original reports abstract

Chemoradiation in Stage IIIB Cancer of the Uterine Cervix: A Review of the Zimbabwean Experience

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PURPOSE Cervical cancer remains the leading cause of cancer morbidity and mortality among Zimbabwean women. Many patients present with stage IIIB disease. Although definitive concurrent chemoradiation (CCRT) is the standard of care, there is a paucity of data on the effect(s) of this intervention in resource-constrained and high HIV-prevalence settings. We investigated the differences in CCRT initiation practices, tolerability, and outcomes in this group.

PATIENTS AND METHODS We performed a retrospective analysis of data from hospital records for patients with stage IIIB disease who were treated over a 2-year period at Parirenyatwa Group of Hospitals. Outcome measures were documented treatment-related adverse events and early clinical tumor response.

RESULTS One hundred twenty-eight (37%) of 346 patients received CCRT, and 65 (51%) of 128 patients were infected with HIV. CCRT was prescribed mostly in patients with less extensive disease—not involving lower third vaginal walls, minimal pelvic sidewall involvement ($P = .002$), and higher CD4$^+$ count ($P = .02$). Eighteen percent of recorded adverse events were high grade (≥ 3). One patient did not complete treatment, and 68.5% achieved complete clinical tumor response at 3 months post-CCRT. A higher proportion of complete clinical tumor response was noted in those patients who were young, HIV uninfected, had less extensive disease, CD4$^+$ of 500 cells/mm^3 or greater, received four or more cycles of chemotherapy, received brachytherapy, and had no treatment breaks.

CONCLUSION The study revealed that the use of CCRT to treat stage IIIB cervical cancer is low in Zimbabwe. Although several factors contribute, low CCRT uptake is mostly attributed to financial barriers. Well-selected patients tolerate the treatment and have good early clinical tumor response as expected. The role of CCRT for this patient group (and methods to make it available in resource-limited settings) must be further evaluated.

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INTRODUCTION

Carcinoma of the uterine cervix is the world's fourth most common cancer and cause of cancer death affecting women.[1] In lower Human Development Index settings, cervical cancer ranks second in incidence and mortality; however, it is the most commonly diagnosed cancer in 28 countries and the leading cause of cancer death in 42 countries. The majority of these are in sub-Saharan Africa, including Zimbabwe, and South Eastern Asia.[1] Incidence and mortality rates in lower- and middle-income countries are reported to be $> 85\%$ and $> 87\%$, respectively, with the highest regional rates observed in Africa and elevated mostly in Southern Africa.[1] Patients in these countries present late with advanced disease, which is not amenable to surgical intervention. When available and affordable, definitive concurrent chemoradiation (CCRT) takes a central role in the management of most of these patients.[2]

In Zimbabwe, cervical cancer accounts for 19% of yearly incident cancers.[3] Commonly, patients present late with advanced disease. Stage IIIB disease accounts for close to 48% of all incident cervical cancer cases yearly. A high HIV prevalence of 44% among patients with cervical cancer has been noted at our institute. HIV-infected patients tend to present at a younger age, with more advanced disease, and tend to have poor treatment tolerance and outcomes.[4] Squamous cell carcinoma is the most common histologic subtype, accounting for approximately 92% of cases, followed by adenocarcinoma and adenosquamous histologies, with 7% and 1% of cases, respectively. Furthermore, there is a slight dominance of moderately differentiated over poorly differentiated

ASSOCIATED CONTENT

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Definitive chemoradiation (CCRT) breakthrough studies for treatment of locally advanced cervical cancer (LACC) were conducted in well-resourced settings. Due to limited screening services, most patients present with more advanced disease in Zimbabwe compared with populations included in the studies. Is the CCRT being used and well-tolerated among stage IIIB patients in this low-resourced, high HIV prevalence setting?

Knowledge Generated

The use CCRT for stage IIIB cervical cancer is low in Zimbabwe. Patients tolerate CCRT well and have early clinical tumor response as expected.

Relevance

Weak screening programs, compounded with high HIV prevalence in the developing world are associated with more advanced disease at presentation and poorer outcomes. Local data to guide evidence-based management is limited. CCRT breakthrough studies in LACC were conducted in well-resourced countries. This study highlights how, in the local population, a low-resourced and high HIV prevalence setting, patients fare on these treatments.

histology, which is consistent with figures documented elsewhere in the literature.

Platinum-based CCRT for locally advanced cervical cancer (LACC) has been a standard treatment for decades.[5] A meta-analysis demonstrated that CCRT improves overall survival and progression-free survival, with absolute benefits of 10% and 13%, respectively, the effect being greater in trials that include a high proportion of patients with stage 1 and 2 disease.[6] CCRT also showed significant benefit for local recurrence and a suggestion of a benefit for distant recurrence. Acute hematologic and GI toxicities were significantly greater in the CCRT group.

Data are lacking on the utility and tolerability of CCRT in patients with LACC in Zimbabwe. The breakthrough studies from which CCRT was adopted as a standard treatment were conducted in a different population with different population characteristics and environment.[2] Moreover, the stage IIIB subgroup of patients were a minority in these studies. We investigated the uptake of CCRT as the treatment of choice as the primary outcome, and its tolerability and early clinical tumor response as secondary outcomes among our patients with stage IIIB cervical cancer. For the purposes of this study, clinical tumor response was defined as documented disease response by the reviewing physicians at 3 months post-CCRT, including findings on vaginal examination and imaging when available. Tolerability was measured by the occurrence, frequency, and grade of acute adverse events on treatment and the impact it had on treatment continuity.

Although CCRT is considered the standard of care for the management of stage IIIB cervical cancer, associated comorbidities, patients' general condition, and financial toxicity can affect its use as a treatment option much more in lower Human Development Index countries. Criteria should be set to guide physicians' selection between CCRT or radiotherapy only (RT) in such settings.

PATIENTS AND METHODS

Patients and Staging

Consecutive records of all patients with cervical cancer seen at Parirenyatwa Radiotherapy Centre from January 1, 2013, to December 31, 2014, were reviewed and stage IIIB cases were identified for analysis according to the eligibility criteria (Fig 1). Documented clinical findings by the consulting physicians and, if available, imaging results (chest X-rays and ultrasound scans of the abdomen and pelvis in most cases) were used for staging purposes. A coded data collection sheet was used to extract patient, disease, and treatment data from hospital records. Records from a total of 906 patients with cervical cancer were reviewed, of which 898 had histologic confirmation and 357 (40%) were stage IIIB. Eleven patients were excluded for insufficient data or previous treatment. On the basis of the treatment received, patients were grouped into CCRT, RT, and lost to follow-up (LTFU) groups. Adverse events during CCRT were scored and assessed using WHO criteria for grading of acute toxicity effects (Table 1). All patients analyzed were black Zimbabweans. Parirenyatwa Radiotherapy Centre was the only functional radiotherapy unit in Zimbabwe during this study period, and the country's economic status was stable and representative of the usual socioeconomic environment.

Laboratory Data

Weekly CBCs and metabolic panels were routinely done for patients on CCRT; therefore, captured results were accessible in medical records. Viral load tests were not routinely performed in these patients.

Treatment

The CCRT group consisted of patients who received pelvic external beam radiotherapy (EBRT) to a total dose of 46-50 Gy at 180-200 Gy per fraction per day. Treatment was administered 5 days per week, over 6-7 weeks, with weekly

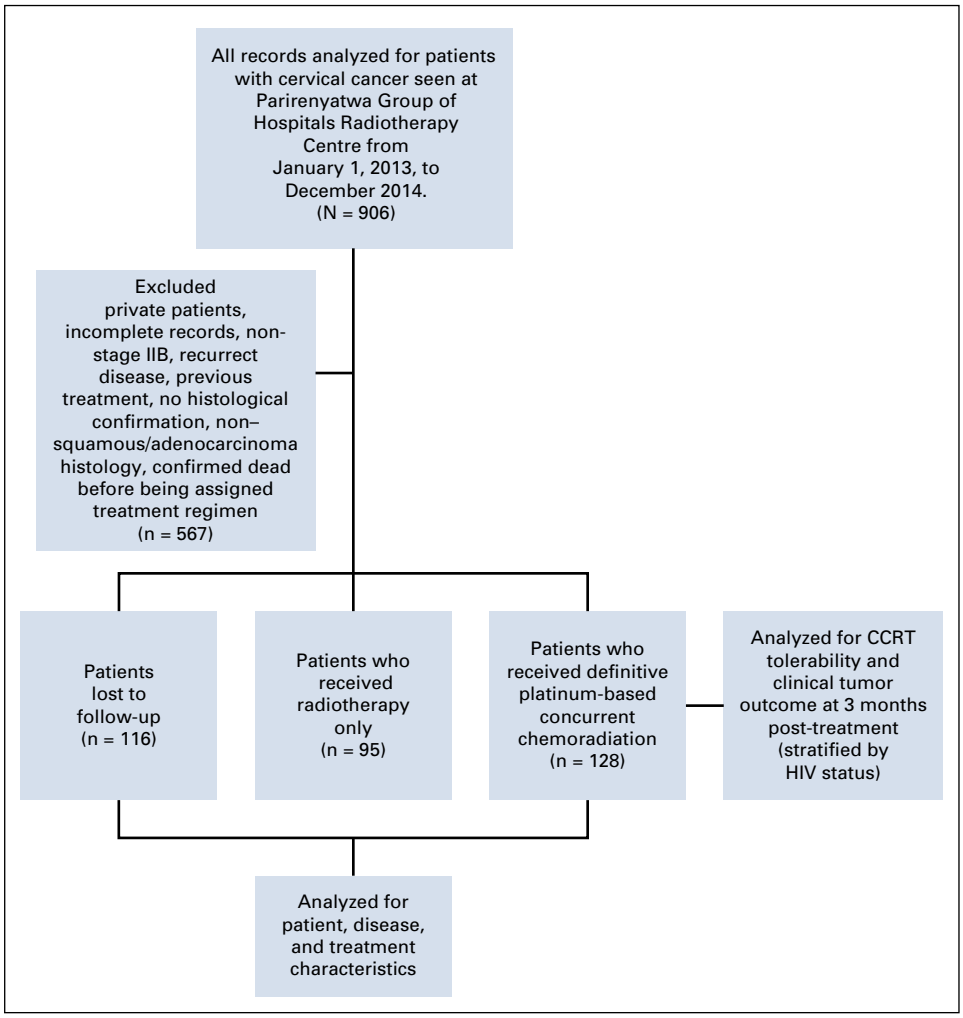

FIG 1. All consecutive records for patients with cervical cancer seen at Parirenyatwa Radiotherapy Centre during the study period were reviewed and stage IIIB cases were identified for analysis according to the eligibility criteria. Analysis for treatment tolerability and clinical tumor outcome was performed on patients who received definitive platinum-based concurrent chemoradiation, stratified by HIV status (n = 128).

concurrent cisplatin at a dose of 35-40 mg/m^2 or carboplatin at a dose of area under curve 2 and 3 to 4 high-dose rate brachytherapy insertions at 6-7 Gy per weekly insertion. Patients who were ineligible for brachytherapy received a total pelvic EBRT of 60 Gy over a period of 6-7 weeks. All radiotherapy was planned on the Eclipse Treatment Planning System and administered using three-dimensional conformal radiotherapy technique.

TABLE 1. WHO Criteria for Grading of Acute Toxic Effects

	Grade				
Effect	**0**	**1**	**2**	**3**	**4**
Hematologic					
Hemoglobin, mmol/L	6.8	5.6-6.7	4.9-5.8	4.0-4.9	< 4.0
Leukocytes (WBC)	4.9	3.0-3.9	2.0-2.9	1.0-1.9	< 1.0
Platelets	100	75-99	50-74	25-49	< 25
GI					
Nausea and vomiting	None	Nausea	Transient vomiting	Vomiting requiring therapy	Intractable vomiting
Diarrhea	None	Transient, two per day	Tolerable, more than two per day	Intolerable, requires therapy	Hemorrhagic plus dehydration
Genitourinary					
Dysuria	None	Intermittent	Persistent	Persistent with fever	Obstructive uropathy
Cutaneous	No change	Erythema	Dry desquamation	Moist desquamation, ulceration	Exfoliative dermatitis, necrosis

TABLE 2. Patient Characteristics in Different Treatment Groups for All Patients With Stage IIIB Disease

Variable	Chemoradiation Group (n = 128)	Radiotherapy Only Group (n = 95)	Lost to Follow-Up After First Visit (n = 116)	*P*
Median age, years (range)	51 (31-75)	53.0 (40-71)	51.2 (31-73)	.41
Residency				
Urban	53 (41.4)	36 (37.9)	40 (34.5)	
Rural	75 (58.6)	59 (62.2)	76 (65.5)	.43
Employment status				
Employed	15 (12)	4 (4)	3 (3)	
Unemployed	113 (88)	89 (96)	112 (97)	.02
Documented KPS, %				
< 80	3 (4)	12 (26)	23 (59)	
≥ 80	78 (96)	34 (74)	16 (41)	.07
HIV status				
Positive	65 (50.8)	43 (45.3)	51 (44.0)	
Negative	59 (46.1)	49 (51.6)	51 (44.0)	
Unknown	4 (3.1)	3 (3.1)	14 (12.0)	.15
Means of $CD4^+$ count, cells/mm^3 (± SD)	526 (± 223)	394 (± 336)	392 (± 227)	.02

NOTE. Data presented as No. (%) unless otherwise indicated.
Abbreviations: KPS, Karnofsky Performance Status; SD, standard deviation.

Neoadjuvant chemotherapy was administered in cases in which CCRT had to be delayed in qualifying patients because of machine downtime issues. These patients received a chemotherapy doublet of either cisplatin or carboplatin and paclitaxel at doses of 75 mg/m^2, area under curve 4-6 mg/mL per min and 175 mg/m^2, respectively, administered on day 1 of every 3 weeks up to six cycles. The effect of this intervention on CCRT outcomes was analyzed in this study.

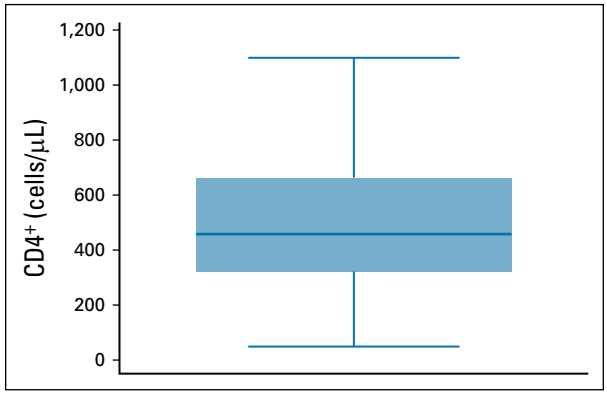

FIG 2. HIV-infected patients who received definitive chemoradiation for stage IIIB cervical cancer had a mean $CD4^+$ count of 526 cells/mm^3 (± 233 cells/mm^3 standard deviation) and a median of 534 cells/mm^3 (range, 155-1,099 cells/mm^3). This was higher than in patients who received radiotherapy only. The difference in the means of baseline $CD4^+$ was statistically significant (P = .02).

Statistical Methods

For normally distributed continuous variables, means and standard deviations were generated. Skewed continuous variables were described using medians and range. Associations between categorical variables were computed using χ^2 tests and the corresponding P values were used to test for association between categorical variables. A P value of $< .05$ was considered significant. Epi Info version 7 and Stata statistical packages were used for data analysis.

Ethical Considerations

Ethical approvals were obtained from the Joint Research and Ethics Committee of University of Zimbabwe and Parirenyatwa Group of Hospitals (JREC/3/16).

RESULTS

Patient and Treatment Characteristics

A total of 346 patients with stage IIIB cervical cancer were evaluated for patient and disease characteristics. One hundred ninety-three (55.7%) of 346 patients were prescribed CCRT, abd 128 (66.3%) of 198 patients eventually received this treatment. Thirty (8.7%) of 346 patients were prescribed RT treatment from the initial consultation. One hundred twenty-eight patients who received CCRT were eligible for analysis on CCRT tolerability and outcome (Fig 1).

Characteristics for all patients with stage IIIB disease seen during the study period are highlighted in Table 2. There was an association between the type of treatment received and patient characteristics, which included employment

TABLE 3. Disease Characteristics in Different Treatment Groups for All Patients With Stage IIIB Disease

Variable	Chemoradiation Group (n = 128)	Radiotherapy Only Group (n = 95)	Lost to Follow-Up After First Visit (n = 116)	*P*
Histologic subtype				
Squamous	118 (92.2)	88 (92.6)	109 (94)	
Adenocarcinoma	9 (7)	5 (5.3)	7 (6)	
Adenosquamous	1 (0.8)	2 (2.1)	0 (0.00)	.57
Tumor differentiation				
Poorly	60 (46.9)	49 (51.6)	58 (50)	
Moderately	63 (49.2)	44 (46.3)	54 (46.6)	
Well	5 (3.9)	2 (2.1)	4 (3.4)	.92
Tumor size, cm	(n = 110)	(n = 81)	(n = 69)	
< 7	62 (56.4)	39 (48.1)	39 (56.5)	
≥ 7	48 (43.6)	42 (51.9)	30 (43.5)	.46
PSW				
Involved	115 (89.8)	86 (90.5)	103 (88.8)	
Uninvolved	13 (10.2)	9 (9.5)	13 (11.2)	.92
PSW laterality	(n = 115)	(n = 86)	(n = 103)	
Unilateral	67 (58.3)	38 (44.2)	36 (35)	
Bilateral	48 (41.7)	48 (55.8)	67 (65)	.002
Lower third vagina				
Involved	59 (46.1)	62 (65.3)	77 (66.4)	
Uninvolved	69 (53.9)	33 (34.7)	39 (33.6)	.002
Hydronephrosis				
Present	55 (43)	64 (67.4)	63 (54.3)	
Absent	73 (57)	29 (30.5)	27 (23.3)	
Unknown	0 (0)	2 (2.1)	26 (22.4)	.06
Hydronephrosis laterality	(n = 55)	(n = 64)	(n = 63)	
Unilateral	38 (69.1)	32 (50)	31 (49.2)	
Bilateral	17 (30.9)	32 (50)	32 (50.8)	.06

NOTE. Data presented as No. (%) unless otherwise indicated.
Abbreviation: PSW, pelvic side wall involvement.

status ($P = .02$) and CD4$^+$ count ($P = .02$). The association with performance status, however, was not significant ($P = .07$). One third of all patients were LTFU after the first visit. Of 223 patients who received treatment, 128 (57.3%) received CCRT and 95 (42.6%) received RT.

Median age for the CCRT, RT, and LTFU groups were 51 years (range, 31-75 years), 53 year (range, 40-71 years), and 51 years (range, 31-73 years), respectively. A greater proportion of patients in the CCRT group were younger than age 50 years compared with the RT group. Fifty-nine percent of patients on CCRT lived in rural areas and 88% were unemployed. The association of employment status and treatment received was statistically significant ($P = .02$). Sixty-five (52%) of 124 patients on CCRT with documented HIV status were infected with HIV. There was no association between HIV status and treatment received across the different groups ($P = .15$). Younger patients dominated the HIV-infected group (68% were age ≤ 50 years and 5% were older than age 60 years).

Ninety-one percent of HIV-infected patients on CCRT had documented baseline CD4$^+$ counts, with a mean baseline of 526 cells/mm^3 (SD, ± 233 cells/mm^3) and a median of 534 cells/mm^3 (range, 155-1,099 cells/mm^3). CD4$^+$ counts in the RT only group were lower, with a mean baseline CD4$^+$ count of 394 cells/mm^3 (SD, ± 336 cells/mm^3) and a median of 176 cells/mm^3 (range, 24-1,141 cells/mm^3). The difference in the means of baseline CD4$^+$ counts between treatment groups was statistically significant ($P = .02$). Figure 2 illustrates the distribution of the CD4$^+$ counts in this group. Ninety-nine percent of HIV-infected patients on CCRT were on combination antiretroviral therapy (cART). Proportions of patients on tenofovir-, stavudine-, and

zidovudine-based regimens were 89%, 8% and 3%, respectively, combined with either nevirapine or efavirenz.

Four percent of patients in the CCRT group, consisting mostly of those infected with HIV, had a baseline Karnofsky Performance Status (KPS) of less than 80%. KPS values in the RT only group were lower, with 26% less than the score of 80%. However, the difference between the two groups was not statistically significant ($P = .07$)

Disease Characteristics

Squamous cell carcinoma histology constituted 92.2% of patients in the CCRT group, 7.0% had adenocarcinoma, and 0.8% had adenosquamous histologies. Poorly, moderately, and well-differentiated histology constituted 46.9%, 49.2%, and 3.9%, respectively. Bilateral pelvic side wall involvement was present in 41.7% and 55.8% in the CCRT and RT groups, respectively. The association between treatment received and the extent of pelvic side wall involvement was significant ($P = .002$). The proportions of patients with lower third vaginal involvement in the CCRT, RT, and LTFU groups were 46.1%, 65.3%, and 66.1%, respectively. This difference was statistically significant ($P = .002$). Forty-three percent of patients in the CCRT group had hydronephrosis compared with 68.8% and 70.0% for the RT and LTFU groups, respectively. The proportion of bilateral hydronephrosis was 30.9% in CCRT group, but was 50.0% in the RT and LTFU groups (Table 3). HIV-infected patients had slightly bigger tumors, even though there was marked overlap.

TABLE 4. Overall Recorded Weekly Acute Adverse Events for Patients With Stage IIIB Disease Receiving Chemoradiation (by WHO criteria)

	Week		
System	1-3	4-6	Total
Hematologic			
Grade 0	184	98	282
Grade1-2	61	144	205
Grade 3	0	12	12
Grade 4	0	2	2
Grade 1-4	61	158	219
GI			
Grade 0	264	111	375
Grade 1-2	78	199	277
Grade 3	23	64	87
Grade 4	0	2	2
Grade 1-4	101	265	366
Skin			
Grade 0	344	171	515
Grade 1-2	22	146	168
Grade 3	2	56	58
Grade 4	0	0	0
Grade 1-4	24	202	226
Genitourinary			
Grade 0	307	180	487
Grade 1-2	40	162	202
Grade 3	6	12	18
Grade 4	0	4	4
Grade 1-4	46	178	224

Treatment Characteristics

Most patients (78%) received EBRT, chemotherapy, and brachytherapy, as per initial prescription. Brachytherapy was withheld in the other 22% of patients for various reasons, the most commonly reported being persistent bulky disease after EBRT.

Total pelvic EBRT doses of 46 Gy in 23 fractions and 50 Gy in 25 fractions were administered to 61% and 17% of patients, respectively. In 22% of patients, EBRT dose was escalated to 60 Gy in 30 fractions to a small volume of pelvis for bulky disease.

Weekly cisplatin was administered to 94% of patients while the remainder received weekly carboplatin. Twenty-nine percent received four or more cycles of chemotherapy. None of the 128 patients was able to complete six cycles. Of the 768 scheduled chemotherapy cycles that were expected to be completed by the 128 patients in the CCRT group over the 6-week treatment period, 372 cycles (48%) were completed. The most-cited reason for deferring chemotherapy was financial, accounting for 44%. In 45% of patients, there was at least one episode of unscheduled RT treatment break, prolonging treatment duration. The most-cited reason for treatment breaks was holidays, accounting for 43%. Hospital admissions during

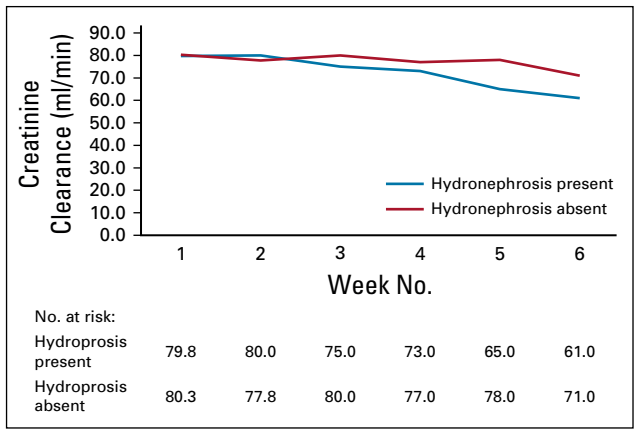

FIG 3. Weekly mean creatinine clearance at week 6 decreased by an average of 12.5% from the pretreatment value in patients with stage IIIB cervical cancer without hydronephrosis who received definitive chemoradiation. The decrease was doubled in the group of patients with hydronephrosis.

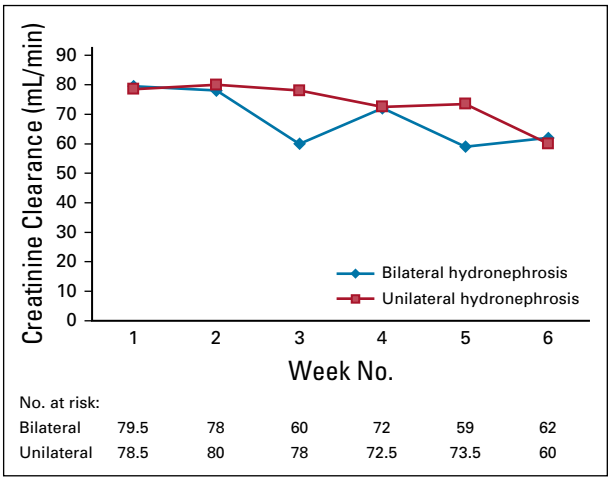

FIG 4. Renal function was maintained at the pretreatment value until week 3 on definitive chemoradiation in patients with stage IIIB cervical cancer with unilateral hydronephrosis, decreasing by 25% at week 6. Marked fluctuations in the weekly mean creatinine clearance (CrCl) was noted in patients with bilateral hydronephrosis; the decrease at week 6 remained at the same level as with patients with unilateral hydronephrosis (n = 55).

the 6-week period occurred for 12% of patients on CCRT; 50% of these admissions were because of treatment-related adverse events. One patient died as a result of a GI adverse event.

TABLE 5. Effect of Patient Characteristics on Tumor Response

Variable	Complete Response	Partial Response	Disease Progression	*P*
Age group, years				
< 45 (n = 43)	25 (58.1)	15 (34.9)	3 (7.0)	
≥ 45 (n = 84)	62 (74)	16 (19)	6 (7)	.22
HIV status				
Positive (n = 65)	43 (66.2)	15 (23.1)	7 (10.8)	
Negative (n = 58)	43 (72.9)	14 (23.7)	1 (1.7)	
Unknown (n = 4)	1 (25)	2 (50)	1 (25)	.17
$CD4^+$ count, cells/mm^3				
< 500 (n = 28)	17 (60.7)	8 (28.6)	3 (10.7)	
≥ 500 (n = 31)	23 (74.2)	5 (16.1)	3 (9.7)	.49
Comorbidities other than HIV				
Absent (n = 96)	65 (67.70)	24 (25)	7 (7.3)	
Present (n = 31)	22 (70.97)	7 (22.58)	2 (6.45)	.93
BSA, m^2				
≤ 1.7 (n = 84)	56 (66.67)	21 (25)	7 (8.33)	
> 1.7 (n = 43)	30 (69.77)	10 (23.26)	3 (6.98)	.79
Pretreatment hemoglobin, g/dL				
< 10 (n = 34)	22 (64.71)	10 (29.41)	2 (5.88)	
≥ 10 (n = 93)	69 (74.19)	18 (19.36)	6 (6.45)	.95

NOTE. Data presented as No. (%) unless otherwise indicated.
Abbreviation: BSA, body surface area.

Adverse Events of Chemoradiation

A total of 1,035 adverse events were recorded for all the systems, and 18% were grade ≥ 3. GI adverse events were the most commonly recorded, accounting for 34% (Table 4). Seventy-one percent of grade ≥ 3 hematologic adverse events occurred in HIV-infected patients, none of whom was on a zidovudine-based cART regimen.

Hydronephrosis and Renal Function During Chemoradiation

At week 6 on CCRT, mean creatinine clearance decreased by an average of 12.5% from the pretreatment value in patients without hydronephrosis. The decrease was doubled in the group of patients with hydronephrosis (Fig 3). In patients with unilateral hydronephrosis, renal function was maintained until week 3, decreasing by 25% at week 6. Marked fluctuations in mean creatinine clearance was noted in patients with bilateral hydronephrosis; however, the decrease at week 6 remained at the same level as that of patients with unilateral hydronephrosis (Fig 4).

Tumor Response to CCRT

Complete clinical tumor response (cCR) at 3 months post-CCRT was reported in 73% of HIV-uninfected patients compared with 66% of HIV-infected patients. A higher proportion of patients ≥ 45 years of age achieved cCR versus the younger population (P = .22). Seventy-four percent of HIV-infected patients with $CD4^+$ counts ≥ 500 cells/mm^3 achieved cCR and compared with 60% in those with counts < 500 cells/mm^3.

Seventy-four percent of patients without hydronephrosis achieved cCR compared with 60% in those with hydronephrosis. A higher proportion of patients with squamous cell carcinoma histology achieved cCR compared with those with adenocarcinoma (P = .12). Seventy-three percent of patients who received four or more chemotherapy cycles achieved cCR compared with 67% of patients who received fewer than four cycles. Complete responses were observed in 30 (52.63%) of 57 patients who had unscheduled breaks during their treatment. A higher proportion of cCR (81%) was recorded in those who did not have unscheduled treatment breaks (P = .003). Tables 5-7 summarize the patient, disease, and treatment characteristics association with tumor response.

DISCUSSION

The study revealed that most patients with cervical cancer in this setting present late and with advanced disease. HIV-infected patients present at a younger age, as noted elsewhere in the literature.[4] LTFU in cancer care remains a challenge, as is the case in most lower- and middle-income countries.[7] One third of our participants could not be accounted for after the first visit. Contributing factors to high LTFU could not be established in this study, but unreported deaths, low socioeconomic status, low education levels, lack of adequate patient education, and

TABLE 6. Effect of Disease Characteristics on Tumor Response

Variable	Complete Response	Partial Response	Disease Progression	*P*
Histologic type				
Squamous cell carcinoma (n = 117)	83 (70.94)	25 (21.37)	9 (7.69)	
Adenocarcinoma (n = 9)	3 (33.3)	6 (66.7)	0 (0)	
Adenosquamous carcinoma (n = 1)	1 (100)	0 (0)	0 (0)	.12
Tumor differentiation				
Moderately differentiated (n = 62)	41 (66.13)	19 (30.65)	2 (3.23)	
Poorly differentiated (n = 60)	44 (73.3)	9 (15)	7 (11.67)	
Well differentiated (n = 5)	2 (40)	3 (60)	0 (0)	.08
Hydronephrosis				
Absent (n = 72)	54 (74)	14 (19.2)	4 (5.5)	
Present (n = 55)	33 (60)	17 (30.9)	5 (9.1)	.26
Bilateral (n = 17)	10 (58.8)	5 (29.4)	2 (11.8)	
Unilateral (n = 38)	23 (60.5)	12 (31.6)	3 (7.9)	.9
Vaginal lower third				
Uninvolved (n = 69)	48 (69.6)	14 (20.3)	7 (10.1)	
Involved (n = 58)	39 (67.24)	17 (29.31)	2 (3.45)	.24
Pelvic side walls				
Uninvolved (n = 13)	11 (84.6)	1 (7.7)	1 (7.7)	
Involved (n = 114)	76 (66.7)	30 (26.3)	8 (7.0)	.50
Bilateral (n = 47)	32 (68.1)	11 (23.4)	4 (8.5)	
Unilateral (n = 67)	44 (65.67)	19 (28.36)	4 (5.97)	.59
Tumor size, cm				
< 7 (n = 79)	58 (73.42)	16 (20.25)	5 (6.33)	
≥ 7 (n = 48)	35 (72.92)	10 (20.83)	3 (6.25)	.08

NOTE. Data presented as No. (%) unless otherwise indicated.

higher levels of alternative medicine use are among the reasons cited in other sources.[8] Only one third of patients with stage IIIB disease received CCRT in this study, indicating low use of this modality, which is considered the standard management of LACC.[2] The CCRT group had a higher proportion of patients with high KPS (≥ 80%), and the RT group had a higher proportion of patients with lower KPS (< 80%), reflecting the possible role this parameter has in guiding the treating doctor on choice of treatment in this setting. Chemoradiation was generally reserved for patients with good performance status, although the association in this study was not significant ($P = .07$). The role of RT only treatment in LACC is not only unique in our situation, but has been noted to be a valid option in other lower- and middle-income countries, like the Indian subcontinent, where patients also usually present in poor general condition and have limited supportive care.[9]

The CCRT group's median age of 51 years (range, 31-75 years) correlated with age at presentation for patients with cervical cancer in the general population.[1,4,8] Median age in the RT group was higher, indicating a higher likelihood of older patients not being considered for concurrent chemotherapy. It is a common practice in our setting to withhold CCRT in older patients as they are often times too frail to tolerate the treatment; however, age did not seem to have much effect on the tumor response to CCRT. The majority of participants lived in rural areas and were unemployed, echoing poor socioeconomic background. Most could not afford to meet the financial requirements for CCRT, as is the case in most resource-constrained settings.[2] A considerable proportion of patients could not complete at least four cycles of chemotherapy, which may explain the poor response. Other studies correlated tumor response to the number of chemotherapy cycles, and the negative effect of noncompletion of chemotherapy is reflected in this study.

A higher HIV prevalence (50.8%) was reported in this stage IIIB subgroup study compared with that reported for the combined cervical cancer stages in other centers within the region, such as 16.7% in Côte d'Ivoire and 13.1% in South Africa.[4] This may reflect the association between HIV and LACC at presentation as concluded in other studies.[8] HIV-

TABLE 7. Effect of Treatment Characteristics on Tumor Response

Variable	Complete Response	Partial Response	Disease Progression	*P*
Neoadjuvant chemotherapy				
Administered (n = 8)	5 (62.5)	3 (37.5)	0 (0)	
Not administered (120)	82 (68.33)	29 (24.17)	9 (7.50)	.72
Granulocyte stimulating factor used (n = 9)	8 (88.9)	1 (11.1)	0 (0)	.03
Pretreatment transfusion				
Administered (n = 9)	5 (55.6)	3 (33.3)	1 (11.1)	
Not administered (n = 19)	9 (47.4)	9 (47.4)	1 (5.3)	.72
Unscheduled treatment breaks				
Yes (n = 57)	30 (52.63)	20 (35.09)	7 (12.28)	
No (n = 70)	57 (81.4)	11 (15.7)	2 (2.9)	.003
No. of chemotherapy cycles received				
1 (n = 14)	6 (42.9)	7 (50)	1 (7)	
2 (n = 29)	17 (58.6)	8 (27.6)	4 (13.8)	
3 (n = 47)	37 (78.7)	9 (19.1)	1 (2.1)	
4 (n = 29)	20 (69)	7 (24.1)	2 (6.9)	
5 (n = 8)	7 (87.5)	0 (0)	1 (12.5)	.25
EBRT dose received, Gy				
60 in 30 fractions (n = 27)	8 (29.63)	16 (59.26)	3 (11.11)	
50 in 25 fractions (n = 22)	12 (54.55)	8 (36.36)	2 (9.09)	
46 in 23 fractions (n = 78)	67 (85.90)	7 (8.97)	4 (5.13)	< .001
Brachytherapy dose received, Gy				
24 in 4 fractions (n = 1)	0 (0)	1 (100)	0 (0)	
21 in 3 fractions (n = 94)	76 (81)	12 (13)	6 (6)	
18 in 3 fractions (n = 5)	3 (60)	2 (40)	0 (0)	.07

NOTE. Data presented as No. (%) unless otherwise indicated.
Abbreviation: EBRT, external beam radiotherapy.

infected patients were younger, as previously reported.[4] HIV status did not seem to influence choice of treatment. A higher median $CD4^+$ count in the CCRT group compared with the RT group demonstrated the role that this parameter plays in guiding treatment decisions in HIV-infected patients in relation to chemotherapy treatment. The significance of pretreatment $CD4^+$ count on outcome and treatment tolerance of HIV-infected patients has been documented in other studies. CCRT is reserved for patients with higher $CD4^+$ counts in our setting, a 200-cells/mm^3 cutoff is typically used. CCRT was well tolerated in this study, with expected early clinical tumor response regardless of HIV status and $CD4^+$ count, which is in agreement with other studies in the literature. Tenofovir-based cART was the most common regimen in this study population, accounting for 89%. Zidovudine- and stavudine-based combinations accounted for 3% and 8%, respectively. Zidovudine-based combinations have been associated with anemia and high incidences of myelosuppression in several studies. Two patients who were on zidovudine-based combination in this study had pretreatment hemoglobin of less than 8 g/dL, but tolerated the treatment with low-grade hematologic toxicities.

Higher proportions of bilateral hydronephrosis and involvement of the lower third of vagina in the RT group versus the CCRT group indicate the possible role of these disease characteristics in guiding physicians on the choice of treatment in patients with bulky disease. Patients with bilateral hydronephrosis were more likely to receive RT versus CCRT. cCR was observed in patients with less bulky disease as expected. Treatment breaks were associated with a lower cCR rate (P = .003). Protracted treatment time has been associated with poor disease response in several studies.

Pretreatment hemoglobin and blood transfusion were not significantly associated with cCR. This finding is in agreement with the results in another study by Bishop et al,[10] which concluded that the use of transfusion is not correlated with benefit. Anemia was not noted to be an independent predictor of central recurrence in patients with cervical cancer treated with definitive RT with or without chemotherapy.[10]

In conclusion, the current study reveals that the use of CCRT for treatment of stage IIIB cervical cancer is low in Zimbabwe. Although several factors contribute, low CCRT uptake is mostly attributed to financial barriers. Well-selected patients, however, tolerate treatment and have good early clinical tumor response as expected. The role of CCRT as the standard treatment in this patient group, and methods to make it available in resource-limited settings, need to be further evaluated.

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