

Is Advanced Age a Limiting Factor in the Practice of High Dose Rate Brachytherapy in Patients Treated for Cervical Cancer?

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Abstract:

➤ Purpose:

To assess the percentage of elderly patients not receiving brachytherapy in our practice and identify the factors influencing the decision to forgo this therapeutic modality in this population.

➤ Materiel and Methods:

A retrospective study including patients aged ≥ 65 years old admitted in the brachytherapy unit, at the radiotherapy department of the national institute of oncology Sidi Mohamed ben Abdellah in Rabat, for a year. The characteristics of the included patients were examined as well as the modality of administration of brachytherapy. For cases where intracavitary ICBT could not be feasible, reasons behind its non-practice were determined.

➤ Results:

Patients ≥ 65 years old represented 31% (n=38) of all patients admitted in one year in the brachytherapy unit (average age was 71,8 years). Comorbidities were present in 20 patients (53%). All patients received treatment using external beam radiation therapy (EBRT), 81,6% with concurrent chemotherapy. HDR brachytherapy was performed in 65,8 % of our patients, delivered in three or four sessions. Causes of impractical intracavitary brachytherapy in elderly patients with cervical cancer revealed that the size of the residual tumor was the most common factor Identified.

➤ Conclusion:

Age is not a limiting factor for receiving suitable brachytherapy treatment, moreover elderly cervical cancer patients should receive brachytherapy if their performance status is adequate and the extent and severity of comorbidities do not contraindicate it. The most commonly cited reasons for not performing brachytherapy was tumor-related factors, Hence the importance of early diagnosis and screening in this age group

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I. INTRODUCTION

Based on scientific publications and recognized organizations (World health organization (WHO), National Institute on Aging (NIA), Eurostat), older women are considered from the age of 65 years, especially in the context of health care and gerontology, because this age is often associated with significant changes in physical and mental health.

The World Health Organization projects that the population aged over 60 will double by 2050, representing

22% of the total global population. [1] The number of cancers in the elderly is also increasing due to the increase in life expectancy, 83.0 years for women and 77.9 years for men [2], Since the rate of tumors diagnosed in patients aged over 65 years is expected to rise 70% by 2030 [3], the management of elderly cancer patients poses difficulties seen the potential increased risk of morbidities.

Focusing particularly on cervix cancer, the standard treatment is concomitant radiochemotherapy followed by brachytherapy performed on the uterus and vagina. However, elderly patients may not be always able to

complete curative radiotherapy, and some of them cannot benefit from the practice of brachytherapy due to many factors: severe comorbidities, tumor size, or technical problems.

Elderly patients should be managed carefully during the treatment, especially when brachytherapy is giving, so as to reduce acute and late complications. Treatment policy should be sometimes optimized by shortening the treatment duration, changing the brachytherapy fractionation strategy and even adapting the drugs regimens combined to radiotherapy so as to be tolerable and effective for fragile old patients.

➤ *Purpose:*

The aim of this study is to explore the use of brachytherapy in old patients treated for locally advanced cervical cancer, and how can this treatment be adapted to the specificities of this age group. We also aim through this work to research the causes of impractical brachytherapy in elderly.

II. MATERIEL AND METHOD

➤ *Population:*

This retrospective study included 38 patients aged 65 to 89 years old, who were diagnosed with invasive cervical cancer, admitted in the brachytherapy unit at the radiotherapy department of the national institute of oncology Sidi Mohamed ben Abdellah in Rabat, between October 2023 and October 2024.

None of the patients underwent radical hysterectomy as their initial treatment and none of the participants was excluded because of incomplete data.

➤ *Procedures:*

All patients were treated with curative intent. The treatment plan involved curative radiotherapy, consisting of external beam radiation therapy (EBRT) with or without concomitant chemotherapy (based on the patient's tolerance), followed by 3D (scan guided) high-dose-rate (HDR) intracavitary brachytherapy.

EBRT was delivered at a total dose of 46 Gy due to 2 Gy per fraction, with 5 fractions per week, regardless of the tumor stage. Typically we use conformational techniques with 18 MV X-ray photons (box technique: two fields AP, PA, and two lateral fields). External radiotherapy using VMAT technique was employed in certain patients who required lomboarctic irradiation, particularly for tumors at stage IIIC, to achieve better dose distribution and homogeneity, as well as optimal protection of organs at risk. This was done using 6 MV photons generally in 2 arcs.

A dose overlay on the parameters (10 GY, 2GY per fractions) and lymphadenopathy (10- 14 GY, 2GY per fractions) by external radiotherapy was also indicated based on the tumor stage, considering both parametrial invasion and the presence of lymph node involvement.

For patients who received brachytherapy after radical cervical cancer treatment, an HDR-ICBT dose of 24 to 28 Gy was administered at point A using a FLEXITRON source projector, following a protocol of either 4x7 Gy weekly or 3x8 Gy weekly. The applicators were loaded remotely with 192-Iridium, and the ONCENTRA brachytherapy planning system was used for HDR-ICBT treatment planning.

We referred to cases where intracavitary brachytherapy (ICBT) could not be feasible as "impractical." Conformal radiotherapy boost by VMAT technique (20-24GY, 2GY per fraction) to the primary tumor was considered when ICBT could not be performed.

➤ *Statistical Analysis:*

The data for the patients included in our study were collected retrospectively from electronic medical records in the ENOVA system, as well as from the Excel file used for planning and scheduling patients in the brachytherapy unit. Information regarding: age, comorbidities, current medications, the course of external radiotherapy treatment (tolerance, scheduling, side effects, and whether it was combined with concurrent chemotherapy or not), as well as whether or not brachytherapy was performed (protocol, tolerance, applicator details), and the reasons behind its non-practice, were all documented in an Excel file for the study. All statistical analyses were performed on a personal computer with SPSS version 11.0.1.

III. RESULTS

Between October 2023 and October 2024, a total of 121 patients have been admitted for intracavitary brachytherapy for cervical carcinoma in the brachytherapy unit at the radiotherapy department at the National Institute of Oncology in Rabat. Of these, patients over 65 years old represented 31,4 % (n=38).

➤ *Patients and Tumor Characteristics:*

The average age was 71,8years (range: 65 –87, median age= 70). 81,6% of the patients presented An histology of squamous cell carcinoma, with well-differentiated tumors identified in 64% of cases . Comorbidities were present in 20 patients (53%), including cardiovascular issues (hypertension in 12 patients, congestive heart failure in 4 cases), metabolic disorders (diabetes in 6 cases, thyroid dysfunction in 3 patients), and respiratory conditions (chronic obstructive pulmonary disease in 3 cases). 97,4% patients were deemed suitable for anesthesia for the uterovaginal brachytherapy procedure. An history of vaginal birth was present in 87% of cases.

The majority of patients had initial tumors larger than 4 cm (with a minimum classification of IIb). Negative pelvic and lomboarctic nodal statuses were observed in 50% and 79% of patients, respectively.

The patient and tumor characteristics of elderly patients with cervical cancer admitted in the brachytherapy unit of our department are detailed in Table 1.

➤ *Treatment:*

All patients received treatment using combined external beam radiation therapy (EBRT), 81,6% with concurrent chemotherapy, while 18,4% of patients didn't receive chemotherapy concurrently with radiotherapy. The average number of chemotherapy sessions received concurrently with external radiotherapy is 3, with a good tolerance to the chemotherapy regimen in 26 cases.

A pelvic examination was conducted for all patients at the brachytherapy first consultation and in the operating room before the first insertion. Tumor response to external beam radiation therapy (EBRT) was assessed as follows:

NRT Response (No Gross Residual Tumor): This indicated complete or nearly complete regression of the cervical tumor, with non-specific fibrosis or granulation observed on the cervix. This response was observed in 23 patients.

GRT Response (Gross Residual Tumor): This was characterized by the presence of a gross tumor or palpable nodularity on the cervix, and/or palpable induration of the parametrium. This response was observed in 15 patients.

General anaesthesia was not routinely performed for the brachytherapy insertions, only one patient required general anaesthesia as she experienced vagal discomfort at the time of spinal anaesthesia.

HDR brachytherapy was performed in 65,8 % of our patients aged over 65 years, whereas the indication for brachytherapy was rejected in 34,2% of cases due to multiple factors that we will detail later.

The intracavitary brachytherapy characteristics are summarized in Table 2. Brachytherapy was delivered in three or four sessions. The dose was prescribed to

encompass the residual tumor while considering the initial tumor extension. Twelve patients benefited from an HDR endocavitary brachytherapy protocol in 3 fractions, i.e. 3x8GY weekly, taking into account their general condition (PS score), a localized residual disease, as well as the prior lengthening of the overall treatment time, in order to remain within the theoretical treatment timeframe (not exceeding 55 days in overall treatment time EBRT+BT). On another hand, thirteen patients received brachytherapy according to the 4x7GY weekly protocol, indicated for fit patients, with slightly more advanced residual disease.

The 3x8 and 4x7 protocols for endocavitary brachytherapy, as recommended by the GEC-ESTRO (Groupe Européen de Curiethérapie - European Society for Radiotherapy and Oncology), are commonly used in the treatment of certain gynecological cancers, particularly cervical cancer. Both protocols aim to balance effective tumor control with the minimization of toxicity to surrounding healthy tissues. The 3x8 and 4x7 protocols are generally considered equivalent in terms of EQD2 (Equivalent Dose in 2 Gy fractions) for the tumor. The median overall duration time was 54 days (extremes: 49-59 days).

Regarding the applicator used, 72% of our patients (those who have benefited from brachytherapy) were treated with a uterine probe applicator plus a ring. The most commonly used angle for the uterine probe was 60 degrees (generally chosen for uterus located along the umbilical-coccygeal line), and the most frequently used ring diameter was 34 mm. Besides, 29% of patients were treated using uterine probe applicators combined with ovoids (FLETCHERS) when there was residual disease extending to the upper third of the vagina, or in cases of specific anatomical conditions such as a funnel-shaped or barrel-shaped cervix.

Table 1 Baseline Characteristics of all Patients

Patients (n= 38)	
Age (years)	
65-75	22
75-87	16
Average age	71,8 years
Performance status	
0	10
1	15
2	10
3	3
FIGO stage	
I	0
II	16
III	10
IVA	12
Histology	
SCC	31
Non-SCC	7
Lymph node involvement	
N0	19

N+	17
Comorbidities	
NA	18
Diabetes	6
Hypertension	12
Heart disease	4
Respiratory pathology	3
More than one	6
Vaginal birth	
NA	5
Present	33
EBRT (total dose=46 GY ,2GY/Fr)	
3D	16
VMAT	22
Concurrent chemotherapy	
NA	7
Done	31
ICBT (total dose =24-27 GY)	
NA	13
Done	25

EBRT, external beam radiation therapy; FIGO, International Federation of Gynecology and Obstetrics; ICBT, intracavitary brachytherapy; NA, not applicable; SCC, squamous cell carcinoma.

Table 2 Brachytherapy Modality

Brachytherapy	
Equipment	Flexitron Ir-192 remote after loading system
Anaesthesia	Spinal anaesthesia
fractionation	
4X7GY once/week	13
3X8GY once/week	12
Applicator	
RING	18
FLETCHER	7
Break between EBRT and ICBT	0-14J (median =7 days)

The investigation into the causes of impractical intracavitary brachytherapy in elderly patients with cervical cancer revealed that the size of the residual tumor was the most common factor Identified (see Table 3). Age related reason such as comorbidities and patient's vulnerability was behind only 2 impractical brachytherapy in our series, also anatomical causes such as very narrow vagina was found in one patient, whereas in one patient, the non-practice of

brachytherapy was due to her personal conviction (refusal of the patient) and not to a medical cause.

We found that having no history of vaginal births was an independent risk factor for impractical application. Other clinical risk factors, such as body mass index, and performance status, did not show any association with the impractical application.

Table 3 Clinical Courses of Impractical Intracavitary Brachytherapy Patients

	Age (years)	PS	Comorbidity	Vaginal births	Stage	Residual Tumor diameter (APxTxH mm)	Reason of impractical brachytherapy
1	69	1	—	+	IIIC2	35X40X39	Tumor size
2	81	3	—	+	IVA	34X36X29	Bladder invasion
3	67	1	—	+	IIIB	39X49X48	Tumor size
4	65	2	—	—	IIB	38X45X50	Tumor size
5	74	0	+	+	IVA	39X47X58	Bladder invasion+ tumor size
6	68	1	—	—	IIIA	30X25	Anatomical/very narrow vagina
7	80	3	+	+	IIB	25X20	anesthetic risk/comorbidity
8	72	0	—	+	IIB	30X20	Patient's refusal
9	82	3	+	+	IIB	22X18X16	Posture difficulty
10	76	2	—	—	IVA	38X35X29	Bladder invasion
11	66	1	+	+	IVA	35X39X42	Bladder invasion

12	68	0	+	+	IVA	39X51X45	bladder invasion+ tumor size
13	66	2	+	—	IVA	44x56X43	Tumor size

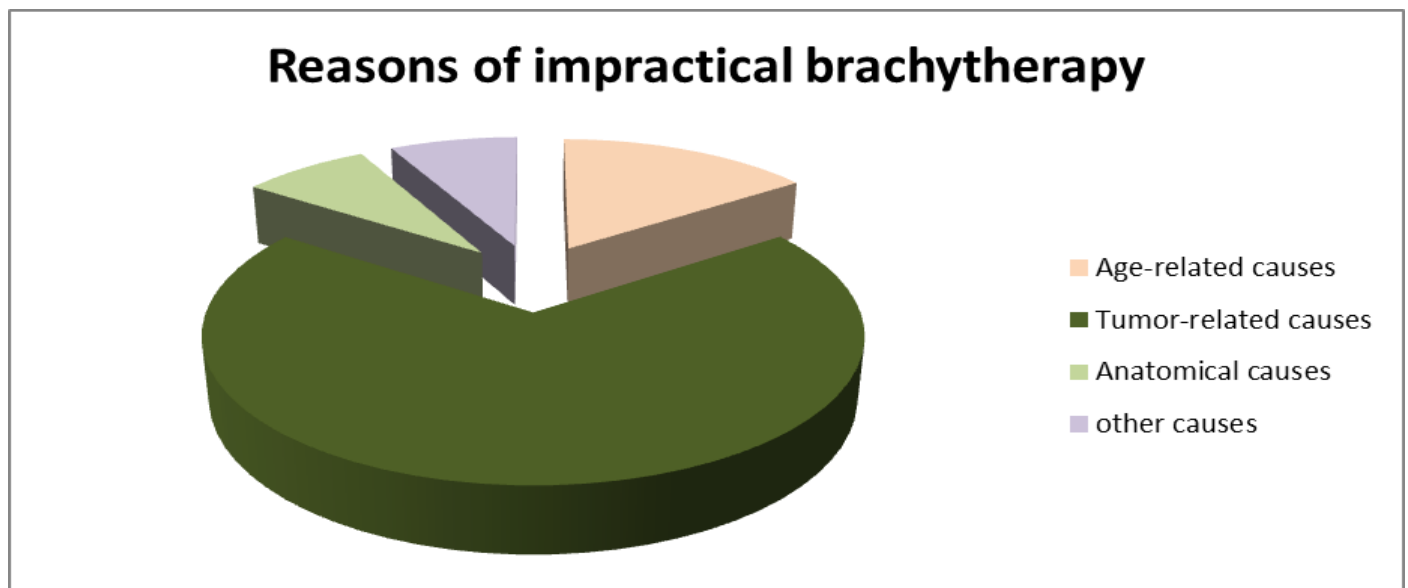


Fig 1 Reasons of the Non-Practice of Brachytherapy

IV. DISCUSSION

The number of elderly patients is rising in many countries. The treatment outcomes of radiation therapy in elderly are considered acceptable when compared to younger patients, especially when complete radiation therapy can be administered.

Although chemoradiotherapy including brachytherapy, is the standard treatment for locally advanced or inoperable cervical cancer, existing data primarily come from studies involving patients mostly under 70 years old. The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database includes information on 28,902 patients with cervical cancer, but only 13.5% were aged 70 or older. Elderly women often presented with squamous cell tumors, grade 3, and advanced-stage disease [4] and they received different treatment approaches compared to younger patients [5,6]. For instance, 20% of patients aged 70–79 and 40% of those over 80 did not receive brachytherapy. Our study revealed that 34.2% of patients aged over 65 years old did not receive brachytherapy.

Many older patients have concomitant medical conditions, which often lead to decreased tolerance, slower recovery, and reduced life expectancy following radiation therapy (RT) treatment. Therefore, it is essential to manage older patients more carefully during treatment to minimize both acute and chronic complications, especially when combining external beam radiation therapy (EBRT) with high-dose-rate intracavitary brachytherapy. Kennedy et al. reported that 78% of patients aged 75 years and older have pre-existing medical issues [7]. Likewise, Mitchell et al. found that the primary reason for not performing intracavitary brachytherapy (ICBT) in elderly patients was complications related to comorbidities (50%), while technical issues accounted for only 7% in low-dose-rate

ICBT[8]. In contrast, in the non-elderly group, impractical ICBT was primarily due to technical problems (41.7%). Significant risk factors for impractical application included a large tumor size and a lack of history of vaginal births [8].

Medical comorbidities and anesthetic risk are also frequently mentioned as reasons for the omission of brachytherapy; however, no formal anesthetic risk assessments were performed in these clinical trials. Furthermore, cervical brachytherapy can be administered using regional or local anesthesia, and both the number of fractions and the treatment workflow can be customized to enhance patient comfort [12]. In our study, and despite the fact that comorbidities were significantly present in our patients (53%), they did not really impact the performance of spinal anesthesia and did not constitute a major cause of non-practice of brachytherapy and only 2 patients were rejected for reasons related to age.

The presence of bulky tumors was identified as a significant risk factor for the impractical application of the ICBT device in multivariate analysis [9,10]. It has been suggested that the survival rate for patients with bulky tumors may decline due to a reduced radiation effect on the tumor and limitations in the radiation dose resulting from incomplete ICBT in elderly patients. [11]

Our study confirmed that size of residual tumoral after EBRT is the major reason of impractical brachytherapy with 69% of cases rejected for cervical residue exceeding 4 cm in more than one dimension, or the persistence of bladder or rectal involvement.

Magné et al have shown that Elderly women with cervical cancer tolerated brachytherapy (BT) well and achieved excellent rates of local disease-free and specific survival. Age did not affect the effectiveness of BT in older

patients, and it should be considered whenever feasible, even for elderly patients diagnosed with cervical cancer [13]. It was demonstrated by Yanazume et al. that incomplete high-dose-rate intracavitary brachytherapy (HDR-ICBT) led to decreased survival rates in elderly patients. Factors such as larger tumor size and a lack of vaginal birth history were linked to incomplete HDR-ICBT, which proved fatal, especially for elderly patients with bulky tumors [11].

Although, it has been shown in the literature that aged skin has lower hydration levels, decreased elasticity, increased permeability, and is more challenging for applying the ICBT device in patients without a history of vaginal births [14]. The impact of a history of vaginal births on the application of ICBT has not been demonstrated in our study. This can be explained by the advancements in techniques, such as image guided BT utilizing CT or magnetic resonance imaging,

The underutilization of brachytherapy in cases of locally advanced cervical cancer is widely acknowledged, and this issue is especially significant among the elderly. Studies from North America indicate that 20% of women aged 70 to 79 and up to 60% of women over 80 do not receive brachytherapy [15, 16].

Analysis of clinical trials from cooperative oncology groups (COG), which include some of the largest stage IVA patient populations in the literature, found that brachytherapy was not completed in 35% of patients aged 70 and older, compared to only 13% of patients under 40. This discrepancy persists even though these clinical trials are conducted at large tertiary centers with well-established brachytherapy programs [17].

A retrospective cohort study examining the effects of CT-based brachytherapy in 105 elderly patients (aged 70 to 89) reported 5-year local control and cancer-specific survival rates of 89% and 78%, respectively, with a toxicity profile comparable to that of younger cohorts [18]. Brachytherapy is a crucial component in the treatment for curative intent in cervical cancer (beyond Stage IB) and should not be omitted in elderly patients unless they are medically unfit. Replacing brachytherapy by external beam radiation therapy (EBRT) or stereotactic body radiation therapy (SBRT) boosts is associated with poorer outcomes [19].

The benefits of both definitive and palliative brachytherapy in the elderly population were emphasized in a recent literature review. For aged or frail patients, a comprehensive geriatric assessment is recommended to evaluate individual fitness for brachytherapy. This assessment should consider tumor biology, potential toxicities, physiological age, patient preferences, quality of life, and remaining life expectancy. In case of cervical cancer, brachytherapy is a mandatory component of curative treatment and should not be readily omitted in elderly patients [20].

V. CONCLUSION

Regardless of their advanced age and existing comorbidities, older patients should be considered for definitive cancer treatments. Brachytherapy is an essential part of radical treatment of uterine cervix cancer, unless significant medical contraindications prevent its use. The results of our study are consistent with those of the literature and suggest that age does not pose a barrier to receiving appropriate brachytherapy treatment. Tumor-related causes such as tumor size and invasion of neighboring organs (bladder, rectum) are most often incriminated in the non-practice of brachytherapy. This finding highlights the importance of early diagnosis of cervical cancer in elderly women, which allows a better therapeutic approach and therefore better local control.

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