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Adjuvant electronic brachytherapy for endometrial carcinoma: A 4-year outcomes report

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ABSTRACT

PURPOSE: The purpose of the study was to report the outcomes of a single-center adjuvant electronic brachytherapy (e-BT) experience for patients with endometrial carcinoma.

METHODS AND MATERIALS: Patients were retrospectively assessed. Intracavitary e-BT was applied through a cylindrical applicator (diameters 2.5−3.5 cm). e-BT single doses ranged between 4 and 7 Gy (EQD2 ~ 6−12, α/β of 10 Gy and an relative biological effectiveness of 1.3) at 5-mm depth. Adverse events are reported at first week, 1−3 months, 3−12 months, 12−24 months, and >24 months. The overall survival, disease-free survival, distant disease control rate, and local control rate were estimated using the Kaplan−Meier method.

RESULTS: Twenty-nine patients were assessed. The median age was 68 [48−86] years. External beam radiotherapy was added in $n = 8$ (27.6%) patients. Staging was 13.8% for T1a, 51.7% for T1b, 24.1% for T2, 6.9% for T3a, and 3.4% for T3b. Grading was G3 in 51.7% ($n = 15$), G2 in 20.7% ($n = 6$), and G1 in 27.6% ($n = 8$). Median followup was 47 months [5−88]. Overall Grade 1, 2, and 3 toxicity was 89.7% ($n = 26$), 17.2% ($n = 5$), and 6.9% ($n = 2$), respectively. No Grade 3 cystitis or proctitis or any Grade 4 or 5 toxicity occurred during followup. No local recurrences were detected. Estimated distant disease control rate was 92.1% ($n = 2$, distant metastasis at 7 and 11 months). Estimated 4-year overall survival was 84.8% ($n = 4$ events, two unrelated to disease) and disease-free survival was 84.6%.

CONCLUSIONS: Our data suggest that e-BT resembles a very-low-toxicity profile and a high local control rate in the adjuvant scenario for patients with endometrial carcinoma. © 2020 The Authors. Published by Elsevier Inc. on behalf of American Brachytherapy Society. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Keywords: Electronic brachytherapy; Intracavitary brachytherapy; Kilovoltage; Endometrial carcinoma

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Introduction

Intracavitary brachytherapy (BT) has played a fundamental role in the treatment of gynecological malignancies along the last century. As historical techniques have developed progressively, since the first description of radium isotope applications until the most modern high-dose-rate (HDR) afterloading delivery (1), their efficacy, safety, and importance have already been widely addressed (2,3).

However, it seems to be that for the past few years, the implementation and use of BT techniques have decayed because of factors such as the lack of access to well-implemented centers, trained personnel, and logistic or reimbursement issues, among many others (2,4,5). Despite this problem, there might be a willingness to increase the use of BT, according to evidence presented in poll-based publications among the practitioners from different countries, demonstrating their awareness of the potential benefit of this approach (6–8). Specifically, an elevated tendency toward greater BT utilization for endometrial carcinoma (EC) treatment has been reported (9,10), being the modality of vital importance to achieve optimal oncologic and quality-of-life outcomes for this group of patients (11,12).

An interesting option to overcome these problems may rise with the introduction of kilovoltage electronic brachytherapy (e-BT) to centers where the investment in a fully operational isotope-based BT facility could result unaffordable (13–15).

Herein, we present the longest followup of gynecological patients so far published worldwide of e-BT with low-energy photons performed in our institution.

Methods

Procedure and treatment

Patients with EC and an indication for adjuvant intracavitary BT were retrospectively analyzed, regardless of the indication of combined external beam radiotherapy (EBRT). BT was performed with a portable low-energy X-ray linear accelerator (INTRABEAM, Carl Zeiss Meditec, Oberkochen, Germany). A cylinder-shaped applicator with different diameter ranges (2.5–3.5 cm) was used to deliver the prescribed dose to a depth of 5 mm according to the anatomy of the patient. A dedicated fixation device allowed immobilization of the applicator. Multidwelling was possible due to an adjustable multistepping set of semicircular sleeves, allowing an application range between 17 and 19.5 mm per dwelling point (proportional to each cylinder diameter), outward from the tip of the applicator (Fig. 1). Patients received treatment on a simulation CT scan table, and images were acquired for dosimetry documentation (Fig. 2). Treatment length was chosen at physician's discretion according to risk factors and the vaginal length, to cover the upper 1/3 or 1/2 of the vagina. Single e-BT doses ranged between 4 and 7 Gy (EQD2 ~ 6–12 Gy assuming an α/β of 10 Gy and an relative biological effectiveness (RBE) 1.3) (16), which were delivered during and/or after EBRT treatment or as a sole application. Intensity-modulated radiotherapy based EBRT was added in 1.8–2.0 Gy per fraction up to a cumulative dose of 45–50 Gy, including the upper half of the vagina; in addition, two fractions of 4 Gy each were delivered as boost,

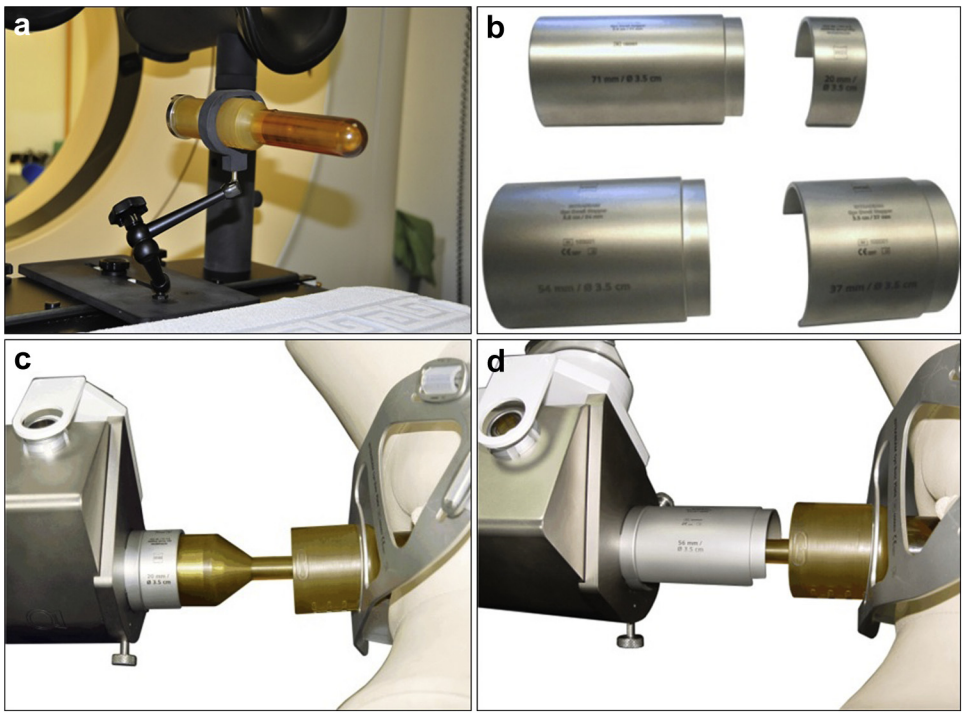


Fig. 1. †Cylinder and fixation device (a). Multidwell rings with different lengths (b). Application procedure (c and d).

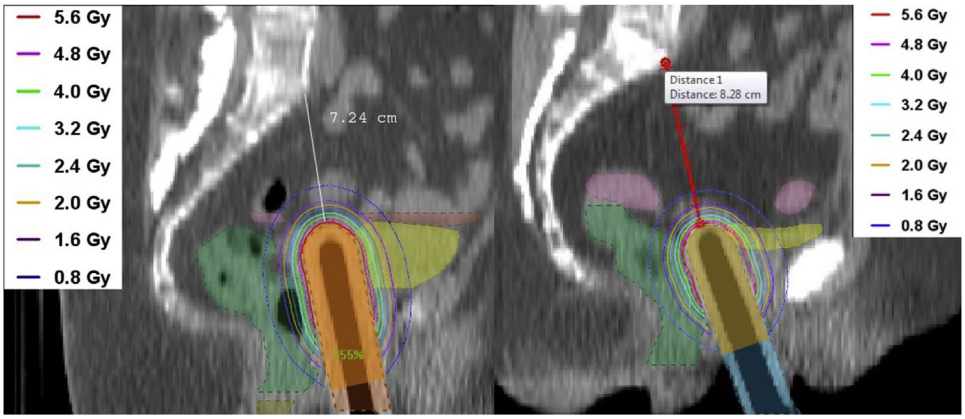


Fig. 2. †Representative images of dosimetry with different prescription lengths. Surface dose reaches ~150% of prescription.

whereas a combination of endovaginal BT and external radiotherapy was indicated.

This study was approved by the local institutional review board, according to local protocols and in compliance with the Helsinki Declaration. All patients gave informed consent before therapy.

End points and statistics

Followup intervals were established after the first post-treatment week and month, every 3 months for the first year, 6 months until the second year, and annually afterward. Arbitrary toxicity assessment intervals were defined as "immediate" (after 1 week), "acute" (1−3 months), "subacute" (3−12 months), "late" (1−2 years), and "chronic" (>2 years). Information was thoroughly collected according to patients' reference, physical examination, and imaging. Main points of interest included toxicity rates per time interval (pelvic pain, cystitis, proctitis, vaginal stricture, and vaginal pain) and were graded per the Common Terminology Criteria for Adverse Events v. 5.0 criteria (17). Cross-sectional analysis of toxicity rates was performed showing the cumulative rates of certain toxicity over time by first occurrence. Estimated overall survival, disease-free survival, distant disease control rates, and local disease control rates (defined as vaginal vault or D_{90} volume area) evaluated according to the Kaplan−Meier method are also reported as secondary end points. Statistical analysis was performed with the SPSS 24.0 software.

Results

Twenty-nine patients, treated between August 2011 and December 2015, were included in the analysis. The median age was 73 [48−86] years. All patients were treated using the first-line approach. The median time from surgery to first EBRT or e-BT fraction was 46 days [21−210]. Intensity-modulated radiotherapy based EBRT (45−50.4 Gy) was added in $n = 8$ (27.6%) patients. Endometrial adenocarcinoma was confirmed in all the cases, whereas 13.8% were staged as T1a, 51.7% as T1b, 24.1% as T2, 6.9% as T3a, and 3.4% as T3b (American Joint Committee on Cancer TNM seventh edition (18)). No different high-risk histologies were found in the specimens. Endometrial histology grade was G3 in 51.7% ($n = 15$), G2 in 20.7% ($n = 6$), and G1 in 27.6% ($n = 8$). According to each individual prescription, dwelling points were two in 13.8%, three in 65.5%, and four in 20.7%, to encompass different vaginal lengths. Treatment schemes included 16 Gy in four fractions (58.6%), 20 Gy in 4 (13.8%), 8 Gy in 2 (24.1%), and 14 Gy in 2 ($n = 1$, 3.4%) (Table 1).

The median followup was 48 months [5−88]. Baseline pelvic pain was found in 41.4% of the entire cohort, whereas grades G1 and G2 were present in $n = 11$ patients and $n = 1$ patient, respectively. The cumulative incidence of G1, G2, and G3 toxicity at the end of the followup period was 89.7% ($n = 26$), 17.2% ($n = 5$), and 6.9% ($n = 2$), respectively, with an overall median first onset of 1 [1−227] week after treatment, as most of the patients (65.8%) reported G1 events during the first week after the procedure. Median onset times per interval were 1 week for "immediate," 1 [1−3] month for "acute," 6 [3−12] months for "subacute," 20 [12−24] months for "late," and 49 [24−227] months for "chronic." The rates of toxicity per time intervals and prevalence are shown in Fig. 3. The two G3 events were one "acute" pelvic pain as well as one "acute" vaginal stricture in the combined modality subgroup. No G3 cystitis or proctitis or any G4 or G5 toxicity occurred during followup.

Most notably, the local disease control rate was 100% during the entire observation period, whereas the estimated 4-year distant disease control rate was found to be 92.1% ($n = 2$ patients with distant metastases at 7 and 11 months). Estimated 4-year overall survival was 84.8% ($n = 4$ events, two unrelated to disease) and 4-year disease-free survival was 84.6% (Fig. 4).

Discussion

Principal findings of the study

These results, with a median 4-year followup, the longest to date regarding this topic, point out the value of

Table 1
Patients and treatment characteristics

Characteristics	Median	Rate (%)
Age	73 [48–86]	
Endometrial histology grade		
G1		27.6
G2		20.7
G3		51.7
Endometrial T-stage[a]		
T1a		13.8
T1b		51.7
T2		24.1
T3a		6.9
T3b		3.4
EBRT[b]		
Yes		27.6
No		72.4
Dwell points		
2		13.8
3		65.5
4		20.7
Total e-BT doses (Gy)/fractions		
16/4		58.6
20/4		13.8
8/2[c]		24.1
14/2		3.4

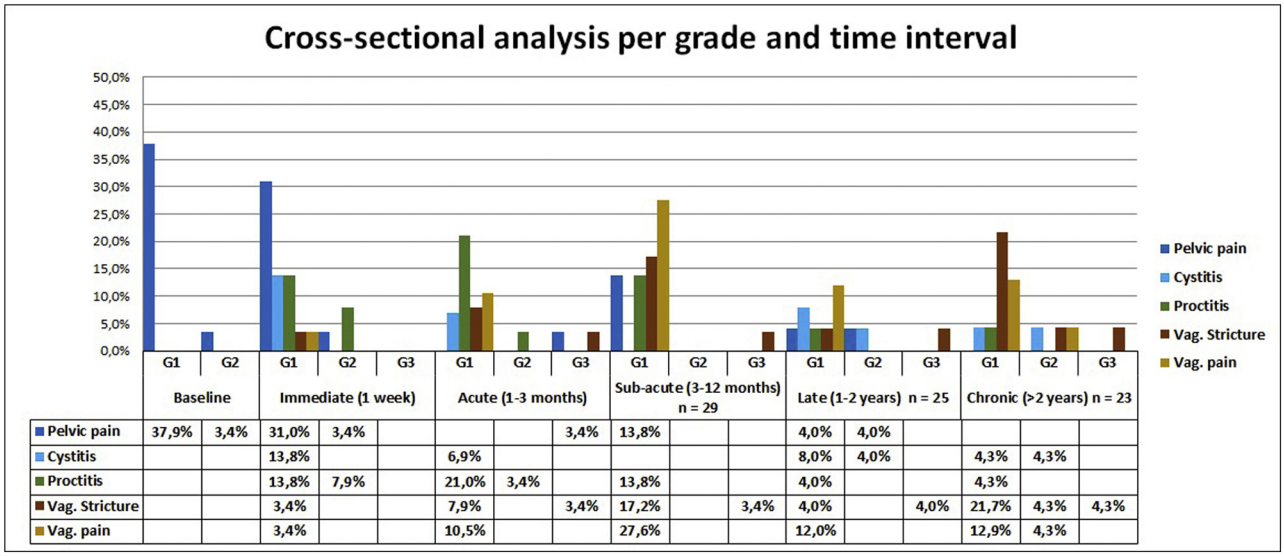
AJCC = American Joint Committee on Cancer; e-BT = electronic brachytherapy; EBRT = external beam radiotherapy.
[a] AJCC TNM seventh edition classification.
[b] Doses ranging from 45 to 50 Gy.
[c] Combined modality scheme.

e-BT in terms of the toxicity profile and suggest a strong correlation for local disease control in comparison to larger series studies. The low G3 event rate (n = 2 patients) and the high local control rate (100%) confirm our statement. The absence of cystitis or proctitis and G3 or higher grade toxicity is remarkable as well.

Results

Interesting preliminary results have been previously published (19–21); however, none of them have shown long followup periods as presented herein. This lack of evidence led therefore to the American Brachytherapy Society consensus for e-BT, recommending recruitment of patients only in the context of safety and efficiency evaluations (22).

The rationale for e-BT includes dosimetric and logistic advantages. The dosimetry profile of the portable linear accelerator (INTRABEAM, Carl Zeiss Meditec, Oberkochen, Germany) has been described in a previous publication through a comparison between an Ir^{192} afterloader and this device. For cylindrical applicators, at a 5-mm depth prescription, the surface relative dose varied between 140 and 150% of the intended delivery for the former and the latter, respectively. In addition, the measured dose at 1 cm showed a relative dose delivery of 74% for the isotope-based afterloader and 67% for the kilovoltage device (23). Diverse experiences with other devices from different manufacturers have been as well reported. In two dosimetric reports, where another kilovoltage device was compared to Ir^{192} and Co^{60} afterloaders, the investigators found a 15% to 23% increase on the relative surface dose delivery; this might resemble a minor problem regarding toxicity by reducing the single doses and simultaneously increasing the number of fractions per treatment (24,25). A higher RBE factor should also be taken into consideration, as this could potentially increase the toxicity profile (26). Despite these prior dosimetric concerns about elevated doses to the vaginal mucosa, we found no clinical correlation. This might be related to the lower dose-per-fraction strategy applied to our patients. In relation to the latter, dose selection was performed after obtaining the



	Baseline G1	Baseline G2	Immediate (1 week) G1	Immediate (1 week) G2	Immediate (1 week) G3	Acute (1-3 months) G1	Acute (1-3 months) G2	Acute (1-3 months) G3	Sub-acute (3-12 months) n = 29 G1	Sub-acute (3-12 months) n = 29 G2	Sub-acute (3-12 months) n = 29 G3	Late (1-2 years) n = 25 G1	Late (1-2 years) n = 25 G2	Late (1-2 years) n = 25 G3	Chronic (>2 years) n = 23 G1	Chronic (>2 years) n = 23 G2	Chronic (>2 years) n = 23 G3
Pelvic pain	37,9%	3,4%	31,0%	3,4%				3,4%	13,8%			4,0%	4,0%				
Cystitis			13,8%			6,9%						8,0%	4,0%		4,3%	4,3%	
Proctitis			13,8%	7,9%		21,0%	3,4%		13,8%			4,0%			4,3%		
Vag. Stricture			3,4%			7,9%		3,4%	17,2%		3,4%	4,0%		4,0%	21,7%	4,3%	4,3%
Vag. pain			3,4%			10,5%			27,6%			12,0%			12,9%	4,3%	

Fig. 3. †Cross-sectional analysis showing prevalence of adverse events according to time frames.

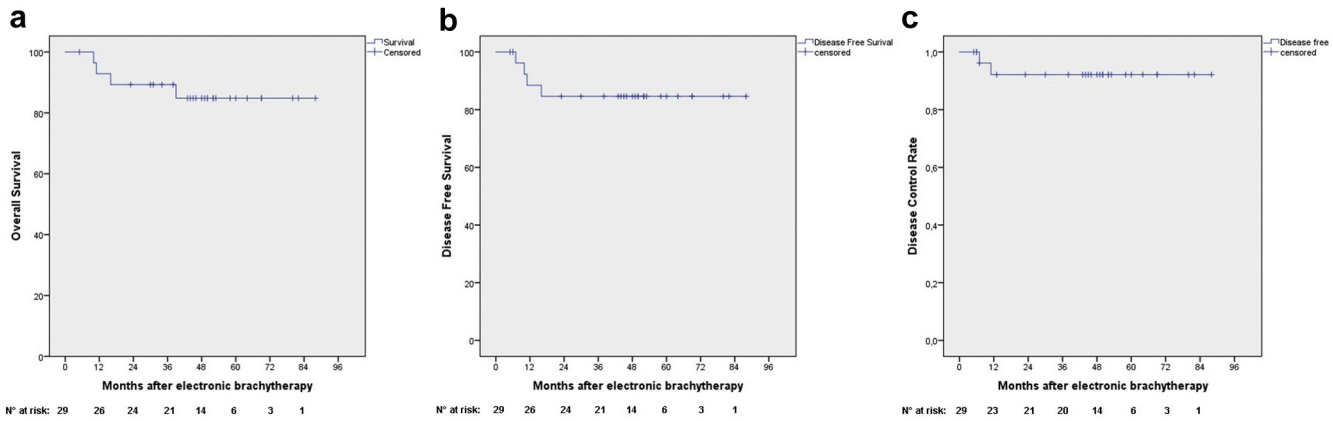


Fig. 4. †Estimated OS (a) and DFS (b). Distant control rate (c). OS = overall survival; DFS = disease-free survival.

product of EQD_2 and RBE values (1.3−1.5) (16), to achieve a total EQD_2 of ~70 Gy for the combined modality patient group and ~25−30 Gy for the monotherapy group (27). Although the PORTEC-2 trial reported EQD_2 doses of approximately 30 Gy, there is additional evidence from a randomized trial supporting the application of six fractions of 2.5 Gy (EQD_2 ~16 Gy) with similar outcomes after 5-year followup (28). After considering these factors and the previously mentioned RBE profile, single doses of 4−5 Gy in four applications were chosen. Only one patient from our cohort received two 7-Gy single doses ($\sum EQD_2$ 26 Gy) because of personal desire of treatment shortening.

Despite the prompt onset of acute toxicity in this study, it is not of major concern, as most of these were G1, were solved spontaneously, and were strictly related to the procedure's nature. Safety profile achieved by this technique reveals a low incidence and prevalence of overall adverse events, with only two G3 events reported in the acute subgroup. Our data show great correlation to the toxicity reports of the PORTEC-2 and Swedish trials. In our study, G3 vaginal stricture is reported in two (5.3%) cases compared with the ~2% cases reported in the aforementioned trials. However, the given difference between the samples (n = 38 vs. 213 and 264) and the addition of EBRT in 27.6% of our patients should be noticed. Interestingly, the reported rates in the combined-treatment arm (EBRT + BT, n = 264) of the Swedish trial differ from their only-EBRT arm (0.8%) and the PORTEC-2 results, with no G3 events after a median followup of 45 months (29,30). Another recent systematic review of 11 publications, including 2404 patients who underwent vaginal BT without EBRT, supports our findings reporting an overall 2% G3 vaginal toxicity (31). Compared to the reported toxicity profile from the PORTEC-2 trial, based on the vaginal mucosa assessment, our study was focused on a more descriptive symptomatic report, as these patient-reported symptoms and clinical evaluation are directly correlated with mucosal atrophy. Vaginal dilators were not routinely prescribed for patients in our cohort because of the low incidence of vaginal toxicity; therefore, an evaluation in regard of this subject could not be performed. However, it is to be remarked that although the retrospective nature of this analysis carries inherent limitations, toxicity data are thoroughly collected in a registry-like format for all patients who underwent intraoperative radiotherapy and e-BT since the very first treatment in our center, over 15 years ago.

In regard of the previously described dosimetric profile, the cystitis and proctitis rates appear to be lower as expected compared with isotope-based techniques. In stretch relationship, lower G1 and G2 urinary and rectal toxicity values are here reported, with prevalence late rates between 6.9% and 3.4% and a decrease tendency curve between acute and late events, while seminal studies report up to 26.9% urinary and 9.8% rectal late toxicity (29,30). Additional reports with larger cohorts of patients, in addition to the aforementioned reports, have shown comparable results regarding toxicity (32−34).

It is worth mentioning that the local control remained to be 100% during the entire observation period. The results obtained here follow the trend of previously published reports from the last 20 years, including the cornerstone PORTEC-2 and Swedish trials, as well as other long followup results that ranged between 93% and 100% (11,29,35,36).

Clinical implications

The outcomes presented here, in addition to prior publications from different groups, have set the basis profile for safe applications. The dosimetric background, as mentioned previously, is directly correlated with these results. As detailed herein, the described toxicity profile might be a useful tool for clinicians to better know the inherent secondary events' onset characteristics. Based on this experience, the 8 Gy in two fractions scheme has been selected at our institution to be the standard fractionation

for the combined modality (plus 45−50 Gy EBRT) and 16 Gy in four fractions for monotherapy managements.

This technique might represent a lower budget approach for the center where HDR facilities are not a viable option because of shielding or other logistic reasons.

Research implications

Although joining our data to prior publications suggests good outcomes in terms of disease control, prospective data assessment comparing outcomes between techniques (HDR−e-BT) to answer this question is strongly recommended. Caution is suggested while delivering on an RBE-based calculation, as this mathematical model has not been widely proven in clinical settings. In addition, prospective information regarding the toxicity impact on sexual activity is required, as this might imply a great quality-of-life limiting factor for sexually active patients. The real cost-benefit relationship of this approach should also be evaluated, as this technique might represent an interesting option in centers where building an isotope-based BT facility would not be feasible.

Strengths and limitations

The main strength of this study relies on the long-term followup period, which is the longest period published to date, regarding e-BT for gynecological malignancies. In addition, the well-described toxicity cross-sectional analysis represents a useful tool for practitioners, as onset times related to grading often lack in BT reports. The limitations of this study include its retrospective nature and staging inhomogeneity of the population. Despite the promising results reported herein, prospective assessment of quality-of-life and oncological outcomes should be carried out aiming to generate definitive evidence on the impact of e-BT in patients with EC, according to stage. An evaluation of sexual life status could not be performed for this cohort due to poor registration on this matter, which is a recurrent problem in BT studies; although some other efforts have successfully reported this information (37,38).

Conclusion

With the longest followup time published to date, e-BT represents a safe and effective option for postsurgical patients with EC. Prospective data are warranted to confirm the disease control outcomes and a real economic impact.

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Authors' contributions: G.R.S. contributed to data and statistical analysis, manuscript production, and review; E.S. contributed to data and statistical analyses; F.W. contributed to study design and manuscript review; F.S. contributed to dosimetric analysis and manuscript review; Y.A. contributed to study design and data collection; F.A.G. contributed to the design of the study and data and manuscript review; M.E. contributed to the design of the study, data collection, and manuscript review.

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