Effect of total laparoscopic hysterectomy vs total abdominal hysterectomy on disease-free survival among women with stage I endometrial cancer. A randomized clinical trial.

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Short title: Laparoscopic Approach to Cancer of the Endometrium Trial

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Key points

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

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 compared to 81.3% with total abdominal hysterectomy (difference 0.3% (favouring TLH), 95%CI, -5.53% to 6.13%) meeting pre-specified 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. New and proposed better surgical methods of treating early stage endometrial cancer should be tested against total laparoscopic hysterectomy in the future.

Abstract

IMPORTANCE Current standard treatment for endometrial cancer involves removal of uterus, adnexa ± 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 Multinational, randomized equivalence trial evaluating the laparoscopic approach to endometrial cancer (LACE). Between October 7, 2005 and June 30, 2010, 27 surgeons from 20 tertiary gynaecological cancer centres in Australia, New Zealand, and Hong Kong randomised 760 women with stage I endometrioid endometrial cancer to either TLH or TAH. Follow-up ended 3rd March 2016.

INTERVENTIONS 353 patients were randomized to TAH, 407 to TLH.

MAIN OUTCOMES AND MEASURES Analysis according to intention-to-treat assessed the primary outcome of disease-free survival (DFS, time interval between surgery and date of first recurrence including any new localized or distant endometrial cancer recurrence or any new cancers, at 4.5 years post-randomization). The pre-specified equivalence boundary was $\Delta=\pm 7\%$. Among seven pre-specified secondary outcomes, disease recurrence and overall survival are reported.

RESULTS Patients were followed 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 follow-up, DFS was 81.3% in the TAH and 81.6% in the TLH group. Equivalence was established with a DFS rate difference of 0.3% (favoring TLH) [95% CI: -5.53% to 6.13], p for equivalence =0.007. There was no statistical difference in endometrial cancer recurrences between the two groups (TAH 28 of 353 (7.9%) and TLH 33 of 407 (8.1%), risk difference 0.2%, 95% CI: -3.7 to 4.0%, p=0.93) or in overall survival (TAH 24 of 353 (6.8%) and TLH 30 of 407 (7.4%), risk difference 0.6%, 95% CI: -3.0 to 4.2%, p=0.76).

CONCLUSIONS AND RELEVANCE Among women with stage I endometrioid endometrial cancer, the use of TAH compared with TLH resulted in equivalent DFS at 4.5 years and no difference in overall survival was observed. These findings support the use of laparoscopic hysterectomy for stage 1 endometrial cancer.

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Endometrial cancer is the most common gynaecological cancer in developed countries.[1] Obese, nulliparous and women with Lynch syndrome are at risk.[2] Treatment is mainly surgical and includes a total hysterectomy and bilateral salpingo-oophorectomy.[3] Surgical staging, to determine the extent of disease, is controversial. Postoperative treatment is tailored to histopathological risk factors and disease stage.[3, 4]

At the start of the laparoscopic approach to endometrial cancer (LACE) trial in 2005, few patients were offered a laparoscopic hysterectomy (LH). At the time concerns included that it could pose greater risks in obese patients, have a higher risk of intraoperative injuries, inferior disease-specific survival, or port-site metastases.[5] Subsequent data by three large randomized trials suggested that total LH may be equally safe as total abdominal hysterectomy (TAH)[6] and have short-term advantages including less pain, better quality of life (QoL),[7-9] decreased risk of surgical adverse events,[10] and economic savings.[11] A Cochrane review and meta-analysis summarized the wider literature.[12]

These now well-characterized short-term advantages have supported the global trend to adopt LH despite little data to confirm its efficacy in regard to disease-free and overall survival.[13, 14] A meta-analysis [12] found only three small (each had n<160) and one large trial (n=2,616) formally evaluating survival endpoints. These trials are heterogeneous with respect to their LH technique; just two trials focused on patients with stage 1 endometrial cancer, and only one trial used a total LH, while the other three trials allowed laparoscopic-assisted vaginal hysterectomy.

The ***primary hypothesis*** of the present trial was that Total Laparoscopic Hysterectomy (TLH) is associated with equivalent disease-free survival (DFS) when compared to the standard treatment of TAH for women with apparent Stage I endometrial cancer.

Methods

Study design and Procedures

This multinational, randomized, phase 3, equivalence trial compared TAH ± lymphadenectomy to TLH ± lymphadenectomy in women with apparent stage 1 endometrial cancer (EC). Between October 7, 2005 and June 30, 2010, patients were recruited through one of 20 participating tertiary gynaecological cancer centres in Australia, New Zealand, and Hong Kong. Recruiting centres came on board as site specific ethics approval was obtained. They differed greatly in size and commonly recruited 0-10 patients/month. Ethics approval was obtained from each hospital's Human Research and Ethics Committees.

The full trial protocol and statistical analysis plan are included in the online supplement. The trial's design and methods were described in 2006.[15] The rationale for an equivalence trial was based on retrospective studies which showed promising morbidity and survival results.

Written informed consent was obtained from patients prior to randomization. Eligibility and exclusion criteria were described in detail previously.[15] In brief, the trial enrolled patients with histologically confirmed endometrioid adenocarcinoma of the endometrium of any FIGO grade without evidence of extra-uterine disease by imaging (computed tomography (CT) or Magnetic Resonance Imaging (MRI) of the abdomen and pelvis and chest radiograph or chest CT). Women with a histological cell-type other than endometrioid on curettage, clinically advanced disease (stage II – IV using FIGO 2009 criteria for stage or bulky lymph nodes on imaging), uterine size greater than 10 weeks of gestation were ineligible.

Patient-related assessments were collected prior to surgery, and at week 1, and months 1, 3, and 6, post-surgery. All patients were followed at 12 months, and then annually for survival outcomes. Patients without events were censored at the date of data lock (3rd March 2016) or date of last contact for patients lost to follow up.

Verification of surgery, histopathology and baseline eligibility assessment documents was conducted for all patients. Presence of recurrent disease was confirmed histologically whenever feasible.

There were two phases in the study design. In the event that the study would not be able to proceed to the clinical endpoint of DFS, a 2:1 allocation TLH:TAH for the first 150 patients was performed to gain key information on the effect of the intervention on QoL. Thereafter patients were randomized to TAH or TLH by mixed permuted blocks of size 3 and 6 using computer-

generated random number sequences. Randomization was performed centrally (School of Population Health, University of Queensland) to ensure allocation concealment. The first phase of the trial focused on QoL. Randomization for the remainder of the study to evaluate clinical outcomes commenced with a ratio of 1:0.76 ratio to re-balance the treatment allocation. This however did not prove to be practical and the allocation ratio was changed to 1:1. Due to the 2:1 allocation of the first 150 patients, it was expected that about 55 more patients would be allocated to TLH compared to TAH at the end of the trial. Randomization was stratified by treating centre, grade of differentiation and history of cancer (second phase only). Blinding of treatment allocation was impractical in this setting (see **online supplement trial protocol** page 17 for details about allocation and stratification).

The surgical procedures and their steps have been described in detail previously.[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, haematology). For the TLH an anatomically curved silicone tube with a proximal airtight cap that prevents loss of pneumoperitoneum, enables instrument access and facilitates the safe removal of specimens transvaginally was used (McCartney Tube™, The O.R. Company, Melbourne, Australia). TAH 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. A lymph-node dissection could only be omitted if one of the following criteria were met: morbid obesity, Grade 1 (well-differentiated) or Grade 2 (moderately-differentiated) without myometrial invasion or with a depth of invasion of less than the inner half of the myometrium based on frozen section, or the patient was medically unfit for lymph-node dissection, or institutional guidelines advising 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 carried out according to local institutional clinical practice guidelines. Data on dosimetry or chemotherapy dosing was recorded.

All clinical Adverse Events (AEs) encountered during the clinical study were documented. The intensity of AEs was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (CTC-AE v3.0). The incidence of, and risk factors for, AEs was reported previously.[16, 17]

For quality assurance, a rigorous accreditation process was followed as described in detail previously.[15] Surgeons were required to (i) be certified gynecological oncologists proficient in TAH or under the direct supervision of a certified gynecological oncologist in theatre; and (ii) provide evidence of a minimal number of 20 supervised and documented TLHs performed as the main surgeon; and (iii) have submitted an unedited video of a TLH for assessment by the trial credential committee. Finally, all prospective surgeons had to perform a live TLH for endometrial cancer evaluated by one of the LACE accredited surgeons prior to their own accreditation.

The specific requirements for a surgeon to participate on the trial were: 1. Able to secure uterine vessels at the level of the uterus laparoscopically; 2. Able to perform a laparoscopic retroperitoneal node dissection (pelvic); 3. Able to suture vaginal vault laparoscopically. These surgical steps were checked at accreditation of every trial surgeon. Given that all participating surgeons were certified gynecological oncologists and given that there are variations how those tasks could be achieved, no further standardisation of surgical technique was attempted.

Patients were seen for follow-up every three months after surgery for the first two years and every six months until their postsurgical year five. 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 recurrence.

Imaging was performed if there was a patient complaint or clinical finding justifying such procedure. Clinical assessment, radiological work-up ± histological confirmation of recurrence proved the presence of recurrent disease. As per protocol, the presence of a recurrence had to be biopsy proven whenever possible. However in exceptional circumstances, where it would have been ethically not justifiable to take a biopsy and if clinical and/or radiological and tumour marker evidence was overwhelming we relied on clinical findings.

The independent Data and Safety Monitoring Committee (IDSMC) included two gynecological oncologists who were not otherwise involved in this trial, a medical oncologist and a biostatistician. The IDSMC met biannually and monitored patient safety and toxicity data, serious AEs and mortality.

Outcomes

The primary outcome was DFS, which was measured as the time interval between surgery and 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 tumours during the course of the study would move to a different risk profile compared with those not developing a new primary. As this was a pragmatic study, to account for this risk, DFS was defined to include the development of new primary disease.[20] Similarly death (from any cause) was also considered as an event.

Prespecified secondary outcomes reported here included recurrence, patterns of recurrence, and overall survival (OS). Prespecified secondary outcomes not reported here, but previously reported elsewhere are morbidity, pain, analgesic consumption, QoL, and cost-effectiveness.[7,16, 17, 21, 22] In early recovery (up to 4 weeks after surgery), patients treated with TLH compared to TAH had a 13% and 11% greater improvement in their functional and physical well-being, respectively. Smaller QoL benefits for TLH persisted into the late recovery phase 3–6 months after surgery. [7] While intraoperative adverse events were similar between the two groups, postoperative adverse events were less frequent in patients after TLH compared to TAH. [17] Costs were lower for TLH.[11]

Statistical Analysis

The statistical design and sample size calculations were based on a 4·5-year DFS rate of 90% in the TAH arm,[3] and a 7% margin at 4·5 years. This corresponded to a DFS rate of 83%, and was deemed to be sufficiently small to declare TLH to be equivalent to TAH. A sample size of 755 patients would be sufficient to declare TLH equivalent to TAH with 90% power and a pre-specified margin, $\Delta = \pm 7\%$, 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 in this and other disease sites.[23-25]

Equivalence would be declared if both the lower and upper bounds of the 95% confidence interval (CI) for difference in the DFS rates between surgical groups at 4·5-years post-randomization were not greater than $\Delta = \pm 7\%$. A p value of <0.05 rejects the null hypothesis, and confirms equivalence.

All statistical analyses were conducted according to the intention-to-treat (ITT) principle. Additional exploratory analyses according to per-protocol (excluding patients that did not receive their randomized treatment allocation) and by the surgery patients actually received was performed. Treatment comparisons of continuous data were performed using *t*-tests and categorical variables using chi-square tests. DFS rates at 4·5-years were estimated using the method of Kaplan-Meier.[16] Hazard ratios for DFS and OS in bivariate and multivariable models were obtained using proportional hazards models.

Exploratory multivariable analyses for DFS and OS was performed adjusting for pre-specified prognostic factors including treatment type, age, BMI, FIGO surgical stage, grade of differentiation,

lymph node involvement, history of malignancy and ECOG status. Subgroup analyses were performed according to stratification variables and other pre-specified clinically relevant groups, with tests for interaction by logistic regression in which the outcome was DFS at 4.5-years (yes vs no).

All analyses were performed at the 5% level of significance (two-sided) and conducted in SAS version 9.3 (SAS Institute, Inc, Cary, NC) and STATA version 14.1 (Statacorp, Texas). No statistical adjustments to the analysis were made for multiple testing or to account for missing data.

Results

Study Population and Assigned Treatment

760 patients were randomized to TAH (n=353) or TLH (n=407) (**Figure 1**). A total of 27 surgeons were accredited and enrolled patients into the trial. The median follow-up time was 4.5 years. The two groups were well balanced across stratification and other baseline factors (**Table 1**). Medical comorbidities were equally distributed across both surgical arms. There were no statistical differences in the types of tumour between the two groups, with the majority being endometrioid adenocarcinomas (97%). There were no significant differences between the groups in FIGO surgical staging, histological grade, number of metastatic lymph nodes or adjuvant treatment (**Table 2**).

Twenty-seven (7%) of patients randomized to TLH did not receive the assigned surgical procedure, twenty-four (6%) being converted from laparoscopy to laparotomy (15 for anatomical reasons (incision to remove the uterus; uterus too large, vagina too narrow etc.), 7 due to complications and 2 for technical reasons). In the remaining 3 patients that did not undergo a TLH, 2 withdrew prior to surgery and 1 patient had their surgery abandoned due to clinically advanced disease with vaginal involvement that was unrecognized until the day of surgery (**Figure 1**). Similarly, five (2%) patients randomized to TAH received TLH due to refusal of TAH and two patients withdrew prior to surgery. There were 81 (11%) patients lost to follow up by 4.5 years; baseline characteristics did not differ in these patients compared to those who completed follow-up (**Supplementary Table 1**). All patients were included in their randomized treatment group for ITT analysis.

Disease-free survival

In the ITT analysis of the primary outcome, 60 (17.0%) of patients who had been assigned to TAH, and 70 (17.2%) of patients assigned to TLH experienced an event by 4.5 years post-randomization. Based on the Kaplan-Meier estimates, the probability of DFS at 4.5 years was 81.3% in the TAH group and 81.6% in the TLH group with a DFS difference of 0.3% (95% CI: -5.53% to 6.13) favouring TLH. Both the lower and upper boundary of the two-sided 95% confidence interval

excluded the pre-specified equivalence margin of Δ= ±7% (p for equivalence=0.007), supporting the conclusion that TLH is equivalent to TAH. Supporting per-protocol (PP) analyses revealed the probability of not having a DFS event as 81.4% (346 patients) in the TAH group vs 83.0% (381 patients) in the TLH group at 4.5 years giving a difference of 1.6% (95% CI: -4.3% to 7.5%) in favour of TLH. For the treatment-received groups the DFS rates were 80.0% in TAH group vs 82.9% in TLH group giving a difference of 2.9% (95% CI: -2.9% to 8.7%).

Secondary outcomes:

There was no statistical difference in DFS between patients assigned to TAH or TLH over the study period (HR 1.03 95% CI 0.73 to 1.44; p=0.87) (**Figure 2a**), or in the primary site of recurrence, with 12 (3%) patients in the TAH group and 14 (3%) in the TLH group relapsing at the vaginal vault, and 2% or less of patients experiencing a relapse in the pelvis, abdomen, at distant organs or multiple sites in both groups (**Table 3**). A post-hoc sensitivity analysis of DFS excluding the new primary cancers and deaths found a difference of -0.02% (95% CI: -4.22% to 4.18) from Kaplan-Meier estimates (**Supplementary Figure 1**).

There were two patients with port-site metastases in the TLH group and both patients presented with multiple peritoneal metastases including at the port site(s). Similarly, two patients in the TAH group developed recurrences at the site of the abdominal wound. One of these patients presented with multiple metastases including liver and lung and another patient had an isolated recurrence at the vertical midline scar.

In total, 24 (6.8%) patients in the TAH group and 30 (7.4%) in the TLH group died, with an estimated 4.5-year OS 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 difference in OS between the two groups (HR 1.08 95% CI 0.63 to 1.85; p=0.78) (**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 DFS and OS are given in **Supplementary Table 2** and include history of malignancy, increasing age and higher surgical stage and stage of differentiation but not randomized treatment.

Prognostic factors for disease-free survival

Exploratory analyses for differences in rates of DFS between the pre-specified prognostic subgroups are presented in **Supplementary Figure 2**. A significant interaction (P=0·038) for BMI (<30 vs ≥ 30) was found, in which patients with lower BMI had higher rates of DFS in the TAH group compared to TLH (86·6% vs 77·4%), whereas the TLH group had higher DFS rates at 4.5 years for patients with BMI ≥ 30 (78·9% vs 84·4%). There were no statistically significant

differences between TAH and TLH in any of the other subgroups, including age (<65 vs ≥ 65 years), FIGO staging (1 vs >1), ECOG (0 vs 1), Charlson index (<3 vs ≥ 3) or history of malignancy (yes vs no).

A multivariable analysis using proportional hazard regression of DFS adjusting for pre-specified prognostic factors did not materially change the treatment effect (**Supplementary Table 2**). The unadjusted hazard ratio (HR) was 1·03 [95% CI: 0·74 to 1·45, P=0·85] compared to an adjusted HR of 1·02 [95% CI: 0·68 to 1·52, P=0·94].

Discussion

In this clinical trial of 760 women with stage I endometrial cancer, DFS at 4.5 years was 81.6% with total laparoscopic hysterectomy compared to 81.3% with total abdominal hysterectomy (difference 0.3%, 95% CI, -5.5% to 6.13%) meeting criteria for equivalence. Although a limited number of clinical trials have attempted to address the performance and safety of these two modalities, the current trial represents the first multi-centre, international trial where all surgeons were tasked to perform the hysterectomy totally laparoscopically. Surgeon screening procedures were done to achieve a high standard of surgery and this was reflected in a low conversion rate, and a high DFS rate. The incidence of post-operative wound metastases was of low incidence (0.0047%) and no different in frequency between the arms. The results reported here are robust across survival rates and hazard ratios, intention-to-treat and as-treated analyses, DFS and endometrial cancer specific-recurrence free survival, and the 4.5-year time point is sufficiently long to capture any separation in the survival curves.[26] The apparent DFS benefit of TLH in women with BMI ≥ 30 is counter-intuitive but as the CI's for estimates in the individual subgroups overlap this may well be a statistical artefact. Laparoscopic surgery has benefits for patients with regards to QoL, recovery after surgery, hospital stay and adverse events.[12] Given its better short-term outcomes, updated meta-analyses should now be conducted to determine whether TLH should become the standard of care for the majority of patients with stage 1 endometrial cancer.

Published reports from trials have been summarised in a Cochrane meta-analysis.[12] Until now, the only randomized evidence assessing long-term survival outcomes from a sufficiently powered and multicentre trial was the U.S. LAP2 Trial (GOG 222). LAP2 recruited a total of 2,616 women and formally failed to meet the criteria for noninferiority based on a HR boundary of 1·4,[25] potentially due to the smaller than expected rate of recurrences. There were some important differences between the trial reported here and the LAP2 trial. LAP2 trial enrolled patients with all cell types, whereas the present trial focused on endometrioid cell type on preoperative uterine curettings. All patients enrolled into LAP2 had to have a retroperitoneal node dissection, including para-aortic nodes. It has been argued that the high conversion rate from laparoscopy to laparotomy (25·8% in

LAP2, compared to only 6% in this trial) was due to that requirement.[27] Only half of all patients enrolled in this trial received a retroperitoneal node dissection and patients who received TLH were less likely to have a node dissection. This reflects the existing, wide variation in opinions about the need of comprehensive surgical staging and lymphadenectomy.[2]

Previously reported adverse event results of this trial,[16, 17] confirmed LAP2 trial results[10] and the results from other studies summarised in the Cochrane review.[12] Intraoperative surgical complications were comparable between patients assigned to TAH and TLH in the three large trials conducted worldwide to date.[9, 10, 17] In regards to postoperative surgical adverse events, the Dutch trial [9] recorded similar postoperative surgical complications in the abdominal and the laparoscopic group, whereas LH led to fewer postoperative surgical complications in LAP2[10] and the present trial.[17] QOL outcomes favoured TLH over TAH in all three of these trials. The present analyses now showed that endometrial cancer patients treated by TLH had equivalent survival outcomes up to 4.5 years after surgery. Others reported that long-term survival outcomes of patients are also promising for TLH. [28]

Limitations of this trial include that blinding of patients or surgeons was not undertaken, however it is unlikely to affect the DFS or OS outcomes reported here, which were collected independently from the treating surgeons by dedicated clinical trial staff. Furthermore, randomization was not deferred until the patient entered the operating room, due to the different set-up required for the surgical procedures. Due to funding constraints, the trial followed a pragmatic 2-phase design,[29] first focussing on QOL initially, then on DFS and OS once the recruitment of a sufficiently large number of patients was supported by the funders of this trial. In this trial the matter of pelvic and aortic retroperitoneal node dissection followed the current clinical practice guidelines of the participating surgeons and institutions.

Conclusions

Among women with stage I endometrioid endometrial cancer, the use of TAH compared with TLH resulted in equivalent DFS at 4.5 years. These findings support the use of laparoscopic hysterectomy for stage 1 endometrial cancer. The results come from a multinational trial boosting confidence that a consistent high quality surgery result can be achieved within different hospitals and healthcare systems. Given the well documented and wide-ranging health benefits of laparoscopic hysterectomy compared to TAH, [12, 30] and the absence of increased adverse events, TLH should become widely used in the surgical treatment of early stage endometrial cancer. New and emerging surgical methods of treating early stage endometrial cancer should now be tested against TLH in the future with regards to QOL, safety, AEs, pain, cost and survival outcomes.

Declaration of interest: AO received travel grants from the O.R. Company (formerly Tyco Healthcare) and is a consultant for Covidien, NSW, Australia. Other authors reported no conflict of interest.

Contributors:

Dr Janda and Dr Gebski had full access to all of the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Janda, Gebski, Forder, McCartney, Obermair. Acquisition, analysis or interpretation of data: All authors. Drafting of manuscript: Janda, Gebski, Davies, Obermair. Critical revision of manuscript for important content: All authors. Administrative, technical, or material support: All authors. Study supervision: Janda, Gebski, Obermair.

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Role of the funding source

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.

Trial registration:

This study is registered with ClinicalTrials.gov, number NCT00096408, and the Australian New Zealand Clinical Trials Registry, number CTRN12606000261516.

Figure captions:

Figure 1: Consort flow diagram of the LACE trial

[a] The trial proceeded in two phases. During the first phase that focussed on quality of life outcomes, randomization was 2:1 TLH:TAH. After that, randomization for the second phase, started with a 1:0.76 ratio in an attempt to re-balance sample sizes between the two arms, but when this proved unworkable in the field, the allocation ratio was changed to 1:1.

[b] 1 patient withdrew as unable to return for follow-up visits, 1 patient withdrew as did not want to remain on study

[c] 2 patients withdrew

[d] Surgery abandoned due to clinically advanced disease with vaginal involvement

[e] Reasons for not meeting the inclusion criteria: Histology not confirmed diagnosis of primary endometriod adenocarcinoma of the endometrium n=12; Performance status of ECOG >1 n=20; Age less than 18 = 0; Other histologic type than endometriod adenocarcinoma of the endometrium n=164; Clinically advanced disease (stages II-IV) n=150; Uterine size larger than 10 week gestation n=78; Estimated life expectancy of less than 6 months n=0; Enlarged aortic lymph nodes n=11; Serious concomitant systemic disorders incompatible with the study n=134; Patient compliance and geographic proximity do not allow for adequate follow-up n=30; Patient unfit to complete QoL measurements n=49.

Figure 2a: Cumulative incidence of recurrence or death by surgical group

Figure 2b*:* Cumulative incidence of death by surgical group

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***Table 1*: Baseline Characteristics of the intention-to-treat population**

		Total Laparoscopic Hysterectomy (N=407)	Total Abdominal Hysterectomy (N=353)
Age at randomization (Years)	Mean(SD)	63.3 (10.0)	63.1 (10.6)
	<65	231 (57%)	198 (56%)
	≥65	174 (43%)	157 (44%)
BMI, N(%)	Median(range)	33.1 (18.8 to 63.3)	32.7 (19.1 to 63.2)
	<30	143 (35%)	119 (34%)
	≥30	244 (60%)	222 (63%)
Grade of differentiation upon Dilation & Curette, N(%)	Grade 1	259 (64%)	223 (63%)
	Grade 2	120 (29%)	107 (30%)
	Grade 3	28 (7%)	23 (7%)
Any malignancy [a], N(%)		28 (9%)	20 (7%)
Charlson Index[b], N(%)	Median(range)	3 (0 to 10)	3 (0 to 8)
	<3	171 (42%)	159 (45%)
	≥3	230 (57%)	196 (55%)
Ongoing Medication[c], N(%)		332 (82%)	273 (77%)
ECOG Performance Status[d], N(%)	0	352 (86%)	303 (86%)
	1	55 (14%)	50 (14%)

Data are n (%), Mean (SD) or Median (range). Abbreviations: BMI = body-mass index; ECOG = Eastern Cooperative Oncology Group. [a] Refers to any malignancy prior to the index malignancy. Numbers are based on TAH=303 and TLH=306 due to the different stratification schemes between Phase 1 and Phase 2 [b] The Charlson index summarises the patient's comorbidity burden, with higher scores indicating greater burden [c] Ongoing medications are those without an end-date during trial participation noted, indicating comorbidity burden [d] ECOG- Performance scale (range of scores 0 - perfect health to 5 - death)

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Table 2: **Surgery and Adjuvant Treatment Details**

		Total Laparoscopic Hysterectomy (N=407)	Total Abdominal Hysterectomy (N=353)	Risk Difference, % (95% CI)	p-value
Surgical and Pathological Outcomes					
Days to surgery (from randomization), Median (range)		7 (0 to 62)	7 (0 to 74)		0.70
Duration of operation (minutes), Median (range)		130 (50 to 300)	105 (35 to 249)		<0.001
Change in haemoglobin levels from baseline to one week post-surgery (g/dl), Median (range)		-17 (-55 to 15)	-19 (-111 to 31)		0.14
Pelvic/Aortic Lymph Node Dissection, N(%)		161 (40%)	206 (58%)	-18.8 (-25.8 to -11.8)	<0.001
FIGO Surgical Stage [a], N(%)	IA	286 (70%)	237 (67%)	3.1 (-3.5 to 9.7)	0.27
	IB	55 (14%)	44 (13%)	1.0 (-3.7 to 5.8)	
	II	32 (8%)	45 (13%)	-4.9 (-9.2 to -0.5)	
	IIIA	11 (3%)	4 (1%)	1.6 (-0.4 to 3.5)	
	IIIB	4 (1%)	1 (<1%)	0.7 (-0.4 to 1.8)	
	IIIC1	11 (3%)	12 (3%)	-0.7 (-3.2 to 1.7)	
	IIIC2	1 (<1%)	3 (1%)	-0.6 (-1.7 to 0.5)	
	IIIIA	0 (<1%)	1 (<1%)	-0.3 (-0.8 to 0.3)	
	IIIIB	3 (1%)	3 (1%)	-0.1 (-1.4 to 1.2)	
	Unknown	4 (1%)	3 (1%)	0.1 (-1.2 to 1.5)	
Cell type, N(%)					
Endometrioid		395 (97%)	340 (96%)	0.7 (-1.8 to 3.3)	
Clear cell		4 (1%)	7 (2%)	-1.0 (-2.7 to 0.7)	
Adenocarcinoma		1 (<1%)	5 (1%)	-1.2 (-2.5 to 0.2)	
Mixed Epithelial		0 (0%)	3 (1%)	-0.8 (-1.8 to 0.1)	
Sarcoma		2 (<1%)	1 (<1%)	0.2 (-0.7 to 1.0)	
Serous		7 (2%)	12 (3%)	-1.7 (-4.0 to 0.6)	
Mucinous		7 (2%)	2 (1%)	1.1 (-0.3 to 2.6)	
Small cell		2 (<1%)	0 (0%)	0.5 (-0.2 to 1.2)	
FIGO Grade[b], N(%)	1	231 (57%)	185 (52%)	4.3 (-2.7 10 11.4)	0.27
	2	129 (32%)	124 (35%)	-3.5 (-10.2 to 3.3)	
	3	43 (11%)	40 (11%)	-0.8 (-5.2 to 3.7)	
	Unknown	4 (1%)	4 (1%)	-0.2 (-1.6 to 1.3)	
Number of lymph nodes examined	Median (range)	11 (7 to 15)	10 (5 to 28)		0.88

Number of metastatic lymph nodes	Median (range)	0 (0 to 2)	0 (0 to 1)		0.84
Adjuvant Treatment, N(%)	Chemotherapy Only	8 (2%)	7 (2%)	-0.01 (-2.0 to 2.0)	0.99
	Radiation Treatment Only	61 (15%)	66 (19%)	-3.7 (-9.1 to 1.6)	0.17
	Both Chemotherapy and Radiation Treatment	22 (5%)	19 (5%)	0.02 (-3.2 to 3.2)	0.99

[a] International Federation of Gynecology and Obstetrics (FIGO) surgical stage: Stage Ia Tumor limited to the endometrium; Stage Ib Invasion to less than half of the myometrium
Stage Ic Invasion equal to or more than half of the myometrium; Stage IIa Endocervical glandular involvement only; Stage IIb Cervical stromal invasion; Stage IIIa Tumor invades the serosa of the corpus uteri and/or adnexae and/or positive cytological findings; Stage IIIb Vaginal metastases [b] Figo grade: G1: Well differentiated; G2: Moderately differentiated; G3: Poorly or undifferentiated

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Table 3: Survival Outcomes

		Total Laparoscopic Hysterectomy (N=407)	Total Abdominal Hysterectomy (N=353)	Risk Difference, % (95% CI)	p-value
Survival Outcomes					
Probability of DFS at 4.5 years		81.6%	81.3%		
Difference in TAH and TLH based on equivalence boundary of Δ=±7%		0.3% (-5.53% to 6.13)			0.007*
Recurrences or deaths[a], N(%)		70 (17%)	60 (17%)	0.2 (-5.1 to 5.6)	0.54
Recurrences alone[a,b], N(%)		33 (8%)	28 (8%)	0.2 (-3.7 to 4.0)	0.93
Primary site of relapse	Vault	14 (3%)	12 (3%)	0.04 (-2.5 to 2.6)	0.98
	Pelvis	2 (<1%)	4 (1%)	-0.6 (-1.9 to 0.7)	0.32
	Abdomen	6 (1%)	6 (2%)	-0.2 (-2.0 to 1.6)	0.84
	Distant	5 (1%)	4 (1%)	0.1 (-1.4 to 1.6)	0.90
	Multiple	6 (1%)	2 (1%)	0.9 (-0.5 to 2.3)	0.22
New primary cancer	Any type	37 (9%)	27 (8%)	1.4 (-2.5 to 5.4)	0.48
	Breast	7	10		
	Colorectal	3	5		
	Skin	19	9		
	Haematological	4	1		
	Lung	3	1		
	Pancreatic	1	0		
	Thyroid	0	1		
	Other				
Deaths[c]		30 (7%)	24 (7%)	0.6 (-3.0 to 4.2)	0.76
Cause of Death	Endometrial Cancer	16 (4%)	14 (4%)	-0.03 (-2.8 to 2.7)	0.98
	Unrelated Morbidity	5 (1%)	2 (1%)	0.7 (-0.6 to 2.0)	
	Unknown	9 (2%)	8 (2%)	-0.05 (-2.2 to 2.1)	

484 Abbreviations: DFS = disease-free survival *P-value for equivalence testing the null-hypothesis that the two groups are
485 different by at least 7%. A p value of 0.007 rejects the null hypothesis, and confirms equivalence.
486 [a]Any event that occurred between randomization and 4.5-years post-randomization
487 [b] Definition excludes deaths and new primary cancers
488 [c]Any event that occurred between randomization and data lock (3rd March 2016)
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