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CLINICAL INVESTIGATION

Endometrium

IMPACT OF EXTERNAL BEAM ADJUVANT RADIOTHERAPY ON HEALTH-RELATED QUALITY OF LIFE FOR LONG-TERM SURVIVORS OF ENDOMETRIAL ADENOCARCINOMA: A POPULATION-BASED STUDY

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Purpose: To compare the health-related quality of life (HRQOL) among 5–10-year survivors of Stage I-II endometrial (adeno-)carcinoma (EC) treated with surgery alone or surgery with external beam adjuvant radiotherapy (EBRT) and an age-matched norm population.

Methods and Materials: A population-based, cross-sectional survey was conducted by the Eindhoven Cancer Registry. All patients were included who had been diagnosed with EC between 1994 and 1998 ($n = 462$). Information from the questionnaires returned was linked to data from the Eindhoven Cancer Registry on patient, tumor, and treatment characteristics.

Results: Responses were received from 75% of the patients. The analyses were restricted to women with Stage I-II disease at diagnosis, treated with either surgery alone or surgery with adjuvant EBRT, and without recurrent disease or new primary malignancies ($n = 264$). The patients who had received adjuvant EBRT ($n = 80$) had had a significantly higher tumor stage and grade at diagnosis ($p < 0.0001$) and a longer mean time since diagnosis ($p = 0.04$). Age, number of comorbid diseases, current marital status, nulliparity, education, and occupation were similar for both treatment groups. On multivariate analyses, adjuvant EBRT was independently and negatively associated with the vitality and physical and social well-being scale scores. The HRQOL scores of both treatment groups, however, were similar to those of an age-matched norm population.

Conclusion: In general, the HRQOL of EC survivors is good. EC survivors treated with surgery alone had a better HRQOL than women treated with surgery and adjuvant EBRT, although for both groups, the HRQOL was in the range of the norm population. © 2007 Elsevier Inc.

Endometrial cancer, Long-term survivors, Quality of life, Radiotherapy.

INTRODUCTION

Endometrial cancer (EC) is the most common malignancy of the female genital tract. The American Cancer Society estimated that 40,880 women were diagnosed with, and 7,310 women died of, EC in 2005 (1). Endometrial cancer most often occurs in postmenopausal women, with a peak incidence at 55–70 years of age (2) (median, ~66). About 95% are adenocarcinomas. The survival rates of EC have improved during the past decades, with an overall 5-year relative survival rate for 1995–2001 from nine Surveillance, Epidemiology, and End Results geographic areas of 84.4% (1). The 5-year

relative survival in the Eindhoven Cancer Registry (ECR) area was 85% for 1996–2001 (3). An aging population with more cases of EC, public awareness resulting in an earlier diagnosis, and improved treatment have all resulted in increasing numbers of EC survivors. Using data from The Netherlands Cancer Registry, the Dutch Cancer Society estimated that in 2005 about 1,700 women were diagnosed with EC in The Netherlands, with an estimated prevalence of >17,000, which is expected to increase to 25,000 by 2015 (3). In the United States, on January 1, 2002, 571,854 women were alive with a history of EC (1).

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Because most cancer cases are diagnosed at an early stage (75–80% are Stage I) (2), many patients are treated primarily with surgery. Three randomized trials have established that adjuvant pelvic radiotherapy (RT) provides a highly significant improvement in local control, but without a survival advantage for intermediate-risk EC (4–7). Therefore, in The Netherlands, pelvic RT is now considered to be indicated for “high-intermediate risk” Stage I EC. High-intermediate Stage I EC is defined as Stage I EC in the presence of at least two of the following three risk factors: (1) grade 3, (2) age ≥ 60 years, and (3) deep ($>50\%$) myometrial invasion. However, it is unknown whether RT is indicated for these subgroups, because the treatment-related morbidity has been 25% of the irradiated patients; also, the effect of this morbidity on patient quality of life (QOL) is not known (8).

Health-related quality of life (HRQOL) has never been evaluated in relation to adjuvant RT for intermediate-risk EC. Only a few small studies have investigated HRQOL among EC survivors (9–13), but they had low ($<40\%$) response rates (10, 11) or did not associate different EC treatments with outcome (9, 11–13). The aim of the present study was to obtain insight into the long-term effects of EC and its treatment on HRQOL. Therefore, we assessed HRQOL in a population-based study of 5–10-year survivors of Stage I or II EC treated with surgery alone or surgery with adjuvant external beam RT (EBRT). Furthermore, a comparison of HRQOL was made between EC survivors and an age-matched norm population (14). The results of this study are expected to provide the growing group of (long-term) EC survivors and specialists with additional information to help make an informed decision about adjuvant EBRT and/or to anticipate possible late consequences of EC and its treatment.

METHODS AND MATERIALS

Setting and participants

A population-based, cross-sectional survey was conducted by the ECR. The ECR records data on all patients newly diagnosed with cancer in the southern part of The Netherlands, an area with 2.3 million inhabitants, 17 hospital locations, and two large RT institutes. In November 2004, we selected all patients diagnosed with EC between 1994 and 1998 ($n = 642$). To exclude all those who had died before November 1, 2004, our database was linked with the database of the Central Bureau for Genealogy, which collects data on all deceased Dutch citizens through the civil municipal registries. Of the 642 patients, 180 had died, 65% of whom had initially been diagnosed with Stage I or II EC. Of all deceased women, 63 had undergone surgery alone at diagnosis, 77 had undergone surgery and EBRT, 27 were treated with a combination of surgery and systemic treatment, and 13 had received other, or no, treatment. After exclusion of all deceased patients, data collection was started in November 2004. Participants >75 years at diagnosis were excluded from the survey 5–10 years later, because it was expected that they would have difficulty in completing a self-report questionnaire without assistance owing to their age. The Medical Ethics Committee of Máxima Medical Centre in Veldhoven, The Netherlands, approved this study.

Data collection

Gynecologists sent their (former) patients a questionnaire, together with a letter to inform them about the study. By replying,

the patients explicitly agreed to participate and consented to linkage of the outcome of the questionnaire with their disease history as registered in the ECR. If the questionnaire was not returned within 2 months, a reminder letter was sent. Returned questionnaires only contained a study number to guarantee anonymity.

Measures

The ECR routinely collects data on tumor characteristics such as the date of diagnosis, subsite, histologic type, stage (TNM clinical classification), and primary treatment and patient characteristics, including gender, date of birth, and (since 1993) comorbidities at diagnosis (a slightly adapted version of the Charlson comorbidity index) (15).

External beam RT was administered to the pelvic region. The total dose consisted of 46 Gy, using 2-Gy daily fractions, 5 d/wk. The radiation was delivered by anteroposterior and posteroanterior parallel ports or a four-field box technique (anteroposterior, posteroanterior, and two lateral fields). Vaginal brachytherapy consisted of seven applications of 5 Gy specified at 5 mm of the surface of the application.

The Dutch version of the Medical Outcomes Study Short Form 36-item Health Survey (SF-36) questionnaire was used to measure generic QOL (16). As prescribed, the scores were standardized on a scale from 0 to 100, with higher scores indicating better functioning. To compare the generic QOL in long-term EC survivors with a norm population, we used age matched SF-36 scores available from the general Dutch female population (14).

Generic QOL survivorship issues were assessed with the Dutch version of the Quality of Life-Cancer Survivors (QOL-CS) instrument (17). The QOL-CS is a 45-item visual analogue scale, based on a scale of 0 (worst outcome) to 10 (best outcome). The questionnaire contains four multi-item subscales: physical, psychological, social, and spiritual well-being. It examines issues of particular concern to long-term cancer survivors, such as fear of a second tumor, recurrence or metastasis, survivorship guilt, and the role of spirituality and religion (18). The QOL-CS proved to be psychometrically valid and reliable in American populations (17, 19, 20), as well as in a Dutch population of prostate cancer survivors in the ECR region, except for the subscale spiritual well-being, which showed low reliability and validity in the latter cohort (21). Cronbach's alpha in the current group of endometrial cancer survivors was 0.84 for the physical, 0.85 for the psychological, 0.69 for the social, and 0.38 for the spiritual subscale, respectively. For the total score, it was 0.89.

Four additional items on sexual activity in the past 4 weeks were added using a scale of 1–4.

Statistical analysis

All statistical analyses were performed using Statistical Analysis Systems, version 9.1, for Windows (SAS Institute, Cary NC). Routinely collected data from the ECR on patient and tumor characteristics enabled us to compare nonrespondents with respondents, using chi-square statistics or Fisher's exact test for categorical variables and *t* test for continuous variables. These tests were also used to compare women who underwent surgery alone with those who also received adjuvant EBRT. For a comparison of outcomes between the treatment groups and the norm population, analysis of covariance was used to adjust for the effects of age, tumor stage, and tumor grade. Multivariate linear regression analyses were done to investigate the independent association between patient characteristics (age, comorbidity, marital status, education, and occupation) and tumor characteristics (stage, grade, treatment, time since diagnosis) with the composite and subscale scores of the SF-36 and QOL-CS.

RESULTS

Patient characteristics

On November 1, 2004, 462 of 642 endometrial adenocarcinoma patients diagnosed between 1994 and 1998 were alive (Fig. 1). Of the 462 women, 57 were excluded because their addresses could not be verified, leaving 405 women who received a questionnaire. The patient and tumor characteristics of the 57 women whose addresses could not be verified did not differ from those of the 405 who received a questionnaire (data not shown). Responses were received from 305 patients (75%). The nonrespondents were somewhat older, but no significant differences were found with the respondents in the years since diagnosis, stage at diagnosis, or primary treatment (Table 1). Additional analyses were then restricted to women with Stage I or II disease at diagnosis, who had undergone either surgery alone or surgery and EBRT, without recurrent disease or new primary malignancies ($n = 264$), thereby excluding 41 patients from the final analyses. Of these 41 patients, 21 had initially been diagnosed with Stage III/IV/unknown and 20 had initially been diagnosed with Stage I-II but had recurrent disease or

a new primary malignancy. Of these 20 women, 2 had local recurrence (both had initially undergone surgery alone), 2 had distant metastases (one had initially undergone surgery alone, and 1 had undergone surgery and EBRT), and 16 had been diagnosed with a new primary tumor (14 had initially undergone surgery alone and 2 surgery and EBRT).

Twenty-two irradiated patients received a combination of vaginal brachytherapy and EBRT; the other 58 women received only EBRT. The women who received both brachytherapy and EBRT more often had Stage II EC. However, because the RT subgroups did not differ from each other in all other characteristics or HRQOL outcomes (data not shown), the results are presented for the two RT groups combined. Women who underwent surgery and adjuvant EBRT appeared to be somewhat older compared with those receiving surgery alone, although this was not statistically significant (Table 2). Irradiated patients had a significantly higher tumor stage and grade at diagnosis ($p < 0.0001$), even though they had a longer mean time since diagnosis ($p = 0.04$). Current age, number of comorbid diseases, current marital status, nulliparity, education, and current occupation were similar for the two treatment groups.

Fig. 1. Study population.

Table 1. Demographic and clinical characteristics of respondents and nonrespondents

Characteristic	Respondents (n = 305)	Nonrespondents (n = 100)	p
Age at survey (y)			
Mean $\pm$ SD	67.9 $\pm$ 8	71.2 $\pm$ 8	<0.001
Range	43–85	52–85	
<64	113 (37)	22 (22)	0.001
65–69	76 (25)	17 (17)	
70–74	48 (16)	26 (26)	
$\geq$ 75	68 (22)	35 (35)	
Interval since diagnosis (y)			
Mean $\pm$ SD	8.0 $\pm$ 1	7.9 $\pm$ 1	0.43
5–6 y	91 (30)	32 (32)	0.82
7–8 y	142 (47)	43 (43)	
9–10 y	72 (24)	25 (25)	
Stage at diagnosis			
I	268 (88)	89 (89)	0.47
II	23 (7)	4 (4)	
III	8 (3)	5 (5)	
IV	1 (0)	1 (1)	
Unknown	5 (2)	1 (1)	
Primary treatment			
Surgery alone	205 (67)	68 (68)	0.93
Surgery and adjuvant EBRT*	91 (30)	28 (28)	
Systemic with/without surgery	6 (2)	3 (3)	
Other/none	3 (1)	1 (1)	

Abbreviations: SD = standard deviation; EBRT = external beam radiotherapy.

Data presented as numbers, with percentages in parentheses, unless otherwise noted.

* With or without vaginal brachytherapy.

Health-related QOL

Compared with the women who underwent surgery alone, the women who also underwent RT reported lower scores on all subscales of the SF-36 and QOL-CS. The analysis of covariance revealed a significant effect of treatment on the subscales of vitality, social functioning, and mental health, after adjustment for differences in age at the survey, years since diagnosis, tumor stage, and tumor grade (Table 3). The physical and social well-being scores, as measured by the QOL-CS, were also significantly less for those who received EBRT, as was the total QOL-CS score. No differences in sexual activity were found, but vaginal dryness was reported more often by the 25 sexually active women who had undergone EBRT ($p = \text{NS}$).

In a direct comparison between the treatment groups and an age-matched SF-36 norm population, both groups of cancer survivors scored significantly better on the subscale of bodily pain (*i.e.*, less pain; Fig. 2). Women treated with surgery alone had similar or even better scores on all subscales, and the irradiated women almost always had nonstatistically significant lower scores compared with the norm population.

Multivariate linear regression analyses with SF-36 (Table 4) and QOL-CS (Table 5) subscales as outcome variables showed the independent association of tumor and patient

Table 2. Sociodemographic and clinical characteristics of EC survivors with stage I or II disease

Characteristic	Surgery alone (n = 184)	Surgery and EBRT*	p
Age at survey (y)			
Mean $\pm$ SD	67.8 $\pm$ 7	69.4 $\pm$ 8	0.10
Range	54–85	44–82	
<64	71 (38)	19 (24)	0.07
65–69	49 (27)	21 (26)	
70–74	27 (15)	19 (24)	
$\geq$ 75	37 (20)	21 (26)	
Interval since diagnosis (y)			
Mean $\pm$ SD	7.7 $\pm$ 1	8.1 $\pm$ 1	0.04
5–6 y	61 (33)	17 (21)	0.14
7–8 y	84 (46)	41 (51)	
9–10 y	39 (21)	22 (28)	
Stage at diagnosis			<0.0001
IA	49 (27)	4 (6)	
IB	96 (52)	25 (31)	
IC	30 (16)	40 (50)	
IIA	7 (4)	8 (10)	
IIB	2 (1)	3 (4)	
Grade			<0.0001
1	91 (49)	18 (23)	
2	67 (36)	46 (58)	
3	16 (9)	16 (20)	
Unknown	10 (5)	—	
Lymphadenectomy	12 (7)	1 (1)	0.05
Comorbidity at survey			0.95
None	49 (27)	20 (25)	
1	66 (36)	30 (38)	
$\geq$ 2	69 (38)	30 (38)	
Most frequent comorbid conditions			
Arthritis	70 (38)	31 (39)	0.91
Hypertension	69 (38)	32 (40)	0.70
Diabetes	29 (16)	12 (15)	0.88
Marital status			0.72
Married	108 (59)	53 (66)	
Not married/divorced	18 (10)	8 (10)	
Widowed	50 (27)	16 (20)	
Unknown	8 (4)	3 (4)	
Nulliparous	32 (17)	15 (19)	0.90
Educational level			0.60
Low	103 (56)	50 (63)	
Medium	53 (29)	21 (26)	
High	20 (11)	5 (6)	
Unknown	8 (4)	4 (5)	
Current occupation			0.33
Employed	22 (12)	6 (8)	
Unemployed	91 (49)	35 (44)	
Retired	63 (34)	36 (45)	
Unknown	8 (4)	3 (4)	

Abbreviations: EC = endometrial (adeno-)carcinoma; other abbreviations as in Table 1.

Data presented as numbers, with percentages in parentheses, unless otherwise noted.

* With or without vaginal brachytherapy.

characteristics. Older women exhibited lower scores for physical functioning, role limitations due to physical health, and the physical component scale as measured by the SF-36, but their psychological and social well-being and total QOL

Table 3. Analysis of covariance of outcome variables for patients who underwent surgery alone or surgery and adjuvant EBRT

Variable	Surgery alone (<i>n</i> = 184)	Surgery and EBRT* (<i>n</i> = 80)	<i>p</i> (For treatment effect [†])
SF-36 [‡]			
PF	68.3 (27.6)	65.2 (27.3)	0.22
RP	65.7 (40.8)	58.7 (44.0)	0.22
BP	74.5 (24.0)	72.7 (25.2)	0.26
GH	63.2 (19.8)	58.2 (20.6)	0.12
VT	65.7 (18.6)	59.1 (19.0)	0.01
SF	82.2 (20.0)	76.1 (23.2)	0.04
RE	74.3 (40.1)	66.2 (44.4)	0.21
MH	75.7 (17.3)	70.1 (18.0)	0.02
PCS	45.1 (11.2)	45.5 (10.6)	0.40
MCS	51.9 (10.3)	49.9 (9.5)	0.08
QOL-CS [‡]			
Physical well-being	7.8 (1.7)	7.5 (2.1)	0.04
Psychological well-being	6.6 (1.5)	6.4 (1.5)	0.08
Social well-being	7.6 (1.8)	7.2 (1.5)	0.03
Spiritual well-being	4.8 (1.4)	4.7 (1.3)	0.62
Total score	6.8 (1.2)	6.5 (1.2)	0.02
Sexual functioning in past 4 wks	<i>n</i> = 133	<i>n</i> = 51	
Interested in sex	1.6 (0.7)	1.6 (0.7)	0.90
Sexually active	1.6 (0.6)	1.5 (0.6)	0.78
If sexually active:	<i>n</i> = 70	<i>n</i> = 25	
Enjoyable sex	2.0 (0.8)	2.1 (0.9)	0.45
Dry vagina during sexual activity	2.2 (1.2)	2.6 (1.1)	0.17

Abbreviations: SF-36 = short form-36; PF = physical functioning; RP = role limitations due to physical health; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role limitations due to emotional problems; MH = mental health; PCS = physical component scale; MCS = mental component scale; QOL-CS = Quality of Life in Cancer Survivors; other abbreviations as in Table 1.

Data presented as mean, with SD in parentheses.

* With or without vaginal brachytherapy.

[†] Adjusted for age at survey and tumor stage and grade at diagnosis.

[‡] Higher score correlates with better quality of life.

scores, as measured by the QOL-CS, were better. Tumor stage was positively associated with physical functioning (SF-36), and tumor grade was positively associated with social well-being and the total QOL, both measured by the QOL-CS. Women who had undergone EBRT scored significantly lower on the SF-36 vitality subscale, the QOL-CS subscales of physical well-being and social well-being, and the total QOL-CS. Comorbidity at the time of the survey appeared to be the only variable that was negatively and independently associated with all subscales of the SF-36 and QOL-CS.

Women with a higher education reported better physical functioning (SF-36) and better social well-being (QOL-CS).

DISCUSSION

The results of this study have shown that 5–10 years after diagnosis, EC survivors who underwent surgery alone had a better HRQOL than women treated with surgery and adjuvant EBRT. EBRT appeared to be independently and negatively associated with vitality (SF-36) and physical and social well-being (QOL-CS) among long-term EC survivors.

The HRQOL scores for both treatment groups were in the range of those of an age-matched norm population.

Although adjuvant RT in EC is associated with tissue damage that can result in treatment-related morbidity (22, 23) and is assumed to lead to a diminished HRQOL (24), only a few studies have investigated long-term HRQOL in EC survivors and its association with treatment. A Swedish study comparing HRQOL of 61 EC survivors with that of healthy controls showed a poorer HRQOL among EC survivors but did not have information about tumor or treatment characteristics (9). In contrast, a retrospective analysis of 70 EC Stage I survivors ≥5 years after diagnosis demonstrated that adjuvant RT significantly worsened the HRQOL of patients undergoing surgery (10). A study of 20 irradiated EC survivors, 3–4 years after diagnosis revealed that survivors scored lower than the general population on role functioning and higher on diarrhea (12). HRQOL was also significantly lower for 49 irradiated EC survivors, 2 years after diagnosis, compared with healthy controls (13). In contrast, a study of 73 EC survivors 5–20 years after diagnosis found HRQOL scores that approximated those of healthy controls and no association with treatment modality (11). All studies were conducted in

SF-36= Short Form-36, PF= Physical Functioning, RP= Role limitations Physical health, BP= Bodily Pain, GH= General Health, VT= Vitality, SF= Social Functioning, RE= Role limitations Emotional problems, MH= Mental Health, PCS= Physical Component Scale, MCS= Mental Component Scale, EBRT= External Beam Radiotherapy with or without vaginal brachytherapy.

* $p < 0.05$: Statistically significant difference between both treatment groups

$p < 0.05$: Statistically significant difference between age weighed norm-data and both treatment groups

Fig. 2. Medical Outcomes Study Short Form 36-item Health Survey (SF-36) subscale scores for endometrial cancer survivors, Stage I or II, who underwent surgery alone or surgery and adjuvant external beam radiotherapy vs. age-matched norm population of Dutch women.

small samples of EC populations. The response rate was (sometimes) very low (10, 11). The outcomes often were not associated with the different treatment modalities (9, 11–13) and were analyzed in combination with other gynecologic cancers (11). Therefore, it is difficult to compare these results with ours or to draw firm conclusions. The diminished

HRQOL across many subscales of both SF-36 and QOL-CS measures for irradiated women is, however, consistent with the results from a study of irradiated long-term cervical cancer survivors (25). Fatigue, as measured by the vitality subscale of the SF-36 and the physical well-being subscale of the QOL-CS, was consistently reported more often by the

Table 4. Multivariate linear regression model evaluating independent variables for SF-36 subscale scores for all patients ($n = 264$)

Independent variable	SF-36 subscales (standardized β coefficients)									
	PF	RP	BP	GH	VT	SF	RE	MH	PCS	MCS
Age	−0.38*	−0.21 [†]	NS	NS	NS	NS	NS	NS	−0.29*	NS
Time since diagnosis	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Tumor stage	0.12 [†]	NS	NS	NS	NS	NS	NS	NS	NS	NS
Tumor grade	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
EBRT [‡]	NS	NS	NS	NS	−0.15 [†]	NS	NS	NS	NS	NS
Comorbidity	−0.28*	−0.29*	−0.36*	−0.27*	−0.25*	−0.15 [†]	−0.16 [†]	−0.14 [†]	−0.38*	NS
Marital status	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Education	0.17 [†]	NS	NS	NS	NS	NS	NS	NS	NS	NS
Occupation	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

Abbreviations: NS = nonsignificant; other abbreviations as in Tables 1 and 3.

* $p < 0.001$.

[†] $p < 0.05$.

[‡] With or without vaginal brachytherapy.

Table 5. Multivariate linear regression model evaluating independent variables for QOL-CS subscale scores for all patients ($n = 264$)

Independent variable	QOL-CS subscales (standardized β coefficients)				
	Physical well-being	Psychological well-being	Social well-being	Spiritual well-being	Total score
Age	NS	0.19*	0.25*	NS	0.20*
Time since diagnosis	NS	NS	NS	NS	NS
Tumor stage	NS	NS	NS	NS	NS
Tumor grade	NS	NS	0.19*	NS	0.18*
EBRT [†]	−0.18*	NS	−0.17*	NS	−0.18*
Comorbidity	−0.29 [‡]	−0.30 [‡]	−0.17*	−0.22*	−0.34 [‡]
Marital status	NS	NS	NS	NS	NS
Education	NS	NS	0.15*	NS	NS
Occupation	NS	NS	NS	NS	NS

Abbreviations: NS = nonsignificant; other abbreviations as in Tables 1 and 3.

* $p < 0.05$.

[†] With or without vaginal brachytherapy.

[‡] $p < 0.001$.

irradiated EC survivors. RT-induced fatigue is a common early and chronic side effect of RT, reported in $\leq 30\%$ of patients at follow-up visits (24). In contrast to studies of cervical cancer survivors (25, 26), sexual dysfunction was not associated with EBRT in our population of EC survivors, although only 70% completed the questions on these issues and only 36% completed additional questions about sexual pleasure and a dry vagina. Because the mean age of the EC survivors is older than that of cervical cancer survivors, and the women who did not respond to these questions were significantly older than those who did, it is possible that sexuality did not play an important role in the lives of these older women.

Patients in this study were treated 5–10 years ago, when no national treatment guidelines were available with respect to the indication for adjuvant EBRT. After the Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC) trial (6), the indication for RT was restricted to “high-intermediate” risk patients (EC Stage I in the presence of at least two of the following three risk factors: grade 3, age ≥ 60 , and deep [$>50\%$] myometrial invasion), resulting in a reduction in the referral for RT for EC patients in South-Eastern Netherlands (27).

Three randomized clinical trials have shown that adjuvant RT improves locoregional control but does not translate into an overall survival benefit (4–7), meaning that most patients with locoregional relapse after surgery alone can be salvaged with repeat therapy. Furthermore, the 5-year actuarial rate of treatment-related morbidity was 26% for patients who received adjuvant RT and 4% for those who received surgery alone (22). In the high-risk group of patients with Stage IC and grade 3 tumors, adjuvant RT improved local control but did not decrease the frequency of metastatic disease (28). A recent retrospective analysis in the United States, however, revealed a significant association between improved overall and relative survival and adjuvant RT for Stage IC disease (29).

Although optimization of survival and local control of cancer is the first priority, HRQOL after treatment is increasingly being recognized as an important aspect of patient care. When different treatment options result in similar survival, or the survival benefit is unclear, then the HRQOL becomes

even more important. The results of our large population-based analyses, therefore, add information to the ongoing discussion about whether to prescribe adjuvant EBRT, and for whom. The current randomized PORTEC-2 trial was designed to compare the efficacy, morbidity, and QOL among patients treated with either EBRT or brachytherapy alone to evaluate whether vaginal brachytherapy provides equal local control, less morbidity, and better QOL for patients with high-intermediate risk EC.

The present study had a few limitations. Although the response rate was high, we could not determine the current health status of the nonrespondents or the women whose addresses could not be verified. The characteristics of the women whose addresses could not be verified were similar to those of the others. Also, the nonrespondents appeared to be fairly similar to the respondents with regard to tumor or treatment characteristics; however, they were somewhat older. Although all analyses were adjusted for the effect of age, it is possible that our results cannot be generalized to very old women with EC. Furthermore, we did not have information about physical activity or the prevalence of obesity in the two treatment groups, although it has been shown that exercise and body weight are important correlates of QOL for EC survivors (30). However, as comorbidities, in particular, diabetes, was equally prevalent in both treatment groups, we did not expect to find large differences in body weight or exercise. In addition, differences between patient groups (disease characteristics, but also HRQOL) at diagnosis might have influenced the outcomes. However, because all analyses were restricted to disease-free survivors and adjusted for differences in tumor stage and grade, it seemed unlikely that the outcomes could be explained fully by the characteristics at diagnosis.

Future studies comparing HRQOL between treatment groups should also include disease- or treatment-specific questionnaires. We received several comments from irradiated women about the specific radiation-induced morbidity they experienced. The response shift, when persons change their internal standards or when they redefine their concept of HRQOL (31), is another explanation for not finding an association between treatment and generic HRQOL. For

example, that EC survivors experienced less bodily pain than the general Dutch population of the same age could possibly be explained by the response shift phenomenon. However, we have not investigated this phenomenon in our study population.

The results of the present study contribute to the limited information available about HRQOL associated with different treatment modalities in the growing group of long-term survivors of EC. It has been suggested that a trade-off has to be made between the risk of locoregional recurrence and

the survival rate after salvage treatment, on the one hand, and the morbidity and cost of adjuvant RT, on the other (6). We believe that HRQOL should also be included in this trade-off analysis. The challenge, therefore, remains to select high-risk patients who would benefit the most from adjuvant therapy, taking into account disease-free and overall survival, but also HRQOL. The results from the randomized PORTEC-2 trial will show whether EBRT can be replaced by brachytherapy to optimize local control with less morbidity and better QOL for patients with high-intermediate risk EC.

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