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Chapter 2

Long-Term Impact of Endometrial Cancer Diagnosis and Treatment on Health-Related Quality of Life and Cancer Survivorship: Results From the Randomised PORTEC-2 Trial

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ABSTRACT

Purpose

To evaluate the long-term health-related quality of life (HRQL) after external beam radiation therapy (EBRT) or vaginal brachytherapy (VBT) among PORTEC-2 trial patients, evaluate long-term bowel and bladder symptoms, and assess the impact of cancer on these endometrial cancer (EC) survivors.

Patients and Methods

In the PORTEC-2 trial, 427 patients with stage I high-intermediate-risk EC were randomly allocated to EBRT or VBT. The 7- and 10-year HRQL questionnaires consisted of EORTC QLQ-C30; subscales for bowel and bladder symptoms; the Impact of Cancer Questionnaire; and 14 questions on comorbidities, walking aids, and incontinence pads. Analysis was done using linear mixed models for subscales and (ordinal) logistic regression with random effects for single items. A two-sided P value <.01 was considered statistically significant.

Results

Longitudinal HRQL analysis showed persisting higher rates of bowel symptoms with EBRT, without significant differences in global health or any of the functioning scales. At 7 years, clinically relevant fecal leakage was reported by 10.6% in the EBRT group, versus 1.8% for VBT (P=.03), diarrhea by 8.4% versus 0.9% (P=.04), limitations due to bowel symptoms by 10.5% versus 1.8% (P=.001), and bowel urgency by 23.3% versus 6.6% (P<.001). Urinary urgency was reported by 39.3% of EBRT patients, 25.5% for VBT, P=.05. No difference in sexual activity was seen between treatment arms. Long-term impact of cancer scores was higher among the patients who had an EC recurrence or second cancer.

Conclusions

More than 7 years after treatment, EBRT patients reported more bowel symptoms with impact on daily activities, and a trend for more urinary symptoms, without impact on overall quality of life or difference in cancer survivorship issues.

INTRODUCTION

Randomised trials have shown that pelvic external beam radiation therapy (EBRT) significantly reduced locoregional relapse compared with observation after surgery, but without survival benefit, and at the cost of mainly gastrointestinal adverse events.[1-5] The Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC)-2 trial showed that vaginal brachytherapy (VBT) was highly effective as compared with EBRT, with 2% vaginal recurrence at 5 years in both arms, and similar rates of locoregional relapse and overall survival.[6] Health-related quality of life (HRQL) analysis among PORTEC-2 trial patients at 5 years showed that women treated with VBT reported significantly fewer bowel symptoms, without limitations in daily activities, and higher social functioning scores than those who underwent EBRT. Symptom ratings of VBT patients remained similar to that of an age-matched normal population. Sexual functioning scores were lower in both groups compared with the age-matched population.[7] On the basis of these results VBT became the standard adjuvant treatment for patients with high-intermediate-risk endometrial cancer (EC).

Analysis of long-term HRQL in the previous PORTEC-1 trial, in which patients were randomised to EBRT or observation after surgery, showed that even after 10 to 15 years, bowel symptoms were still more frequent among patients who underwent EBRT. Urinary symptoms had become more frequent over time in both groups, but more clearly so among EBRT patients, with a significantly increased use of incontinence pads ("day and night usage" 42.9% vs 15.2% and "never use" 39% vs 60% for EBRT vs VBT, P<.001).[4, 8] For radiation therapy-related toxicity it is known that the bladder is a late-responding organ.[9, 10]

Little is known about the long-term impact of diagnosis and treatment on survivors of EC. The Impact Of Cancer (IOC) scale is a questionnaire measuring the positive and negative impact of cancer experience among long-term survivors.[11] Translation and validation of the IOC for use in The Netherlands have been reported.[12] The IOC version 2 (IOCv2) had similar impact domains in the Dutch sample, providing evidence that IOCv2 measured common and important survivor concerns across two different Western nations.

The present analysis was done to evaluate long-term HRQL after EBRT or VBT among PORTEC-2 trial patients, evaluate long-term bowel and bladder symptoms, and assess the impact of cancer on these EC survivors.

PATIENTS AND METHODS

Patient selection and study design of the PORTEC-2 trial

Between 2002 and 2006, 427 patients with stage I high-intermediate-risk EC who participated in the PORTEC-2 trial were randomised to EBRT or VBT. Details on patient selection, treatment, and HRQL have been described in previous publications.[6, 13] Baseline questionnaires and at least 1 follow-up questionnaire were received from 348 of 427 patients (81% of responders). Almost all patients had multiple follow-up questionnaires.[7] For the present analysis, patients were considered eligible if they were previous responders and were alive and disease-free according to the trial database.

HRQL assessment

Cancer-specific general HRQL was measured with the EORTC (European Organization for Research and Treatment of Cancer) Core questionnaire (QLQ-C30 v3.0).[14] Because the EC-specific EN24 module was not yet available, subscales from EORTC modules were combined into a bowel, bladder, and sexual symptom module.[15, 16] Likert-type response scales were used with a 4-point response scale, except for items 29 and 30 of the EORTC QLQ-C30 (7-point scale). All subscales and item responses were converted to 0 to 100 scales. Higher scores for functioning items and global quality of life scale represent a better level of functioning. For the symptom items, a higher score reflects a higher level of symptoms.

The HRQL questionnaire had been sent to the trial patients at 6-months intervals in the first 2 years and annually until 5 years. The 7- and 10-year questionnaires were supplemented with the IOCv2 and 14 extra questions on general health, comorbidities, and use of (walking) aids and incontinence pads.

The most recent scaling of the IOC questionnaire yielded the 37-item IOCv2, divided into 4 positive subscales and 4 negative subscales.[17] Respondents indicated their level of agreement from 1 (strongly disagree) to 5 (strongly agree). The PORTEC-1 trial patients had completed the IOCv1, which has 7 items less than IOCv2. An algorithm by Crespi et al[18] was used to impute these missing IOCv2 items for the PORTEC-1 patients for comparison. In view of overlapping questions, the IOCv1 question "ongoing cancer-related or treatment-related symptoms interfere with my life" was not asked. Therefore, the subscale "life interferences" was not computed. As a consequence, the overall scale "negative impact domains" consisted of 3 instead of 4 subscales.

Statistical methods

All statistical analyses were performed with SPSS version 20.0. The χ^2 test or Fisher exact test for categorical variables and t test for continuous variables were used to compare patient and tumour characteristics and to compare mean scores of symptoms at single

time points (P<.05 considered significant). Because of ongoing follow up, the 10-year results were only used for longitudinal analysis.

Analysis of HRQL was done according to EORTC Quality of Life Group guidelines. Baseline scores were compared with a t test, or Armitage trend test for single items. To obtain estimates of the EORTC QLQ-C30 and subscales at each of the fixed time points, a linear mixed model was used with patient as random effect and time (categorical), random assignment, and their interaction as fixed effects. Single items were analyzed using (ordinal) logistic regression with random effects. Differences in HRQL between the two treatment groups were tested by the Wald test in the linear or ordinal logistic mixed model (P random assignment), which excluded the baseline value.

The same test was applied to analyze significant changes of QOL scores over time (P-time), and score changes over time were compared between treatment groups (P-time by random assignment), which included the baseline value. To guard against false-positive results because of multiple testing, a 2-sided P value ≤.01 was considered statistically significant.

Guidelines on the interpretation of clinically relevant changes of EORTC QLQ-C30 scores were applied[19, 20]. Scales not included in the guideline were evaluated according to Osoba et al[21], who reported that patients valued a change of 5 to 10 as "little," 10-20 as "moderate," and more than 20 as "very much" difference.

The IOC scores were compared with a t test. Analysis of covariance was done to evaluate whether patient-related factors influenced scores between PORTEC-1 and PORTEC-2 patients.

RESULTS

HRQL population and compliance

Questionnaires were sent to 265 eligible patients with correct current address at the time points 7 years and 10 years from date of randomization. Response rate at 7 years was 205 of 265 (77%). Three patients only answered the comment page and were therefore not evaluable. One hundred nineteen patients had reached the 10-year time point, of whom 80 (67%) returned the questionnaire (Figure 1).

Of the 282 evaluable questionnaires (202 7-year and 80 10-year questionnaires), 76.2% had completed all items of the QLQ-C30, with rates of completion for the bladder and bowel items of 90.8% and 93.97%, respectively, and 69.8% for sexuality items. Among the responders who indicated to be sexually active (n=45), 86.7% had completed the sexual symptom subscale.

In the "remarks" section, 7 patients (2 EBRT, 5 VBT, of whom 1 only at 10 years) noted having been diagnosed with a second cancer in the pelvic region or an EC recurrence.

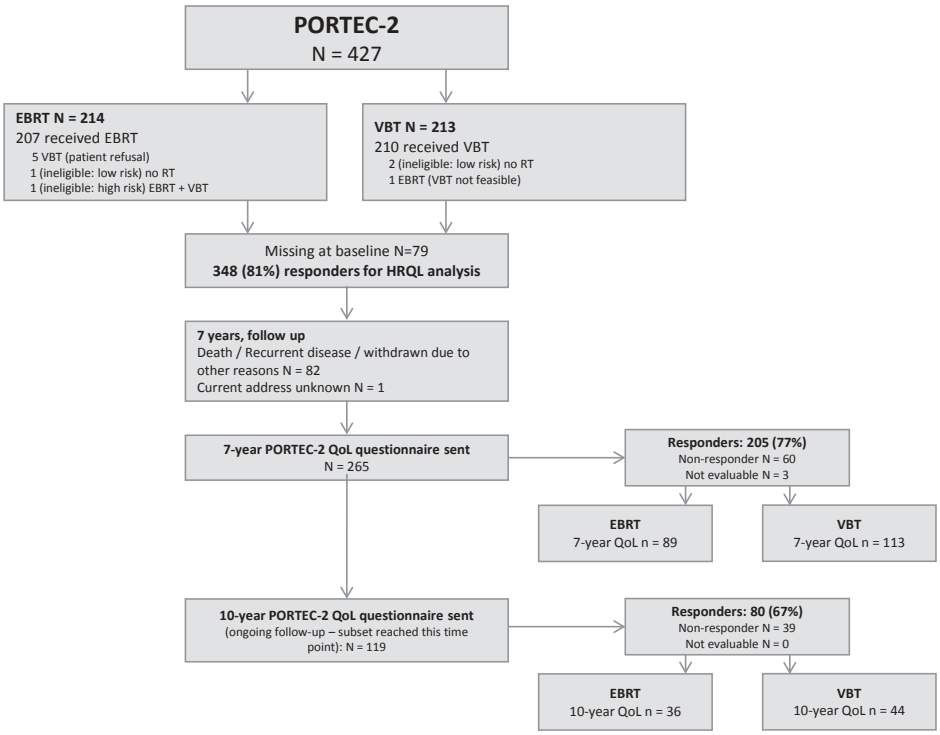


Figure 1. Consort diagram

Because this was not yet known in the trial database, this information was verified and proved correct in all cases. A second cancer outside the pelvic region was reported by another 5 patients. To avoid analysis of symptoms that could have been caused by a second cancer or recurrence, patients with an EC recurrence or a second cancer in the pelvic region were excluded for longitudinal and symptom analysis. The patients with an EC recurrence or a second malignancy (n=12) were analyzed separately for the IOC items.

General functioning

Table 1 shows the patient characteristics, both of the current participants and for the complete PORTEC-2 trial population. Responders at 7 years were slightly younger and had fewer comorbidities compared with the whole PORTEC-2 cohort; no other significant differences were found.

Scores on the QLQ-C30 functioning and global health scales did not significantly differ between the 2 treatment groups (Figure 2, Table 2). Although the overall longitudinal analysis found higher social functioning scores in the VBT group (P=.04), these higher scores were observed in the first 2 years after treatment, and similar thereafter. Sexual

activity was reported by only 19.4% of the patients, sexual interest by 28.1%. No difference in sexual interest and sexual activity was seen between treatment arms. Among patients who were sexually active, 87% (n=20) of EBRT patients reported sex to be enjoyable, compared with 50% (n=15) of VBT patients (P=.001). Symptoms ratings of vaginal dryness, shortening, or pain were not significantly different between the treatment arms.

Table 1. Patient characteristics of patients at 7 years compared to all PORTEC-2 patients

	Responders and evaluable at 7 years (n = 202)					**All patients PORTEC-2 (n=427)**				
	EBRT (n = 89)		**VBT (n = 113)**			**EBRT (n = 214)**		**VBT (n = 213)**		
	No. of patients	**%**	**No. of patients**	**%**	**p-Value[1]**	**No. of patients**	**%**	**No. of patients**	**%**	**p-Value[2]**
Age at randomisation, years										
Mean	67.1		68.1		0.28	69.3		69.8		**0.001**
Range	51-84		46-85			51-89		46-85		
< 60 years	6	6.7%	4	3.5%		8	3.7%	8	3.8%	
≥ 60 years	83	93.3%	109	96.5%		206	96.3%	205	96.2%	
Figo-stage (1988)[#]					0.94					0.81
IB	5	5.6%	6	5.3%		19	8.9%	16	7.5%	
IC	77	86.5%	98	86.7%		172	80.4%	171	80.3%	
IIA	7	7.9%	9	8.0%		23	10.7%	26	12.2%	
Histologic grade					0.55					0.74
Grade 1	39	43.8%	56	49.6%		99	46.3%	103	48.4%	
Grade 2	45	50.6%	50	44.2%		97	44.1%	94	44.1%	
Grade 3	5	5.6%	7	6.2%		18	8.4%	16	7.5%	
WHO performance					0.83					0.32
0	64	71.9%	87	77.0%		157	73.4%	141	66.5%	
1	25	28.1%	22	19.5%		56	26.2%	66	31.1%	
≥2	0	0.0%	4	3.5%		1	0.5%	5	2.4%	
Comorbidity										
IBS	1	1.1%	0	0.0%	0.32	4	1.9%	2	0.9%	0.23
Diabetes	6	6.7%	16	14.2%	0.08	28	13.1%	34	16.0%	0.19
Hypertension	32	36.0%	40	35.4%	0.94	75	35.2%	75	35.5%	0.95
Cardiovascular	16	18.2%	20	17.7%	0.93	47	22.2%	51	24.1%	0.13
Other	10	11.2%	9	8.0%	0.43	33	15.4%	33	15.6%	**0.02**

Abbreviations: EBRT, external beam radiation therapy; VBT, vaginal brachytherapy; WHO, World Health Organisation performance score; IBS, irritable bowel syndrome

[#]FIGO, International Federation of Gynaecology and Obstetrics (1988 staging criteria)

[1] p-value for comparison EBRT versus VBT of responders and evaluable at 7 years.

[2] p-value for comparison responders and evaluable at 7 years (present analysis) versus the initial PORTEC-2 cohort.

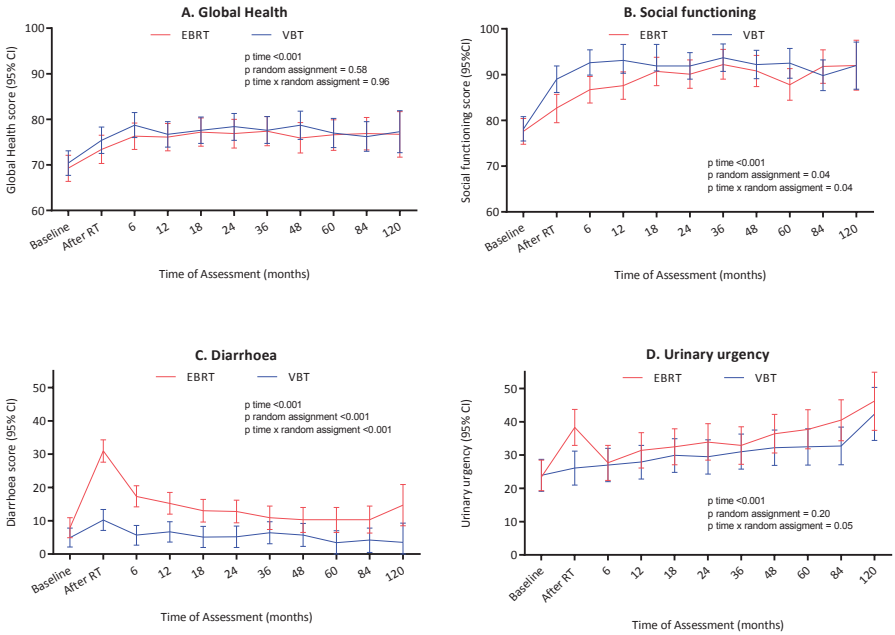


Figure 2. Patient functioning subscales and single-item symptom scores on the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and prostate cancer questionnaire module (EORTC PR-25). For (A) (Global Health score) and (B) (Social functioning score), a higher score indicates a higher level of functioning or activity. For (C) (Diarrhea) and D (Urinary urgency), a higher score indicates a higher level of symptoms. Abbreviations: EBRT = external beam radiation therapy; RT = radiation therapy; VBT = vaginal brachytherapy.

Bowel and bladder symptoms

Longitudinal analysis throughout the 10-year HRQL follow-up period showed higher rates of diarrhea, fecal leakage, and limitations in daily activities due to bowel symptoms in the EBRT group as compared with VBT (all P<.001; Table 2), similar to previous analyses.[8] At 7 years, significant and clinically relevant differences between EBRT and VBT patients were found for all bowel symptoms except for rectal blood loss, flatulence, and bowel cramps (Figure 3, Table 3). Moderate or severe symptoms of fecal leakage were reported by 10.6% versus 1.8% of EBRT versus VBT patients (P=.03), and moderate or severe diarrhea by 8.4% versus 0.9% (P=.037). Limitations in daily activities due to bowel symptoms were reported by 10.5% versus 1.8% (P=.001) and bowel urgency by 23.3% versus 6.6% (P<.001).

No differences were found in use of incontinence pads for fecal soiling (10.6% vs 8.1% for EBRT vs VBT). Fifty percent of patients who reported limitations in daily functioning due to bowel symptoms or fecal leakage used incontinence pads.

Table 2. Mean scores of QLQ-C30 functioning scales and symptom ratings by treatment arm

		Questionnaire time points			p-value		
		Months			Time	Randomization	Time by randomization
		Baseline	84	120			
EORTC QLQ-C30							
Global health	EBRT	69.3	76.9	76.7	**<0.001**	0.58	0.96
	VBT	70.4	76.2	77.3			
Functioning scales							
Social functioning	EBRT	77.6	91.8	92.0	**<0.001**	0.04	0.04
	VBT	78.1	89.8	92.0			
Cognitive functioning	EBRT	84.3	86.5	84.7	0.35	0.30	0.60
	VBT	86.7	85.5	86.7			
Emotional functioning	EBRT	75.6	82.9	83.7	**<0.001**	0.33	0.71
	VBT	76.3	84.7	87.5			
Physical functioning	EBRT	72.0	74.9	68.4	**<0.001**	0.34	0.75
	VBT	73.7	73.3	69.2			
Role functioning	EBRT	61.0	80.3	71.2	**<0.001**	0.34	0.15
	VBT	59.1	76.9	77.5			
QLQ C-30 symptom scoring							
Fatigue	EBRT	34.8	25.6	25.0	**<0.001**	0.14	0.37
	VBT	34.1	26.2	25.6			
Nausea and vomiting	EBRT	4.6	2.8	3.9	**<0.001**	0.04	0.34
	VBT	5.0	2.4	3.7			
Pain	EBRT	18.5	14.2	22.1	**<0.001**	0.33	0.46
	VBT	19.4	17.0	15.1			
Dyspnoea	EBRT	13.0	18.6	21.8	**<0.001**	0.53	0.05
	VBT	11.6	14.6	19.6			
Insomnia	EBRT	27.4	20.2	29.6	**0.003**	0.17	0.58
	VBT	25.9	23.3	21.5			
Appetite loss	EBRT	13.7	8.6	8.8	**<0.001**	0.03	0.02
	VBT	10.6	8.2	4.3			
Constipation	EBRT	13.4	8.3	5.7	**<0.001**	0.56	0.79
	VBT	12.9	7.4	9.1			
Diarrhoea	EBRT	7.9	10.3	14.7	**<0.001**	**<0.001**	**<0.001**
	VBT	4.9	4.2	3.5			
Financial difficulties	EBRT	2.0	2.3	2.0	**0.003**	0.85	0.26
	VBT	5.5	2.3	3.1			
Bowel symptoms (BS)							
Limitation daily activities due to BS	EBRT	9.0	12.7	14.1	**<0.001**	**<0.001**	**0.001**
	VBT	5.0	4.9	6.2			

Table 2. Mean scores of QLQ-C30 functioning scales and symptom ratings by treatment arm (continued)

		Questionnaire time points			p-value		
			Months		Time	Randomization	Time by randomization
		Baseline	84	120			
Faecal leakage	EBRT	4.0	12.1	13.4	**<0.001**	**<0.001**	0.06
	VBT	1.5	5.6	3.0			
Rectal blood loss	EBRT	0.4	1.2	1.0	0.08	0.06	0.51
	VBT	0.2	1.1	0.1			
Bloated feeling	EBRT	15.8	16.0	11.2	**<0.001**	0.16	0.78
	VBT	15.5	10.9	8.0			
Urinary symptoms (US)							
Frequency daytime	EBRT	33.2	35.0	43.4	**<0.001**	0.16	0.09
	VBT	36.5	32.0	33.1			
Frequency at night	EBRT	31.5	36.3	46.4	**<0.001**	0.21	0.05
	VBT	34.3	35.3	37.2			
Urinary urgency	EBRT	23.4	40.5	46.2	**<0.001**	0.20	0.05
	VBT	23.9	32.7	42.3			
Sleep deprivation due to urinary frequency	EBRT	15.3	18.9	25.8	**0.001**	0.10	0.18
	VBT	16.2	14.0	17.4			
Need to remain close to the toilet	EBRT	7.8	16.2	23.4	**<0.001**	**0.001**	**0.004**
	VBT	7.0	10.2	12.8			
Incontinence for urine	EBRT	11.5	20.4	29.8	**<0.001**	0.19	0.24
	VBT	10.6	20.8	25.5			
Dysuria	EBRT	5.3	3.9	2.2	**<0.001**	0.91	0.87
	VBT	7.9	3.2	2.0			
Limitation daily activities due to US	EBRT	3.6	12.4	14.2	**<0.001**	0.03	0.25
	VBT	3.0	7.3	7.3			
Sexual functioning and symptoms							
Sexual interest	EBRT	7.7	13.8	8.1	**<0.001**	0.24	0.26
	VBT	4.9	8.1	2.2			
Sexual activity	EBRT	5.3	7.3	5.3	**<0.001**	0.34	0.82
	VBT	2.8	6.4	0,0			
To what extent was sex enjoyable	EBRT	45.7	46.1	19.7	**0.004**	0.30	**<0.001**
	VBT	20.0	25.1	43.5			
Vaginal dryness	EBRT	30.9	29.6	25.3	0.83	0.66	0.07
	VBT	36.4	28.9	51.9			

P time: changes of quality of life scores over time. P random: difference in health-related quality of life between the two treatment groups. P time x random: quality of life score changes over time between the two treatment groups. EBRT, external-beam radiotherapy; VBT, vaginal brachytherapy;
Mean scores of earlier time points have previously been reported by Nout et al (EJC 2012).

Longitudinal analysis of 10-year HRQL follow-up for urinary symptoms showed increasing rates of urinary urgency and nocturnal frequency over time in both groups, but more so among EBRT patients (P=.05). Patients treated with EBRT reported higher rates of remaining close to the toilet because of urinary symptoms (P=.001; Table 2). Over time, increasing rates of urinary urgency were found, and at 7 years significantly more EBRT patients reported urinary urgency, a difference that was not seen in the 5-year HRQL analysis. Moderate or severe symptoms of urinary urgency were reported by 39.3% versus 25.5% (EBRT vs VBT, P=.05). Rates of sleep disturbance due to urinary frequency (13.1% vs 6.7%, P=.06) and the need to remain close to the toilet (8.4% vs 5.7%, P=.07) were slightly but nonsignificantly higher among EBRT patients (Figure 3, Table 3).
Overall, 50% of patients reported use of incontinence pads, without differences between the groups (50.6% vs 50.9%). Use of incontinence pads was reported by 85.2% of patients with urinary incontinence and 87.2% of those with limitations in daily activities due to urinary symptoms.

Table 3. Single item scores bowel, bladder and sexual symptoms at 7 years (n=196)*

	Treatment	N missing	N patients without symptoms	% of patients	N patients with mild symptoms$	% of patients	N patients with moderate/severe symptoms$	% of patients	t-test mean scores
Bowel symptoms (BS)									
Diarrhoea	EBRT	5	65	78.3%	11	13.3%	7	8.4%	**0.037**
	VBT	2	93	87.7%	12	11.3%	1	0.9%	
Limitation daily activities due to BS	EBRT	2	58	67.4%	19	22.1%	9	10.5%	**0.001**
	VBT	2	93	87.7%	11	10.4%	2	1.8%	
Faecal leakage	EBRT	3	64	75.3%	12	14.1%	9	10.6%	**0.03**
	VBT	1	91	85%	14	13.1%	2	1.8%	
Rectal blood loss	EBRT	2	84	97.7%	1	1.2%	1	1.2%	0.83
	VBT	2	103	97.2%	3	2.8%	0	0.0%	
Bloated feeling	EBRT	2	56	65.1%	21	24.4%	9	10.5%	**0.04**
	VBT	2	81	76.4%	21	19.8%	4	3.8%	
Bowel urgency	EBRT	2	38	44.2%	28	32.6%	20	23.3%	**<0.001**
	VBT	2	71	67%	28	26.4%	7	6.6%	
Flatulence	EBRT	3	36	42.4%	31	36.5%	18	21.2%	0.76
	VBT	2	54	50.9%	40	37.7%	12	11.3%	
Stomach/bowel cramps	EBRT	2	63	73.3%	18	20.9%	5	5.9%	0.12
	VBT	2	88	83.0%	14	13.2%	4	3.8%	

Table 3. Single item scores bowel, bladder and sexual symptoms at 7 years (N=196)* (continued)

	Treatment	N missing	N patients without symptoms	% of patients	N patients with mild symptoms$	% of patients	N patients with moderate/severe symptoms$	% of patients	t-test mean scores
Urinary symptoms (US)									
Frequency daytime	EBRT	5	29	34.9%	31	37.3%	23	27.7%	0.58
	VBT	2	40	37.7%	41	38.7%	25	23.6%	
Frequency at night	EBRT	3	20	23.5%	40	47.1%	25	29.4%	0.56
	VBT	2	35	33.0%	42	39.6%	29	27.4%	
Urinary urgency	EBRT	4	27	32.1%	24	28.6%	33	39.3%	**0.05**
	VBT	2	41	38.7%	38	35.8%	27	25.5%	
Sleep deprivation due to urinary frequency	EBRT	4	50	59.5%	23	27.4%	11	13.1%	0.06
	VBT	3	77	73.3%	21	20.0%	7	6.7%	
Need to remain close to the toilet	EBRT	4	54	64.3%	23	27.4%	7	8.4%	0.07
	VBT	4	82	78.8%	16	15.4%	6	5.7%	
Incontinence for urine	EBRT	4	48	57.1%	26	31.0%	10	11.9%	0.89
	VBT	4	57	54.8%	38	36.5%	9	8.7%	
Dysuria	EBRT	4	76	90.5%	5	6.0%	3	3.6%	0.35
	VBT	6	96	94.1%	4	3.9%	2	2.0%	
Limitation daily activities due to US	EBRT	1	63	72.4%	20	23.0%	4	4.6%	0.11
	VBT	1	90	84.1%	13	12.1%	4	3.7%	
Difficulties emptying of the bladder	EBRT	4	66	78.6%	13	15.5%	5	6.0%	0.19
	VBT	4	89	85.6%	12	11.5%	3	2.9%	
Sexual symptoms**									
To what extent was sex enjoyable	EBRT	65	3	13.0%	8	34.8%	12	52.2%	**0.001**
	VBT	78	15	50.0%	9	30.0%	6	20.0%	
Vaginal dryness	EBRT	67	11	52.4%	3	14.3%	7	33.4%	0.763
	VBT	78	18	60.0%	4	13.3%	8	26.7%	
Short or narrow vagina	EBRT	66	13	59.1%	8	36.4%	1	4.5%	0.190
	VBT	79	16	55.2%	7	24.1%	6	20.6%	
Pain during intercourse	EBRT	66	17	77.3%	4	18.2%	1	4.5%	0.122
	VBT	81	17	63.0%	6	22.2%	4	14.8%	

* At 7 years there were 202 responders; 6 patients were exlcuded owing to endometrial cancer recurrence or second cancer in the pelvic region.

Abbreviations: EBRT, external beam radiotherapy; VBT, vaginal brachytherapy

$ mild symptoms: response 'a little'; moderate/severe symptoms: response "quite a bit" or "very much"

** responses to these questions were only expected if the respondent indicated to be sexually active

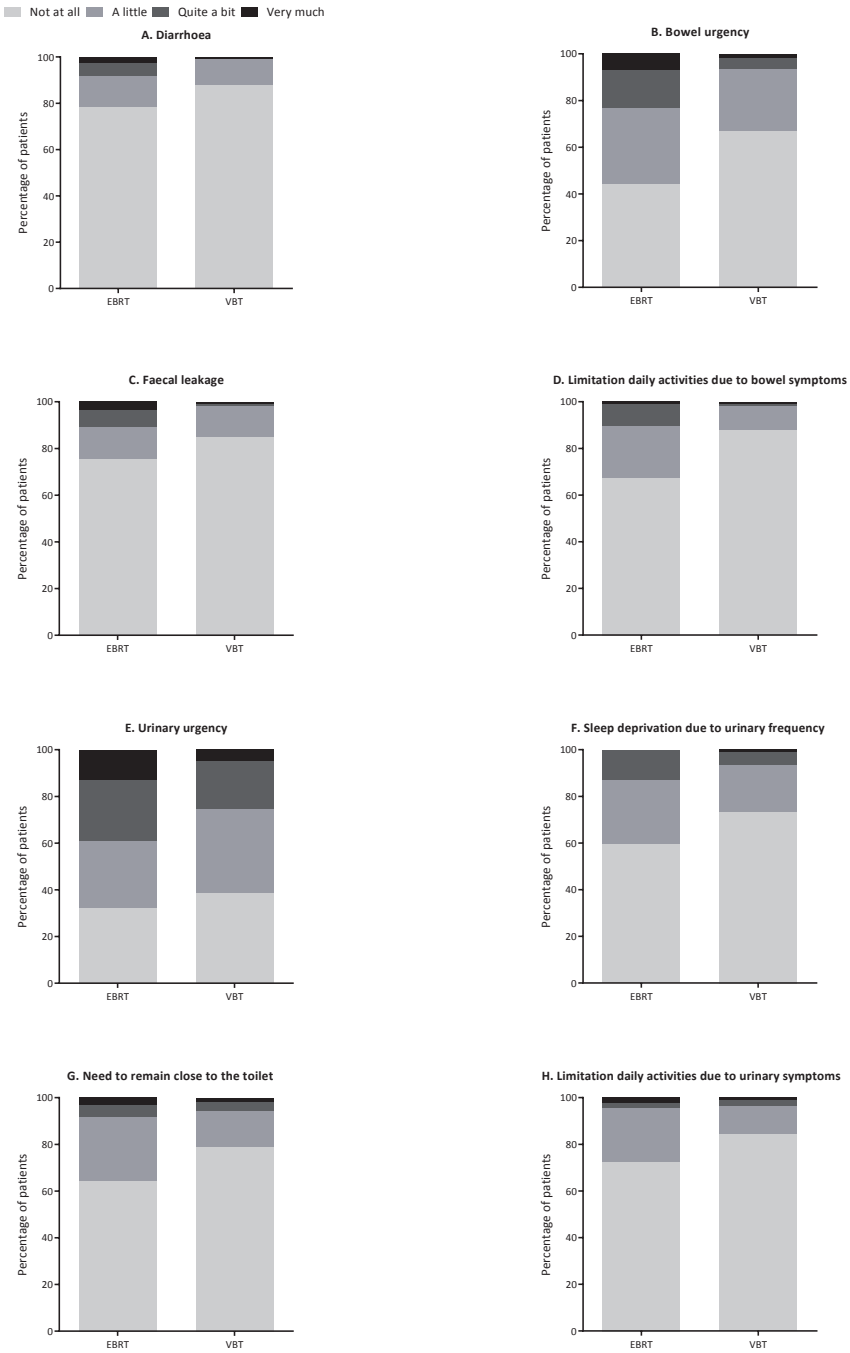
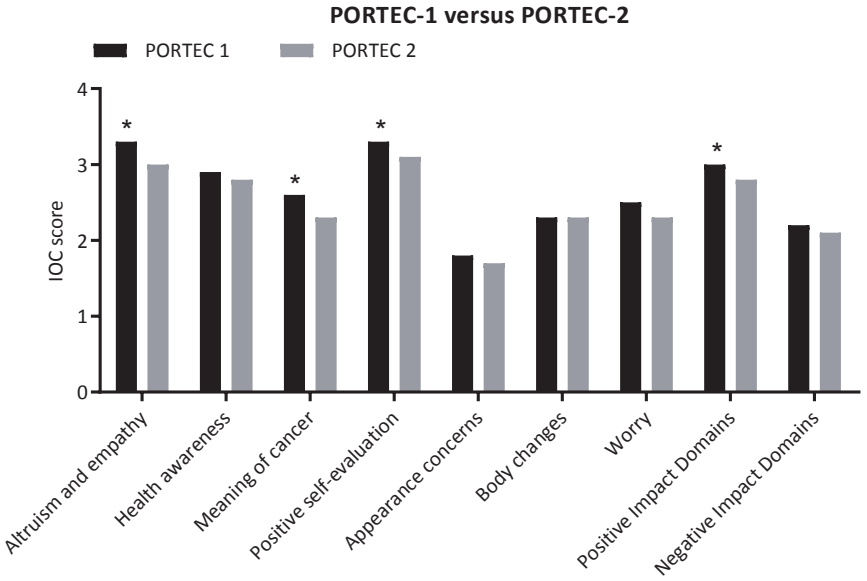


Figure 3. Patient symptom scores at 7 years for (A) diarrhea, (B) bowel urgency, (C) fecal leakage, (D) limitation of daily activities due to bowel symptoms, (E) urinary urgency, (F) sleep deprivation due to urinary frequency, (G) need to remain close to the toilet, and (H) limitation of daily activities due to urinary symptoms.



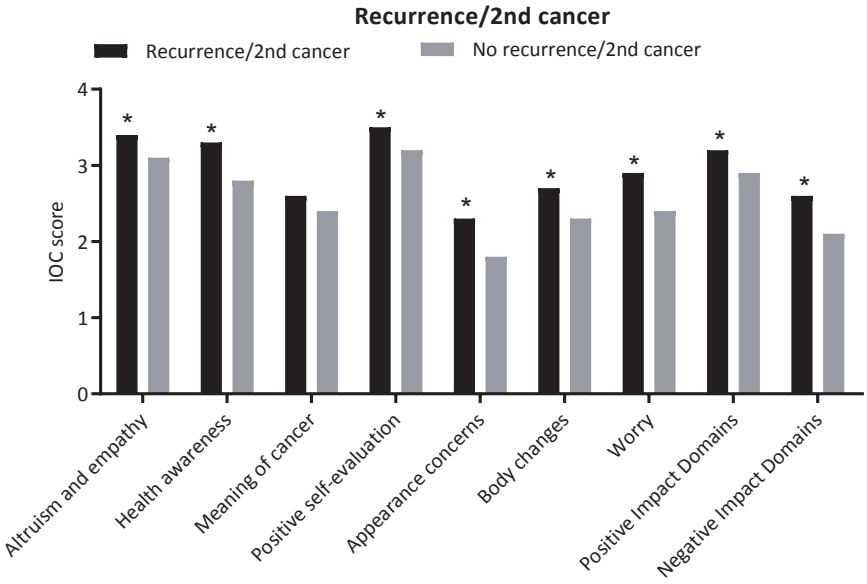


Figure 4. Impact of cancer scores at 7 years of (A) patients treated in the Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC)-1 versus PORTEC-2 trial; and (B) patients in PORTEC-1 and PORTEC-2 with recurrence or a second cancer versus patients without recurrence or second cancer.

IOC scores

All scales for the IOC questionnaire could be computed for 176 of 190 patients (92.6%). No differences in any of the subscales were seen between the 2 PORTEC-2 treatment arms. Comparison of PORTEC-2 IOC scores with PORTEC-1 scores showed that PORTEC-1 patients tended to have higher scores on every subscale and overall scales (Figure 4 and Table S1. Analysis of covariance (adjusted for the presence of bone problems, having a partner, and age) showed that PORTEC- 1 patients scored higher on the positive impact domain (3.03 vs 2.82, P=.002).

Differences in IOC scores were found between the 51 patients who had reported to have been diagnosed and treated for EC recurrence or second cancer (PORTEC-1 n=39, PORTEC-2 n=12), compared with the combined general PORTEC-1 and -2 patients. These patients had significantly higher scores on all IOC subscales, except for meaning of cancer (Figure 4).

DISCUSSION

This long-term analysis of HRQL in the PORTEC-2 trial shows that EBRT may have a long-lasting, clinically relevant, mostly bowel symptom-related negative impact on HRQL, with moderate or severe limitation of daily activities reported by 10% of the patients. Patients treated with EBRT reported significantly more diarrhea, fecal leakage, urgency, and limitations in daily activities due to bowel symptoms compared with VBT. At 7 years, for the first time significantly more urinary urgency was reported by patients treated with EBRT.

This is one of the few long-term analyses of patient reported gastrointestinal and bladder symptoms after pelvic EBRT in a randomised trial, with the strengths of exclusion of biases due to the randomised comparison and the complete follow-up. Our results are consistent with the rates of gastrointestinal and bladder toxicity found in other studies.[22-24] Although the differences in mean scores were small, 10% of patients reported to have moderate or severe limitations of daily activities, and this is clinically relevant.[19, 20]

These patient-reported outcomes provide a complete picture of survivorship issues after treatment of EC, because agreement between patient- and physician-based scoring of toxicities is low, with significant underreporting of lower-grade toxicities that do impact daily life.[25] Similar to the long-term quality-of-life analysis of the PORTEC-1 trial, we found that urinary symptoms with use of incontinence pads was not reported until more than 5 years after treatment, showing the combined effects of aging and EBRT on the bladder and pelvic floor. It is known from previous studies that the bladder is a late-responding organ[8-10] and that pelvic floor dysfunction gradually develops over time.

General functioning and global health did not significantly differ between EBRT and VBT patients, suggesting that diagnosis and treatment of EC have a transient impact on patient functioning and that many patients adjust their lives to bothersome but manageable symptoms.

Sexual activity and interest were reported by only 19.4% and 28.1% of the patients at 7 years, without differences between EBRT and VBT. Patients treated with EBRT more often (87% vs 51%) reported sex to be enjoyable, whereas there were no differences in symptoms such as vaginal dryness or pain. The low activity rates together with the low completion rate of the sexual functioning questions are a limitation to these findings.

The challenge is to develop preventive and intervention measures that might reduce or prevent such long-lasting symptoms caused by EBRT. Andreyev et al[26] reported clinical improvement in bowel function with a structured, algorithm-driven approach. Pelvic floor muscle training programs for gynecologic cancer survivors with pelvic floor dysfunction showed improved results compared with no intervention[27, 28]. It remains to be seen whether instruction on simple pelvic floor exercises for all patients will reduce symptoms and dysfunction over time.

Another possible limitation to this analysis is the inherent selection of responders at long-term analysis, because participants had to be alive and disease-free. Previous analyses had shown no differences in patient or tumour characteristics between responders and non-responders.[7] The patients in the present analysis were slightly younger and had fewer comorbidities. With a mean age of the PORTEC-2 patients of 69 years, the older patients with more comorbidities were at higher risk to die of intercurrent disease compared with the younger patients. Another explanation could be that the older patients were not able to respond owing to other reasons, such as vision problems or cognitive disorders. With the high response rate of 77% at 7 years, however, these results are generally applicable.

No differences in IOC scores were seen between patients in the PORTEC-2 treatment arms. Comparison of PORTEC-1 and PORTEC-2 patients showed higher scores on positive impact scales among PORTEC-1 patients. Younger patients and those with a partner had higher scores on the positive impact domain scales, whereas patients with bone or joint problems scored higher on the negative impact scales. Oerlemans et al[12] reported in a study among non-Hodgkin lymphoma survivors fewer positive and more negative impacts of cancer in Dutch survivors compared with American non-Hodgkin lymphoma survivors. They suggested that IOC scores might be more dependent on cultural background than type of cancer. Age, length of follow-up, female gender, education level, relationship, and employment were factors of influence.[12] In Table S1 an overview of the IOC scores from these 4 different study groups is shown.

The higher IOC scores among patients who had been diagnosed with EC recurrence or second cancer reflect their having to cope with the stresses and anxieties of having had cancer for the second time, and additional symptoms of renewed treatment.

In conclusion, this study shows the long-lasting, clinically relevant, mostly bowel symptom-related negative impact of EBRT on HRQL of a significant minority of the patients, although not significantly influencing general health and overall quality of life. External beam radiation therapy should be used only when the benefit outweighs the risks of toxicity. These results provide important information to be used for patient counselling and shared decision making regarding costs and benefits of adjuvant treatment. Future studies should be aimed at methods to prevent or improve these symptoms. The reduction of such long-term symptoms might be achieved by using new radiation techniques. First studies of intensity modulated radiation therapy have shown lower rates of both acute and late symptoms.[29-31] Preventive measures for pelvic floor function should be investigated.

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SUPPLEMENTARY MATERIAL

Table S1. IOC scores of the PORTEC studies compared with Dutch and American NHL survivors

	PORTEC-1	PORTEC-2	Dutch NHL cohort	American NHL cohort
	N = 246	N = 202	N = 491	N = 738
Median age at time of questionnaire	75	75	63	63
Mean follow up duration (years)	13.4	7.1	5.3	10.2
IOC psychological: Altruism and Empathy	3.3	3.0	3.3	3.9
IOC physical: health awareness	2.9	2.8	3.2	3.7
IOC psychological: meaning of cancer	2.6	2.3	2.7	2.7
IOC psychological: positive self-evaluation	3.3	3.1	3.4	3.9
IOC physical: Appearance concerns	1.8	1.7	1.8	1.7
IOC physical: body changes	2.3	2.3	2.6	2.4
IOC worry	2.5	2.3	2.8	2.6
IOC Positive Impact Domains	3.0	2.8	3.1	3.5
IOC Negative Impact Domains	2.2	2.1	2.4	2.2

IOC, impact of cancer; NHL, non-hodgkin lymphoma; Dutch NHL cohort; Eindhoven registration study, American NHL cohort; North-Carolina registration study

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