JAMA | Original Investigation

Effect of Total Laparoscopic Hysterectomy vs Total Abdominal Hysterectomy on Disease-Free Survival Among Women With Stage I Endometrial Cancer
A Randomized Clinical Trial

Monika Janda, PhD; Val Gebski, MStat; Lucy C. Davies, MSc; Peta Forder, MBiost; Alison Brand, FRANZCOG; Russell Hogg, FRANZCOG; Thomas W. Jobling, FRANZCOG; Russell Land, FRANZCOG; Tom Manolitsas, FRANZCOG; Marcelo Nascimento, FRANZCOG; Deborah Neesham, FRANZCOG; James L. Nicklin, FRANZCOG; Martin K. Oehler, FRANZCOG; Geoff Otton, FRANZCOG; Lewis Perrin, FRANZCOG; Stuart Salfinger, FRANZCOG; Ian Hammond, FRANZCOG; Yee Leung, FRANZCOG; Peter Sykes, FRANZCOG; Hextan Ngan, MD; Andrea Garrett, FRANZCOG; Michael Laney, FRANZCOG; Tong Yow Ng, MD; Karfai Tam, MB, BS; Karen Chan, MB, BChir; C. David Wrede, MD; Selvan Pather, FRANZCOG; Bryony Simcock, FRANZCOG; Rhonda Farrell, FRANZCOG; Gregory Robertson, FRANZCOG; Graeme Walker, MD; Nigel R. Armfield, PhD; Nick Graves, PhD; Anthony J. McCartney, FRANZCOG; Andreas Obermair, MD, FRANZCOG

IMPORTANCE Standard treatment for endometrial cancer involves removal of the uterus, tubes, ovaries, and lymph nodes. Few randomized trials have compared disease-free survival outcomes for surgical approaches.

OBJECTIVE To investigate whether total laparoscopic hysterectomy (TLH) is equivalent to total abdominal hysterectomy (TAH) in women with treatment-naive endometrial cancer.

DESIGN, SETTING, AND PARTICIPANTS The Laparoscopic Approach to Cancer of the Endometrium (LACE) trial was a multinational, randomized equivalence trial conducted between October 7, 2005, and June 30, 2010, in which 27 surgeons from 20 tertiary gynecological cancer centers in Australia, New Zealand, and Hong Kong randomized 760 women with stage I endometrioid endometrial cancer to either TLH or TAH. Follow-up ended on March 3, 2016.

INTERVENTIONS Patients were randomly assigned to undergo TAH (n = 353) or TLH (n = 407).

MAIN OUTCOMES AND MEASURES The primary outcome was disease-free survival, which was measured as the interval between surgery and the date of first recurrence, including disease progression or the development of a new primary cancer or death assessed at 4.5 years after randomization. The prespecified equivalence margin was 7% or less. Secondary outcomes included recurrence of endometrial cancer and overall survival.

RESULTS Patients were followed up for a median of 4.5 years. Of 760 patients who were randomized (mean age, 63 years), 679 (89%) completed the trial. At 4.5 years of follow-up, disease-free survival was 81.3% in the TAH group and 81.6% in the TLH group. The disease-free survival rate difference was 0.3% (favoring TLH; 95% CI, −5.5% to 6.1%; $P = .007$), meeting criteria for equivalence. There was no statistically significant between-group difference in recurrence of endometrial cancer (28/353 in TAH group [7.9%] vs 33/407 in TLH group [8.1%]; risk difference, 0.2% [95% CI, −3.7% to 4.0%]; $P = .93$) or in overall survival (24/353 in TAH group [6.8%] vs 30/407 in TLH group [7.4%]; risk difference, 0.6% [95% CI, −3.0% to 4.2%]; $P = .76$).

CONCLUSIONS AND RELEVANCE Among women with stage I endometrial cancer, the use of total abdominal hysterectomy compared with total laparoscopic hysterectomy resulted in equivalent disease-free survival at 4.5 years and no difference in overall survival. These findings support the use of laparoscopic hysterectomy for women with stage I endometrial cancer.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00096408; Australian New Zealand Clinical Trials Registry: CTRN12606000261516

JAMA. 2017;317(12):1224-1233. doi:10.1001/jama.2017.2068

Editorial page 1215

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Andreas Obermair, MD, FRANZCOG, Royal Brisbane and Women's Hospital, Sixth Floor, Ned Hanlon Building, Brisbane, Queensland, Australia 4029 (obermair@powerup.com.au).

Endometrial cancer is the most common gynecological cancer in developed countries.[1] Obese or nulliparous women, and those with Lynch syndrome have a particularly high risk for the disease.[2] Endometrial cancer is usually treated surgically by removing the uterus and performing a bilateral salpingo-oophorectomy.[3] It is not known how beneficial surgical staging is for early-stage disease, although postoperative treatment is tailored to histopathological risk factors and disease stage.[3,4]

Laparoscopic hysterectomy is associated with less morbidity and results in better recovery than open operations, but it is not known if the operation results in equivalent survival outcomes. Laparoscopic hysterectomy could also pose greater risks of complications in obese patients, have a higher risk of intraoperative injuries, or result in port-site metastases.[5] Three large randomized trials suggested that total laparoscopic hysterectomy may be equally safe as total abdominal hysterectomy[6] and may have short-term advantages, including less pain, better quality of life,[7-9] decreased risk of surgical adverse events,[10] and economic savings.[11]

These short-term advantages have supported the global trend to adopt laparoscopic hysterectomy despite little data to confirm its efficacy in regard to disease-free and overall survival.[12,13] A meta-analysis[14] included only 3 small trials (each had <160 participants) and 1 large trial (N = 2616) formally evaluating survival end points. The included trials were heterogeneous with respect to their laparoscopic hysterectomy technique; just 2 of the trials focused on patients with stage I endometrial cancer, and only 1 of the trials used total laparoscopic hysterectomy, whereas the other 3 trials allowed laparoscopic-assisted vaginal hysterectomy.

The primary hypothesis of the present trial was that total laparoscopic hysterectomy is associated with equivalent disease-free survival compared with the standard treatment of total abdominal hysterectomy for women with apparent stage I endometrial cancer.

Key Points

Question Is total laparoscopic hysterectomy equivalent to total abdominal hysterectomy for early-stage endometrial cancer surgery?

Findings In this clinical trial of 760 women with stage I endometrial cancer, disease-free survival at 4.5 years was 81.6% with total laparoscopic hysterectomy vs 81.3% with total abdominal hysterectomy (difference, 0.3% [favoring total laparoscopic hysterectomy], 95% CI, −5.5% to 6.1%), meeting prespecified criteria for equivalence.

Meaning In this trial of women with early-stage endometrial cancer, disease-free survival was equivalent following total laparoscopic hysterectomy compared with total abdominal hysterectomy. Laparoscopic hysterectomy is an appropriate approach for treatment of stage I endometrial cancer.

Methods

Study Design and Procedures

The Laparoscopic Approach to Cancer of the Endometrium (LACE) trial was a multinational, phase 3, randomized equivalence trial. Women with apparent stage I endometrial cancer were randomized to undergo total abdominal hysterectomy (with or without lymphadenectomy) or total laparoscopic hysterectomy (with or without lymphadenectomy). Patients were recruited between October 7, 2005, and June 30, 2010, while receiving treatment at 1 of 20 participating tertiary gynecological cancer centers in Australia, New Zealand, and Hong Kong.

Recruiting centers were eligible to participate after site-specific ethics approval was obtained. The centers differed greatly in size and commonly recruited between 0 and 10 patients per month. Ethics approval was obtained from each hospital's human research and ethics committees. Written informed consent was obtained from patients prior to randomization.

The trial protocol and statistical analysis plan appear in Supplement 1. The design and methods of the LACE trial were described in 2006.[15] The rationale for an equivalence trial was based on retrospective studies that showed promising morbidity and survival results.

Eligibility and exclusion criteria were previously described in detail.[15] In brief, the trial enrolled patients with histologically confirmed endometrioid adenocarcinoma of the endometrium with any grade from the International Federation of Gynecology and Obstetrics (FIGO) staging system and without evidence of extrauterine disease determined by imaging (computed tomography or magnetic resonance imaging of the abdomen and pelvis and chest radiograph or chest computed tomography). Women were ineligible if they had a histological cell type other than endometrioid on curettage, clinically advanced disease (stages II-IV using FIGO 2009 criteria or bulky lymph nodes on imaging), or uterine size greater than 10 weeks' gestation.

Patient-related assessments were collected prior to surgery, at week 1, and at months 1, 3, and 6 after surgery. Patients were followed up at 12 months, and then annually for survival outcomes. Patients without events were censored on March 3, 2016, or on the date of last contact for those lost to follow-up. Investigators verified the surgery performed and the histopathological diagnosis, and collected patient baseline eligibility documents. The presence of recurrent disease was histologically confirmed whenever feasible.

There were 2 phases of the study design. The first phase focused on quality of life. In the event that the study would not be able to proceed to the clinical end point of disease-free survival, an allocation ratio of 2 patients to total laparoscopic hysterectomy and 1 patient to total abdominal hysterectomy for the first 150 patients was used to gain information on the quality-of-life effects of the intervention. Thereafter, to evaluate clinical outcomes in the second phase, a ratio of 1:0.76 was used to rebalance the treatment allocation using mixed-permuted block sizes of 3 and 6 via computer-generated random-number sequences. However, this did not prove to be practical and the allocation ratio was changed to 1:1. Randomization was performed centrally (School of Population Health, University of Queensland) to ensure allocation concealment.

Due to the 2:1 allocation for the first 150 patients, it was expected that about 55 more patients would be allocated to total laparoscopic hysterectomy vs total abdominal hysterectomy by the end of the trial. Randomization was stratified by treatment center, grade of differentiation, and history of cancer (during the second phase only). Blinding of treatment allocation was impractical in this setting (details about allocation and stratification appear in Supplement 1).

The surgical procedures and their steps have been described in detail.[15] Prior to surgery, all patients had to have a complete physical examination, imaging (as described above), an electrocardiogram, and routine blood tests (clinical chemistry and hematology). For total laparoscopic hysterectomy, an anatomically curved silicone tube with a proximal airtight cap (McCartney Tube, OR Company), which prevents loss of pneumoperitoneum, was used that enables instrument access and facilitates the safe removal of specimens transvaginally. Total abdominal hysterectomy was performed through a vertical midline or lower transverse incision.

Surgeons were required to perform pelvic (with or without para-aortic) lymph-node dissection as part of the treatment in both groups. Lymph-node dissections were performed unless (1) the patient was morbidly obese, (2) the patient had grade 1 (well differentiated) or grade 2 (moderately differentiated) without myometrial invasion or had a depth of invasion of less than the inner half of the myometrium based on the frozen section, (3) the patient was medically unfit for lymph-node dissection, or (4) institutional guidelines advised against the lymphadenectomy. Morcellation was not allowed.

Histopathological findings were used to determine the need for adjuvant treatment according to local institutional clinical practice guidelines, and typically were discussed in multidisciplinary meetings. The delivery and management of radiation therapy or chemotherapy was performed according to local institutional clinical practice guidelines. Data on dosimetry or chemotherapy dosing were recorded.

All adverse events encountered during the clinical study were documented. The intensity of adverse events was graded using version 3.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events. The incidence and risk factors for adverse events were previously reported.[16,17]

For quality assurance, a rigorous accreditation process was followed as previously described.[15] Surgeons were required to (1) be certified gynecological oncologists proficient in total abdominal hysterectomy or under the direct supervision of a certified gynecological oncologist in theater; (2) provide evidence of a minimal number of 20 supervised and documented total laparoscopic hysterectomies performed while serving as the main surgeon; and (3) have submitted an unedited video of a total laparoscopic hysterectomy for assessment by the trial credential committee. In addition, prospective surgeons had to perform a live total laparoscopic hysterectomy for treatment of endometrial cancer evaluated by 1 of the accredited surgeons from the LACE trial.

In addition to the above requirements, surgeons had to be (1) able to secure uterine vessels at the level of the uterus laparoscopically; (2) able to perform a laparoscopic retroperitoneal node dissection (pelvic); and (3) able to suture the vaginal vault laparoscopically. These surgical steps were checked during the accreditation process for every trial surgeon. Given that all participating surgeons were certified gynecological oncologists and there are variations in how these tasks can be achieved, no further standardization of surgical technique was attempted.

Patients were seen for follow-up every 3 months after surgery for the first 2 years and then every 6 months until they reached postsurgical year 5. Clinical assessments including gynecological examinations were performed at each visit. Routine medical imaging of asymptomatic women was not performed.[18,19] However, medical imaging was performed to evaluate patients with symptoms that are consistent with disease recurrence.

Imaging was performed if there was a patient complaint or clinical finding to justify it. Clinical assessment and radiological workup with or without histological confirmation of disease recurrence proved the presence of recurrent disease. As per protocol, the presence of disease recurrence had to be proven by biopsy results whenever possible. However, clinical findings were relied on in exceptional circumstances where it would not have been ethically justifiable to take a biopsy, and if clinical, radiological, and tumor marker evidence was overwhelming.

The independent data and safety monitoring committee included 2 gynecological oncologists who were not otherwise involved in this trial, a medical oncologist, and a biostatistician. The committee met biannually and monitored patient safety and toxic effects data, serious adverse events, and mortality.

Outcomes

The primary outcome was disease-free survival, which was measured as the interval between surgery and the date of first recurrence, including disease progression or the development of a new primary cancer or death. Patients who were disease-free at the end of the study were censored at their last follow-up visit. Patients developing new primary tumors during the course of the study would be moved to a different risk profile compared with those not developing a new primary tumor. Because this was a pragmatic study, disease-free survival included the development of new primary disease to account for this risk.[20] Similarly, death (from any cause) also was considered an event.

The reported prespecified secondary outcomes included disease recurrence, patterns of recurrence, and overall survival. The previously reported prespecified secondary outcomes were morbidity, pain, analgesic use, quality of life, and cost-effectiveness.[7,16,17,21,22] Quality of life was assessed using the Functional Assessment of Cancer Therapy General Questionnaire. The proportion of women who showed an improvement of at least 10% or greater from baseline to 4 weeks after surgery was assessed; 55 of 179 women (31%) in the total laparoscopic hysterectomy group and 17 of 121 women (14%) in the total abdominal hysterectomy group achieved this threshold (between-group difference, 13.0% [95% CI, 7.7%-28.9%]; $P < .001$).[7] Smaller quality-of-life benefits

for total laparoscopic hysterectomy persisted into the late recovery phase 3 to 6 months after surgery.[7] Although intraoperative adverse events were similar between the 2 groups, postoperative adverse events were less frequent in patients after total laparoscopic hysterectomy compared with those who received total abdominal hysterectomy.[17] Costs were lower for total laparoscopic hysterectomy.[11]

Statistical Analysis

The statistical design and sample size calculations were based on a 4.5-year disease-free survival rate of 90% in the total abdominal hysterectomy group,[3] and a 7% equivalence margin at 4.5 years. This corresponded to a disease-free survival rate of 83% and was deemed to be sufficiently small to declare total laparoscopic hysterectomy to be equivalent to total abdominal hysterectomy. A sample size of 755 patients was deemed sufficient to declare total laparoscopic hysterectomy equivalent to total abdominal hysterectomy with 90% power and a prespecified equivalence margin of 7% or less based on 5 years of patient accrual and 4.5 years of follow-up. An equivalence margin of 7% or less was determined to be clinically acceptable, as established for this and other disease sites.[23-25] The PORTEC trial,[26] evaluating the effect of postoperative radiotherapy on overall survival in endometrial cancer, used a 10% difference at 5 years and the LAP2 trial[25] used a 5.3% difference in disease-free survival at 3 years.

Equivalence would be declared if both the lower and upper bounds of the 95% CI for the differences in the disease-free survival rates between surgical groups at 4.5 years after randomization were not greater than 7%. A *P* value of less than .05 rejects the null hypothesis and confirms equivalence.

All statistical analyses were conducted according to the intention-to-treat principle. Additional exploratory analyses were performed by exclusion of patients who did not receive the allocated surgery and by the surgery received. Treatment comparisons of continuous data were performed using *t* tests and using χ^2 tests for categorical variables. Disease-free survival rates at 4.5 years were estimated using the Kaplan-Meier method.[16] The hazard ratios (HRs) for disease-free and overall survival in the bivariate and multivariable models were obtained using proportional hazards models.

Exploratory multivariable analyses for disease-free and overall survival were performed with adjustment for prespecified prognostic factors including treatment type, age, body mass index (calculated as weight in kilograms divided by height in meters squared), FIGO surgical stage, grade of differentiation, lymph node involvement, history of malignancy, and Eastern Cooperative Oncology Group performance status score. Subgroup analyses were performed according to stratification variables and other prespecified clinically relevant groups, with tests for interaction by logistic regression in which the outcome was disease-free survival at 4.5 years (yes vs no).

All analyses were performed at the .05 level of significance (2-sided) and conducted using SAS version 9.3 (SAS Institute Inc) and STATA version 14.1 (StataCorp). No statistical adjustments to the analyses were made for multiple testing or to account for missing data.

Results

Study Population and Assigned Treatment

Of 760 patients who were randomized (353 to total abdominal hysterectomy and 407 to total laparoscopic hysterectomy), 679 (89%) completed the trial (**Figure 1**). A total of 27 surgeons were accredited and enrolled their patients into the trial. The median follow-up time was 4.5 years. The 2 groups were well balanced across stratification and other baseline factors (**Table 1**). Medical comorbidities were equally distributed across both surgical groups. There were no statistically significant between-group differences in the types of tumor, with the majority being endometrioid adenocarcinomas (97%). There were no significant between-group differences in FIGO surgical staging, histological grade, number of metastatic lymph nodes, or adjuvant treatment (**Table 2**).

Of patients randomized to total laparoscopic hysterectomy, 27 (7%) did not receive the assigned surgical procedure, 24 (6%) were converted from laparoscopy to laparotomy (15 for anatomical reasons [ie, related to the incision to remove the uterus, uterus too large, vagina too narrow], 7 due to complications, and 2 for technical reasons). In the remaining 3 patients that did not undergo a total laparoscopic hysterectomy, 2 withdrew prior to surgery and 1 had her surgery abandoned due to clinically advanced disease with vaginal involvement that was unrecognized until the day of surgery (Figure 1).

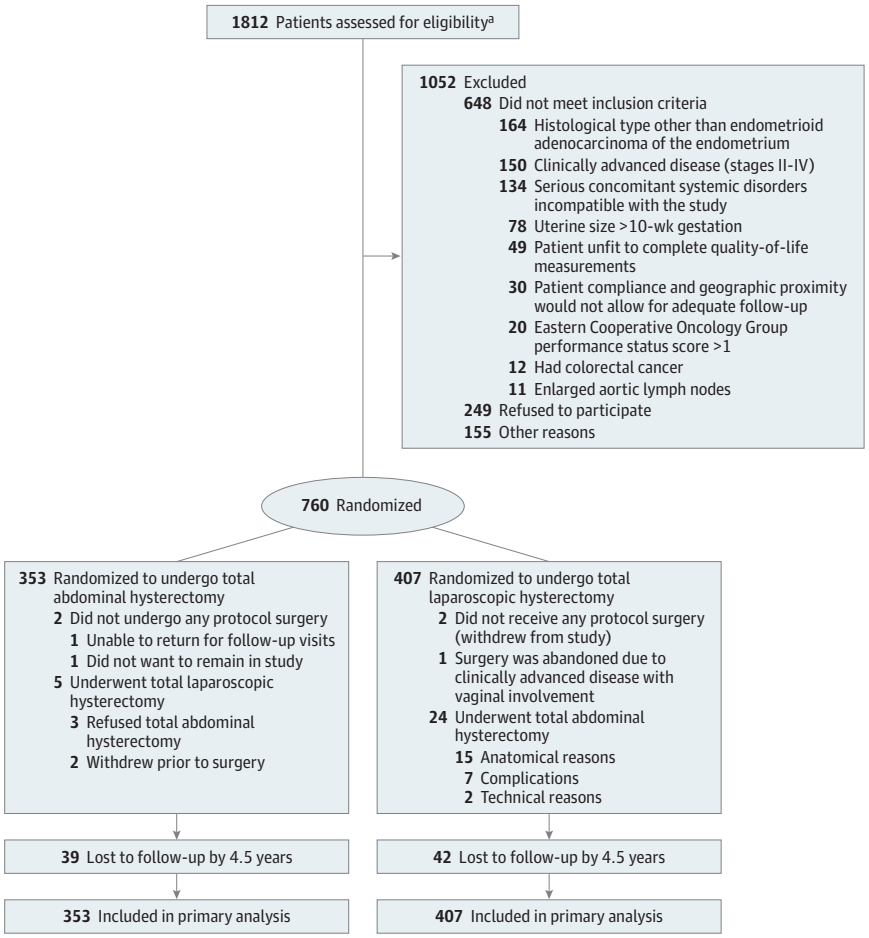
Similarly, 5 patients (2%) randomized to total abdominal hysterectomy received total laparoscopic hysterectomy due to refusal of total abdominal hysterectomy and 2 patients withdrew prior to surgery. There were 81 patients (11%) lost to follow-up by 4.5 years; baseline characteristics did not differ in these patients compared with those who completed follow-up (eTable 1 in Supplement 2). For the primary analysis, all patients were included in their randomized treatment group.

Disease-Free Survival

In the intention-to-treat analysis of the primary outcome, 60 patients (17.0%) who had been assigned to total abdominal hysterectomy and 70 patients (17.2%) who had been assigned to total laparoscopic hysterectomy experienced an event by 4.5 years after randomization. Based on the Kaplan-Meier estimates, the probability of disease-free survival at 4.5 years was 81.3% in the total abdominal hysterectomy group and 81.6% in the total laparoscopic hysterectomy group (disease-free survival difference, 0.3% [95% CI, −5.5% to 6.1%], favoring total laparoscopic hysterectomy). Both the lower and upper boundary of the 2-sided 95% CI excluded the prespecified equivalence margin of 7% or less (*P* = .007), supporting the conclusion that total laparoscopic hysterectomy is equivalent to total abdominal hysterectomy.

Supporting per-protocol analyses revealed the probability of not having a disease-free survival event as 81.4% (346 patients) in the total abdominal hysterectomy group vs 83.0% (381 patients) in the total laparoscopic hysterectomy group at 4.5 years (providing a difference of 1.6% [95% CI, −4.3% to 7.5%] in favor of total laparoscopic hysterectomy).

Figure 1. Flow Diagram of the Laparoscopic Approach to Cancer of the Endometrium (LACE) Trial



[a] The trial proceeded in 2 phases. During the first phase that focused on quality-of-life outcomes, randomization was conducted using a ratio of 2 patients to total laparoscopic hysterectomy and 1 patient to total abdominal hysterectomy. For the second phase, randomization started with a ratio of 1:0.76 in an attempt to rebalance sample sizes between the 2 groups; however, when this proved unworkable in the field, the allocation ratio was changed to 1:1.

In analyzing patients according to the surgery they received, the disease-free survival rates were 80.0% in the total abdominal hysterectomy group vs 82.9% in the total laparoscopic hysterectomy group (providing a difference of 2.9% [95% CI, −2.9% to 8.7%]).

Secondary Outcomes

In the intention-to-treat analysis, there was no statistically significant between-group difference in disease-free survival (HR, 1.03 [95% CI, 0.73 to 1.44]; $P = .87$) (**Figure 2**A), or in the primary site of recurrence, with 12 patients (3%) in the total abdominal hysterectomy group and 14 patients (3%) in the total laparoscopic hysterectomy group experiencing a cancer relapse at the vaginal vault, and 2% or less of patients experiencing a relapse in the pelvis, in the abdomen, at distant organs, or at multiple sites in both groups (**Table 3**). A post hoc sensitivity analysis of disease-free survival excluding the new primary cancers and deaths found a difference of −0.02% (95% CI, −4.22% to 4.18%) from Kaplan-Meier estimates (eFigure 1 in Supplement 2).

There were 2 patients with port-site metastases in the total laparoscopic hysterectomy group and both patients presented with multiple peritoneal metastases including those located at the port sites. Similarly, 2 patients in the total abdominal hysterectomy group developed recurrences at the site of the abdominal wound. One of these patients presented with multiple metastases affecting the liver and lung, and another patient had an isolated recurrence at the vertical midline scar.

In total, 24 patients (6.8%) in the total abdominal hysterectomy group and 30 patients (7.4%) in the total laparoscopic hysterectomy group died, with an estimated 4.5-year overall survival rate (based on Kaplan-Meier estimates) of 92.4% vs 92.0%, respectively (survival difference, −0.34% [95% CI, −4.4% to 3.7%]). There was no significant between-group difference in overall survival (HR, 1.08 [95% CI, 0.63 to 1.85]; $P = .78$) (Figure 2B). The cause of death was balanced across the treatment groups with the majority of deaths (56%) due to endometrial cancer (Table 3). Prognostic factors associated with disease-free survival and overall survival appear in eTable 2 in Supplement 2 and include history of malignancy, increasing age, and higher surgical and differentiation stage, but not randomized treatment.

Prognostic Factors for Disease-Free Survival

Exploratory analyses for differences in the rates of disease-free survival between the prespecified prognostic subgroups

Table 1. Baseline Characteristics

	Total Hysterectomy	
	Abdominal (n = 353)	Laparoscopic (n = 407)
Age, mean (SD), y	63.1 (10.6)	63.3 (10.0)
Age group, No. (%)		
<65 y	197 (55.8)	232 (57.0)
≥65 y	156 (44.1)	175 (43.0)
Body mass index, median (range)[a]	32.7 (19.1-63.2)	33.1 (18.8-63.3)
Body mass index group, No. (%)		
<30	118 (33.0)	145 (36.0)
≥30	222 (62.9)	244 (60.0)
FIGO differentiation grade determined by dilation and curette, No. (%)		
1 (Well differentiated)	223 (63.2)	259 (63.6)
2 (Moderately differentiated)	107 (30.3)	120 (29.5)
3 (Poorly or undifferentiated)	23 (6.5)	28 (6.9)
Any malignancy prior to the index malignancy, No./total (%)[b]	20/303 (6.6)	28/306 (9.2)
Charlson comorbidity index, median (range)[c]	3 (0-8)	3 (0-10)
Charlson comorbidity index group, No. (%)		
<3	158 (44.7)	172 (42.3)
≥3	195 (55.2)	231 (56.8)
Medication use, No. (%)[d]	271 (76.8)	334 (82.1)
ECOG performance status score, No. (%)[e]		
0	303 (85.8)	352 (86.5)
1	50 (14.2)	55 (13.5)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Change in denominators for this variable are due to phase 1 and phase 2 stratification scheme differences.

[c] Higher scores indicate greater burden.

[d] Ongoing without an end date (indicator of comorbidity burden).

[e] Range is 0 (perfect health) to 5 (death).

appear in eFigure 2 in Supplement 2. A significant interaction (P = .04) for body mass index (<30 vs ≥30) was found, in which patients with a lower body mass index had higher rates of disease-free survival in the total abdominal hysterectomy group (86.6%) vs the total laparoscopic hysterectomy group (77.4%), whereas the total laparoscopic hysterectomy group had higher disease-free survival rates at 4.5 years for patients with a body mass index of 30 or greater (78.9% vs 84.4%, respectively). There were no statistically significant between-group differences in any of the other subgroup categories, including age (<65 years vs ≥65 years), FIGO stage (1 vs >1), Eastern Cooperative Oncology Group performance status score (0 vs 1), Charlson comorbidity index (<3 vs ≥3), or history of malignancy (yes vs no).

A multivariable analysis using proportional hazard regression of disease-free survival adjusting for prespecified prognostic factors did not materially change the treatment effect (eTable 2 in Supplement 2). The unadjusted HR was 1.03 (95% CI, 0.73-1.44; P = .87) and the adjusted HR was 1.00 (95% CI, 0.67-1.50; P = .98).

Discussion

In this clinical trial of 760 women with stage I endometrial cancer, disease-free survival at 4.5 years was 81.6% with total laparoscopic hysterectomy vs 81.3% with total abdominal hysterectomy (between-group difference, 0.3% [95% CI, −5.5% to 6.1%), meeting the criteria for equivalence. Although a limited number of clinical trials have attempted to address the performance and safety of these 2 surgical approaches, the current trial represents, to our knowledge, the first multicenter, international trial in which all surgeons were tasked to perform the total hysterectomy laparoscopically. Surgeons were assessed to ensure that they had sufficient technical competence to participate in this trial. Their proficiency in performing the operations was manifested by a low conversion rate and a high-disease-free survival rate.

The overall incidence of postoperative wound metastases was low (0.0047%); there was no between-group difference in frequency. The outcomes for the 2 groups were consistent irrespective of the analytic approach. Outcomes were similar for survival rates and HRs in both the intention-to-treat and as-treated analyses for disease-free and overall survival without endometrial cancer-specific recurrence and the 4.5-year time point was sufficiently long to capture any separation in the survival curves.[27]

The apparent disease-free survival benefit of total laparoscopic hysterectomy in women with a BMI of 30 or greater is counterintuitive; however, because the 95% CIs for estimates in the individual subgroups overlap, this finding may be a statistical artifact. Laparoscopic surgery has benefits for patients with regard to quality of life, recovery after surgery, hospital stay, and adverse events.[14] Given its better short-term outcomes, updated meta-analyses should now be conducted to determine whether total laparoscopic hysterectomy should become the standard approach for patients with stage I endometrial cancer.

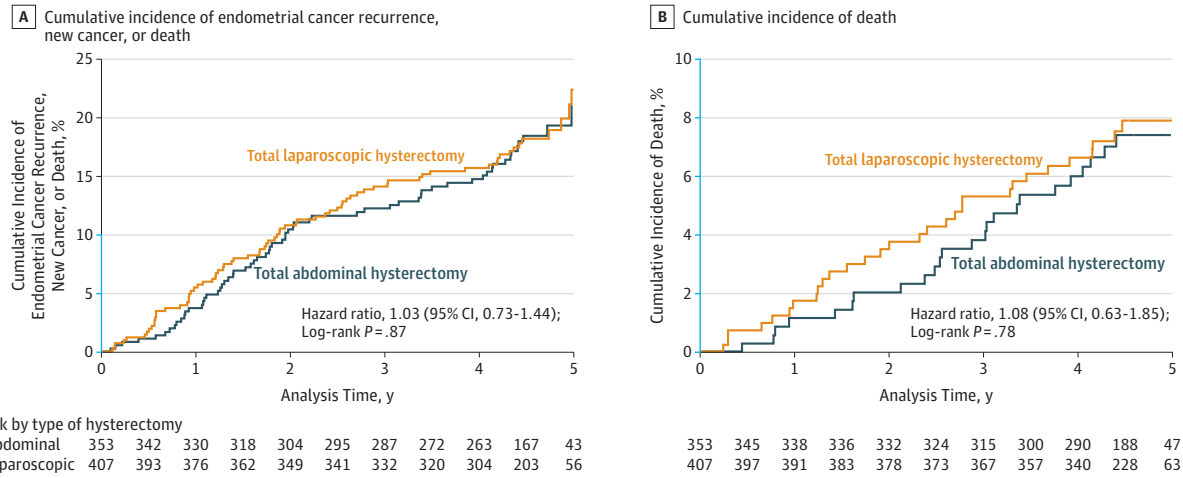
Table 2. Surgery and Adjuvant Treatment Characteristics

	Total Hysterectomy		Risk Difference (Laparoscopic Group Minus Abdominal Group), % (95% CI)	P Value
	Abdominal (n = 353)	Laparoscopic (n = 407)		
Surgical and pathological characteristics, median (range)				
Time to surgery from randomization, d	7 (0 to 74)	7 (0 to 62)		.70
Duration of operation, min	105 (35 to 249)	130 (50 to 300)		<.001
Hemoglobin level (change from baseline to 1 wk after surgery), g/dL	−19 (−111 to 31)	−17 (−55 to 15)		.14
Pelvic or aortic lymph node dissection, No. (%)	206 (58.4)	161 (39.6)	−18.8 (−25.8 to −11.8)	<.001
International Federation of Gynecology and Obstetrics surgical stage, No. (%)				
IA (tumor limited to the endometrium)	237 (67.1)	286 (70.3)	3.1 (−3.5 to 9.7)	.27
IB (invasion to <half of the myometrium)	44 (12.5)	55 (13.5)	1.0 (−3.7 to 5.8)	
II	45 (12.7)	32 (7.9)	−4.9 (−9.2 to −0.5)	
IIIA (tumor invades the serosa of the corpus uteri, adnexa, or positive cytological findings)	4 (1.1)	11 (2.7)	1.6 (−0.4 to 3.5)	
IIIB (vaginal metastases)	1 (0.3)	4 (1.0)	0.7 (−0.4 to 1.8)	
IIIC1	12 (3.4)	11 (2.7)	−0.7 (−3.2 to 1.7)	
IIIC2	3 (0.8)	1 (0.2)	−0.6 (−1.7 to 0.5)	
IVA	1 (0.3)	0	−0.3 (−0.8 to 0.3)	
IVB	3 (0.8)	3 (0.7)	−0.1 (−1.4 to 1.2)	
Unknown	3 (0.8)	4 (1.0)	0.1 (−1.2 to 1.5)	
Cell type, No. (%)				
Endometrioid	340 (96.3)	395 (97.1)	0.7 (−1.8 to 3.3)	.59
Clear cell	7 (2.0)	4 (1.0)	−1.0 (−2.7 to 0.7)	.28
Adenocarcinoma	5 (1.4)	1 (0.2)	−1.2 (−2.5 to 0.2)	.06
Mixed epithelial	3 (0.8)	0	−0.8 (−1.8 to 0.1)	
Sarcoma	1 (0.3)	2 (0.5)	0.2 (−0.7 to 1.0)	.80
Serous	12 (3.4)	7 (1.7)	−1.7 (−4.0 to 0.6)	.14
Mucinous	2 (0.6)	7 (1.7)	1.1 (−0.3 to 2.6)	.14
Small cell	0	2 (0.5)	0.5 (−0.2 to 1.2)	
International Federation of Gynecology and Obstetrics differentiation grade, No. (%)				
1 (Well differentiated)	185 (52.4)	231 (56.8)	4.3 (−2.7 to 11.4)	.27
2 (Moderately differentiated)	124 (35.1)	129 (31.7)	−3.5 (−10.2 to 3.3)	
3 (Poorly or undifferentiated)	40 (11.3)	43 (10.6)	−0.8 (−5.2 to 3.7)	
Unknown	4 (1.1)	4 (1.0)	−0.2 (−1.6 to 1.3)	
No. of lymph nodes examined, median (range)	10 (5 to 28)	11 (7 to 15)		.88
No. of metastatic lymph nodes, median (range)	0 (0 to 1)	0 (0 to 2)		.84
Adjuvant treatment, No. (%)				
Chemotherapy only	7 (2.0)	8 (2.0)	−0.01 (−2.0 to 2.0)	.99
Radiation treatment only	66 (18.7)	61 (15.0)	−3.7 (−9.1 to 1.6)	.17
Both chemotherapy and radiation treatment	19 (5.4)	22 (5.4)	0.02 (−3.2 to 3.2)	.99

Published reports from previous trials evaluating the differences in outcomes between open and laparoscopic hysterectomy have been summarized in a recent Cochrane meta-analysis.[14] Until now, the only randomized evidence assessing long-term survival outcomes from a sufficiently powered and multicenter trial was the US Gynecologic Oncology Group's LAP2 trial (GOG 222).[25] The LAP2 trial recruited a total of 2616 women and did not meet the criteria for noninferiority based on a HR boundary of 1.4,[25] potentially due to the smaller than expected recurrence rate. The results of this previous trial suggested that laparoscopic hysterectomy was not as good as the open operation in terms of recurrent disease. In that trial, laparoscopic hysterectomy had an estimated 3-year recurrence rate of 11.4% compared with 10.2% for open hysterectomy.[25]

There are some important differences between the trial reported herein and the LAP2 trial. The LAP2 trial enrolled patients with all types of cancer histology, whereas the present trial enrolled patients with endometrioid cell type on preoperative uterine curetting. All patients enrolled into LAP2 had a retroperitoneal node dissection, including para-aortic nodes. The high conversion rate from laparoscopy to laparotomy (25.8% in LAP2 vs only 6% in this trial) can be explained by the requirement of aortic node dissection in LAP2.[28]

Figure 2. Cumulative Incidence of the Composite Outcome of Endometrial Cancer Recurrence, New Cancer, or Death and Cumulative Incidence of Death by Surgical Group



No. at risk by type of hysterectomy

Total abdominal	353	342	330	318	304	295	287	272	263	167	43	
Total laparoscopic	407	393	376	362	349	341	332	320	304	203	56	
Total abdominal	353	345	338	336	332	324	315	300	290	188	47	
Total laparoscopic	407	397	391	383	378	373	367	357	340	228	63	

The y-axis segment shown in blue indicates the interval from 0% to 10%.

Table 3. Survival Outcomes

	Total Hysterectomy		Risk Difference (Laparoscopic Group Minus Abdominal Group), % (95% CI)	*P* Value
	Abdominal (n = 353)	Laparoscopic (n = 407)		
Primary Outcome				
Disease-free survival (Kaplan-Meier estimates) at 4.5 y, %	81.3	81.6	0.3 (−5.5 to 6.1)	.007[a]
Secondary Outcomes				
Endometrial cancer recurrence, new primary cancer, or death, No. (%)	60 (17.0)	70 (17.2)	0.2 (−5.1 to 5.6)	.54
Endometrial cancer recurrence, No. (%)[b]	28 (7.9)	33 (8.1)	0.2 (−3.7 to 4.0)	.93
Primary site of relapse, No. (%)				
Vaginal vault	12 (3.4)	14 (3.4)	0.04 (−2.5 to 2.6)	.98
Pelvis	4 (1.1)	2 (0.5)	−0.6 (−1.9 to 0.7)	.32
Abdomen	6 (1.7)	6 (1.5)	−0.2 (−2.0 to 1.6)	.84
Distant organs	4 (1.1)	5 (1.2)	0.1 (−1.4 to 1.6)	.90
Multiple sites	2 (0.6)	6 (1.5)	0.9 (−0.5 to 2.3)	.22
Any new primary cancer, No. (%)	27 (7.6)	37 (9.1)	1.4 (−2.5 to 5.4)	.48
Breast	10 (37.0)	7 (18.9)	−18.1 (−40.3 to 4.0)	.11
Colorectal	5 (18.5)	3 (8.1)	−10.4 (−27.5 to 6.7)	.21
Skin	9 (33.3)	19 (51.4)	18.0 (−6.0 to 42.0)	.15
Hematological	1 (3.7)	4 (10.8)	7.1 (−5.2 to 19.4)	.30
Lung	1 (3.7)	3 (8.1)	4.4 (−6.9 to 15.7)	.47
Pancreatic	0	1 (2.7)	2.7 (−2.5 to 7.9)	
Thyroid	1 (3.7)	0	−3.7 (−10.8 to 3.4)	
Deaths by cause, No. (%)[c]	24 (6.8)	30 (7.4)	0.6 (−3.0 to 4.2)	.76
Endometrial cancer	14 (58.3)	16 (53.3)	−5.0 (−31.6 to 22.0)	.71
Unrelated morbidity	2 (8.3)	5 (16.7)	8.3 (−9.0 to 25.7)	.37
Unknown	8 (33.3)	9 (30.0)	−3.3 (−28.3 to 21.7)	.79

[a] Rejects the null hypothesis and confirms equivalence.

[b] Any event that occurred between randomization and 4.5 years after randomization. Recurrence excludes deaths and new primary cancers.

[c] Any event that occurred between randomization and March 3, 2016.

In contrast, only half of all patients enrolled in the current trial received a retroperitoneal node dissection, and patients who received total laparoscopic hysterectomy were less likely to have a node dissection. This reflects the existing, wide variation in opinions about the need for comprehensive surgical staging and lymphadenectomy.[2]

Previously reported adverse event results of this trial[16,17] confirmed results from the LAP2 trial[10] and the results from other studies summarized in the Cochrane review.[14] Intraoperative surgical complications were comparable between patients assigned to total abdominal hysterectomy and total laparoscopic hysterectomy in the 3 large trials conducted worldwide to date.[9,10,17] In regard to postoperative surgical adverse events, the Dutch trial[9] recorded similar postoperative surgical complications in the abdominal and the laparoscopic groups, whereas laparoscopic hysterectomy led to fewer postoperative surgical complications in LAP2[10] and in the present trial.[17] Quality-of-life outcomes favored total laparoscopic hysterectomy over total abdominal hysterectomy in all 3 of these trials.

The present analyses showed that patients with endometrial cancer treated by total laparoscopic hysterectomy had equivalent survival outcomes up to 4.5 years after surgery. Other investigators reported that long-term survival outcomes are also promising for patients who undergo total laparoscopic hysterectomy.[29]

Limitations

The limitations of this trial include that the blinding of patients and surgeons was not possible; however, lack of blinding is unlikely to affect the disease-free or overall survival outcomes reported herein, which were collected independently from the treating surgeons by dedicated clinical trial staff. Furthermore, randomization was performed prior to the patient being scheduled for surgery due to the different setup required for the surgical procedures.

Due to funding constraints, the trial followed a pragmatic 2-phase design,[30] first focusing on quality of life, and then on disease-free and overall survival once the recruitment of a sufficiently large number of patients was supported by the funders of this trial. In this trial, performance of pelvic and aortic retroperitoneal node dissection was left to the discretion of the surgeons, resulting in inconsistent application of this component of the operation in the study.

Conclusions

Among women with stage I endometrial cancer, the use of total abdominal hysterectomy compared with total laparoscopic hysterectomy resulted in equivalent disease-free survival at 4.5 years and no difference in overall survival. These findings support the use of laparoscopic hysterectomy for women with stage I endometrial cancer.

ARTICLE INFORMATION

Author Affiliations: School of Public Health and Social Work, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Australia (Janda, Graves); NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia (Gebski, Davies); Research Centre for Generational Health and Ageing, University of Newcastle, Newcastle, Australia (Forder); Westmead Hospital, Department of Gynaecologic Oncology, Sydney, Australia (Brand); University of Sydney and Northern Sydney Local Health District, Sydney, Australia (Hogg); Department of Gynaecologic Oncology, Monash Medical Centre, Melbourne, Australia (Jobling); Queensland Centre for Gynaecological Cancer, University of Queensland, Herston, Australia (Land, Nascimento, Nicklin, Perrin, Garrett, Walker, Armfield, Obermair); School of Medicine, University of Queensland, Herston, Australia (Land, Nascimento, Nicklin, Perrin, Garrett, Armfield, Obermair); Box Hill Hospital, Melbourne, Australia (Manolitsas); Royal Women's Hospital, Melbourne, Australia (Neesham, Wrede); Department of Gynaecology, Royal Adelaide Hospital, Adelaide, Australia (Oehler); John Hunter Hospital, Newcastle, Australia (Otton); Department of Gynaecologic Oncology, University of Newcastle, Callaghan, Australia (Otton); St John of God Hospital, Perth, Australia (Salfinger, Leung, McCartney); Gynaecological Cancer Service, King Edward Memorial Hospital, Subiaco, Australia (Salfinger, Leung, McCartney); University of Notre Dame, Perth, Australia (Salfinger); School of Women's and Infants' Health, University of Western Australia, Perth (Salfinger, Hammond, Leung); Christchurch Women's Hospital, Christchurch, New Zealand (Sykes, Laney, Simcock); Department of Obstetrics and Gynecology, Queen Mary Hospital, Hong Kong (Ngan, Ng, Tam, Chan); Royal Prince Alfred Hospital, Sydney, Australia (Pather); School of Women's and Children's Health, University of New South Wales, St George Hospital, Sydney, Australia (Farrell, Robertson).

Author Contributions: Dr Janda and Mr Gebski had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Janda, Gebski, Forder, Manolitsas, McCartney, Obermair.
Acquisition, analysis, or interpretation of data: Janda, Gebski, Davies, Brand, Hogg, Jobling, Land, Manolitsas, Nascimento, Neesham, Nicklin, Oehler, Otton, Perrin, Hammond, Salfinger, Leung, Sykes, Ngan, Garrett, NG, Tam, Chan, Wrede, Pather, Simcock, Farrell, Robertson, Walker, Armfield, Graves, McCartney, Obermair.
Drafting of the manuscript: Janda, Gebski, Davies, Obermair.
Critical revision of the manuscript for important intellectual content: Janda, Gebski, Forder, Brand, Hogg, Jobling, Land, Manolitsas, Nascimento, Neesham, Nicklin, Oehler, Otton, Perrin, Hammond, Salfinger, Leung, Sykes, Ngan, Garrett, Laney, NG, Tam, Chan, Wrede, Pather, Simcock, Farrell, Robertson, Walker, Armfield, Obermair.
Statistical analysis: Gebski, Davies, Forder, Graves.
Obtained funding: Janda, Forder, Hogg, Manolitsas, McCartney, Obermair.
Administrative, technical, or material support: Gebski, Brand, Hogg, Land, Manolitsas, Nascimento, Neesham, Nicklin, Otton, Hammond, Salfinger, Sykes, Garrett, Laney, Tam, Chan, Pather, Farrell, Robertson, Walker, Armfield, Obermair.
Supervision: Gebski, Land, Manolitsas, Oehler, Salfinger, Leung, Obermair.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Obermair reported receiving travel grants from the O. R. Company; being the founder and managing director of SurgicalPerformance Pty Ltd; and being a consultant for Covidien. No other disclosures were reported.

Funding/Support: This study was funded by the Cancer Council Queensland, the Cancer Council New South Wales, the Cancer Council Victoria, and the Cancer Council Western Australia; by project grant 456110 from the National Health and Medical Research Council, project grants 631523 and 1098905 from Cancer Australia, and a Smart health research grant from QLD Health; and funding from the Women and Infants Research Foundation, Royal Brisbane and Women's Hospital Foundation, Wesley Research Institute, Gallipoli Research Foundation, Gynetech, Tyco Healthcare, Johnson & Johnson Medical, Hunter New England Centre for Gynaecological Cancer, Genesis Oncology Trust, and the Cherish Foundation.

Role of the Funder/Sponsor: The funders of the study had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript or the decision to submit for publication.

Additional Contributions: We are deeply grateful to the patients who volunteered to participate in the Laparoscopic Approach to Cancer of the Endometrium trial. We also thank the study staff, including Trudi Cattley, BSc (Queensland Centre for Gynaecological Cancer), who was the clinical trial manager and study employee. In addition, we thank Rob Coleman, MD (University of Texas M. D. Anderson Cancer Center, Houston), for insightful comments on an earlier version of this article. Dr Coleman did not receive any compensation.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136(5):E359-E386.

2. Morice P, Leary A, Creutzberg C, Abu-Rustum N, Darai E. Endometrial cancer. *Lancet*. 2016;387 (10023):1094-1108.

3. Creasman WT, Odicino F, Maisonneuve P, et al. Carcinoma of the corpus uteri: FIGO 26th annual report on the results of treatment in gynecological cancer. *Int J Gynaecol Obstet*. 2006;95(suppl 1): S105-S143.

4. Frost JA, Webster KE, Bryant A, Morrison J. Lymphadenectomy for the management of endometrial cancer. *Cochrane Database Syst Rev*. 2015;(9):CD007585.

5. Johnstone PA, Rohde DC, Swartz SE, Fetter JE, Wexner SD. Port site recurrences after laparoscopic and thoracoscopic procedures in malignancy. *J Clin Oncol*. 1996;14(6):1950-1956.

6. Obermair A, Manolitsas TP, Leung Y, Hammond IG, McCartney AJ. Total laparoscopic hysterectomy for endometrial cancer: patterns of recurrence and survival. *Gynecol Oncol*. 2004;92(3):789-793.

7. Janda M, Gebski V, Brand A, et al. Quality of life after total laparoscopic hysterectomy versus total abdominal hysterectomy for stage I endometrial cancer (LACE): a randomised trial. *Lancet Oncol*. 2010;11(8):772-780.

8. 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(32):5337-5342.

9. Mourits MJ, Bijen CB, Arts HJ, et al. Safety of laparoscopy versus laparotomy in early-stage endometrial cancer: a randomised trial. *Lancet Oncol*. 2010;11(8):763-771.

10. 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(32):5331-5336.

11. Graves N, Janda M, Merollini K, Gebski V, Obermair A; LACE Trial Committee. The cost-effectiveness of total laparoscopic hysterectomy compared to total abdominal hysterectomy for the treatment of early stage endometrial cancer. *BMJ Open*. 2013;3(4):e001884.

12. Wright JD, Burke WM, Tergas AI, et al. Comparative effectiveness of minimally invasive hysterectomy for endometrial cancer. *J Clin Oncol*. 2016;34(10):1087-1096.

13. National Institute for Health and Clinical Excellence. *Laparoscopic Hysterectomy for Endometrial Cancer*. London, England: National Institute for Health and Clinical Excellence; 2010.

14. Galaal K, Bryant A, Fisher AD, Al-Khaduri M, Kew F, Lopes AD. Laparoscopy versus laparotomy for the management of early stage endometrial cancer. *Cochrane Database Syst Rev*. 2012;(9): CD006655.

15. Janda M, Gebski V, Forder P, Jackson D, Williams G, Obermair A; LACE Trial Committee. Total laparoscopic versus open surgery for stage 1 endometrial cancer: the LACE randomized controlled trial. *Contemp Clin Trials*. 2006;27(4): 353-363.

16. Kondalsamy-Chennakesavan S, Janda M, Gebski V, et al. Risk factors to predict the incidence of surgical adverse events following open or laparoscopic surgery for apparent early stage endometrial cancer: results from a randomised controlled trial. *Eur J Cancer*. 2012;48(14):2155-2162.

17. Obermair A, Janda M, Baker J, et al. Improved surgical safety after laparoscopic compared to open surgery for apparent early stage endometrial cancer: results from a randomised controlled trial. *Eur J Cancer*. 2012;48(8):1147-1153.

18. Agboola OO, Grunfeld E, Coyle D, Perry GA. Costs and benefits of routine follow-up after curative treatment for endometrial cancer. *CMAJ*. 1997;157(7):879-886.

19. Morice P, Levy-Piedbois C, Ajaj S, et al. Value and cost evaluation of routine follow-up for patients with clinical stage I/II endometrial cancer. *Eur J Cancer*. 2001;37(8):985-990.

20. Punt CJ, Buyse M, Köhne CH, et al. Endpoints in adjuvant treatment trials: a systematic review of the literature in colon cancer and proposed definitions for future trials. *J Natl Cancer Inst*. 2007; 99(13):998-1003.

21. Baker J, Janda M, Belavy D, Obermair A. Differences in epidural and analgesic use in patients with apparent stage I endometrial cancer treated by open versus laparoscopic surgery: results from the randomised LACE trial. *Minim Invasive Surg*. 2013; 2013:764329.

22. Belavy D, Janda M, Baker J, Obermair A. Epidural analgesia is associated with an increased incidence of postoperative complications in patients requiring an abdominal hysterectomy for early stage endometrial cancer. *Gynecol Oncol*. 2013;131(2):423-429.

23. Fleshman J, Branda M, Sargent DJ, et al. Effect of laparoscopic-assisted resection vs open resection of stage II or III rectal cancer on pathologic outcomes: the ACOSOG Z6051 randomized clinical trial. *JAMA*. 2015;314(13):1346-1355.

24. Stevenson AR, Solomon MJ, Lumley JW, et al; ALaCaRT Investigators. Effect of laparoscopic-assisted resection vs open resection on pathological outcomes in rectal cancer: the ALaCaRT randomized clinical trial. *JAMA*. 2015;314 (13):1356-1363.

25. Walker JL, Piedmonte MR, Spirtos NM, et al. Recurrence and survival after random assignment to laparoscopy versus laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group LAP2 Study. *J Clin Oncol*. 2012;30(7):695-700.

26. Creutzberg CL, van Putten WL, Koper PC, et al; Post Operative Radiation Therapy in Endometrial Carcinoma. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial: PORTEC Study Group. *Lancet*. 2000;355 (9213):1404-1411.

27. Fung-Kee-Fung M, Dodge J, Elit L, Lukka H, Chambers A, Oliver T; Cancer Care Ontario Program in Evidence-based Care Gynecology Cancer Disease Site Group. Follow-up after primary therapy for endometrial cancer: a systematic review. *Gynecol Oncol*. 2006;101(3):520-529.

28. Berchuck A, Secord AA, Havrilesky LJ. Minimally invasive surgery for endometrial cancer: the horse is already out of the barn. *J Clin Oncol*. 2012;30(7):681-682.

29. Koskas M, Jozwiak M, Fournier M, et al. Long-term oncological safety of minimally invasive surgery in high-risk endometrial cancer. *Eur J Cancer*. 2016;65:185-191.

30. Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. *JAMA*. 2003;290(12):1624-1632.