PErsonalized TReatment for Endometrial Carcinoma (PETREC): study design and methods of a prospective Finnish multicenter trial

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ABSTRACT

Background Endometrial carcinomas can be classified into four molecular subgroups – mismatch repair deficient (MMRd), p53 abnormal (p53abn), polymerase-ϵ (*POLE*) ultramutated, and 'no specific molecular profile' (NSMP). Retrospective data imply that the response to adjuvant therapies may depend on the molecular subgroup. These findings emphasize the need for adjuvant therapy trials where patients are randomized to treatment arms separately within each molecular subgroup.

Primary Objective The PErsonalized TReatment for Endometrial Carcinoma (PETREC) trial clarifies the value of molecular classification in the determination of adjuvant therapies of high-intermediate risk and early-stage high-risk endometrial carcinoma.

Study Hypothesis Compared with vaginal brachytherapy, the utilization of whole pelvic radiotherapy may result in improved outcomes for either MMRd or NSMP high-intermediate risk carcinomas. Early-stage high-risk p53abn and nonendometrioid carcinomas are postulated to gain benefits from chemoradiotherapy, as opposed to chemotherapy alone. *POLE* ultramutated carcinomas harboring high-intermediate or high-risk clinicopathologic features are speculated to have favorable prognosis without any adjuvant therapy.

Trial Design This prospective, multicenter, phase 3 trial compares the efficacy of vaginal brachytherapy vs whole pelvic radiotherapy in high-intermediate risk MMRd and NSMP molecular subgroups, and chemotherapy vs chemoradiotherapy in early-stage high-risk p53abn subtype and nonendometrioid carcinomas. Eligible women who consent to participation in the trial are randomly allocated (1:1) to treatment arms.

Major Inclusion/Exclusion Criteria Women with stages I–II molecular integrated high-intermediate risk or high-risk endometrial carcinoma will be included.

Primary Endpoint The primary endpoint is the 5 year cumulative incidence of disease recurrence.

Sample Size A total sample size of 294 patients (49 subjects in each treatment arm of the three subgroups intended for randomization) was estimated to be sufficient.

Estimated Dates for Completing Accrual and Presenting Results Patient recruitment will be completed in 2025, and follow-up will be completed in 2030.

Trial Registration NCT05655260.

INTRODUCTION

Endometrial carcinoma is the most common cancer of the female genital tract in women living in developed countries. In Finland, the age-standardized rate was 27.92 per 1 00 000 women in 2014. About 800 new cases are diagnosed annually.[1]

The mainstay of the initial treatment for endometrial carcinoma is surgery with total hysterectomy, bilateral salpingo-oophorectomy, and peritoneal washings, complemented with regional lymph node staging in selected cases. Adjuvant therapy is tailored according to stage and final pathology findings, that is, histology and grade, depth of myometrial invasion, and lymphovascular space invasion.[2]

In 2013, The Cancer Genome Atlas (TCGA) consortium performed a genomic, transcriptomic, and proteomic characterization of 373 endometrial carcinomas and identified four prognostically distinct molecular subgroups: polymerase-ϵ (*POLE*) ultramutated (7% of cases), microsatellite unstable hypermutated (28%), copy-number low (39%), and copy-number high (26%).[3] Of these, the *POLE* ultramutated and copy-number high subgroups are associated with an excellent outcome and poor outcome, respectively. Meantime, the microsatellite unstable hypermutated and copy-number low subgroups are associated with an intermediate outcome. Apart from the *POLE* ultramutated subgroup, molecular classification can be reproduced by using surrogate markers, thus providing a clinically feasible method for risk-stratification of endometrial carcinomas in gynecologic oncology practices.[4]

Pooled data of retrospective studies confirmed that molecular subgroups of endometrial carcinoma provide independent prognostic information beyond established clinicopathologic risk factors.[5] However, the role of molecular-integrated risk profiles in the triage of patients to adjuvant therapies has not been established in a prospective setting. The PErsonalized

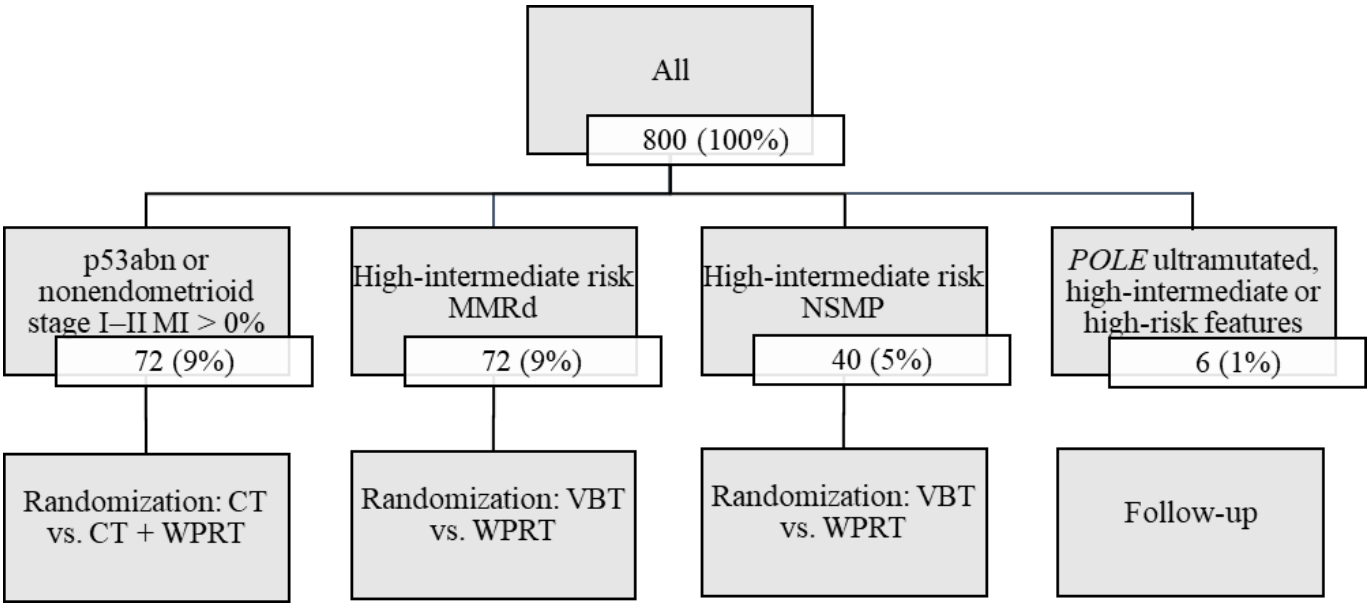

Figure 1 Patient subgroups along with their estimated rates and proportions in Finland per year, and allocation to treatment arms in the PETREC trial.

Abbreviations: CT, chemotherapy; MI, myometrial invasion; MMRd, mismatch repair deficient; NSMP, no specific molecular profile; p53abn, p53 abnormal; *POLE*, polymerase-ϵ; VBT, vaginal brachytherapy; WPRT, whole pelvic radiotherapy.

TReatment for Endometrial Carcinoma (PETREC) trial was designed to assess the role of molecular subgroups in determining adjuvant therapies in high-intermediate risk and early-stage high-risk endometrial carcinoma.

METHODS

Trial Design

The PETREC trial is a prospective, Finnish, multicenter, phase 3 trial that compares the efficacy of vaginal brachytherapy vs whole pelvic radiotherapy in mismatch repair deficient (MMRd, surrogate to microsatellite unstable hypermutated in the TCGA classification system) and 'no specific molecular profile' (NSMP, surrogate to copy-number low) molecular subgroups, and chemotherapy vs chemoradiotherapy in p53 abnormal (p53abn, surrogate to copy-number high) and nonendometrioid carcinomas (figure 1). Quality of life and toxicity are evaluated in each group. The trial protocol has been approved by the institutional review boards of the participating centers. The trial is registered with ClinicalTrials.gov (NCT05655260). Anticipated recruitment rates are based on a cohort of 604 women with a molecularly characterized endometrial carcinoma who underwent surgery at the Department of Obstetrics and Gynecology, Helsinki University Hospital, between January 1, 2007 and December 31, 2012.[6]

Participants

Women with a newly diagnosed endometrial carcinoma are eligible for the trial when one of the molecular integrated histopathologic inclusion criteria, shown in table 1, is met. Patients must have undergone hysterectomy with bilateral salpingo-oophorectomy

Table 1 Molecular integrated histopathologic inclusion criteria

Tumor characteristics	ESGO-ESTRO-ESP risk group
MMRd/NSMP stage IA–B grade 1–2, substantial LVSI	High-intermediate
MMRd/NSMP stage IA grade 3, substantial LVSI	
MMRd/NSMP stage IB grade 3	
MMRd/NSMP stage II grade 1–3	
p53abn stage I–II MI>0%	High
MMRd/NSMP nonendometrioid stage I–II MI>0%	
POLE ultramutated (including *POLE* ultramutated–MMRd and *POLE* ultramutated–p53abn double classifiers) stage I–II with high-intermediate or high-risk pathology features as defined above	Low

ESGO, European Society of Gynecological Oncology; ESP, European Society of Pathology; ESTRO, European SocieTy for Radiotherapy and Oncology; LVSI, lymphovascular space invasion; MI, myometrial invasion; MMRd, mismatch repair deficient; NSMP, no specific molecular profile; POLE, polymerase-ϵ; p53abn, p53 abnormal.

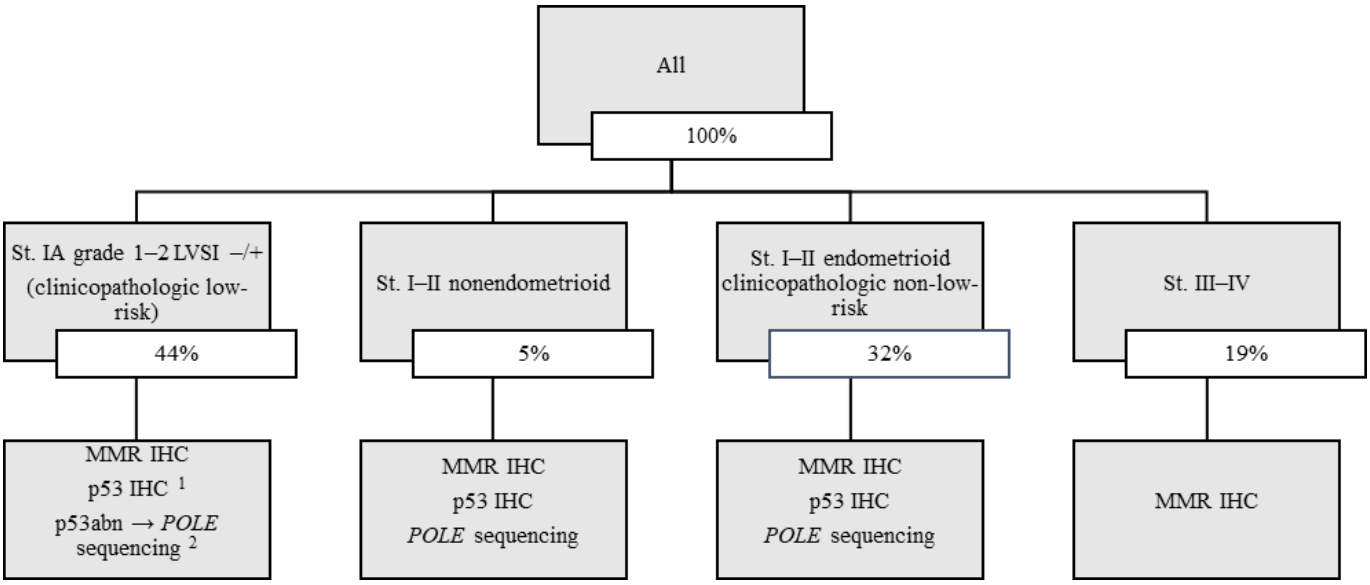

Figure 2 Targeting of molecular characterization and estimated proportions for each type of tumor.
Abbreviations: IHC, immunohistochemistry; LVSI, lymphovascular space invasion; MMR, mismatch repair; *POLE*, polymerase-ϵ.
Notes: [1] p53 abnormal in about 3% of clinicopathologic low-risk cases.[2] *POLE* ultramutated–p53 abnormal double classifiers are classified as *POLE* ultramutated (= low risk).

and peritoneal washing, with or without pelvic-aortic lymphadenectomy or pelvic sentinel node biopsy before enrollment. Given that the trial is restricted to molecular integrated high-intermediate risk and high-risk carcinomas,[2] most patients will have undergone lymphatic staging.

Exclusion criteria are age <18 years, WHO performance status >2, uterine sarcoma, a history of malignancy within 5 years, previous pelvic radiotherapy, and an interval of >30 days between surgery and start of chemotherapy or >8 weeks between surgery and start of radiotherapy (longer intervals may be permitted with investigator's approval).

The review of histopathological slides will be performed at the Departments of Pathology of the participating centers. Standard items to be determined are histologic type and grade, depth of myometrial invasion, and semi-quantification of lymphovascular space invasion (LVSI).[2]

Molecular characterization of the tumors is carried out as shown in figure 2. In clinicopathologic low-risk carcinomas, *POLE* sequencing can be restricted to those with abnormal p53 staining, whereby *POLE* ultramutated–p53abn double classifiers can be identified.[6] *POLE* testing can be further reduced by omitting it in advanced (stage III–IV) carcinomas, in which adjuvant therapy decisions are not altered by molecular classification.[6] Mutations of *POLE* in the exonuclease domain (exons 9–14) are analyzed by direct sequencing. Expression of p53 and MMR proteins (MLH1, PMS2, MSH2, MSH6) is analyzed by immunohistochemistry.

The pelvic radiotherapy dose is 45 to 50.4 Gy over 5 to 6 weeks (1.8 Gy per day for 25 to 28 fractions). Patients randomized to vaginal brachytherapy will receive cuff brachytherapy at 21 Gy in 3 fractions of 7 Gy at 0.5 cm depth. Patients assigned to chemotherapy, i.e. those with stage I–II high-risk carcinoma (table 1), will receive paclitaxel (175 mg/m2) and carboplatin (area under curve, 5) every 3 weeks for six cycles. Treatment adjustments are allowed at the discretion of the physician.

Patients are evaluated at follow-up visits every 4 months for year 1, every 6 months up to year 3, and every 12 months up to year 5. Whole body computed tomography will be the standard imaging modality to diagnose a relapse in a symptomatic patient, and to assess disease extent when a relapse is diagnosed by physical examination or bedside ultrasound. In case of recurrence, patients are treated as appropriate and remain in follow-up thereafter. In case of death, information on its cause is required. Assessments of toxicity and health-related quality of life are done using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and the EORTC QLQ-EN24 module for endometrial cancer, respectively, at baseline and at each follow-up visit.

Stage I–II *POLE* ultramutated carcinomas with clinicopathologic high-intermediate risk or high-risk features are defined as low-risk carcinomas in the molecular integrated risk model.[2] Although not randomized, these patients are evaluated at 6 months and then annually up to the year 5 for confirmation of their good outcome (figure 1).

Primary Endpoints

The primary outcome of the PETREC trial is the 5 year cumulative incidence of disease recurrence. Secondary outcomes are vaginal, pelvic, and distant recurrence rates, 5 year recurrence-free and overall survival, adverse events, and patient-reported symptoms and quality of life.

Sample Size

Sample size was calculated assuming a relapse rate of 10% vs 30% in the two treatment arms of the three molecular subgroups intended for randomization. Using an alpha level of 0.05 and a power of 80%, a sample size of 49 subjects in each treatment arm of the three subgroups was estimated to be sufficient.

Of all patients with newly diagnosed endometrial carcinoma, 23% can be expected to be eligible for randomization in the PETREC trial.

The anticipated proportions for the risk groups of interest are 9% for MMRd high-intermediate risk, 5% for NSMP high-intermediate risk, and 9% for stage I–II high-risk. In addition, about 5% of clinicopathologic high-intermediate risk tumors and 1% of clinicopathologic high-risk tumors may be shifted to the low-risk group based on *POLE* mutation. With the rate of about 800 endometrial carcinomas diagnosed in Finland per year, roughly 180 patients could be screened annually.

The investigation has been authorized in eight centers in Finland between February 8, 2022 and May 12, 2022. A total of 94 patients have been accrued to date (August 2023).

Randomization and Blinding

Eligible women who consent to participation in the trial are randomly allocated (1:1) to treatment arms. Management of patients who consent to follow-up within the trial but not to randomization is based on multidisciplinary meeting decisions and patient preference. Blinding will not be applied in the PETREC trial.

Statistical Methods

Recurrence rates are estimated by the Kaplan-Meier method. Data are analyzed using the Statistical Package for the Social Sciences software (International Business Machines Corporation, Armonk, NY, USA).

DISCUSSION

Six randomized trials established the role of adjuvant radiotherapy in decreasing the risk of pelvic and vaginal relapse without improving overall survival in early-stage endometrial carcinoma.[7–12] Compared with whole pelvic radiotherapy, vaginal brachytherapy provides equivalent vaginal control with a lower risk of acute gastrointestinal toxicity and improved quality of life.[13] However, it is important to consider that opting for vaginal brachytherapy entails a greater risk of pelvic (nonvaginal) recurrence compared with pelvic radiation.[13] The use of adjuvant chemotherapy to treat early-stage endometrial carcinomas is not supported by available evidence. However, decisions regarding early-stage nonendometrioid carcinomas remain challenging as available studies were not adequately powered for subset analyses.[13] Given these uncertainties, adjuvant chemotherapy is often recommended, with or without radiotherapy.

Knowledge of the relationship between molecular subgroups of endometrial carcinoma and benefit from adjuvant therapies is restricted by the lack of randomized trials. As commented in the joint statement by the European Society of Gynecological Oncology (ESGO), the European SocieTy for Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP), prospective evaluation of the molecular characteristics of endometrial carcinoma is highly recommended in randomized trials.[2] Molecular subgroups may play a dual role in determining the optimal adjuvant therapy. First, clinicopathologic risk factors may differently modify the prognostic impact of molecular subgroups so that, compared with NSMP, prognosis of MMRd is worsened by unfavorable clinicopathologic factors.[5] Second, retrospective data imply that the response to adjuvant therapies may depend on the molecular subgroup, so that either MMRd carcinomas or NSMP carcinomas may gain the most benefit.[4] Compared with whole pelvic radiotherapy, chemoradiotherapy improved recurrence-free survival for stage I–III p53abn endometrial carcinomas.[14] These findings emphasize the need for adjuvant therapy trials where patients are randomized to treatment arms separately within each molecular subgroup.

The PETREC trial is a prospective trial that investigates the use of molecular classification in the assessment of optimal adjuvant therapy in high-intermediate risk and stage I–II high-risk endometrial carcinoma, as determined by the ESGO-ESTRO-ESP criteria.[2] The high-intermediate risk group includes stage IB MMRd/NSMP patients with grade 3 tumors, any stage I MMRd/NSMP patients with substantial LVSI, and any stage II MMRd/NSMP patients. Stage I–II high-risk tumors include p53abn and nonendometrioid carcinomas with myometrial invasion.

As per the ESGO-ESTRO-ESP guidelines, adjuvant therapy decisions are based on classification of endometrial carcinomas into five risk groups with specific clinicopathologic features.[2] Integration of molecular classification is encouraged to improve prognostication and triage to adjuvant therapy when molecular tools are available. For high-intermediate risk carcinomas, vaginal brachytherapy is recommended as the standard adjuvant therapy. In patients who did not undergo lymph node staging, whole pelvic radiotherapy can be recommended, especially in patients at highest risk for lymph node involvement (substantial LVSI and/or stage II). For stage I–II high-risk carcinomas, chemotherapy with or without whole pelvic radiotherapy is recommended.

Eligibility is restricted to high-intermediate risk and early-stage high-risk endometrial carcinomas due to their indeterminate prognoses and variable options for adjuvant therapy. Because of the rather strict tumor-related inclusion criteria, we anticipate that 23% of all patients may be eligible for screening in the PETREC trial.[6] These patients are divided into three subgroups that are randomly allocated to treatment arms. Each subgroup comprises 5% to 9% of all patients.

The proportion of patients consenting to randomization cannot be predicted in advance. To improve recruitment rates, patients who reject randomization remain eligible for the trial. Non-randomized patients are enrolled in a prospective observational study after giving informed consent. Management of these patients is based on multidisciplinary meeting decisions and patient preference. Besides improving recruitment rates, the comprehensive cohort study design may reduce selection bias and improve generalizability of the findings. As a trade-off, the option to enter non-randomized patients into the trial may reduce clinicians' efforts in encouraging patient consent to randomization.

About 6% of tumors harboring either high-intermediate risk or high-risk clinicopathologic features are shifted to the low-risk group because of *POLE* mutation.[6] These patients will not be treated with adjuvant therapy. Their follow-up will hopefully confirm that the outcome of the *POLE* ultramutated molecular subgroup is intrinsically good, as opposed to good outcome due to exceptional response to adjuvant therapies.

In summary, the PETREC trial clarifies the value of molecular classification in the determination of adjuvant therapies of high-intermediate risk and early-stage high-risk endometrial carcinoma. The findings of the trial may eventually help to decrease under- and over-treatment and, consequently, improve patient outcomes and decrease treatment-associated adverse events.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Helsinki University Hospital Institutional Review Board, reference number HUS/2360/2021 Participants gave informed consent to participate in the study before taking part.

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