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Prognostic Factors of Locally Advanced Cervical Cancers Seen at the Only Public Radiotherapy Center in Madagascar

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Abstract

Introduction: In Madagascar, cervical cancer ranks second among cancer pathologies after breast cancer. It is diagnosed at a locally advanced stage in 79% of cases, where chemoradiotherapy followed by brachytherapy is the standard treatment. In the absence of brachytherapy, our objectives were to describe the evolution of locally advanced cervical cancers treated with chemoradiotherapy and to identify prognostic factors for progression and recurrence. **Materials and Methods**: This was a retrospective study including cervical cancers from stage IB3 to IVA between January 1, 2020, and December 30, 2021, at the Radiotherapy Department of the Joseph Ravoahangy Andrianavalona University Hospital. The median follow-up time was 15 months. Kaplan Meier analysis was used for disease-free survival. Proportion comparisons were made using the log-rank test and Cox model. **Results**: We collected data from 64 patients. The remission rate was 51.5% compared to a 48.4% therapeutic failure rate, of which 34.3% was progression and 14% was recurrence. The median time to progression and recurrence was 4 months and 8 months, respectively. The 15-month recurrence-free survival rate was 50%. Fixation to the pelvic wall ($p = 0.0001$), pelvic and/or lomboaortic lymph node involvement ($p = 0.03$), and stage ($p = 0.001$) were significantly associated with the occurrence of therapeutic failure. **Conclusion**: The prognosis for locally advanced cervical cancers is reserved, largely explained by the very advanced stage of the disease. To improve the therapeutic index, efforts should focus on prevention, and access to brachytherapy equipment is essential.

Keywords

Cervical Cancer, Chemotherapy, Prognosis, Radiotherapy

1. Introduction

The global incidence of cervical cancer is estimated at 570,000 new cases per year, with over 80% occurring in developing countries according to GLOBOCAN 2018 [1]. It is considered the leading cause of cancer-related death in women in Africa [2].

In Madagascar, the establishment of a national cancer registry is currently underway, and data is limited to studies from various departments. According to a multicenter study conducted in six cancer centers across Madagascar in 2020, cervical cancer ranks second among cancer pathologies after breast cancer, representing 30% of cancers in women [3]. Patients come for treatment at a locally advanced stage in 70% of cases [4] and it is the second most common cause of cancer-related death after breast [5]. Overall survival is 90% at two years for stage IB and 25% at one year for stage IVB [6]. Cervical cancer represents a threat to women's lives in resource-limited countries like ours, compared with wealthy countries that have implemented screening programs.

The standard treatment for these locally advanced cervical cancers involves chemoradiotherapy, followed by uterovaginal brachytherapy [7]. According to GEC-ESTRO (European Brachytherapy Group—European Society of Radiotherapy and Oncology) recommendations for locally advanced cervical cancer, the radiation dose to 90% of the total volume should be between 85 Gy and 90 Gy, while protecting organs at risk (bladder, rectum, sigmoid) with brachytherapy guided by three-dimensional imaging, and with a hypothetical local control rate of 86.7% in 2 years [8]. The probability of local control depends on the minimum dose in 90% of the volume to be irradiated: it is less than 65% for a dose of around 70 Gy, and greater than 90% for a dose of 90 Gy [9].

In literature reviews, particularly in developed countries, despite the radiosensitivity of cervical carcinomas and therapeutic advancements, progressive disease and tumor recurrences can occur, darkening the prognosis of the disease with a 5-year survival rate of less than 5% [10]. In 75% of cases, they occur within the first 2 years post-therapy [11] [12]. Recurrence rates are estimated to be between 50% and 70% in locally advanced stages [10]-[12].

Several prognostic factors are associated with the risk of recurrence, such as tumor size, advanced stage, non-squamous histological type, presence of vascular emboli, lymph node involvement, extension of the pelvic radiotherapy-brachytherapy sequence beyond 56 days, hemoglobin (Hb) concentration below 10 g/dl, and persistence of a lesion after treatment [11]-[13].

Since January 2020, after 11 years of downtime, cobalt radiotherapy has returned to Madagascar, and brachytherapy has not been available. The objectives of our study were, therefore, to describe the evolution of locally advanced cervical cancers treated with chemoradiotherapy without brachytherapy and to identify the prognostic factors for progression and recurrence.

2. Methods

We conducted a descriptive retrospective study on patients treated in the Radio-

therapy Department of the Joseph Ravoahangy Andrianavalona University Hospital from January 1, 2020, to December 30, 2021 (24 months). Included were patients with histologically proven locally advanced cervical cancer from stage IB3 to stage IVA, who received external-beam radiation therapy (EBRT) with or without concomitant chemotherapy, without brachytherapy, and with curative intent. Excluded patients were those who received a dose of less than 66 Gy, patients who were lost to follow-up during or after treatment despite a telephone call, and patients with another synchronous tumor.

The parameters studied related to the patients were age and hemoglobin (Hb) level. Tumor-related parameters included histological type, vascular emboli, infiltration of parameters, fixation to the pelvic wall(s), pelvic and/or lomboaortic lymph node involvement, tumor size, and tumor stage. Treatment-related parameters included the duration of radiotherapy, the number of concomitant chemotherapy cycles, and closure surgery.

The treatment device was Telecobalt with a two-dimensional simulator. The standard protocol of the department was irradiation of the large pelvis at 46 Gy or 45 Gy over 5 weeks in conventional fractionation. The additional dose was given on a reduced field (boost) of 20 Gy with or without direct perineal irradiation of 4 Gy for a total dose of 66 Gy to 70 Gy. Concomitant chemotherapy with weekly Cisplatin (40 mg/m^2) was administered in the absence of contraindications during the radiotherapy period. After radiotherapy treatment, closure surgery was proposed in cases of complete or partial remission with a tumor < 4 cm limited to the cervix. Patients were transfused at the beginning of treatment and during the week of discovering an Hb level < 10 g/dl.

The median follow-up time after treatment was 15 months [12; 25]. Evaluation methods included gynecological examination (without anesthesia by at least two clinicians), associated or not with abdominal-pelvic ultrasound and/or thoracic-abdominal-pelvic CT scan and/or pelvic Magnetic Resonance Imaging (MRI) (depending on presenting signs and the patient's financial means), and the pathological result of the surgical specimen in patients who underwent closure surgery. Patients were seen 1 month after the end of treatment and then every 3 or 6 months. Patients lost to follow-up could be reviewed after a phone call invitation. WHO (World Health Organization) criteria were used to assess tumor response: complete remission (absence of macroscopically visible tumor), tumor reduction > 50% (reduction greater than half the tumor volume before the very start of treatment), tumor reduction < 50% (reduction less than half the tumor volume before the very start of treatment), and no response.

Progression was defined by the occurrence of local tumor recurrence (tumor progression) or distant (metastasis) during treatment or within 6 months following treatment. Recurrence (or relapse) local or metastatic was defined by the occurrence of tumor recurrence 6 months or more after the end of treatment. Remission was defined as the absence of tumor lesions. Therapeutic failure was defined by the appearance of progression or recurrence, local or distant. Disease-

free survival was defined as the time after treatment during which the disease does not worsen. Kaplan Meier analysis was used for disease-free survival.

Comparisons of proportions were made using Fisher's exact test and the chi-square (chi2) test on Stata 13 software. Results were considered significant at the $p < 0.05$ threshold. The chi2 test was used when the contingency table data had cells with expected frequencies greater than 5; Fisher's exact test was used if frequencies were less than 5.

3. Results

Out of 98 patients recorded for cervical cancer in the department, 64 were included. The average age was 50 years ± 10. Patients presented with anemia below 10 g/dl in 31.2% of cases (Table 1). In the pathological examination, squamous cell carcinoma predominated at 84.3%, and vascular emboli were present at 20.3%. The gynecological examination revealed infiltration of parameters in 57.8% and fixation to the pelvic wall in 29.6%. Radiological examination confirmed lymph node involvement in 29.6% and an average tumor size of 5 cm ± 18. The majority of our patients were at stage IVA (34.3%) (Table 2). The median overall treatment time was 54 days [45; 162]. The number of concomitant chemotherapy cycles was greater than 6 in 70.4%. Closure surgery was performed in 18.7% of cases (Table 3).

Table 1. Distribution of patients according to patient-related parameters.

Patient-related parameters	REMISSION n (%)	FAILURE n (%)	N= 64 (%)	p-value
Average age (years)	50 ± 10			
≥50	19 (57.5)	16 (51.6)	35 (54.4)	0.6 (Pearson Chi2)
<50	14 (42.4)	15 (48.3)	29 (45.3)	
Hemoglobin (Hb) level (g/dl)				
<10 corrected	11 (33.3)	9 (29)	20 (31.2)	0.7 (Pearson Chi2)
≥10	22 (66.6)	22 (70.9)	44 (68.7)	
Therapeutic response (N)	33	31		

Among the 64 patients followed, 51.5% (n = 33) were in remission and 48.4% (n = 31) experienced therapeutic failure, of which 34.3% (n = 22) were progressions and 14% (n = 9) were recurrences. The median time to progression was 4 months [1; 6]. The median time to recurrence was 8 months [7; 13]. Among the 31 patients with therapeutic failure, 71% (n = 22) had locoregional failure, 22.5% (n = 7) had locoregional and metastatic failure, and 6.4% (n = 2) had metastatic failure. The disease-free survival at 15 months for the entire population was 50% (Figure 1).

Patients under 50 years old experienced therapeutic failure in 51.7%. Patients aged 50 and over were in remission in 54.2%. There was no significant correlation between age and the occurrence of therapeutic failure ($p = 0.6$). Among patients in the group with Hb < 10 g/dl then corrected, the therapeutic response was comparable to the group whose hemoglobin level was ≥10 g/dl. Nearly 50% of each group was in remission and had therapeutic failure ($p = 0.7$) (Table 1). The his-

tological type adenocarcinoma (ADC) tended to resist treatment with 60% therapeutic failure. For squamous cell carcinoma (SCC), there was remission in 53.7% (p = 0.5). There was a therapeutic failure in 69.2% of patients with vascular emboli (p = 0.1). Among patients with infiltration of parameters, 56.7% experienced therapeutic failure. For patients without infiltration, remission was 62.9% (p = 0.1). Of the 15 patients with fixation to the pelvic wall(s), 14 patients, or 93%, had therapeutic failure (p = 0.0001). Sixty-eight percent (68%) of patients with lymph node involvement experienced therapeutic failure. Sixty percent (60%) of patients without lymph node involvement were in remission (p = 0.03). Tumors ≤ 4 cm had therapeutic failure in 53.8%. Tumors > 4 cm had remission in 52.9% (p = 0.6). Stage IVA presented 72.7% therapeutic failure. Stage III presented 57.8% therapeutic failure. Stages IB3 and II presented 25% and 13.3% therapeutic failure, respectively (p = 0.001) (Table 2). Patients whose overall treatment time exceeded 56 days experienced therapeutic failure in 53.8%. For those with a duration of less than 56 days, 55.2% experienced remission (p = 0.47). Among patients receiving less than 6 chemotherapies, there was therapeutic failure in 63.1% compared to those receiving more than 6 cycles who had 42.2% therapeutic failure (p = 0.12). After radiotherapy, 12 out of 64 patients, or 18.7%, underwent surgery. There was remission in 66% of patients who underwent surgery (p = 0.4) (Table 3).

Table 2. Distribution of patients according to tumor-related parameters.

Tumor-related parameters	REMISSION n (%)	FAILURE n (%)	N = 64 (%)	p-value
Histological type				
Squamous cell carcinoma	29 (87.8)	25 (80.6)	54 (84.3)	0.5
Adenocarcinoma	4 (12.1)	6 (19.3)	10 (15.6)	(Fisher's exact)
Vascular emboli				
Yes	4 (12,1)	9 (29)	13 (20.3)	0,1
No	29 (87,8)	22 (70,9)	51 (79.6)	(Fisher's exact)
Infiltrations infiltration of parameters				
Yes	16 (48.8)	21 (67.7)	37 (57.8)	0.1
No	17 (51.2)	10 (32.2)	27 (42.1)	(Pearson chi2)
Fixation to the pelvic wall				
Yes	1 (3)	14 (45.1)	15 (23.4)	0.0001
No	32 (96.9)	17 (54.8)	49 (76.5)	(Fisher's exact)
Fixation to the pelvic wall				
Yes	6 (18.1)	13 (41.9)	19 (29.6)	0.03
No	27 (81.8)	18 (58)	45 (70.4)	(Pearson chi2)
Average tumor size (cm)	5 ± 18			
≤ 4	6 (18.1)	7 (22.5)	13 (20.4)	0.6
> 4	27 (81.8)	24 (77.4)	51 (79.6)	(Pearson chi2)

Continued

Stage (FIGO)				
IB3	6 (18.1)	2 (6.4)	8 (12.5)	
II	13 (39.3)	2 (6.4)	15 (23.4)	0,001
III	8 (24.2)	11 (35.4)	19 (29.6)	(Fisher's exact)
IVA	6 (18.1)	16 (51.6)	22 (34.3)	
Therapeutic response (N)	33	31		

Table 3. Distribution of patients according to treatments-related parameters.

Parameters related to treatments	REMISSION n (%)	FAILURE n (%)	N= 64 (%)	p-value
Median overall treatment time/radiotherapy duration (days)	54 [45; 162]			
≤56	21 (63.6)	17 (54.8)	38 (59.3)	0.4
>56	12 (36.3)	14 (45.1)	26 (40.7)	(Pearson chi2)
Chemotherapies				
<6	7 (21.2)	12 (38.7)	19 (29.6)	0.1
≥6	26 (78.7)	19 (61.2)	45 (70.4)	(Pearson chi2)
Closure surgery after radiotherapy				
Yes	8 (24.2)	4 (12.9)	12 (18.7)	0.4
No	25 (75.7)	27 (87.1)	52 (81.3)	(Fisher's exact)
Total: therapeutic response (N)	33	31		

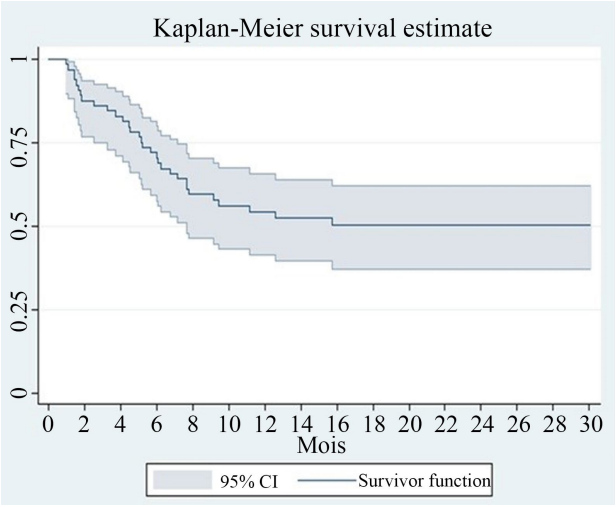

Figure 1. Kaplan-Meier disease-free survival curve for the general population.

4. Discussion

Two-thirds of locoregional recurrences occur within 2 years of initial treatment, and 90% within 3 years [11] [14] [15]. They are characterized by their rapid evolution and often by the complexity of the anatomical extension, making treatment difficult and rarely satisfactory [16].

According to GEC-ESTRO recommendations, for locally advanced cervical cancers: the irradiation dose in 90% of the total volume should be between 85 Gy and 90 Gy, while protecting organs at risk with brachytherapy guided by three-dimensional imaging, and with a hypothetical local control rate of 86.7% in 2 years [8]. The probability of local control is less than 65% for a dose of around 70 Gy and over 90% for a dose of 90 Gy [9].

In our study, 33 patients (51.5%) were in remission, 22 patients (34.3%) had progressed and 9 patients (14%) had relapsed (for a therapeutic failure rate of 48.4%). The median time to progression was 4 months [1] [6]. The median time to recurrence was 8 months [7] [13]. Of these therapeutic failures, 71% were locoregional, 22.58% locoregional and metastatic, and 6.45% metastatic alone. In the same center in 2009, a retrospective study of 46 patients diagnosed with locally advanced cervical cancer treated with EBRT at a dose of 65 to 75 Gy was carried out. Short-term results, at the patient's gynaecological examination one month after the end of radiotherapy, showed 45% complete remission, a partial remission rate ≥ 50% assessed at 30.42%, and 21.74% partial remission < 50% [17].

According to PEREZ, stage, tumor size and dose are the main prognostic factors for cervical cancer [18].

Several studies have shown that for a total dose less than or equal to 80 Gy, with or without chemotherapy, with or without brachytherapy, with stage II and stage III predominating, the therapeutic failure rate varied between 30% and 33% in 12 months to 7 years of median follow-up [19]-[25] (**Table 4**). The high failure rate in our study compared with the literature may be due to the fact that stage IVA predominated at 34.3%.

With a dose greater than 80 Gy using brachytherapy in combination with chemotherapy, the failure rate is lower the earlier the stage [10] [26] [27]. It ranged from 27% for stages IIIB and IVA to 23% for stages IB2 and II over a median follow-up time of 5 to 10 years (**Table 5**). However, despite a high brachytherapy dose in excess of 80 Gy, some studies report a fairly high failure rate ranging from 56% to 71% over 3 years and 7 years of median follow-up [15] [28]. YEUNG's retrospective study found a very high 5-year failure rate of 71.4%. He explained this by the absence of chemotherapy and interstitial brachytherapy, whose geometric dose distribution over the tumour was inadequate compared with uterovaginal brachytherapy [15]. KHAYAT showed a 56% failure rate at 3 years, linked to a total spread of between 35 and 149 days, with a median spread of 118 days [28] (**Table 5**).

This suggests that factors other than stage and dose come into play in relation to therapeutic response. According to CHAO, population heterogeneity and tumor cell characteristics make it extremely difficult to correlate precise irradiation doses with the probability of tumor control [29].

Disease-free survival of patients treated for locally advanced cervical cancer with radiochemotherapy ranged from 46% to 83% in the literature over a follow-

up period of between 3 and 7 years [7] [20]-[22] [26] [27] [30] [31] (**Table 4**, **Table 5**). In our series, disease-free survival was 50% at 15 months. Even with a median follow-up time that was short compared with the literature, we can see a high failure rate on disease control and a recurrence-free survival rate that drops to 50% in less than 2 years in our study. It is, therefore, pertinent to identify the main poor prognostic factors for Malagasy patients.

Table 4. Therapeutic response according to the literature to a radiotherapy dose of 80 Gy or less

Studies	Studies characteristics	Therapeutic failure Time to Onset	Disease-free survival
Our series	64 patients, **IVA/III** EBRT **without brachytherapy + CT**, **66 - 70 Gy** median follow-up time: 15 months	48.4% 4 to 8 months	50%
ULMER, Germany, 1981 [19]	150 patients, **III** EBRT **without UVB/CT**, **80 Gy** median follow-up time: 5 years	33% 14 months	
GIRINSKI, France, 1989 [20]	386 patients, **IIB/III** EBRT + UVB **without CT, 60 Gy** median follow-up time: 7 years	30%	46%
NGUYEN, France, 2002 [21]	92 patients, **IIB/III** EBRT + CT + UVB, 70 – 75 Gy median follow-up time: 5 years	30%	47%
HIRAKAWA, Japan, 2008 **[22]**	108 patients, **IIB/IIIB** EBRT + CT + UVB, 75 - 80 Gy median follow-up time: 4 years	30%	77%
HONG, Taiwan region, 2004 **[23]**	1292 patients, IIB EBRT + UVB **without CT**, 70 - 77 Gy, median follow-up time: 3 years	32% 18 - 20 months	
PATHY, India, 2014 **[24]**	128 patients, IIIB EBRT + CT + UVB, 80 Gy median follow-up time: 12 months	33%	

EBRT: external-beam radiation therapy; UVB: uterovaginal brachytherapy; CT: chemotherapy.

Table 5. Therapeutic response according to the literature to a radiotherapy dose greater than 80 Gy.

Studies	Studies characteristics	Therapeutic failure Time to Onset	Disease-free survival
ERRACHDI, Morocco, 2014 [10]	184 patients, **IIIB/IVA** EBRT + CT + UVB, **82 - 85 Gy** median follow-up time: 5 years	27.5% 2 years	
NUGENT, Washington, 2010 [26]	118 patients, **IB2/II** EBRT + CT + UVB, **95 Gy** median follow-up time: 4 years	23% 28 months	83%
KATANYO, Thailand, 2012 [27]	423 patients, **IIB** EBRT + CT + UVB, **75 - 85 Gy** median follow-up time: 10 years	24%	58.5% (ADC) 59.7% (SCC)

Continued

YEUNG, Florida, 2006 [15]	91 patients, **IIIB** EBRT + **interstitial brachytherapy without CT**, **85 Gy** median follow-up time: 8.8 years	71.4% 90 % at 2 years
KHAYAT, Morocco, 2020 **[28]**	250 patients, **IIB/IIIC** EBRT + CT + UVB, **82 - 85 Gy Median overall treatment 118 days** median follow-up time: 3 years	56% 11 months

EBRT: external-beam radiation therapy; UVB: uterovaginal brachytherapy; CT: chemotherapy; SCC: squamous cell carcinoma; ADC: adenocarcinoma.

A few studies report a local control rate of between 70% and 93% in patients aged 50 and over with a median follow-up time of 5 years, compared with 63% to 78% in those under 50 [10] [32] [33]. Age was not a significant factor in our study (**Table 1**). Patients aged 50 and over had a better 2-fold complete response compared with those under 50 [20] [24]. This finding has been reported since 1913, but the reason remains unclear [34]. According to SERUR, drug addiction in young people (smoking, alcoholism, cocaine use) was a likely contributing factor that could explain these results [35].

A hemoglobin concentration lower than 10 g/dl has a detrimental role on the local control rate of solid tumors, particularly for cervical tumors. Anemia during radiotherapy was associated with a relative risk of local recurrence of 1.6 and a risk of local and metastatic recurrence of 1.8 [20]. The mechanism of the relationship between anemia and poor prognosis in patients with cervical cancer is not clear. One hypothesis was that tumor-related anemia was more a sign of tumor aggressiveness, such as weight loss and general condition. In these cases, correcting hemoglobin levels during treatment would have no impact. The other hypothesis was that tissue hypoxia (partial pressure of oxygen < 5 mm Hg) is a factor of radioresistance, and anemia worsens hypoxia; in this case, correcting anemia should improve treatment outcomes [36]. In our series, the therapeutic response was comparable for the group with anemia that was then corrected and the group without anemia during radiotherapy ($p = 0.7$) (**Table 1**). This fact is supported by the studies of GROGAN and BUSH: compensating for anemia through transfusion certainly modifies the prognosis in patients who were initially anemic or became so during irradiation. Correcting anemia with a hemoglobin concentration lower than 10 g/dl diagnosed before or during radiotherapy for cervical cancer should be systematic [36] [37].

The literature reports that invasive adenocarcinoma is characterized by a worse prognosis compared to squamous cell carcinoma, particularly in advanced stages, with a higher frequency of lymph node involvement, a delayed response to standard treatment, and a greater risk of recurrence. However, in the long term, with a follow-up of 5 years or more, the prognosis of these two histological types is similar in terms of disease control and overall survival [27] [38] [39]. In our series, the histological type adenocarcinoma tended to resist treatment with a 60% ther-

apeutic failure rate (Table 2).

There was a therapeutic failure rate of 69.2% in our patients presenting with vascular emboli (Table 2). Most studies focus on the early stages. The ESGO (European Society of Gynaecological Oncology) has described the presence of vascular emboli as a risk factor for recurrence of cervical cancer at an early stage, with three times the risk of recurrence. The 5-year disease-free survival rate is 82.5% for the presence of emboli compared to 95.8% without emboli ($p = 0.04$) [40].

According to several authors, the recurrence rate exceeded 15% in cases of unilateral parametrial involvement, and this rate is higher when the involvement is bilateral, reaching up to 50% [18] [33] [41] [42]. In our series, patients with infiltration of the parameters tended to resist treatment with a 56.7% therapeutic failure rate (Table 2).

Attachment to the pelvic wall was significantly associated with the occurrence of therapeutic failure in our study ($p = 0.0001$) (Table 2). Of the 15 patients with attachment to the pelvic wall (s), 14 patients, or 93%, had a therapeutic failure. Some studies report a therapeutic failure rate exceeding 40% in cases of unilateral attachment to the pelvic wall and can reach 100% when the attachment is bilateral [10] [18] [41].

Patients with lymph node involvement have a relative risk of 1.6 to 2.6 for distant recurrence and within a shorter timeframe (18 months) than those whose lymph nodes are not affected [20] [23] [43]. The literature reports a therapeutic failure rate of 43% to 56.7% for patients with invaded pelvic and/or lomboaortic lymph nodes [10] [22]. This rate is even higher in our series; lymph node involvement was significantly associated with the occurrence of therapeutic failure, where 68.4% of patients with therapeutic failure had invaded lymph nodes ($p = 0.03$) (Table 2).

At the same stage, the prognosis for tumors with a diameter greater than 4 cm is worse than that for smaller tumors [44]. DELGADO reports a relative risk of developing a recurrence of 2.9 for tumors larger than 4 cm [45]. Some authors, such as PEREZ [18], and PATHY [24] reported a recurrence rate over a follow-up period of 1 year to 10 years, ranging from 16% to 32% for tumors smaller than 4 cm and a rate between 37% and 50% for tumors of 4 cm and larger. However, in our study, our results are contradictory: tumors larger than 4 cm tended to show remission (52.9%), while tumors smaller than 4 cm tended to show therapeutic failure (53.8%) (Table 2). This is likely related to the presence of other associated prognostic factors and the clinical assessment of tumor size, which is operator-dependent. Indeed, many studies have confirmed the value of MRI as the only standard examination for staging, without substituting it for clinical and gynecological examination under general anesthesia. The unavailability of this modern method in most sub-Saharan African countries, including ours, restricts the staging assessment to clinical examination and abdominal ultrasound, which remain, as in the West, operator-dependent [46].

The stage of cancer is the most important prognostic factor for patients diag-

nosed with cervical cancer [47]. This prognostic factor significantly influences the therapeutic response in our series, where the failure rate increases with the stage. Indeed, patients at stage IVA and stage III had therapeutic failure rates of 72.7% and 57.8%, respectively (p = 0.001) (**Table 2**). Those at stage IB3 and stage II had failure rates of 25% and 13.3%. Our results are similar to the literature. Studies report that the therapeutic failure rate increases with the stage. Over a follow-up period of 6 months to 10 years, this rate varied between 8% and 35% for stage I, 13% and 43% for stage II, 28% and 83% for stage III, and 64% to 100% for stage IVA [18] [24] [30] [33] [48]-[50]. According to HONG [23], the relative risk of local recurrence was 1.45 for stages I and IIA, 4.41 for stage IIB, 8.5 for stage III, and 14.5 for stage IVA.

Cervical cancer had a doubling time ranging from 3 to 5 days. The overall treatment time was thus identified as a prognostic factor in cervical carcinomas, as this time correlates with accelerated repopulation of clonogens during treatment, particularly for advanced stages [43]. The longer the spread, the higher the therapeutic failure rate. The entire treatment of chemoradiotherapy followed by brachytherapy should be completed in less than 56 days (8 weeks) [51]. PETEREIT found a failure rate of 28% compared to 13% for an overall treatment time of more and less than 55 days [52]. In our study, patients whose overall treatment time lasted more than 56 days tended to have a therapeutic failure rate of 53.8% (**Table 3**). For those with an overall treatment time of less than 56 days, there was a tendency towards remission at 55.2%.

According to FYLES, the loss of local control would be approximately 1% (0.6% to 0.86%) per day when treatment is extended beyond 30 days, but this repopulation would be compensated by the delivery of high doses during brachytherapy in the case of cervical cancer treatment [53]. This loss is 1.1% per day and 0.85% per day when treatment is extended beyond 52 days and 55 days, respectively, for GIRINSKY and PEREZ [54] [55].

Chemotherapy acts synergistically with radiotherapy by inhibiting the repair of radiation-induced lesions and reducing the fraction of hypoxic cells resistant to radiation [21] [56]. It reduces the risk of death by decreasing distant or local recurrence by 30% to 50% [22]. A study conducted by NUGENT demonstrated that patients who received fewer than 6 cycles had worse disease-free survival (p = 0.0045) [26]. SIRAK observed a 3-year disease-free survival rate ranging from 74% to 54% between patients who received 5 cycles and those who received 2 cycles of chemotherapy [25]. In our study, we found that among patients who received fewer than 6 cycles of chemotherapy, there was a tendency toward therapeutic failure at 63.1% (p = 0.12) (**Table 3**).

A meta-analysis by KOKKA studied the role of surgery following radiotherapy or chemoradiotherapy combined with brachytherapy for advanced cervical tumors, and no significant improvement in overall survival or progression-free survival was shown with complementary surgery [57]. There is no solid data to suggest that complementary surgery would improve oncological outcomes after

chemoradiotherapy followed by a boost dose of brachytherapy. Nevertheless, for patients who did not receive brachytherapy, the role of surgery deserves to be evaluated in the therapeutic strategy for locally advanced stages after EBRT. In our study, we found a tendency towards remission (66%) among patients who underwent surgery (p = 0.4) (**Table 3**). The results of TRAORE in Senegal are similar to ours, showing a 60.4% locoregional control at 40 months (3 years) of follow-up in 48 patients (II - IVA) who underwent hysterectomy after EBRT of 65 Gy with chemotherapy without brachytherapy [58].

Due to the recent reopening of the department in January 2020, the sample size was small, and the median follow-up time was short. Due to the retrospective nature of our study, some important information—therapeutic response at the end of treatment, and time to tumor regression—was not mentioned in the majority of files. A study with a 3-year and then a 5-year follow-up for these patients is in progress.

5. Conclusion

In the absence of brachytherapy, our patients were treated with EBRT at doses of 66 Gy to 70 Gy and concomitant chemotherapy. The 15-month disease-free survival rate was 50%. This high failure rate is explained by a dose delivered to the tumor below 80 Gy. However, other prognostic factors are also involved, which is consistent with the literature. Our results demonstrated that therapeutic failure is largely explained by the very advanced stage of the disease: fixation to the pelvic wall(s) (p = 0.0001), pelvic and/or lomboaortic lymph node involvement (p = 0.03), and the advanced stage of the disease at diagnosis (p = 0.001) were significantly associated with the occurrence of therapeutic failure. To improve the therapeutic index, efforts should focus on primary prevention through the widespread use of the HPV (Human Papillomavirus) vaccine, as well as early-stage screening, which involves fewer poor prognostic factors. Access to brachytherapy equipment is essential.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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