Review Article

High Dose Rate Intracavitary Brachytherapy in Locally Advanced Cervical Cancer: A Retrospective Serie Analysis

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ABSTRACT

Introduction: The treatment of locally advanced cervical cancer is based on radio chemotherapy followed by brachytherapy. The aim of this study was to evaluate the tolerance and efficacy of image-guided high dose rate (HDR) intracavitarybrachytherapy in a context of limited resources.

Materials and Methods: The clinical and dosimetric data of 60 patients with locally advanced cervical carcinoma treated by concomitant radio-chemotherapy (RCC) follow-up of brachytherapy between January 2019 and December 2023 at the CHU Dalal Jamm in Dakar were retrospectively analyzed. The toxicities of brachytherapy had been evaluated according to the Common Terminology Criteria for Adverse Events V4.0 (CTCAE) criteria. Estimates of overall survival and recurrence-free survival rates were analyzed by the Kaplan-Meier method, comparisons were made with the log-rank test and the cox model, with a 95% confidence interval. The statistical analyses were carried out using SPSS software in version 21.

Results: The average age was 53.8 ± 11.8 years. All patients had locally advanced tumors with FIGO stages IIB and IIIC1 respectively predominant 37.1% each. The median time from completion of external irradiation to brachytherapy was 28 days [0–124]. The dosimetry was in 3D for all patients. The average dose delivered at the high risk CTV (D90) was 82.2 Gy and 71.7 Gy at the low risk CTV. The D2cc (minimum dose received by the most irradiated 2 cm3) were 79.5 Gy for the bladder, 72.1 Gy for the rectum, 55.4 Gy for the sigmoid and 60.1 Gy for the small intestine. The main toxicities of brachytherapy were digestive (16.7%) and genitourinary (33.3%) all grades combined. With a median follow-up of 19.5 months, the evolution was marked by 12 locoregional recurrences (21.4%), 8 metastatic relapses (14.5%) and 6 deaths (10%). Overall survival and local relapse-free survival rates were 76.6% and 64.5% at 3 years, respectively.

Conclusion: Brachytherapy is essential in the optimal management of cervix cancer in advanced stages. Our institutional experience shows that it allows good local control and better overall survival. Interstitial brachytherapy could further improves these results in our context where tumors are advanced to diagnosis.

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Introduction

Cervix cancer is the second most common cancer in women with 85% of cases observed in low and middle income countries [1]. The treatment is stage-dependent; surgery, external beam radiation therapy (EBRT), brachytherapy and chemotherapy can be used alone or in combination in a multidisciplinary setting. Since Green's meta-analysis published in 2001, concomitant radio chemotherapy (CRC) is the standard of care for locally advanced cervix tumours [2,3]. This CRC is completed by brachytherapy, which constitutes a major component of the success of the treatment. It delivers a very high dose to the tumor while sparing organs at risk (OAR). It has long shown better effectiveness in terms of local control and tolerance of the treatment [3]. This efficiency is based on the very high dose gradient related to the position of the radioactive source in contact with the tumor. This allows the received dose to be increased to levels that could never be reached by EBRT tumor boost [2,4,5]. International Commission on Radiation Units and Measurements (ICRU 38) report 38 defined three types of brachytherapy based on dose rate: high dose rate brachytherapy (HDR) with more than 12 Gy/h (0.2 Gy/min); brachytherapy at average rate (between 2 to 12 Gy/h) and low dose rate brachytherapy (LDR) between 0.4 to 2 Gy/h [3]. The development of HDR brachytherapy is the result of technological developments, particularly in computed tomography (CT) imaging and even more magnetic resonance imaging (MRI), treatment planning software, new applicators, and miniaturized sources [4-6]. HDR brachytherapy is easier to use and therefore more accessible in terms of feasibility and costs. It brings major advantages, notably outpatient treatment, patient comfort, as well as better radiation protection for staff [7]. The objective of this study was to evaluate the efficacy and tolerance of HDR brachytherapy in locally advanced cervical cancers in a context of limited resources.

Materials and Methods

This is a retrospective study involving 60 patients treated in the radiotherapy department of Dalal Jamm Hospital between January 2019 and December 2023, for locally advanced cervical carcinomas confirmed at the histology and having received curative HDR brachytherapy in addition to CRC.

Processing

Sixty-five percent of patients received neoadjuvant chemotherapy with the Carboplatin – Paclitaxel protocol. External radiotherapy was delivered at a dose of 45 or 46 Gy, in classic fractionation from 1.8 to 2 Gy/fraction with an average spread of 41 days. Fifteen patients received a 10 to 15 Gy node boost, sequential (10 patients) or integrated mode (SIB) in 5 patients. The concomitant chemotherapy performed in 91.7% of patients was based on weekly Cisplatin (40 mg/m2).

All patients received intracavitary brachytherapy in HDR guided by computed tomography imaging. The radioactive source was Cobalt 60.

Practical Application

The brachytherapy applications were carried out under local sedation (paracervix block and analgesic). The applicator was composed of a uterine probe (SU), a vaginal ring of variable dimensions, a rectal retractor and a perineal fixator. The first step was to set up a balloon urinary catheter. The clinical examination allowed an accurate assessment of the tumor residue and its extensions. The cervical orifice was identified and the uterine height measured by a hysterometer. In a second step, the SU was established after dilation of the endo-uterine tract. The incurvation of the SU was chosen according to the uterine angle–vagina (CT scan, MRI). The vaginal applicator (ring) was then threaded onto the SU and inserted into the vagina. The diameter of the ring was chosen based on the vaginal capacity that was assessed by the clinical examination. The Ring was plated at the vaginal bottom and secured to the SU by an interlocking and screwing system. A tamping of the vaginal cavity was then performed using compresses soaked with Betadine. A perineal fixator was used to better fix the applicator (Figure 1). At the end of the application, a radioscopic check was performed to assess the quality of the application using dummy sources dedicated for the Ring and the SU. Contiguous 5 mm thick scan cuts were made using a dedicated simulator scanner.
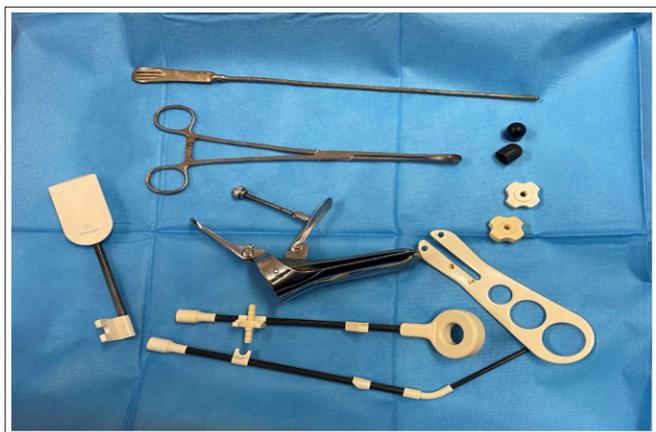

Figure 1: Composition of Brachytherapy Equipment

Dosimetry

After the CT, a delineation of the anatomoclinical target volumes (high-risk CTV and intermediate-risk CTV) and the organs at risk (OAR) (bladder, rectum, sigmoid) was done. We prescribed 4 to 3 sessions of 7Gy, twice a week. The physicist was reconstructing the catheters. The dose was prescribed at point A of Manchester as in 2D. The dose constraints for OARs in 2 Gy equivalent dose (EQD2) taking into account the dose received in EBRT followed the recommendations of EMBRACE II; bladder: D2ccc $\leq$ 90 Gy, rectum, sigmoid and small intestine: D2cc $\leq$ 75 Gy [8]. D2cc being the minimum dose received by the most irradiated 2 cubic centimeters of the organ. After the validation of the treatment plan, patients received the first session on the same day.

Evaluation

The follow-up of brachytherapy was carried out twice a week and allowed to search for acute toxicities. The post-therapeutic follow-up was monthly then quarterly for the first two years and after every six months until five years. It included a clinical and gynecological examination (vaginal touch, speculum exam, digital rectal examination) for the assessment of local control and the evaluation of late side effects. Monitoring medical imaging based on stage and call signs: (pelvic MRI, CT scan, cystoscopy, rectoscopy).

Analysis and Statistics

Data were collected using a pre-established data collection sheet and entered into Microsoft Excel. Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences), version 21.

Descriptive statistics included the calculation of frequencies and proportions for qualitative variables, and means with standard deviations for quantitative variables.

For analytical analysis, cross-tabulations were used. Comparisons of frequencies were conducted using Pearson's chi-square test or Fisher's exact two-sided test, depending on the applicability conditions. Mean comparisons were performed using analysis of variance (ANOVA), with a significance level set at $p < 0.05$.

Survival probabilities were estimated using the Kaplan-Meier method.

Results

The average age of the patients was 51.8 ± 11.8 years. The tumors were locally advanced with FIGO stages IIB and IIIC1 respectively predominant 37.1% each. Squamous cell carcinoma was the most common histological type with 93.3%. The median time between the end of EBRT and brachytherapy was 28 days [0–124]. The main characteristics of the population and treatment are presented in Table I.

Table 1: Population Characteristics

Characteristics	N value= 60
Age (y)	53.8 ± 11.8
Stages	
IIB	19 (37,1)
IIIC1	19 (37,1)
IVA	10 (16,7)
IIA	6 (10)
Type of Histology	
SCC	56 (94,3)
Adenocarcinoma	6 (10,7)
NA Chemotherapy	39 (65)
EBRT	
Alone	5 (8,3)
CRC	55(91,7)
Type of EBRT	
RC3D	50 (83,3)
VMAT	10 (16,7)
Applicator	
45°/26/40	11(19,6)
45°/26/40	7(11,6)
45°/26/40	46(43,8)
Protocol	
4 x 7	51 (85)
3 x 7	7 (11,7)
3 x 8	1 (1,7)
Number of Implementation	
1	143(80,8)
2	34(19,2)

The dosimetry was in 3D for all patients. The average dose (D90) delivered at the high risk CTV and intermediate risk CTV were 82.2 Gy and 71.7 Gy, respectively. The average D2cc for the bladder was 79.5 Gy, 72.1 Gy for the rectum, 55.4Gy for the sigmoid and 60.1 Gy for the small intestine. The different dosimetric characteristics are summarized in Table II.

Table 2: Dosimetric Characteristics

Constraints	Objective (Gy)	Number of patients with full respect of the constraints (%)	Average ± SD	Median [min-max]
D90CTVHR	>85	19 (31,7)	82,2 ± 7,5	80,8 [67,8 – 100,8]
D90CTVIR	>60	44 (78,6)	71,7 ± 14,9	64,7 [50,8 – 102,3]
D2cc-Bladder	<90	57 (95)	79,5 ± 10,5	81,7 [53,6 – 97,8]
D2cc-Rectum	<75	29 (48,3)	72,1 ± 6,8	75,2 [51,2 – 87,6]
D2cc-Sigmoid	<75	48 (94,1)	55,4 ± 8,7	53,6 [46,0 – 75,2]
D2cc- intestine bowel	<75	25 (80,6)	60,1 ± 13,5	55,5 [40,0 – 95,2]

The main toxicities of brachytherapy were digestive (16.7%), genitourinary (33.3%). (Table III). It's was a majority Grade 1 and 2. Only 3 patients had grade 4 toxicities at vesico-vaginal fistula.

Table 3: Toxicity of Brachytherapy

			Number (%)
Digestive toxicity	Non		50 (83,3%)
	Yes	Grade 1	8 (13,4%)
		Grade 2	2 (3,3%)
GU Acute toxicity	Non		40 (66,7%)
	Yes	Grade 1	6 (10,0%)
		Grade 2	10 (16,7%)
		Grade 3	1 (1,6%)
		Grade 4	3 (5,0%)

The median total treatment time was 175 Days [34–577]. Early response to treatment was complete in 46 patients (76.3%), partial in 12 patients (20%) and stable in 2 patients (3.3%).

After a median follow-up of 19.5 months, the evolution was marked by 12 loco regional recurrences (21.4%) and 8 metastatic relapses (14.5%) in the lung, liver and bone. Six deaths (10%) were noted. The overall and local relapse-free survival rates at 3 years were 76.6% and 64.5%, respectively. The survival curves are in Figure 2.
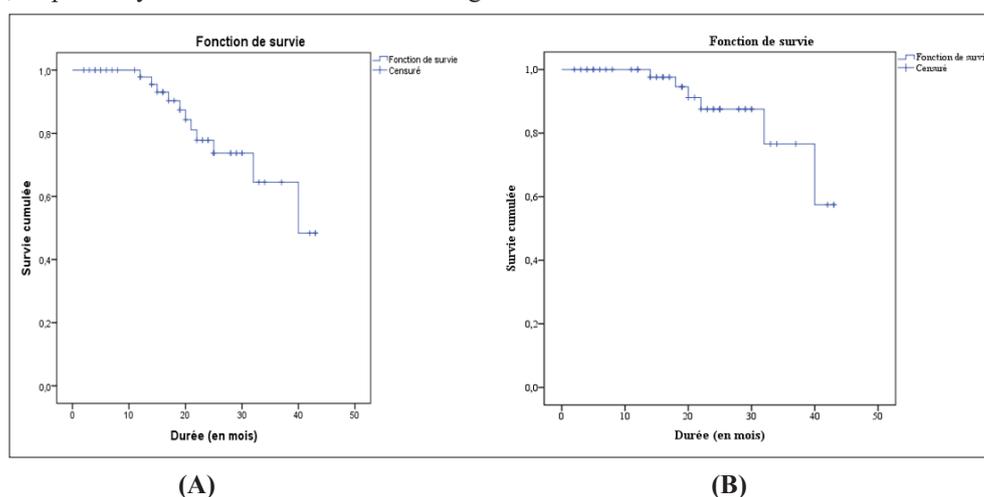

(A)   (B)

Figure 2: Survival Curves
A: Overall Survival
B: Local Relapse-Free Survival

Discussion

Cervix cancer represents a public health problem, particularly in the tropical countries of sub-Saharan Africa. It is the leading cancer in Senegal in terms of incidence (17.4%) and morality (16.1%) [9]. Its management is multidisciplinary, concomitant radio chemotherapy followed by brachytherapy is the standard treatment in locally advanced stages [10]. Brachytherapy is a better dose overprinting technique compared to EBRT alone [11]. It offers better control and good tolerance of the treatment. Unfortunately, its availability in low middle income countries (LMICs) particularly in Africa poses a problem, the IAEA's directorate of radiotherapy centers lists 37 brachytherapy devices for all sub-Saharan Africa (excluding South Africa). In Senegal, only one brachytherapy unit exists entirely dedicated to gynecological intracavitary brachytherapy.

Brachytherapy, which complements EBRT, is associated with good local control of the disease and therefore an increase in overall survival. It allows, with a very high dose gradient due to the direct contact of the radioactive source with the tumor, to obtain a better tumor coverage and good tolerance through less exposure of organs at risk. It is an independent prognostic factor for disease survival. In our context, only intracavitary brachytherapy is available. Although superior to the boost by EBRT, it has shortcomings related to a deficient coverage of tumor volumes in the case of significant distal and vaginal parametric invasions. From this point of view, interstitial brachytherapy would offer much better dose coverage, especially in our context where diseases are discovered at a locally advanced stage [12].

Conventionally and before the advent of 3D brachytherapy, it was difficult to evaluate the relationship between the dose at the level of the OAR and the risk of complications. This evaluation is especially difficult at the bladder level due to the lack of relationship between the dose at the bladder point of the ICRU and the risk of complications [13]. The current dosimetric data based on imaging has allowed a better characterization of the dose actually received by the bladder. Kirisits et al. reported the dosimetric parameters of a series of 22 patients treated at high dose rate; the average dose at D2ccc of the bladder was 83 Gy versus 79.5 Gy in our study [3,14]. Doses for the rectum are relatively simpler, in fact the dose received by the D2ccc generally being close to that received by the ICRU rectum point [15]. Even if there are dose variations during brachytherapy, the recommendations on dose constraints at the volume D2ccc are 75 Gy for the rectum and 90 Gy for the bladder in EQD2 [3,16,17]. In this study, the maximum doses received at the D2ccc bladder were 79,5Gy and

72,1 Gy for the rectum. This is the result of a good preparation and a better conformation and optimization that 3D dosimetry offers us and consequently a better protection of organs at risk.

The toxicities were mostly of grade 1-2. Only one patient had grade 3 toxicities and three patients had grade 4 (late) toxicity. No patient in our study had stopped their treatment due to severe toxicity. These results are similar to those of Pedersen et al, who had found a predominance of grade 1 and 2 toxicities in a study of 442 patients [18].

Optimized image-guided brachytherapy represents an opportunity to improve local control in patients with cervix cancer. The major advantage of this technique is represented by the possibility of conforming the dose delivered by brachytherapy taking into account both the initial tumor volume and the tumor regression during the concomitant chemo-radiotherapy.

In our context of limited resources in radiation therapy, the primary means of dose overprinting in cervix cancer was external radiation therapy. A study conducted at the Joliot Curie Institute in Dakar on a radiosurgical association using a two-dimensional technique in locally advanced cervix cancers found local control and an overall survival at 3 years of 60.4% and 55%, respectively [19]. Another study conducted at the International Cancer Center in Dakar, combining concomitant radio-chemotherapy and tumor boost in an integrated mode (SIB), reported a local control at 3 years of 62% and an overall survival of 74% [20]. In this study, local control and overall survival at 3 years all stages combined are respectively 64.5% and 76.6%, indicating the superiority of brachytherapy compared to other boost modalities by external radiotherapy.

Moreover, these results, although quite interesting, are weaker than those of the meta-analyses on EBRT followed by brachytherapy which found local control at 3 years of 85% and 92% at 5 years in Embrace II [21,22,8]. This difference can be explained by various factors, notably the nature of locally advanced tumors, the extension of the total treatment time with a significant use of neoadjuvant chemotherapy, the frequency of anemia with its corollary of cellular hypoxia which constitutes a radioresistance factor, but also the absence of interstitial brachytherapy.

No statistically significant correlation was found between prognostic factors and overall survival outside of the FIGO stage.

The limitations of this study are mainly related to the weakness of the hindsight, a difficult comparison of the results with those published due to the use of CT instead of MRI as a modality guiding brachytherapy.

Conclusion

Brachytherapy is an essential modality in the optimal management of cervix cancer. Its use is recent in our center and this study constitutes a first evaluation of our practice. The results in terms of local control and overall survival are satisfactory compared to the tumour boost in external radiotherapy. To our knowledge, this is the first study in Senegal on 3D image-guided intracavitary brachytherapy. However, the development of interstitial brachytherapy in our context is a necessity for optimal management of locally advanced cervical cancer.

Conflict of Interest
The authors declare no conflict of interest

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