

# Tumour and treatment factors influencing the outcome of chemo-radiation in stage IIB cervical cancer: a single institution experience

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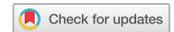
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**Objective:** This study examined the effects of treatment and tumour factors on the overall survival of patients completing chemo-radiation for stage IIB cervical cancer, to identify modifiable factors that might improve outcome.

**Materials and methods:** A retrospective audit was undertaken of 228 patients with stage IIB cervical cancer treated between 1995 and 2010, who received chemo-radiation with at least 45 Gy external beam radiation, two to four brachytherapy sessions, and one to six weekly cycles of concurrent cisplatin (40 mg/m<sup>2</sup>, capped at 60 mg/week).

**Results:** Mean total dose to Point A from external beam radiation and brachytherapy was 83 Gy (range 61–96 – expressed as the linear quadratic equivalent dose to 2 Gy/fraction). Mean overall treatment time was 45 days. The average weekly haemoglobin (AWHB) during treatment was 11.6 g/dl (range 8.8–15.5). Overall, one-third of patients received blood transfusions before or during chemo-radiation, and two-thirds of patients completed five or six cycles of weekly cisplatin. Reasons for fewer than five cycles were scheduling failures, neutropenia, renal impairment and side effects. No outcome differences were observed for Monday vs. Thursday cisplatin administration. The five-year overall survival was 60%. Patients completing fewer than six cycles had a worse survival (55 vs. 76%,  $p = 0.02$ ). By multiple regression for survival only six cycles of cisplatin, squamous histology and AWHB >10 g/dl were significant.

**Conclusions:** Maintaining HB >10.0 and administering six cycles of weekly cisplatin are associated with better survival from chemo-radiation for stage IIB cervical cancer.

**Keywords:** average weekly haemoglobin, cervical cancer, concurrent chemo-radiation, non-squamous histology, number of cisplatin cycles, overall treatment time, stage IIB

## Introduction

Cervical cancer is one of the commonest cancers in women in developing countries.<sup>1</sup> The impact on limited treatment facilities of large numbers of patients with locally advanced cervical cancer is considerable. Stage IIB is the commonest stage, and in some centres hypofractionated radiation regimens are used to cope with patient numbers.<sup>2,3</sup> Stage IIB has a better prognosis and definitive concurrent chemo-radiation (CRT) and brachytherapy is recommended, even in developing countries.<sup>4</sup>

Clinical audits of cervical cancer cohorts can determine factors that modify the effect of CRT on survival. In stage IIB, these include histological type, tumour volume and haemoglobin level during therapy. Treatment-related factors include CRT versus radiation alone, minimising overall treatment time, and total radiation doses to Point A.<sup>5</sup> A positive human immunodeficiency virus (HIV) status, especially if untreated with antiretroviral therapy, has a deleterious effect on outcome after CRT and increases acute epithelial side effects within the radiation volume.<sup>6,7</sup>

Questions remain concerning how best to administer concurrent chemotherapy. 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 weekly concurrent cisplatin cycles may also impact outcomes; Nugent *et al.* conducted a retrospective analysis of the effect of the number of cycles completed with radiotherapy in 118 patients and found that fewer than five cycles were associated with

reduced survival rates when compared with five or six cycles.<sup>8</sup> The optimal day of the week for the administration of concurrent cisplatin has not been investigated. Potentially, administering chemotherapy during the early part of the week could increase the interaction of drug and radiation when compared administration later in the week.

This is a retrospective clinical audit of 228 patients with stage IIB cervical cancer treated with CRT over a 15-year period at a single institution. The study examines the impact of several factors on patient survival to identify priorities for optimising outcomes.

## Methods

Institutional ethics approval was obtained (HREC 832/2014). Patient informed consent for data assembly and analyses was not required due to the retrospective nature of this study with anonymous data handling. Data were extracted for all patients with FIGO stage IIB cervical cancer registered during 1995–2010 at the Groote Schuur Hospital, Cape Town, South Africa. Inclusion criteria included: proven histological diagnosis of squamous, adeno-squamous or adenocarcinoma of the uterine cervix; receiving an external beam radiotherapy (EBRT) dose of at least 45 Gy to the whole pelvis; receiving two to four sessions of brachytherapy (BT); and receiving one to six weekly cycles of concurrent cisplatin (40 mg/m<sup>2</sup>, capped at 60 mg per week). Data were extracted for selected tumour and treatment-related factors and the HIV status was recorded. Tumour volume was measured as cervical diameter in centimetres, determined from CT images or clinical palpation, while involvement of parametria

and vagina were determined clinically. Individual patient haemoglobin (HB) values were expressed as the average weekly levels during treatment (AWHB in g/dl). Treatment duration was measured from the first to the last day of radiation, regardless of whether the last exposure was from EBRT or BT, and it is reported as overall treatment time (OTT) in days. Total radiation doses to Point A were expressed as the summation of EBRT and BT doses, as expressed by linear quadratic equivalent dose to 2 Gy per fraction (LQED2). Radiation on the day of cisplatin administration was given within two hours, either before or after chemotherapy.

Analysis was conducted using Prism v6.05 (GraphPad Software Inc., San Diego, CA, USA). Numerical variables were summarised by means, or dichotomised at various cut-off points and compared with the log-rank test for the outcome of survival. Categorical variables were summarised by frequencies and percentages. Survival was estimated using the Kaplan–Meier 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, otherwise censored at the date of last patient 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 < 0.05. A multivariable Cox regression model with proportional hazards was used to assess the independent significance of potential predictive factors for the outcome of OS.

**Results**

Of 410 patients with stage IIB cervical cancer managed between 1995 and 2010, 228 met the criteria for inclusion in the study (see Figure 1). Patient, disease and treatment characteristics are presented in Table 1.

EBRT was administered 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 all other patients were 46 Gy in 20 fractions, delivered as 2.3 Gy four times a week, or in 23 fractions delivered as 2 Gy five times a week. BT commenced during the last week of EBRT and was given twice a week. High dose rate iridium192 after-loading tandem and ring applicators

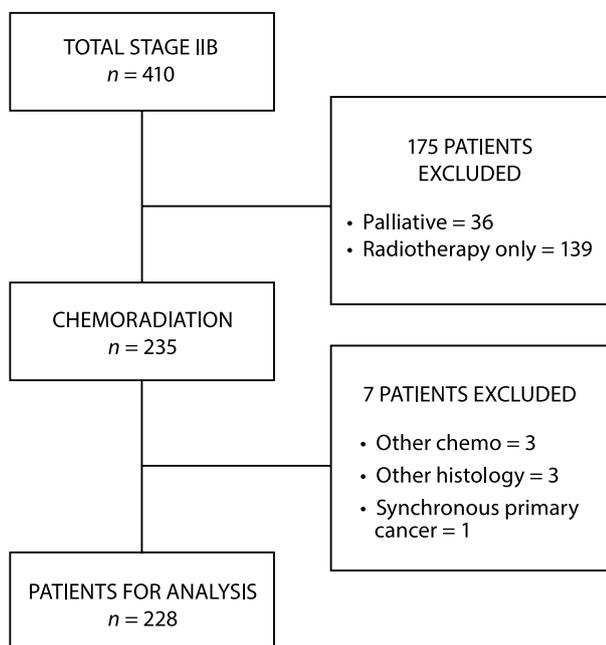
**Table 1:** Patient, disease and treatment characteristics (n = 228)

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

were used 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). 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. Where receiving fewer 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 to < 2.5 10<sup>9</sup>/l, platelet count to < 75 000 10<sup>9</sup>/l, or an increase in 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.

Overall survival for all patients was 60% at five years. There was no significant influence on OS for: age; whether the cisplatin was administered on Mondays or Thursdays; tumour volume differences; total LQED2 to Point A; and HIV-positive or -negative

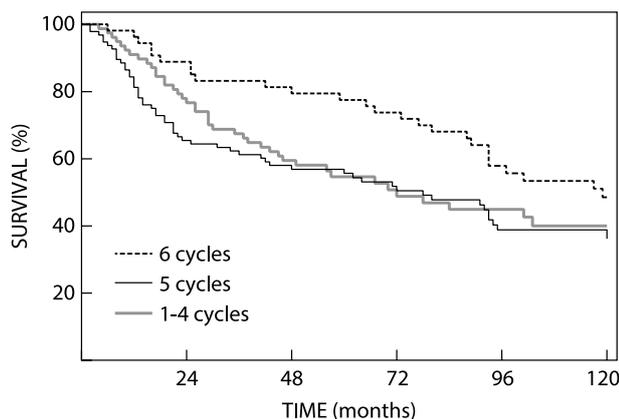


**Figure 1:** Exclusions and cases for analyses

**Table 2:** Univariate and multivariate analysis of the selected covariates

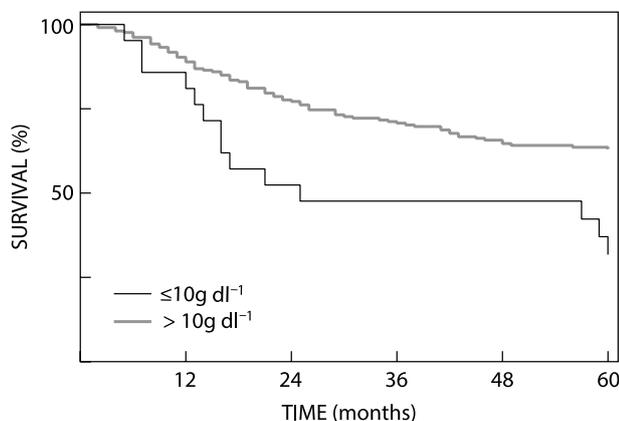
Univariate (Crude)			Multivariate (Adjusted)	
Covariate	H.R. (95% C.I.)	p-value	H.R. (95% C.I.)	p-value
Histology: non-squamous	1.88 (1.23, 2.86)	0.003	2.08 (1.35, 3.22)	0.001
AWHB: ≤10	1.77 (1.05, 3.00)	0.032	1.83 (1.06, 3.15)	0.031
OTT: > 45 days	1.56 (1.09, 2.21)	0.013	1.32 (0.92, 1.90)	0.14
No. of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

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

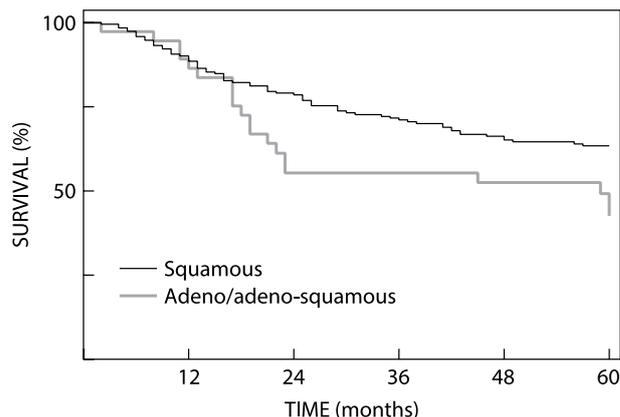


**Figure 2:** Kaplan–Meier overall survival curves for number of cycles (sustained benefit shown by 10-year survival).

status (all HIV-positive patients received antiretroviral therapy). Variables found to be significant for differences in OS were: weekly cisplatin for six as compared with one to five cycles ( $p < 0.026$ ); six as compared with five cycles ( $p < 0.01$ ); squamous vs. non-squamous histology ( $p < 0.003$ ); AWHB at cut-off level  $> 10.0$  ( $p < 0.032$ ); and OTT with cut-off 45 days ( $p < 0.03$ ). By Cox regression, on multivariate analysis only squamous histology, AWHB  $> 10$  g/dl, and weekly cisplatin of six cycles remained significant (Table 2, Figures 2–4).



**Figure 3:** Kaplan–Meier overall survival curves for AWHB.



**Figure 4:** Kaplan–Meier overall survival curves for histology type.

**Discussion**

This study surveyed which tumour or treatment parameters appear to influence overall survival in stage IIB cervical cancer, and which could potentially be managed to maximise treatment outcomes. Only the following factors were significantly associated with a better OS on multivariate analysis: six cycles of weekly cisplatin, an AWHB of  $> 10.0$  g/dl during CRT, and squamous histology.

**Non-squamous pathology**

Squamous histology conferred a better prognosis in the present study. Yokio et al. (2017),<sup>9</sup> in a retrospective survey of patients with locally advanced disease, had similar findings; 9.6% of their cohort had adenocarcinoma or adeno-squamous histology and did significantly worse than patients with squamous tumours. The authors recommended that a specific chemotherapy regimen be developed for CRT of non-squamous histologies.

**Concurrent chemotherapy**

Cisplatin-based concurrent chemo-radiation has become the established curative treatment for cervical cancer worldwide.<sup>10</sup> The preferred regimen is weekly cisplatin during EBRT, 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 randomised studies was cisplatin 40 mg/m<sup>2</sup>, with capping at 70 mg absolute weekly dose in one of the two studies using this regimen.<sup>11,12</sup> A meta-analysis of pooled individual patient data has found a 7% absolute improvement in five-year OS for stage IIB with CRT vs. RT alone (and only 3% in stage IIIB).<sup>13</sup>

Three studies warrant mention because the benefit of CRT over RT alone could not be demonstrated. Chen et al. reported a control-cohort retrospective study that included 171 patients with stages IIB and IIIB, of whom 80% completed five cycles of weekly cisplatin (40 mg/m<sup>2</sup>, capped at 60 mg/week).<sup>14</sup> This is a dose regimen similar to the one used in the current study, hence perhaps six cycles are required at this dosage, as suggested by our findings. A randomised study from Canada included substantial numbers of stage IIB patients. Some 70% of patients completed the planned five cycles (40 mg/m<sup>2</sup> 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.<sup>15</sup> In another randomised trial, conducted by the International Atomic Energy Agency, 601 patients with IIB/IIIB cervical cancer received either RT or CRT; 66% completed five weekly cycles of cisplatin. Cancer-specific survival was of marginal significance ( $p = 0.078$ , but intention-to-treat  $p = 0.2$ ).<sup>16</sup> All three of these studies were probably underpowered because of the inclusion of stage IIIB cancers.

The optimal dose of cisplatin has also not been well defined. Weekly doses of 40 mg/m<sup>2</sup> for six cycles deliver cumulative doses of 240 mg/m<sup>2</sup>. Capping at 60 mg, assuming that most patients have a body surface area of 1.7 m<sup>2</sup>, will reduce the prescribed dose to 35 mg/m<sup>2</sup>, or 210 mg/m<sup>2</sup>. Restricting the maximum cisplatin weekly dose to 60–70 mg is presumably a manoeuvre to improve tolerability to, and compliance with, a planned course of either five or six cycles, to maintain relative dose intensity. Serkies and Jassem<sup>17</sup> found in a retrospective review that 74% of their patients received four cycles (40 mg/m<sup>2</sup>, capped at 70 mg). Only 45% completed five cycles, mostly because of acute toxicity. Relative dose intensity for all patients was 0.8, or 32 mg/m<sup>2</sup>.

An alternative, simpler way to examine a possible dose effect of weekly cisplatin during CRT is to compare the number of cycles received with the outcome of survival. Sirak *et al.*<sup>18</sup> reviewed 73 patients (78% with stage IIB) who received CRT at 40 mg/m<sup>2</sup> without dose capping. Only 28% of patients completed five cycles, with improved three-year survival rates compared with those patients who received four or fewer cycles. Another retrospective study of the number of cycles in locally advanced cervical cancer was that of Nugent and co-workers<sup>8</sup> who treated 118 patients with CRT at 40 mg/m<sup>2</sup> (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 vs. one to four cycles) but there was no difference between five and six cycles. The reasons why patients did not complete five or six cycles included patient non-adherence, side effects and laboratory test deviations.

In the present study, six cycles of chemotherapy were associated with greater overall survival. The reasons are speculative but could be related to the slightly lower drug dose (capping at 60 mg). Clinical experience shows that whilst CRT with weekly cisplatin is generally well tolerated, some patients experience symptoms or develop laboratory abnormalities that result in fewer cycles received than intended. Markman<sup>19</sup> has suggested lower weekly cisplatin doses of 30–35 mg/m<sup>2</sup> to increase compliance further, although this would require an RCT to test the idea or, alternatively, detailed retrospective analyses of relative dose intensities as a function of numbers of cycles.

Whilst one cannot directly compare CRT in cervical cancer with CRT in head and neck cancer, a recent review found that 200–300 mg/m<sup>2</sup> of cisplatin was required for optimum results in head and neck cancer.<sup>20</sup> 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<sup>2</sup>/week gave superior results compared with fewer than six cycles.<sup>21</sup> Whether this a function of cumulative dose, or of a larger number of cycles giving optimum radiosensitisation, is uncertain.

Alternative strategies to improve chemotherapy delivery include a finding by Ruy *et al.* in an RCT in which the standard weekly regimen was compared with cisplatin 75 mg/m<sup>2</sup> every three

weeks for three cycles: survival rates were better, and side effects fewer, in the three-weekly arm.<sup>22</sup> Weekly CRT with carboplatin (area under curve = 2) is another apparently equipotent option, with less morbidity according to a randomised study of cisplatin vs. carboplatin in locally advanced disease, reported by Tharvichitkul *et al.* (2016).<sup>23</sup> Lastly, efforts to reduce treatment toxicity could improve tolerance. Intensity modulated radiotherapy (IMRT) was recently studied in locally advanced disease by Mell and co-workers,<sup>24</sup> with the hypothesis that a reduction in radiation exposure to bowel and functioning bone marrow would improve tolerability to CRT. Compared with historical data, a significant decrease in gastrointestinal and haematological side effects was seen, and 82% of patients could complete five or more cycles of cisplatin at 40 mg/m<sup>2</sup> without dose capping.

The present study 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 EBRT than when given closer to the following weekend, is diminutive, or non-existent. We could not find reports in the literature which mention the day of the week, except to 'start CRT on day one of radiation'.

#### Anaemia and transfusions

Anaemia in cervical cancer theoretically increases the hypoxic cell component within tumours, which would contribute to radio-resistance and poorer outcomes.<sup>25</sup> There is debate as to whether anaemia in itself is prognostic, or whether it is the phenotype of a more aggressive underlying cancer. Low HB levels during radiotherapy may be more significant than pre-treatment levels, as first described by Dr Raymond Bush in 1986.<sup>26</sup> In 2009, Grogan *et al.*, also from Canada, retrospectively studied the impact of anaemia and blood transfusion on the outcome of cervical cancer patients treated with definitive radiotherapy.<sup>27</sup> An intra-therapy AWHB level of  $\geq 12$  g/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 Gynecology Oncology Group trials, affirmed these findings; an AWHB level  $\geq 12$  g/dl during treatment was an independent predictor of disease-free experience for locally advanced disease. Reduced levels in the last part of the EBRT course were most predictive of local recurrence.<sup>28</sup>

Kapp and co-workers (2002) concluded that red cell transfusions are beneficial, using a threshold HB of 11 g/dl. Multivariate analysis, correcting for tumour size and nodal status, confirmed that only HB during treatment was significant.<sup>29</sup> Another retrospective study, by Obamair *et al.* (2000), also found that pre-treatment HB levels were not prognostic. An HB nadir of  $> 11$  g/dl during CRT had a 90% chance of a complete clinical response and was significantly related to better progression-free survival.<sup>30</sup> In a study of 88 patients with locally advanced disease, Mayr and co-workers measured tumour perfusion using dynamic contrast-enhanced magnetic-resonance imaging. Patients with a combination of low tumour perfusion and AWHB  $< 11.2$  g/dl had significantly worse outcomes, suggesting synergistic negative effects. These authors recommended dual assessment of both perfusion and AWHB to guide the management of anaemia during CRT, especially in the poorly diffusing tumours.<sup>31</sup>

In a retrospective review of a large patient cohort, Bishop *et al.* (2015) questioned the relationship between low HB level and outcomes after treatment. The only significant association on multivariate analysis was that HB < 10 during radiotherapy was associated with disease-specific survival. The benefit of blood transfusions was unclear from their data.<sup>32</sup> Fyles and colleagues from the Princess Margaret Hospital in Toronto maintained that anaemia in cervical cancer correlates with tumour size and therefore may not be independently prognostic. A randomised study of transfusion in cervical cancer, previously performed at their institution, failed to demonstrate any benefit.<sup>33</sup>

### Overall radiation treatment time

Protracted radiation (generally defined as OTT ≥ 8 weeks), has been reported in several retrospective studies to have statistically significant associations with poor pelvic control and survival. Saibishkumar *et al.*<sup>34</sup> 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.<sup>35</sup> Conversely, Huang *et al.* (2016),<sup>36</sup> in a study of stage IIB patients treated with uniform RT doses, with high dose rate BT started after completion of teletherapy, showed that OTT did not impact either survival or local recurrence, although if OTT were ≤ 56 days there was a negative effect on proctitis. For this reason, these authors recommended a one-week gap between teletherapy and commencing BT. Another group of investigators found that when concurrent cisplatin was added to RT, an extended OTT had no effect on treatment outcome.<sup>37</sup> Our finding of a significant difference in survival for OTT > 45 days on univariate analysis was not sustained on multivariate analysis. It is generally accepted, however, that prolongation of treatment should be avoided.

### Other factors

Perez *et al.* (1992) conducted a retrospective assessment of the impact of tumour extent and size on local control and distant failure in 1 178 patients treated with definitive radiotherapy, 353 of whom had stage IIB disease. Tumours were described in terms of size (cut-off 5 cm) and anatomic extent (unilateral vs. bilateral, and medial vs. lateral parametrial involvement), reflecting intra-stage volume differences. The 10-year actuarial pelvic failure rate was significantly associated with tumour size and lateral parametrial involvement in Stage IIB. There was no difference between unilateral vs. bilateral disease. Larger tumours (≥ 5 cm) also had a higher incidence of distant failure and lower disease-free survival. These data pre-date the CRT era, however.<sup>38</sup> Our study did not confirm any effect of disease volume, possibly because of smaller patient numbers, or less precise recording of disease extent than in the Perez study.

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.<sup>6,39</sup> Untreated HIV is also associated with anaemia, a factor with a negative influence on CRT outcome in cervical cancer.<sup>40</sup> Only 6.8% of the patients tested for HIV in this study were positive, which is below the current prevalence of 25% at our institution (L. van Wijk, personal communication). This is most likely due to the low prevalence and inconsistent testing during the early years of the study. The relatively small numbers of HIV-positive patients, who were all receiving antiretroviral therapy, could explain why they did not experience a worse overall survival. It is crucial, however, that patients with newly discovered HIV infection at the time of a cervical cancer diagnosis be promptly started on antiretroviral therapy prior to commencing CRT.<sup>41</sup>

### Study limitations

Limitations inherent to this retrospective study include potential bias from inconsistent examiner-dependent assessments of tumour volume at baseline. Further, RT treatment schedules changed over the study period. Parameters such as progression-free survival, tumour responses and complication rates were deliberately not used, given the risk of detection bias from non-uniform follow-up intervals.

### Conclusions

Concurrent CRT with weekly cisplatin is the standard therapy in squamous cervical cancer but optimal scheduling and drug dosage may require further refinement. In this retrospective study of CRT in stage IIB, better survival occurred with six cycles at the dose-schedule described. Whether the six cycles are needed for continuous radiosensitisation, or to reach a cumulative cisplatin threshold, is not clear. We aim to strengthen departmental systems to strive for the six planned administrations in all patients and to commence concurrent chemotherapy during the first week of EBRT. Despite dose capping, patients still miss weekly cycles because of either side effects or laboratory deviations, but removing the dose cap of 60 mg/week may increase delays from acute toxicity.

Whilst anaemia of AWHB ≤ 10.0 g/dl during CRT was a negative prognostic factor in this study, uncertainties regarding the benefit of transfusions can only be resolved by a randomised trial. Our practice is to transfuse all symptomatic anaemic patients, as well as those whose HBs have dropped < 10 g/dl as there is sufficient evidence in the literature to suggest that levels of > 10 g/dl should be maintained during therapy. Non-squamous cervical cancer histology might benefit from exploring other concurrent chemotherapy options (e.g. taxanes).

*Funding* – No funding received.

*Disclosure statement* – No potential conflict of interest was reported by the authors.

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

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Received: 14-12-2017 Accepted: 14-02-2018