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

Nanda Horeweg, Remi A Nout, Ina M Jürgenliemk-Schulz, Ludy C H W Lutgens, Jan J Jobsen, Marie A D Haverkortv, Jan Willem M Mens, Annerie Slot, Bastiaan G Wortman, Stephanie M de Boer, Ellen Stelloo, Karen W Verhoeven-Adema, Hein Putter, Vincent T H B M Smit, Tjalling Bosse, Carien L Creutzberg; PORTEC Study Group

J Clin Oncol. 2023 Sep 20;41(27):4369-4380. doi: 10.1200/JCO.23.00062. Epub 2023 Jul 24.

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.