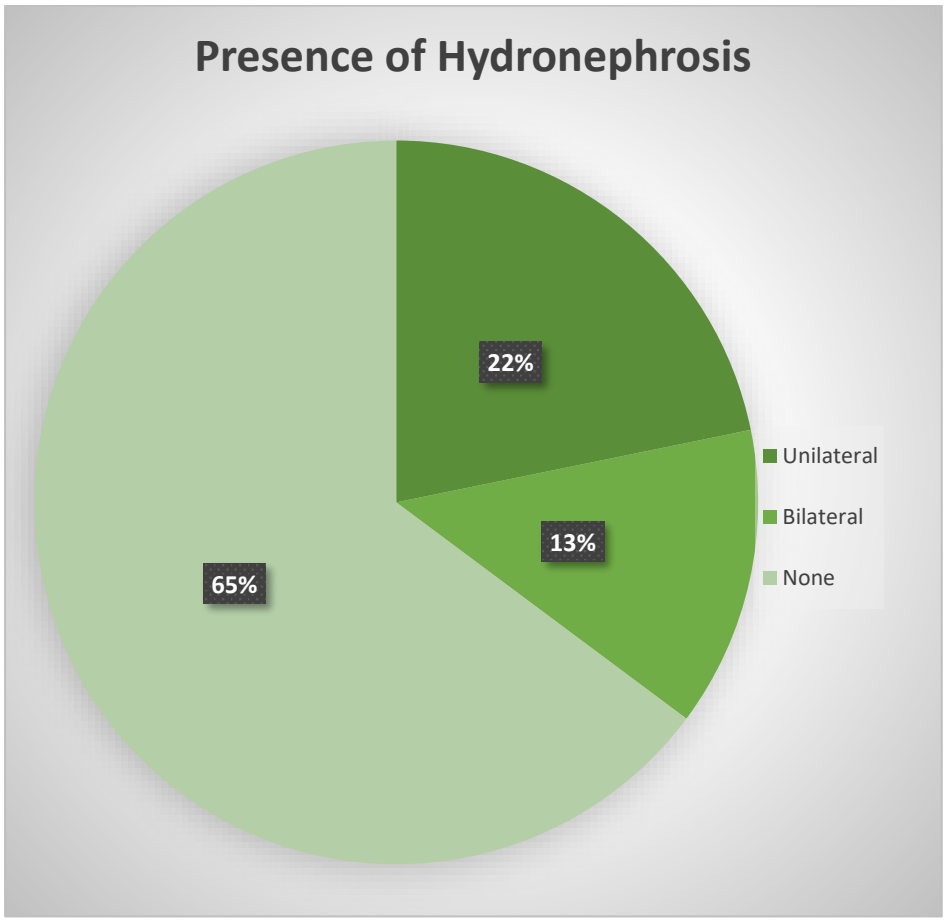


Figure 9: Percentage of patients presenting with stage IIIB disease defined by the presence of hydronephrosis and laterality.

3.2 Treatment modalities of stage IIIB cervical cancer among study participants

3.2.1 EBRT Fractionation

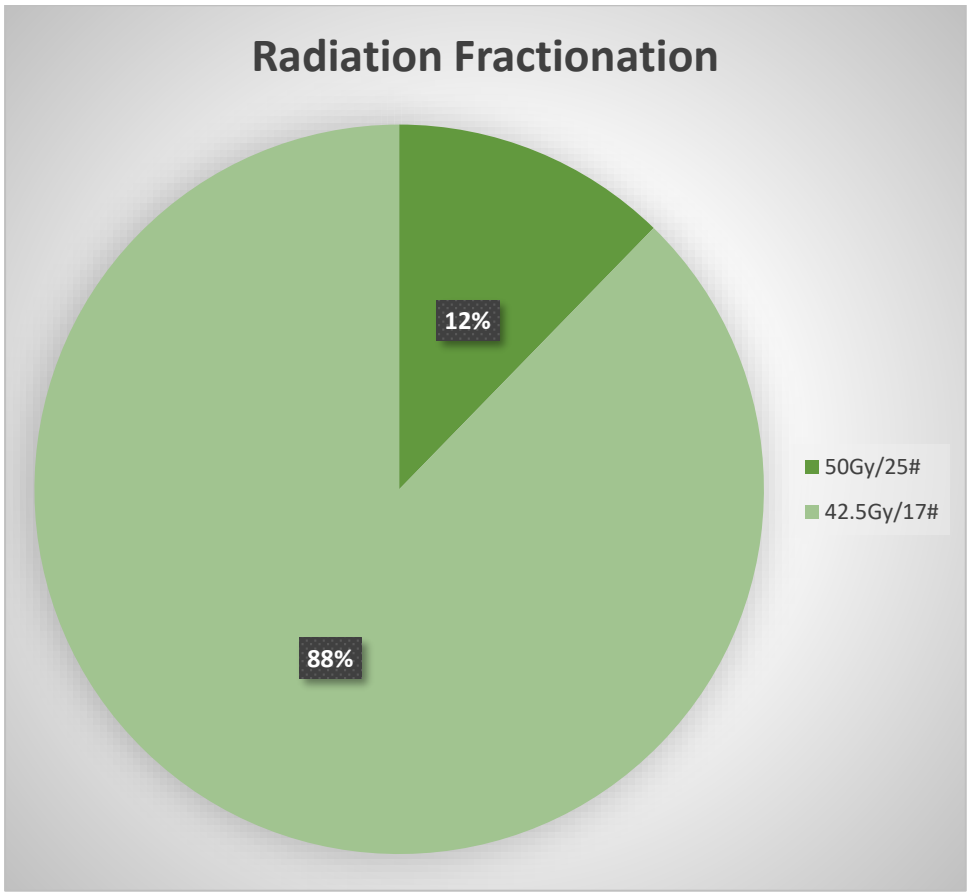


Figure 10: Breakdown of fractionation schemes used for study participants.

3.2.2 Brachytherapy Applicators Used

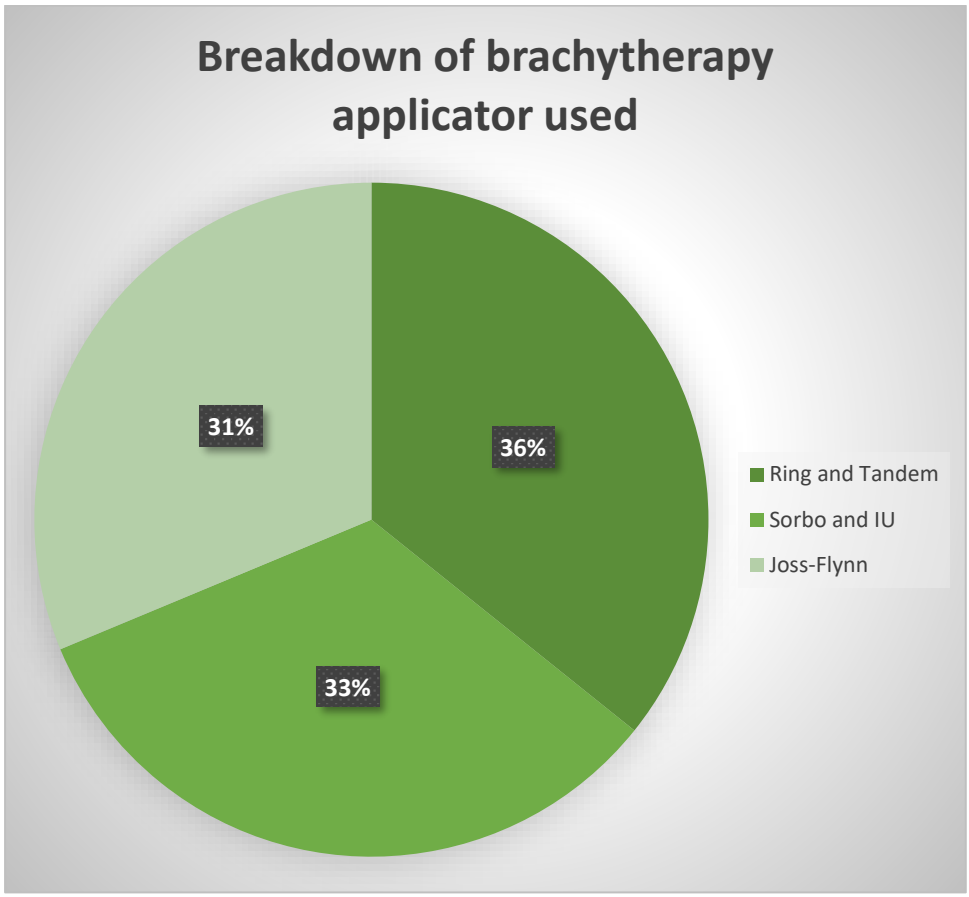


Figure 11: Breakdown of different brachytherapy applicators used

The choice of brachytherapy applicator used was left to the discretion of the physician in the brachytherapy theatre. 64 patients were treated using a tandem and ring, 56 patients were treated with a Joss-Flynn applicator and 59 patients were treated using a sorbo and intra-uterine tandem.

3.2.3 Use of Chemotherapy

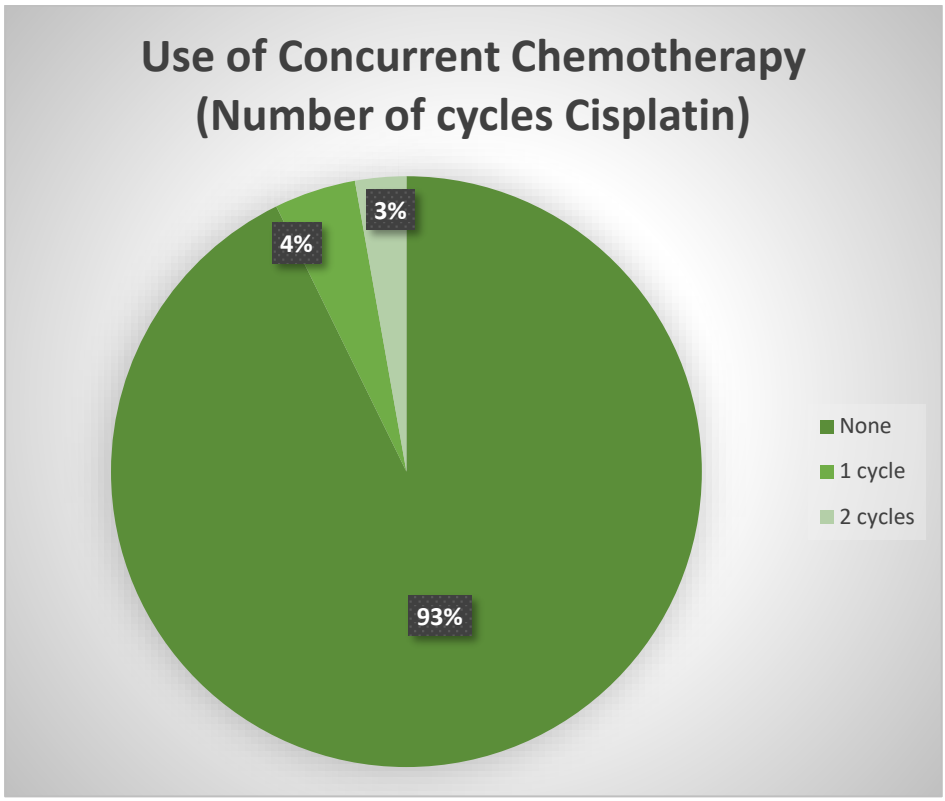


Figure 12: Percentage of patients receiving concurrent chemotherapy and number of cycles cisplatin received.

The use of concurrent cisplatin-based chemotherapy was permitted for patients who received standard fractionated EBRT. Most patients did not receive chemotherapy because they received hypofractionated radiation therapy. 9 of the 22 patients who were prescribed standard fractionated EBRT did not receive concurrent chemotherapy. One patient did not receive chemotherapy because of low CD4 count, 5 patients did not receive chemotherapy due to compromised renal function, one patient did not get chemotherapy because of age (77-year-old) and two patients did not get chemotherapy though no reason was cited in the clinical notes. Of the remaining patients eligible for chemotherapy, 5 completed the prescribed 2, 3 weekly cycles of cisplatin and 8 patients received only one cycle of chemotherapy.

3.3 Follow up Rates

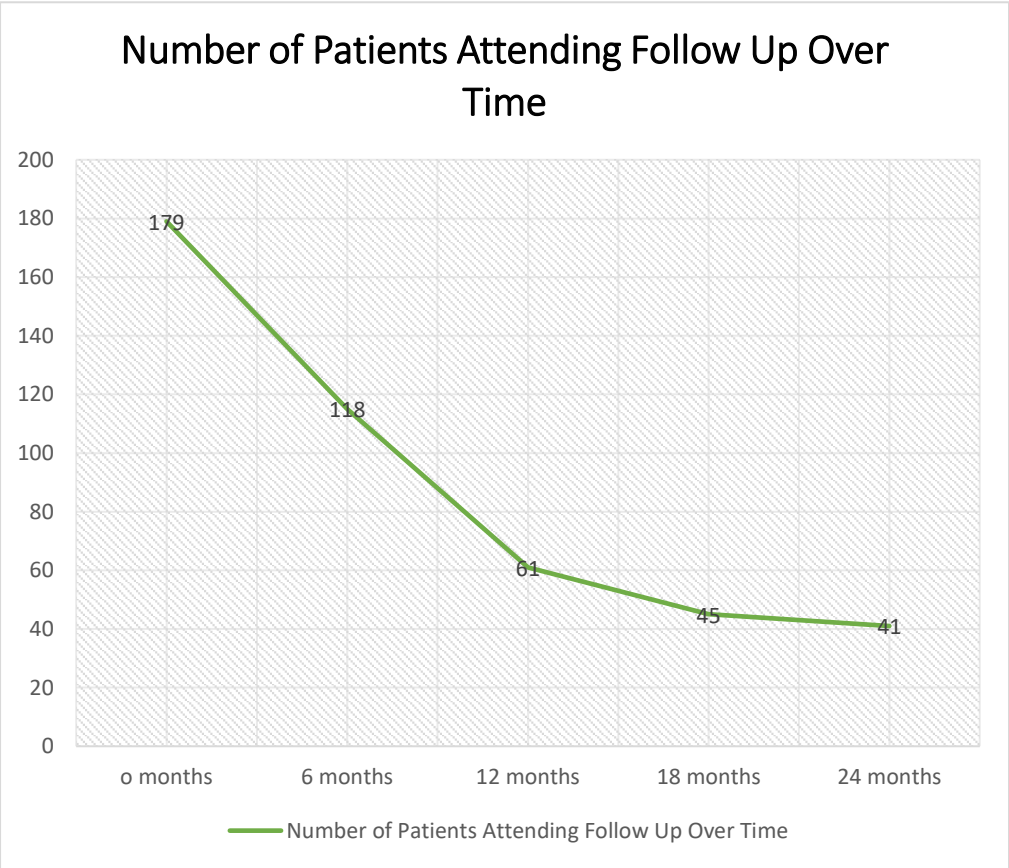


Fig 13: Number of study participants attending follow up over 24 months post completion of treatment.

3.4 Local Control at 6 months

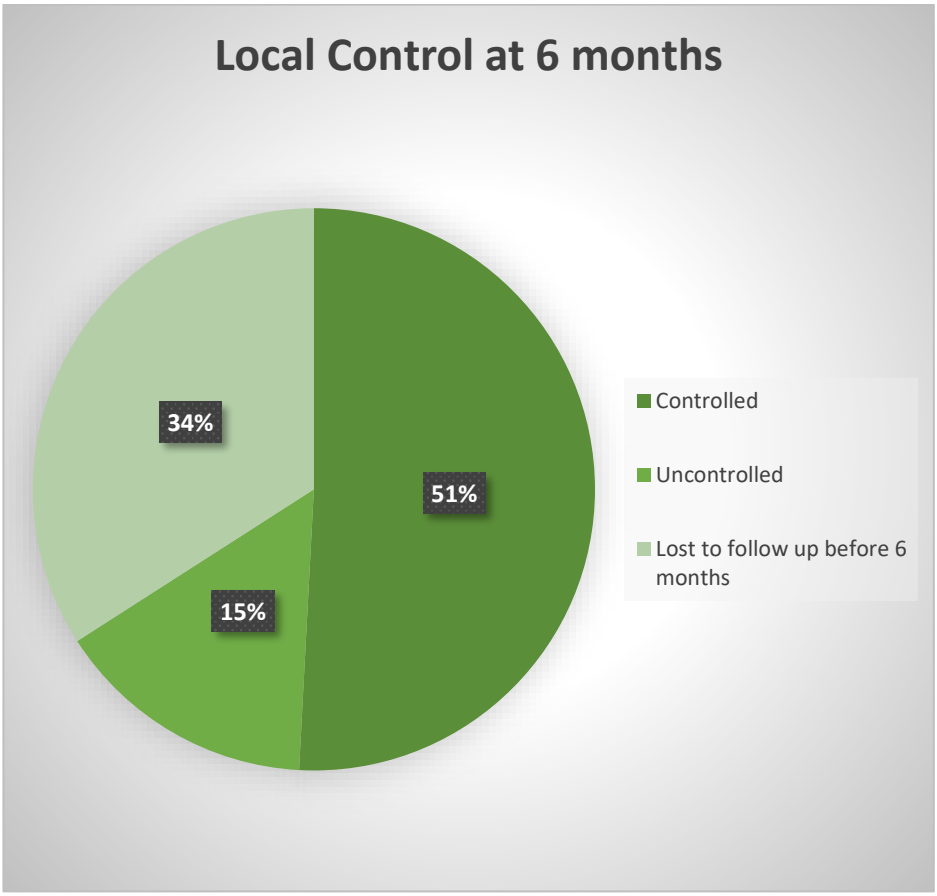


Figure 14: Status of local control at 6 months post treatment among study participants.

3.5 Overall survival at 24 months post treatment among study participants

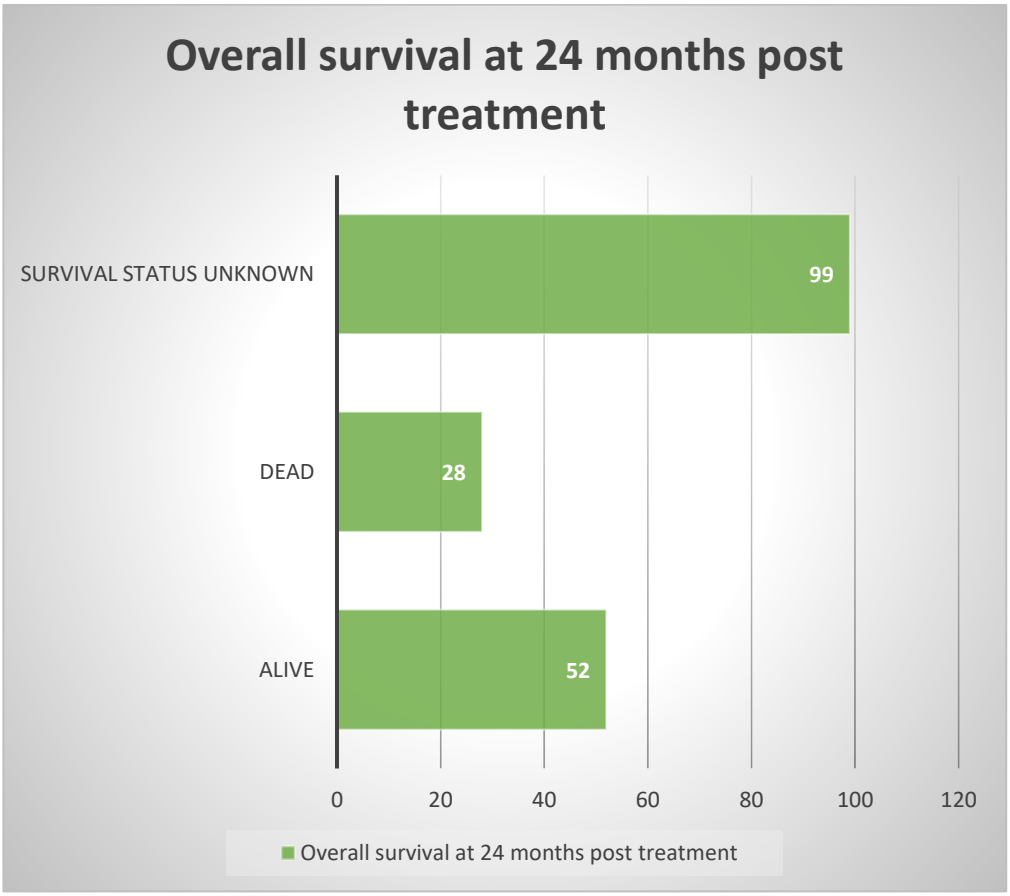


Figure 15: Overall survival at 24 months post treatment among study participants.

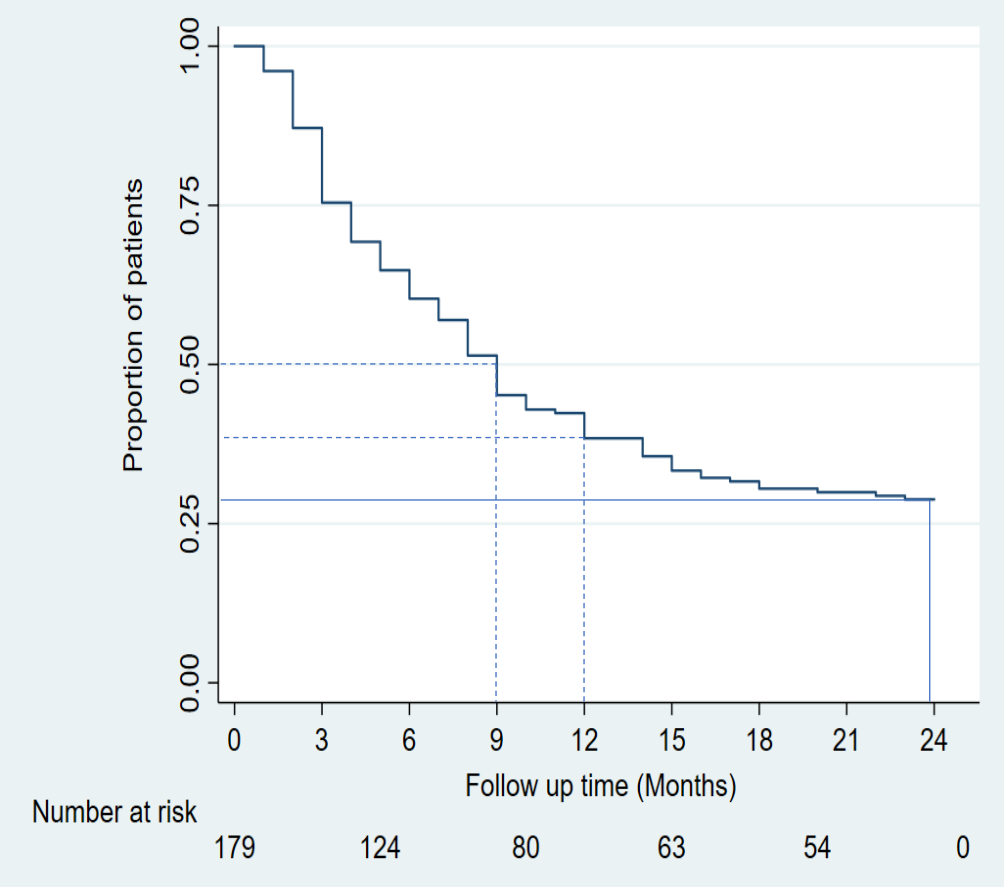


Figure 16: Kaplan Meier analysis of Overall Survival.

A total of 127 patients died or were lost to follow up. Patients who were lost to follow up were censored at their last visit. Median overall survival was 9 months and one year survival was 37%. The attrition rate was 60.6 per 1000 person months, 95% CI [50.8-71.9]

3.6 Association between treatment variables and treatment outcomes

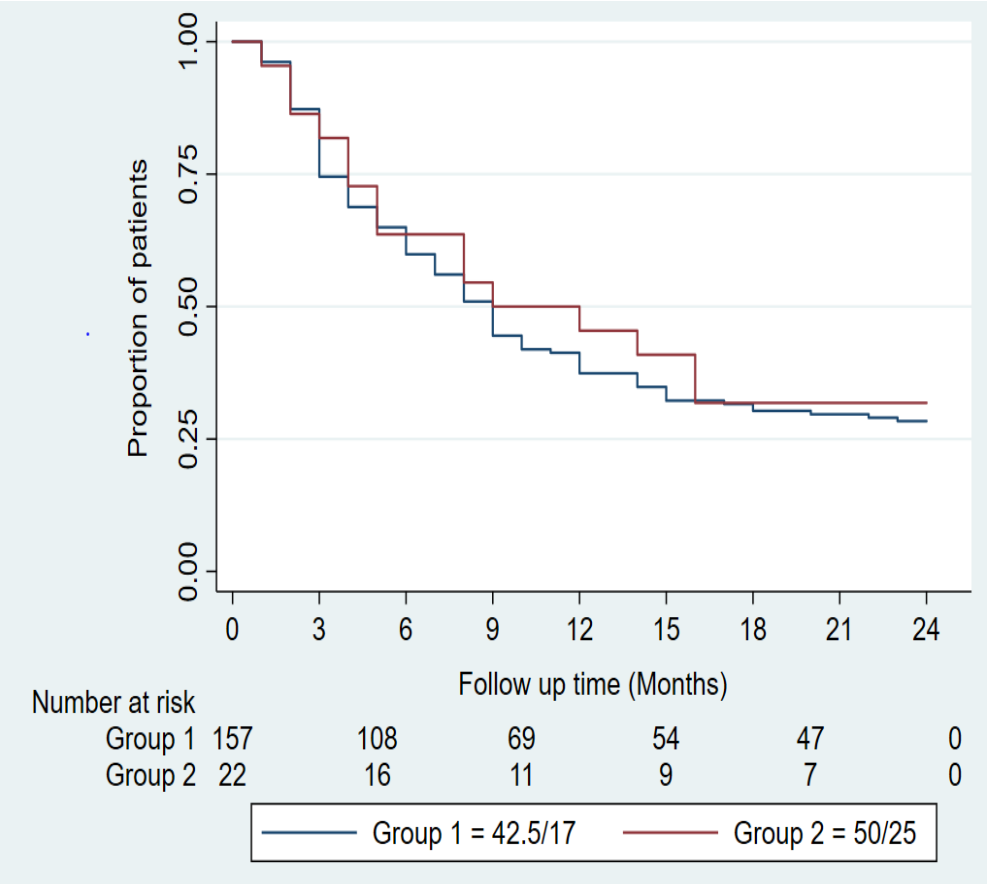


Figure 17: Kaplan Meier analysis of overall survival of standard fractionation versus hypofractionated external beam radiation therapy

No difference in survival rates at 24 months was noted between the two radiation schedules, (log rank test p value= 0.673)

Table 3: Association between treatment variables and local control.

Variable	Local control at 6 months		P value
	Uncontrolled n=27	***Controlled n=91***	
Radiation fraction			0.391
42.5/17#	22	80	
50G/25#	5	11	
Brachytherapy applicator type			0.395
Sorbo®	6	33	
Joss Flynn®	9	25	
Tandem and Ring®	12	33	

A non-significant association was found between local control and radiation fractionation used [$x^2(1, N=118) = 0.7346$, $p=0.391$], with an odds ratio of 0.61 [95% CI 0.19-1.92 favouring hypofractionated radiation therapy. The association between local control and brachytherapy applicator did not reach statistical significance either [$x^2(2, N=118) = 1.8558$, $p=0.395$].

Table 4: Sensitivity analysis of treatment variables and their effect on local control

	Variable	Local control at 6 months		P value
		Uncontrolled n=27	***Controlled n=152***	
Scenario 1: 1. Unknown assigned controlled status 2. status LTFU assigned dead status	**Radiation fraction**			0.285
	42.5/17#	22	135	
	50G/25#	5	17	
	Brachytherapy applicator type			0.401
	Sorbo®	6	53	
	Joss Flynn®	9	47	
	Tandem and Ring®	12	52	
Scenario 2: 1. Unknown assigned uncontrolled status 2. LTFU assigned alive status		***Uncontrolled n=88***	***Controlled n=91***	
	Radiation fraction			0.933
	42.5/17#	77	80	
	50G/25#	11	11	
	Brachytherapy applicator type			0.476
	Sorbo®	26	33	
	Joss Flynn®	31	25	
	Tandem and Ring®	31	33	

Due to large number of patients being lost to follow up, a sensitivity analysis was performed to assess for possible associations between radiation fractionation used or brachytherapy applicator used and local control rates. In neither scenario was there a significant correlation between these treatment variables and local control rates.

Table 5: Association between treatment variables and survival.

Variable	Survival at 24 months post treatment		P value
	Alive n=51	***Dead n=28***	
Radiation fraction			0.59
42.5/17#	45	23	
50G/25#	7	5	
Brachytherapy applicator type			0.41
Sorbo®	18	13	
Joss Flynn®	16	9	
Tandem and Ring®	18	6	

There was no association between survival and radiation fractionation [$x^{2(}$1, N=118) = 0.2578, p=0.59] or survival and choice of brachytherapy applicator [x^2(2, N=118) = 0.422871, p=0.41].

Table 6: Sensitivity analysis of treatment factors and their effect on survival.

	Variable	Survival at 24 months post treatment		P value
		Alive n=52	***Dead n=127***	
Scenario 1: 1. Unknown assigned controlled status 2. status LTFU assigned dead status	**Radiation fraction**			0.760
	42.5/17#	45	112	
	50G/25#	7	15	
	Brachytherapy applicator type			0.954
	Sorbo®	18	41	
	Joss Flynn®	16	40	
	Tandem and Ring	18	46	
Scenario 2: 1. Unknown assigned uncontrolled status 2. LTFU assigned alive status		***Alive n=151***	***Dead n=28***	
	Radiation fraction			0.329
	42.5/17#	134	23	
	50G/25#	17	5	
	Brachytherapy applicator type			0.154
	Sorbo®	46	13	
	Joss Flynn®	47	9	
	Tandem and Ring	58	6	

In neither of the scenarios was there a statistically significant correlation between radiation fraction used and survival or brachytherapy applicator choice and survival.

3.7Factors associated with lack of local control

Table 7: Prognostic factors associated with local control

Prognostic factors	**Unadjusted OR [95% CI]**	**P value**	**Adjusted OR [95% CI]**	**P value**
Age group (Years)				
<50	1.0		1.0	
≥50	0.51 [0.18-1.50]	0.223	0.64 [0.17-2.45]	0.515
Haemoglobin (g/dL)				
<10	1.0		1.0	
≥10	0.42 [0.17-1.10]	0.054	0.55 [0.20-1.47]	0.230
HIV status				
Negative	1.0		1.0	
Positive	1.91 [0.78-4.70]	0.160	1.54 [0.49-4.85]	0.456
CD4 count category				
<200 cells/mm^3	1.0		1.0	-
≥200 cells/mm^3	0.30 [0.03-1.24]	0.052	0.10[0.01-1.12]	0.062

Logistic regression analysis was performed to identify the effect of the various prognostic factors in this population. Due to 34% of patients being lost to follow up before 6 months, and therefore having no documentation of local control, the resultant odds ratios had wide confidence intervals and none of the analysed prognostic factors in this sample had a statistically significant p value.

3.8 Factors associated with decreased survival

Table 6: Prognostic factors associated with death by 24 months post completion of treatment

Prognostic factors	**Unadjusted OR [95% CI]**	**P value**	**Adjusted OR [95% CI]**	**P value**
Age group (Years)				
<50	1.0		1.0	
≥50	0.81 [0.26-2.53]	0.714	1.16 [0.29-4.63]	0.834
Race				
Black	1.0		1.0	
Other	0.58 [0.11-3.07]	0.519	0.62 [0.10-3.83]	0.609
Haemoglobin (g/dL)				
<10	1.0		1.0	
≥10	0.62 [0.23-1.62]	0.325	0.73 [0.25-2.16]	0.572
HIV status				
Negative	1.0		1.0	
Positive	1.63 [0.63-4.21]	0.160	2.31 [0.58-9.20]	0.234
CD4 count category				
<200 cells/mm^3	1.0		1.0	
≥200 cells/mm^3	0.26 [0.25-2.81]	0.241	0.34 [0.03-4.42]	0.414

None of the analysed variables reached statistical significance in this study as a result of a large number of patients being lost to follow up. Confidence intervals were wide and thus no conclusions can be drawn from this analysis.

3.9 Treatment failure

Treatment failure was defined as death, failure to obtain local control by 6 months (i.e., persistent local disease), local recurrence after obtaining control at 6 months or the progression to metastatic disease.

3.9.1 Time to treatment failure

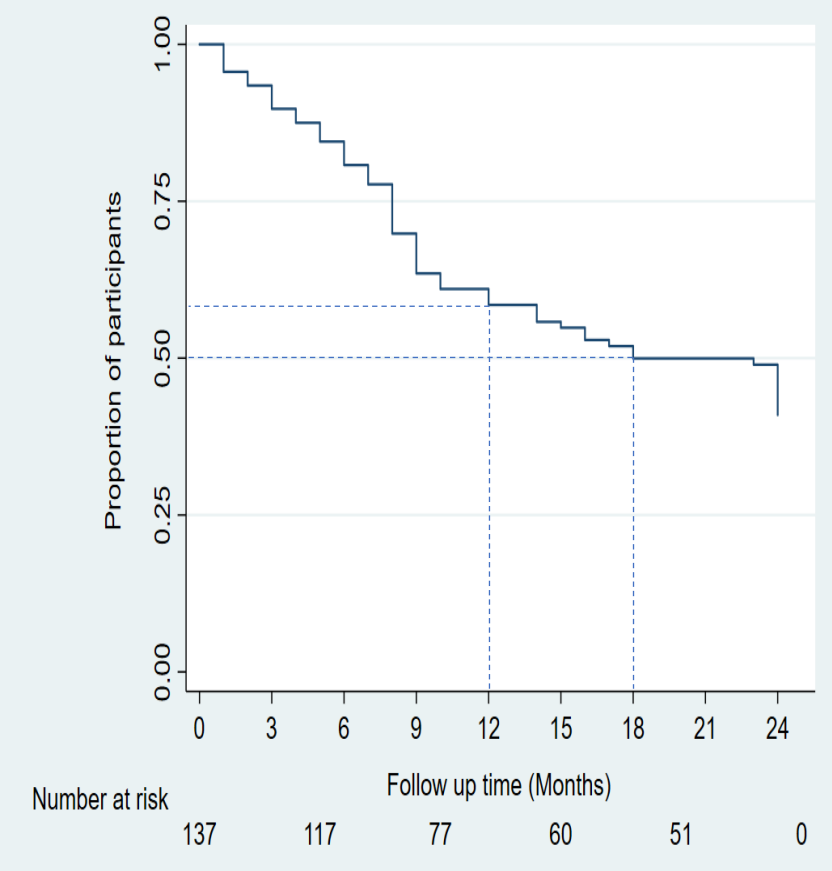


Figure 18: Kaplan Meier analysis for treatment failure in the study sample

A total of 72 participants failed treatment representing a treatment failure rate of 37.6 per 1000 person months, 95% CI [29.8-46.4] among participants with a documented treatment outcome. Median time to treatment failure was 18 months and one-year TTF was 58%

3.9.2 Patterns of failure

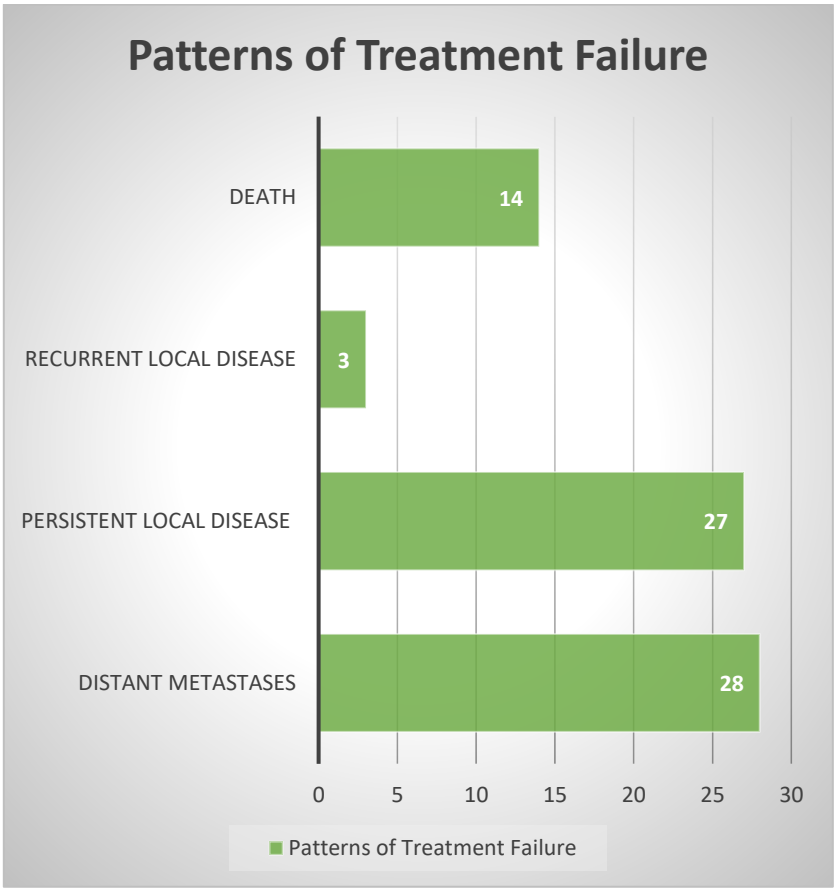


Figure 19: Patterns of treatment failure

3.9.3 Metastasis free survival

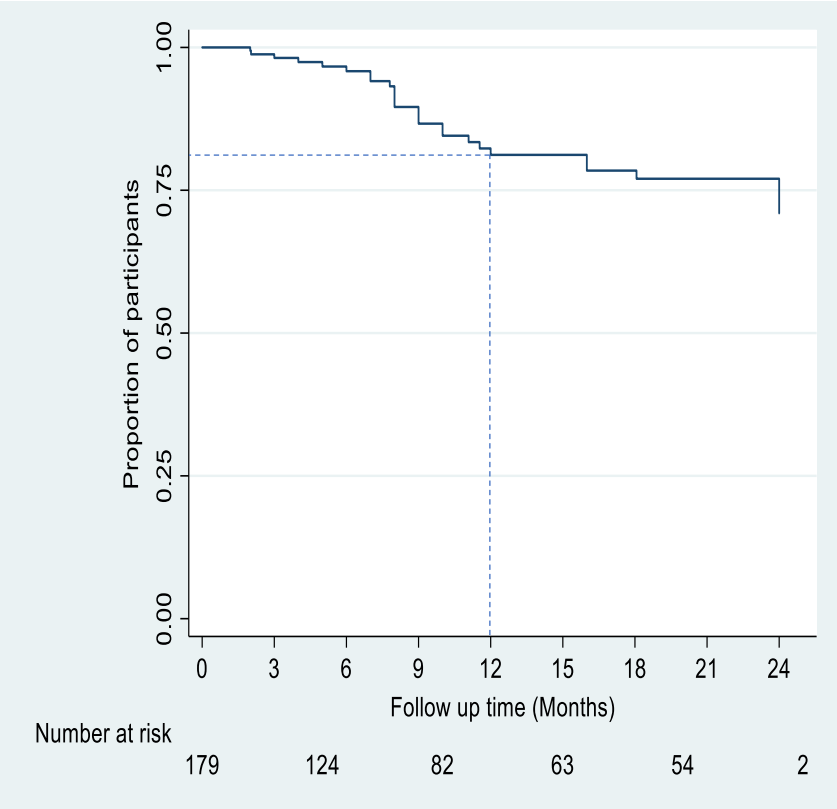


Figure 20: Metastasis free survival.

Patients contributed 2 153.9 person months as total analysis time at risk, with metastases documented in 28 patients. Median MFS not reached, one year MFS 80%. The incidence rate of metastases in the study population was 12.9 per 1 000 person-months, 95% CI [9.0-18.8].

3.9.4 Patterns of metastatic failure

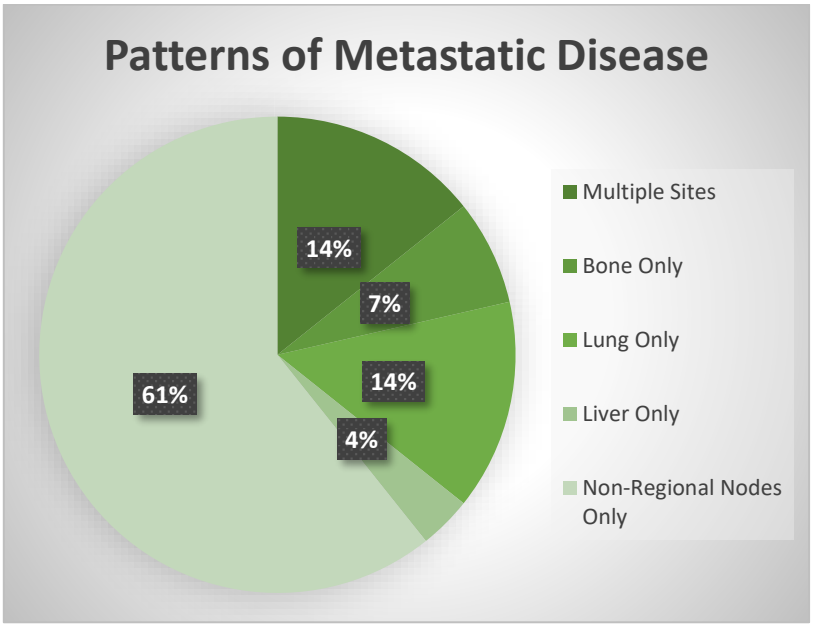


Figure 21: Patterns of Metastatic disease.

28 patients developed metastatic disease:

- 2 patients developed bone only metastases
- 1 patient developed liver only metastases
- 4 developed lung only metastases
- 17 patients developed nodal only metastases
- 4 patients developed metastases in multiple sites:
    - 1 had spread to bone, lung and nodes
    - 1 had spread to bone and lung
    - 1 patient had spread to liver and nodes
    - 1 patient had metastases detected in the lung and nodes.

4 Discussion

Stage IIIB cervical cancer with lower third vaginal involvement has been studied only in an Asian population, with only two previous reports published. The purpose of this study was to describe and analyse the treatment outcomes for this group of patients within a South African, public funded quaternary hospital, with the main objectives being to describe local control at 6 months and 2-year survival. In total, 2030 patients were treated for cervical cancer between January 2016 and December 2019, of which184 patients were identified who met the criteria for Stage IIIB with lower third vaginal involvement. A single patient underwent treatment for recurrence following a total abdominal hysterectomy and 4 patients were excluded because they either received a palliative course of radiation therapy or did not complete the full prescribed course of external beam radiotherapy and brachytherapy. The remaining 179 patients were available for analysis.

4.1 Local control

This study was limited by poor patient follow up. Data for six-month local control was unavailable for 34% of patients. Of the patients who attended at least 6 months of follow up and were available for assessment of local control (n=118), 77% (n=91) had no evidence of pelvic disease on clinical exam while the remaining 23% (n=27) of patients had persistent vaginal/pelvic disease. A further 3 patients who had complete clinical response at 6 months then developed a local recurrence.

In the study by Katanyoo (2017), 20% of patients with stage IIIB cervical cancer with lower third vaginal involvement (LTVI) had persistent disease as the end of treatment which was defined as persistent disease at 3 months post treatment. In addition, treatment failure in terms of persistent pelvic disease and pelvic recurrence occurred in 34.4% of their sample after a median follow up period of 9.7 years. These rates of local control were worse than the 3B counterparts without lower third involvement. Patients within the study were staged similarly to this trial without the routine use of CT for staging. All patients were treated with standard fractionation radiation therapy (40-46Gy in 2Gy/#) with a parametrial boost dose to 54-60Gy and intracavitary brachytherapy. Not all patients received platinum-based chemotherapy (59).

In the only other paper published looking at patients with lower third vaginal involvement in stage IIIB cervical cancer patients, persistent disease was defined as residual disease at 3 months post completion of treatment and was also higher for patients with LTVI than those without (16.2% vs 9.1%, p=0.064%). These patients were also treated with standard fractionated EBRT (46-50Gy in 1.8-2Gy/#) with a parametrial boost (8-10Gy in 2Gy/#), intracavitary brachytherapy and concurrent chemotherapy in 75% of their patients (60).

Thus, treatment failure rates for this study group are in keeping with the only 2 other published studies for this group of patients (15-20%). This is despite the use of a hypofractionated external beam radiation schedule and lack of concurrent chemotherapy given.

It should be highlighted that the time used to define treatment failure is different between this study and the other 2 (6 months versus 3). It is possible that some disease present at 3 months would continue to respond to treatment though this needs to be balanced against the possibility that some patients who have obtained local control at 3 months may still develop local recurrence/progression as was seen in the Katanyoo (2017) study from Thailand where local treatment failure over the study period was 30% while failure at 3 months was only 20%. The time from completion of radiation therapy to define persistent disease has not been officially characterised with most recommending a period between 3 and 6 months. 6 months was used in this instance based on institutional policy.

The similarity in local control rate between this and the two other Asian studies, despite different radiation fractionation schedule used, is supported by the lack of association on chi-square analysis of fractionation and local control in this study ($p=0.391$). Sensitivity analysis also failed to demonstrate an association between local control and EBRT fractionation even when all patients lost to follow up were assumed to have either persistent disease or complete response. EQD2 calculations

are not too dissimilar between the two EBRT schedules; 44.27Gy ($^{a}/_{ß}$ =10) versus 50Gy ($^{a}/_{ß}$ =10) which could explain the comparable outcomes. NCCN recommends an EBRT dose of approximately 45Gy, with a range of 40-50Gy being provided (66). Although the total EQD2 dose for the hypofractionated schedule was lower than that received by patients in the conventionally fractionated scheme, the hypofractionated regimen delivers the total dose in 8 less fractions which equates to nearly 2 weeks shorter treatment duration than the 50Gy/25# schedule, considering that only 5 fractions are delivered in a week. Given the rapid tumour doubling time of cervical cancer, this accelerated dose delivery is likely to be advantageous in overcoming tumour repopulation during treatment and could be one reason why no difference was observed in local control rates between the two different fractionated regimens.

The choice of brachytherapy applicator used also had no influence on local control rate as evidenced by a non-significant analysis (p=0.3960) for the portion of the study that was available for analysis and on sensitivity testing. The reason for brachytherapy applicator used other than TC was not stated in the patient file. It is possible that the lack of correlation between local control and brachytherapy applicator used may be due to selection of applicator based on extent of disease at time of brachytherapy rather than at initial presentation. Image guided brachytherapy with MRI has been demonstrated in the RETRO-EMBRACE and EMBRACE I trials to be effective in controlling local disease and producing a favourable toxicity profile in patients with all stages of locally advanced cervical

cancers (109,123). Acknowledging that MRI is not universally available, CT based adaptive brachytherapy guidelines have been published by the IBS-GEC ESTRO-ABS collaborative group (124). As per the IBS-GEC ESTRO-ABS guidelines, volumetric imaging is a minimum requirement for adaptive brachytherapy and to date, adaptive brachytherapy based only on clinical examination cannot be recommended. In this study, the extent of disease at time of first brachytherapy insertion was not recorded as a study variable and this represents a shortfall of this study, however the objective of this study was not to evaluate effectiveness of adaptive brachytherapy in the absence of 3D imaging. The results obtained are interesting and should be evaluated in a separate retrospective study.

4.2 Survival

At one year post completion of treatment 40% (n=68) of patients were documented as being alive, 14.5% (n=21) of patients were documented as dead and the remaining 45.5% (n=90) had missing survival data due to loss of follow up and inability to trace survival status. If only patients with survival data are considered (n=89), 76.4% are alive at one year after treatment. This figure represents an overestimate of survival due to an attrition bias as some of the patients who were lost to follow up would have died of their cancer before one year. The Kaplan-Meier analysis of survival reveals overall survival to be 38%, a figure which over-estimates the number of deaths since patients must be regarded as being at risk of death at time of censorship. True one year survival rates are impossible to determine due to the high attrition rate seen in this group of patients.

Analysis of 2-year survival revealed that 55.3% of patients were lost to follow up before 2 years, 29.1% of patients were alive and 15.6% were dead at 2 years. If only the patients with survival information are analysed (n=80) 65% (n=52) of patients were alive 2 years post treatment and 35% (n=28) were dead. These calculations are limited by an attrition bias in that many of the patients who were lost to follow up may have died from their cancers. The attrition rate in this group was high at a rate of 60.6 per 1000 person months 95% CI [50.8-71.9].

Both Katanyoo and Fang found inferior survival in patients with lower third vaginal involvement compared to those without. In the study by Katanyoo (2017), 2- and 5-year survival for patients with stage IIIB with LTVI were 43.8% and 28.9% respectively and for those without LTVI these survival rates were 66.5% and 46.8% respectively (59). Fang et al. (2021) documented 2- and 5- year survival rates of 68.9% and 38.8% respectively for patient with LTVI and 79.9% and 58.9% respectively in those without LTVI (60). Thus, the 2-year survival rates obtained in this study are comparable to those obtained by Fang and higher than those obtained by Katanyoo, despite the use of a different radiation dose and fractionation scheme, and lack of use of concurrent chemotherapy. This may be explained by the possible equi-effectiveness of a hypofractionated radiation schedule compared to a standard fractionated radiation schedule. It is also possible that chemotherapy provides little benefit to this group of patients, and it known that the benefit of concurrent

chemotherapy declines with advancing tumour stage (111). In Katanyoo's study, there was also no association between survival and the use of concurrent chemotherapy; HR for OS 0.91 (0.64-1.29), p=0.595 (59).

In a previous study on the effects of hypofractionated radiation therapy conducted at the same radiation oncology centre as this study, the author found a 600-day OS and DFS of 94.92% and 59.04% respectively for patients with stage IIIB cervical cancer not stratified based on presence of lower third vaginal involvement. These patients were treated with the same EBRT and BT schedule used in this study (103). These are considerably higher survival rates than those obtained in either this study or those obtained in the other 2 studies on patients with LTVI. While evidence from Katanyoo (2017) and Fang et al. (2021) demonstrate worse prognosis for patients with lower third vaginal involvement compared to those without, the survival outcomes from patients without LTVI are not comparable to those obtained by Komen (2014). In another study looking at the prognosis of patients with stage III disease, 3-year OS and PFS rates were 69.0% and 55% respectively (125), which are more comparable to this study and those by Katanyoo or Fang than to the survival outcomes obtained by Komen. Muckaden et al. (2002) also reported a 3-year OS of 50% at a mean follow up period of 40 months, for stage IIIB cervical cancer patients treated with hypofractionated EBRT which again is in keeping with the results found in this study (126). It remains possible that the excellent results obtained by Komen may be due to a sampling anomaly. Considering this unusually high survival rate

for patients with stage IIIB disease and that Komen had not stratified patients based on LTVI, it makes it impossible to compare outcomes between this trial and this one even though both studies looked at patients from a similar demographic and received a comparable radiation schedule.

The survival rates obtained in this study are therefore comparable to those obtained in other published studies for patients treated with hypofractionated EBRT for stage IIIB cervical cancer but the loss to follow up may have over-exaggerated survival data due to an attrition bias. Survival analysis of this sample also demonstrated no correlation between brachytherapy applicator used or EBRT fractionation.

4.3 Treatment failure

For analysis of treatment failure, TTF was defined as time to first event of either persistent disease at 6 months, local recurrence, development of metastatic disease or unexplained treatment death. In this study group, 72 patients were available for analysis and this resulted in a failure rate of 37.6 per 1000 person months, 95% CI [29.8-46.4].) Treatment failure due to incomplete response at 6 months occurred in 37.5% (n=27) of participants.

Of the group of patients who had not obtained a complete response by 6 months, 7% (n=2) had isolated vault persistence based on clinical examination and 11% (n=3) had persistent disease localised only to the

vagina, though the clinical notes did not document whether this persistent disease was in the lower third of the vagina or whether it was located more proximally. These findings are in keeping with the 6.7% isolated central recurrences following chemoradiation therapy documented by Liu et al (2103) (China) (127).

In this study, 3 patients developed recurrent disease after obtaining a clinical complete response. In a retrospective review of treatment failures following a previous complete response, Bandoyopadhyay et al. (2018) (India) demonstrated that 8% of patients experienced a central recurrence (128). This result is similar (6.7% vs 8%) to what was obtained in this study when calculated as a ratio of treatment failures, excluding those who had persistent disease.

Distant metastases occurred in 28 patients. The majority of these (61%, n=17) occurred in the non-regional lymph nodes. Within this group, 10 patients had inguinal nodal failure, though only 3 patients had isolated groin failures. The next most frequent sites of metastatic disease were lung only metastases and metastases in multiple sites (14% each, n=4). Bone only metastases occurred in 7% of patients and liver only metastases were the least frequent site of distant disease (4%, n=1). There were no patients in this sample who developed distant spread to other sites such as the CNS. The patterns of distant failure seen in this study are similar to those seen in other published papers. diSibio and French (2008) (USA) demonstrated in an autopsy series that cervical

cancer has a propensity for lymphatic dissemination and that non regional nodal metastases are the most common site of distant spread in cervical cancer patients (129). Zhou et al. (2020)(China), reported on metastatic patterns of 1347 patients retrospectively reviewed from the SEER data base and found that the most common sites of single organ metastases were (in order) lung, bone, liver then brain (130).

Surveillance guidelines from NCCN recommend surveillance with cross sectional imaging and even a single PET-CT in the post treatment setting (66). Contrary to this, FIGO guidelines which were developed for use in LMICs do not recommend the routine use of imaging in the surveillance period unless there is suspicion of metastatic disease based on clinical findings (131). The number of patients who experienced treatment failure in this study is most likely understated due to the high attrition rate and lack of cross-sectional imaging used in the follow up period.

4.4 Effect of age

Logistic regression analysis for age as a prognostic factor revealed no statistically significant correlation with either local control or survival. Confidence intervals were wide, and this makes interpretation impossible. In this study sample, the calculated odds ratios imply that patients older than the age of 50 were 36% more like to have complete response to radiation therapy than patients younger than 50. When survival was analysed, there was a trend for decreasing survival with advancing age. There is therefore a discrepancy between the effect of local control and

survival, and one would expect local control to be directly related to survival since salvage surgery is rarely performed in this institution.

This study was limited by poor patient follow up and this is one possible explanation for the lack of association between age as a prognostic factor and local control or survival. The available literature on this topic is conflicting with some authors documenting young age as a poor prognostic factor(25), others commenting older age is a poor prognostic factor (27)and other authors finding no association between age and treatment outcomes(28). The resultant trends obtained from this study are in keeping with those found by Wang et al. (2019)(China) who found that while survival was lower amongst older women, age was not predictive for either disease free survival or cancer specific survival (29). Ultimately, this study has found no evidence for age being prognostic for either local control or survival.

4.5 Effect of self-reported race

Black patients made up 92.7% of the study group, 2.8% were white, 1.1% of patients were of Indian origin and 3.4% were classified as mixed race. Race did not reach statistical significance as a prognostic factor for survival, however within this sample, non-black participants were 38% less likely to die compared to black participants, adjusted OR 0.62 [0.10-3.83, p=0.609]. Grisby et al. (2000)(USA) noted that for patients treated for stage II or III cervical cancer, overall survival was different for black and non-black patients however cancer specific survival was the same for

both groups, suggesting that other factors may be responsible of lower survival in black race patients (35). Rodrigues et al. (2018)(Brazil) similarly showed that after correcting for other factors such as treatment and pre-treatment Hb levels, survival was the same between black and non-black patients (34). In this study, all patients received the same treatment for the same stage of cancer, and although the association between race and survival was not significant, the greater likelihood of black women to die could be explained that deaths may have been due causes other than cancer. Cause of death was not available for most patients and a cancer specific survival could not be ascertained. Out of the 13 non-black patients, 4 (30%) were HIV positive, while. Of the black patients, 9 had unknown status and the remaining 53.5% (83 out of 155) were HIV positive. Since HIV positivity is a poor prognostic indicator for survival this could be one possible explanation why survival was lower for black patients. This however is an explanation of the trends seen in this study however the odds ratios obtained and had wide confidence intervals. Due to the lack of statistical significance (p value = 0.609), this study has failed to show any prognostic value of race on survival in this group of patients.

4.6 Effect of HIV status and CD4 count

HIV positive patients made up 48.6% of the study group, 48.0% were negative and 3.4% had unknown status. Of the patients who were HIV positive, 78.2% had CD4 counts greater than 200 cell/mm3 and only 11.5% had CD4 counts less than 200 cells/mm3. All HIV positive patients

were on antiretroviral therapy at time of presentation to the oncology clinic. Using regression analyses, HIV positive patients were 1.5 times more likely to be uncontrolled 6 months post treatment compared to their HIV negative counterparts though this value did not reach statistical significance, adjusted odds ratio=1.54 [95% CI 0.49-4.85, p value=0.456]. In addition, HIV positive patients were 2.3 times more likely to die by 24 months post treatment compared to HIV negative participants, adjusted odds ratio 2.31 [95% CI 0.58-9.20, p=0.234]. For 2-year survival, the odds ratio has a wide confidence interval, and the p value is not significant.

The correlation between HIV seropositivity and cervical cancer treatment outcomes has never been evaluated formally in a randomised controlled trial. There are however several retrospective trials that have provided some contrasting results. Dryden-Peterson et al. (2016)(USA) found that HIV positivity correlated with poorer 3-year survival rates when compared to patients who were HIV negative (56). Contrary to this, Ntekim et al. (2015)(Nigeria) found that HIV positivity did not lead to decreased survival and Trejo et al. (2020)(Zambia) demonstrated how pelvic control rates were the same between women living with HIV and those without (53,55).

Regarding CD4 count, this did not establish a significant correlation between CD4 count and treatment outcomes (p=0.062 for local control and p=0.414 for survival). Of note, patients with CD4 counts greater than 200 cells/mm2 in this sample were 90% more likely to achieve local control at 6 months and 75% less likely to die before 2 years post

treatment. These results are similar to those obtained by Grover et al. (2020)(USA) who also demonstrated that higher CD4 count showed a trend towards increased survival following chemoradiation (132).

Although the trends observed for the correlation between HIV status and CD4 counts are comparable to other published papers, neither of these two variables achieved any statistically relevant correlation. It is possible that the sample size and loss to follow up were major limiting factors of this study. The trends lend support to the evidence provided in other studies that HIV positivity and low CD4 count may negatively predict for poorer treatment outcomes however this study has ultimately failed to prove this correlation.

4.7 Effect of pre-treatment haemoglobin level

Within this sample of patients with stage IIIB cervical cancer with LTVI, logistic regression analysis suggested that there was no association between low pre-treatment Hb levels and local control rates or survival with analysis returning non-significant p values (0.23 for local control and 0.52 for 2-year survival).

Despite this lack of statistical significance, patients with a pre-treatment Hb level greater than 10mg/dL were 45% more likely to obtain local control and 27% more likely to be alive at 2 years post completion of therapy than their anaemic counterparts.

The interaction between Hb and treatment outcomes is controversial. Bishop et al (2014)(USA) and Shin et al. (2014)(Korea) demonstrated that low Hb levels before treatment correlated with increased local and distant failure and/or decreased survival (39,41). Barkati et al (2013)(Canada) and Thomas (2001)(Canada) both found that pre-treatment anaemia did not predict for poorer treatment outcomes, but that on-treatment anaemia did (36, 37).

In addition to the problems of poor follow up limiting this study and lack of clarity in the literature regarding the relationship between low pre-treatment Hb and treatment outcomes, this study is also limited by the uncertainty in the delivery of blood transfusions prior to presentation at the radiation oncology clinic. Only Hb levels recorded at presentation were documented, and some patients document as Hb greater than 10g/dL may have presented with a more severe anaemia and were corrected with blood products prior to referral to this oncology department. While some authors have documented that blood transfusions do not improve treatment outcomes (38,41), others have shown that correcting anaemia through repeated transfusion improves pelvic control for patients treated with radiation therapy (43).

In summary, no conclusions can be drawn from this study about the relationship between pre-treatment Hb levels and treatment outcomes for patients with this advanced stage of cervical cancer.

4.8 Limitations of study

This study was a retrospective study performed in a single centre. Due to its retrospective design, data was limited to information documented in patient files. Due to large losses of numbers of patients in the follow up period, statistical analysis of treatment variables was compromised and there was failure to detect statistically meaningful correlations that might otherwise have been found. This limited follow up may be due to several reasons including the COVID-19 pandemic which prevented movement and access to non-emergency medical treatments and investigations. CMJAH also serves patients who often come from different provinces or neighbouring countries for treatment and who then return home following radiation treatment rendering them unavailable for routine post treatment surveillance. Patients in this study were treated for an advanced stage of cancer and death may be another reason why these patients were lost to follow up. Unfortunately, only those patients who provided ID numbers at registration in the clinic could be traced for survival analysis if they were lost to follow up before the 24 months surveillance period. The majority of patients did not supply ID numbers and their survival information was therefore not traceable. Only 27% (n=50) patients had documented ID numbers. Bindu et. al (2017) reported a loss to regular follow up rate of 69.6% in his retrospective study of patients treated for cervical cancer in Kerala, India. In the same study advanced age and advanced FIGO stage were identified as having a statistically meaningful correlation with loss to follow up (133). In a retrospective study conducted on cervical cancer patients from Rwanda, 40% of patients were reported as loss to follow up.

Travelling long distances was one of the statistically relevant correlations with loss to follow up noted in this study (134). Studies into factors that affect regular follow up in malignancies other than cervical cancer have identified factors such as black race, fewer than 5 contact numbers, and long travelling distances as reasons for patients discontinuing regular follow up (135,136). Compared to the above-mentioned studies, this study had exceptionally high loss to follow up rates, with only 22.9% of patients attending regular follow up for the full 24-month period. The high rates of attrition can partly be explained the reasons identified in these studies on loss to follow up, the COVID-19 pandemic exacerbated this problem and the fire that occurred at CMJAH in April 2021 also limited the 2-year follow up for the patients who were treated in 2019.

Another limitation of this study was the staging tests used. While FIGO staging guidelines were followed, more economically developed countries would have greater access to cross sectional and physiological based imaging with CT scans, MR imaging and PET-CT scans as recommended by international guidelines such as NCCN. Had more sensitive staging investigations been used; it is likely that a proportion of patients may have been upstaged. Similarly, if patients had more sophisticated imaging used in the post treatment follow-up period, the rates of treatment failure would likely have been higher.

In addition to this, the findings of a non-significant association between treatment outcomes and the EBRT fractionated scheme arms may have

been due to a bias in patient selection for different arms and it is a short coming of this study that the reason for the choice of using standard fractionation for these patients was not determined at the time of data collection. Total treatment time was not recorded as a treatment variable. Since current recommendations are that total treatment time should be completed in under 8 weeks, it is acknowledged that time to completion of treatment is an important factor. Patients receiving 50Gy/25# are at greater risk of experiencing extended treatment times and this could have affected analysis when comparing the outcomes of the different schedules. The purpose of this study however was not to evaluate hypofractionated radiation therapy as an alternative to conventionally fractionated EBRT. Retrospective evidence has been provided about stage IIIB patients treated at CMJAH in terms of treatment outcomes and toxicity of this same hypofractionated schedule (90). This study has however managed to demonstrate that patients with the added poor prognostic factor of lower third vaginal involvement can still achieve meaningful treatment outcomes in terms of local control and survival as this was the main objective of this study.

Similarly, the clinical findings at the time of first brachytherapy insertion was not recorded as a study variable. This would potentially have allowed for insight into why no difference was seen in local control between different brachytherapy applicators despite the current standard requiring adequate coverage of initial disease, which could only be accomplished with a TC applicator. This raises interesting questions about adaptive

brachytherapy based on clinical exam findings only, in the absence of volumetric imaging, which could guide practice in resource constrained settings. This should be evaluated in future studies.

5 Conclusions and Recommendations

This study has demonstrated that patients with this advanced stage of cervical cancer can obtain meaningful local control with definitive radiation therapy. The hypofractionated EBRT regimen used at CMJAH produced comparable results to those obtained in other retrospective trials using standard EBRT fractionation schemes and Chi square analysis in this study showed no correlation between fractionation scheme used and local control or survival rates. This should prompt investigation into prospective, randomised controlled studies in this regard. Indeed, studies such as the Canadian phase II HEROICC (Hypofractionated External Beam Radiotherapy for Intact Cervical Cancer, NCT04583254) study and the Mexican National Institute of Cancerologia phase II study (NCT04070976) are currently recruiting in this regard and results are awaited.

Local control rates may also potentially be improved through the use of improved brachytherapy. One recommendation would be to have patients examined by a senior registrar or consultant in the department prior to brachytherapy to ensure all disease is covered by the appropriate brachytherapy applicator. For locoregionally advanced disease, modern techniques such as 3D planned brachytherapy and interstitial brachytherapy would also provide better tumour coverage and improve outcomes (95, 96).

This study was limited by poor follow up and departmental efforts should be made to improve this. This could include better counselling for patients at the time of completion of treatment, obtaining ID numbers and multiple contact numbers. The use of cancer therapy navigators has also been demonstrated to improve adherence to cancer care and this could be another consideration for the department (137).

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