NOdal METastasis in high risk Endometrial Cancer (NOMETEC): detection methods and the prevalence of lymph node micrometastasis

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OBJECTIVE NOMETEC PART I: "Mapping the lymphatic drainage of the uterus: a feasibility study of the sentinel node procedure"Our aim is to find out which out of two injection methods with technetium labelled nanocolloid is the best to...

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

Summary

ID

NL-OMON39933

Source
ToetsingOnline

Brief title
NOMETEC

Condition

- Reproductive neoplasms female malignant and unspecified

Synonym
(high risk) endometrial cancer

Research involving
Human

Sponsors and support

Primary sponsor: Diakonessenhuis Utrecht

Source(s) of monetary or material Support: Een aanvraag voor een zgn. AGIKO subsidie werd ingediend bij ZONMW. Daarnaast benaderen wij Stichting KWF Kankerbestrijding. Er werd ons inmiddels 5100 euro vergoeding toegezegd door de Aart Huisman Stichting verbonden aan het Diakonessenhuis te Utrecht.

Intervention

Keyword: (Micro)metastasis, Endometrial cancer, High risk, Lymph node metastasis, Sentinel node

Outcome measures

Primary outcome

Primary outcome parameter PART I

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Both techniques will be compared for:

- sentinel node detection rate (min. 80% DR)

- the location and level of the sentinel nodes (pelvic and/or para-aortal, high

and/or low)

- patient friendliness (questionnaire)

- doctor friendliness (questionnaire)

Primary outcome parameter PART II

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The reliability of the sentinel node procedure in high risk endometrial cancer,

which will be determined by the false negative rate after histological

examination of all removed nodes using the *gold standard* (= multiple

sectioning Hematoxylin and Eosin (H&E) staining and immunohistochemistry (IHC))

Secondary outcome

Secondary outcome parameters PART II:

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1) The prevalence location of lymphnode metastasis (pelvic and/o high/low para-aortal).

2) The prevalence of lymphnode micrometastasis in high risk endometrial cancer.

3) The feasibility and reliability of the OSNA CK19 test as an intraoperative method to diagnose lymph node macro- and micrometastasis in sentinel nodes will be tested. Histopathological examination (H&E) will be used as control method. In case of discordant cases immunohistochemistry will be used as reference method. The reliability will be defined by the true histological false negative rate.

Study description

Background summary

Endometrial cancer is the most common gynaecological malignancy in industrialized countries. The disease has a relatively good prognosis because most patients (75%) present early with complaints about postmenopausal bleeding. Although the mortality rate is rather low compared to other malignancies; still, yearly an estimated 9000 women die of endometrial cancer in Europe [1]. Disease related mortality is the result of distant metastasis and recurrent disease.

The prognosis of endometrial cancer patients depends on the tumour stage, histological differentiation grade and histological type; moreover it depends on the woman*s age and the therapeutical possibilities [3,4].

Involvement of the lymph nodes has been proven to be one of the most important prognostic factors in most other malignant tumours. The lymphatic drainage routes of the uterus are complex and the evidence on lymphatic spread of endometrial cancer is scarce.
Current non-invasive imaging techniques are restricted in their ability to detect metastatic lymph node spread. On the other hand, the benefits of invasive surgery like a complete lymphadenectomy as part of the routine staging procedure remain controversial, given the potential morbidity [10,11].

There*s an ongoing discussion about the (primary) surgical treatment of endometrial cancer. Standard treatment for all patients consists of total hysterectomy, bilateral salpingo-oöphorectomy, peritoneal cytology and lymph node palpation/assessment. The recently revised national guideline clearly recommends a systematic lymfadenectomy in cases of clear cell and serous papillary endometrial carcinoma. Furthermore, the authors point out the actual risk of extra uterine disease in type I grade 3 tumours, implying that lymphadenectomy would be reasonable option in this group of patients [7, 8, 9]. Therefor we need to understand more about the routes of nodal spread to truly tailor surgical treatment and use targeted adjuvant therapy. Thus potentially increasing quality if life as well as survival of these patients.

Lymphatic mapping with the sentinel node procedure has emerged as an alternative to systematic lymphadenectomy. The technique is widely used in cases with breast cancer and melanoma (12, 13), while it is also used in cases with vulvar or cervical cancer (14). Burke e.a was the first to study the sentinel node procedure in endometrial cancer patients in 1996 [15]. So far, there*s an ongoing dicussion about which site of injection would be most feasible: cervical vs. submucosal per hysteroscopy vs. subserosal per laparoscopy or -tomy [16-26].

An estimated 20% of the patients with high risk endometrial cancer have lymph node involvement. Though current diagnotic work up and treatment guidelines don*t seem to focus enough on the actual possibility of lymphatic spread. A surgical-pathological study, performed by the US Gynecologic Oncology Group (GOG) provides the most reliable data on the relationship between the FIGO stage of the tumour, the myometrial invasion and the presence of lymph node metastasis. It has been proven that -among patients with lymph node metastases- 50% have pelvic LNM only, 30% have both pelvic and para-aortic metastases and 20% have para-aortic LNM only [27]. A estimated 50% of all para-aortal metastasis is situated in the high para-aortal regions. This is probably the result of various lymph drainage routes of the uterus, wich would explain the difference in sentinel node detection after each injectionmethod [16-26].

There*s not enough evidence on the prevalence and clinical relevance of para-aortal metastasis. It is unclear weather a systematic pelvic and para-aortal lymfadenectomy up to the level of the v. renalis would improve the disease free survival because there*s a lack of reliable prognostic data [28].

Finally, not only are we interested in the clinical significance of the location of nodal involvement, but we also wish to know the extent of metatasis: macroscopic vs. microscopic.

Up till now, only the presence of lymph node macrometastasis has therapeutical consequences. But, detailed pathological study of a lymph node biopsy with ultrastaging and immunohistochemical or PCR analysis can identify lymph node micrometastases (measuring 0.2mm - 2mm) that conventional methods would identify as negative for metastatic disease. The relation between micrometastases and the risk of recurrence and prognosis has been demonstrated in an increasing number of malignancies including breast cancer, vulvar cancer, gastric cancer, oesophageal cancer, colon cancer, prostate cancer and melanoma, suggesting that micrometastases should be an indication for adjuvant therapy.

Pushing the limits of diagnostic possibilities, we need to gain more insight in the clinical consequences of micrometastasis and isolated tumour cells [29, 30].

(References are listed in the research protocol!)

Study objective

OBJECTIVE NOMETEC PART I: "Mapping the lymphatic drainage of the uterus: a feasibility study of the sentinel node procedure"

Our aim is to find out which out of two injection methods with technetium labelled nanocolloid is the best to describe the lymphatic drainage routes of the uterus:
1. SMI: sub-mucosal injection after hysteroscopy
2. SSI: laparoscopic/laparotomic sub-serosal (fundus) injection.
In addition, we aim to learn which technique is most accurate and/or feasible for sentinel node mapping in endometrial cancer.

OBJECTIVE NOMETEC PART II: "Nodal metastases in high risk endometrial cancer (NOMETEC): detection methods and the prevalence of lymph node micrometastases"

The feasibility study (NOMETEC PART I) will result in the proposal of either SMI or SSI as the preferred method for lymph node detection. The SN detection should be possible in at least 80% of patients.
The next step in our investigation is to find out the correlation between Sentinal Node (SN) involvement and involvement of other pelvic and para-aortal lymph nodes in high risk endometrial cancer patients.
Finally, we are interested in the feasibility and reliability of the OSNA CK19 test as an intraoperative method to diagnose lymph node macro- and micrometastasis in sentinel nodes.

Study design

The study is a multicenter cross-sectional diagnostic intervention study, consisting of two sub-studies. Patient enrolment starts medio 2011 and will take place in the University Medical Center Maastricht, the University Medical Center Utrecht and the Diakonessenhuis in Utrecht.

NOMETEC PART I is a feasibility study, investigating two methods for sentinel lymph node detection and drainage system visibility in patients suspicious for endometrial cancer, undergoing hysteroscopy and laparoscopic or laparotomic hysterectomy. Both methods will be used in all patients. The methods will be used independent of each other: the second method will be conducted without knowledge of the results of the first method. PART I will result in the proposal of either SMI or SSI as the preferred method for lymph node detection. The SN detection should be possible in at least 80% of patients.

The next step in our investigation is to find out the correlation between Sentinal Node (SN) involvement and involvement of other pelvic and para-aortal lymph nodes in a group of high risk endometrial cancer patients (NOMETEC PART II). Based on several characteristics of the patients and the tumour, the risk of lymph node involvement is computed. Among these patients approximately 15-20% has lymph node involvement. The question is whether SN involvement further improves the prediction of concurrent lymph node involvement in addition to characteristics such as tumor grade, histological tumour type, myometrium invasion and age. If so, this may result in a better selection of patients for adjuvant therapy and/or lympadenectomy, a procedure with relatively high rates of morbidity.

The determinant is whether information about SN involvement improves the prediction of lymph node involvement The outcome is lymph node involvement determined in lymph nodes obtained through lymphadenectomy and histologically examined (gold standard).
There will be several cut-off points used for defining whether a SN is malignant: 1) macrometastasis, 2) micrometastasis, 3) isolated tumour cells. Different pathological tests will also be explored.

Study burden and risks

As the diagnostic work-up and surgical treatment will be carried out according to the national guideline, complications during or after surgery will not be considered as *research risk*.
The administration of the radioactive tracer 99m Tc-nanocolloid for the sentinel node procedure has been widely experienced and investigated in other tumours. Adverse effects or complications have been proven to be very rare. Moreover, the dosage has been approved by the radiological health and safety officer of the Diakonessenhuis in Utrecht.

The extra burden for the patients, participating in this study, would consist of the injection with the radioactive tracer 99m Tc-nanocolloid and a lymfoscintigrafic examination respectively 30 minutes and 2 hours after the injection. The injection will be performed under adequate anaesthesia.

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

This study is a multicenter cross-sectional diagnostic invention study, consisting of two sub-studies. ;Inclusion criteria PART I:
==========;All women, undergoing a hysteroscopic curettage and a hysterectomy because of suspicion for a (malignant) lesion of the endometrium.;Inclusion criteria PART II:
==========;Only patients with high risk endometrial cancer will be

included in this study, because - according to the recently revised national guideline - standard care in these patients includes a pelvic and para-aortal lymphadenctomy. High risk patients are defined as having at least one of the following characteristics: differentiation grade 3, > 50% myometrial invasion, suspicious for extra-corporal spread, high risk histological type (serous papillary, clear cell or carcinosarcoma tumour type)

Exclusion criteria

Exclusion criteria PART I and PART II:
==========;Patients with contraindications for open abdominal or laparoscopic surgery will be excluded: cervical or pelvic infection, severe cardio-pulmonal or other co-morbidity contra-indicating extensive surgery and anaesthesia.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-02-2012
Enrollment:	290
Type:	Actual

Ethics review

Approved WMO

Date:	07-07-2011
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	13-04-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-02-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	NL36526.100.11