Quality of life in patients with cervical cancer after open versus minimally invasive radical hysterectomy (LACC): a secondary outcome of a multicentre, randomised, open-label, phase 3, non-inferiority trial

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Summary

Background In the phase 3 LACC trial and a subsequent population-level review, minimally invasive radical hysterectomy was shown to be associated with worse disease-free survival and higher recurrence rates than was open radical hysterectomy in patients with early stage cervical cancer. Here, we report the results of a secondary endpoint, quality of life, of the LACC trial.

Methods The LACC trial was a randomised, open-label, phase 3, non-inferiority trial done in 33 centres worldwide. Eligible participants were women aged 18 years or older with International Federation of Gynaecology and Obstetrics (FIGO) stage IA1 with lymphovascular space invasion, IA2, or IB1 adenocarcinoma, squamous cell carcinoma, or adenosquamous carcinoma of the cervix, with an Eastern Cooperative Oncology Group performance status of 0 or 1, who were scheduled to have a type 2 or 3 radical hysterectomy. Participants were randomly assigned (1:1) to receive open or minimally invasive radical hysterectomy. Randomisation was done centrally using a computerised minimisation program, stratified by centre, disease stage according to FIGO guidelines, and age. Neither participants nor investigators were masked to treatment allocation. The primary endpoint of the LACC trial was disease-free survival at 4·5 years, and quality of life was a secondary endpoint. Eligible patients completed validated quality-of-life and symptom assessments (12-item Short Form Health Survey [SF-12], Functional Assessment of Cancer Therapy–Cervical [FACT-Cx], EuroQoL-5D [EQ-5D], and MD Anderson Symptom Inventory [MDASI]) before surgery and at 1 and 6 weeks and 3 and 6 months after surgery (FACT-Cx was also completed at additional timepoints up to 54 months after surgery). Differences in quality of life over time between treatment groups were assessed in the modified intention-to-treat population, which included all patients who had surgery and completed at least one baseline (pretreatment) and one follow-up (at any timepoint after surgery) questionnaire, using generalised estimating equations. The LACC trial is registered with ClinicalTrials.gov, NCT00614211.

Findings Between Jan 31, 2008, and June 22, 2017, 631 patients were enrolled; 312 assigned to the open surgery group and 319 assigned to the minimally invasive surgery group. 496 (79%) of 631 patients had surgery completed at least one baseline and one follow-up quality-of-life survey and were included in the modified intention-to-treat analysis (244 [78%] of 312 patients in the open surgery group and 252 [79%] of 319 participants in the minimally invasive surgery group). Median follow-up was 3·0 years (IQR 1·7–4·5). At baseline, no differences in the mean FACT-Cx total score were identified between the open surgery (129·3 [SD 18·8]) and minimally invasive surgery groups (129·8 [19·8]). No differences in mean FACT-Cx total scores were identified between the groups 6 weeks after surgery (128·7 [SD 19·9] in the open surgery group *vs* 130·0 [19·8] in the minimally invasive surgery group) or 3 months after surgery (132·0 [21·7] *vs* 133·0 [22·1]).

Interpretation Since recurrence rates are higher and disease-free survival is lower for minimally invasive radical hysterectomy than for open surgery, and postoperative quality of life is similar between the treatment groups, gynaecological oncologists should recommend open radical hysterectomy for patients with early stage cervical cancer.

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Introduction

New technologies are frequently adopted in surgical oncology subspecialties before randomised studies are done to confirm their safety and efficacy. One example is the widespread acceptance of minimally invasive radical hysterectomy for the treatment of early-stage cervical cancer on the basis of individual experiences and opinions and subsequent institutional retrospective studies.[1–3] The

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Research in context

Evidence before this study

In August 2007, we searched PubMed and ClinicalTrials.gov without date or language restrictions for publications about the use of minimally invasive radical hysterectomy for the treatment of early stage cervical cancer. We used the search terms "radical hysterectomy", "cervical cancer", "minimally invasive", "laparoscopic", "robotic", "robotic-assisted", and "quality of life". We identified several small, single-institution, retrospective reports detailing the use of minimally invasive radical hysterectomy for early-stage cervical cancer. We identified no randomised studies comparing open and minimally invasive radical hysterectomy, or any studies comparing quality of life after open or minimally invasive radical hysterectomy. Additionally, few randomised studies had compared quality of life after open and minimally invasive surgeries across all surgical subspecialties and procedures.

Added value of this study

Contrary to a common expectation that minimally invasive surgery would be better than open surgery with regard to quality of life after surgery, the LACC trial showed no difference in quality of life between patients who had open and minimally invasive radical hysterectomy for early-stage cervical cancer.

Implications of all the available evidence

The quality-of-life results of this study combined with previously reported findings of shorter disease-free survival and overall survival after minimally invasive radical hysterectomy than after open surgery and the fact that no difference in early or late postoperative morbidity has been identified between the procedures, suggest that surgeons should re-evaluate the use of minimally invasive surgery in the treatment of early-stage cervical cancer. We recommend that minimally invasive radical hysterectomy no longer be offered to women with early stage cervical cancer.

LACC trial[4] showed that in patients with early-stage cervical cancer, the risk of death after minimally invasive surgery is higher than that after a radical hysterectomy done using a traditional open incision (laparotomy). The minimally invasive procedure is also associated with higher recurrence rates than is open surgery.[4] A review comparing minimally invasive surgery with open radical hysterectomy based on population-level data from the National Cancer Database confirmed that women with cervical cancer who have minimally invasive surgery have worse outcomes than do those who have the procedure done via laparotomy.[5] Multiple retrospective studies have since been published confirming these findings.[6–9]

Although previous studies have shown that survival is shorter with minimally invasive radical hysterectomy than with open surgery, some surgeons might continue to use the minimally invasive approach because of the possibility that the procedure results in lower operative morbidity and mortality. However, data on adverse events from the LACC trial showed that although blood loss was significantly higher for women who had open surgery than those who had minimally invasive surgery, no differences were identified between the treatment groups in terms of intraoperative complications, early or delayed postoperative adverse events, or major adverse events.[10]

Surgeons might also argue that substantial improvements in quality of life after minimally invasive surgery justifies continuing to offer patients minimally invasive radical hysterectomy.[11] However, prospective studies are far from conclusive regarding the quality-of-life benefits of the minimally invasive approach. For women with endometrial cancer who have simple hysterectomy, two randomised trials, LAP2[12] and LACE,[13] reported contrasting findings for quality of life in the postoperative period. The LAP2 study showed a modest advantage 6 weeks after surgery for minimally invasive surgery in terms of body image and the proportion of patients who had returned to work, but scores from the Functional Assessment of Cancer Therapy—General (FACT-G) questionnaire from the two treatment groups did not meet the predefined minimally important difference at this early timepoint. At 6 months after surgery, no differences were identified between the open and minimally invasive surgery groups in any of the quality-of-life measurements assessed.[12] In contrast, the LACE study showed improved FACT-G scores favouring the minimally invasive approach over open surgery for endometrial cancer at 6 weeks after surgery, and this difference persisted even at 6 months after surgery.[13]

To date, no randomised studies comparing quality of life after the open and minimally invasive approaches have been done in women following radical hysterectomy for the treatment of cervical cancer. Observational studies found no difference in long-term quality of life between the two approaches in survivors of cervical cancer.[14] Furthermore, long-term quality of life does not seem to differ between patients who have had open radical hysterectomy and matched controls who have not had any type of hysterectomy (simple or radical).[15] The primary outcome of the LACC trial was to compare disease-free survival between the open and minimally invasive surgery treatment groups. Here, we report the quality-of-life results, assessed as a secondary outcome.

Methods

Study design and participants

The LACC trial was a randomised, open-label, phase 3, non-inferiority trial done in 33 medical centres

(appendix p 9). Detailed methods of the LACC trial have been published previously.[4] Briefly, eligible patients were women aged 18 years or older with adenocarcinoma, squamous cell carcinoma, or adenosquamous carcinoma of the cervix scheduled to have a type 2 or 3 radical hysterectomy, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and International Federation of Gynaecology and Obstetrics (FIGO) 2008 clinical stage IA1 disease with lymphovascular space invasion, IA2 disease, or IB1 disease (tumour size ≤4 cm limited to the cervix). Patients were excluded if they had a tumour larger than 4 cm in size, FIGO stage IB2–IVB disease, a history of pelvic or abdominal radiotherapy, evidence of metastatic disease, or were deemed unfit for surgery by the investigators. Full details of the eligibility criteria are included in the study protocol (appendix pp 11–115). All patients were eligible to enter the quality-of-life part of the study, but patients enrolled at Korean sites were not included because none of the questionnaires were available in Korean. The trial was approved by the institutional review boards at each of the participating centres and patients gave written informed consent.

Randomisation and masking

Patients were randomly assigned (1:1) to receive open or minimally invasive radical hysterectomy. Randomisation was done using a computerised minimisation program stratified by centre, disease stage according to FIGO guidelines, and age (≤70 or >70 years). Randomisation was done centrally at the Biostatistical Department of the School of Population Health, University of Queensland (Brisbane, QLD, Australia). Neither participants nor investigators were masked to treatment allocation.

Procedures

Patients were scheduled to have a type 2 or a type 3 radical hysterectomy (Piver classification) and pelvic lymphadenectomy. Postoperative adjuvant radiotherapy was recommended according to the widely accepted Sedlis criteria.[16]

Four self-administered quality-of-life questionnaires (the Functional Assessment of Cancer Therapy–Cervical [FACT-Cx], the MD Anderson Symptom Inventory [MDASI], the 12-item Short Form Health Survey [SF-12], and the EuroQoL-5D [EQ-5D]) were administered to patients by study coordinators in person at baseline (before surgery) and at each follow-up appointment after surgery. These instruments were chosen on the basis of previous publications and consultations with experts from the MD Anderson Assessment, Intervention, and Measurement Core Resource Center (MD Anderson Cancer Center, Houston, TX, USA).[12,13] The FACT-Cx was administered before surgery and at 1 and 6 weeks and 3, 6, 18, 30, 42, and 54 months after surgery. The MDASI, SF-12, and EQ-5D were administered before surgery and at 1 week, 6 weeks, and 3 and 6 months after surgery. To reduce the survey burden for patients, we collected quality-of-life data for all four instruments for up to 6 months after surgery and only for the FACT-Cx for an additional 4 years (up to 54 months) since the FACT-Cx is the most commonly used quality-of-life instrument for assessing quality of life in patients with cervical cancer across all types of treatments (eg, surgical, medical, radiotherapy, supportive care). Since no standard schedule exists for the collection of patient-reported outcomes after surgery, timepoints for quality-of-life assessments were chosen on the basis of the patient follow-up schedule for other endpoints in the LACC trial. The instruments comprised 78 items in total, and the estimated time to complete all four instruments was 20–25 min.

The FACT-Cx is a 42-item survey that has been widely used in oncology because it is a multidimensional instrument that is easy to administer. The Cx subscale of FACT was developed to incorporate several issues specific to cervical cancer treatment, both physical and emotional, including sexual function and fertility.[17]

The MDASI is a 19-item questionnaire. The first 13 items assess patient symptoms during the previous 24 h. Symptoms assessed include pain, fatigue, nausea or vomiting, anorexia, sleep symptoms, and distress. The final six items assess how those symptoms have interfered with the patient's general wellbeing, including their general activity, mood, ability to walk and do normal work, and relationships with others and enjoyment of life.[18]

The SF-12 measures generic health concepts regardless of a patient's age, disease, or treatment. This instrument is designed to assess health from the patient's point of view and covers eight areas: physical functioning, role functioning—physical, bodily pain, general health, vitality, social functioning, role functioning—emotional, and mental health. Results are expressed in terms of two meta-scores: a physical component summary and a mental component summary.[19]

The EQ-5D is a standardised instrument that provides a descriptive profile and a single index value for health status. The EQ-5D was originally designed to complement the SF-12. Serial administrations of the EQ-5D can be used to measure changes in health status and quality of life and can be used to calculate the life-years gained with an intervention.[20]

Higher scores on the SF-12 and FACT-Cx instruments correlate with better functioning, whereas on the MDASI and EQ-5D instruments, lower scores correlate with better functioning. However, to aid interpretation, all survey scales were transformed to a 0–100 scale, with higher scores correlating with better quality-of-life outcome.

Outcomes

The primary endpoint of the LACC trial was disease-free survival at 4·5 years, as reported previously.[4] Quality of life was a secondary endpoint, and is reported here.

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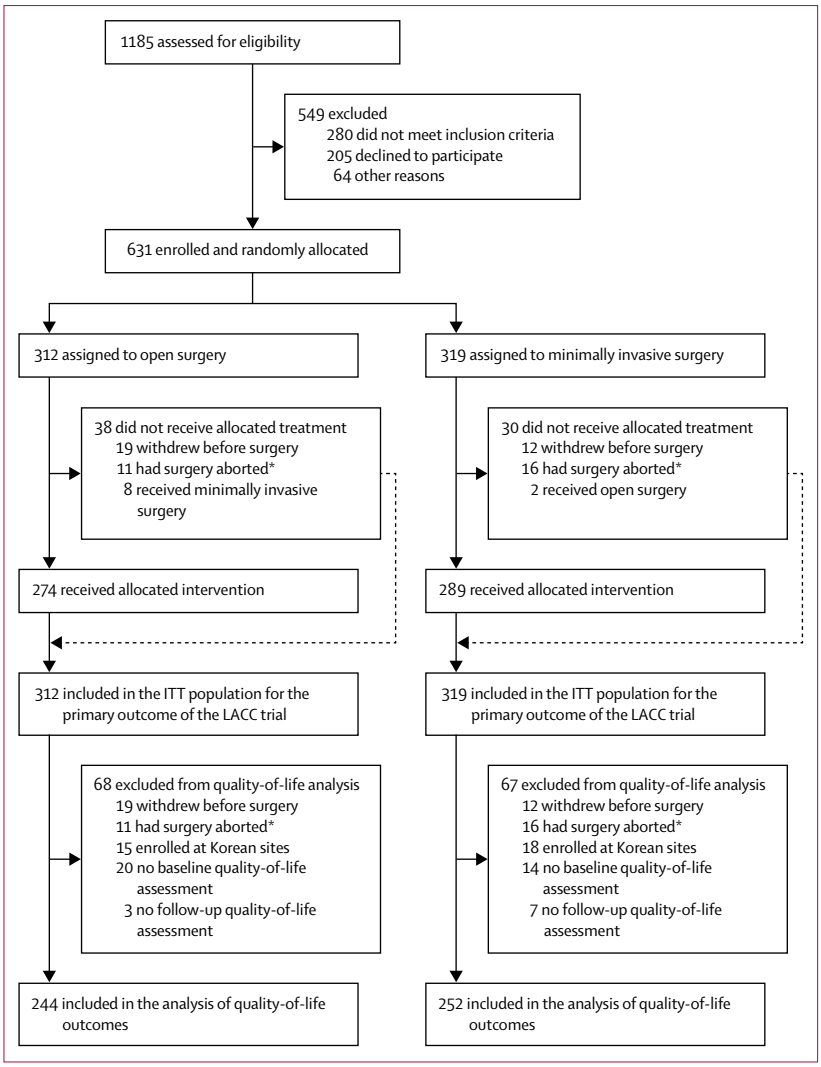

Figure 1: **Trial profile**
ITT=intention to treat. *Surgery was started, but not completed due metastatic disease.

Six quality-of-life outcomes were analysed: FACT-Cx total score, SF-12 physical and mental components, MDASI scores for symptoms (symptom score) and interference of symptoms with daily life (interference score), and EQ-5D total score (body state score).

Statistical analysis

We hypothesized that disease-free survival at 4·5 years would be similar between women who had open surgery and women who had minimally invasive radical hysterectomy, and assuming a 4·5-year accrual and 4·5-year follow-up, a sample size of 740 patients (370 per treatment group) would achieve 80% power to detect non-inferiority at a two-sided α of 0·05. The quality-of-life secondary endpoint was not powered and the quality-of-life analysis in the LACC study is exploratory; our report is primarily descriptive and no formal analysis plan was developed a priori.

The primary endpoint of the LACC trial was assessed by intention to treat. We assessed the secondary endpoint, quality of life, in the modified intention-to-treat population, which included all patients who had surgery and completed at least one baseline (pretreatment) and one follow-up (at any timepoint) questionnaire. Patients were excluded from the analysis if surgery was aborted or if they withdrew from the study prior to surgery; however, patients who were randomly assigned to the minimally invasive group but had a conversion to open surgery were included in the minimally invasive group for the analysis. Since 38 patients in the open surgery group and 30 patients in the minimally invasive surgery group did not receive the allocated treatment, we did not do an analysis by actual treatment received. No statistical adjustments to the analysis were made for multiple testing or to account for missing data.

We recorded the number of completed questionnaires at each timepoint of interest. Patient demographic and clinical characteristics were presented as frequencies for categorical variables and mean (SD) or median (IQR) for continuous variables. Quality-of-life scores were summarised as mean (SD) at each timepoint by treatment group. Mean scores with corresponding 95% CIs over time were plotted for each quality-of-life outcome.

Change in quality of life was calculated from baseline to an early (6 weeks) and a late (3 months) postoperative timepoint for each variable. Change in quality-of-life scores from baseline to postoperative timepoint were summarised by treatment group. Differences between treatment groups in change from baseline in quality-of-life scores were assessed at each time period using generalised estimating equations with a time-by-treatment interaction term included in addition to the main effects of time since surgery and treatment. This method allows the inclusion of all participants, regardless of whether they have missing data at the early or late timepoint, and was adopted to take into account the within-patient correlation. Since no other covariates were included in the model, the assumption is that treatment and time explained any missing data. We generated forest plots, in which positive differences between treatment groups in the change in quality of life between baseline and 6 week or 3 month timepoints represented an absolute advantage for minimally invasive surgery and negative differences represented an absolute advantage for open surgery.

Change in scores were used to assess change in quality of life over time for all four instruments. Change in quality-of-life scores between baseline and the early and late timepoints was dichotomised to show improvements of 5% and 10% from baseline. The changes in quality-of-life scores were set at 5% and 10% to identify which patient's quality of life improved over time since the overall means do not provide information about which individual patients have improvements or declines in quality of life. The assessment of these change in scores

were predefined based on previous studies that showed 5% and 10% improvements in scores were clinically significant.[13,21–23] The difference in the proportion of patients who had a 5 or 10% improvement in quality of life at the 6-week and 3-month timepoints between the open surgery and minimally invasive surgery groups was calculated and is presented with the corresponding 95% CI and p values.

We did a post-hoc subgroup analysis for FACT-Cx total score at early and late timepoints stratified by age (<60 *vs* ≥60 years), country of residence (developed *vs* developing countries according to the UN Department of Economic and Social Affairs), ECOG performance status (0 *vs* 1), incision type for laparotomy (vertical *vs* transverse), body-mass index (BMI; <30 kg/m² *vs* ≥30 kg/m²), and adverse events (grade 0–1 *vs* grade 2 or worse adverse events graded according to Common Terminology Criteria for Adverse Events [CTCAE] version 3.0). Adverse events data used in the analysis have been published previously.[10] Since grade 2 or worse adverse events were the only subgroup associated with quality-of-life score on the FACT-Cx total score, we also did post-hoc subgroup analysis for the remaining five composite scores obtained from the other three instruments at the early and late timepoints. All analyses were done using SAS (version 9.3) and STATA (version 14.1). This study is registered with ClinicalTrials.gov, NCT00614211.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. MF, KPR, VG, RA, AO, and PTR had access to all the raw data. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

Results

Between Jan 31, 2008, and June 22, 2017, 631 patients were enrolled in the LACC trial, of whom 312 were randomly assigned to receive open radical hysterectomy and 319 patients were randomly assigned to receive minimally invasive radical hysterectomy. 244 (78%) of 312 patients in the open surgery group and 252 (79%) of 319 patients in the minimally invasive surgery group had surgery and completed at least one baseline and one follow-up quality-of-life questionnaire, and thus were included in the modified intention-to-treat population (figure 1). Median follow-up was 3·0 years (IQR 1·7–4·5). Completion rates for each instrument at each timepoint are shown in the appendix (pp 2–5). Baseline patient characteristics for each group are summarised in table 1. No baseline characteristics were identified as being associated with missing quality-of-life forms suggesting that non-completion of forms was random (data not shown).

In the open surgery group, the median time from surgery to response (ie, completion of follow-up questionnaire) was 6 weeks (IQR 6·0–6·4) for the early timepoint and 3 months (3·0–3·3) for the late timepoint. For the minimally invasive surgery group, the median time from surgery to response was 6 weeks (IQR 6·0–6·6) for the early timepoint and 3 months (3·0–3·2) for the late timepoint.

Transformed and untransformed scores for each quality-of-life instrument at each timepoint are shown in the appendix (pp 2–5).[13,24] At baseline, no differences in the mean FACT-Cx total score were identified between the open surgery (129·3 [SD 18·8]) and minimally invasive surgery groups (129·8 [19·8]; appendix pp 4–5). No differences in mean FACT-Cx total scores were identified between the groups 6 weeks after surgery

	Open surgery (n=244)	Minimally invasive surgery (n=252)
Age, years		
Mean (SD)	45·6 (10·4)	45·4 (1·4)
Median (IQR)	45·0 (22·0–73·1)	44·1 (22·4–71·3)
Body-mass index, kg/m²	26·5 (5·5)	27·3 (5·7)
ECOG performance status		
0	223 (91%)	229 (91%)
1	21 (9%)	23 (9%)
Geographical region		
Asia	37 (15%)	40 (16%)
Australia or New Zealand	42 (17%)	41 (16%)
Europe	20 (8%)	27 (11%)
North America	27 (11%)	29 (12%)
South America	118 (48%)	115 (46%)
Histological subtype		
Squamous cell carcinoma	174 (71%)	175 (69%)
Adenocarcinoma	64 (26%)	71 (28%)
Adenosquamous	6 (2%)	6 (2%)
FIGO clinical disease stage		
IA1 (with lymphovascular space invasion)	4 (2%)	4 (2%)
IA2	15 (6%)	17 (7%)
IB1	225 (92%)	231 (92%)
Treatment received		
Open	243 (100%)	0
Minimally invasive surgery	1 (<1%)	244 (97%)
Surgery converted to TARH	NA	8 (3%)
Adjuvant therapy		
Chemotherapy or radiotherapy	66 (27%)	66 (26%)
≥1 cycle of chemotherapy	48 (20%)	47 (19%)
≥1 dose of radiotherapy	55 (23%)	57 (23%)
Incision type		
Vertical midline	141 (58%)	7 (3%)
Low transverse	103 (42%)	1 (<1%)
Did not have open surgery	0	244 (97%)

Data are mean (SD), or n (%), unless stated otherwise. ECOG=Eastern Cooperative Oncology Group. FIGO=International Federation of Gynaecology and Obstetrics. TARH=total abdominal radical hysterectomy. NA=not applicable.

Table 1: **Baseline characteristics in the modified intention-to-treat population**

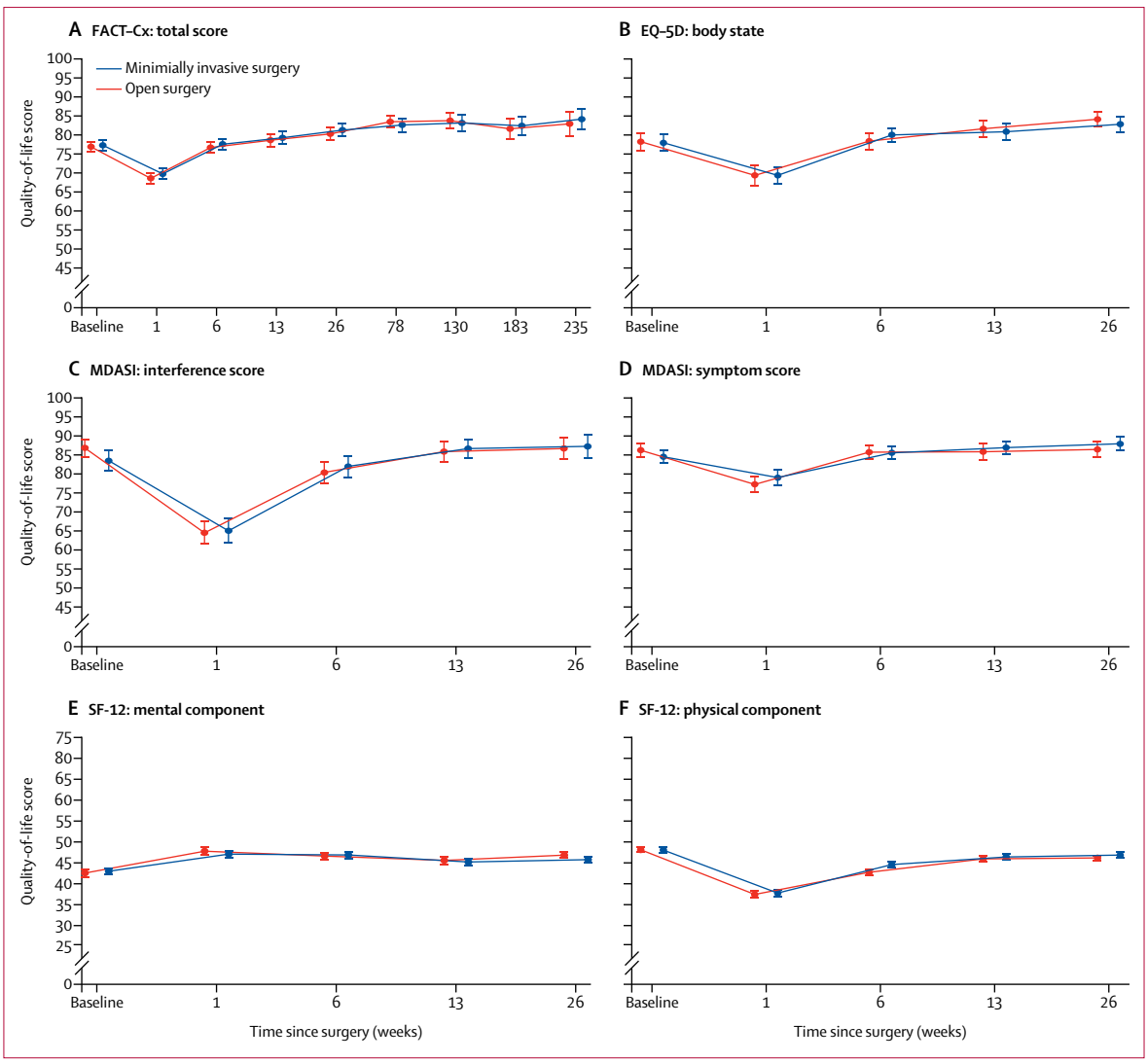

Figure 2: **Change in quality-of-life scores over time**
Datapoints represent means and error bars denote 95% CIs. Higher quality-of-life scores represents better quality of life. Timepoints for all surveys were the same for both treatment groups. Figure timepoints have been offset slightly to better show data without overlap. FACT-Cx=Functional Assessment of Cancer Therapy–Cervical. EQ-5D=EuroQoL-5D. MDASI=MD Anderson Symptom Inventory. SF-12=12-item Short Form Health Survey.

(128·7 [SD 19·9] in the open surgery group *vs* 130·0 [19·8] in the minimally invasive surgery group) or 3 months after surgery (132·0 [21·7] *vs* 133·0 [22·1]; appendix pp 4–5). Scores for the remaining five composite quality-of-life scores (SF-12 physical and mental components, MDASI symptom and interference scores, and EQ-5D body state score) were also similar between the open and minimally invasive surgery groups at baseline and all post-surgery timepoints (figure 2; appendix pp 2–5, 10).

At the early timepoint (6 weeks), patients in both the open surgery and minimally invasive surgery groups had a significant reduction from baseline in the physical component score of the SF-12, with patients in the open surgery group reporting a greater reduction than those in the minimally invasive surgery group (p=0·003; appendix p 6). Between baseline and 6 weeks, both groups had a significant increase in the mental component score of the SF-12; however, there was no significant difference between groups in the reduction from baseline (appendix p 6). At 6 weeks after surgery, no difference in the change scores for any of the other quality-of-life measures were identified between the open surgery and minimally invasive surgery groups (figure 2; appendix pp 6, 10).

At the late timepoint (3 months), no significant differences were identified between the two groups for change from baseline for any of the quality-of-life measures analysed (figure 2; appendix p 7). No differences were identified between the open and minimally invasive surgery groups in change from baseline to early or late

timepoints when patients were dichotomised by 5% or 10% improvement (table 2).

In post-hoc subgroup analyses, BMI was significantly associated with FACT-Cx total score at 6 weeks but was not significantly associated at 3 months (appendix p 8). Age, country of residence, ECOG performance status, and incision type for laparotomy were not associated with FACT-Cx score at either timepoint (appendix p 8).

In an additional post-hoc subgroup analysis, patients who had a grade 2 or worse adverse event in the first 6 weeks after surgery had worse quality of life on all six composite scores than did patients who did not have a grade 2 or worse adverse event (table 3). At the 3 month timepoint, patients with grade 2 or worse adverse events continued to have worse quality of life than those who did not have a grade 2 or worse adverse event as measured by the FACT-Cx total score, MDASI symptom and interference scores, and SF-12 physical component score, but not as measured by the SF-12 mental component or EQ-5D body state scores (table 3).

	Open surgery	Minimally invasive surgery	Difference (95% CI)*	p value
FACT-Cx total score				
5% improvement at 6 weeks	75/210 (36%)	69/214 (32%)	−3·5% (−18·9 to 12·0)	0·66
5% improvement at 3 months	78/198 (39%)	91/211 (43%)	3·7% (−11·1 to 18·6)	0·62
10% improvement at 6 weeks	38/210 (18%)	33/214 (15%)	−2·7% (−20·0 to 14·7)	0·76
10% improvement at 3 months	46/198 (23%)	45/211 (21%)	−1·9% (−19·0 to 15·2)	0·83
MDASI: interference score				
5% improvement at 6 weeks	50/211 (24%)	57/213 (27%)	3·1% (−13·4 to 19·5)	0·72
5% improvement at 3 months	53/199 (27%)	69/210 (33%)	6·2% (−10·0 to 22·5)	0·45
10% improvement at 6 weeks	34/211 (16%)	43/213 (20%)	4·1% (−13·2 to 21·3)	0·64
10% improvement at 3 months	38/199 (19%)	54/210 (26%)	6·6% (−10·5 to 23·7)	0·45
MDASI: symptom score				
5% improvement at 6 weeks	73/210 (35%)	70/215 (33%)	−2·2% (−17·7 to 13·3)	0·78
5% improvement at 3 months	73/202 (36%)	79/211 (37%)	1·3% (−14·0 to 16·6)	0·87
10% improvement at 6 weeks	43/210 (20%)	42/215 (20%)	−0·9% (−17·9 to 16·1)	0·91
10% improvement at 3 months	47/202 (23%)	52/211 (25%)	1·4% (−15·4 to 18·2)	0·87
SF-12: mental component				
5% improvement at 6 weeks	84/195 (43%)	87/204 (42%)	−0·9% (−15·7 to 14·0)	0·91
5% improvement at 3 months	78/185 (42%)	72/202 (35%)	−6·9% (−22·5 to 8·6)	0·38
10% improvement at 6 weeks	48/195 (25%)	46/204 (22%)	−2·3% (−19·5 to 14·9)	0·79
10% improvement at 3 months	41/185 (22%)	39/202 (19%)	−3·1% (−20·8 to 14·7)	0·73
SF-12: physical component				
5% improvement at 6 weeks	18/195 (9%)	26/204 (13%)	3·4% (−15·1 to 21·9)	0·72
5% improvement at 3 months	26/185 (14%)	24/202 (12%)	−2·3% (−20·9 to 16·3)	0·81
10% improvement at 6 weeks	9/195 (5%)	7/204 (3%)	−1·2% (−20·5 to 18·0)	0·90
10% improvement at 3 months	9/185 (5%)	9/202 (4%)	−0·5% (−19·9 to 19·0)	0·96
EQ-5D: body state				
5% improvement at 6 weeks	69/213 (32%)	78/215 (36%)	3·9% (−11·5 to 19·2)	0·62
5% improvement at 3 months	79/202 (39%)	84/211 (40%)	0·7% (−14·3 to 15·7)	0·93
10% improvement at 6 weeks	44/213 (21%)	54/215 (25%)	4·5% (−12·2 to 21·1)	0·60
10% improvement at 3 months	47/202 (23%)	59/211 (28%)	4·7% (−12·0 to 21·3)	0·58

Data are n/N (%). FACT-Cx=Functional Assessment of Cancer Therapy–Cervical. MDASI=MD Anderson Symptom Inventory. SF-12=12-item Short Form Health Survey. EQ-5D=EuroQoL-5D. *Change in score from baseline (minimally invasive surgery group minus open surgery group).

Table 2: **Proportion of patients whose quality of life had improved by at least 5% or 10% from baseline at 6 weeks and 3 months after surgery by treatment group**

Discussion

In this study, we found a small difference in the SF-12 physical component score at 6 weeks, but no other differences in the other measures of quality of life between women who had open radical hysterectomy and those who had minimally invasive radical hysterectomy in the early (≤6 weeks) or late (≥3 months) phase of recovery. The four validated instruments have been used to assess the effects on quality of life for a variety of acute and chronic health conditions. In addition to cross-cohort comparisons at multiple timepoints, we assessed within-patient changes in quality-of-life scores from baseline to 6 weeks and 3 months for the two groups. In these 12 comparisons, significant differences were only identified in the physical component score of the SF-12 at 6 weeks after surgery favouring the minimally invasive surgery group (ie, suggesting a less severe decrease in quality of life). Although significant, the absolute difference was only 2% between the two groups, which suggests the difference is not clinically meaningful, and by 3 months, this difference was no longer significant. In a subgroup analysis, we found that adverse events (CTCAE grade ≥2) correlated with worse quality of life on all scales at 6 weeks after surgery and this association persisted on multiple instruments 3 months after surgery.

These findings might be surprising to some who anecdotally hypothesise that minimally invasive surgery correlates with better quality of life than does laparotomy. The literature, however, does not consistently support this hypothesis. Few randomised surgical studies have been done comparing open and minimally invasive approaches for cancer treatment and even fewer studies have been published that incorporate quality-of-life outcomes. The few studies done have shown generally short-lived or minimal quality-of-life advantages for minimally invasive surgery. For example, in a large randomised study comparing open and minimally invasive colectomy for colon cancer, Weeks and colleagues[25] found a difference in the single-item global rating scale at 2 weeks after surgery favouring minimally invasive surgery, but no difference at the same timepoint on the Symptom Distress Scale pain intensity score, the Symptom Distress Scale summary score, or the Quality of Life Index. Furthermore, at 2 months after surgery, no differences were identified in any of the scales measured. Other randomised studies on the surgical treatment of colon cancer have shown a difference in quality of life favouring a minimally invasive approach persisting up to 1 year after surgery.[26,27] Quality of life at 6 weeks after surgery has also been found to be better for patients who had oesophagectomy via a minimally invasive approach than for those who had open oesophagectomy for the

	Grade 0–1 adverse events		Grade ≥2 adverse events		p value*
	Patients, n	Mean score† (SD)	Patients, n	Mean score† (SD)	
FACT-Cx total score					
6 weeks	357	78·0 (11·6)	78	73·2 (12·8)	0·0058
3 months	360	79·8 (12·9)	59	73·8 (13·3)	0·0023
SF-12: physical component					
6 weeks	343	44·0 (6·4)	77	42·1 (7·3)	0·025
3 months	349	46·6 (5·8)	56	43·6 (7·3)	0·0051
SF-12: mental component					
6 weeks	343	47·2 (6·9)	77	44·6 (7·8)	0·0016
3 months	349	45·5 (7·5)	56	44·5 (6·1)	0·38
MDASI: symptom score					
6 weeks	357	86·8 (13·9)	78	80·5 (17·7)	0·0014
3 months	362	87·4 (14·8)	58	80·4 (18·2)	0·0092
MDASI: interference score					
6 weeks	357	83·3 (20·6)	77	71·7 (26·2)	0·0002
3 months	360	87·6 (19·4)	57	78·3 (23·5)	0·026
EQ-5D body state score					
6 weeks	354	80·6 (15·5)	80	73·2 (17·2)	0·0033
3 months	361	82·2 (16·1)	58	75·2 (21·5)	0·066

FACT-Cx=Functional Assessment of Cancer Therapy–Cervical. SF-12=12-item Short Form Health Survey. MDASI=MD Anderson Symptom Inventory. EQ-5D=EuroQoL-5D. *Two-sided. †All quality-of-life scores were transformed to a 0–100 scale, with higher scores indicating better quality of life.

Table 3: **Subgroup analysis of quality-of-life scores at 6 weeks and 3 months after surgery, stratified by adverse event severity**

treatment of oesophageal cancer.[28] However, in that study, quality of life was not measured after the 6-week timepoint.

The LAP2 and LACE studies reported conflicting results for quality of life measured with the FACT-G survey after open and minimally invasive simple hysterectomy for endometrial cancer.[12,13] In the LAP2 study, a statistically significant difference favouring minimally invasive surgery was identified at 6 weeks, but this difference did not meet the predetermined value for a so-called minimally important difference, and by 6 months, no difference was identified between the groups.[12] In the LACE study, a difference in all subscales of the FACT-G at 6 weeks favouring the minimally invasive surgery group was identified, and this difference persisted at 6 months.[13]

Multiple possible explanations exist for the lack of a difference in quality of life between the two cohorts in the LACC trial. Early postoperative quality-of-life scores might correlate more closely with surgical morbidity than with surgical approach.[29] In explaining their results, authors of the LAP2 study hypothesised that one reason clinically significant quality-of-life differences were not observed between the open and laparoscopic surgery groups was that clinical outcomes (including intraoperative complications) were similar between the two cohorts.[12] Similarly, in the LACC trial, no differences were identified in intraoperative complications or postoperative morbidities between the minimally invasive and open surgery groups.[10] However, when we assessed quality of life in patients who had a grade 2 or worse adverse events associated with the surgical procedure, we found worse quality of life across all scales, regardless of surgical approach. We hypothesise that surgical approach (open *vs* minimally invasive) might be irrelevant for quality-of-life outcomes if patients have an uncomplicated postoperative course.

The lack of difference in intraoperative and postoperative complications might be due to the relatively low rates of obesity in the patient population studied. Women with obese and morbid obesity have more postoperative complications and longer hospital stays than women with a BMI of less than 30 kg/m² (a BMI of >30 kg/m² is the threshold for obesity).[30] In the LACC trial, the mean BMI in both the open and minimally invasive surgery groups was approximately 27 kg/m². In the LAP2 study, in which no clinically meaningful differences were identified in postoperative quality-of-life scores between groups, the median BMI was also lower than the obesity threshold (28–29 kg/m²).[12] In contrast, in the LACE study, in which postoperative quality-of-life scores did differ between the open and minimally invasive surgery groups, the median BMI in the overall patient population was 33 kg/m².[13] In our exploratory analyses, the change in quality-of-life scores between baseline and the early timepoint differed between patients who were obese and morbidly obese (BMI ≥30 kg/m²) and those of a normal weight or patients who were overweight (BMI <30 kg/m²).

The adoption of so-called enhanced recovery after surgery programmes in many institutions worldwide might add to the multifactorial influences that could affect postoperative quality of life. These programmes apply standardised, evidence-based treatment algorithms or so-called bundles to the patient's surgical journey starting days before the surgery and lasting until discharge and after.[31] This multidisciplinary approach, which involves surgeons, anaesthesia teams, and nursing support, has led to substantial decreases in postoperative pain and length of hospital stay, and faster return to baseline functioning after laparotomy in a variety of surgical fields.[32] Implementation of an enhanced recovery programme in patients who have laparotomy for ovarian cancer resection showed improvement in MDASI scores in the cohort of women who had their postoperative care managed under enhanced recovery compared with those who had conventional perioperative management.[33] Although no data are available on the number of centres in the LACC trial that had adopted enhanced recovery pathways for patients having laparotomy, this approach has become ubiquitous in all surgical fields and is likely to contribute to the improvement of postoperative quality of life in patients who had laparotomy.

Our study has limitations inherent to international surgical trials. Although patients were randomly

assigned to open or minimally invasive surgery, masking researchers and patients to treatment allocation was not possible. Furthermore, patients were randomised before surgery, and patients' knowledge of their group assignment might have biased the results. Also, the study was powered to show non-inferiority in disease-free survival between the two treatment groups, thus the sample size might not be have been adequate to detect a difference in the quality-of-life outcomes. The exclusion of Korean patients, due to the lack of validated instruments in that language, might also have introduced bias. Additionally, although we did exploratory analyses on confounders that might affect quality of life (eg, age, country of residence, ECOG performance status, incision type, BMI, and postoperative morbidity [adverse events]), we were unable to evaluate other possible factors such as length of hospital stay. Because the study was done at 33 sites across multiple countries, duration of post-operative hospital stay varied widely. It would be difficult to determine the association between quality of life and length of stay, since duration of hospital stay is dependent on a wide variety of factors such as varying clinical practice, surgeon preference, patient or cultural expectations, and institutional norms, and not necessarily on surgical approach or adverse events or complications alone. Most patients were recruited from academic centres around the world, so the applicability of our results to specific patient populations could be limited.

In conclusion, our analysis of quality-of-life outcomes in the LACC trial shows that women with early stage cervical cancer had similar postoperative quality of life 6 weeks after surgery and beyond regardless of whether they had open or minimally invasive radical hysterectomy. Considering these results and the previously reported findings of worse progression-free survival and overall survival after minimally invasive radical hysterectomy than after open surgery and no difference in early or late postoperative morbidity between these two surgical approaches, the role of minimally invasive surgery in the treatment of early-stage cervical cancer should be re-evaluated. We would recommend that minimally invasive radical hysterectomy should no longer be offered to women with early stage cervical cancer.

Contributors

MF, AO, RLC, PTR, RA, KPR, and VG participated in study conception and design. MF, AO, RLC, PTR, RP, AL, DI, GR, MQB, AB, RM-M, RR, AZ, MAV, TZ, RPL, and JN collected data. MF, AO, RLC, PTR, RA, KPR, and VG participated in data analysis and interpretation of data. MF, AO, RLC, PTR drafted the manuscript. All authors critically revised and approved the manuscript before publication.

Declaration of interests

MF reports grants and personal fees from Stryker; grants from Navidea and AstraZeneca; and personal fees from Johnson and Johnson and Genentech, outside the submitted work. AO reports personal fees from, and holds intellectual property on, SurgicalPerformance, a surgical audit software; travel expenses from the OR Company; and is a consultant for Covidien, outside the submitted work. RLC reports grants from the National Institutes of Health, the Gateway Foundation, and the V Foundation, during the conduct of the study; grants and personal fees from AstraZeneca, Clovis, Genmab, Roche, and Janssen; grants from Merck; and personal fees from Tesaro, Medivation, Gamamab, Agenus, Regeneron, and OncoQuest, outside the submitted work. All other authors declare no competing interests.

Data sharing

De-identified individual participant data that underlie the results reported in this Article and the study protocol will be shared. Data will become available 9 months after publication until 36 months after publication. Data can be shared with investigators whose proposed use of the data has been approved by an independent review committee identified for this purpose. Data can be used for indiviudal participant data meta-analysis. Proposals can be submitted up to 36 months after publication. After 36 months, data will be available in our university's data repository but without investigator support other than deposited metadata.

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