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Electronic brachytherapy for gynecological cancers — a systematic review

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ABSTRACT

Background: The purpose of this manuscript is to provide an in-depth literature review of the management of endometrial and cervical cancers with electronic brachytherapy.

Materials and methods: An extensive literature search was performed and 9 articles were selected based on preset criteria.

Results: The reviewed studies provided dosimetric and clinical results. Patient populations were diverse and prescribed doses varied. When treatment plans were compared to those using cobalt 60 (^{60}Co) and iridium 192 (^{192}Ir) sources researchers found lower or equivalent doses in organs at risk while the doses at the applicator surface were significantly higher for electronic brachytherapy. In the eligible studies, a total of 72 patients received treatment with AxxentXoft vaginal applicator, 29 were treated with the Intrabeam vaginal applicator, and 8 with AxxentXoft cervical applicator.

Conclusions: All authors found that electronic brachytherapy was safe and well tolerated as higher mucosal doses did not present as adverse clinical effects. Electronic brachytherapy for gynecological cancers has the potential to achieve equivalent tumor control while minimizing bowel and urinary toxicity thus improving the quality of life. More clinical data is needed to stratify patients who would benefit the most.

Key words: cervical cancer; endometrial cancer; electronic brachytherapy

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Introduction

Oncologic diseases are a leading cause of death. The burden of cancer morbidity and mortality is increasing [1]. In 2020 over one million new cases of cervical and endometrial carcinoma were diagnosed accounting for 10% of cancer cases in women [2].

The contemporary treatment of gynecologic cancers is multidisciplinary, tailored to the individual patient risk and prognostic factors. Surgery, chemotherapy, external beam radiotherapy (EBRT), and brachytherapy (BT) can be recommended alone or combined.

Brachytherapy is a form of radiation therapy that consists of placing radioactive sources inside or in proximity of a tumor, most often in treatment of cervical, prostate, breast and skin cancer. This modality has been used since the discovery of radio-

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activity and allows an optimal dose distribution enabling higher dose of radiation in a short period of time directly to the target volume with minimal exposure of surrounding tissues [3]. In the treatment of the most common gynecological cancers, cervical and vaginal applicators as well as needles are used to position the radioactive source in place.

Image guided adaptive high dose rate (HDR) BT with iridium 192 (^{192}Ir) is an essential component of the standard treatment of locally advanced cervical cancer [4–6]. Definitive chemoradiation with brachytherapy is recommended as a primary treatment in American and European guidelines [7, 8]. Enough data has been collected to prove that dose-volume parameters of treatment plans have an impact on morbidity as well [9–11]. However, omitting BT is linked to increased cancer related mortality [12].

Brachytherapy is also indicated in the postoperative setting as an adjuvant treatment for cervical cancer with high risk of local recurrence [7, 8, 13, 14]. In these cases a vaginal applicator is used.

Vaginal BT is the adjuvant treatment of choice for patients with endometrial carcinoma of high-intermediate risk as it achieves excellent vaginal control and low rates of locoregional recurrence. High risk groups are subject to combined treatment (EBRT + BT ± chemotherapy) due to possibility of distant recurrence [15–18].

Electronic brachytherapy (EBT) has been evolving since the start of the 21st century and has become a treatment option for various tumor sites. EBT devices deliver electronically generated radiation and have a low energy output; they are mobile and versatile, do not involve a radioactive source thus obviating the need for an extra shielded room and for storage and handling of isotopes [19, 20].

It is recommended that EBT is used in prospective clinical trials by the American Brachytherapy Society [21] and the necessity for more clinical data is pointed out [22].

The purpose of this review is to survey and analyze the currently available research articles about treatment of endometrial and cervical cancers with electronic brachytherapy.

Materials and methods

This is a systematic review of studies on treatment planning or delivery of electronic brachytherapy with gynecological applicators. Our report follows the PRISMA guidelines [23]. Two independent researchers performed a systematic survey in PubMed and ScienceDirect individually (28.01.2022). The survey strategy included using the search terms "electronic brachytherapy", "Xoft", "Intrabeam" alone and combined in pairs with "endometrial", "cervical", and "vaginal cuff" (Tab. 1).

Table 1. Search strategy and key words

Search strategy and key words			
№	Key words	Pubmed	Science Direct
1	Electronic brachytherapy endometrial	218	158
2	Electronic brachytherapy vaginal cuff	47	59
3	Electronic brachytherapy cervical	760	332
4	Xoft endometrial	4	11
5	Axxent endometrial	3	8
6	Intrabeam endometrial	1	4
7	Intrabeam vaginal cuff	0	2
8	Intrabeam cervical	3	9
9	Xoft vaginal cuff	0	6
10	Xoft cervical	11	11
11	Axxent vaginal cuff	0	5
12	Axxent cervical	8	6
Total		1055	611
		1666	

Only full-text research articles were included by using the automation filter tool. All results which did not concern planning or treatment of gynecological cancer with electronic brachytherapy were excluded after a careful review of the searchers. The most common reasons for excluding articles was that they were either about conventional isotope-based brachytherapy, or about electronic brachytherapy applied for other cancers, i.e. breast, brain, skin.

Results

A total of 1666 results were found. 9 articles met the inclusion criteria.

The databases contained 7 studies on EBT with a vaginal applicator of which 5 concerned Xoft Axxent Electronic Brachytherapy (Xoft Inc., Sunnyvale, CA) and 1, INTRABEAM (Carl Zeiss

Meditec, Oberkochen, Germany). There were two studies on EBT with a cervical applicator using XoftAxxent EBT. The results are grouped according to the applicator used and by the topic of the study: dosimetric or clinical.

Vaginal applicator — dose-volume results

The first study dedicated to the possibilities of EBT in gynecological cancer was published in 2008 by Dickler et al. [24] who compared XoftAxxent EBT and ^{192}Ir based HDR BT plans for treatment of endometrial cancer. It is a dosimetric study on 11 patients previously treated with HDR BT with 21 Gy in 3 fx prescribed to 0.5 mm depth over the first 5 cm of the vaginal cuff as a PTV. Sizes of applicators varied. PLATO treatment planning software, version 14.3.2 (Nucletron, B.V., Veenendaal, the Netherlands) was used. The calculated parameters were: the mean V95%, V100%, V150% for PTV, V35% and V50% for the bladder and rectum. The two methods showed equivalent target coverage while V150% for EBT was higher and reached statistical significance. EBT demonstrated significantly lower V35% and V50% for both the rectum and bladder (see Tab. 2). The authors concluded that EBT has the capacity to reduce the risk of BT toxicity.

In 2012 a study by Rava et al. [25] compared the biologically effective doses absorbed for vaginal brachytherapy with ^{192}Ir and 50 kV EBT considering the relative biological effectiveness (RBE) value of 1.5. They used 15 data sets from 5 patients who were previously treated with EBT using the Axxent Vaginal Applicator (Xoft, Inc., Sunnyvale, CA). All patients were simulated with the 3 cm diameter applicator. Treatment plans were generated using PLATO software (Nucletron B.V., Veenendaal, The Netherlands). 21 Gy/3fx was prescribed to 0.5-cm depth from the surface of the applicator over a 5.0-cm length. All plans had similar target coverage. Treatment plans were compared with respect to physical dose, BED3, and BED10. Mucosal dose (surface dose), as well as the dose at 0.5 cm, was determined at the applicator apex and at midshaft. Bladder and rectum were evaluated using dose to 50% volume of the organ (D50) and dose to 1.0 cc of the organ (D1cc). The authors report that when a RBE of 1.5 is taken into account for calculating BED of EBT, the doses in the rectum and bladder are not significantly lower than ^{192}Ir (Tab. 2). They also find that the lateral aspects of the applicator have an increased BED of approximately 70%. They state that they do not know if the calculated higher BEDs would translate into clinical effects, and think that if dose is prescribed based on BED, high target coverage with low doses in OARs will be again achieved.

A new dosimetric study concerning EBT with vaginal applicators was published in 2016 by Mobit et al. [26] to compare ^{192}Ir, cobalt 60 (^{60}Co), and Xoft electronic BT source for treatment of endometrial cancer. 10 patients who were previously treated with vaginal vault BT were replanned for the other two modalities. The prescribed dose was 18 Gy/3 fx to 5 mm depth. The size of the cylinder applicator varied. The total number of treatment plans was 90 generated by Varian® BrachyVision™ treatment planning system (TPS) v. 10.8.9. The reported parameters were: PTV V90%, V150%, and V200%; the cylinder surface dose; organs at risk (OAR) D2cc, V35% and V50%. PTV coverage was similar for ^{60}Co and ^{192}Ir while EBT covered much higher volumes of PTV with 150% and 200% of the prescribed dose. These differences increased proportionally to the diameter of the cylinder. The surface dose was also the highest in EBT source. D2cc for the rectum and sigmoid were similar for all modalities while D2cc for the bladder, as well as V35% and V50% for the rectum and bladder were lower with EBT and proved statistically significant (Tab. 2). The authors comment on cases in which the dose in the rectum was higher with EBT and point out that the distance between the organ and applicator was less than 5 mm, i.e. it was partially inside PTV. Considering the higher surface dose, patients with this specific anatomical feature might still benefit from EBT as the volume that receives lower doses is smaller but is at risk of local toxicity due to proximity to the applicator. Authors recommended that increasing the number of fractions and reducing the dose per fraction and the total dose per treatment course should be considered.

Vaginal applicator — clinical implementation

In 2010 the first multicenter studies on usage of Xoft EBT with a vaginal applicator were published. The retrospective survey performed by Dooley et al. [27] evaluated the feasibility and safety of EBT for vaginal cuff irradiation. 41 patients were enrolled. 25 patients received EBRT and 16 patients were

treated with EBT only (18–24 Gy/3 to 4 fx). Dose was prescribed to 5 mm depth to the upper third or upper half of the vagina. BrachyVision™ treatment planning software (Varian Medical Systems, Palo Alto, CA) or Plato™ treatment planning software (Nucletron, Columbia, MD) were used at most centers. The median follow-up was 3.8 months. Patients who were treated with EBT alone had no adverse events in the first 3 months while four grade 1 and 2 (according to CTCAE ver. 3.0.) toxicities were recorded later in this group. The total number of G2 events in both groups was 8 and 4 of them were recorded to be due to EBRT. There was one G3 toxicity in the combined treatment group in a patient who had vaginal recurrence and who had received prior chemotherapy; the patient's vaginal mucosa was not intact beforehand. However, some of the recorded toxicities were not scored at all. The authors concluded that electronic brachytherapy was feasible and well tolerated.

Also in 2010 Dickler et al. [28] published their prospective multi-center trial to evaluate the success of treatment delivery, safety and toxicity of XoftAxxentEBT as post-surgical adjuvant radiation therapy in 15 patients with early-stage endometrial cancer. Five patients received combined treatment of 45–50.4 Gy/25–28 fx EBRT and 16–20 Gy/2–4 fx EBT prescribed to the vaginal surface. Ten patients were treated with EBT only with doses of 21 Gy/3 fx or 22 Gy/4 fx prescribed to 0.5 mm depth. The length of irradiated vagina ranged from 4 to 7 cm. Three applicator sizes were used. The follow-up period was 3 months. There were 4 grade 1 toxicities and 2 grade 2 toxicities (Common Terminology Criteria for Adverse Events; CTCAE ver. 3.0). The authors reported achieved dose-volume parameters specifically stressing on their previous results comparing ^{192}Ir to EBT. The percent of PTV receiving 150% of the prescribed dose was 58.9% *vs.* 35.8% for the EBT and 192Ir treatments while their more current study achieved a mean value of 34.1%, which is however not comparable since the PTV coverage is also lower. The conclusion of this study was that all treatment sessions were delivered successfully without serious adverse events.

In 2013 a retrospective study by Kamrava et al. [29] examined the effect of XoftAxxent EBT as a vaginal cuff treatment (Tab. 2). The study included 16 patients. Eleven patients were treated with EBRT first (dose 45–49.2 Gy), 7 patients received chemotherapy. The EBT dose was 30-34 Gy in 5 to 6 fx for patients who received BT as a single modality and 9–20 Gy in 2 to 4 fx for patients on combined treatment. EBT dose was prescribed to a depth of 5 mm from the surface of the applicator in 10 patients and 2 mm in 6 patients. Treatment planning was performed using the BrachyVision™ planning system version 8.2 (Varian Medical Systems, Inc., Palo Alto, CA, USA). PTV was defined as a 2 mm shell around the upper 4 cm of the applicator. Dosimetric data that was reported includes: PTV V95%, V100%, V150%, the volumes of the bladder and rectum V35% and V50% as well as D0, 1cc and D2cc. The median follow-up was 20.5 months. The authors used CTCAE ver. 4.0 to evaluate toxicity. All G2 (n = 5) and G3 (n = 2) toxicities were in the group of combined modalities treatment. The G3 adverse events were vaginal strictures. These patients had the highest V150 in the whole group. The local control rate was 94%, locoregional control was 94%, and overall survival was 88%. The authors recommended careful patient selection, especially stressing comorbidity and compliance.

The first published 4-year outcomes report of patients treated with EBT for endometrial cancer by Sarria et al. [30] came out in 2020. The study was conducted in Germany and 29 patients were treated with EBT for endometrial cancer. Eight patients received EBRT (IMRT 45–50 Gy ± 2 x 4 Gy boost) beforehand. BT was performed with INTRABEAM, Carl Zeiss Meditec, Oberkochen, Germany. Physician's prescriptions varied both in terms of target volume (1/2 or 1/3 of the vagina) and doses (16 Gy/4 fx, 20 Gy/4 fx, 8 Gy/2 fx, 14 Gy/2 fx). The median follow-up was 48 months. The authors report two G3 toxicity events – one acute pelvic pain and one acute vaginal stricture, and both of these patients were treated with combined modality RT. There were 5 G2 toxicities. Local disease control rate was 100%; 4-year distant disease control rate was 92.1% (2 patients with distant metastases at 7 and 11 months). Estimated 4-year overall survival was 84.8% (4 events, two unrelated to disease) and 4-year disease-free survival was 84.6%. The authors concluded that the dosimetric concerns about mucosal dose had no clinical consequences. They report EBT is safe and effective compared to isotope-based BT while finding that the patient cohort is quite non-homogenous.

Cervical applicator

The dosimetric results of planning EBT with a cervical applicator and their comparison with ^{60}Co and ^{192}Ir sources were published by Mobit et al. [31] in 2015. They replanned 10 patients treated by 4 fractions of brachytherapy for cervical cancer using ^{192}Ir , ^{60}Co, and Xoft electronic brachytherapy source. 40 treatment plans for each radiation source were generated. The treatment planning systems were Varian BrachyVision v. 8.9 (Varian® Medical Systems, Palo Alto, CA). The parameters that were reported were: the OAR V35% and V50%, the highest dose to 2 cm^3 of an OAR (D2cc); the volume of tissue surrounded by the 200%, 150%, 100%, and 50% of the prescription dose isodose lines; doses to point B. The OARs were the bladder, rectum, sigmoid and small bowel. The planning objective was to keep D2cc for them < 80% (22.4 Gy or 5.6 per fx) of the prescription dose. The study found that volumes of tissue (including the applicator) surrounded by the isodose lines receiving 200%, 150%, 100%, and 50% of the prescribed dose were similar for ^{60}Co and ^{192}Ir source. Electronic BT presented with a 74% greater 200% volume and 34% greater 150% volume. The volume surrounded by the prescription dose was quite similar to the other sources; however, the 50% isodose volume was 23% smaller. The average dose for EBT was 45% lower in point B compared with the other two sources. The OAR dose per fraction was calculated as a mean value of all the four plans per modality. D2cc for the rectum, small bowel, and sigmoid showed no statistically significant difference while for the bladder there was a 25% reduction in D2cc. V35% and V50% for both the rectum and bowel demonstrated a significant decrease in the EBT plans (see Tab. 2). The authors conclude that ^{60}Co is equivalent to ^{192}Ir while electronic brachytherapy source provides the same target coverage while reducing doses to OARs; the central doses inside the target volume of 200% and 150% are higher and of higher biological effectiveness. The authors speculated that this could raise toxicity but could be managed by changing fractionation. In 2019 Lozares-Cordero et al. [32] published their report on first cases of cervical cancer treated at their facility with XoftAxxent EBT. Eight patients were treated with EBT and plans for ^{192}Ir were generated for comparison. The parameters that were evaluated for OARs were D0.1cc, D1cc, D2cc; V150 and V200 of irradiated tissue (Tab. 3). The prescribed dose was 28 Gy/4 fx after 46 Gy/23 fx EBRT (IMRT). Patients with tumor expected to be < 3 cm and with no parametrial invasion after EBRT were eligible for the study. The treatment planning system (TPS) used was Brachyvision-Eclipse (Varian Medical System Inc., Palo Alto, CA, USA). Each patient had 2 EBT plans (for the first and third session) and two ^{192}Ir plans — a total of 32 plans were evaluated. All plans were normalized by the dose received by 90% and 98% of CTV — the planning aim was to achieve equal coverage. Dosimetric statistical significance was reached for D1cc and D2cc of the rectum where EBT had lower doses than ^{192}Ir. There were no other significant differences in parameters. The median follow-up was 13 months. There was one Grade 2 acute vaginal mucositis that lasted no longer than a month. No relapses were observed. The authors express that higher mucosal toxicity was expected due to higher doses near the applicator surface but find the clinical result promising.

Discussion

Brachytherapy performed by low-energy X-ray generators can save the costs of radioactive isotopes and room shielding but also eliminates risks of accidents with radionuclides [33]. The available devices are mobile with applicators of various sizes, shapes and materials. For the treatment of gynecological tumors, vaginal and cervical applicators by Xoft have received Food and Drug Administration (FDA) clearance and CE marking for commercial trade and usage. However, there are still no international recommendations on gynecological application of electronic brachytherapy up to this day. The studies comparing treatment plans using EBT and radioactive sources have found that EBT has the potential to be superior in sparing organs at risk while dose near the applicator and inside the treated volume might be much higher. This fact, alongside supposed calculated higher RBE [34], raised the concern about local mucosal toxicity. All authors of dosimetry studies suggested de-escalation of dose per fraction and total dose. A study on skin electronic brachytherapy has observed that dose reduction in accordance with RBE was associated with lower cure rate. Toxicity was never-

Table 2. Bladder and rectum receiving prescription dose volumes

Study	Percentage of rectum and bladder receiving 35% and 50% of prescription dose [V50%/V35%], Gy			
	Bladder [V50%]	Bladder [V35%]	Rectum [V50%]	Rectum [V35%]
EBT data — Dickler [20]	15.90	27.40	17.00	28.30
HDR data — Dickler [20]	26.50	47.70	27.80	48.30
EBT data — Rava [21]	6.60	NA	4.20	NA
HDR data — Rava [21]	9.3	NA	7.2	NA
EBT data — Mobit 2016 [22]	15.6 ± 11.8	37.9 ± 17.9	20.4 ± 10.3	36.9 ± 14.4
HDR data — Mobit 2016 [22]	33.9 ± 18.7	73.2 ± 23.4	32.7 ± 14.1	58.9 ± 17.5
^{60}Co data — Mobit 2016 [22]	32.2 ± 17.6	70.3 ± 24	31.8 ± 13.9	57.9 ± 16.7
EBT data — Kamrava 2013 [25]	7.2 ± 5,4	16.8 ± 9.0	10.1 ± 5.8	20.7 ± 8.7
EBT data — Mobit 2015 [27]	22.5 ± 12.9	42.1 ± 24	13.7 ± 10.1	27.7 ± 15.9
HDR data — Mobit 2015 [27]	48.5 ± 27	80.0 ± 23.0	21.7 ± 15.8	47 ± 17.2
^{60}Co data — Mobit 2015 [27]	47.9 ± 27.1	79.1 ± 23.7	23.5 ± 16.2	48.9 ± 17.2

EBT — electronic brachytherapy; HDR — high dose rate; ^{60}Co — cobalt-60; NA — non available

Table 3. Doses to the volume of 2 cc, 1 cc, or 0.1 cc mean [Gy] per fraction for organs at risk (OARs)

D2cc, D1cc, D0.1cc: Doses [Gy] to the volume of 2 cc, 1 cc, or 0.1 cc mean [Gy] per fraction for OAR						
	Bladder D2cc	Bladder D1cc	Bladder D0,1cc	Rectum D2cc	Rectum D1cc	Rectum D0,1cc
EBT data — Lozares-Cordero (28)	4.40	4.90	5.90	2.10	2.50	3.50
HDR data — Lozares-Cordero (28)	4.60	5.10	6.00	2.60	3.00	3.90

EBT — electronic brachytherapy; HDR — high dose rate

theless higher in the regular dose regimen group [35]. Clinical studies on gynecologic application of EBT have currently found no translation of higher mucosal doses into clinical effects and have reported low toxicity rates.

According to the International Commission on Radiation Units and Measurements (ICRU) Report 89 [36], it is recommended for research-oriented reporting that vaginal volume or subvolumes' doses are reported, which could add valuable information since PTV coverage is not precisely indicative for dose absorbed by vaginal mucosa as it is usually generated by adding a margin to the applicator surface. What is more, our personal experience with planning EBT (BrachyCare treatment planning system by Técnicas Radiofísicas, Zaragoza, Spain) is that V200% and V150% inside the PTV are actually partially inside the applicator itself, which means that the highest calculated doses are absorbed by the device and not the patient. This could explain why high grade adverse events were not observed, but further investigation on the matter is necessary.

The main limitation was the limited number of patients. There is one study of 94 patients who were treated with XoftAxxent EBT for endometrial cancer and the median follow-up was 14 months. Toxicity was scored according to Radiation Therapy Oncology Group — European Organization for Research and Treatment of Cancer (RTOG-EORTC). There was 1 (1.1%) acute G2 event and 1 month after treatment there were none [37].

There are no currently registered ongoing clinical trials on EBT for gynecological cancers even though much data is needed. Results of the published studies cannot be directly summarized as they varied in patient population, dose prescription, target volume, sizes of applicator. Quality of life has not been assessed in any of the available published surveys.

The latest article on EBT for cervical cancer was published in 2022 and offers an analysis of 48 EBT treatment plans of patients who were previously treated with ^{192}Ir by an Utrecht type applicator [38]. This is the first study that includes patients with stage III and stage IV carcinoma which usually

require interstitial needles for better target coverage. However, XoftAxxent EBT offers no opportunity to use needles. Plans were calculated using the BrachyCare treatment planning system (Técnicas Radiofísicas, Zaragoza, Spain) for EBT and Oncentra Brachy planning system, version 4.5.3 (Elekta AB, Stockholm, Sweden) for ^{192}Ir. All plans had to meet the EMBRACE criteria for organs at risk and achieve D90% > 90% of the prescribed dose to be classified as good, or D90>85% to be classified as acceptable. Good and acceptable plans were achieved in 95.8% of patients with stage I-II disease and in 62.5% of stage III–IV cases. According to the authors, EBT could replace conventional BT in 100% of cases with high risk clinical target volume (HR-CTV) lower than 30cc. Surprisingly, good plans were achieved even in the very locally advanced group which is encouraging. There is no clinical data to support the expectations that EBT could provide effective treatment to stage III–IV cervical cancer.

In addition, results of these studies cannot be directly summarized as they varied in patient population, dose prescription, target volume, sizes of applicator. Quality of life has not been assessed in any of the available published surveys.

Conclusion

Electronic brachytherapy can be alternative to ^{192}Ir HDR brachytherapy in the treatment of gynecological cancer. It has the potential to make BT accessible in regions where conventional HDR BT is not available. While eligibility and safety have been demonstrated, more prospective research is needed to define the late toxicity, local control, OS, and DFS rates as well as achieved quality of life.

Conflict of interest

None declared.

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