GYNECOLOGY

Open vs minimally invasive radical trachelectomy in early-stage cervical cancer: International Radical Trachelectomy Assessment Study

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BACKGROUND: Minimally invasive radical trachelectomy has emerged as an alternative to open radical hysterectomy for patients with early-stage cervical cancer desiring future fertility. Recent data suggest worse oncologic outcomes after minimally invasive radical hysterectomy than after open radical hysterectomy in stage I cervical cancer.

OBJECTIVE: We aimed to compare 4.5-year disease-free survival after open vs minimally invasive radical trachelectomy.

STUDY DESIGN: This was a collaborative, international retrospective study (International Radical Trachelectomy Assessment Study) of patients treated during 2005–2017 at 18 centers in 12 countries. Eligible patients had squamous carcinoma, adenocarcinoma, or adenosquamous carcinoma; had a preoperative tumor size of ≤2 cm; and underwent open or minimally invasive (robotic or laparoscopic) radical trachelectomy with nodal assessment (pelvic lymphadenectomy and/or sentinel lymph node biopsy). The exclusion criteria included neoadjuvant chemotherapy or preoperative pelvic radiotherapy, previous lymphadenectomy or pelvic retroperitoneal surgery, pregnancy, stage IA1 disease with lymphovascular space invasion, aborted trachelectomy (conversion to radical hysterectomy), or vaginal approach. Surgical approach, indication, and adjuvant therapy regimen were at the discretion of the treating institution. A total of 715 patients were entered into the study database. However, 69 patients were excluded, leaving 646 in the analysis. Endpoints were the 4.5-year disease-free survival rate (primary), 4.5-year overall survival rate (secondary), and recurrence rate (secondary). Kaplan-Meier methods were used to estimate disease-free survival and overall survival. A post hoc weighted analysis was performed, comparing the recurrence rates between surgical approaches, with open surgery being considered as standard and minimally invasive surgery as experimental.

RESULTS: Of 646 patients, 358 underwent open surgery, and 288 underwent minimally invasive surgery. The median (range) patient age was 32 (20–42) years for open surgery vs 31 (18–45) years for minimally invasive surgery (P=.11). Median (range) pathologic tumor size was 15 (0–31) mm for open surgery and 12 (0.8–40) mm for minimally invasive surgery (P=.33). The rates of pelvic nodal involvement were 5.3% (19 of 358 patients) for open surgery and 4.9% (14 of 288 patients) for minimally invasive surgery (P=.81). Median (range) follow-up time was 5.5 (0.20–16.70) years for open surgery and 3.1 years (0.02–11.10) years for minimally invasive surgery (P<.001). At 4.5 years, 17 of 358 patients (4.7%) with open surgery and 18 of 288 patients (6.2%) with minimally invasive surgery had recurrence (P=.40). The 4.5-year disease-free survival rates were 94.3% (95% confidence interval, 91.6–97.0) for open surgery and 91.5% (95% confidence interval, 87.6–95.6) for minimally invasive surgery (log-rank P=.37). Post hoc propensity score analysis of recurrence risk showed no difference between surgical approaches (P=.42). At 4.5 years, there were 6 disease-related deaths (open surgery, 3; minimally invasive surgery, 3) (log-rank P=.49). The 4.5-year overall survival rates were 99.2% (95% confidence interval, 97.6–99.7) for open surgery and 99.0% (95% confidence interval, 79.0–99.8) for minimally invasive surgery.

CONCLUSION: The 4.5-year disease-free survival rates did not differ between open radical trachelectomy and minimally invasive radical trachelectomy. However, recurrence rates in each group were low. Ongoing prospective studies of conservative management of early-stage cervical cancer may help guide future management.

Key words: disease-free survival, fertility, hysterectomy, laparoscopy, minimally invasive surgical procedures, recurrence, retrospective studies, robotic surgical procedures, trachelectomy, uterine cervical neoplasms

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Introduction

Radical hysterectomy with pelvic lymphadenectomy is the standard treatment for early-stage cervical cancer. However, radical trachelectomy has emerged as an alternative to radical hysterectomy in patients with early-stage disease who wish to preserve fertility.[1] In 2011, minimally invasive radical trachelectomy became more common than open trachelectomy.[2]

A randomized noninferiority trial comparing open vs minimally invasive radical hysterectomy showed that the minimally invasive approach was associated with lower rates of disease-free survival (DFS) and overall survival (OS).[3] Subsequent studies confirmed the

AJOG at a Glance

Why was this study conducted?

A randomized prospective trial has demonstrated worse disease-free survival (DFS) in patients undergoing minimally invasive radical hysterectomy. Whether there is a difference in DFS or overall survival (OS) between open and minimally invasive radical trachelectomy for patients with early-stage cervical cancer (≤2 cm) has not been established.

Key findings

There was no difference in the rates of disease recurrence, 4.5-year DFS, or OS between open radical trachelectomy and minimally invasive radical trachelectomy.

What does this add to what is known?

Based on this large multicenter retrospective study, surgical approach (minimally invasive vs open) for radical trachelectomy in patients with early-stage cervical cancer (≤2 cm) may not affect oncologic outcomes.

findings from that trial.[4–6] The unanticipated results of the Laparoscopic Approach to Cervical Carcinoma (LACC) trial[3] raised concern regarding the oncologic safety of minimally invasive radical trachelectomy. Given the limited number of patients who were candidates for radical trachelectomy and the low recurrence rate, a randomized controlled trial comparing open surgery with minimally invasive surgery (MIS) was unlikely. Therefore, we performed an international retrospective study comparing 4.5-year DFS rates in patients with preoperative early-stage cervical cancer (≤2 cm) who underwent open vs minimally invasive radical trachelectomy.

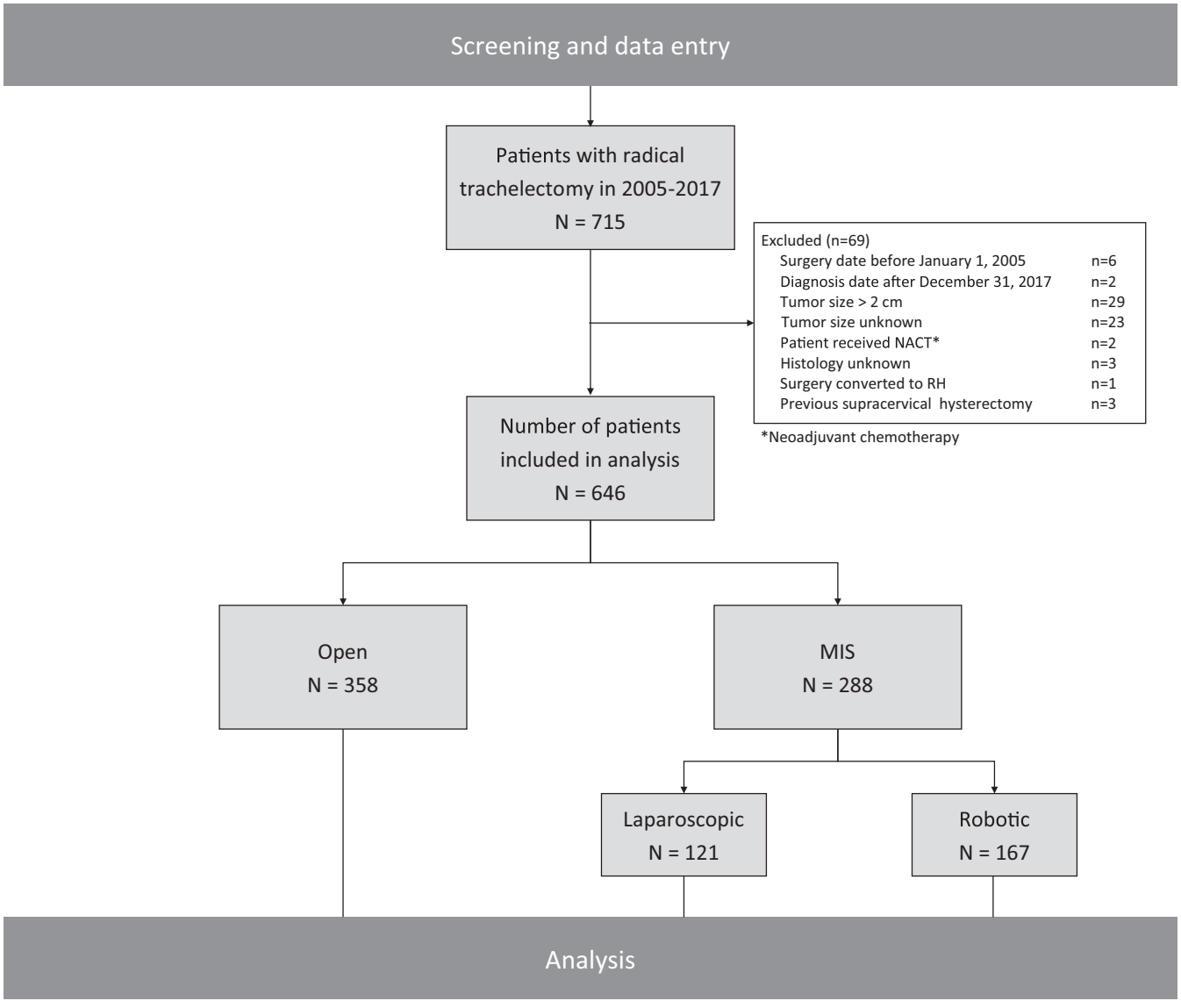
Materials and Methods

After obtaining approval from each center's institutional review board, we obtained data from 18 centers in 12 countries on all patients with early-stage cervical cancer who underwent open or minimally invasive (robotic or laparoscopic) radical trachelectomy. Eligible patients had squamous carcinoma, adenocarcinoma, or adenosquamous carcinoma; had a preoperative tumor size of ≤2 cm (via physical examination, imaging, or pathology assessment); and underwent radical trachelectomy with nodal assessment (pelvic lymphadenectomy and/or sentinel lymph node biopsy) during 2005−2017. The exclusion criteria included neoadjuvant chemotherapy or preoperative pelvic radiotherapy, previous lymphadenectomy or pelvic retroperitoneal surgery, pregnancy, stage IA1 disease with lymphovascular space invasion, aborted trachelectomy (conversion to radical hysterectomy), or vaginal approach. Surgical approach, indication, and adjuvant therapy regimen were at the discretion of the treating institution. Written informed consent was waived because the data were deidentified. The study design was previously published.[7]

Patient characteristics were summarized using descriptive statistics. Categorical variables were compared using the chi-square or the Fisher exact test; continuous variables were compared using the Wilcoxon rank-sum test. Preoperative tumor size was categorized as <1 cm and 1 to 2 cm using tumor size reported at conization, tumor size on imaging if conization was not performed or tumor size was not reported at conization, or tumor size on physical examination if tumor size from conization or imaging was not available. DFS was measured from the radical trachelectomy date until the date of first recurrence or death from any cause. Patients were censored at the date of the last clinic visit when they were known to be disease-free. An evaluation of DFS and recurrence rates at 4.5 years was performed as defined in the LACC trial.[3] OS was measured from the diagnosis date until death. Patients were censored at their last contact date. Kaplan-Meier methods were used to estimate DFS and OS. Survival distributions were compared using the log-rank test. The proportion of patients with recurrence was calculated for each group (open surgery vs MIS), and associations were tested using the chi-square or the Fisher exact test. The methods of Gooley et al[8] were used to estimate the cumulative incidence of disease recurrence (with 95% confidence interval [CI]) as a function of the surgical method with noncervical cancer death as a competing risk. The methods of Fine and Gray[9] were used to compare the 2 groups concerning a cumulative incidence of recurrence. Exploratory analyses in subsets of patients investigated possible associations among variables using proportions and logistic regression modeling when possible and recurrence and survival endpoints using Kaplan-Meier methods. Given the low number of events, a multivariable proportional-hazards model for DFS and overall survival (OS) could not be performed. Separate Cochran-Mantel-Haenszel tests were used to test the association of surgical approach and recurrence between the groups while adjusting for variables. Except for the primary endpoint, DFS, all testing methods were 2-sided using α=0.05. A 2-sided test with α=0.10 was used for DFS. Missing data were ignored when completing the analyses, but the impact on the primary analyses was minimal because of the low number of missing data. All patients had information regarding survival endpoints. Furthermore, when examining recurrence adjusting for propensity scores, only 33 of 646 patients (5%) had missing data when calculating the propensity scores. Therefore, bias owing to casewise deletion should be minimal.

Previous studies have shown that recurrence rates in the open surgery group range from 3.8% to 7.6%. If the 4.5-year disease-free survival rate for patients who underwent open surgery was 92.4%, we had 80% power to detect a 0.53 hazard ratio using a 2-sided test with α=0.10.

FIGURE 1
CONSORT diagram



CONSORT, Consolidated Standards of Reporting Trials; *MIS*, minimally invasive surgery; *RH*, radical hysterectomy.

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This corresponds to an 86.1% DFS rate at 4.5 years in the MIS group. An estimated 845 patients would need to be included in this study: 456 open surgery and 389 MIS. This power calculation was performed with PASS 13 (Power Analysis and Sample Size Software [2014]; NCSS, LLC, Kaysville, UT; ncss.com/software/pass).

A post hoc weighted analysis was performed to compare the recurrence rates between the surgical approaches. Propensity score methods were used to assign weights to each observation with adjustment for body mass index, International Federation of Gynecology and Obstetrics (FIGO)-defined stage, tumor size, preoperative cone biopsy, and preoperative histologic type. Open surgery was considered standard, and MIS was considered experimental. The risk of recurrence and 95% CI were estimated. This report summarized the data collected through July 12, 2020. Statistical significance was defined as $P<.05$. Statistical analyses were completed using SAS (version 9.4; SAS Institute Inc, Cary, NC) and R (version 3.6.1; R Core Team [2019]; R Foundation for Statistical Computing, Vienna Austria).

Results

The study included 646 patients, 358 with open surgery and 288 with MIS (121 laparoscopic; 167 robotic) (Figure 1). The median age was 32 years in the open surgery group and 31 years in the MIS group. Moreover, 549 of 646

TABLE 1
Demographic, clinical, and tumor characteristics and perioperative outcomes

Characteristic	Number of patients		
	Open surgery (n=358)	Minimally invasive surgery (n=288)	*P* value
Age (y)	32.0 (20.0–42.0)	31.0 (18.0–45.0)	.11
BMI (kg/m^2)	21.8 (16.0–36.6)	23.5 (16.1–48.4)	<.001
FIGO 2009 stage			.54
IA2	51 (14.2)	46 (16.0)	
IB1	307 (85.8)	242 (84.0)	
Preoperative tumor size (cm)			.54
<1	137 (38.3)	117 (40.6)	
1–2	221 (61.7)	171 (59.4)	
Cone biopsy	217 (60.6)	229 (79.5)	<.001
Preoperative histologic type			.01
Squamous carcinoma	234 (65.4)	168 (58.3)	
Adenocarcinoma	108 (30.2)	115 (39.9)	
Adenosquamous carcinoma	16 (4.5)	5 (1.7)	
Preoperative grade			.02
I	36 (10.1)	32 (11.1)	
II	80 (22.3)	99 (34.4)	
III	58 (16.2)	35 (12.2)	
Unknown or not reported	184 (51.4)	122 (42.4)	
Surgical time (min)	171 (50–425)	262 (120–472)	<.001
Estimated blood loss (mL)	200 (50–4500)	50 (0–3000)	<.001
Nodal assessment			<.001
Pelvic lymphadenectomy only	267 (74.6)	163 (56.6)	
SLN only	17 (4.7)	28 (9.7)	
SLN and pelvic lymphadenectomy	74 (20.7)	97 (33.7)	
Number of nodes removed	17 (2–63)	18 (2–65)	.79
Length of stay (d)	6 (1–23)	2 (0–24)	<.001
Readmission	7 (2.0)	28 (9.7)	<.001
Reoperation	6 (1.7)	10 (3.5)	.14

Data are presented as median (interquartile range) or number (percentage), unless otherwise indicated.

BMI, body mass index; *FIGO*, International Federation of Gynecology and Obstetrics; *SLN*, sentinel lymph node.
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patients (85.0%) had FIGO 2009 stage IB1 disease (Table 1). Residual disease was present in the final specimen in 204 patients (57%) with open surgery and 118 patients (41%) with MIS (*P*<.001) (Table 2).

Median follow-up time was 5.5 (0.20–16.70) years for open surgery and 3.1 (0.02–11.10) years for MIS (*P*<.001). Rates of adjuvant treatment in the open surgery and MIS groups were 13% and 5%, respectively (*P*<.001). The odds of adjuvant treatment did not differ by tumor size (Breslow-Day, *P*=.88). At 4.5 years, 4.7% of patients with open surgery and 6.2% with MIS had recurrence (*P*=.40). (Supplemental Table 1). DFS did not differ between surgical approaches (log-rank *P*=.31). Recurrence rates did not differ between robotic surgery (9 of 167 patients [5.4%]) and laparoscopy (9 of 121 patients [7.4%]) (*P*=.48). The 4.5-year DFS rates were 94.3% (95% CI, 91.6–97.0) for open surgery and 91.5% (95% CI, 87.6–95.6) for MIS (log-rank *P*=.37) (Figure 2, A).

On univariate analysis, factors associated with recurrence regardless of surgical approach were lack of cone biopsy, preoperative visible lesion, FIGO 2009 stage IB1 disease, lymphovascular space invasion, and adenosquamous carcinoma (Supplemental Table 2). Patients with adenosquamous carcinoma had worse DFS overall (*P*=.02) (Figure 3, A) but not OS (*P*=.58) (Figure 3, B). In stratified analysis, surgical approach remained not associated with recurrence (Figure 4). Because of unbalanced groups, a post hoc propensity score analysis to assess the risk of recurrence by surgery type was performed. It showed no differences in recurrence by approach (*P*=.42), but this should be interpreted with caution because the propensity score analysis failed to completely control for preoperative grade, nodal assessment, pathologic histology, and continent of site.

Of patients who had a cone biopsy, 146 (67.6%) in the open surgery cohort did not have residual disease in the final pathology report. In the MIS cohort, 162 (72.3%) did not have residual disease. Because it pertains to outcomes based on whether patients underwent a previous conization and association with surgical approach, the Breslow-Day test did not indicate an interaction effect (*P*=.11), but the study was underpowered to detect such a difference. However, recurrence by surgical type varied differentially when each cervical conization stratum was evaluated separately. Specifically, the odds ratio and 95% CI for recurrence among patients who did not have a cone biopsy was 3.0 (95% CI, 1.2–7.3; *P*=.011) and it was 0.9 (95% CI, 0.3–3.0; *P*=.995) among patients who did have a cone biopsy.

At 4.5 years, there were 6 disease-related deaths (open surgery, 3; MIS, 3)

TABLE 2
Histopathologic findings, adjuvant treatment, and recurrences

Characteristic	Number of patients		*P* value
	Open surgery (n=358)	Minimally invasive surgery (n=288)	
Histologic type			<.001
No residual disease[a]	150 (42.0)	165 (57.3)	
Squamous carcinoma	138 (38.5)	61 (21.2)	
Adenocarcinoma	58 (16.2)	53 (18.4)	
Adenosquamous carcinoma	8 (2.2)	4 (1.4)	
Not reported	4 (1.1)	5 (1.7)	
Tumor size (mm)[b]	15 (10.00–18.00)	12 (0.89–17.00)	.33
Tumor size (cm)[b]			.02
<1	55 (27.00)	42 (35.6)	
1–2	124 (60.8)	49 (41.5)	
Not reported	25 (12.2)	27 (22.9)	
Grade[b]			<.001
I	31 (15.2)	14 (11.8)	
II	58 (28.4)	54 (45.8)	
III	65 (31.9)	19 (16.1)	
Unknown or not reported	50 (24.5)	31 (26.3)	
LVSI[b]			.40
Yes	43 (21.1)	28 (23.7)	
No	144 (70.6)	74 (62.7)	
Not reported	17 (8.3)	16 (13.6)	
Depth of invasion (mm)[b]			.06
<10	85 (41.7)	91 (77.1)	
≥10	16 (7.8)	7 (5.9)	
Not reported or unknown	103 (50.5)	20 (17.0)	
Pelvic nodal involvement	19 (5.3)	14 (4.9)	.81
Adjuvant treatment[c]			<.001
Yes	46 (12.9)	15 (5.2)	
No	310 (86.6)	273 (94.8)	
Not reported or unknown	2 (0.6)	0 (0.0)	
Follow-up time (y)	5.5 (3.40–8.30)	3.1 (2.0–4.80)	<.001
Recurrence	17 (4.7)	18 (6.3)	.40
Time to recurrence (range)[d]	0.3–3.0	0.3–3.6	.34
Location of recurrence			.27
Local	15	13	
Regional	1	0	
Distant	0	1	
Local and regional	1	4	

Data are presented as number (percentage) or median (interquartile range), unless otherwise indicated.

LVSI, lymphovascular space invasion.

[a] No residual disease after conization or initial biopsy; [b] Only patients with residual disease in the final pathology (204 with open surgery and 118 with minimally invasive surgery); [c] Radiation therapy, chemotherapy, chemoradiation, and/or brachytherapy; [d] For current number of events, the median time to recurrence could not be estimated.

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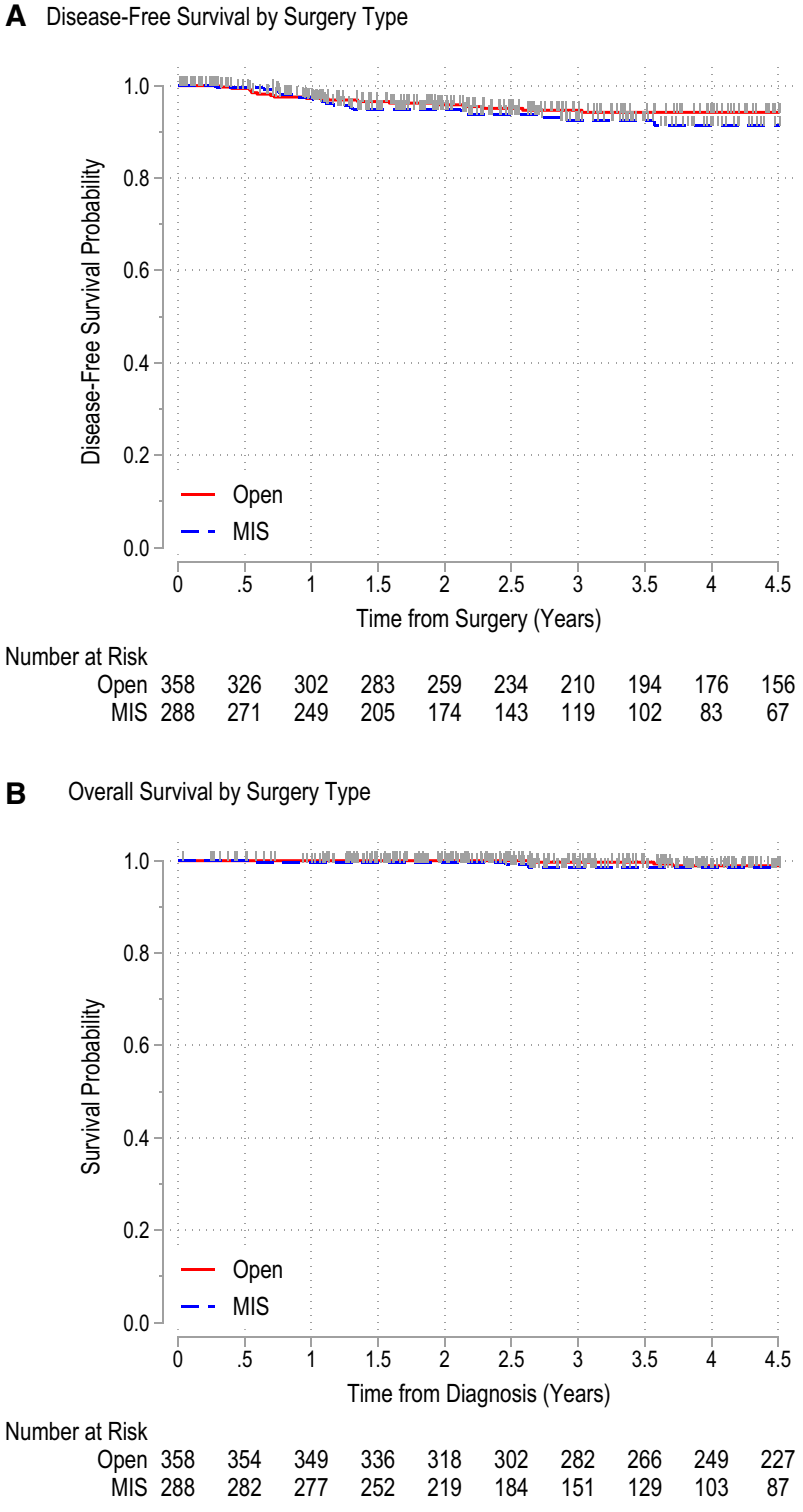
FIGURE 2
Kaplan-Meier estimates of DFS and OS



The graphs show the (**A**) DFS and (**B**) OS by type of surgery in patients with early-stage cervical cancer (≤2 cm) who underwent open radical trachelectomy or minimally invasive radical trachelectomy.

DFS, disease-free survival; *MIS*, minimally invasive surgery; *OS*, overall survival.

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(log-rank *P*=.49). The 4.5-year OS rates were 99.2% (95% CI, 97.6–99.8) for open surgery and 99.0% (95% CI, 97.0–99.8) for MIS (log-rank *P*=.49) (Figure 2, B).

Comment

Principal findings

In this multicenter retrospective study, we found no difference in the 4.5-year DFS rates between open radical trachelectomy and minimally invasive radical trachelectomy, even after adjusting for potential confounding variables because of unbalanced groups. Furthermore, we found no difference in the OS rates or recurrence rates between the open surgery and MIS groups. Risk factors for relapse were more common in the open surgery group, but oncologic outcomes were similar for the open and minimally invasive approaches.

Results in context of what is known

A retrospective National Cancer Database study[2] of 246 patients with early-stage cervical cancer who underwent open radical trachelectomy (102 patients) or minimally invasive radical trachelectomy (144 patients) found 4-year OS rates of 92.3% for open surgery and 95.7% for MIS. With median follow-up times of 40 months for open surgery and 37 months for MIS, there were 11 deaths (5.3%) (open surgery, 7 [7.6%]; MIS, 4 [3.5%]) (*P*=.25). The authors acknowledged that the effects of MIS on survival remained unknown as the oncologic outcome was not the primary endpoint of the study.

A recent systematic review[10] included 1075 patients with early-stage cervical cancer who underwent open radical trachelectomy (955) or laparoscopic (120) radical trachelectomy. With median (range) follow-up times of 38 months for open surgery and 25 months for laparoscopic surgery, the authors found recurrence rates of 3% and 0%, respectively. The 5-year relapse-free survival rate was 96.3% for open surgery and not reported for laparoscopy. The 5-year OS rate was 98.6% for open surgery and not reported for

laparoscopy. The authors concluded that a particular approach could not be recommended, but overall oncologic outcomes were favorable.

In addition, the following 3 prospective studies are evaluating oncologic results in patients with a tumor size of ≤2 cm undergoing conization or simple hysterectomy: Conservative Surgery for Women with Cervical Cancer trial,[11] Radical versus simple hysterectomy and pelvic node dissection with low-risk early stage cervical cancer (SHAPE) (NCT01658930) and Gynecologic Oncology Group-278 trial (ClinicalTrials.gov Identifier: NCT01649089). The results will hopefully shed light on whether conservative surgery is sufficient for patients with low-risk disease and could render radical trachelectomy obsolete in such patients.

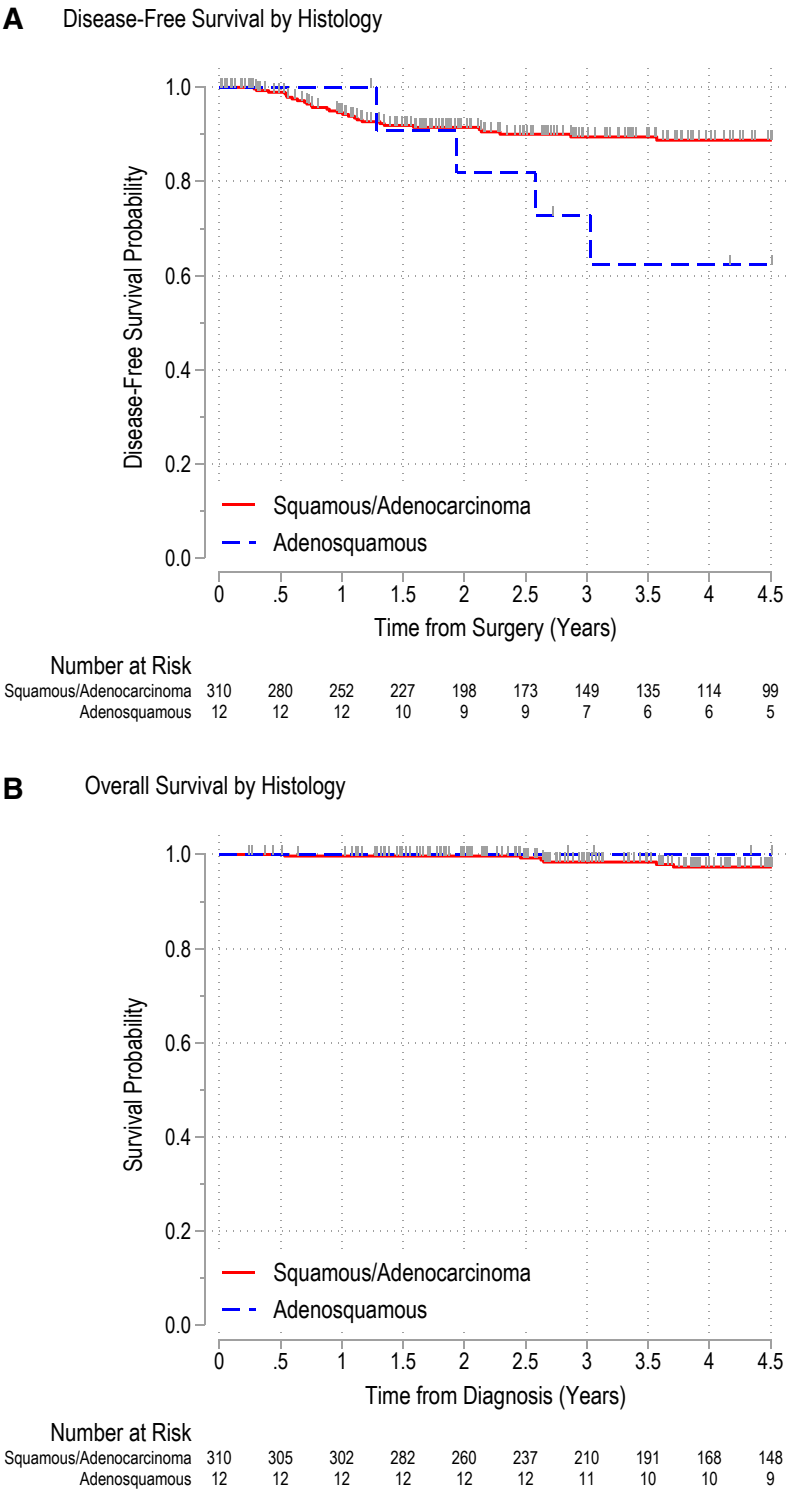
Clinical implications

Our results demonstrating no difference in recurrence rate, DFS, and OS between open and minimally invasive radical trachelectomy provided grounds for discussion and counseling patients with early cervical cancer who wish to preserve future fertility. However, it should be highlighted that this finding may reflect the small number of recurrences in each group and this study limitation should be integrated into such discussions. The ongoing prospective studies of conservative management in patients with small tumors (≤2 cm) will add valuable information on the best management of low-risk cervical cancer.

Research implications

Future research studies should explore comparisons of oncologic outcomes between the open approach and minimally invasive approach and radical trachelectomy in patients with grossly visible tumors vs those with microscopic disease. Similarly, there remains a gap in knowledge on whether histologic subtypes might impact recurrence rates and survival based on the surgical approach. Lastly, there were unanswered questions regarding equivalency comparison between laparoscopic or robotic surgery and radical trachelectomy.

FIGURE 3
Kaplan-Meier estimates of DFS and OS



The graphs show the (**A**) DFS and (**B**) OS by histologic type in patients with early-stage cervical cancer (≤2 cm) who underwent open radical trachelectomy or minimally invasive radical trachelectomy.

DFS, disease-free survival; *OS*, overall survival.

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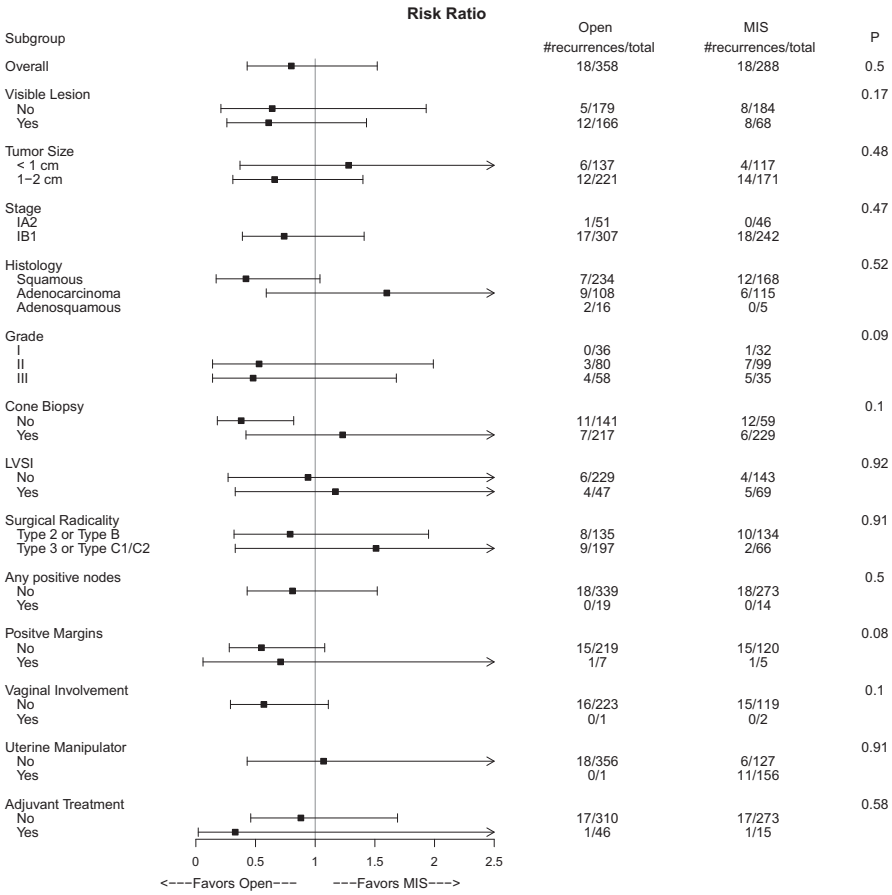
FIGURE 4
Forest plot displaying RRs and 95% CIs



The forest plot displays the RRs and 95% CIs for recurrence by surgical approach adjusted by subgroups defined by tumor characteristics, surgical procedures, and whether or not the patient received adjuvant treatment. *P* values reflect the statistical significance of the association of recurrence and surgical approach adjusted by subgroup.

CI, confidence interval; *RR*, risk ratio.

Strengths and limitations

Our study had several strengths, including a large sample of radical trachelectomy. All centers that participated performed radical hysterectomy in addition to trachelectomy, confirming proficiency in radical pelvic surgery. A data dictionary was available for each variable to reduce differences in interpretation. The database was periodically monitored by the Study Management Committee to find missing or incorrect values, and for 10% of the patients entered per site, source documents were reviewed. Limitations of the study included its retrospective nature, which made the study prone to bias in patient selection and choice of surgical approach. Although the largest sample size reported was included, the number of patients might have been limited considering that recurrences in this population were low. In addition, the results of our study may have not reflected outcomes in low-volume centers. In addition, here, we have not included details on intraoperative or postoperative complications as this information will be submitted as a separate article. Moreover, 1 potential concern when evaluating open surgery vs MIS for any procedure was that with the increasing trend in MIS, comparisons have often been flawed by a sequential pattern and cases could not be concurrently evaluated: in other words, an "old vs new practice" comparison. To that end, we evaluated this principle and demonstrated the following: our study collection time was 2005−2017. From 2005 to 2011, most cases were by open surgery, as shown in the Supplemental Figure; however, from 2012 to 2017, given the fact that many institutions did not change their approach to MIS and continued to perform radical trachelectomy by laparotomy, we noted balanced rates of open surgery vs MIS over the last 6 years of the study. Supplemental Table 3 demonstrates the distribution of surgical approach by center. In addition, ideally, one could perform a comparison of recurrences or similar oncologic outcomes among continents. However, given the small frequencies of events of recurrence in this group of patients, it would be difficult to draw an adequate statistical analysis with such a small number of patients once these are separated by continents. The issue of surgical volume per center has been previously explored. In a study by Matsuo et al,[12] the authors evaluated data from 89 centers that performed 815 trachelectomies and noted that 76.4% of the centers had a surgical volume of 1 procedure per year and only 6.7% of centers performed ≥2.5 trachelectomies per year. Based on these data, it was difficult to categorize any center as a "high-volume" center.

Conclusion

Here, in patients with early-stage cervical cancer (≤2 cm), the surgical approach for radical trachelectomy had no impact on oncologic outcomes. However, in this very select group of patients, recurrence rates were low. Patients with cervical cancer in this low-risk group (≤2 cm) may benefit from less radical surgery. ■

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Supplemental online content

This appendix has been provided by the authors to give readers additional information about their work.

Study Management Committee

The Study Management Committee consisted of the following investigators: Gloria Salvo, MD; Pedro T. Ramirez, MD; and Rene Pareja, MD.

Data entrance and monitoring

Each participating site was invited by the Study Management Committee and was asked to include at least 15 cases (either their first 15 cases or subsequent cases) performed by an open surgery approach, minimally invasive surgery approach, or both. We included centers that had performed at least 15 cases with the aim of excluding those centers whose outcomes reflected their initial learning curve. This goal would assure that we included centers with higher level of expertise.

After each site obtained institutional review board approval, it was provided access to a Research Electronic Data Capture database[1] maintained by The University of Texas MD Anderson Cancer Center. Participating sites were responsible for entering patient data from their institutions. Data monitoring was assessed by auditing all participating sites by random selection of 10% of patients entered in the database per site. Each site was asked for all source documents pertaining to selected patients. Data monitoring was performed by the Study Management Committee, which was responsible for checking the accuracy, completeness, and credibility of all data and their compliance with the protocol.

Supplementary References

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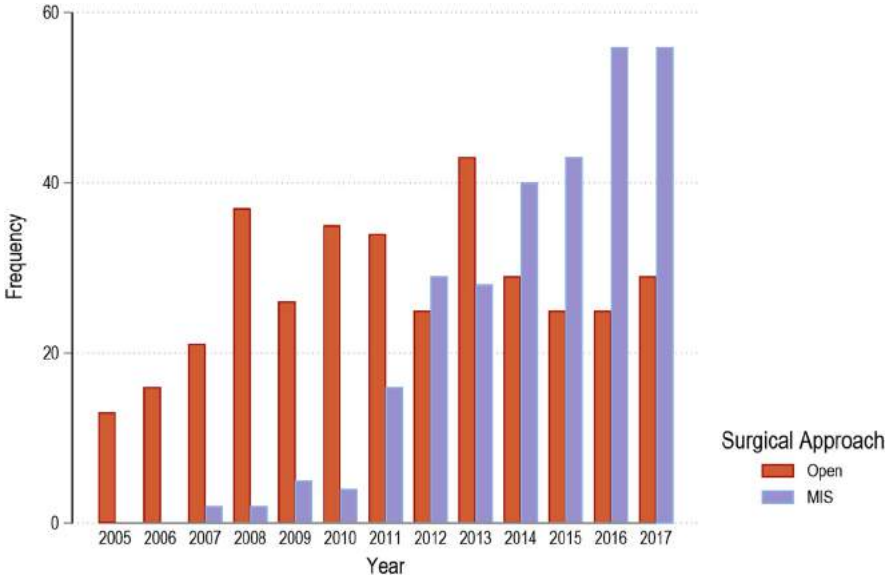
SUPPLEMENTAL FIGURE

Surgical approaches per year



MIS, minimally invasive surgery.

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SUPPLEMENTAL TABLE 1
Characteristics of patients with recurrent disease

Surgical approach	Age (y)	FIGO stage	Preoperative tumor size (categorized) (cm)	Final pathology						Adjuvant therapy	DFS time (y)
				Histology	Tumor size (cm)	Grade	Parametrial involvement	LVSI	Positive nodes		
MIS	22	IB1	1–2	Squamous	—	III	No	No	No	No	1
MIS	22	IB1	1–2	Squamous	—	II	No	No	No	No	0.8
MIS	39	IB1	<1	Adenocarcinoma	<1	III	Unknown	No	No	No	1.2
MIS	34	IB1	<1	Squamous	<1	II	No	No	No	No	2.9
MIS	34	IB1	1–2	Squamous	—	III	No	No	No	No	2.1
MIS	29	IB1	1–2	Squamous	1–2	III	No	No	No	No	1.1
MIS	31	IB1	1–2	Adenocarcinoma[a]	No residual disease	I[a]	No	Unknown	No	No	2.2
MIS	33	IB1	1–2	Squamous	1–2	II	No	No	No	No	1.3
MIS	31	IB1	1–2	Squamous	1–2	II	No	No	No	No	0.9
MIS	26	IB1	1–2	Squamous[a]	No residual disease	III[a]	No	Unknown	No	No	2.7
MIS	36	IB1	1–2	Squamous	<1	II	No	No	No	No	0.8
MIS	25	IB1	1–2	Adenocarcinoma	—	II	No	Yes	No	No	0.6
MIS	37	IB1	1–2	Adenocarcinoma	1–2	II	No	Yes	No	No	1.3
MIS	26	IB1	<1	Adenocarcinoma	—	III	No	Yes	No	No	1.1
MIS	41	IB1	1–2	Adenocarcinoma	—	I	No	Unknown	No	No	3.6
MIS	40	IB1	<1	Adenocarcinoma	<1	II	No	No	No	No	0.7
MIS	31	IB1	1–2	Squamous	1–2	II	No	No	No	No	0.9
MIS	22	IB1	1–2	Squamous	—	Unknown	No	No	No	No	0.3
Open	41	IB1	1–2	Adenocarcinoma	—	II	No	No	No	No	0.5
Open	29	IB1	1–2	Adenocarcinoma	1–2	II	No	No	No	No	0.6
Open	26	IB1	< 1	Adenocarcinoma	<1	III	No	No	No	No	0.3
Open	37	IB1	1–2	Adenocarcinoma	1–2	I	No	No	No	No	0.7
Open	29	IB1	1–2	Adenocarcinoma	1–2	I	No	Unknown	No	No	1.9
Open	29	IB1	1–2	Adenocarcinoma	1–2	Unknown	No	Unknown	No	No	0.6
Open	24	IB1	1–2	Squamous	—	III	No	Yes	No	No	1.1
Open	27	IB1	<	Adenocarcinoma	<1	Unknown	No	No	No	No	2.1
Open	33	IB1	1–2	Squamous	1–2	III	No	No	No	No	0.5

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(continued)

SUPPLEMENTAL TABLE 1
Characteristics of patients with recurrent disease *(continued)*

Surgical approach	Age (y)	FIGO stage	Preoperative tumor size (categorized) (cm)	Final pathology						Adjuvant therapy	DFS time (y)
				Histology	Tumor size (cm)	Grade	Parametrial involvement	LVSI	Positive nodes		
Open	33	IB1	1–2	Squamous	1–2	I	No	Yes	No	No	1
Open	30	IB1	1–2	Adenocarcinoma	1–2	III	No	No	No	No	3
Open	30	IB1	1–2	Squamous	1–2	III	No	Yes	No	No	1.6
Open	32	IB1	<1	Squamous	1–2	III	No	No	No	No	2.3
Open	38	IB1	<1	Adenocarcinoma[a]	No residual disease	Unknown[a]	No	Unknown	No	No	0.7
Open	34	IB1	1–2	Squamous	1–2	III	No	No	No	No	0.4
Open	31	IB1	1–2	Adenocarcinoma	1–2	III	No	No	No	No	2.6
Open	34	IB1	< 1	Squamous	—	III	No	Unknown	No	No	1.3

DFS, disease-free survival; *FIGO*, International Federation of Gynecology and Obstetrics; *LVSI*, lymphovascular space invasion; *MIS*, minimally invasive surgery.

[a] For patients with no residual disease, preoperative grade and histology were entered.

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SUPPLEMENTAL TABLE 2

Univariate analysis of associations with 4.5-year recurrence regardless of surgical approach

Variable	Number of patients with recurrence/total number of patients (%)	*P* value
Surgical approach		.40
Open	17/358 (4.7)	
MIS	18/288 (6.3)	
Tumor size (cm)		.09
<1	9/254 (3.5)	
1–2	26/392 (6.6)	
Visible lesion		.02
No	12/363 (3.3)	
Yes	20/234 (8.6)	
Unknown	3/49 (6.1)	
FIGO 2009 stage (preoperative)		.01
IA2	0/97 (0)	
IB1	35/549 (6.4)	
Histologic type		.50
Squamous carcinoma	19/402 (4.7)	
Adenocarcinoma	14/223 (6.3)	
Adenosquamous carcinoma	2/21 (9.5)	
Grade (preoperative)		.09
I	1/68 (1.5)	
II	10/179 (5.6)	
III	9/93 (9.7)	
LVSI		.05
No	10/372 (2.7)	
Yes	8/116 (7.8)	
Cone biopsy		<.001
No	23/200 (11.5)	
Yes	12/446 (2.7)	
Radicality of surgery		.32
Type II or class B	18/269 (6.7)	
Type III or class C1 or C2	10/263 (3.8)	
Neither method	7/114 (6.1)	
Any positive nodes		.25
No	35/612 (5.7)	
Yes	0/33 (0)	
Histologic type (pathology)		<.001
Squamous carcinoma	17/199 (8.5)	
Adenocarcinoma	11/111 (9.9)	
Adenosquamous carcinoma	4/12 (33.3)	
No residual disease	3/315 (1.0)	

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SUPPLEMENTAL TABLE 2

Univariate analysis of associations with 4.5-year recurrence regardless of surgical approach *(continued)*

Variable	Number of patients with recurrence/total number of patients (%)	*P* value
Positive margins		.30
No	30/339 (8.9)	
Yes	2/12 (16.7)	
Vaginal involvement		1.00
No	31/342 (9.1)	
Yes	0/3 (0)	
Uterine manipulator		.28
No	23/483 (4.8)	
Yes	11/157 (7.0)	
Colpotomy		.71
Abdominal	32/591 (5.4)	
Vaginal	1/37 (2.7)	
Order		.40
Cervical amputation first	7/102 (6.9)	
Colpotomy first	24/497 (4.8)	
Adjuvant treatment		.76
No	33/583 (5.7)	
Yes	2/61 (3.3)	

Surgical margin status refers to any surgical margin status.

FIGO, International Federation of Gynecology and Obstetrics; *LVSI*, lymphovascular space invasion; *MIS*, minimally invasive surgery.

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SUPPLEMENTAL TABLE 3
Surgeries included per site

Institution	Open, n (%)	MIS, n (%)	Total, n (%)
Fudan University Shanghai Cancer Center, Shanghai (China)	187 (52)	0 (0)	187 (29)
Memorial Sloan Kettering Cancer Center, New York (United States)	42 (12)	24 (8)	66 (10)
Md Anderson Cancer Center, Houston (United States)	21 (6)	31 (11)	52 (8)
Copenhagen University Hospital Rigshospitalet, Copenhagen (Denmark)	0 (0)	48 (17)	48 (7)
Karolinska Institute, Stockholm (Sweden)	0 (0)	41 (14)	41 (6)
Queen Elizabeth Hospital, Gateshead (United Kingdom)	10 (3)	20 (7)	30 (5)
Hospital Italiano de Buenos Aires, Buenos Aires (Argentina)	14 (4)	16 (6)	30 (5)
North-Western State Medical University. N.N. Petrov Research Institute of Oncology, St. Petersburg (Russia)	25 (7)	1 (0)	26 (4)
Instituto de Cancerología de Las Américas, Medellín (Columbia)	10 (3)	15 (5)	25 (4)
Skåne University Hospital, Lund (Sweden)	0 (0)	23 (8)	23 (4)
First Faculty of Medicine, General University Hospital in Prague, Charles University, Prague (Czech Republic)	20 (6)	0 (0)	20 (3)
Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai (China)	0 (0)	19 (7)	19 (3)
Barretos Cancer Hospital, Barretos (Brazil)	0 (0)	17 (6)	17 (3)
First Clinic of Obstetrics and Gynecology, University of Medicine and Pharmacy of Târgu Mures, Târgu Mureş (Romania)	16 (4)	0 (0)	16 (2)
Imperial College London, London (United Kingdom)	4 (1)	10 (3)	14 (2)
A.C. Camargo Cancer Center, São Paulo (Brazil)	1 (0)	11 (4)	12 (2)
Kazakh Institute of Oncology and Radiology, Almaty (Kazakhstan)	7 (2)	4 (1)	11 (2)
Instituto de Oncología Panama, Curitiba (Brazil)	1 (0)	8 (3)	9 (1)
Total	358	288	646

MIS, minimally invasive surgery.

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