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# Fifteen-year radiotherapy outcomes of the randomized PORTEC-1 trial for endometrial carcinoma

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# Abstract

**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 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 (OS) was 52% vs 60% ($p=0.14$), and failure-free survival 50% vs 54% ($p=0.94$). For patients with high-intermediate risk criteria (HIR), 15-year OS was 41% vs. 48% ($p=0.51$), and 15-year EC-related death 14 vs 13%. Most LRR in the NAT group were vaginal recurrences (11% out 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 versus expected ratios of 1.6 (EBRT) and 1.2 (NAT) compared with a matched population (p=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 HR 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 high-intermediate risk 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 endometrial carcinoma.

# 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 radiotherapy (EBRT) provides a highly significant improvement of 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 5-year survival of 70%, while outcomes after pelvic and distant relapse were poor.[5] EBRT was associated with 26% risk of side effects, mainly grade 1-2 gastro-intestinal (GI) toxicity.[6]

As a result of these trials, the indication for EBRT has become limited to patients with a relative high risk of recurrence. Risk factors have been identified: grade 3; age 60 years or older; and deep myometrial invasion. Patients with at least 2 of these 3 risk factors have been designated 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 radiotherapy has been maintained after PORTEC-1, and EBRT was abandoned for the 55% patients with stage I EC who were designated as low-intermediate risk (LIR).

In the Gynecology Oncology Group (GOG) 99 trial, which included patients with stage I-IIA EC after surgery which including lymphadenectomy (LA) with negative nodes, a similar HIR group was identified.[4] EBRT resulted in a hazard reduction of 58% both for 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.[4] 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 in 1990-1997. Details on patient evaluation and treatment have been described in previous publications.[3,6] 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 Organisation performance score 0-2, with endometrial adenocarcinoma stage I, grade 1 with deep (³50%) 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. Total dose was 46 Gy in 2-Gy daily fractions. The PORTEC trial was done before 3-D conformal treatment planning techniques had been introduced. Radiation was delivered by AP-PA parallel opposed fields (30%), three-field (18%) or four-field techniques (52%) with calculation of the dose distribution on the central axis and specification at isocentre or midplane.[6]

**Pathology review**

Central pathology review was done after patient inclusion.[13] Histopathological slides of 567 patients (79%) were obtained. The diagnosis of endometrial carcinoma was confirmed in all patients. The histological 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% 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, histological grades determined at review have been 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 in their regional hospitals until 7 years after treatment. The LRRs were confirmed by histology. LRR was 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 the present 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). The analysis of long-term 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). 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.[3,5]

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[16] using the subject-years method.
Prognostic factors considered in the analysis were: 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 no additional treatment (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).

*Table 1: Patient characteristics after central pathology review*

| Characteristic | RT (n = 354) | NAT (n = 360) |
|---|---|---|
| | number of patients (%) | |
| **Age (years)** | | |
| <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 (09) | 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 (06) | 35 (10) |
| IC grade 1 | 138 (39) | 123 (34) |
| IC grade 2** | 68 (19) | 62 (17) |
| IC grade 3 | 10 (03) | 19 (05) |
| **Vascular space invasion** | | |
| present | 22 (06) | 19 (05) |
| **HIR** | | |
| no | 170 (48) | 178 (49) |
| yes | 184 (52) | 182 (51) |

*nd = no review grade; # at review ineligible; ** includes grade nd;
RT= radiotherapy; NAT= no additional treatment; sd= standard deviation;
HIR = high-intermediate risk

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 in the analysis and censored at the date of last follow-up. 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 LLR rates were 4.2% vs. 13.7%; 4.6% vs. 14.3% and 5.8% vs. 15.5%. Among 50 LRR 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 (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 one patient in the RT group, a large (6 cm) abdominal recurrence was diagnosed 16 years after treatment. She was started on hormonal therapy and is currently alive with partial remission. In two patients in the NAT group, vaginal recurrence and vaginal and pelvic recurrences were found after 9 and 14 years, respectively. These were treated with EBRT, and are currently without evidence of disease.

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

| Outcome | RT (n = 354) | | NAT (n = 360) | |
|---|---|---|---|---|
| | **Events** | **15-yr % (SE)** | **Events** | **15-yr % (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) |

RT= radiotherapy; NAT= no additional treatment; EC= endometrial carcinoma; NED=no evidence of disease; HIR= high-intermediate risk; GI = gastro-intestinal; se= standard error

A total of 288 patients had died: 67 due to EC (13 pelvic disease; 47 metastases; 1 related to primary treatment; 3 related to treatment of metastases; and 3 of unknown cause, but with previous diagnosis of relapse); and 221 due to other causes (51 second cancers; 165 intercurrent diseases; 5 unknown). The rates of death were compared with those of an age-matched population. Observed versus expected ratios were 1.14 for the total group; 1.22 in the EBRT group vs. 1.06 in the NAT group (p=N.S.).

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.

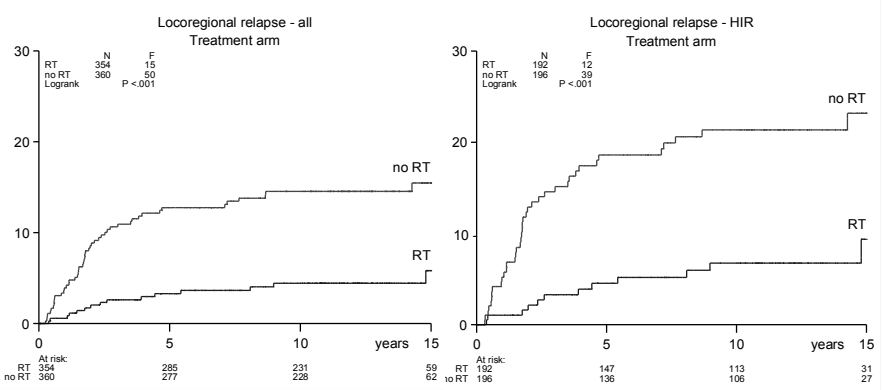


*Fig. 1. Probability of locoregional (vaginal and/or pelvic) relapse for patients assigned to postoperative radiotherapy (RT) or no additional treatment (NAT) for the total group (left) and for patients with high-intermediate-risk (HIR) features (right).*

**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 ($p<0.01$). Survival rates after vaginal recurrence were 70% (NAT) vs. 38% (EBRT) at 5 years, and 51% vs. 25% at 10 years. 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: two after surgical excision of a solitary pulmonary metastasis and a solitary omental metastasis, respectively; the third after salvage RT for vaginal recurrence and complete prolonged response on hormonal treatment of histologically verified pulmonary metastasis which had occurred 3 years after vaginal recurrence.

**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=N.S.).

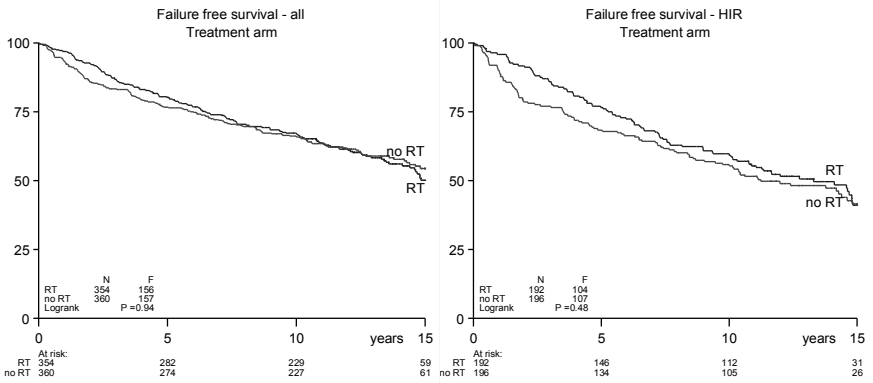


*Fig. 2. Probability of failure-free survival for patients assigned to postoperative radiotherapy (RT) or no additional treatment (NAT) for the total group (left) and for patients with high-intermediate-risk (HIR) features (right).*

Second cancer types were breast cancer (6% at 15 years), cancers of the GI tract (5%), and any 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 ³60 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 ³60 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 data, which excluded a survival benefit of EBRT in intermediate-risk endometrial cancer of more than 3%.2 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.17,18 This was confirmed in the current analysis, with results showing a trend for lower OS after EBRT, whereas 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 effects6, and has been shown in our recent analysis to have a very long-term negative impact on HRQL.16 Moreover, we found a trend towards more second cancers among EBRT patients, especially cancers of the GI tract. EBRT can therefore not be justified in absence of survival benefit, and in 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 rates19, 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 risk 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 vaginal brachytherapy (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 and urgency, resulting in 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.

*Table 3. Cox regression analysis*

| | Locoregional relapse | | | Death related to endometrial cancer | | |
|---|---|---|---|---|---|---|
| **Variable** | **HR** | **95% CI** | ***p*–value** | **HR** | **95% CI** | ***p*–value** |
| **NAT arm** | 3.46 | 1.93 - 6.18 | <0.0001 | 0.71 | 0.43 - 1.16 | 0.17 |
| **Age ≥ 60** | 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 |

NAT= no additional treatment; CI= confidence interval; HIR= high-intermediate risk

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 high-risk EC. Although two randomized trials comparing chemotherapy alone to pelvic EBRT alone did not show differences in OS, progression-free survival, or relapse rates20,21, the Nordic Society of Gynaecological Oncology / European Organisation fo 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 overall survival (p=0.08) in the combined arm.22 The current international randomized PORTEC-3 trial for patients with high-risk and advanced-stage EC investigates survival benefit, toxicities, and impact on quality of life of EBRT +chemotherapy compared

with EBRT alone. Both treatments are started early (2 cycles of cisplatin during EBRT and 4 cycles of carboplatin and paclitaxel after the completion of EBRT), which obviates the need to decide which treatment should be given first.23 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 carboplatin and paclitaxel vs. six cycles of carboplatin and paclitaxel).

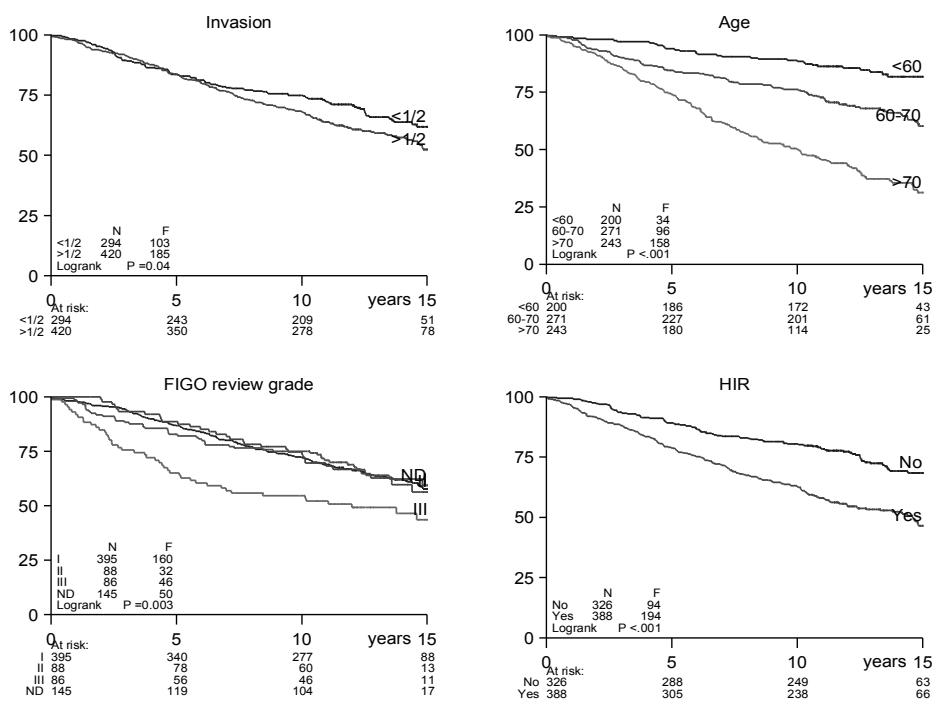


*Fig. 3. Probability of overall survival according to prognostic factors: depth of myometrial invasion (<50% vs. $50%, top left), patient age (<60 vs. 60–70 vs. >70 years, top right), revised International Federation of Gynecology and Obstetrics (FIGO) Grade (1 vs. 2 vs. 3 vs. ND grade, bottom left),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

PORTEC-1 and 2, GOG 99, and ASTEC trials2-4,8 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% EC patients with HIR features. It should be noted that the favorable results in the control arm of PORTEC-1 and 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 only included patients who were node-negative. Two recent large randomized trials investigated the role of LA and did not find survival benefit or any differences in patterns and sites of relapse.[24,25] The Italian trial[24], which had median node count of 23 to 30 in the LA arm, showed identical rates of vaginal (2.6% for LA vs 2.4% for no-LA), lymph node recurrence (1.5% vs 1.6%) and intraperitoneal (3% vs 2.8%) relapse in both arms. The abandonment of EBRT for 85% of EC patients should thus not encourage 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.[24,26] Lymphedema has been shown to affect HRQL, and women with LA reported more clinically relevant edema symptoms (25.6% vs. 16.9%, $p<0.001$).[27] Powerful prognostic factors, especially grade 3 (with HR of 7.3 for EC death in the current analysis), and lymphovascular space invasion[28,29] 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, 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 presence of effective salvage treatment, the rationale for the abandonment of EBRT for intermediate-risk EC has been confirmed.

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