High Dose Rate Brachytherapy in The Treatment of Cervical Cancer: Retrospective Study About 380 Patients, Experience of The National Institute of Oncology, Rabat

Introduction and aim of the study:

Brachytherapy is a fundamental step in the treatment of patients with cervical cancer. It increases local control and global survival rates.

The objective of our study is to present the Moroccan experience of the Rabat National Institute of Oncology in high-dose-rate brachytherapy for cervical cancer.

Material and methods:

Retrospective study from January 2019 to December 2023 carried out in the radiotherapy department at the National Oncology Institute Rabat describing the clinical, paraclinical, technical, dosimetric and evolutionary modalities of three-dimensional high-dose-rate brachytherapy in 380 patients with cervical cancer. These data were then entered and processed on Microsoft Excel 2019.

Results:

The mean age of the patients was 54 years. The predominant histological type was squamous cell carcinoma in 88% and adenocarcinoma in 12%.

In our study, pelvic MRI was performed in 98% of patients, with tumor stages according to the FIGO 2018 classification being IB (6.6%), IIA (5,8%), IIB (34,2%), IIIC1 (21.6%), IIIC2 (14.7%), and IVA bladder and rectal (17.4%) respectively.

All patients were treated with external radiotherapy with a dose of 46 Gy concomitantly with weekly cisplatin at a dose of 40mg/m2.

The average total course of external radiotherapy combined with brachytherapy was 66 days [44 - 75].

90% of applications were endocavitary and 10% were vaginal brachytherapy. The applications were controlled by per-brachytherapy ultrasound.

The protocols used for endocavitary brachytherapy were 4x7Gy weekly in 29.5% of cases, 4x7Gy in two series in 50% of cases, 3x8Gy weekly in 12% of cases, and for barrage brachytherapy were 2x5Gy weekly in 4% of cases, 2x6Gy weekly in 2% of cases and 3x6Gy weekly in 2.5% of cases.

Brachytherapy dosimetry was performed on a dosimetric scanner for all patients, except for barrage brachytherapy.

The mean total DQE2 (α/β 10) external radiotherapy and brachytherapy for high-risk CTV was 94.93Gy. For organs at risk, the mean total EQD2 (α/β 3) external radiotherapy and brachytherapy was 65.5Gy, 61.4Gy, 53.5Gy and 50.2Gy respectively for the bladder, rectum, sigmoid and small bowel.

Acute toxicity during brachytherapy was mainly represented by minimal bleeding in 9% of patients, grade I cystitis in 3.5% of patients, and grade I radio-mucositis in 2.5%, while 85% of patients had no side effects during the treatment.

After a 32-month follow-up, a complete remission was observed for 89,73% of patients, a stable tumor for 2,36% and a local recurrence for 7,89% of patients with initial stages IIB, IIIC1 and IVA.

Conclusion:

HDR brachytherapy has an important place in the treatment of cervical cancer. It improves local control by reducing locoregional recurrence and toxicity in organs at risk, and improves quality of life after irradiation.

Keywords: Brachytherapy, Cervical Cancer, Patients

Introduction:

Cancer of the cervix is the second most frequent cancer in women worldwide and the fourth cause of death by cancer in women [1], nearly 85% of the population suffering from cervical cancer live in developing countries.

Infection with oncogenic types of HPV sexually transmissible is primary cause. In Morocco, this cancer poses a major public health issue for women [2]. Two preventive methods are currently available: primary prevention through vaccination and secondary prevention through early diagnosis.

Squamous cell carcinomas present approximately 80% of cervical cancers, while adenocarcinomas account for 20% with less favorable prognosis [3].

The management of cervical cancer is stratified based on the tumor stage, for locally advanced stages, five randomized trials have demonstrated a survival benefit both progression free survival and overall survival due the combination of external radiotherapy and concomitant chemotherapy, combined with brachytherapy [4,5,6,7,8].

High dose brachytherapy has become a key approach in the treatment of cervical cancer, as evidenced by advancements in techniques and clinical outcomes over the years. In a study by Yin et al. (9), the use of high-dose-rate brachytherapy for treating cervical cancer was highlighted, emphasizing its growing importance in treatment protocols.

Brachytherapy involves placing a radioactive source, for a set duration, in contact with or within the structure to be irradiated, aiming to treat only the tumor while sparing adjacent tissues as much as possible, thereby ensuring better local control.

Our study aims to present the Moroccan experience at the National Oncology Institute in Rabat with high-dose-rate brachytherapy in the management of locally advanced cervical cancer.

Materials and Methods

Retrospective study from January 2019 to December 2023 carried out in the radiotherapy department at the National Oncology Institute Rabat describing the clinical, paraclinical, technical, dosimetric and evolutionary modalities of three-dimensional high-dose-rate brachytherapy in 380 patients with cervical cancer. These data were then entered and processed on Microsoft Excel 2019.

The inclusion criteria were: a cervical cancer diagnosis confirmed by biopsy according to the WHO classification, starting from stage IB according to the 2018 FIGO classification, and all patients having received concurrent chemoradiotherapy followed by brachytherapy.

Exclusion criteria included: patients with initial metastases, those who received only concurrent chemoradiotherapy, and those lost to follow-up immediately after treatment.

Concurrent Radio-Chemotherapy

All of our patients received 3D conformational radiotherapy technique, with a dose of 46 Gy delivered to the pelvic region in 23 fractions of 2 Gy per day, 5 days a week. This radiotherapy was combined with weekly cisplatin-based chemotherapy at a dose of 40 mg/m², not exceeding a total dose of 70 mg/m²/week. Macroscopic pelvic lymphadenopathy was treated with a dose of 60 Gy, while lombo-aortic lymph nodes and the parametria received 56 Gy.

The target volumes were delineated using axial slices acquired from a dosimetric scanner. The use of multi-leaf collimators allows for precise dose adjustment based on the geometry of the target volume. Treatment fields were defined using bony landmarks as reference points, then adjusted according to the organs at risk and the target volumes delineated on the scanner.

Brachytherapy

All patients underwent high-dose rate (HDR) brachytherapy, delivered in one of the following protocols: four fractions of 7 Gy with 2 or 4 insertions (one insertion per week), three fractions of 8 Gy, or two fractions of 9 Gy, each administered in a single insertion per week. HDR brachytherapy was planned during the final week of external beam radiotherapy (EBRT) to maintain an optimal overall treatment duration of less than 56 days.

A consultation was systematically held during the 13th radiotherapy session to evaluate tumor response and determine the most appropriate application technique (intracavitary or interstitial). Applicator selection was based on tumor residue, vaginal tumor extension, uterine anteflexion, and vaginal capacity. The available applicators included Fletcher, Utrecht, Ring, Vienna-type Ring, or vaginal cylinder models. For locally advanced tumors or large residual tumors, a pelvic MRI was performed at the end of EBRT to evaluate tumor response.

The accuracy of the application was initially evaluated using ultrasound during the insertions. A dosimetric CT scan was then conducted with the applicator in place, and the position was verified using scout views. Contiguous CT images (2-mm slice thickness) were acquired from the mid-sacroiliac joint to the ischial tuberosities. Applicator positioning was further confirmed in three planes: axial, sagittal, and coronal.

CT images were imported into the ONCENTRA treatment planning system (TPS) for delineation of target volumes and organs at risk (OAR), following GEC-ESTRO guidelines [10]. The high-risk clinical target volume (HR-CTV) was defined as the post-radiochemotherapy residual tumor, including the cervix and gray zones observed on pelvic MRI (if performed). The intermediate-risk CTV (IR-CTV) includes the HR-CTV, the initial tumor extent, and margins of 1.5 cm cranio-caudally, 1 cm laterally, and 0.5 cm antero-posterior. OARs included the rectum, bladder, and sigmoid colon.

HDR brachytherapy dose prescription was based on Point A, as defined by the Manchester system. Total HDR brachytherapy EBRT doses to Point A were calculated using the linear-quadratic model with an α/β ratio of 10, aiming for cumulative doses between 85 and 95 Gy. Cumulative dose constraints for OARs, combining HDR brachytherapy and EBRT were set at 65–70 Gy for the rectum and 80–90 Gy for the bladder, in accordance with International Commission on Radiation Units and Measurements (ICRU) Report 38 recommendations, using an α/β ratio of 3.

HDR brachytherapy dose prescription was determined based on Point A, as defined by the Manchester system. The cumulative dose delivered to Point A, combining HDR brachytherapy and external beam radiotherapy (EBRT), was calculated using the linear-quadratic model with an α/β ratio of 10, targeting a

total dose range of 85–95 Gy. Dose constraints for organs at risk (OARs) were established in accordance with the recommendations of the International Commission on Radiation Units and Measurements (ICRU) Report 38, with cumulative dose limits of 65–70 Gy for the rectum and 80–90 Gy for the bladder, calculated using an α/β ratio of 3.

Follow-up

Throughout treatment, patients underwent weekly clinical surveillance. Following completion of treatment, they were monitored every 3 months for 2 years, subsequently every 6 months for 3 years, and then annually. Local recurrence was initially suspected based on clinical examination and later confirmed through MRI and biopsy.

Disease-free survival was defined as the duration from the initiation of treatment to the confirmation of either local or metastatic recurrence.

Local recurrence was defined as the reactivation of the disease within the irradiated area, whereas distant recurrence was characterized by the onset of metastases outside the treated region. The date of recurrence was determined by the date of imaging or histopathological confirmation.

Results

A total of 380 patients with locally advanced cervical cancer were included in this study. All patients were treated with concomitant chemoradiotherapy combined with high-dose-rate (HDR) brachytherapy.

The median age of the patients was 54 years (range: 33–87 years). The predominant histological type was squamous cell carcinoma for 88% of cases, while adenocarcinoma was present in 12%. The most common symptom was metrorrhagia.

Pelvic magnetic resonance imaging (MRI) was performed in 98% of the patients to assess locoregional extension. According to the 2018 FIGO classification, the distribution of tumor stages was as follows: 25 patients (6.6%) at stage IB, 22 patients (5.8%) at stage IIA, 130 patients (34.2%) at stage IIB, 82 patients (21.6%) at stage IIIC1, 56 patients (14.7%) at stage IIIC2, and 66 patients (17.4%) at stage IVA with bladder and/or rectal involvement.

The average initial tumor size was 5.4 cm, which reduced to 1.8 cm after completion of the chemoradiotherapy. The average total duration of external radiotherapy combined with brachytherapy was 66 days (range: 44–75 days). (Table 1)

All patients received external beam radiotherapy (EBRT) at a dose of 46 Gy, delivered in 2 Gy per fractions, 5 sessions per week. This was combined with weekly cisplatin-based chemotherapy at a dose of 40 mg/m², not exceeding 70 mg/m²/week.

90% of brachytherapy applications were endocavitary, while 10% were endovaginal, with ultrasound guidance used to control the applications. The brachytherapy protocols were as follows: 4x7 Gy weekly in 29.5% of patients, 4x7 Gy in two series in 50% of patients, 3x8 Gy weekly in 12% of patients, 2x5 Gy weekly in 4% of interstitial cases, 2x6 Gy weekly in 2% of interstitial cases, and 3x6 Gy weekly in 2.5% of endovaginal cases.

Brachytherapy dosimetry was performed using a dosimetric CT scan for all patients. The total average EQD2 ($\alpha/\beta = 10$) for EBRT and brachytherapy for the high-risk clinical target volume (CTV) was 94.93 Gy. For the organs at risk, the total average EQD2 ($\alpha/\beta = 3$) was as follows: (Table 2)

- ✓ 65.5 Gy for the bladder,
- ✓ 61.4 Gy for the rectum,
- ✓ 53.5 Gy for the sigmoid colon, and
- ✓ 50.2 Gy for the small bowel.

The treatment was well tolerated by all patients, with no severe side events necessitating discontinuation of treatment. No treatment-related mortality was observed during the study.

The median follow-up time was 32 months (range: 19–48.7 months). At the end of the follow-up period, 89.73% of patients achieved complete remission, 2.36% had stable disease, and 7.89% experienced locoregional or distant recurrence for patients with initial stages IIB, IIIC1, IIIC2, and IVA, the recurrence rates were as follows:

- ✓ 6.15% for stage IIB,
- ✓ 10.97% for stage IIIC1,
- ✓ 19.64% for stage IIIC2, and
- ✓ 16.66% for stage IVA.

In total, 28 patients (7.36%) experienced locoregional recurrence, and 11 patients (2.89%) experienced distant recurrence.

TABLE 1: The patients' and tumors' characteristics

The patients and tumors characteristics	
Characteristics	**Number of patients (%)**
Median age= 54 years	
Range Age 33-87	
<40 years	120 (31,57)
>40 years	260 (68,42)
Symptomatology	
Métrorrhagia	245 ()
Pelvic pain	69 ()
Vaginal discharge	28 ()
Autres	38 ()
Histology	
Squamous cell carcinoma	334 (88)
Adenocarcinoma	46 (12)
FIGO stage	
IB	24 (6,5)
IIA	22 (6)
IIB	130 (34)
IIIC1	82 (21,5)
IIIC2	56 (14,5)
IVA	66 (17,5)
Initial tumors size	

<4 cm	
>4 cm	
Residue tumor size after CCRT	
<2 cm	272 (71,57)
>2 cm	108 (28,42)

TABLE 2 : Treatment details

Treatment details	
Radiotherapy	
Dose	46
Fraction	23
Chemotherapy (nombre of seances)	
1	28
2	42
3	158
4	152
Brachytherapy	
Applicator	
Fletcher	150
Ring	148
Vienna	20
Utrecht	24
Cylindre vaginale	38
CTV-HR (Gy)	95,93
Bladder (Gy)	65,5
Rectum (Gy)	61,4
Sigmoïde (Gy)	53,5
Grêle (Gy)	50,2
Overall treatement	66 (44 et 76 jours)

Discussion

This study aimed to describe the clinical, paraclinical, technical, dosimetric, and evolutionary aspects of high-dose-rate brachytherapy following concurrent chemoradiotherapy.

Concurrent radiotherapy combined with platinum-based chemotherapy followed by brachytherapy is the standard treatment for women with locally advanced cervical cancer.
Radiotherapy aims to eradicate the macroscopic tumor and control microscopic disease in the pelvic region, while the addition of concurrent chemotherapy has been shown to reduce both distant and local recurrences, providing a 12% benefit [11].

In this study, cisplatin was administered as the cytotoxic agent at a weekly dose of 40 mg/m², initiated concurrently with external beam radiotherapy. Prior to chemotherapy initiation, patients underwent a

laboratory evaluation, including complete blood count, renal function tests, and Fasting Blood Glucose and Electrolytes, to monitor potential treatment-related toxicities.

Conformal radiotherapy was delivered to the entire pelvic region using a four-field technique, encompassing an anteroposterior field and two opposing lateral fields, and a boost for macroscopic pelvic and lombo-aortic lymphadenopathy nodes and the parametria. Post concurrent chemoradiotherapy, 71.5% of patients demonstrated residual tumor dimensions of less than 2 cm.

Although no randomized study has directly compared patients treated with and without brachytherapy, studies based on international databases have shown that brachytherapy boost is the standard treatment for locally advanced cervical cancer, with improvements in overall survival (OS) and clinical outcomes. Logsdon et al. [12] demonstrated a significant 45% increase in the 5-year recurrence-free survival rate in 907 patients with stage IIIB cervical cancer treated with radiotherapy and brachytherapy, compared to 24% for exclusive radiotherapy.

This efficacy is based on delivering a high dose by placing a radioactive source in contact with or inside the primary tumor for a specific period of time, allowing for increased dose delivery to the tumor with a rapid dose drop-off at the periphery, thereby better preserving adjacent tissues (rectum and bladder) [13,14].

High-dose rate (HDR) brachytherapy is currently considered the standard in gynecological brachytherapy, as it is administered at a dose rate at point A exceeding 12 Gy/hour. HDR brachytherapy offers several advantages: it allows for dose fractionation, reduces irradiation time (less than 15 to 20 minutes), and provides a sufficient interval between fractions to promote the repair of sublethal damage. Additionally, when a fraction is administered weekly over a period of 4 to 6 weeks, it can also encourage cellular repopulation.

utero-vaginal brachytherapy is planned according to the Manchester method, which specifies the dose prescription at two distinct points: point A and point B. Point A is defined 2 cm laterally from the central canal of the uterus, at the tangent of the vaginal sources, and 2 cm above the lower end of the cervical canal. It corresponds to the intersection of the ureter and uterine artery, located in a region with a steep dose gradient. Point B, located 3 cm laterally from point A, is used to assess the dose delivered to organs at risk, particularly the bladder and rectum.

However, patients with larger tumors are likely to receive an insufficient dose with endocavitary brachytherapy, which may result in reduced local control. The dose optimization at point A is not suitable for the variability in tumor diameters, shapes, and extensions between patients. In other words, overdose could occur for small-volume tumors, and underdose for larger tumors.

Brachytherapy for cervical cancer can be performed using intracavitary, interstitial, or combined approaches. The choice of technique depends on the initial tumor extent, the size of the residual tumor after chemoradiotherapy, and the patient's anatomy. Intracavitary brachytherapy is the most commonly used technique in the treatment of cervical cancer. Tandem with ovoids or a ring applicator are the most frequently used applicators. In this study, tandem with ovoids was used in 45.78% of cases, and tandem with a ring in 44.21% of cases.

Interstitial brachytherapy is indicated for large residual lesions after EBRT, lower vaginal involvement, and lateral parametric or pelvic wall extension [15]. The interstitial brachytherapy technique involves

inserting multiple small hollow tubes to cover the residual tumor, but it was never applied in our study. In our study, 90% of patients underwent intracavitary brachytherapy, while 10% received endovaginal brachytherapy.

Image-guided adaptive brachytherapy has become increasingly common, and 3D planning using MRI or CT has improved treatment quality by providing greater precision in the dose delivered to target volumes and organs at risk [16,17]. MRI-guided brachytherapy remains the gold standard for intracavitary brachytherapy due to its high soft-tissue resolution, allowing precise delineation of the gross tumor and potential invasion of adjacent normal organs. The implementation of MRI-guided brachytherapy in clinical practice has significantly improved the ability to optimize, document, and report doses reproducibly, as demonstrated by numerous institutional reports [18,19].

The European Brachytherapy Group of the European Society for Radiotherapy and Oncology (GEC-ESTRO) has provided recommendations for target volume definitions and 3D imaging-based dosimetry [20,10].

These guidelines consider tumor response after chemo-radiotherapy, according to the American Brachytherapy Society (ABS), a total dose (EBRT and brachytherapy) > 80 Gy is administered to patients with a complete response or a partial response with residual disease < 4 cm, and 85–90 Gy for patients with poor response or residual disease > 4 cm [21].

Image-guided brachytherapy planning, based on GEC-ESTRO guidelines, was used for all patients in our study, with a dose administered for utero-vaginal brachytherapy was most often 7 Gy × 4 in 79.5% of cases, and in 66.6% of cases for vaginal brachytherapy, the dose administered was predominantly 5 Gy × 2.

Dose-volume histograms (DVH) were used to evaluate the treatment plan, with the objective of delivering a dose exceeding 85 Gy to the high-risk clinical target volume (CTV-HR) and greater than 60 Gy to the intermediate-risk clinical target volume (CTV-IR), while ensuring that less than 100% of the prescribed dose was administered to less than 2 cc of the organs at risk (OARs), namely the rectum, bladder, and sigmoid.

In our study, the total average EQD2 ($\alpha/\beta = 10$) for EBRT and brachytherapy for the high-risk clinical target volume (CTV) was 94.93 Gy. For the organs at risk, the total average EQD2 ($\alpha/\beta = 3$) was as follows: 65.5 Gy for the bladder, 61.4 Gy for the rectum, 53.5 Gy for the sigmoid colon, and 50.2 Gy for the small bowel.

Pelvic magnetic resonance imaging (MRI) represents a pivotal modality in assessing tumor response in patients with locally advanced cervical cancer following concurrent chemoradiotherapy and high-dose rate brachytherapy. Early pelvic MRI, conducted 3 months after the completion of treatment, is instrumental in detecting potential residual tumor tissue, which can inform subsequent salvage therapeutic strategies [[22]]. Post-therapeutic positron emission tomography (PET) scans are reserved for select cases. In the study, 185 (48,68%) patients underwent post-treatment MRI evaluations, while PET scans were not indicated.

The median follow-up duration in our cohort was 32 months (range: 19–48.7 months). At the conclusion of follow-up, complete remission was achieved in 89.73% of patients, lesion stability was observed in

2.36%, and 7.89% experienced loco-regional or distant recurrences. Recurrence rates were stratified by stage as follows: 6.15% for stage IIB, 10.97% for stage IIIC1, 19.64% for stage IIIC2, and 16.66% for stage IVA. Notably, the rate of local and metastatic recurrence was 26.3% among patients with treatment durations exceeding 65 days, compared to 11% for those whose treatment duration was ≤65 days.

A retrospective analysis evaluating the impact of total treatment time (EBRT and brachytherapy) on cervical cancer outcomes demonstrated a 1% reduction in local disease control for each day of delay beyond the median treatment duration [23]. Furthermore, a study by Williams et al., published in 2020, highlighted the detrimental effects of the COVID-19 pandemic on cervical cancer management, including prolonged treatment timelines, which adversely affected local disease control (24).

Conclusion:

This study suggests that concomitant pelvic radiation with cisplatin-based chemotherapy and 3D-HDR brachytherapy, following international recommendations regarding treatment duration (OTT), provides promising results in terms of short-term local control in the treatment of locally advanced cervical cancer.

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