

University of Groningen

Safety of laparoscopy versus laparotomy in early-stage endometrial cancer

Mourits, Marian J.E.; Bijen, C.B.; Arts, H.J.; Ter Brugge, H.G.; van der Sijde, R.; Paulsen, L.; Wijma, J.; Bongers, M.Y.; Post, W.J.; van der Zee, Ate

Published in:
Lancet Oncology

DOI:
[10.1016/S1470-2045\(10\)70143-1](https://doi.org/10.1016/S1470-2045(10)70143-1)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2010

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Mourits, M. J. E., Bijen, C. B., Arts, H. J., Ter Brugge, H. G., van der Sijde, R., Paulsen, L., ... de Bock, G. H. (2010). Safety of laparoscopy versus laparotomy in early-stage endometrial cancer: a randomised trial. *Lancet Oncology*, 11(8), 763-771. DOI: 10.1016/S1470-2045(10)70143-1

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Safety of laparoscopy versus laparotomy in early-stage endometrial cancer: a randomised trial



Marian J E Mourits, Claudia B Bijen, Henriëtte J Arts, Henk G ter Brugge, Rob van der Sijde, Lasse Paulsen, Jacobus Wijma, Marlies Y Bongers, Wendy J Post, Ate G van der Zee, Geertruida H de Bock

Summary

Background The standard surgery for early-stage endometrial cancer is total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy, which is associated with substantial morbidity. Total laparoscopic hysterectomy (TLH) and bilateral salpingo-oophorectomy is less invasive and is assumed to be associated with lower morbidity, particularly in obese women. This study investigated the complication rate of TLH versus TAH in women with early-stage endometrial cancer.

Methods This randomised trial was done in 21 hospitals in the Netherlands, and 26 gynaecologists with proven sufficient skills in TLH participated. 283 patients with stage I endometrioid adenocarcinoma or complex atypical hyperplasia were randomly allocated (2:1) to the intervention group (TLH, n=187) or control group (TAH, n=96). Randomisation by sequential number generation was done centrally in alternate blocks of six and three participants, with stratification by trial centre. After assignment, the study coordinators, patients, gynaecologists, and members of the panel were not masked to intervention. The primary outcome was major complication rate, assessed by an independent panel. Data were analysed by a modified intention-to-treat analysis, since two patients in both groups were excluded from the main analysis. This trial is registered with the Dutch trial registry, number NTR821.

Findings The proportion of major complications was 14·6% (27 of 185) in the TLH group versus 14·9% (14 of 94) in the TAH group, with a difference of -0·3% (95% CI -9·1 to 8·5; p=0·95). The proportion of patients with an intraoperative major complication (nine of 279 [3·2%]) was lower than the proportion with a postoperative major complication (32 of 279 [11·5%]) and did not differ between TLH (five of 185 [2·7%]) and TAH (four of 94 [4·3%]; p=0·49). The proportion of patients with a minor complication was 13·0% (24 of 185) in the TLH group and 11·7% (11 of 94) in the TAH group (p=0·76). Conversion to laparotomy occurred in 10·8% (20 of 185) of the laparoscopic procedures. TLH was associated with significantly less blood loss (p<0·0001), less use of pain medication (p<0·0001), a shorter hospital stay (p<0·0001), and a faster recovery (p=0·002), but the procedure took longer than TAH (p<0·0001).

Interpretation Our results showed no evidence of a benefit for TLH over TAH in terms of major complications, but TLH (done by skilled surgeons) was beneficial in terms of a shorter hospital stay, less pain, and quicker resumption of daily activities.

Funding The Dutch Organization for Health Research and Development (ZonMw), programme efficacy.

Introduction

Endometrial cancer is the third most common cancer in women in North America and Europe, accounting for 6–9% of all cancers in female patients. Endometrial cancer mainly occurs in postmenopausal women and 90% of patients are older than 50 years. Incidence of this cancer increases in overweight individuals, and almost half of patients have a body-mass index (BMI) higher than 30 kg/m². Additionally, a substantial number of patients present with a comorbidity. Because postmenopausal bleeding is an early sign, most patients (75%) are diagnosed at an early stage. Standard treatment for patients with early-stage endometrial cancer is total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy.¹ Treatment guidelines vary between countries as to whether a lymphadenectomy is part of the standard surgical procedure. In the Netherlands, standard surgery for clinical stage I endometrial cancer (ie, confined to the uterine corpus) is TAH without

lymphadenectomy. The effectiveness of this treatment policy was confirmed by two large randomised studies that compared the outcome of surgery for early endometrial cancer with and without lymphadenectomy; these studies found no evidence that a lymphadenectomy provided a benefit over no lymphadenectomy in women with early endometrial cancer.^{1,2}

Although TAH is an effective treatment, morbidity associated with laparotomy can be substantial (particularly wound complications) because of the high incidence of obesity and comorbidity in this population.^{3,4} An alternative approach for patients with early endometrial cancer is total laparoscopic hysterectomy (TLH) with bilateral salpingo-oophorectomy. Several prospective controlled studies showed that laparoscopic hysterectomy was an effective, minimally invasive, safe alternative to TAH for benign indications. Most of these studies found a comparable or significantly lower incidence of treatment-related morbidity, a shorter hospital stay, less

Lancet Oncol 2010; 11: 763–71

Published Online

July 17, 2010

DOI:10.1016/S1470-

2045(10)70143-1

See [Reflection and Reaction](#)

page 707

See [Articles](#) page 772

Department of Gynaecology

(Prof M J E Mourits PhD,

C B Bijen MD, H J Arts PhD,

Prof A G van der Zee PhD) and

Department of Epidemiology

(W J Post PhD,

Prof G H de Bock PhD),

University Medical Center

Groningen, University of

Groningen, Netherlands;

Department of Obstetrics and

Gynaecology, Isala Clinics

Zwolle, Netherlands

(H G ter Brugge MD);

Department of Obstetrics and

Gynaecology, Hospital Group

Twente Hengelo, Netherlands

(R van der Sijde MD);

Department of Obstetrics and

Gynaecology, Wilhelmina

Hospital Assen, Netherlands

(L Paulsen MD); Department of

Obstetrics and Gynaecology,

Martini Hospital Groningen,

Netherlands (J Wijma PhD); and

Department of Obstetrics and

Gynaecology, Máxima Medical

Centre Veldhoven, Netherlands

(M Y Bongers PhD)

Correspondence to:

Prof Marian J E Mourits,

Department of Gynaecologic

Oncology, University Medical

Center Groningen, University of

Groningen, 9700 RB Groningen,

Netherlands

m.j.e.mourits@og.umcg.nl

blood loss, less pain, and quicker resumption of daily activities with the laparoscopic approach compared with laparotomy.^{5–11} However, patients with benign disease are typically younger, less obese, and healthier than are patients with endometrial cancer, and these patients also have the option of vaginal hysterectomy. Randomised studies of laparoscopy versus laparotomy in patients with endometrial cancer are limited, and, more importantly, are not powered for morbidity.^{12–16} A recent study reported secondary outcomes from a large randomised trial of laparoscopy versus laparotomy in endometrial cancer, powered for survival.^{17,18} However, the standard treatment protocol included pelvic and para-aortic lymphadenectomy; thus, the outcome was not applicable to the standard Dutch treatment, which does not include lymphadenectomy for stage I disease. The aim of the present randomised controlled trial was to assess the major complication proportion, minor complication proportion, treatment-related outcome, and quality of life (QoL) in patients with clinical stage I endometrial cancer who received TLH or TAH. To avoid bias associated with comparing an established procedure (TAH) with an experimental surgical procedure (TLH), the latter was done only by surgeons who were proven competent in performing a TLH by independent assessment.

Methods

Study design and patients

Patients were enrolled and randomised between Feb 1, 2007, and Jan 15, 2009, at 21 teaching and non-teaching hospitals in the Netherlands.¹⁹ We included women with histologically proven grade 1–2 endometrioid adenocarcinoma or complex atypical hyperplasia, clinically confined to the uterine corpus (ie, clinical stage I). Exclusion criteria were any non-endometrioid adenocarcinoma histological types, uterine size larger than that

expected at 12 weeks of pregnancy, and cardiopulmonary contraindications for laparoscopy or laparotomy.

The study was done in accordance with the Declaration of Helsinki and the Medical Research Involving Human Subjects Act (WMO). Approval was obtained from local research ethics committees. Patients were informed that there was no proven advantage for either TLH or TAH in early endometrial cancer, and all gave written, informed consent before randomisation.

Randomisation and masking

Eligible patients, enrolled by the participating gynaecologists, were randomly allocated to the intervention group (TLH) or control group (TAH). Randomisation was done via a computerised, unbalanced (2:1) method, favouring TLH to obtain more data on the experimental laparoscopic procedure. Randomisation by sequential number generation was done centrally in alternate blocks of six and three, with stratification by trial centre. Study coordinators, patients, gynaecologists and members of the panel were not masked to intervention after assignment.

Procedures

In 21 centres, 26 specialist gynaecological surgeons with experience in laparoscopy were trained and assessed by a visiting gynaecological oncologist with experience in laparoscopy. The assessment used preset scores from an Objective Structured Assessment of Technical Skills.²⁰ The gynaecological surgeons were allowed to participate in the study only after achieving, according to the assessment, sufficient laparoscopic skills for performing a TLH.¹⁹ Two gynaecologists did not show the required sufficient skills within the study period and did not perform a TLH in this study. All TLH procedures were done by these 24 certified surgeons. Centres that participated in the study were not allowed to offer a TLH to patients with early endometrial cancer outside the study. TAH procedures were done by fully trained, established, gynaecological surgeons; either one of the 24 certified surgeons or a colleague. Gynaecologists who were trained in TAH during their residency, and therefore proven skilled, were allowed to perform a TAH in the study.

In the laparotomy group, a vertical midline incision was recommended, followed by peritoneal washings, and a TAH (panel 1). In the laparoscopy group, a TLH (panel 2) was done after peritoneal washings, according to a standardised surgical protocol.¹⁹ Thromboprophylaxis and antibiotics were given according to the local clinical practice and this practice was similar for both surgical procedures.

The primary outcome was major complications, recorded intraoperatively and postoperatively until 6 weeks after surgery. The different categories of complications have been previously described in detail.¹⁹ The severity of a complication was assessed according to the Common Terminology Criteria of Adverse Events (CTCAE), version 3.0. An independent panel of three skilled clinicians

For the published protocol of this trial see <http://www.biomedcentral.com/1471-2407/9/23>

Panel 1: Surgical treatment protocol for laparotomy (TAH) for early-stage endometrial cancer

- Preoperative thrombosis prophylaxis administered
- Preoperative antibiotics given at least 15 min before skin incision
- Patient positioned in the lithotomy position
- Vertical midline incision
- Abdominal washings for cytology
- Bipolar coagulation or sealing the round ligament before cutting; opening the peritoneum of the bladder and the pelvic sidewall
- Bipolar coagulation or sealing the infundibulopelvic ligament before cutting with monopolar scissors
- Preparation of the bladder off the vagina
- Skeletting the uterine vessels, coagulating or sealing the vessels after identification of the ureter
- Coagulating or sealing and cutting the sacrouterine ligaments
- Taking out the uterus; closing the vaginal cuff with abdominal stitching
- Mass closure of sheath; skin closure

TAH=total abdominal hysterectomy.

familiar with laparoscopic surgery (one surgeon, H S Hofker; one anaesthesiologist, G B Eindhoven; and one gynaecologic oncologist, H W Nijman) met once every 3 months to differentiate between major and minor complications, based on consensus. The panel also assessed whether, and to what extent, the complication was related to the surgical procedure. The clinicians were given a random sample of complications twice, to assess consistency of judgment. Moreover, the panel assessed whether the rate or severity of complications in the TLH group exceeded that in the TAH group. All major complications were reported to the medical ethics committee of the coordinating centre immediately. The study coordinators had no access to data during the study.

Secondary outcomes were minor complications, treatment-related outcomes, and QoL. Treatment-related outcomes were the conversion rate (ie, from laparoscopy to laparotomy), operating time, blood loss, hospital stay, use of pain medication, and resumption of daily activities. QoL was assessed with questionnaires given to all patients before surgery and at 6 weeks, 3 months, and 6 months after surgery. Questionnaires included the Short Form-36 Health Survey (SF-36), the Sexual Activity Questionnaire (SAQ), the Body Image Scale (BIS), and the Visual Analogue Scale (VAS) for general health perception.^{21–24} The SF-36 is organised into eight subscales assessing physical functioning, role-physical, bodily pain, general health, mental health, role-emotional, social functioning, and vitality. The first four subscales comprise the physical dimension of SF-36 and latter four comprise the mental dimension.²¹ The SAQ was completed only by patients that had been sexually active in the month before receiving the questionnaire.

Statistical analysis

The study required 275 patients, assuming a 10% drop-out rate, to detect a difference of 15% in the major complication rate between procedures (80% power; $\alpha=0.05$). Primary and secondary endpoints were analysed according to the intention-to-treat principle (based on the allocated intervention) and according to the as-treated principle (based on the received intervention; figure 1). In the as-treated analyses, patients who were allocated to laparoscopy but did not receive this procedure because of reasons known preoperatively ($n=8$), were analysed in the laparotomy group (figure 1). Patients converted to laparotomy remained in the laparoscopy group for both analyses. Since incorrectly randomised patients were excluded from the analyses, the intention-to-treat analyses should be considered as modified.

Descriptive statistics for QoL were calculated for both groups at each postoperative assessment. Operating time was defined as time (min) from the first incision to the last suture. Length of stay was defined as the number of days from the day of surgery to the day of discharge. Variables were summarised as frequencies or proportions. Differences in the variables between groups were evaluated

Panel 2: Surgical treatment protocol for laparoscopy (TLH) for early-stage endometrial cancer

- Preoperative thrombosis prophylaxis administered
- Preoperative antibiotics given at least 15 min before skin incision
- Patient positioned in the lithotomy position
- Insufflation of CO₂ and placing of the four troicarts
- Abdominal washing for cytology
- Bipolar coagulation or sealing the round ligament before cutting with monopolar scissors; opening the peritoneum of the bladder and the pelvic sidewall
- Bipolar coagulation or sealing the infundibulopelvic ligament before cutting with monopolar scissors
- Placing the vaginal tube (McCartney tube); preparation of the bladder off the vagina
- Skeleting the uterine vessels, coagulating or sealing the vessels after identification of the ureter
- Coagulating or sealing and cutting the sacrouterine ligaments
- Cutting the vaginal wall on the rim of the vaginal tube; keeping the ureter in sight
- Taking out the uterus; closing the vaginal cuff with abdominal or vaginal stitching

TLH=total laparoscopic hysterectomy.

with χ^2 tests. Changes in QoL scores at 6 weeks, 3 months, and 6 months after baseline, within and between treatment groups, were assessed with mixed-effects analysis-of-variance models for repeated measures. All tests were two-sided and p values less than 0.05 were considered significant. Analyses were done with SPSS software, version 17.0 for Windows (SPSS Inc, Chicago, IL, USA) and MLwiN version 1.10 (Institute of Education, University of London, London, 2001). The trial is registered with the clinical Dutch trial registry, number NTR821.

Role of the funding source

The sponsor reviewed and approved the study design, but had no role in collecting, analysing, or interpreting the data, writing the report, or the decision to submit the paper for publication. The authors had full access to all data after inclusion of patients and to external data monitoring. All authors participated in writing the report. The corresponding author had final responsibility for the decision to submit for publication.

Results

Of the 283 randomised patients, 187 were assigned to the TLH group and 96 to the TAH group. Patient characteristics did not differ between groups (figure 1). In each group, two patients were randomised even though it was known that they did not fulfil the inclusion criteria. These patients were not included in the intention-to-treat analysis. Of the 94 abdominal procedures, 33 were done by the 24 surgeons assessed for skill in laparoscopy and 61 by their colleagues. Eight of 185 (4.3%) of patients allocated to the laparoscopic procedure had abdominal surgery, for reasons shown in figure 1. No patient was lost to follow-up in the case record form, although not all completed the questionnaires at each timepoint. Two centres did not

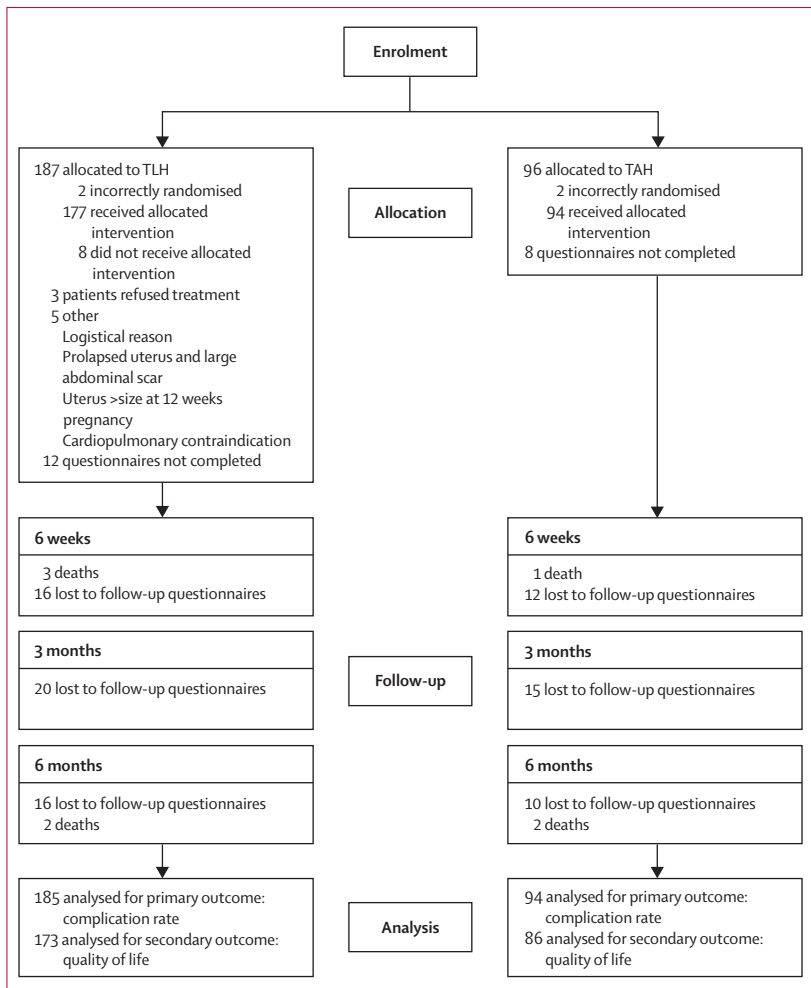


Figure 1: Study flowchart
TLH=total laparoscopic hysterectomy. TAH=total abdominal hysterectomy.

comply with the randomisation procedure and were banned from participation shortly after the beginning of the study. These centres assumed an advantage for laparoscopy and intended to first offer laparoscopy and subsequently randomise patients who had no preference. One of these centres had not yet randomised patients. The other centre randomised four patients before beginning the selective randomisation; therefore, these patients were not excluded from the study.

Baseline characteristics were equally distributed between treatment groups in both the intention-to-treat analysis (table 1) and the as-treated analysis. Median age was 63.0 years (range 39.0–89.0) and median BMI was 29 kg/m² (range 17–55). Comorbidity was reported in nearly 60% (165 of 279) of included patients. 78 of 279 (28.0%) patients had previous abdominal surgery. Based on the final pathology report, most patients (235 of 279 [84.2%]) had International Federation of Gynaecologists and Obstetricians (FIGO 1988) stage I endometrioid adenocarcinoma or complex atypical

	TLH (n=185)	TAH (n=94)
Age in years, median (range)	62 (40–89)	63 (39–86)
>65 years	70 (37.8)	40 (42.6)
BMI kg/m ² , median (range)†	29 (17–55)	28 (19–48)
>30 kg/m ²	80 (43.5)	37 (39.8)
Comorbidity (including previous malignancy)	107 (57.8)	58 (61.7)
Previous abdominal surgery	55 (29.7)	23 (24.5)
Histological subtype‡		
No dysplasia or malignancy	11 (6.0)	1 (1.1)
Complex atypical hyperplasia	24 (13.0)	7 (7.4)
Endometrioid adenocarcinoma	147 (79.9)	83 (88.3)
Papillary adenocarcinoma	1 (0.5)	2 (2.1)
Sarcoma	1 (0.5)	1 (1.1)
FIGO 1988 stage§		
I	130 (87.2)	75 (87.2)
II	15 (10.1)	8 (9.3)
III	2 (1.3)	2 (2.3)
IV	2 (1.3)	1 (1.2)
Grade¶		
I	107 (71.8)	55 (64.0)
II	32 (21.5)	26 (30.2)
III	10 (6.7)	5 (5.8)
Adjuvant radiotherapy	38 (20.5)	25 (26.6)

Data are number of patients (%) unless otherwise stated. TLH=total laparoscopic hysterectomy. TAH=total abdominal hysterectomy. BMI=body-mass index. FIGO=International Federation of Gynaecologists and Obstetricians. *For the intention-to-treat analysis (distribution for the as-treated analysis did not differ significantly). †Two patients had missing BMI data. ‡One patient had missing data in the TLH group. §One patient had missing data. The patients with complex atypical hyperplasia or no dysplasia in the final uterine specimen were not given a FIGO stage and were therefore not included in the analysis. ¶One patient had missing data.

Table 1: Baseline characteristics according to treatment group*

hyperplasia. Postoperative radiotherapy was given to 22.6% (63 of 279) of patients, according to the Postoperative Radiation Therapy for Endometrial Carcinoma (PORTEC)-I criteria.²⁵

Overall, 49 major complications (49 of 279 [17.6%]) were noted in 41 patients (41 of 279 [14.7%]; table 2). According to the intention-to-treat analysis, 27 patients with major complications were in the TLH group (27 of 185 [14.6%]) and 14 were in the TAH group (14 of 94 [14.9%]), with a difference of –0.3% (95% CI –9.1 to 8.5; p=0.95). According to the as-treated analysis, major complications were noted in 24 patients in the TLH group (24 of 177 [13.6%]) versus 17 in the TAH group (17 of 102 [16.7%]), with a difference of –3.1% (95% CI –11.9 to 5.7; p=0.48). The proportion of patients with intraoperative major complications (nine of 279 [3.2%]) was lower than the proportion with postoperative major complications for both groups (32 of 279 [11.5%]) and did not differ between TLH (five of 185 [2.7%]) and TAH groups (four of 94 [4.3%]; p=0.49). In the TAH group, the proportion of major complications did not differ

	TLH (n=185)†	TAH (n=94)
Patients with major complications (n=41)		
Total	27 (14.6)	14 (14.9)
Intraoperative	5 (2.7)	4 (4.3)
Postoperative	22 (11.9)	10 (10.6)
Related to surgery	27 (14.6)	14 (14.9)
Related to procedure	4 (2.2)	3 (3.2)
Patients with minor complications (n=35)		
Total	24 (13.0)	11 (11.7)
Intraoperative	15 (8.1)	1 (1.1)
Postoperative	18 (9.7)	13 (13.8)
Type of major complication (n=49 events)‡		
Total	33 (17.8)	16 (17.0)
Bowel injury	4 (2.2)	2 (2.1)
Ureter injury	2 (1.1)	0 (0.0)
Bladder injury	2 (1.1)	1 (1.1)
Infection >38.0°C	4 (2.2)	3 (3.2)
Haematoma requiring intervention	1 (0.5)	0 (0.0)
Haemorrhage requiring transfusion	6 (3.2)	2 (2.1)
Wound dehiscence requiring intervention	2 (1.1)	3 (3.2)
Wound infection requiring intervention	3 (1.6)	1 (1.1)
Other major complications	9 (4.9)	4 (4.3)
Ileus requiring intervention	3 (1.6)	1 (1.1)
Death	3 (1.6)	1 (1.1)
Type of minor complication (n=58 events)		
Total	39 (21.1)	19 (20.2)
Pulmonary infection <38.0°C	0 (0.0)	1 (1.1)
Urinary-tract infection, fever <38.0°C	13 (7.0)	7 (7.4)
Urinary retention needing catheter	4 (2.2)	0 (0.0)
Fever <38.0°C	3 (1.6)	2 (2.1)
Wound infection not requiring intervention or prolonged stay	0 (0.0)	1 (1.1)
Minor anaesthetic problems	2 (1.1)	0 (0.0)
Haemorrhage or haematoma without transfusion or intervention	4 (2.2)	2 (2.1)
Other minor complications	13 (7.0)	6 (6.4)

Data are number of patients (%) unless otherwise stated. TLH=total laparoscopic hysterectomy. TAH=total abdominal hysterectomy. *For the intention-to-treat analysis (as-treated analysis not shown). †20 of 185 (10.8%) were converted to TAH. ‡Not tested because groups were too small to test for a significant difference. No patients had fistulas, pulmonary embolism, nerve damage, or vaginal cuff dehiscence.

Table 2: Numbers and types of complications per treatment group*

significantly according to whether the procedure was done by one of the 24 skilled surgeons or a colleague (five of 33 [15.2%] vs nine of 61 [14.8%]; $p=0.96$). The major complication proportion in obese patients (BMI >30 kg/m²) was 16.3% (13 of 80) in the TLH group and 18.9% (seven of 37) in the TAH group, and did not differ between groups ($p=0.72$). The proportion of major complications did not differ significantly between teaching ($n=17$) and non-teaching centres ($n=4$) in either the TLH group (18 of 145 [12.4%] vs nine of 40 [22.5%]; $p=0.11$) or the TAH group (11 of 73 [15.1%] vs three of 21 [14.3%]; $p=0.93$). All 41 major complications were

	Intention-to-treat analysis		As-treated analysis	
	TLH (n=185)	TAH (n=94)	TLH (n=177)	TAH (n=102)
Median duration of surgery (min)	115 (35–267)	71 (31–239)*	115 (52–267)	73 (31–239)*
Median amount of blood loss (mL)	100 (10–1500)	200 (50–2500)*	100 (10–1500)	200 (50–2500)*
Median hospital stay (days)	3 (1–25)	5 (3–32)*	3 (1–25)	5 (3–32)*
Median hospital stay after surgery (days)	2 (1–25)	5 (3–32)*	2 (1–25)	5 (2–32)*
Pain medication (days)	3 (0–7)	5 (0–7)*	3 (0–7)	5 (0–7)*

Data are median (range). TLH=total laparoscopic hysterectomy. TAH=total abdominal hysterectomy. *The p value for all comparisons was <0.0001.

Table 3: Secondary outcomes

assessed as surgery-related (ie, hysterectomy), but only seven were assessed as procedure-related (ie, laparoscopy or laparotomy). Four patients died (grade 5 complication) within 6 weeks of surgery; three died after TLH (three of 185 [1.6%]) and one after TAH (one of 94 [1.1%]; figure 1; webappendix). Two patients died of progressive metastatic disease; one death was probably due to a pulmonary embolism 5 days after surgery, and one was because of progressive hypoxia leading to a hypoxic coma, in a patient with pre-existing cardiopulmonary problems. All the deaths were related to surgery, but none to the type of surgical procedure. Four major complications were graded as life-threatening (grade 4); two in the TLH group (two of 185 [1.1%]) and two in the TAH group (two of 94 [2.1%]). Types of major complications recorded are specified in table 2.

Minor complications, a secondary endpoint, did not differ between groups, with 13.0% (24 of 185) in the TLH group versus 11.7% (11 of 94) in the TAH group ($p=0.76$; table 2). The most common minor complication was urinary-tract infection in both groups. The as-treated analysis for minor complications did not differ significantly (data not shown).

Conversion from laparoscopy to laparotomy was reported in 20 of 185 (10.8%) patients. The reasons for conversions were as follows: inadequate exposure (nine of 185 [4.9%]), uterus too large (nine of 185 [4.9%]), bleeding (one of 185 [0.5%]), technical problems (two of 185 [1.1%]), obesity or anaesthetic complications due to obesity (five of 185 [2.7%]), additional pathology (three of 185 [1.6%]), or other reasons (one of 185 [0.5%]). Some patients had more than one reason for conversion. The median duration of surgery was significantly longer in the TLH group (115 min, range 35–267) compared with the TAH group (71 min, 31–239; table 3). The median amount of blood loss during laparoscopy was 100 mL (range 10–1500) versus 200 mL (50–2500) during laparotomy ($p<0.0001$). Patients who had laparoscopy had a shorter hospital stay after surgery (2 days, range 1–25) than did those who had abdominal surgery (5 days, 3–32; $p<0.0001$). Patients used less analgesic after laparoscopy than after laparotomy ($p<0.0001$). In the questionnaires, 129 of 169 (76.3%)

See Online for webappendix

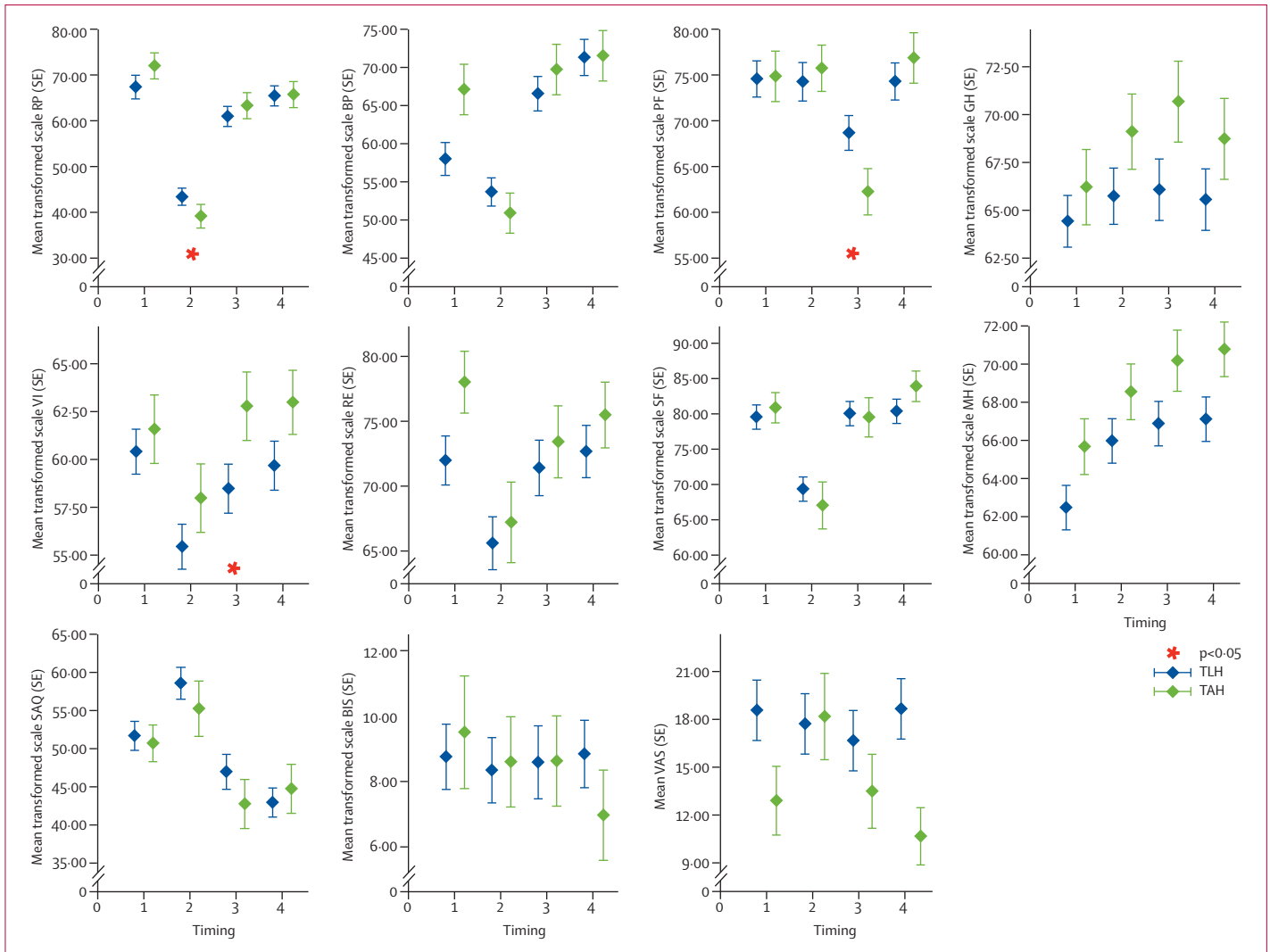


Figure 2: Quality of life as measured at four timepoints after TLH or TAH

Timing: 1=baseline, 2=6 weeks, 3=3 months, and 4=6 months after surgery. Top panels show SF-36 physical components, middle panels show SF-36 mental components, and bottom panels show mean transformed scores for SAQ, BIS, and VAS. TLH=total laparoscopic hysterectomy. TAH=total abdominal hysterectomy. SF-36=Short Form-36. SAQ=Sexual Activity Questionnaire. BIS=Body Image Scale. VAS=Visual Analogue Scale. RP=role-physical. BP=bodily pain. PF=physical functioning. GH=general health. VI=vitality. RE=role-emotional. SF=social functioning. MH=mental health.

patients in the TLH group reported resumption of daily activities at 6 weeks, versus 51 of 82 (62.2%) patients in the TAH group ($p=0.002$). The proportion of patients returning to work 6 weeks after surgery did not differ between the TLH (37 of 167 [22.2%]) and TAH groups (22 of 82 [26.8%]) ($p=0.42$).

For the QoL assessment, overall response rate was 90.1% (1006 of 1116 questionnaires from the four timepoints), with a range of 87.5–92.8% at various assessment points. Compliance did not differ significantly between groups, nor did the median scores at baseline for all QoL scales. Patients who had laparoscopy scored significantly higher on the physical functioning subscale of the SF-36 at 6 weeks, and on the role-physical subscale at 3 months after the procedure (webappendix; figure 2). Patients who had laparotomy

scored significantly higher on the vitality subscale of the mental dimension 3 months after surgery. No differences between groups were recorded for the other subscales. No differences between groups were noted over time in the sums of the mental and physical dimensions. The TLH and TAH groups did not differ significantly at baseline or over time in the VAS, BIS, or SAQ. 38.2% of women (426 of 1116) were sexually active (range 29.4–45.5%; webappendix; figure 2).

Discussion

This randomised trial showed no evidence of a lower proportion of major complications with TLH versus TAH, given that the laparoscopic procedure was done by a skilled surgeon. Additionally, no differences over time in the summed dimensions of QoL scales were noted

between groups. However, a benefit was observed for TLH with regard to treatment-related outcomes. TLH was associated with significantly less blood loss, less use of pain medication, shorter hospital stay, and faster recovery than TAH.

The complication rate was higher than expected in the TLH group (14.6% observed vs 10.0% expected) and much lower than expected in the TAH group (14.9% observed vs 25.0% expected). The power analysis was based on expected rates, which were mainly derived from the results of retrospective single-centre studies that investigated both surgical procedures in patients with endometrial cancer.^{3,4,26,27} These studies all reported a favourable outcome for laparoscopy and substantial (wound) complications after laparotomy. However, the studies were non-randomised—patient selection was biased against TAH (ie, more high-risk or obese patients)—which might explain the higher complication proportion in the laparotomy group. Additionally, two of four studies did not analyse data according to intention-to-treat principles; this might have led to substantial disparity in the results and an overoptimistic report from the innovators of the new laparoscopic surgical technique. Unfortunately, current opinion of laparoscopy is based on these reports, because of the paucity of randomised controlled trials that meet quality standards for optimum reporting of surgical practices.

To minimise bias in studies of well-established surgical techniques, large, multicentre, randomised, controlled trials are needed that are similar in design, definitions, outcomes, and analytical methods.²⁸ The present study was rigorously designed to decrease bias; the study protocol was registered before patient recruitment and the design was published before outcomes were analysed.¹⁹ We used random allocation to treatment, recruited in a multicentre setting, and strictly preplanned the study, with on-site data monitoring to ensure minimum selection and information bias. Additionally, we required the following: a uniform surgical protocol with no variation in laparoscopic hysterectomy (panels 1 and 2); training and assessment of surgeons with preset competence scores for laparoscopy, to avoid learning curve evaluations during the study; universally accepted criteria for complications and strict monitoring to ensure that all adverse events were documented; and an independent panel that assessed all complications, to standardise the primary outcome (major complication rate) and facilitate reproducibility. An alternative to such a rigorously designed trial aimed at diminishing bias is an expertise-based design.^{29,30}

Recently, a large, randomised, multicentre trial (GOG-2222) compared laparoscopy and laparotomy for comprehensive surgical staging of uterine cancer, powered for recurrence-free survival.^{17,18} So far, the investigators have reported only the secondary outcomes of QoL and short-term morbidity. Patient characteristics were similar to those in our study, with similar

distributions of age and BMI. However, because lymphadenectomy was advocated in all patients, the GOG-2222 study does not apply to the Dutch situation and the results cannot be fully compared with those in our study. Furthermore, the requirements imposed in our study were not met by the GOG-2222, because they allowed different surgical laparoscopic techniques (including robotics), omitted a uniform surgical protocol, and did not use an independent panel to assess complications. GOG-2222 showed that laparoscopy had fewer moderate to severe postoperative complications than laparotomy (14% vs 21%), and similar rates of intraoperative complications (10% vs 8%). Conversion to laparotomy was required in 25.8% of the laparoscopic procedures. Intraoperative complications, postoperative complications, and conversion rates were much higher than reported in our trial. This discrepancy could be partly attributed to the surgical skills of clinicians in our study, but might be mainly because the GOG-2222 study included lymphadenectomy as part of their standard procedure. Therefore, the results of GOG-2222 are not applicable in the Netherlands, where surgical treatment of early endometrial cancer is mainly done by general gynaecologists in teaching and non-teaching centres, and does not dictate lymphadenectomy.^{1,2}

Assessments of a new surgical technique versus an established procedure have been criticised, because of a perceived imbalance in surgical experience that favours the established procedure.³¹ Therefore, to avoid comparisons among surgeons with various skill levels for the new intervention (TLH), we only included surgeons who were active in laparoscopy and had completed their learning curve, as proven by an assessment. To the best of our knowledge, this is the first study to implement a safety procedure to overcome intraoperative complications due to surgeons with skill levels at the start of the learning curve.¹¹ Garry and colleagues did a randomised study in an earlier stage of surgical innovation in laparoscopy (ie, the development and exploration stage), in which the level of refinement of this new technique was lower than in our study.^{11,32} To avoid this problem, surgeons in our study were required to pass an Objective Structured Assessment of Technical Skills before they were allowed to recruit patients.²⁰ Only one or two surgeons at every centre were trained in TLH, to ensure that each surgeon was proficient in the laparoscopic procedures. The fact that the major complication proportion for the TAH group did not differ between the proven skilled surgeons and their colleagues confirmed the assumption that all gynaecologists were fully skilled in the abdominal procedure.

The summed QoL dimensions did not differ between groups over the study period. One reason that laparoscopy did not show a clinically significant benefit for QoL might be that the groups had similar major complication outcomes. Furthermore, problems coping

with a malignant disease might have had more effect on QoL than the sequelae of the surgical procedures, a factor that has been noted by others.¹¹ Therefore, because the surgical interventions were comparable for both surgeon-selected clinical outcome and patient-reported outcome, the question of superiority must be based on treatment-related outcomes and cost-effectiveness. Our study was not powered for equivalence, so we cannot conclude that the two procedures are equally safe. We tested the hypothesis that TLH had a lower complication rate than TAH. This hypothesis was rejected and we conclude that there is no evidence of a lower rate of major complications with TLH versus TAH, given that the laparoscopic procedure is done by proven, skilled surgeons. Our study suggests a benefit for TLH over TAH because of shorter hospital stay, less pain after surgery, and quicker return to daily activities. This finding agrees with the GOG-2222 trial, in which laparoscopy also resulted in less pain, faster recovery, and a significantly reduced length of hospital stay.¹⁸

In conclusion, to our knowledge, this study is the largest randomised trial of surgery without lymphadenectomy for early endometrial cancer. By contrast with previous reports, we did not find a safety benefit for laparoscopy over laparotomy, given that TLH is done by proven, skilled surgeons. However, our results show a benefit for TLH in patients with early-stage endometrial cancer in terms of shorter hospital stay, less pain, and quicker resumption of daily activities. Laparoscopy could develop further, which might result in an increased benefit (shorter duration of surgery and hospital stay) over laparotomy, because of improvements in technical equipment and quality of surgical teams. Our study clearly showed that randomised controlled trials are warranted for making rational decisions about the introduction of new surgical techniques.

Contributors

GHdB, HJA, and MJEM wrote the grant application and obtained funding for the study. MJEM and HJA assessed participating gynaecologists. MJEM, CBB, WJP, AGvdZ, and GHdB participated in the study design. MJEM, CBB, HJA, HGtB, RvdS, LP, JW, MYB, and AGvdZ recruited patients. CBB collected data, coordinated the study, and analysed the data. CBB drafted the manuscript, and all authors contributed to review and revision. All authors approved the final version. For a list of study collaborators, see webappendix.

Conflicts of interests

The authors declared no conflicts of interest.

Acknowledgments

This trial was funded by the Dutch Organization for Health Research and Development (ZonMw), programme efficacy (945-07-101). We thank the research nurses of our consortium, particularly José Keurentjes and Lida Ulkeman, and the residents, nurses, and gynaecologists of the participating centres for their help with patient recruitment and data collection. We thank the Trial Coordination Centre for coordinating the entry and validation of data. We thank the independent panel (Hans Nijman, Sybrand Hofker, and Boukes Eindhoven) for their assessments and judgments of the complications.

References

- 1 Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. *Lancet* 2009; **373**: 125–36.
- 2 Benedetti Panici P, Basile S, Maneschi F, et al. Systematic pelvic lymphadenectomy vs no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. *J Natl Cancer Inst* 2008; **100**: 1707–16.
- 3 Obermair A, Manolitsas TP, Leung Y, Hammond IG, McCartney AJ. Total laparoscopic hysterectomy versus total abdominal hysterectomy for obese women with endometrial cancer. *Int J Gynecol Cancer* 2005; **15**: 319–24.
- 4 Manolitsas TP, McCartney AJ. Total laparoscopic hysterectomy in the management of endometrial carcinoma. *J Am Assoc Gynecol Laparosc* 2002; **9**: 54–62.
- 5 Marana R, Busacca M, Zupi E, Garcea N, Paparella P, Catalano GF. Laparoscopically assisted vaginal hysterectomy versus total abdominal hysterectomy: a prospective, randomized, multicenter study. *Am J Obstet Gynecol* 1999; **180**: 270–75.
- 6 Lumsden MA, Twaddle S, Hawthorn R, et al. A randomised comparison and economic evaluation of laparoscopic-assisted hysterectomy and abdominal hysterectomy. *Br J Obstet Gynaecol* 2000; **107**: 1386–91.
- 7 Persson P, Wijma K, Hammar M, Kjolhede P. Psychological wellbeing after laparoscopic and abdominal hysterectomy—a randomised controlled multicentre study. *Br J Obstet Gynaecol* 2006; **113**: 1023–30.
- 8 Olsson JH, Ellstrom M, Hahlin M. A randomised prospective trial comparing laparoscopic and abdominal hysterectomy. *Br J Obstet Gynaecol* 1996; **103**: 345–50.
- 9 Kluivers KB, Hendriks JC, Mol BW, et al. Quality of life and surgical outcome after total laparoscopic hysterectomy versus total abdominal hysterectomy for benign disease: a randomized, controlled trial. *J Minim Invasive Gynecol* 2007; **14**: 145–52.
- 10 Perino A, Cucinella G, Venezia R, Castelli A, Cittadini E. Total laparoscopic hysterectomy versus total abdominal hysterectomy: an assessment of the learning curve in a prospective randomized study. *Hum Reprod* 1999; **14**: 2996–99.
- 11 Garry R, Fountain J, Mason S, et al. The eVALuate study: two parallel randomised trials, one comparing laparoscopic with abdominal hysterectomy, the other comparing laparoscopic with vaginal hysterectomy. *BMJ* 2004; **328**: 129.
- 12 Malzoni M, Tinelli R, Cosentino F, et al. Total laparoscopic hysterectomy versus abdominal hysterectomy with lymphadenectomy for early-stage endometrial cancer: a prospective randomized study. *Gynecol Oncol* 2009; **112**: 126–33.
- 13 Malur S, Possover M, Michels W, Schneider A. Laparoscopic-assisted vaginal versus abdominal surgery in patients with endometrial cancer—a prospective randomized trial. *Gynecol Oncol* 2001; **80**: 239–44.
- 14 Fram KM. Laparoscopically assisted vaginal hysterectomy versus abdominal hysterectomy in stage I endometrial cancer. *Int J Gynecol Cancer* 2002; **12**: 57–61.
- 15 Zorlu CG, Simsek T, Ari ES. Laparoscopy or laparotomy for the management of endometrial cancer. *JLS* 2005; **9**: 442–46.
- 16 Zullo F, Palomba S, Russo T, et al. A prospective randomized comparison between laparoscopic and laparotomic approaches in women with early stage endometrial cancer: a focus on the quality of life. *Am J Obstet Gynecol* 2005; **193**: 1344–52.
- 17 Walker JL, Piedmonte MR, Spirtos NM, et al. Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group Study LAP2. *J Clin Oncol* 2009; **27**: 5331–36.
- 18 Kornblith AB, Huang HQ, Walker JL, Spirtos NM, Rotmensch J, Cella D. Quality of life of patients with endometrial cancer undergoing laparoscopic international federation of gynecology and obstetrics staging compared with laparotomy: a Gynecologic Oncology Group study. *J Clin Oncol* 2009; **27**: 5337–42.
- 19 Bijen CB, Briet JM, de Bock GH, Arts HJ, Bergsma-Kadijk JA, Mourits MJ. Total laparoscopic hysterectomy versus abdominal hysterectomy in the treatment of patients with early stage endometrial cancer: a randomized multi center study. *BMC Cancer* 2009; **9**: 23.
- 20 Goff BA, Nielsen PE, Lentz GM, et al. Surgical skills assessment: a blinded examination of obstetrics and gynecology residents. *Am J Obstet Gynecol* 2002; **186**: 613–17.

- 21 Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol* 1998; **51**: 1055–68.
- 22 Madalinska JB, Hollenstein J, Bleiker E, et al. Quality-of-life effects of prophylactic salpingo-oophorectomy versus gynecologic screening among women at increased risk of hereditary ovarian cancer. *J Clin Oncol* 2005; **23**: 6890–98.
- 23 Stead ML, Fountain J, Napp V, Garry R, Brown JM. Psychometric properties of the Body Image Scale in women with benign gynaecological conditions. *Eur J Obstet Gynecol Reprod Biol* 2004; **114**: 215–20.
- 24 Rorarius MG, Kujansuu E, Baer GA, et al. Laparoscopically assisted vaginal and abdominal hysterectomy: comparison of postoperative pain, fatigue and systemic response. A case-control study. *Eur J Anaesthesiol* 2001; **18**: 530–39.
- 25 Creutzberg CL, van Putten WL, Koper PC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. *Lancet* 2000; **355**: 1404–11.
- 26 Scribner DR Jr, Walker JL, Johnson GA, McMeekin SD, Gold MA, Mannel RS. Surgical management of early-stage endometrial cancer in the elderly: is laparoscopy feasible? *Gynecol Oncol* 2001; **83**: 563–68.
- 27 Eltabbakh GH, Shamonki MI, Moody JM, Garafano LL. Laparoscopy as the primary modality for the treatment of women with endometrial carcinoma. *Cancer* 2001; **91**: 378–87.
- 28 McCulloch P, Altman DG, Campbell WB, et al. No surgical innovation without evaluation: the IDEAL recommendations. *Lancet* 2009; **374**: 1105–12.
- 29 Devereaux PJ, Bhandari M, Clarke M, et al. Need for expertise based randomised controlled trials. *BMJ* 2005; **330**: 88.
- 30 Waler SD, Ismaila AS, Devereaux PJ. Statistical issues in the design and analysis of expertise-based randomized clinical trials. *Stat Med* 2008; **27**: 6583–96.
- 31 Cook JA. The challenges faced in the design, conduct and analysis of surgical randomised controlled trials. *Trials* 2009; **10**: 9.
- 32 Barkun JS, Aronson JK, Feldman LS, et al. Evaluation and stages of surgical innovations. *Lancet* 2009; **374**: 1089–96.