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Open Versus Minimally Invasive Radical Hysterectomy in Cervical Cancer: The CIRCOL Group Study

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ABSTRACT

Purpose. To analyze the survival outcomes of patients in a Brazilian cohort who underwent minimally invasive surgery (MIS) compared with open surgery for early stage cervical cancer.

Methods. A multicenter database was constructed, registering 1280 cervical cancer patients who had undergone radical hysterectomy from 2000 to 2019. For the final analysis, we included cases with a tumor $\leq$ 4 cm (stages Ia2 to Ib2, FIGO 2018) that underwent surgery from January 2007 to December 2017. Propensity score matching was also performed.

Results. A total of 776 cases were ultimately analyzed, 526 of which were included in the propensity score matching analysis (open, n = 263; MIS, n = 263). There were 52 recurrences (9.9%), 28 (10.6%) with MIS and 24 (9.1%) with open surgery (p = 0.55); and 34 deaths were recorded, 13 (4.9%) and 21 (8.0%), respectively (p = 0.15). We noted a 3-year disease-free survival (DFS) rate of 88.2% and 90.3% for those who received MIS and open surgery, respectively (HR 1.32; 95% CI: 0.76–2.29; p = 0.31) and a 5-year overall survival (OS) rate of 91.8% and 91.1%, respectively (HR 0.80; 95% CI: 0.40–1.61; p = 0.53). There was no difference in 3-year DFS rates between open surgery and MIS for tumors $\leq$ 2 cm (95.7% vs. 90.8%; p = 0.16) or $>$ 2 cm (83.9% vs. 85.4%; p = 0.77). Also, the 5-year OS between open surgery and MIS did not differ for tumors $\leq$ 2 cm (93.1% vs. 93.6%; p = 0.82) or $>$ 2 cm (88.9% vs. 89.8%; p = 0.35).

Conclusions. Survival outcomes were similar between minimally invasive and open radical hysterectomy in this large retrospective multicenter cohort.

Cervical cancer is the fourth most common cancer in women worldwide and the fourth leading cause of death[1]. Moreover, nearly 85% of cases occur in low- and middle-income countries (LMICs), rendering cervical cancer the third most frequent cancer overall in Brazilian women and the most prevalent cancer in underserved Brazilian regions.[2]

Early stage disease is usually curable, with 5-year disease-free survival rates of over 90% after radical hysterectomy. In the past several decades, minimally invasive surgery (MIS) had gained widespread acceptance as a standard approach for cervical cancer, primarily due to its improved morbidity profile.[3,4] However, data from the Laparoscopic Approach to Cervical Cancer (LACC) trial[5]

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did not support the oncological safety and theoretical advantages in quality of life and morbidity of MIS, finding that women who were randomized to MIS had over 4 times the risk of recurrence or death that those who underwent open surgery.

Subsequently, several retrospective reports, including well-designed observational studies, were published, mostly confirming the LACC trial data,[6–8] whereas others did not generate the same results.[9–13] Further, a recent systematic review and meta-analysis that comprised 15 studies (n = 9499) reported hazard ratios of recurrence and death that were 71% and 56% higher for patients who underwent MIS.[14]

In the LACC trial,[5] 42% of cases were from Latin America, and a recent large multicenter study (n = 1379) from Latin America confirmed the increased risk of recurrence and death from cervical cancer when women underwent MIS (HR 1.7; 95% CI 1.13–2.57; $p = 0.01$).[6] However, the latter study did not include Brazilian institutions, and data from LMICs on surgical approaches in cervical cancer remain scarce. Our aim was to compare the survival outcomes of women who underwent MIS versus an open approach for early stage cervical cancer in a large Brazilian cohort.

METHODS

Study Population

This retrospective, multicenter study comprised 5 Brazilian tertiary oncology centers: AC Camargo Cancer Center, Aristides Maltez Hospital, Erasto Gaertner Hospital, Barretos Cancer Hospital, and Instituto Brasileiro de Controle do Cancer. The study was approved by the IRBs at each site.

Data were collected from medical records, inputted into Research Electronic Data Capture (REDCap),[15] and audited by the researcher at each institution. Then, the data were extracted for quality assessment (data accuracy and correctness) and analysis. The study group was named CIRCOL, and the databank included the clinical and pathological reports, adjuvant treatment, and outcomes data of 1280 patients with stage Ia2 to IIa1 cervical cancer (FIGO 2018) who underwent radical hysterectomy from 2000 to 2019.

We included patients who were treated from January 2007 to December 2017 and excluded those with tumors that were larger than 4 cm. Moreover, patients who had been in the LACC trial [4] from 2 institutions (Erasto Gaertner Hospital and Barretos Cancer Hospital) were excluded due to contractual agreement with the previous study. Preoperative imaging was performed at each institution, depending on availability. Surgical radicality (radical hysterectomy type B or C) was recorded and indications for adjuvant treatment were determined per the protocols at each institution. Details on uterine manipulator use were not retrieved, but this device was routinely used in nearly all cases of MIS.

Statistical Analysis

The major variable of interest was the surgical approach (open or MIS). Data on disease-free survival, overall survival, and site of first recurrence were collected. Disease-free survival (DFS) was calculated as the time of surgery to the date of recurrence or last follow-up. Overall survival (OS) was calculated as the time of surgery until death or the last follow-up. Patients were censored at the last follow-up if they experienced no recurrence or death. Chi-square and Fisher's exact tests were used to analyze the correlations between categorical variables; continuous variables were analyzed by independent samples *t*-test and Mann-Whitney test.

We first performed multiple analysis to compare clinical and pathological variables between the 2 surgical approaches (open vs. MIS). Next, we conducted an unadjusted survival analysis by the Kaplan-Meier method, comparing the 2 surgical modalities by log rank test. Propensity score-matched analysis was also performed. The score was calculated using a logistic regression model, with the type of surgical approach as the outcome and tumor size ($\leq$ 2 cm vs. $>$ 2 cm), previous conization, and adjuvant radiation as determinants. This predictive probability was used as a score for matching cases 1 to 1 with the nearest neighbor with a difference of 0.001. Survival analysis was performed between matched groups. We calculated the hazard ratios (HRs) for DFS and OS for MIS and for other clinical and pathological variables of interest using weighted Cox proportional hazard models. Significance levels of $\alpha = 5\%$ were used to test all hypotheses. All analyses were performed using SPSS, version 24.0 for Windows (SPSS, Inc, Chicago, IL).

RESULTS

Patients and Demographics

A total of 948 cervical cancer cases were analyzed from January 2007 to December 2017. We excluded cases with tumors $>$ 4 cm (n = 118) and cases without follow-up after surgery (n = 33). Cases that had been included in the LACC trial were also excluded (n = 70). Ultimately, 776 cases with stage Ia2 to Ib2 cancer (FIGO 2018) were analyzed (Fig. 1). Regarding the surgical approach, 384

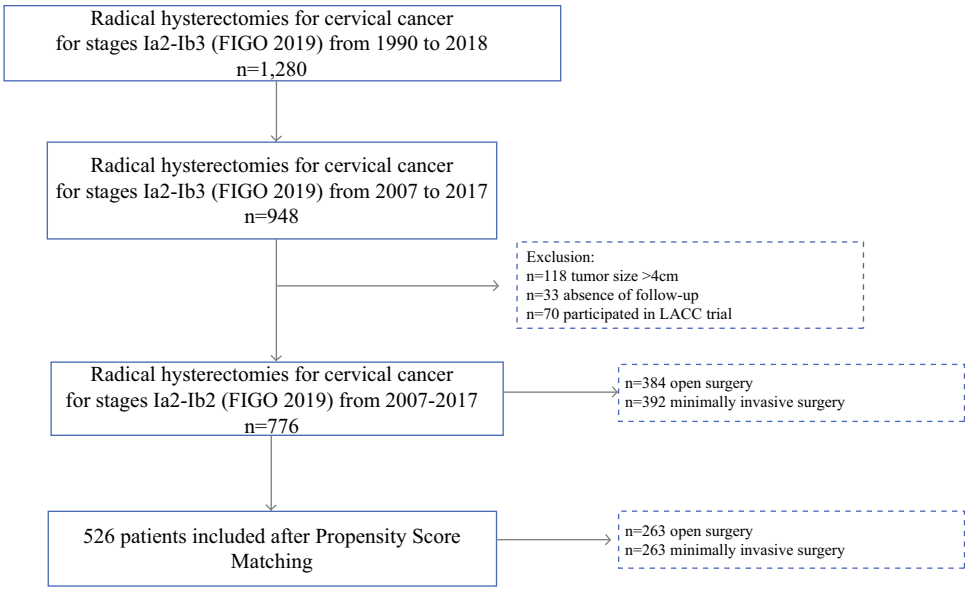

FIG. 1 Flowchart of patient inclusion

(49.5%) patients underwent open surgery, and 392 (50.5%) were subjected to minimally invasive surgery — laparoscopy and robotic-assisted in 365 (47%) and 27 (3.5%) of cases, respectively.

Table 1 summarizes the clinical and pathological variables. Several variables differed between groups. Women who underwent open surgery were older (median: 43 vs. 40 years; $p = 0.003$), had larger tumors (mean: 21.5 vs. 19.6 mm; $p = 0.025$), and deeper stromal invasion (mean: 8.7 vs. 7.3 mm; $p = 0.036$) and were more likely to receive adjuvant radiotherapy (38.3% vs. 28.3%; $p = 0.003$). Patients who underwent open surgery had longer follow-ups (median: 59.1 vs. 39.3 months; $p < 0.001$). However, the median times to recurrence were similar for open and MIS (19.0 vs. 21.1 months; $p = 0.89$).

Recurrence and Survival Outcomes

A total of 73 (9.5%) recurrences were documented — 39 (10.2%) and 34 (8.7%) in the open surgery and MIS groups, respectively. Also, 51 deaths were reported: 33 (8.6%) with open surgery and 18 (4.6%) with MIS ($p = 0.024$) (Table 2).

We found no difference in DFS between those who underwent open surgery and MIS, with 3- and 5-year rates of 90.4% and 89.5% for the former, respectively, and 90.7% and 87.8% for the latter (HR 1.02; 95% CI: 0.64–1.63; $p = 0.91$). OS rates were also similar between open surgery and MIS, yielding 3- and 5-year rates of 95.2% and 90.5% for open surgery, respectively, and 96.2% and 92.8% for MIS (HR 0.71; 95% CI: 0.39–1.02; $p = 0.25$).

Propensity Score Matching Analysis

The propensity score matching analysis comprised 526 cases. A total of 52 (9.9%) recurrences were reported — 24 (9.1%) and 28 (10.6%) in the open surgery and MIS groups, respectively ($p = 0.55$). Moreover, 34 deaths were recorded — 21 (8.0%) and 13 (4.9%), respectively ($p = 0.15$) (Table 2).

Tables 3 and 4 summarize the proportional hazard values for DFS, including the clinical and pathological variables for all cases and after the propensity score matching. Pathological variables, such as parametrial invasion, histological grade 3, tumor size > 2 cm, depth of invasion ≥ 10 mm, and invasion of lymphovascular space, negatively impacted the risk of recurrence. Further, histological grade 3, tumor size > 2 cm, depth of invasion ≥ 10 mm, and lymph node metastasis increased the risk of death. Adjuvant radiation was associated with a lower risk of recurrence and death.

No difference in DFS for the open approach versus MIS was observed. The 3- and 5-year DFS rates were 90.3% and 89.7% for open surgery and 88.2% and 84.5% for MIS, respectively (HR 1.32; 95% CI: 0.76–2.29; $p = 0.31$). Moreover, OS did not differ between open surgery and MIS, with 3- and 5-year rates of 95.4% and 91.1% for the open approach and 96.1% and 91.8% for MIS, respectively (HR 0.80; 95% CI: 0.40–1.61; $p = 0.53$) (Fig. 2).

In this study, the type of surgical approach did not impact DFS when tumor size was considered. The 3-year DFS rates for open surgery and MIS for tumors ≤ 2 cm were 95.7% and 90.8% ($p = 0.16$), respectively, and 83.9% and 85.4% for tumors > 2 cm ($p = 0.77$). The 5-year OS rates were also similar between open surgery and MIS in

TABLE 1 Comparison of clinical and pathological variables between the 776 patients with stage Ia2 to Ib2 (FIGO 2018) submitted to radical hysterectomy according to surgical approach

Variable		Open (n=384)	MIS (n=392)	Total (n=776)	*P*
Age (years)	Median	43 (17-81)	40 (21-70)	42 (17-81)	0.003
	Mean	44.8 ± 11.7	42 ± 9.6	43.4 ± 10.8	
Tumor size (mm)	Median	20 (1-40)	20 (0.4-40)	20 (0.4-40)	0.025
	Mean	21.5 ± 1.0	19.6 ± 0.9	20 ± 1.0	
Depth of invasion (mm)	Median	7 (0.1-30)	6 (0.2-28)	7 (0.1-30)	0.036
	Mean	8.7 ± 6.1	7.3 ± 5.6	8.2 ± 6.0	
LN dissected	Median	18 (1-91)	18 (1-81)	18 (1-91)	0.17
	Mean	22.4 ± 15.2	18.6 ± 8.1	20.5 ± 12.3	
Follow-up (months)	Median	59.1 (4.2-158)	39.3 (4.5-124)	47.9 (4.2-158)	<0.001
Recurrences	Local	19 (51.3%)	25 (75.7%)		
	Distant	10 (27.1%)	5 (15.2%)		
	Local and distant	8 (21.6%)	3 (9.1%)		
	Missing	2	1	4 (0.5%)	
	Total	39 (10.2%)	34 (8.7%)	73 (9.5%)	
Deaths		33 (8.6%)	18 (4.6%)	51 (6.6%)	
Previous conization	No	249	246	495 (64%)	0.45
	Yes	132 (34.6%)	146 (37.2%)	278 (36%)	
	Missing	3	-	3	
Residual neoplasia after conization	No	56	50	106 (40,9%)	0.18
	Yes	68 (54.8%)	85 (63%)	153 (59.1%)	
	Missing	260	257	517	
Adjuvant radiation	No	237	281	518 (66.8%)	0.003
	Yes	147 (38.3%)	111 (28.3%)	258 (33.2%)	
Adjuvant concomitant chemotherapy[a]	No	96	61	156 (60.7%)	0.1
	Yes	51 (34.7%)	50 (45%)	101 (39.3%)	
Parametrial invasion	No	370	364	734 (95.1%)	0.10
	Yes	14 (3.6%)	24 (6.2%)	38 (4.9%)	
	Missing	-	4	4	
Positive margins	No	241	125	366 (94.1%)	0.42
	Yes	17 (6.6%)	6 (4.6%)	23 (5.9%)	
		126	131	261	
Histologic type	SCC	265	265	530 (68.4%)	
	Adenocarcinoma[b]	119 (31%)	126 (32.2%)	245 (31.6%)	0.71
	Not specified	-	1	1	
Grade	G1+G2	244	282	526 (72.1%)	
	G3	110 (31.1%)	94 (25%)	204 (27.9%)	0.068
	Missing	30	16	46	
Tumor size	<2cm	147	211	358 (56.2%)	0.065
	≥2cm to <4cm	135 (47.9%)	144 (40.6%)	279 (43.8%)	
	Missing	102	37	139	
Depth of invasion	<10mm	143	88	231 (64.3%)	0.08
	≥10mm	91 (38.9%)	37 (29.6%)	128 (35.7%)	
	Missing	150	125	267	
LVSI	No	281	297	578 (79.4%)	0.38
	Yes	67 (19.3%)	83 (21.8%)	150 (20.6%)	
	Missing				
Perineural invasion	No	224	117	341 (88.3%)	0.67
	Yes	31 (12.2%)	14 (10.7%)	45 (11.7%)	

Table 1 (continued)

Variable		Open (n=384)	MIS (n=392)	Total (n=776)	*P*
	Missing	129	131	261	
LN metastasis	No	321	338	659 (85.5%)	0.19
	Yes	62 (16.2%)	50 (12.9%)	112 (14.5%)	
	Missing	1	4	5	

MIS minimally invasive surgery, *LN* lymph node, *CIN* or invasive cancer, *SCC* squamous cell carcinoma, *LVSI* lymphovascular space invasion

[a]Considering cases submitted to adjuvant radiotherapy

[b]Adenocarcinoma all types including adenosquamous

TABLE 2 Description of recurrences and deaths of stages Ia2 to Ib2 (FIGO 2018) cervical cancer submitted to radical hysterectomy according to surgical approach

All cases		Open (n=384)	MIS (n=392)	Total (n=776)	*P*
Recurrences	Locoregional	19 (51.3%)[a]	25 (75.7%)[a]		0.46
	Distant	10 (27.1%)[a]	5 (15.2%)[a]		
	Locoregional and distant	8 (21.6%)[a]	3 (9.1%)[a]		
	Missing	2	1	4 (0.5%)	
	Total	39 (10.2%)[b]	34 (8.7%)[b]	73 (9.5%)	
Deaths		33 (8.6%)	18 (4.6%)	51 (6.6%)	0.024
After PSM		Open (n=263)	MIS (n=263)	Total (n=526)	*P*
Recurrences	Locoregional	11 (45.8%)[a]	20 (71.4%)[a]		0.55
	Distant	6 (25%)[a]	6 (21.4%)[a]		
	Locoregional and distant	7 (29.1%)[a]	2 (7.1%)[a]		
	Total	24 (9.1%)[b]	28 (10.6%)[b]	52 (9.9%)	
Deaths		21 (8.0%)	13 (4.9%)	34 (6.5%)	0.15

MIS minimally invasive surgery, *PSM* propensity score matching

[a]Percentage referred to the total of recurrences

[b]Percentage referred to the total of cases

tumors $\leq$ 2 cm (93.1% vs. 93.6%; $p = 0.82$) and $>$ 2 cm (88.9% vs. 89.8%; $p = 0.35$) (Fig. 3).

DISCUSSION

Based on the unexpected results of the phase 3 LACC trial in 2018,[5] which reported a higher recurrence rate and worse overall survival for patients with early stage cervical cancer who underwent MIS, several subsequent retrospective studies addressed this important topic, supporting the current consensus of the detrimental effects of MIS in cervical cancer.[6–8] Further, four main concerns were raised after the LACC trial: the role of the manipulator and the type of colpotomy in recurrence, and the safety of MIS in small tumors ($\leq$ 2 cm) or after conization.

In contrast to the LACC trial, we did not find any difference in DFS or OS for MIS compared with open surgery. Notably, when we analyzed the whole cohort, there were major clinical and pathological differences between groups, such as tumor size, stromal invasion, and adjuvant radiotherapy, but no difference in survival was seen. After adjustments for variables, the similarities in DFS and OS were maintained, even for tumors that were larger than 2 cm. Further, no tumor containment was performed before the colpotomy, as suggested by Kohler et al.[16] In this large (n = 389) multicenter German study, with combined vaginally assisted laparoscopic radical hysterectomy, in which a cervical tumor is encased vaginally before resection, a favorable long-term outcome was reported. The 4.5- and 10-year DFS rates were 95.8% and 93.1%, respectively, and the 4.5- and 10-year OS rates were 97.8% and 95.8%. Also, we found that previous conization did not affect survival after adjustments for size and adjuvant radiation, and nearly all cases that underwent MIS used a uterine manipulator.

TABLE 3 Cox proportional hazards for disease-free survival of clinical and pathological variables between patients with stage Ia2 to Ib2 (FIGO 2018) submitted to radical hysterectomy

Variable		All cases (n=776) Hazard ratio (95% CI)	*P*	Propensity score matching (n=526) Hazard ratio (95% CI)	*P*
Type of surgery	Open	Reference	0.91	Reference	0.31
	Minimally invasive	1.02 (0.64-1.63)		1.32 (0.76-2.29)	
Age (years)	Continuous	0.75 (0.97-1.01)	0.75	0.99 (0.97-1.02)	0.76
Previous conization	No	Reference	0.029	Reference	0.50
	Yes	0.55 (0.32-0.94)		0.79 (0.41-1.55)	
Residual neoplasia after conization	No	Reference	0.024	Reference	0.13
	Yes	10.4 (1.3-79.2)		49.9 (0.27-895)	
Adjuvant radiation	No	Reference	0.016	Reference	0.038
	Yes	0.56 (0.35-0.89)		0.56 (0.32-0.97)	
Adjuvant concomitant chemotherapy[a]	No	Reference	0.087	Reference	0.38
	Yes	1.67 (0.92-3.0)		1.35 (0.68-2.68)	
Parametrial invasion	No	Reference	0.032	Reference	0.015
	Yes	2.34 (1.07-5.11)		2.69 (1.21-5.98)	
Histologic type	SCC	Reference	0.39	Reference	0.96
	Adenocarcinoma[b]	1.2 (0.76-2.0)		1.01 (0.57-1.79)	
Grade	G1+G2	Reference	0.045	Reference	0.002
	G3	1.63 (1.01-2.64)		2.34 (1.35-4.05)	
Tumor size	$\leq$ 2 cm	Reference	<0.001	Reference	<0.001
	> 2 cm to $\leq$ 4 cm	3.1 (1.78-5.58)		2.85 (1.58-5.14)	
Depth of invasion	< 10 mm	Reference	<0.001	Reference	0.001
	$\geq$ 10 mm	3.69 (1.92-7.07)		4.42 (1.85-10.5)	
LVSI	No	Reference	0.039	Reference	0.024
	Yes	1.76 (1.02-3.01)		1.97 (1.09-3.57)	
Perineural invasion	No	Reference	0.16	Reference	0.41
	Yes	1.77 (0.78-4.02)		1.05 (0.57-3.95)	
LN metastasis	No	Reference	0.07	Reference	0.14
	Yes	1.69 (0.95-2.99)		1.62 (0.85-3.09)	

MIS minimally invasive surgery, *LN* lymph node, *CIN* or invasive cancer, *SCC* squamous cell carcinoma, *LVSI*: lymphovascular space invasion

[a]Considering cases submitted to adjuvant radiotherapy

[b]Adenocarcinoma all types including adenosquamous

Nevertheless, other studies found that MIS did not have inferior oncological outcomes. In two population-based cohort studies in Nordic countries (Denmark and Sweden), nationwide adoption of robot-assisted MIS for cervical cancer did not negatively impact survival outcomes.[12,17] Moreover, Li et al. recently published a large multi-institutional retrospective (1484 patients: 585 laparoscopy vs. 899 open surgery), reporting comparable oncological outcomes between laparoscopic and open radical hysterectomy in patients with tumors < 2 cm, unmatched and after propensity score matching, regardless of whether the tumor was visible. The 5-year DFS rate for open surgery and laparoscopy was 94.3% and 93.7%, respectively (p = 0.49).[9]

Similarly, Kwon et al. found no differences in patients who were treated with open surgery (258) and laparoscopy (252), finding similar 5-year DFS (84.4% vs. 86.6%, p = 0.467) and OS rates (85.8% vs. 88.0%, p = 0.919). Further, in the subgroup of patients with tumors > 2 cm, the 5-year DFS (77.6% vs. 79.0%, p = 0.682) and OS rates (79.2% vs. 81.5%, p = 0.784) did not differ between groups.[11] An institutional retrospective cohort study from Korea reported that laparoscopy does not influence disease recurrence for tumors $\leq$ 2 cm by preoperative magnetic resonance, which included stages Ib1 to IIa2 (open, n = 435; MIS, n = 158).[10] However, in the 349 patients with stage Ib1 disease, MIS was associated with worse recurrence rates (HR 2.27; 95% CI 1.03–4.98; p = 0.04).

TABLE 4 Cox proportional hazards for overall survival of clinical and pathological variables between patients with stage Ia2 to Ib2 (FIGO 2018) submitted to radical hysterectomy

Variable		All cases (n=776) Hazard ratio (95% CI)	*P*	Propensity score matching (n=526) Hazard ratio (95% CI)	*P*
Type of surgery	Open	Reference	0.25	Reference	0.53
	Minimally invasive	0.71 (0.39–1.02)		0.80 (0.40–1.61)	
Age (years)	Continuous	1.0 (0.97-1.02)	0.89	1.01 (0.98–1.04)	0.39
Previous conization	No	Reference	0.12	Reference	0.34
	Yes	0.61 (0.33–1.14)		0.65 (0.27–1.57)	
Residual neoplasia after conization	No	Reference	0.048	Reference	0.39
	Yes	7.8 (1.01–60.9)		2.59 (0.29–23.2)	
Adjuvant radiation	No	Reference	<0.001	Reference	0.004
	Yes	0.29 (0.16–0.51)		0.35 (0.17–0.72)	
Adjuvant concomitant chemotherapy[a]	No	Reference	0.005	Reference	0.056
	Yes	2.5 (1.32–4.75)		2.18 (0.97–4.87)	
Parametrial invasion	No	Reference	0.19	Reference	0.073
	Yes	1.96 (0.70–5.47)		2.60 (0.91–7.41)	
Histologic type	SCC	Reference	0.26	Reference	0.13
	Adenocarcinoma[b]	0.7 (0.37–1.31)		0.54 (0.24–1.20)	
Grade	G1 + G2	Reference	0.16	Reference	0.016
	G3	1.50 (0.84–2.68)		2.31 (1.16–4.57)	
Tumor size	$\leq$ 2 cm	Reference	0.008	Reference	0.040
	$>$ 2 cm to $\leq$ 4 cm	2.42 (1.26–4.67)		2.06 (1.03–4.12)	
Depth of invasion	$<$ 10 mm	Reference	<0.001	Reference	0.020
	$\geq$ 10 mm	4.44 (1.93–10.2)		4.74 (1.28–17.5)	
LVSI	No	Reference	0.001	Reference	0.003
	Yes	2.82 (1.56–5.1)		2.92 (1.42–6.0)	
Perineural invasion	No	Reference	0.038	Reference	0.45
	Yes	2.43 (1.04-5.66)		1.60 (0.45–5.65)	
LN metastasis	No	Reference	0.001	Reference	0.030
	Yes	2.71 (1.48-4.96)		2.26 (1.08–4.73)	

MIS minimally invasive surgery, *LN* lymph node, *CIN* or invasive cancer, *SCC* squamous cell carcinoma, *LVSI* lymphovascular space invasion

[a]Considering cases submitted to adjuvant radiotherapy

[b]Adenocarcinoma all types including adenosquamous

In contrast to the results above, an American multi-institutional retrospective cohort study by Uppal et al.[7] reported that after risk adjustment analysis, patients with tumors $\leq$ 2 cm in the final pathology examination had significantly worse DFS after MIS versus the open approach (HR 6.31; 95% CI: 1.24–31). However, cases with no residual tumor were excluded, whereas 2009 FIGO stage Ia1 with lymphovascular space invasion, Ia2, and Ib1 tumors were included. They reported that conization before surgery correlated with a lower risk of recurrence, similar to Kim et al.[10]

Also, a large European retrospective cohort study (SUCCOR)[8] comprised 693 patients with 2009 FIGO stage IB1 cervical cancer by preoperative MRI, whereas those who received conization before surgery were excluded. After inverse probability weighting, the authors noted that MIS was associated with higher rates of recurrence (HR 2.07; 95% CI: 1.35–3.15; $p = 0.001$) and death (HR 2.45; 95% CI 1.30–4.60; $p = 0.005$) compared with open surgery. However, in a subgroup of patients with tumors $\leq$ 2 cm, survival outcomes were similar between MIS and open surgery. Notably, patients without the use of a uterine manipulator and those who had a protective vaginal closure had similar DFS rates as those who underwent open surgery. We also had longer follow-ups for patients who underwent open surgery, and that may have impacted the OS. However, the median times to recurrence were similar for open and MIS ($<$ 24 months), probably having a low impact on DFS.

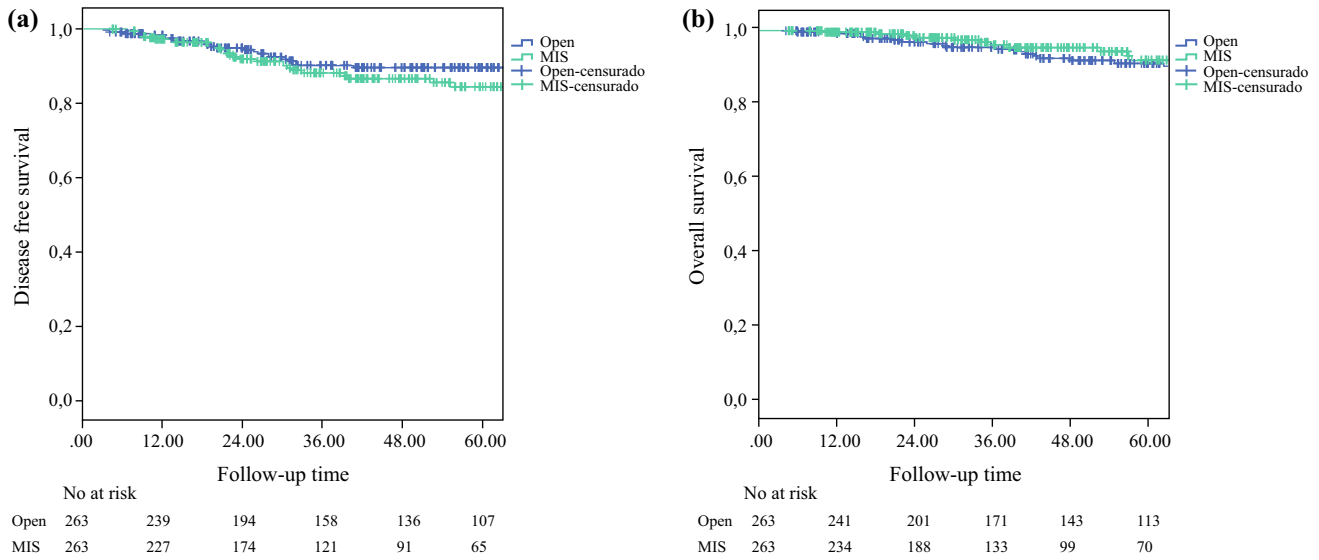

FIG. 2 **a** Disease-free survival curves for open surgery and minimally invasive surgery (MIS) ($p = 0.31$); **b** overall survival curves for open surgery and MIS ($p = 0.53$). (Adjusted analysis)

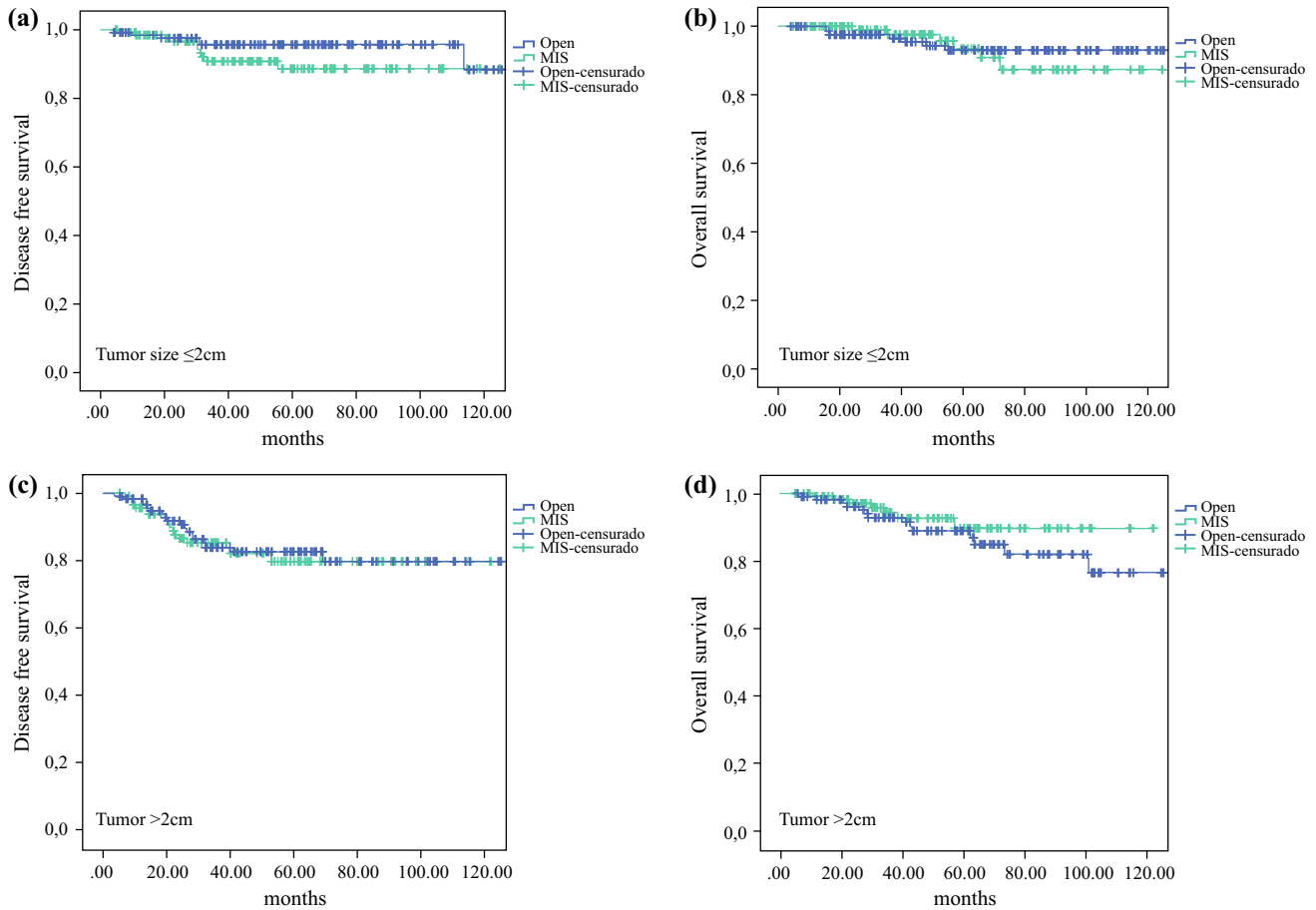

FIG. 3 **a** Disease-free survival ($p = 0.16$) and **b** overall survival ($p = 0.82$) curves for open surgery and minimally invasive surgery (MIS) for tumors $\leq$ 2cm; **c** disease-free survival ($p = 0.82$) and **d** overall survival ($p = 0.35$) curves for open surgery and MIS for tumors $>$ 2 cm. (Adjusted analysis)

One of the criticisms of the LACC trial was its high 4.5-year DFS rate of 96.5% for the open surgery group versus 86% with MIS.[5] We found a similar DFS rate for those who underwent MIS (4.5-year DFS 85.6%) but a lower rate for the open surgery approach (89.7%) compared with the LACC trial. Ramirez et al. hypothesized that the unexpectedly high DFS rate for open surgery was related to the evolving treatment of cervical cancer, although other recent series that included up to stage Ib2 disease (FIGO 2019) did not report the same favorable DFS. Notably, Kohler et al. reported a 4.5-year DFS of 95.8% after tumor containment, but their study population had a lower percentage of lymph node positivity versus the LACC trial (3% vs. 12.4%).[5,16]

Despite the "all or none" approach that has been adopted since the landmark LACC trial, the "one size fits all" method might not be appropriate for treating cervical cancer by surgery. Many concerns have been raised, and the LACC trial was not designed or powered to evaluate the safety of previous conization, tumors $\leq$ 2 cm, or the impact of the surgical technique (uterine manipulator and vaginal tumor containment). In parallel, the ESGO,[18] FIGO,[19] and NCCN[20] have revised their guidelines, stating that open abdominal radical hysterectomy is the standard approach for the surgical treatment of early stage cervical cancer.

Although it is imperfect and prone to criticism, the LACC trial has generated the best evidence to date. However, researchers should examine the reasons for the unexpected findings, refine the selection of patients, and revise the principles of the oncological technique. As discussed, in our study MIS did not negatively impact survival, despite the use of a uterine manipulator and the lack of tumor containment. Because we could not retrieve the details on all surgical techniques that could have impacted the surgical results, we believe that an unrecorded technique explains our result, rather than differences in tumor biology. Moreover, the LACC should not be considered the definitive trial for surgical approaches in cervical cancer. Fortunately, 2 randomized noninferiority trials are ongoing,[21,22] and a third will be launched soon, sponsored by the GOG Foundation (NCT04831580).

In our opinion, propensity score matching can be a valuable tool for confounding adjustment in observational investigations, and we decided to add this analysis to our study. Despite some existing controversy and inherent limitations, the propensity score intends to analyze an observational study trying to simulate some characteristics of a randomized controlled trial. Moreover, other key advantages should be addressed such as a clear definition of the target population and the ability to identify and exclude patients in atypical circumstances.[23]

Despite suffering from the inherent limitations of any retrospective study, our series is comparable in size with the most important studies in the literature on this topic and contributes valuable data. Moreover, we included patients from the same period as the LACC trial and from Brazilian institutions that are dedicated to cancer treatment. However, its weaknesses include the absence of preoperative imaging (MRI) for all cases, a centralized pathological review, and intraoperative surgical details. In conclusion, we did not find any difference in survival outcomes for patients with stage Ia2 to Ib2 disease who underwent radical hysterectomy between MIS and an open surgery approach.

AUTHORS' CONTRIBUTIONS Study concept and design: GB, RR, RdR, HM, BTG, AL, PHZ; data acquisition: GB, RR, RdR, AL, DFF, LYK, HM, TFF, LOP, BTG, CCF, PHZ; quality control of data: GB, RR, AL, RRLRC, GLSP, MAV, DFF, CCF, LBF, CECMA; data analysis and interpretation: GB, RR, RDR, AL, ATT, BTG, HM, PHZ; statistical analysis: GB, BTG; manuscript preparation and editing: GB, RR, RdR, AL, BTG, ATT, PHZ, DFF; manuscript review: all authors

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