UNIVERSITY OF CAPE TOWN
FACULTY OF HEALTH SCIENCES

MMed Part III (minor dissertation)

"The influence of cisplatin dose variations during concurrent weekly chemo-radiation in stage IIB cervical cancer at Groote Schuur Hospital"

by

STUDENT: MTABENI JEMU
JMXMTA001

SUBMITTED TO THE UNIVERSITY OF CAPE TOWN
In partial fulfilment of the requirements for the degree

MMed in Radiation Oncology

Supervisor: Leon Van Wijk, (Division of Radiation Oncology)

Groote Schuur Hospital / University of Cape Town

Date of submission: 17 June 2017

DECLARATION

I, Dr Mtabeni Jemu, hereby declare that the work on which this minor dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ACKNOWLEDGEMENTS:

I thank God for providence and sustenance.

I acknowledge Dr Leon Van Wijk for his immeasurable insight, support and mentorship without which the research described in this dissertation would have been an insurmountable task. My gratitude goes to my wife Yabwile for believing in me and encouraging me to do better. I thank my son Ethan for giving me a reason to work for a better world.

To my father: for the lifetime lesson of leaving a mark with your handwork. I thank Michelle Parker for the many times that she reviewed the statistics, tables and text.

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PART A

PART A: ABSTRACT AND STUDY PROTOCOL

ABSTRACT OF THE MINI-THESIS (PUBLICATION-READY FORMAT):

Objectives: To examine the effect of treatment and tumour factors, in particular the influence of cisplatin dose variations, on the survival of patients completing concurrent chemo-radiation (CRT) for stage IIB cervical cancer.

Design and method: A retrospective audit of 228 patients with stage IIB cervical cancer who were treated between 1995 and 2010 at Groote Schuur Hospital. Inclusion criteria were: patients with squamous, adeno-squamous or adenocarcinoma who had competed chemo-radiation with at least 45 Gy external beam radiation; received between two and four brachytherapy insertions; and, one or more cycles of concurrent weekly cisplatin (40mg/m², capped at 60 mg/week). Institutional ethics clearance was obtained. Collected data was tabulated as descriptive statistics. Overall Survival (OS) rates were estimated by the Kaplan-Meier method, and differences between groups by log-rank test and Cox regression. Statistical significance was taken as $p<0.05$.

A literature review was performed. The study methods, findings and discussion were prepared as a draft manuscript for the South African Journal of Gynaecological Oncology but with a slight variation made to the title because the authors believe that the manuscript title is more likely to be accepted for publication than the original one.

Results: Mean age of the cohort was 50.3 years; 84% had squamous histology. Mean tumour size was 5.5cm (range 2-10 cm), with bilateral parametrial involvement in 40% of patients, lateral parametrial involvement in 50%, and vaginal spread in 43%. Mean total dose to Point A was 83 Gy (range 61-96), expressed as linear quadratic equivalent dose to 2 Gy/fraction (LQED2) of brachytherapy plus teletherapy. Mean overall treatment time (OTT) was 45 days (range 36-80). The average weekly haemoglobin (AWHB) during treatment was 11.6 g/dL (range 8.8-15.5). Red cell transfusions before or during chemo-radiation were given in 33% of patients, aiming to maintain a HB of at least 10 g/dL.

Two thirds of patients completed either five or six cycles of weekly cisplatin. Reasons for fewer than five cycles were scheduling failure, neutropaenia, and/or renal impairment. Most patients received weekly cisplatin on Thursdays (82.5%), with the balance receiving administration on Mondays.

The 5-year OS was 60%. Patients with fewer than six cycles of treatment had a worse OS (55 vs. 76%, $p=0.02$). Multivariable analysis for OS showed that 6 vs. <6 cycles, squamous histology, and an AWHB>10g/dL were all significant.

None of the following was associated with OS: age, Thursday vs Monday administration of cisplatin, total LQED2 to point A, or tumour volume. OTT with cut-off of 45 days was significant on univariate, but not multivariate analysis.

Conclusion: The observed data supports the position that an average HB >10 during chemo-radiation for stage IIB cervical cancer is beneficial to treatment outcome. The study suggests that scheduling failures with weekly cisplatin administration should be avoided, since six cycles of weekly cisplatin at the dose regimen used (40 mg/m^2 capped at 60 mg per cycle) are required to ensure maximum benefit. Non-squamous histological types of stage IIB cervical cancer probably require concurrent chemotherapy regimens that differ from those for squamous cancer.

(Word counts:

Thesis abstract: 499- limit 500
Literature review: 3441 - limit 3000-4000
Publication-ready manuscript (abstract): 250 - limit 250.
Publication-ready manuscript (body of text): 3206 - limit 3500

Referencing style: Vancouver)

STUDY PROTOCOL:

Title of the study:

"The influence of cisplatin dosing variations during concurrent weekly chemo-radiation in stage IIB cervical cancer at Groote Schuur Hospital"

Research Question**:**

What is the influence on treatment outcome of the number of weekly doses of cisplatin given concurrently with pelvic radiation for stage IIB cervical cancer, and does it matter when in the week these doses are administered (Mondays vs Thursdays)?

Aim of the study:

To examine the research question by means of a retrospective analysis of patients with stage IIB cervical cancer treated with concurrent chemo-radiation (CRT) at Groote Schuur Hospital (GSH) between Jan 1995 and Dec 2010.

Hypothesis: The null hypothesis is that the number of cycles of weekly cisplatin administered during CRT of stage IIB cervical cancer has no effect on treatment outcome, neither has the day of week on which it is administered.

Primary endpoint

- Overall survival

Secondary endpoints

- Disease free survival
- Response rate
- Treatment toxicity

Background

Globally, cervical cancer is the fourth most-common cancer in women, accounting for more than 500,000 new cases in 2012. The developing world accounts for most of these cases, as well as the largest incidence of mortality caused by cervical cancer (87%). Southern Africa is a high risk region with an Age Standardized Rate of 31.5 per 100,000 (Globocan, 2012).[1] In South Africa, cervical cancer ranks second to breast cancer as far as the most common cancers in women are concerned (South African National cancer registry, 2012). Most patients present late with advanced disease. At Groote Schuur Hospital, 76 % of the patients present with locally advanced cancer not amenable to surgical therapy (Van Wijk L. Personal communication 2014).

These patients require concomitant chemo-radiotherapy (CRT) as definitive therapy. Several randomized controlled trials have established concomitant chemo-radiation as the standard treatment for locally advanced cervical cancer.[2,3,4,5,6] Based on these trials the National Cancer Institute issued an alert in 1999 advocating the use of CRT with concurrent cisplatin in the treatment of locally advanced cervical cancer. The evidence is corroborated in a meta-analysis of 24 randomized controlled trials by Green et al.[7] which reported a significantly superior overall survival rate in patients treated with combined chemo-radiotherapy (HR 0.69, 95% CI = 0.61 to 0.77, p< 0.00001) representing a 31% reduction in the risk of death or a 10% absolute improvement in survival. Progression free survival was better in the chemo-radiotherapy group (HR 0.66, 95% CI = 0.59 to 0.73, p<0.0001) compared to radiotherapy alone. However this was at the cost of higher rates of severe toxicity. A Chemo-radiotherapy for Cervical Cancer Meta-analysis Collaboration (2008) conducted a meta-analysis of 15 trials, 13 of which compared chemo-radiotherapy with radiotherapy alone; it demonstrated a 6% improvement in 5-year survival with CRT (HR = 0.81, p< 0.001). Further chemotherapy after chemo-radiotherapy increased the survival benefit. Chemo-radiotherapy also reduced the risk of local and distant recurrence and progression.[8]

There is evidence to suggest that the number of chemotherapy cycles given concurrently with radiotherapy impacts the treatment outcome. Nugent et al. (2010) conducted a retrospective analysis of the effect of the number of cycles completed concurrent with radiotherapy in 118 patients; they found that patients receiving less than five cycles of chemotherapy had reduced survival rates compared to those who completed either five or six cycles.[9]

The optimal day for the administration of concomitant cisplatin has not been investigated. A change in the day of administration of cisplatin in our unit was made purely on practical grounds; this change offered a rare opportunity to assess whether the day of administration affects outcome. Intuitively, administering the cisplatin in the early part of the week will increase the concurrency of the drug with the radiation as compared to later in the week, when a weekend intervenes, which could potentially reduce interactions with radiation.

Materials and Methods:

The study period was from January 1995 to December 2010.

Inclusion criteria:

- Proven histological diagnosis of squamous, adeno-squamous, or adenocarcinoma of the uterine cervix.
- Stage IIB cancers based on the FIGO staging of cervical cancer.
- Patients who received an external beam radiotherapy dose of at least 45 Gy (LQED2) to the whole pelvis, as well as at least two fractions of intracavitary brachytherapy.
- Patients who received at least one weekly dose of concurrent cisplatin.

- Patient case files available for analysis.

Exclusion criteria:

- Small cell cancer of the cervix.

Permission to conduct the study will be sought from the Head of Department of Radiation Oncology of GSH, the Clinical Directorate of GSH, and the Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town.

At the Gynaecological Oncology Clinic, new patients are assessed by a combined (multi-disciplinary) team where the initial staging assessment is done. The treatment decision is made by the multi-disciplinary team after taking into account factors such as the patient's age, co-morbidities, performance status and extent of disease. All these factors as well as any subsequent events are recorded in the patient's hospital record and the Gynaecology Oncology database. (HREC No: 2016/2013)

The unit file numbers of all patients with stage IIB cervical cancer referred to the Radiation Oncology Department between January 1995 and December 2010 will be extracted from the departmental Gynaecological Oncology database. The patient data is anonymous except for the unit file numbers and patient initials as identifiers for purposes of quality control. No direct patient contact is required for this study.

The required data will be extracted from the database and supplemented from individual patient case files. Such data will be captured on individual data sheets, then transferred to an Excel spreadsheet (for an example of individual data sheet, see Appendix I).

Statistical analysis will include descriptions of basic patient data (age), disease data (histological diagnosis, stage, HIV status, CD4 count) and treatment data (total radiotherapy dose, average weekly haemoglobin, blood transfusion, number of weekly cycles of cisplatin and the day of the week on which cisplatin was administered.)

The treatment toxicity for radiation will be recorded only for grade 3 or 4 toxicity for skin, bladder, rectum and bone marrow, according to the Radiotherapy Oncology Group scale.

Prognostic variables taken into account in the assessment of treatment outcomes, apart from the number of weekly chemotherapy cycles, are as follows:

- Tumour volume – as per pre-treatment clinical assessment.
- Haemoglobin levels during chemo-radiation (CRT) – expressed as average weekly haemoglobin (AWHB).
- Overall treatment time (OTT) – number of days from first day of CRT to last day of brachytherapy or external beam radiation, whichever was given last.

- Total radiation dose to Point A, external beam plus brachytherapy, expressed as Linear Quadratic Equivalent Dose to 2 Gy per fraction (LQED2).

Numerical variables are to be summarized by means and standard deviations. Categorical variables will be summarized by frequencies and percentages.

Survival rates will be calculated using the Kaplan-Meyer method, with differences between rates assessed by the log-rank method. For the survival analysis, patients who had not died will be censored at their last follow-up visit.

A discussion of the findings incorporating relevant reviewed literature will be prepared. All the literature consulted is cited appropriately.

Limitations of the study

There were variations in the treatment techniques and doses used during the study period. The population under study is therefore not as homogenous regarding treatment parameters as would have been the case with a prospective trial. The clinical records in use were not designed for this study and thus some information may be missing. The different periods of follow-up present a potential source of bias, rendering untenable the assessment of other time-to-event parameters, such as progression free survival.

Ethical considerations

The retrospective nature of the study makes the acquisition of informed consent impracticable. However utmost care was taken to uphold the confidentiality and privacy of the patients. All data will be de-identified.

Dr Mtabeni Jemu

Department of Radiation Oncology

Groote Schuur Hospital.

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PART B

PART B: STRUCTURED LITERATURE REVIEW

OBJECTIVES:

The aim of the literature review is to provide a basis for the research question by exploring the context in which it arose. An analysis of previous studies will investigate what has already been discovered and described about the subject matter. That analysis may possibly demonstrate the paucity of information surrounding the inquiry. The current study may serve to confirm previous research, or may reveal new information. Paradoxically, the literature review evolves with the research question upfront, and later shapes the entire process, including the methodology and contextualization.[1]

Taylor[2] has indicated that "writing a literature review tries to convey what knowledge and ideas have been established on a topic and what their strengths and weaknesses are".

LITERATURE REVIEW STRATEGY

The keywords "prognostic factors in cervical cancer", "treatment of cervical cancer", and "stage IIB cervical cancer" were entered in the following databases: EBSCO, Science Direct, Medline, The Cochrane Library, Google scholar and PubMed. Perusal of an abstract was followed by assessment of the full publication if it was deemed relevant and the evidence showed the need for further scrutiny.

Meta-analysis of randomized controlled trials (RCTs) was considered to be the epitome of evidence followed by individual RCTs, cohort, case control, and cross-sectional studies, in that order.

INTRODUCTION

The Globocan report of 2012 states that cervical cancer is globally the fourth most-common cancer in women, accounting for more than 500,000 new cases in 2012. [3] The developing world accounts for most of these cases, as well as for the largest incidence of mortality attributable to cervical cancer (87% of deaths). [3] Southern Africa is a high risk region with an Age Standardized Rate of 31.5 per 100,000.[3] In South Africa, cervical cancer ranks second to breast cancer as far as the most common cancers in women are concerned (South African National Cancer Registry, 2007).[4] Most patients present late, at an advanced stage of the disease. At Groote Schuur Hospital, 76 % of the patients present with locally advanced cervical cancer (LACC) which is not amenable to surgical therapy (Van Wijk, L. Personal communication 2014). These patients require definitive concomitant chemo-radiation (CRT) to the whole pelvis, as well as intracavitary brachytherapy, with weekly cisplatin administration during the external beam radiation course.

This retrospective study examines the influence on treatment outcome of the number of weekly doses of cisplatin and the day of the week on which these doses are administered (Mondays vs Thursdays) for those stage IIB cervical cancer patients who had completed a potentially curative course of treatment. The literature review focuses largely on CRT, although a limited number of other factors which could potentially affect treatment outcome are briefly reviewed. Where found, data about stage IIB was highlighted. The available literature was reviewed, focusing on:

a. Treatment of cervical carcinoma with CRT.
b. The type of CRT used in the treatment of cervical cancer.
c. Correlation of number of cycles of cisplatin, and day of week administered, vs outcome.
d. Role of haemoglobin (HB) level during treatment.
e. Effect of treatment duration.
f. Effect of tumour volume and histological subtype on treatment outcome in stage IIB cervical cancer.

a. Treatment of cervical carcinoma with CRT:

CRT is now the standard of treatment for all stages of cervical cancer; this was established as a result of evidence obtained from five RCTs, collated by the National Cancer Institute (NCI) in America.[5,6,7,8,9] These studies demonstrated a reduction in both the risk of death and recurrence when CRT was used. Based on the evidence obtained from these trials, the NCI issued an alert in 1999 advocating the use of CRT with concurrent cisplatin-based chemotherapy in the treatment of locally advanced cervical cancer.[10]

The evidence in favour of CRT was corroborated in a meta-analysis by Green et al,[11] in which most of the patients had stage I and II disease. The authors reported a significant superior overall survival rate in patients treated with CRT (HR 0.69, 95% CI = 0.61 to 0.77, P < 0.00001) representing a 31% reduction in the risk of death or a 10% absolute improvement in survival. Progression free survival was better in the CRT group (HR 0.66, 95% CI = 0.59 to 0.73, P<0.0001) compared to radiotherapy alone. However this was at the cost of higher rates of acute toxicity.

The "Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration" published a further meta-analysis in 2008. Thirteen of fifteen trials compared CRT with radiotherapy alone, and demonstrated a somewhat lesser absolute improvement of 6% in 5-year survival with CRT (HR = 0.81, P < 0.001). The hazard ratio for stage IIB translated into an estimated survival benefit of 7%. CRT reduced the risk of both local and distant recurrence and progression. While radio-sensitization of the primary tumour cells probably accounts for the improved pelvic control, it is more difficult to explain the reduction in distant metastases; it could be direct cancer cell kill, or reduced seeding from better pelvic control. There was no detectable difference attributable to dose intensity or chemotherapy scheduling.[12]

While there are no published accounts of CRT in solely stage IIB cervical cancer, a retrospective control-cohort study was conducted in Taiwan which included 171 patients with stages IIB and IIIB. The cisplatin dose was 40 mg/m^2, capped at a maximum weekly dose of 60 mg. Patients treated in the pre-CRT era were compared to those treated with CRT, using an identical radiotherapy (RT) protocol. Eighty per cent received "at least five weekly cycles". No survival benefit could be demonstated.[13] Another well-known negative study of CRT was a randomized study performed by the Canadian NCI.[14] This study included substantial numbers of stage IIB patients. The weekly cisplatin dose was 40mg/m^2 x 5, without capping the dose, and delivered within two hours of the RT administration of that day. It should be noted that the protocol did not specify the day of week; this applies also to the methods sections of the other studies mentioned in this literature review. Seventy per cent of patients received "the full dose on time". Reasons given for the failure to find a survival benefit for CRT in the Canadian NCI study include being not powered to show a 5-year benefit <15%, more anaemia in the CRT arm and higher RT doses than in the American CRT studies .

b. The type of CRT used in the treatment of cervical cancer:

Whitney et al. (1999)[7] randomized 388 patients with locally advanced cervical cancer to receive radiotherapy concurrent with cisplatin and 5-fluorouracil (5FU) or hydroxyurea. The former group had better 5-year overall survival rates and toxicity profiles than the latter (63 % vs 47%). Rose and co-workers[6] conducted a Gynecology Oncology Group (GOG 120) trial comparing chemo-radiotherapy with either cisplatin alone, cisplatin with hydroxyurea and 5-FU, or hydroxyurea alone; they demonstrated the benefit in overall survival in patients receiving a platinum containing regimen. In this study the single agent weekly cisplatin had a favourable toxicity profile without compromising on survival or local control. It has become the preferred method of CRT administration, and is given on an outpatient basis.

A pooled analysis from a meta-analysis, mentioned before,[12] of controlled trials using platinum based, or non-platinum based CRT, could not demonstrate differences in the survival benefit of platinum chemotherapy (HR = 0.83, p= .017) over other drugs (HR= 0.77, p = .009). The heterogeneity in chemotherapy and radiotherapy doses as well as the disease characteristics in these studies are sources of bias and make the interpretation of the results difficult. The authors could not demonstrate that any particular treatment type, dose or schedule were superior, with the exception of two studies where additional chemotherapy was given after CRT. In these studies the benefit seems superior to CRT only: this question is being studied currently in the Australian "Outback" trial, which has been joined by the GOG and other cooperative groups.[15]

c. Correlation of number of cycles of cisplatin, and day of week administered, vs outcome:

As stated above, no study could be found which specified the day of the week on which cisplatin should be administered. The protocols of some of the clinical trials of CRT in cervical cancer indicated only that chemotherapy "start on day one of radiotherapy".[5,6] The

day of the week on which cisplatin should be administered remains an unknown, or possibly irrelevant parameter in CRT.

Of the five original NCI-sponsored CRT trials, two studies used the weekly cisplatin regimen in one of the study arms. Thus, Rose et al. (GOG 120)[6] used a dose of 40 mg/m^2, with 83% of patients completing five or more cycles (49% completing six cycles), whilst in the study by Keyes et al. (GOG 123)[5], the dose was also 40 mg/m^2 but with capping the weekly dose at 70 mg. Ninety percent of patients completed four or more cycles. In neither of these two studies was there a subset analysis of outcome depending on the number of weekly cycles received.

It is somewhat difficult to ascertain from published studies how to compare optimum cisplatin administration. Regarding average total doses of cisplatin received, if one assumes that all patients in GOG 120 have an average body surface area (BSA) of 1.7 m^2 , then for six cycles the total dose was 40 x 1.7 x 6 = 408 mg (or 240mg/m2). In the Keyes study (GOG 123), although doses were capped at 70 mg, one could come to similar speculative dose ranges if one still assumes an average BSA of 1.7 m^2; thus, 40 mg/m2 x 1.7 is 68 mg per cycle, or approximately 340 or 400 mg cumulative doses for five to six cycles respectively. Capping the dose of weekly concurrent cisplatin is presumably done to improve tolerability to, and compliance with, a course of six cycles.

Many retrospective single institution studies of CRT have been published. One of the larger studies is mentioned here in order to record the doses used. Thus, Kong et al., in 2012 reported a retrospective study of 255 patients in which two cisplatin regimens were used. Eighty-two percent of their cohort had stage IIB cancer. Weekly doses were 40 mg/m^2, capped at 70 mg, starting 1-4 hours prior to RT on day 1 of the RT course. Acute adverse events (grade 3/4) were reported as being haematological in 8% and gastrointestinal in 14.5% of instances. Renal toxicity was not mentioned. Eighty-four per cent of the patients completed five or more cycles.[16] Maltefano et al. (1993)[17] capped the weekly dose at 60 mg; 51% of patients completed five cycles, and 31% completed six cycles. Side effects were described as tolerable and not interfering with CRT. Laboratory abnormalities such as neutropenia <3000 were seen in 33% of patients, with grade 3/4 present in <10% of patients.

In contrast, although Serkies and Jassem,[18] used 40 mg/m^2 capped at 70mg, they found that whilst 74% of their patients received four cycles, only 45% received five planned cycles (29% at planned doses); this was mostly due to acute toxicity. Moreover, an additional reason for non-compliance with the planned schedule was scheduling failure; for example, failure to administer the first cycle, or missing a subsequent cycle for reasons that are unclear. The overall relative dose intensity (ratio between actual and planned doses) for all patients was 0.8, or 32 mg/m^2. Regarding such compliance issues, it is probable that patients treated in clinical trials will have fewer non-protocol delays.

For patients receiving six concurrent cycles, cisplatin dose intensity is 40mg/m^2/week. For example, for patients receiving only five cycles over the six weeks, with no dose adjustments or capping, the relative dose intensity is 33.3mg/m^2/week. While it is uncertain how best to express the total amount of weekly cisplatin received, there is evidence to suggest a dose

effect, in that the amount of cisplatin a patient receives concurrently with radiotherapy impacts treatment outcome, whether expressed as cumulative doses in mg, or mg/m^2, or simply as number of weekly cycles received.

A limited number of retrospective reports suggest such a dose-related trend, of outcome versus dose vs number of cycles. Thus, Sirák et al. (2008)[19] conducted a retrospective review of 73 patients with locally advanced cervical carcinoma (LACC), (78% with stage IIB) treated with weekly cisplatin 40mg/m^2 during CRT (without dose capping); they found that only 28 % of patients completed the intended five cycles. The main reason for delays was neutropaenia. There was a significant improvement in overall survival at three years for those patients who received five as opposed to four or fewer cycles, although the authors caution that the numbers in the subgroups were small. Nugent et al. (2010) reported an analysis of 118 patients receiving radiotherapy concurrent with cisplatin 40 mg/m² (capped at 70 mg for six planned cycles) for LACC. In multivariate analysis, both progression-free and overall survival were independently impacted by the number of cycles; patients receiving fewer than five cycles of chemotherapy fared significantly worse than those who completed six cycles (p=0.001). Interestingly, there were no differences in survival rates between five and six cycles. Seventy percent could complete six cycles.[20]

In a response to the Nugent et al. (2010) report, Markman, in a letter to the Editor,[21] suggested lower weekly cisplatin doses of 30-35 mg/m^2 to improve compliance rates, although this would require a RCT, or retrospective analyses of relative dose intensities as a function of number of cycles. An alternative strategy was suggested by Ruy et al. in a RCT in which the standard weekly regimen was compared to cisplatin 75 mg/m^2 every three weeks times three cycles: survival rates were better, and side effects were fewer, in the 3-weekly arm.[22] Weekly CRT with carboplatin (area under curve = 2) is another apparently equipotent option, with less morbidity, according to a randomized study of cisplatin vs carboplatin reported by Tharvichitkul et al. in 2016.[23]

Lastly, a recent study by Mell and co-workers[24] examined the hypothesis that intensity modulated RT for locally advanced cervix cancer can reduce exposure to bowel and functioning bone marrow, hence improve tolerability to CRT. A comparison with historical data revealed a significant reduction in gastrointestinal and haematological side effects, while 82% of patients could complete five or more cycles of cisplatin at 40mg/m^2, without dose capping. A RCT will be required to prove that it is a worthwhile endeavour.

d. Role of haemoglobin (HB) level during treatment:

Anaemia may increase the hypoxic component within tumours, which would contribute to radio-resistance and poorer outcomes.[25] There is debate on the issue of whether anaemia by itself is prognostic, or whether it is the phenotype of a more aggressive underlying cancer. Some studies have shown that the pre-treatment HB level is an independent predictor of treatment outcome, although a more convincing finding is that HB levels during RT may be more significant. The impacts of anaemia and blood transfusion on the outcome of cervical cancer patients who were treated with definitive RT were investigated retrospectively by

Grogan et al. (2009).[26] They established that an intra-therapy average weekly HB (AWH) level of ≥ 12g/dL from start of treatment, or maintained during treatment with blood transfusion, was prognostic, while pre-treatment HB level was not prognostic in their study that entailed a multivariate analysis.

Winter et al. (2004) conducted a retrospective assessment of patients treated on two consecutive GOG trials and they reiterated these findings; thus, an AWHB level ≥12g/dL during treatment was an independent predictor of disease-free survival (DFS) for LACC. Levels during the last part of the treatment were most predictive of local recurrence.[27]

Kapp and co-workers (2002) have reported findings that confirm the work of Grogan et al. concerning the beneficial effects of red cells transfusions, using a HB cut-off of 11. Multivariate analysis, correcting for tumour size and nodal status, confirmed that only HB levels during treatment were significant.[28] Another retrospective study also found that pre-treatment HB levels was not prognostic, although the lowest value during RT was; Obamair et al. (2000)[29] found that a HB nadir of >11g/dL during CRT had a 90% chance of a complete clinical response and was significantly related to better progression free survival. In an elegant study of 88 patients with LACC, Mayr and co-workers measured tumour perfusion using dynamic contrast enhanced magnetic resonance imaging. Patients with a combination of low tumour perfusion and AWHB <11.2 had significantly worse outcomes, suggesting synergistic negative effects. These authors recommend dual assessment of both perfusion and AWHB, to guide the management of anaemia during CRT, especially in the poorly diffusing tumours.[30]

This issue of the negative effects of anaemia during RT/CRT in LACC has intrigued many investigators; Bishop et al (2015) questioned, in a retrospective review of a large cohort, the relationship between low haemoglobin level and outcomes after treatment in cervical cancer. The only significant association they could establish on multivariate analysis was that HB <10 during RT was associated with disease-specific survival only. The benefit of blood transfusions was unclear from their data.[31] Fyles and colleagues from the Princess Margaret Hospital in Toronto maintain that anaemia in cervical cancer correlates with tumour size and therefore may not be independently prognostic. A randomized study of transfusion in cervical cancer, previously performed at their institution, failed to demonstrate any benefit.[32]

e. Effect of treatment duration:

Protracted radiation is generally defined as overall treatment time (OTT) of eight weeks or longer. Various retrospective analyses have reported statistically significant associations between prolongation of OTT and poor pelvic control and survival in cervical cancer. Some investigators found the cut-off to be shorter than eight weeks; Saibishkumar et al. describe a cut-off of 7 weeks,[33] whilst a loss of pelvic tumour control of 0.68%/day was found by Perez et al. if OTT exceeds seven weeks in stage IIB.[34]

On the contrary, Huang et al. (2016),[35] in a study of stage IIB patients treated with uniform RT doses, high dose rate brachytherapy (BT) was started after completion of teletherapy. The

OTT did not impact on either survival or local recurrence; however, if OTT was ≤56 days, there was a significant impact on proctitis. For this reason, these authors recommend a gap of one week between teletherapy and onset of BT to spare rectal effects. Another group of investigators found that when concurrent cisplatin is added to RT, an extended OTT had no effect on treatment outcome.[36]

f. Effect of tumour volume and histological subtype on treatment outcome in stage IIB cervical cancer:

Perez et al. (1992) conducted a retrospective assessment of the impact of tumour size and extent on local control and distant failure in 1178 patients treated with definitive radiotherapy, 353 of whom had stage IIB disease. Tumours were described in terms of size (cut-off 5 cm) and volume (unilateral/ bilateral parametrial involvement, and medial or lateral parametrium). The 10-year actuarial pelvic failure rate correlated significantly with tumour size and lateral parametrial involvement in Stage IIB. There was no difference between unilateral vs bilateral disease. Larger tumours (≥ 5cm) also had a higher incidence of distant failure and a lower disease free survival rate. This data predates the chemo-radiotherapy era in the treatment of cervical carcinoma.[37] Investigators from Turkey conducted a retrospective analysis of parameters such as age, tumour size, parametrial extent and total dose to point A in their patients with stage IIB cervical cancer; tumour size >5 cm was the only parameter which correlated with local control and 5-year OS.[38]

Regarding histological type, Yokio et al. (2017),[39] conducted a retrospective survey of patients with locally advanced cervical cancer and found that the 9.6% of the cohort with adenocarcinoma or adeno-squamous histology had significantly worse outcomes than patients with squamous tumours. The authors recommend that a specific CRT regimen be developed for these non-squamous histological types.

Conclusions: For almost two decades, CRT has been the gold standard and definitive therapy for LACC, as well as for postoperative adjuvant therapy in early cervical cancer. The benefits of CRT over RT alone are best illustrated by the published meta-analyses. The fact that two studies could not demonstrate a benefit is probably a chance finding; alternatively, the studies could have been inadequately powered. The CRT regimen of choice is weekly cisplatin as an outpatient therapy, with purportedly a lower toxicity profile compared to the 3-weekly cisplatin plus 5-fluorouracil regimen.

The amount of cisplatin required in order to arrive at the best therapeutic ratio, with or without a capping of the weekly dose, is not known. Likewise, it is not known whether a threshold cumulative dose, or a maximum number of weekly cycles, or both, are needed. It appears that at least five or six cycles are needed for benefit. Other tumour and treatment-related parameters have varying and complex relationships with treatment outcomes in cervical cancer in general, and stage IIB in particular. This literature review revealed some of these interactions; furthermore, not all study findings were in agreement for multiple possible reasons, which can be a topic for discussion by itself. The results of the current study are given in the next chapter.

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PART C

PART C: PUBLICATION-READY MANUSCRIPT - TITLE PAGE.

"The influence of tumour and treatment factors on the outcome of chemo-radiation of stage IIB cervical cancer – a single institution experience"

Mtabeni Jemu MB BS*, Leon van Wijk*[δ] FFRad(T)SA, Michelle Parker[θ] MSc,

Glen Jones[ß] MD.

(*Division of Radiation Oncology, Groote Schuur Hospital and University of Cape Town, Anzio Road, Observatory, Cape Town, South Africa. [δ]Member of the South African Medical Research Council Gynaecological Cancer Research Centre, [θ]Radiobiology Section, Division of Radiation Oncology, Groote Schuur Hospital and University of Cape Town, [ß]The School of Clinical Medicine and Research, The University of the West Indies, Nassau, Bahamas).

Correspondence to: Dr M Jemu, e-mail: mtabeni@yahoo.co.uk

Keywords: Cervical cancer, stage IIB, concurrent chemo-radiation, number of cisplatin cycles, average weekly haemoglobin, overall treatment time.

Funding support or Conflict of Interest: Nothing to declare. No funding received.

Word count of abstract: 249 - limit 250.
Word count of manuscript (body of text): 3439 - limit 3500

"The influence of tumour and treatment factors on the outcome of chemo-radiation of stage IIB cervical cancer – a single institution experience"

Mtabeni Jemu*MB BS, Leon van Wijk*[δ] FF Rad(T)SA, Michelle Parker[θ] MSc,

Glen Jones [ß] MD.

(*Division of Radiation Oncology, Groote Schuur Hospital and University of Cape Town, Anzio Road, Observatory, Cape Town, South Africa. [δ]Member of the South African Medical Research Council Gynaecological Cancer Research Centre, [θ]Radiobiology Section, Division of Radiation Oncology, Groote Schuur Hospital and University of Cape Town, [ß]The School of Clinical Medicine and Research, The University of the West Indies, Nassau, Bahamas).

ABSTRACT:

***Objective*:** To examine the effect of treatment and tumour factors on the overall survival (OS) of patients completing chemo-radiation (CRT) for stage IIB cervical cancer.

***Materials and methods*:** Retrospective audit of 228 patients with stage IIB cervical cancer treated between 1995 and 2010, who received CRT with at least 45 Gy external beam radiation, two to four brachytherapy insertions, and one or more cycles of concurrent weekly cisplatin (40mg/m², capped at 60 mg/week).

***Results*:** Mean tumour size was 5.5 cm, bilateral parametrial involvement in 40% of patients, lateral parametrial involvement in 50%, and vaginal spread in 43%. Mean total dose to Point A was 83 Gy (range 61-96) linear quadratic equivalent dose to 2 Gy/fraction. Mean overall treatment time (OTT) was 45 days. The average weekly haemoglobin (AWHB) during treatment was 11.6 g/dL (range 8.8-15.5). Blood transfusions before or during chemo-radiation were given in 33% of patients. Two thirds of patients completed five or six cycles of weekly cisplatin. Reasons for fewer than five cycles were: scheduling failure, neutropaenia, and/or renal impairment. No outcome differences were observed for Monday vs. Thursday cisplatin administration.

The 5-year OS was 60%. Patients completing fewer than six cycles had a worse OS (55 vs. 76%, p=0.02). By multiple regression analysis for OS, only six cycles of cisplatin, squamous histology, and AWHB>10g/dL were significant.

***Conclusions*:** Maintaining HB >10 and administering six cycles of weekly cisplatin at the dose regimen used appear to be requirements for maximal benefit during CRT of stage IIB cervical cancer.

Key words: Cervical cancer, stage IIB, concurrent chemo-radiation, number of cisplatin cycles, average weekly haemoglobin, overall treatment time.

INTRODUCTION:

Cervical cancer ranks with breast cancer as being one of the commonest cancers in women in developing countries.[1] The burden that large numbers of patients with locally advanced cervical cancer (LACC) place on limited treatment facilities is considerable. Stage IIIB is the commonest stage, and in some centres, hypofractionated radiation regimens are used to cope with patient numbers.[2] In stage IIB, with a better prognosis, definitive concurrent chemo-radiation (CRT) and brachytherapy (BT) is recommended, even in developing countries.[3] It is important to audit treatment results to ascertain which factors modify the effect of treatment during CRT and which of those factors could be manipulated to optimise the patient's outcome.

Factors which are either known to, or suspected of, being important in influencing treatment outcome in stage IIB include histological type, tumour volume, and haemoglobin level during therapy. Treatment related factors which may be prognostic are CRT versus radiation alone, the avoidance of treatment with an extended duration, and total radiation doses to Point A.[4] A positive Human Immunodeficiency Virus (HIV) status, especially if untreated with antiviral therapy, not only has a deleterious effect on outcome after CRT for cervical cancer, but increases acute epithelial side effects within the radiation volume.[5]

In the case of CRT with weekly cisplatin, the literature does not give detailed guidance on the cumulative drug dose required for optimal benefit. The number of concurrent chemotherapy cycles given with radiotherapy may also impact the treatment outcome; Nugent and co-workers, conducted a retrospective analysis of the effect of the number of cycles completed with radiotherapy in 118 patients; they found that patients completing fewer than five cycles of chemotherapy had reduced survival rates when compared to those patients who completed five or six cycles.[6] The optimal day of the week for the administration of concomitant cisplatin has not been investigated. Intuitively, administering the cisplatin during the early part of the week will increase the interaction of the drug with the radiation as compared to later in the week.

This retrospective audit of 228 patients with stage IIB cervical cancer, treated with curative intent over a 15-year period at a single institution, proposed to examine the impact of some of these factors on patient survival.

METHODS:

Institutional ethics clearance was obtained. (HREC 832/2014). Patient consent was not sought because of the retrospective and anonymous data collection. A departmental database was used to extract data applicable to all patients with FIGO stage IIB cervical cancer registered during the chosen study period of 1995-2010. The inclusion criteria to select patients for data analysis were as follows:

- Proven histological diagnosis of squamous, adeno-squamous, or adenocarcinoma of the uterine cervix.

- Patients who received an external beam radiotherapy (EBRT) dose of at least 45 Gy to the whole pelvis, as well as between two and four fractions of BT,
- One or more weekly dose of concurrent cisplatin administered (40 mg/m^2, capped at 60 mg per week).

Data was extracted for selected tumour and treatment-related parameters from both the database and patient files and entered onto a spreadsheet. The HIV status was also recorded. The study cohort is summarized by descriptive statistics. Tumour volume was described as cervical diameter in cm, determined from either CT scanning or clinical palpation, and clinical assessment of parametrial and vaginal extent. Individual patient haemoglobin (HB) was expressed as the average weekly levels during treatment (AWHB in g/dL) instead of pre-treatment estimations. Treatment duration was measured from the first to last day of radiation, regardless of whether it was EBRT or BT, and reported as Overall Treatment Time (OTT) in days. Total radiation doses to Point A were expressed as the summation of EBRT and BT doses, expressed as Linear Quadratic Equivalent Dose to 2 Gy per fraction (LQED2). The radiotherapy session on the day of cisplatin administration was given within two hours, either before or after chemotherapy.

Analysis was performed using Prism v6.05 (GraphPad Software Inc., San Diego, California). Numerical variables were summarized by means, or dichotomized at various cut-off points and compared with the log-rank test. Categorical variables were summarized by frequencies and percentages. Survival rates were calculated using the Kaplan-Meyer method, with differences between groups assessed by the log-rank method. Overall survival (OS) was defined as extending from the first day of treatment to death from any cause, or censored at date of last contact. Other time-to-event outcomes were not considered because follow-up intervals were variable over the study period. Statistical significance was defined as p-value < 0.5. Variables found to be significant were evaluated with multiple regression by the Cox model of proportional hazards, with OS as the dependent outcome.

RESULTS:

Of 410 patients with stage IIB cervical cancer managed between 1995 and 2010, 228 met the criteria for inclusion in the study (see flow diagram below).

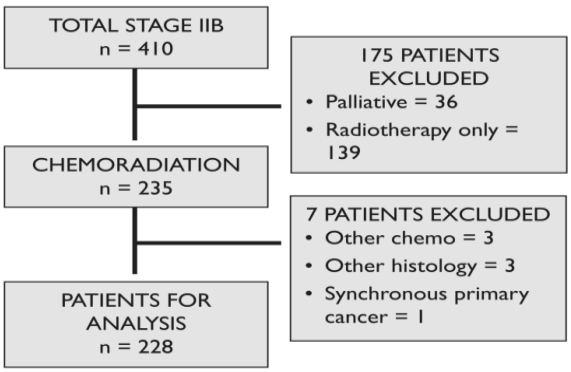

Table I summarizes the patient, disease and treatment characteristics. One third of patients received red cell transfusions in an attempt to maintain their HB ≥ 10 g/dL. Most cisplatin cycles were administered on Thursdays because of logistical considerations within the department. Two thirds of patients received either five or six cycles of weekly cisplatin.

In the case of those patients receiving between one and four cycles, administrative or scheduling issues were responsible in 32% of instances, mostly failure to start cisplatin during the first week of RT. In the remainder, deterioration of the weekly white cell <2.5 10^9/L, platelet count <75 000 10^9/L, or of serial creatinine measurements, were responsible for delaying or suspending chemotherapy; these reasons are regarded as unpreventable. Chemotherapy was not delayed for low HB levels. A total of 15.5% of patients declined to complete all the cycles because of nausea or personal reasons.

The EBRT was with four portals in 160 patients, anterior-posterior in 60, while eight patients received extended field radiation for suspicious para-aortic lymph nodes (1.8 Gy x 28 fractions). Fractionation schedules for the other patients were 46 Gy in 20 fractions, delivered as 2.3 Gy four times a week, or in 23 fractions five times a week. BT commenced during the last week of EBRT, given twice a week. High dose rate iridium192 afterloading tandem and ring applicators were used were in 213 patients, and a single linear applicator in 15 patients. Individual BT doses were adjusted to tumour size at insertion, dose constraints to organs at risk, or applicator type used (5-7 Gy to Point A for 3-4 insertions).

There was no significant influence on OS as far as the following factors were concerned: age, whether the cisplatin was administered on Mondays or Thursdays, tumour volume differences, or total LQED2 to Point A. The OS of HIV-positive patients was similar to those with negative status. All the HIV-positive patients were receiving antiviral therapy. Variables found to be significant for differences in OS were: weekly cisplatin for six as opposed to between one and five cycles ($p<0.026$); six as opposed to five cycles ($p<0.01$); squamous vs non-squamous histology ($p<0.003$); AWHB at cut-off level >10 ($p<0.032$), and OTT with cut-off 45 days ($p<0.03$). The only parameters that remained significant on multivariate analysis were squamous histology, AWHB >10 g/dL, and weekly cisplatin of six cycles (Table II, Fig. 1-3). Overall survival for all patients was 60% at five years.

Table I: Patient, disease and treatment characteristics: (n = 228)

Characteristic	n (%)
Mean age (range):	50.3 (25-84) years
HIV status (n = 190 patients tested): Positive Negative	 13 (6.8%) 177 (93.2%)
Mean tumour size (range):	5.5 (2-10) cm
Parametria: Unilateral } n = 228 Bilateral Medial } n = 228 Lateral	 137 (60%) 91 (40%) 114 (50%) 114 (50%)
Vaginal involvement: Nil 1/3-2/3	 130 (57%) 98 (43%)
Histology: Squamous Adenocarcinoma Adeno-squamous	 191 (83.8%) 27 (11.8%) 10 (4.4%)
Mean AWHB (range):	11.6 (8.8-15.5) g/dL
Completed cisplatin cycles: 6 cycles 5 cycles 4 cycles 3 cycles 1-2 cycles	 56 (24.5 %) 95 (41.7%) 50 (22%) 19 (8.3%) 8 (3.5%)
Reason for not completing 5-6 cycles (n = 78): Administrative failure Haematological Renal Nausea/refusal Unknown	 25 (32%) 22 (28.5%) 15 (19%) 12 (15.5%) 4 (5%)
Day in week of cisplatin administration: Mondays Thursdays Mixed	 32 (14%) 187 (82%) 9 (4%)
Median OTT (range):	45 (36-80) days
Mean total LQED2 dose to Pt A (range):	83 (61-96) Gy

Table II: Univariate and multivariate analysis of the selected covariates.

Univariate (Crude)			Multivariate (Adjusted)	
Covariate	H.R. (95% C.I)	p-value	H.R. (95% C.I)	p-value
Histology: non-squamous	1.88 (1.23, 2.86)	0.003	2.08 (1.35, 3.22)	0.001
AWHB: ≤10	1.77 (1.05, 3.00)	0.032	1.83 (1.06, 3.15)	0.031
OTT: > 45 days	1.56 (1.09, 2.21)	0.013	1.32 (0.92, 1.90)	0.14
No. of cycles: 1-5 cycles	1.62 (1.05, 2.45)	0.026	1.90 (1.23, 2.96)	0.004

Reference groups = Histology: Squamous, AWHB: >10 mmHg, OTT: ≤45 days, No. of cycles: = 6 cycles

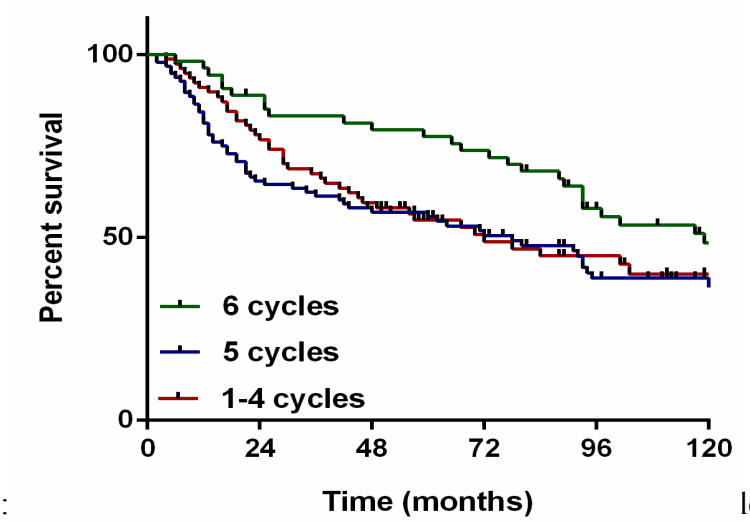

Figure 1: les (sustained benefit shown by 10-year survival).

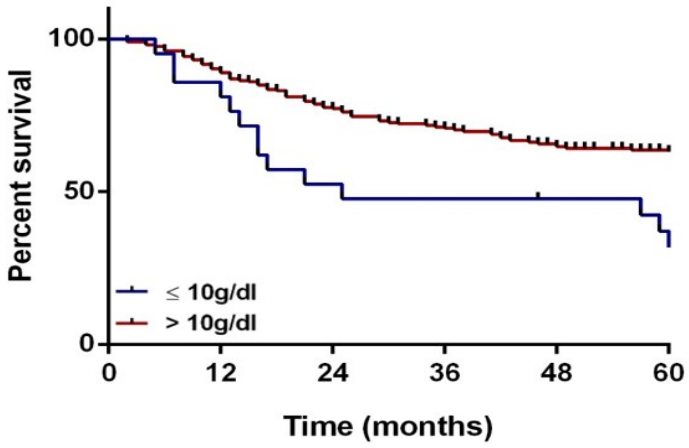

Figure 2: Kaplan Meyer overall survival curves for AWHB.

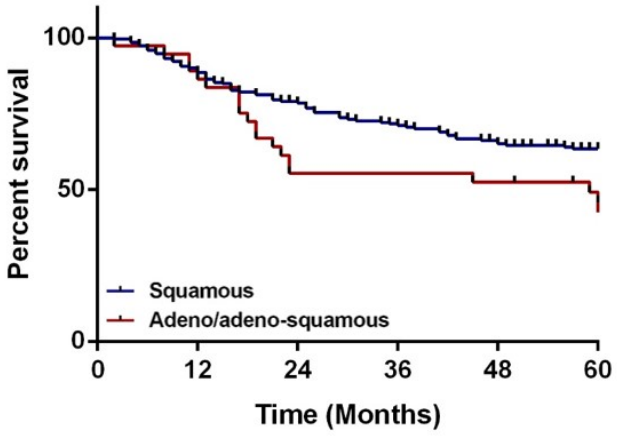

Figure 3: Kaplan Meyer overall survival curves for histology type.

DISCUSSION:

Our study surveyed which tumour or treatment parameters appear to influence overall survival, and which could potentially be manipulated to maximize treatment outcomes. We found that only the following factors were significantly associated with a better OS on multivariate analysis: six cycles of weekly cisplatin, an AWHB of >10 g/dL during CRT, and squamous histology.

Cisplatin-based concurrent chemo-radiation of cervical cancer has become the established treatment worldwide for all stages of the disease.[7] The preferred regimen is weekly cisplatin during RT, because of the relative convenience of outpatient administration and fewer side effects than other schedules. The weekly dosage established in two of the five originator randomized studies was cisplatin 40mg/m^2, with capping at 70 mg absolute weekly dose in one of the two studies using this regimen.[8,9] A meta-analysis of pooled individual patient data has found a 7% absolute improvement in 5-year OS for stage IIB with CRT vs. RT alone.[10]

Two studies warrant mention because the benefit of CRT over RT alone could not be demonstrated: Chen et al. reported a control-cohort retrospective study which included 171 patients with stages IIB and IIIB, of whom 80% completed five cycles of weekly cisplatin (40 mg/m^2, capped at 60 mg/week).[11] This is a dose regimen similar to the one used in the current study, and perhaps six cycles are required at this dosage, as suggested by our findings. A randomized study from Canadian included substantial numbers if stage IIB patients. Seventy percent of patients completed the planned five cycles (40mg/m^2 without capping). The reasons given for the failure to show benefit for CRT in this study included: the study was underpowered; more anaemia in the CRT arm, and/or higher RT doses in the RT-alone arm than used in the American studies of CRT.[12]

The optimal dose of cisplatin has also not been well described. Weekly doses of 40 mg/m^2 for six cycles deliver cumulative doses of 240 mg/m^2. Capping at 60 mg, assuming that most patients have a body surface area of 1.7 m^2, will reduce the prescribed dose to 35 mg/m^2, or 210 mg/m^2. Restricting the maximum cisplatin weekly dose to 60-70 mg is presumably a

manoeuver to improve tolerability to, and compliance with a planned course of either five or six cycles. Missing cycles for whatever reason reduces the relative dose intensity, or ratio between actual and planned doses. Serkies and Jassem[13] found in a retrospective review that 74% of their patients received four cycles (40mg/m^2, capped at 70 mg). Only 45% completed five cycles, mostly because of the intervention of acute toxicity. Relative dose intensity for all patients was 0.8, or 32mg/m^2.

An alternative, simpler way to examine a possible dose effect of weekly cisplatin during CRT is to compare number of cycles received to outcome. Sirak et al[14] reviewed 73 patients (78% with stage IIB) who received CRT at 40mg/m^2 without dose capping. Only 28% of patients completed five cycles, with improved 3-year survival rates compared to those patients who received four or more cycles. Another retrospective study of the number of cycles in LACC was that of Nugent and co-workers[4] who treated 118 patients with CRT at 40mg/m^2 (70 mg cap/dose) for a planned six doses. Altogether, 72% completed six cycles. Multivariate analysis showed that number of cycles was independently significant for survival (six cycles vs one to four) but there was no difference between five or six cycles. The reasons why patients did not complete five or six cycles included noncompliance, side effects and laboratory test deviations.

This situation is different from the current study, where six cycles were needed to achieve the best results. The reasons are speculative but include the following: it could be related to the slightly lower drug dose (capping at 60 mg), only stage IIB being included, and different radiation parameters. Clinical experience shows that whilst CRT with weekly cisplatin is generally well tolerated, some patients experience symptoms, or develop laboratory abnormalities, resulting in fewer than the planned number of cycles being received. Markman[15] has suggested lower weekly cisplatin doses of 30-35 mg/m^2 to increase compliance further, although this would require a RCT to test, or at least retrospective analyses of relative dose intensities as a function of number of cycles.

Whilst one cannot directly compare CRT in head and neck cancer, a recent review found that 200-300 mg/m^2 of cisplatin is required for optimum results.[16] This cumulative dose was not dependent on scheduling of the chemotherapy. A large single institution study of Head and Neck cancer found that six or more cycles of cisplatin at 30 mg/m^2/week gave superior results compared with fewer than six cycles.[17] Whether this a function of cumulative dose, or of a larger number of cycles giving optimum radiosensitization, are uncertain.

Alternative strategies to improve chemotherapy deliverance include a finding by Ruy et al in a RCT in which the standard weekly regimen was compared to cisplatin 75 mg/m^2 every three weeks for three cycles: survival rates were better, and side effects fewer, in the 3-weekly arm.[18] Weekly CRT with carboplatin (Area Under Curve = 2) is another apparently equipotent option, with less morbidity, according to a randomized study of cisplatin vs carboplatin in LACC, reported by Tharvichitkul et al., (2016).[19] Lastly, efforts to reduce treatment toxicity could improve tolerance. Intensity Modulated Radiotherapy (IMRT) was recently studied in LACC by Mell and co-workers,[20] with the hypothesis that a reduction in radiation exposure to bowel and functioning bone marrow would improve tolerability to

CRT. Compared to historical data, a significant decrease in gastrointestinal and haematological side effects was seen, while 82% of patients could complete five or more cycles of cisplatin at 40mg/m^2, without dose capping.

We did not demonstrate any difference in outcome between Monday or Thursday administration of concurrent cisplatin. Although patient numbers were small, it is more likely that any benefit effect of Monday administration, with potentially more interaction with radiation than closer to the weekend, is diminutive, or non-existent. We could not find reports in the literature which mention the day of week, except to "start on day one of radiation".

Anaemia in cervical cancer theoretically increases the hypoxic cell component within tumours, which would contribute to radio-resistance and poorer outcomes.[21] There is debate as to whether anemia in itself is prognostic, or whether it is the phenotype of a more aggressive underlying cancer. HB levels during RT may be more significant than pre-treatment levels. Grogan et al. (2009) retrospectively studied the impact of anaemia and blood transfusion on the outcome of cervical cancer patients treated with definitive RT.[22] An intra-therapy AWHB level of ≥ 12g/dL from start of treatment, or maintained during treatment with blood transfusion, was prognostic, while pre-treatment HB level was not, in a multivariate analysis. Winter et al. (2004), in a retrospective assessment of patients treated on two consecutive GOG trials, reiterated these findings; an AWHB level ≥12g/dL during treatment was an independent predictor of DFS for LACC. Reduced levels in the last part of the EBRT course were most predictive of local recurrence.[23]

Kapp and co-workers (2002) support the notion that red cell transfusions are beneficial, using a threshold HB of 11g/dL. Multivariate analysis, correcting for tumour size and nodal status, confirmed that only HB during treatment was significant.[24] Another retrospective study also found that pre-treatment HB levels were not prognostic, although the lowest value during RT was; Obamair et al. (2000)[25] found that an HB nadir of >11g/dL during CRT had a 90% chance of a complete clinical response and was significantly related to better progression free survival. In a study of 88 patients with LACC, Mayr and co-workers measured tumour perfusion using dynamic contrast enhanced magnetic resonance imaging. Patients with a combination of low tumour perfusion and AWHB <11.2 had significantly worse outcomes, suggesting synergistic negative effects. These authors recommend dual assessment of both perfusion and AWHB to guide the management of anaemia during CRT, especially in the poorly diffusing tumours.[26]

Bishop et al. (2015) questioned, in a retrospective review of a large patient cohort, the relationship between low haemoglobin level and outcomes after treatment in cervical cancer. The only significant association they could establish on multivariate analysis was that HB <10 during RT was associated with disease-specific survival. The benefit of blood transfusions was unclear from their data.[27] Fyles and colleagues from the Princess Margaret Hospital in Toronto maintain that anaemia in cervical cancer correlates with tumour size and therefore may not be independently prognostic. A randomized study of transfusion in cervical cancer, previously performed at their institution, failed to demonstrate any benefit.[28]

Squamous histology conferred a better prognosis in our cohort. Yokio et al. (2017),[29] in a retrospective survey of patients with locally advanced cervical cancer made similar findings; 9.6% of their cohort had adeno-carcinoma or adeno-squamous histology and did significantly worse than patients with squamous tumours. The authors recommend that a specific CRT regimen be developed for these non-squamous histological types.

Protracted radiation (generally defined as OTT ≥ 8 weeks), has been reported to have statistically significant associations with poor pelvic control and survival in cervical cancer in various retrospective analyses. Saibishkumar et al.[30] found the cut-off to be seven weeks, while Perez's group calculated a loss of pelvic tumour control of 0.68%/day if OTT >7 weeks in stage IIB.[31] On the contrary, Huang et al. (2016),[32] in a study of stage IIB patients treated with uniform RT doses, high dose rate BT started after completion of teletherapy. The OTT did not impact upon either survival or local recurrence, although if it were ≤56 days, there was a negative effect on proctitis. For this reason, these authors recommend a one-week gap between teletherapy and onset of BT. Another group of investigators found that when concurrent cisplatin is added to RT, an extended OTT had no effect on treatment outcome.[33] Our finding of a significant difference in survival if OTT were more than 45 days was not borne out on multivariate analysis. It is generally accepted, however, that prolongation of treatment should be avoided.

Perez et al. (1992) conducted a retrospective assessment of the impact of tumour size and extent on local control and distant failure in 1178 patients treated with definitive radiotherapy, 353 of whom had stage IIB disease. Tumours were described in terms of size (cut-off 5 cm) and volume (unilateral/ bilateral parametrial involvement, and medial or lateral parametrium). The 10-year actuarial pelvic failure rate significantly correlated with tumour size and lateral parametrial involvement in Stage IIB. There was no difference between unilateral vs bilateral disease. Larger tumours (≥ 5cm) also had a higher incidence of distant failure and a lower disease free survival period. This data predates the chemo-radiotherapy era in the treatment of cervical carcinoma.[34] Our data could not confirm any effect of disease volume, possibly because of much smaller patient numbers than in the Perez review.

Adverse outcomes associated with HIV infection in cervical cancer patients include shorter overall survival, increased pelvic failures, and increased risk of multi-organ radiation-related acute toxicity and treatment interruption.[5,35] Untreated HIV is also associated with anaemia, a factor with a negative influence on chemo-radiotherapeutic outcome in cervical cancer.[36] Only 6.8% of the patients tested for HIV in this study were positive, which is below the current prevalence at our institution (25% in 2015 - L van Wijk, Personal communication). This is most likely due to the low prevalence during the early years of the study. The relatively small numbers of HIV-positive patients, who were all receiving antiviral therapy, could explain why they did not show worse outcome. It is crucial, however, that newly discovered HIV infection at time of cervical cancer diagnosis be promptly commenced on antiviral therapy prior to commencement of CRT.[37]

Limitations inherent to the retrospective nature of this study include bias from inconsistent examiner-dependent assessments of tumour size or parametrial involvement. Furthermore,

other time-event parameters such as progression free survival, also tumour responses and complication rates are unreliable as a result of non-uniform follow-up periods and could not be assessed accurately.

In conclusion, concurrent CRT with weekly cisplatin has become standard therapy in cervical cancer although the optimal scheduling and drug dosage may require further refinement. In our study of CRT in stage IIB cervical cancer, the best survival rate was found in patients receiving six cycles at the dosage schedule used. We speculate that the number of weekly cycles may outweigh cumulative dose of cisplatin for interaction with radiation. We aim to strengthen departmental systems to strive for the six planned administrations, from day one of CRT, in the majority of our patients. Despite dose capping, patients still miss weekly cycles because of either side effects or laboratory deviations. Removing the dose cap of 60mg/week may increase delays from acute toxicity.

Anaemia of AWHB ≤ 10 g/dL during CRT was a negative prognostic factor for our patients with stage IIB. While our study was not designed to examine benefit from blood transfusion, the uncertainty regarding this issue can only be resolved by a randomized trial. Our practice is to transfuse all symptomatic anaemic patients, although there is sufficient evidence in the literature to suggest that levels of >10 g/dL should be maintained during therapy; in view of this, we use oral antifibrinolytic agents liberally, and transfuse if HB is <10 g/dL. Non-squamous cervical cancer histology of either the adenocarcinoma or adeno-squamous type needs exploration of CRT with other concurrent drugs; for example, taxanes.

Acknowledgements: The authors thank the Clinical Directorate of Groote Schuur Hospital for permission to perform this study.

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PART D

PART D: APPENDICES

I: *Data collection instrument:*

The influence of cisplatin dosing variations during concurrent weekly chemo-radiation in stage IIb cervical cancer.

EXCLUDED + REASON: Other Hist : Other chemo : Other

RT number: Initials:

Age: numeric

Hist: Sq : Ad : Ad-Sq

HIV: Y : N : NS

CD4: Numeric : 000 if unknown

Size: numeric in cm

Para: Uni : Bil

Vag: Nil : 1/3 : 2/3

AWHB: numeric

BTF?: Y : N : NS

Field: POP : Box

 # size: numeric **No #:** numeric **EBRT:** numeric

ID2Ext: numeric

No # ICT: numeric **ID2ICT:** numeric **Total ID2:** numeric

Type ICT: T+R : TBH : Combo : Mix

WC: Mon : Thurs : Other....

No. WC: numeric

Reason: N/V : Renal : Haem : Refuse : Admin : other

OTT: numeric (Can excel calc this from dates???)

CR: Y : N : NS

Rel: (ONLY IF CR) Loc : Dist : L+D

Gr 3-4: Nil : GIT : Uro : Oth

	Date last contact/death	**Status at last contact**			**Cause of death**				
		A-Well	A-Dis	Dead	Dis	Rx	Unrel	Unkn	

OS: numeric

DFI: numeric

……..

ID2 (10) of EBRT: 2.3 Gy x 20# : 47 Gy

2.1 Gy x 22# : 46.5

ID2 (10) of BT:

4Gy x 4 = 19 (4.75 9.5 14.25 19 - for 1,2,3 4 #)

4.5Gy x 4 = 22 (5.5 11 16.5 22)

5Gy x 4 = 25 (6.25 12.5 18.75 25)

5.5Gy x 4 = 28 (7 14 21 28)

6 Gy x 4 = 32 (8 16 24 32)

6.5Gy x 4 = 36 (9 18 27 36)

7 Gy x 4 = 40 (10 20 30 40)

7.5Gy x 4 = 44 (11 22 33 44)

II: *Official Ethics approval letters.*

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: shureta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

21 November 2014

HREC REF: 832/2014

Dr L van Wijk
Radiation Oncology
LE32

Dear Dr van Wijk

PROJECT TITLE: THE INFLUENCE OF CISPLATINUM DOSING VARIATIONS DURING CONCURRENT WEEKLY CHEMORADIATION IN STAGE IIB CERVICAL CANCER AT GROOTE SCHUUR HOSPITAL (MMed candidate- Dr MG Jenu)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th November 2015.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

We acknowledge that the student, Dr Mtabeni George Jenu will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB0001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical

HREC 832/2014

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☐ Approved	Annual progress report	Approved until/next renewal date	30/03/2017
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	30/3/2016

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	29/3/16		
HREC REF Number	832/2014	Current Ethics Approval was granted until	30/11/15
Protocol title	"The influence of cisplatinum dosing ...		
Protocol number (if applicable)	MA		
Are there any sub-studies linked to this study?	☐ Yes ☑ No		
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	DR A.L. MANWELL (MMED STUDENT		
Department / Office Internal Mail Address	LE33 CCMC GSH	DR M. JEMAL	

1.1 Does this protocol receive US Federal funding?	☐ Yes	☑ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval?	☐ Yes	☐ No
1.3 Has sponsorship of this study changed? If yes, please attach a revised summary of the budget.	☐ Yes	☐ No

MA

RESEARCH ETHICS COMMITTEE
2016 -03- 30
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

Western Cape Government
Health

GROOTE SCHUUR HOSPITAL

Enquiries: Dr Bernadette Eick
E-mail : Bernadette.Eick@westerncape.gov.za

Dr L. Van Wijk
Radiation Oncology
L-BLOCK

E-mail: leon.vanwijk@uct.ac.za / mtabeni@yahoo.co.uk

Dear Dr Van Wijk

RESEARCH PROJECT EXTENSION: The Influence of Cisplatinum Dosing Variations During Concurrent Weekly Chemoradiation in Stage 11B Cervical Cancer at Groote Schuur Hospital (Mmed Dr M. G. Jemu)

Your recent communication to the hospital refers.

The extension of your research has been approved until **30 March 2017**.

As previously mentioned:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) No hospital consumables and stationary may be used.
d) **No patient folders may be removed from the premises or be inaccessible.**
e) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
f) Confidentiality must be maintained at all times.
g) Once the research is complete, please submit a copy of the publication or report.

I would like to wish you every success with the project.

Yours sincerely

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 31st
BE/vms

C.C. Mr L. Naidoo, Professor E. Weimann, Professor J. Parkes

G46 Management Suite, Old Main Building,
Observatory 7925

Private Bag X,
Observatory, 7935

Tel: +27 21 404 6288 fax: +27 21 404 6125

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7. Select Author.
   - Click on CLICK HERE TO FOLLOW THE FIVE STEPS TO SUBMIT YOUR MANUSCRIPT.
   - Follow the five steps to submit your paper.

Please submit a cover letter as a supplementary file with the following:

1. Surnames, initials and qualifications of all authors in the correct sequence
2. Full contact details of corresponding author: Title, first name, surname, e-mail address, mobile, office and fax number and postal address.
3. Declaration on copyright and originality of paper and acknowledgement of any third party sources (references and images) exempting the author(s), journal and publisher of plagiarism.
4. Declaration regarding authorship
5. Ethics committee approval
6. Conflicts of interest

Review policy and timelines

1. Immediate notification if submitted successfully
2. Notification within 3 weeks if not accepted for further review
3. Notification within 3 months if accepted for publication, if revisions are required or if rejected by both reviewers.
4. Publication within 6 months after submission.

The Journal aims to be the prime journal on women's cancer for local health care workers and gynaecologists, focusing on all aspects of cancer prevention, detection, diagnosis and treatment. The SAJGO is also a specialist journal catering for sub-specialist gynaecologic oncologists, for other specialists with a specific interest in breast and gynaecologic cancer, including medical oncologists, radiation oncologists, surgeons, radiologists, pathologists, geneticists, specialised nurses and research scientists.

The Journal includes all aspects of female cancer prevention, diagnosis and treatment and aims to serve a broad readership. As such it should be of interest to the clinical, scientific and academic community, policy makers, government and non-government stakeholders and industry.

Cancer control programmes include primary and secondary prevention, early detection and effective treatment. These aspects form part of public health, general and specialist services and together form the important priorities of the journal.

HIV and AIDS remain problematic in the region with a severe impact on gynaecologic oncology. Papers focusing on gynaecological malignancies in HIV infected women will be prioritised. Research in this field needs to be encouraged.

The Journal encourages articles from all investigators in the fields of gynaecological and breast cancer. In particular young researchers and researchers from historically disadvantaged backgrounds will be encouraged and supported to submit their research work for publication.

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- *Conflict of interest and funding* statements.
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Correspondence to the Editor-in-Chief:
Prof Greta Dreyer, Department of Obstetrics and Gynaecology, University of Pretoria
E-mail: gretadreyer@mweb.co.za or greta.dreyer@up.ac.za
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