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Five-year quality of life of endometrial cancer patients treated in the randomised Post Operative Radiation Therapy in Endometrial Cancer (PORTEC-2) trial and comparison with norm data

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Abstract

Background: The PORTEC-2 trial showed efficacy and reduced side-effects of vaginal brachytherapy (VBT) compared with external beam pelvic radiotherapy (EBRT) for patients with high-intermediate risk endometrial cancer. The current analysis was done to evaluate long-term health related quality of life (HRQL), and compare HRQL of patients to an age-matched norm population.

Methods: Patients were randomly allocated to EBRT (n=214) or VBT (n=213). HRQL was assessed using EORTC QLQ-C30 and subscales from PR25 and OV28 (bladder, bowel, sexual symptoms); and compared to norm data.

Findings: Median follow-up was 65 months; 348 (81%) patients were evaluable for HRQL (EBRT n=166, VBT n=182). At baseline, patient functioning was at lowest level, increasing during and after radiotherapy to reach a plateau after 12 months, within range of scores of the norm population. VBT patients reported better social functioning (p=0.005) and lower symptom scores for diarrhoea, faecal leakage, need to stay close to a toilet, and limitation in daily activities due to bowel symptoms ($p \leq 0.001$), compared to EBRT. There were no differences in sexual functioning or symptoms between the treatment groups; however, sexual functioning was lower and sexual symptoms more frequent in both treatment groups compared to the norm population.

Interpretation: Patients who received EBRT reported clinically relevant higher levels of bowel symptoms and related limitations in daily activities with lower social functioning, 5 years after treatment. VBT provides a better HRQL, which remained similar to that of an age-matched norm population, except for sexual symptoms which were more frequent in both treatment groups.

Introduction

Endometrial carcinoma (EC) is the most common gynaecological malignancy among postmenopausal women in Western countries.[1] Surgery, consisting of total abdominal (or laparoscopic) hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) is the cornerstone of treatment.

Randomised trials have shown that pelvic external beam radiotherapy (EBRT) significantly reduced locoregional relapse, but without survival benefit, and at the cost of more (predominantly mild) gastro-intestinal toxicity.[2-6] Risk factors for locoregional recurrence were tumour grade 3, outer 50% myometrial invasion, age over 60 years, and lymph-vascular space invasion. Patients with these high-intermediate risk features had the largest benefit from EBRT (20% locoregional relapse without radiotherapy vs. 5% with EBRT). As most (75%) locoregional relapses were located in the vagina, the randomised PORTEC-2 trial was initiated to investigate if vaginal brachytherapy (VBT) would be equally effective for vaginal control, while reducing treatment toxicity and improving health related quality of life (HRQL) as compared to EBRT. Final results showed that VBT was indeed very effective in preventing vaginal recurrence with an estimated vaginal recurrence rate of 2% at 5 years, similar to the results obtained with EBRT.[7] Short-term HRQL results up to two years after treatment showed that rates of bowel symptoms such as diarrhoea and faecal leakage were significantly lower among women treated with VBT, with better social functioning compared to women treated with EBRT.[8] Symptom levels among VBT patients were very low. These results prompted adoption of VBT as standard of care for patients with high-intermediate risk EC in the Netherlands. Analysis of HRQL among PORTEC-1 patients 15 years after treatment showed that EBRT is associated with long-lasting symptoms impacting on patient functioning.[9] This finding underscores the importance of longitudinal HRQL analysis and reporting of late outcomes.

The current analysis was done to evaluate 5-year HRQL after EBRT and VBT of PORTEC-2 trial patients and compare their HRQL with that of an age-matched Dutch norm population.

Patients and Methods

Patient selection, treatment and study design of the PORTEC-2 trial

The multicenter PORTEC-2 trial randomly allocated EC patients with high-intermediate risk features to EBRT or VBT. Details on patient selection, treatment and HRQL have been described in previous publications.[7,8] In short, surgery consisted of TAH-BSO; clinically suspicious pelvic and/or periaortic lymph nodes were removed, but no routine lymphadenectomy was performed. FIGO 1988 staging was assigned on the basis of surgical and pathological findings.[10] Patients were eligible if they had one of the following combinations of age, grade and FIGO stage: (1) Age ≥60 years and stage 1C grade 1 or 2, or stage 1B grade 3; (2) stage 2A, any age (except grade 3 with outer 50% myometrial invasion). Written informed consent was obtained from all patients. The protocol was approved by the Dutch Cancer Society and the Ethics Committees of participating centres.

EBRT was given to a total dose of 46 Gy in 2 Gy daily fractions, 5 fractions/week. VBT was delivered to the upper half of the vagina using a vaginal cylinder. Brachytherapy dose schedules were used, equivalent to 45-50 Gy to the vaginal mucosa: high-dose-rate (90% of patients) 21 Gy at 5 mm depth in 3 fractions of 7 Gy over 2 weeks; low-dose-rate (10%) 30 Gy at 5 mm depth, in one session at 50-70 cGy/hr.

The primary endpoint was 5-year vaginal relapse (VR) as cumulative incidence, accounting for death as competing risk.[11] Secondary endpoints were HRQL, treatment related toxicity, pelvic lymph node and distant relapse and overall survival.

Quality-of-Life Assessment

Cancer-specific HRQL was measured with the EORTC (European Organization for Research and Treatment of Cancer) Core questionnaire (QLQ-C30 version 3.0).[12] No endometrial cancer-specific symptom questionnaire was available at the time; with approval of the EORTC Quality of Life Group, relevant subscales from existing published EORTC modules were combined into a symptom module (subscales for bowel and bladder symptoms from PR25 and subscale for sexual functioning and symptoms from OV28).[13,14] For all items Likert-type response scales were used, with response scales ranging from 1-4 points for all items except for items 29 and 30 (response scale 1-7). 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 represents a better level of functioning. For the symptom scales and items, a higher score reflects a higher level of symptoms and decreased HRQL.

Baseline HRQL questionnaires were handed out at first consultation with the radiation oncologist 3-4 weeks after surgery, and were returned prior to RT. The end-of-treatment HRQL questionnaire was completed 2-4 weeks after RT. With consent, subsequent questionnaires were sent directly to the patient home address at 6, 12, 18, 24, 36, 48 and 60 months from randomization.

Patients were considered evaluable for the HRQL assessment if they had returned the baseline questionnaire and at least one of the follow-up questionnaires ('responders').

Statistical methods

All statistical analyses were performed using SPSS, version 17.0 (SPSS, Inc, Chicago, IL). Chi-square statistics or Fisher's exact test for categorical variables and *t* test for continuous variables were used to compare patient and tumour characteristics (significance p-value < 0.05).

HRQL analysis was done according to the guidelines provided by the EORTC Quality of life Group.[15] Descriptive median scores are presented in the tables. Baseline scores of both treatment groups were compared with a *t* test, or Armitage trend test for single items. In order 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, PR25 and OV28 subscales at each of the fixed time points, a linear mixed model was used with patient as random effect and time (categorical), randomization and their interaction as fixed effects. Single items were analyzed using (ordinal) logistic regression with random effects. The difference in HRQL between the two treatment groups was tested by Wald's test in the linear or ordinal logistic mixed model (*p*-randomization), excluding 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 randomization), including the baseline value. Age-matched Dutch norm population means[16] were compared with both treatment groups at each time point using the *t* test. To guard against false positive results due to multiple testing, a two sided *p*-value of 0.01 was considered statistically significant.

Recently published guidelines on the interpretation of clinical relevant changes of EORTC QLQ-C30 scores were applied (trivial, small, medium or large differences per scale).[17] For scales not included in the guideline, changes were evaluated according to Osoba, who found for the EORTC QLQ-C30 that patients valued a change of 5-10% as 'little', 10-20% as 'moderate' and more than 20% as 'very much' difference.[18]

Results

Study population and compliance

The PORTEC-2 trial accrued 427 patients between 2002 and 2006; 214 patients were allocated to EBRT and 213 to VBT. Baseline questionnaires and at least one follow-up questionnaire were received from 348 patients (81%), hereafter referred to as 'responders'. At the time of analysis (June 30th 2011), 268 of the 348 responders were alive, disease free and had reached the 5-year follow-up time point, of whom 206 (76%) returned the 5-year questionnaire (Web Appendix A). The median follow-up was 65 months (range 18-106 months), both for the whole trial population and for the responders.

All returned questionnaires were complete for all items of the QLQ-C30 in 82% of the responders, and for PR25 items in 92%; when allowing up to two missing items, these rates were 95% and 97%. In contrast, the sexual functioning subscale was complete for all items in 65%, and the sexual symptom subscale could be calculated for 81% of responders who were sexually active. The treatment groups did not differ with regard to questionnaire response rates and missing items. Although there were more EBRT patients among the non-responders (51 EBRT vs. 31 VBT patients p=0.02), patient characteristics were equally balanced between the EBRT and VBT group and between responders and non-responders (Table 1).

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	%	p-Value*
	No. of Patients	%	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.*

Patient functioning

For both treatment groups, global heath status and functioning scales were low at baseline and showed a medium to large improvement during radiotherapy and in the first 6 months, reaching a plateau within range of the scores of the norm population at 6-12 months (Fig. 1 and Table 2). Cognitive functioning remained unchanged from baseline onwards.

Patients treated with vaginal brachytherapy (VBT) reported significantly better social functioning scores, both at completion of VBT and during follow-up, than patients treated with EBRT. The maximum difference in mean social functioning scores between the groups was small (EBRT 83 vs. VBT 89, *p*-randomization = 0.005); this difference remained during the first year of follow-up.

Sexual activity and interest were lowest at baseline (i.e. after surgery), when 15% of the patients indicated that they were sexually active. There was a large increase of both interest and activity increased during the first 6 months to reach a plateau (39% active), without significant differences between the treatment groups (Fig. 1 and Table 2). For both EBRT and VBT patients however, mean sexual interest and activity scores were significantly lower than those of the age-matched norm-population. The maximum difference between EBRT or VBT patients and the norm population in mean sexual interest after 12 months was small and ranged between 6-10 points, and in sexual activity between 4-8 points. Among the patients who indicated they were active, 81% reported on their sexual symptoms. There were no significant differences in sexual symptoms between patients treated with EBRT or VBT. However, the norm population reported significantly less vaginal dryness and higher levels of sexual enjoyment.

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

	Questionnaire Time Points										p-Value		
				Month									Time by
	Baseline	p*	After RT	6	12	18	24	36	48	60	Time	Randomization	Randomization
EORTC QLQ-C30													
Global healt EBRT	69.3	0.55	73.4	76.3	76.1	77.2	76.9	77.5	75.9	76.7	**<0.001**	0.46	0.85
VBT	70.4		75.4	78.7	76.7	77.6	78.4	77.7	78.7	77.0			
Norm	75.4[F‡]		75.4	75.4	75.3	75.3	75.2	75.1	75.1	75.0			
Functional scales													
Physical func EBRT	72.0	0.42	76.5	79.3	78.4	78.8	77.8	76.4	76.6	75.2	**<0.001**	0.23	0.97
VBT	73.7		79.5	81.7	80.3	80.3	79.3	78.7	77.2	77,7			
Norm	82.0[F‡]		82.0[‡]	82.0	81.7	81.7	81.4	81.0	81.0	80.7[‡]			
Role functior EBRT	61.0	0.49	71.8	79.4	80.5	82.2	81.1	80.1	81.5	77.0	**<0.001**	0.27	0.26
VBT	59.1		76.8	83.3	81.6	83.3	81.5	83.3	81.6	81.5			
Norm	82.1[F‡]		82.1[F]	82.1	81.9	81.9	81.6	81.3	81.3	81.1			
Emotional fu EBRT	75.6	0.77	82.0	83.6	83.7	85.1	86.0	84.6	85.4	83.0	**<0.001**	0.39	0.58
VBT	76.3		83.5	84.4	84.3	87.0	85.3	87.6	85.8	87.2			
Norm	87.2[F‡]		87.2[F]	87.2	87.2	87.2	87.2	87.1	87.1	87.1			
Cognitive fur EBRT	84.3	0.26	86.0	85.9	86.5	86.4	86.1	86.1	87.6	83.4	0.28	0.24	0.66
VBT	86.7		87.5	89.2	88.7	88.8	87.4	87.9	87.0	87.8			
Norm	90.0[F]		90.0	90.0	89.9	89.9	89.8	89.7	89.7	89.6[F]			
Social functic EBRT	77.6	0.84	82.7	86.6	87.6	90.7	90.1	92.2	90.8	87.8	**<0.001**	**0.005**	0.09
VBT	78.1		89.1	92.6	93.1	93.7	91.9	93.7	92.2	92.4			
Norm	90.4[F‡]		90.4[F]	90.4	90.3	90.3	90.2	90.1	90.1	89.9			
EORTC OV-28													
Sexual functioning													
Sexual intere EBRT	8.0	0.08	10.0	14.4	13.6	15.0	14.2	14.9	14.2	14.0	**<0.001**	0.35	0.40
VBT	4.9		9.9	15.2	14.4	13.3	10.6	11.4	10.3	11.8			
Norm	22.3[F‡]		22.3[F‡]	22.3[F‡]	21.7[F‡]	21.7[F‡]	21.1[F‡]	20.5[‡]	20.5[‡]	20.0[‡]			
Sexual activit EBRT	5.4	0.07	9.6	12.9	12.8	12.1	11.1	12.8	10.8	8.3	**<0.001**	0.46	0.86
VBT	2.9		6.6	12.5	11.8	12.0	10.3	10.2	8.6	8.7			
Norm	18.2[F‡]		18.2[F‡]	18.2	17.6	17.6	17.1[‡]	16.5[‡]	16.5[‡]	15.9[F‡]			
Sexual symptoms													
extent was EBRT	46.8	0.02	40.6	44.3	49.1	48.9	46.5	47.8	49.2	50.7	0.068	0.27	0.025
sex VBT	21.0		45.5	47.2	42.8	49.9	40.6	36.1	42.7	42.4			
Norm	57.1[‡]		57.1[F]	57.1[F]	56.5[‡]	56.5	56.0[‡]	55.4[‡]	55.4	54.8			
Vaginal dryn EBRT	31.5	0.21	32.4	33.4	34.3	40.8	35.4	39.2	30.3	30.4	0.89	0.73	0.063
VBT	38.3		37.3	39.8	40.6	25.0	31.7	37.6	38.0	37.2			
Norm	19.4		19.4[‡]	19.4[‡]	19.8[F‡]	19.8[F]	20.3	20.7[F‡]	20.7	21.2[‡]			

*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, Norm: age matched Dutch population. After RT: after radiotherapy. * p-Value for baseline comparison, t test for comparing means, Armitage trend test for single items.F: p<0.01 for EBRT vs Norm; ‡: p<0.01 for VBT vs Norm.*

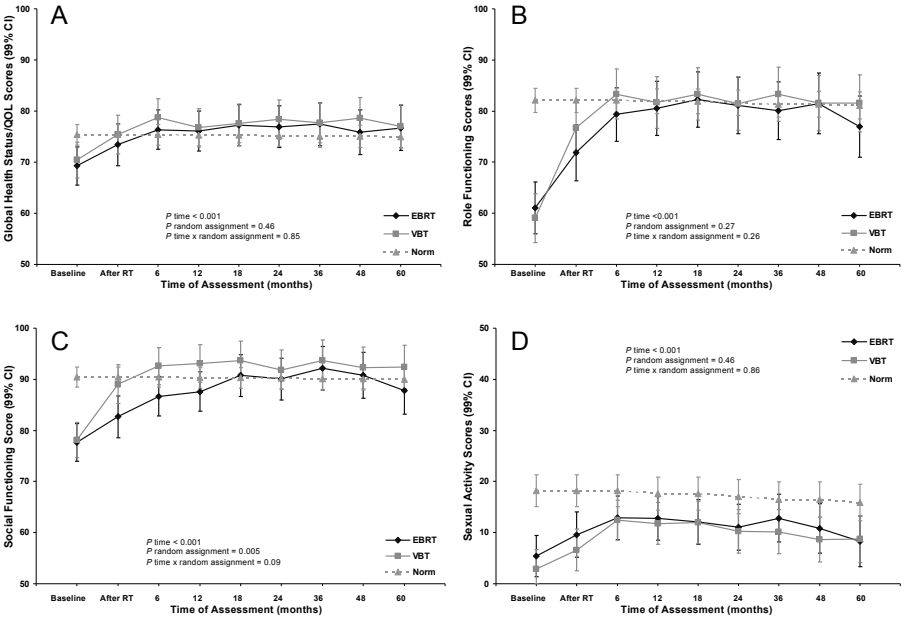

Fig. 1 - Patient functioning on subscales from European Organization for Research and Treatment of Cancer C30 questionnaire (EORTC QLQ-C30) and sexual activity score of the ovarian cancer questionnaire module (EORTC OV-28). A higher score indicates a higher level of functioning or activity. For EBRT and VBT error bars represent 99% Confidence Interval (CI), for Norm the error bars represent the 95% CI. The vertical axis is in the (A-C) upper-50% range; and (D) lower-50% range. VBT, vaginal brachytherapy; EBRT, external-beam radiotherapy; Norm, age-matched Dutch norm population; RT, radiation therapy.

Symptom scores

Patients treated with EBRT reported a large increase of diarrhoea scores at completion of RT, in contrast to VBT patients (31 EBRT vs. 10 VBT, *p*-randomization <0.001, Table 3 and Fig. 2). Diarrhoea scores of EBRT patients, although decreasing, remained at significantly higher levels throughout the 5-year follow-up period, whereas diarrhoea scores in the VBT group remained at baseline level (p-time < 0.001). There were no significant differences between diarrhoea scores of VBT patients and those of the norm population, whereas the diarrhoea scores of EBRT patients remained increased throughout 5 years after treatment. In addition, EBRT patients reported a little increase of faecal leakage 6 months after radiotherapy (11% EBRT vs. 3% VBT, *p*-randomization <0.001), remaining stable with further follow-up. Among the bowel symptoms, the item 'limitations of daily activities due to bowel problems' showed the largest difference between the treatment groups, in favour of VBT (23% EBRT vs. 7% VBT, *p*-randomization: <0.001). Moreover, EBRT patients reported a moderately increased need to remain close to the toilet.

Fatigue scores of both EBRT and VBT patients returned to levels in range with the norm-population after 6 months, while pain scores of both treatment groups were lower than those of the norm population.

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

		Questionnaire Time Points										p-Value		
					Month									Time by
		Baseline	p*	After RT	6	12	18	24	36	48	60	Time	Randomization	Randomization
EORTC QLQ-C30														
Symptom scales														
Fatigue	EBRT	34.8	0.79	33.0	25.7	25.7	23.6	24.7	24.0	23.8	26.0	<0.001	0.061	0.54
	VBT	34.1		26.9	22.2	21.9	21.3	21.0	20.2	21.4	20.8			
	Norm	21.0[F‡]		21.0[F‡]	21.0	21.0	21.0	21.1	21.2	21.2	21.2			
Nausea and vomiting	EBRT	4.6	0.76	6.5	2.9	4.6	2.5	3.2	2.6	3.2	4.5	<0.001	0.017	0.23
	VBT	5.0		4.0	2.4	1.6	2.2	1.8	2.2	3.2	1.9			
	Norm	3.6		3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6			
Pain	EBRT	18.5	0.71	16.1	13.7	14.4	13.4	11.9	14.5	12.1	13.2	<0.001	0.38	0.75
	VBT	19.4		13.3	11.5	12.9	10.1	12.1	11.5	12.1	11.6			
	Norm	24.1		24.1[F‡]	24.1[F‡]	24.4[F‡]	24.4[F‡]	24.7[F‡]	25.0[F‡]	25.0[F‡]	25.4[F‡]			
Dyspnoea	EBRT	13.0	0.58	15.2	14.0	14.9	14.6	14.0	15.6	16.3	20.1	<0.001	0.72	0.032
	VBT	11.6		10.6	12.6	14.4	15.1	17.9	15.4	17.0	15.2			
	Norm	10.2		10.2	10.2	10.4	10.4	10.5[‡]	10.6	10.6[‡]	10.8[F]			
Insomnia	EBRT	27.4	0.60	23.5	22.4	21.7	21.4	22.8	24.4	24.0	26.1	0.001	0.17	0.93
	VBT	25.9		21.3	19.6	18.9	21.2	21.0	20.9	20.1	20.8			
	Norm	22.4		22.4	22.4	22.6	22.6	22.9	23.2	23.2	23.4			
Appetite loss	EBRT	13.7	0.22	16.8	9.7	8.9	5.6	7.5	7.8	6.3	8.4	<0.001	0.017	0.012
	VBT	10.6		7.7	3.7	4.5	5.1	6.5	5.3	5.5	5.6			
	Norm	5.0[F‡]		5.0[F]	5.0[F]	5.0	5.0	5,1	5,1	5,1	5,1			
Constipation	EBRT	13.4	0.78	7.6	6.4	6.2	6.9	9.0	8.3	8.9	10.7	<0.001	0.42	0.76
	VBT	12.9		6.7	6.2	8.0	7.5	7.7	7.0	9.3	7.1			
	Norm	8.7[F]		8.7	8.7	8.8	8.8	8.9	9.1	9.1	9.2			
Diarrhoea	EBRT	7.9	0.10	31.0	17.3	15.2	13.0	12.7	10.9	10.3	10.3	<0.001	<0.001	<0.001
	VBT	4.9		10.2	5.7	6.7	5.1	5.2	6.4	5.7	3.4			
	Norm	3.9		3.9[F‡]	3.9[F]	3.9[F]	3.9[F]	3.9[F]	3.9[F]	3.9[F]	3.9			
Financial difficulties	EBRT	2.0	0.02	5.4	3.5	2.3	3.2	2.2	1.1	2.0	3.7	0.002	0.95	0.14
	VBT	5.5		4.8	3.9	3.1	3.3	2.9	1.9	2.3	2.0			
	Norm	4.4		4.4	4.4	4.5	4.5	4.5	4.6[F]	4.6	4.6			

EORTC PR-25														
Urinary symptoms														
31. Frequency daytime	EBRT	33.2	0.26	39.0	30.9	32.9	31.4	29.1	34.1	31.6	31.3	<0.001	0.23	0.068
	VBT	36.5		37.3	28.7	25.3	26.9	28.7	28.6	27.5	28.5			
32. Frequency at night	EBRT	31.5	0.31	37.5	30.4	30.3	30.5	29.9	36.2	32.9	36.5	<0.001	0.24	0.033
	VBT	34,3		34.2	26.1	25.3	29.0	31.1	29.7	29.1	31.0			
33. Urinary urgency	EBRT	23.4	0.80	38.3	27.7	31.4	32.6	34.0	33.1	36.4	37.8	<0.001	0.21	0.022
	VBT	23.9		26.0	26.9	27.9	29.8	29.5	31.0	32.3	32.5			
34. Sleep deprivation due to US	EBRT	15.3	0.52	19.9	14.3	16.9	13.8	14.8	17.7	17.0	20.2	0.005	0.17	0.15
	VBT	16.3		13.6	10.2	14.1	12.6	14.3	15.1	15.0	14.0			
35. Need to remain close to toilet	EBRT	7.7	0.93	21.0	15.0	15.0	13.9	13.4	15.8	13.6	15.5	<0.001	0.001	0.001
	VBT	7.0		9.1	6.8	7.9	8.2	8.5	9.3	11.4	10.2			
36. Incontinence for urine	EBRT	11.4	0.76	17.7	13.7	17.3	17.1	17.9	21.5	20.4	24.2	<0.001	0.16	0.17
	VBT	10.6		13.3	14.2	15.7	14.9	16.8	17.3	18.9	17.1			
37. Dysuria	EBRT	5.3	0.14	8.6	3.4	2.9	1.5	2.6	1.3	1.2	2.0	<0,001	0.97	0.79
	VBT	7.9		9.5	3.7	3.5	1.5	1.7	1.6	1.0	1.4			
38. Limitation daily activities due to US	EBRT	3.6	0.82	8.4	6.0	6.7	5.6	8.9	9.8	7.2	10.2	<0.001	0.071	0.34
	VBT	3.0		6.0	4.4	3.9	4.7	6.1	4.4	4.6	5.9			
Bowel symptoms														
39. Limitation daily activities due to BS	EBRT	9.0	0.05	22.5	15.2	14.3	13.4	13.2	12.6	11.8	11.4	<0.001	<0.001	<0.001
	VBT	5.0		7.1	5.3	4.0	4.7	3.3	5.0	7.7	5.0			
40. Faecal leakage	EBRT	4.0	0.05	9.8	10.8	8.0	8.6	8.4	8.6	6.6	8.4	<0.001	<0.001	0.050
	VBT	1.5		4.7	2.5	2.5	3.6	2.0	3.0	4.8	2.9			
41. Rectal blood loss	EBRT	0.4	0.49	2.2	2.1	1.0	2.4	1.5	1.3	0.0	0.8	0.037	0.040	0.34
	VBT	0.2		1.2	0.9	0.9	0.3	0.8	0.4	0.6	0.0			
42. Bloated feeling	EBRT	15.5	0.84	16.4	16.3	14.6	12.8	10.6	12.7	11.7	12.1	<0.001	0.25	0.76
	VBT	15.5		14.2	13.0	10.6	10.4	9.6	9.5	13.2	9.6			

*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, PR-25: prostate cancer module. US: urinary symptoms, BS: bowel symptoms, EBRT: external beam radiotherapy, VBT: vaginal brachytherapy, Norm: age matched Dutch population. After RT: after radiotherapy. * p-Value for baseline comparison, t test for comparing means, Armitage trend test for single items. ǂ: p<0.01 for EBRT vs Norm; ǂ: p<0.01 for VBT vs Norm.*

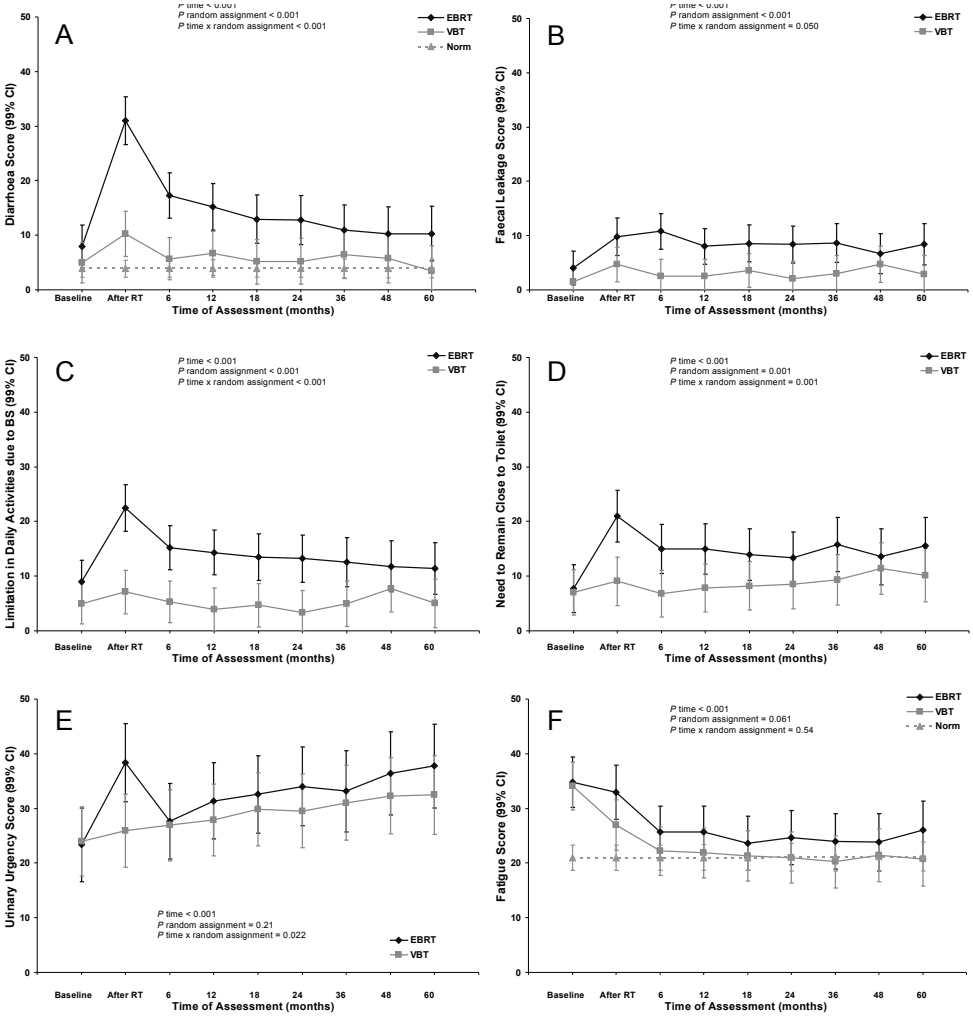

Fig. 2 - Single item symptom scores from European Organization for Research and Treatment of Cancer C30 questionnaire (EORTC QLQ-C30) and prostate cancer questionnaire module (EORTC PR-25). A higher score indicates a higher level of symptoms. For EBRT and VBT error bars represent 99% Confidence Interval (CI), for Norm the error bars represent the 95% CI. The vertical axis is in the (A-F) lower-50% range. VBT, vaginal brachytherapy; EBRT, external-beam radiotherapy; Norm, age-matched Dutch norm population; RT, radiation therapy.

Discussion

The current analysis of long-term HRQL of patients treated in the PORTEC-2 trial with a median follow-up of 65 months found a continuing long-term impact of EBRT on HRQL. Especially diarrhoea and faecal leakage were increased after EBRT, leading to a higher need to remain close to a toilet; more limitations of daily activities due to bowel problems; and a lower level of social functioning. HRQL of patients treated with VBT remained very similar to that of a healthy age-matched norm population. In contrast, sexual aspects of HRQL after treatment for endometrial cancer were lower than that of the norm population, irrespective of the type of adjuvant radiotherapy.[16]

Diarrhoea scores of VBT patients remained at the norm population level, while the scores of EBRT patients remained significantly increased up to 5 years after treatment. Furthermore, scores on the global health status scale and functioning scales of both EBRT and VBT patients were significantly lower than norm data at baseline (after surgery), and recovered in the first 6 months to reach a plateau within range of the age-matched norm population. A similar pattern was found for fatigue scores. These results indicate that for most women the stressful period of diagnosis and treatment for endometrial cancer has a clear but transient influence on their general functioning.

The persisting increased rates of bowel symptoms after EBRT are consistent with the increased gastrointestinal toxicity rates after EBRT found in randomised trials and retrospective studies on long-term morbidity after pelvic radiotherapy.[19-21] In the HRQL analysis of PORTEC-1 trial survivors 15 years after treatment, increased bowel symptom rates were reported by EBRT patients as compared to those treated with surgery alone, indicating the persistence of these symptoms over time.[9]

Reported late side effects of vaginal brachytherapy include atrophic changes in the vaginal mucosa leading to vaginal dryness, painful intercourse, and vaginal fibrosis leading to tightening and/or shortening. Analysis of vaginal mucosal changes as assessed at gynaecological examinations showed an increase of grade 1 and 2 mucosal atrophy from 6 months onwards (at 3 years 17% after EBRT vs. 35% after VBT).[7] Despite the increased rate of grade 1-2 mucosal atrophy, there were no significant differences in sexual functioning and sexual symptoms between patients treated with EBRT or VBT. However, sexual functioning (activity and interest) scores of both EBRT and VBT were

lower than those of the age-matched norm-population, and sexual symptoms were increased. The rates of sexual activity and symptom scores reported by PORTEC-2 trial patients were similar to the long-term scores of PORTEC-1 trial survivors, also those treated with surgery alone, suggesting an impact of cancer diagnosis and treatment on sexual aspects of HRQL.[9] Limitations to any conclusion are the low rate of sexual activity in this elderly population, and the lower completion rate of the sexual functioning questions.
A striking finding of the 15-year HRQL analysis of the PORTEC-1 trial was the increase rate of urinary urgency and incontinence. In the current analysis of 5-year HRQL in the PORTEC-2 trial, there were no differences in urinary symptoms between the groups. However, from 12 months onwards a trend towards higher incontinence and urgency scores after EBRT seemed to emerge. Possibly, these late urinary symptoms develop as a result of added long-term impact of EBRT upon normal ageing changes of the pelvic floor muscles. A future analysis of very long-term HRQL in PORTEC-2 will include questions on incontinence pad usage. Future studies should investigate preventive measures to maintain pelvic floor functioning to diminish the added effect of RT on normal ageing.

In conclusion, up to 5 years after treatment, EBRT has a clinically relevant, bowel symptom-related negative impact on HRQL, with limitation of daily activities. Global health status and functioning scores of all patients returned to levels of an age-matched Dutch norm population after 6-12 months, indicating that for most women diagnosis and treatment for endometrial cancer has a clear but transient influence on their general functioning. Compared to the norm population, EC patients reported lower levels of sexual functioning and more sexual symptoms after treatment, without differences between patients who received EBRT or VBT.

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