PORTEC-4: Randomised Phase III Trial Comparing Vaginal Brachytherapy (two doses schedules: 21 or 15 Gy HDR in 3 fractions) and Observation after Surgery in patients with Endometrial Carcinoma with High-Intermediate Risk Features

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

Summary

ID

NL-OMON39610

Source
ToetsingOnline

Brief title
PORTEC-4

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 aanvraag voor datamanagement en trialcoordinatie bij KWF kankerbestrijding ingediend

Intervention

Keyword: adverse effects, endometrial cancer, radiotherapy, vaginal brachytherapy

Outcome measures

Primary outcome

Primary objectives:

Establish vaginal recurrence and 5-year vaginal control including treatment for relapse in patients with high-intermediate risk endometrial carcinoma, treated after surgery with vaginal brachytherapy (21 Gy or 15 Gy in 3 fractions), in comparison with no additional treatment

Primary endpoint: vaginal recurrence

Second primary endpoint: 5-year vaginal control including treatment for relapse

Secondary outcome

Secondary objectives:

Establish and compare the rates of vaginal toxicity, quality of life, pelvic recurrence, and overall and failure-free survival.

Secondary endpoints:

Overall and failure-free survival;

Pelvic recurrence;

Vaginal adverse effects;

General and specific quality of life (including sexual functioning and

symptoms, if applicable).

Study description

Background summary

Endometrial cancer is the most common gynaecological cancer. Surgery (hysterectomy and oophorectomy) is the primary treatment. Previous randomized trials, among which the PORTEC-1 trial, have shown that postoperative radiation therapy (RT) significantly reduces the risk of vaginal and pelvic recurrence from 14 to 4%, but without difference in overall survival. Most (75%) local recurrences are located in the proximal vagina, and can effectively be treated with radiation therapy (external beam radiation followed by brachytherapy) at the time of recurrence. After completion of the PORTEC-1 trial, the indication for RT has become limited to patients with high-intermediate 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 pelvic radiotherapy. Patients treated with vaginal brachytherapy had higher rates of vaginal atrophy (recorded at pelvic examination), although without measurable effects on general or sexual quality of life of functioning. However, treating all patients with risk factors with brachytherapy is still significant overtreatment. If a watchful waiting policy would be adopted, with prompt treatment in case of vaginal relapse, the eventual local control (including treatment for relapse) might be very similar to the local control after adjuvant brachytherapy. A range of published brachytherapy dose schedules has equal efficacy, and the rate of vaginal atrophy changes in PORTEC-2 suggests that the standard dose schedule of 21 Gy in 3 fractions of 7 Gy could be compared to a lower dose schedule.

Study objective

The primary objective of this study is to establish and compare the rates of vaginal relapse in patients with high-intermediate risk endometrial carcinoma treated with vaginal brachytherapy (standard versus reduced brachytherapy dose schedule of 21 vs 15 Gy HDR in 3 fractions, respectively), versus no additional treatment after surgery. Second primary objective is to establish overall vaginal control, including salvage treatment for patients with vaginal relapse, at 5 years.
Secondary objectives are to establish and compare the rates of pelvic nodal recurrence; overall and failure-free survival; vaginal toxicity; and quality of life. The objective of the brachytherapy dose comparison is to estimate the

differences in vaginal relapse, toxicity and quality of life (with emphasis on sexual symptoms and functioning) between the two dose levels with sufficient precision.

Study design

In this prospective multicenter randomized Phase III trial, 500 patients with endometrioid type endometrial adenocarcinoma with high-intermediate risk features will be randomised in 2:1 distribution to one of the following arms:
1. vaginal brachytherapy (standard arm), 1:1 randomized to
a. brachytherapy dose 21 Gy HDR in 3 fractions of 7 Gy each (standard dose)
b. brachytherapy dose 15 Gy HDR at 5 mm depth, in 3 fractions of 5 Gy (reduced dose).
2. observation (experimental arm).

Stratification will be done for:
1. participating centre
2. grade (1 vs 2 vs 3)
3. type of surgery (laparoscopic vs abdominal hysterectomy; lymphadenectomy yes/no)

Patients will be followed closely and prospectively evaluated for outcome (vaginal control; local, pelvic or distant recurrence, survival) after primary treatment (and, if applicable, after treatment for recurrence), for vaginal changes, atrophy and symptoms, and general and site-specific quality of life.

Intervention

Postoperative vaginal brachytherapy, dose 21 Gy in 3 fractions of 7 Gy each, using high-dose-rate (HDR) equipment in outpatient setting, within 2 weeks (standard treatment)
Postoperative vaginal brachytherapy, dose 15 Gy in 3 fractions of 5 Gy each, using high-dose-rate (HDR) equipment in outpatient setting, within 2 weeks (vaginal brachytherapy - reduced dose)
No further treatment, close follow-up, and prompt treatment in case of recurrence (experimental arm, no further treatment)

Study burden and risks

Burden and risks of the study:
- potential distress and/of feelings of doubt and insecurity during the decision making process;
- psychological distress and/or anxiety of no treatment and during the 'watchful waiting' period for the patients randomized to no furhter treatment
- psychological and practical burnden 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
- 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 and 10 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, with the only exception that during standard pelvic examination, vaginal length and width are measured using standard smooth perspex cilinders, at baseline and once annually thereafter, up to a maximum of 5 years.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

To be eligible for this trial, patients will need to meet all of the following inclusion criteria:
1. Histologically confirmed endometrioid type endometrial carcinoma, FIGO stage I, with one of the following combinations of substage, age, and grade:
a. Stage IA, any age, grade 3 without lymph-vascular space invasion (LVSI)
b. Stage IB, age 60 years or older and grade 1 or 2
c. Stage IB, any age, grade 1 or 2 with documented lymph-vascular space invasion (LVSI)
2. Surgery consisted of Total Abdominal or Laparoscopic Hysterectomy and Bilateral Salpingo-Oophorectomy (TH-BSO). Although pelvic lymphadenectomy is not recommended; if this has been done the patient is still eligible.
3. WHO-performance status 0-2
4. Written informed consent

Exclusion criteria

The following criteria exclude the patient from enrolment in this trial:
1. Any other stage of endometrial carcinoma
2. Non-endometrioid endometrial carcinoma, such as serous or clear cell carcinoma
3. Uterine sarcoma (including carcinosarcoma)
4. Previous malignancy (except for non-melanomatous skin cancer) < 5 yrs
5. Previous pelvic radiotherapy
6. 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)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-09-2012
Enrollment:	150
Type:	Actual

Ethics review

Approved WMO

Date:	11-01-2012
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	08-03-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	14-03-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	16-04-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	02-05-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	04-06-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	04-07-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	18-07-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	22-01-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	05-06-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	17-03-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	22-04-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	26-06-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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
ISRCTN	ISRCTN16228756
CCMO	NL37861.058.11