Adjuvant radiotherapy for endometrial cancer - a comparative review of radiotherapy technique with acute toxicity

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Summary

Objectives: The addition of pelvic radiotherapy to brachytherapy (EBRT-BT) in early-stage endometrial cancer is controversial and may cause unnecessary toxicity. The incidence of acute toxicity of EBRT-BT will have an impact on clinical decision and patient compliance but is currently poorly understood. This study compares the acute toxicities of EBRT-BT versus BT alone. *Materials and Methods:* Seventy-nine patients with FIGO Stage IA-II endometrial cancer who underwent adjuvant radiotherapy, (EBRT-BT or BT alone) from 2001 to 2011 were included in the study. Medical records of these patients were reviewed retrospectively and toxicity graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Patients were followed up for at least three months post-treatment to assess resolution of toxicity. *Results:* The mean age of the study group was 60.6 years. Median follow-up was four years. Forty patients received EBRT-BT. There was a 37% increase in Grade 1-3 diarrhea with the addition of pelvic radiotherapy (OR 18.67, $p < 0.0005$) and a 34% increase in lethargy ($p < 0.0005$). There was also an increased occurrence of genitourinary and skin toxicities. Two patients in the EBRT-BT group required hospitalisation for severe diarrhea and three patients were unable to complete the treatment. All acute toxicities had resolved by three months post treatment. *Conclusion:* EBRT-BT causes significantly more acute toxicities compared to BT alone. Patients should be informed of this during counselling.

Keywords: Endometrial cancer; Brachytherapy; Radiotherapy; Toxicity.

Introduction

Radiotherapy is the most common form of adjuvant therapy used in the clinical management of endometrial cancer after surgery. The GOG-99, PORTEC 1 & 2, and the ASTEC trials [1-3] were large trials which evaluated the role of adjuvant therapy in reducing loco-regional recurrence for moderate to high-risk early-stage endometrial cancer. However, the mode of radiotherapy used differed in all the studies.

External beam radiotherapy (EBRT) delivered to the pelvis or brachytherapy (BT) have been shown to be equivalent in early-stage endometrial adenocarcinoma in the recent PORTEC 2 trial. However, EBRT is still indicated for certain subgroups [4-5] of patients who would benefit from sterilisation of microscopic disease in the tumour bed and draining lymphatics. This is the case for patients [6] who did not undergo a pelvic lymph node dissection, or those who were found to have positive lymph nodes after pelvic lymph node dissection. Certain histological subtypes [7] have also been shown to be more aggressive with higher local recurrence rates. In such patients, delivering EBRT followed by BT (EBRT-BT) may be beneficial if the treatment is well tolerated.

Sorbe *et al.* [8] demonstrated that EBRT-BT decreased locoregional relapse rates at five years from 5% to 1.5% compared with BT alone. In light of these findings, the acute toxicity of this treatment has become clinically relevant. Toxicities may have an impact on treatment compliance, requiring symptomatic treatment when necessary. Acute toxicities may also be worsened by the addition of chemotherapy and is likely to lead to increased risk of late complications. [9] Most studies have however focussed on the long term toxicity of EBRT in the pelvis.

The quality of life analysis of the patients in the PORTEC 2 trial showed that EBRT caused more gastrointestinal disturbances when compared with BT and was therefore relatively poorly tolerated. While it may seem intuitive that EBRT-BT would have worse side effects compared with BT alone, there appears to be a lack of data on its severity in patients and how well-tolerated the treatment is.

The aim of this retrospective study is to assess and compare the severity and incidence of acute toxicities experienced by patients who underwent EBRT-BT and those who received BT only.

Materials and Methods

Patient selection and eligibility criteria

Seventy-nine patients who were treated with curative intent for endometrial cancer at the present centre between 2001 and 2011 were included in the study. The information was retrieved from medical records and entries made by the radiation oncologists and nurses during weekly consults while on radiotherapy. During these consults, radiation oncologists routinely graded and recorded toxicities according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 and these were recorded in the centre's computerised Local Area Network Therapy Information System (LANTIS). Patients were asked a fixed set of questions during these consults regarding the toxicities they experienced.

Permission to retrieve the records of the patients was obtained

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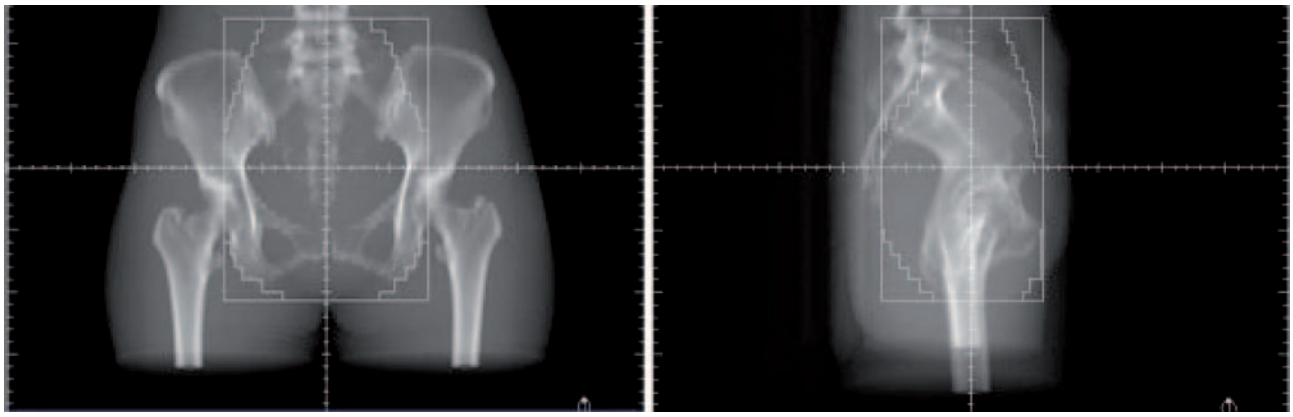

Figure 1. — Digitally reconstructed radiograph of the anterior and lateral treatment fields for pelvic radiotherapy

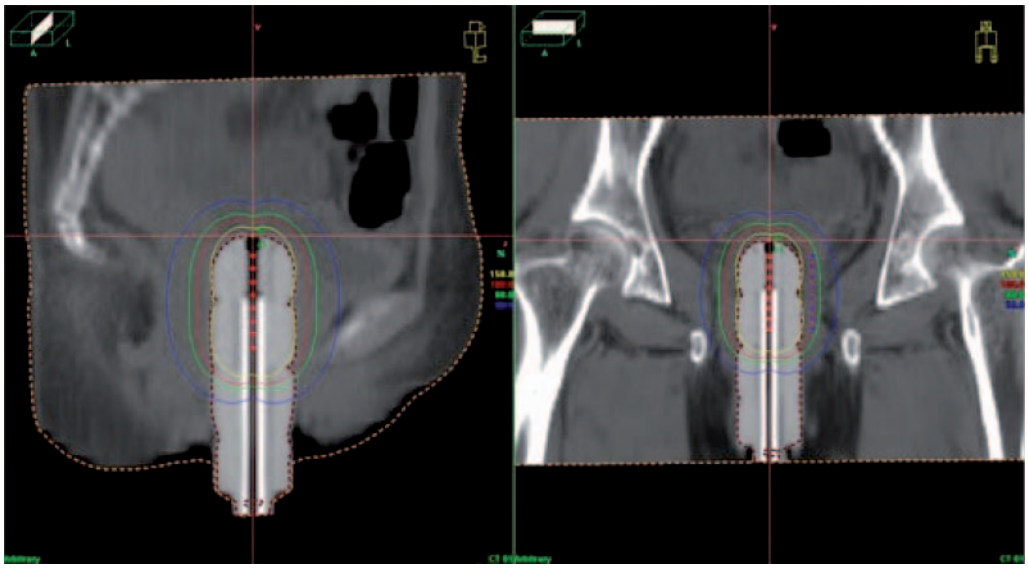

Figure 2. — Sagittal and coronal views of the applicator in position during vaginal BT.

from the medical ethics committee of the hospital. (Domain Specific Reference B/09/576).

Patients with early stage endometrial cancer who had undergone surgery followed by radiotherapy were included and classified according to low-risk, early-stage disease (FIGO IA or IB and low grade pathology [G1, G2]) and intermediate-risk to high-risk, early-stage disease (FIGO IA or IB with high grade pathology [G3], FIGO IIA). Other factors used in decision making were: presence of lymphovascular invasion, presence of pelvic lymph node dissection, and age. All patients were discussed at a multidisciplinary tumour board with a gynaecologist, pathologist, and an oncologist. Decision regarding use of BT and EBRT - BT was discussed.

Prior to the use of FIGO 2009, majority of patients was staged using the FIGO 1988 staging system and these patients were restaged according to FIGO 2009 for this study. Surgery consisted of total abdominal hysterectomy and bilateral salpingo-oophrectomy; clinically suspicious pelvic and/or para-aortic lymph nodes were removed and pelvic lymph node dissection was performed according to surgeon preference. International Federation of Gynaecology and Obstetrics 2009 staging was assigned on the basis of the surgical and pathological findings.

Exclusion criteria were: 1) patients with missing records, 2) patients who had refused surgery and had only received primary radiotherapy (EBRT-BT or BT), 3) patients who had autoimmune diseases (eg. systemic lupus erythematosus, ulcerative colitis), 4) patients who received concurrent chemotherapy and radiotherapy, and 5) patients who had an Eastern Cooperative Oncology Group (ECOG) score of more than 2.

Procedures

EBRT was delivered to the whole pelvis in a total dose of 45-50.4 Gy in 1.8 Gray daily fractions treating from Monday to Friday, five days a week in 25-28 fractions with 10 MV photons. The clinical target volume for EBRT consisted of the proximal half of the vagina, the parametrial tissues, the internal and proximal external iliac lymph node region, and the caudal part of the common iliac lymph node chain (up to the L5-S1 vertebrae junction)(Figure 1). Radiation dose was prescribed to the planning target volume and specified at the isocentre, with homogeneity requirements according to recommendations by the International Commission on Radiation Units and Measurements (ICRU-50). For all patients, computerised treatment planning was used. The beam arrangement consisted of a four- field

Table 1. — *Patient characteristics of the EBRT-BT and BT groups.*

Patient characteristics	EBRT - BT (n = 40)	BT (n = 39)
Median age	62 years (range 46-80 years)	57 years (range 50-78 years)
ECOG post surgery		
0	26	27
1	11	8
2	3	4
FIGO		
IA	10	13
IB	10	19
II	15	7
FIGO		
G1	13	14
G2	13	10
G3	15	15
N. of patients with pelvic lymphadenectomy	4	26
Lymphovascular invasion	20	5
Low risk	15	17
Intermediate risk	25	22

n =number of patients in each study group.

plan with an anterior- posterior beam arrangement and two lateral beams. Shielding was achieved with multi-leaf collimators.

BT was delivered to the upper half of the vagina using a vaginal cylinder applicator (Figure 2). A high dose rate (HDR) iridium source was used to deliver the treatment via a remote afterloader. If the patient had received EBRT, two to three fractions of five to six Gray per fraction prescribed to a 0.5 cm depth of vaginal mucosa was delivered two fractions per week. Patients receiving BT alone were treated with a total of four to five fractions of the same dose per fraction delivered two to three times a week. Selection of fractionation and dose was a clinical decision and depended on the patient's histology, margin positivity, and the type of surgery performed. Fractionation schedules included five Gray per fraction for five fractions, six Gray per fraction for five fractions and 8.5 Gray per fraction for four fractions. Doses to the bladder and rectum reference points (according to ICRU-38 criteria) as well as at the vaginal mucosal surface were documented.

Follow-up

Patients were seen on a weekly basis by the radiation oncologists throughout the course of radiotherapy. They were assessed for acute toxicities and medication providing symptomatic relief was administered if indicated. Patients who tolerated the treatment poorly were hospitalised for observation. At the completion of treatment, patients were reviewed at one week, four weeks, and at three months post-treatment for resolution of acute side effects. A pelvic examination was performed at every visit.

The primary endpoint of this study was to assess the incidence of acute toxicity in patients who received EBRT-BT and compare this with those who received BT alone. The secondary endpoint was the severity of acute side effects experienced.

The results were analysed using chi square test or Fischer's exact test where applicable. The *p*-value was set at < 0.05 for significance.

Logistic regression analysis was used to analyse the risk factors associated with each toxicity. The authors reported the odds ratios and their corresponding 95% confidence Intervals as estimates of effect size. Data analysis was done in Stata V11 and level of significance set at five percent.

Results

Study population and compliance

The authors enrolled 79 patients from the years 2001 to 2011 with Stage IA to II endometrial cancer using the ear-

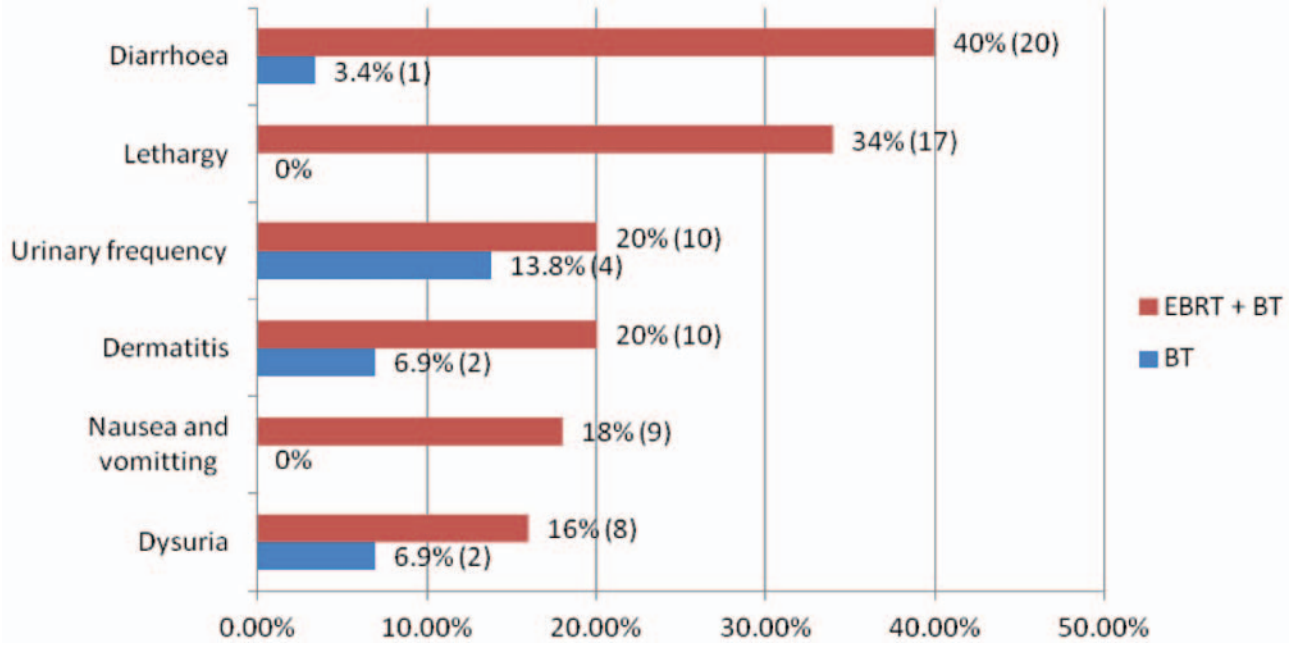

Figure 3. — Incidence of acute toxicities in the EBRT-BT and BT groups, respectively. Absolute numbers are shown in brackets.

Table 2. — *Significance levels between the EBRT-BT and BT groups for each toxicity.*

	p-value	Odds ratio	Confidence interval
Diarrhea	<0.0005	18.67	2.35 - 148.42
Lethargy	<0.0005	-	-
Urinary frequency	0.486	1.56	0.44 -0.52
Dermatitis	0.193*	3.38	0.68 -16.63
Nausea and vomitting	0.023*	-	-
Dysuria	0.310*	2.57	0.51 - 13.04

*Fischer's exact test used.

lier mentioned criteria. The median follow-up was four years. The median age of the study population was 60 years (range 45 - 80 years; mean age 60.6 years).

Seven (8.8%) patients were ECOG score 2 after surgery with the majority 53 (67%) of them being ECOG score 0.

Forty (50.6%) patients were treated with EBRT-BT as part of their treatment for various stages of endometrial cancer. Patient characteristics in the two groups are shown in Table 1.

The total dose prescribed to patients receiving BT only varied according to stage and physician preference. Patients with Stage IA disease received a median total dose delivered by BT of 25 Gray with doses ranging from 24 Gray to 34 Gray. Patients with Stage IB and II disease received a median total dose of 30 Gray with total doses ranging from 24 Gray to 34 Gray.

Toxicity of treatment

Diarrhea was the most common toxicity affecting patients who received EBRT-BT. Patients receiving EBRT-BT were noted to have a 37% increase in incidence of grade 1-3 diarrhea during treatment compared to those who received only BT (40% vs 3% in the BT alone group; p = 0.001, Figure 3). The group receiving EBRT-BT also experienced more lethargy (34% vs 0%), nausea and vomiting (18% vs 0%).

There was an increase in occurrence of dysuria (16% vs 6.9% - BT alone), skin changes (20% vs 6.9% - BT alone) and urinary frequency (20% vs 13.8% - BT alone), although the difference was not statistically significant (Table 2).

The authors also noticed an increase in the occurrence of dysuria in elderly patients (p = 0.078, OR 0.94, 95% CI) and an increase in the occurrence of urinary frequency in patients with poor ECOG post surgery (p = 0.063, OR 1.86, 95% CI), although the findings were not statistically significant.

Severity of acute toxicity

Some patients experienced severe toxicity requiring hospitalisation for rehydration (grade 3 diarrhea). One patient in the EBRT-BT group experienced grade 2 lethargy and required a caregiver at home. Three (7.5%) patients in the EBRT-BT group did not complete the treatment prescribed due to toxicity. By the first follow-up at three months post-treatment, all the symptoms experienced during the radiotherapy had resolved.

Disease recurrence

There were two recurrences in this study group. Both were of intermediate risk and did not undergo pelvic lymph node dissection. They received EBRT-BT and subsequently recurred with distant metastases.

Discussion

In this study, the authors demonstrated that endometrial cancer patients treated with a combination of post-operative EBRT-BT experienced greater acute toxicities as up to 40% of patients had increased nausea and vomiting, diarrhea, and lethargy compared to BT alone. This resulted in a few patients not completing the treatment prescribed.

Studies in cervical cancer and prostate cancer have shown that up to 45% of patients experienced grade 2-3 gastrointestinal toxicities while receiving pelvic EBRT [10-14]. The follow-up study on the PORTEC 2 trial on toxicity of treatment also found significant gastrointestinal toxicity which affected quality of life in the patients receiving EBRT alone. [15]

The present results are meaningful at the cusp of a fundamental shift in the delivery of adjuvant radiotherapy for endometrial cancer. While the results of the PORTEC 2 trial showed that BT alone may be sufficient for adjuvant therapy for early stage endometrial cancer, the combined modality approach has been shown to reduce pelvic recurrences by up to 93% [8] in medium risk patients. The acute toxicity and tolerability of EBRT-BT is important as it will impact clinical decision-making.

Patients with unstaged endometrial cancer present a difficult dilemma in that BT alone is inadequate treatment for women with unrecognised nodal disease. Adjuvant pelvic irradiation is commonly offered in clinical practice when a pelvic lymph node dissection has not been performed [16]. This was reflected in the present study as almost all the patients in the EBRT-BT group did not have a pelvic lymph node dissection. Pelvic lymph node dissections, however, have not been shown to improve overall survival or disease free survival [17-19] while increasing systemic morbidity from surgery, lymphoedema, and lymphocyst formation [17-19]. EBRT-BT and its tolerability will need to be further evaluated before it can be used in all medium risk patients. This study contributes to the evaluation of adjuvant therapies in the treatment of endometrial cancer.

This study required its authors to restage the patients according to the FIGO 2009 staging criteria. Also, they excluded histologies other than endometriod carcinoma from

the analysis as chemotherapy was frequently used concurrently with the radiotherapy for adjuvant treatment of more aggressive histologies. This would worsen the acute toxicity experienced by the patient.

The limitations of this study are its small sample size and its retrospective study design. Unlike the PORTEC 2 trial which was a prospective study and used questionnaires to assess the patients after radiotherapy, this study used notes entered by the doctors caring for the patient during the treatment and their assessment of the severity of toxicity using the CTC grading. This helped us focus on the clinically relevant toxicities experienced by the patient. Bias was also limited as most of the entries were made by the radiation oncologist on duty who was usually not the physician who performed the BT.

In this study, the authors also noticed an increase in the incidence of urinary symptoms with increasing age and ECOG status. Current studies of concurrent chemotherapy and radiotherapy in cervical cancer [20-21] show increased toxicity and treatment breaks in patients above 60 years of age with up to 44% of patients in this group requiring treatment breaks due to grade 3- 4 symptoms. While the present study group did not experience such severe toxicity, a larger sample size in the authors' future studies could give a clearer picture regarding the relationship with age.

Treatment toxicity has a great impact on the patient both physically and psychologically and every effort should be made to decrease its frequency.

Advances in treatment delivery have allowed radiotherapy to pelvic organs to be delivered more precisely [22] (eg. intensity modulated radiotherapy) resulting in well-tolerated treatment [23-24]. This is especially significant as studies have shown that the gastrointestinal toxicity experienced from external beam irradiation of the pelvic organs is directly related to the volume of small bowel irradiated [25-26]. Lactobacillus supplements and amifostine [27] have also shown some promise in preliminary trials in decreasing diarrhea symptoms and radiation colitis [28].

Future research should focus on vaginal BT with concurrent targeted therapies or chemotherapy, especially for intermediate to high risk endometrial cancer to eliminate the need for external beam radiotherapy in these patients. More studies are needed before intensity modulated radiotherapy is used routinely for pelvic radiotherapy.

Conclusion

EBRT-BT causes significantly more acute toxicities compared to BT alone. With the option of vaginal BT alone, postoperative patients with endometrial cancer should be carefully evaluated regarding indications for EBRT-BT and better informed of risk-benefit considerations.

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