Improved surgical safety after laparoscopic compared to open surgery for apparent early stage endometrial cancer: a randomized-controlled clinical trial

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Abstract

Aim: To compare Total Laparoscopic Hysterectomy (TLH) and Total Abdominal Hysterectomy (TAH) with regards to surgical safety.

Methods: Between October 2005 and June 2010, 760 patients with apparent early stage endometrial cancer were enrolled in a multicentre, randomized clinical trial (LACE) comparing outcomes following TLH or TAH. The main study end points for this analysis were surgical adverse events (AE), hospital length of stay, conversion from laparoscopy to laparotomy, including 753 patients who completed at least 6 weeks of follow-up. Postoperative AEs were graded according to Common Toxicity Criteria (V3), and those immediately life-threatening, requiring inpatient hospitalization or prolonged hospitalization, or resulting in persistent or significant disability/incapacity were regarded as serious AEs.

Results: The incidence of intra-operative AEs was comparable in either group. The incidence of post-operative AE CTC Grade 3+ (18.6% in TAH, 12.9% in TLH, p 0.03) and serious AE (14.3% in TAH, 8.2% in TLH, p 0.007) was significantly higher in the TAH group compared to the TLH group. Mean operating time was 132 minutes and 107 minutes, and median length of hospital stay was 2 days and 5 days in the TLH and TAH group, respectively ($p < 0.0001$). The decline of haemoglobin from baseline to day 1 postoperatively was 2 g/L less in the TLH group (p 0.006).

Conclusions: Compared to TAH, TLH is associated with a significantly decreased risk of major surgical AEs. A laparoscopic surgical approach to early stage endometrial cancer is safe.

Clinical Trial Registration: NCT00096408

Keywords: Endometrial cancer; safety; surgery

Introduction

Endometrial cancer is the most common gynecological cancer among women in developed countries. Worldwide, more than 300,000 women were diagnosed with uterine cancer in 2010 and this number is projected to increase to 471,061 by 2030.(1) Treatment is primarily surgical, and includes the removal of the uterus, the tubes and the ovaries with or without surgical staging.

Previously we reported that patients undergoing a Total Laparoscopic Hysterectomy (TLH) reported significantly greater postsurgical improvement of Quality of Life (QoL) compared to Total Abdominal Hysterectomy (TAH) (Laparoscopic Approach to Carcinoma of the Endometrium trial; LACE) (2). This improvement in QoL continued to favor the laparoscopic approach for up to 6 months post-surgery. Two randomized clinical trials reported results on surgical Adverse Events (AE) (3, 4). The US Gynecologic Oncology Group (GOG) LAP2 showed that a laparoscopic surgical approach resulted in fewer post-operative moderate/severe surgical complications and shorter hospital stay than surgery through laparotomy (4). In contrast, the Dutch TLH study suggested that the incidence of major and minor surgical complications is similar in patients undergoing a TLH or TAH (3).

The LACE trial was initiated to compare TLH and TAH with regards to QoL outcomes and disease-free survival in patients with apparent early-stage endometrial cancer. For the aim of this report, measures of surgical safety were examined.

Patients and Methods

The LACE trial commenced enrolment in 2005, was registered with clinicaltrials.gov (NCT00096408) and the Australian New Zealand Clinical Trials Registry (CTRN12606000261516), and approved by all relevant hospital and university ethics

committees. A detailed description of the surgical method (5) and study methodology including details of the two surgical approaches has been published previously (6).

Patients were recruited through one of 20 participating tertiary gynaecological oncology centers in Australia, New Zealand, Hong Kong and Scotland. Women were eligible if they were aged 18 years or older, with histologically confirmed endometrioid adenocarcinoma of the endometrium of any International Federation of Gynecology and Obstetrics (FIGO) grade, and had an Eastern Cooperative Oncology Group (ECOG) score of less than 2. Further inclusion criteria included imaging studies (computed tomography (CT) of the abdomen and pelvis and chest radiograph or chest CT) suggesting the absence of extra-uterine disease. Patients were excluded from the study if any of the following criteria were met: histological cell-type other than endometrioid on curettage, clinically advanced disease (stage II – IV) or bulky lymph nodes on imaging, uterine size greater than 10 weeks of gestation, estimated life expectancy of less than 6 months, medically unfit for surgery, patient compliance or geographic proximity preventing adequate follow-up, or unfit to complete quality of life questionnaires. The FIGO criteria for stage (2009) were used.

We followed a two-stage clinical trial design. During the first stage, the QoL substudy, we randomized 361 patients into TLH versus TAH to assess QoL. To establish the feasibility of enrolment and to maximize the evidence for the new procedure, a 2:1 randomization scheme was used for the first 180 patients, followed by 1:1 allocation for all remaining patients. When the trial was attractive for granting bodies offering seed funds, it allowed us to apply for substantial funding for stage 2 of the LACE trial evaluating the two surgical procedures in an equivalence trial design with respect to survival. Hence, another 580 patients were enrolled for a total of 760 patients (stage 2; completed enrolment in June 2010).

Randomization using stratified permuted blocks was carried out centrally and independent from other study procedures through a web-based system at the University of Queensland, ascertaining concealment of the next allocated treatment to study staff. Randomization was stratified according to treating centre and by grade of differentiation (as taken from the endometrial biopsy/D&C) (2, 6).

All surgeons on the trial had to be accredited gynaecological oncologists, had to have completed at least 20 TLHs and submitted video footage about a TLH, and finally had to have performed a TLH live in the presence of a senior accredited surgeon before being eligible to enroll patients into the trial. Surgeons discussed the study with the patients and obtained informed consent. Study staff then completed eligibility criteria and received notification of the allocated treatment via the web-based case report system. Blinding was not possible due to ethical considerations and the nature of the treatment.

A full blood count as well as a range of blood chemistry tests was conducted at baseline (preoperatively) as a routine measure.After surgery, patients were assessed on a daily basis by their clinicians until discharge from hospital. A full blood count was repeated on the first day after surgery (Day 1).

Adverse events during the first six weeks past surgery were recorded according to Common Toxicity Criteria (CTC) Version 3.

Statistical considerations

Patients with a minimum of 6 weeks of follow-up after surgery were included in this analysis. Analyses were based on 'intention to treat'. Descriptive statistics were used to compare the incidence of three classifications of AE: a) intra-operative, b) postoperative CTC grade ≥ 3, and c) serious AEs, between the two treatment groups. A serious AE was defined as any event that results in death, is immediately life-threatening, requires inpatient hospitalization

or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity. Chi-square tests were used to compare the frequency of AE distribution between treatment groups. T-test was used to compare the operating time and blood loss as well as length of hospital stay (after log transformation) between the treatment arms. No data were imputed.

Results

A total of 753/760 (99.1%) patients who completed at least 6 weeks of follow up were included in the analysis. Four patients withdrew from the trial between randomization and surgery and three additional patients withdrew within a week after surgery. Mean (SD) age was 63 (10) years at diagnosis. Of these, 349 were allocated to TAH and 404 to TLH (Table 1). The treatment groups were balanced in terms of relevant clinical and demographic factors. Three hundred and seventy-one (49.3%) patients underwent lymph node dissection, 210 (60.2%) in the TAH compared to 161 (39.9%) in the TLH groups ($p<0.001$).

There were 24/404 and 26/349 readmissions in the TLH and TAH groups, respectively ($p=0.40$). A total of 51 (6.8%) patients had at least one intra-operative AE, 117 (15.5%) patients had at least one post-operative AE CTC grade ≥ 3, and 83 (11.0%) patients had at least one serious AE (Table 2). The incidence of intraoperative AE was similar between the treatment allocation arms (TAH 4.6%; TLH 7.4%; p 0.105). There were 12 cases of vaginal laceration in the TLH compared to 0 in the TAH group, resulting from a disproportion of uterine size and vaginal width. Patients randomized to TAH had a 44% higher incidence of postoperative AE CTC grade ≥ 3 (18.6% in TAH, 12.9% in TLH, p 0.03) when compared to those randomized to TLH. The incidence of serious AE was 74% higher in the TAH group compared with the TLH group (14.3% in TAH, 8.2% in TLH, $p = 0.007$). Wound infection

or dehiscence contributed to the statistically significant differences between the treatment arms for post-operative AE and serious AE (Table 1). Risk factors for the development of surgical AEs will be presented elsewhere (Kondalsamy-Chennakesavan et al; submitted for publication in a companion paper). There were no deaths within 30 days from surgery in either treatment arm.

Duration of surgery was 25 minutes longer in the TLH compared to the TAH arm ($p < 0.001$), while the drop in hemoglobin from baseline to day 1 postoperatively was 2.3 g/L lower in the TLH compared to the TAH arm (p 0.006). The median length of hospital stay was 2 days in the TLH arm and 5 days in the TAH arm ($p < 0.001$) (Table 3). Table 4 describes the incidence of AEs stratified by treatment arm in the subgroups according to nodal dissection status. No significant differences in the incidence of AEs (CTC 3+) were noted between the treatment arms when stratified by nodal dissection status. However, serious AEs were lower in the TLH arm when nodal dissection was not performed.

Treatment Crossovers: Overall, 29 conversions (3.8%) were recorded, 5 from TAH to TLH due to patient decision after randomization and 24 from TLH to TAH (15 for anatomical reasons of which 6 needed an abdominal incision to remove the uterus, 2 for technical reasons, and 7 due to intra-operative complications). The odds of conversion to TAH were 1.07 (95% CI 1.02 – 1.12) with each unit increase in BMI in univariate analysis, and 1.08 (1.03 – 1.14) when BMI was adjusted for age.

Discussion

Laparoscopic surgical approaches are becoming increasingly popular for surgical cancer treatment, and randomized trials such as the LACE trial are important to provide the evidence whether a minimally invasive surgical approach to the treatment of apparent early-stage

endometrial cancer is at least equivalent to open abdominal surgery. This analysis shows that patients allocated to TLH had a 74% decreased risk of a serious AE from their surgery when compared to patients allocated to TAH. Results on disease-free and overall survival are still pending and will be reported once follow up data collection has been completed.

Patients in the laparoscopic arm (39.9%) were less likely to have a retroperitoneal node dissection than in the open arm (60.2%). While there was no data collected on the reason for surgeons' decision for or against a lymphnode dissection, the decision not to proceed with a node dissection in laparoscopic cases was most likely based on the feasibility of a node dissection in obese and super-obese patients, surgeons attitude to avoid harm ,and the absence of a dogmatic approach to node dissection in the trial protocol. Patients' mean body mass index in the present trial was 35 compared to only 30 in LAP2 (4) and the Dutch (3) trial. Modern evidence suggests that the gain from a pelvic and aortic node dissection is questionable (7,8) but the harm of a conversion to laparotomy in obese and super-obese women is significant (9). In a case where TAH is performed, the harm of laparotomy is already done and surgeons may thus have based the decision to proceed with a node dissection mainly on tumour (grade, depth of invasion) and patient (BMI, medical co-morbidities) factors.

While it could be argued that lympnode dissection rather than the surgical approach contributed to the difference in the AE prevalence between the two surgical arms, our results indicate that this is not the case. When compared to patients in the TLH group, the odds of patients treated with TAH to develop an AE group was consistently higher regardless of whether the patients had no, any, a pelvic or an aortic lymphnode dissection. However, the numbers within individual cells are small as the LACE trial was not powered to detect differences of AEs within various lymphnode dissection subgroups.

The results of two other randomized controlled clinical trials comparing open versus laparoscopic surgery for endometrial cancer were published recently. The GOG LAP2 trial enrolled 2616 patients with stage 1 to 4 uterine cancers of all cell types (4). All patients had to have a comprehensive surgical staging including a pelvic and aortic lymph node dissection regardless of FIGO grade and depth of invasion. Conversion to laparotomy was 25.8% in the laparoscopy group. The incidence of intraoperative surgical complications was 10% and 8% in the laparoscopic and open treatment group, respectively. Postoperatively moderate to severe surgical complications developed in 14% of patients in the laparoscopic group and 21% in the open group.

The Dutch trial enrolled 283 patients with stage 1 endometrioid adenocarcinoma of the endometrium or endometrial hyperplasia with atypia (3). Conversion to laparotomy was 10.8%. Intraoperative complications developed in 2.7% (laparoscopic) and 4.3% (open) of patients. The incidence of major postoperative complications related to the surgical procedure was almost identical in both groups (14.6% and 14.9% in the laparoscopic and open group, respectively). In contrast to LAP2 and the present LACE trial, the outcomes of the Dutch trial suggested that major complication rates were similar in both the arms.

There are key differences between the US LAP2 trial, The Dutch trial and the LACE trial that could explain some of the differences in outcomes. All patients recruited for the LAP2 trial underwent a comprehensive surgical staging including a pelvic and aortic lymph node dissection whereas none of the patients in the Dutch study underwent a nodal dissection. In the Australian LACE trial approximately half of all patients had a full surgical staging involving nodal dissection. The LAP2 trial enrolled patients with all histological cell-types and grades whereas the Dutch study enrolled patients with endometrioid cell type on

curettings with FIGO grades 1 or 2, including patients with endometrial hyperplasia with atypia. In our study, only patients with endometrioid cell type of all FIGO grades were included.

A comparison of the crude incidence rates of AE reveals that the GOG LAP2 trial applied CTC Grade 2 criteria and reported lower incidence rates of post-operative AE (14% in laparoscopic vs. 21% in laparotomy) than the LACE trial, which used CTC Grade 3 criteria (12.9%, TLH vs. 18.6%, TAH). Similar to the Dutch study, we collected data on AE for a period of 6 weeks from surgery whereas collection of data on AE in the LAP2 trial was limited to 30 days from surgery.

Conversions were lower in our LACE trial when compared to both these two trials. Reduced conversion rates in our study can potentially be attributed to the strict adherence to accreditation criteria of surgeons; to exclusion criteria of patients with a uterine size >10 weeks; who had presence of extrauterine disease at diagnosis; or high-risk histological cell types. Moreover, patients with grade 1 or grade 2 tumors invading not more than half into the myometrium did not require a node dissection. Therefore, only half of patients in the LACE trial underwent a comprehensive surgical staging, and this may have assisted in keeping the conversion rate low. The lowest rates of AEs were noted in the TLH arm when a retroperitoneal node dissection was not performed.

In the present study, risk factors increasing the risk of conversion to open hysterectomy included patient's body mass index and patient's age. The independent contribution of various risk factors for the development of major AEs will be presented elsewhere (Kondalsamy-Chennakesavan et al; submitted for publication).

In summary, an open surgical approach with TAH is associated with a significantly increased risk of developing AEs when compared to treatment with TLH in apparent early stage

endometrial cancer. The risk of conversion from laparoscopic to open is acceptably low when the indication for lymph node dissection is individualized. This randomized trial prospectively confirms previous reports that a laparoscopic surgical approach is feasible, safe and should become the standard treatment once survival data confirmed equivalence with respect to patterns of recurrence, disease-free and overall survival.

Conflict of interest statement:

AMcC had shares and stock ownership of Gynetech. He had received occasional consultancy honoraria from Gate Healthcare. AO has been an occasional adviser for Genzyme, with honoraria for presentations. AO has received research support from Bristol-Myers Squibb. SKC and AO have received research support from Abbott Australia. All other authors have declared that there no conflicts of interest.

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Table 1: Patient characteristics

	TLH n=404	TAH n=349
Age < 50 years n(%)	35 (8.7)	32 (9.2)
BMI, kg/m^2		
Normal (<25 kg/m^2), n(%)	47 (12.1)	46 (13.6)
Overweight (25 to <30kg/m^2), n(%)	97 (25.0)	72 (21.3)
Obesity Class I (30 to <35 kg/m^2), n(%)	77 (19.8)	86 (25.4)
Obesity Class II (35 to <40 $kg/m^{2)}$, n(%)	81 (20.9)	61 (18.1)
Obesity Class III (40+ kg/m^2), n(%)	86 (22.2)	73 (21.6)
Charlson's Index (mean, SD)	3.0 (1.8)	2.9 (1.8)
Nodal dissection, n (%)[a]		
Any	161/404 (39.9)	210/349 (60.2)
Pelvic	147/161 (91.3)	205/210 (97.6)
Aortic	11/161 (6.8)	43/210 (20.5)
Other (not specified)	13/161 (8.1)	16/210 (7.6)
FIGO Surgical Stage, n(%)		
IA	285 (70.4)	237 (67.5)
IB	55 (13.8)	44 (12.5)
II	33 (8.2)	44 (12.5)
IIIA	11 (2.7)	4 (1.1)
IIIB	3 (0.7)	1 (0.3)
IIIC1	11 (2.7)	11 (3.4)
IIIC2	1 (0.2)	3 (0.8)
IVA	-	1 (0.3)
IVB	3 (0.7)	3 (0.8)
Other[b]	2 (0.5)	1 (0.3)
Grade on curettings, n(%)		
1	258 (63.8)	220 (63.0)
2	119 (29.5)	106 (30.4)
3	27 (6.7)	23 (6.6)
ECOG, n(%)		
0	349 (86.4)	299 (85.7)
1	55 (13.6)	50 (14.3)

Abbreviations: TLH = total laparoscopic hysterectomy; TAH=total abdominal hysterectomy; BMI: Body Mass Index; FIGO: International Federation of Gynecology and Obstetrics; ECOG: Eastern Cooperative Oncology Group; [a] numbers do not add up to total due to overlap between the patients with pelvic, aortic or other nodal dissection [b] found to have cervical cancer

Table 2: Intraoperative, postoperative and serious adverse events

	TLH n=404 (%)	TAH n= 349 (%)	p-value
Intraoperative			
Any	30 (7.4)	16 (4.6)	0.105
Bowel injury	7 (1.7)	6 (1.7)	
Vaginal injury	12 (3.0)	-	
Vascular injury	4 (1.0)	5 (1.4)	
Bladder injury	6 (1.5)	1 (0.3)	
Blood transfusion	3 (0.7)	4 (1.1)	
Ureteric injury	-	2 (0.6)	
Nerve injury	1 (0.2)	-	
Postoperative, CTC[a] ≥3			
Any	52 (12.9)	65 (18.6)	0.030
Wound infection/dehiscence	8 (2.0)	31 (8.9)	
Pulmonary/upper respiratory	16 (4.0)	13 (3.7)	
Cardiac general	15 (3.7)	4 (1.1)	
Gastrointestinal/hepatobiliary	4 (1.0)	15 (4.3)	
Infection	12 (3.0)	7 (2.0)	
Metabolic/laboratory	7 (2.7)	9 (2.6)	
Haemorrhage/bleeding	8 (2.0)	3 (0.9)	
Blood/bone marrow	3 (0.7)	10 (2.9)	
Renal/genitourinary	4 (1.0)	5 (1.4)	
Constitutional symptoms	3 (0.7)	4 (1.1)	
Neurology	6 (1.5)	2 (0.6)	
Others[b]	5 (1.2)	2 (0.6)	
Vascular	3 (0.7)	2 (0.6)	
Musculoskeletal/soft tissue	1 (0.2)	2 (0.6)	
Cardiac arrhythmia	-	5 (1.4%)	
Lymphatics	1 (0.2)	-	
Dermatology/Skin	-	1 (0.3)	
Endocrine	-	1 (0.3)	
Serious adverse events			
Any	33 (8.2)	50 (14.3)	0.007
Wound infection/dehiscence	6 (1.5)	27 (7.7)	
Haemorrhage/bleeding	8 (2.0)	7 (2.0)	
Cardiac general	9 (2.2)	3 (0.9)	
Pulmonary/upper respiratory	6 (1.5)	7 (2.0)	
Infection	6 (1.5)	6 (1.7)	
Neurology	5 (1.2)	1 (0.3)	
Gastrointestinal/hepatobiliary	1 (0.2)	6 (1.7)	
Renal/genitourinary	3 (0.7)	2 (0.6)	
Surgery/Intra-operative injury	2 (0.5)	2 (0.6)	
Vascular	2 (0.5)	1 (0.3)	
Blood/bone marrow	-	2 (0.6)	

Constitutional symptoms	-	2 (0.6)
Cardiac arrhythmia	1 (0.2%)	7 (2.0)
Endocrine/ Metabolic/laboratory	-	2 (0.6)
Others[c]	1 (0.2%)	1 (0.3)

Abbreviations: TLH = total laparoscopic hysterectomy. TAH=total abdominal hysterectomy.
[a]Common Toxicity Criteria
[b]Includes return to theatre same admission, depression, anxiety, panic attack
[c]Includes return to theatre same admission

Table 3: Comparison of clinical factors using intention-to-treat analysis

	TLH (n=404)	TAH (n=349)	Difference	Lower 95% CI limit	Upper 95% CI limit	p-value
Duration of surgery (mins), mean (sd)	132 (40.7)	107 (33.6)	25.6	20.3	30.9	<0.001
Drop in haemoglobin (g/dL), mean (sd)	17.0 (10.4)	19.3 (10.8)	-2.25	-3.84	-0.66	0.006
Log length of stay, mean (sd)	0.874	1.613	-0.740	-0.798	-0.681	<0.001
Exponentiated estimates for length of stay (days)	2.396	5.018	2.1	1.98	2.22	

Abbreviations: TLH = total laparoscopic hysterectomy; TAH=total abdominal hysterectomy; CI = Confidence Interval

Table 4. Adverse Events by treatment arm and nodal dissection status

	LND performed (n=371)				LND not performed (n=382)			
	TLH (n=161) n (%)	TAH (n=210) n (%)	OR (TAH:TLH)	p-value	TLH (n=243) n (%)	TAH (n=139) n (%)	OR (TAH:TLH)	p-value
Postoperative CTC 3+	23 (14.3)	42 (20.0)	1.40	0.15	29 (11.9)	23 (16.6)	1.39	0.21
Serious adverse event	18 (11.2)	32 (15.2)	1.36	0.26	15 (6.2)	18 (13.0)	2.10	0.02
	Pelvic LND performed* (n=352)				Pelvic LND not performed (n=401)			
	TLH (n=147)	TAH (n=205)	OR (TAH:TLH)	p-value	TLH (n=257)	TAH (n=144)	OR (TAH:TLH)	p-value
Postoperative CTC 3+	21 (14.3)	38 (18.5)	1.29	0.29	31 (12.1)	27 (18.8)	1.55	0.14
Serious adverse event	17 (11.6)	29 (14.1)	1.22	0.48	16 (6.2)	21 (14.6)	2.35	0.006
	Aortic LND performed (n=54)				Aortic LND not performed (n=699)			
	TLH (n=11)	TAH (n=43)	OR (TAH:TLH)	p-value	TLH (n=393)	TAH (n=306)	OR (TAH:TLH)	p-value
Postoperative CTC 3+	3 (27.3)	15 (34.9)	1.28	0.63	49 (12.5)	50 (16.3)	1.30	0.15
Serious adverse event	2 (18.2)	9 (20.9)	1.15	0.84	31 (7.9)	41 (13.4)	1.70	0.02

Abbreviations: LND: Lymph Node Dissection; TAH: total abdominal hysterectomy; TLH: total laparoscopic hysterectomy