2

Quality of life after pelvic radiotherapy or vaginal brachytherapy for endometrial cancer: first results of the randomized PORTEC-2 trial

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Abstract

Purpose: Studies on quality of life (QOL) among women with endometrial cancer have shown that patients who undergo pelvic radiotherapy report lower role functioning and more diarrhea and fatigue. In the Post Operative Radiation Therapy in Endometrial Cancer (PORTEC) trial endometrial carcinoma patients were randomly assigned to receive external beam radiotherapy (EBRT) or vaginal brachytherapy (VBT). QOL was evaluated using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 and subscales from the prostate cancer module, PR-25, and the ovarian cancer module, OV-28.

Patients and Methods: PORTEC-2 accrued 427 patients between 2002 and 2006, of whom 214 were randomly assigned to EBRT and 213 were randomly assigned to VBT. Three-hundred forty-eight patients (81%) were evaluable for QOL. QOL outcomes were analyzed at a median follow-up of 2 years.

Results: At baseline, after surgery, patient functioning was at the lowest level, and it increased during and after radiotherapy to reach a plateau after 12 months. Patients in the VBT group reported better social functioning ($p<0.002$) and lower symptom scores for diarrhea, fecal leakage, the need to stay close to the toilet, and limitation in daily activities because of bowel symptoms ($p<0.001$). At baseline, 15% of patients were sexually active; this increased significantly to 39% during the first year ($p<0.001$). Sexual functioning and symptoms did not differ between the treatment groups.

Conclusions: Patients who received EBRT reported significantly higher levels of diarrhea and bowel symptoms. This resulted in a higher need to remain close to a toilet and, as a consequence, more limitation of daily activities because of bowel symptoms, and decreased social functioning. Vaginal brachytherapy provides a better QOL, and should be the preferred treatment from a QOL perspective.

Introduction

Endometrial carcinoma is the most common gynecological malignancy among postmenopausal women in western countries.[1] Most patients are diagnosed at an early stage, and surgery, which consists of total abdominal hysterectomy and bilateral salpingo-oophorectomy is the cornerstone of treatment.

Randomized trials on postoperative radiotherapy in endometrial carcinoma have shown that pelvic external-beam radiotherapy (EBRT) significantly reduced the rate of locoregional relapse. However, reduction of relapse did not translate into a survival benefit, and was achieved at the cost of more (predominantly mild) gastro intestinal toxicity.[2-7]

As a result of the first Post Operative Radiation Therapy in Endometrial Cancer (PORTEC) trial, the indication for radiotherapy was abandoned in the Netherlands for patients with a very low risk of locoregional recurrence.3 For the remaining so-called 'high-intermediate risk' patients (ie, age 60 years or older and stage IC grades 1 or 2, or stage IB grade 3) the benefit in terms of locoregional control (ie,19% locoregional relapse without radiotherapy vs. 5% with EBRT) and disease-free survival was considered to outweigh the risks in terms of treatment-related toxicity. As most (75%) locoregional relapses were located in the vagina, the multicenter, randomized, PORTEC-2 trial was initiated to investigate if vaginal brachytherapy (VBT) would be equally effective in reducing the risk of locoregional recurrence, while at the same time reducing treatment-related toxicity and improving health-related quality of life (HRQOL).

Little is known about HRQOL and the impact of adjuvant radiotherapy on HRQOL in endometrial cancer survivors. All studies are retrospective, most are quite small and have low questionnaire return rates (<40%).[8-12] One retrospective study with an adequate return rate (75%) found that EBRT was negatively associated with vitality and physical and social well-being, but scores of patients treated both with or without radiotherapy were similar to those of an age-matched population.[13] Although patient-perceived HRQOL is

an important factor to be used in the decision making process, whether or not postoperative radiotherapy should be recommended, there is a clear lack of data on HRQOL among patients with endometrial cancer.

The aim of this analysis was to investigate short-term HRQOL of patients with high-intermediate risk endometrial carcinoma treated in the PORTEC-2 trial and to evaluate the impact of EBRT compared with VBT on patient-perceived HRQOL.

Tabel 1. Patient characteristics of responders and non-responders

	Responders (n=348)					**Non-responders** (n=79)		
	EBRT (n=166)		**VBT** (n=182)					
	No. of Patients	%	No. of Patients	%	*P*-value‡	No. of Patients	%	*P*-value*
Age, years								
mean	69,5		70,1		0,45	71,3		0,16
range	52-88		46-86			52-89		
<60 years	7	4,2	6	3,3	0,29	3	3,8	0,33
≥60 years	159	95,8	176	96,7		75	96,2	
FIGO-stage					0,73			0,99
1B	11	6,1	13	7,2		8	9,2	
1C	137	82,9	147	80,7		58	75	
2A	18	11	22	12,2		9	11,8	
Histologic Grade					0,83			0,42
Grade 1	77	46,4	89	48,9		36	46,1	
Grade 2	78	47	79	43,4		34	43,4	
Grade 3	11	6,6	14	7,7		9	10,5	
KPS					0,18			0,10
0	118	71,1	119	65,4		61	78,2	
1	47	28,3	59	32,4		16	20,5	
2	1	0,6	4	2,2		1	1,3	
Comorbidity								
IBD	2	1,2	2	1,1	0,93	2	2,6	0,34
Diabetes	19	11,4	31	17	0,14	12	15,4	0,82
Hypertension	61	37	63	34,8	0,68	26	33,3	0,68
Cardiovascular	38	23	42	23,1	0,99	18	23,4	0,95
Other	24	14,5	28	15,5	0,79	14	17,9	0,51

EBRT: external beam radiotherapy; VBT: vaginal brachytherapy

KPS: Karnofski Performance Score; IBD: inflammatory bowel disease

FIGO: International Federation of Gynaecology and Obstetrics

‡: *P*-value for comparison EBRT vs. VBT

*: *P*-value for comparison responders vs. non-responders

Patients and Methods

Patient selection and study design of the PORTEC-2 trial

The PORTEC-2 trial was a multicenter, randomized trial that was conducted throughout the Netherlands to compare EBRT and VBT. Surgery consisted of total abdominal hysterectomy and bilateral salpingo-oophorectomy; clinically suspicious pelvic and/or periaortic lymph nodes were removed, but no routine lymphadenectomy was performed. The diagnosis of endometrial carcinoma, grade, histological subtype and depth of myometrial invasion were made by the regional pathologist. International Federation of Gynecology and Obstetrics 1988 staging was assigned on the basis of surgical and pathological findings.[14] Patients were eligible for the study if they had one of the following combinations of age and postoperative International Federation of Gynecology and Obstetrics stage: age ≥60 years and stage 1C grade 1 or 2, or stage 1B grade 3 disease; or any age and stage 2A disease (except grade 3 disease with >50% myometrial invasion). All patients had a WHO-performance score of ≤2. Written informed consent was obtained from all patients. The protocol was approved by the Dutch Cancer Society and the medical ethics committees of all participating centers.

EBRT was given to a total dose of 46 Gy in 2-Gy daily fractions, and five fractions were given per week. VBT was delivered to the upper half of the vagina using a vaginal cylinder. High-dose-rate (HDR; 90% of patients) and low-dose-rate (LDR; 10% of patients) schedules were used, aiming at an equivalent of 45-50 Gy to the vaginal mucosa with HDR schedules of 21 Gy at 5-mm depth, given in 3 fractions of 7 Gy, each 1 week apart; and LDR schedules of 30 Gy at 5-mm depth, in one session at 0.50 Gy/hr.

The primary endpoint was 5-year vaginal relapse rate (VRR) as cumulative incidence, with death as a competing risk.[15] Secondary endpoints were HRQOL, treatment-related toxicity, pelvic lymph node and distant relapse rates, and overall survival. To detect a clinical relevant difference in VRR with sufficient precision, a total of 400 patients were required during an accrual period of 4

years. For evaluation of HRQOL this sample size would be more than sufficient to obtain significant and clinically relevant results, even when taking dropout into account.

QOL Assessment

Cancer-specific HRQOL was measured with the European Organization for Research and Treatment of Cancer C30 questionnaire (EORTC QLQ-C30, version 3.0).[16] The EORTC QLQ-C30 is a multidimensional, cancer-specific quality of life questionnaire developed for repeated assessments in clinical trials and has been found valid and reliable in various cancer populations. The QLQ-C30 questionnaire contains five functional scales (physical, cognitive, emotional, social and role functioning), a global health status/quality of life scale, three symptom scales (pain, fatigue and nausea/vomiting), and six single items assessing additional symptoms (dyspnea, insomnia, loss of appetite, constipation, diarrhea) and perceived financial impact.

Although an endometrial cancer module is currently being developed by the EORTC Quality of Life Group, no endometrial cancer-specific symptom questionnaire was available when PORTEC-2 was active. With approval of the EORTC Quality of Life Group, relevant subscales from existing published EORTC modules, which had previously undergone psychometric evaluation and validation, were combined into a symptom module for this study. The subscales for bowel and bladder symptoms from the prostate cancer module (PR-25) and the subscale for sexual functioning and symptoms from the ovarian cancer module (OV-28) were used.[17, 18]

For all items, Likert-type response scales were used, and the response scale ranged from 4 to 7 points. All subscales and individual-item responses were linearly converted to 0 to 100 scales. A higher score for a functional and global quality of life scale represented a better level of functioning. For the symptom scales and items, a higher score reflected a higher level of symptoms and decreased QOL.

Baseline QOL questionnaires were handed out at the first consultation with the radiation oncologist, usually 3 to 4 weeks after surgery, and had to be returned before the start of radiotherapy. The end-of-treatment QOL questionnaire was handed out 2 to 4 weeks after the completion of radiotherapy. After that time,

the questionnaires were sent directly to each patient's home address at 6, 12, 18, 24, 36, 48 and 60 months from the date of random assignment. Patients were considered evaluable for the QOL assessment if they had returned the baseline questionnaire and at least one of the follow-up questionnaires (ie, responders).

Statistical methods

All statistical analyses were performed using SPSS, version 14.0 (SPSS, Chicago, IL). Data on patient and tumor characteristics from the trial register enabled us to compare responders with nonresponders, using chi-square statistics or Fisher's exact test for categorical variables and t test for continuous variables ($p= 0.05$ was considered significant). These tests were also used to compare the VBT group with the EBRT group.

QOL analysis was done according to the guidelines provided by the EORTC Quality of life Group.[19] Descriptive median scores are listed in the tables. Baseline scores of both treatment groups were compared with a t test or the Armitage trend test for single items. To exclude a treatment effect on baseline scores, baseline forms completed later than the first day of radiotherapy were excluded for this comparison. To obtain estimates of the EORTC QLQ-C30, PR-25 and OV-28 subscales at each of the fixed time points, a linear mixed model was used with the patient as random effect and time (categorical), random assignment and their interaction as fixed effects. Single items were analyzed by using (ordinal) logistic regression with random effects. The difference in QOL between the two treatment groups was tested by Wald's test in the linear or ordinal logistic mixed model (p random assignment), which excluded the baseline value. The same test was applied to look for significant changes of QOL scores over time (p time), and score changes over time were compared between both treatment groups (p time by random assignment), which included the baseline value. To guard against false-positive results because of multiple testing, a two-sided p value of 0.01 was considered statistically significant.

Table 2. Patient functioning scores from EORTC QLQ-C30 and sexual functioning and symptom scores from OV-28.

		Questionnaire Timepoints							*P*-value		
		Baseline	*p**	After RT	6	12	18	24	Time	Randomization	Time by Randomization
EORTC QLQ-C30											
Global health status	EBRT	69,1	0,97	73,2	76,8	75,7	77,0	75,7	**<0.001**	0,35	0,82
	VBT	70,3		76,2	79,2	77,7	78,9	80,3			
Functional scales											
Physical functioning	EBRT	72,0	0,47	76,3	80,7	79,0	80,4	77,3	**<0.001**	0,24	0,98
	VBT	73,6		79,4	82,3	81,7	81,8	81,1			
Role functioning	EBRT	61,0	0,18	71,5	80,5	81,0	82,9	80,7	**<0.001**	0,29	0,66
	VBT	59,1		77,5	83,6	82,9	84,4	82,9			
Emotional functioning	EBRT	75,6	0,54	82,4	84,0	83,4	85,4	86,1	**<0.001**	0,73	0,81
	VBT	76,2		83,2	85,0	85,0	87,9	87,1			
Cognitive functioning	EBRT	84,3	0,46	86,6	86,3	86,9	87,3	85,9	0,22	0,21	0,76
	VBT	86,6		87,9	89,3	89,3	89,8	88,6			
Social functioning	EBRT	77,7	0,72	82,5	87,0	87,1	90,4	89,9	**<0.001**	**0,002**	0,42
	VBT	78,0		89,3	92,7	93,4	93,8	92,1			
EORTC OV-28											
Sexual functioning											
43. Sexual interest	EBRT	9,6	0,14	12,0	15,5	16,3	16,7	16,4	**<0.001**	0,63	0,50
	VBT	6,2		11,7	16,2	15,5	15,0	13,0			
44. Sexual activity	EBRT	6,8	0,34	11,2	14,1	14,9	13,0	13,5	**<0.001**	0,35	0,42
	VBT	3,9		8,8	13,9	12,2	13,0	10,6			
Sexual symptoms											
45. To what extent was sex enjoyable	EBRT	52,9	0,05	46,4	48,5	51,0	53,1	53,7	0,053	0,05	0,54
	VBT	23,3		50,0	47,2	42,5	50,0	42,6			
46. Vaginal dryness	EBRT	26,7	0,20	30,3	31,2	35,5	40,5	37,0	0,725	0,13	0,02
	VBT	44,4		31,6	38,9	35,6	24,4	29,6			

NOTE: for functioning scales a higher score indicates higher functioning, for symptom scales a higher score indicates more symptoms.

EORTC: European Organisation of Research and Treatment of Cancer, QLQ-C30: Core Questionnaire, OV-28: ovarian cancer module.

EBRT: external beam radiotherapy, VBT: vaginal brachytherapy, After RT: after radiotherapy

* p-value for baseline comparison, *t* test for comparing means, Armitage trend test for single items.

Results

Study population and compliance

The PORTEC-2 trial accrued 427 patients between 2002 and 2006; 214 patients were allocated to EBRT and 213 were allocated to VBT. The median follow-up at the time of analysis (January 2008) for all randomly assigned patients was 2.7 years (range, 0.9 to 5.3 years). Baseline questionnaires and at least one follow-up questionnaire were received from 348 patients (81%), who were considered responders. The median follow-up of responders was 2.7 years; because of ongoing follow-up at the time of analysis, the rate of responders at the 2-year time point was 53% (Appendix 1).

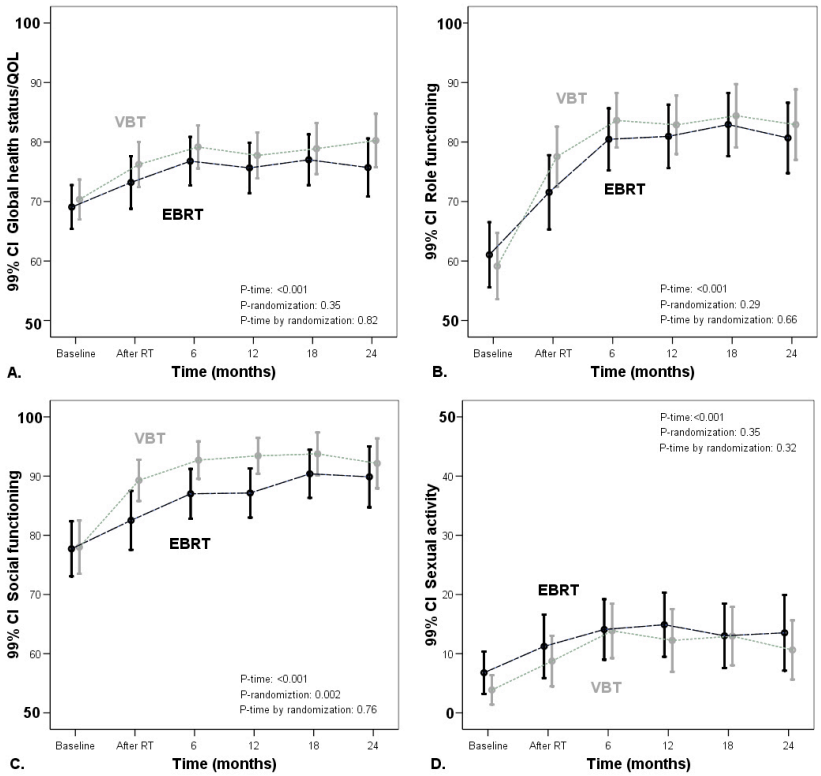
All returned questionnaires were complete for all items of the QLQ-C30 in 83% of the responders and for items on bladder and bowel symptom subscales (PR-25) in 92%. When up to two missing items were allowed, these rates were 96% and 97%, respectively. In contrast, patients were more reluctant about responding to questions about their sexual functioning and symptoms. The sexual functioning subscale (OV-28) was complete for all items in 66%; the sexual symptom subscale was complete for all items in 80% among responders who were sexually active. Overall, the treatment groups did not differ significantly with regard to questionnaire response rates and missing items. Although there were more patients who received EBRT among the nonresponders (48 patients in EBRT vs. 31 patients in VBT; p=0.04), patient characteristics were equally balanced between the EBRT and VBT groups and between responders and nonresponders (Table 1).

Table 3. Symptom scores of EORTC QLQ-C30 and PR-25.

		Questionnaire Timepoints							*P*-value		
		Baseline	*p**	After RT	6	12	18	24	Time	Randomization	Time by Randomization
EORTC QLQ-C30											
Symptom scales											
Fatigue	EBRT	34,8	0,83	32,3	24,6	25,5	23,9	24,7	**<0,001**	0,06	0,84
	VBT	34,1		26,3	21,1	20,1	19,9	18,9			
Nausea and v	EBRT	4,6	0,60	6,4	2,9	4,5	2,5	3,4	**0,001**	0,013	0,54
	VBT	5,1		3,8	2,3	1,4	2,3	1,8			
Pain	EBRT	18,4	0,25	15,7	12,9	14,4	13,2	12,6	**<0,001**	0,23	0,74
	VBT	19,5		13,6	10,5	11,7	8,9	10,6			
Dyspnoea	EBRT	13,1	0,54	14,9	11,9	20,9	13,1	11,8	0,13	0,35	**0,008**
	VBT	11,7		10,1	12,4	22,2	15,2	18,1			
Insomnia	EBRT	27,5	0,59	22,9	21,4	26,4	22,3	21,4	**0,006**	0,77	0,94
	VBT	25,7		21,0	19,3	23,6	20,4	20,7			
Appetite loss	EBRT	13,7	0,24	15,7	8,7	20,5	5,1	6,9	**<0,001**	0,10	0,02
	VBT	10,7		7,2	3,2	11,0	4,6	5,5			
Constipation	EBRT	13,7	0,74	8,2	6,5	15,1	6,6	9,0	**<0,001**	0,92	0,76
	VBT	12,8		6,5	5,4	18,0	7,1	7,5			
Diarrhea	EBRT	7,9	0,10	30,6	17,4	25,9	13,1	12,8	**<0,001**	**<0,001**	0,08
	VBT	5,0		9,1	5,4	17,5	5,2	5,6			
Financial diffic	EBRT	2,2	0,02	5,1	3,5	9,2	3,0	2,2	0,025	0,70	0,82
	VBT	5,5		4,9	3,7	9,8	3,0	2,5			
EORTC PR-25											
Urinary symptoms											
31. Frequency	EBRT	32,9	0,11	40,0	29,4	32,6	30,6	30,2	**<0,001**	0,09	0,32
	VBT	36,6		36,9	29,6	24,0	26,7	29,4			
32. Frequency	EBRT	31,2	0,11	38,3	28,7	29,5	29,8	29,5	**<0,001**	0,19	0,17
	VBT	34,3		34,3	27,0	25,2	30,6	31,6			
33. Urinary ur	EBRT	22,4	0,33	39,4	26,3	31,9	32,3	34,3	**0,005**	0,015	0,02
	VBT	23,3		24,6	28,0	27,3	30,2	28,3			
34. Sleep	EBRT	14,4	0,07	20,0	13,1	16,7	13,4	13,2	**0,009**	0,05	0,10
deprivation	VBT	16,3		13,8	10,9	13,9	13,2	15,4			
35. Need to	EBRT	7,3	0,39	21,4	14,2	15,0	13,3	12,9	0,02	**<0,001**	0,42
remain close	VBT	7,1		8,7	7,0	7,3	8,4	7,9			
36.	EBRT	11,0	0,95	18,1	12,3	16,8	15,7	16,2	0,016	0,40	0,35
Incontinence	VBT	10,6		13,0	14,0	15,4	14,8	16,0			
37. Dysuria	EBRT	5,3	0,37	8,6	3,2	2,9	1,4	2,5	**<0,001**	0,61	0,80
	VBT	8,0		9,4	3,6	3,3	1,2	1,1			
38. Limitation	EBRT	3,4	0,54	8,6	5,2	7,0	5,1	8,3	**0,005**	0,85	0,88
daily	VBT	3,1		5,4	4,4	3,8	4,9	6,2			
Bowel symptoms											
39. Limitation	EBRT	8,9	0,08	21,8	15,2	14,5	13,8	13,7	**<0,001**	**<0,001**	0,48
daily	VBT	5,2		6,3	5,0	3,6	4,6	2,8			
40. Fecal	EBRT	4,0	0,26	9,3	10,5	7,8	8,4	8,7	**0,002**	**<0,001**	0,12
leakage	VBT	1,5		3,8	2,3	2,2	3,6	1,7			
41. Rectal blo	EBRT	0,4	0,95	2,2	2,1	1,0	2,5	1,6	0,162	0,04	0,57
	VBT	0,2		1,2	0,8	0,9	0,2	0,8			
42. Bloated fe	EBRT	16,1	0,61	16,8	15,4	14,4	12,6	10,8	**0,006**	0,15	0,96
	VBT	15,5		14,2	12,4	9,6	9,6	8,8			

NOTE: for functioning scales a higher score indicates higher functioning, for symptom scales a higher score indicates more symptoms.
EORTC: European Organisation of Research and Treatment of Cancer, QLQ-C30: Core Questionnaire, PR-25: prostate cancer module.
US: urinary symptoms, BS: bowel symptoms, EBRT: external beam radiotherapy, VBT: vaginal brachytherapy after RT: after radiotherapy
* p-value for baseline comparison, t test for comparing means, Armitage trend test for single items.

Figure 1. Patient functioning, subscales from EORTC QLQ-C30 and OV-28



Note: for functioning scales a higher score indicates a higher level of functioning. Bars represent 99% confidence intervals. For figures A, B and C the vertical axis is in the upper 50% range, for figure D in the lower 50% range.

Patient functioning

Mean scores of the EORTC QLQ-C30 functioning subscales and global health status, and for the OV-28 subscales on sexual functioning and symptoms are summarized in Table 2. Development of the functioning scores over time is displayed in Figure 1. Baseline functioning scores did not differ significantly between the treatment groups. For both treatment groups, global heath status and functioning scales were low at baseline, showed a significant improvement in the first 6 months, and reached a plateau at 12 months (Fig 1).

Patients treated with VBT reported significantly higher social functioning scores after radiotherapy and with additional follow-up than patients treated with EBRT. The maximum difference between both treatment groups was 6%

after radiotherapy (EBRT 83% vs. VBT 89%, p random assignment = 0.002); this difference remained at approximately the same level during the first year of follow-up. Mean scores for global health status and for the remaining functioning scores were somewhat higher for patients treated with VBT, but these differences were not statistically significant.

Sexual activity and interest were lowest at baseline (ie, after surgery), when 15% of the patients indicated that they were sexually active. Both interest and activity increased significantly during the first 6 months to reach a plateau (39% active), without significant differences between the treatment groups. Of the patients who indicated they were active, 80% reported on their sexual symptoms; in these patients there were no significant differences in sexual symptoms.

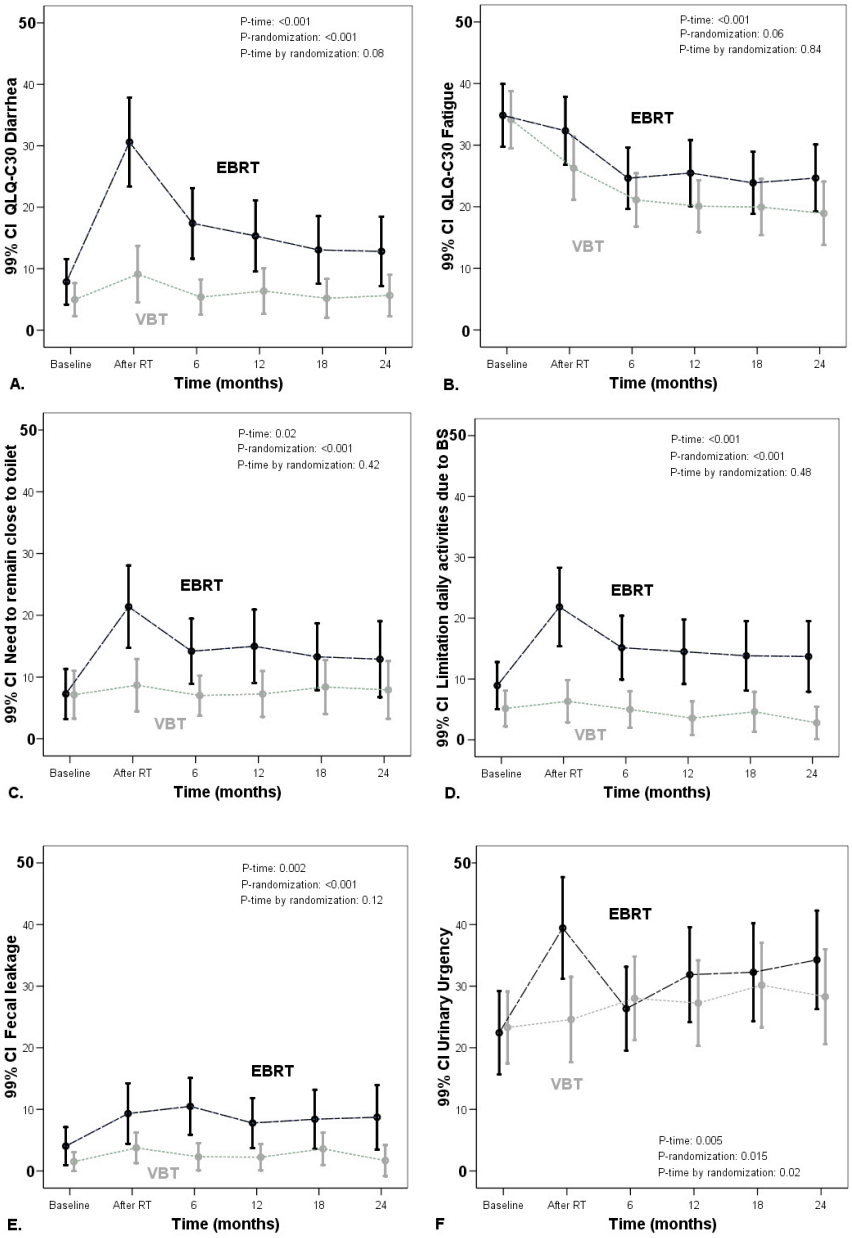
Symptom scores

Mean scores on the symptom scales of EORTC QLQ-C30, PR-25 and OV-28 are summarized in Table 3. Development of the mean symptom scores over time is displayed in Figure 2, and development of patient responses is in Figure 3. Baseline symptom scores did not differ significantly between the treatment groups. Patients treated with EBRT reported a 21% increase in mean diarrhea scores after radiotherapy, as compared to patients treated with VBT (30% EBRT vs. 9% VBT, p random assignment <0.001). After EBRT, 15.4% and 7.3% of the patients reported “quite a bit” or “very much” diarrhea, respectively, whereas these rates were 2.8% and 2.8%, respectively after VBT (Fig 3). Although diarrhea scores of the patients in the EBRT group decreased, they remained at significantly higher levels with additional follow-up. Conversely, diarrhea scores in the VBT group remained low, at baseline level (p time < 0.001).

In addition, patients treated with EBRT reported an 8% increase in mean scores of fecal leakage 6 months after radiotherapy (10% EBRT vs. 2% VBT, p random assignment <0.001), and scores remained stable with additional follow-up. Within the bowel symptom subscale the item on ‘limitations of daily activities due to bowel problems’ showed the largest difference (15%) between the treatment groups, in favor of VBT (22% EBRT vs. 6% VBT, p random assignment <0.001). Although there was a trend toward a higher level of urinary urgency after EBRT (p random assignment = 0.015), the same question on limitation of daily

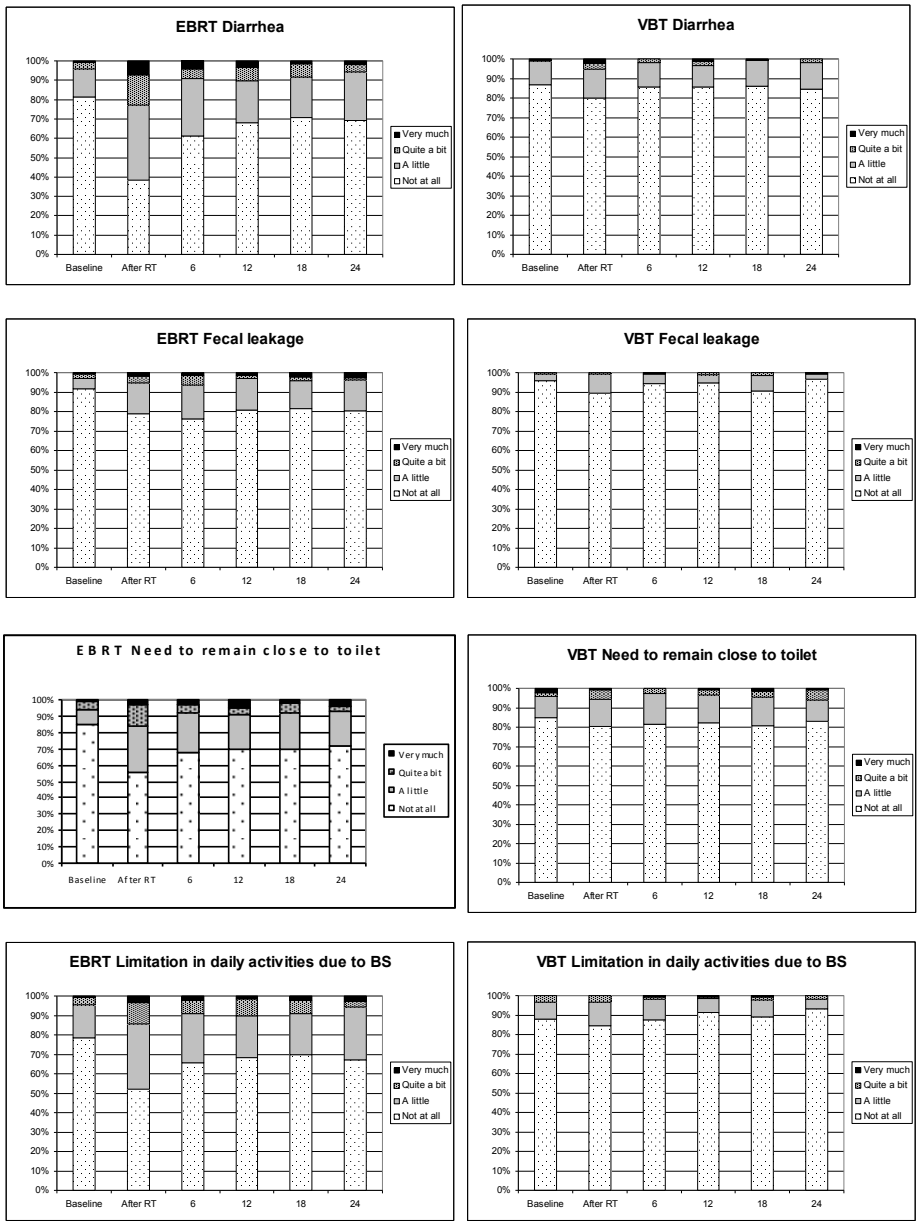
activities because of bladder problems did not show a significant difference. In fact, the only urinary symptom item that showed a significant difference between treatment groups, both after radiotherapy and with additional follow-up, was the question, "Have you had difficulty going out of the house because you needed to be close to a toilet?" This question is however not specific for urinary symptoms, and could also be related to bowel symptoms. Two general patterns of change in symptom scores over time could be distinguished (Fig 2). In the first pattern baseline symptom scores were high, and decreased in the subsequent time points to reach a plateau around 12 months. Fatigue, nausea and vomiting, pain, appetite loss, and constipation are examples of this first pattern and are considered symptoms related to recovery from surgery. The second pattern is associated with RT, as baseline scores are low, but increase significantly during and after radiotherapy before declining again (eg, bowel and urinary symptoms).

Figure 2. Summary scores for symptom scales of EORTC QLQ-C30 and PR-25.



Note: for symptom scales a higher score indicates more symptoms. Bars represent 99% confidence intervals. For all figures the vertical axis is in the lower 50% range. Scores correspond to summary scores presented in Table 3. BS: bowel symptoms.

Figure 3. Patient responses on single item symptom scales of: diarrhea, fecal leakage, need to remain close to the toilet and limitation in daily activities due to bowel symptoms.



Discussion

To our knowledge, PORTEC-2 is the first phase III, randomized, multicenter trial to compare the efficacy of VBT and EBRT, to determine which treatment provides optimal local control with least morbidity and best QOL for patients with high-intermediate risk endometrial cancer. In this first analysis of patient-reported QOL during the first two years after treatment, marked differences between the treatment groups were found.

Bowel symptoms such as diarrhea and fecal leakage were significantly increased after EBRT compared with VBT. Furthermore, patients treated with EBRT reported a significantly higher need to remain close to a toilet, which resulted in a higher level of limitation of daily activities because of bowel problems. Finally, social functioning after EBRT was at a significant lower level than after VBT. These differences remained stable with additional follow-up.

Although higher fatigue rates among the patients who underwent EBRT were expected[13], a sharp decrease of fatigue rates during radiotherapy and during the first year after treatment in both groups was observed. The trend was towards less fatigue after VBT compared with EBRT (p=0.06).

Reported late side effects of vaginal brachytherapy include vaginal dryness with painful intercourse and tightening and/or shortening of the vagina.[20-23] Little is known about the influence of these adverse effects on sexual functioning. Patients generally were more reluctant to respond to questions on this subject; 66% completed the questions on sexual activity. Nonetheless, 39% of these elderly women indicated they were sexually active at 6 months after surgery, which is in the range of results reported in elderly women.[24] Other than the significant increase in sexual activity in both treatment groups, there were no significant differences in sexual functioning or symptoms between the groups.

The observed increases in diarrhea scores (on QLQ-C30) and bowel symptoms (on PR-25) show the internal consistency of these main findings. The same is true for the lower levels of social functioning and increased limitation of daily activities reported by patients treated with EBRT. Increased bowel symptoms and diarrhea scores after EBRT are consistent both with clinical experience and the higher rates of gastro-intestinal toxicity reported in the randomized trials.[4,6]

In the PORTEC-1 trial the rate of grade 1-4 late toxicity for EBRT patients was

26%, of which 20% was gastro-intestinal toxicity (grades 1 to 2, 17%; grades 3 to 4, 3%).4 Phase II studies of VBT reported very low rates of gastro-intestinal toxicity, consistent with the finding that symptom scores among the PORTEC-2 VBT arm remained at baseline level.[20-23]

Reference values of the Swedish and Danish norm-population for the EORTC QLQ-C30 show higher functioning scores and lower symptom rates as compared to the baseline scores for both EBRT and VBT groups.[25,26] However, the plateau that occurred in most scores 6 to 12 months after treatment is in the range of these reference values, which indicates that, for most women, the stressful period of diagnosis and treatment for endometrial cancer has a clear but transient influence on their functioning. This observation is in concordance with the largest retrospective HRQOL study among patients with endometrial cancer at 5 to 10 years after treatment; in this study, scores of patients treated with and without EBRT were similar to those of an age matched population, although scores on vitality and physical and social well-being were significantly lower when EBRT patients were compared to patients who had received no radiotherapy.[13]

When changes in QOL scores are interpreted, definition of a clinically relevant change in a score is important. Earlier studies on the magnitude of clinically relevant differences agree on a difference of 5% to 10% of the instrument range as being clinically relevant.[27-29] For the EORTC Core questionnaire, Osoba et al[28] found that patients valued a change of 5-10% as little, 10-20% as moderate and more than 20% as very much difference. For these results, this would mean that there was very much improvement in functioning scales in the first 6 months after surgery for both groups. Furthermore, patients treated with EBRT reported very much diarrhea and little symptoms of fecal leakage, while patients treated with VBT did not report an increase in these symptoms. In addition, patients treated with EBRT reported a moderate increase in the need to remain close the toilet because of bowel symptoms and limitation of daily activities. This resulted in little reduction of social functioning for EBRT patients.

In conclusion, patients who received external beam radiotherapy reported significant and clinically relevant higher levels of diarrhea and fecal leakage. This resulted in a higher need to remain close to a toilet, more limitation of daily activities because of bowel symptoms, and decreased social functioning. VBT did not have this negative effect on HRQOL and can be regarded the preferred treatment from a HRQOL perspective. This QOL benefit will have to be balanced against the outcome of the efficacy analysis. First results suggest that VBT is effective and should be regarded as the treatment of choice for patients with high-intermediate risk endometrial carcinoma.[30]

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Appendix 1.

Web appendix Table: Follow-up of Responders

	Baseline		After RT		6 months		12 months		18 months		24 months	
	No. of responders	%	No. of responders	%	No. of responders	%	No. of responders	%	No. of responders	%	No. of responders	%
EBRT	166	48,3	123	46,2	145	46,3	146	48,5	129	47,6	107	46,9
VBT	182	52,9	143	53,8	168	53,7	155	51,5	142	52,4	121	53,1
Total Responders	344		266		313		301		271		228	
Responders as % of total randomized (N=427)	80,6		62,3		73,3		70,5		63,5		53,4	

EBRT: External Beam Radiotherapy; VBT: Vaginal Brachytherapy
Responders: patients who handed in the baseline questionnaire and at least one follow-up questionnaires.
NOTE: Due to ongoing follow-up at time of analysis, the rate of responders gradualy decreased to 53% at 24 months.