Potential prognostic factors for cervical cancer patients undergoing radiotherapy at Charlotte Maxeke Johannesburg Academic Hospital: A retrospective analysis.

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Master of Science in Epidemiology and Biostatistics

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DECLARATION

I Maleshwane Lettie Pule declare that this research report is my own work. It is being submitted for the degree of Master of Science in Epidemiology and Biostatistics in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree examination at this or any other University.

Furthermore, I certify that this research report has the approval of the Human Research Ethics Committee at the University of the Witwatersrand. (Protocol Number: M120370)

Maleshwane Lettie Pule

19th day of May 2014

DEDICATION

In loving memory of my parents, Masetimela Alina Pule and Molahlehi Petrus Pule for their sacrifices and guidance through the years. For instilling in me the value of knowledge and education.

To my husband Thulani Nyathi, for the love and undying support.

To my sisters and brother for their encouragement and faith in me.

To the rest of my family and friends for their prayers and support.

ABSTRACT

Introduction: Although cervical cancer can be prevented through known interventions it still remains a major cause of mortality in developing countries. Currently in South Africa there is little literature on cervical cancer radiotherapy treatment and its prognostic factors. Knowledge of prognostic factors helps in understanding the determinants of a disease better and optimize treatment strategies. The aim of this study was to determine overall survival rate and to investigate potential prognostic factors for cervical cancer in patients who underwent radiotherapy during the period of 1 January 2004 to 31 December 2006 at the Division of Radiation Oncology, Charlotte Maxeke Johannesburg Academic Hospital.

Methods: This was a retrospective cohort study of 900 patients who were treated with radiotherapy between 1 January 2004 and 31 December 2006. Patient and treatment related data was obtained from the hospital treatment records. Follow-up was then censored as of 31st of December 2008. Subjects of this study had either mono-therapy or a combination of therapies: external beam radiotherapy, brachytherapy and chemotherapy. A Cox regression model was fitted to determine the prognostic and predictive factors of cervical cancer. Kaplan Meier methods were used to establish the effect of different socio-demographic and clinic-pathological factors on overall survival. The overall two year survival was also determined.

Results: At 2 years post-treatment for each individual patient, 26 out of 900 patients had died, 281 were still alive and 593 lost to follow up leaving 307 patients available for analysis. The overall 2 year mortality rate was 45 per 1000 person years and highest in the period of 0-6 months. In the final model, completion of brachytherapy remained a significant predictor of survival (HR=0.04, 95% CI: 0.01-0.11, $p<0.001$) after adjusting for all other factors. Furthermore, HIV status was the only significant prognostic factor (HR=3.23, 95% CI: 1.04-

10, p=0.042). Patients who had brachytherapy treatment prescribed and completed the prescription were 96% less likely to die compared to those who didn't complete it at any point in time, after adjusting for age and HIV status. Patients who were HIV positive were approximately three times more likely to die as compared to HIV negative patients at any point in time after adjusting for age and completed brachytherapy. The overall 2-year survival rate was 92% for this group of patients.

Conclusion: Completion of the brachytherapy prescription was a significant predictor of treatment outcome, while the patient's HIV status was also a significant prognostic factor for treatment. Patients who were HIV positive were three-times more likely to die compared to HIV negative patients. The overall 2-year survival rate was 92%, however, these results need to be interpreted with caution due to the large loss to follow-up in this patient population. Prospective clinical trials are recommended in the future to confirm the validity of the findings of this work in a representative patient population. In addition this work puts forward some suggestions to optimize treatment of cervical cancer patients in typical university teaching public health centres in South Africa.

KEY WORDS: prognostic factors, predictors, cervical cancer, overall survival

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Disclaimer

Any opinions, findings, conclusions, or recommendations expressed in this research report are those of the author and do not necessarily reflect the views of the Division of Radiation Oncology, Charlotte Maxeke Johannesburg Academic Hospital.

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ABBREVIATIONS

AS	Age standardized
BRACHY	Brachytherapy
CANSA	Cancer Association of South Africa
CI	Confidence Interval
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CT	Computed Tomography
EBRT	External Beam Radiotherapy
FIGO	International Federation of Gynaecology and Obstetrics
GAVI	Global Access to Vaccines Initiative
HPV	Human Papilloma Virus
HR	Hazard Ratio
IARC	International Agency for Research on Cancer
ICC	Invasive Cervical Cancer
IQR	Inter quartile range
MRI	Magnetic Resonance Imaging
NCR	National Cancer registry
PET	Positron Emission Tomography

PH	proportional hazards
TNM	Tumor, Lymph Node, Metastases
WHO	World Health Organisation

CHAPTER ONE

INTRODUCTION

1.1 What is Cervical Cancer?

The cervix is the lower portion of the uterus that connects the upper vagina to the uterus [1]. It is cylindrical or conical in shape and it protrudes through the upper anterior vaginal wall. The cervix allows flow of menstrual blood from the uterus into the vagina and directs sperms into the uterus. This structure or organ can sometimes be diseased with cancer. Cervical cancer is a disease which affects the cervix in the female reproductive system where malignant (cancer) cells can form in the tissues of the cervix [1]. This is a slow growing cancer which starts as a precancerous condition called dysplasia and its symptoms are thus not always immediately evident [2][3]. This condition can develop into cervical cancer after several years [3]. Cervical cancer can be detected or diagnosed through a regular Pap smear test, a procedure in which cells are scraped from the cervix and looked at under a microscope [2][4]. A persistent infection with human papillomavirus (HPV) of certain subtypes is a necessary condition which leads to the development of most cases of cervical cancer [5][3].

Cervical cancer is the third most common gynaecological malignancy after ovarian and uterine corpus cancers. More than 90% of cervical squamous cell cancers contain DNA evidence of human papillomavirus (HPV). This virus is acquired through sexual activity [6]. HPV is a common sexually transmitted infection (STI) in South Africa and worldwide thus anyone who is sexually active is at risk of being exposed to HPV [7]. In 2004, it was estimated that about 6 800 new infections and 3 700 deaths from cervical cancer were caused by HPV every year in South Africa [8]. Although, studies have shown that the development and inclusion of an HPV vaccine into the national screening programme would decrease HPV

infections which would in turn reduce HPV related cancers, studies published in 2004 showed that the vaccine was still not provided at South African government clinics although available in the private sector [9]. In November 2011, the Global Access to Vaccines Initiative (GAVI) announced the decision to support HPV vaccines in the world's poorest countries even though South Africa as a middle-income country did not qualify for access to the vaccine by GAVI [10]. Recently in South Africa the health ministry announced that from February 2014 a pilot programme will be launched whereby the HPV vaccine will be administered to girls aged between 9 and 12 at some schools [11]. Currently due to the poor health infrastructure and relatively high costs of the vaccine it remains out of reach for most members of the public.

In general as people become more economically viable they will live longer and thus be more prone to cancer. Fortunately cervical cancer is both a preventable and curable disease, however it still poses a serious health problem in the developing world [5][7]. In developing countries cervical cancer is still unnecessarily causing mortality [12]. This unnecessary mortality in developing countries is largely due to a lack of disease awareness programs, lack of screening in order to detect precancerous and early stage cervical cancer, lack of clinical equipment, limited staff training and HIV infection. Analysis of worldwide cervical cancer mortality rates will reveal a lower rate however a targeted analysis of data from developing countries shows that both the mortality and incidence rates are very high [12]. The critical factor in the fight against this disease is early detection and diagnosis given the fact that in its early stages the cancer is curable.

1.2 Signs and Symptoms of Cervical Cancer

In its early stages, the symptoms for cervical cancer are not readily noticeable to the patient. However in advanced stages the affected woman is likely to have the following symptoms:

- Vaginal bleeding
- Bleeding after sexual intercourse
- Heavy and longer menstrual periods
- Pelvic pains
- Post –menopause bleeding
- Pain during sexual intercourse
- Vaginal smelling discharge
- Pain during urination
- Loss of appetite and weight loss
- Changes to bowel and bladder habits

In most cases vaginal bleeding is the most noticeable symptom of cervical cancer [3].

1.3 Risk Factors of Cervical Cancer

Prevention and therapy interventions measures to a disease are likely to succeed if the risk factors are known. Below we look in detail at the various risk factors for cervical cancer.

Human Papillomavirus (HPV)

HPV is a sexually transmitted disease that has been proven to be necessary condition for cervical cancer. Approximately 100% of all cervical cancer cases are caused by HPV [5]. There are different types of HPV and not all of them cause cervical cancer. In general, HPV is classified into two categories according to their risk of causing cervical cancer: high risk type and low risk type. The high risk type HPV causes cervical cancer while the low risk type such as type 6 and 11 causes genital warts[5] [14]. There are 15 HPV types in the high risk category and 12 HPV types in the low risk category. In a study by Denny et al it was showed that HPV types 16, 18, 45 and 35 were the most common HPV types in sub-Saharan African women with invasive cervical cancer and HPV infections were more common in HIV-positive women [14].

Age

Young age at the first full term pregnancy has been shown to increase the risk of cervical cancer. In particular women who were younger than 17 years of age at the first full term pregnancy had 2 times more risk of developing cervical cancer at a later stage in life as compared to those who had their first above age 25 [15]. In South Africa, according to the NCR 2005 women between the age of 40-59 years were more prone to cervical cancer [2].

Risky Sexual Behaviour

The risk factors for cervical cancer closely resemble those of sexually transmitted diseases, some of the risk factors are: first coitus at a young age, multiple sexual partners, history of other sexually transmitted diseases [16]. Given that HPV which is a sexually transmitted disease is the most prominent cause of cervical cancer, it follows that sexual behaviour is a huge factor in causing cervical cancer. A strong association has been observed between

Chlamydia trachomatis with cervical cancer OR = 5.0 (95% CI 1.6 – 15.7) after adjustment for smoking and other STIs. Women with multiple sexual partners have been shown to be more prone to cervical cancer than the control group. In women with only one lifetime sexual partner, the sexual behavior of the male partner has a substantial role in the development of cervical carcinogenesis [17]. In Tunisia a very low rate of incidence was attributed to the late age of first sexual activity.

High Parity

Studies have proved an association between parity and cervical cancer. Women who had more births were more prone to cervical cancer than those who had only 1 or 2 births, OR =2.6 (95% CI 1.6 – 4.3), 3 – 4 births, OR = 5.7 (95% CI 3.0 – 11.1), 5 -6 births and for greater than 7 births, OR = 5.7 (95% CI 2.4 -13.3) [18]. Women who had 3 or more, full term pregnancies also were at increased risk of developing cervical this might have been due to their increased exposure to HPV through unprotected intercourse [15].

Smoking

Tobacco smoking increases the risk of cervical cancer incidence in women. Researchers have found tobacco by products in the cervical mucus of women who smoke and this is believed to cause damage to the DNA of cervix cells as such increasing the development of cervical cancer [15]. Berrinton et al proved a significant increased risk of squamous cell carcinoma OR = 1.47 (95%CI 1.15-1.88) but not of adenocarcinoma OR = 0.82(95%CI 0.60-1.11) [19]

Oral Contraceptives

Women who use oral contraceptives for 5 years or more have been shown to have a higher risk of cervical cancer but the risk goes back down again after the oral contraceptives are stopped [15].

Socio-economic Status

Low socio-economic status and education are risk factors in cervical cancer, in the sense that such people are less likely to take up to cervical cancer screening. Uneducated, poor women are also less likely to access information about cervical cancer and cervical cancer screening. In countries where healthcare is not free then most likely the poor will only present with advanced tumours as they fail to go for screening.

1.4 International Cervical Cancer Screening Recommendations

Much of the success of cervical cancer management worldwide has not only been due to the efficiency of the treatment modalities but also due to the success of mass screening [20][21]. Despite the clear benefits of screening in the fight against cervical cancer, it is not readily accessible in African countries because of lack of resources. In comparison to the primary healthcare demands, HIV pandemic and other urgent health care needs, African countries cannot afford to fund cervical cancer screening and its associated activities.

There are conflicting recommendations on the frequency of screening; the American Cancer Society has recommended that asymptomatic women 20 years of age or older or sexually active have two initial consecutive annual Pap smears and thereafter have at least triennial Pap smears. However the American College of Obstetricians and Gynaecologists strongly advocates for women to undergo Pap smears on an annual basis.

A significant number of women still remain unscreened despite the benefits of screening. In the United States 50% of the women with newly diagnosed invasive cervical cancer have never had a Pap smear, another 10% have not had a Pap smear in 5 years [22]. Interestingly, based on data from the United States, women who are underscreened tend to be postmenopausal, uninsured, ethnic minority, elderly black and poor in rural areas.

1.5 Cervical Cancer Staging

Cancer staging gives a description of the size and spread of the disease. This is done at the time of diagnosis and sometimes also before the treatment where there has been a long gap between diagnosis and treatment, as this can change depending on how quickly the cancer is growing or spreading. Staging describes the extent or spread of the disease at the time of diagnosis. This staging also helps in determining the choice of treatment and it is based on the primary tumour's size and location and whether it has spread to other areas of the body [23]. There are different staging systems such as TNM are used to classify tumours according to the size and extent of the primary tumour (T), absence or presence of regional lymph node involvement (N) and absence and presence of distant metastases (M). Once the T, N, and M are determined, stages are assigned from I, II, III, or IV with stage I being early stage and stage IV being advanced [23]. Figure 2.5 below shows a summary of the description of cervical cancer staging according to FIGO [24].

Table 1.1: The revised FIGO staging for carcinoma of the cervix [24].

Stage I	The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded)
IA	Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤5 mm and largest extension ≥7 mm
IA1	Measured stromal invasion of ≤3.0 mm in depth and extension of ≤7.0 mm
IA2	Measured stromal invasion of >3.0 mm and not >5.0 mm with an extension of not >7.0 mm
IB	Clinically visible lesions limited to the cervix uteri or pre-clinical cancers greater than stage IA *
IB1	Clinically visible lesion ≤4.0 cm in greatest dimension
IB2	Clinically visible lesion >4.0 cm in greatest dimension
Stage II	Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina
IIA	Without parametrial invasion
IIA1	Clinically visible lesion ≤4.0 cm in greatest dimension
IIA2	Clinically visible lesion >4 cm in greatest dimension
IIB	With obvious parametrial invasion
Stage III	The tumor extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney **
IIIA	Tumor involves lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney
Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to Stage IV
IVA	Spread of the growth to adjacent organs
IVB	Spread to distant organs

The International Federation of Gynaecology and Oncology (FIGO) staging classification for cervical cancer is clinically staged, thus failing to officially incorporate modern radiologic methods of staging, including magnetic resonance imaging (MRI), computed tomography (CT) and positron emission tomography (PET). Furthermore the FIGO staging system fails to consider important prognostic variables such as lymph node involvement and to some extent tumor size (tumor size is only recognized for Stage 1B1, IB2 and stage 2 tumors) [25].

1.6 Treatment Options for Cervical Cancer

There is a variety of treatment options for patients with cervical cancer, some of them being surgery, radiation therapy, chemotherapy, therapeutic conization, laser therapy and cryotherapy [26][27][28]. Presently in South Africa the most common treatment modalities of choice are surgery, chemotherapy and radiation therapy. Surgery in the form of hysterectomy involves removal of the uterus. Chemotherapy is the use of drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. These drugs can either be given by mouth, injected into a vein or muscle, or placed directly into a spinal column, organ or cavity. The method used for the administration of chemotherapy depends on the type and the stage of the cancer. Radiation therapy uses high-energy x-rays or other types of ionizing radiation to kill cancer cells or keep them from growing [29]. There are two types of radiation therapy which are external beam radiation therapy uses a machine outside the body to send radiation toward the cancer and brachytherapy also known as short distance therapy which uses a radioactive sources sealed in needles, seeds, wires, or catheters that are placed directly into or near the cancer. The way the radiation therapy is given also depends on the type and stage of the cancer being treated [29].

Surgery is generally the preferred option in young women with small squamous carcinoma to avoid radiation-related ovarian failure and minimize the risk of sexual dysfunction. Aggressive radiation therapy, involving a combination of external beam radiotherapy and brachytherapy, concurrent with cisplatin-based chemotherapy is now the standard of care in treating bulky and loco-regionally advanced tumors [30]. Figure below gives a summary of the treatment options for different stages in cervical cancer.

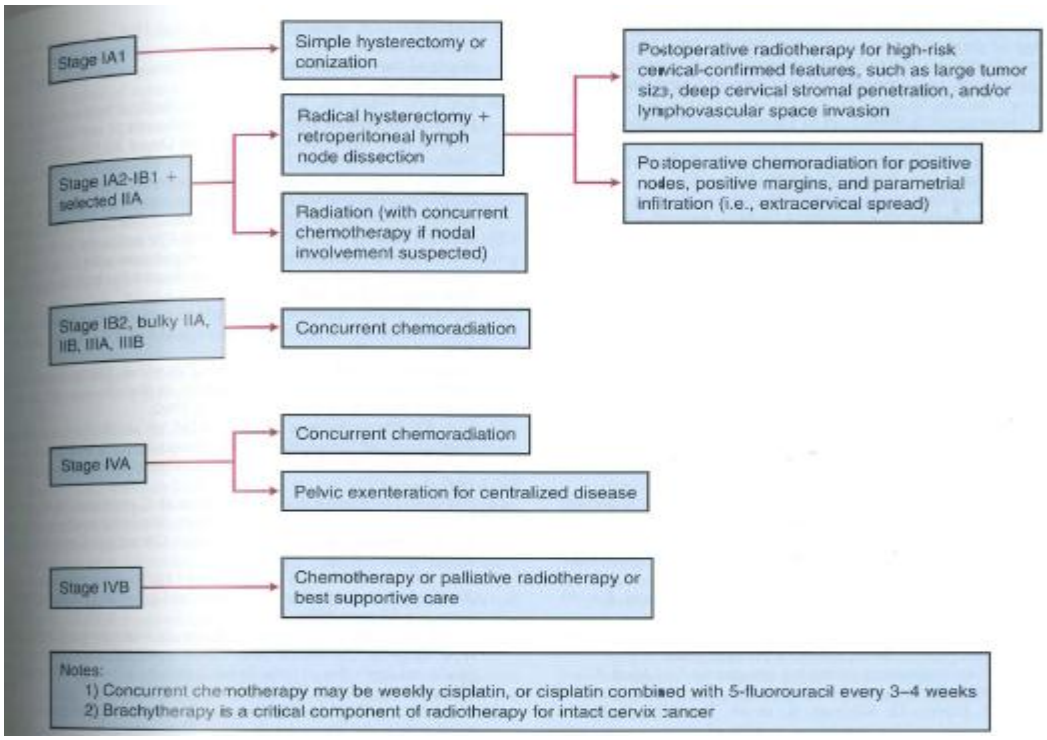

Figure 1.1: Treatment options for the different stages in cervical cancer [30].

1.7 Epidemiology - Worldwide

Worldwide cervical cancer is the fourth most common malignancy in women [12]. The wide range in the incidence rates across the globe potentially reflects the variation in epidemiologic risk factors that is compounded by lack of screening resources in poor communities or countries. Figure 1.2 below shows the worlds' age standardized incidence and mortality rates estimates as at 2012 [12].

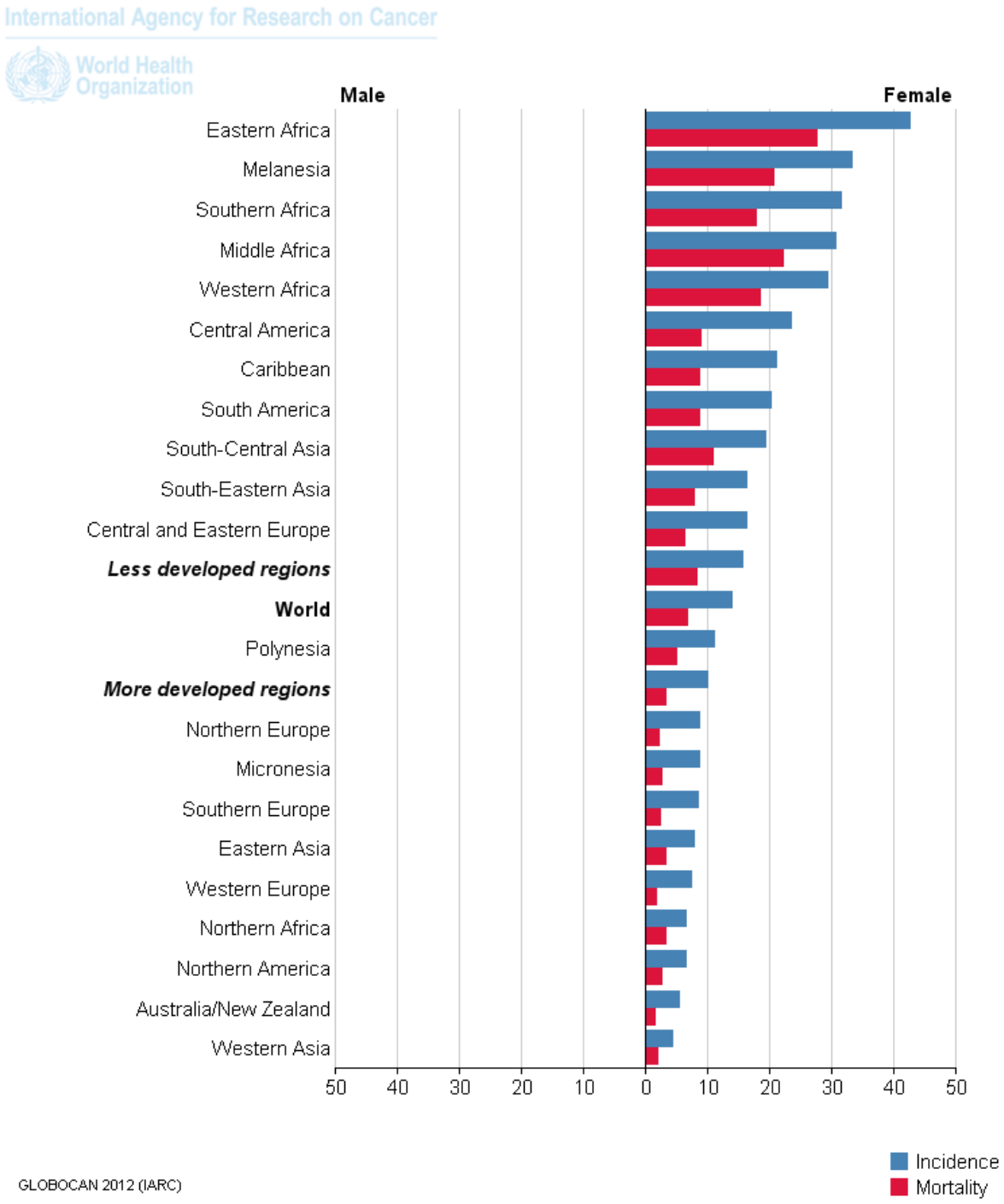

Figure 1.2: Estimates of world cervical cancer age-standerdized incidence and mortality rates in 2012 [12].

The above graphs shows that cervical cancer incidence rates were lowest in Western Asia and highest in Eastern Africa [12].

A full representation of the incidence rates worldwide is given in Figure 1.3. Below is a representation of the cervical cancer incidence rates in the world as of the year 2012. There is a wide variation in the incidence rates across the world, with rates ranging from 5.5 per 100 000 in Australia/New Zealand and 4.4 per 100 000 in Western Asia to 42.7 per 100 000 in Eastern Africa in 2012 [12].

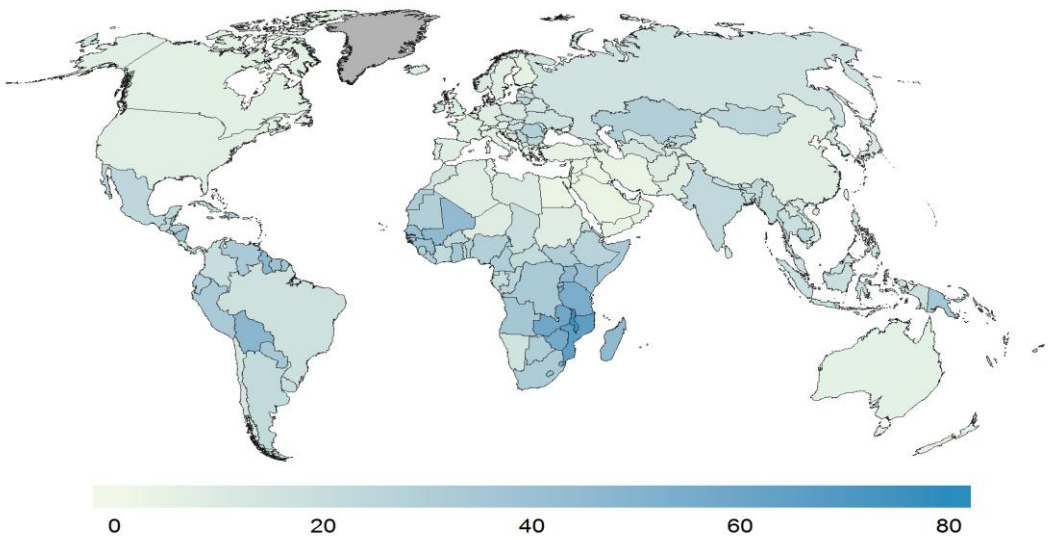

Figure 1.3: Estimated cervical cancer incidence worldwide in 2012 [12].

The trend in most countries all over the world shows that there is a general decline in cancer incidence rates. Below are trend graphs for different countries showing the incidence rates [12].

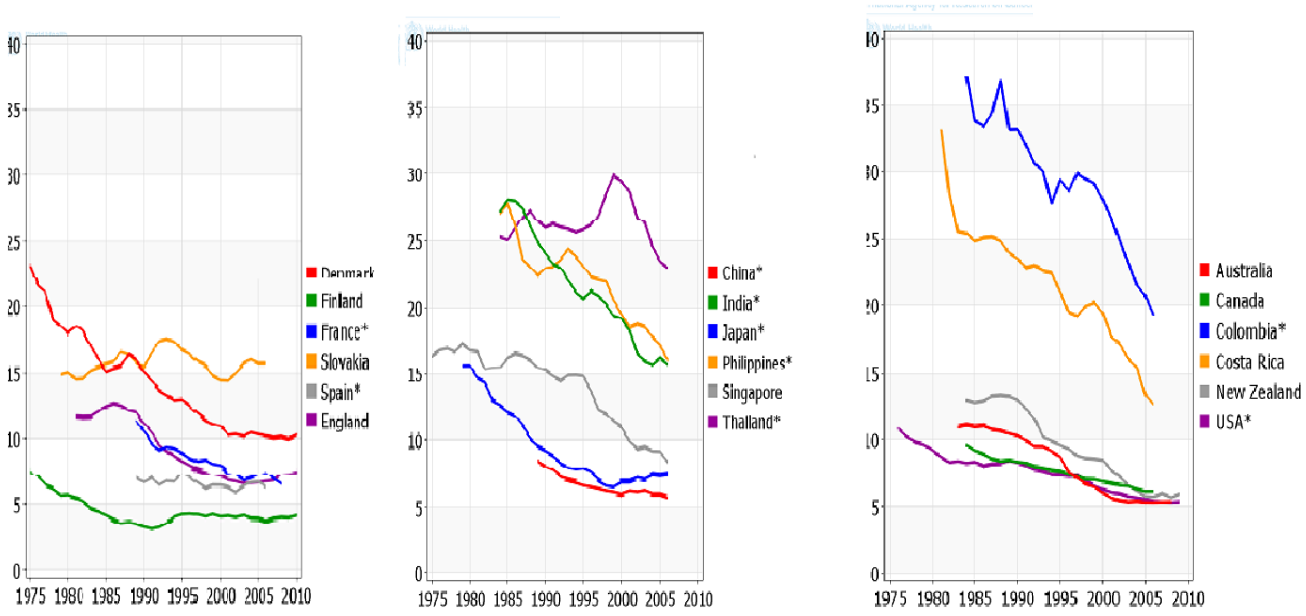

Figure 1.4: Trends in incidence of cervical cancer in a few selected countries: age standardized rate per 100 000 in 2012[12].

India, despite still having high incidence rates has managed to reduce these rates over the last decade. The Indian experience can be compared to South Africa as their healthcare challenges are similar.

In 2012 there were 266 000 deaths from cervical cancer worldwide, which accounted for 7.5% of the total cancer deaths in women. Of these deaths, 87% occurred in developing countries. Below is a world map showing mortality rates world-wide [12].

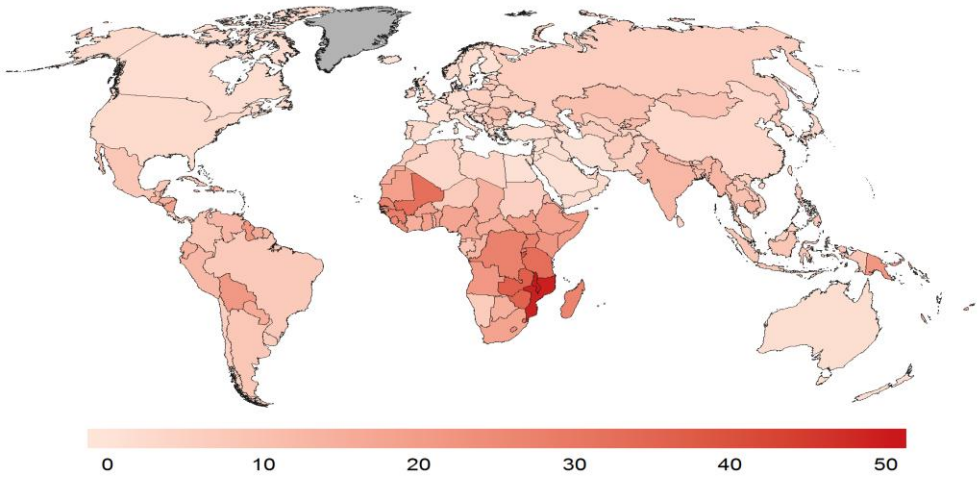

Figure 1.5: Age standardized cervical cancer mortality rates per 100 000 worldwide in 2012 [12].

As the case with incidence rates there is a wide variation between the mortality rates across the world. The mortality rates are generally high in developing countries, for example in 2012 the mortality rates ranged from 2 per 100 000 in Western Europe, Western Asia and Australia/New Zealand to 27.6 per 100 000 in East Africa [12].

1.8 Epidemiology – South Africa

Cervical cancer is the fourth most common cancer in women worldwide [12]. In 2012, about 85 % of the cancers occurred in developing countries, representing 12% of all female cancers [12]. According to South African statistics, cervical cancer is the second most common

female cancer in South Africa [7]. Figure 1.6 below shows the incidence for cervical cancer compared to other cancers among South African women of all ages [5].

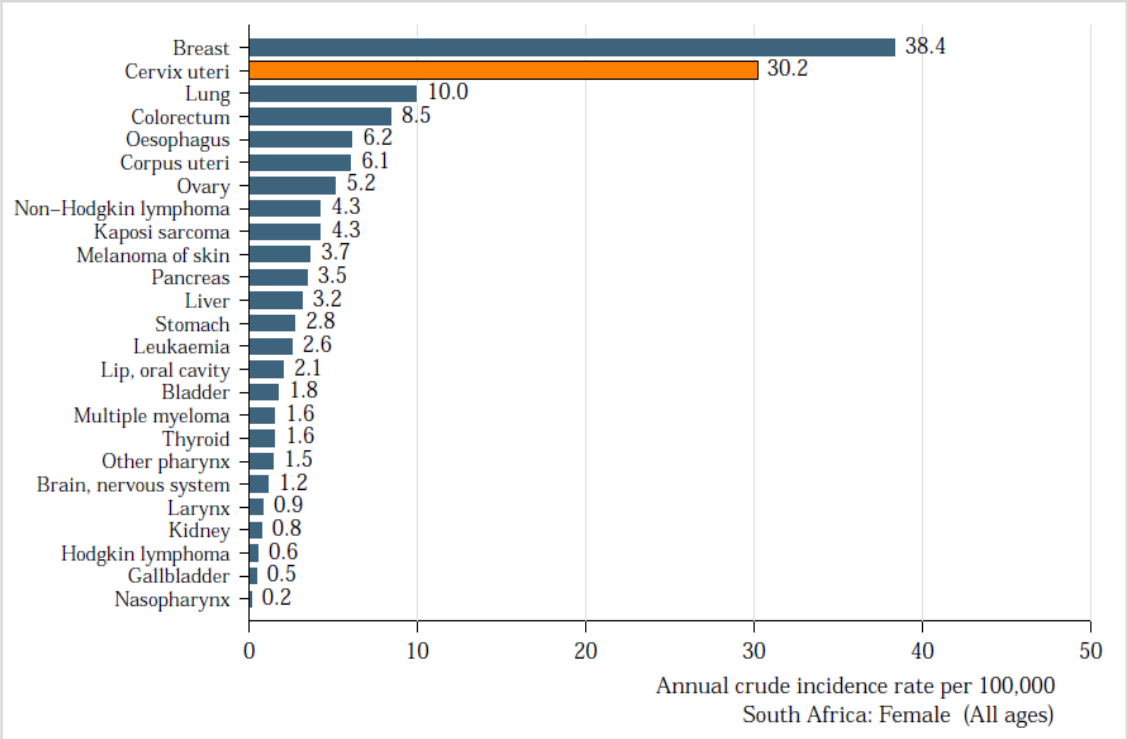

Figure 1.6: Annual crude incidence rate per 100 000 in South African women of all ages, 2014 [5]

According to the South African National Cancer Registry (2005) the lifetime risk of developing cervical cancer is 1 in 39 for all females, 1 in 92 for Asian, 1 in 33 for black, 1 in 44 for coloured and 1 in 81 for white females [2]. The number of histologically diagnosed cervical cancer per age group in South Africa is shown in Table 1.2 below [2]

Table 1.2: The number of histologically diagnosed cervical cancer among South African women according to age and ethnicity (SA NCR 2005) [2]

Group	Age groups (years)					
	0 – 29	30 – 39	40 – 49	50 – 59	60 – 69	70+
All	115	676	1158	1077	847	608
Asian	1	8	17	14	15	2
Black	84	495	840	804	646	438
Coloured	14	65	105	102	62	34
White	7	62	127	94	55	91

CHAPTER TWO

LITERATURE REVIEW

2.1 Prognostic Factors

Determination of prognostic factors helps in predicting the outcome or occurrences of diseases in the population and guides use of health care system resources. This also helps in designing public health prevention and intervention measures in order to reduce the incidences and severity of these particular diseases based on the results of these studies. Prognostic factors of cervical cancer have mostly been studied in the US, Canada, India to name a few, below are examples of such studies. A literature search shows an apparent scarcity of data from low-to-middle income countries, thus the motivation for this study. Below a number of potential prognostic factors for the cervical cancer are discussed.

2.2 Studies from Developed Countries

Below is a discussion of cervical cancer prognostic factors as determined by studies in first world countries.

Age

The issue of age as a prognostic factor in cervical cancer has been surrounded with controversy with some investigators being of the view that age is not a prognostic factor [31]. In addition there has been conflicting conclusions with some studies observing decreased survival rates in younger patients while others have findings to the contrary. Dattoli et al. observed a decrease in survival rates for patients younger than 35 or 40 years [32]. In

contrast, two European studies showed improved treatment outcomes in younger patients [33]. In contrast, Kastritis et al observed younger patients (less than 35 years) and older patients (above 70 years) to have the worst survival post treatment [34]. A review based on American data by Duarte-Franco and Franco concluded that in general patient survival decreased with increasing age [35]. Given the different conclusions from different studies the proposed study will derive home grown data and thus relevant conclusions to our local patient population.

Human Immunodeficiency Virus (HIV)

The International Atomic Energy Agency (IAEA) technical document on the role of radiotherapy in HIV infected patients recommends that for patients presenting with early stage disease and profound immunosuppression, the HIV infection rather than the tumour should dictate the prognosis [36]. Conversely for those patients presenting with advanced disease but with normal CD4 counts, the prognosis is dominated by the tumour. In the developed world, some studies have shown that HIV positive patients are at a higher risk for tumor recurrence after treatment and death as a consequence of the malignant process [37][38].

Tumor Stage

The clinical stage of the cervical cancer at the time of commencement of treatment has proved to have an effect on treatment outcome. Cervical cancer is classified into four stages (Stage I to Stage IV), each stage with sub categories; however the tumour size increases from Stage I through to Stage IV. Chances of disease control decreases from 95% to 10% for Stage I and Stage IV tumours respectively [7][1]. Patients with advanced clinical stage had poor prognosis as compared to those with early stage. Hopkins and Morley [39] and two other

authors also confirmed that the higher the cancer stage the poorer the prognosis in their studies [40][35].

The spread of the cancer to nearby lymph nodes has an effect on treatment outcome. For example for a Stage IA cancer the 5-year survival rates are 25% to 60% lower in women with positive lymph nodes in comparison to those with negative status [35]. Based on clinicopathologic review of patients Hopkins and Morley also showed that urethral obstruction and renal failure lead to a poor prognosis for patients being treated for cervical cancer [39]. A striking recommendation of their research was that for advanced Stage IVa there is a chance of significant survival. This is particularly encouraging in the South African set-up where patients normally present with advanced disease.

Treatment Modalities

The treatment of cervical cancer is normally achieved by use of multi-therapy strategies, which is through radiation therapy, surgery and chemotherapy. It has been postulated that a combination of chemotherapy and radiation leads to superior treatment outcomes in comparison the use of radiation therapy only. However, the study by Duval revealed that there was a doubtful survival benefit when postoperative external beam radiotherapy is used alone as compared to being used in conjunction with chemotherapy [41]. In a study published in 2000 by William et al based on data collected from 1991 to 1996 post-operative radiation therapy alone and radiation therapy in combination with chemotherapy as a prescribed treatment was investigated with regard to improved overall survival of early stage cervical cancer patients [42]. This study showed a 71% overall survival in patients treated with radiation therapy only and 81% overall survival in those treated with both chemotherapy and

radiation therapy. There is however, conflicting findings from clinical researchers on the effect of chemotherapy drugs given concurrently with radiation on treatment outcomes [42][43][44].

Treatment Time/Duration

Time is an important parameter in the management of cancer, i.e. initiation of treatment and duration of treatment. Cancer cells are in a state of perpetual growth and multiplication so the timing of the intervention procedure is critical. If the intervention is done late in the life of the cancer then it is difficult to control the disease as most likely it would have metastasized. On the other hand if the intervention occurs over a prolonged period it won't be able to suppress or catch-up with the tumour growth, bearing in mind that an intervention naturally triggers repopulation of the tumour. Duval showed in his literature review that an increase in the overall treatment time due to treatment interruptions (for example lack of adherence to treatment, machine breakdown), reduced the biological effect and hence the probability of cure [41]. In radiation therapy, it has been estimated that for every one day increase in total treatment time, the loss in biological effect is equivalent to a 0.6 Gy dose reduction [45]. In addition, Fyles et al studied the effect of treatment time on disease/pelvic local control and also found that there was 1% loss of control per day of treatment prolonged beyond 30 days. This effect was even more in stages III and IV as compared to stages I and II [46]. These effects remained significant after accounting for other factors thought to may have had influence in the local control such as, treatment complications and many more. In their conclusion unnecessary delays especially in stage III and IV patients should therefore be avoided.

2.3 Studies from Developing Countries

As has been pointed elsewhere in this research report, published data on cervical cancer from low-to-middle income countries is sparse. Below is a review of the few data from African studies and other developing countries. Rogo et al carried out a study to describe the prevalence and distribution of cervical cancer in sub-Saharan Africa, using Kenyan data [47]. All the patients were staged according to the FIGO clinical staging and allocated to either receive radical hysterectomy and/or radiotherapy for early stages and radiotherapy only for those in late stages. The results showed no correlation between prevalence and ethnic patterns, geographical and socioeconomic status. Also showed a large number of late stages for younger age groups in contrast to the data from Geetha [40]. Thus confirming that in developing countries the disease is mostly detected at its late stage. Survival rates were however shown to be best for patients given combined teletheraphy and brachytherapy which contradicts the study by Melahat et al [48].

Age

In a retrospective study by Geetha et al done in India, the effect of the patient's age as a prognostic factor was investigated [40]. Their results showed that the incidence of cervical cancer was less in young women below the age of 30 and older women above 70. In addition, the study found that younger patients (less than or equal to 30 years) had longer post treatment survival as well as older patients above age 70.

HIV

The scourge of HIV AIDS has affected every facet of disease management. Studies done around the world have shown that people with HIV have a higher risk of some types of cancers than uninfected people due to a weakened immune system caused by HIV

[49][50][51][52][53]. Cancers like cervical cancer, non-Hodgkin lymphoma and Kaposi sarcoma have been labeled as "AIDS-defining conditions" meaning that they signify AIDS in HIV infected people. HIV infected women are at a high risk of cervical intraepithelial neoplasia (CIN), however, there is no demonstration of an excess risk of invasive cervical cancer [54]. The IAEA points out the need to establish the effect of radical radiotherapy on HIV positive women with cervical cancer. In addition they suggest that such data be from countries with high prevalence of both HIV and cervical cancer of which South Africa suits the criteria.

In agreement with other studies done in developed countries, Campbell et al have studied HIV positive patients with carcinoma of uterine cervix and they concluded that HIV positive patients had more advanced tumors and a shorter remission period [55]. Kigula-Mugambe and Kavuma found that, the survival probabilities for HIV positive patients were less than that of HIV negative ones, and at 4 years the survival probability had dropped to 0% and 46% respectively [56]. This was in agreement with another study by Maiman et al which showed that HIV positive patients had a poorer response to treatment than their HIV negative counterparts [57]. In addition both studies showed that HIV positive patients presented with more advanced stage disease and their survival probabilities had a rapid fall off. This shows the importance of screening programs in high risk groups such as HIV positive patients which can lead to an increase in early disease detection and better treatment outcomes [56][57].

Tumour Stage

A Thai study demonstrated that cancer stage as a prognostic factor was statistically significant (p-value < 0.001) in survival of patients. In this study Stage III patients had a 1.65-fold mortality risk compared to Stage I patients (95% CI 1.05 – 2.59) [58]. This is in agreement with studies done in developed countries which proved that, patients with

advanced clinical stage had poor prognosis as compared to those with early stage. In a study by Pesee et al it was established that patients with tumours less than 2 cm had superior 5 year overall survival compared to those with tumours greater than 2 cm [59].

Timing of Treatment Commencement

A study conducted by Pomros and co-investigators proved that the timing of administration of brachytherapy was a significant (p-value < 0.001) prognostic factor in cancer of the cervix. This study showed that patients who had their brachytherapy administered in over 28 days since the start of external beam therapy had a 2.28-fold mortality risk compared to those who had brachytherapy within a day of external beam therapy (95% CI =1.40 – 2.44) [58].

2.4 Status of screening in South Africa

A persistent infection of some oncogenic strains of HPV has been proven to be a necessary condition for the development of most cases of cervical cancer [5]. There are a number of HPV subtypes, namely, types 16, 18, 31, 33, 35 and 45 of which types 16 and 18 present the highest risk of inducing cervical cancer globally [60]. However availability of vaccines against the oncogenic strains of HPV provides hope in the fight against cervical cancer in South Africa. This hope is premised on the idea that a lower HPV infection rate should in turn drastically reduce the incidence rates of cervical cancer. Success of the vaccination programs is pinned on aggressive awareness and screening campaigns.

In 2001, South Africa launched the national cervical cancer screening programme, which offered women aged 30 years and above 3 free Pap smears per lifetime every 10 years [61]. The program's goal was to screen about 70% of women attending public sector services, over

the age of 30 years within 10 years, after the implementation of the policy. A study conducted by Moodley *et al* 2006, showed difficulties with implementation of the cervical cancer screening programme in South Africa [61]. Although in South Africa there has been implementation of such policies, there has been a lot of debate as to what is the most suitable policy with regards to the age at which the smear should be done and time interval between smears as well as how often for HIV positive women [62][63]. The jury is still out on whether the programmes have been effective in reducing the incidence of invasive cancer in South Africa. In a paper by Hoffman et al, it was shown that screening had been done mostly for young age groups who are relatively at low risk [62]. This is because the services are performed when women attend public health services for family planning and antenatal clinics and the majority of these women would be below 30 years of age. The study was done to investigate the effect of Pap smear screening on the incidence of invasive cervical cancer among women below age 65 years in the Western Cape, South Africa where screening is said to be limited. The results confirmed that there was a decrease in the incidence of invasive disease due to screening. There was 57% reduction in coloured women and 37% in black African women. The reduction in the risk was greater with frequent screening regardless of the acknowledged limitations in the quality and quantity of the screening programme [62]. It therefore stands to reason that further risk reduction is expected with improved screening performance standards and widespread use of Pap smear tests targeted to the appropriate age groups at risk.

Hoque et al conducted a study to assess the level of knowledge of the risk factors of and attitude towards cervical cancer among female university students in South Africa, through a self-administered and anonymous questionnaire. The results revealed that a large number of students were sexually active, had more than one partner and had previously contracted STDs, had long use of contraceptives and smoked [64]. Risky sexual behaviour leads to an

increase in HPV prevalence which would in turn increase the risk of cervical cancer. Most of these students had never heard of Pap smear test, cervical cancer and its risk factors. Those who knew about it did not know it was preventable and that the Pap smear test was used as a detection and prevention method for cervical cancer. This shows that a lot of work still has to be done to promote health education in order to reduce the spread of preventable health conditions.

2.5 Problem Statement

Research publications on the determination of the prognostic factors of cervical cancer in South Africa are scarce. As a result the treatment protocols used in South Africa are adopted from international studies without appropriately taking into consideration local circumstances and context. The proposed study will elucidate prognostic factors for treatment of cervical cancer with the aim to identify factors which will optimize the treatment protocol at Charlotte Maxeke Johannesburg Academic Hospital, South Africa and potentially be relevant to any typical developing world clinical setting.

2.6 Justification

Health systems use valuable resources and personnel as such it is important that the system is regularly evaluated and improved in order to use it to its fullest effect. This can be done by examining factors which can help with patient's prognosis on individual basis, this is important for a number of reasons, for example it aids in identifying those patients who are most likely to benefit from early detection and treatment. In addition knowledge of

prognostic factors helps health workers understand the determinants of a disease better and thus encourage and stimulate future research. Furthermore, with knowledge of prognostic factors health workers can ably give recommendations and support for the planning of future clinical trials, for example, selection of patients, stratification, development of new local treatment protocols etc. Current clinical practice in radiation therapy is informed by protocols designed in developed countries, which is not a necessarily representative patient population and the challenges of the healthcare systems are different. It is therefore important that local data is collected and analysed with the aim of developing treatment protocols based on the local patient population. In the specific context of this study, it is envisaged that results of this study will lead to an optimized radiotherapy strategy informed by statistically significant prognostic factors of cervical cancer in a typical South African patient population.

2.7 Objectives

The aim of this study is to investigate potential prognostic factors for cervical cancer in patients who underwent radiotherapy during the period of 1 January 2004 to 31 December 2006 at the Division of Radiation Oncology, Charlotte Maxeke Johannesburg Academic Hospital, with follow-up visits up to 31 December 2008 post-treatment completion. Some of the patients would have in addition to radiotherapy had other forms of therapy, for example surgery or chemotherapy.

The specific objectives of this study are:

1. To describe socio-demographic characteristics of cancer patients who underwent radiotherapy at Charlotte Maxeke Johannesburg Academic Hospital treated during the period: 1 January 2004 to 31 December 2006.

2. To identify potential prognostic factors for cervical cancer patients undergoing radiotherapy.

3. To determine the 2 year overall survival rate for the same group of patients.

4. To determine the effect of the tested prognostic factors on overall survival rate.

CHAPTER THREE

METHODS

3.1 Study design

A retrospective cohort study on cervical cancer patients treated at the Division of Radiation Oncology, Charlotte Maxeke Johannesburg Academic Hospital during the period 1 January 2004 to 31 December 2006 with treatment data available was conducted. For any study on prognostic factors to be statistically sound the patients have to be followed up for a minimum period of 5 years. Given this requisite for a fairly long follow-up period, a prospective study is not feasible thus a retrospective study has been adopted.

3.2 Study area

The study was conducted at the Division of Radiation Oncology, Charlotte Maxeke Johannesburg Academic Hospital which is a public/government hospital based at Johannesburg, Gauteng. The hospital receives patients from most parts of Gauteng and some parts of the North West province. The number of patients with cervical cancer treated in the hospital ranges between 500 and 600 yearly. This hospital's Radiation Oncology department is the largest of the two available public oncology centres thus this is likely to be representative of cervical cancer population in the South African public sector.

3.3 Study population

All cervical cancer patients who had undergone radiotherapy treatment at Charlotte Maxeke Johannesburg Academic Hospital, during the period 1 January 2004 to 31 December 2006 were eligible for this study.

3.4 Inclusion and Exclusion Criteria

All cervical cancer patients treated during the period of 1 January 2004 to 31 December 2006 with follow up visits of at least two years post treatment were eligible for the study.

All cervical cancer patients, who were lost to follow up before cut off date/end of study period 31 December 2008 were excluded from the study.

3.5 Sampling and Sample Size

At the end of the 2 years follow up period post treatment, only 307 patients who had complete follow up data were included in the analysis.

3.6 Data collection

To evaluate all the objectives of the study, a data collection sheet was designed for recording the information gathered from the patients' hospital records. Information collected included patient demographics, clinical history and treatment regime and post treatment follow up dates. From the hard copy data collection sheet the data was manually transferred into the software Epi Info Version 3.5.1 database. To avoid transcription errors all the collected raw data was verified and validated (cleaned) before analysis. All the analysis was done with STATA Version 12.

3.7 Data Collection and Management

Data was collected from patients' hospital records, from which various socio-demographic characteristics of the patient population were recorded. In addition patient clinical data and dosimetry parameters were collected from the patient's file. Follow-up information was obtained from doctors review/follow up notes in patient's hospital file (patients see the consulting radiation oncologist as follows: weekly while patient is on treatment, every three months post treatment during the first year, bi-annual in the second year post treatment and thereafter once a year). Patients who were lost to follow up were dropped from the study. All the data collection was exclusively done by the author.

3.8 Definition of terms

For the purposes of this study the following definitions apply:

Table 3.1: Definition of terms used in this study.

Term	**Definition**
Alive	All patients who are alive two years after treatment (living with nor without the disease)
Dead	All patients who had died or got lost to follow up before 31 December 2008.
Age	Date of birth to date of diagnosis.
Treatment duration days	Treatment Start Date – Treatment End Date
Waiting period	Date of Diagnosis – Treatment Start Date
Last follow up date	Date last seen alive at the clinic post treatment.

3.9 Statistical Analysis Plan

The statistical analysis plan is described below.

3.9.1 Descriptive Statistics

The data was subdivided into demographic characteristics, clinical presentation of the disease and treatment history. The study populations' demographic characteristics were summarized in the tabular form. Continuous variables were summarized and described using their mean and standard deviation if their distribution was normal or median and inter-quartile range if they were not normally distributed. Categorical variables were tabulated and described using their frequencies and percentages. The participants were then grouped according to their mortality status and the differences between these groups tabulated. To test whether the difference was significant a chi squared test was used for all categorical variables. The difference was considered significant if the p-value was < 0.2.

3.9.2 Inferential Statistics

Inferential statistics was used to determine the impact of the potential prognostic factors on treatment outcome in terms of the overall survival of cancer patients on radiotherapy**.**

Treatment outcome in terms of patient overall 2 years survival was described using Kaplan Meier survival curves. The influence of different socio-demographic and clinico-pathological factors was analysed using Kaplan Meier survival curves. To tests whether the difference observed on the survival curves was significant, a log-rank test was done. The difference was considered significant if the p-value was less than 0.2.

Cox proportional hazard regression model was used to assess the impact of potential prognostics factors on the overall survival. The underlying time variable in the counting process was treatment end date with entry time defined as the subject's date at the end of

treatment and exit time as date of last follow up/death, whichever came first. Factors identified in univariate analysis with a p-value ≤ 0.20 were considered as potential candidates of the final model and therefore added in the multivariate model. Factors that were found to be significant prognostic factors from previous studies were also included in the multivariate analysis. For the final model factors that had a p-value <0.05 in the multivariate model were included. Proportionality assumption, which is one of the main assumptions of Cox proportional hazard model was tested for using the Schoenfeld and scaled Schoenfeld residual method. Also the goodness of fit of the model was tested using Cox Snell residuals.

3.10 Ethical Considerations

To maintain confidentiality and protect patients' identity, all the participants in the study were given a unique identifier and their personal details such as names were removed before any data was described and analyzed. This study was approved by Human Research Ethics Committee at the University of the Witwatersrand.

CHAPTER FOUR

RESULTS

This chapter gives a summary of the study results. The descriptive characteristics of the study participants are first reported then the association between mortality and study variables are explored and finally the potential prognostic and predictive factors identified. The incident rates and cumulative probabilities of mortality were also reported.

4.1 Descriptive Statistics

4.1.1 Descriptive statistics of the cohort

There were 1119 patients treated between the periods of 1 January 2004 – 31 December 2006 although not all of them met the inclusion criteria. 202 of the 1119 patients didn't have any follow up data and 17 were duplicates and were therefore dropped. A further 593 were lost to follow up and dropped, resulting in 307 study participants for the analysis who had complete treatment data 2 years post treatment. Table 4.1 below gives a description of the demographic characteristics of patients who were enrolled in the study.

Table 4.1: Frequency table of demographic characteristics of participants

Variables	Number N=307	Percentage %
Age group: <30	7	2.3
30-39	54	17.6
40-49	102	33.2
50-59	78	25.4
60-69	39	12.7
70+	14	4.6
Missing*	13	4.2
Marital Status		
Married	127	41.4
Single	136	44.3
Missing	44	14.3
Parity: 0	4	1.3
1-4	36	11.7
5-8	146	47.6
9+	64	20.8
Missing[1]	57	18.6
HIV Status		
Positive	71	23.1
Negative	231	75.2
Missing	5	1.6
CD4 Count		
≤ 200	19	26.8
>200	49	69.0
Missing	3	4.2
Province		
Gauteng	278	90.6
North West	29	9.4
Alive at 2 Years		
Alive	281	31.2
Dead	26	2.9
Lost to follow up	593	65.9

The average age of participants was 49.1 years (standard deviation 11 years). The majority of women (33%) were between the age of 40 and 49 years and only five percent (5%) were above the age of 70. Forty one percent (41%) of them were married. Twenty three percent (23%) of the women were HIV positive; two thirds (69%) had a CD4 count above 200. The majority of these women (91%) came from different areas in Gauteng province. At the end of

* Missing: Not documented

follow up (2 years), only 3% out of the 307 with known outcome were dead. There was 66% loss to follow up at the end of study follow up period.

Furthermore the patient population was stratified according to their clinico-pathology characteristics. Table 4.2 below gives a descriptive summary of the clinical presentation of the disease of the patients.

Table 4.2: Descriptive summary of clinical presentation of the disease

Variables	**Number N=307**	**Percentage %**
Type of Cancer		
Adeno Carcinoma	29	9.5
Squamous Cell Carcinoma	269	87.6
Missing[†]	9	2.9
Patient General Condition		
Ecog 0-1	265	86.3
Ecog 2	29	9.5
Ecog 3-4	3	1.0
Missing	10	3.3
Cancer Stage at Treatment		
I	47	15.3
II	157	51.1
III	96	31.3
IV	7	2.3

Squamous cell carcinoma was the leading histological type (88%) followed by adeno carcinoma (9%) and the other 3% had missing type. Eighty six percent of the patients (86%) had good general conditions according to their ECOG score. Most patients had stage II (51%) and stage III (31%) and only fifteen percent (15%) had early stage I.

[†] Missing: Not documented

Patients in this study had mono-therapy or multi-therapy, the available therapy options being: EBRT, brachytherapy or chemotherapy. Table 4.3 below gives a descriptive summary of the treatment modality used.

Table 4.3: Descriptive summary of treatment modality history

Variables	**Number N=307**	**Percentage %**
Treatment Modality		
EBRT[1] Only	10	3.3
EBRT + Brachytherapy	116	37.8
EBRT+ Brachytherapy+ Chemotherapy	181	59.0
EBRT Completed		
Yes	273	88.9
No	34	11.1
Brachytherapy Completed		
Yes	277	90.2
No	20	6.5
Not Prescribed	10	3.3
Chemotherapy Prescribed		
Yes	181	59.0
No	117	38.1
Missing[2]	9	2.9
Completed Follow UP		
Yes	281	91.5
No	26	8.5
Treatment Duration[3] days group		
≤ 60 days	299	97.4
>60 days	8	2.6
Waiting Period[4](Diagnosis-Treat)		
0-6 months	225	73.3
6-12 months	52	16.9
12+ months	17	5.5
Missing[2]	13	4.2
Total Follow Up Completed		
< 6 Months	13	4.2
6 – 12 months	9	2.9
12 – 18 months	3	1.0
18 – 24 months	282	91.9

[1]EBRT: External beam radiotherapy
[2] Missing: Not documented
[3] Treatment duration days: Treatment Start Date – Treatment End Date
[4] Waiting period: Date of Diagnosis – Treatment Start Date

Most patients (59%) were treated with a combination of external beam radiotherapy plus brachytherapy and chemotherapy, followed by those treated with external beam radiotherapy plus brachytherapy only (38%). Only three percent (3%) of the patients were treated with external beam radiotherapy only. Eighty nine percent (89%) of the patients receiving external beam radiotherapy completed it while 90% of those prescribed brachytherapy completed it. 97% of patients finished the prescribed treatment within 60 days. 92% of the patients completed the 2 years follow up period.

4.1.2 Descriptive characteristics and association of the cohort with mortality

At the end of follow up period (30 December 2008) only 26 patients out of 900 enrolled between 1 January 2004 and 31 December 2006, were known to be dead. A total of 593 became lost to follow up and were dropped. 281 patients were still alive at the end of the study period. Table 4.4 shows the descriptive characteristics of patients who died and those who were still alive. The difference between these two groups (Alive/Dead), were then tested using Chi-squared test for all categorical variables. In Table 4.4 the percentages in brackets represent the proportion in that particular group.

Table 4.4: Demographic factors associated with crude mortality

Variable	**Mortality = 0 (Alive) N=281**	**Mortality= 1 (Dead) N=26**	**p-value**[‡]
Age group: 0-29	6 (85.7%)	1 (14.3%)	
30-39	49 (90.7%)	5 (9.26%)	
40-49	93 (91.2%)	9 (8.8%)	
50-59	75 (96.2%)	3 (3.9%)	0.544
60-69	35 (89.7%)	4 (10.3%)	
70+	14 (100%)	0 (0.00%)	
Marital Status			
Married	120(94.5%)	7 (5.5%)	
Single	128(94.1%)	8 (5.9%)	0.897
Parity group			
No Children	3 (75.0%)	1 (25.0%)	
1-4	34 (94.4%)	2 (5.6%)	0.594
5-8	134 (91.8%)	12 (8.2%)	
9+	58 (90.6%)	6 (9.4%)	
HIV status			
Negative	217 (93.9%)	14 (6.1%)	**0.012**[§]
Positive	60 (84.5%)	11 (15.5%)	
CD4 Count group			
≤ 200	16 (84.2%)	3 (15.8%)	0.875
>200	42 (85.7%)	7 (14.3%)	
Province			
Gauteng	255 (91.7%)	23 (8.3%)	0.703
North West	26 (89.7%)	3 (10.3%)	

The relationship between demographic factors with crude mortality was determined using chi squared test. Factors which had a p-value < 0.2 were considered to have a significant relationship with crude mortality. Only HIV status (p-value 0.012) had a statistically significant relationship with mortality. As a proportion HIV positive patients died more in comparison to HIV negative patients.

[‡] p-value from chi squared test for categorical variables

[§] Statistically significant

Table 4.5: Clinical presentation and treatment modality factors associated with crude mortality

Variable	Mortality = 0 (Alive) N=282	Mortality= 1 (Dead) N=26	p-value
Type of Cancer			
Adeno Carcinoma	26 (89.7%)	3 (10.3%)	
SCC	247 (91.8%)	22 (8.2%)	0.689
Cancer Stage at Treatment			
Stage I	45 (95.7%)	2 (4.3%)	
Stage II	150 (95.5%)	7 (4.5%)	**0.002**♦
Stage III	81 (84.4%)	15 (15.6%)	
Stage IV	5 (71.4)	2 (28.6%)	
EBRT Completed			
No	24 (70.6%)	10 (29.4%)	**0.001**♦
Yes	257 (94.1%)	16 (5.9%)	
Brachytherapy Completed			
No	7(35.0%)	13 (65.0%)	**0.001**♦
Yes	266 (96.0%)	11 (4.0%)	
Chemotherapy Prescribed			
No	101 (86.3 %)	16 (13.7%)	**0.008**♦
Yes	172 (95.0%)	9 (5.0%)	
Total Followup Completed			
< 6 months	0 (0%)	13 (100.0%)	
6 - 12 months	0 (0%)	9(100.0%)	
12 – 18 months	0 (0%)	3(100.0%)	**0.001**♦
18 – 24 months	281 (99.6%)	1(0.4%)	
Treatment Modality			
EBRT Only	8 (80.0%)	2 (20.0%)	
EBRT + Brachytherapy	101 (87.0%)	15 (13.0%)	**0.023**♦
EBRT+Brachy+Chemotherapy	172 (95.0%)	9 (5.0%)	
Treatment Duration Days			
≤ 60	275 (92.0%)	24 (8.0%)	**0.089**♦
>60	6 (75.0%)	2 (25.0%)	
Waiting Period			
0- 6 months	209 (92.9%)	16 (7.1%)	
6-12 months	48 (92.3%)	4 (7.7%)	0.779
>12 months	15 (88.3%)	2 (11.8%)	

Table 4.5 shows the relationship of clinical factors and treatment modality factors with crude mortality.

♦ Significant p - value

All variables were categorical and chi squared test was performed. From the above table, it can be concluded that, patients who had at least 18 months or more follow up post treatment were most likely to survive and attain 24 months overall survival, however, patients who had less than 18 months follow up period died within that same period. Completion of prescribed EBRT, completion of prescribed brachytherapy and completion of treatment within 60 days also showed a significant association with mortality.

4.2 Inferential Statistics

4.2.1 Overall Survival and Mortality

These patients contributed in total 576 person years by the end of the study period. The incidence of mortality for the entire follow up period was 45 per 1000 person years (95% CI 30.7 – 66.3). Results of the period incidence rates of mortality at specific time points are summarised in Table 4.6 below.

Table 4.6: Period incidence rates of mortality at specified time points per 1000 person years

Period (years)	**Person-time (years)**	**Failures**	**Mortality Rate**	**95% CI**
0 - 0.5 year	148.4	13	87.6	50.8 - 150.9
0.5 - 1 year	145.1	9	62.0	32.3 - 119.2
1 - 1.5 years	141.7	3	21.2	65.6
1.5 - 2 years	141.0	1	7.1	50.3
Total	**576.3**	**26**	**45.1**	**30.7 - 66.3**

The overall 2 year mortality rate was 45.1 per 1000 person years. During period 0 – 0.5 year, the incidence mortality rate was the highest 87.6 per 1000 person years (95% CI 50.8 –

150.9). The incidence rate decreased to 62.0 per 1000 person years (95% CI 32.3 - 119.2) during the period 0.5- 1 year, 21.2 per 1000 person years in the 1-1.5 years reaching a low of 7.1 per 1000 person years during 1.5 - 2 years. The majority of patients died within the first 6 months of follow up. Also the number of patients followed up over 2 years decreased every year.

Survival analysis is one of the tools used to assess the success of treatment. In this study, Kaplan Meier curve was used to determine the overall 2 years survival. Figure 4.1 shows the overall survival of patients during the study period.

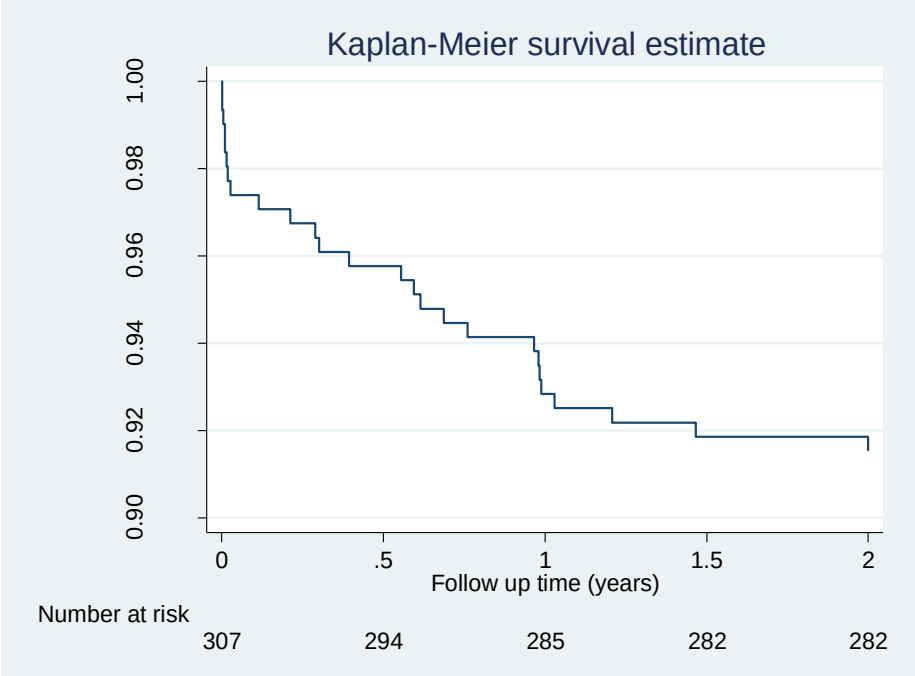

Figure 4.1: Kaplan Meier curve of the 2 years overall survival

4.2.2 Predictors of survival

Figures 4.2 - 4.7 below show the Kaplan Meier curves with significant logrank test. This was done to test the effect of different variables on overall survival. From Kaplan Meier curves, the null hypothesis, Ho: no overall difference between the survival curves was tested using a non-parametic logrank test. When the p-value is significant ($p<0.2$) it indicates that the null hypothesis should be rejected. Therefore, we can conclude that there was a significant difference in the KM survival curves between the different groups

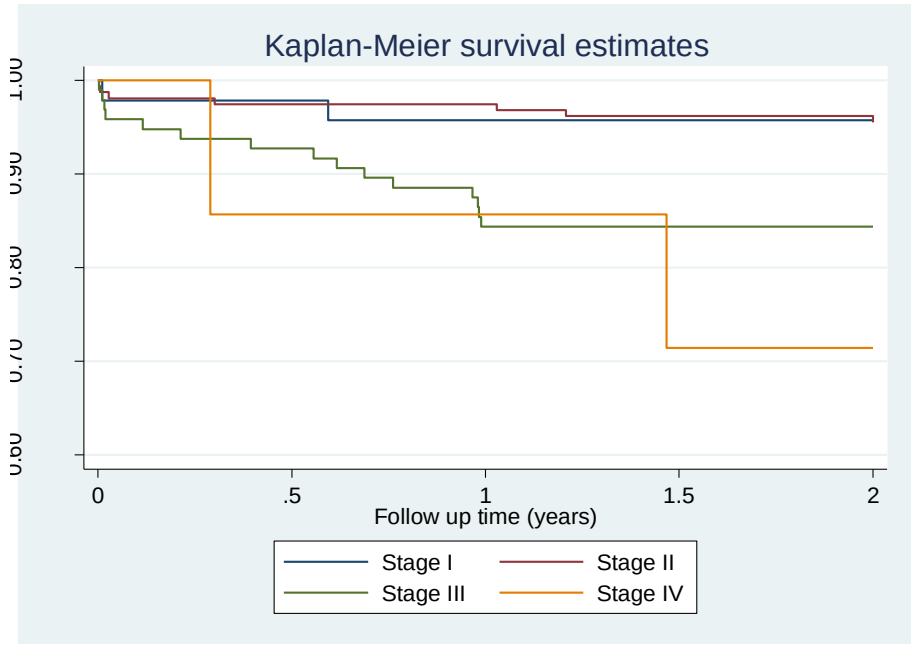

Figure 4.2: Kaplan Meier overall survival curve by cancer stage at treatment

Early stage I and stage II patients had better survival as compared to late stages III and IV. This difference was significant (p-value: 0.023)

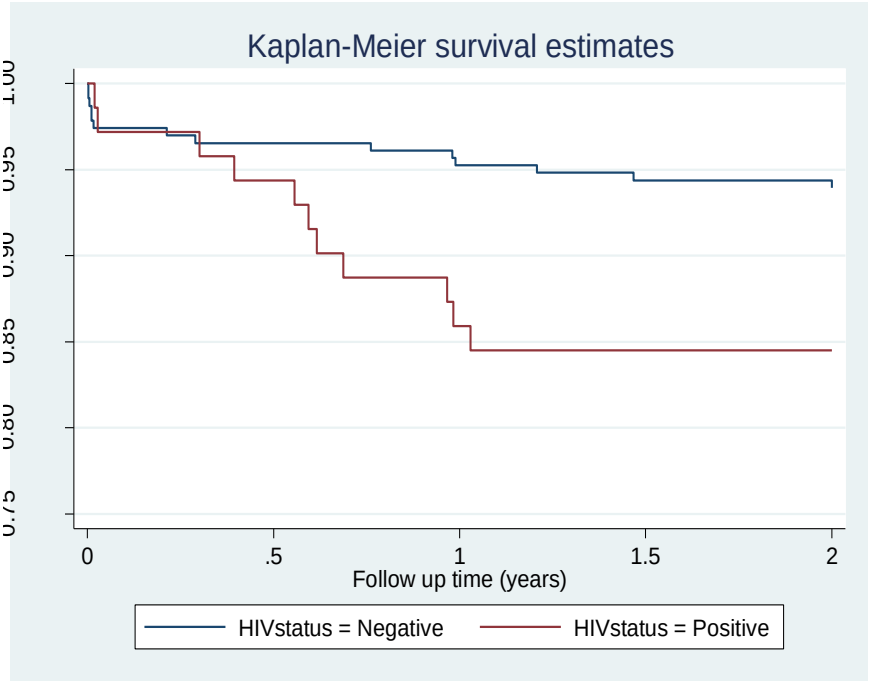

Figure 4.3: Kaplan Meier curve showing overall survival by HIV status

HIV negative patients had better survival compared to HIV positive patients. This difference was significant (p-value: 0.012)

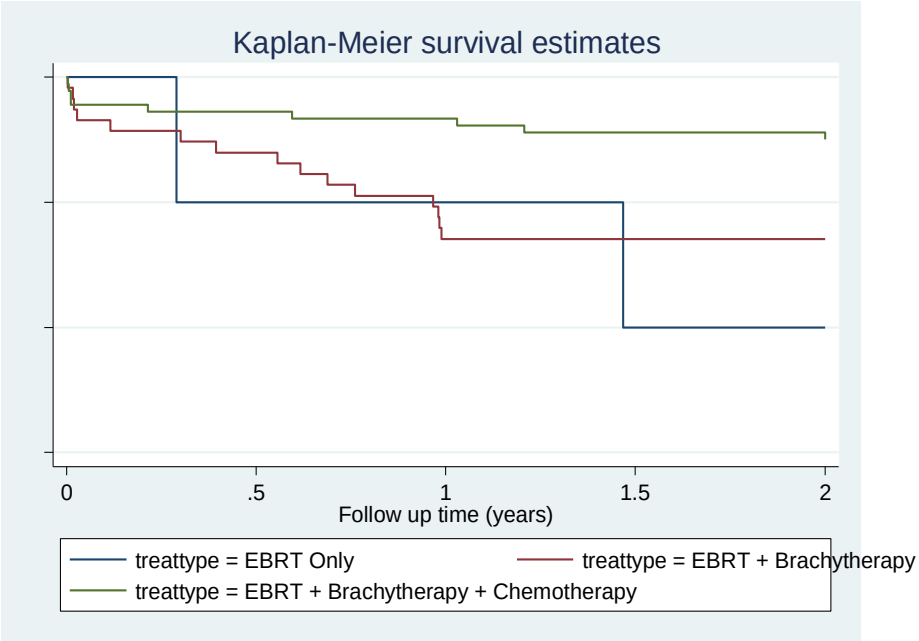

Figure 4.4: Kaplam Meier overall survival curve by treatment modality

Patients who were treated with a combination of EBRT, brachytherapy and chemotherapy had better survival compared to those who just received EBRT only. This difference was significant (p-value: 0.024)

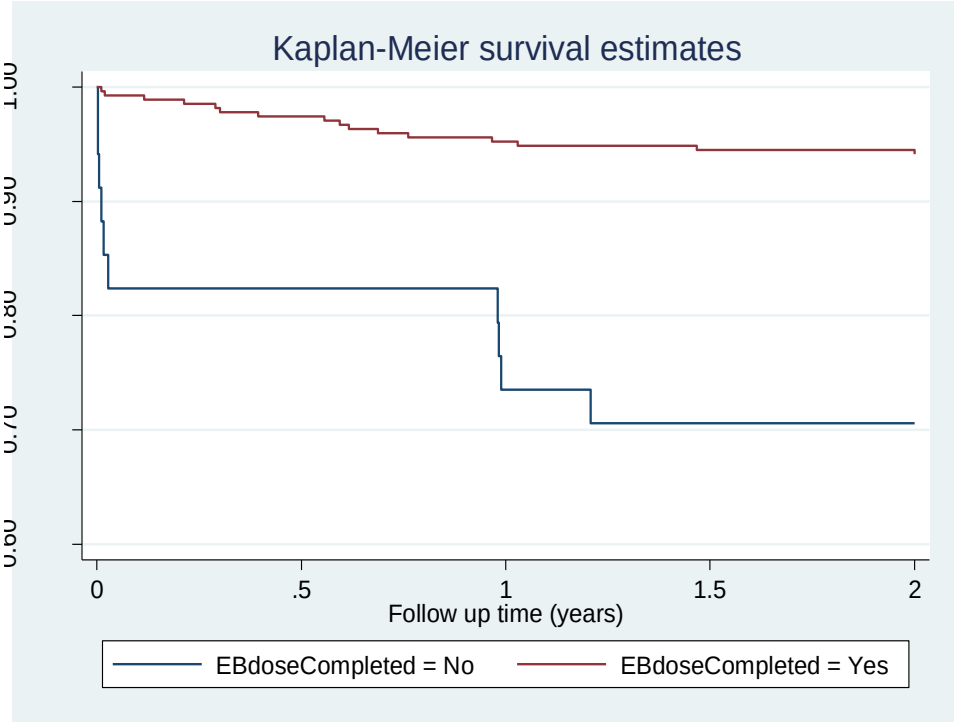

Figure 4.5: Kaplan Meier curve showing the effect of EBRT completion on overall survival

Patients who completed the prescribed EBRT had better survival compared to those who didn't. This difference was significant (p-value <0.001)

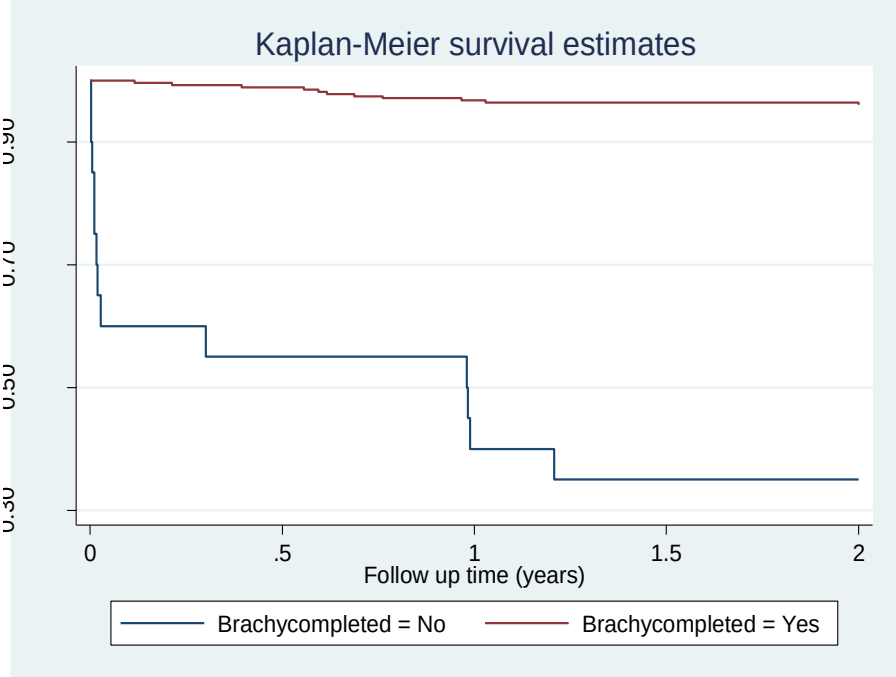

Figure 4.6: Kaplan Meier curve showing the effect of brachytherapy treatment on overall survival

Patients who completed the prescribed brachytherapy had better survival compared to those who didn't complete treatment. This difference was significant (p-value < 0.001)

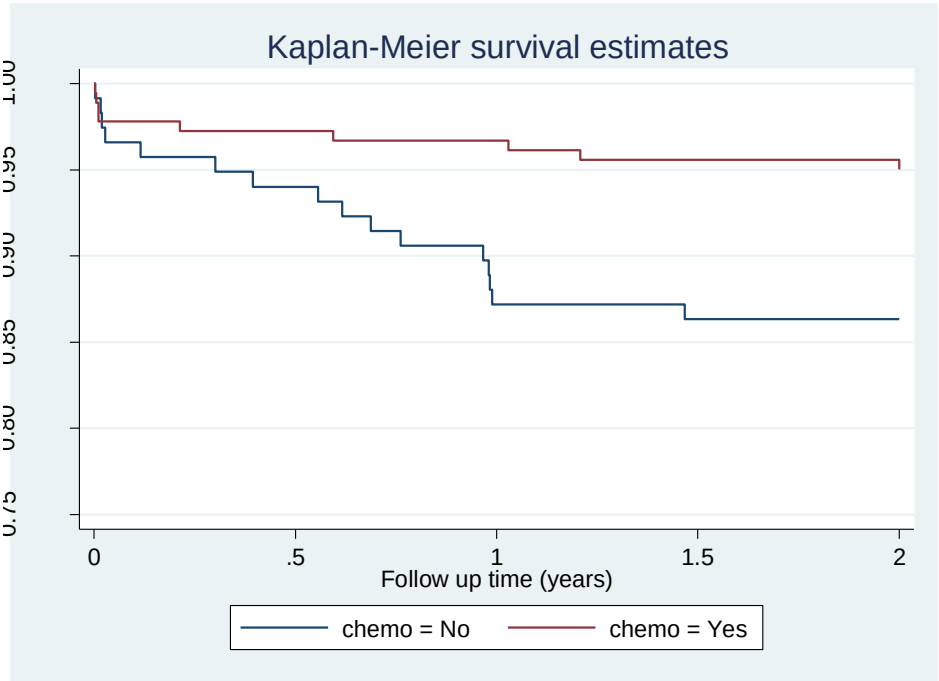

Figure 4.7: Kaplan Meier curve showing the effect of chemotherapy treatment on overall survival

Patients who received chemotherapy had better survival compared to those who didn't receive it. This difference was significant (p-value: 0.083)

This significant difference in KM survival curves between different groups was also seen for CompletedFollowup and Treatmentduration days.

The equality of survival curves was tested using logrank test. These results are shown in Table 4.7 below. From the results, a p-value <0.2 was considered significant.

Table 4.7: Logrank test of equality of survival functions

	Log-rank Chi square	p-value
Age group	3.92	0.562
HIV status	6.38	0.012*
CD4count group	0.05	0.818
Cancer Stage at Treatment	14.50	0.023*
Treatment Modality	7.47	0.024*
Chemotherapy Prescribed	6.98	0.083*
EBRTCompleted	24.94	0.001*
BrachyCompleted	143.66	0.001*
Treatment Duration days	3.32	0.0685*
WaitingPeriod	0.44	0.801
Province	0.11	0.735

*:significant p-value <0.2

Table 4.8 below shows the results of the univariate analysis. To identify the predictors of survival of cervical cancer and potential prognostic factors, Cox proportional hazards model was fitted starting with univariate analysis. The proportional hazard assumption was also

tested using Schoenfeld residuals and variables which showed violation of this assumption were not included in the final model. From the univariate analysis variables which were found significant at 0.2 percent level were added into a multivariate model, starting with the most significant variable. Also variables which were found to be significant prognostic factors of cervical cancer from previous studies were forced into the model.

Table 4.8: Cox proportional hazards univariate analysis

Variable	Hazard Ratio	95% CI	p-value
EBRT Completed			
No	Ref		
Yes	0.17	0.08 – 0.37	0.001**
Brachytherapy Completed			
No	Ref*		
Yes	0.037	0.02 – 0.08	0.001**
HIV status			
Negative	Ref*		
Positive	2.66	1.21 – 5.86	0.015**
Treatment Duration Days			
<=60	Ref*		
>60	3.51	0.83 – 14.9	0.088**
Chemo			
No	Ref*		
Yes	0.35	0.15 – 0.79	0.012**
Stage at treatment			
Stage I	Ref*		
Stage II	1.04	0.22 – 5.01	0.960
Stage III	3.88	0.89 – 17.0	0.072
Stage IV	7.12	1.01 – 51.0	0.049
Treatment Modality			
EBRT Only	Ref*		
EBRT + Brachytherapy	0.65	0.15 – 2.83	0.562
EBRT+ Brachytherapy +Chemotherapy	0.24	0.05 – 1.11	0.067
Province			
Gauteng	Ref*		
Northwest	1.23	0.37 – 4.10	0.735
CD4 Count group			
<=200	Ref*		
>200	0.85	0.22 – 3.30	0.818
Waiting Period			
0- 6 months	Ref*		
6-12 months	1.10	0.37 – 3.30	0.864
12+ months	1.63	0.38 – 7.11	0.512
Age (years)	0.98	0.94 – 1.01	0.220

**

** Significant p-value

* Ref – the first group used as a reference in STATA

The following factors were found to be significant predictors of survival in the univariate analysis: EBRT completed, brachytherapy completed and chemotherapy prescribed. HIV status and treatment duration days also proved to be significant prognostic factors. These factors were then tested for proportional hazard assumptions and showed no evidence of violating the proportional hazard assumption.

In the univariate analysis, patients who completed EBRT and brachytherapy treatment had 83% and 96% respectively less risk of dying compared to those who did not complete their treatment. Patients who had in addition chemotherapy prescribed, had 65% less risk/chance of dying compared to those who did not receive chemotherapy. HIV positive patients were 2.66 times more likely to die as compared to those who were HIV negative. Patients who took over 60 days to complete treatment were 3.5 times more likely to die compared to those who completed treatment within 60 days. Cancer stage at treatment, completion of follow up, treatment modality, province, CD4 Count, waiting period and age were not associated with mortality in the univariate analysis.

Table 4.9 below shows the results of the multivariate analysis. Factors which were significant at 5% level were considered to be potential predictors and prognostic factors of cervical cancer.

Table 4.9: Cox proportional hazard multivariate analysis

Variables	Hazard Ratio	95% CI	p-value
Age	0.98	0.93-1.04	0.573
EBRT Completed			
No	Ref		0.199
Yes	0.48	0.16-1.47	
Brachytherapy Completed			
No	Ref		0.001*
Yes	0.04	0.01-0.11	
HIV status			
Negative	Ref		0.042*
Positive	3.23	1.04-10.0	
Chemo			
No	Ref		0.775
Yes	0.83	0.24-2.91	
Treatment Duration Days			
<= 60 days	Ref		0.246
>60 days	2.67	0.51-14.0	

*$p<0.05$

In the multivariate analysis completion of brachytherapy remained significant predictor of survival after adjusting for all other factors. HIV status was the only significant prognostic factor. Patients who completed brachytherapy treatment were 96% less likely to die compared to those who didn't complete it at any point in time, after adjusting for age and HIV status. Patients who were HIV positive were 3.2 times more likely to die as compared to HIV negative patients at any point in time after adjusting for age and brachytherapy completed. The final model didn't show any violation of the proportional hazard assumption, global test p-value = 0.614

The results of the global tests for proportional hazard assumptions based on Schoenfeld residuals are shown in Table 4.10 below.

Table 4.10: Proportionality hazard assumption test

Variables	**PH assumption p-value**
EBRT Completed	0.408
Brachy Completed	0.217
Completed FollowUp	1.000
Treatment Duration Days	0.490
HIV status	0.934
Chemotherapy Prescribed	0.962
Age	0.678
Cancer Stage at Treatment	0.630
Treatment Modality	0.617
Province	0.057
CD4 Count	0.068
Waiting Period	0.178

Table 4.10 above shows the p-values from the global test of the proportional hazard assumption. When $p>0.05$ then the assumption is not violated.

CHAPTER FIVE

DISCUSSION

This study investigated the several prognostic factors of cervical cancer patients undergoing radiotherapy at CMJAH and the overall survival rates of this patient population. Results of this work add to the local knowledge of the epidemiology and statistics of cervical cancer patients undergoing radiotherapy in a typical public university teaching hospital. In the paragraphs that follow the results of this work are discussed in the context of the present literature and public health service delivery in South Africa.

5.1 Overall survival rate

This study established that the 2-year overall survival rate was 92 % for this patient population. This high survival rate can be attributed to the high loss to follow-up. In a developing country loss to follow-up is typically high for various reasons, ranging from financial implications of travelling to the radiotherapy centre, lack of understanding of its importance and doctor-patient encounter being non-meaningful post treatment. Incentives can be introduced to make patients honour their follow-up appointments (incentives can be in the form of bus fare). Follow-up statistics can be possibly be improved by having the follow-up visits done at local clinics by trained nurses and the results faxed to the attending radiation oncologist for review. A national health insurance system is envisaged to be an ideal platform for easier sharing of patient data across the country. The overall 2 year mortality rate was calculated to be 45 per 1000 person years. It is of interest that in this present data set patient deaths occurred in the first 18 months, which implies that follow-up is critical in the first 24 months post radiotherapy.

5.2 Potential prognostic factors

This study investigated the potential prognostic factors for cervical cancer patients presenting for radiotherapy at CMJAH. Below some pertinent results of the various potential prognostic factors tested are discussed:

In this study patient age, HIV status, treatment duration, administration of chemotherapy drugs, completion of external beam radiotherapy and completion of brachytherapy were found to be significant predictors of mortality in the univariate cox regression model. These findings are in agreement with the work of other researchers. However, further subjection of the same predictors to multivariate Cox regression model showed that only HIV status and completion of brachytherapy remained significant after adjusting for all other factors. Furthermore, these two factors didn't show signs of violating the proportional hazard assumption.

Age

There has been a lot of controversy surrounding age, whether its a prognostic factor for cervical cancer or not. In this study, KM survival curves showed that patients who were less than 30 years of age had the worst survival, in contrast Geetha et al found that younger patients (less than or equal to 30 years) had longer post treatment survival. However, the results in this study were similar to that of Kastritis et al where they observed younger patients (less than 35 years) to have worst survival post treatment. In this study, 85% of the patients in the less than 30 years group were HIV positive this might have led to their survival being low. This further show that there could be a link between HIV and cervical cancer therefore studies have to be done to investigate this possibility. Also in this study,

patients above 70 years had a better survival although this difference was not statistically significant. This is similar to findings by Geetha et al who found that older patients above age 70 had longer post treatment survival. In contrast to what has been widely reported in literature that patients above 50 years are the ones with a high risk of cervical cancer, this study population showed that it was indeed patients less than 30 years having a greater chance of having cervical cancer. It deserves mentioning that this age group of less than 30 years had a high proportion of HIV positive patients. The current national health policy on cervical cancer screening targets women at least 30 years old, which means significant number of cervical cancer cases are being missed in the population aged less than 30 years. It was found that the peak age group of this population was 40-49 years which is alarming as this age group is the countries' productive work force hence efforts of prevention of the disease have to be put forward to protect this population for the countries' benefit.

HIV

In this study, from the Kaplan Meier survival curves HIV positive women had poorer survival as compared to HIV negative women. This also remained only significant prognostic factor in the multivariate analysis. Poor survival rates in HIV positive women have been observed elsewhere, for example in studies by Kigula-Mugambe and Kavuma and by Maiman et al. With HIV pandemic in Africa, this shows further motivation to increase screening coverage directed at HIV positive women who are also at more risk of cervical cancer due to high infection of HPV which has been found to be a risk factor for cervical cancer. Also because of the increased access of ARV treatment, the lifespan of people living with HIV has increased therefore putting them at more risk of developing cancer. This study also showed that HIV positive women presented more with late stage II and III, which emphasises the need for early detection of these abnormal lesions in order to prevent new cases of cervical cancer also to have better treatment outcome. Another aspect which needs to

be looked at in future is the response of HIV positive patients on ARVs compared to those who were not yet on ARVs.

Stage at Treatment

Presentation of patients with advanced cancer is a consistent feature in most studies done in the developing world. This study showed that a large number of patients at CMJHA presented with late stages with 51%, 31% and 2% in stage II, stage III and stage IV respectively. Late presentation by patients might be due to lack of dedicated and effective screening programmes within the government policy, lack of HPV vaccines and its high costs and also lack of access and knowledge of such services by patients. However, in general these results confirm that patients with higher clinical stage have poor prognosis as compared to those with early stage. From the univariate analysis, stage III and stage IV patients had higher risk of dying from cervical cancer compared to stage I and stage II patients. These findings are in agreement with a study done by Hopkins and Morley. This can be because at stage III and IV the disease would have spread to other areas of the body making it more difficult to treat and control.

Treatment Modality

Cancer management in most cases involves multi-therapies and in most cases the choice of the therapy given to a patient influences treatment outcomes and eventually survival of the patient. For example a study by William et al showed that a combination of radiation therapy and chemotherapy had superior survival rates compared to radiation therapy alone on cervical cancer patients (81 % for radiation therapy in combination with chemotherapy vs 71 % for radiation therapy alone). Despite there being evidence of superior treatment outcomes for combined radiotherapy and chemotherapy some of the patients in this study did not receive or benefit from chemotherapy. These were patients who where HIV positive and had a CD4

count of less than 200, this is because this patient group generally cannot tolerate toxic chemotherapy drugs and would develop severe side effects on patients. This study underscores the effectiveness of combined therapy (external radiation beam therapy, chemotherapy and brachytherapy) in the management of cervical cancer.

Treatment Duration

Tumour control is affected by the timing of the diagnosis, treatment commencement and length of the therapy intervention. This is mainly because the cancer cells will continue to grow and multiply, the more these cells grow the more difficult it will be to kill them as they may spread to other surrounding area. Thus it is important to finish the treatment without any gaps in between and also within a short space of time. This study showed that patients who completed their treatment within 60 days had a better survival compared to those who took over 60 days to complete treatment. In the univariate analysis those who took longer to complete treatment were four times more at risk of dying. Thus emphasis should be put on educating patients about the importance of not absconding during the treatment. These results are similar to a study done by Fyles where he found that there was 1% loss of disease control per day of treatment prolonged beyond 30 days. A number of patients in this retrospective analysis did not comply with the treatment schedule, skipping treatments in between thus prolonging their treatment duration which has potential to compromise tumour control. It is therefore important for patients to be encouraged and shown the importance of completing the treatment within the prescribed time. Provision of lodging facilities outside the normal ward set-up should be explored as an alternative to patients travelling from home, which should potentially get rid of skipping of treatment due to lack of transport.

Since disease control is affected by timing of treatment commencement, it is important to ensure that the waiting period between diagnosis and the start of treatment is not too long.

This might be difficult to achieve in settings where radiotherapy centers are limited or not available in the developing world hence increasing mortality due to untreated cervical cancer. In this study, patients who had more than 6 months waiting period had less survival as compared to those with less waiting period. Patients whose waiting period was 12 months or more had 63% more risk of dying than those who had less than 6 months waiting but these results were not significant. Furthermore machine breakdowns compromise patient care as it extends the treatment period to an extent that the therapy intent is negated by the tumour kinetics. Public health administrators should be encouraged to pay the vendors who supply and repair radiotherapy equipment in time such that they continue providing service. In recent years it has been widely reported in media where public hospital radiotherapy services are not available due to non-payment of private service providers.

Histology type

Squamous cell carcinoma has been the leading type of histology in most studies and in the present one. In this study, 88% of the patients had squamous cell carcinoma compared to only 9% with adenocarcinoma. Similar findings have been reported in a Thailand study by Pomros et al. This is in agreement with this study finding where squamous cell carcinoma had a better survival compared to adenocarcinoma. This type of cancer has good response to radiotherapy as compared to adenocarcinoma and therefore a favourable prognostic factor.

5.3 Limitations

This research work had some limitations which have to be considered when interpreting the results. For example the significant proportion of patients lost to follow-up should be taken into account when interpreting the survival rates. In this study 66% of patients who were treated during the study period were lost to follow up. A number of possibilities can be put forward to explain this significant loss to follow up, for example, a large proportion of the patients presented with late stage tumors which possibly meant early mortality after treatment. As shown from the study demographics, CMJAH served patients outside the Johannesburg metropolitan area meaning the majority of the patients had to travel long distances to the hospital, which can be daunting in terms of the finance aspects especially for the low income and pension groups. This significant proportion of patients lost to follow up weakens the statistical power of the study; however the challenges of cancer treatment in a typical public hospital in South Africa have been exposed by this study. Therefore a cautionary approach is recommended in interpreting the survival rates.

This significant number of patients lost to follow up also brings with it bias to this study, which needs acknowledging for proper conclusions to be drawn from this study. The concept of censoring assumes that censored patients have the same survival prospects or prognosis as those who remained in the study and completed follow up. This may not always be true, as some of these patients feel fully recovered after receiving treatment and thus deem it not necessary to return for follow up. On the other hand, some these patients either have poor treatment outcomes or succumb to illness and die. In both cases, censoring brings unavoidable bias into the study which needs to be taken into context when conclusions or inferences are drawn from the study. In this study overall survival was based on those patients who completed follow up, meaning either the survival rate was overestimated if

those lost to follow up had died or underestimated if those lost to follow up were still alive, a limitation which this study acknowledges.

Another limitation to this study was that all patient deaths were attributed to cervical cancer which is not always the case in a clinical setting. During the period under review a total of 2212 patients had histologically confirmed cervical cancer, however only 900 had complete treatment data records although not all of them were eligible for the study. The ineligibility of the other two-thirds of the patient population reduces the statistical power of this work. It needs mentioning that the ineligibility of most patients was due to lack of recorded treatment data: see Chapter Six for recommendations to alleviate this problem.

A significant proportion of the cervical cancer patient population who was treated at CMJAH which were not eligible for this study was mainly due to lack of proper recording of patient – or treatment related data. Out of a total patient population of 2212 during the study period, a significant 1092 patients had missing treatment data thus making them ineligible for the study. A number of reasons can be postulated for this, for example, some of these patients could be referrals from the private health sector thus there was no need for comprehensive data collection and recording into the CMJAH filing system as the patients data is already captured into their private health clinic filing system or due to simple poor data capture by the clerical staff at CMJAH.

This research work exposed some fascinating facts about the demographics of cervical cancer patients presenting at CMJAH for radiotherapy treatment. This work showed that the radiotherapy patient catchment area went beyond the borders of Gauteng Province. In this study 91% patients came from Gauteng Province and 9% from North West Province. From

1092 patients excluded in the study, about 50% of that was from Botswana (private sector/ Netcare) and about 5% from Zambia and Zimbabwe. In 2010 the North West Province started providing radiotherapy services at Klerksdorp Hospital as such the numbers from North West Province are no longer presenting. In recent years International Atomic Energy Agency (IAEA) funded projects to equip neighbouring countries with radiotherapy equipment should lead to no patients presenting from outside the South African boarders.

In this study all patient deaths were attributed to cervical cancer which is not necessarily true. It is not a trivial task to establish the cause of a patient's death as that can only be established through the access to the patient's death certificate. The current practice does not capture the patient's national identity number thus making it impossible to trace the cause of death through the Department of Home Affairs database. The impact of surgery was not investigated in this present study despite some of the patients having benefited from it.

CHAPTER SIX

RECOMMENDATIONS AND FUTURE STUDIES

6.1 Recommendations and Future Studies

A number of recommendations are hereby put forward based on the practical experience of this research work.

1. The long treatment waiting period experienced by public hospital cancer radiotherapy patients in general motivates for additional radiotherapy centres be available within Gauteng province in order to reduce the long waiting period and possible lead to better treatment outcomes.

2. Teaching of patients in understanding the benefit of adhering and completing the treatment within the prescribed time as well as encouraging patients to present for follow-up post treatment. The financial implication of travelling for an average of four weeks for radiotherapy treatment is acknowledged in a developing country, thus government and non-governmental organisations interventions to assist deserving patients with travel costs would be welcome. Most countries in the world house their cancer patients in government funded lodgings during their treatment.

3. Since most patients in this study died in the first 2 years post treatment it is recommended that patients present for follow up every three months in the first two years after treatment as opposed to the present six months interval.

4. Continued community based education and awareness of the risk factors and prevention of cervical cancer, this can reduce the burden of patients needing radiotherapy treatment which is can cut costs in the health system.

5. HIV positive women to be screened more regularly in order to prevent late presentation with cervical cancer.

6. For more meaningful analysis of survival data it is recommended that all radiotherapy patients have their national identity numbers recorded in addition to their *"radiotherapy centre treatment numbers"* such that it could be possible to link the data between the national mortality database and hospital database.

7. Training of personnel on the importance of correct an accurate record keeping of patients for future studies. Quality control measures can be easily implemented to ensure that clerical staff enter and record all the necessary patient treatment specific data. Moving away from paper forms to digital forms can help in ensuring that all data is captured by employing software programs which won't *sav*e the form without all pre-requisite information.

From a public health scientist's perspective there was a lot learnt from this study about radiotherapy treatment of cervical cancer, however, there still remains some local knowledge gaps and thus some aspects deserve to be explored further in future studies in order to have a sustainable cost-effective public service radiotherapy delivery service. Below are some suggestions for future work:

1. A study designed to link survival rate to quality of life and cause of death would be appropriate and more informative to health practitioners and policy makers.

2. The long waiting periods can be shortened by conducting of peer-reviewed prospective hypofractionation clinical trials.

3. Studies to identify prognostic factors should be extended to other cancer sites with the aim of cost-effective healthcare delivery.

CHAPTER 7

CONCLUSIONS

7.1 Conclusions

This present retrospective study involved 307 cervical cancer patients treated during the period 1 January 2004 to 31 December 2006 at CMJAH and met the inclusion criteria. From this study the 2 year overall survival rate of cervical cancer patients was 92%. Based on this study, only HIV status was found to be a statistically significant prognostic factor (p-value =0.04), while completion of the brachytherapy prescription proved to be a significant predictor of mortality (p-value < 0.001). Nearly 66% of the eligible patients in the study were lost to follow-up, therefore results of this study have to be interpreted bearing this in mind. The statistics from this study further reinforces the importance of screening in the fight against cervical cancer. It is recommended that prospective clinical trials be conducted in the future to confirm the validity of the findings of this work. This study has successfully contributed to the local body of knowledge with regards to treatment of cervical cancer in typical a public teaching hospital in South Africa.

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APPENDIX 1: ETHICAL CLEARANCE FORM

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Miss Maleshwane L Pule

CLEARANCE CERTIFICATE	**M120370**
PROJECT	Potential Prognostic Factors for Cervical Cancer Patients undergoing Radiotherapy at CM Johannesburg Academic Hospital: A Retrospective Analysis
INVESTIGATORS	Miss Maleshwane L Pule.
DEPARTMENT	Department of Radiation Sciences
DATE CONSIDERED	30/03/2012
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 30/03/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr Danuta Kielkowski

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

APPENDIX 2: DATA COLLECTION SHEET

Table 1: Demographics

GT Nr	DXT No	Hospital Name	Dob	Home Area	Occupation	Type of cance Squam/adeno	ECOG	No Of kids, Age

Hb Levels and Brachy Dates

Dxt No	HB level Date1	HB Date 2	HB Date3	Brachy Date1	Brachy Date2	Brachy Date3	Brachy Date4

Treatment Data – Tumor related

DXT Number	Date of Diagnosis	Stage at diag	Simulation Date	Waiting period (diag-tx)	Stage at Tx	Tx dates: Start	Treatment : Finish	Last follow up date - post tx

Treatment data

DXT No	EBRT (dose)	EBRT Cm (Y/N)	Brachy dose	Brc Cm (Y/N)	Chemo (Y/N)	Chemo regime	HIV +/-	Cd4 - date	Status (Alive/Dead)	Status End Date