A RANDOMIZED TRIAL COMPARING RADICAL HYSTERECTOMY AND PELVIC NODE DISSECTION VS SIMPLE HYSTERECTOMY AND PELVIC NODE DISSECTION IN PATIENTS WITH LOW RISK EARLY STAGE CERVICAL CANCER

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Primary objective:To evaluate whether treatment with simple hysterectomy and pelvic node dissection is non-inferior to treatment with radical hysterectomy and pelvic node dissection in terms of pelvic relapse-free survival.Secondary objectives:To...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cervix disorders (excl infections and inflammations)
Study type	Interventional

Summary

ID

NL-OMON55443

Source
ToetsingOnline

Brief title
SHAPE-trial

Condition

- Cervix disorders (excl infections and inflammations)

Synonym
cancer of the cerivx, cervical cancer

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,KWF kankerbestrijding

Intervention

Keyword: cervical cancer, conservative surgery, quality of life, radical surgery

Outcome measures

Primary outcome

Primary Endpoint: pelvic relapse-free survival.

Pelvic Relapse-Free Survival is defined as the date from randomization to the date of first documented reappearance (recurrence) of disease provided that this recurrence is in the pelvis. A pelvic recurrence is defined as a recurrence within the pelvis, below the pelvic brim and inferior to the L4-L5 vertebral level. Pelvic recurrences will include disease recurrence in the vaginal vault, parametrium and pelvic lymph nodes (including the common iliac nodes). In the intent-to-treat analysis, patients found to have more advanced stages of cervical cancer on sentinel node mapping, pelvic node dissection or other intraoperative findings consistent with pelvic disease will be considered to have pelvic disease relapse as of the date of the surgical procedure. These patients will be excluded from the per-protocol analysis.

Secondary outcome

To compare the two treatment arms with respect to:

- Extrapelvic relapse-free survival

- Relapse-free survival (any site)

- Overall survival

- Treatment-related toxicity

- Patient Reported Outcomes including global quality of life and measures of

sexual health

- Cost-effectiveness and cost-utility

To observe rates of the following in this patient population:

- Sentinel node detection

- Parametrial involvement

- Involvement of surgical margins

- Pelvic node involvement

Study description

Background summary

Cancer of the cervix is the second leading worldwide cause of cancer death in women. Most recent global statistics indicate that in 2002, the estimated incidence was 493,243 new cases with 273,505 deaths [Parkin 2006]. The disease is much more prevalent in developing as opposed to developed nations. There is an almost two-fold increase in lifetime probability risk of developing cervical cancer (1.48% vs. 0.76%) and a more than three-fold increase in dying from it (0.84% vs. 0.25%) in underdeveloped countries [Global Cancer Facts and Figures 2007]. In Canada, the projected number of new cases in 2010 was 1300, with 370 deaths [Canadian Cancer Statistics, 2010].
As a result of effective screening in developed countries, the overall incidence of cervical cancer has decreased over the past 20 years, while the proportion of younger women presenting with low-risk early-stage disease has increased. As surgical therapy is highly efficacious in providing durable disease control in women with low-risk disease, these patients are at risk of suffering *survivorship* issues related to long-term surgical effects, including compromised sexual, bowel and bladder function, as well as

infertility. The NCIC CTG CX.5 / GCIG SHAPE trial uses a non-inferiority design to test whether, in the long-term, less invasive surgical approaches can maintain high rates of disease control and improve quality of life through a reduction in late-effects associated with the surgical procedure.
Data from the recent 24th annual International Federation of Gynecology and Obstetrics (FIGO) report indicates that the 5-year stage-specific overall survivals of patients with stage IA2 squamous carcinoma were 99.1% (97.1% for adenocarcinoma) and for stage IB1 squamous carcinoma were 92.3% (91.8% for adenocarcinoma) [FIGO Annual Report, 2009]. The FIGO report emphasizes that from an international perspective, extensive practice variation occurs in managing patients with micro-invasive disease. Overall, 75% of patients were treated with surgery alone. Among these patients, one-third underwent conization, one-third simple hysterectomy (with or without lymphadenectomy) and one-third radical hysterectomy (again with or without lymphadenectomy). The remaining 25% of patients received some form of adjuvant therapy. Overall, 20% of patients underwent lymph node removal, presumably when lymphovascular involvement was detected on the conization specimen [FIGO Annual Report, 2009].
The major reason for such discrepant practices is the lack of high-quality evidence upon which clinicians can base their decisions and advice to these women. There is a need to standardize treatments and potentially identify the patient and disease specifics associated with advantages with radical or more limited surgical approaches.
There are no studies comparing the efficacy and morbidity of simple hysterectomy to that of radical hysterectomy in patients with early-stage disease. However, as the purpose of removing the parametria at the time of the hysterectomy is to ensure safe and wide margins around the cervical tumour and/or to remove potential spread to the parametrial lymph nodes and, as will be described below, the occurrence of disease in these locations is essentially nonexistent in patients with low-risk disease, important advantages may be associated with a simple hysterectomy. This premise provides the foundation for this trial.

Study objective

Primary objective:
To evaluate whether treatment with simple hysterectomy and pelvic node dissection is non-inferior to treatment with radical hysterectomy and pelvic node dissection in terms of pelvic relapse-free survival.

Secondary objectives:

To compare the two treatment arms with respect to:
- Extrapelvic relapse-free survival
- Relapse-free survival (any site)
- Overall survival
- Treatment-related toxicity
- Patient Reported Outcomes including global quality of life and measures of

sexual health
- Cost-effectiveness and cost-utility

To observe rates of the following in this patient population:
- Sentinel node detection
- Parametrial involvement
- Involvement of surgical margins
- Pelvic node involvement

Study design

This is a multi-centre, international, prospective, randomized phase III trial of radical hysterectomy and pelvic node dissection versus simple hysterectomy and pelvic node dissection in patients with previously untreated, low-risk cervical cancer. The planned sample size is 700 participants (1:1 randmization in both arms). The smple size is calculated based on non-inferiority at 0.05 level with 80% power.

Intervention

Arm 1 - Radical Hysterectomy (Type 2)
This procedure may be performed abdominally, laparoscopically, robotically or vaginally. The uterus, cervix, medial 1/3 of parametria, 2 cm of the uterosacral ligaments and upper 2 cm of the vagina are to be removed en bloc. The uterine artery is ligated laterally to the ureters and the ureters are unroofed to the ureterovesical junction.

Arm 2 - Simple Hysterectomy (Extrafascial Hysterectomy)
This procedure may be performed abdominally, laparoscopically, robotically or vaginally. Extrafascial hysterectomy involves removal of the uterus with cervix without adjacent parametria. The uterine arteries are transected medial to the ureters at the level of the isthmus and the uterosacral ligaments are transected at the level of the cervix. Surgeons should pay special attention to make sure that the whole cervix is removed. As such, a maximum 0.5 cm of vaginal cuff can be removed to ensure the complete removal of the cervix.

Both arms: Lymphadenectomy and Sentinel Node Mapping
Protocol therapy on both treatment arms will include pelvic lymph node dissection. Centres may choose to perform sentinel node mapping for some or all of their CX.5 patients if that is part of their usual practice. For centers not performing sentinel node mapping, a complete pelvic node dissection is considered protocol therapy. All the nodes are submitted for routine pathological analysis as per the Surgery/Pathology Manual. Frozen section analyses of sentinel nodes are not permitted for this trial unless the node is visually suggestive of metastatic spread.

Pelvic Lymphadenectomy
This procedure can be performed by open or laparoscopic technique. Bilateral skeletonization is to be performed with removal of all lymph node tissue from lower half of common iliac vessels, external iliac vessels, internal iliac vessels and the obturator fossa. The anatomic boundaries are to include the lower half of the common iliac artery proximally, the deep circumflex iliac vein distally, the mid portion of the psoas muscle laterally, to the ureters medially and above the obturator nerve in the obturator fossa inferiorly. Following the complete bilateral pelvic node dissection, the nodes are submitted for routine pathological analysis as per the Surgery/Pathology Manual.

Sentinel Node (SN) Mapping
Only experienced surgeons are permitted to perform sentinel node biopsies as part of this trial. In order to be eligible for this procedure, individual surgeons will be required to have successfully performed at least 10 previous SN procedures in cervix or endometrial cancer patients. Following the surgery, a quality assurance exercise will be conducted in the first 5 CX.5 patients treated by each surgeon.

Study burden and risks

With regard to possible benefit there is evidence that especially long term urological complication after surgery for cervical cancer depend on the extend of parametrial dissection. Hence women in whom the parametrium is not dissected (arm 2: experimental arm, simple hysterectomy) may have benefit with regard to less long term (urological) morbidity compared to women in whom the parametrium is dissected (amr 1: control arm, radical hysterectomy)

The possible risk associated with participation is, if randomized into the experimental arm, that parametrial involvement is not diagnosed nor treated, however there is a body of evidence justiying testing the less radical approach in both stage IA2 and 1B1.Based on the data below, routine parametrectomy in patients with low-risk cervical cancer appears to be potentially unnecessary given the very low rate of parametrial extension seen with retrospective reviews and acknowledging the morbidity of the procedure. However, there are no randomized trials demonstrating the safety of simple hysterectomy in low-risk stage IB1 patients. This trial will provide a unique opportunity to compare the rate of lymph node metastasis, parametrial infiltration and outcome between the two procedures, and produce results that can drive a change in clinical practice.

Outcomes Justifying Testing of Less Radical Approaches in Stage IA2
There is a growing body of literature suggesting that more conservative surgery can safely be performed in patients with stage IA2 disease, providing careful pathological evaluation is undertaken. A literature review performed by van Meurs identified 1063 patients with stage IA2 disease and reported an overall recurrence rate of 3.6% [van Meurs 2009]. No patients had parametrial

infiltration and 4.8% (range 0 to 9.7%) were found to have lymph node metastasis, indicating the importance of accurate measurement of depth and lateral extension of microinvasive disease, particularly with adenocarcinomas. This principle is highlighted by the author*s finding that following a thorough review of 47 cases that were previously identified in the Netherland registry as having IA2 disease, only 14 cases (30%) fulfilled criteria for stage IA2 [van Meurs 2009]. These authors also noted that the rate of lymph node metastasis was 12% in patients with lymphovascular space involvement (LVSI) compared with 1.3% in LVSI negative patients [van Meurs 2009].

However, other investigators have not observed the same risks to be associated with LVSI. Rogers conducted an extensive literature review and compared the rate of lymph node metastasis and recurrence in a series that used strict FIGO-defined selection criteria for microinvasion with a series that did not comply with this definition [Rogers 2009]. In the former group, the rates of node metastasis and recurrence were 0.5% and 2.9%, whereas rates were 7.3% and 3.1% in the latter group. Careful pathological assessment is thus essential when considering conservative treatment.

These data are supported by findings of Bisseling, who reviewed more than 1565 patients with microinvasive adenocarcinomas, of which 52% (814) underwent lymph node dissection [Bisseling 2007]. Lymph node metastases were identified in only 1.5% of cases. The presence of LVSI did not seem to be associated with nodal metastasis. Parametria were removed in 713 cases (46%) and reported in 356 cases; none of these cases were found to have parametrial involvement. The authors emphasized the difficulty in distinguishing microinvasive adenocarcinoma from adenocarcinoma in situ and the importance of obtaining multiple serial sections for review by an experienced gynecologic pathologist. The authors conclude that: i) in cases with extensive LVSI positivity, lymph node dissection is advised; ii) given the low-risk of lymph node metastasis, lymph node dissection may not be necessary in the vast majority of stage IA2 cases, although sentinel node mapping may be of interest as a less morbid alternative; and, iii) the very low rate of parametrial infiltration does not justify its routine removal. Therefore, local treatment together with lymph node assessment, particularly in the presence of LVSI would be the favored approach for patients with stage IA2 adenocarcinomas [Bisseling 2007]. Of note, microinvasive adenocarcinomas do not appear to be associated with higher rates of lymph node metastasis as compared with stage-matched squamous carcinoma [Rogers 2009].

In 92 patients with IA2 disease treated with radical hysterectomy, Jones found no cases with pathologic involvement of the parametrial or regional lymph nodes [Jones 1993]. On a subsequent pathologic analysis of 25 patients with microinvasive adenocarcinomas, again no cases with lymph node metastasis and no parametrial invasion were detected. Poynor concluded that conisation alone (if fertility preservation is desired) or simple hysterectomy should be considered adequate treatment for microinvasive adenocarcinomas [Poynor 2006].

The Gynecologic Oncology Group (GOG) reported results of a prospective study of 51 patients with stage IA2 disease confirmed by conization and treated with radical hysterectomy [Creasman 1998]. No patients had residual disease detected with the pathologic hysterectomy specimen, including none with lymph node metastasis [Creasman 1998]. Recently, Suri confirmed that patients with IA2 disease and negative pathologic margins following a loop electrosurgical excision procedure (LEEP) or cone procedure have a very low-risk of disease detection on the radical hysterectomy pathology specimen [Suri 2009]. In their series of 42 patients, only one patient was found to have positive nodes (2.4%) and in this patient LVSI was present on her cone specimen. The authors concluded that in carefully selected women with IA2 disease and negative pathology margins with LEEP or cone procedures could be treated more conservatively, but patients with LVSI may require nodal assessment [Suri 2009].

Outcomes Justifying Testing of Less Radical Approaches in Stage IB1

Fewer data are available regarding the safety of conservative treatment for the subset of patients with early-stage IB1 disease, defined as a tumour measuring less than 2 cm. In a retrospective study of 842 patients, Covens questioned the necessity of the parametrectomy based on observing a rate of parametrial extension of 0.6% and 2 and 5-year recurrence-free survivals of 98% and 96% in patients with low-risk features (tumour < 2cm, depth of stromal invasion < 10mm and negative pelvic nodes) [Covens 2002]. Wright conducted a retrospective review of 594 patients who underwent a radical hysterectomy; 0.4% of patients with lesions measuring < 2cm, negative nodes and no LVSI had parametrial spread and their recurrence rate was 0.7% [Wright 2007]. The authors concluded that simple hysterectomy in combination with pelvic lymphadenectomy may be adequate treatment for these patients. In a similar study plus literature review of 799 patients, only 0.63% of those with low-risk features had parametrial spread [Stegeman 2007]. Further supporting data include:

• In a retrospective analysis of 120 patients by Steed, no patients with negative nodes had parametrial infiltration. Parametrial infiltration was associated with tumour size (3 vs. 2 cm) and depth of stromal invasion [Steed 2006].

• In a retrospective analysis of 83 patients by Kinney, no parametrial node metastases were seen in those with lesions measuring < 2cm in diameter and negative LVSI. Only 4 patients had pelvic node metastasis (4.8%), and the 5-year survival was 97.6% [Kinney 1995].

• In a retrospective analysis of 136 patients by Frumovitz, no patients with tumours measuring < 2cm with negative LVSI had parametrial infiltration [Frumovitz 2009]. This group is now prospectively testing conservative surgery for patients with

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

squamous of adenocarcinoma of the cervix
< 20 mm AND < 50% stromal infiltration OR < 10 mm depth of invasion
Grade 1, 2 or 3

Exclusion criteria

High risk histology (clear cell, small cell)
Stage IA1
Evidence of lymph node metastasis or extra-uterine spead on pelvic MRI
Neo-adjuvant chemotherapie
Pregnancy

Desire to preserve fertility

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:	Recruitment stopped
Start date (anticipated):	24-12-2014
Enrollment:	110
Type:	Actual

Ethics review

Approved WMO

Date:	29-10-2013
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	19-02-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	23-12-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	15-04-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	30-09-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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

Approved WMO Date:	06-07-2021
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
ClinicalTrials.gov	NCT01658930
CCMO	NL42532.058.13