

Patterns of care and outcomes for women with locally advanced cervical cancer treated with curative intent between 2013-2018 at a tertiary center in South Africa

Research dissertation

by

Dr Maina Juliet

for the degree of

Master of Medicine (Radiation Oncology)

at the

University of Cape Town



Supervisor: Dr Fakie Nazia

Co supervisor: Dr Surbhi Grover

12th December 2021

The copyright of this thesis vests in the author. No quotation from it or information derived from it is to be published without full acknowledgement of the source. The thesis is to be used for private study or non-commercial research purposes only.

Published by the University of Cape Town (UCT) in terms of the non-exclusive license granted to UCT by the author.

DECLARATION

I, Dr Maina Juliet , hereby declare that the work on which this dissertation/thesis 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.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signed by candidate

Signature:

Date: 12/10.2021

INTRODUCTION

According to Global Cancer Statistics (GLOBOCAN), cervical cancer is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer related death in women. It is estimated that there were 604,000 new cases and 342,000 deaths worldwide in 2020 with the highest regional incidence and mortality seen in Sub-Saharan Africa[1]. Cervical cancer in sub-Saharan Africa accounts for 22.2% of all cancers in women and it is also the most common cause of cancer related death among women[2].

In South Africa, cervical cancer also ranks as the leading cause of female cancer deaths, particularly affecting women in the reproductive age group from 15 to 44 years. Recent estimates suggest that given a population of 19.35 million women, 7,735 women are diagnosed annually with cervical cancer and 4,248 women die from the disease[3].

The incidence and mortality of cervical cancer has declined in developing countries in the past 50 years because of increased availability of Papanicolaou (Pap) smear screening programs and decline in fertility rates[4]. However in Sub-Saharan Africa the overall incidence of cervical cancer incidence has been increasing [5]. The onset of the human immunodeficiency virus (HIV)/ acquired immunodeficiency syndrome (AIDS) epidemic and the widespread lack of resources highly impacted the rate of progression of cervical cancer in the Sub-Saharan region[6]. However, sub-Saharan Africa still has a high burden of cervical cancer due to high prevalence of HIV and lack of cervical cancer screening programs. Women living with HIV (WLWH) are at increased risk of human papillomavirus virus (HPV), cervical cancer, and precancerous lesions compared to women without HIV[7, 8]. Current WHO guidelines recommend cervical cancer screening for the general population of women and all WLWH[9]. Despite these recommendations aimed to reduce their higher risk, cervical cancer screening for WLWH are poor, especially in Sub-Saharan Africa[10].

Most women with cervical cancer in SA present with locally advanced cervical cancer. The current guidelines for treatment of for patients with LACC, is external beam radiotherapy followed by intracavitary brachytherapy offered with concurrent platinum based chemotherapy[11].

Although there have been significant advancements made in screening, workup, and management of patients with cervical cancer in Sub-Saharan Africa, further improvement is still needed. Enrollment in clinical trials remains a struggle[12]. Cervical cancer research in African countries has increased steadily over the past decade, yet several countries in Africa reside with little to no research ever conducted on cervical cancer[13]. Therefore, availability of data on patterns of care and outcomes in Sub-Saharan Africa is both limited and lacking.

This study describes the real-world treatments patterns for patients with LACC in South Africa compared to treatment guideline recommendations and evaluates factors related to the outcomes.

PATIENTS AND METHODS

Patient inclusion

We retrospectively evaluated women with histologically confirmed LACC, clinically staged according to the International Federation of Gynecology and Obstetrics (FIGO) (stages IB2-IVA)[14], and eligible for treatment with curative intent between July 2013 - July 2018 treated at Groote Schuur Hospital (GSH) in Cape Town, South Africa. Patients who underwent primary surgery and age <18 years were excluded from the study.

Data collection

The initial patient demographics and clinical data were collected from medical records, which included the following characteristics: age, marital status, physical examinations, vaginal pelvic examinations, any past anti-retroviral treatment (ART), and histological sub type. Baseline laboratory investigations included haemoglobin (Hb), HIV status, and cluster of differentiation (CD4) counts. Baseline

imaging included chest x-rays and abdominal ultrasounds. All patients were staged by both a gynaecological and radiation oncologist according to FIGO 2009 staging system[14].

Treatment

Standard curative treatment at the time of the study period entailed external beam radiotherapy (EBRT) with or without chemotherapy followed by intracavitary brachytherapy (ICT). EBRT delivered to the pelvis was a total dose of 46 Gy in 23 fractions using 3D conformal radiotherapy technique or Volumetric Modulated Arc Therapy (VMAT) and 6MV or 18MV energy, 4 field beam arrangement from a linear accelerator. Concurrent cisplatin (40 mg/m²) capped at 60mg was given weekly for four to five cycles during EBRT unless the estimated glomerular filtration rate was <60 mL/min/1.73 m² or poor performance status or hydronephrosis was present. Alternatively, carboplatin area under the curve (AUC 2) was administered weekly if cisplatin was contraindicated.

Following completion of the EBRT, an additional 14 to 25 Gy was delivered through high dose-rate intracavitary brachytherapy in two to four fractions of 5 to 7 Gy per fraction. At the time of the study, no image-guided brachytherapy was available. Patients who were not suitable for brachytherapy received EBRT boost 18 Gy. The total dose delivered for all patients was calculated as a combined dose of 2 Gy per fraction radiobiologic equivalence (EQD2) [15] as recommended by American Brachytherapy Society[16].

All patients with LACC are routinely tested for HIV at first presentation. Patients who were newly diagnosed with HIV, those who were not on treatment, or had defaulted treatment were initiated ART either just before or as soon as possible after commencing radiation treatment. Standard first-line therapy for HIV at the time of the study was co-formulated Tenofovir, Emtricitabine, and Efavirenz. Data on viral load, compliance, medication changes, and ART toxicities were unable to be recorded for this study.

Response was assessed by subjective and objective response 3 months after treatment completion. For the next 1-2 years, they were followed up every 3 – 6 months and then for the following 3 - 4 years for every 6 - 12 months. Objective

response was graded as complete response, residual disease, locoregional recurrence, or progressive disease[17]. During follow-up, response and toxicities were assessed clinically and managed appropriately.

Outcome

Primary outcome for the study was overall survival (OS) and factors associated with survival in patients with LACC treated with curative intent. OS was defined as the time from the end of treatment until death or until last contact with the patient.

Secondary outcome was disease free survival (DFS) and factors associated with recurrence free survival. DFS was defined as the time from end of treatment time until disease recurrence including both local recurrence and distant metastases.

Statistical Analysis

The primary analytic objective was to evaluate the OS, DFS and factors associated with improved survival in women with LACC. The OS and DFS were evaluated using the Kaplan–Meier method. The log-rank tests were used to compare these survival rates among subgroups. Factors associated with these outcomes were analyzed using Cox proportional hazards regression modeling. Multivariate logistic regression modeling was performed adjusting for age, stage, and HIV status to assess factors associated with chemotherapy receipt and baseline hemoglobin ≥ 10 g/dL. Statistical significance was considered with a p-value of <0.05 .

Ethics

Ethics approval was obtained from the University of Cape Town (UCT) human ethics committee.

RESULTS

Patient Characteristics

A total of 278 women were eligible to participate in this study, of which 28.4% (n=79) were WLWH and 71.6% (n=199) were women without HIV. Patient demographics, clinical, and treatment characteristics are summarized in Table 1. Among the WLWH, median CD4 count was 441 cells/ μ L (IQR; 315-581) and all had been initiated ART prior to commencing treatment. Median age at diagnosis

was 51 years (IQR; 41-60). Among all the patients in this study, 35% had a smoking history. . Most patients had stage II and stage III disease accounting for 48.6% (n=135) and 45.6% (n=126) respectively. Most women, 89.5% (n= 246) had squamous cell carcinoma (SCC). Median Hb evaluated at baseline laboratory investigation for all patients was 11.3 g/dl (IQR; 9.70 - 12.8).

Chemoradiotherapy

Sixty four % (n=180) of the patients received chemoradiation (CRT) with a median of 5 cycles of concurrent chemotherapy. Median EQD2 dose was 74.5 Gy (IQR; 69.00-80.9) and 13 patients (4.5%) received external beam boost in place of intracavitary brachytherapy.

Overall survival and disease-free survival for entire population

One hundred and seventeen (61.5%) patients were alive and well at the end of study period, 28 (10.1%) were lost to follow-up, and 79 (28.4%) died. Causes of death include: 19 deaths (24%) due to local recurrence, 27 (34.2%) deaths due to metastatic disease, 2 (2.5%) deaths due to HIV related illness, 24 deaths (30.4%) due to unknown causes, and 7 deaths (8.9%) due to unrelated/accidental cause. Sixty-four patients (23%) were noted to have a disease recurrence Table 2. Median follow-up in the whole cohort was 18 months (23 months for living patients).

The 2-year OS and DFS rates for the entire population were 73.3% and 72.3% respectively. Factors associated with improved OS in the cohort were receipt of chemotherapy (Hazard Ratio [HR] 0.32; 95% CI 0.14-0.69, p=0.004) and higher baseline Hb (HR 0.86; 95% CI 0.77-0.98, p=0.018) (Table 3). Higher baseline Hb (HR 0.88; 95% CI 0.77-1.00, p=0.047) was associated with improved DFS in the cohort (Table 4).

Factors associated with chemotherapy receipt and Hb \geq 10 g/dL

On multivariate logistic regression, adjusting for age, stage, and HIV status showed that patients with stages III-IVA disease were less likely to receive chemotherapy (Odds Ratio [OR] 48.17; 95% CI 20.59-128.95, p<0.001) and less likely to have Hb \geq 10 g/dL (OR 0.20; 95% CI 0.10-0.36, p<0.001) as illustrated in

Table 5 and Table 6 respectively. Stage III/IVA patients who received chemotherapy were 38 (29.9%) vs. 89 (70.1%) who did not.

Overall survival and disease-free survival for CCRT vs RT alone

The 2-year OS was 87.4% for patients who received CCRT vs. 52.8% for those who received radiotherapy alone (log-rank, $p < 0.001$). The 2-year DFS was 80.2% for patients who received CCRT vs 58.3% for those who received radiotherapy alone (log-rank, $p < 0.001$).

DISCUSSION

In this retrospective study of women with locally advanced cervical cancer at a tertiary center in South Africa, a total of 278 women were eligible to participate. Factors associated with improved OS in the cohort were receipt of chemotherapy and higher baseline Hb. In our study most patients with stage III/IV did not receive concurrent chemotherapy, which was detrimental to their survival.

Our results are similar to cited literature showing significant survival benefit of concurrent chemotherapy (HR 0.32, $p = 0.004$) in patients with LACC. Similar studies have emphasized the importance of platinum-based regimens as a crucial component of treatment. Several meta – analysis conducted have shown CCRT is associated with improved outcomes, including overall survival (OS), disease free survival (DFS) and locoregional control rates[17-19] .

The current recommended treatment guidelines in South Africa for patients with LACC, International Federation of Gynecology and Obstetrics (FIGO) 2009 stage IB2-IVA[14, 20] is external beam radiotherapy (EBRT) followed by intracavitary brachytherapy (ICT) administered concurrently with platinum-based chemotherapy. This is now standard practice and therefore does not substantially differ from the guidelines developed by the FIGO[11, 20] or other available guidelines in other countries[21-24]. Brachytherapy is essential to include when delivering definitive CCRT [25-28].

Even with the current treatment guidelines supporting the need for CCRT for patients with LACC, this has been a challenge in most African countries. A study conducted in Zambia by Sibusiso M. et al[29] illustrated that full and timely

cisplatin dose was administered to only 26% of their patients with LACC. A study conducted in Zimbabwe by Nyamhunga A. et al[30] in patients FIGO stage IIIB found that only 128 (37%) of 346 patients received CCRT mainly attributed to financial barrier. Both of these studies reported insufficient use of concurrent chemotherapy in the African context. Similarly, in our study we found that in the entire population, 64.7% (n=180) received chemotherapy while 36.3% (n=98) did not. In our study receipt of chemotherapy was found to be significantly improve the OS (HR 0.32; 95% CI 0.14-0.69, p=0.004).

One explanation as to why these patients with stage III/IV disease did not receive chemotherapy may be due to some controversial evidence in certain studies that showed little to no benefit of CCRT over RT alone hence negating the need for chemotherapy. A study conducted by Chen et al[31] did not show a survival benefit of CCRT with weekly cisplatin and high dose intracavitary brachytherapy over RT alone for stage II–III cervical cancer. Another study conducted Pearcey et al[32] demonstrated no significant difference found in progression free survival (p=0.33) and in the 3- and 5-year survival rates which was found (69% vs. 66%) and (62% vs. 58%), CCRT vs. RT respectively (p=0.42). Furthermore, a study conducted in India by Srivastava K et al[33] also demonstrated no improvement in outcome seen with addition of cisplatin. An alternate explanation may be further highlighted by some studies that emphasized greater benefit for patients with early stage I/II disease vs. stage III/IV disease. The meta-analysis conducted by Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC) [19] demonstrated a benefit of only 3% shown in stages IIIB and IVA. Hence, the role of chemotherapy was lessened in patients with more advanced disease. However, a study conducted by Green J et al compared treatment of patients with LACC with radiation therapy alone vs CCRT, showed that CCRT has been shown to improve both overall and progression-free survival in this population, and may also reduce local and distant recurrence[34].

Higher baseline Hb has been associated with increased survival for patients with LACC in our study. Adverse impact of low Hb levels in patients undergoing radiotherapy (RT) was demonstrated in various solid tumors including cervical cancer[35-43]. The impact of anaemia on survival has also been evaluated in trials that have shown haemoglobin levels ≥ 12 mg/L during radiotherapy to be a significant prognostic factor for successful radiotherapy and disease-free

survival[44]. A study conducted by Mayr, N.A, et al[45] suggests that the compounded effects of Hb level and tumor perfusion during RT influence the radio responsiveness and survival in cervical cancer patients[46]. A study conducted in Botswana by George J et al[47] demonstrated improved survival was largely associated with a higher Hb. Similarly, in our study a higher baseline Hb ≥ 10 g/dL was associated with increased OS (HR 0.86; 95% CI 0.77-0.98, $p=0.018$) and DFS (HR 0.88; 95% CI 0.77-1.00, $p=0.047$).

Further evaluation showed a direct relationship between patients with more advanced disease and low Hb. We found patients with stage III/IVA disease had lower Hb of <10 g/dL in comparison to the entire population and on multivariate logistic regression adjusting for age, stage, and HIV status, this patients were less likely to receive chemotherapy (OR 0.20;95% CI 0.10-0.36, $p<0.001$). This may be a possible explanation as to why patients with more advance disease stage III/IVA may have not received chemotherapy. This raises a question concerning the role of blood transfusion in these patients to necessitate chemotherapy receipt. However, the role of blood transfusion in anemic patients with LACC treated with radiotherapy has been controversial. Santin A. D, et al[48] study results suggest that routine blood transfusion of anemic cervical cancer patients does not improve outcomes. Furthermore, , a study conducted by Zayed S et al[49] on red blood cell transfusion practices for patients with cervical cancer undergoing radiotherapy indicated baseline Hb was highly predictive of outcome and hence, blood transfusion appeared to overcome the negative prognostic effects of low presenting Hb levels. This hypothesis is further supported by Kapp Karin S et al[9], who evaluated the impact of routine transfusion in patients with hemoglobin level (Hb) <11 g/dL, multivariate analysis showed a therapeutic benefit for patients whose Hb was corrected. Therefore, , further studies are strongly warranted to confirm this hypothesis.

Our study indicated no difference in survival between HIV-infected and HIV-uninfected patients (HR 1.13; 95% CI 0.64-1.99, $p=0.668$)) with LACC. WLWH had well-managed HIV with majority initiating ART before starting treatment. These results are supported by studies conducted by Shah S. et al[50] that indicated no differences in treatment outcomes including overall toxicity, treatment response, or mortality, on the basis of HIV infection status. These results suggest CCRT should continue to be the treatment of choice for locally invasive cervical cancer

regardless of HIV status. Similar results were found by Grover et al[51] in a large prospective, observational cohort study of women with locally advanced cervical cancer beginning curative CRT in Botswana in which they did not identify differences in 2-year OS rates between WLWH and taking ART and women without HIV.

The study is not without its limitations. As a retrospective study, the overall number of patient may have not be adequately captured due to lack of proper record keeping. We were unable to ascertain why a greater proportion of patients with stage III/IV disease did not receive chemotherapy. The study data does not include clinical decision-making regarding the type of radiotherapy received and thus cannot account for provider bias implemented when prescribing brachytherapy versus a boost. Further, we did not include toxicity data, which is an important predictor of survival. Another important consideration is the outdated staging, which was done according to 2009 FIGO criteria Despite these limitation, this study remains the first of its kind, both characterizing the cervical cancer patients in South Africa and detailing the treatment regimens received.

Further research is warranted to further reinforce the body of evidence available especially in the African context. This will allow further evaluation of the outcomes in the developed and developing counties, and therefore allow us to address any challenges that may be faced.

Conclusion

The results our study reinforce the body of evidence confirming that CCRT improves therapeutic outcomes and survival in patients with locally advanced cervical cancer. In this study, patients with stage III/IVA treated with curative intent did not receive chemotherapy, which was detrimental to their survival. Therefore, if performance status allows, it is essential for all to receive chemotherapy. However, patients with low Hb may require transfusion to necessitate they receive chemotherapy.

References

1. Sung, H., et al., *Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries*. CA: A Cancer Journal for Clinicians, 2021. **71**(3): p. 209-249.
2. Parkin, D., et al., *Cancer in Africa*. Epidemiology and prevention, 2003. **4**: p. 268-276.
3. South Africa Human Papillomavirus and Related Cancers, F.S., 2018.
4. Franco, E.L., E. Duarte-Franco, and A. Ferenczy, *Cervical cancer: epidemiology, prevention and the role of human papillomavirus infection*. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne, 2001. **164**(7): p. 1017-1025.
5. Jedy-Agba, E., et al., *Trends in cervical cancer incidence in sub-Saharan Africa*. British Journal of Cancer, 2020. **123**(1): p. 148-154.
6. Williamson, A.L., *The Interaction between Human Immunodeficiency Virus and Human Papillomaviruses in Heterosexuals in Africa*. J Clin Med, 2015. **4**(4): p. 579-92.
7. Saslow, D., et al., *American Cancer Society guideline for the early detection of cervical neoplasia and cancer*. CA Cancer J Clin, 2002. **52**(6): p. 342-62.
8. Massad, L.S., et al., *Prevalence and predictors of squamous cell abnormalities in Papanicolaou smears from women infected with HIV-1*. Women's Interagency HIV Study Group. J Acquir Immune Defic Syndr, 1999. **21**(1): p. 33-41.
9. Kapp, K.S., et al., *Evaluation of the effect of routine packed red blood cell transfusion in anemic cervix cancer patients treated with radical radiotherapy*. International Journal of Radiation Oncology*Biophysics, 2002. **54**(1): p. 58-66.
10. Yimer, N.B., et al., *Cervical cancer screening uptake in Sub-Saharan Africa: a systematic review and meta-analysis*. medRxiv, 2021: p. 2020.12.26.20248864.
11. Benedet, J.L., et al., *FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology*. Int J Gynaecol Obstet, 2000. **70**(2): p. 209-62.
12. Burt, L.M., et al., *Cervix Cancer in Sub-Saharan Africa: An Assessment of Cervical Cancer Management*. JCO Global Oncology, 2021(7): p. 173-182.
13. Finocchiaro-Kessler, S., et al., *Cervical cancer prevention and treatment research in Africa: a systematic review from a public health perspective*. BMC Women's Health, 2016. **16**(1): p. 29.
14. Pecorelli, S., L. Zigliani, and F. Odicino, *Revised FIGO staging for carcinoma of the cervix*. Int J Gynaecol Obstet, 2009. **105**(2): p. 107-8.
15. Nag, S. and N. Gupta, *A simple method of obtaining equivalent doses for use in HDR brachytherapy*. Int J Radiat Oncol Biol Phys, 2000. **46**(2): p. 507-13.
16. Viswanathan, A.N., et al., *American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part II: high-dose-rate brachytherapy*. Brachytherapy, 2012. **11**(1): p. 47-52.
17. Miller, A.B., et al., *Reporting results of cancer treatment*. Cancer, 1981. **47**(1): p. 207-14.
18. Green, J.A., et al., *Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis*. The Lancet, 2001. **358**(9284): p. 781-786.
19. Cochrane Database of Systematic Reviews 2010, I.A.N.C., *Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis*. Cochrane Database Syst Rev, 2010. **2010**(1): p. Cd008285.

20. Bhatla, N., et al., *Cancer of the cervix uteri*. International Journal of Gynecology & Obstetrics, 2018. **143**(S2): p. 22-36.
21. Kang, Y.-J., et al., *Effect of changes in treatment practice on survival for cervical cancer: results from a population-based study in Manitoba, Canada*. BMC Cancer, 2015. **15**(1): p. 642.
22. Morris, M., et al., *Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer*. N Engl J Med, 1999. **340**(15): p. 1137-43.
23. Cibula, D., et al., *The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines for the management of patients with cervical cancer*. Radiotherapy and Oncology, 2018. **127**(3): p. 404-416.
24. Eifel, P.J., et al., *Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: An update of Radiation Therapy Oncology Group Trial (RTOG) 90-01*. Journal of Clinical Oncology, 2004. **22**(5): p. 872-880.
25. Han, K., et al., *Trends in the Utilization of Brachytherapy in Cervical Cancer in the United States*. International Journal of Radiation Oncology*Biography*Physics, 2013. **87**(1): p. 111-119.
26. Peterit, D.G., et al., *Brachytherapy: Where has it gone?* Journal of Clinical Oncology, 2015. **33**(9): p. 980-982.
27. Sturdza, A., et al., *Image guided brachytherapy in locally advanced cervical cancer: Improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study*. Radiotherapy and Oncology, 2016. **120**(3): p. 428-433.
28. Tanderup, K., et al., *Curative Radiation Therapy for Locally Advanced Cervical Cancer: Brachytherapy Is NOT Optional*. International Journal of Radiation Oncology*Biography*Physics, 2014. **88**(3): p. 537-539.
29. Mdletshe, S., H. Munkupa, and K. Lishimpi, *Acute toxicity in cervical cancer HIV-positive vs. HIV-negative patients treated by radical chemo-radiation in Zambia*. Southern African Journal of Gynaecological Oncology, 2016. **8**(2): p. 37-41.
30. Nyamhunga, A., et al., *Chemoradiation in Stage IIIB Cancer of the Uterine Cervix: A Review of the Zimbabwean Experience*. JCO Global Oncology, 2020(6): p. 1554-1564.
31. Chen, S.W., et al., *Concurrent weekly cisplatin plus external beam radiotherapy and high-dose rate brachytherapy for advanced cervical cancer: a control cohort comparison with radiation alone on treatment outcome and complications*. Int J Radiat Oncol Biol Phys, 2006. **66**(5): p. 1370-7.
32. Pearcey, R., et al., *Phase III Trial Comparing Radical Radiotherapy With and Without Cisplatin Chemotherapy in Patients With Advanced Squamous Cell Cancer of the Cervix*. Journal of Clinical Oncology, 2002. **20**(4): p. 966-972.
33. Srivastava, K., et al., *Concurrent chemoradiation versus radiotherapy alone in cervical carcinoma: A randomized phase III trial*. Asia-Pacific Journal of Clinical Oncology, 2013. **9**(4): p. 349-356.
34. Green, J., et al., *Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix*. Cochrane Database Syst Rev, 2005(3): p. Cd002225.
35. Caro, J.J., et al., *Anemia as an independent prognostic factor for survival in patients with cancer: a systemic, quantitative review*. Cancer, 2001. **91**(12): p. 2214-21.
36. Chatani, M., et al., *High-dose rate intracavitary irradiation for carcinoma of the uterine cervix. The adverse effect of treatment prolongation*. Strahlenther Onkol, 1997. **173**(7): p. 379-84.
37. Dunst, J., et al., *Anemia in cervical cancers: impact on survival, patterns of relapse, and association with hypoxia and angiogenesis*. Int J Radiat Oncol Biol Phys, 2003. **56**(3): p. 778-87.
38. Fyles, A.W., et al., *Prognostic factors in patients with cervix cancer treated by radiation therapy: results of a multiple regression analysis*. Radiother Oncol, 1995. **35**(2): p. 107-17.
39. Serkies, K., A. Badzio, and J. Jassem, *Clinical relevance of hemoglobin level in cervical cancer patients administered definitive radiotherapy*. Acta Oncologica, 2006. **45**(6): p. 695-701.

40. Girinski, T., et al., *Prognostic value of hemoglobin concentrations and blood transfusions in advanced carcinoma of the cervix treated by radiation therapy: results of a retrospective study of 386 patients*. *Int J Radiat Oncol Biol Phys*, 1989. **16**(1): p. 37-42.
41. Karolewski, K., et al., *Prognostic significance of pretherapeutic and therapeutic factors in patients with advanced cancer of the uterine cervix treated with radical radiotherapy alone*. *Acta Oncol*, 1999. **38**(4): p. 461-8.
42. Logsdon, M.D. and P.J. Eifel, *Figo IIIB squamous cell carcinoma of the cervix: an analysis of prognostic factors emphasizing the balance between external beam and intracavitary radiation therapy*. *Int J Radiat Oncol Biol Phys*, 1999. **43**(4): p. 763-75.
43. Pedersen, D., et al., *Prognostic value of pretreatment factors in patients with locally advanced carcinoma of the uterine cervix treated by radiotherapy alone*. *Acta Oncol*, 1995. **34**(6): p. 787-95.
44. Thomas, G., *The effect of hemoglobin level on radiotherapy outcomes: the Canadian experience*. *Semin Oncol*, 2001. **28**(2 Suppl 8): p. 60-5.
45. Mayr, N.A., et al., *Synergistic effects of hemoglobin and tumor perfusion on tumor control and survival in cervical cancer*. *Int J Radiat Oncol Biol Phys*, 2009. **74**(5): p. 1513-21.
46. Grogan, M., et al., *The importance of hemoglobin levels during radiotherapy for carcinoma of the cervix*. *Cancer*, 1999. **86**(8): p. 1528-1536.
47. George, J., et al., *Stage and Outcomes of Cervical Cancer With or Without HIV Infection in Botswana 2013-2020*. *International Journal of Radiation Oncology*Biological*Physics*, 2021. **111**(3, Supplement): p. e612-e613.
48. Santin, A.D., et al., *Influence of Allogeneic Blood Transfusion on Clinical Outcome during Radiotherapy for Cancer of the Uterine Cervix*. *Gynecologic and Obstetric Investigation*, 2003. **56**(1): p. 28-34.
49. Zayed, S., et al., *Red Blood Cell Transfusion Practices for Patients With Cervical Cancer Undergoing Radiotherapy*. *JAMA Network Open*, 2021. **4**(4): p. e213531-e213531.
50. Shah, S., et al., *Differences in Outcomes of Chemoradiation in Women With Invasive Cervical Cancer by Human Immunodeficiency Virus Status: A Systematic Review*. *Pract Radiat Oncol*, 2021. **11**(1): p. 53-65.
51. Grover, S., et al., *Impact of Human Immunodeficiency Virus Infection on Survival and Acute Toxicities From Chemoradiation Therapy for Cervical Cancer Patients in a Limited-Resource Setting*. *Int J Radiat Oncol Biol Phys*, 2018. **101**(1): p. 201-210.

Table 1
Patient demographic, clinical, and treatment characteristics

Demographics	All N=287 (100%)
Age (years)	51 (41-60)
Smoking, yes	97 (35.0%)
Marital status	

Single	94 (33.8%)
Married	102 (36.7%)
Divorced	32 (11.5%)
Widowed	49 (17.6%)
Unknown	1 (0.4%)
Tumour characteristics	
Histology	
Squamous	246 (89.5%)
Adenocarcinoma	18 (6.5%)
Other	11 (4.0%)
Stage	
I	16 (5.8%)
II	135 (48.6%)
III-IV	127 (45.6%)
Baseline investigation	
CD4 (cells/mm ³)	441 (315-581)
Hb (g/dL)	11.3 (9.70-12.8)
Creatinine (μmol/L)	79 (69-81.8)
Treatment characteristics	
Concurrent chemotherapy	180 (64.8%)
Number chemo cycles	5 (4-5)

Completed brachytherapy	265 (95.5%)
Received external beam boost	13 (4.5%)
EQD2 (Gy)	74.5 (69-80.9)

Abbreviations: CD4 - cluster of differentiation 4 (T cells); Hb – Haemoglobin; HIV - Human Immunodeficiency Virus; IQR - interquartile range; EQD2 = Equivalent dose in 2 Gy fractions. Values are presented as number (percentage) or median (interquartile range).

Table 2

Patient outcomes

Characteristic	Total N=278 (100%)
Treatment outcome	
Alive and well	171 (61.5%)
Lost to follow up	28 (10.1%)
Dead	79 (28.4%)
Recurrence	
Yes	64 (23%)
No	214 (77%)
Cause of death	
Local disease	19 (24%)
Metastatic disease	27 (34.2%)

HIV related	2 (2.5%)
Other	7 (8.9%)
Unknown	24 (30.4%)
Died	
Yes	199 (71.6%)
No	79 (28.4%)

Table 3

Factors associated with overall survival among study participants: univariate and multivariate analyses [N=278]

Characteristics		All	OS, UVA HR (95% CI)	OS, MVA HR (95% CI)
Age (years)	20-39	51	--	--
	40-59	142	0.77 (0.44-1.35, p=0.359)	1.03 (0.56-1.87 p=0.928)
	>60	67	0.79 (0.40-1.52, p=0.476)	1.27 (0.59-2.73 p=0.536)
HIV status	HIV-	199	--	--

	HIV+	79	1.73 (1.09-2.75, p=0.020)*	1.39 (0.82-2.33, p=0.221)
Stage	I-II	151	--	--
	III-IV	127	3.09 (1.94-4.91, p<0.001)*	0.96 (0.43-2.15, p=0.927)
Hb	Mean	11.2	0.84 (0.76-0.93, p=0.001)*	0.86 (0.76-0.97, p=0.015)*
Chemotherapy received	No	98	--	--
	Yes	180	0.26 (0.17-0.42, p<0.001)*	0.32 (0.14-0.69, p=0.004)*
EQD2	Mean	73.9	0.98 (0.96-1.00, p=0.091)	0.98 (0.96-1.01, p=0.182)

Abbreviations: HIV, human immunodeficiency virus; Hb, Hemoglobin; IQR, interquartile range; EQD2, equivalent dose in 2 Gy fractions; OS, Overall Survival, UVA, Univariable Analysis; MVA, Multivariable Analysis.

*Statistically significant

**Multivariate logistic regression adjusting for: age, stage, Hb, receipt of chemotherapy, EQD2 and HIV status

Table 4

Factors associated with on disease free survival among study participants: univariate and multivariate analyses [N=278]

Characteristics		All	DFS, UVA HR (95% CI)	DFS, MVA HR (95% CI)
HIV Status	HIV-	199	--	--

	HIV+	79	1.68 (1.00-2.81, p=0.050)	1.13 (0.64-1.99, p=0.668)
Stage	I-II	151	--	--
	III-IV	127	3.44 (2.04-5.82, p<0.001)*	2.04 (0.92-4.52, p=0.080)
Age (years)	20-39	51	--	--
	40-59	142	0.64 (0.37-1.14, p=0.131)	0.84 (0.46-1.52, p=0.560)
	>60	67	0.29 (0.12-0.70, p=0.006)*	0.48 (0.19-1.24, p=0.132)
Hb	Mean	11.2	0.81 (0.73-0.91, p<0.001)*	0.88 (0.77-1.00, p=0.047)*
Chemotherapy received	No	98	--	--
	Yes	180	0.34 (0.20-0.55, p<0.001)*	0.59 (0.28-1.24, p=0.163)
EQD2	Mean	73.9	1.01 (0.98-1.03, p=0.721)	1.01 (0.98-1.04, p=0.490)

Abbreviations: HIV, human immunodeficiency virus; Hb, Hemoglobin; IQR, interquartile range; EQD2, equivalent dose in 2 Gy fractions; DFS, Disease Free Survival, UVA, Univariable Analysis; MVA, Multivariable Analysis.

*Statistically significant

**Multivariate logistic regression adjusting for: age, stage, Hb, receipt of chemotherapy, EQD2 and HIV status.

Table 5

Factors associated with chemotherapy receipt: univariate and multivariate analyses [N=278]

Chemo received		Yes	No	UVA OR (95% CI)	MVA OR (95% CI)
Age (years)	20-39	30 (58.8)	21 (41.2)	--	--
	40-59	97 (68.3)	45 (31.7)	0.66 (0.34-1.29, p=0.222)	1.19 (0.46-3.11, p=0.723)
	>60	43 (64.2)	24 (35.8)	0.80 (0.38-1.69, p=0.553)	1.15 (0.39-3.44, p=0.804)
Stage	I-II	142 (94.0)	9 (6.0)		
	III-IV	38 (29.9)	89 (70.1)	36.95 (17.87-85.10, p<0.001)*	48.17(20.59-128.95, p<0.001)*
HIV Status	HIV-	138 (69.3)	61 (30.7)	--	--
	HIV+	42 (53.2)	37 (46.8)	1.99 (1.17-3.41, p=0.012)*	2.32 (1.01-5.54, p=0.051)
Hb	Mean (SD)	11.4 (2.3)	10.8 (2.1)	0.88 (0.78-0.98 p=0.028)*	1.18 (0.99-1.40, p=0.063)

Abbreviations: HIV, human immunodeficiency virus; Hb, Hemoglobin; IQR, interquartile range; EQD2, equivalent dose in 2 Gy fractions; UVA, Univariable Analysis; MVA, Multivariable Analysis.

*Statistically significant

**Multivariate logistic regression adjusting for: age, stage, Hb and HIV status.

Table 6

**Factors associated with Hb \geq 10 g/dL: univariate and multivariate analyses
[N=278]**

Hb		<10	\geq 10	UVA OR (95% CI)	MVA OR (95% CI)
Age	20-39	22 (44.0)	28 (56.0)		
	40-59	37 (26.8)	102 (73.9)	2.23 (1.13-4.38, p=0.020)*	1.74 (0.81-3.70, p=0.153)
	60+	11 (17.5)	52 (82.5)	3.71 (1.61-9.02, p=0.003)*	3.30 (1.28-8.85 p=0.015)*
Stage	I-II	19 (13.3)	124 (86.7)		
	III-IV	56 (44.4)	70 (55.6)	0.19 (0.10-0.34, p<0.001)*	0.20 (0.10-0.36, p<0.001)*
HIV Status	HIV-	46 (23.7)	148 (76.3)	--	--
	HIV+	29 (38.7)	46 (61.3)	0.49(0.28-0.87, p=0.015)*	0.57 (0.29-1.12, p=0.099)

Abbreviations: HIV, human immunodeficiency virus; Hb, Hemoglobin; UVA, Univariable Analysis; MVA, Multivariable Analysis; OR, Odds Ratio.

*Statistically significant

**Multivariate logistic regression adjusting for: age, stage, and HIV status.