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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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HIGHLIGHTS

- Molecular-integrated risk profiling holds promise to improve individualization of treatment in endometrial cancer (EC).
- PORTEC-4a is the first randomized clinical trial investigating molecular profile-based adjuvant treatment in EC.
- The trial design was proven feasible with a good patient acceptance rate and logistical feasibility; accrual is ongoing.

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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 to 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 >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.

☆ Trial registration numbers – clinicaltrials.gov (NCT03469674); ISRCTN11659025; NTR5841.

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1. 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, β 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 Fig. 1A and B.

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.

2. Methods

2.1. 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 (UL 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).

2.2. 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 ≥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 >8 weeks between surgery and start of radiotherapy.

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