Prognostic relevance of the molecular classification in high-risk endometrial cancer: Analysis of the PORTEC-3 trial

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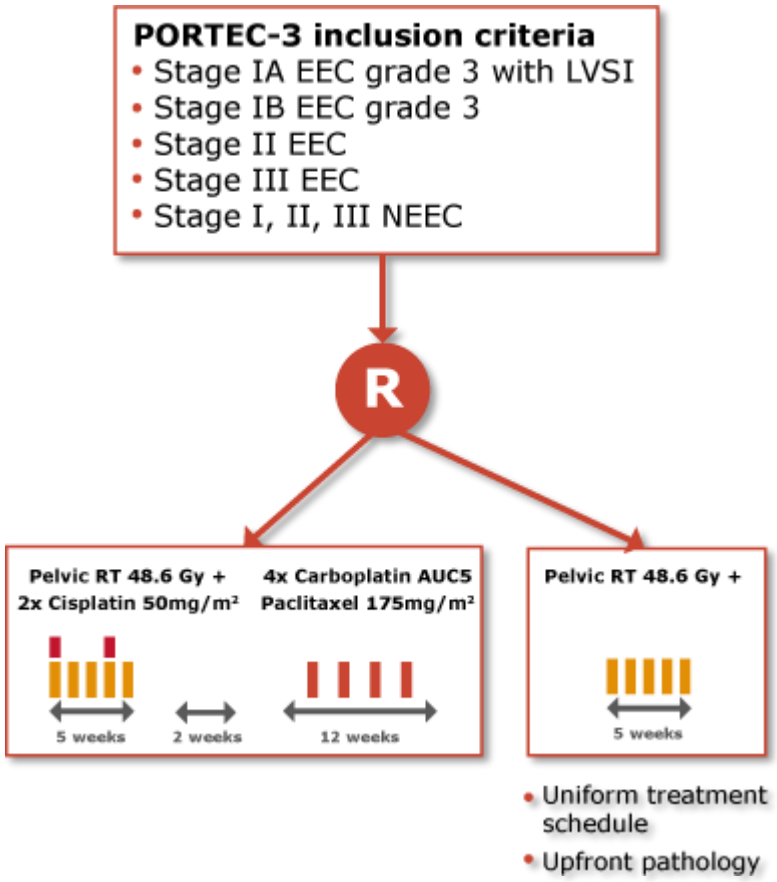
Objectives & Methods

OBJECTIVES

PORTEC-3 trial investigated the benefit of combined adjuvant chemotherapy and radiotherapy versus pelvic radiotherapy alone for women with high-risk endometrial cancer (HREC).

Recent studies have discovered and confirmed four different molecular subclasses in EC, with each having a distinct prognosis; POLE-ultramutated, microsatellite unstable, copy-number low, and copy-number high.



Objectives & Methods

The aim of this study:

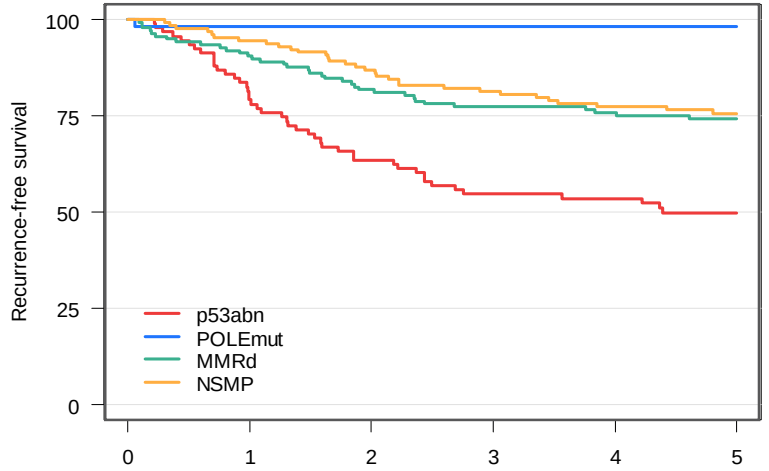
- evaluate the prognostic significance of the molecular classification in HREC using tissues from consenting PORTEC-3 trial participants
- evaluate molecular subclass specific benefit of combined chemotherapy and radiotherapy.

METHODS

- tissue samples obtained from 410 of the 660 participants in the PORTEC-3 trial
- tumours classified into four molecular subgroups of endometrial cancer with prognostic value:
  - 92 (22%) samples were p53 mutant staining (p53abn)
  - 2 (13%) POLE ultramutated (POLEmut)
  - 137 (33%) MMR deficient (MMRd)
  - and 129 (32%) no specific molecular profile (NSMP).
- treatment well balanced between molecular subgroups

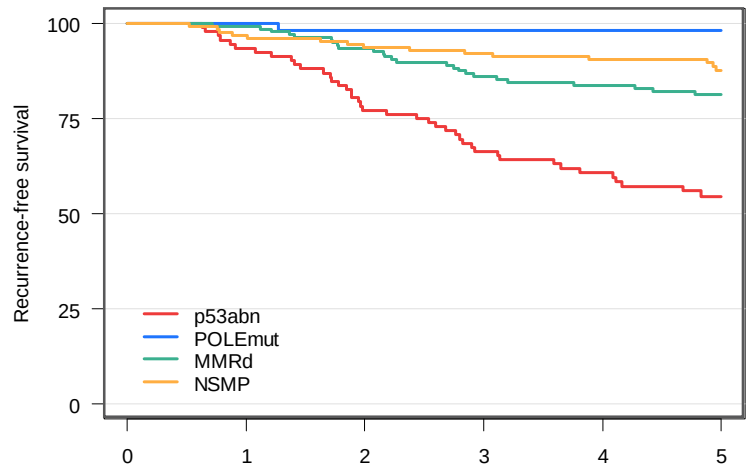
Results

RECURRENCE-FREE SURVICAL (RFS)



Five-year RFS for patients with *POLE*mut, p53abn, MMRd and NSMP EC was 98%, 50%, 74% and 76%, respectively (p<0.0001)

OVERALL SURVIVAL (OS)



OS for patients with *POLE*mut, p53abn, MMRd and NSMP EC was 98%, 55%, 81% and 88% (p<0.0001).

- p53abn was the strongest prognostic factor for decreased survival, while pathogenic POLE EDM was the strongest favourable factor
- Patients with p53abn HREC had significant benefit of combined adjuvant chemotherapy and radiotherapy (5-year RFS with CTRT 61% versus 37% for RT, log-rank p=0.015).

Conclusions

The **molecular classification** provides **better risk stratification** than histopathology alone.

Patients with **POLEmut HREC have excellent clinical outcome**, suggesting these should be **classified as low-risk**, independent of other pathologic variables.

P53abn EC is the strongest predictor of poor clinical outcome, and these patients had significant benefit from added chemotherapy.

Molecular characteristics should be incorporated in clinical diagnostics and decision making and future trials should address molecular subgroup-based treatments.