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BRACHYTHERAPY

Brachytherapy 21 (2022) 389–396

Feasibility of electronic brachytherapy in cervix cancer–A dosimetric comparison of different brachytherapy techniques

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ABSTRACT

INTRODUCTION: This study analyzes cases in which electronic brachytherapy (eBT) led to acceptable treatment plans in cervical cancer. Findings were compared with dosimetry values obtained in ^{192}Ir-based treatments according to the high-risk clinical target volume (HR-CTV) and the disease stage.

MATERIAL AND METHODS: We retrospectively analyzed 48 patients with cervical cancer from two centers. The patients were treated with ^{192}Ir based on MRI. It was possible to use interstitial needles via an Utrecht-type applicator. Dosimetry was simulated using eBT and the parameters D90 and D98 (HR-CTV) and D2cc, D1cc, and D0.1cc (bladder, rectum, and sigmoid colon) were evaluated. The Mann-Whitney *U* test was used for comparison. The overall cohort of patients was analyzed, as were the sub-cohorts based on stage (FIGO stages *I*+IIA, IIB and III–IV). Finally, the dosimetry of the eBT plans was evaluated, and the plans obtained were classified as "good", "acceptable", or "poor".

RESULTS: Statistically significant differences were found between the eBT and ^{192}Ir plans for D98 (HR-CTV), D1cc and D0.1cc (bladder), and D1cc and D0.1cc (sigmoid colon). A total of 31 cases (64.6%) were considered good, seven (14.6%) were considered acceptable, and 10 (20.8%) were considered poor. For volumes <30 cc, all the plans were good or acceptable; for volumes >30 cc, 54.3% were good, and 71.4% were good or acceptable. By stage, eBT plans for patients with stage IB–IIA disease were good in 100%, whereas those for patients with stage IIB were good in 70.6% and III–IV disease were good in 50%.

CONCLUSIONS: eBT provides appropriate dosimetry for treatment of cervical cancer in selected cases.

Keywords: Electronic brachytherapy; Cervical cancer; MRI guided radiotherapy; Embrace study

Received 20 October 2021; received in revised form 3 January 2022; accepted 4 January 2022

Disclosures: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. None of the authors have any conflict of interest related to this publication and the research conducted.

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1538-4721/$ - see front matter
https://doi.org/10.1016/j.brachy.2022.01.006

Introduction

External beam radiation therapy (EBRT) delivered to the pelvis combined with (cisplatin-based) chemotherapy and followed by intracavitary brachytherapy or interstitial brachytherapy (ISBT) as a boost to the gross tumor volume has become the standard of care in locally advanced cervical cancer (1–5).

According to the American Brachytherapy Society Task Group Report (6), cervical cancer in clinical stages IB2–IVA should be treated primarily with chemoradiation followed by brachytherapy. Many clinical studies have shown that the efficacy of high-dose-rate (HDR) brachytherapy is similar to that of low-dose-rate brachytherapy for patients with early-to-advanced cervical cancers (7,8).

Many cancer centers in the developed world have thus adopted HDR brachytherapy for patients with cervical and endometrial cancer. The main limitations to widespread adoption of HDR brachytherapy in low-middle income countries (LMICs) are the high cost of the after loader and the fact that a new shielded bunker may need to be constructed if for some reason the after loader cannot be located in one of the preexisting teletherapy bunkers. ^{192}Ir has been the radioactive source of choice for most HDR brachytherapy devices, although it needs to be changed at least three to four times per year because its half-life is 73.8 days. In resource-limited settings, this ongoing cost may be prohibitive (9).

The setup and maintenance costs of electronic brachytherapy (eBT) are lower than those of HDR owing to the low requirements for protection against radiation: no bunker is necessary, and health professionals require minimal personal protection (10–12). Consequently, eBT could overcome cost-related problems in LMICs. eBT has been evolving since the start of the 21st century (13) and has become a treatment option for various tumor sites in different situations (14–18). The advantages of eBT include the reduced dose absorbed by treating staff, absence of radiation leakage in the off state, reduced shielding requirement, and absence of radioactive waste. It can be used to treat cervical cancer in protocols that require treatment with HDR brachytherapy after chemotherapy and EBRT with a dedicated applicator. A key disadvantage of the technique in gynecology is the fact that it is not compatible with the needles used in the interstitial component of the implant.

Clinical data have been published for patients whose cervical cancer was treated with eBT (19). Treatment was based on small high-risk clinical target (HR-CTV) volumes (<16 cc), and the disease was in stages IB-IIIB, thus illustrating the practical viability of eBT in cervical cancer.

In the present study, which was based on a broad range of HR-CTVs volumes and disease stages, we analyze cases where brachytherapy enabled acceptable treatment plans and compare our findings with dosimetry values obtained in treatment using magnetic resonance–based ^{192}Ir, which enabled us to use interstitial needles via an Utrecht-type applicator. Therefore, our objective was to demonstrate that for a certain percentage of patients, implementation of eBT is feasible in LMICs.

Table 1
Study patients divided by stage

Stage	Patients
IB+IIA	7
IIB	17
IIIB+IIIC	20
IVA+IVB	4
Total	48
Average HR-CTV (cc)	44.2 ± 25.2

Materials and methods

We performed a retrospective analysis of 48 patients from two centers who had been treated with ^{192}Ir-based ISBT. Both centers used an Utrecht-type applicator (Elekta AB, Stockholm, Sweden) and MRI for image planning. The treatment protocol consisted of two implants separated by one week. Patients were treated with two schedules, either 50 Gy of EBRT in 25 sessions plus four sessions of 6.5 Gy with ISBT, or 45 Gy in 25 sessions plus four sessions of 7 Gy. For a better comparison all plans have been recalculated to 45 Gy and four sessions of 7 Gy for both ISBT and eBT. The use of interstitial needles was at the discretion of the oncology radiotherapy team in each case, with a median of 2.2 needles per plan (range 0–6). Treatments followed the recommendations for contouring and planning of the main international guidelines (20–22). During selection, we tried to include a sufficient number of patients for each stage, with an equal number (24 patients) in each set of FIGO stages (23) I–II and III–IV. The number was representative of all the HR-CTVs treated. Finally, we selected 48 patients treated between January 2017 and January 2020, with a mean ± standard deviation HR-CTV of 44.2 ± 25.2 cc (Table 1). For these cases, we used the images for the first implant, which were replanned for an eBT source.

The source used for planning eBT was Xoft Axxent eBT (Xoft, Inc., subsidiary of iCAD, San José, CA), which is based on an electronic radiation source, rather than a radioisotope, such as ^{192}Ir. The Axxent S700 is a miniature X-ray device in a flexible catheter. The source is a vacuum tube (10 mm in length, 2 mm in diameter) encased in a cooling catheter (5.6 mm diameter). It is typically operated at 50 kVp with 300 μA of electrons striking a thin tungsten film target on the inner surface of a ceramic X-ray-transparent anode (24).

We used the BrachyCare treatment planning system (Técnicas Radiofísicas, Zaragoza, Spain). Dosimetry was simulated using eBT. The eBT applicator was positioned based on the intracavitary tandem and colpostats of the Utrecht applicator and ignoring the presence of interstitial needles during planning (Fig. 1).

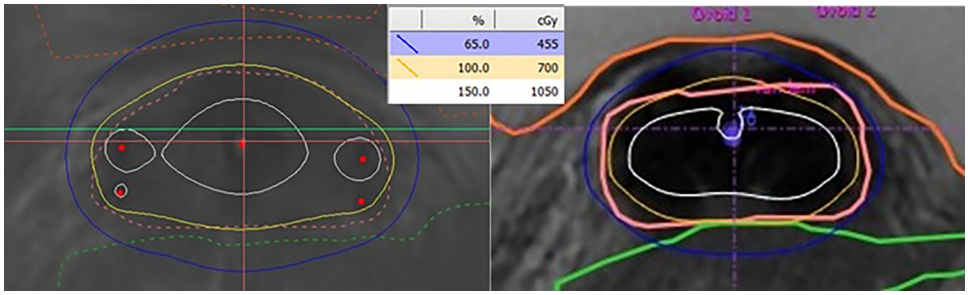

Fig. 1. Treatment planning based on ^{192}Ir (left) and eBT (right) in a patient with a stage IIIC1 disease. The interstitial needles used with the Utrecht-type applicator in the ^{192}Ir plan enable better D90 and D98 for HR-CTV vs. eBT (7.1 Gy and 6.7 Gy vs. 6.1 Gy and 5.2 Gy, respectively). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Planning with ^{192}Ir was based on the Oncentra Brachy planning system, version 4.5.3 (center A and center B) (Elekta AB, Stockholm, Sweden). The specific details of the planning process carried out using ^{192}Ir HDR can be found in the guidelines of the Cervical Brachytherapy Working Group of the Spanish Society of Medical Physics (Grupo de Trabajo de Braquiterapia de Cérvix de la Sociedad Española de Física Médica) (25). Planning based on eBT followed an approach normalized at the A points. Stopping times were then modified to ensure the best coverage possible for HR-CTV, whereas the dose absorbed by the organs at risk (rectum, sigmoid colon, and bladder) was maintained within the limits set out in the EMBRACE II guidelines (21). Calculations were based on the TG-43U1 algorithm (26) for ^{192}Ir and the TG-43 algorithm, which is specific for eBT (27).

Even though planning was only used in the first implant, the same dose was theoretically used for the second implant, thus making it possible to add it to previous EBRT treatments and calculate the global equivalent dose in 2 Gy fractions (EQD2) for a better interpretation of the results. Consequently, the dosimetry variables evaluated with both techniques were as follows: D90 and D98 for HR-CTV (absorbed dose that reaches 90% and 98% of the HR-CTV); D2cc, D1cc, and D0.1cc (maximum dose absorbed at 2 cc, 1 cc, and 0.1 cc, respectively) for the main organs at risk (bladder, rectum, and sigmoid colon). The comparison was based on the Mann-Whitney U test, and statistical significance was set at $p < 0.05$. The statistical analysis was performed using SPSS v22 (IBM, Armonk, NY). Patients were analyzed both as a single cohort and separately as FIGO subgroups I–IIA, IIB and III–IV.

Finally, the eBT plans generated were evaluated according to both their FIGO stage and their volume (above and below 30 cc). A plan was considered "good" when it fulfilled the EMBRACE II recommendations, with respect to the dose delivered to the organ at risk and had a D90>90% of the prescribed dose. "Acceptable" when it fulfilled the dose for the organ at risk, at the expense of the EQD2 of the HR-CTV being between 85% and 90% of the prescribed dose, and "poor" when, in order to fulfill the dose delivered to the organs at risk, it had to reduce the D90 to below the 85% threshold of the prescribed dose.

Table 2
Degree of compliance with acceptance criteria by FIGO stage

Stage	Patients	Good (%)	Acceptable (%)	Poor (%)
IB+IIA	14.6%	7 (100%)	0 (0%)	0 (0%)
IIB	35.4%	12 (70.6%)	4 (23.5%)	1 (5.9%)
IIIB+IIIC	41.7%	11 (55%)	2 (10%)	7 (35%)
IVA+IVB	8.3%	1 (25%)	1 (25%)	2 (50%)
Total	**100.0%**	**31 (64.6%)**	**7 (14.6%)**	**10 (20.8%)**

Results

The plans created retrospectively with eBT were good or acceptable according to the study criteria in 38 of the 48 patients included (79.2%), compared with 10 cases that did not meet the criteria for acceptance and were therefore considered poor (20.8%).

In terms of interstitial needles used in the ISBT plans, the average number of needles used in the "good" or "acceptable" plans was 1.5, while in the "poor" plans it was 5.1 needles on average.

By stage, we observed that stage IB and IIA fulfilled the criteria to be considered good in 100% of cases; stage IIB fulfilled the "good" plan criteria in 70.6% of cases. Therefore, if we include both "good" and "acceptable" cases, the validity percentage was 94.1% for stage IIB. From stage III, the validity of the plan decreased slightly to 55% and rose to 65% when acceptable plans were included. The degree of fulfillment was 25% for patients in stage IV, rising to 50% when acceptable plans were included (Table 2).

If we compare HR-CTV volume and the validity of the plan, we find that for volumes lower than 30 cc, all the plans are good (92.3%) or acceptable (7.7%), and that for volumes greater than 30 cc, the plans are good in 54.3% of cases and good or acceptable in 71.4%.

In cases where the results were good or acceptable, the mean biological equivalent dose was calculated for all the plans, thus fulfilling the requirements of EMBRACE (Table 3).

Table 3
Mean dosimetry parameters for ISBT and Axxent treatments achieving the acceptance criteria

$N=38$	Mean ± SD		EMBRACE recommendation
7 Gy x fraction	ISBT (Gy)	eBT (Gy)	
HR-CTV			
D90	7.7 ± 2.1	8.0 ± 2.0	
EQD2	90	92.3	>90 Gy
D98	6.6 ± 1.9	6.3 ± 2.0	
Bladder			
D2cc	4.7 ± 0.9	4.5 ± 1.4	
EQD2 D2cc	72.2	70.2	<90 Gy
D1cc	5.1 ± 1.0	5.1 ± 1.4	
D0.1cc	5.9 ± 1.1	6.1 ± 1.3	
EQD2 D0.1cc	85.2	87.6	<110 Gy
Rectum			
D2cc	3.6 ± 1.2	3.2 ± 1.3	
EQD2 D2cc	62.2	59.8	<75 Gy
D1cc	4.0 ± 1.4	3.6 ± 1.5	
D0.1cc	4.9 ± 1.7	4.8 ± 2.0	
EQD2 D0.1cc	74.2	73.2	<80 Gy
Sigmoid colon			
D2cc	3.6 ± 0.9	3.7 ± 1.0	
EQD2 D2cc	62.2	63	<75 Gy
D1cc	4.1 ± 0.9	3.9 ± 1.2	
D0.1cc	4.9 ± 1.2	4.9 ± 1.4	
EQD2 D0.1cc	74.2	74.2	<80 Gy

The EQD2 value corresponds to the sum of four brachytherapy sessions with the plan calculated added to 45 Gy of EBRT at 1.8 Gy/session.

Table 4
Mean dosimetry parameters for ISBT and eBT treatments consider as "poor" plans

$N=10$	Average + SD	
7Gy x fraction	ISBT (Gy)	**eBT (Gy)**
HR-CTV		
D90%	6.9 ± 0.3	5.5 ± 0.7
D98%	5.7 ± 0.5	4.2 ± 0.9
OAR		
Bladder		
D2cc	4.5 ± 0.6	5.9 ± 1.0
D1cc	4.7 ± 0.9	6.5 ± 1.1
D0.1cc	5.4 ± 1.0	7.9 ± 1.3
Rectum		
D2cc	3.3 ± 1.0	3.9 ± 1.3
D1cc	3.7 ± 1.2	4.5 ± 1.5
D0.1cc	4.5 ± 1.4	5.9 ± 2.1
Sigmoid		
D2cc	3.4 ± 0.7	4.3 ± 0.8
D1cc	4.0 ± 0.7	5.1 ± 1.0
D0.1cc	4.9 ± 0.8	6.2 ± 1.2

Cases where the requirements for the plan were not met showed different coverage results (Table 4). Plans considered as "poor" with eBT had much better results with ISBT. They meet EMBRACE requirements for all OARs, with 50% of patients achieving a D90>100% and 100% achieving a D90>90%.

The results of the Mann-Whitney *U* test in the comparison of both techniques are presented (Table 5). Statistically significant differences were found in the overall cohort for D98 in HR-CTV and D0.1cc in bladder. However, it is noteworthy that no statistically significant differences were found for the stage I–IIA and IIB cohort, whereas for the stage III–IV cohort, we found statistically significant differences for D98 in HR-CTV, D1cc and D0.1cc in bladder, and D1cc and D0.1cc in the sigmoid colon, suggesting that differences in dosimetry are more pronounced for higher stages. The box-and-whiskers plots for parameters with statistically significant differences in the stage III–IV subgroup are shown (Fig. 2).

Likewise, no significant differences were found if we examined the "good" or "acceptable" cases as a whole, except for D2cc of rectum with lower absorbed dose in the case of eBT. On the other hand, the cases considered "poor" were considered and significant differences were found in the D90 and D98 of HR-CTV and in the parameters D2cc, D1cc and D0.1cc of bladder.

Discussion

The present study is the first to compare planning dosimetry values obtained from ISBT with those obtained from eBT in gynecological brachytherapy. Furthermore, the treatment planning system used for the eBT calculations is the first that has been specifically designed for this purpose.

The patients selected for the comparison were based on the percentages used in the EMBRACE study (28), attempting to ensure that those studied had higher volumes and higher stages. A comparison of the stages of the present cohort with those of the EMBRACE study (28) is provided (Table 6), which retrospectively analyzes data from 24 centers and 1341 patients treated with ^{192}Ir following the recommendations of EMBRACE. The distribution of stages I and IIA in EMBRACE was 23.2% compared with 14.6% in the present study. Similarly, the HR-CTV volumes studied are greater than the average in EMBRACE. The mean study volume was 44.2 ± 25.2 cc compared with 28 cc in EMBRACE.

If we consider the total number of patients, stages I and IIA, which would ensure a "good" plan, represent 23.2% in EMBRACE and stage IIB represents 51.7%. Thus, being our percentage of "good" plan in stage IIB 70.6%, applied to the percentage of patients in EMBRACE, would represent 36.5% of patients, which added to the previous 23.2%, would give us a total of 59.7% of cases that would ensure a "good" plan with eBT.

Stage is a key aspect when attempting to obtain a good plan in eBT treatment. The plan obtained with eBT was considered good in 100% of patients with stage I and IIA disease and 70.6% of those with stage IIB disease. Combining these values yields an 79.2% possibility of obtaining a plan with optimal dosimetry, which increases to 95.8% if we add the acceptable plans in stages I and II, which accounted for 74.9% of the cases in EMBRACE. This im-

Table 5
Mann-Whitney *U* test for dosimetry parameters in ISBT and eBT

Variable	Overall cohort (*p*)	Stage I–IIAsub-cohort (*p*)	Stage IIBsub-cohort (*p*)	Stage III–IVsub-cohort (*p*)
HR-CTV D90	0.591	0.394	0.737	0.152
HR-CTV D98	**0.016**[a]	1.000	0.602	**0.010**[a]
Bladder D2cc	0.330	0.589	0.710	0.107
Bladder D1cc	0.078	0.180	0.941	**0.048**[a]
Bladder D0.1cc	**0.026**[a]	0.093	0.911	**0.011**[a]
Rectum D2cc	0.129	0.937	0.06	0.758
Rectum D1cc	0.370	1.000	0.076	0.800
Rectum D0.1cc	0.762	1.000	0.331	0.190
Sigmoid colon D2cc	0.210	0.485	0.478	0.058
Sigmoid colon D1cc	0.312	0.394	0.189	**0.028**[a]
Sigmoid colon D0.1cc	0.272	0.699	0.246	**0.024**[a]

[a] $p < 0.05$ statistically significant.

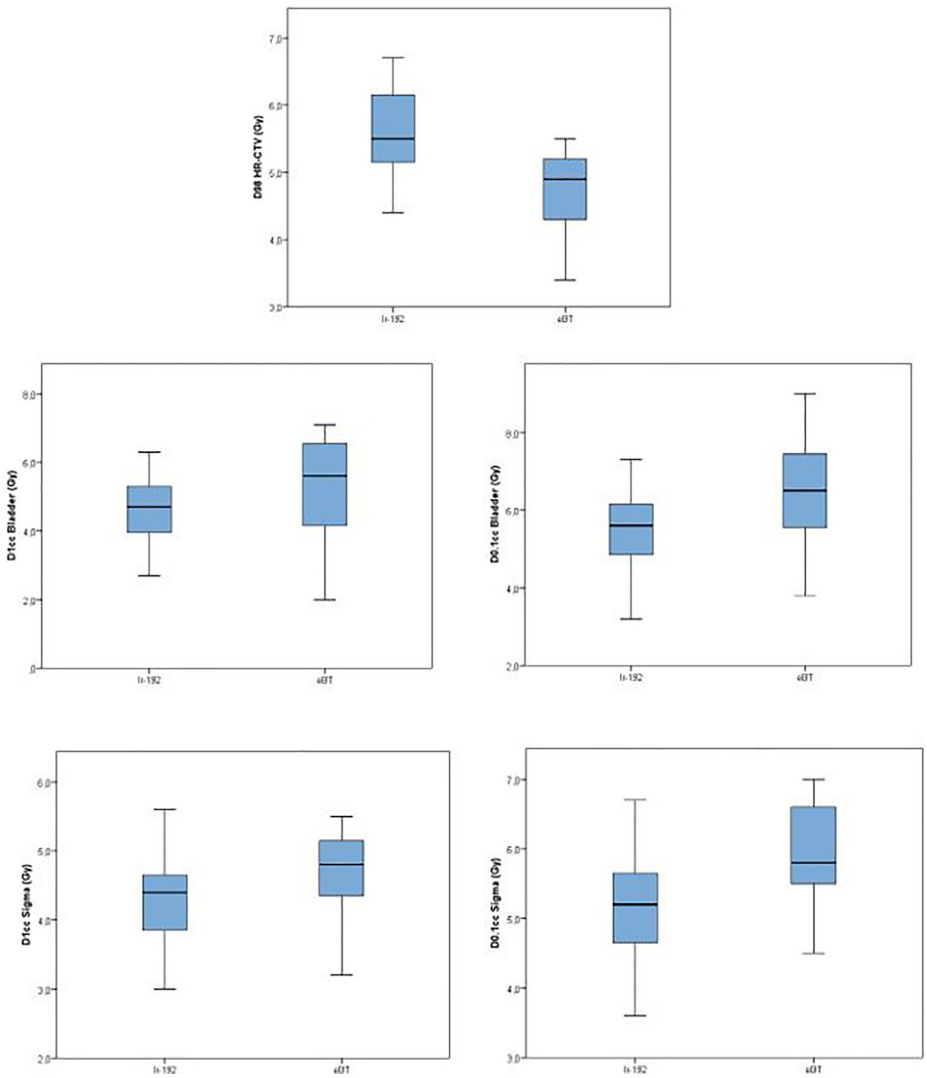

Fig. 2. Box-and-whiskers plots for dosimetry parameters with statistically significant differences between ^{192}Ir and eBT plans for the stage III–IV sub-cohort. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 6
Comparative analysis of stages in EMBRACE and the present study

	Study	EMBRACE
IB	12.5%	18.1%
IIA	2.1%	5.1%
IIB	35.4%	51.7%
IIIA	0.0%	1.0%
IIIB	16.7%	14.2%
IIIC	25.0%	0.0%
IV	8.3%	9.8%
Total patients	48	1341

plies a very large majority of low stages in these patients, that is, eBT would lead to a good plan in a very high percentage of cases.

The cases in this study with "good" or "acceptable" results averaged 1.5 interstitial needles in the ISBT plans, which made the results more achievable with eBT, while the "poor" plans achieved 5.1 needles. This led to good results mainly in those cases without parametrial involvement (I and IIA) or stage IIB, where it exists, although with an average volume of 27.5 cc of HR-CTV in the present study (IIB).

Therefore, we believe that treating cervical cancer with eBT is a good alternative in cases where the technique based on ISBT with ^{192}Ir is not available. The mobility of eBT and the fact that it can be administered at several centers make this approach a potentially useful addition in cervical cancer in LMICs, although in these countries there tend to be found many cases of advanced stages and the results of this study were more positive for stages I–II.

In stages III and IV, the percentage for obtaining a plan equivalent to those for ISBT falls to 50.0% if we add both stages. While far from the value for stages I and II, this is still a high percentage for these cases; the percentage increases to 62.5% if we add the acceptable plans.

Statistical analysis confirmed that as disease stage increased, the likelihood of obtaining a good plan decreased. Stage III and IV cases were also those with a higher HR-CTV volume, which made it more difficult to obtain a good plan with eBT. Parametrial involvement, from stage IIB cases onwards, reflected a decline in results, although the fact that the average volumes were smaller meant that the percentage of good or acceptable results remained at 70.6%.

Mobit et al. (29) compared ^{192}Ir-based plans with eBT plans calculated retrospectively based on CT images. Their retrospective data on 10 patients revealed differences in the dose absorbed in the bladder, rectum, and sigmoid colon. In D2cc for bladder, the mean difference was 25% of the dose absorbed, and the difference was significant ($p < 0.05$). In the case of the rectum and sigmoid colon, the dose absorbed was lower in the eBT plans, although the difference was not significant. The study did not differentiate by stage or by HR-CTV and was limited to comparing plans. In the present study, we differentiate between the parameters. This seems essential if we are to maintain that eBT is acceptable for treatment of cervical cancer.

Recently reported data for patients with cervical cancer treated with eBT (19) also showed lower doses absorbed in the organs at risk. The doses absorbed in the bladder (eBT vs. ^{192}Ir) were 63% of the prescribed dose versus 66% for D2cc, 70% versus 73% for D1cc, and 84% versus 86% for D0.1cc. The differences were greater in the rectum (30% vs. 37% for D2cc, 32.9% vs. 36% for D1cc, and 50% vs. 56% for D0.1cc) and in the sigmoid colon (D2cc, 54% vs. 57%; D1cc, 63% vs. 66%; and D0.1cc, 86% vs. 89%) with an average HR-CTV of 16.6 cc.

In the abovementioned study (19), mean HR-CTV was much lower (16.6 cc) than in the present study (44.2 cc). Furthermore, the comparison with ^{192}Ir-based plans did not include interstitial needles, although the data reported are the only data available on patients with cervical cancer treated with eBT.

It is noteworthy that the images and planning used were from the first implant only. In the case of suboptimal dosimetry with ^{192}Ir, we could attempt a correction in the second implant using more interstitial needles; therefore, the published results could be worse than the real results for ^{192}Ir. In order to rule out this possibility, we ran a Mann-Whitney *U* test to compare the results of this single application and the sum of all the applications. We found no statistically significant differences for any dosimetry parameter.

The dose for eBT was prescribed without taking into account the relative biologic efficiency factor (RBE) or the fact that the mean energy of the beam was much lower than with ^{192}Ir (26keV vs. 355keV) (30,31). Modification of the prescribed dose continues to be controversial in low-energy cases (32). We based our approach on previous experience in that the prescription dose was not modified owing to differences in RBE with respect to ^{192}Ir, and good results were obtained with eBT in endometrium (33) and cervical cancer (19). Similarly, a clinical study showed that modifying the prescription dose by including the RBE factor for treatment of nodular and superficial basal cell carcinoma using eBT reduced the control of the tumor from 95%–90% (34).

Conclusions

According to the analyzed dosimetric parameters, HR-CTV coverage and maximum doses at OARs volumes, our data show that eBT administered using the eBTsystem could be a good alternative to ISBT in a selection of cases. The doses absorbed in the target volume are good or acceptable according to the criteria set out for 79.2% of the cases studied. The results revealed no statistically significant differences with ^{192}Ir in the dosimetry of plans for FIGO stages I–IIA and IIB. For volumes lower than 30 cc, good plans were achieved in 92.3% of cases. If we in-

clude acceptable plans, this percentage increases to 100% compared with the ISBT values for absorbed doses similar to those in our technique.

Thus, the dosimetric targets of the plan could be achieved whenever interstitial needles were not necessary, in stages I and IIA, without parametrial involvement, and in those stages IIB where they are not needed in large numbers.

Therefore, it can be concluded that cases without parametrial involvement and with small volumes of HR-CTV would ensure an appropriate plan with eBT versus ISBT.

The doses absorbed in the organs at risk are similar to those obtained with ISBT for stage I–IIA disease, and IIB; although significant differences were observed in the sub-cohort of patients with stage III–IV disease, where the impossibility of conforming the dose with the help of interstitial needles led to an increase in the doses delivered to the organs at risk and a clear decrease in HR-CTV coverage.

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