Randomised Phase III Trial Comparing Concurrent Chemoradiation and Adjuvant Chemotherapy with Pelvic Radiation Alone in High Risk and Advanced Stage Endometrial Carcinoma: PORTEC-3.

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The addition of concurrent and adjuvant chemotherapy to postoperative radiation therapy will increase 5-year overall survival and failure-free survival of patients with high-risk and advanced stage endometrial carcinoma.

Ethische beoordeling	Positief advies
Status	Werving gestopt
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON25773

Bron
NTR

Verkorte titel
PORTEC-3

Aandoening

Endometrial carcinoma

Ondersteuning

Primaire sponsor: Leiden University Medical Center (LUMC), Department of Clinical Oncology
Overige ondersteuning: Dutch Cancer Society (KWF Kankerbestrijding, CKTO 2006-04)

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

5-year actuarial overall suvival
5-year actuarial failure-free survival (with failure defined as relapse or death due to endometrial carcinoma or to treatment complications).

Toelichting onderzoek

Achtergrond van het onderzoek

Background:
The PORTEC-1 trial (1990-1997) has demonstrated that postoperative external beam radiation therapy (EBRT) for stage 1 endometrial cancer significantly increases 5-year local control (96% versus 85%), but without a difference in survival. The currently ongoing PORTEC-2 trial for intermediate-risk endometrial carcinoma patients investigates whether vaginal brachytherapy, compared to EBRT, provides equally high rates of vaginal control and survival, with less toxicity and better quality of life.
Patients with stage IC (deep myometrial invasion) grade 3 tumors have a higher risk of recurrence and endometrial carcinoma related death. These patients were registered during the PORTEC-1 accrual period and received EBRT. Compared to the PORTEC-1 patients who were randomized to EBRT, stage IC grade 3 cases had an inferior prognosis, with 58% 5-year survival versus 83-86% for grade 1-2 and 74% for IB grade 3, mainly due to a higher risk of distant metastases. In multivariate analyses grade 3 was the most important adverse prognostic factor with hazard ratios for relapse and for endometrial carcinoma related death of 5.4 (p=0.0001) and 5.5 (p=0.0004). These findings are confirmed by literature data. Stage I and II grade 3 tumors, unfavorable histologic types (serous and clear cell cancers) and stage III tumors are at increased risk of relapse and death (50% 5-year survival).
First results of trials using adjuvant chemotherapy for advanced stage endometrial carcinoma show reduction of recurrence rates and increased survival rates. Omitting pelvic radiation would increase the risk of pelvic relapse. The concurrent use of chemotherapy and radiotherapy has become standard for many tumor sites, as both local control and survival rates are improved. However, this has not yet been investigated for endometrial carcinoma.
A RTOG phase II trial of concurrent chemotherapy and radiation therapy followed by adjuvant chemotherapy for high-risk and advanced stage endometrial carcinoma used 2 cycles of cisplatin during radiotherapy, followed by 4 adjuvant cycles of cisplatin and paclitaxel at 4-week intervals. This phase II trial, showing combination therapy to be feasible and having promising outcome data, was the basis for the PORTEC-3 study. However, in PORTEC-3 the cisplatin has in the adjuvant phase been replaced by carboplatin to reduce toxicity.
Objectives:

Establish whether treatment with concurrent radiotherapy and chemotherapy, followed by adjuvant chemotherapy, improves overall survival and failure-free survival of patients with high-risk and advanced stage endometrial carcinoma, in comparison with pelvic radiation therapy alone. Secondary objectives are to establish and compare the rates of severe (grades 3 and 4) treatment-related toxicity, pelvic and distant recurrence, and compare quality of life.
Study design, population, intervention:
In this multicenter trial 500 patients with stage I or II endometrial adenocarcinoma with high-risk features or stage IIIA or IIIC endometrial carcinoma who meet the inclusion criteria will be randomly allocated to external beam pelvic radiotherapy (control arm; 48.6 Gy in 1.8 Gy fractions), or pelvic radiotherapy with concurrent chemotherapy (2 cycles of cisplatin 50 mg/m2 in week 1 and 4), followed by adjuvant chemotherapy (4 cycles of carboplatin AUC 5 and paclitaxel 175 mg/m2 at 3-week intervals; experimental arm).
Patients will be stratified for participating group (Dutch CGOG vs. UK NCRI); mode of surgery; stage (IB vs. IC vs. II vs. III); and histological type (endometrioid carcinoma vs. serous and clear cell carcinoma). The accrual period will be 5 years.
Endpoints and statistics:
Primary study endpoints will be 5-year actuarial overall survival, and 5-year actuarial failure-free survival (FFS). Failure is defined as relapse, or death due to endometrial carcinoma or due to treatment complications. Secondary endpoints will be quality of life, severe treatment related morbidity, and rates of vaginal, pelvic and distant relapse.
The principal aim is to detect with sufficient power (80%) a difference in the 5-year overall survival rate of 12.5% (based on an expected 5-year OS in the RT arm of 50%; hazard ratio for combined modality treatment (CMT) 0.68) with a two–sided test at significance level alpha=0.05. This requires 215 events to be observed, and a target number of 500 patients for this trial.
Collaboration in the Intergroup setting with the NCRI will ensure sufficient and timely patient inclusion in this trial. In case of rapid inclusion (150 patients per year) the target number will be increased to 800 patients within the 5-year accrual period to detect a 10% difference in 5-year OS with a power of 80%.
Side studies:
Tumour samples will be collected and saved in a dedicated tissue bank for immunohistochemical studies and tissue micro-array analysis. Aims are to identify new prognostic and predictive markers, compare these to traditional factors, and develop targets for molecular therapy.

Doel van het onderzoek

The addition of concurrent and adjuvant chemotherapy to postoperative radiation therapy will increase 5-year overall survival and failure-free survival of patients with high-risk and advanced stage endometrial carcinoma.

Onderzoeksopzet

Primary outcomes are 5-year OS and FFS
Long-term results at 7 and 10 years will be evaluated

Onderzoeksproduct en/of interventie

Patients are randomised (1:1) to receive external beam pelvic radiotherapy (atandard arm; 48.6 Gy in 1.8 Gy fractions), or pelvic radiotherapy with concurrent chemotherapy (2 cycles of cisplatin) followed by adjuvant chemotherapy (4 cycles of carboplatin and paclitaxel; experimental arm).

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. Histologically confirmed endometrial carcinoma, with one of the following postoperative FIGO 2009 stages and grade:

A. Stage IA with myometrial invasion, grade 3 with documented LVSI;

B. Stage IB grade 3;

C. Stage II;

D. Stage IIIA or IIIC; or IIIB if parametrial invasion only;

E. Stage IA (with myometrial invasion), IB, II, or III with serous or clear cell histology.

2. WHO-performance status 0-2;

3. WBC >= 3.0 x 109/L;

4. Platelets >= 100 x 109/L;

5. Bilirubin <= 1.5 x UNL;

6. ASAT/ALAT <= 2.5 x UNL;

7. Written informed consent.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Previous malignancy, except for basal cell carcinoma of the skin, < 10 yrs;
2. Previous pelvic radiotherapy;
3. Hormonal therapy or chemotherapy for this tumor;
4. Macroscopic stage IIB for which Wertheim type hysterectomy;
5. Prior diagnosis of Crohn's disease or ulcerative colitis;
6. Residual macroscopic tumor after surgery;
7. Creatinine clearance <= 60 ml/min (calculated according to Cockroft) or <= 50 ml/min (EDTA clearance, or measured creatinine clearance);
8. Impaired cardiac function, prohibiting the infusion of large amounts of fluid during cisplatin therapy;
9. Peripheral Neuropathy >= grade 2.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Blindering:	Open / niet geblindeerd
Controle:	Geneesmiddel

Deelname

Nederland

Status:	Werving gestopt
(Verwachte) startdatum:	01-10-2006
Aantal proefpersonen:	500
Type:	Werkelijke startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

Toelichting
After publication of long-term results, IPD will be shared after a scientific proposal has been evaluated and approved by the trial group (e.g., for meta analysis)

Ethische beoordeling

Positief advies

Datum:	10-07-2006
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL719
NTR-old	NTR729
Ander register	METC Leiden-Den Haag-Delft : METC LUMC P06.031

Register	ID
ISRCTN	ISRCTN14387080

Resultaten

Samenvatting resultaten

Wortman BG, Post CCB, Powell ME, et al.
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Clinical consequences of upfront pathology review in the randomised PORTEC-3 trial for high-risk endometrial cancer.
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Jameson MG, McNamara J, Bailey M, et al.
Results of the Australasian (Trans-Tasman Oncology Group) radiotherapy benchmarking exercise in preparation for participation in the PORTEC-3 trial.
J Med Imaging Radiat Oncol. 2016 Aug;60(4):554-9. doi: 10.1111/1754-9485.12447.