Molecular Classification Predicts Response to Radiotherapy in the Randomized PORTEC-1 and PORTEC-2 Trials for Early-Stage Endometrioid Endometrial Cancer

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ABSTRACT

PURPOSE The molecular classification of endometrial cancer (EC) has proven to have prognostic value and is predictive of response to adjuvant chemotherapy. Here, we investigate its predictive value for response to external beam radiotherapy (EBRT) and vaginal brachytherapy (VBT) in early-stage endometrioid EC (EEC).

METHODS Data of the randomized PORTEC-1 trial (n = 714) comparing pelvic EBRT with no adjuvant therapy in early-stage intermediate-risk EC and the PORTEC-2 trial (n = 427) comparing VBT with EBRT in early-stage high-intermediate-risk EC were used. Locoregional (including vaginal and pelvic) recurrence-free survival was compared between treatment groups across the four molecular classes using Kaplan-Meier's methodology and log-rank tests.

RESULTS A total of 880 molecularly classified ECs, 484 from PORTEC-1 and 396 from PORTEC-2, were included. The majority were FIGO-2009 stage I EEC (97.2%). The median follow-up was 11.3 years. No locoregional recurrences were observed in EC with a pathogenic mutation of DNA polymerase-ε (POLEmut EC). In mismatch repair–deficient (MMRd) EC, locoregional recurrence-free survival was similar after EBRT (94.2%), VBT (94.2%), and no adjuvant therapy (90.3%; P = .74). In EC with a p53 abnormality (p53abn EC), EBRT (96.9%) had a substantial benefit over VBT (64.3%) and no adjuvant therapy (72.2%; P = .048). In EC with no specific molecular profile (NSMP EC), both EBRT (98.3%) and VBT (96.2%) yielded better locoregional control than no adjuvant therapy (87.7%; P < .0001).

CONCLUSION The molecular classification of EC predicts response to radiotherapy in stage I EEC and may guide adjuvant treatment decisions. Omitting radiotherapy seems to be safe in POLEmut EC. The benefit of radiotherapy seems to be limited in MMRd EC. EBRT yields a significantly better locoregional recurrence-free survival than VBT or no adjuvant therapy in p53abn EC. VBT is the treatment of choice for NSMP EC as it is as effective as EBRT and significantly better than no adjuvant therapy for locoregional tumor control.

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INTRODUCTION

Endometrial cancer (EC) is currently classified into four molecular groups with a distinct tumor biology and prognosis. EC with a pathogenic mutation of DNA polymerase-ε (POLEmut EC) has an excellent prognosis, and EC with mismatch repair–deficient (MMRd EC) has an intermediate prognosis. EC with a p53 abnormality (p53abn EC) has a poor prognosis, whereas EC with no specific molecular profile (NSMP EC) has a stage-dependent prognosis.[1,2]

Several studies have confirmed the independent prognostic impact of the molecular class.[3-5] The molecular class also has predictive value for benefit of chemotherapy in women with high-risk EC.[6] A number of international guidelines recently incorporated the molecular classification in risk assessment and adjuvant treatment recommendations, although mainly for high-risk EC.[7-9] The molecular class might also have clinically relevant implications in (high-) intermediate-risk EC, for which adjuvant radiotherapy is often recommended.[7-10]

CONTEXT

Key Objective
To determine the predictive value of the molecular class of endometrial cancer (EC) for the efficacy of vaginal brachytherapy (VBT) and pelvic external beam radiotherapy (EBRT) in women with stage I endometrioid EC.

Knowledge Generated
Analyses of data from 880 women included in the randomized PORTEC-1 and PORTEC-2 radiotherapy trials showed at 5 years the following: (1) no locoregional recurrences in *POLE*-mutant EC regardless of adjuvant radiotherapy; (2) similar locoregional recurrence-free survival in mismatch repair–deficient EC after EBRT (94.2%), VBT (94.2%), and no adjuvant therapy (90.3%; *P* = .74); (3) significantly better locoregional recurrence-free survival in p53-abnormal EC with EBRT (96.9%), compared with VBT (64.3%) and no adjuvant therapy (72.2%; *P* = .048); and (4) significantly better locoregional recurrence-free survival in EC with no specific molecular profile, with both EBRT (98.3%) and VBT (96.2%) compared with no adjuvant therapy (87.7%; *P* < .0001).

Relevance *(G.F. Fleming)*
Systemic therapy for EC is being adapted for different TCGA groups, and this report adds to our knowledge about also adapting radiotherapy for biologic subsets.*

*Relevance section written by *JCO* Associate Editor Gini F. Fleming, MD.

Whether the molecular classification has predictive value for benefit of radiotherapy has not yet been investigated. There are several studies that show differences between the molecular classes in the ways cancer cells respond to damage induced by radiation.[11,12] For example, homologous recombination (HR)–deficient p53abn EC[13,14] is unable to repair radiation-induced double-strand breaks, which might translate into radiosensitivity.[15] MMRd EC has an impaired base mismatch repair apparatus, which is normally activated by radiotherapy-induced single-strand breaks.[11] However, as these cancers are typically HR-proficient,[16] it is uncertain whether this translates into a clinical benefit. The majority of NSMP ECs have an endometrioid histotype,[3,6] of which 80% have aberrant activation of the PI3K/PTEN/AKT/mTOR-signaling pathway.[11] Loss of *PTEN* is common[17] and associated with increased radiosensitivity.[18] Finally, it is likely that patients with *POLE*mut EC do not benefit from radiotherapy as recurrences are rare, even in the absence of adjuvant therapy.[19]

Here, we investigate the efficacy of radiotherapy across the four molecular classes of EC using data of two large, randomized radiotherapy trials in women with early-stage endometrioid EC.

METHODS

Study Population

Data of all women included in the intention-to-treat populations of the randomized PORTEC-1 (n = 714) and PORTEC-2 trials (n = 427) were used for this study. The design and outcomes of both trials have been published.[20,21] In PORTEC-1, pelvic external beam radiotherapy (EBRT) was compared with no adjuvant treatment, and in PORTEC-2, vaginal brachytherapy (VBT) was compared with EBRT. From 1990 to 1997, PORTEC-1 trial recruited women with FIGO-1988 stage I endometrioid EC (EEC), grade 1-2 with deep myometrial invasion or grade 2-3 with superficial invasion. From 2000 to 2006, PORTEC-2 trial recruited women with EEC with high-intermediate-risk features, defined as (1) FIGO-1988 stage IB with age >60 years and grade 3, (2) stage IC with age >60 years and grade 1-2, or (3) stage IIA (except grade 3 with deep invasion).

Study Protocols (online only) of the PORTEC-1 and PORTEC-2 trials were approved by the medical ethics committees of all participating centers, and all patients provided informed consent.

Central Pathology Review and Molecular Analysis

Tumor characteristics and treatment outcomes were obtained from the trial databases. Tumor characteristics were based on the central pathology review that was performed after random assignment.[3,22,23] This process identified a few women who were in hindsight not eligible. For this study, tumor stage was reclassified according to FIGO-2009.

For all EC, Sanger sequencing of exons 9 and 13 was performed for detection of pathogenic DNA-polymerase-ε exonuclease domain variants.[24] Mismatch-repair status was determined using the Promega MSI analysis system (version 1.2) or immunohistochemistry (IHC) for the four mismatch-repair proteins.[2] The p53 status was defined as abnormal if p53-IHC

in >10% of tumor cells showed a null pattern, nuclear overexpression, or cytoplasmic expression.[25] Details on primers and antibodies have been reported.[3] The molecular class of EC was assigned according to WHO-2020 classification.[1]

Statistical Analysis

Statistical analyses were optimized for causal inference of any difference in treatment effects across the molecular classes. Exchangeability of treatment groups was preserved as much as possible by working with the intention-to-treat populations, excluding as few patients as possible and using the randomly allocated treatment.

The primary analysis of this study consists of two parts: (1) locoregional (vaginal and/or pelvic) recurrence-free survival by treatment across the molecular classes in PORTEC-1 and (2) pelvic recurrence-free survival by treatment across molecular classes in PORTEC-2. These end points were chosen to evaluate recurrences in locations that were exposed to radiotherapy in one treatment group and not exposed to radiotherapy in the other treatment group. Hence, in PORTEC-1, this comprises all recurrences in the pelvis, including in the lymph node regions and the vaginal vault, as no adjuvant therapy was compared with pelvic EBRT. In PORTEC-2, in which VBT was compared with EBRT, this only comprises pelvic recurrences as the vaginal vault region was irradiated in both treatment groups. For the secondary analysis, data of PORTEC-1 and PORTEC-2 were pooled to investigate locoregional recurrence-free survival by treatment across the molecular classes.

Time to recurrence was defined as the time from random assignment to recurrence, with censoring at last follow-up or death in the case of no recurrence. Actuarial survival times were estimated according to Kaplan-Meier's methodology and compared between groups using log-rank tests. Median follow-up was calculated by the reverse Kaplan-Meier method.[26] Multivariable regression analysis was performed using a Cox, proportional hazards model stratified by trial with prespecified covariates on the basis of previous work,[27] with the number of covariables adapted to minimize risk of overfitting. The model used all informative cases and excluded those with missing covariable data (only for lymphovascular space invasion [LVSI] 6.4% missingness). Model validation was performed by analysis of discrimination and indices of optimism determined by means of model fitting to 1,000 bootstrap resamples.[28] Proportionality of hazards was evaluated by inspection of scaled Schoenfeld residuals.

Continuous variables were analyzed by either parametric or nonparametric methods depending on their distribution. Categorical variables were analyzed by nonparametric methods.

As a sensitivity analysis, the primary and secondary analyses were repeated using the competing risk method.[29] Distant
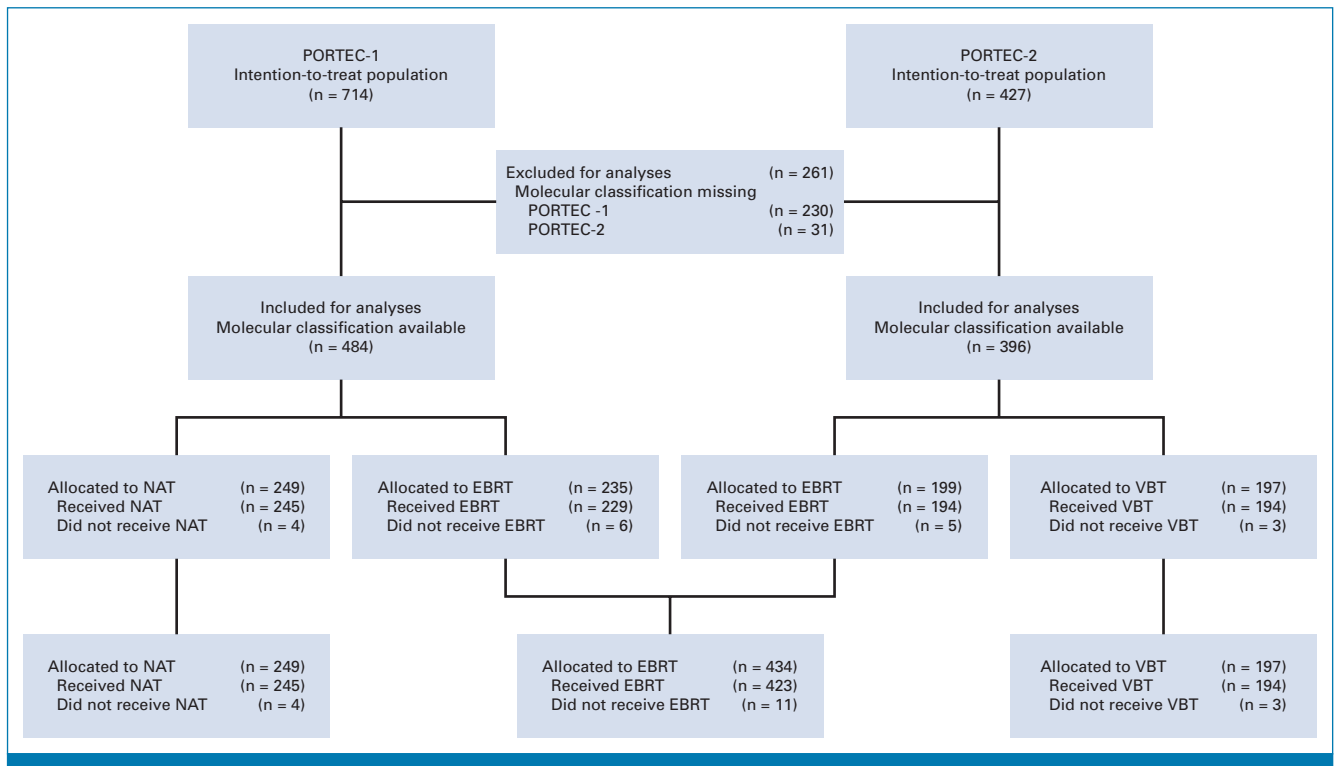

FIG 1. CONSORT diagram. EBRT, external beam radiotherapy; NAT, no adjuvant therapy; VBT, vaginal brachytherapy.

recurrences and deaths were considered competing events for both pelvic and locoregional recurrences. Cumulative incidences were estimated using a Fine and Gray model and compared between treatments across molecular classes using Gray's test.[30]

All *P* values were two-sided, and statistical significance was accepted at *P* < .05. Statistical analyses were performed using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). R packages used in this study included rms, survival, ggPlot2, survminer, and cmprsk.

RESULTS

Of all women (n = 1141) included in the intention-to-treat populations of PORTEC-1 (n = 714) and PORTEC-2 (n = 427), 880 (77.1%) were molecularly classified and included in the current study (Fig 1). The included and excluded women had similar tumor characteristics and treatment outcomes (Appendix Tables A1 and A2, online only).

Characteristics of the 880 included women are presented in Table 1. Almost all had stage I endometrioid EC (97.2%). Few women with higher-stage disease (0.5%) and non-endometrioid histotypes (2.3%) were classified as such at central pathology review, which was performed after random assignment. Substantial LVSI was found in 39 women (4.4%). The most common molecular class was NSMP (56.5%), followed by MMRd (28.1%). Both *POLE*mut EC (7.5%) and p53abn EC (8.0%) were relatively rare. Substantial LVSI was present in one (1.5%) *POLE*mut EC, in 20 (8.1%) MMRd ECs, two (2.8%) p53abn ECs, and 19 (3.8%) NSMP ECs.

The median follow-up was 12.4 years (95% CI, 12.0 to 12.8) in PORTEC-1, 10.5 years (95% CI, 10.2 to 10.7) in PORTEC-2, and 11.3 years (95% CI, 11.1 to 11.6) in the combined PORTEC-1 and PORTEC-2 cohort.

The 5-year risk of vaginal, pelvic, and locoregional recurrences without adjuvant therapy for each molecular class is

TABLE 1. Characteristics of the 880 Women Included From the PORTEC-1 and PORTEC-2 Trials

Characteristic	PORTEC-1 (n = 484)	PORTEC-2 (n = 396)	PORTEC-1 and PORTEC-2 (N = 880)
Age at random assignment, years, median (IQR)	67 (13)	69 (10)	68 (11)
Randomly allocated adjuvant treatment, No. (%)			
None	249 (51.4)		249 (28.3)
Pelvic external beam radiotherapy	235 (48.6)	199 (50.3)	434 (49.3)
Vaginal brachytherapy		197 (49.7)	197 (22.4)
Histotype and grade, No. (%)			
Endometrioid grade 1-2	401 (82.9)	344 (86.9)	745 (84.7)
Endometrioid grade 3	75 (15.5)	40 (10.1)	115 (13.1)
Serous	3 (0.6)	11 (2.8)	14 (1.6)
Clear cell	1 (0.2)	0 (0.0)	1 (0.1)
Others[a]	4 (0.8)	1 (0.3)	5 (0.6)
Stage (2009 classification), No. (%)			
IA	202 (41.7)	67 (16.9)	269 (30.6)
IB	282 (58.3)	324 (81.8)	606 (68.9)
II	0 (0.0)	2 (0.5)	2 (0.2)
IIIA	0 (0.0)	2 (0.5)	2 (0.2)
IIIB	0 (0.0)	1 (0.3)	1 (0.1)
Lymphovascular space invasion, No. (%)			
None	397 (82.0)	307 (77.5)	704 (80.0)
Focal	32 (6.6)	49 (12.4)	81 (9.2)
Substantial	20 (4.1)	19 (4.8)	39 (4.4)
Unknown	35 (7.2)	21 (5.3)	56 (6.4)
Molecular class, No. (%)			
POLE mutant	42 (8.7)	24 (6.1)	66 (7.5)
MMRd	137 (28.3)	110 (27.8)	247 (28.1)
p53-abnormal	40 (8.3)	30 (7.6)	70 (8.0)
NSMP	265 (54.8)	232 (58.6)	497 (56.5)

Abbreviations: MMRd, mismatch repair–deficient; NSMP, no specific molecular profile; *POLE* mutant, pathogenic variants in the exonuclease domain of DNA polymerase epsilon.
[a]Cases reclassified as nonendometrioid after central pathologic review without specification of the histologic subtype.

presented in Appendix Table A3 (online only) on the basis of data of the PORTEC-1 trial. No recurrences were detected among women with *POLE*mut EC. In MMRd EC, vaginal recurrences (6.4%) were slightly more common than pelvic recurrences (4.9%). In p53abn EC, risk of vaginal recurrence was high (24.4%) and pelvic recurrences (6.2%) were also more common than in the other three molecular classes. In NSMP EC, vaginal recurrences were more common (10.0%) than pelvic recurrences (2.2%).

Primary Analysis

In the PORTEC-1 trial, 5-year locoregional recurrence-free survival was significantly better in women treated with EBRT (97.4%) than those with no adjuvant therapy (88.3; $P = 6.0 \times 10^{-4}$; Fig 2A). Locoregional recurrence-free survival by adjuvant therapy for each molecular class is shown in Table 2 and Figure 3. No locoregional recurrences were observed among women with *POLE*mut EC. A small, but nonsignificant, benefit of EBRT (5-year locoregional recurrence-free survival 95.7%) over no adjuvant therapy (90.3%; $P = .52$) was found in MMRd EC. A substantial, but nonsignificant, benefit of EBRT (96.2%) compared with no adjuvant therapy (72.2%; $P = .15$) was observed in the 40 women with p53abn EC. A significant benefit of EBRT (98.3%) over no adjuvant therapy (87.7%; $P = 4.6 \times 10^{-4}$) was detected in NSMP EC.

In the PORTEC-2 trial, no difference in 5-year vaginal recurrence-free survival was observed between the VBT arm (97.8%) and the EBRT arm (97.9%; $P = .98$). Pelvic recurrence-free survival was significantly better in the EBRT group (98.9%) than in the VBT group (94.6%; $P = .010$; Fig 2B). Five-year pelvic recurrence-free survival by adjuvant therapy across the four molecular classes is shown in Table 2 and Figure 4. None of the women with *POLE*mut EC had a pelvic recurrence. Women with MMRd EC who underwent VBT and those who received EBRT had a low risk of pelvic recurrence (96.2% v 100%; $P = .20$). None of the 11 women with p53abn EC in the EBRT group had a locoregional recurrence (100%) in contrast to five of 19 women in the VBT group (68.6%; $P = .055$). No differences in pelvic recurrence-free survival were observed between women with NSMP EC who underwent EBRT (98.2%) or VBT (97.2%; $P = .38$).

Secondary Analysis

The 880 women included in the combined cohort of the PORTEC-1 and PORTEC-2 trials had been randomly assigned to EBRT (49.3%), VBT (22.4%), or no adjuvant treatment (28.3%), which resulted in significantly different 5-year locoregional recurrence-free survival rates of 97.1% (95% CI, 95.5 to 98.7), 93.0% (95% CI, 89.4 to 96.7), and 88.3% (95% CI, 84.3 to 92.5; $P = .0001$; Fig 2C), respectively. Table 2 and Figure 5 show the benefit of radiotherapy for each molecular class. Women with *POLE*mut EC had no recurrences and thus no benefit of radiotherapy. Women with MMRd EC who underwent EBRT (94.2%) or VBT (94.2%) had a small and nonsignificant benefit compared with those
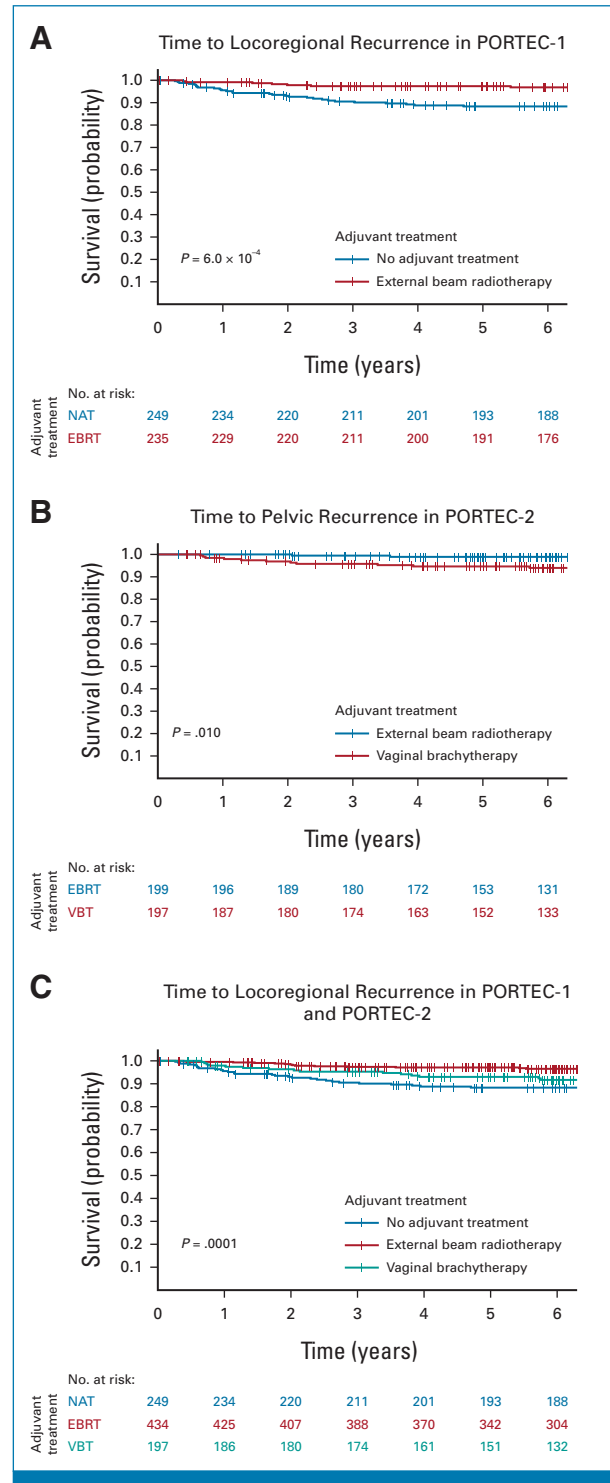
FIG 2. Time to recurrence by adjuvant treatment in the PORTEC-1 and PORTEC-2 trials. (A) Time to locoregional recurrence in PORTEC-1 by adjuvant treatment. (B) Time to pelvic recurrence in PORTEC-2 by adjuvant treatment. (C) Time to locoregional recurrence in the combined PORTEC-1 and -2 cohort by adjuvant treatment. EBRT, external beam radiotherapy; NAT, no adjuvant therapy; VBT, vaginal brachytherapy.

with no adjuvant therapy (90.3%; $P = .74$). In p53abn EC, locoregional recurrence-free survival with no adjuvant therapy (72.2%) and VBT (64.3%) was worse than that with

TABLE 2. Outcome by Adjuvant Treatment Per Molecular Class of EC

	Actuarial Estimates 5 Years After Random Assignment (95% CI)				
	*POLE*mut EC	MMRd EC	p53abn EC	NSMP EC	Total
PORTEC-1: locoregional recurrence-free survival					
EBRT (n = 235)	No events	95.7 (91.0 to 100)	96.2 (89.0 to 100)	98.3 (96.1 to 100)	97.4 (95.3 to 99.5)
NAT (n = 249)	No events	90.3 (83.2 to 98.0)	72.2 (54.2 to 96.2)	87.7 (82.4 to 93.4)	88.3 (84.3 to 92.5)
All (n = 484)	No events	93.0 (88.7 to 97.5)	84.5 (73.9 to 96.7)	92.6 (89.5 to 95.9)	92.7 (90.3 to 95.1)
P	—	.52	.15	4.6×10^{-4}	6.0×10^{-4}
PORTEC-2: pelvic recurrence-free survival					
EBRT (n = 199)	No events	No events	No events	98.2 (95.8 to 100)	98.9 (97.4 to 100)
VBT (n = 197)	No events	96.2 (91.1 to 100)	68.6 (48.8 to 96.3)	97.2 (94.2 to 100)	94.6 (91.4 to 97.9)
All (n = 396)	No events	98.1 (95.5 to 100)	80.9 (67.0 to 97.7)	97.7 (95.8 to 99.7)	96.8 (95.0 to 98.6)
P	—	.20	.055	.38	.010
PORTEC-1 and PORTEC-2: locoregional recurrence-free survival					
EBRT (n = 434)	No events	94.2 (90.1 to 98.5)	96.9 (91.0 to 100)	98.3 (96.6 to 100)	97.1 (95.5 to 98.7)
VBT (n = 197)	No events	94.2 (87.9 to 100)	64.3 (44.8 to 92.3)	96.2 (92.7 to 99.9)	93.0 (89.4 to 96.7)
NAT (n = 249)	No events	90.3 (83.2 to 98.0)	72.2 (54.2 to 96.2)	87.7 (82.4 to 93.4)	88.3 (84.3 to 92.5)
All (N = 880)	No events	93.1 (89.9 to 96.4)	81.6 (72.6 to 91.6)	94.8 (92.8 to 96.8)	93.7 (92.1 to 95.4)
P	—	.74	.048	5.0×10^{-5}	.0001

NOTE. Data maturity was confirmed on the basis of the number of patients at risk at a 5-year follow-up, which was 400 in PORTEC-1 and 325 in PORTEC-2, and by determining the sensitivity index ∆* at 5 years, which was 0.002 in PORTEC-1 and 0.003 in PORTEC-2, both under the threshold of 0.025 proposed by Gebski et al[31] for clinical trials.

Abbreviations: EBRT, external beam radiotherapy; EC, endometrial cancer; MMRd EC, EC with mismatch repair deficiency (*POLE* wild type); NAT, no adjuvant therapy; NSMP EC, EC with no specific molecular profile (*POLE* wild-type, MMR-proficient and p53 wild-type); *POLE*mut EC, EC with a pathogenic mutation of DNA polymerase-ε; p53abn EC, EC with a p53 abnormality (*POLE* wild-type and MMR-proficient); VBT, vaginal brachytherapy.

EBRT (96.9%; *P* = .048). In NSMP EC, EBRT (98.3%) and VBT (96.2%) were associated with a significantly better locoregional recurrence–free survival than no adjuvant therapy (87.7%; *P* = 5.0×10^{-5}).

Multivariable analysis of locoregional recurrence–survival of the combined PORTEC-1 and PORTEC-2 cohort showed that the interaction between the molecular class and the type of adjuvant therapy was not significant (*P* = .13). However, both molecular class and adjuvant therapy had independent prognostic value after correction for age, tumor grade, and the presence of LVSI (Appendix Table A4, online only).

Sensitivity Analysis

An overview of the recurrence rates of first events in provided in Appendix Table A5 (online only). Results of the competing risk analyses are provided in Appendix Table A6 (online only). The cumulative incidences of pelvic and locoregional recurrences were similar to the estimates of locoregional and pelvic recurrence–free survival according to the Kaplan–Meier method. The comparisons of the treatment groups across molecular classes using Gray's test yielded the same findings as the comparisons by the log-rank test.

DISCUSSION

In this study, we determined the predictive value of the molecular classification of EC for response to radiotherapy

using data of two large, randomized radiotherapy trials. A total of 880 women with stage I EEC who had been allocated to EBRT, VBT, or no adjuvant therapy were included for analyses. At 5 years, no locoregional recurrences were observed in women with *POLE*mut EC. In women with MMRd EC, EBRT and VBT yielded a small, nonsignificant benefit compared with no adjuvant therapy. For women with p53abn EC, locoregional recurrence–free survival was excellent after EBRT, but poor after VBT or no adjuvant therapy. In women with NSMP EC, VBT was as effective as EBRT and both yielded a significantly better locoregional control than no adjuvant therapy.

Although *POLE*mut is the rarest molecular class of EC, the evidence for excellent outcomes regardless of adjuvant therapy is accumulating.[6,32,33] Even in the absence of adjuvant treatment, the risk of recurrence seems to be very low, as shown here in 21 women participating in the PORTEC-1 trial and previously in 26 women with high-grade *POLE*mut EC included in a Danish study.[19] This supports prospective investigation of treatment de-escalation, which is currently ongoing in the PORTEC-4a trial (stage I-II EEC with high- to intermediate-risk features)[34] and the *POLE*mut-BLUE trial (stage I-III EEC and non-EEC).[35]

This study found a small, but nonsignificant, benefit of adjuvant radiotherapy in women with stage I MMRd EEC, which is in line with a large, retrospective single-center
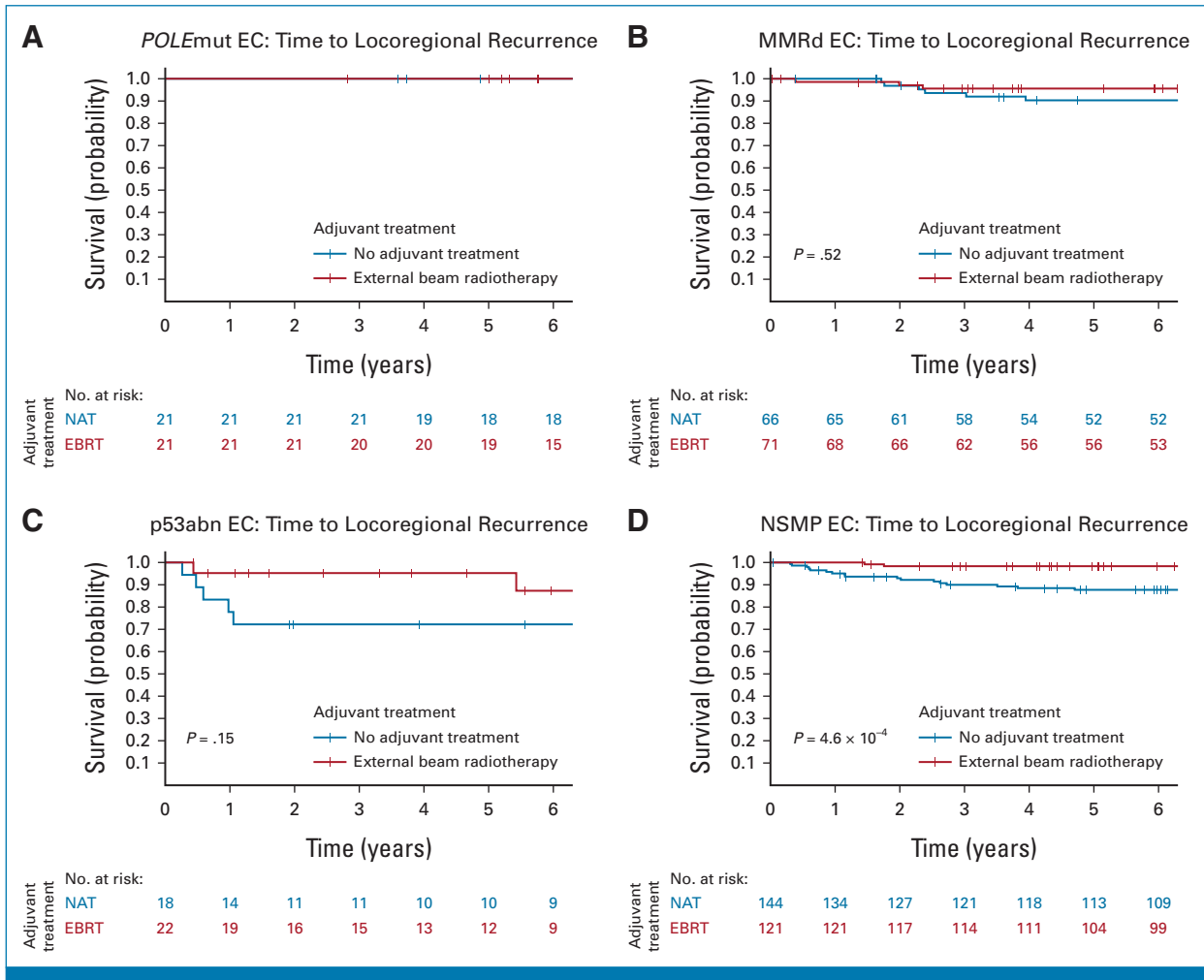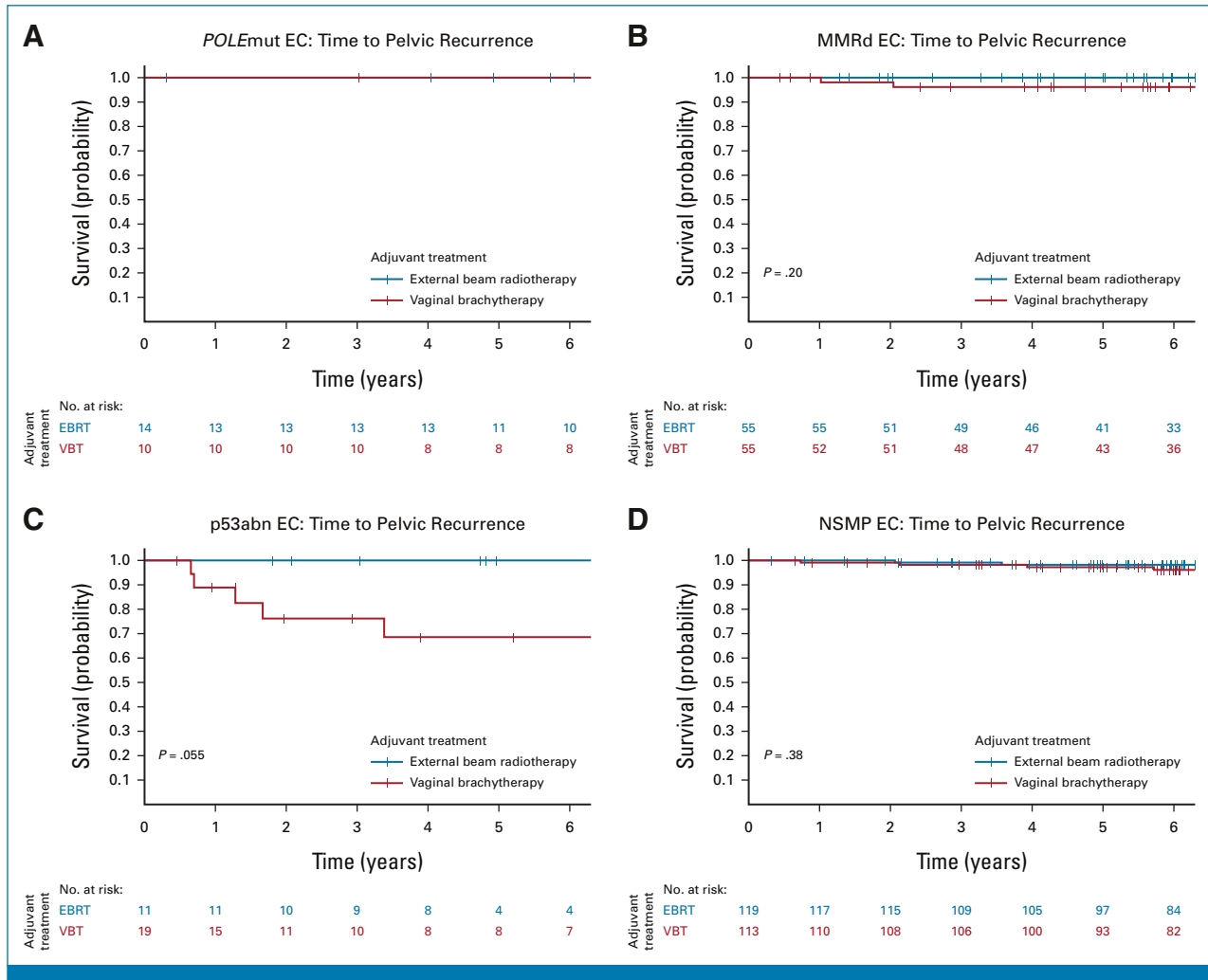
FIG 3. Time to locoregional recurrence per molecular class in PORTEC-1. (A) Time to locoregional recurrence in *POLE*-mutated endometrial cancer. (B) Time to locoregional recurrence in mismatch-repair deficient endometrial cancer. (C) Time to locoregional recurrence in p53 abnormal endometrial cancer. (D) Time to locoregional recurrence in no specific molecular profile endometrial cancer. EBRT, external beam radiotherapy; EC, endometrial cancer; MMRd EC, EC with mismatch repair deficiency (*POLE* wild-type); NAT, no adjuvant therapy; NSMP EC, EC with no specific molecular profile (*POLE* wild-type, MMR-proficient, and p53 wild-type); *POLE*mut EC, EC with a pathogenic mutation of DNA polymerase-ε; p53abn EC, EC with a p53 abnormality (*POLE* wild-type and MMR-proficient).

study conducted in Finland.[36] As these women have a relatively low risk of locoregional recurrence,[3] the absolute benefit of EBRT might not outweigh the risk of toxicity.[37,38] However, in early-stage MMRd EEC, substantial LVSI is associated with a significantly higher risk of recurrence and death.[3] The PORTEC-4a trial currently investigates whether MMRd and NSMP EC with substantial LVSI benefit more from EBRT than standard VBT.[34] A recent study among women with high-risk MMRd EC showed that grade 3 is not associated with an increased risk of recurrence,[39] possibly because high-grade morphological features in MMRd EC result from its hypermutated genotype. Nonetheless, a retrospective study among 57 women with stage IB-II grade 3 MMRd EEC found a significantly better progression-free survival and overall survival with radiotherapy.[40] Therefore, this study supports the current guidelines that recommend adjuvant VBT to reduce risk of vaginal recurrence.[7,9] Further research to identify subgroups within stage I endometrioid MMRd EC that would benefit from EBRT is of interest.

Locoregional recurrence–free survival in early-stage p53abn EEC was poor (70.6% at 5 years) without adjuvant therapy. Although the numbers were limited, this study showed a large significant benefit of adjuvant EBRT over VBT and no adjuvant therapy. The size of the treatment effect seems to indicate that p53abn ECs are particularly radiosensitive. This is probably because p53abn ECs have high genomic instability[16] and are often HR-deficient.[13,14] Since radiotherapy and platinum-based chemotherapy synergistically act upon this, the combination of chemotherapy and radiotherapy should be considered for invasive stage I endometrioid p53abn EC.[6]

This study demonstrates that women with stage I endometrioid NSMP EC have significant benefit from adjuvant
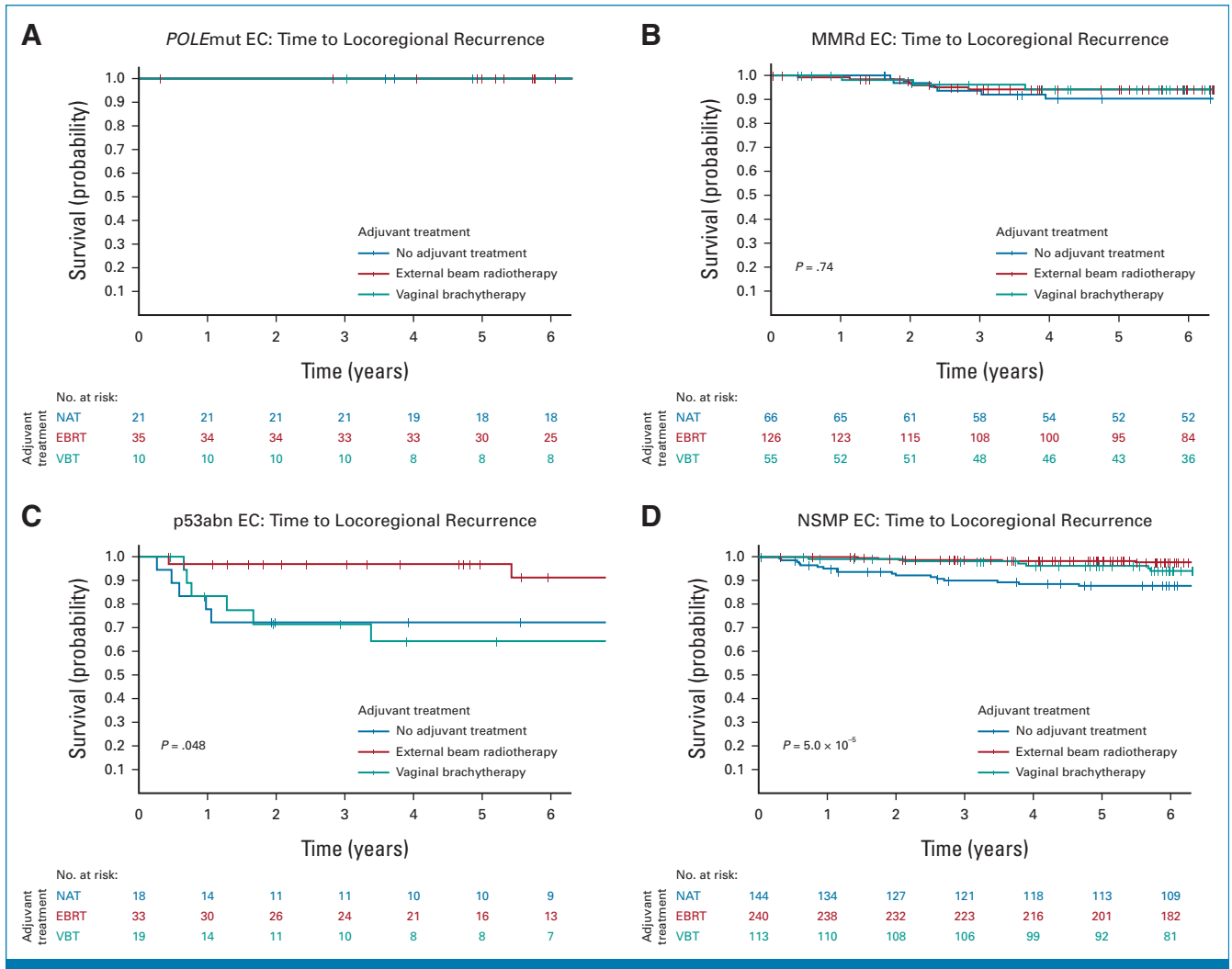
FIG 4. Time to pelvic recurrence per molecular class in PORTEC-2. (A) Time to pelvic recurrence in *POLE*-mutated endometrial cancer. (B) Time to pelvic recurrence in mismatch-repair deficient endometrial cancer. (C) Time to pelvic recurrence in p53 abnormal endometrial cancer. (D) Time to pelvic recurrence in no specific molecular profile endometrial cancer. EBRT, external beam radiotherapy; EC, endometrial cancer; MMRd EC, EC with mismatch repair deficiency (*POLE* wild-type); NSMP EC, EC with no specific molecular profile (*POLE* wild-type, MMR-proficient, and p53 wild-type); *POLE*mut EC, EC with a pathogenic mutation of DNA polymerase-ε; p53abn EC, EC with a p53 abnormality (*POLE* wild-type and MMR-proficient); VBT, vaginal brachytherapy.

radiotherapy for locoregional disease control. This effect is probably the main driver of radiotherapy effects that have been observed in clinical trials[20,41-43] as NSMP is the most common molecular class in early-stage EEC.[3] Since vaginal recurrences are more common (approximately 10%) than pelvic recurrences (approximately 2%) and the toxicity profile of VBT is much milder than that of EBRT,[37] VBT seems to be the preferred radiotherapeutic modality in these women. However, a recent study showed that estrogen re-ceptor (ER)–negative-NSMP EC may represent a biologically distinct subgroup with a higher risk of recurrence.[39] No subgroup analyses by ER status were performed in this study as only 14 of the 497 included NSMP ECs were ER-negative.

The assessment of the molecular classification is currently recommended for all women with high-risk EC.[7-9] Several guidelines encourage molecular profiling also in women with

(high–)intermediate-risk EC,[7-9] and this and other studies show that it has clinically relevant implications. In 5%-10%, molecular testing will show *POLE*mut EC, which is associated with an excellent prognosis and should lead to consideration of de-escalation of adjuvant therapy.[3,6-9,19,32] Around 30% will have MMRd EC, which requires in 70% further testing (for MLH1 promotor hypermethylation) and/or genetic counseling to detect Lynch syndrome (approximately 3% of all EC).[44,45] In another 5%-10%, the molecular classification will reveal p53abn EC, which reclassifies these women to the high-risk group.[7] For them, VBT alone is not sufficient for locoregional and distant disease control and chemotherapy and EBRT should be considered.[6-9] In the remaining ap-proximately 55%, molecular testing will show NSMP for which this study showed a clinically relevant difference in risk of locoregional recurrence between adjuvant radio-therapy and observation.

FIG 5. Time to locoregional recurrence per molecular class in PORTEC-1 and PORTEC-2. (A) Time to locoregional recurrence in *POLE*-mutated endometrial cancer. (B) Time to locoregional recurrence in mismatch-repair deficient endometrial cancer. (C) Time to locoregional recurrence in p53 abnormal endometrial cancer. (D) Time to locoregional recurrence in no specific molecular profile endometrial cancer. EBRT, external beam radiotherapy; EC, endometrial cancer; MMRd EC, EC with mismatch repair deficiency (*POLE* wild-type); NAT, no adjuvant therapy; NSMP EC, EC with no specific molecular profile (*POLE* wild-type, MMR-proficient, and p53 wild-type); *POLE*mut EC, EC with a pathogenic mutation of DNA polymerase-ε; p53abn EC, EC with a p53 abnormality (*POLE* wild-type and MMR-proficient); VBT, vaginal brachytherapy.

The body of evidence on the relevance of molecular testing in EC is growing, but clinical implementation remains challenging. Assessment of mismatch repair deficiency has become the standard of care in many countries because of the clinical importance of detecting Lynch syndrome, which is more effective by MMR IHC than age-based triage.[44,46-48] IHC for p53 is increasingly performed as well, although often limited to selected patients, for example, with non-endometrioid histotypes. The main bottleneck, however, is DNA sequencing of the *POLE* gene, which is mainly performed by next-generation sequencing or Sanger sequencing, techniques that are expensive and/or time-consuming. The increasing number of places where *POLE* testing is offered and reimbursed indicates that many women in high-income countries will probably have access to molecular testing in this decade. Cheap alternatives for

POLE sequencing have already been developed; examples are a quantitative polymerase chain reaction assay called *QPOLE*,[49] a multiplex SNaPshot assay,[50] and a droplet digital polymerase chain reaction assay.[51] These tests may find their way to the clinic more rapidly and could make molecular testing and tailored adjuvant therapy available to women around the world.

To our knowledge, this is the first study to investigate the predictive value of the molecular classification for response to radiotherapy in early-stage EC using two randomized trials with high-quality long-term outcome data. Although an unprecedented number of 880 molecularly characterized ECs were included, some subgroup analyses were limited by insufficient power. For this reason, no further molecular class−specific analyses stratified by risk factors such as LVSI

were performed. This study's design was optimized for the detection of a causal impact of the molecular class on treatment effects. Patients with protocol violations (such as nonendometrioid histotypes or treatment crossovers) were not removed from the analyses, which could have introduced some noise and may dilute differences between groups. The fact that the patterns of treatment effects across the four molecular classes were similar in the independent analyses of PORTEC-1 and PORTEC-2, and sensitivity analysis showing robustness against competing events, makes a strong case for transferability of this result. Nonetheless, external validation on another RCT comparing radiotherapy with no adjuvant therapy has not been performed. This could best be done for EC of the GOG-99,[41] ASTEC/EN.5,[41] and Swedish[43] trials, which have not been molecularly characterized to our knowledge.

In conclusion, the molecular classification is predictive of benefit from radiotherapy in women with stage-I EEC.

Results of this study support decisions on adjuvant therapy. Omitting radiotherapy is safe in women with *POLE*mut EC and will reduce toxicity, improve quality of life, and reduce health care utilization and costs. The impact of both EBRT and VBT seems to be limited in stage I *MMRd* EC and was not significantly different from no adjuvant therapy in this study. However, this result could be due to insufficient power and should be prospectively validated. Women with stage I p53abn EC have a high risk of recurrence, but these cancers seem to be particularly radiosensitive. EBRT is recommended as it yields an excellent locoregional control, in contrast to VBT or no adjuvant therapy. Women with stage I NSMP EC have significant benefit from adjuvant radiotherapy. Here, VBT is the treatment of choice as it is as effective as EBRT but has a much milder toxicity profile. This implies that assessment of the molecular classification is needed to provide women with stage I EEC with the most suitable adjuvant treatment strategy.

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DATA SHARING STATEMENT

The syntax used for data analysis are available upon request. Requests for data sharing can be addressed, with a scientific study proposal, to the corresponding author within 15 years from the date of publication. The PORTEC study group will evaluate the request. Depending on the specific research proposal, the PORTEC study group will determine when, for how long, for which specific purposes, and under which conditions the requested data can be made available, subject to ethical consent.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Molecular Classification Predicts Response to Radiotherapy in the Randomized PORTEC-1 and PORTEC-2 Trials for Early-Stage Endometrioid Endometrial Cancer

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APPENDIX 1. THE PORTEC STUDY GROUP

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TABLE A1. Comparison of Included and Excluded PORTEC-1 Participants

Characteristic	Included (n = 484)	Excluded (n = 230)	P
Age at random assignment, years, median (IQR)	67 (13)	66 (14)	.16
Randomly allocated adjuvant treatment, No. (%)			.43
None	249 (51.4)	111 (48.3)	
Pelvic external beam radiotherapy	235 (48.6)	119 (51.7)	
Histotype and grade, No. (%)			.006
Endometrioid grade 1-2	401 (82.9)	200 (87.0)	
Endometrioid grade 3	75 (15.5)	20 (8.7)	
Nonendometrioid	8 (1.7)	10 (4.3)	
Stage (2009 classification), No. (%)			.66
IA	202 (41.7)	92 (40.0)	
≥IB	282 (58.3)	138 (60.0)	
Lymphovascular space invasion, No. (%)			.72
None or focal	429 (95.5)	108 (94.7)	
Substantial	20 (4.5)	6 (5.3)	
Survival outcomes (survival probability), % (SE)			
Pelvic recurrence-free survival (at 5 years)	98.2 (0.6)	96.7 (1.2)	.73
Locoregional recurrence-free survival (at 5 years)	92.7 (1.2)	90.3 (2.0)	.70
Overall survival (at 5 years)	83.6 (1.7)	81.7 (2.5)	.95

TABLE A2. Comparison of Included and Excluded PORTEC-2 Participants

Characteristic	Included (n = 396)	Excluded (n = 31)	P
Age at random assignment, years, median (IQR)	69 (10)	69 (11)	.92
Randomly allocated adjuvant treatment, No. (%)			.84
Pelvic external beam radiotherapy	199 (50.3)	15 (48.4)	
Vaginal brachytherapy	197 (49.7)	16 (51.6)	
Histotype and grade, No. (%)			.14
Endometrioid grade 1-2	344 (86.9)	30 (96.8)	
Endometrioid grade 3	40 (10.1)	1 (3.2)	
Nonendometrioid	12 (3.0)	0 (0.0)	
Stage (2009 classification), No. (%)			.55
IA	67 (16.9)	4 (12.9)	
≥IB	329 (83.1)	27 (87.1)	
Lymphovascular space invasion, No. (%)			1.00
None or focal	356 (94.9)	17 (94.4)	
Substantial	19 (5.1)	1 (5.6)	
Survival outcomes (survival probability), % (SE)			
Pelvic recurrence-free survival (at 5 years)	96.8 (0.9)	100.0 (-)	.97
Locoregional recurrence-free survival (at 5 years)	94.9 (1.1)	96.3 (3.6)	.85
Overall survival (at 5 years)	83.8 (1.9)	86.8 (6.1)	.46

TABLE A3. Five-Year Recurrence Rates Among Women Who Received No Adjuvant Treatment in PORTEC-1 by Molecular Class

	POLEmut (n = 21)	MMRd (n = 67)	p53abn (n = 17)	NSMP (n = 146)	
Clinical Outcome		Actuarial Estimate, % (SE)			Log-Rank P
PORTEC-1: no adjuvant therapy group					
Vaginal recurrence	0	6.4 (3.1)	24.4 (10.6)	10.0 (2.5)	.046
Pelvic recurrence	0	4.9 (2.7)	6.2 (6.1)	2.2 (1.3)	.69
Locoregional recurrence	0	11.2 (4.0)	29.4 (11.1)	12.1 (2.8)	.028

Abbreviations: MMRd, mismatch repair–deficient; NSMP, no specific molecular profile; POLEmut, pathogenic mutation of DNA polymerase-ε; p53abn, p53 abnormality (POLE wild-type and MMR-proficient).

TABLE A4. Predictors of Locoregional Recurrence-Free Survival in the Combined PORTEC-1 and PORTEC-2 Cohort

Predictor	HR (95% CI)	P
Molecular class		
POLEmut	No events	
MMRd	Reference	
p53abn	4.04 (1.86 to 8.77)	<.0001
NSMP	0.91 (0.49 to 1.71)	.78
Adjuvant therapy		
None	Reference	
EBRT	0.25 (0.12 to 0.53)	<.0001
VBT	0.47 (0.13 to 1.64)	.23
Stage		
IA	Reference	
≥IB	1.98 (1.05 to 3.73)	.035
LVSI	3.90 (1.71 to 8.87)	.001
Grade		
1-2	Reference	
3	2.12 (1.12 to 4.04)	.022

NOTE. Multivariable analysis using a Cox proportional hazard's model with stratification by trial.
Abbreviations: EC, endometrial cancer; HR, hazard ratio; MMRd EC, EC with mismatch repair deficiency (POLE wild type); NSMP EC, EC with no specific molecular profile (POLE wild-type, MMR-proficient, and p53 wild-type); POLEmut EC, EC with a pathogenic mutation of DNA polymerase-ε; p53abn EC, EC with a p53 abnormality (POLE wild-type and MMR-proficient).

TABLE A5. Overview of Failure Rates of First Events in the Combined PORTEC-1 and PORTEC-2 Cohort

Clinical Outcome	Cumulative Incidence at 5 Years, % (95% CI)
Vaginal recurrence	3.8 (2.7 to 5.2)
Pelvic recurrence	2.1 (1.3 to 3.3)
Locoregional recurrence	5.9 (4.5 to 7.6)
Distant recurrence	7.7 (6.1 to 9.6)
Death without failure	8.6 (6.8 to 10.5)

TABLE A6. Sensitivity Analyses: Outcome by Adjuvant Treatment Per Molecular Class of EC Using Competing Risk Analysis

Adjuvant Therapy Group	Cumulative Incidence at 5 Years After Random Assignment, % (95% CI)			
	POLEmut EC	MMRd EC	p53abn EC	NSMP EC
PORTEC 1: locoregional recurrence-free survival (n = 484)				
EBRT (n = 235)	No events	4.2 (1.1 to 10.8)	4.5 (0.3 to 19.4)	1.7 (0.3 to 5.3)
NAT (n = 249)	No events	9.1 (3.7 to 17.6)	27.8 (9.7 to 49.5)	11.8 (7.2 to 17.7)
P	—	.30	.12	.00056
PORTEC 2: pelvic recurrence-free survival (n = 396)				
EBRT (n = 199)	No events	No events	No events	0.8 (0.1 to 4.2)
VBT (n = 197)	No events	3.6 (0.6 to 11.2)	26.3 (9.1 to 47.6)	2.7 (0.7 to 7.0)
P	—	.16	.069	.16
PORTEC-1 and PORTEC-2: locoregional recurrence-free survival (n = 880)				
EBRT (n = 434)	No events	5.6 (2.5 to 10.6)	3.0 (0.2 to 13.6)	1.3 (0.3 to 3.4)
VBT (n = 197)	No events	5.5 (1.4 to 13.8)	31.6 (12.3 to 53.0)	3.6 (1.2 to 8.2)
NAT (n = 249)	No events	9.1 (3.7 to 17.6)	27.8 (9.7 to 49.5)	11.8 (7.2 to 17.7)
P	—	.60	.042	3×10^{-5}

Abbreviations: EBRT, external beam radiotherapy; EC, endometrial cancer; MMRd EC, EC with mismatch repair deficiency (POLE wild-type); NAT, no adjuvant therapy; NSMP EC, EC with no specific molecular profile (POLE wild-type, MMR-proficient, and p53 wild-type); POLEmut EC, EC with a pathogenic mutation of DNA polymerase-ε; p53abn EC, EC with a p53 abnormality (POLE wild-type and MMR-proficient); VBT, vaginal brachytherapy.