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CLINICAL INVESTIGATION

Endometrium

FIFTEEN-YEAR RADIOTHERAPY OUTCOMES OF THE RANDOMIZED PORTEC-1 TRIAL FOR ENDOMETRIAL CARCINOMA

CARIEN L. CREUTZBERG, M.D., PH.D.,* REMI A. NOUT, M.D.,* MARNIX L. M. LYBEERT, M.D.,[†]
 CARLA C. WÁRLÁM-RODENHUIS, M.D.,[‡] JAN J. JOBSEN, M.D., PH.D.,[§] JAN-WILLEM M. MENS, M.D.,[¶]
 LUDY C. H. W. LUTGENS, M.D., PH.D.,** ELISABETH PRAS, M.D., PH.D.,^{††}
 LONNEKE V. VAN DE POLL-FRANSE, PH.D.,^{‡‡} AND WIM L. J. VAN PUTTEN, M.Sc.^{||}
 FOR THE PORTEC STUDY GROUP

*Department of Clinical Oncology, Leiden University Medical Center; [†]Department of Radiotherapy, Catharina Hospital Eindhoven; [‡]Department of Radiation Oncology, University Medical Center Utrecht; [§]Department of Radiotherapy, Medisch Spectrum Twente, Enschede; [¶]Departments of Radiation Oncology and ^{||}Biostatistics, ErasmusMC-Daniel den Hoed Cancer Center, Rotterdam; **MAASTRO clinic, Maastricht; ^{††}Department of Radiotherapy, University Medical Center Groningen; and ^{‡‡}Comprehensive Cancer Centre South, Eindhoven and Center of Research on Psychology in Somatic Diseases, Tilburg University, The Netherlands

Purpose: To evaluate the very long-term results of the randomized Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC)-1 trial for patients with Stage I endometrial carcinoma (EC), focusing on the role of prognostic factors for treatment selection and the long-term risk of second cancers.

Patients and Methods: The PORTEC trial (1990–1997) included 714 patients with Stage IC Grade 1–2 or Stage IB Grade 2–3 EC. After surgery, patients were randomly allocated to external-beam pelvic radiotherapy (EBRT) or no additional treatment (NAT). Analysis was by intention to treat.

Results: 426 patients were alive at the date of analysis. The median follow-up time was 13.3 years. The 15-year actuarial locoregional recurrence (LRR) rates were 6% for EBRT vs. 15.5% for NAT ($p < 0.0001$). The 15-year overall survival was 52% vs. 60% ($p = 0.14$), and the failure-free survival was 50% vs. 54% ($p = 0.94$). For patients with high-intermediate risk criteria, the 15-year overall survival was 41% vs. 48% ($p = 0.51$), and the 15-year EC-related death was 14% vs. 13%. Most LRR in the NAT group were vaginal recurrences (11.0% of 15.5%). The 15-year rates of distant metastases were 9% vs. 7% ($p = 0.25$). Second primary cancers had been diagnosed over 15 years in 19% of all patients, 22% vs. 16% for EBRT vs. NAT ($p = 0.10$), with observed vs. expected ratios of 1.6 (EBRT) and 1.2 (NAT) compared with a matched population ($p = \text{NS}$). Multivariate analysis confirmed the prognostic significance of Grade 3 for LRR (hazard ratio [HR] 3.4, $p = 0.0003$) and for EC death (HR 7.3, $p < 0.0001$), of age >60 (HR 3.9, $p = 0.002$ for LRR and 2.7, $p = 0.01$ for EC death) and myometrial invasion $>50\%$ (HR 1.9, $p = 0.03$ and HR 1.9, $p = 0.02$).

Conclusions: The 15-year outcomes of PORTEC-1 confirm the relevance of HIR criteria for treatment selection, and a trend for long-term risk of second cancers. EBRT should be avoided in patients with low- and intermediate-risk EC.

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Endometrial carcinoma, Long-term outcome, Randomized trial, Radiation therapy, Prognostic factors.

INTRODUCTION

The Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC)-1 trial was one of four randomized trials that have established the role of radiotherapy (RT) in intermediate-risk endometrial carcinoma (EC), showing that

pelvic external-beam RT (EBRT) provides a highly significant improvement in local control, but without a survival advantage (1–4). The majority (75%) of the locoregional (vaginal and/or pelvic) recurrences were located in the vagina, and treatment for vaginal recurrence was effective, with a 5-year survival

Reprint requests to: Carien L. Creutzberg, M.D., Ph.D., Department of Clinical Oncology, postzone K1-P, Leiden University Medical Center, Albinusdreef 2, P.O. Box 9600, 2300 RC Leiden, The Netherlands. Tel: (+31) 71-526-5120; Fax: (+31) 71-526-6760; E-mail: c.l.creutzberg@lumc.nl

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Conflict of interest: none.

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of 70%, whereas the outcomes after pelvic and distant relapse were poor (5). EBRT was associated with a 26% risk of side effects, mainly Grade 1–2 gastrointestinal (GI) toxicity (6).

As a result of these trials, the indication for EBRT has become limited to patients at a relatively high risk of recurrence. Risk factors have been identified: Grade 3, age 60 years or older, and deep myometrial invasion. Patients with at least two of these three risk factors have been designated as high-intermediate-risk (HIR). Patients with HIR features have a 20% risk of locoregional recurrence (LRR) after no additional treatment (NAT), which is reduced to 5% with EBRT. For these HIR patients, the indication for RT has been maintained after PORTEC-1, and EBRT was abandoned for the 55% patients with Stage I EC who were designated as low to intermediate risk (LIR).

In the Gynecology Oncology Group (GOG) 99 trial, which included patients with Stage I–IIA EC after surgery including lymphadenectomy (LA) with negative nodes, a similar HIR group was identified (3). EBRT resulted in a hazard reduction of 58% for both LIR and HIR, but this reduction was clinically relevant only in the HIR group. The 4-year isolated local relapse rate was reduced from 13% to 5% in the HIR group (3). These results were essentially the same as those from PORTEC-1, showing that both with and without LA, the risk factors Grade 3, deep invasion, older age, and lymphovascular space invasion are associated with local recurrence.

The subsequent randomized PORTEC-2 trial for International Federation of Gynecology and Obstetrics (FIGO) 1988 Stage I–IIA EC patients with HIR factors confirmed that EBRT could safely be substituted by vaginal brachytherapy (VBT), with less toxicity and better quality of life (7, 8). However, for high-risk EC—FIGO 2009 (9) Stages IB Grade 3, II, III; or Stages IB–III with serous/clear cell histology—EBRT continues to be the most effective adjuvant treatment for pelvic control (10–12).

The present analysis was done to evaluate very long-term outcomes of the PORTEC-1 trial, to investigate whether patients with HIR EC benefited more from EBRT than those without HIR factors, and to analyze the long-term risk of second cancers.

PATIENTS AND METHODS

Patient selection and treatment

The PORTEC-1 trial was a multicenter trial accruing during 1990 to 1997. The details of patient evaluation and treatment have been described in previous publications (2, 6). Surgery consisted of total extrafascial hysterectomy and bilateral salpingo-oophorectomy without LA (only biopsy of any suspicious lymph nodes). Women of any age, World Health Organization performance score 0–2, with 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. The protocol was approved by the Protocol Review Committee of the Dutch Cancer Society and by the ethics committees of the Daniel den Hoed Cancer Center and of the participating centers.

Radiation therapy

Pelvic EBRT was administered with a target volume that included the parametrial tissues, the 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. The total dose was 46 Gy in 2-Gy daily fractions. The PORTEC trial was done before three-dimensional conformal treatment planning techniques had been introduced. Radiation was delivered by antero-posterior–posteroanterior parallel opposed fields (30%), by use of three-field (18%) or four-field techniques (52%), with calculation of the dose distribution on the central axis and specification at isocenter or midplane (6).

Pathology review

Central pathology review was done after patient inclusion (13). Histopathologic slides of 567 patients (79%) were obtained. The diagnosis of endometrial carcinoma was confirmed in all patients. The histologic grade was determined at review according to the FIGO 1988 grading criteria (14, 15). Systematic grading according to these criteria led to the assignment of Grade 1 to significantly more tumors: 60% of the tumors were Grade 1, 32% were Grade 2, and 8% were Grade 3, in contrast to the initial assignment of 21% Grade 1, 68% Grade 2, and 11% Grade 3. The outcomes in patients with Grade 1 or 2 tumors were similar, in contrast to Grade 3 (13). In the present analysis, histologic grades determined at review were used. In cases without pathology review the grade was assigned not done.” For determination of HIR and LIR groups, patients with review grade “not done” were assigned Grade 2.

Follow-up

Patients were followed up in their regional hospitals until at least 7 years after treatment. The LRR were confirmed by histology. LRR was defined as vaginal and/or pelvic recurrence. Distant failures included paraaortic lymph node metastases; abdominal relapses; liver, lung, and bone metastases; and diffuse metastatic disease.

For the present analysis, the 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/or the governmental local population administration.

The analysis of long-term health-related quality of life (HRQL) has been addressed in a separate publication (16). The current analysis was done to evaluate prognostic factors, to establish the role of HIR factors for treatment selection, and to evaluate the long-term risk of second cancers after EBRT.

Statistical methods

The primary endpoints for the study were LRR and overall survival (OS). The secondary endpoints were morbidity and survival after relapse.

The analysis was by intention to treat. All randomized patients were kept in the analysis, including those who did not meet eligibility criteria ($n = 10$) and those with protocol violations ($n = 31$). The Kaplan-Meier method, log-rank test, and Cox regression analysis were used for time-to-event analyses (2, 5). Competing risk probabilities of failure were calculated with the following competing risks of first failure type: LRR, distant metastasis, and death without relapse. If metastases were detected together with LRR, the failure type was metastases. Competing risk analysis was also applied to calculate probabilities of risk of death split by cause of death, and LRR split by type (vaginal or pelvic). Combined vaginal and pelvic recurrences were scored as pelvic recurrence.

The observed numbers of secondary cancers and deaths were compared with the expected numbers based on Dutch sex- and age-specific incidence rates of cancer and death (17), using the subject-years method.

Prognostic factors considered in the analysis were as follows: age, depth of myometrial invasion, and (review) grade. Age (at randomization) was classified *a priori* in three groups: <60, 60–70, and >70 years. Differences between the treatment groups in risk of relapse or death were tested with the log-rank test without adjustment for prognostic factors, and with the likelihood ratio test in Cox regression analysis with adjustment. All reported *p* values are based on two-sided tests with *p* values <0.05 considered statistically significant.

RESULTS

Outcomes

A total of 715 eligible patients with Stage I EC were enrolled; 354 patients were randomly assigned to EBRT, and 361 to NAT. One patient was excluded because all information was irretrievably missing. Thus, 714 patients were evaluated. The study groups were well balanced with regard to patient and tumor characteristics (Table 1).

The present analysis was done on data frozen on March 1, 2009. Forty-eight patients were lost to follow-up (41 of whom were lost after >5 years' follow-up); they were included

Table 1. Patient characteristics after central pathology review

Characteristic	No. of patients (%)	
	RT (<i>n</i> = 354)	NAT (<i>n</i> = 360)
Age (y)		
<60	93 (26)	108 (30)
60–70	136 (38)	134 (37)
>70	125 (35)	118 (33)
Mean (SD)	66.3 (SD 9)	65.7 (SD 9)
Range	41–85	43–90
Myometrial invasion		
<50%	138 (39)	156 (43)
≥50%	216 (61)	204 (57)
Revised histologic grade		
1	198 (56)	197 (55)
2	49 (14)	39 (11)
3	32 (9)	54 (15)
ND*	75 (21)	70 (19)
Revised FIGO 1988 stage		
IB Grade 1 [†]	60 (17)	74 (21)
IB Grade 2 [‡]	56 (16)	47 (13)
IB Grade 3	22 (6)	35 (10)
IC Grade 1	138 (39)	123 (34)
IC Grade 2 [‡]	68 (19)	62 (17)
IC Grade 3	10 (3)	19 (5)
Vascular space invasion		
Present	22 (6)	19 (5)
HIR		
No	170 (48)	178 (49)
Yes	184 (52)	182 (51)

Abbreviations: RT = radiotherapy; NAT = no additional treatment; SD = standard deviation; FIGO = International Federation of Gynecology and Obstetrics; HIR = high to intermediate risk.

* ND = no review grade.

[†] Ineligible at review.

[‡] Includes ND grade.

in the analysis and censored at the date of last follow-up. The median follow-up for patients alive was 13.3 years (range, 2.8–18.5 years).

Table 2 shows the 15-year rates of LRR, metastases, OS, and failure-free survival (FFS) by treatment group. The 15-year LRR rates were 5.8% in the RT group and 15.5% in the NAT group (hazard ratio [HR] for NAT 3.46; 95% CI 1.93–6.18; log-rank test *p* < 0.0001). For comparison, the 5-year, 10-year, and 15-year LRR rates were 4.2% vs. 13.7% (2); 4.6% vs. 14.3% (13), and 5.8% vs. 15.5%. Among 50 LRR in the NAT arm, 37 (74%) were located in the vagina. The 15-year rates of distant metastases were similar in the treatment groups: 9.3% for EBRT and 7.1% for NAT (*p* = 0.25).

In both treatment arms, some very late recurrences were diagnosed (Fig. 1). All late recurrences were histologically confirmed, showing adenocarcinoma similar to the previous endometrial carcinoma. In 1 patient in the RT group, a large (6-cm) abdominal recurrence was diagnosed 16 years after treatment. The patient was given hormonal therapy and at this writing is alive with partial remission. In 2 patients in the NAT group, vaginal recurrence and vaginal and pelvic recurrences were found after 9 and 14 years, respectively. These patients were treated with EBRT and at this writing are without evidence of disease.

A total of 288 patients had died: 67 as a result of EC (13 pelvic disease, 47 metastases, 1 related to primary treatment,

Table 2. Long-term outcomes at 15 years (actuarial probabilities) by treatment arm

Outcome	RT (<i>n</i> = 354)		NAT (<i>n</i> = 360)	
	Events	15-year % (SE)	Events	15-year % (SE)
Survival				
Alive	202	52% (3)	224	60% (3)
Death EC	37	11% (2)	30	8% (1)
Death other causes	115	38% (3)	106	31% (3)
Survival: HIR				
Alive	85	41% (4)	93	48% (4)
Death EC	25	14% (3)	24	13% (3)
Death other causes	74	45% (4)	65	39% (4)
Recurrence				
Vaginal	8	2.5% (0.6)	37	11.0% (1.3)
Pelvic	7	3.4% (1.6)	13	4.5% (1.4)
Distant	32	9.3% (1.6)	24	7.1% (1.4)
First failure				
No failure	198	50.1% (3.3)	203	54.4% (3.0)
Death NED	115	38.1% (3.2)	94	27.7% (3.0)
Vaginal recurrence	8	2.3% (0.8)	37	10.3% (1.6)
Pelvic recurrence	7	2.5% (1.0)	13	4.0% (1.1)
Distant recurrence	26	7.1% (1.4)	13	3.6% (1.0)
Second cancer				
Breast	11	4.8% (1.6)	18	6.6% (1.6)
GI	19	6.2% (1.4)	10	3.2% (1.0)
Other	25	10.6% (2.3)	14	6.0% (1.7)

Abbreviations: RT = radiotherapy; NAT = no additional treatment; EC = endometrial carcinoma; NED = no evidence of disease; HIR = high to intermediate risk; GI = gastrointestinal; SE = standard error.

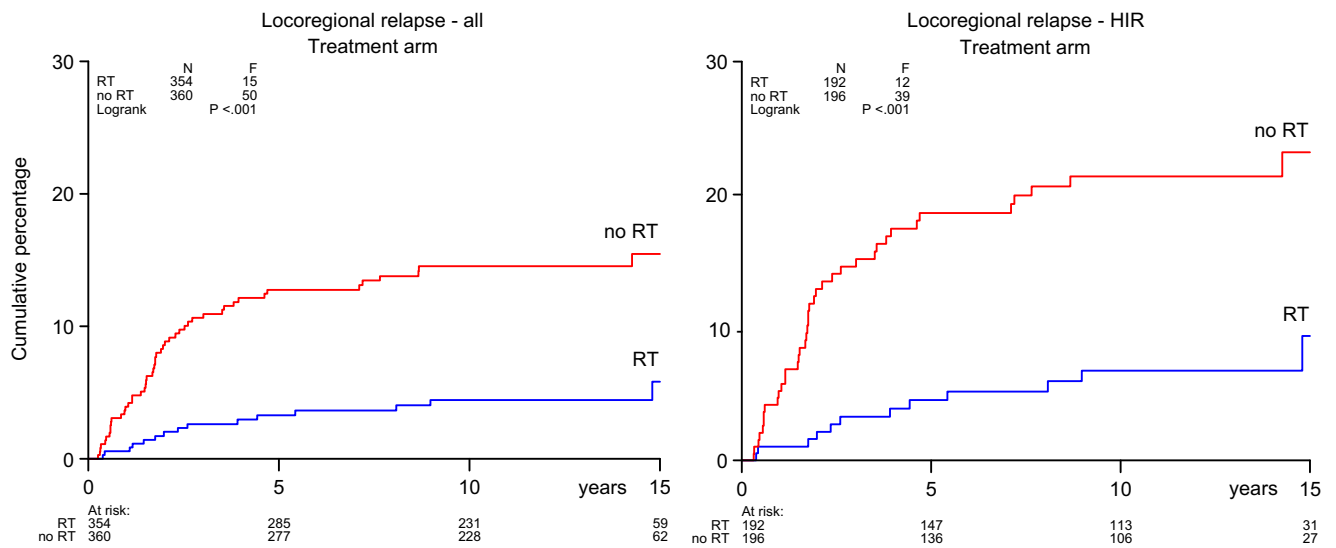


Fig. 1. Probability of locoregional (vaginal and/or pelvic) relapse for patients assigned to postoperative radiotherapy (RT) or no additional treatment (NAT) for the total group (left) and for patients with high-intermediate-risk (HIR) features (right).

3 related to treatment of metastases, and 3 of unknown cause but with previous diagnosis of relapse) and 221 of other causes (51 second cancers, 165 intercurrent diseases, 5 unknown). The OS rates were 81% vs. 85% at 5 years (2), 68% vs. 74% at 10 years, and 52% vs. 60% at 15 years ($p = 0.14$). For patients with HIR features, the OS rates at 10 and 15 years were 60% vs. 64% and 41% vs. 48%, respectively ($p = 0.35$). The rates of death were compared with those of an age-matched population. The observed vs. expected ratios were 1.14 for the total group: 1.22 in the EBRT group vs. 1.06 in the NAT group ($p = NS$).

In Fig. 2 the FFS rates by treatment group are shown for all patients and for those with HIR features. The FFS at 15 years was 50% vs. 54% ($p = 0.94$), and among HIR patients FFS was nonsignificantly slightly higher in the EBRT group.

Survival after recurrence

The 5- and 10-year survival rates after recurrence were significantly better in the NAT group: 48% (NAT) vs. 12% (EBRT) at 5 years and 35% vs. 7% at 10 years ($p < 0.01$).

The survival rates after vaginal recurrence were 70% (NAT) vs. 38% (EBRT) at 5 years and 51% vs. 25% at 10 years. The estimated 10-year survival rates for NAT vs. EBRT were 18% vs. 0% for pelvic relapse and 8% vs. 4% for distant relapse.

Three patients with distant metastases were still alive and progression-free after 14, 12, and 10 years: 2 after surgical excision of a solitary pulmonary metastasis and a solitary omental metastasis, respectively; the third after salvage RT for vaginal recurrence and prolonged complete response during hormonal treatment of histologically verified pulmonary metastasis which had occurred 3 years after vaginal recurrence.

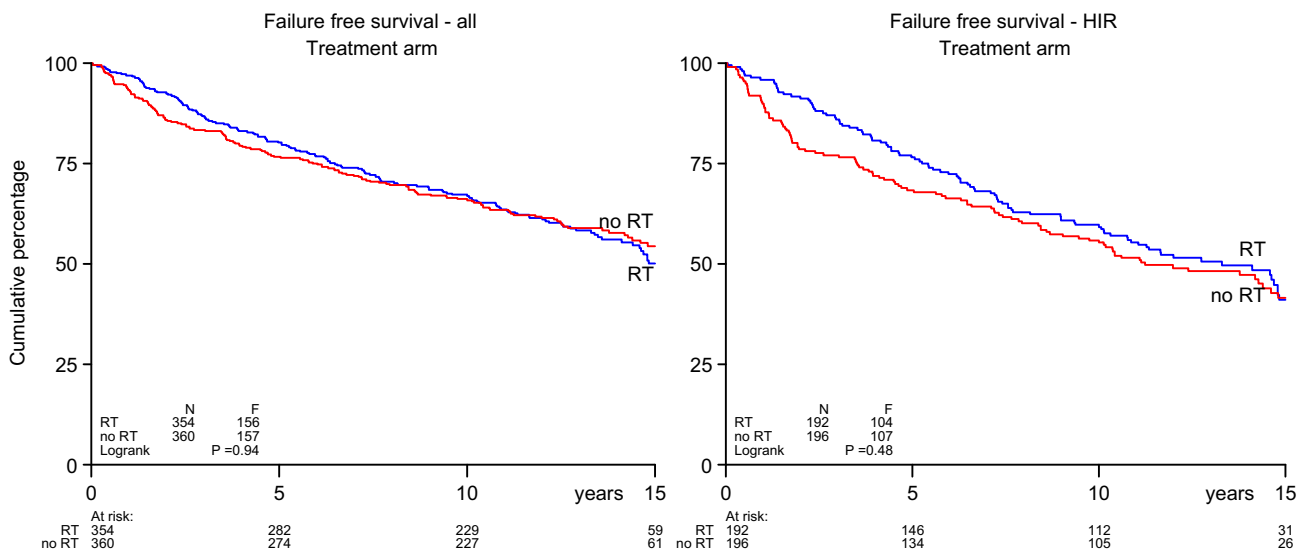


Fig. 2. Probability of failure-free survival for patients assigned to postoperative radiotherapy (RT) or no additional treatment (NAT) for the total group (left) and for patients with high-intermediate-risk (HIR) features (right).

Second cancers

Second cancers were diagnosed in 97 patients, with 15-year rates of 22% in the EBRT group vs. 16% in the NAT group ($p = 0.10$). The incidence rates were compared with those of an age- and sex-matched population: the observed vs. expected ratios were 1.40 for the total group: 1.62 for EBRT and 1.20 for NAT ($p = \text{NS}$).

Second cancer types were breast cancer (6% at 15 years), cancers of the GI tract (5%), and various other types (8%). The predominant cancer type among EBRT patients was GI cancer (6.2% vs. 3.2% among NAT patients), and breast cancer was most frequent in the NAT group (6.6% vs. 4.8% in the EBRT group). These differences did not reach statistical significance ($p = 0.10$).

Prognostic factors

Table 3 shows multivariate analysis of prognostic factors for LRR and EC-related death. The HR for LRR, adjusted for major prognostic factors, were 3.46 for NAT compared to EBRT ($p < 0.0001$), 3.35 for review Grade 3 ($p < 0.001$) and 1.66 for Grade 2 ($p = 0.19$) as compared to Grade 1; and 3.90 for age 60 years compared to <60 years ($p = 0.0017$). Figure 3 shows OS split by prognostic factors.

The risk of EC-related death was significantly higher for patients ≥ 60 years and especially for patients with Grade 3 tumors (HR 7.3, $p < 0.0001$). After adjustment for age, grade, and invasion there was no evidence of benefit of EBRT for OS or EC-specific survival.

DISCUSSION

The recent publication of the results of the ASTEC trial included a meta-analysis of the ASTEC, GOG 99, and PORTEC-1 trials, which excluded a survival benefit of EBRT in intermediate-risk endometrial cancer of more than 3% (4). Moreover, the results of previous meta-analyses suggested that EBRT may even be harmful for patients with features of low to intermediate risk, given that these patients have a low risk of recurrence after surgery alone, and EBRT adds toxicity and risks without improving survival (18, 19). This was confirmed in the current analysis, with results showing a trend for lower OS after EBRT,

whereas the FFS curves overlapped. However, for patients with HIR features, the OS rates were similar, and FFS was slightly (but nonsignificantly) higher after EBRT.

The abandonment of EBRT for patients with LIR features has been confirmed to be a correct decision. EBRT causes side effects (6) and has been shown in our recent analysis to have a very long-term negative impact on HRQL (16). Moreover, we found a trend toward more second cancers among EBRT patients, especially cancers of the GI tract. EBRT can therefore not be justified in the absence of survival benefit and in the presence of effective salvage RT for the very few LIR patients who develop locoregional recurrence. Although current sophisticated EBRT planning techniques (intensity-modulated RT) may be expected to have lower GI toxicity rates (20), the irradiated volume in the lower pelvis remains large, and the long-term risks of pelvic floor dysfunction, GI symptoms, and second cancers cannot be disregarded.

For patients with HIR features, the indication for RT was maintained because their 5-year risk of LRR was 20%, which was considered sufficiently high to justify adjuvant treatment significantly improving local control. For these patients, the subsequent PORTEC-2 trial showed that VBT was highly effective, with fewer side effects and better HRQL than after EBRT (8). Patients who received VBT did not have the increased bowel symptoms reported by EBRT patients, most notably diarrhea, urgency, and higher need to remain close to a toilet (7). As a result of the PORTEC-2 trial, patients with HIR EC are currently treated with VBT.

External-beam RT has remained indicated only for the 15% of EC patients with high-risk features (Grade 3 with deep invasion and/or lymph-vascular space invasion (LVSI), serous or clear cell histology) or advanced stages. Omitting EBRT for those patients has been shown to result in significantly lower pelvic control rates and may even affect survival (10, 12). The use of high-risk and HIR factors for decisions on adjuvant treatment underlines the critical importance of complete and reproducible pathology evaluation in the treatment of EC patients.

Adjuvant chemotherapy might be considered in view of the higher risk of distant metastases among patients with

Table 3. Cox regression analysis

Variable	Locoregional relapse			Death related to endometrial cancer		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
NAT arm	3.46	1.93–6.18	<0.0001	0.71	0.43–1.16	0.17
Age ≥ 60 y	3.90	1.67–9.11	0.0017	2.66	1.26–5.61	0.010
Review Grade 2	1.66	0.78–3.52	0.19	2.20	1.07–4.51	0.032
Review Grade 3	3.35	1.75–6.41	0.0003	7.30	3.94–13.53	<0.0001
Invasion >50%	1.86	1.07–3.24	0.027	1.86	1.09–3.17	0.024
HIR patients						
NAT arm	3.31	1.73–6.35	0.0003	0.87	0.50–1.50	0.61
Review Grade 2	1.53	0.62–3.79	0.35	1.93	0.81–4.60	0.14
Review Grade 3	2.15	1.10–4.21	0.026	4.31	2.28–8.12	<0.0001

Abbreviations: HR = hazard ratio; NAT = no additional treatment; CI = confidence interval; HIR = high to intermediate risk.

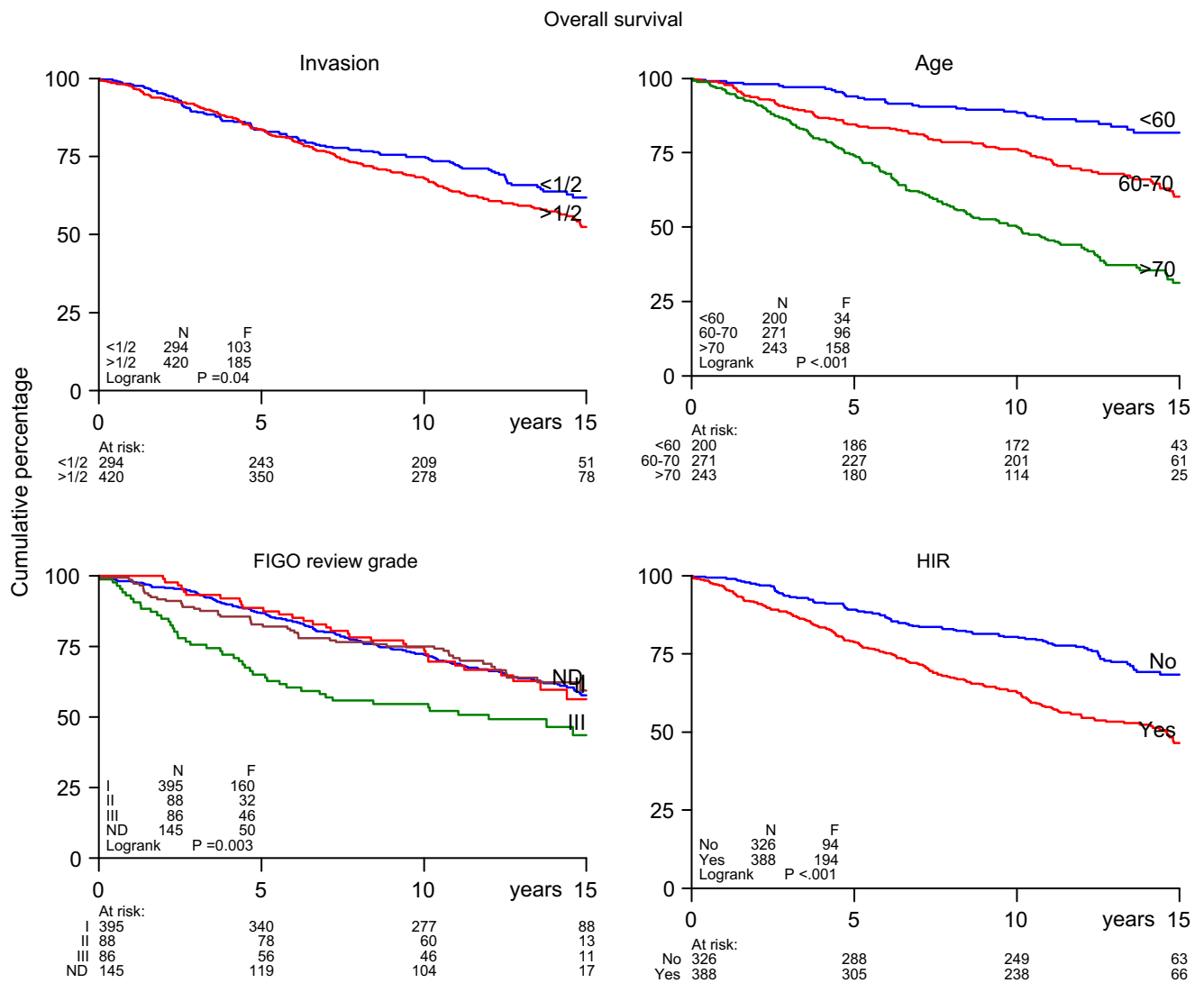


Fig. 3. Probability of overall survival according to prognostic factors: depth of myometrial invasion (<50% vs. ≥50%, top left), patient age (<60 vs. 60–70 vs. >70 years, top right), revised International Federation of Gynecology and Obstetrics (FIGO) Grade (1 vs. 2 vs. 3 vs. ND grade, bottom left), and presence vs. absence of high-intermediate-risk (HIR) features (bottom right).

high-risk EC. Although two randomized trials comparing chemotherapy alone with pelvic EBRT alone did not show differences in OS, progression-free survival, or relapse rates (21, 22), the Nordic Society of Gynaecological Oncology/European Organisation for the Research and Treatment of Cancer (NSGO9501/EORTC55991) trial comparing EBRT alone with EBRT preceded or followed by chemotherapy showed a 7% increase in progression-free survival ($p = 0.03$) and a trend for improved OS ($p = 0.08$) in the combined EBRT + chemotherapy arm (23). The current international randomized PORTEC-3 trial for patients with high-risk and advanced-stage EC investigates the survival benefit, toxicities, and impact on quality of life of EBRT + chemotherapy compared with EBRT alone. Both treatments are started early (two cycles of cisplatin during EBRT and four cycles of carboplatin and paclitaxel after the completion of EBRT), which obviates the need to decide which treatment should be given first (24). Two current ongoing GOG trials (GOG

249 and 258) investigate the role of chemotherapy for early-stage HIR and high-risk EC (three cycles of carboplatin and paclitaxel and VBT vs. EBRT), and advanced-stage EC (EBRT plus two cycles of cisplatin followed by four cycles of carboplatin and paclitaxel vs. six cycles of carboplatin and paclitaxel), respectively.

The PORTEC-1 and -2, GOG 99, and ASTEC trials (2–4, 8) have resulted in a significant reduction of the treatment burden for a large number of patients with endometrial carcinoma, abandoning EBRT for 85% of EC patients and introducing VBT as adjuvant treatment for the 30% of EC patients with HIR features. It should be noted that the favorable results in the control arm of PORTEC-1 and in the VBT arm of PORTEC-2 were obtained in the absence of LA, whereas only 30% of patients in the ASTEC trial underwent LA. These results were very similar to those of GOG 99 (3), which required LA and included only patients who were node negative. Two recent large randomized trials

investigated the role of LA and did not find a survival benefit or any differences in patterns and sites of relapse (25, 26). The Italian trial (26), which had a median node count of 23 to 30 in the LA arm, showed identical rates of vaginal recurrence (2.6% for LA vs. 2.4% for no LA), lymph node recurrence (1.5% vs. 1.6%), and intraperitoneal relapse (3% vs. 2.8%) in both arms. The abandonment of EBRT for 85% of EC patients should thus not encourage the increased use of LA to identify the 9% of patients with microscopic node metastases. This will not affect their survival and add morbidity: 18.6% vs. 8.8% risk of late complications for LA vs. no LA, most notably 10.2% vs. 1.6% lymphedema (26, 27). Lymphedema has been shown to affect HRQL, and women with LA reported more clinically relevant edema symptoms (25.6 vs. 16.9, $p < 0.001$) (28). Powerful

prognostic factors, especially Grade 3 (with HR of 7.3 for EC death in the current analysis), and lymphovascular space invasion (29, 30), are available at histologic examination and are associated with increased risk of distant spread. These factors can be used to select patients who might benefit from systemic treatments reaching areas that neither radiation nor the surgical knife can effectively treat.

In conclusion, the 15-year results of the PORTEC-1 trial have confirmed the highly significant improvement of local control obtained by EBRT but an absence of survival benefit. HIR features were shown to be useful for selection for RT (currently VBT). In view of the long-term negative impact of EBRT, the absence of survival benefit, and the presence of effective salvage treatment, the rationale for the abandonment of EBRT for intermediate-risk EC has been confirmed.

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