Randomised Phase III Trial of molecular profile-based versus standard recommendations for adjuvant radiotherapy for women with early stage endometrial cancer: PORTEC-4a

Published: 10-05-2016
Last updated: 20-04-2024

To determine if individual tailored treatment recommendation based on the integrated molecular risk profile will (strongly) reduce the number of women that will unnecessarily receive vaginal brachytherapy, with comparable local control and...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Reproductive neoplasms female malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON54837

Source
ToetsingOnline

Brief title
PORTEC-4a

Condition

- Reproductive neoplasms female malignant and unspecified

Synonym
Endometrial cancer; cancer of the womb

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Subsidie voor datamanagement en trialcoordinatie van KWF kankerbestrijding (buitenlandse groepen zullen eigen subsidie voor locaal datamanagement en coordinatie aanvragen)

Intervention

Keyword: endometrial cancer, molecular risk factors, radiation therapy, vaginal brachytherapy

Outcome measures

Primary outcome

Primary endpoint: vaginal recurrence

Secondary outcome

Secondary endpoints:

Adverse events and patient-reported symptoms and health-related quality of life

Recurrence-free and overall survival

Pelvic and distant recurrence

5-year vaginal control (including treatment for relapse if applicable)

Endometrial cancer - related healthcare costs

Study description

Background summary

Endometrial cancer (EC) is the most common gynaecological cancer. Surgery (hysterectomy and oophorectomy) is the primary treatment. Previous randomized trials including the Dutch PORTEC-1 trial have shown that postoperative radiation therapy (RT) significantly reduces the risk of vaginal and pelvic recurrence, but without difference in overall survival. Most (75%) recurrences occur locally in the vaginal vault, and can effectively be treated with RT at the time of recurrence. The indication for RT has since been limited to patients with risk factors. The PORTEC-2 trial has shown that for these

patients, vaginal brachytherapy alone is highly effective in preventing vaginal recurrence, with fewer side effects and better quality of life than external beam RT. However, standard vaginal brachytherapy for all patients with risk factors is still significant overtreatment, as 85% of women will not have local recurrence. In a patient preference study it has been shown that women strongly prefer a treatment to avoid recurrence over a watchful waiting policy, especially when this involves a short treatment with few side effects. More precise individual risk prediction could avoid both over- and undertreatment.
In recent years molecular-genetic characterisation of endometrial cancer has been done in The Cancer Genome Atlas project, and four prognostic groups have been defined which have been confirmed and validated in analysis of tissue samples of the PORTEC-1 and -2 trial cohorts on paraffin embedded tissue. With additional validated risk factors an integrated molecular profile has been developed with which an individual risk assessment (favourable, intermediate, unfavourable) can be given to patients previously all included in the group with early stage endometrial carcinoma with classic high-intermediate risk features. .

Study objective

To determine if individual tailored treatment recommendation based on the integrated molecular risk profile will (strongly) reduce the number of women that will unnecessarily receive vaginal brachytherapy, with comparable local control and recurrence-free survival compared to standard treatment, to reduce overtreatment with related symptoms; retain best quality of life and save health care costs.

Study design

Randomised multicenter phase Ill trial in which 550 patients with endometrioid type EC with risk features will be randomised (1:2) to vaginal brachytherapy (standard arm) or to molecular profile-based treatment recommendations for observation (favourable group, about 55%), vaginal brachytherapy (intermediate group, 40%) or E8RT (unfavorable group, 5%), the experimental arm.
Primary study endpoint is vaginal relapse. Secondary objectives are adverse events and quality of life; recurrence-free and overall survival; pelvic and distant recurrence; 5-year vaginal control (including treatment for relapse if applicable); and EC-related health care costs.
The first 50 patients will be included in a pilot phase to confirm the logistics and patient acceptance of the molecular profile; if positive this trial will continue to a total of 550 evaluable patients (including 22 patients already included in the previous PORTEC4 design).

Intervention

Patients in the standard arm will be treated with vaginal brachytherapy (21 Gy

HDR in 3 fractions of 7 Gy each, specified at 5 mm from the applicator surface and top, within overall time of 2 weeks).
Patients in the experimental arm will, based on the integrated molecular profile, be either observed after surgery (55%), or will receive vaginal brachytherapy as above (40%). The 5% who will be recommended pelvic external beam radiotherapy will received a dose of 45-48.6 Gy in 1.8-2 Gy fractions according to the centre's policy and technique.

Study burden and risks

Burden and risks of the study:
- potential distress and/of feelings of doubt and insecurity during the decision making process;
- in the standard treatment group: psychological and practical burden of 3 hospital visits for vaginal brachytherapy (outpatient procedure, duration of 1 hour at 1st session, and 0.5-1 hr at 2nd and 3rd session) - this is the standard treatment and is also applicable outside the scope of this trial
- in the experimental treatment group: psychological burden of the results of the molecular profile: 'favourable', 'intermediate', or 'unfavourable'. In the 'favourable' group (about 55%) on the one hand reassurance of 'favourable' profile, but on the other hand psychological distress and/or anxiety of no treatment and feeling of 'waiting', even if the risk of recurrence is very low. In the 'intermediate' group (about 40%) the situation and burden are the same as for the standard arm described above. In the 'unfavourable' group (about 5%) the psychological burden of 'unfavourable' results, and the burden of external beam radiation treatments daily (working days) for 5 weeks with more side effects such as bowel frequency, cramps and diarrhea and also bladder frequency and fatigue which will continue for at least 1-2 weeks after completion of therapy.
- no extra risks as to survival as this will be similar in both groups; aim is reduction of overtreatment with similar overall outcomes
- low (3-5%) risk of result of possible lynch syndrome in both groups, with referral to a clinical geneticist for information and analysis, with related distress but potential advantages of adequate information and screening ..
- completing quality of life questionnaires - these are standard validated EORTC questionnaires (QLQ C-30 core questionnaire and EN24 module specific for endometrial cancer), with 2 additional questions regarding sexual activity (partner yes/no and if not active, reason). Duration of completing the questionnaires: 10-15 min. Our experience with similar questionnaires in previous PORTEC-trials shows that patients gererally feel positive about quality of life questionnaires, which shows that their feedback is valued and may influence future treatments, and that the response rates are high, also at long term (70-80%)
The questionnaires before and after treatment are distributed by their own doctor or research nurse, and IF the patient gives separate consent and submits an address form, the questionnaires are sent directly to their home address at 6, 12, 24, 36 and 60 months and after 7 years. With each questionnaire an

accompanying letter is sent stating that the patient is free to decide not to complete the questionnaire, and in that case is asked to sent back the blank questionnaire in order to stop further sending. The database with address forms is kept SEPARATELY from the
general trial base and documents, and is managed by a datacenter secretarial employee who does not have any other relation to the trial.
- hospital visits to the radiation oncologist and gynaecologist, and procedures and tests such as general and pelvic examination are identical to those for patients who do not participate in the trial.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Adult patients with histologically confirmed endometrioid type endometrial carcinoma, FIGO 2009 stage I, with one of the following combinations of stage,

grade, age, and LVSI:
1. Stage IA, grade 3 (any age, with or without LVSI)
2. Stage IB, grade 1 or 2 and age >60 years
3. Stage IB, grade 1-2 with documented LVSI
4. Stage IB, grade 3 without LVSI
5. Stage II (microscopic), grade 1
Surgery consisted of Total Abdominal or Laparoscopic Hysterectomy and Bilateral Salpingo-Oophorectomy (TH-BSO) with or without pelvic lymphadenectomy, lymph node sampling or sentinel node procedure (not recommended, but permitted)
WHO-performance status 0-2
Written informed consent

Exclusion criteria

The following criteria exclude the patient from enrolment in this trial:
1. Any other stage and type of endometrial. carcinoma
2. Non-endometrioid endometrial carcinoma, such as serous or clear cell carcinoma (at least 10% in mixed types), or undifferentiated or neuroendocrine carcinoma
3. Uterine sarcoma (including carcinosarcoma)
4. Previous malignancy (except for non-melanomatous skin cancer) < 5 yrs
5. Previous pelvic radiotherapy
6. Verwacht interval between the operation and start of radiotherapy exceeding 8 weeks

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-06-2016
Enrollment:	450
Type:	Actual

Ethics review

Approved WMO Date:	10-05-2016
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	27-06-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	12-10-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	14-08-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	05-07-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO Date:	05-10-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL56828.058.16
Other	NTR5841; ISRCTN11659025; NCT03469674