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RESEARCH ARTICLE

HIGH DOSE RATE BRACHYTHERAPY IN THE TREATMENT OF CERVICAL CANCER: RETROSPECTIVE STUDY ABOUT 380 PATIENTS, EXPERIENCE OF THE NATIONAL INSTITUTE OF ONCOLOGY, RABAT

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Abstract

Introduction: Brachytherapy is an essential component in the treatment of women with cervical cancer, significantly improving overall survival and local control rates.The objective of the study is to present the Moroccan experience of the Rabat National Institute of Oncology in high-dose-rate (HDR) brachytherapy for cervical cancer.

Material and Methods: Retrospective study from January 2019 to December 2023carried 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 patients had a mean age of 54 years, with squamous cell carcinoma as the predominant histological type (88%), followed by adenocarcinoma (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 beam radiotherapy with a dose of 46 Gy concomitantly with weekly cisplatin at a dose of 40mg/m2. The average total course of external beam radiotherapy combined with brachytherapy was 66 days [44-75]. 90% of applications were intracavitary and 10% were vaginal brachytherapy. The applications were controlled by per-brachytherapy ultrasound.The protocols used for intracavitary 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 EQD2 (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 ofbrachytherapy was represented by minimal bleeding in 9% of patients, grade I cystitis in 3.5% of patients, and grade I radio-

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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 women 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.

Introduction:

Cervical cancer is the second most common cancer in women worldwide and the fourth leading cause of cancer-related death in women[1], nearly 85% of the population suffering from cervical cancer occurring 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 tumorstage, with locally advanced stages, five randomized trials have proved a survival benefit, improving both progression-free survival and overall survivalwith the combination of external radiotherapy and concomitant chemotherapy, and brachytherapy [4,5,6,7,8].

High dose Rate brachytherapyhas 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 with HDR brachytherapy in the management of locally advanced cervical cancer at the National Oncology Institute in Rabat.

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 HDR brachytherapy in 380 women 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, receiving a total dose of 46 Gy to the pelvic region in twenty-three fractions of 2 Gy per day, five days a week. This treatment was combined with weekly

cisplatin-based chemotherapy at a dose of 40 mg/m², with a maximum of 70 mg/m² per week. Macroscopic pelvic lymphadenopathy was treated with a dose of 60 Gy, while the lombo-aortic lymph nodes and 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

The patients received HDR brachytherapy following one of the treatment protocols.: four fractions of 7 Gy with 2 or 4 insertions (one insertion per week), 3 fractions of 8 Gy, or 2 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 responseand 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 target volume and organ-at-risk (OAR) delineation, following GEC-ESTRO guidelines[10]. The high-risk clinical target volume (HR-CTV) was defined as the residual tumor post-radiochemotherapy, including the cervix and gray zones observed on pelvic MRI (if performed). The intermediate-risk CTV (IR-CTV) included the HR-CTV, the initial tumor extent, and margins of 1,5 cm cranio-caudally, 1cm laterally, and 0.5cm antero-posteriorly. The OARs considered were the rectum, bladder, and sigmoid colon.

HDR brachytherapy dose prescription was based on Point A, as defined by the Manchester system. The cumulative dose to Point A, combining HDR brachytherapy and EBRT, was calculated using the linearquadratic model with an α/β ratio of 10, targeting a total dose of 85 to 95 Gy. Dose constraints for organs at risk (OARs) followed the recommendations of ICRU Report 38, with cumulative dose limits of 65 to 70 Gy for the rectum and 80 to 90 Gy for the bladder, using an α/β ratio of 3.

Follow-up

Throughout treatment, women underwent weekly clinical surveillance. Following completion of treatment, they were monitored every three months for two years, subsequently every six months for three years, and then every year. Local recurrence was initially suspected based on clinical examination and later confirmed through MRI and biopsy.

Diseasefree survival was defined as the time from treatment initiation to the confirmation of either local or metastatic recurrence.

Local recurrence was identified as disease reactivation within the irradiated area, while distant recurrence referred to the appearance of metastases outside the treated region. The date of recurrence was established based on imaging or histopathological confirmation.

Results:

A total of 380 patients with locally advanced cervical cancer were included in this study, all treated with concomitant chemoradiotherapy combined with HDR brachytherapy.

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

Pelvic magnetic resonance imaging (MRI) was performed in 98% of patients to assess locoregional extension. According to the 2018 FIGO classification, tumor stage distribution 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 chemoradiotherapy. The average total duration of external radiotherapy combined with brachytherapy was 66 days (range: 44–75 days) (Table 1).

All patients received EBRT at a total dose of 46 Gy, administered in 2 Gy\fractions, five sessions per week. Concomitant chemotherapy consisted of weekly cisplatin at a dose of 40 mg/m², with a maximum of 70 mg/m² per week.

90% of brachytherapy applications were intracavitary, 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 endovaginalcases,2x6 Gy weekly in 2% of endovaginal cases, and 3x6 Gy weekly in 2.5% of endovaginalcases.

Brachytherapy dosimetry was performed using a dosimetric CT scan for all patients. The total average EQD2 (α/β = 10) for EBRT and brachytherapy for the HR-CTV was 94.93 Gy. The mean total EQD2 (α/β = 3) for organs at risk 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 treatmentrelated mortality was observed during the study.

The median followsup time was 32 months (range: 19–48.7 months). At the end of the follow-up period, 89.73% of women 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 (%)**
Medianage= 54 years	
Range Age 33-87	
<40 years	120 (31,57)
>40 years	260 (68,42)
Symptomatology	
Métrorrhagia	245 (64,47)
Pelvic pain	69 (18,15)
Vaginal discharge	28 (7,36)

Autres	38 (10)
Histology	
Squamouscellcarcinoma	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 tumor size	
<4 cm	298 (78,42)
>4 cm	82 (21,57)
Residue tumor size after CCRT	
<2 cm	272 (71,57)
>2 cm	108 (28,42)

Table 2: Treatmentdetails.

Treatmentdetails	
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
Cylindrevaginale	38
CTV-HR (Gy)	95,93
Bladder (Gy)	65,5
Rectum (Gy)	61,4
Sigmoïde (Gy)	53,5
Grêle (Gy)	50,2
Overalltreatement	66 (44 et 76 jours)

Discussion:

The objective of this study was to analyze the clinical, paraclinical, technical, dosimetric, and therapeutic outcomes of high-dose-rate brachytherapy following concomitant chemoradiotherapy in patients with locally advanced cervical cancer.

The standard treatment for locally advanced cervical cancer consists of external beam radiotherapy (EBRT) combined with platinum-based chemotherapy, followed by brachytherapy. Radiotherapy aims to eradicate macroscopic tumor lesions while controlling microscopic disease within the pelvic region. The addition of concurrent chemotherapy has been demonstrated to enhance both local and distant disease control, resulting in a 12% improvement in overall therapeutic benefit[11].

In this study, cisplatin was used as the cytotoxic agent, administered at a weekly dose of 40 mg/m², starting concomitantly with radiotherapy. Before initiating chemotherapy, patients underwent a comprehensive laboratory assessment, including complete blood count, renal function tests, fasting blood glucose, and electrolyte analysis, to monitor potential treatment-related toxicities.

Conformal radiotherapy was delivered to the entire pelvic region using a fourfield technique, encompassing an antero-posterior 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 45% increase in thefive-year recurrence-free survival rate in 907 women with stage IIIB cervical cancer treated with radiotherapy and brachytherapy, compared to 24% for exclusive radiotherapy.

This efficacy is achieved by delivering a high dose through the placement of a radioactive source in direct contact with or inside the primary tumor for a specified duration. This approach allows for an increased dose concentration within the tumor while ensuring a rapid dose drop-off at the periphery, thereby better preserving adjacent organs such as the rectum and bladder[13,14].

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-vaginalbrachytherapy 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 may receive an insufficient dose with endocavitary brachytherapy, potentially leading to reduced local tumor control. Dose optimization at point A does not suitable for interpatient variations in tumor diameter, shape, and extent. Consequently, small-volume tumors may be overtreated, whereas larger tumors may be undertreated.

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 following chemoradiotherapy, and the patient's anatomical characteristics. Intracavitary brachytherapy is the most commonly utilized method, with tandem and ovoid or ring applicators being the most frequently employed. In this study, tandem and ovoid applicators were used in 45.78% of cases, while tandem and ring applicators were used in 44.21% of cases.

Interstitial brachytherapy is recommended for patients with large residual lesions after EBRT, involvement of the lower vagina, or lateral parametric and pelvic wall extension[15]. This technique involves inserting multiple small hollow tubes to ensure adequate dose coverage of the residual tumor. However, it was not utilized in this study. Among the patients included, 90% underwent intracavitary brachytherapy, while 10% received endovaginal brachytherapy.

Imageguided 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 OAR [16,17]. MRI-guided brachytherapy is considered the gold standard for intracavitary brachytherapy due to its superior soft-tissue contrast, enabling precise delineation of the gross tumor and potential invasion of adjacent organs. Its integration into clinical practice has significantky enhanced dose optimization, documentation, and reproducibility, as evidenced by multiple institutional studies[18,19].

The European Brachytherapy Group of the European Society for Radiotherapy and Oncology (GEC-ESTRO) has establishedguidelinesfor target volume definitions and 3D imaging-based dosimetry [20,10].
These guidelines consider tumor response following chemoradiotherapy,according to the American Brachytherapy Society (ABS), a total dose (including external beam radiotherapy and brachytherapy) exceeding 80 Gy is recommended for patients demonstrating a complete response or a partial response with residual disease < 4 cm, while a dose of 85–90 Gy is advised for patients with a poor response or residual disease > 4 cm[21].

Imageguided 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 utilized for treatment plan evaluation, aiming to deliver a dose exceeding 85 Gy to CTV-HR and greater than 60 Gy to CTV-IR. Additionally, dose constraints were applied to organs at risk (OARs), ensuring that the volume receiving 100% of the prescribed dose remained below 2 cc for 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 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 MRI is a key imaging modality for evaluating tumor response in patients with locally advanced cervical cancer following concurrent chemoradiotherapy and high-dose-rate brachytherapy. An early pelvic MRI, performed three months after treatment completion, plays a crucial role in detecting residual tumor tissue, thereby guiding potential 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 assessing the influence of total treatment time (including external beam radiotherapy and brachytherapy) on cervical cancer outcomes revealed a 1% decrease in local disease control for each day of treatment delay beyond the median 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 radiotherapy combined with cisplatin-based chemotherapy and three-dimensional high-dose-rate brachytherapy, in accordance with international recommendations regarding overall treatment time, achieves promising short-term local control outcomes in the management of locally advanced cervical cancer.

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