

IMPACT OF WAITING TIMES FOR RADIOTHERAPY FOR CERVICAL CANCER

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A research report submitted to the Faculty of Health Sciences, University of the
Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of
Master of Medicine in the branch of Radiation Oncology

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DECLARATION

I, Kim Nicole Lohlun, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in Radiation Oncology in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.



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Kim Nicole Lohlun

Signed at Johannesburg on the 30th day of October 2013.

Dedicated to my parents,
who have always encouraged hard work, diligence and perseverance.

Your love, support and guidance have been unwavering.

For my father,
Richard Kaikhong Lohlun

(1935-2004)

and my mother,
Pearl Angela Lohlun.

ABSTRACT

Title

Impact of waiting times for Radiotherapy for Cervical Cancer

Background

Radiotherapy plays a vital role in cervical cancer management. However, due to high patient load and limited resources, waiting lists are unacceptably long. This prospective study aimed to evaluate the potential impact of radiotherapy delays.

Patients and methods

Eighty-one patients requiring radical radiotherapy for cervical cancer were selected. Patients were re-evaluated every four weeks while waiting, and again at simulation.

Results

Median delay from first consultation to simulation was 55 days. Longer delays were not statistically correlated to tumour progression. Most of the upstaging occurred around 40 to 65 days. One in four patients received blood transfusions and required hospital admission. Four patients needed haemostatic brachytherapy for bleeding.

Conclusion

A relationship between time waited and disease progression could not be proven. However, numbers were small and statistical tests were likely underpowered. The study does, however, highlight unacceptably long delays for radiotherapy and a wait of less than 40 days is recommended.

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NOMENCLATURE

ALARA	As Low As Reasonably Achievable
ASARA	As Short As Reasonably Achievable
CD4	Cluster of Differentiation 4
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
FIGO	International Federation of Gynecology and Obstetrics
g/dL	Grams per deciliter
Gy	Gray (unit of radiation)
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
IARC	International Agency for Research on Cancer
ICO	Institut Catalià d'Oncologia
PR	Per rectum (examination)
PSW	Pelvic side wall
PV	Per vagina (examination)
RTOG	Radiation Therapy Oncology Group
RVF	Recto-vaginal fistula
TCP	Tumour Control Probability
VVF	Vesico-vaginal fistula
WHO	World Health Organization

1.0 INTRODUCTION

1.1 Burden of disease

Despite significant advances in screening and management over the past few decades, cervical cancer remains a significant burden, particularly in developing countries, where more than 80% of cases are diagnosed (Denny 2012). Figure 1.1.1 demonstrates a clear difference in the global age-standardized incidence rates of cervical cancer between developed and developing nations (WHO/ICO 2010).

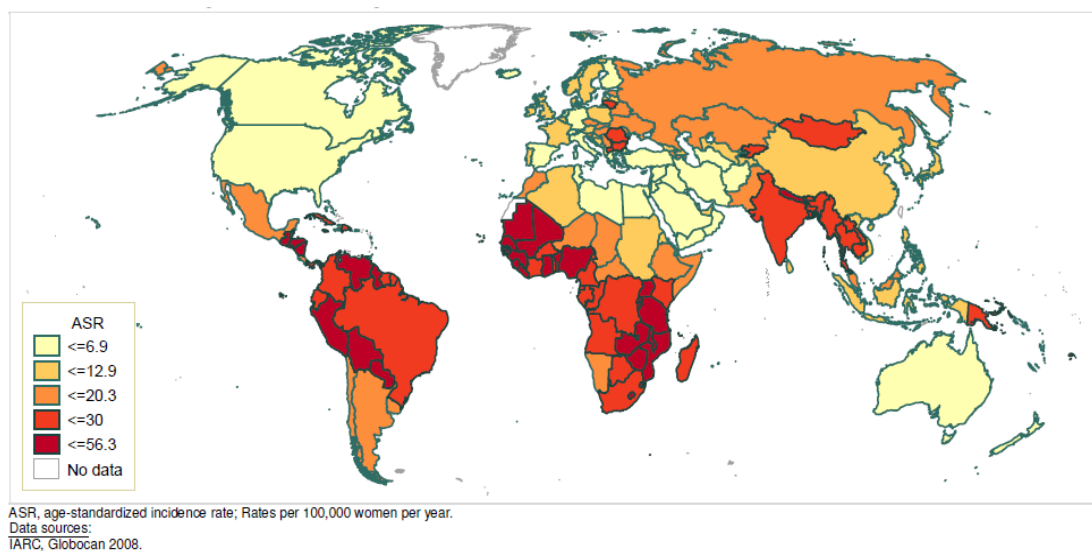
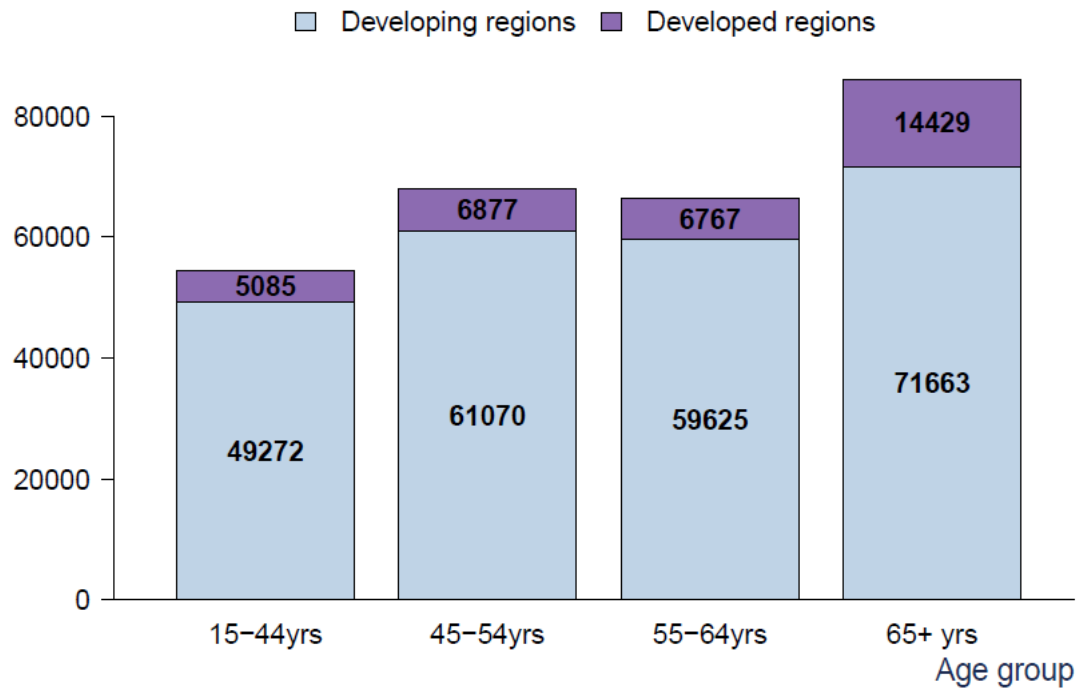


Figure 1.1.1 World age-standardized incidence rates of cervical cancer

Cervical cancer comprises 22,2% of all cancers in women of Sub-Saharan Africa and carries the highest rate of cancer-related mortality (Anorlu 2008). In 2002, Anorlu (2008) reported survival rates of 21% in Sub-Saharan Africa, while those of the United States and Western Europe were 70% and 66% respectively. Figure 1.1.2 demonstrates the annual number of deaths by age group. From this graph, we

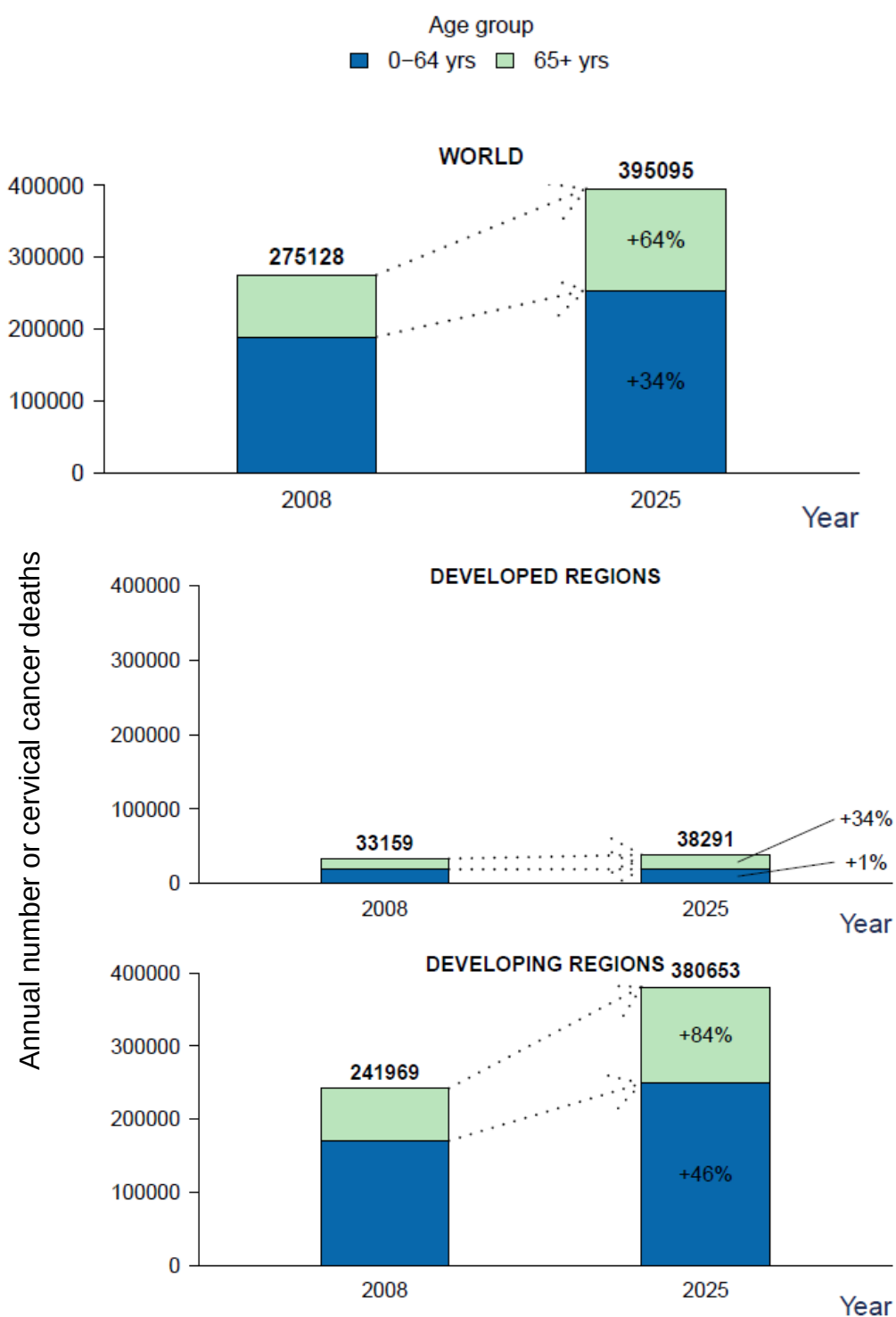
can see that mortality rates in developing nations are over seven times those in developed nations (WHO/ICO 2010).



Data sources:
IARC, Globocan 2008. Age-specific data from GLOBOCAN 2008 were obtained from IARC, personal communication.

Figure 1.1.2 Annual number of deaths due to cervical cancer by age in developing and developed regions

The National Cancer Registry of 2003 showed that cervical cancer is the third leading malignancy in South African women, second only to breast and basal cell carcinomas. In black women, it is the leading cancer (National Cancer Registry 2003). The lifetime risk of developing cervical cancer for South African women is one in 31 (Mqoqi *et al.* 2004).



Projected burden in 2025 is estimated by applying current population forecasts for the country and assuming that current mortality rates of cervical cancer are constant over time.
 Data sources:
 IARC, Globocan 2008.

Figure 1.1.3 Global estimated number of deaths from cervical cancer by age group and regions for 2008 and projected in 2025

Thus, the burden of disease in developing countries, including South Africa, remains high. GLOBOCAN (WHO/ICO 2010) predicts that mortality rates will have risen by 130% from 2008 to the year 2025 (Figure 1.1.3). Meanwhile, radiation and other treatment facilities are poorly staffed and poorly equipped, ultimately leading to the inability to cope with the large numbers of patients.

1.2 Aetiology

The vast majority (99%) of cervical cancers can be attributed to the Human Papilloma Virus (Wallboomers *et al.* 1999). Infection by this virus is most often sexually acquired. Whilst most infections are self-limiting and resolve within a few months, some may go on to cause changes in the cervical mucosa, which ultimately leads to dysplasia and subsequent malignancy. Infection by oncogenic types of Human Papilloma Virus (HPV), notably HPV 16 and HPV 18, account for 70% of high-grade dysplasia and cancerous lesions (Ault 2008).

Risk factors for the development of cervical cancer include: early age of first coitus, multiple sexual partners and early age of first pregnancy (Eifel *et al.* 2008). These factors all correlate to increased risk of acquiring an HPV infection.

1.3 Natural history

Cervical cancer usually originates at the transformation zone of the endocervical canal. It arises from cervical carcinoma-in-situ, which may be present for as long as 20 years before developing into invasive disease. From the uterine cervix, the

tumour may then grow to involve the vagina and adjacent parametrial tissues. Significant parametrial spread may result in hydronephrosis of the kidney(s), due to ureteric obstruction. Anteriorly, tumours may invade the bladder wall and posteriorly, the rectum (Perez & Lavanagh 2008). In such cases, fistulae may form. Distant spread may be lymphatic to pelvic, para-aortic and supraclavicular nodes or haematogenous to lungs, abdominal cavity, liver or bone (Denny 2011; Fagundes *et al.* 1992).

1.4 Preventative measures

1.4.1 Screening

Cervical cancer screening has been shown to decrease both incidence and mortality rates (World Health Organization 2005), as pre-cancerous lesions can be detected and treated before they become invasive. This has mostly been seen in developed nations, where effective screening programmes have been implemented. In the developing world, there are few screening programmes, while those that do exist garner a mere 19% coverage, versus the 63% seen in developed countries (Gakidou *et al.* 2008). This is reflected by the high burden of disease in developing nations.

Cytology laboratories for cervical screening were first introduced in South Africa in the mid to late 1950's. From the mid-1960's, a decline in age-specific mortality rates from cervical cancer was seen in white South Africans, proving that screening has had an impact. Unfortunately, the

benefits of screening were limited to patients in the private sector (mainly white women at the time), who also fell into the lowest risk category for cervical cancer (Bailie *et al.* 1996).

In 2000, a national screening programme was introduced, whereby women in the public sector would be offered three cervical smears at ten year intervals, from the age of 30. The goal was to achieve 70% coverage of the target age-group, nationally, within ten years of implementation (Department of Health). Unfortunately, coverage remains sub-optimal and a significant proportion of patients with precursor lesions still do not get treatment (Kawonga & Fonn 2008).

1.4.2 Vaccination

As most cervical cancers stem from infection by the Human Papilloma Virus (see 1.2), it follows that prevention of this infection would decrease the incidence of cervical cancer.

There are currently two vaccines available for prevention of HPV infection - a bivalent vaccine that protects against HPV 16 and 18, and a quadrivalent vaccine that also offers protection against HPV 6 and 11, which are largely responsible for genital warts. These vaccines have shown close on 100% efficacy (Ault 2008) and are registered for use in females between the ages of nine and 26.

The World Health Organization (WHO) recommends that the HPV vaccine be routinely included as a part of the national immunization programme in any country where cervical cancer or HPV-related disease prevention measures are a public health priority, where such a programme is feasible, where adequate financing is available and where adequate consideration has been given to cost effectiveness (World Health Organization 2009).

The HPV vaccine was approved for use in South Africa in 2008. However, due to high costs, this vaccine has only been available in the private sector. The quadrivalent vaccine, Gardasil (Merck and Co.), costs R770 per dose, which amounts to R2 310 for all three required doses. The bivalent vaccine, Cervarix (GlaxoSmithKline), has reduced its cost per dose from R700 to R450, but even at this reduced price, the total cost of the vaccine still amounts to R1 350. Thus, HPV vaccination in South Africa remains an option for only a small percentage of the population.

1.5 Staging

Invasive cervical carcinomas are classified according to the FIGO (International Federation of Gynecology and Obstetrics) staging system (Pecorelli 2009). This is a clinical, as opposed to surgical or radiological, staging system and it relies on physician experience and interpretation.

At Charlotte Maxeke Johannesburg Academic Hospital, stages IIB and IIIB have been further subdivided. In other words, a distinction has been made between stage

IIB₁ and IIB₂, depending on whether only inner parametria is involved or both inner and outer parametria are involved by tumour. This was a combined decision amongst gynaecologic oncologists and radiation oncologists and it has enabled the department to offer different radiation schedules according to tumour extent. The same has been done with stage IIIB, which has been subdivided into stages IIIB₁, IIIB₂ and IIIB₃. This differentiates tumours that involve one or both pelvic side walls (stages IIIB₁ and IIIB₂ respectively) and those where hydronephrosis of the kidney(s) is present (stage IIIB₃). (Appendix 7.1).

1.6 Management of cervical cancer

Early cervical tumours can be treated by surgery. If the stage of the cancer is more than IA₁, a lymph node dissection must be included. If this is not done (for example, if hysterectomy is done for reasons other than malignancy), if nodes are found to be positive or if surgical margins are positive, then post-operative radiotherapy is indicated. For stage IB₁, either surgery or radiotherapy may be given.

For stage IB₂ or greater, surgery is no longer an option and definitive radiotherapy is given (Perez & Lavanagh 2008). Radiotherapy involves daily radiation sessions, given Monday to Friday for about six weeks.

The release of results from five key studies, showing improved response rates and significant survival benefit with the addition of chemotherapy, lead to changes in standard management (Eifel *et al.* 2004; Keys *et al.* 1999; Peters *et al.* 2000; Rose &

Eifel 2001; Whitney *et al.* 1999). Chemotherapy is now given concurrently with radiation as an intravenous infusion of cisplatin, either weekly, or every three weeks. However, this may be withheld in patients with compromised renal function, or in HIV-positive patients with a low CD4 count as both radiation and chemotherapy will cause a drop in CD4, which may compromise the patient (Nel *et al.* 2006).

For stage IV cancers, cure is no longer the aim of management and palliation of symptoms is offered, using two fractions of radiation given one month apart. For distant metastases, systemic chemotherapy may be offered if performance status permits.

1.7 Prognosis

If diagnosed early, five-year survival rates for cervical cancer are relatively high - over 80% for early, localized disease, such as stages IB and IIA. Even patients with more advanced disease have a fair outcome with stages IIB and III having five-year survival rates of 65% and 40% respectively (Cannistra & Niloff 1996). Therefore, treatment of these cancers should be a priority.

1.8 Rationale for the study

The Gauteng province diagnoses 40% of the country's malignancies, probably due to this region having the highest number of cancer-diagnosing laboratories. At our Gauteng-based institution, we see approximately 750 cases of cervical cancer each year. This constitutes about 20% of the total number of cases referred to us, which is

comparable with the 17-20% noted for national statistics (Denny 2006; Mqoqi *et al.* 2004).

Patients seen at our clinic tend to present with more advanced disease to those in first world countries. This corresponds to findings in other South African cities, such as Cape Town and Durban, where 66% of women with cervical cancer presented with stage III or IV disease (Denny 2006; Walker *et al.* 2002). This may be due to several factors, including poor education and lack of awareness, inadequate screening programmes, poor access to health care facilities, lack of funding and staff shortages. As radiotherapy (as opposed to surgery) is the mainstay of treatment for advanced disease, it plays a vital role in the management of cervical cancer in our country. Adewole *et al.* (2005) noted that 80% of cervical cancer cases from developing countries present with stage III disease, while a further ten per cent have stage IV disease. The sources which he sites are all from Nigerian studies. At that time, there were only four established radiotherapy units to serve the entire country of 136 million, 32 million of which were women between the ages of 15 and 64.

Due to large numbers of patients and insufficient machine time to cater for all these patients, Charlotte Maxeke Johannesburg Academic Hospital was experiencing waiting lists of up to 16 weeks for patients with cervical cancer. Patients are seen within a week of referral. They are then seen four to six weekly until a simulation date is allocated. At simulation, radiographs are taken and files are sent for calculations and quality checks. Once a treatment slot is available, the patient is telephoned and told when her treatment will start. This may take another week or two.

During the delay, patients may require blood transfusions, hospital admissions and haemostatic doses of brachytherapy to stop bleeding per vagina. This increases financial costs of patient care. On follow-up reviews, it is sometimes noted that the tumour has progressed or that performance status has deteriorated, thus prompting alterations in radiotherapy from radical to palliative regimens. Delays in treatment become a burden not only to the patient and her family, but also to doctors, nurses and other staff (Dische 2000). These unwanted events could possibly be prevented or reduced if waiting times for radiation were decreased. In order to do this, the extent of the problem needs to be properly assessed.

In our experience, patients do not always arrive on their given simulation dates, a problem that is exacerbated by long delays. This problem may be due to patients' lack of education, money and transport, as well as absence of contact details such as telephone numbers. However, it could also be the result of miscommunication or poor correspondence with peripheral hospitals. Clinical management may vary substantially between different hospitals due to a lack of protocol, differing patient loads, budget and equipment, and differing levels of oncology training. There are currently no studies exploring this. It is possible that patients being seen at peripheral hospitals receive different interim management as compared to those who are referred from tertiary institutions, where multi-disciplinary discussion and meetings have been set up. The care, while not standardized, is not necessarily sub-standard.

This study was conducted to assess the extent of waiting times for radiation treatment and the potential impact that these delays might have on both the patients

and the health care system, in terms of disease progression and the need for extra supportive measures. It also aims to highlight any discrepancies in management between different referring hospitals, where the introduction of standardized policies may be of benefit.

2.0 LITERATURE REVIEW

2.1 Waiting time for radiotherapy

Guidelines from The Joint Council for Clinical Oncology (1993) recommend that radical radiotherapy should start within 14 days for good practice, while 28 days should be the maximum acceptable.

In 2009, Mr M Waters, of the Democratic Alliance, posed a question to the Minister of Health regarding radiotherapy waiting lists in public hospitals. The response was published on the Parliamentary Monitoring Group website, www.pmg.org.za. The information collected by the Minister indicated that, while some hospitals were able to keep within the recommended time interval of two weeks between consultation and start of treatment, there were other hospitals whose delays were up to six months for gynaecological malignancies (Minister of Health 2009).

Waiting times for treatment are by no means isolated to the South African setting. Even so-called first world countries struggle with this problem.

Mackillop *et al.* (1994) reviewed waiting times for carcinoma of the cervix, larynx, lung, prostate and breast in Ontario from 1982 to 1991. The overall waiting time for each patient was divided up into time from diagnosis to referral, time from referral to consultation, time from consultation to initiation of radiotherapy. The longest time delay was found to be from time of consultation to initiation of

treatment. According to the Committee on Standards of the Canadian Association of Radiation Oncologists, this interval should not exceed two weeks. These requirements were met in 1982, but were not maintained up to 1991, at which time, few patients started treatment within the two weeks after consultation. During the ten-year study period, waiting times for cervical cancer doubled, the median time increasing by 105,6%. This resulted from an increase in the incidence of new cases, due to an ageing population, without a parallel increase in radiation resources.

Coles *et al.* (2003) conducted a survey looking at delays both before and during radical radiotherapy. Overall treatment time was reduced from 1996 to 2001 in the majority of the 62 UK hospitals surveyed. However, the median waiting time to start of treatment increased from 14 to 35 days.

2.2 Impact of delay on tumour control

For ethical reasons, there are no prospective randomized studies specifically evaluating the effect of delays in radiation therapy on tumour control. Therefore, most of the information gathered is either retrospective or theoretical.

Wyatt *et al.* (2003) used biological models to demonstrate that long waiting times for radiotherapy may have a negative effect on tumour control. From his study, he concluded that slowly growing tumours, such as prostate cancers, are less likely to be affected by treatment delays, with only 0,1% reduction in tumour control probability (TCP) per week of delay. In contrast, more rapidly growing tumours,

such as squamous cell carcinomas of the head and neck region, may see a one per cent reduction in TCP. By Mackillop's calculations, this figure could be up to ten per cent for tonsillar tumours that have been delayed by one month (Mackillop *et al.* 1996). An audit on patients with lung cancer (O'Rourke & Edwards 2000) showed that 21% of the 29 patients who were waiting for radiotherapy became incurable during this time, while the patients who eventually made it to treatment planning had tumour sizes (cross-sectional diameter) increase by up to 373%.

Cervical cancers are regarded as having similar doubling times to squamous cell carcinomas of the head and neck. The Royal College of Radiologists (2008) has classified tumours into three categories, depending on the rapidity of growth (Appendix 7.2). This classification is used as a guideline to indicate which tumours will be more affected by prolonged treatment due to shorter doubling times. Potential doubling time (T_{pot}) is defined as the time taken for a cell population to double if there is no cell loss. Squamous cell carcinomas of the head and neck region and of the cervix have similar doubling times and they both fall under category I, which are, by definition, rapidly growing tumours.

Glioblastomas and other high-grade gliomas have extremely rapid growth rates, even more so than squamous cell carcinomas. There is clear evidence that delay in starting therapy for these tumours has a negative effect on outcome. A retrospective study (Do *et al.* 2000) of 182 patients with high grade gliomas showed a two per cent increased risk of death per day of delay. Another such study (Irwin *et al.* 2007) showed that each additional week of delay increased risk of death by 8,9%. This translated to a 1,2% risk per day.

Other studies have found conflicting results. Barton *et al.* (1997) looked at 581 patients with early laryngeal carcinoma (stage T1 or T2) who received radical radiotherapy. After a median follow-up of 6,8 years, waiting times did not seem to correlate with risk of relapse. However, median times from biopsy and first consult to start of treatment were 24 and 16 days respectively, which are not significantly longer than general recommendations. Brouha *et al.* (2000), also, could not link length of waiting times to outcomes in 361 patients with early glottic carcinomas. In this retrospective study, median time between diagnosis and start of radiotherapy was 43 days, with a range of nine days to 180. Waiting time was divided into three groups: less than 31 days, 31 to 60 days, and more than 60 days. Two patients of 49 in the first group recurred locally. Of the 102 patients who waited 31 to 60 days, five recurred, while the 19 who waited more than 60 days showed no recurrence. No significant differences in recurrence were found between the three groups.

Fortin *et al.* (2002) defined delay as the time from first oncology consultation, and not biopsy, to start of treatment. In this retrospective study, 623 patients with early squamous cell carcinomas of the head and neck region were evaluated. Delay intervals were again divided into three groups: <30 days, 31 to 40 days, and >40 days. Results indicated that delays of >40 days were associated with poorer loco-regional control and poorer overall survival. The difference in local recurrence was not observed in the first 600 days of follow-up, but thereafter, the difference became evident (Figure 2.2.1). At three years' follow-up, the survival rate in patients who waited more than 40 days was approximately 15% lower than that of patients who waited less than 40 days (Figure 2.2.2).

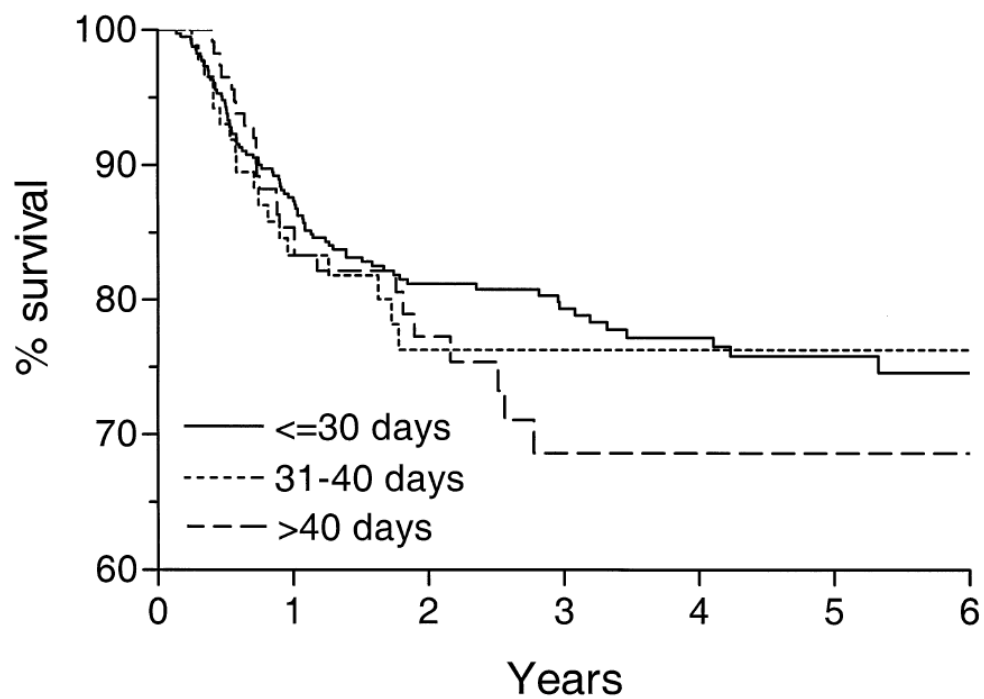


Figure 2.2.1 Local recurrence-free survival rate according to delay interval

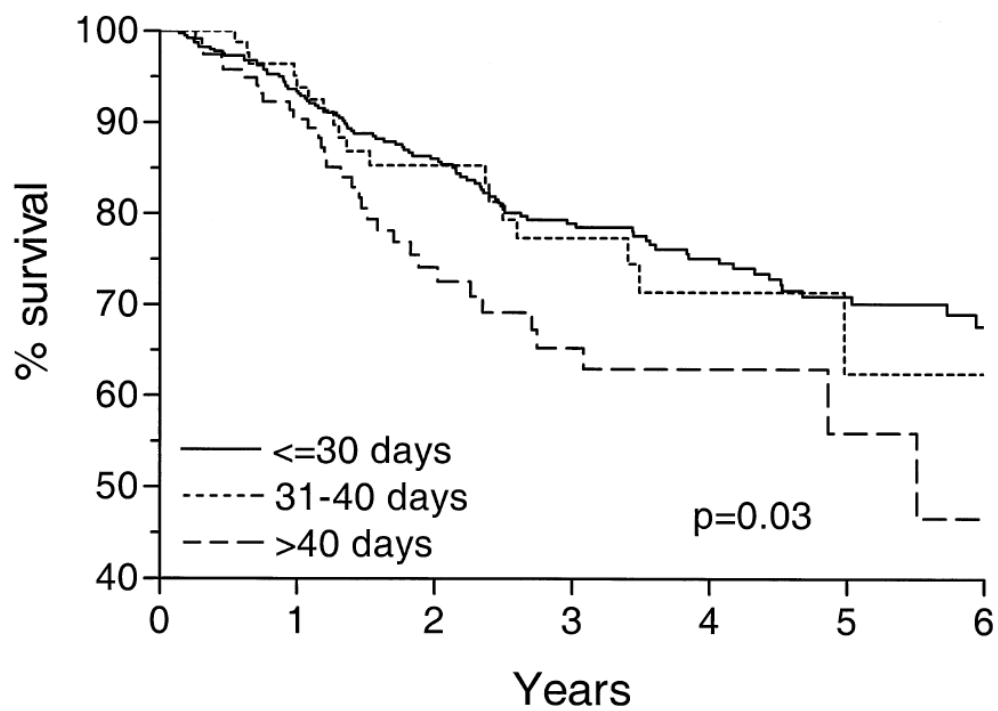


Figure 2.2.2 Survival rate according to delay interval

Given that the delay period in this study was calculated from time of first consultation rather than biopsy, and that times from biopsy to referral and from referral to first oncology consult were relatively constant at nine and 8,5 days respectively, it can be deduced that patients who start radiotherapy more than two months after biopsy show significantly worse outcomes. The results of this study could explain why Barton *et al.* (1997) and Brouha *et al.* (2000) could not attribute relapse risk to treatment delays. In both those studies, waiting times were less than 40 days from first consult to start of radiotherapy.

2.3 Strategies to improve management

From the above studies, we can deduce that delays in commencement of radiotherapy may be detrimental to tumour control. One means to try and improve outcomes is to implement effective screening programmes for early cancer detection and diagnosis.

Strategies that were adopted in Quebec to decrease delays to radiotherapy included centralized management of the waiting lists, so that patients could be transferred to centres with shorter waiting lists; opening of new radiation units; and increased admissions to oncology training programmes (Fortin *et al.* 2006).

A phase II study conducted in South Africa (Goedhals *et al.* 2005) looked at administering a combination of vinorelbine and cisplatin to patients with advanced (stages III and IV) squamous cell carcinomas of the cervix for whom no previous treatment was given. Forty-two patients received up to six cycles of

chemotherapy (discontinued if tumour progressed or if toxicity was unacceptable). There was a 57% overall response rate, with seven per cent of the patients showing complete response, 50% partial response and 19% stable disease. The median duration of response was 17,5 months (range 2,5 to 57 months). Median disease-free survival was 13,2 months and median overall survival 20,6 months. The regimen did not cause excessive toxicity. This study demonstrates that squamous cell carcinomas of the cervix are responsive to chemotherapy and that these regimens have acceptable safety profiles. The administration of such chemotherapy is a strategy that could be adopted while waiting for radiotherapy to begin.

Other ways to shorten waiting times for radiotherapy would be to introduce hypofractionated radiotherapy regimens (see 2.4), to improve national screening programmes or to administer the anti-Human Papilloma Virus vaccine to appropriate individuals (see 1.4).

2.4 Hypofractionation

Conventional fractionation delivers radiation doses of 1,8 - 2,0Gy (Gray) per treatment session, ie.1,8 - 2,0Gy per fraction of radiation. Five fractions are given per week, with a two-day break over weekends. A standard course of radiation takes, on average, six weeks. Hypofractionation entails giving a higher dose per fraction, ie.more than 2Gy per treatment session. As a result, fewer fractions are required and the overall treatment time is reduced. This has the advantage of decreasing overall treatment duration, which has a positive effect on both local

control and survival (Fyles *et al.* 1992; Muckaden *et al.* 2002), as well as easing the patient load at busy radiation units. The compromise is a possible increase in late adverse effects, which increase with increasing dose per fraction (Muckaden *et al.* 2002).

Shortly after the writing of this protocol, our department introduced a hypofractionated radiation regimen for patients with stage IIIB cervical cancer. The regimen adopted consisted of giving 2,5Gy per treatment, five times a week, to a total dose of 40Gy. Brachytherapy was administered twice during the treatment at 9Gy per dose. Thus, overall treatment time was reduced from six weeks to four. This aimed to address two problems – the first being to reduce waiting times, and the second, to complete all radiotherapy within the recommended 30 days (Fyles *et al.* 1992).

Muckaden *et al.* (2002) looked at the role of hypofractionated radiotherapy in stage III cervical cancers. Forty-eight patients received external beam radiation to a total dose of 39Gy in 13 fractions (3Gy per fraction), followed by intracavitary brachytherapy. Eighty-five percent of the patients achieved a complete response by the end of the treatment. At a mean follow-up of 40 months, five-year disease-free survival was 59% and overall survival was 50%. These figures were no worse than those predicted for standard, conventionally fractionated treatments (Cannistra & Niloff 1996). At standard follow-up intervals, the patients were assessed for radiation reactions according the RTOG scale (Appendix 7.3). Acute and late complications were higher than those documented for conventional fractionation. However, the authors feel that, as these were mainly grade I and II

reactions, there is still a role for hypofractionation in patients with more extensive local disease.

Similarly, Campbell *et al.* (2000) found complete response rates, overall five-year survival and local tumour control to be similar in patients receiving hypofractionated radiotherapy and conventionally fractionated radiotherapy, with the late adverse effects also being increased with hypofractionation.

3.0 PATIENTS AND METHODS

We prospectively looked at waiting times for radiation treatment for cervical cancer and the impact that delay had on the patients and their overall management. Patients with cervical cancer who presented to the Radiation Oncology department at the Charlotte Maxeke Johannesburg Academic Hospital were recruited. Ethical clearance was obtained from the Human Research Ethics Committee at the University of the Witwatersrand (Appendix 7.4).

3.1 Patient characteristics

Eighty-one (81) patients, who presented to the department between May 2010 and July 2011, were included in the study. These patients were all to receive radical radiotherapy. Patients planned for palliative radiation regimens (either due to advanced-stage disease or poor performance status), with poor expected overall survival, were excluded, as well as patients who required post-operative radiation. Cases where clinical stage was in doubt were also excluded. Performance status was evaluated using the ECOG scale (Appendix 7.5). Patient characteristics are presented in Table 3.1.1.

Table 3.1.1 Patient characteristics

Characteristic	Number of patients (%) (n=81)
Age group	
20-30 years	4 (5%)
31-40 years	11 (14%)
41-50 years	28 (35%)
51-60 years	26 (32%)

61-70 years	10 (12%)
71-80 years	2 (2%)
Histological type	
Squamous cell carcinoma	71 (88%)
Adenocarcinoma	6 (7%)
Adenosquamous carcinoma	1 (1%)
Basaloid squamous carcinoma	1 (1%)
Unknown	2 (3%)
Tumour grade	
I (well differentiated)	1 (1%)
II (moderately differentiated)	51 (63%)
III (poorly differentiated)	14 (17%)
IV (undifferentiated)	1 (1%)
Unknown	14 (17%)
Tumour stage	
IB ₁	1 (1%)
IB ₂	2 (2%)
IIA	1 (1%)
IIB ₁	29 (36%)
IIB ₂	15 (19%)
IIIA	2 (2%)
IIIB ₁	5 (6%)
IIIB ₂	5 (6%)
IIIB ₃	21 (26%)
HIV status	
Negative	44 (54%)
Positive	37 (46%)
ECOG performance status	
0	0 (0%)
1	80 (99%)
2	1 (1%)
Hospital level	
Secondary	4 (5%)
Tertiary	77 (95%)

3.2 Recruitment and follow-up reviews

Patients were counselled about their disease, intended treatment and about the study. Written informed consent for both radiation and participation in the study was obtained at first visit.

Standard hospital policy was followed, whereby patients were reviewed every four weeks until simulation. At each visit, each patient's history was noted, including whether the patient received any blood transfusions, how many units were received, whether they had been admitted for any reason, whether they were experiencing any bleeding per vagina (and severity of bleeding) and whether or not they were having any bladder or bowel complaints. The administration of haemostatic brachytherapy (due to excessive bleeding or the requirement of multiple blood transfusions) was also documented. A physical examination was done. Special note was taken of the overall performance status, and of local tumour extent, to assess for tumour progression. (Appendix 7.6: 4-weekly clinic review form).

Once patients had been assigned a date for simulation, they were telephoned to come in. At the simulator, they were asked the same questions as those asked at the four-weekly clinic reviews and a local examination was, once again, repeated. In addition, blood was drawn to reassess renal function and blood counts. This was necessary as original/previous blood results were often up to four months old. It also allowed us to evaluate changes or deterioration in counts and renal function for patients who were waiting for treatment.

Once a treatment date was assigned, this was recorded to complete the required data.

3.3 Statistical methods

Statistical tests were performed using IBM SPSS version 20.0. A p-value of $<0,05$ was considered statistically significant.

Firstly, a one-sample Kolmogorov-Smirnov Test was used to test whether time from consultation to simulation was normally distributed. As demonstrated in Figure 3.3.1 and Table 3.3.2, the distribution was positively skewed, with a skewness value of +3,85. The graph is also very peaked, with a high kurtosis of 23. Both the skewness and the high kurtosis indicate that the data is not normally distributed. Reporting of average values might, therefore, not be a relevant reflection of the average patient's experience due to higher than normally expected values. In such cases, the median value provides a more accurate reflection of the average patient's experience.

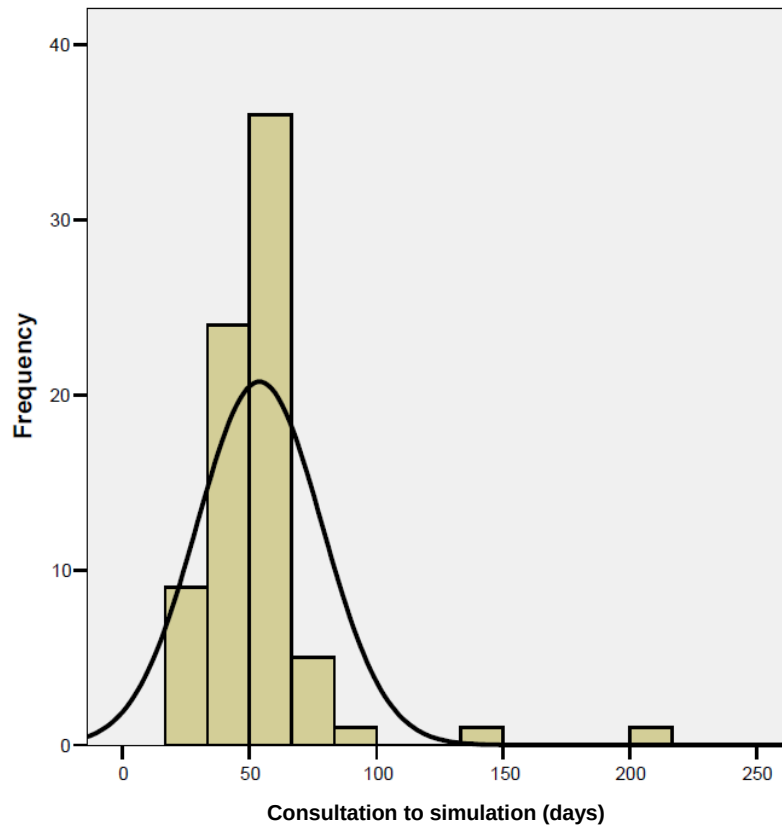


Figure 3.3.1 One-Sample Kolmogorov-Smirnov Test for normality

Table 3.3.2 One-Sample Kolmogorov-Smirnov Test looking at time from consultation to simulation

Valid N	77
Missing	4
Mean	53,87
Standard Error of Mean	2,81
Median	55,00
Standard Deviation	24,66
Skewness	3,85
Standard Error of Skewness	0,27
Kurtosis	22,69
Standard Error of Kurtosis	0,54
Minimum	18,00
Maximum	211,00
Kolmogorov-Smirnov Z	2,08
Asymmetric Significance (2-tailed)	0,00

The p-value was 0,00. The test was, thus, statistically significant and the null hypothesis was rejected. This confirms non-normality and, therefore, non-parametric tests were chosen for further data analysis. Where relevant, median values were also reported in favour of averages.

The Mann-Whitney test was used to determine if the distributions differed statistically in relation to time waited between first consultation and simulation.

Exact significance testing was performed to confirm results on stage changes and time waited. Exact tests provide a more direct calculation of probabilities for groups with very low n-values ($n < 30$).

Kaplan-Meier estimates were used to determine the length of time elapsed while waiting for simulation before stage progression occurred. These methods were also used to evaluate differences in stage progression according to original tumour stage, HIV status and histological differentiation (grade).

4.0 RESULTS

4.1 Time delays

The median time from first consultation at the department to simulation was just short of two months (55 days). The wait from simulation to commencement of radiation treatment took, on average, another 19 days, as illustrated in Table 4.1.1. The median total delay in starting treatment as a consequence of departmental waiting lists was, therefore, 74 days. This, however, does not take into account delays due to other factors, such as patients defaulting or being unreachable by both telephone and telegram.

Table 4.1.1 Delay times

Time interval (days)	Valid N	Mean	Median	Mode	Min	Max	Std. Dev.
Diagnosis to Consultation	81	45	36	30	6	274	34
Consultation to Simulation	77	54	55	57	18	211	25
Simulation to Treatment	77	20	19	19	1	76	11
Diagnosis to Treatment	77	119	108	90	65	324	39
Consultation to Treatment	77	73	74	75	30	222	26

Min,minimum; Max,maximum; Std. Dev., standard deviation.

One of the rationales for doing this study was the observation that some patients were waiting up to four months for their treatment to begin. In this study, the

maximum delay from day of first consultation to simulation was 211 days. This patient did not come for her follow-up appointment and could not be contacted on the telephone number that she had provided. She eventually returned, 25 weeks later, citing “social problems” as her reason for defaulting follow-up. She returned complaining of a vaginal discharge and dysuria. She was treated for pelvic inflammatory disease and the local tumour was assessed as “unchanged”. However, at simulation, three-and-a-half weeks later, she was indeed upstaged from stage IIB₁ to IIB₂.

The patient with the next longest wait was simulated 139 days after her first consultation. Again, this was a defaulter who was difficult to contact. She had, apparently, moved to Vrede in the Free State Province and cited various reasons for defaulting (she did not get the messages left with her brother to return to the hospital; she was too ill to walk, so could not travel to the hospital; her house had burned down). Unfortunately, on her return, her tumour had progressed and she was re-staged as having stage IVA disease with a vesico-vaginal fistula. She was given palliative radiotherapy of 20Gy in two fractions, one month apart.

These two patients represent extreme outliers. Five patients of the valid population (six per cent) waited longer than 70 days from first consultation to simulation. If we exclude these five patients from our analysis, the median waiting time would still be 55 days, although the mean time would drop from 54 to 50 days. For this reason, median values have been chosen for comparison rather than the mean, as they give a more accurate picture given the typically non-Gaussian distributions (Figure 4.1.2 and Figure 4.1.3).

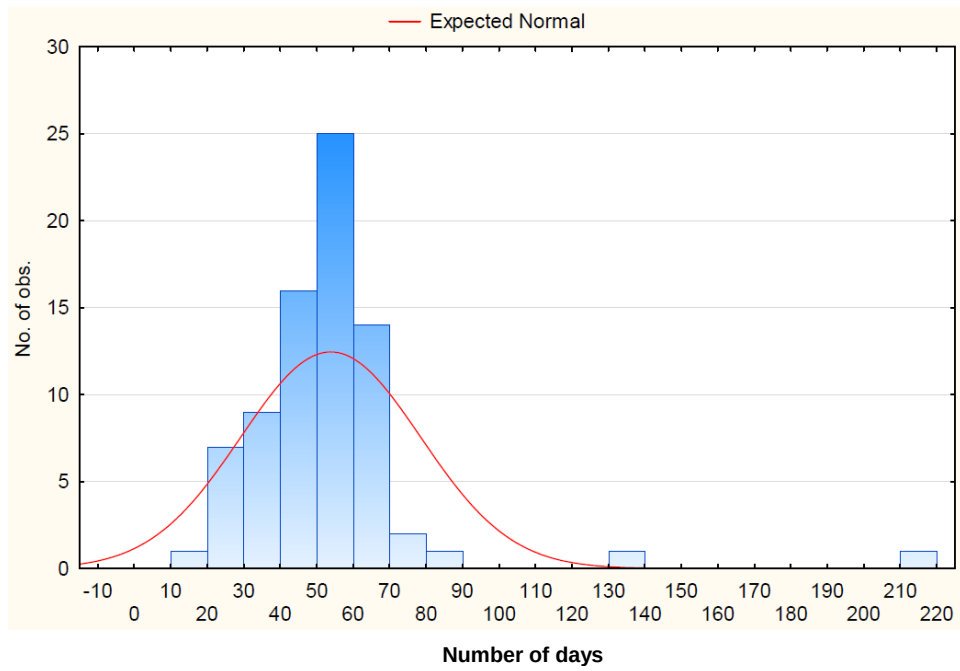


Figure 4.1.2 Histogram showing time from first consultation to simulation

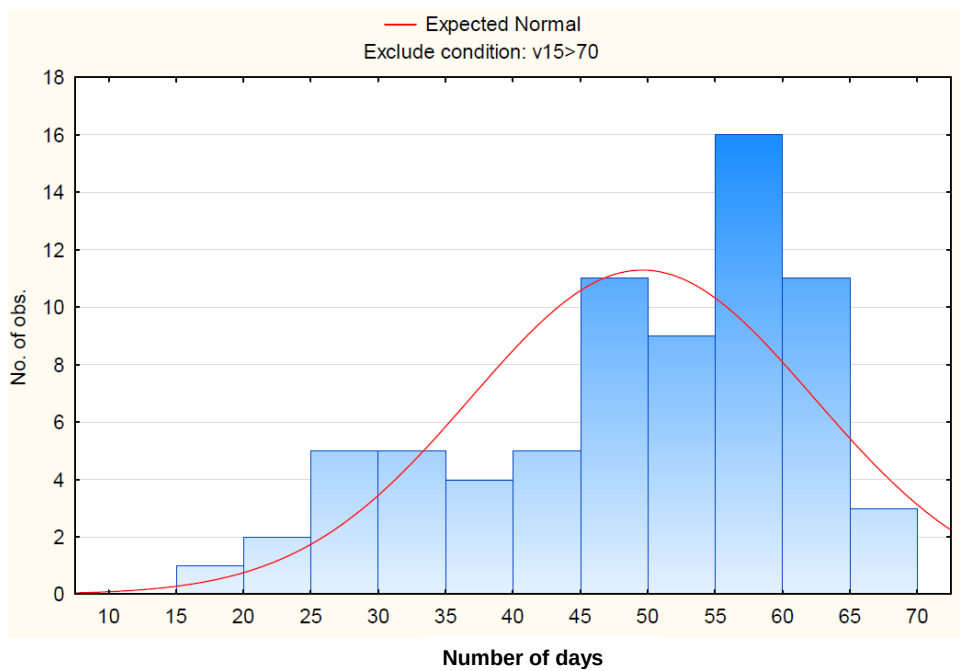


Figure 4.1.3 Histogram showing time from first consultation to simulation
(Values >70 days excluded)

The interval between simulation and the commencement of treatment, again, shows a skewed distribution (Figure 4.1.4), with a range of one day to 76 days. Again, the patient who waited 76 days for treatment was a patient who did not arrive on her treatment day. It is unclear why she defaulted. On her return, she was found to be pale and blood tests were done. She then complained of vomiting and was admitted for intravenous fluids and correction of electrolyte imbalances. Excluding this patient from our analysis, the median time from simulation to start of treatment remains 19 days. However, standard deviation is reduced from 11 to eight.

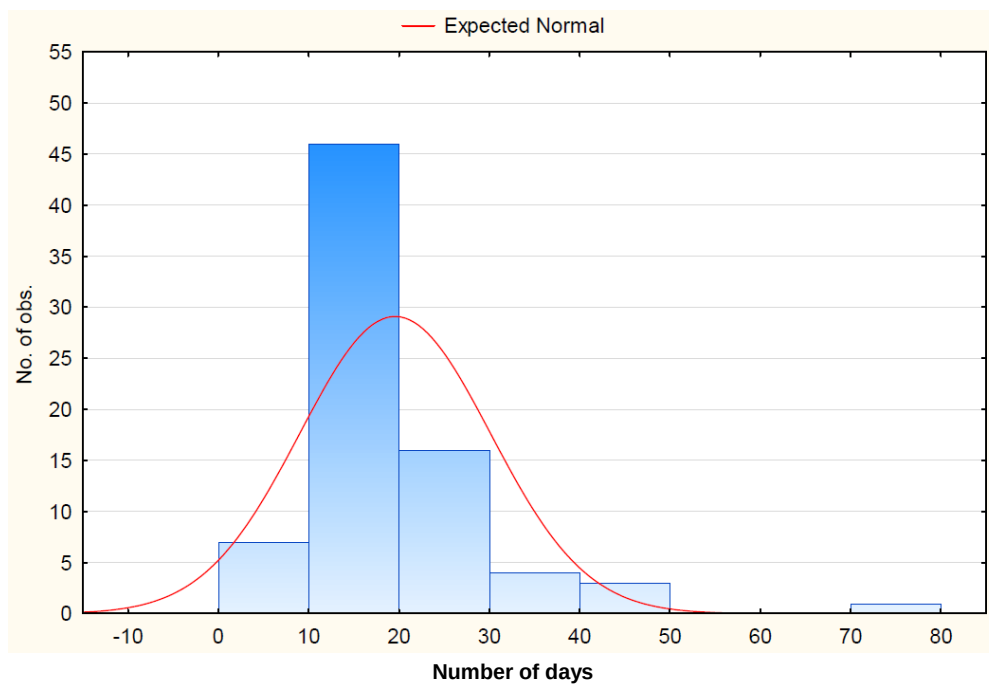


Figure 4.1.4 Histogram showing time from simulation to start of treatment

In order to reduce standard deviation even further (to a value of six), we would have to exclude the four patients (five per cent of the valid population) who waited the longest for treatment to start. Thus, we would include all patients who

waited less than or up to 40 days from simulation to treatment. This would produce a more normal curve as seen in Figure 4.1.5.

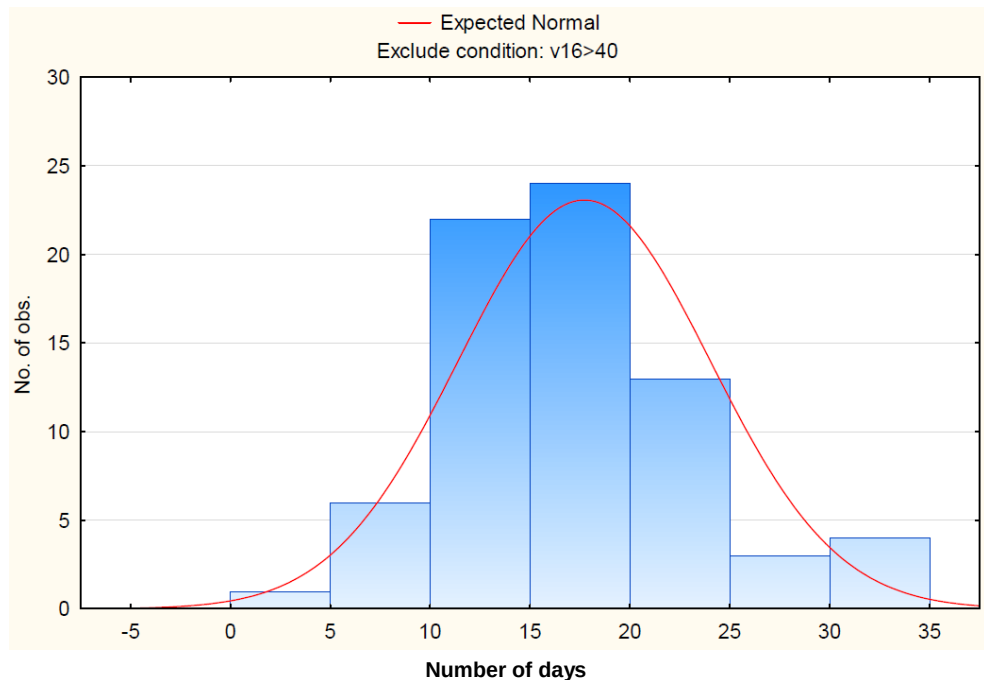


Figure 4.1.5 Histogram showing time from simulation to start of treatment (Values >40 days excluded)

4.2 Procedures

From the time of first consultation to simulation, one in four patients received blood transfusions. However, the median haemoglobin level was only 11,1g/dL, with the minimum referral haemoglobin being as low as 3,8g/dL. The Mann-Whitney Test showed no statistical difference in waiting time (first consultation to simulation) for those who received blood transfusions and those who did not ($p=0,70$).

Of the 79 patients who returned for follow-up, 21 (27%) were admitted to hospital during the wait. This constitutes one quarter. Most of the admissions were for anaemia and related symptoms, whereby a blood transfusion was required. Only three were admitted and did not receive a blood transfusion. Two of these were admitted for transport reasons, as they had no other means to get to the radiation unit. The third patient says she was admitted for “an operation to treat the cancer”, but this was not done. As she had already presented with a stage IIB cancer, this admission was most likely the result of a mix-up or miscommunication problem. Longer waiting times from first consultation to simulation did not predict for admission ($p=0,84$).

Four (5%) of the participants were given brachytherapy for haemostasis while awaiting treatment. Due to the small number of patients (four) in this group, the Mann-Whitney Test was not valid. Interestingly, the median time from first consultation to simulation for those who received brachytherapy was 50 days, while those who had no brachytherapy waited median times of 55 days. Although numbers are too small for accurate comparison, a possible explanation for this discrepancy is that the patients who were bleeding enough to require haemostasis in the form of brachytherapy may have been given an earlier treatment date to obviate the need for further intervention.

4.3 Progression

From the time of first consultation to simulation, 35 (43%) of the 79 evaluable patients had progression of their tumours. Twenty-two (27%) were upstaged.

Nineteen (23%) required modification of their planned treatments to a less radical regimen (eg. hypofractionated radiation), as per departmental protocol. It was suspected that one patient had developed a vesico-vaginal fistula at simulation review, which would have upstaged the tumour to stage IVA. However, this was not verified and the patient's good performance status suggested a fair prognosis. Therefore, she was given radical radiation as planned.

In terms of both tumour progression and stage changes, the time waited from first consultation to simulation was not statistically significant, with p-values of 0,08 and 0,21 respectively. However, median values were slightly higher for the average patient whose disease became more advanced (Table 4.3.1).

Table 4.3.1 Median waiting times (in days) from first consultation to simulation

	TUMOUR PROGRESSED		STAGE CHANGED	
	NO	YES	NO	YES
Mean	48	61	52	67
Standard deviation	14	33	10	40
Minimum	18	22	34	22
Percentile 25	36	50	46	50
Median	53	55	55	57
Percentile 75	57	62	58	69
Maximum	69	211	71	211
Valid n	42	34	13	21

An exact (significance) test was done to confirm that waited times from first consultation to simulation were not significant with respect to stage changes. None of the results reached statistical significance.

Figure 4.3.2 is a Kaplan-Meier plot of time from consultation to simulation against the proportion of patients whose tumour stage did not change. The steep drop in the curve indicates that the majority of those patients whose tumours progressed, and were upstaged, experienced these changes between 40 and 65 days of waiting.

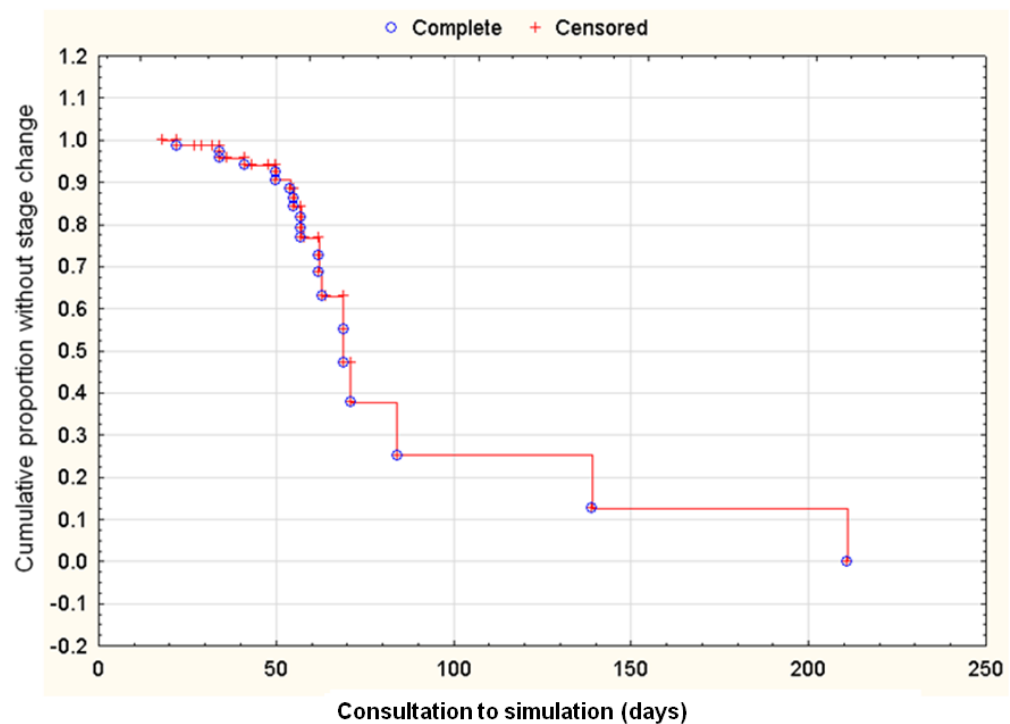


Figure 4.3.2 Kaplan-Meier estimate of stage changes against time waited

Figure 4.3.3 suggests that earlier tumours may progress more rapidly than later stage tumours. However, this was not statistically significant, with a p-value of 0,55.

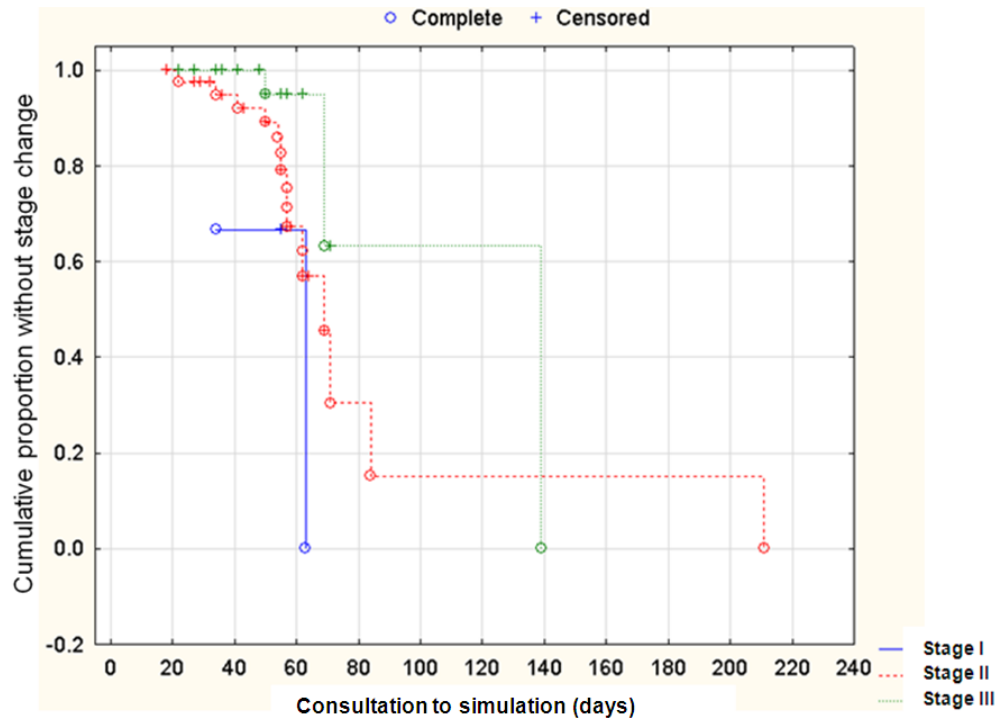


Figure 4.3.3 Kaplan-Meier estimate of stage changes according to original stage ($p=0,55$)

Neither HIV status nor histological differentiation (grade) was significant with regards to stage progression, with p-values of 0,20 and 0,18 respectively (Figures 4.3.4 and 4.3.5).

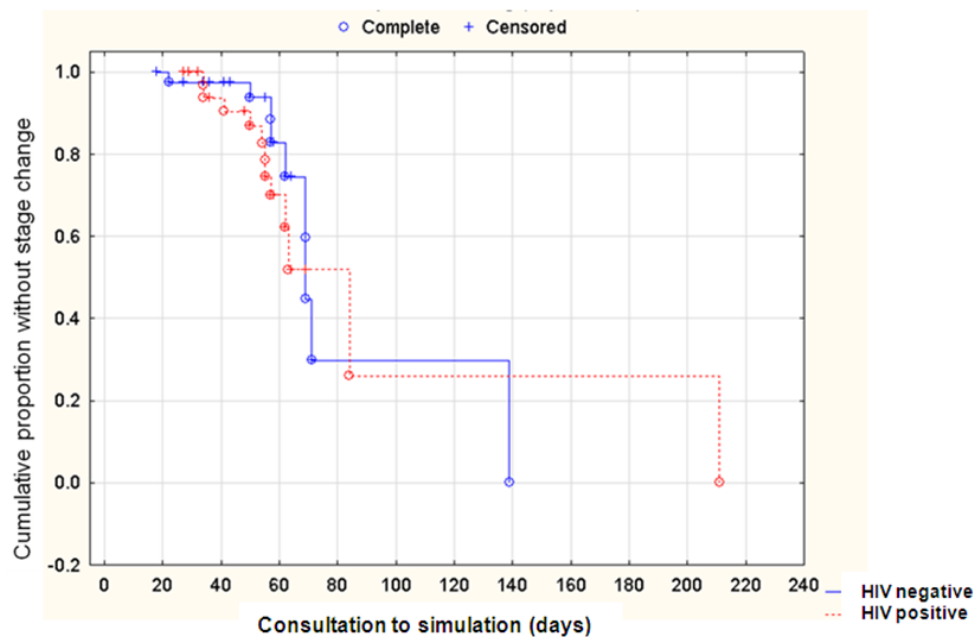


Figure 4.3.4 Kaplan-Meier estimate of stage changes according to HIV status ($p=0,20$)

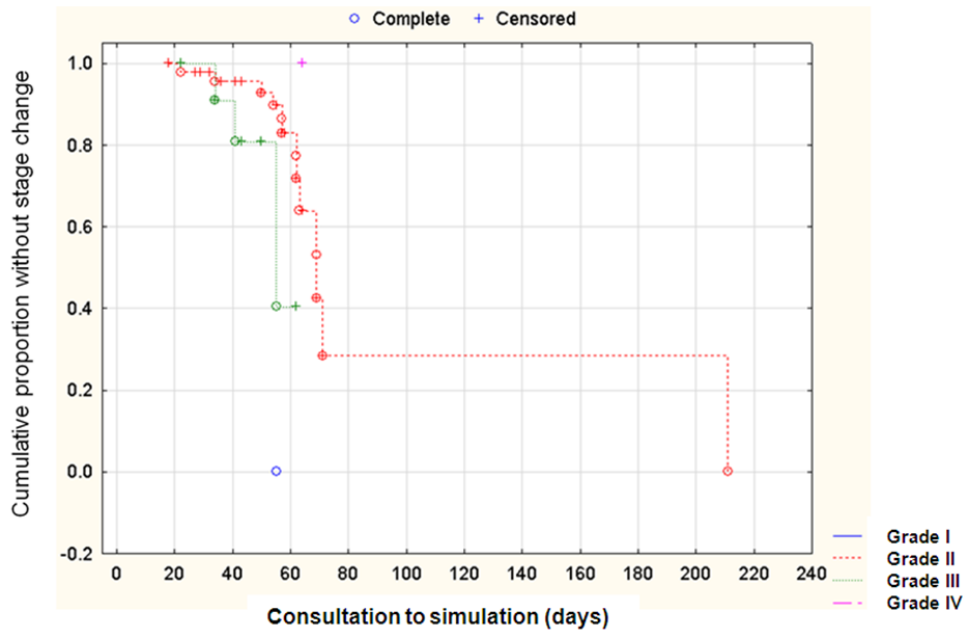


Figure 4.3.5 Kaplan-Meier estimate of stage changes according to histological differentiation/grade ($p=0,18$)

Only five patients (six per cent) were evaluated as having a deterioration in ECOG performance status, with the majority staying at an ECOG of I. There were too few changes in performance status to evaluate significance with respect to time waited. No deaths were reported.

Median haemoglobin levels at first consultation were 11,1g/dL and this value was unchanged at time of simulation, despite the large number of patients who were transfused blood. There was no significant change in renal functions from time of first consultation to time of simulation.

4.4 Defaulting and death

Ten of the 81 patients on the study defaulted follow-up or declined treatment at some point. Reasons for defaulting were often unclear, with some stating social problems and others giving no real explanation. Problems such as “forgetting about” follow-up appointments could possibly be attributed to the long wait. Some patients were delayed as they had returned home to other provinces while waiting to be phoned with a date from the hospital. One such patient had gone back to Limpopo and decided to get her treatment there instead. Another felt that the wait was too long and opted to go to Germany, where she had family. Some patients could not be contacted on the telephone numbers provided. One patient decided not to return to the hospital as she was “dissatisfied” with the service she was receiving. She did not clarify whether her dissatisfaction was due to the wait or due to other reasons; she did not answer her phone thereafter.

As seen with the patients who had brachytherapy or whose performance status’ deteriorated, numbers were too low to do statistical tests on those who had defaulted. The patients who defaulted had median waiting times from first consultation to simulation of 67 days, whereas those who did not default waited a median time of 55 days. This is expected as patients who default will logically wait longer, having missed a review, simulation or treatment appointment.

Of the patients who were treated or could be reached, none had demised while awaiting radiation. However, at least one patient had progressed to stage IV disease and was given palliative radiation of 10Gy monthly, for two fractions. A

second patient had a suspected vesico-vaginal fistula at simulation. However, as this was not verified, she was treated radically as planned.

5.0 DISCUSSION

5.1 Delays in radiotherapy and the impact

The median delay from first consultation until commencement of treatment was 74 days. The patients waited, on average, two months to have a simulation done, and a further three weeks after simulation. At the time of writing a protocol for this study, it was noted that some patients were waiting up to four months for simulation alone. The reason for this discrepancy is due to the introduction of a hypofractionated radiation protocol, which was introduced with the aim of decreasing waiting times. Similar manipulations in fractionation, which reduce overall treatment time by increasing daily doses, have been adopted by other resource-constrained centres, including those in some first world countries like the United Kingdom (Dodwell & Crellin 2006).

All patients with stage IIIB disease were placed on a four-week course of radiation, as opposed to the conventional six weeks. This strategy appears to have had some impact. However, there are still significant waiting lists and there is still an unacceptably long delay in starting treatment.

Mackillop *et al.* (1994) found that the median waiting time for patients with cervical cancer in Ontario was 27,2 days from diagnosis to commencement of radiotherapy. He observed, as with this study, that most of the wait lay in the period following the first consultation, but he gives no figure for this time interval. We, therefore, compare his median total time of 27,2 days to our median total

time of 108 days from diagnosis to treatment. Although Mackillop cites waiting times as a problem in Ontario, it is clear that the delays in the Canadian setting are in no way comparable to those in our institution, where the wait is four times as long.

At the time of simulation, over one quarter (27%) of the study patients had tumours which had progressed to a more advanced stage since the time of first consultation to the unit. This would, theoretically, translate to a poorer prognosis and decreased survival, given that five-year survival rates are roughly 80%, 65% and 40% for stages I, II and III respectively (Cannistra & Niloff 1996). A longer follow-up of these patients would be required to assess lives lost as a result of treatment delay. The study, however, failed to show that tumour progression was increased with a longer delay. This could, possibly, be explained by the fact that only 77 patients were evaluable for analysis and this small number could have lead to statistical tests being underpowered.

Mackillop *et al.* (1996) conclude that there is no theoretical reason to believe that any delay is safe and the best course would then be to adopt an ASARA principle, ie. to keep delays “As Short As Reasonably Achievable”, this being modeled from the ALARA principle of keeping radiation doses “As Low As Reasonably Achievable”. While this principle is both logical and sensible, it may be of benefit to define specific goals towards which radiation departments can aim.

In order to determine if there is a cut-off delay period below which would be “acceptable” for patients to wait, a similar study could be done, recruiting a much

larger number of participants. More directed studies cannot, for obvious reasons, be done as it would be ethically unsound to delay treatment intentionally. In this study, progression of the tumours that were upstaged was noted between 40 and 65 days, using Kaplan-Meier plots (see 4.3). Fortin *et al.* (2002) looked at time waited from consultation to start of treatment for radically-treated head and neck tumours, which are considered to have similar doubling times to cervical cancers. Their study demonstrated diminished loco-regional control and overall survival for patients who waited longer than 40 days for radiation treatment. These patients had a 15% lower survival rate at three years. Although we looked at time from first consultation to simulation, rather than time to start of treatment, the trend of the plot (Figure 4.3.2) implies that should patients have been re-evaluated at the start of treatment, the sharp drop between 40 and 65 days would still be relevant. Thus, this study, in accordance with Fortin's study, supports the conclusion that a delay of more than 40 days may compromise tumour control and subsequent patient survival.

This study has focussed largely on local tumour progression and upstaging. A more complete assessment would include the development of distant metastases. With a longer follow-up, one could also look at responses to treatment and overall survival.

Apart from the obvious consequences of disease progression, patients' quality of life needs to be considered. This includes the psychological anxiety of living with an untreated cancer, as well as the symptoms of the cancer itself, which may manifest as severe pain, vaginal bleeding, malodorous vaginal discharge and

general asthenia due to anaemia and chronic illness. Many patients fail to receive adequate analgesia and many struggle to collect medication due to lack of transport money and poor social support.

Bleeding per vagina is a common clinical presentation of cervical cancer. This may be mild or heavy, intermittent or constant. Clearly, anaemia is a real risk for these patients and the longer they wait for radiation treatment, the higher the chances that they will require multiple blood transfusions or haemostatic brachytherapy to stop the bleeding. In this study, one in four patients received a blood transfusion while waiting for simulation. The cost of one unit of Red Cell Concentrate is R1 369,39 in the state sector, while blood administration sets cost a further R796,05 each (South African National Blood Service 2012). This is over and above the price of the hospital stay.

Most of the patients who were transfused were admitted to hospital to receive the transfusion. According to statistics compiled by economist, Mike Schüssler, only two per cent of the cost of a public sector admission is charged to the patient. The remaining 98% is borne by the taxpayer (Zietsman 2012). Zietsman (2012) concludes, in his analysis of hospital costs, that while public health care appears cheaper than private care, the opposite is actually true when one takes into consideration the overall cost to the economy and the effectiveness of providing that care.

Brachytherapy for haemostasis is only available at hospitals that have radiation facilities, and these facilities are already burdened with high patient volumes and

insufficient treatment time. Four patients of 79 received haemostatic brachytherapy for bleeding.

There were no significant changes in haemoglobin, urea or creatinine levels from the time of first consultation to the time of simulation. In some cases, haemoglobin levels had actually improved. This could have been due to blood transfusions that were given during the waiting period.

Ninety-five per cent of the patients were referred from tertiary institutions. This made it impossible to assess whether management differed between level two and level three hospitals. Many patients are diagnosed at secondary hospitals and local clinics, but are then referred to specialized centres for further work-up and staging. The referral hospital (often a tertiary centre) will then take over management and refer patients to the oncology department when all results are available.

5.2 Strengths and limitations of the study

This study has the advantage of being conducted prospectively, so notes were complete and patients could be assessed at each visit. Almost all reviews were done by one oncologist, which minimized chances of subjectivity.

Unfortunately, only original staging was done by oncological gynaecologists, and not always the same ones. Although the International Federation of Gynecology and Obstetrics (FIGO) still stages cervical carcinoma by clinical examination and

minimal diagnostic tests are permitted (Pecorelli 2009), there is clearly an element of subjectivity that may result in incorrect assessment of tumour extent and stage.

Limitations of the study include the small number of patients (81) recruited. As there were too few patients referred from secondary institutions, comparisons between secondary and tertiary hospitals were not done. Due to the small size of the study, there were insufficient numbers of patients who received brachytherapy, who defaulted and whose general performance status' deteriorated. Therefore, accurate statistical analyses could not be performed to see if these patients waited longer median times than their counterparts.

Although the time between simulation and start of treatment should have been more or less standard for all patients, it was found that some did wait significantly longer than others, whether due to patient or departmental factors. Thus, it may have been more beneficial to compare the time waited from first oncology consultation to the start of radiation treatment, rather than analyze time from first consultation to time of simulation. However, as this was not part of the original study protocol, patients were not re-examined at the commencement of treatment.

Web addresses were checked prior to submission of this research report. The web address for the Department of Health, which was accessed on 30 May 2012, was no longer available on 25 January 2013. The same guideline was able to be accessed via a different web address and the reference was updated. Such problems may arise when readers are attempting to find references online.

6.0 CONCLUSION

Carcinoma of the uterine cervix remains a problem in the developing world, particularly in sub-Saharan Africa. Despite the large burden of disease, treatment facilities are still lacking. Supply is unable to keep up with demand and waiting lists for radiotherapy are unacceptably long.

This study was conducted to assess the potential impact that treatment delays may be having on the health care system, the patients and their disease. As squamous cell carcinomas are classified as category I tumours and, by definition, rapidly growing, these patients need to start treatment as soon as possible. The prolonged wait for machine time has been of theoretical concern. It was hoped that this study would demonstrate the clinical impact that delays have on tumour progression and upstaging. Results did not reach statistical significance. However median delay times of ten weeks from first consultation to commencement of treatment, 43% of the patients having progressive disease and 27% having their tumours upstaged are all figures that remain a concern for both medical staff and patients alike. Although tumour progression could not be correlated to time waited, it was noted that most of the tumours that were upstaged were upstaged between 40 and 65 days. Thus, reasonable goals for the department would be to decrease the wait from first consultation to simulation to less than 40 days.

In this study, two patients decided to seek treatment elsewhere, which may not have happened had they been offered immediate care. It is difficult to measure patients' anxiety levels caused by delayed cancer care. This study did not look at quality of life issues, which would be another useful parameter for future assessment.

Delays in starting radiotherapy result in unnecessary and, often, costly interventions. The cost of blood transfusions, especially in a setting where blood is in short supply, as well as the cost of hospital admissions, places further strain on hospital budgets and, ultimately, results in a vicious cycle of unsatisfactory service delivery. In this study, one in four patients required blood transfusions while awaiting treatment.

In conclusion, this study provides a basic overview of times waited for radiotherapy for cervical cancer at Charlotte Maxeke Johannesburg Academic Hospital. This will provide a platform for future comparisons and for assessment of progress and improvement within the department. Further studies may look at quality of life for patients awaiting treatment, patient satisfaction with the care received, staff and equipment requirements for improving waiting times, and outcomes for patients who were treated using a hypofractionated protocol.

7.0 APPENDICES

APPENDIX 1

7.1 Staging of carcinoma of the cervix uteri (comparison between FIGO staging and CMJAH modifications)

STAGE	FIGO	CMJAH modifications
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 $\leq 5\text{mm}$ and largest extension $\geq 7\text{mm}$	
IA ₁	Measured stromal invasion of $\leq 3.0\text{mm}$ in depth and extension of $\leq 7.0\text{mm}$	
IA ₂	Measured stromal invasion of $> 3.0\text{mm}$ and not $> 5.0\text{mm}$ with an extension of not $> 7.0\text{mm}$	
IB	Clinically visible lesions limited to the cervix uteri or pre-clinical cancers greater than stage IA	
IB ₁	Clinically visible lesion $\leq 4.0\text{cm}$ in greatest dimension	
IB ₂	Clinically visible lesion $> 4.0\text{cm}$ in greatest dimension	
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	
IIA ₁	Clinically visible lesion $\leq 4.0\text{cm}$ in greatest dimension	
IIA ₂	Clinically visible lesion $> 4.0\text{cm}$ in greatest dimension	
IIB	With obvious parametrial invasion	
IIB ₁		Only inner half of parametria invaded
IIB ₂		Outer half of parametria invaded
III	The tumour extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney	
IIIA	Tumour involves lower third of the vagina, with no extension to the pelvic wall	
IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney	
IIIB ₁		One pelvic wall involved
IIIB ₂		Both pelvic walls involved
IIIB ₃		Hydronephrosis
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous oedema, as such, does not permit a case to be allotted to Stage IV	
IVA	Spread of the growth to adjacent organs	
IVB	Spread to distant organs	

7.2 Royal College of Radiologists: patient categorization for prioritization of patients according to need

- Category I patients

These are patients with rapidly growing tumours, such as squamous carcinomas, being treated with radical intent. The effects of interruptions on the outcomes of such cancers have been assessed by a number of international studies. Treatment duration must not be prolonged by more than two days over the original prescription.

- Category II patients

These are patients with slower growing tumours, usually adenocarcinomas, being treated with radical intent. There are reports that prolongation of five days may not always be deleterious, but no safe minimum has been established. It is advised that their treatment should not be prolonged by more than two days over the original prescription

- Category III patients

These are patients being treated with palliative intent. Overall time is less critical in achieving the desired palliative outcomes. Prolonged interruptions, which may occur because of intercurrent illness, may require compensation, particularly if longer than seven days.

APPENDIX 3

7.3 RTOG/EORTC Late Radiation Morbidity Scoring Schema

ORGAN TISSUE	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	5
SKIN	None	Slight atrophy; Pigmentation change; Some hair loss	Patch atrophy; Moderate telangiectasia; Total hair loss	Marked atrophy; Gross telangiectasia	Ulceration	D E A T H D I R E C T L Y R E L A T E D T O R A D I A T I O N
SUB-CUTANEOUS TISSUE	None	Slight induration, (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; Slight field contracture; <10% linear reduction	Severe induration and loss of subcutaneous tissue; Field contracture; >10% linear measurement	Necrosis	
MUCOUS MEMBRANE	None	Slight atrophy and dryness	Moderate atrophy and telangiectasia; Little mucous	Marked atrophy with complete dryness; Severe telangiectasia	Ulceration	
SALIVARY GLANDS	None	Slight dryness of mouth; Good response on stimulation	Moderate dryness of mouth; Poor response on stimulation	Complete dryness of mouth; No response on stimulation	Fibrosis	
SPINAL CORD	None	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurological findings at or below cord level treated	Mono, para, quadraplegia	
BRAIN	None	Mild headache; Slight lethargy	Moderate headache; Great lethargy	Severe headaches; Severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or paralysis Coma	
EYE	None	Asymptomatic cataract; Minor corneal ulceration or keratitis	Symptomatic cataract; Moderate corneal ulceration; Minor retinopathy or glaucoma	Severe keratitis; Severe retinopathy or detachment; Severe glaucoma	Pan-opthalmitis/ Blindness	
LARYNX	None	Hoarseness; Slight arytenoid edema	Moderate arytenoid edema; Chondritis	Severe edema Severe chondritis	Necrosis	
LUNG	None	Asymptomatic or mild symptoms (dry cough); Slight radiographic	Moderate symptomatic fibrosis or pneumonitis (severe cough) Low grade fever	Severe symptomatic fibrosis or pneumonitis; Dense radiographic	Severe respiratory insufficiency/ Continuous O ₂ / Assisted ventilation	

		appearances	Patchy radiographic appearances	changes		L A T E E F F E C T S
HEART	None	Asymptomatic or mild symptoms; Transient T wave inversion & ST changes; Sinus tachycardia >110 (at rest)	Moderate angina on effort; Mild pericarditis; Normal heart size; Persistent abnormal T wave and ST changes; Low ORS	Severe angina; Pericardial effusion; Constrictive pericarditis; Moderate heart failure; Cardiac enlargement; EKG abnormalities	Tamponade/ Severe heart failure/ Severe constrictive pericarditis	
ESOPHAGUS	None	Mild fibrosis; Slight difficulty in swallowing solids; No pain on swallowing	Unable to take solid food normally; Swallowing semi-solid food; Dilatation may be indicated	Severe fibrosis; Able to swallow only liquids; May have pain on swallowing; Dilation required	Necrosis/ Perforation; Fistula	
SMALL/ LARGE INTESTINE	None	Mild diarrhea; Mild cramping; Bowel movement 5 times daily; Slight rectal discharge or bleeding	Moderate diarrhea and colic; Bowel movement >5 times daily; Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis/ Perforation Fistula	
LIVER	None	Mild lassitude; Nausea, dyspepsia; Slightly abnormal liver function	Moderate symptoms; Some abnormal liver function tests; Serum albumin normal	Disabling hepatic insufficiency; Liver function tests grossly abnormal; Low albumin Edema or ascites	Necrosis/ Hepatic coma or encephalopathy	
KIDNEY	None	Transient albuminuria; No hypertension; Mild impairment of renal function Urea 25-35 mg% Creatinine 1.5-2.0 mg% Creatinine clearance >75%	Persistent moderate albuminuria (2+); Mild hypertension; No related anemia; Moderate impairment of renal function Urea>36-60 mg% Creatinine clearance (50-74%)	Severe albuminuria; Severe hypertension; Persistent anemia (<10g%); Severe renal failure Urea >60 mg% Creatinine >4.0 mg% Creatinine clearance <50%	Malignant hypertension; Uremic coma/Urea >100%	
BLADDER	None	Slight epithelial atrophy; Minor telangiectasia (microscopic hematuria)	Moderate frequency; Generalized telangiectasia; Intermittent macroscopic hematuria	Severe frequency and dysuria; Severe generalized telangiectasia (often with petechiae); Frequent hematuria; Reduction in	Necrosis/ Contracted bladder (capacity <100 cc); Severe hemorrhagic cystitis	

				bladder capacity (≤150 cc)		
BONE	None	Asymptomatic No growth retardation; Reduced bone density	Moderate pain or tenderness; Growth retardation; Irregular bone sclerosis	Severe pain or tenderness; Complete arrest of bone growth; Dense bone sclerosis	Necrosis/ Spontaneous fracture	
JOINT	None	Mild joint stiffness; Slight limitation of movement	Moderate stiffness; Intermittent or moderate joint pain; Moderate limitation of movement	Severe joint stiffness; Pain with severe limitation of movement	Necrosis/ Complete fixation	

7.4 Ethics clearance certificate

<u>UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG</u>	
Division of the Deputy Registrar (Research)	
 <u>HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)</u>	
R14/49 Dr Kim N Lohlun	
<u>CLEARANCE CERTIFICATE</u>	<u>M10440</u>
<u>PROJECT</u>	Impact of Waiting Times for Radiotherapy for Cervical Cancer
<u>INVESTIGATORS</u>	Dr Kim N Lohlun.
<u>DEPARTMENT</u>	Department of Radiation Oncology
<u>DATE CONSIDERED</u>	30/04/2010
<u>DECISION OF THE COMMITTEE*</u>	Approved unconditionally
 <u>Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.</u>	
<u>DATE</u>	03/05/2010
<u>CHAIRPERSON</u>	 (Professor PE Cleaton-Jones)
*Guidelines for written 'informed consent' attached where applicable	
cc: Supervisor : Dr J Kotzen	
<u>DECLARATION OF INVESTIGATOR(S)</u>	
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. <u>I agree to a completion of a yearly progress report.</u>	
PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...	

7.5 ECOG Performance Status Scale

	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

As published in Am. J. Clin. Oncol.:

Oken, M.M., Creech, R.H., Tormey, D.C., et al. 1982. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. *American Journal of Clinical Oncology* 5: 649-655.

7.6 Form: 4-weekly clinic review

Trial: Impact of waiting times for Radiotherapy for Cervical Cancer

4-WEEKLY CLINIC REVIEW

Patient no.:

Visit no.:

Date:

Please complete this form in full, for all patients on the trial.

For queries, please contact Dr Kim Lohlun. Dr Kotzen or Prof Lakier can assist if Dr

Lohlun is unavailable.

Questions to ask the patient (may check file from local hospital if available)

- Blood transfusions since last seen at 348

YES	NO
-----	----

If yes,

- How many units were transfused?
- Dates of transfusion (if available)
- Haemoglobin level before (if available)
- Haemoglobin level after (if available)

- Hospital admissions since last seen at 348

YES	NO
-----	----

If yes, please elaborate.

- Place of admission
- Reason for admission
- Procedures/investigations done
- Dates of admission

- PV Bleeding

YES	NO
-----	----

If yes, number of pads used per day (average)

- Urinary incontinence

YES	NO	Suspected
-----	----	-----------

If yes/suspected, please elaborate

- Bowel complaints (eg. faeces in vagina)

If yes, elaborate.

YES	NO
-----	----

Haemostatic brachytherapy details:

Dates given

Reason / details

Examination:

ECOG performance status	0	1	2	3	4
Comment:					

Supraclavicular nodes	YES	NO
Inguinal nodes	YES	NO
Comment:		

LOCAL EXAMINATION (Findings on PV / PR)

Size of cervical tumour (cm)				
Vaginal involvement	NONE	UPPER 2/3	LOWER 1/3	
VVF felt	YES	NO		
RVF felt	YES	NO		
Parametrial involved – left	NONE	INNER 1/2	OUTER 1/2	PSW
Parametrial involved - right	NONE	INNER 1/2	OUTER 1/2	PSW

Summary

Has tumour stage changed?

YES	NO
-----	----

If yes, state new stage:

.....

Has intended radiotherapy prescription changed (eg. radical to palliative)?

YES	NO
-----	----

If yes, give reasons:

.....
.....

DATE OF NEXT VISIT (in 4 weeks)

(Please ensure this is written clearly in the patient's blue hospital card.)

Doctor's name & signature

.....

8.0 REFERENCES

1. Adewole, I.F., Benedet, J.L., Crain, B.T., et al. 2005. Evolving a strategic approach to cervical cancer control in Africa. *Gynecologic Oncology* 99: S209-12.
2. Anorlu, R.I. 2008. Cervical cancer: The Sub-Saharan African perspective. *Reproductive Health Matters* 16: 41-9.
3. Ault, K.A. 2008. Human papilloma virus vaccines: An update for gynecologists. *Clinical Obstetrics and Gynecology* 51: 527-32.
4. Bailie, R.S., Selvey, C.E., Bourne, D., et al. 1996. Trends in cervical cancer mortality in South Africa, *International journal of epidemiology* 25: 488-493.
5. Barton, M.B., Morgan, G., Smee, R., et al. 1997. Does waiting time affect the outcome of larynx cancer treated by radiotherapy? *Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology* 44: 137-41.
6. Brouha, X.D., Op De Coul, B., Terhaard, C.H., et al. 2000. Does waiting time for radiotherapy affect local control of T1N0M0 glottic laryngeal carcinoma? *Clinical Otolaryngology and Allied Sciences* 25: 215-8.
7. Campbell, O.B., Akinlade, I.B., Arowojolu, A., et al. 2000. Comparative evaluation of hypofractionated radiotherapy and conventional fractionated radiotherapy in the management of carcinoma of the cervix in Ibadan, Nigeria. *African Journal of Medicine and Medical Sciences* 29: 253-8.
8. Cannistra, S. A. & Niloff, J.M. 1996. Cancer of the uterine cervix. *The New England Journal of Medicine* 334: 1030-8.

9. Coles, C.E., Burgess, L., & Tan, L.T. 2003. An audit of delays before and during radical radiotherapy for cervical cancer - effect on tumour cure probability. *Clinical Oncology (Royal College of Radiologists (Great Britain))* 15: 47-54.
10. Denny, L. 2006. Cervical cancer: The South African perspective. *International Journal of Gynecology & Obstetrics* 95: S211-4.
11. Denny, L. 2011. Cervical cancer treatment in Africa. *Current Opinion in Oncology* 23: 469-74.
12. Denny, L. 2012. Cytological screening for cervical cancer prevention. *Best Practice & Research. Clinical Obstetrics & Gynaecology* 26: 189-196.
13. Department of Health. "National guideline on cervical cancer screening programme". <<http://screening.iarc.fr/doc/SAcervical-cancer.pdf>> [Accessed 25 January 2013]
14. Dische, S. 2000. Tumour growth while waiting: does it really matter? *Clinical oncology (Royal College of Radiologists (Great Britain))* 12: 139.
15. Do, V., Gebiski, V. & Barton, M.B. 2000. The effect of waiting for radiotherapy for grade III/IV gliomas. *Radiotherapy and Oncology : Journal of the European Society for Therapeutic Radiology and Oncology* 57: 131-6.
16. Dodwell, D. & Crellin, A. 2006. Waiting for radiotherapy. *BMJ (Clinical Research Ed.)* 332: 107-9.
17. Eifel, P.J., Berek, J.S. & Markman, M.A. 2008. Section 2: Cancer of the cervix, vagina, and vulva. In: DeVita VT, Lawrence TS, Rosenberg SA, Editors. *Cancer: Principles & Practice of Oncology (8th Ed.)*. Lippincott Williams & Wilkins: 1496-1543.
18. Eifel, P.J., Winter, K., Morris, M., et al. 2004. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical

- cancer: An update of radiation therapy oncology group trial (RTOG) 90-01. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* 22: 872-80.
19. Fagundes, H., Perez, C.A., Grigsby, P.W., et al. 1992. Distant metastases after irradiation alone in carcinoma of the uterine cervix. *International Journal of Radiation Oncology, Biology, Physics* 24: 197-204.
 20. Fortin, A., Bairati, I., Albert, M., et al. 2002. Effect of treatment delay on outcome of patients with early-stage head-and-neck carcinoma receiving radical radiotherapy. *International Journal of Radiation Oncology, Biology, Physics* 52: 929-36.
 21. Fortin, B., Goldberg, M.S., Mayo, N.E., et al. 2006. Waiting time for radiation therapy in breast cancer patients in Quebec from 1992 to 1998: A study of surgically treated breast cancer patients in Quebec documents and helps to explain increased waiting times for radiation therapy. *Healthcare Policy = Politiques De Sante* 1: 152-67.
 22. Fyles, A., Keane, T.J., Barton, M., et al. 1992. The effect of treatment duration in the local control of cervix cancer. *Radiotherapy and Oncology : Journal of the European Society for Therapeutic Radiology and Oncology* 25: 273-9.
 23. Gakidou, E., Nordhagen, S. & Obermeyer, Z. 2008. Coverage of cervical cancer screening in 57 countries: Low average levels and large inequalities. *PLoS Medicine* 5: e132.
 24. Goedhals, L., Falkson, G., Smith, B.L., et al. 2005. Vinorelbine and cisplatin in advanced squamous cell carcinoma of the cervix: the South African experience. *Anticancer Research* 25: 2489-2492.

25. Irwin, C., Hunn, M., Purdie, G., et al. 2007. Delay in radiotherapy shortens survival in patients with high grade glioma. *Journal of Neuro-Oncology* 85: 339-43.
26. Joint Council for Clinical Oncology. 1993. *Reducing delays in cancer treatment: Some targets*. London: Royal College of Physicians: 6-7.
27. Kawonga, M. & Fonn, S. 2008. Achieving effective cervical screening coverage in South Africa through human resources and health systems development. *Reproductive Health Matters* 16: 32-40.
28. Keys, H. M., Bundy, B.N., Stehman, F.B., et al. 1999. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *The New England Journal of Medicine* 340: 1154-61.
29. Mackillop, W. J., Bates, J.H., O'Sullivan, B. et al. 1996. The effect of delay in treatment on local control by radiotherapy. *International Journal of Radiation Oncology, Biology, Physics* 34: 243-50.
30. Mackillop, W. J., Fu, H., Quirt, C.F., et al. 1994. Waiting for radiotherapy in Ontario. *International Journal of Radiation Oncology, Biology, Physics* 30: 221-8.
31. Minister of Health. Parliamentary Monitoring Group. 21 October 2009. <<http://www.pmg.org.za/node/14826>> [Accessed 21 January 2013]
32. Mqoqi, N., Kellet, P., Sitas, F., et al. 2004. Incidence of histologically diagnosed cancer in South Africa, 1998-1999. *National Cancer Registry of South Africa. National Health Laboratory Service, Johannesburg, 2004: viii, 23.*
33. Muckaden, M.A., Budrukhar, A.N., Tongaonkar, H.B., et al. 2002. Hypofractionated radiotherapy in carcinoma cervix IIIB: Tata Memorial Hospital experience. *Indian journal of cancer* 39: 127-134.

34. National Cancer Registry. Incidence of histologically diagnosed cancer in South Africa. National Institute for Occupational Health [database online]. 2003. <<http://www.nioh.ac.za/assets/files/Cancer%20tables%202003.pdf>> [Accessed 25/01/2013]
35. Nel, C.P.G., Schoeman, L.C., Van Wyngaardt, M., et al. 2006. The prevalence of HIV amongst women with cervix cancer. *SA Fam Pract* 48: 17.
36. O'Rourke, N. & Edwards, R. 2000. Lung cancer treatment waiting times and tumour growth. *Clinical Oncology (Royal College of Radiologists (Great Britain))* 12: 141-4.
37. Pecorelli, S. 2009. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics* 105: 103-4.
38. Perez, C.A., & Lavanagh, B.D. 2008. Chapter 66: Uterine cervix. In *Perez and Brady's Principles and Practice of Radiation Oncology*, eds. EC Halperin, CA Perez and LW Brady. Fifth ed. Philadelphia, USA: Lippincott Williams & Willkins: 1532-1609.
39. Peters, W. A., 3rd, Liu, P.Y., Barrett, R.J. 2nd, et al. 2000. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* 18: 1606-13.
40. Rose, P. G., & Eifel, P.J. 2001. Combined radiation therapy and chemotherapy for carcinoma of the cervix. *Cancer Journal (Sudbury, Mass.)* 7: 86-94.

41. Royal College of Radiologists. 2008. The timely delivery of radical radiotherapy: Standards and guidelines for the management of unscheduled treatment interruptions. Third edition.
42. South African National Bloods Service. SANBS state patients price list 2012. <<http://www.sanbs.org.za/images/pdfdocs/state%20patients%202012.pdf>> [Accessed 25 January 2013]
43. Walboomers, J. M., Jacobs, M.V., Manos, M.M., et al. 1999. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *The Journal of Pathology* 189: 12-9.
44. Walker, A. R., Michelow, P.M. & Walker, B.F. 2002. Cervix cancer in African women in Durban, South Africa. *International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics* 79: 45-6.
45. Whitney, C. W., Sause, W., Bundy, B.N., et al. 1999. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: A Gynecologic Oncology Group and Southwest Oncology Group study. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* 17: 1339-48.
46. WHO/ICO (Institut Catalià d'Oncologia) Information Centre on HPV and Cervical Cancer (HPV Information Centre) 2010. Human Papilloma Virus and Related Cancers in World. Summary Report 2010. [Accessed 25/01/2013]
47. World Health Organization. IARC Press, 2005. Cervix cancer screening. *IARC Handbooks of Cancer Prevention* 10: 1-57.

<<http://www.iarc.fr/en/publications/pdfs-online/prev/handbook10/index.php>>

[Accessed 25/01/2013]

48. World Health Organization. 2009. Human papillomavirus vaccines WHO position paper. *WHO Weekly Epidemiological Record* 84: 118-132.
<<http://www.who.int/wer/2009/wer8415.pdf>> [Accessed 25 January 2013]
49. Wyatt, R. M., Beddoe, A.H, & Dale, R.G. 2003. The effects of delays in radiotherapy treatment on tumour control. *Physics in Medicine and Biology* 48: 139-55.
50. Zietsman G. “Why Motsoaledi's wrong about private sector hospital costs.” 13 April 2012. <www.politicsweb.co.za> [Accessed 25 January 2013]