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Long-Term Outcome and Quality of Life of Patients With Endometrial Carcinoma Treated With or Without Pelvic Radiotherapy in the Post Operative Radiation Therapy in Endometrial Carcinoma 1 (PORTEC-1) Trial

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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ABSTRACT

Purpose
To determine the long-term outcome and health-related quality of life (HRQL) of patients with endometrial carcinoma (EC) treated with or without pelvic radiotherapy in the Post Operative Radiation Therapy in Endometrial Carcinoma 1 (PORTEC-1) trial.

Patients and Methods
Between 1990 and 1997, 714 patients with stage IC grade 1 to 2 or IB grade 2 to 3 EC were randomly allocated to pelvic external-beam radiotherapy (EBRT) or no additional treatment (NAT). HRQL was evaluated with the Short Form 36-Item (SF-36) questionnaire; subscales from the European Organisation for Research and Treatment of Cancer (EORTC) PR25 module for bowel and bladder symptoms and the OV28 and CX24 modules for sexual symptoms; and demographic questions. Analysis was by intention-to-treat.

Results
Median follow-up was 13.3 years. The 15-year actuarial locoregional recurrence rates were 5.8% for EBRT versus 15.5% for NAT ($P < .001$), and 15-year overall survival was 52% versus 60% ($P = .14$). Of the 351 patients confirmed to be alive with correct address, 246 (70%) returned the questionnaire. Patients treated with EBRT reported significant ($P < .01$) and clinically relevant higher rates of urinary incontinence, diarrhea, and fecal leakage leading to more limitations in daily activities. Increased symptoms were reflected by the frequent use of incontinence materials after EBRT (day and night use, 42.9% *v* 15.2% for NAT; $P < .001$). Patients treated with EBRT reported lower scores on the SF-36 scales "physical functioning" ($P = .004$) and "role-physical" ($P = .003$).

Conclusion
EBRT for endometrial cancer is associated with long-term urinary and bowel symptoms and lower physical and role-physical functioning, even 15 years after treatment. Despite its efficacy in reducing locoregional recurrence, EBRT should be avoided in patients with low- and intermediate-risk EC.

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INTRODUCTION

Four randomized trials have established the role of radiotherapy in intermediate-risk endometrial carcinoma (EC).[1-4] The Post Operative Radiation Therapy in Endometrial Carcinoma 1 (PORTEC-1) trial (1990-1997) was among the first to randomly compare pelvic external-beam radiotherapy (EBRT) to no additional treatment (NAT), and it showed that EBRT provides a highly significant improvement of local control but without a survival advantage.[3,5] Furthermore, EBRT was associated with a 26% risk of adverse effects, mainly grade 1 to 2 GI toxicity.[6]

It was concluded that in view of the absence of survival benefit, EBRT would be justified only for patients at relatively high risk of recurrence. The risk factors identified were grade 3, age 60 years or older, and deep myometrial invasion. Patients with at least two of these three risk factors were designated high-intermediate risk (HIR). Patients with HIR features had a 20% risk of locoregional recurrence (LRR) after NAT, which was reduced to 5% with EBRT.[3,5] For these HIR patients, the indication for radiotherapy (RT) was maintained after PORTEC-1, although EBRT was abandoned for the 50% of patients with stage I EC who were designated low-intermediate risk (LIR).

The PORTEC-2 trial confirmed that vaginal brachytherapy (VBT) could safely be substituted for EBRT in HIR patients.[7,8] After a median follow-up of 24 months, health-related quality-of-life (HRQL) analysis showed that bowel symptoms such as diarrhea and fecal leakage were significantly increased after EBRT, leading to more limitation in daily activities and a significantly lower level of social functioning.[7]

Only a few studies[9-13] have investigated long-term HRQL of EC survivors, and most studies included few patients or had low response rates (< 40%). One retrospective study with an adequate response rate (75%) found that EBRT was negatively associated with vitality and physical and social well-being, but scores were similar to those of an age-matched population.[14]

The short-term PORTEC-2 findings prompted this analysis of long-term HRQL of EC survivors treated in the PORTEC-1 trial 11 to 18 years ago to investigate whether the impact of EBRT would have resolved over time.

PATIENTS AND METHODS

Between 1990 and 1997, 714 patients with stage I EC who participated in the PORTEC-1 trial were randomly allocated to EBRT or NAT. Information on patient selection and treatment have been provided in previous publications[3,5,6] and in the CONSORT diagram (Fig 1).

Surgery consisted of total extrafascial hysterectomy and bilateral salpingo-oophorectomy without lymphadenectomy (only biopsy of any suspicious lymph nodes). Women of any age with a WHO performance score 0 to 2; endometrial adenocarcinoma stage I, grade 1 with deep (≥ 50%) myometrial invasion; grade 2 with any invasion; or grade 3 with superficial (< 50%) invasion were eligible. Informed consent was obtained from all patients.

Pelvic EBRT was administered with the target volume including the parametrial tissues, proximal two thirds of the vagina, and lymphatic drainage regions along the internal iliac vessels up to the promontory. The superior field border was at the L5-S1 disc. Total dose was 46 Gy with 2 Gy daily fractions.

The original trial protocol was approved by the Protocol Review Committee of the Dutch Cancer Society and by the ethics committees of the participating centers. Because HRQL investigation was not included in the original protocol, ethics approval for this study was sought and obtained in 2007 from the Ethics Committee of Leiden University Medical Center.

Follow-Up and HRQL Patient Selection

Patients were followed in their regional hospitals at least until 7 years after treatment. LRRs were confirmed by histology. Patterns of failure were recorded by sites of failure: locoregional, distant, or both. LRRs were defined as vaginal and/or pelvic recurrences. Distant failures included para-aortic lymph node metastases; abdominal relapses; liver, lung, and bone metastases; and diffuse metastatic disease.

For this analysis, vital status of all patients considered to be alive and disease-free according to the trial database was checked with the Dutch Bureau for Genealogy and the governmental local population administration (GBA). Patients confirmed to be alive (n = 428; January 2008) and for whom a correct mailing address was available (n = 351) were sent a questionnaire to evaluate

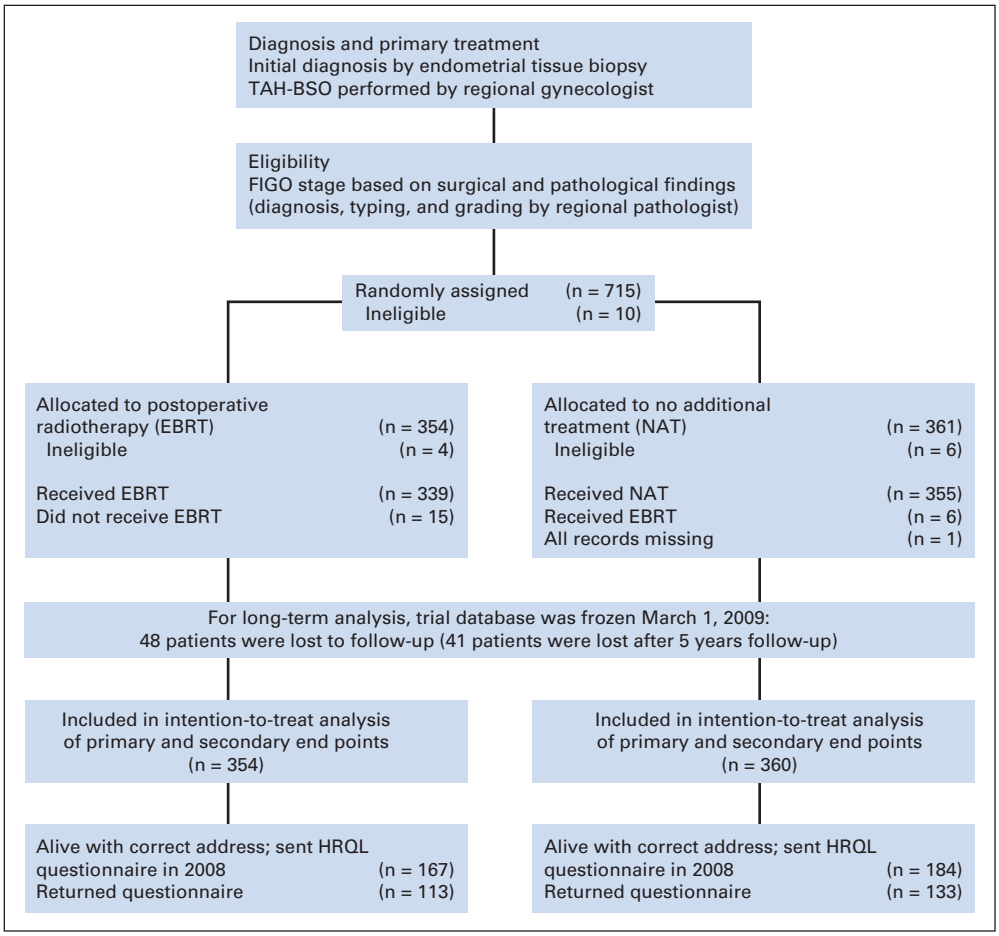

Fig 1. CONSORT diagram. TAH-BSO: total abdominal hysterectomy and bilateral salpingo-oophorectomy; FIGO, International Federation of Gynecology and Obstetrics; EBRT, external-beam radiotherapy; NAT, no additional treatment; HRQL, health-related quality of life.

long-term HRQL. The questionnaire was accompanied by a letter written by each patient's own radiation oncologist explaining the background and purpose of the questionnaire. A reminder was sent to patients who had not returned the questionnaire after 3 months.

Patients who returned the questionnaire were noted alive with the date of completing their questionnaire. For patients who did not respond, vital status was noted as on the date of GBA confirmation. For patients who had died, the date of death according to GBA registry was noted, and local study coordinators were contacted to obtain causes of death. Follow-up information was updated, especially for patients with previously known recurrences and those who noted events on their questionnaires, by obtaining information from their local hospital or general practitioner.

HRQL Assessment

General health status was measured with the Dutch version of the Medical Outcomes Study Short Form 36-Item (SF-36) Health Survey.[15] The scores were standardized on a scale of 0 to 100, with higher scores indicating better health status. To compare the health status of survivors with the general population, we used age-matched SF-36 scores available from the general Dutch female population.[16]

Although an EC module has recently been developed by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Group,[17] no EC-specific symptom questionnaire was available at the time of this study. With approval of the EORTC Quality of Life Group, relevant subscales from EORTC modules were combined into a symptom module, similar to that used in the PORTEC-2 trial.[7] Subscales for bowel and bladder symptoms from PR25, for sexual functioning and symptoms from OV28, and additional single items from CX24 were used.[18-20] Likert-type response scales were used for all items with a four-point response scale. All subscales and individual-item responses were linearly converted to 0 to 100 scales. Higher scores for functioning items represent a better level of functioning. For the symptom items, a higher score reflects a higher level of symptoms and decreased quality of life.

The Impact of Cancer (IOC) questionnaire, a specific questionnaire assessing the long-term impact of diagnosis and treatment of cancer, was also included in the survey.[21,22] Since analysis of the IOC did not show differences between both treatment groups, the results are not further discussed in this article.

Statistical Methods

All statistical analyses were performed by using SPSS version 17.0 (SPSS, Chicago, IL). Primary end points for the study were LRR and overall survival (OS). The analysis was by intention to treat. All randomly assigned patients were kept in the analysis, including those who did not meet eligibility criteria (n = 10) or with protocol violations (n = 31). The Kaplan-Meier method, log-rank test, and Cox regression analysis were used for time-to-event analyses with the following end points: LRR and distant metastasis from random assignment with censoring at date of last contact or death; OS from random assignment with failure defined as death irrespective of the cause and censoring at the date of last contact for patients alive.

χ^2 statistics or Fisher's exact test for categorical variables and *t* test for continuous variables ($P = .05$ was considered significant) were used to compare patient and tumor characteristics of EBRT with NAT and respondents with nonrespondents. Explanatory comparison of HRQL scores was done with the *t* test; descriptive median scores are presented in Table 1. To guard against false-positive results due to multiple testing, a two-sided *P* value of .01 was considered statistically significant. Differences between the groups were considered clinically relevant if they exceeded 10 points on a scale of 100 points.[23] Amount of variance (R^2) explained by EBRT was analyzed in a linear regression model with age, comorbidity, and treatment arm entered in that order (Fig 2).

RESULTS

Fifteen-Year Outcomes

The outcome analysis was done on data frozen on March 1, 2009. Of the 714 evaluable patients, 48 patients were lost to follow-up (41 of them were lost after > 5 years of follow-up); they were included in the analysis and censored at the date of last follow-up (Fig 3). Median follow-up for patients alive was 13.3 years (range, 2.8 to 18.5 years). The study groups were well balanced with regard to patient and tumor characteristics.[3]

LRRs at 15 years were 5.8% in the RT group and 15.5% in the NAT group (hazard ratio [HR], 3.46; 95% CI, 1.93 to 6.18; log-rank test $P < .001$; Fig 3). Among 50 LRRs in the NAT arm, 37 (74%) were located in the vagina. The 15-year rate of distant metastases was similar in the treatment groups: 9.3% for EBRT and 7.1% for NAT (HR, 0.73; 95% CI, 0.43 to 1.25; log-rank test $P = .25$). OS rate at 15 years was 52% after EBRT versus 60% after NAT (HR, 0.84; 95% CI, 0.67 to 1.06; log-rank test $P = .14$; Fig 4).

HRQL Population and Compliance

Quality-of-life questionnaires were sent to 351 patients for whom the correct address could be confirmed. In all, 246 patients (70%) responded to the questionnaire. Median follow-up of the respondents was 13.3 years (range, 9.4 to 18.3 years). Nonrespondents were slightly older; all other tumor and treatment characteristics were equally balanced between responders and nonrespondents and between the EBRT and NAT groups (Table 2). As expected, more respondents in the NAT arm had been diagnosed with a locoregional recurrence (n = 14) than in the EBRT arm (n = 1; $P = .007$). There were no significant differences in the rates of second cancers or distant metastases between respondents in both arms.

Six patients returned the questionnaire responding only to the demographic questions. Excluding these six patients, the rate of missing data was 8.7% for the SF-36, 5.3% for EORTC items, and 7.4% for IOC. Patients were more reluctant to respond to questions about their sexual functioning (activity and interest: 29% missing). Among the patients who indicated they were sexually active, 91% responded to the items on sexual symptoms. Overall, the treatment groups did not differ significantly with regard to questionnaire response rates and missing items.

General Health Status (SF-36)

Patients treated with EBRT reported lower scores on all scales of the SF-36 (Table 1 and Fig 2). These differences were significant and clinically relevant for physical functioning (EBRT, 50.5 *v* NAT, 61.6; $P = .004$) and role-physical (EBRT, 40.3 *v* NAT, 58.5; $P = .003$).

EBRT was a significant explanatory variable for deteriorated score on the physical functioning scale (R^2 change, 3.0%; $P = .002$) and role-physical scale (R^2 change, 3.1%; $P = .006$) after correction for age and comorbidity (Fig 2). There were no clinically relevant differences between the SF scores of either of the treatment groups and those of an age-matched Dutch general population (data not shown).

Symptom Items (EORTC modules)

Compared with patients in the NAT arm, patients treated with EBRT reported significantly higher levels of urinary urgency (mean, 45.6 *v* 31.7; $P < .001$), and of urinary incontinence, a higher need to remain close to the toilet, and more limitations in daily activities due to bladder symptoms (Table 1 and Fig 5). As for bowel symptoms, patients treated with EBRT reported increased levels of diarrhea, fecal leakage, and more limitations in daily activities due to bowel symptoms (25.8 *v* 14.6; $P = .006$). As a result of these increased symptoms, significantly more patients treated with EBRT indicated they used

Table 1. Scores on Medical Outcomes Study SF-36 Health Survey and EORTC Module Symptom Items

	EBRT (n = 113)	NAT (n = 133) Mean ± SD	P*	Recurrence After NAT (n = 14) Mean ± SD	P†
SF-36					
General health	58 ± 22	62 ± 17	.082	67 ± 18	.311
Physical function	**50 ± 30**	**62 ± 27**	**.004**	62 ± 22	.973
Role-physical	**40 ± 44**	**59 ± 45**	**.003**	66 ± 48	.572
Bodily pain	**62 ± 27**	**70 ± 23**	**.009**	70 ± 22	.999
Vitality	57 ± 30	62 ± 19	.055	60 ± 17	.744
Social functioning	*71 ± 29*	*79 ± 24*	*.030*	77 ± 24	.817
Role-emotional	*64 ± 47*	*77 ± 36*	*.033*	83 ± 24	.579
Mental health	71 ± 22	73 ± 18	.526	81 ± 15	.135
Physical component scale	*38 ± 12*	*42 ± 11*	*.014*	*42 ± 13*	.794
Mental component scale	51 ± 12	52 ± 10	.614	53 ± 9	.745
Urinary symptoms					
Frequency during the day	*47 ± 31*	*37 ± 31*	*.015*	42 ± 29	.601
Frequency during the night	*48 ± 27*	*39 ± 27*	*.017*	45 ± 34	.416
Urinary urgency	**46 ± 33**	**32 ± 32**	**.001**	47 ± 33	.078
Sleep deprivation because of urinary symptoms	21 ± 27	20 ± 30	.716	27 ± 36	.395
Need to remain close to toilet	**26 ± 32**	**10 ± 20**	**< .001**	18 ± 31	.392
Incontinence for urine	**30 ± 31**	**16 ± 23**	**< .001**	27 ± 25	.090
Dysuria	6 ± 16	6 ± 16	.810	12 ± 22	.344
Difficulty with voiding	16 ± 25	11 ± 22	.121	12 ± 31	.876
Limitation of daily activities because of urinary symptoms	**11 ± 21**	**4 ± 13**	**.006**	3 ± 10	.755
Bowel symptoms					
Limitation of daily activities because of bowel symptoms	**26 ± 34**	**15 ± 26**	**.006**	33 ± 36	.062
Fecal urgency	**44 ± 37**	**25 ± 33**	**< .001**	**64 ± 32**	**< .001**
Fecal leakage	**19 ± 30**	**8 ± 19**	**.002**	*28 ± 30*	*.021*
Diarrhea	**25 ± 33**	**10 ± 20**	**< .001**	21 ± 29	.165
Rectal blood loss	2 ± 11	1 ± 5	.416	3 ± 10	.441
Bloated feeling	18 ± 27	13 ± 23	.199	9 ± 16	.505
Flatulence	30 ± 29	26 ± 29	.240	45 ± 43	.129
Abdominal cramps	*20 ± 28*	*12 ± 21*	*.011*	15 ± 26	.512
Vaginal symptoms					
Vaginal irritation	9 ± 19	9 ± 19	.993	22 ± 30	.112
Vaginal discharge	5 ± 15	4 ± 13	.523	18 ± 31	.136
Vaginal blood loss	1 ± 5	1 ± 4	.816	6 ± 13	.167
Sexual functioning					
Sexual interest	14 ± 20	10 ± 18	.212	3 ± 11	.079
Sexual activity	11 ± 18	8 ± 17	.393	4 ± 11	.394
Sexual symptoms					
Sexual enjoyment	36 ± 28	31 ± 27	.532	17 ± 33	.255
Vaginal dryness	33 ± 38	26 ± 30	.384	8 ± 17	.229
Body image					
Decreased feeling of attractiveness	9 ± 22	5 ± 15	.093	6 ± 19	.888
Less feminine	6 ± 18	3 ± 11	.180	0 ± 0	.002
Dissatisfied with body	17 ± 27	11 ± 19	.094	15 ± 23	.481
Remaining single items					
Lymphoedema	22 ± 30	20 ± 26	.590	21 ± 31	.882
Pain lower back	33 ± 36	24 ± 30	.054	24 ± 34	.978
Hot flashes	16 ± 28	9 ± 22	.060	11 ± 22	.758

NOTE. *P* values < .01 are shown in bold; *P* values < .05 are shown in italics.
Abbreviations: SF-36, Short Form 36-Item; EORTC, European Organisation for Research and Treatment of Cancer; EBRT, external-beam radiotherapy; NAT, no additional treatment; SD, standard deviation.
*EBRT *v* NAT; there were no differences when excluding patients with a recurrence and/or with second cancer.
†Patients with a recurrence after NAT *v* patients without a recurrence after NAT.

incontinence materials. "Day and night usage" was reported by 42.9% of patients treated with EBRT in contrast to 15.2% of patients who had NAT, and "never use" was reported by 39.0% versus 60.0% (overall $P < .001$).

There were no significant differences in vaginal symptoms, body image, lymph edema, lower back pain, or menopausal symptoms between the groups. Among the patients that answered questions on their sexual functioning and symptoms, 24.3% reported being

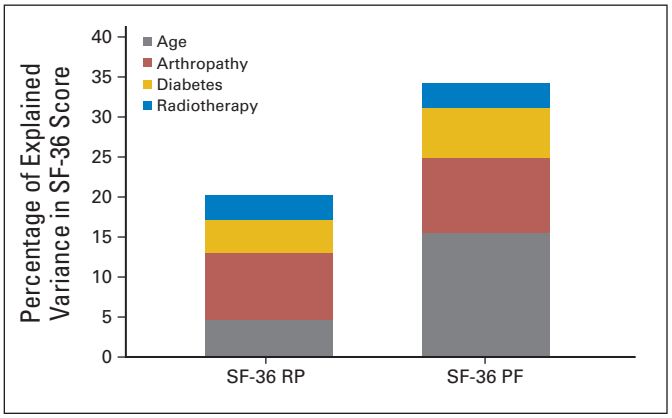

Fig 2. Percentage of explained variance in scores for all patients on Short Form 36-Item (SF-36) scales Role-Physical (RP) and Physical Functioning (PF). Blue represents the percentage of variance in the SF-36 score that is explained by the addition of radiotherapy, after correction for age and comorbidity (arthropathy and diabetes as significant explanatory variables).

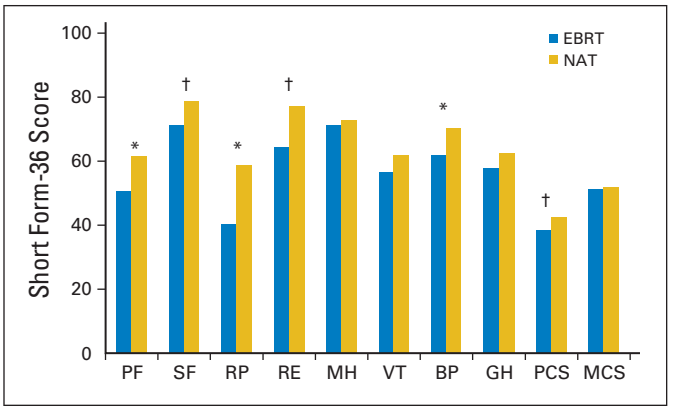

Fig 4. Scores of both treatment groups on Medical Outcomes Study Short Form 36-Item Health Survey. EBRT, external-beam radiotherapy; NAT, no additional treatment; PF, physical functioning; SF, social functioning; RP, role-physical; RE, role-emotional; MH, mental health; VT, vitality; BP, bodily pain; GH, general health; PCS, physical component scale; MCS, mental component scale. (*) *P* values ≤ .01. (†) *P* values ≤ .05.

sexually active, with no differences in functioning or symptoms between the EBRT and NAT groups.

HRQL After Having Survived a Locoregional Recurrence or a Second Cancer

Patients who had survived a locoregional recurrence in the NAT arm (n = 14) reported significantly more fecal urgency and fecal leakage, with a trend toward more urinary urgency and urinary incontinence on the EORTC items compared with the other patients who had NAT, although there were no significant differences between the patients who had a recurrence after NAT and the patients treated with EBRT (Table 1).

A sensitivity analysis was undertaken on the main HRQL analysis to estimate a possible effect of having survived a recurrence or a second cancer. In this analysis, HRQL outcomes were compared between both treatment arms after exclusion of patients with a recurrence and/or a second cancer. This analysis did not alter the previously described findings.

DISCUSSION

This analysis of the long-term outcomes of the PORTEC-1 trial confirms the highly significant reduction of locoregional recurrence obtained by pelvic EBRT but any survival benefit is absent. EBRT was found to be associated with a clinically relevant increase of patient-reported long-term bowel and bladder symptoms, most notably urinary urgency, incontinence, diarrhea, and fecal urgency and leakage compared with surgery alone. These symptoms resulted in more limitations of daily activities. The increased symptom rates are reflected by the frequent use of incontinence materials after EBRT. Moreover, patients treated with EBRT reported significant and clinically relevant

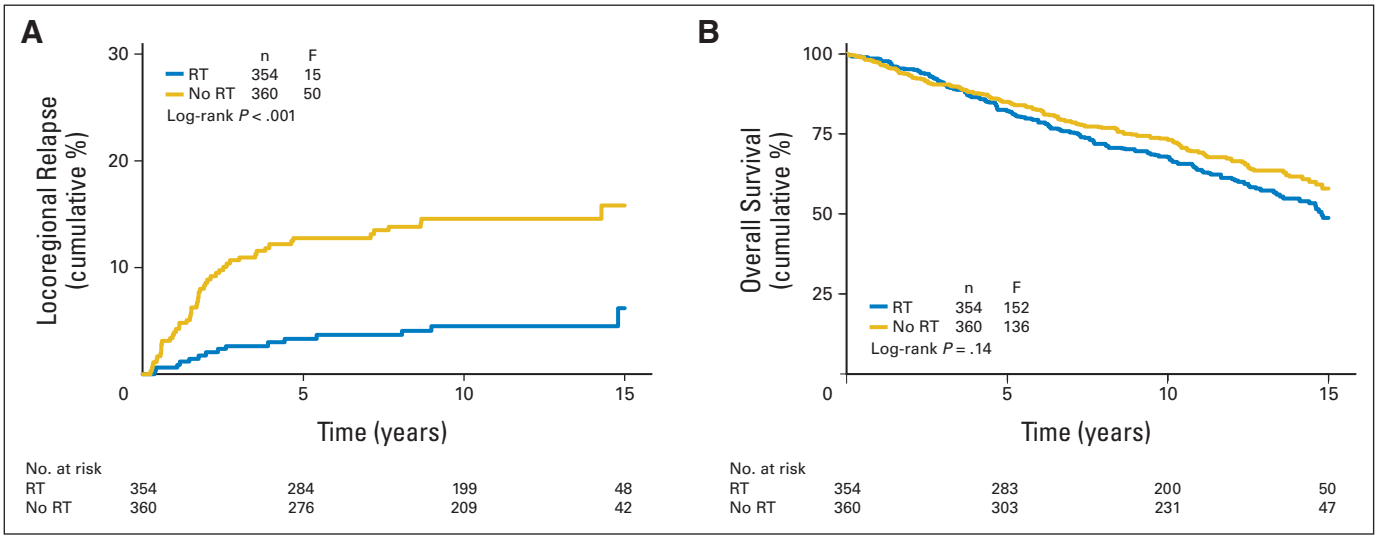

Fig 3. Probability of locoregional (vaginal and/or pelvic) relapse (A) and overall survival (B) for patients assigned to postoperative radiotherapy (RT) or no additional treatment (no RT). F, total number of events.

Table 2. Patient, Tumor, and Treatment Characteristics of HRQL Respondents*

Characteristic	EBRT No.	EBRT %	NAT No.	NAT %	*P*
Total	113	46	133	54	
Age, years					.64
Mean	75.5		76.0		
Range	56-94		59-93		
≤ 70	36	32	28	21	.02
71-80	38	34	68	51	
> 80	39	34	37	28	
Marital status					
Married	54	50	57	44	.54
Not married	12	11	14	11	
Divorced	6	6	5	4	
Widowed	35	33	54	41	
Partner and living together					
Yes, together	42	46	54	45	.68
Yes, living apart	0	0	1	1	
No	50	54	66	54	
Children					
Yes	81	76	91	72	.41
No	25	24	36	28	
Living with children					
Yes	7	8	8	8	.98
No	77	92	87	92	
Comorbidities					
Asthma	15	14	9	7	.08
Heart disease	10	9	7	6	.26
Hypertension	44	41	66	52	.10
Stroke	6	6	3	2	.20
Kidney disease	4	4	1	1	.12
Diabetes	26	24	23	18	.26
Malignancy	5	5	2	2	.17
Arthropathy	48	44	53	41	.64
Skin disease	3	3	9	7	.14
Liver disease	1	1	1	1	.90
Thyroid disease	8	7	6	5	.38
No comorbidity	17	16	14	11	.28
Medication for comorbidity					
Yes	79	76	97	81	.59
No	25	24	23	19	
Grade					
1	90	80	103	77	.13
2	14	12	10	8	
3	9	8	20	15	
Myometrial infiltration, %					
< 50	45	40	61	46	.34
> 50	68	60	72	54	
FIGO stage and grade					
IB 2	40	35	52	39	.53
IB 3	5	4	9	7	
IC 1	21	19	28	21	
IC 2	47	42	44	33	

Abbreviations: HRQL, health-related quality of life; EBRT, external-beam radiotherapy; NAT, no additional treatment; FIGO, International Federation of Gynecology and Obstetrics.

*Age and demographic characteristics at time of questionnaire; tumor characteristics at time of randomization (before central pathology review).

lower physical and role-physical functioning (the extent to which role-related activities are limited by physical functioning).

As expected, there were more patients in the NAT group who had survived a locoregional recurrence and had undergone salvage therapy.[24] These patients reported higher levels of fecal urgency and fecal leakage, with a trend toward more urinary urgency and urinary incontinence, similar to the patients in the EBRT group.

Randomized controlled trials on adjuvant RT for EC[4,6,25] have published acute toxicity rates after EBRT of approximately 60% (predominantly grade 1 to 2 GI symptoms), although late toxicity rates show a decline to approximately 20% grade 1 to 2 symptoms at 5 years and, overall, 3% grade 3 to 4 late complications. Patient-reported toxicity outcomes that provide insight into the impact of low-grade toxicity on HRQL are lacking in these trials, and follow-up of reported toxicity generally does not exceed 5 years.

The 2-year HRQL results of the PORTEC-2 trial showed that bowel symptoms (diarrhea, fecal leakage) were significantly increased in patients treated with EBRT, leading to a higher level of limitation of daily activities due to bowel problems, which resulted in a significant lower level of social functioning for these patients compared with patients who received brachytherapy.[7] These short-term results reflect the long-term HRQL findings of PORTEC-1, suggesting that although the negative impact of EBRT decreases in the first 6 months after treatment, there is a long-term component that persists during subsequent years. The few retrospective studies that evaluated long-term patient-reported symptoms after pelvic RT confirm the increased rate of prolonged bowel and bladder symptoms after RT.[26-28] The increase of urinary incontinence and fecal leakage after EBRT are suggestive for a decreased pelvic floor function, although the exact etiology remains unclear. In addition to the chronic effects of radiation to the GI epithelium, a recent study[29,30] in patients with prostate cancer found that besides dose volume, parameters regarding the anal sphincter, colonic dismotility resulting in a faster colonic transit, and reduced rectal compliance contribute to anorectal dysfunction.

Techniques for RT have improved over the last two decades, with the introduction of 3D-conformal RT as a standard, and the more recent introduction of intensity-modulated RT (IMRT), with significantly improved bowel sparing.[31] Approximately 52% of the patients in PORTEC-1 were treated with a four-field box technique and 18% with a three-field technique with some form of individualized shielding, although 30% were treated with parallel opposing fields. The use of multiple fields was associated with a lower rate of late complications compared with parallel opposing fields.[6] Standard use of IMRT might further decrease the rate of late radiation toxicity. However, even with sophisticated IMRT techniques, the target volume for gynecologic cancers remains relatively large, with significant exposure of bowel, rectum, bladder, and pelvic floor muscles to the full radiation dose. This necessitates research into etiology and preventive measures.[32,33]

One of the most illustrative results of this long-term HRQL analysis is the increased use of incontinence materials among patients treated with EBRT. The prevalence of incontinence among the general population of elderly women in the Netherlands is 30% to 40%, with higher rates among women with comorbid conditions such as diabetes.[34] In our study, urinary incontinence was reported by 38.2% of the patients in the NAT arm, much in line with the general population, in contrast to 57.8% of the patients treated with EBRT. After EBRT, significantly more women used incontinence materials during the day and at night (EBRT, 42.9% *v* NAT, 15.2%; $P < .001$).

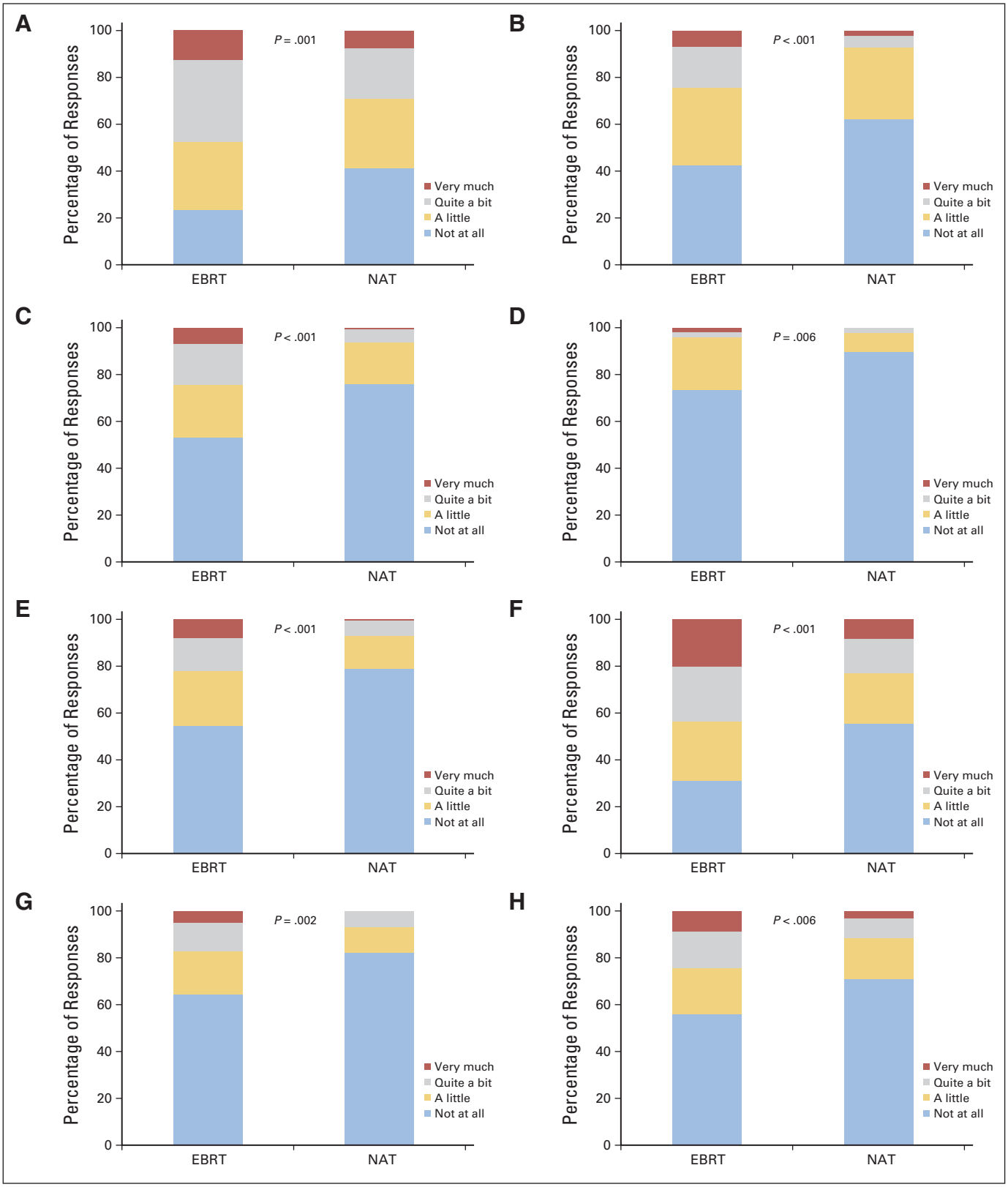

Fig 5. Patient responses to single-item symptom scores of (A) urinary urgency, (B) urinary incontinence, (C) need to remain close to the toilet because of urinary symptoms, (D) limitation in daily activities because of urinary symptoms, (E) diarrhea, (F) fecal urgency, (G) fecal leakage, and (H) limitation in daily activities because of bowel symptoms. EBRT, external-beam radiotherapy; NAT, no additional treatment.

Sexual functioning has long been identified as an important part of quality of life after cancer treatment.[35] In this group of elderly women (median age, 76 years), 24.3% reported to be sexually active-,which is in accordance with population data.[36] There were no differences between treatment groups with regard to sexual functioning or symptoms.

The abandonment of EBRT for the 55% of patients who had EC and LIR features has been confirmed to be a correct decision. Adverse effects of EBRT have a long-term negative impact on HRQL, and EBRT therefore cannot be justified in the absence of survival benefit and in the presence of effective salvage RT for the few LIR patients who develop locoregional recurrence.

For patients with HIR features, the indication for RT was maintained. For these patients, the subsequent PORTEC-2 trial has shown that VBT was highly effective, with fewer adverse effects and better HRQL.[8] As a result of the PORTEC-2 trial, HIR patients are currently treated with VBT, thus sparing a further 30% of patients with EC the risks and morbidity of EBRT.

According to the PORTEC-1 and PORTEC-2 data, EBRT has remained indicated as adjuvant therapy only for the 15% of patients with EC who have high-risk features. Several randomized trials (PORTEC-3, Gynecologic Oncology Group 29 [GOG-249], GOG-258) are currently investigating the role of chemotherapy for patients with high-risk EC.

In conclusion, pelvic EBRT for EC is associated with long-term urinary and bowel symptoms, leading to lower physical and role-physical functioning, even 15 years after treatment. Combined with the 15-year outcome results of the PORTEC-1 trial, it is clear that EBRT should be avoided in patients with low- and intermediate-risk EC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Appendix

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