Quality of life after total laparoscopic hysterectomy versus total abdominal hysterectomy for stage I endometrial cancer (LACE): a randomised trial

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Running Head: Quality of life recovery after TLH for endometrial cancer

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ABSTRACT

Background: The two-stage Total Laparoscopic Hysterectomy (TLH) versus Total Abdominal Hysterectomy (TAH) for stage I endometrial cancer (LACE) randomised controlled trial was initiated in 2005. The primary objective of stage 1 was to assess whether TLH results in equivalent or improved QoL up to 6 months after surgery compared to TAH. The primary objective of stage 2 was to test the hypothesis that disease-free survival at 4.5 years is equivalent for TLH and TAH. Results addressing the primary objective of stage 1 of the LACE trial are presented here.

Methods: The first 361 LACE participants (TAH n= 142, TLH n=190) were enrolled in the QoL substudy at 19 centres across Australia, New Zealand and Hong Kong, and 332 completed the QoL analysis. Randomisation was performed centrally and independently from other study procedures via a computer generated, web-based system (providing concealment of the next assigned treatment) using stratified permuted blocks of 3 and 6, and assigned patients with histologically confirmed stage 1 endometrioid endometrial adenocarcinoma and ECOG performance status <2 to TLH or TAH stratified by histological grade and study centre. No blinding of patients or study personnel was attempted. QoL was measured at baseline, 1 and 4 weeks (early), and 3 and 6 months (late) after surgery using the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire. The primary endpoint was the difference between the groups in QoL change from baseline at early and late time points (a 5% difference was considered clinically significant). Analysis was performed according to the intention-to-treat principle using generalized estimating equations on differences from baseline for the early and late QoL recovery. The LACE trial is registered with clinicaltrials.gov (NCT00096408) and the Australian New Zealand Clinical Trials Registry (CTRN12606000261516). Patients for both stages of the trial have now been recruited and are being followed up for disease-specific outcomes.

Findings: The proportion of missing values at the 5%, 10% 15% and 20% differences in the FACT-G scale was 6% (12/190) in the TLH and 14% (20/142) in the TAH group. There were 8/332 conversions (2.4%, 7 of which were from TLH to TAH). In the early phase of recovery, patients undergoing TLH reported significantly greater improvement of QoL from baseline compared to TAH in all subscales except the emotional and social well-being subscales. Improvements in QoL up to 6 months post-surgery continued to favour TLH except for the emotional and social well-being of the FACT and the visual analogue scale of the EuroQoL five dimensions (EuroQoL-VAS). Length of operating time was significantly longer in the TLH group (138±43 mins), than in the TAH group at (109±34 mins; p=0.001). While the proportion of intraoperative adverse events was similar between the treatment groups (TAH 8/142, 5.6%; TLH 14/190, 7.4%; p=0.55), postoperatively, twice as many patients in the TAH group experienced adverse events of CTC grade 3+ than in the TLH group (33/142, 23.2% and 22/190, 11.6%, respectively; p=0.004). Postoperative serious adverse events occurred more frequently in patients who had a TAH (27/142, 19.0%) than a TLH (15/190, 7.9%) (p=0.002).

Interpretation: QoL improvements from baseline during early and later phases of recovery, and the adverse event profile significantly favour TLH compared to TAH for patients treated for Stage I endometrial cancer.

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Introduction

Endometrial cancer is the most common gynaecological malignancy in developed countries and 80% will be diagnosed at early stages 1 or 2 (1, 2). Primary treatment of early-stage endometrial cancer is surgical and includes a total hysterectomy, bilateral salpingo-oophorectomy, with or without pelvic and aortic lymph node dissection (3). Traditionally, an extrafascial total abdominal hysterectomy (TAH) has been performed through a laparotomy in most centres worldwide (4, 5). However laparoscopic hysterectomy techniques have gained popularity in recent years as summarised in two systematic reviews and one meta-analysis (6-9). Laparoscopic Assisted Vaginal Hysterectomy (LAVH) has been associated with less tissue trauma, lower estimated blood loss, less pain, shorter hospital stay, and less time off work compared to TAH (10-15). A further potential advantage of laparoscopic techniques over TAH is improved quality of life (QoL) post-surgery. A small trial comparing QoL following LAVH or TAH (15) found that the laparoscopic group had significantly better QoL values at one, three, and six months post-surgery. In a recent Gynecologic Oncology Group (GOG LAP-2) trial, patients in the laparoscopy group (various laparoscopy-assisted procedures allowed) had superior short-term QoL outcomes compared to the TAH group up to six weeks post-surgery, but by six months both groups had similar QoL except for body image in favour of the laparoscopic procedure (16). The focus of the present study is on *Total Laparoscopic Hysterectomy* (TLH). Compared to previous laparoscopic techniques TLH represents a new and innovative approach, as the procedure can be completed entirely laparoscopically without the need for a vaginal surgical phase (17).

To collect high quality outcome data for this new surgical procedure (18), we initiated a two-stage international phase 3 multi-centre randomised-controlled surgical trial. The primary objective of stage 1 was to test the hypothesis that TLH results in equivalent or improved QoL up to 6 months after surgery compared to TAH. The primary objective of stage 2 was to

test the hypothesis that disease-free survival at 4.5 years is equivalent for TLH and TAH. Results addressing the primary objective of stage 1 are presented here.

Methods

The trial was initiated in 2005, registered with clinicaltrials.gov (NCT00096408) and the Australian New Zealand Clinical Trials Registry (CTRN12606000261516), and approved by all relevant hospital and university ethics committees. The protocol can be found http://www.gyncan.org/page/attachment/24/lace-protocol-v6-march-2009.

Trial design: A detailed description of the study methods including details of the two surgical approaches has been published previously (19). In brief, we followed a two-stage clinical trial design. During the formal QoL substudy we randomised 361 patients into TLH versus TAH to assess QoL. To establish the feasibility of enrolment and to maximise the evidence for the new procedure, a 2:1 randomisation scheme was used for the first 180 patients, followed by 1:1 allocation for all remaining patients. Following on from stage 1, another 575 patients were enrolled for a total of 755 patients (completion June 2010) randomisation.

Eligibility criteria: Patients were recruited through one of 19 participating tertiary gynaecological cancer centres in Australia, New Zealand, and Hong Kong. Women were eligible if they were older than 18 years, with histologically confirmed stage 1 endometrioid endometrial adenocarcinoma (irrespective of histological grade) and ECOG performance status <2. Patients had to have a CT scan of the abdomen and the pelvis suggesting the absence of extrauterine disease in the abdomen, and a chest X-Ray or a CT scan of the chest to suggest absence of pulmonary metastasis. All patients provided written informed consent. Patients were excluded if they met any of the following conditions: histological cell type other than endometrioid on curettings, clinically advanced disease (stage 2 to 4) or bulky

lymph nodes based on imaging, uterine size larger than 10 weeks of gestation, estimated life expectancy less than 6 months, medically unfit for surgery, patient compliance and geographic proximity not allowing adequate follow-up, or unfit to complete QoL assessments. The FIGO 2009 staging classification was used (20).

Randomisation and masking: Randomisation 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. During stage 1 of the trial, randomised permuted blocks were used to allocate patients between the two treatment groups with an allocation ratio of 2:1, favouring the intervention of TLH (mixed blocks of sizes 3 and 6). Randomisation was stratified according to treating centre and by grade of differentiation (as taken from the endometrial biopsy/D&C).

The 2:1 randomisation was initially selected in order to gain insight into the new laparoscopic procedure. As a result, enrolment was above expectations and the trial was attractive for granting bodies offering seed funds, which 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. When funding for the larger study was secured, the randomisation reverted to 1:1 but it was also felt that the QoL study should continue to a sample size of 360. After 180 patients were randomised the programme was adjusted to allow a 1:1 randomisation stratified according to treating centre, grade of differentiation and history of cancer but not to be influenced by the 2:1 imbalance in the strata.

All surgeons on the trial had to be accredited gynaecological oncologists, had to complete at least 20 TLHs, had to submit video footage about a TLH, and finally had to perform a TLH live in the presence of a senior accredited surgeon. Surgeons discussed the study with the patients and obtained informed consent. Study staff then completed baseline assessments and

obtained the allocated treatment via the web-based case report system. Blinding was not possible due to ethical considerations and the nature of the treatment.

Surgical technique: The surgical procedures have been described in detail previously (19). Briefly, TLH is a four-point laparoscopic procedure. A silicone tube with a diameter of 45 or 35mm and a lid on its outer end is inserted transvaginally (McCartney Transvaginal tube®), and aids reflecting the bladder peritoneum, outlining the vaginal fornices, securing the uterine vessels laparoscopically and finally acts as a conduit to remove the specimens from the patient. The vaginal vault was sutured laparoscopically.

Surgeons were required to perform pelvic ± para-aortic lymph node dissection as part of the treatment in both arms. However a lymph node dissection could be omitted if any of the following criteria were met: morbid obesity, well-differentiated or moderately differentiated tumours invading only to the inner half of the myometrium, or medically unfit for lymph node dissection.

Conversion from assigned treatment was noted in 8/332 cases (2.4%). Of these, 1/332 patient changed from TAH to TLH after randomisation due to patient preference, while 7/332 changed from TLH to TAH (five for anatomical reasons preventing the completion of TLH; one due to intra-operative complications; and one patient was found to have advanced disease).

Baseline assessments were performed before randomisation (up to 28 days prior to surgery), collecting demographic information, height and weight, and QoL data. Follow-up assessments for QoL and short-term surgical outcomes were performed at 1 week, 4 weeks, 3 months, and 6 months post-surgery (± 3 days), to assess early (up to 4 week) and late (up to 6 months) post-surgical recovery, respectively.

Quality of Life Measurements

The primary outcome measure of QoL was the Functional Assessment of Cancer Therapy-General (FACT-G) Version 4 questionnaire (21). Patients raw scores on the physical (PWB) (7 items, range: 0-28), social (SWB) (7 items, range: 0-28), emotional (EWB) (6 items, range: 0-24), and functional (FWB) (7 items, range: 0-28) well-being subscales were measured (22). Patients also completed a 17-item endometrial subscale, which together with the FACT-G forms the FACT-Endometrial (EnWB). All subscales and summary scores were recoded and scored according to standard FACT scoring algorithms such that higher scores indicate better QoL (22).

Body Image Scale

The Body Image Scale is a ten-item scale designed for cancer patients. The ten items were rated on a 0-3 scale (0 = "not at all", 1= "a little", 2= "quite a bit", 3 = "very much") and summed to produce an overall summary score ranging from 0 (best body image – no symptoms or distress) to 30 (worst body image) (23).

EuroQoL five dimensions (EQ-5D)

The EQ-5D is a simple measure of generic QoL. It allows patients to rate their overall health on a visual analogue scale of 1-100 (EuroQoL-VAS) (24) which was used for the present analysis.

For ease of interpretation all QoL scales were subsequently transformed to 0-100 scales with higher scores indicating better QoL (25). Based on the literature a 5% difference or more in the QOL scores were predefined as clinically significant (26-28). Difference scores were calculated to assess change in QOL from baseline (pre-surgery). Forest plots (see statistical

analysis) were used to represent early and late recovery of QoL from baseline and assess the relative recovery comparing TLH to TAH treated patients, with positive values favouring TLH.

Documentation of surgery details, adverse events and length of hospital stay (LOS)

Pre-existing surgical and medical history was taken prior to surgery. After surgery, patients were assessed on a daily basis by their gynaecological oncologist until discharge from hospital. Surgical outcomes including length of operating time, intraoperative complications, cross-overs (e.g., conversion to laparotomy) and reasons for conversion, were documented immediately following surgery. Intraoperative injuries were coded in the categories of visceral injury, blood transfusion, uterus rupture, vaginal laceration or vascular injury. Post-operative adverse events (AEs) were recorded at predefined time points up to six months using the NCI Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Serious AEs were defined as any event that resulted in death, was immediately life threatening, required inpatient hospitalization or prolongation of an existing hospitalization or that resulted in persistent or significant disability/incapacity. Length of hospital stay (LOS) was measured from the day after surgery (day 1) to discharge. Length of operating time was measured from skin incision to completion of wound closure.

Statistical analysis

Sample size: For the stage I QoL component, recruitment commenced in 2005 with a 2:1 randomisation scheme. For the QoL outcomes, aassuming 80% power, 10% overall non-compliance, a 5% type I error rate (95% confidence level) and a 2-tailed comparison, a sample size of at least 180 patients (120 allocated to TLH, 60 patients to TAH) was estimated

to detect a 10% difference (and standard deviation of 20) in the FACT-G between intervention and control group participants (26). However, when literature suggested a 5% difference in QoL to be clinically important (27-29) the collection of QoL data was extended to include 361 patients, (and standard deviation revised from 20 to 16.9 units).

QoL over time was analysed by computing change scores between baseline measurements and each post-operative time point measurement. The primary endpoint for the QoL analysis was the difference between the groups in QoL changes from baseline. The main analysis was broken into two parts, *early* (1 and 4 weeks) and *late* (3 and 6 months) for each QoL variable. Differences in change scores between the TAH and TLH were then compared separately for *early and late recovery* periods using Generalized Estimating Equations (GEE), with an exchangeable correlation structure to account for repeated measures. This method enables the inclusion of observations from subjects who have either dropped out or have intermittent missing data (30). Mean group differences between TAH and TLH, together with the 95% confidence intervals (95% CI), for each of the QoL domains were compiled, with positive percent differences representing an absolute advantage for the TLH group compared to TAH and were presented in a forest plot. Differences were considered statistically significant if the p-value was less than 0.05. No adjustment for multiple comparisons were made, and as such, the results should be viewed with some caution with special attention to the *size* of any difference, the plausible range (95% CI) of this difference together with any relevant clinical benefit rather than just the statistical p-value.

FACT-G change scores were used to examine QoL improvement over time. *Early recovery* in QoL was derived by taking the maximum improvement from weeks 1 and 4 measurements, except where the participant had not completed measurements at both time

points, in which case the single available measurement was used. The maximum improvement was then dichotomized in a number of different ways showing at least 5%, 10%, 15% and 20% improvement. Contingency tables were then used to compare improvement for TAH and TLH, and chi square tests were used to assess difference between the groups. In a similar way, *late recovery* in QoL was derived by using the change scores at 3 and 6 months. Missing value patterns were investigated by examining the association of baseline variable using univariate and multivariate logistic models to the presence of missing QoL outcomes for both the early and late periods (30). All comparisons between groups were evaluated on an intention-to-treat principle. SAS™ statistical software, version 9.1 (31) and ACCoRD, version 1.68 (32) was used. All comparisons are two-sided with a nominal significance level of 5%.

Role of the funding source

The study sponsors had no role in study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

In total, 784 patients were screened for inclusion between October 7, 2005 and April 16, 2008, and 361 were found eligible. Of those, 29 patients did not complete the QoL measurements (14 refused, 15 other reasons). Overall, 332 patients were included in the QoL component, 142 in the TAH group, and 190 in the TLH group (Figure 1). Patients randomised to TAH or TLH had similar demographic characteristics but patients assigned to TAH had better QoL at baseline (although most confidence intervals overlapped) (Table 1).

Patients treatment characteristic are reported in Table 2. Patients who had a TLH were less likely to have received a lymph node dissection for surgical staging purposes (Table 2). A significantly higher proportion of patients who were assigned to TAH stayed in hospital for 2 days or more (139/142 after TAH compared to 72/190 after TLH, p<0.0001). The median (IQR) time to surgery was 7 (4-13) days for TAH and 7 (4-13) days for TLH (p= 0.90).

Quality of Life recovery

Figure 2 presents the mean values and 95% confidence intervals for patients randomised to the TAH and TLH groups at predetermined time points. For the domains measuring PWB, FWB, EnWB, FACT-G, EuroQol-VAS and body image scale there was a decrease in QoL one week post surgery with a gradual QoL recovery up to six months. This is not unexpected and may reflect the trauma of the surgical intervention. EWB and SWB showed a gradual QoL recovery where at baseline these scores reflect low (poor QoL) values prior to surgery, followed by an improvement once the threat of cancer had been removed.

Figure 3 presents the change in QoL scores from baseline, comparing early and late recovery among patients who received TLH to those who received TAH (forest plot). For ease of comparison, the scores have been rescaled on a 0-100 point scale and benefits can be interpreted as a percentage benefit/detriment. In early recovery (up to 4 weeks post surgery), patients with TLH experienced a clinically and statistically significantly greater improvement in most QoL measurements, compared to patients receiving TAH. The greatest differences were noted in functional well-being (13% greater improvement for patients with TLH), followed by physical well-being (11% greater), endometrial cancer-specific well-being (6% greater) and overall FACT-G summary score (7% greater) (p=0.001 for all comparisons). Patients with TLH also reported 5% (p=0.001) greater improvements in their body image and 7.5% (p=0.001) in overall QoL (EQ-VAS) compared to patients with TAH. There was no

significant difference during early recovery in emotional (p=0.39) or social wellbeing (p=0.59) between patients assigned TAH or TLH. During the late post-operative recovery phase (3 to 6 months post surgery), patients with TLH compared to patients with TAH recovered significantly more in their physical (p=0.008), functional (p=0.009), endometrial cancer-specific (p=0.003), and overall well-being (FACT-G) (p = 0.03), and also experienced superior QoL recovery with regards to body image (p=0.001).

There was an imbalance in the number of lymph node dissections (LND) performed between the two treatments. Patients who received LND had significantly lower QoL in FWB and FACT-G at early recovery (1 to 4 weeks postoperatively) compared to those without LND. QoL was not different in all other subscales and in any subscales at late recovery (3 to 6 months postoperatively). LND was significantly related to FACT-G (p=0.01) and FWB (p=0.04) at early recovery, with treatment remaining highly significant in favour of TLH even after adjustment for LND. For all other subscales and all subscales at late recovery there was no significant interaction between LND and treatment allocation.

While the QoL scales provide for changes on a continuous scale, of clinical value is a comparison by treatment of those patients who benefited by a threshold amount. The proportion of women who experienced an improvement in QoL by 5% or more, as measured by the FACT-G, was significantly greater among patients assigned to TLH compared to TAH in both the early (51% (92/179) TLH compared to 29% (36/122) TAH, p <0.0001) and late (69% (121/175) TLH compared to 58% (67/116) TAH, p =0.04) post-operative recovery period (Table 3). This table also shows that the improvement in the FACT-G is maintained as the clinical threshold is increased and is maintained at the late recovery period.

The number of women with completely missing QoL assessments was low, from 8/332 (2.4%) at baseline increasing to 42/332 (12.7%) at six months post-surgery. Overall, 263/332

(79.2%) of participants provided data at all five time points, and a further 30/332 (9%) completed measures at all but one timepoint. A higher proportion of patients assigned to TAH compared to TLH did not complete any QoL forms at 1 week (12/142 (8.5%) versus 4/190 (2.1%), and 6 months (24/142 (16.9%) versus 18/190 (9.5%), post surgery.

The proportion of missing values data at the 5%, 10% 15% and 20% differences in the FACT-G scale was 6% (12/190) in the TLH and 14% (20/142) in the TAH group. This imbalance was investigated further to determine whether there was any signal of a systematic pattern in the missing values during the early and late periods, we examined the association of the baseline variables: Age, obesity, grade, ECOG, lymph node dissection and whether there was a correlation with the FACT-G changes being missing. No such patterns were found in either the early or late missing periods in a univariate or multivariate logistic analysis, other than a treatment imbalance. There was no significant interaction between treatment and these variables on whether the response was missing suggesting that any systematic pattern which could be present would be well within the play of chance. The missing data patterns for the other outcomes were similar (i.e. no discernable trend).

Surgical and short term outcomes

Length of operating time was significantly longer in the TLH group (138±43 mins), than in the TAH group at (109±34 mins; p=0.001). There was no significant difference in numbers of patients with intraoperative adverse events between the TLH (14/190,7.4%) and TAH (8/142,5.6%) groups (p = 0.55). Two patients had an SAE intraoperatively (one TLH, one TAH). The first patient experienced an inadvertent cystostomy at TLH, resulting in prolonged hospitalisation. The second patient, in the TAH group, had a rotten tooth knocked out during intubation, causing oropharyngeal bleeding resulting in a difficult endotracheal intubation. This patient was transferred to the Intensive Care Unit postoperatively for

monitoring. Postoperatively, more than twice as many patients in the TAH group experienced AEs CTC grade 3+ than in the TLH group (33/142, 23.2% and 22/190, 11.6% respectively; p=0.004). Postoperative serious AEs occurred more frequently in patients who had a TAH (27/142, 19.0%) than a TLH (15/190, 7.9%) (p=0.002). Specific complications are presented in Table 4. No treatment-related patient deaths were recorded.

The mean haemoglobin decline from pre-surgery to first day post-surgery was 1.8±1.1 g/dL in the TLH group and 2.1±1.1 g/dL in the TAH group (p = 0.013). A larger proportion of patients stayed at hospital post-surgery for 2 days or more after TAH (139/141, 98.6%) compared to patients after TLH (72/191, 37.7%) (p<0.0001).

Discussion

QoL improvements from baseline during early and later phases of recovery, and the adverse event profile significantly favour TLH compared to TAH for patients treated for Stage I endometrial cancer.QoL was measured on a variety of validated subscales. Patients treated with TLH had significantly greater improvements in QoL from pre-surgery levels at both, early (up to four weeks) and late post-operative recovery (up to 6 months) compared to patients treated by TAH. Differences in subscale scores reflected superior physical, functional and overall QoL as well as body image in the TLH group, while social and emotional components of QoL remained largely stable across post-surgery time-points and between groups. Better physical and functional well-being reflects our clinical experience that patients who had a TLH return to normal activities more quickly, which seems especially relevant given the ageing of the population (33). A larger proportion of patients treated with TLH had improvements of 5% or more from baseline QoL during the early and late recovery after surgery for endometrial cancer.

To date, two prospective clinical trials compared QoL following laparoscopic and open surgery using a validated self-reported QoL scale, although neither studied TLH specifically (15, 16). An Italian trial randomised 84 patients comparing LAVH with TAH and found that patients treated with LAVH had significantly better overall QoL at four weeks, three and six months post-surgery, compared to patients treated with open surgery (15), which is similar to the more prolonged improvement of QoL found in the current study. The Gynecologic Oncology Group (GOG) LAP-2 trial randomly assigned patients to either open or laparoscopic (LAVH or TLH) treatment (n=802). As in the current trial, the FACT scale was used as the primary measure of QoL. Completion rates of QoL questionnaires were similar. Patients in the laparoscopic group had superior QoL compared to the open surgery group up to six weeks postoperatively but QoL scores were similar between the laparoscopic and the open arm at 6 months (16, 34).

A persistent QoL difference in the LACE trial favouring TLH at six months was thus maybe unexpected and may be due to a number of reasons. In the LAP-2 trial 25.8% of patients were converted from laparoscopic to open surgery and those patients had the lowest QoL at all but one time point, compared to successful open or laparoscopy patients. While both trials required surgeons' accreditation, the LAP-2 trial required a full pelvic and aortic lymph node dissection in all patients regardless of pre- or intraoperative findings. The need for a full pelvic and aortic node dissection was the most common reason for conversion to laparotomy in LAP-2. In the LACE trial, surgeons were also required to perform pelvic ± para-aortic lymph node dissection as part of the treatment in both arms but they could elect to omit a lymph node dissection if patients met specific criteria as outlined above. In LACE, 52% of patients had a pelvic and/or aortic lymph node dissection, which is comparable with previous reports (35). However, a lower proportion of patients receiving TLH than TAH underwent a lymph node dissection, which may have contributed to better QoL outcomes in the

laparoscopic group in the early phase of surgical recovery. Indeed, when we assessed the effect of lymph node dissection on QoL outcomes adjusted for treatment received, LND only influenced FACT-G and FWB at early recovery.

Another reason for the good QoL results in the TLH group could be that the LACE trial started enrolment later than the LAP-2 trial and the trial management committee made an enormous effort to ascertain that all surgeons were beyond their individual learning curve. All surgeons had to complete 20 unsupervised TLH procedures, had to submit video footage of one procedure, which qualified them to perform a live TLH and node dissection, which was witnessed by one of the senior LACE trial surgeons attending in person. Comparing QoL scores from early enrolment to QoL scores from late enrolment found no differences (data not shown). One further explanation for the QoL differences between LACE and LAP-2 could also be that no LAVH was performed in the LACE trial, and all procedures were completed totally laparoscopically, whereas the majority of procedures were LAVH in the LAP-2 trial (36).

Last but not least, the statistical analysis model differed between the two RCTs. In LACE, we compared individual QoL differences for each patient between baseline and early (up to 3 months) and late (up to 6 months) after surgery in the TLH and the TAH group. In contrast, adjusted mean QoL values were compared for the laparoscopic and the open group and compared within the specified time points (1, 3, 6 weeks and 6 months) in the LAP-2 trial. Therefore, our statistical analysis approach is not influenced by statistically significant differences in QoL values at baseline as seen in the subscale “physical functioning” in the LAP-2 trial (16).

Past prospective studies have indicated that the laparoscopic approach is comparable to or better than the abdominal approach in terms of short-term outcomes such as complications,

blood loss, and length of hospital stay (6, 8, 36). TLH specifically has been shown to be advantageous for these outcomes in retrospective series (17, 37) and this has been confirmed in the present analysis, with a smaller proportion of patients randomised to TLH experiencing post-operative adverse events. Quicker recovery from surgery and freedom from post-operative adverse events will thus likely have contributed to better QoL outcomes in patients with TLH.

Limitations of our study include those frequently encountered by surgical trials. Blinding of patients and treatment team has not been attempted. Randomisation was well ahead of surgery and for ethical reasons patients had to be aware of the treatment they were to receive. Recruitment for the study was conducted in hospitals well equipped to deal with patients after major abdominal surgery and the new laparoscopic technique.

In summary, the results of this randomised-controlled trial demonstrate that QoL recovery in endometrial cancer patients undergoing surgery by TLH is clinically and statistically significantly superior during the early and late post-operative phases, compared to QoL in those treated with TAH. The QoL findings are more pronounced than those of some earlier trials, most likely because the conversion rate from TLH to TAH was very low. Further follow-up of the patients in this trial will ascertain the equivalence of disease-free survival.

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Author contributions:

BA, HR, JT, LR, MT, McCA, NM, ND, NJ, OM, OG, PL, SS, HI, LY, WTT, SP, NgH, GA, LM, NTY, TK, CK, WD, PS, SB, FR, OA recruited and treated patients. JM, GV and OA contributed to the design and analysis of the trial. All authors reviewed the manuscript before submission.

Conflicts of interest:

McCA has shares and stock ownership of Gynetech. He has received occasional consultancy honoraria from Gate Healthcare. OA has been an occasional advisor for Genzyme, with honoraria for presentations. OA received research support from Bristol-Myers Squibb. All other authors declared no conflicts of interest.

Table 1. Patient characteristics (by treatment group)**

Characteristic	Total 332 (%)	TAH 142 (%)	TLH 190 (%)
Age			
mean	62.8	62.7	62.8
Standard deviation	9.9	9.7	10.0
BMI category*			
Normal (18.50-24.99)	45 (14.4)	21 (15.6)	24 (13.6)
Overweight (25.00-29.99)	70 (22.4)	26 (19.3)	44 (24.9)
Obesity Class I (30.00-34.99)	76 (24.4)	39 (28.9)	37 (20.9)
Obesity Class II (35.00-39.99)	54 (17.3)	23 (17.0)	31 (17.5)
Obesity Class III (≥40)	67 (21.5)	26 (19.3)	41 (23.2)
Education			
Completed 12 years of schooling or less	230 (75.2)	94 (74.6)	136 (75.6)
Completed >12 years of schooling	76 (24.8)	32 (25.4)	44 (24.4)
Employment			
Retired	135 (44.1)	51 (40.5)	84 (46.7)
Employed full-time	38 (12.4)	18 (14.3)	20 (11.1)
Employed part-time or casual	41 (13.4)	20 (15.9)	21 (11.7)
Other	92 (30.1)	37 (29.4)	55 (30.6)
Marital Status			
Married/living together	206 (67.3)	85 (67.5)	121 (67.2)
Other	100 (32.7)	41 (32.5)	59 (32.8)
Private health insurance			
Yes	219 (28.4)	41 (32.5)	46 (25.6)
No	87 (28.4)	85 (67.5)	134 (74.4)
Income			
Less than $40,000	201 (65.7)	76 (60.3)	125 (69.4)
$40,000+	64 (20.9)	31 (24.6)	33 (18.3)
Not answered	41 (13.4)	19 (15.1)	22 (12.2)
Birth Country			
Australia	212 (69.3)	88 (69.8)	124 (68.9)
Other	94 (30.7)	38 (20.2)	56 (31.1)
ECOG Performance Status			
0	282 (84.9)	122 (85.9)	160 (84.2)
1	50 (15.1)	20 (14.1)	30 (15.8)
Quality of life at baseline	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
PWB	85.1 (83.2,87.1)	87.6 (85.0,90.2)	83.4 (80.7,86.1)
SWB	82.7 (80.8,84.6)	83.0 (80.0,86.0)	82.5 (80.0,85.0)
EWB	73.7 (71.4,75.2)	74.6 (71.1,78.0)	73.0 (70.1,76.0)
FWB	74.6 (72.3,76.9)	78.2 (75.0,81.5)	71.9 (68.8, 75.1)
ENWB	81.0 (79.3, 82.7)	83.3 (80.9,85.7)	79.3 (77.0,81.6)
FACT-G	79.7 (78.2,81.2)	81.7 (79.5,83.8)	78.4 (76.4,80.3)
Body image scale	88.5 (86.6, 90.4)	91.4 (89.1,93.8)	86.4 (83.8,89.1)
EuroQOLVas	77.8 (75.8,79.9)	78.5 (75.1,81.8)	77.4 (74.7,80.1)

*Based on WHO categories, **n do not always add to 332 due to missing demographic data; Abbreviations: PWB=physical well -being; SWB=social well-being; EWB=emotional well-being; FWB=functional-well being; ENWB=endometrial well-being; FACTG= Functional Assessment of Cancer Therapy-General; EuroQoLVas=Visual analogue scale or the EQ -5D.

Table 2. Clinical characteristics (by treatment group)

Characteristic	**Total**	**TAH**	**TLH**
	332 (%)	**142 (%)**	**190 (%)**
Grade of Differentiation			
Grade 1 – Well differentiated	211 (63.6)	89 (62.7)	122 (64.2)
Grade 2 – Moderately differentiated	105 (31.6)	46 (32.4)	59 (31.1)
Grade 3 – Poorly differentiated	16 (4.8)	7 (4.9)	9 (4.7)
Surgical Stage			
IA	246 (74.1)	104 (73.2)	142 (74.7)
IB	34 (10.2)	13 (9.2)	21 (11.1)
II	30 (9.0)	16 (11.3)	14 (7.4)
IIIA	6 (1.8)	1 (0.7)	5 (2.6)
IIIB	1 (0.3)	-	1 (0.5)
IIIC1	5 (1.5)	3 (2.1)	2 (1.1)
IIIC2	6 (1.8)	3 (2.1)	3 (1.6)
IVB	1 (0.3)	1 (0.7)	-
Other**	3 (0.9)	1 (0.7)	2 (1.1)
Node dissection performed			
No	159 (47.9)	46 (32.4)	113 (59.5)
Yes	173 (52.1)	96 (67.6)	77 (40.5)
Tumour Types			
Endometroid adeno-carcinoma	309 (93.1)	132 (92.9)	177 (93.2)
other	23 (6.9)	10 (7.1)	13 (6.8)
Adjuvant therapy			
none	263 (79.2)	111 (78.2)	152 (80.0)
Chemotherapy and/or radiation	69 (20.8)	31 (21.8)	38 (20.0)
Hospital stay			
≤2 days	121 (36.4)	3 (2.1)	118 (62.1)
>2 days	211 (63.6)	139 (97.9)	72 (37.9)

**Found to have cervical cancer

Table 3. Proportion of women whose quality of life (FACT-G) improved by at least 5, 10, 15 or 20% from baseline during the early and later recovery period

			FACT-G improvement					
	5%	p-value 95% CI*	10%	p-value 95% CI*	15%	p-value 95% CI*	20%	p-value 95% CI*
Early (up to 4 weeks)								
TLH n=179	92 51%	<0.0001 (11%, 33%)	55 31%	0.001 (8%,26%)	32 18%	.001 (7%, 20%)	19 11%	0.01 (3%, 13%)
TAH n=121	36 29%		17 14%		5 4%		3 2%	
Late (up to 6 months)								
TLH n=175	121 69%	0.04 (0.1%, 23%	85 49%	0.02 (3%,25%	46 26%	0.27 (-4%, 15%	25 14%	0.74 (-7%, 9%)
TAH n=116	67 58%		40 34%		24 21%		15 13%	

***95% confidence interval for the difference in proportions showing an improvement between the TAH and TLH groups**

Table 4. Intra and post-operative adverse events in TAH and TLH groups

Adverse Events (n, %)	Total (n=332)	TAH (n=142)	TLH (n=190)	p-value
Intraoperative				
Any	22 (6.6)	8 (5.6)	14 (7.4)	0.549
Visceral injury	9 (2.7)	3 (2.1)	6 (3.1)	
Blood transfusion	3 (0.9)	3 (2.1)	-	
Uterus rupture	1 (0.5)	-	1 (0.5)	
Vaginal laceration	6 (1.8)	-	6 (3.1)	
Vascular injury	3 (0.9)	2 (1.4)	1 (0.5)	
Postoperative*				
Any	55 (16.6)	33 (23.4)	22 (11.5)	0.004
Wound infection	15 (4.5)	13 (9.2)	2 (1.0)	
Cardiac general	10 (3.0)	4 (2.8)	6 (3.1)	
Pulmonary/upper respiratory	9 (2.7)	4 (2.8)	5 (2.6)	
Gastrointestinal	7 (2.1)	5 (3.5)	2 (1.0)	
Wound dehiscence	6 (1.8)	6 (4.3)	-	
Hemorrhage/bleeding	5 (1.5)	3 (2.1)	2 (1.0)	
Blood/bone marrow	4 (1.2)	4 (2.8)	-	
Others**	4 (1.2)	2 (1.4)	2 (1.0)	
Renal/genitourinary	4 (1.2)	2 (1.4)	2 (1.0)	
Constitutional symptoms	3 (0.9)	1 (0.7)	2 (1.0)	
Metabolic/laboratory	3 (0.9)	3 (2.1)	-	
Neurology	3 (0.9)	-	3 (1.6)	
Vascular	3 (0.9)	2 (1.4)	1 (0.5)	
Cardiac arrhythmia	2 (0.6)	1 (0.7)	1 (0.5)	
Infection	2 (0.6)	-	2 (1.0)	
Musculoskeletal/soft tissue	2 (0.6)	1 (0.7)	1 (0.5)	
Lymphatics	1 (0.3)	-	1 (0.5)	
Pain	1 (0.3)	1 (0.7)	-	
Serious Adverse Events				
Any	42 (12.7)	27 (19.1)	15 (7.9)	0.002
Infection	19 (5.7)	14 (9.9)	5 (2.6)	
Haemorrhage/Bleeding	6 (1.8)	4 (2.8)	2 (1.0)	
Cardiac general	5 (1.5)	1 (0.7)	4 (2.1)	
Wound dehiscence	4 (1.2)	4 (2.8)	-	
Cardiac arrhythmia	4 (1.2)	3 (2.1)	1 (0.5)	
Pulmonary/Upper respiratory	2 (0.6)	1 (0.7)	1 (0.5)	
Blood/Bone Marrow	2 (0.6)	2 (1.4)	-	
Other***	3 (0.9)	1 (0.7)	2 (1.0)	

* CTC grade ≥ 3; ** include extended hospital stay, difficult intubation and return to theatre in the same admission

*** extended hospital stay, small bowel obstruction, thrombus, post anaesthesia difficulties

Figure 1. CONSORT diagram

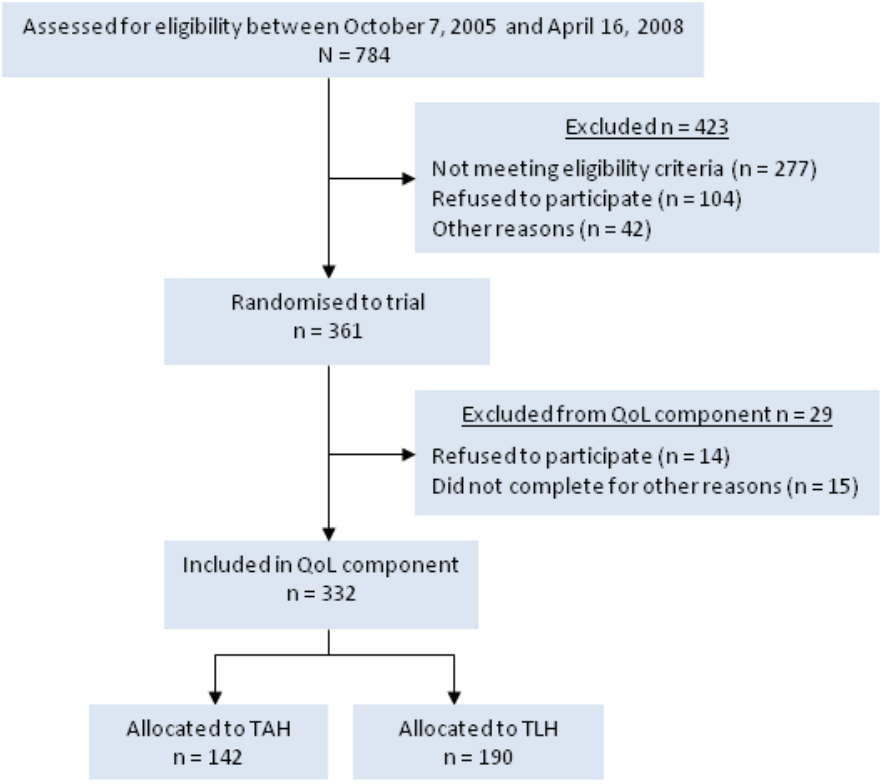
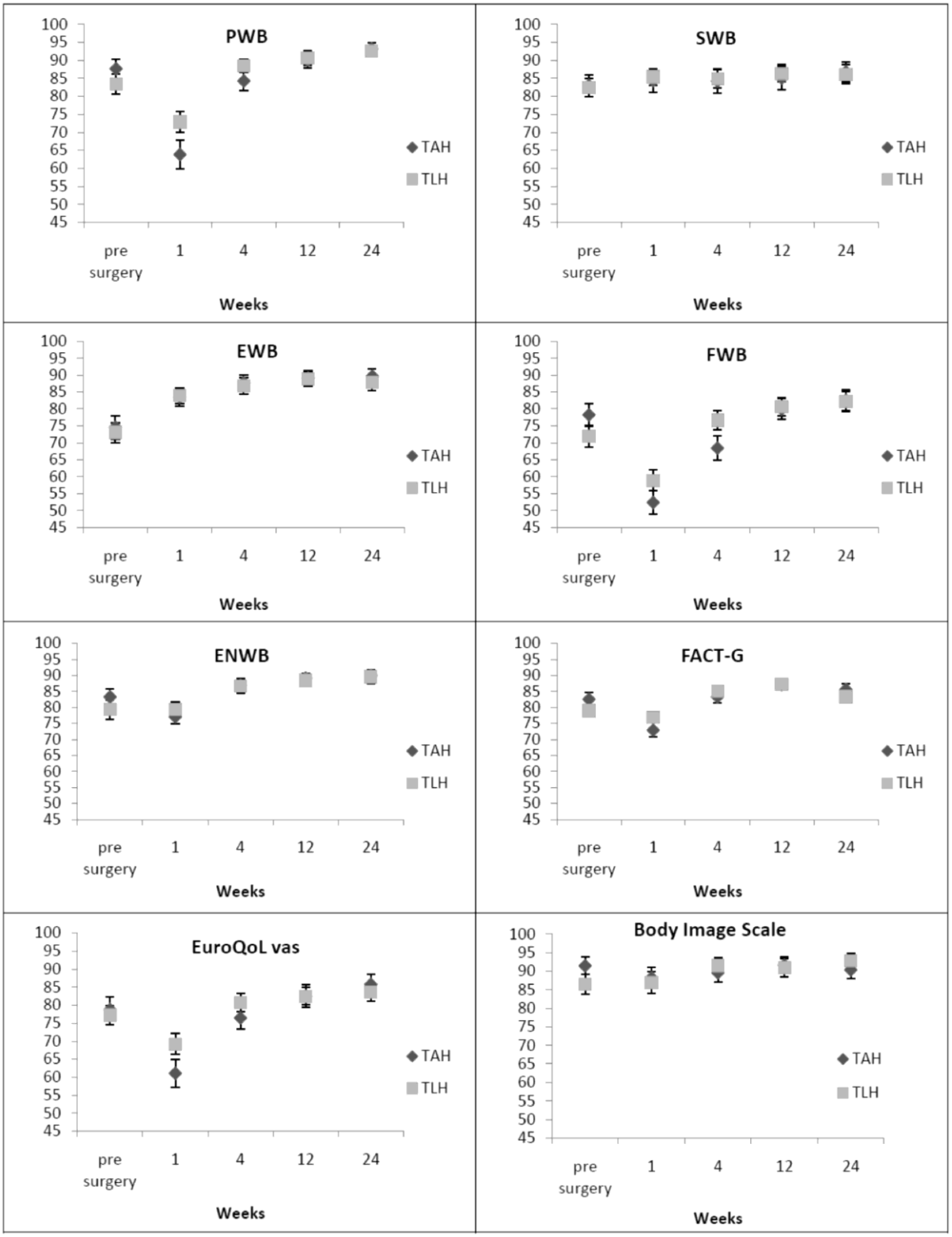
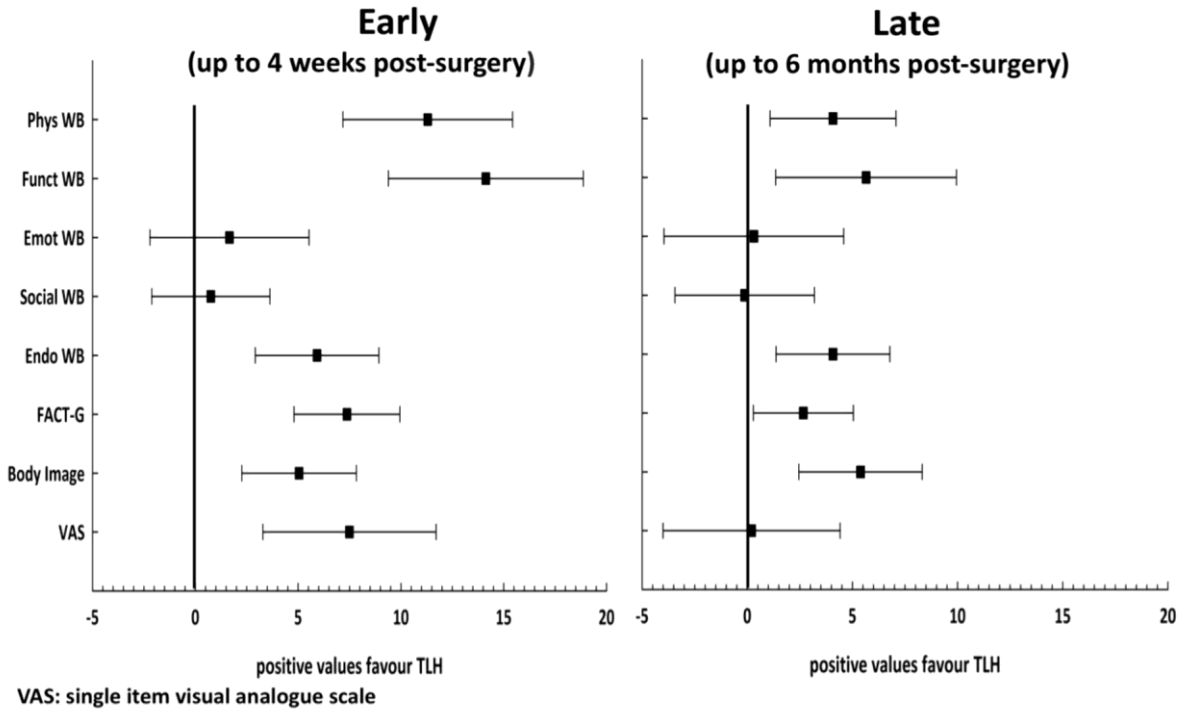


Figure 2. Quality of life scores over time (raw mean scores and confidence intervals on 0-100 scale, with 0 representing low quality of life and 100 representing high quality of life)



Higher score represents better quality of life. Abbreviations: PWB=physical well -being; SWB=social well-being; EWB=emotional well-being; FWB=functional-well being; ENWB=endometrial well-being; FACTG= Functional Assessment of Cancer Therapy-General; EuroQOLVas=Visual analogue scale.

Figure 3. Forest plot of mean difference (95% CI) in QoL improvement from baseline between TLH and TAH groups



VAS: single item visual analogue scale

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