Radiotherapy for endometrial cancer: improved patient selection, techniques and outcomes

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CHAPTER 3

MOLECULAR-INTEGRATED RISK PROFILE TO DETERMINE ADJUVANT RADIOTHERAPY IN ENDOMETRIAL CANCER: EVALUATION OF THE PILOT PHASE OF THE PORTEC-4A TRIAL

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ABSTRACT

Objective: The Post-Operative Radiation Therapy in Endometrial Carcinoma (PORTEC)-4a trial is a randomized trial for women with high-intermediate risk endometrial cancer (EC), comparing individualized adjuvant treatment based on a molecular-integrated risk profile to standard adjuvant treatment; vaginal brachytherapy. To evaluate patient acceptability and pathology logistics of determining the risk profile, a pilot phase was included in the study.

Methods: PORTEC-4a is ongoing and the first 50 patients enrolled were included in the pilot phase. Primary endpoints of the pilot phase were patient acceptance, evaluated by analyzing the screening logs of the participating centers, and logistical feasibility of determination of the risk profile within 2 weeks, evaluated by analyzing the pathology database.

Results: In the first year, 145 eligible women were informed about the trial at 13 centers, of whom 50 (35%) provided informed consent. Patient accrual ranged from 0-57% per center. Most common reasons for not participating were: not willing to participate in any trial (43.2%) and not willing to risk receiving no adjuvant treatment (32.6%). Analysis of the pathology database showed an average time between randomization and determination of the molecular-integrated risk profile of 10.2 days (1-23 days). In 5 of the 32 patients (15.6%), pathology review took more than 2 weeks.

Conclusions: The PORTEC-4a trial design was proven feasible with a satisfactory patient acceptance rate and an optimized workflow of the determination of the molecular- integrated risk profile. PORTEC-4a is the first randomized trial to investigate use of a molecular-integrated risk profile to determine adjuvant treatment in EC.

INTRODUCTION

Endometrial cancer (EC) is the most common gynecological cancer and primarily affects postmenopausal women between ages 60 and 80.[1] Primary treatment consists of surgery, most often laparoscopic hysterectomy and bilateral salpingo-oophorectomy.[2] The current indication for adjuvant radiotherapy depends on clinicopathological risk factors and has been investigated in several randomized trials.[3-6] In the PORTEC-1 and GOG 99 trials women with early stage EC were randomized to pelvic external beam radiotherapy (EBRT) or observation after surgery.[3,4] EBRT significantly reduced the risk of locoregional recurrence, without survival benefit. In the observation group, 75% of the locoregional recurrences were located in the vaginal vault. In the subsequent PORTEC-2 trial which included women with early stage EC with high-intermediate risk (HIR) factors, vaginal brachytherapy (VBT) was compared to EBRT. Results showed adjuvant VBT to be equally effective as EBRT for vaginal control (98% at 5 years in both arms), with less toxicity and improved quality of life.[6-8]

Based on the PORTEC-2 trial, adjuvant VBT became the standard of care for women with HIR EC. However, this may be overtreatment as 7-10 women need to be treated with VBT to prevent one recurrence.[9] An observational Danish population-based study showed that women with intermediate risk EC, who were observed after surgery, had similar survival rates but a higher risk of locoregional recurrence (14%) as compared to previous Danish data with use of radiotherapy.[10]

To prospectively investigate long-term local control and survival, the initial design of the PORTEC-4 study aimed to randomize women with HIR endometrial cancer 1:2 to observation or vaginal brachytherapy (VBT); subsequently, within the VBT arm, they were 1:1 allocated to standard dose VBT (21 Gy in 3 fractions) or reduced dose VBT (15 Gy in 3 fractions).[6] However, patient inclusion was difficult because the majority of eligible patients preferred treatment over observation. A patient preference study showed that patients preferred adjuvant VBT, which has limited toxicity and is highly effective, because of fear for recurrence of the disease and the more intensive salvage treatment in case of recurrence. Additionally, this study showed that even for a small local control benefit, radiation oncologists were likely to recommend VBT over observation.[11] For these reasons, the original PORTEC-4 trial design was not feasible, and new prognostic factors with impact on the risk of recurrence had emerged. After a major change in design, the trial continued as the PORTEC-4a trial as detailed below.

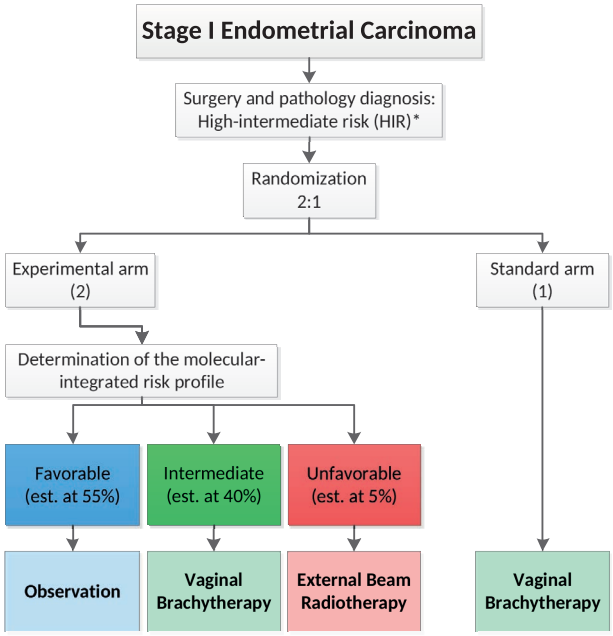
In 2013, the whole genome studies of the Cancer Genome Atlas (TCGA) analyzed the molecular genetic basis of EC development and defined four molecular subclasses, based on mutation burden and copy number alterations. The subclass with the highest mutational load were EC with mutations in the exonuclease domain of *DNA polymerase-epsilon (POLE),* associated with an

excellent prognosis. Microsatellite unstable EC (MSI, driven by mismatch repair deficiency) and the subclass copy number-low EC (also referred to as no specific molecular profile (NSMP)), had an intermediate outcome. The subclass characterized by high somatic copy number alterations, mostly driven by *TP53* mutation, were the most aggressive cancers with unfavorable prognosis.[12] Subsequently, in a comprehensive analysis of 947 EC from the pooled PORTEC-1 and PORTEC-2 biobank, it was shown that by use of surrogate markers for the TCGA subclasses their prognostic value could be confirmed.[13] Additionally, in this and other studies it was shown that L1 cell adhesion molecule (L1CAM) overexpression and substantial lymph-vascular space invasion (LVSI) were significant risk factors for both pelvic and distant recurrences. Within the NSMP group, ß-catenin (*CTNNB1)* was found to be prognostic for distant recurrence.[13-18] An integrated clinicopathologic and molecular risk profile was established for EC with HIR features, separating them in favorable, intermediate and unfavorable groups, each with a clearly different prognosis.[13]

To evaluate the clinical role of this molecular-integrated risk profile in the determination of adjuvant treatment in patients with HIR EC, the PORTEC-4a study was initiated in 2016. Women with HIR endometrial cancer are randomized (2:1) to the experimental arm, in which the molecular-integrated risk profile is determined and used to assign adjuvant treatment, or to standard VBT. Women with a favorable profile (*POLE* mutation, or NSMP without *CTNNB1* mutations) are observed after surgery; women with an intermediate risk profile (mismatch repair-deficient (MMRd) or NSMP with *CTNNB1* mutations) receive adjuvant VBT; and women with any of the unfavorable risk factors (substantial LVSI, *TP53* abnormal immunohistochemical staining or L1CAM overexpression) are treated with EBRT. See Figure 1A and 1B.

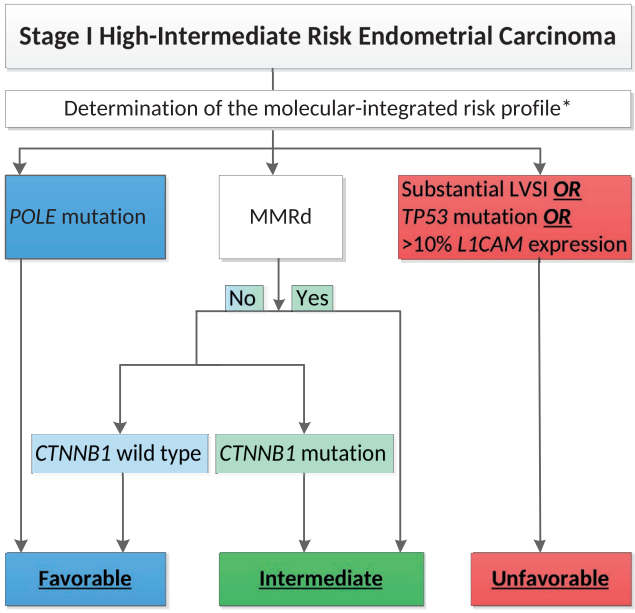
The PORTEC-4a trial was designed with an initial pilot phase of 50 patients. Objectives were to assess patient acceptance of the experimental arm and the logistical feasibility of determining the molecular-integrated risk profile within 2 weeks, as patients must start radiotherapy within a clinically acceptable time frame of 8 weeks from the date of surgery. Here we report on the results on the pilot phase of the PORTEC-4a trial.

Figure 1A. Study design of the PORTEC-4a trial.



**High-intermediate risk (HIR) endometrial cancer:* stage IA (with invasion) and grade 3; stage IB, grade 1 or 2; with either age ≥ 60 or substantial lymph-vascular space invasion (LVSI); stage IB, grade 3 without LVSI; or stage II (microscopic) with grade 1. Est = estimated.

Figure 1B. Decision tree of the molecular-integrated risk profile.



*Patients with multiple characteristics (double classifiers) were designated intermediate risk. MMRd = Mismatch repair-deficiency. For details, see text.

METHODS

Study design and randomization

The PORTEC-4a trial is a multicenter randomized phase 3 trial, led by the Dutch Gynecologic Oncology Group. The trial aims to evaluate vaginal recurrence after adjuvant treatment or observation based on the molecular-integrated risk profile in women with HIR EC, as compared to standard vaginal brachytherapy (VBT), and evaluate quality of life and toxicity in both groups. Eligible women who consent to participation in the PORTEC-4a trial are randomly allocated (1:2) to VBT or the experimental arm using a biased coin minimization procedure with stratification for participating center, tumor grade and type of surgery. The PORTEC-4a trial opened to patient recruitment in June 2016. A total of 500 evaluable patients will be enrolled in the trial. The 54 participants of the previous PORTEC-4 trial design will be included in the analysis by adding those randomized to VBT to the control group (n=36), and those randomized to observation to the experimental arm if their risk profile is favorable. Only approximately 8 women in the observation arm (45% of the 18 in this arm) will have either an intermediate or unfavorable risk profile and will be excluded from the analysis. The first 50 patients who were randomized in the PORTEC-4a trial were included in the pilot phase of the study to evaluate patient acceptability and feasibility of logistics, where after recruitment continued for the main trial endpoints. The trial protocol was approved by the LUMC Ethics Committee (CME P16.054), the Dutch Cancer Society review board (CKTO 2011-5336; amended version) and by the institutional review boards of the participating centers. The trial is registered with the Netherlands Trials Registry (NTR5841), the ISRCTN Registry (ISRCTN11659025) and clinicaltrials.gov (NCT03469674).

Patient selection and eligibility criteria

Women are eligible for the trial when diagnosed with high-intermediate risk (HIR) endometrial cancer, defined as: endometrial cancer of either (1) FIGO stage IA (with invasion) and grade 3; (2) FIGO stage IB grade 1 or 2 with age $\geq$ 60 and/or LVSI; (3) FIGO stage IB grade 3 without LVSI; or (4) FIGO stage II (microscopic) and grade 1. Eligible patients have had surgery using laparoscopic or abdominal hysterectomy and bilateral salpingo-oophorectomy (with or without pelvic lymphadenectomy) and a WHO-performance status of 0-2. Exclusion criteria are non-endometrioid type endometrial cancer, uterine sarcoma, a history of malignancy within 5 years, previous pelvic radiotherapy and an interval of more than 8 weeks between surgery and start of radiotherapy.

Pathology review and molecular-integrated risk profiles

After informed consent and randomization, all histopathological slides and a representative formalin-fixed paraffin-embedded (FFPE) block of the tumor are sent to the Department of

Pathology at LUMC for pathology review and determination of the molecular-integrated profile. Standard items to be determined are histological type and grade, depth of invasion and presence and semi-quantification of LVSI. Immunohistochemistry and molecular analysis are performed to determine the *POLE* (exon 9, 13 and 14) and *CTNNB1* (exon 3) status, L1CAM, p53 and MMR protein expression (MLH1, PMS2, MSH2, MSH6), and, additionally, ER/PR status. During the pilot phase a transition was made in the method of molecular analysis from targeted Sanger sequencing to targeted NGS. In the transition phase, assessment of *POLE* exon 9, 13 and 14 was performed by Sanger sequencing. Later, these exons were included in the Ampliseq Cancer Hotspot NGS panel. In case of loss of MMR-protein expression without *MLH1* promoter hypermethylation (expected in 3-5% of cases[19]), this is reported to the treating physician for patient information and referral to a clinical geneticist for counseling and germline mutation analysis for possible Lynch-syndrome.

The pathology review has to be completed within 2 weeks from randomization, as patients have to start radiotherapy within 8 weeks from surgery. The results of pathology review and the molecular-integrated risk profile are immediately sent back to the local radiation oncologist to determine adjuvant treatment. For patients in the standard arm, a limited set of data (including MMRd and ER/PR) is reported back to the treating center, while the molecular-integrated profile (including all other variables) is reported to the trial database. For all patients who have given informed consent for tissue storage for further translational research, one FFPE-block is stored in the dedicated PORTEC4a tissue repository; all original slides are returned to the local pathology lab. During the pilot phase, pathology review and determination of the integrated profile was conducted at LUMC to ensure uniform procedures and determine the logistical feasibility. After completion of the pilot phase, other regional pathology labs can be authorized to perform the review and determine the profile for trial participants in their region.

Treatment and follow-up

Treatment in the experimental arm is based on the molecular-integrated risk profile: women with a favorable profile are observed after surgery; those with an intermediate profile receive VBT; and those with an unfavorable risk profile receive EBRT (Figure 1). Based on the previous analysis[13], about 55% of those with HIR EC are expected to have a favorable profile, about 40% an intermediate profile and about 5% an unfavorable profile.

Women in the standard arm and those with an intermediate profile in the experimental arm will receive VBT to the vaginal vault (target volume including the upper 3.5-4 cm of the proximal vagina) with a vaginal cylinder and a high-dose-rate (HDR) afterloader. The VBT dose is 21 Gy HDR in 3 fractions of 7 Gy, specified at 5 mm from the applicator surface and top, 5-7 days apart,

with an overall treatment time of 2 weeks. Centers have to complete a dummy-run procedure for vaginal brachytherapy before participation in the trial, and quality assurance is done by evaluation of one treatment plan per year for each participating center.[20] Women in the experimental arm with an unfavorable profile will receive pelvic EBRT to a total dose of 45-48.6 Gy in 1.8-2 Gy daily fractions, 5 times a week, using CT-based intensity modulated radiotherapy planning (IMRT) or a volumetric arc technique (VMAT or RapidArc).

Patients in both arms are evaluated at alternating follow-up visits by their gynecologic oncologist and radiation oncologist every 3 months for the first 2 years, and every 4-6 months up to the 5th year. Information at 7 years is obtained from the GP. In case of recurrence, full evaluation is required and treatment with curative intention is initiated, if appropriate. All patients with recurrent disease remain in follow-up; in case of death, information on its cause is required.

Toxicity is evaluated by the radiation oncologist using CTCAE v 4.0[19] at baseline; at 3-4 weeks after completion of brachytherapy or EBRT; and at each follow-up visit. Assessment of health-related quality of life (HRQL) is done by use of the EORTC QLQ C-30 core questionnaire and endometrial cancer-specific EN24 module in both arms at baseline, at 6 weeks, and at 6, 12, 18, 24, 36, 60 and 72 months from randomization.

Trial endpoints and statistical design

The primary outcome of the PORTEC-4a trial is the 5-year cumulative incidence of vaginal recurrence. Secondary outcomes are pelvic and distant recurrence rates, 5-year vaginal control rate including treatment for relapse, 5-year recurrence-free and overall survival, adverse events, patient-reported symptoms and quality of life, and endometrial cancer-related healthcare costs.

To estimate vaginal recurrence in both groups with sufficient precision and to exclude a clinically relevant difference, the trial is based on a non-inferiority design with an equivalence margin of 7%. For a total of 500 evaluable patients, with 334 in the experimental arm and 167 patients in the standard arm, the estimated power (based on 10.000 simulations) is 84.4% (α=0.05). An additional power calculation was done comparing patients with a favorable profile in the standard arm (receiving VBT) versus those with a favorable profile in the experimental arm (receiving observation), using a non-inferiority design with an equivalence margin of 8.5%. The power for this comparison is dependent on the actual 5-yr cumulative incidence of VR in the favorable subgroup of the experimental arm (power >75% for VR <5%) and analysis will be largely descriptive, estimating the difference with standard error <2.5. The competing risk method will be used with death, pelvic and distant recurrences as competing events for vaginal recurrence. The analysis will be performed according to intention-to-treat. Analysis of HRQL will be based on treatment received, including participants with a valid

baseline and at least one follow-up questionnaire. EC-related healthcare costs, including the costs of the initial treatment by randomized arm, follow-up, care associated with adverse events and with treatment of recurrence, will be evaluated and compared.

Evaluation of the pilot phase

After the first 50 included patients, the results of the pilot phase were evaluated. Endpoints for the pilot phase are patient acceptability of the trial and feasibility of obtaining the molecular-integrated profile within two weeks after randomization. Pathology logistics were evaluated by assessment of all logistical data of the 32 patients that were randomized to the experimental arm. Additional logistical problems concerning the pathology review were evaluated by interviewing the review-pathologists. To evaluate patient acceptability, the screening logs kept by the participating centers on patient assessment and reasons for trial acceptance or refusal were evaluated.

RESULTS

Participants

The first 50 patients of the PORTEC-4a trial were included between June 10th 2016 and June 12th 2017, in 10 radiation oncology centers in The Netherlands. Of those, 32 patients were randomly assigned to the experimental arm and 18 to the standard arm. Currently, 16 centers in The Netherlands have been opened for inclusion, of which some quite recently, and 12 have been actively including patients. A total of 138 patients have been accrued to date (July 2018), of whom 91 were randomly allocated to the experimental arm and 47 to the standard arm (Figure 2).

Patient acceptance

Evaluation of the screenings logs of all participating centers showed that 145 eligible women had been informed about the trial in 13 participating centers. 50 of those 145 (35%) women provided informed consent. Patient accrual ranged from 0 to 57% per center. The remaining 95 of the 145 eligible patients were informed about the trial but did not participate for the following reasons: 41 (43.2%) did not want to participate in any trial and 31 (32.6%) did not want to risk receiving no adjuvant treatment. In 9 (9.5%) cases the radiation oncologist forgot to inform the patient about the trial, and 8 (8.4%) patients had difficulty understanding the trial. Four (4.2%) patients refused participation because of the possibility of receiving external beam radiotherapy instead of vaginal brachytherapy, and 2 (2.1%) patients did not want to participate in quality of life questionnaires (Table 1). Physicians reported that consenting patients were motivated by the added information on their individual risk and necessity to undergo adjuvant treatment, and by contributing to scientific knowledge informing future treatments.

Figure 2. Cumulative accrual of the PORTEC-4a trial.

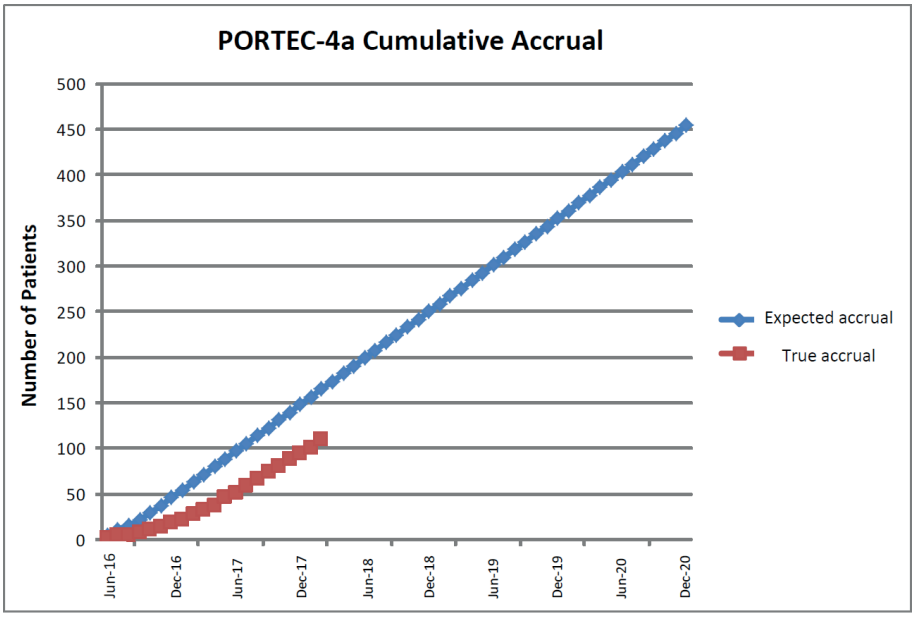


Table 1. Reasons for not participating.

Reasons	Number
Refusal to participate in any trial	41 (43.2%)
Not willing to risk observation	31 (32.6%)
Physician forgot to ask	9 (9.5%)
Difficulty understanding	8 (8.4%)
Not willing to risk EBRT*	4 (4.2%)
Not willing to fill in questionnaires	2 (2.1%)
Total	**95**

** EBRT: external beam radiotherapy*

Logistics of pathology review

By protocol, pathology review had to be performed within 14 days from randomization. Analysis of logistical data of the 32 patients that were randomized to the experimental arm showed an average time between randomization and receipt of all requested materials at the department of Pathology in the LUMC of 5.8 days (range: 1-16 days). Of these 32 cases, 21 were included by institutions other than LUMC. In 7 out of 21 cases (21.9%), material had to be requested more than once. Overall, the average time between randomization and determination of the molecular-integrated profile was 10.2 days (range: 1-23 days); without cases from the LUMC, the average time was 12.2 days (range: 5 – 23 days). In 5 of the 32 patients (15.6%), pathology review took

more than 2 weeks. Causes for the determination of the molecular-integrated profile exceeding the protocol requirement of 2 weeks were: delayed receipt of the requested materials (>7 days after randomization) in 4 cases, and extended duration of the Next-Generation Sequencing (NGS) panel in 1 case (Table 2).

By interviewing the review pathologists on the logistics of the molecular-integrated profile, the main issues were found to be that (1) the logistics of ensuring prompt receipt of all required materials without patient identifiers (in view of the trial setting) involved repeated explanation and multiple phone calls were sometimes needed in the early phase of the trial; and (2) during the pilot phase *POLE* (exon 9, 13 and 14) were added to the next generation sequencing (NGS) panel, which resulted in a slightly longer turnaround time of results as compared to the targeted Sanger sequencing of *POLE* as was performed during the development of the test.

Table 2. Cases with delayed (>14 days) result of the profile.

Number of days	Main reason
2	15 days for NGS*
3	7 days until receipt, 10 days for NGS
4	3x request for material, 12 days until receipt#
6	16 days until receipt#
9	2x request for material, 15 days until receipt

** NGS: Next-Generation Sequencing; in the early phase, NGS runs were only done once a week.*
 # At this time, the Sanger Sequencing method was used to determine the profile

DISCUSSION

In the pilot phase of the PORTEC-4a trial the feasibility and patient acceptance of the trial design were evaluated, as the trial randomizes women with HIR EC between standard VBT and treatment based on an individual molecular-integrated risk profile. Evaluation of the acceptance of the trial design by eligible women showed a patient inclusion rate of 35%. Most common reasons not to participate in the trial were that patients were either not willing to participate in any randomized trial, or preferred to receive standard care.

Evaluation of trial logistics showed that the large majority (84%) of the molecular-integrated risk profiles were assessed within the required timeframe of 14 days. Causes for delay in the logistics were delayed receipt of the requested materials and the turnaround time of NGS. Overall, the PORTEC-4a trial proved to be feasible and patient inclusion was continued at a slightly increased rate due to more centers being activated.

Patient acceptance of the trial design was satisfactory with a patient inclusion rate of 1 in 3 eligible women, which was in accordance with the study protocol expectations. This was substantially higher than in the previous PORTEC-4 design, wherein centers reported that only 1 in about 10 to 15 eligible women accepted randomization, due to their preference of adjuvant VBT over observation, even for a minimal benefit. This is in line with the patient preference study, done in the scope of the PORTEC-4 trial, in which women chose VBT over observation at a lower minimal benefit than clinicians (median 0 vs. 8%).[11] A study on decision making in breast cancer patients showed that women felt more in control of their disease, when opting for an active treatment compared to observation.[20] Chapple et al. investigated treatment decision making in men with prostate cancer and described that patients were afraid to be observed instead of treated and felt pressure from their relatives to choose an active treatment over observation.[21]

The new trial design implemented the recent knowledge of the molecular heterogeneity of EC, including the four molecular-genetic subclasses described by the TCGA and other negative prognostic risk factors such as LVSI, L1CAM and mutations in exon 3 of *CTNNB1*.[12, 14-18] Eligible women accepted the new trial design that evaluated use of the molecular-integrated profile to determine adjuvant treatment much more often; the inclusion rate of 35% included not only patient acceptance but also initial logistical issues.

Currently, 138 patients have been recruited to the trial in the first 2 years. In the Netherlands, 16 centers are open for inclusion, and several international groups have shown interest in participating in the trial.

Evaluation of trial logistics showed that delayed receipt of requested slides and FFPE blocks was the most common difficulty initially. Due to the trial setting, the materials had to be requested without patient identifiers (only the local pathology number), and repeated phone calls and/or emails were sometimes needed. Introduction of standard email text clarifying the urgent request of materials helped to improve this, as well as increased awareness of the trial at other pathology laboratories in the initial phase. Another logistical challenge was the transition from targeted Sanger sequencing to targeted NGS. While Sanger sequencing is a relatively cheap method yielding fast results (<24 hours), NGS is associated with higher costs and has a longer turnaround time, which also depends on the number of NGS-runs initiated per week in the laboratory. We transitioned to targeted NGS for PORTEC-4a as we anticipated that other laboratories will have easy access to NGS platforms, whereas the use of Sanger sequencing in diagnostic pathology is rapidly decreasing. Currently the NGS panel includes *POLE* (exon 9, 13 and 14) and has been fully integrated in the workflow, with 2-3 runs per week, ensuring timely results.

According to the current Dutch guidelines, all women with HIR endometrial cancer should be treated with adjuvant VBT.[2] LVSI has been shown to be an essential risk factor and has been

introduced in the most recent version of the ESMO-ESGO-ESTRO consensus recommendations.[22] However, the recent knowledge on the molecular genetic basis of endometrial cancer has become available by the Cancer Genome Atlas studies, with establishment of four distinct molecular subgroups associated with prognosis, has not yet been introduced into the clinic. Several groups have shown that the four molecular subgroups can be determined in clinical practice using surrogate markers on FFPE tissues and confirmed their prognostic significance.[13, 16] However, these molecular risk factors have not yet been evaluated in clinical practice to determine patient management. Moreover, both our group and the Vancouver group have shown that the molecular risk factors should be integrated with other major risk factors to obtain the strongest prognostic significance and highest clinical relevance.[13, 23]

The PORTEC-4a trial is the first prospective randomized trial that investigates the use of an integrated molecular risk profile in endometrial cancer to determine adjuvant treatment in the clinic. PORTEC-4a aims to avoid overtreatment by omitting VBT in women with endometrial cancer with traditional clinicopathological high-intermediate risk factors, but favorable risk by the molecular-integrated profile. On the other hand, the trial is also aiming to avoid undertreatment of the few women with high-risk factors such as substantial LVSI, *TP53* mutation or L1CAM overexpression by using EBRT in these cases.[14, 15] If the PORTEC-4a trial shows similar local control rates for both the molecular-integrated risk profile arm and the standard VBT arm, integrated risk assessment will become standard practice, tailoring treatment on a more individual basis and sparing health care costs. Furthermore, these women will be spared the burden and toxicity of vaginal brachytherapy, as approximately half of all women with HIR EC currently undergoing VBT will be observed after surgery (Figure 1).

Other opportunities that will emerge with assessment of molecular-integrated risk profiles lie within the fields of pre-operative staging and tailored treatment of metastatic disease. Studies that assessed the concordance of pre-operative curettage samples and surgical specimens showed that molecular alterations detected in curettage samples reliably predicted the alterations found in the subsequent hysterectomy specimens.[24, 25] Pre-operative assessment of molecular risk factors may aid patient counseling and enable tailoring of treatment, especially in the case of high-risk features, for example by more extensive diagnostic work-up (PET-CT scanning), tailored lymph node assessment or even neo-adjuvant treatment.[26] As the molecular groups with *POLE* mutation and mismatch repair deficiency have been shown to be highly immunogenic, first small studies of targeted treatment by checkpoint inhibition have been done, showing promising results.[27, 28] However, especially for molecular high-risk features and non-endometrioid histologies, clinical data are still limited and studies addressing the role of the molecular integrated classifiers to inform and direct treatment of specific high-risk subgroups,

both in treatment of primary and recurrent disease, are needed.

In conclusion, the PORTEC-4a trial design has been proven feasible by assessment of the pilot phase and recruitment is ongoing. PORTEC-4a is the first trial to assess the use of an integrated molecular profile to determine adjuvant treatment, and other studies using molecular-based treatment are eagerly awaited.

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