Advances in Radiation Oncology (2024) 9, 101512

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Monocentric Retrospective Study: Efficacy, Feasibility, and Prognostic Factors of Single-Insertion High-Dose-Rate Brachytherapy With 4 Sessions for Locally Advanced Cervical Cancer

Lucie Houdou, MD,[a] Claire Meynard, MD,[a] Sophie Guillerm, MD,[a] Camille Mimoun, MD,[b] Tiphaine Lambert, MD,[c] Eva Marchand, MD,[b] Diane Jornet, MD,[a] Ingrid Fumagalli, MD,[a] Laurent Quero, MD, PhD,[a,d] Cyrille Huchon, MD, PhD,[a,d] and Christophe Hennequin, MD, PhD[a,d,*]

[a]Radiation Oncology Department, Saint-Louis Hospital, Paris, France; [b]Gynecologic Department, Lariboisière Hospital, Paris, France; [c]Medical Oncology Department, Saint-Louis Hospital, Paris, France; and [d]University of Paris-Cité, Cancer Institute of Oncology, Paris-Nord

Received 27 November 2023; accepted 2 April 2024

Purpose: This study aims to assess the feasibility and efficacy of high-dose rate (HDR) brachytherapy (BT) administered in a single insertion with 4 treatment sessions for locally advanced cervical cancer and to identify the prognostic factors influencing outcomes.

Methods and Materials: We retrospectively analyzed the clinical data of patients with cervical cancer with locally advanced disease (International Federation of Gynecology and Obstetrics 2018 IB-IVB) treated at our institution from January 2014 through December 2021. Each patient received definitive radiation therapy with an external irradiation dosage between 45 and 50.4 Gy along with concurrent chemotherapy. HDR-BT (24 Gy) was prescribed to a high-risk clinical target volume.

Results: One hundred thirty-nine patients were included and the HDR-BT program could be fully performed in 136 patients (98%). Over a median follow-up duration of 40.5 months, the 2-year local control (LC), overall survival (OS), and disease-free survival rates stood at 79.4%, 77.7%, and 61.7%, respectively, with 5-year rates at 78.2%, 61.6%, and 55.7%. Multivariate analysis revealed the primary determinant of LC as the tumor's response to external beam radiation therapy as determined via magnetic resonance imaging before BT. Parametrial involvement demonstrated a significant multivariate association with disease-free survival (P = .04). Regarding OS, parametrial invasion (P = .01) and the tumor's response postchemoradiotherapy (P = .02) emerged as significant factors. Regarding chronic toxicities, 18% (25 patients) experienced grade 3 complications. An optimal D2 cc (bowel) threshold of 70 Gy (P = .001) was identified to limit chronic digestive complications of grade 3 or higher.

Conclusions: The implementation of single-insertion, 4-session HDR-BT could be performed in 98% of the patients. It yields favorable LC and OS rates, coupled with tolerable toxicity in patients with locally advanced cervical cancer. Response to initial chemoradiotherapy evaluated on pre-BT magnetic resonance imaging is an important prognostic factor and could help to individualize therapeutic strategies.

Sources of support: This work had no specific funding.

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

*Corresponding author: Christophe Hennequin, MD, PhD; Email: christophe.hennequin2@aphp.fr

https://doi.org/10.1016/j.adro.2024.101512

Introduction

Cervical cancer is a prevalent gynecologic malignancy and the fourth most common cancer diagnosed in women worldwide. Annually, over 530,000 women are diagnosed, resulting in more than 270,000 deaths globally.[1] In France, there are 3000 new cases and 1100 attributed deaths each year,[2] representing a major public health problem, with three-quarters of cervical cancers diagnosed in women under 65.

Identified risk factors include infection by specific human papillomavirus types,[3] smoking,[4] immunodeficiency,[5] early age at first sexual intercourse, history of sexually transmitted infections, multiple sexual partners, and nonparticipation in screening programs.[6] Cervical carcinogenesis typically initiates from precancerous lesions, which may progress to invasive cancer.[7]

For cervical lesions at stages IB1, IB2, and IIA1, surgical options such as cervical conization or hysterectomy are preferred, typically involving type C radical hysterectomy with pelvic lymphadenectomy.[8]

Prognostic factors for locally advanced cervical cancer (LACC) encompass tumor stage,[9] age,[10] tumor size, lymph node invasion,[11] histologic type, anemia at diagnosis,[12] serum squamous cell carcinoma (SCC) antigen level at diagnosis,[13] and p16 protein expression. Regarding therapeutic parameters, overall treatment time (OTT)[14] and concomitant chemotherapy must be carefully monitored. Previous studies have reported 5-year overall survival (OS) rates ranging from 61.9% to 77.9% in patients with LACC.[9,15] It is necessary to identify patient-, disease-, and treatment-related risk factors and biomarkers for outcomes to define risk groups that can be used for intensification of multimodality treatment in high-risk patients and de-escalation of treatment in low-risk patients.

Treatment for LACC consists of concomitant chemoradiotherapy, followed by uterovaginal brachytherapy (BT).[16] The total uterovaginal BT dose administered depends on several factors, with 2 main techniques: high-dose rate (HDR) and pulsed-dose rate BT. BT is a fundamental component of treatment, exerting a significant effect on prognosis,[17] with no real consensus on HDR-BT fractionation schemes.[18]

Because the organization of multiple insertion under anesthesia is difficult in our country, because of a poor availability of anesthetists, we developed a new schedule of image guided HDR-BT with 1 insertion, performed under general anesthesia, and 4 fractions in 3 days, during a conventional hospitalization.

The aim of this study is to explore the feasibility and efficacy of this image guided HDR-BT protocol with a combined intracavitary and interstitial technique in patients with LACC and to evaluate prognostic factors.

Methods and Materials

Patients

We conducted an observational, retrospective, single institution study for patients with LACC receiving HDR-BT boost. All patients treated for a carcinoma of the cervix with an HDR-BT boost in our institution between 2014 and 2021 were reviewed retrospectively. HDR-BT boost was delivered with a single implant and 4 fractions during a conventional hospitalization.

Inclusion criteria were biopsy-diagnosed cervical SCC, adenocarcinoma or neuroendocrine, locally advanced disease (International Federation of Gynecology and Obstetrics 2018 [FIGO] IB-IVB), and no previous surgery or external-beam radiation therapy for cervical cancer.

At diagnosis, patients had clinical examination, biologic test, pelvic magnetic resonance imaging (MRI), and 18 fluoro-deoxy-glucose positron emission tomography (PET). Tumor size was determined on clinical examination and/or MRI (maximum width on axial T2-weigthed sequence). Para-aortic (with or without pelvic) lymph node (LN) dissection was during the study period recommended to improve the accuracy of the staging in case of PET negative on the para-aortic area.

The exclusion criteria were the absence of BT (exclusive chemo-radiation therapy treatment) and the lack of data concerning recurrence.

Data concerning each patient were recovered using dosimetry records and local clinical files. Before data collection in our center, the consent of all patients was obtained.

Treatment

Treatment consisted of external-beam radiation therapy (EBRT) to the pelvis with concomitant chemotherapy, followed by HDR intracavitary and interstitial BT based on MRI. Para- aortic radiation therapy was applied in patients with para-aortic nodal metastasis after LN dissection or with positive nodes on PET-computed tomography (CT).

Clinical target volume (CTV) covered gross tumor volume (GTV), cervix, uterus, parametrium, upper part of the vagina, and pelvic LNs (common, internal, and external iliac and obturator and presacral LNs). The CTV for para-aortic LNs encompassed the entire lumbo-aortic region. The GTVn included all positive LNs visible on the PET scan.

EBRT was prescribed with 1.8 to 2 Gy daily fractions, 5 days per week, up to a total dose of 45 to 50.4 Gy in 25 to 28 fractions to planning target volume. For patients with positive regional LN, a boost dose was delivered, usually 10 to 15 Gy.

Concomitant platinum-based chemotherapy was administered. In most cases, this was a synchronous sensitization chemotherapy regimen consisting of 5 to 6 weekly cisplatin (40 mg/m^2). For some patients with large tumor volume, a neoadjuvant chemotherapy was administered.

At the end of the EBRT treatment and during the week before BT, a new pelvic MRI was recommended to evaluate tumor response and to better define the target volumes of BT. However, this second MRI could not be done in all patients for logistic reasons. The date of BT was established with an objective of achieving an OTT, including BT, of under 55 days.[19] It must be emphasized that this MRI was not done before the implantation.

All patients were admitted to the radiation therapy inpatient ward for a minimum duration of 3 days to ensure medical monitoring, which included a daily clinical examination. Prophylactic anticoagulation was usually prescribed (eg, enoxaparine 4000 international Unit/subcutaneous injection (UI/SC) daily). On day 1, the uterovaginal BT device was inserted in the operating room by a specialized radiation oncologist, with the patient under general anesthesia. We used the Vienna ring applicator[20]; if possible, interstitial needles (usually 4-6) were inserted inside the cervix to obtain a better coverage of the target volumes. The placement of the intrauterine device was facilitated through suprapubic ultrasonography.

The day after BT device placement, patients had a pelvic CT scan. All high-risk (HR) CTV, intermediate-risk (IR) CTV, and organs at risk (OARs) were delineated according to groupe européen de curiethérapie - european society for radiotherapy and oncology (GEC-ESTRO) and (ICRU) international commission for radiation units recommendations[21] and with the help of preimplant MRI.

HR-CTV consisted of the whole cervix and residual GTV, which was composed of any manifested residual tumor extension at the time of BT and residual pathologic tissue as defined by clinical examination performed during device insertion and post-EBRT MRI.

IR-CTV encompassed tumor extension at diagnosis and a 1-cm margin around HR-CTV. The dosimetry software used was Oncentra Brachy.

The treatment plan aimed to deliver 24 Gy to HR-CTV in 4 fractions. Absorbed doses to these volumes were converted into a radiobiological equivalent of 2 Gy per fraction and biologic effective dose, using the linear-quadratic model, with an α/β value of 10 for tumors and 3 for OARs. Total doses to target volumes and OAR were obtained by adding dose of EBRT and dose of BT.

HDR-BT was delivered with an iridium-192 source with a MicroSelectron Brachytherapy afterloading Platform (Elekta). Four fractions were delivered: 1 fraction on the day after insertion of the device (D2), after obtention of dosimetry, 2 fractions on the third day (D3) with an interval of at least 4 hours between fractions, and 1 on the fourth day (D4) in the morning. A control CT scan was performed in the morning of D3 and D4 before the HDR-BT session. The applicator was removed under local anesthesia and slight sedation just after the fourth session, and the patient was discharged afterward. During the hospitalization, pain medication (World Health Organization level I-II) was systematically prescribed, but morphine derivatives were rarely required.

Follow-up

The follow-up protocol consisted of clinical examinations every 3 to 4 months for the first 3 years, followed by examinations every 6 months up to 5 years of follow-up. A pelvic MRI was performed 3 months after BT, then every 6 months for the first 2 years, and then annually for a total of 5 years. A PET-CT scan was proposed at 3 to 6 months after BT then annually.

In case of persistent or recurrent local disease, without distant metastases, a salvage hysterectomy was discussed.[22] In case of recurrent disease not amenable to surgery, chemotherapy with or without bevazucimab was systematically proposed.

Outcomes

End points of this study are disease-free survival (DFS), OS, and local control (LC). DFS is defined as the absence of recurrence or progression after the primary treatment, and OS refers to the absence of death from any cause. LC represents the absence of any recurrent or progressive local disease in the cervix. All these parameters were calculated from the first day of treatment. Toxicities were graded according to the Common Terminology Criteria for Adverse Events version 5[23] and were retrospectively assessed through the review of patient's electronic medical records.

Statistical analysis

All statistical analyses were conducted using Stata version 14.2, employing Kaplan-Meier survival, log-rank test, Cox regression analysis, t tests, and χ^2 tests. Univariate analysis was performed using Kaplan-Meir survivals with a log-rank test comparison.

Results

Patients

Of the 146 patients who underwent the HDR-BT protocol during the study period, 7 were excluded because of insufficient data, resulting in a total of 139 patients

Table 1 General characteristics of 139 patients

Patient characteristics	
Age (years: mean, min-max)	53 (24-86)
HIV status (number, %)	
Positive	5 (3.6)
Negative	134 (96.4)
Histology (number, %)	
Squamous cell carcinoma	116 (83.5)
Adenocarcinoma	22 (15.8)
Neuro-endocrine	1 (0.7)
Tumor size (mm: mean, min-max)	49 (15-115)
Parametrial involvement (number, %)	
Unilateral	46 (33.1)
Bilateral	64 (46)
No	29 (20.9)
Vaginal involvement (number, %)	
Lower third	11 (7.9)
Upper two-thirds	68 (48.9)
No	60 (43.2)
FIGO 2018 stage	
IB2	2 (1.4)
IB3	5 (3.6)
IIA	4 (2.9)
IIB	31 (22.3)
IIIA	2 (1.4)
IIIB	4 (2.9)
IIIC1	49 (35.2)
IIIC2	19 (13.7)
IVA	18 (13)
IVB	5 (3.6)
PET-CT scan (number, %)	
Yes	135 (97.1)
No	4 (2.9)
LN involvement on the PET-CT scan (number, %)	
Pelvic fixation	55 (40.7)
Para-aortic fixation	22 (16.3)
N0	58 (43)
Performing a pelvic LN dissection (number, %)	
Yes	35 (25.2)
No	104 (74.8)
Performing a para-aortic LN dissection (number, %)	
Yes	91 (65.5)
No	48 (34.5)
Positive LN among LN dissections (number, %)	
On pelvic lymphadenectomy	10 (28.6)
On para-aortic lymphadenectomy	8 (8.9)
Final node stage (number*, %)	
Positive pelvic nodes	50 (36.7)
Positive para-aortic nodes	28 (20.6)
No	58 (42.7)

(*continued on next page*)

Table 1 (*Continued*)

Abbreviations: FIGO = International Federation of Gynecology and Obstetrics; LN = lymph node; PET-CT = positron emission tomography computed tomography scan.
*Final node stage including PET-CT and LN dissection.

included for analysis. Detailed clinical characteristics of these patients are presented in Tables 1 and 2. The patients' mean age was 53 years, and a predominance of SCC (83.5%) was observed. Most of the patients had a FIGO stage IIB and III (25.2% and 53.2%, respectively). The average tumor size was 49 mm. Pelvic lymphadenectomy was performed in 25.2% of the patients, and 65.5% underwent para-aortic lymphadenectomy.

Treatments and outcomes

Most of the patients (97.1%) received platinum-based concomitant chemotherapy, with only 1 patient not receiving concomitant chemotherapy because of altered performance status (asthenia, malnutrition, etc). The average EBRT dose was 48.3 Gy, and the mean overall treatment duration was 59.6 days. Only 70% of patients underwent pre-BT pelvic MRI.

BT program could be fully performed in 136 patients (98%). Three patients received a total dose of 18 Gy only, in 3 sessions of 6 Gy each, because of pain or mental confusion. Mean dose to the HR-CTV was 87.2 Gy but with a large range of dose between 53.1 and 153.1 Gy (Fig. E1).

Over a median follow-up duration of 40.5 months, the 2-year LC, OS, and DFS rates stood at 79.4%, 77.7%, and 61.7%, respectively, with 5-year rates at 78.2%, 61.6%, and 55.7%. Nine patients had a salvage hysterectomy.

Prognostic factors

As detailed in Table 3, in univariate analysis, tumor size, parametrial invasion, FIGO stage (Fig. 1), and neoadjuvant chemotherapy were statistically correlated with DFS. The same parameters were also correlated with LC, but, interestingly, tumor response to EBRT, as identified via MRI before BT, was also highly correlated to LC

Table 2 Treatment characteristics

MRI prior-BT available (number, %)	
Yes	98 (70)
No	41 (30)
Tumoral responses on MRI pre-BT (number, %)	
No response	16 (16.3)
Partial response	52 (53.1)
Complete response	30 (30.6)
Neoadjuvant chemotherapy (number, %)	
Yes	24 (17.3)
No	115 (82.7)
CCRT (number, %)	
Yes	138 (99)
Platine based	134 (97.1)
Other	4 (2.9)
No	1 (1)
RT technique (number, %)	
IMRT	87 (62.6)
3D	52 (37.4)
Dose of RT (Gy: mean, min-max)	48.3 (43.2-60)
Final hysterectomy (number, %)	
Yes	9 (6.5)
No	115 (82.7)
Unknown	15 (10.8)
Node boost	
Yes	47 (33.8)
No	92 (66.2)
OTT (days: mean, min-max)	59.6 (43-93)
Median	58
Interstitial needles	123 (89%)
Dose of BT (Gy: number, %)	
15	1 (0.7)
18	3 (2.2)
24	135 (97.1)
BT dosimetry (Gy: mean, min-max)	
HR-CTV (D_{90})	86.9 (62-119)
HR-CTV	30.6 (5.89-91.7)
IR-CTV (D_{90})	69.1 (50-91.7)
IR-CTV (D_{98})	58.4 (47.7-78.7)
IR-CTV	76.9 (16.8-187.4)
$D_{2\ cc}$ of bowel (EQD2)	65.4 (45.27-85.46)
$D_{2\ cc}$ of rectum (EQD2)	68.6 (49.63-80.26)
$D_{2\ cc}$ of bladder (EQD2)	76.4 (57.36-85.3)

Abbreviations: 3D = 3 dimensional; BT = brachytherapy; CCRT = concomitant chemoradiotherapy; CTV = clinical target volume: EQD2 = equivalent of 2 Gy per fraction; HR = high risk; IMRT = intensity modulated RT; IR = intermediate risk; MRI = magnetic resonance imaging; OTT = overall treatment time; RT = radiation therapy.

(P = .01; Fig. 2). Of note, no dosimetric parameter, such as D90 to HR-CTV or IR-CTV, was correlated with LC or DFS.

Concerning OS, parametrial invasion, final nodal stage, FIGO stage, the implementation of neoadjuvant chemotherapy, and the tumor's response to chemoradiotherapy, as determined by posttreatment MRI, were associated with this parameter. A trend toward poorer OS outcomes was noted in relation to tumor size, albeit without statistical significance (P = .07).

In multivariate analysis (Table 4), tumor response on postchemoradiotherapy MRI was always highly correlated to LC (P = .006) and OS (P = .02). Notably, parametrial involvement was associated with a reduced DFS (P = .04) and OS (P = .01).

Acute complications

Table 5 presents the side effects resulting from the administration of chemoradiotherapy followed by uterovaginal BT. Acute urinary and digestive toxicities were observed in 20.86% and 81.29% of patients, respectively. Notably, among those experiencing acute urinary toxicity, 19.42% presented with grade 1. Conversely, 5.76% of those with acute digestive toxicity had grade 3 symptoms, characterized by recurrent vomiting, diarrhea, and malnutrition, requiring hospitalization for supportive measures. Transfusions of red blood cells or platelets were required in 30 patients (21.6%), either before or after uterovaginal BT.

Chronic complications

Twenty-five patients (18%) experienced late grade 3 complications. Patients with grade 3 chronic urinary toxicity presented with diverse pathologies such as radiation cystitis, pyelocaliceal cavity dilation, radiation-induced ureteral fibrosis (affecting 1 or both ureters), and vesicovaginal fistula. The majority required double J catheter placement to alleviate these conditions. Regarding chronic gastrointestinal toxicity, 11 patients suffered from grade 3 or higher adverse effects. They exhibited conditions like radiation-induced proctitis discovered after a digestive hemorrhage, recurrent occlusive syndromes, and short bowel syndrome. Some required treatments such as argon plasma coagulation or colostomy. Only 28 patients reported dyspareunia during consultation, but this complication was probably underestimated. It must be emphasized that some patients may have manifested toxicities across multiple categories.

Patients manifesting chronic gastrointestinal side effects of grade 3 or higher had a mean D2 cc (bowel) of 73.4 +/- 0.87 (range, 69.4-77.3). In contrast, patients with gastrointestinal side effects of grade 2 or lower showed a

Table 3 Univariate analysis

Characteristic		DFS		LC		OS	
Patient and Tumor characteristics	**N° pts**	**%**	***P* value***	**%**	***P* value***	**%**	***P* value***
Age			0.90		0.80		0.55
<=53 years	68	60		77.9		73.5	
>53 years	71	61.7		80.6		67.5	
HIV			0.81		0.95		0.48
Positive	5	80		80		80	
Negative	134	60.15		79.3		69.9	
Histology			0.46		0.06		0.26
Squamous cell carcinoma	116	61.81		78.8		71.4	
Adenocarcinoma	22	59.08		86		68.2	
Neuro-endocrine	1	-		-		-	
Tumor size			0.07		**0.02**		0.07
<=40 mm	**42**	73.74		**92**		78.4	
>40 mm	**97**	55.65		**74.1**		66.9	
Parametrial involvement			**0.002**		**0.05**		**0.004**
None	**29**	**84.6**		**91.8**		**88.5**	
Unilateral	**46**	**66.7**		**85**		**75.1**	
Bilateral	**64**	**47.1**		**70.2**		**59.5**	
Vaginal involvement			0.06		0.64		0.13
None	**60**	71.4		83.7		76.2	
Lower third	**11**	52.8		75		66.4	
Upper two-thirds	**68**	54.5		80.8		63.6	
Final nodal stage			0.16		0.49		**0.0061**
N0	58	63		81		**71.4**	
Pelvic	50	65.2		81.5		**79**	
Para-aortic	28	43.1		67.1		**48**	
FIGO stage			**0.0002**		**0.02**		**0.0001**
- Stage I-II	**42**	**78.9**		**89.5**		**86.7**	
- Stage III	**74**	**60.2**		**79.5**		**71.2**	
- Stage IV	**23**	**31.9**		**58.5**		**37.6**	
Neoadjuvant chemotherapy			**0.01**		0.09		**0.004**
Yes	**24**	**43.0**		65		**50.8**	
No	**115**	**64.5**		82.1		**74.4**	
Final hysterectomy			0.79		0.47		0.65
Yes	9	55.6		66.7		66.7	
No	130	61.3		80.5		70.7	
Treatment characteristics	N° pts	%	*P* value	%	*P* value	%	*P* value
Tumoral response on MRI to EBRT before BT			0.24		**0.01**		**0.05**
Complete response	30	70.4		**91.9**		**84.3**	
Partial response	52	60.4		**77.3**		**70.4**	

(*continued on next page*)

Table 3 (*Continued*)

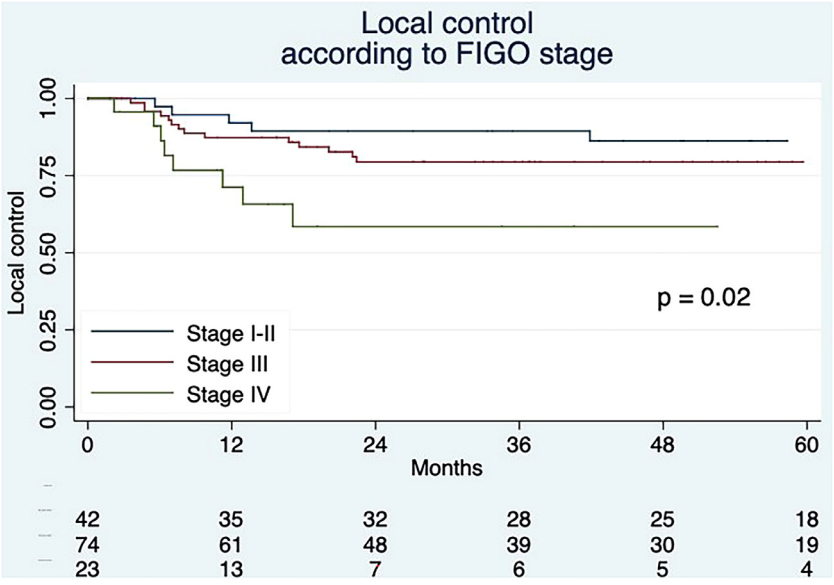
Characteristic		DFS		LC		OS	
Patient and Tumor characteristics	**N° pts**	**%**	***P* value***	**%**	***P* value***	**%**	***P* value***
No response	16	43.8		**61.1**		**62.5**	
EBRT technique			0.997		0.84		0.23
IMRT	87	62.8		79.4		76	
3D	52	58		79.4		61.9	
OTT			0.89		0.34		0.57
<=58 days	72	63.8		84		72.8	
>58 days	67	58.2		74.6		68.3	
BT dose			0.52		0.12		0.20
15 Gy	1	-		-		-	
18 Gy	3	66.7		100		66.7	
24 Gy	135	61.3		85.3		71	
Interstitial needles			0.68		0.50		0.98
No	15	57.1		78.6		71.4	
Yes	123	61		79.3		69.9	
HR-CTV (D_{90})			0.71		0.79		0.89
<=86 Gy	70	58		80.3		69.4	
>86 Gy	69	63.9		78.5		71.4	
HR-CTV			0.82		0.97		0.55
<=25 cm^3	68	61.01		79.3		70.4	
>25 cm^3	71	60.85		79.4		70.3	
IR-CTV (D_{90})			0.13		0.53		0.34
<=68.5 Gy	70	55.7		79		64.7	
>68.5 Gy	69	66.6		80		76.9	
IR-CTV			0.78		0.76		0.72
<=69 cm^3	69	58.7		78		70.8	
>69 cm^3	70	63.1		80.7		70.1	

Abbreviations: 3D = 3 dimensional; BT = brachytherapy; CTV = clinical target volume; DFS = disease-free survival; EBRT = external-beam radiation therapy; FIGO = International Federation of Gynecology and Obstetrics; HR = high risk; IMRT = intensity modulated radiation therapy; IR = intermediate risk; LC = local control; MRI = magnetic resonance imaging; OS = overall survival; OTT = overall treatment time.
Endpoints were assessed for 139 patients. Values are presented as percentages (proportions) unless indicated otherwise.
Significant differences are indicated in bold type.
*Comparisons have been made with a log-rank test.

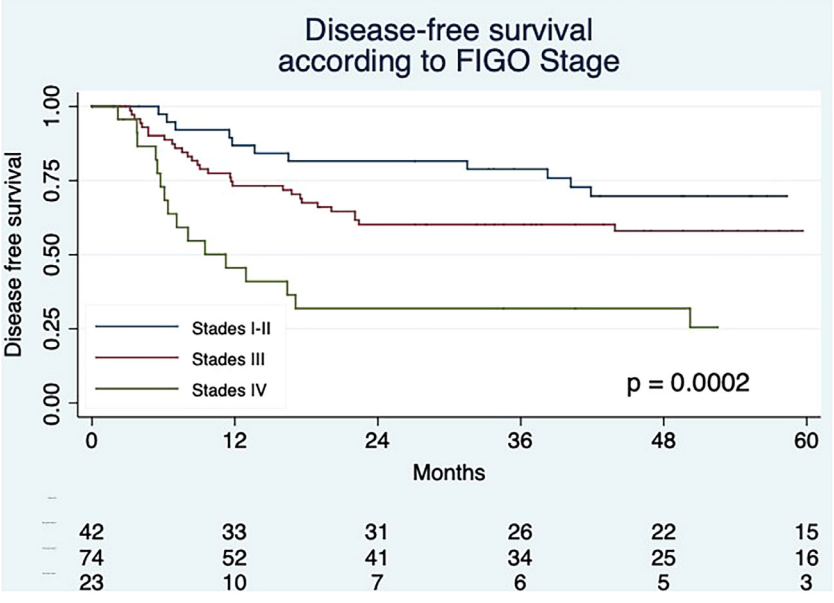
mean D2 cc (bowel) of 64.7 +/- 1.78 (range, 62.9-66.4), with a significant *P* value of .005. The optimal cut-off to discriminate patients with or without grade 3 bowel toxicity was 70 Gy (*P* = .001; Fig. 3). For patients receiving D2 cc (bowel) ≥ 70 Gy, the likelihood of developing chronic gastrointestinal toxicity was 16.13%, as opposed to a considerably lower probability of 1.3% in those receiving D2 cc (bowel) < 70 Gy. No statistical correlation was found between D2 cc (rectum) and severe chronic gastrointestinal toxicity (*P* = .76). Finally, in relation to chronic urinary toxicity, no statistical relationship was discernible with D2 cc (bladder) (*P* = .68).

Discussion

In cervical cancer, recurrences may arise in the cervix itself (local recurrences) or in the pelvic or para-aortic LNs (regional recurrences), while some patients develop distant metastases or a combination of both. Tumor



A



B

Figure 1 (A) Local control based on FIGO stage. Comparison of local control rates among different stages according to the FIGO classification for cervical cancer. (B) Disease-free survival based on FIGO stage. Comparison of disease-free survival rates across various stages using the FIGO classification for cervical cancer. Analysis performed using log-rank test and Kaplan-Meier curves. The FIGO stages are categorized into 3 groups: stage I-II (blue curve, including stages I and II), stage III (red curve, including stages IIIC1, IIIC2), and stage IV (green curve, including stages IVA and IVB). Patients at risk (events) are described below the curve.

Abbreviation: FIGO = International Federation of Gynecology and Obstetrics.

volume directly correlates with the risk of both local and distant failures.[22] Notably, the majority of recurrences present within the first 3 years, and the prognosis remains bleak, with many succumbing to progressive disease.[24] Before the image-based BT, pelvic relapse constituted 70% of these failures, with 50% accompanied by distant metastases.[25,26] With the emergence of the image-based BT, LC has been excellent, and most of the recurrences are regional or distant.[27]

BT is an essential part of the standard treatment. Because of the shortage of anesthetic facilities, we developed a HDR-BT program during a classical hospitalization of 3 days with only 1 insertion and 4 fractions. This retrospective study demonstrates the feasibility of this

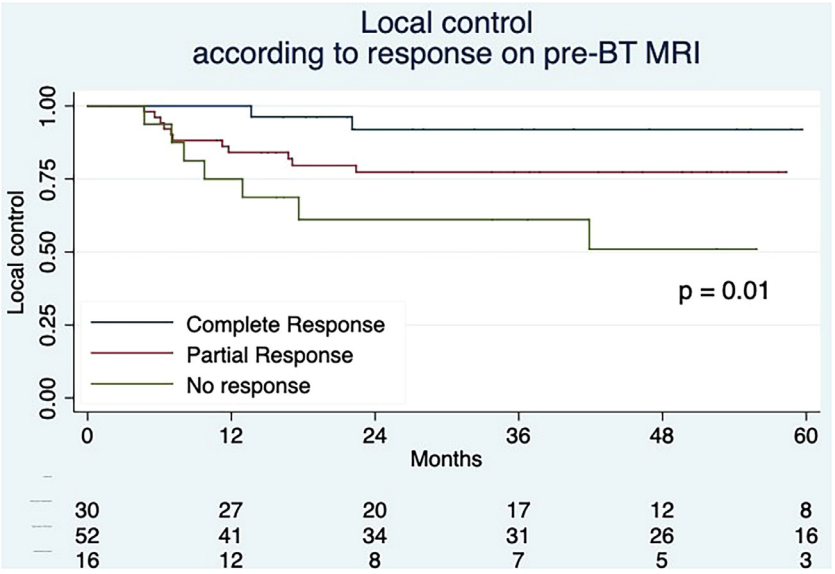


Figure 2 Local control based on response to external beam radiation therapy. Comparison of local control rates based on the response of patients to external beam radiation therapy.

procedure, with 98% of the patients having the full BT dose without any severe complication during the hospitalization.

The present study provides comprehensive clinical evidence supporting the efficacy of MRI-based 3-dimensional HDR-BT for the treatment of LACC. Our findings align with those in the literature regarding efficacy. In a Cochrane review published in 2014,[28] a 3-year OS rate of 66.3% for HDR and 69.6% for low-dose rate was reported, with 5-year rates being 54.9% and 60%, respectively. Five-year LC stood at 75.8% for HDR and 79.7% for low-dose rate. However, our results were slightly lower than those obtained in more recent trials, such as the EMBRACE study[27]: in this prospective study, LC ranges from 89 to 91% for stage IB-IIB (similar to our result of 89.5% for this group) and 92% for stage IIIB (compared with 79.5% in our study). It must be noticed that mean dose to HR volume is slightly lower than in EMBRACE (87 vs 90 Gy). One possible explanation is that we contoured the target volume on CT scan and not directly on MRI, because MRI was performed before the implant. Currently, we have organized our process to perform the MRI after the implant and to contour directly on MRI.

Tumor size, FIGO stage, and parametrial involvement have been classically found to be important prognostic

Table 4 Multivariate analysis

Characteristic	LC		DFS		OS	
Patient and tumor characteristics						
Tumor size	1.62 [0.45-5.91]	0.461	1.24 [0.64-2.42]	0.529	1.10 (0.43-2.85)	0.839
Histology	1.98 [0.50-7.87]	0.33	-	-	-	-
Parametrial involvement	1.55 [0.79-3.04]	0.204	**1.55 [1.01-2.38]**	**0.043**	**2.14 (1.18-3.88)**	**0.012**
Vaginal involvement	-	-	1.27 [0.94-1.71]	0.116	-	-
Neoadjuvant chemotherapy	1.91 [0.63-5.79]	0.250	1.48 [0.76-2.88]	0.249	2.05 (0.83-5.06)	0.118
FIGO 2018 stage	1.13 [0.51-2.47]	0.766	1.48 [0.93-2.37]	0.101	1.35 (0.76-2.39)	0.307
Final nodal stage	-	-	-	-	0.79 (0.47-1.32)	0.365
Treatment characteristics						
Tumoral response on MRI to EBRT before BT	**2.68 [1.32-5.44]**	**0.006**	-	-	**1.86 (1.11-3.13)**	**0.019**

Abbreviations: BT = brachytherapy; DFS = disease-free survival; EBRT = external-beam radiation therapy; FIGO = International Federation of Gynecology and Obstetrics; LC = local control; MRI = magnetic resonance imaging; OS = overall survival.
Endpoints were assessed for 139 patients. Hazard ratio − Cox model 95% CIs are presented. Values are presented as percentages (proportions) unless indicated otherwise.
Significant differences are indicated in bold type.

Table 5 Toxicity

	Grade 1	Grade 2	Grade 3	Grade 4
Acute complications (number, %)				
Urinary	27 (19.42)	2 (1.44)	-	-
Digestive	76 (54.68)	29 (20.86)	8 (5.76)	-
Hematologic	13 (9.35)	21 (15.11)	30 (21.58)	-
Chronic complications (number, %)				
Urinary	1 (0.72)	-	7 (5.04)	-
Digestive	1 (0.72)	3 (2.16)	9 (6.47)	2 (1.44)
Dyspareunia	14 (10.07)	5 (3.60)	9 (6.47)	-

Presentation of acute and chronic toxicities. Results presented as a number (percentage).

factors. Many studies have found a strong association between tumor size and prognosis.[29,30] The Radiation Therapy Oncology Group 90-01 trial, a phase III study, included large tumor size (>5 cm) as a criterion for patient selection.[30] Narayan et al[31] suggested that tumor volume (≥38 mL) was an important risk factor, and Beriwal et al[29] reported that tumor diameter (>5 cm) was a significant predictor of increased risk of local recurrence.

The EMBRACE-I study[27] aimed to report treatment outcomes and risk factors for local failure (LF) in LACC treated with MRI-guided adaptive brachytherapy (MR-IGABT). With a median follow-up of 52 months for 1318 patients, 98 LFs were observed. LFs were predominantly located inside MR-IGABT target volumes. Multivariable analysis revealed significant effects on LF from factors such as histology, minimal dose to 90% of HR-CTV, maximum tumor dimension, HR- CTV > 45 cm^3, OTT, tumor necrosis at diagnosis, and uterine corpus and mesorectal infiltration. Dose-response analysis showed that a minimal dose to 90% of 85 Gy to the HR- CTV resulted in a 95% LC rate for SCC compared with 86% for adenocarcinoma. The study validates the GYN GEC-ESTRO/ICRU-89 target concept and provides large-scale evidence for dose prescription and new risk factors for LF in MR-IGABT-treated cervical cancer. In our study, we did not find a correlation between dose to HR-CTV and LC or DFS. However, most of our patients received a dose around 85 Gy (see Fig. E1).

We emphasized the importance of oncological re-evaluation after chemoradiotherapy: a complete response, as

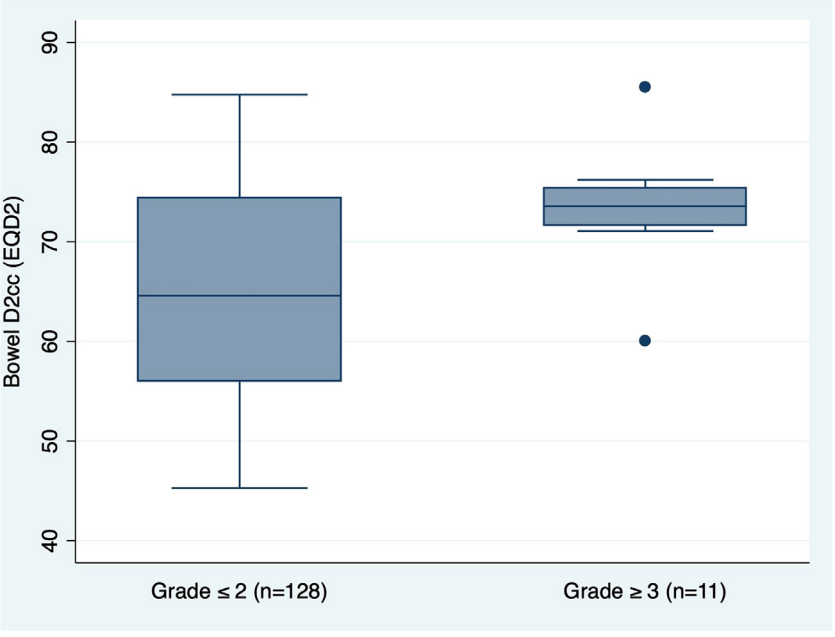


Figure 3 D2 cc of bowel (equivalent dose in 2 Gy fractions) correlated with gastrointestinal toxicity grade. Box plot illustrating the correlation between D2 cc of bowel calculated in equivalent dose in 2 Gy fractions and the corresponding gastrointestinal toxicity grade. Toxicities were classified into 2 groups: grade <= 2 and grade >= 3.

determined by MRI performed in the week before BT, at the end of the chemo-radiation therapy sequence, results in improved LC and OS. A simple scoring system, T-score (TS),[32] evaluating the local extension on clinical examination and MRI, has demonstrated strong prognostic capabilities in predicting LC and survival for patients with advanced cervical cancer treated with chemoradiation and MR-IGABT. Using TS score, calculated at diagnosis and at first implant, it has been shown that a TS regression was observed in 71% of patients and was associated with improved LC, survival, and reduced morbidity.[33] We confirmed that tumor regression evaluated on MRI is an important prognostic parameter, keeping a high significance in multivariate analysis.

Three-dimensional optimization techniques have been shown to enhance coverage of the tumor target volume while simultaneously maintaining a safe dose to OARs.[33] In prior research, the 3-year LC rate was found to be 80% for HR-CTV doses less than 80 Gy, 88.8% for doses ranging between 80 and 85 Gy, and 95.6% for doses greater than or equal to 85 Gy, with this dose-response relationship being more significant in extensive tumors.[34] To achieve this 85 Gy threshold, particularly for larger tumors with significant parametrial infiltration and anatomically unfavorable topography such as asymmetrical tumor growth, narrow vaginal cavity, or vaginal spread of disease, additional interstitial needles along with intracavitary applicators may be necessary.[9] We have used interstitial needles in 89% of our patients. In routine clinical practice, the use of combined intracavitary and interstitial treatment has demonstrated safety and feasibility and has led to significant clinical and statistical improvements in disease progression control and the protection of OAR in LACC.[35]

Regarding toxicity, the majority of side effects observed in patients were of grade 1 to 2 severity. Grade 3 to 4 complication rate (18%) is consistent with those reported in the literature.[36] A maximum threshold of 70 Gy for the D2 cc (bowel) appears to be a reasonable approach to minimize the risk of chronic gastrointestinal adverse effects of grade 3 or higher. In this analysis, there was no evidence that D2 cc (bladder) and D2 cc (rectum) were associated with urinary and gastrointestinal side effects.[37] Because we found that bowel 2 CC dose was highly correlated to late toxicity, and because bowel bag was contoured apart of the rectum, it is probably EBRT that is responsible for this toxicity. So, HDR-BT using a single insertion technique and 4 treatment sessions seems to be acceptable in terms of toxicity. It should be noted that in our study, the reported side effects encompassed those related to initial staging surgery, radiation therapy, chemotherapy, and BT.

Our study has some limitations. First, it is a retrospective, single-center study with a limited number of patients; however, all consecutive patients treated in the study period were included. For some patients, data were missing from the computerized database. Chemoradiotherapy was conducted in 10 different centers across Île-de-France, which may account for the extended treatment duration observed in our patients. Regarding side effects, they are likely underestimated as patients did not complete patient-reported outcome forms for collecting adverse effects. Posttreatment sexual disorders were rarely reported, although we know that many patients suffer from them in the long term.

Conclusion

In conclusion, EBRT with HDR-BT in a single insertion for patients with LACC or IB-IV cervical cancer is both efficacious and safe. For patients with a poor prognosis, more individualized and systemic treatment strategies should be considered for concomitant administration with definitive radiation therapy to improve the therapeutic ratio. The use of other systemic therapies such as immunotherapy is obviously something important to explore. We have demonstrated that HDR-BT could be performed safely with 1 insertion in 3 days, facilitating its use in case of poor availability of anesthetists.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2024.101512.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209-249.
2. Cohen PA, Jhingran A, Oaknin A, Denny L. Cervical cancer. *Lancet*. 2019;393:169-182.
3. Berman TA, Schiller JT. Human papillomavirus in cervical cancer and oropharyngeal cancer: One cause, two diseases. *Cancer*. 2017;123:2219-2229.
4. Roura E, Castellsague X, Pawlita M, et al. Smoking as a major risk factor for cervical cancer and pre-cancer: Results from the EPIC cohort. *Int J Cancer*. 2014;135:453-466.
5. Stier EA, Baranoski AS. Human papillomavirus-related diseases in HIV-infected individuals. *Curr Opin Oncol*. 2008;20:541-546.
6. Petrosky E, Bocchini Jr. JA, Hariri S, et al. Use of 9-valent human papillomavirus (HPV) vaccine: Updated HPV vaccination recommendations of the advisory committee on immunization practices. *MMWR Morb Mortal Wkly Rep*. 2015;64:300-304.

7. Cosper PF, Bradley S, Luo L, Kimple RJ. Biology of HPV mediated carcinogenesis and tumor progression. *Semin Radiat Oncol*. 2021;31:265-273.
8. Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri: 2021 Update. *Int J Gynaecol Obstet*. 2021;155(Suppl 1): 28-44.
9. Sturdza A, Potter R, Fokdal LU, et al. Image guided brachytherapy in locally advanced cervical cancer: Improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study. *Radiother Oncol*. 2016;120:428-433.
10. Moore KN, Java JJ, Slaughter KN, et al. Is age a prognostic biomarker for survival among women with locally advanced cervical cancer treated with chemoradiation? An NRG Oncology/Gynecologic Oncology Group ancillary data analysis. *Gynecol Oncol*. 2016;143:294-301.
11. Queiroz ACM, Fabri V, Mantoan H, et al. Risk factors for pelvic and distant recurrence in locally advanced cervical cancer. *Eur J Obstet Gynecol Reprod Biol*. 2019;235:6-12.
12. Obermair A, Cheuk R, Horwood K, et al. Anemia before and during concurrent chemoradiotherapy in patients with cervical carcinoma: Effect on progression-free survival. *Int J Gynecol Cancer*. 2003;13: 633-639.
13. Charakorn C, Thadanipon K, Chaijindaratana S, Rattanasiri S, Numthavaj P, Thakkinstian A. The association between serum squamous cell carcinoma antigen and recurrence and survival of patients with cervical squamous cell carcinoma: A systematic review and meta-analysis. *Gynecol Oncol*. 2018;150:190-200.
14. Song S, Rudra S, Hasselle MD, et al. The effect of treatment time in locally advanced cervical cancer in the era of concurrent chemoradiotherapy. *Cancer*. 2013;119:325-331.
15. Espenel S, Garcia MA, Trone JC, et al. From IB2 to IIIB locally advanced cervical cancers: Report of a ten-year experience. *Radiat Oncol*. 2018;13:16.
16. Cibula D, Raspollini MR, Planchamp F, et al. ESGO/ESTRO/ESP Guidelines for the management of patients with cervical cancer - Update 2023. *Int J Gynecol Cancer*. 2023;33:649-666.
17. Banerjee R, Kamrava M. Brachytherapy in the treatment of cervical cancer: A review. *Int J Womens Health*. 2014;6:555-564.
18. le Guyader M, Lam Cham Kee D, Thamphya B, et al. High-dose-rate brachytherapy boost for locally advanced cervical cancer: Oncological outcome and toxicity analysis of 4 fractionation schemes. *Clin Transl Radiat Oncol*. 2022;32:15-23.
19. Mazeron R, Castelnau-Marchand P, Dumas I, et al. Impact of treatment time and dose escalation on local control in locally advanced cervical cancer treated by chemoradiation and image-guided pulsed-dose rate adaptive brachytherapy. *Radiother Oncol*. 2015;114:257-263.
20. Kirisits C, Lang S, Dimopoulos J, Berger D, Georg D, Potter R. The Vienna applicator for combined intracavitary and interstitial brachytherapy of cervical cancer: Design, application, treatment planning, and dosimetric results. *Int J Radiat Oncol Biol Phys*. 2006;65:624-630.
21. Potter R, Haie-Meder C, Van Limbergen E, et al. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): Concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. *Radiother Oncol*. 2006;78:67-77.
22. Eifel PJ, Jhingran A, Brown J, Levenback C, Thames H. Time course and outcome of central recurrence after radiation therapy for carcinoma of the cervix. *Int J Gynecol Cancer*. 2006;16:1106-1111.
23. *Common Terminology Criteria for Adverse Events (CTCAE)*. v5.0. Accessed May 17, 2024; https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.
24. Fagundes H, Perez CA, Grigsby PW, Lockett MA. Distant metastases after irradiation alone in carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys*. 1992;24:197-204.
25. Kawaguchi R, Furukawa N, Kobayashi H, Asakawa I. Posttreatment cut-off levels of squamous cell carcinoma antigen as a prognostic factor in patients with locally advanced cervical cancer treated with radiotherapy. *J Gynecol Oncol*. 2013;24:313-320.
26. Mahantshetty U, Krishnatry R, Hande V, et al. Magnetic resonance image guided adaptive brachytherapy in locally advanced cervical cancer: An experience from a tertiary cancer center in a low and middle income countries setting. *Int J Radiat Oncol Biol Phys*. 2017;99:608-617.
27. Potter R, Tanderup K, Schmid MP, et al. MRI-guided adaptive brachytherapy in locally advanced cervical cancer (EMBRACE-I): A multicentre prospective cohort study. *Lancet Oncol*. 2021;22: 538-547.
28. Liu R, Wang X, Tian JH, et al. High dose rate versus low dose rate intracavity brachytherapy for locally advanced uterine cervix cancer. *Cochrane Database Syst Rev*. 2014;2014(10): CD007563.
29. Beriwal S, Kannan N, Sukumvanich P, et al. Complete metabolic response after definitive radiation therapy for cervical cancer: Patterns and factors predicting for recurrence. *Gynecol Oncol*. 2012;127:303-306.
30. Eifel PJ, Winter K, Morris M, et al. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: An update of radiation therapy oncology group trial (RTOG) 90-01. *J Clin Oncol*. 2004;22:872-880.
31. Narayan K, Fisher RJ, Bernshaw D, Shakher R, Hicks RJ. Patterns of failure and prognostic factor analyses in locally advanced cervical cancer patients staged by positron emission tomography and treated with curative intent. *Int J Gynecol Cancer*. 2009;19:912-918.
32. Lindegaard JC, Petric P, Lindegaard AM, Tanderup K, Fokdal LU. Evaluation of a new prognostic tumor score in locally advanced cervical cancer integrating clinical examination and magnetic resonance imaging. *Int J Radiat Oncol Biol Phys*. 2020;106:754-763.
33. Hellebust TP, Kirisits C, Berger D, et al. Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group: Considerations and pitfalls in commissioning and applicator reconstruction in 3D image-based treatment planning of cervix cancer brachytherapy. *Radiother Oncol*. 2010;96:153-160.
34. Castelnau-Marchand P, Chargari C, Maroun P, et al. Clinical outcomes of definitive chemoradiation followed by intracavitary pulsed-dose rate image-guided adaptive brachytherapy in locally advanced cervical cancer. *Gynecol Oncol*. 2015;139:288-294.
35. Benkhaled S, Diakite K, Jullian N, et al. Boost modalities in cervical cancer: Dosimetric comparison between intracavitary BT versus intracavitary + interstitial BT versus SBRT. *Radiat Oncol*. 2023;18:105.
36. Mahantshetty U, Sturdza A, Naga Ch P, et al. Vienna-II ring applicator for distal parametrial/pelvic wall disease in cervical cancer brachytherapy: An experience from two institutions: Clinical feasibility and outcome. *Radiother Oncol*. 2019;141:123-129.
37. Tanderup K, Nesvacil N, Kirchheiner K, et al. Evidence-based dose planning aims and dose prescription in image-guided brachytherapy combined with radiochemotherapy in locally advanced cervical cancer. *Semin Radiat Oncol*. 2020;30:311-327.