LACC Trial: Final Analysis on Overall Survival Comparing Open Versus Minimally Invasive Radical Hysterectomy for Early-Stage Cervical Cancer

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ABSTRACT

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO *or elsewhere, for which the primary end point has already been reported.*

The aim of this study was to compare overall survival between open and minimally invasive radical hysterectomy with participants followed for 4.5 years. The primary objective was to evaluate whether minimally invasive surgery was noninferior in disease-free survival (DFS) to abdominal radical hysterectomy. Secondary outcomes included overall survival. Sample size was based on DFS of 90% at 4.5 years and 7.2% noninferiority margin for minimally invasive surgery. A total of 631 patients were enrolled: 319 assigned to minimally invasive and 312 to open surgery. Of these, 289 (90.6%) patients underwent minimally invasive surgery and 274 (87.8%) patients open surgery. At 4.5 years, DFS was 85.0% in the minimally invasive group and 96% in the open group (difference of −11.1; 95% CI, −15.8 to −6.3; $P = .95$ for noninferiority). Minimally invasive surgery was associated with lower rate of DFS compared with open surgery (hazard ratio [HR], 3.91 [95% CI, 2.02 to 7.58]; $P < .001$). Rate of overall survival at 4.5 years was 90.6% versus 96.2% for the minimally invasive and open surgery groups, respectively (HR for death of any cause = 2.71 [95% CI, 1.32 to 5.59]; $P = .007$). Given higher recurrence rate and worse overall survival with minimally invasive surgery, an open approach should be standard of care.

ACCOMPANYING CONTENT

Appendix

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INTRODUCTION

The current standard surgical approach for International Federation of Gynecology and Obstetrics (FIGO) 2018 stage IA2 to IB2 cervical cancer is open radical hysterectomy and lymph node staging.[1] A prospective noninferiority randomized trial (Laparoscopic Approach to Cervical Cancer [LACC]) evaluating open versus minimally invasive radical hysterectomy demonstrated the rate of disease-free survival (DFS) at 4.5 years was 86% with minimally invasive surgery and 96.5% with open surgery.[2] Similarly, in a population-based study by Melamed et al,[3] the authors found that minimally invasive radical hysterectomy was associated with shorter overall survival than open surgery among women with FIGO 2009 stage IA2 or IB1 cervical carcinoma.

The aim of this study was to report on the overall survival outcomes of the LACC trial after all eligible participants had completed follow-up at 4.5 years. In addition, we performed a prespecified subgroup analysis for tumor size, as well as an exploratory subgroup analysis for previous conization and rates of recurrence as carcinomatosis.

METHODS

Details of the LACC trial design, participants, procedures, and in-depth details on statistical analyses are provided in Appendix 1 (online only).

Outcomes

The primary outcome was DFS, defined as the time from random assignment to disease recurrence or death due to cervical cancer. Secondary outcomes included overall survival and patterns of recurrence. As per protocol, if recurrence was suspected, this was assessed using histologic and/or radiologic confirmation. An independent Recurrence Adjudication Committee reviewed all recurrences to ensure these were due to cervical cancer and to verify date and location of recurrence.

Statistical Analysis

Sample size was based on an expected DFS rate of 90% at 4.5 years and a 7.2% noninferiority margin for minimally invasive surgery. A total sample size of 740 participants gave 87% power to declare minimally invasive surgery to be noninferior to open surgery on the basis of a 4.5-year accrual and a 4.5-year follow-up period. Noninferiority would be declared if the lower bound of the 97.5% CI for the difference in disease-free survival percentages was >−7.2% (minimally invasive minus open surgery).

RESULTS

A total of 631 participants were enrolled. A total of 319 were assigned to minimally invasive surgery and 312 to open surgery (Appendix Fig A1). Baseline characteristics are shown in Table 1. There was no difference in postoperative adjuvant therapy, with rates of 28.8% in the minimally invasive group and 27.6% in the open surgery group. Rates of postoperative treatment remain unchanged from previously reported.[2]

The rate of DFS at 4.5 years was 85.0% in the minimally invasive group and 96% in the open surgery group (difference of −11.1 [95% CI, −15.8 to −6.3]; $P = .95$ for noninferiority; Fig 1). Minimally invasive surgery was associated with lower rate of DFS by almost 4 times compared with open surgery (hazard ratio [HR], 3.91 [95% CI: 2.02 to 7.58]; $P < .0001$), and a similar result was seen after adjustment for age, BMI, stage of disease, lymphovascular space invasion (LVSI), lymph node involvement, and Eastern Cooperative Oncology Group (ECOG) status (Appendix Table A1).

The rate of overall survival at 4.5 years was 90.6% versus 96.2% for the minimally invasive and open surgery groups, respectively (HR for death of any cause = 2.71 [95% CI, 1.32 to 5.59]; $P = .007$). A total of 22/28 deaths were due to cervical cancer in the minimally invasive group compared with 8/10 in the open surgery group, with a HR for disease-specific survival of 2.64 (95% CI, 1.18 to 5.93; $P = .02$).

A total of 48 participants developed a recurrence (37 in the minimally invasive group and 11 in the open surgery group). Rate of locoregional recurrence at 4.5 years was 4.9% versus 1.8% in the minimally invasive versus open surgery group (HR, 4.70 [95% CI, 1.95 to 11.37]; $P = .001$). On post hoc analyses, the rate of recurrence as carcinomatosis for open surgery was 9% (1/11) and for minimally invasive was 23% (8/35). On analysis per protocol, the rates were 0% (0/7) versus 26% (9/35) for open versus minimally invasive. Information on carcinomatosis at recurrence was not available for two patients.

In the prespecified subgroup analysis (Appendix Table A2) for tumor size, we were unable to test for interaction because of no DFS events in patients with <2 cm tumor size in the open surgery group. We can estimate the risk in the <2 cm group by using the

TABLE 1. Baseline Characteristics by Randomized Treatment

Eligible Patients	Open Surgery (n = 312)	Minimally Invasive Surgery (n = 319)
Mean age, years (SD)	46.0 (10.6)	46.1 (11.0)
Mean BMI, kg/m^2 (SD)	26.2 (5.3)	27.2 (5.6)
Histology, No. (%)		
Squamous cell carcinoma	210 (67)	214 (67)
Adenocarcinoma	80 (26)	87 (27)
Adenosquamous	6 (2)	9 (3)
Not documented	16 (5)	9 (3)
Stage of disease, No. (%)		
IA1 (LVSI)	5 (2)	5 (2)
IA2	20 (6)	21 (7)
IB1	287 (92)	293 (92)
ECOG, No. (%)		
0	289 (93)	292 (92)
1	23 (7)	27 (8)
Median days of hospital stay (Q1-Q3)[a]	5 (0-69)	3 (0-72)
Treatment received, No. (%)		
Open surgery	274 (88)	2 (1)
MIS	8 (3)	289 (91)
Withdrawn before surgery	19 (6)	12 (4)
Surgery abandoned	11 (4)	16 (5)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; LVSI, lymphovascular space invasion; MIS, minimally invasive surgery; SD, standard deviation.

[a]A zero length of stay denotes patients who withdrew before surgery, had surgery aborted, or were discharged the same day.

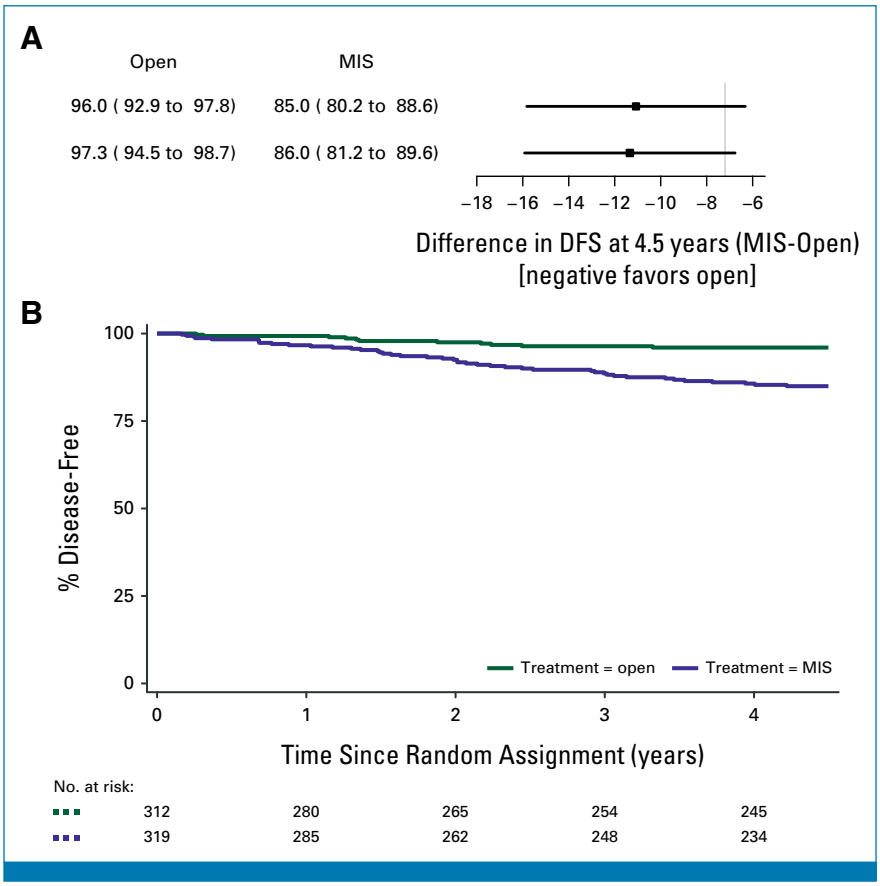

FIG 1. (A) Forest plot of the DFS at 4.5 years with boundaries of noninferiority. Minimally invasive surgery denotes both laparoscopic and robotic-assisted radical hysterectomy. The gray line represents the noninferiority margin of −7.2 percentage points. (B) Kaplan-Meier plot for DFS over 4.5 years by randomized treatment. DFS, disease-free survival; MIS, minimally invasive surgery.

fact that the risk of a rare event such as DFS is $2/(5 \times n)$,[4] in this case 99.5%. We compared this to the upper 95% CI for DFS at 4.5 years in the minimally invasive group (97.4%), which excludes 99.5%. This suggests a treatment effect, which is consistent with lower survival in the minimally invasive arm. For tumors ≥2 cm for DFS, a treatment effect of 4.25 was seen (95% CI, 1.73 to 10.4), favoring the open surgery arm.

For the subgroup analysis by previous conization, the effect of treatment differed between those who had a previous conization compared with those who did not (P-interaction = .042) for DFS. There was no difference between treatment groups in those who had a previous conization (HR, 1.27 [95% CI, 0.39 to 4.17]; P = .69), while in those participants who had not had a previous conization, minimally invasive surgery was associated with higher recurrence rate (HR, 5.85 [95% CI, 2.47 to 13.9]; P < .0001; Fig 2).

DISCUSSION

In this study, we found that overall survival at 4.5 years was 90.6% in minimally invasive compared with 96.2% in open surgery, with over 2.5 times higher risk of death due to cervical cancer in the minimally invasive group. In addition, rate of locoregional recurrence at 4.5 years was higher in the minimally invasive group. We also found that there was over a 4-fold effect in tumors ≥2 cm favoring open surgery for DFS. Finally, the rates of carcinomatosis were higher with the minimally invasive approach.

Nitecki et al[5] reported on the risk of recurrence and death associated with minimally invasive versus open radical hysterectomy for early-stage cervical cancer. A total of 9,499 patients were included (minimally invasive surgery, 4,684 [49%], and open surgery, 4,815 [51%]). The pooled hazard of recurrence or death was 71% higher among patients who underwent minimally invasive radical hysterectomy compared with those who underwent open surgery (HR, 1.71 [95% CI, 1.36 to 2.15]; P < .001). In addition, the hazard of death was 56% higher in the minimally invasive group (HR, 1.56 [95% CI, 1.16 to 2.11]; P = .004).

The SUCCOR study[6] found that patients who underwent minimally invasive surgery using a uterine manipulator had a 2.76 times higher hazard of relapse (HR, 2.76 [95% CI, 1.75 to 4.33]; P < .001) and those without had similar

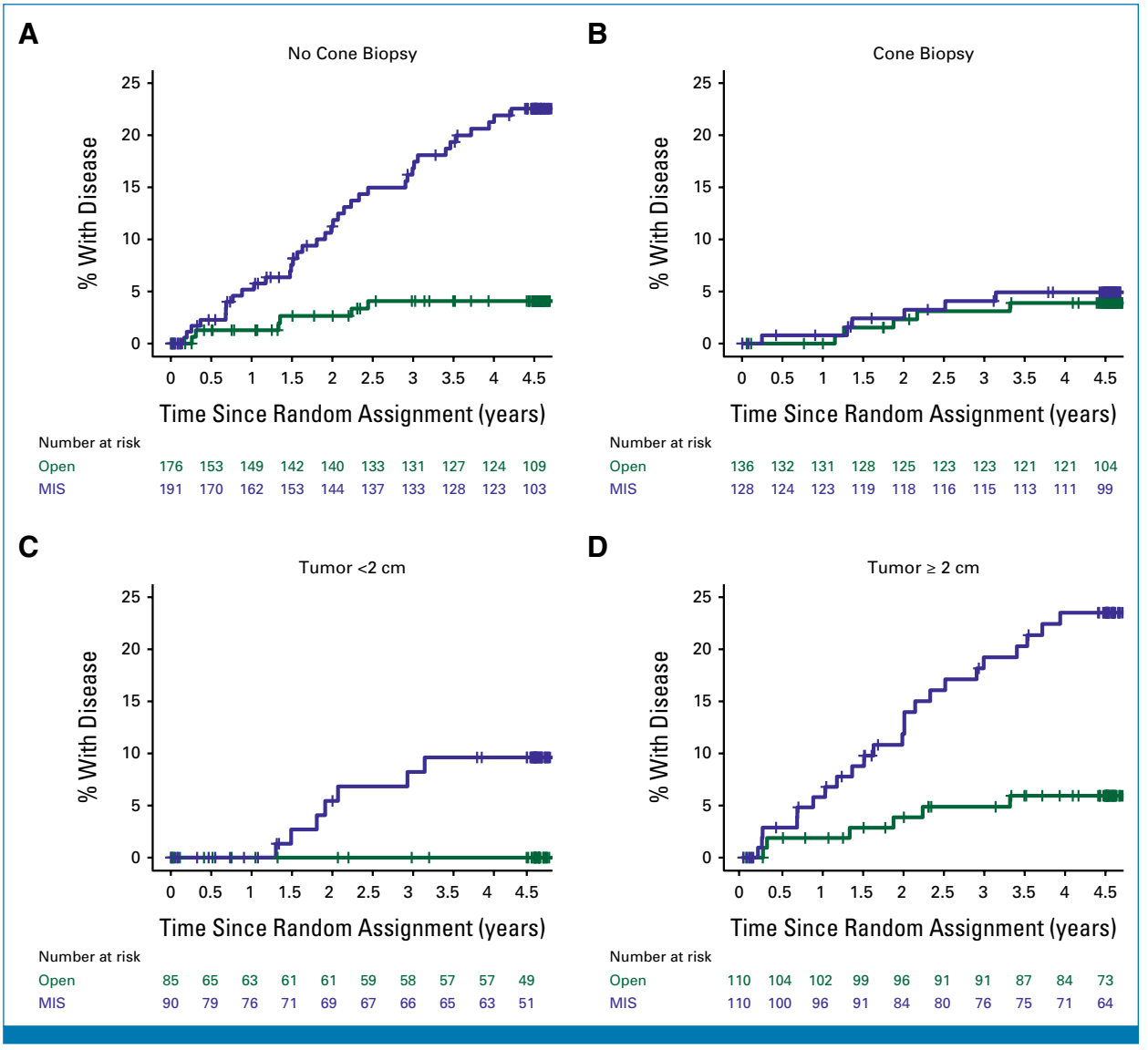

FIG 2. Survival on the basis of previous conization and tumor size (subgroup analysis). (A) In patients who had no previous conization, minimally invasive surgery was associated with higher recurrence rate (HR, 5.85 [95% CI, 2.47 to 13.9]; $P < .0001$). (B) There was no difference between treatment groups in those that had a previous conization (HR, 1.27 [95% CI, 0.39 to 4.17]; $P = .69$). (C) Risk in the <2 cm group by using risk of a rare event 2/(5 × n), in this case 99.5%. The upper 95% CI for DFS at 4.5 years in the minimally invasive group (97.4%), excludes 99.5%. Therefore the treatment effect supports lower survival in the minimally invasive arm. (D) For tumors ≥2 cm for DFS, the treatment effect was 4.25 (95% CI, 1.73 to 10.4), favoring the open surgery. DFS, disease-free survival; HR, hazard ratio; MIS, minimally invasive surgery.

DFS to the open surgery group (HR, 1.58 [95% CI, 0.79 to 3.15]; $P = .20$). From retrospective data, one may not discern if there is association without information on indications for or type of manipulator or documentation of uterine rupture.

Casarin et al[7] found that recurrence rates in patients who underwent previous conization were 1.1% compared with 16.1% for those who only had a cervical biopsy. In the SUCCOR CONE study,[8] the investigator found that risk of recurrence and death was reduced by 65% and 75%, respectively, in patients after cervical conization. These results should be interpreted with caution as it is not unexpected to register lower rates of recurrence in patients who had a cone as these patients generally are considered a lower risk group, as by definition, patients who undergo conization generally have microscopic disease.

In our study, rate of recurrence as carcinomatosis was 9% compared with 23% in open versus minimally invasive surgery. On per protocol analysis, rates were 0% compared with 26% for open versus minimally invasive surgery. In a systematic review and meta-analysis by Hoegl et al,[9] investigators assessed the incidence of peritoneal carcinomatosis in patients undergoing minimally invasive or open radical hysterectomy for early cervical cancer. A total of

7,626 patients were included. Peritoneal carcinomatosis represented 22.2% of recurrences with minimally invasive surgery compared with 8.8% with open surgery (odds ratio, 1.90 [95% CI, 1.32 to 2.74]; $P < .05$).

In conclusion, our analysis of overall survival at completion of follow-up at 4.5 years for the LACC trial showed that the rates of DFS and overall survival were worse for minimally invasive radical hysterectomy when compared with the open approach. In addition, we showed that rates of carcinomatosis as a manifestation of recurrence were higher in the minimally invasive group and that for patients without previous conization, minimally invasive surgery was also associated with higher recurrence rates. On the basis of these findings, patients undergoing radical hysterectomy for early cervical cancer should undergo open surgery as recommended by guidelines and minimally invasive radical hysterectomy should only be performed in clinical trials.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

Deidentified 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 individual 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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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

LACC Trial: Final Analysis on Overall Survival Comparing Open Versus Minimally Invasive Radical Hysterectomy for Early-Stage Cervical Cancer

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No other potential conflicts of interest were reported.

APPENDIX 1

Study Design

This study was a phase III, multicenter, randomized trial with the primary objective to evaluate the hypothesis that laparoscopic or robotic radical hysterectomy was noninferior to abdominal radical hysterectomy in proportion of participants disease-free at 4.5 years after surgery. Secondary objectives of the study included comparing the two groups with regard to recurrence rates and overall survival.

A total of 33 centers recruited participants, from five global regions. Each participating center required accreditation by the Trial Management Committee to ensure proper surgical technique during minimally invasive surgery. Participating centers submitted perioperative outcomes from a minimum of any 10 laparoscopic or robotic radical hysterectomies. Two unedited videos of any laparoscopic or robotic Type III radical hysterectomies were reviewed by the Trial Management Committee before surgeon accreditation. The protocol was approved by the scientific ethics committees of participating centers.[10]

Participants

Participants were eligible if they were age 18 years or older with histologically confirmed primary squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix of International Federation of Gynecology and Obstetrics (FIGO 2009) stages IA1 (lymph-vascular invasion), IA2, or IB1 (tumor ≤4 cm; no evidence of nodal involvement) disease; able to undergo a type II or III radical hysterectomy (Piver classification; Piver MS, et al: Obstet Gynecol 44:265-272, 1974); and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Exclusion criteria included uterine size larger than 12 cm, history of abdominal or pelvic radiotherapy, or metastatic disease by positron emission tomography–computed tomography, magnetic resonance imaging, or computed tomography. Participants were also excluded if unfit for surgery or unable to withstand lithotomy and steep Trendelenburg position.

Procedures

The technique for radical hysterectomy is described in the Study Treatment section of the protocol. Briefly, the open radical hysterectomy was performed either by a midline vertical incision or a low transverse incision. Lymph node assessment was performed to assure no suspicious nodes for metastatic disease; if so, these were sent for frozen section. In the event of metastatic disease, the procedure was abandoned after sampling para-aortic nodes. If lymph nodes were not deemed suspicious for disease, the radical hysterectomy was performed. Lymph node assessment was then performed by complete pelvic lymphadenectomy. For the minimally invasive approach, the same principles were applied. Of note, the trial did not require that surgeons perform a vaginal protective maneuver nor did it restrict use of a uterine manipulator. In addition, the trial did not require the centers to document whether a protective maneuver or uterine manipulator was used, as these were not considered predetermined predictors of outcome at time of study design. Adjuvant chemotherapy and/or radiotherapy was determined on the basis of Sedlis (Sedlis A, et al: Gynecol Oncol 73:177-183, 1999) or Peters criteria (Peters WA III, et al: J Clin Oncol 18:1606-1613, 2000). Surveillance visits were routinely performed every 3 months for the first 2 years and then every 6 months until 4.5 years.

Statistical Analysis

The sample size was based on an expected disease-free survival (DFS) rate of 90% at 4.5 years and a 7.2% noninferiority margin for minimally invasive surgery, reflecting an acceptable decline in expected survival of at most 8%. A total sample size of 740 participants gave 87% power to declare minimally invasive surgery to be noninferior to open surgery on the basis of a 4.5-year accrual, and a 4.5-year follow-up period. Noninferiority would be declared if the lower bound of the 97.5% CI for the difference in disease-free survival percentages was >−7.2% (minimally invasive minus open surgery). DFS rates at 4.5 years were estimated using the Kaplan-Meier method and confidence intervals for the primary end point were calculated using Greenwood's formula (Klien JP, et al: Survival analysis: techniques for censored and truncated data. New York, Springer, 2023:92) No transformations were used.

All analyses were performed on an intention-to-treat basis except for a sensitivity analysis performed according to per-protocol treatment. The prespecified statistical analysis plan was prepared before unblinding the original results to the Trial Management Committee. Survival curves were generated using the Kaplan-Meier method, and proportional hazards models were used to estimate the hazard ratios (HRs) and 95% CIs for the effect of treatment on disease-free survival, progression-free survival, and overall survival. The assumption of proportional hazards was tested by using the approach of Harrel and Lee (and assessed for all analyses reporting HRs; Harrell FE, Lee, KL: Verifying assumptions of the Cox proportional hazards model. SAS Institute 823-828, 1986). Competing-risks models on the basis of the method of Fine and Gray were used to analyze locoregional recurrence and disease-specific survival (Fine JP, et al: J Am Stat Assoc 94:496-509, 1999). A multivariable analysis for DFS was performed with adjustment for important baseline risk factors: age, BMI, stage of disease, depth of cervical invasion, lymphovascular space invasion (LVSI), lymph node involvement, and ECOG status. Subgroup analyses were performed by including an interaction term between subgroup and treatment in the relevant Cox regression model, for the outcome of DFS. Tumor size was a prespecified subgroup, while cone biopsy was exploratory. To estimate the risk of DFS when there are no events, the method of $2/(5 \times n)$ was used.[4] Unless otherwise stated, all analyses were performed using a two-sided significance level of 0.05 and conducted in SAS version 9.4 (SAS Institute Inc) or R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria). No adjustments were made to account for multiple testing or missing data. The trial was registered at ClinicalTrials.org under NCT00614211.

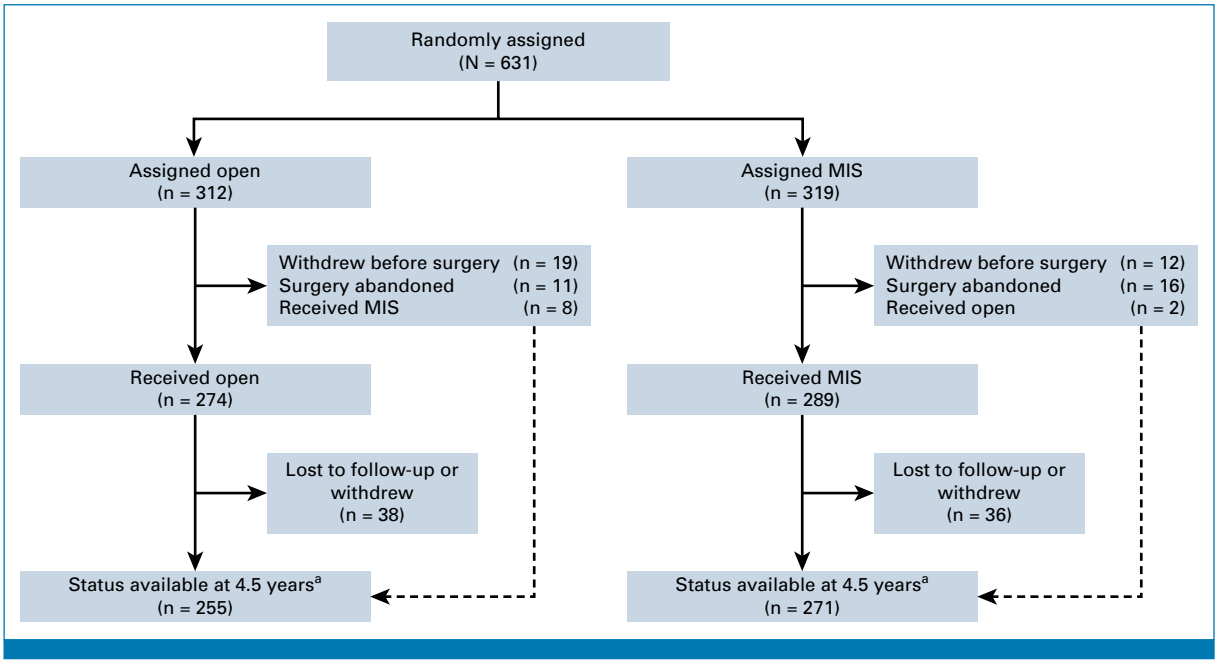

FIG A1. CONSORT diagram for the LACC trial. [a]Participants who were lost to follow-up or withdrawn were censored at date last known alive or recurrence-free, allowing all 631 participants randomly assigned to be included in the analyses. MIS, minimally invasive surgery.

TABLE A1. Results From Proportional Hazards Models for Outcomes

	Open Surgery		Minimally Invasive Surgery			
End Point	Events/No.	Rate at 4.5 years (95% CI)	Events/No.	Rate at 4.5 Years (95% CI)	Hazard Ratio (95% CI)	*P*
Disease-free survival	11/312	96.0 (92.9 to 97.8)	43/319	85.0 (80.2 to 88.6)	3.91 (2.02 to 7.58)	<.0001
Disease-free survival (adjusted[a])	6/199	96.8 (94.3 to 99.4)	31/211	84.3 (79.3 to 89.5)	5.43 (2.22 to 13.2)	.0002
Disease-free survival (adjusted[b])	11/282	95.8 (93.4 to 98.3)	43/295	84.5 (80.3 to 88.9)	4.06 (2.08 to 7.93)	<.0001
Progression-free survival	12/312	95.6 (93.3 to 98.1)	48/319	83.4 (79.3 to 87.8)	3.99 (2.12 to 7.51)	<.0001
Overall survival	10/312	96.2 (94.0 to 98.6)	28/319	90.6 (87.3 to 94.1)	2.71 (1.32 to 5.59)	.0067

Abbreviations: ECOG, Eastern Cooperative Oncology Group; LVSI, lymphovascular space invasion; MIS, minimally invasive surgery.
[a]Adjusted for age, BMI, stage of disease, depth of cervical invasion, LVSI, lymph node involvement, and ECOG status.
[b]Adjusted for age, BMI, stage of disease, LVSI, lymph node involvement, and ECOG status because of large amounts of missing data for depth of cervical invasion and tumor size.

TABLE A2. Subgroup Analyses for Disease-Free Survival

	Open Surgery		Minimally Invasive Surgery		Hazard Ratio	
	Events/No.	Rate at 4.5 years (95% CI)	Events/No.	Rate at 4.5 Years (95% CI)	(95% CI)	*P* interaction
Tumor size						NE
Missing tumor size	5/57	90.9 (83.6 to 98.8)	11/59	79.8 (69.9 to 91.3)	2.28 (0.79 to 6.57)	
No residual disease	0/60[a]	100.0 (100.0 to 100.0)	2/60	96.6 (92.1 to 100.0)	NE	
Tumor <2 cm	0/85[a]	100.0 (100.0 to 100.0)	7/90	90.4 (83.9 to 97.4)	NE	
Tumor ≥2 cm	6/110	94.1 (89.6 to 98.8)	23/110	76.5 (68.5 to 85.4)	4.25 (1.73 to 10.4)	
Cone biopsy						.042
No biopsy	6/176	95.9 (92.8 to 99.2)	37/191	77.5 (71.3 to 84.1)	5.85 (2.47 to 13.9)	
Cone biopsy	5/136	96.1 (92.8 to 99.5)	6/128	95.1 (91.3 to 99.0)	1.27 (0.39 to 4.17)	

Abbreviations: DFS, disease-free survival; MIS, minimally invasive surgery; NE, not estimable.

[a]Although no events were seen, this does not imply zero risk. The risk of a rare event such as disease-free survival is $2/(5 \times n)$, which in this case is 99.5%. The CI for disease-free survival at 4.5 in minimally invasive surgery arm is 97.4%, which excludes the probability of no event. This suggests a treatment effect, which is consistent with a lower disease-free survival in the minimally invasive arm.