Minimally Invasive Surgery for Early-Stage Cervical Carcinoma: Interpreting the Laparoscopic Approach to Cervical Cancer Trial Results

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Traditional extrafascial hysterectomy involves detaching the uterus (and cervix) at the points where the uterine blood supply, cardinal and uterosacral ligaments (ie, the parametria), and vagina join the uterus. The procedure is performed by general gynecologists to manage nonmalignant gynecologic conditions and by gynecologic oncologists to treat women with clinical early-stage endometrial cancer contained within the uterus. By contrast, radical hysterectomy to treat early-stage cervical carcinoma is an anatomically complex operation involving ligation and division of the uterine blood supply at its origin along the internal iliac vessels, bilateral ureterolysis from the pelvic brim to bladder insertion, en bloc resection of the cardinal and uterosacral ligaments at their origin at the pelvic sidewall and pelvic floor, respectively, and removal of the upper vagina. Development of the pararectal, paravesical, rectovaginal, and vesicovaginal spaces facilitates the operation.

Five-year disease-free survival (DFS) after open radical hysterectomy with lymphadenectomy for early-stage cervical carcinoma ranges from 70% to 85%.[1] The operation can result in significant blood loss, packed RBC transfusions, bladder and rectal dysfunction, ureteral injury, lymphocyst formation, and thromboembolism. Minimally invasive surgery (MIS) for early-stage cervical cancer evolved after the implementation of laparoscopy during the 1990s. MIS radical hysterectomy with pelvic lymphadenectomy can be associated with reduced surgical morbidity and earlier recovery compared with open operations. Although randomized trials evaluating oncologic safety were lacking, during the early twenty-first century, surgeons throughout the world adopted MIS to treat patients with International Federation of Gynecology and Obstetrics (FIGO) stage I to IIA cervical carcinoma.

To more formally address this issue, the phase III, international Laparoscopic Approach to Cervical Cancer (LACC) trial (ClinicalTrials.gov identifier: NCT00614211) was activated during 2008 and enrolled patients with FIGO 2014 stage IA_1 (with lymphovascular space invasion), IA_2, and IB_1 squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma. Participants were randomly assigned to MIS radical hysterectomy (laparoscopic or robotic, per surgeon preference) or open radical hysterectomy. The planned sample size of 740 patients was estimated to provide 87% power to declare MIS noninferior to open surgery with 4.5 years of follow-up and a noninferiority margin of −7.2 percentage points. DFS at 5 years from surgery was the primary end point. Overall survival, patterns of recurrence, feasibility of sentinel lymphatic mapping, perioperative morbidity, quality of life, and costs were secondary end points. The study closed prematurely in June 2017 because of an imbalance in deaths, at which time 85% of the trial had been enrolled (MIS, n = 319; open, n = 312), with both arms balanced for preoperative clinicopathologic characteristics and rates of postoperative adjuvant therapy (chemotherapy or radiotherapy).

On March 26, 2018, at the 49th Annual Meeting of the Society of Gynecologic Oncology in New Orleans, Ramirez et al[2] reported that at a median follow-up of 2.5 years (0.0 to 6.33 years), the MIS DFS in the intention-to-treat population was 86.0% compared with 96.5% for open surgery (difference, −10.5 percentage points; 95% CI, −16.4 to −4.7; $P = .87$ for noninferiority). At the time of analysis, 34 patients had experienced recurrence, with MIS relapse (n = 27) almost four times higher than open surgery (n = 7); greater than 40% of recurrences in both arms occurred in the vaginal vault or pelvis, with all nonvaginal vault pelvic recurrences reported in the MIS arm.[2] The per-protocol analysis corroborated these results, with DFS at 4.5 years of 87.1% for MIS versus 97.6% for open (difference, −10.5 percentage points; 95% CI, −16.0% to −5.0%; $P = .88$ for noninferiority). The 3-year DFS was lower with MIS (91.2%) versus open (97.1%; HR for disease recurrence or death as a result of cervical cancer, 3.874; 95% CI, 1.63 to 8.58).[2] The difference persisted after adjustment for age, body mass index, stage of disease, lymphovascular space invasion, lymph node involvement, and Eastern

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on August 5, 2019 and published at jco.org on September 27, 2019: DOI https://doi.org/10.1200/JCO.19.02024

Cooperative Oncology Group performance status score. With 22 deaths reported, 3-year overall survival was also found to be inferior in the MIS group (93.8%, n = 19 deaths), where patients were six times as likely to die during the follow-up period compared with the open group (99.0%, three deaths; HR 6.56; 95% CI, 1.48 to 29.00).[2]

Interpretation of data from the LACC trial has been controversial. Because previous randomized controlled trials comparing MIS with open surgery in clinical early-stage endometrial cancer,[3,4] nonmetastatic colon cancer,[5] and distal gastric cancer[6] had reported equivalent survival rates and reduced surgical morbidity, the results of the LACC trial were met with some skepticism. Inferior mortality rates associated with MIS radical hysterectomy were also reported by Melamed et al[7] using the National Cancer Database (2010 to 2012) and the SEER database (2006 onwards), and in other retrospective studies[8-14] after presentation of LACC (Table 1).

On November 13, 2018, the Society of Gynecologic Oncology issued a statement to its members summarizing the LACC trial findings and encouraged gynecologic oncologists to consider all available data when counseling patients.[15] On February 28, 2019, the US Food and Drug Administration (FDA) posted a safety communication urging the oncology community to exercise caution when using robotically assisted surgical devices in women's health, including mastectomy and other cancer-related surgeries.[16] Although the FDA warning was not restricted to cervical cancer, it is interesting that the only publication cited was that of the LACC trial.[2]

Not all MIS procedures are created equal, and it may not be appropriate to conflate the results of radical hysterectomy performed by traditional (straight-stick) laparoscopy with those of robotic procedures. In the MIS arm of the LACC trial, 84.4% of patients (n = 269) underwent laparoscopic radical hysterectomy, and only 15.6% (n = 50) underwent robotic radical hysterectomy. We can assume that in cases involving carcinoma, the cervix probably does not care how it is removed (whether by open surgery, laparoscopy, robotics, or even vaginally) as long as it is removed correctly.

The anatomic and physiologic considerations concerning radical hysterectomy are complex, and the DaVinci robotic surgical platform may facilitate achieving clear margins and adequate parametrial resection for many MIS surgeons. Specifically, the ergonomics allows the surgeon to remain seated at the console as opposed to having to wrestle with the abdominal wall while standing for 2 to 3 hours; wristed instrumentation and the intuitive nature enhances manual dexterity and precision, essentially mimicking the surgeon's hands; and the 3D camera provides depth perception (Table 2). Collectively, these attributes converge to generate a steeper learning curve compared with laparoscopy in that proficiency with the robot may be achieved with fewer patients. There is no question that there are gifted laparoscopic surgeons who can perform the operation skillfully, but they are likely to be relatively fewer in number compared with those who achieved proficiency with the robot.

In the retrospective studies that have followed on the heels of LACC (Table 1), the findings have not only harmonized with those of the LACC trial, but inferior outcomes also track with robotics.[7-14] These reports are hypothesis generating and do not provide evidence because they are crippled by recognized shortcomings of selection bias, recall bias, incomplete data, and so on. For many years, published retrospective experiences suggested a clinical benefit associated with secondary cytoreductive surgery for recurrent ovarian carcinoma, but the phase III, randomized trial by the Gynecologic Oncology Group (ie, protocol 0213) actually demonstrated no survival benefit with the intervention and, for some patients, worse outcomes.[17]

Due to the lack of a contract research organization, electronic data capture, and serial audits, interpretation of the LACC trial is more difficult compared to studies that use modern standards for clinical trial design and conduct. Fewer than 20% of patients in LACC were recruited in the United States, with the vast majority treated at centers in South America, China, India, Italy, Australia, and Bulgaria, where the training (and performance) of radical hysterectomy has not been standardized. In the United States, the 53 gynecologic oncology fellowships are immersive and audited by the Accreditation Council for Graduate Medical Education. Fellowship training is conducted by American Board of Obstetrics and Gynecology–certified gynecologic oncologists. Eligible graduates are required to take a written examination and a surgical case log oral examination to obtain Board certification. Most who succeed subsequently enroll in annual Maintenance of Certification programs through the American Board of Obstetrics and Gynecology. Although surgical skill per se is not specifically evaluated during the licensing process, the years invested prior are highly regulated in terms of surgical performance and oversight, foundation of knowledge concerning oncology and internal medicine, and professional conduct. In LACC, each participating center was required to submit 10 documented MIS patients, along with two nonedited complete video recordings to the study steering committee. Ten patients (an arbitrary designation) may not be sufficient to generalize competence of MIS radical hysterectomy. In a retrospective review of 84 patients who underwent laparoscopic radical hysterectomy for stage IB cervical cancer, Kong et al[18] reported that approximately 18 patients for surgeons with or without prior open radical hysterectomy experience were required to achieve surgical proficiency. In addition, the outcomes of the video review, particularly exclusions (if any), have not been forthcoming. Consequently, these stipulations may not serve as a reasonable surrogate that is interchangeable across countries. If MIS radical hysterectomy is not equivalent across international borders (specifically,

TABLE 1. Summary of the LACC Phase III Randomized Trial Results and Subsequent Retrospective Studies of Interest

First Author	Design	No.	Findings
Ramirez [2] (LACC trial)	Prospective, randomized trial (FIGO 2014 IA1 with LVSI, IA2, or IB1; SCCA, adenoCA, adenosquamous CA)	Open radical hysterectomy (n = 312)	3-year DFS: 91.2% (MIS) *v* 97.1% (open); HR for disease recurrence or death: 3.74; 95% CI, 1.63 to 8.58; 3-year OS: 93.8% (MIS) *v* 99.0% (open); HR, 6.00; 95% CI, 1.77 to 20.30
		MIS radical hysterectomy (n = 319): 84.4% (n = 269) LSC; 15.6% (n = 50) robotic	
Melamed[7]	Retrospective, SEER database (2000-2010) and National Cancer Database (2010-2013); FIGO 2014 stage IA2-IB1	Open radical hysterectomy (n = 1,236); MIS radical hysterectomy (n = 1,225) with 978 (79.8%) robotic	4-year mortality: 9.1% MIS *v* 5.3% open; HR, 1.65; 95% CI, 1.22 to 2.22; *P* = .002
Uppal[12]	Retrospective, multi-institutional pooled study; FIGO 2014 IA1, IA2, IB1; SCCA, adenoCA, adenosquamous CA	Open radical hysterectomy (26.3%; n = 185); MIS radical hysterectomy (73.7%; n = 519): 9% LSC (n = 58); 91% robotic (n = 469)	MIS associated with higher odds of recurrence: OR, 2.24; 95% CI, 1.04 to 4.87; *P* = .04
Cusimano[8]	Population-based retrospective cohort study using linked administrative databases held at ICES (nonprofit research institute, Ontario); FIGO 2014 IA-II+, SCCA, adenoCA, adenosquamous CA	958 (total)	MIS associated with increased risk of death: HR, 2.20; 95% CI, 1.15 to 4.19 and recurrence: HR, 1.97; 95% CI, 1.10 to 3.50 (stage IB)
		Open: 483	
		MIS: 475 (89.6%, n = 426 LSC; 10.4%, n = 49 robot)	
Paik[9]	Ancillary data analysis of KGOG 1028 (FIGO 2014 IB-IIA)	Open radical hysterectomy (n = 357); LSC radical hysterectomy (n = 119)	LSC compared with open:
			DFS: HR, 2.738; 95% CI, 1.326 to 5.650; *P* = .005
			Pelvic recurrence: HR, 5.110; 95% CI, 1.817 to 14.473; *P* < .001
			Hematogenous recurrence: HR, 3.171; 95% CI, 1.059 to 9.494; *P* = .03
			No differences in OS
Kim[10]	Retrospective, FIGO 2014 IB1-IIA2; subanalysis for IB1 with preoperative MRI, 2000-2018	Open radical hysterectomy (n = 435); MIS radical hysterectomy (n = 158).	PFS: MIS, 78.5% *v* 89.7%, adjusted HR for progression, 2.883; 95% CI, 1.711 to 4.859; *P* < .001
		FIGO IB1 (n = 349, overall)	Recurrence for stage IB1: adjusted HR, 2.276; 95% CI, 1.039 to 4.986; *P* = .040; MIS did not influence PFS of stage IB1 with cervix ≤ 2 cm on MRI (adjusted HR, 1.146; 95% CI, 0.278 to 4.724; *P* = .850)
Fitzsimmons[13]	Retrospective review from institutional database, 2007-2017 (FIGO 2014 IA1 with LVSI, IA2, or IB1; SCCA, adenoCA, adenosquamous CA)	Robotic radical hysterectomy (n = 90): group A (first 10 learning curve patients per surgeon); group B (all subsequent patients)	Positive vaginal margin status: group A, 10% *v* group B, 0%; *P* = .034
			Recurrence: group A (15%; n = 6) *v* group B (2%; n = 1); *P* = .025
Doo[11]	Retrospective review from institutional database, 2010-2016 (FIGO 2014 IB1)	Open radical hysterectomy (n = 56); robotic radical hysterectomy (n = 49)	No differences in recurrence, PFS, or OS
			Tumors > 2 cm, recurrence: MIS, 30% *v* open, 8%; *P* = .006; PFS HR, 0.31; *P* = .04
National Cancer Registration and Analysis Service (British Gynaecologic Cancer Society)[14]	Retrospective review of linked cancer registration and Hospital Episodes Statistics data, 2013-2016 (FIGO 2014 IA2, IB1)	N = 929	4.5-year OS: MIS, 93.1% *v* open, 97.2%: HR, 4.0; 95% CI 1.5 to 11.1; *P* = .013
		Open radical hysterectomy (n = 365, 39%); MIS (n = 564, 61%) (includes LSC and robotic)	

Abbreviations: adenoCA, adenocarcinoma; CA, carcinoma; DFS, disease-free survival; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; ICES, Institute for Clinical Evaluative Sciences; KGOG, Korean Gynecologic Oncology Group; LACC, Laparoscopic Approach to Cervical Cancer trial; LSC, laparoscopy; LVSI, lymphovascular space involvement; MIS, minimally invasive surgery; MRI, magnetic resonance imaging; OS, overall survival; PFS, progression-free survival; SCCA, squamous cell carcinoma.

TABLE 2. Advantages of Open Versus MIS and Comparison of LSC With Robotics

Advantages of Open Surgery Compared to MIS		Disadvantages of Open Surgery Compared to MIS	
Tactile feedback		Requires hospitalization	Hospital-acquired infection
			Hospital costs
Opportunity to remove large structures intact		Longer time to reach postoperative milestones	Voiding
			Ambulation
			Regular diet
			Bowel function
			Pain control
			Discharge home
			Driving
			Exercise
			Return to work
Expeditious control of catastrophic hemorrhage		Wound complications	Cosmesis
			Cellulitis
			Superficial wound separation
			Fascial dehiscence
			Rectus muscle diastasis
			Evisceration
			Adhesions (may result in SBO and complications associated with radiotherapy)
More complex operations possible (eg, liver transplantation)		Visualization not magnified	Larger blood loss
			More transfusions
			Increased complications
Shorter operating time	Less inhalational anesthetic exposure		
	More efficient use of surgeon time		
	Reduced OR costs		
Advantages of LSC Over Robotics		**Advantages of Robotics Over LSC**	
		Camera stabilization	
Fewer and smaller incisions		Ergonomics	
Haptic feedback		Wristed instrumentation	Improved suturing
			Facilitates surgical planes
			Precision in dissection
Intermittent steep Trendelenburg possible		Motion-dampening censors (tremor filtration)	
Ability to interchange instrument configuration more readily		Intuitive nature	
Less costly		Depth perception due to 3D camera	Less blood loss
			Fewer transfusions
			Reduced complications
		Steeper learning curve	
		May facilitate MIS surgery for morbidly obese patients	
		Reduced conversion rate	

Abbreviations: LSC, laparoscopy (traditional, straight stick); MIS, minimally invasive surgery; OR, operating room; SBO, small bowel obstruction.

United States *v* ex–United States) one could argue that any shortcomings would be balanced by similar outcome deficiencies in the open arm. However, given some technical advantages of the open technique compared with MIS (Table 2), surgeons lacking adequate training may be able to better approximate a radical hysterectomy via laparotomy than with traditional straight-stick laparoscopy.

Additional weaknesses include the lack of central pathology review and missing data on tumor size in one third of patients. Preoperative cervical biopsies may not be of sufficient volume to exclude neuroendocrine tumors, which are known to be clinically aggressive. Preoperative surgeon assessment of tumor size less than 4 cm (an eligibility criterion) is also subjective and can ultimately be found to be erroneous. Results from subgroup analyses are needed, particularly to determine whether relapsing disease tracked with a specific histology, surgeon, and/or institution/country. Two additional years of follow-up will also be required to clarify the unusually low rate of recurrence (ie, 2%) in the open arm.

Passing on the trial shortcomings detailed previously, one must take the other side of the argument and consider why MIS radical hysterectomy could indeed be unsafe oncologically whether performed using the laparoscope or with robotics. The use of a uterine manipulator, prolonged steep Trendelenburg position, and intracorporeal vaginal colpotomy in the setting of the high pressure pneumoperitoneum of 12 to 15 mmHg have all been proposed as MIS-specific factors, which conspire to place patients at risk for recurrence. A precedent for this exists in anecdotal reports of port site metastases after laparoscopic evaluation in advanced ovarian cancer,[19] and peritoneal dissemination after hysteroscopy for endometrial cancer.[20] Certainly, placing a manipulator through the cervical canal may result in tumor fragmentation in women with large exophytic squamous cell carcinoma as well as those with expansile, endophytic adenocarcinoma. The aforementioned patient positioning and CO_2 gas may then facilitate seeding of the peritoneal cavity with fractured tumor. Furthermore, uterine perforation (a recognized subclinical complication of using the uterine manipulator in any MIS hysterectomy) may also contribute to this phenomenon.

Extrapolation of the LACC study results to discourage the use of robotic surgery may not be appropriate, because the vast majority of patients in the MIS arm underwent laparoscopic, as opposed to robotic, radical hysterectomy. Most MIS surgeons in the United States would probably agree that the robotics platform offers several technical advantages compared with straight-stick laparoscopy (Table 2). The majority of centers that participated in LACC are in countries where MIS has not been as readily adopted as in the United States, and therefore, there is continued interest in performing additional studies in countries where surgeons are highly experienced in MIS.

During the latter half of the twentieth century, radical hysterectomy was considered the defining surgical procedure in the gynecologic oncologist's armamentarium. With the implementation of successful cervical cancer screening programs using cytology with and without high-risk human papillomavirus DNA testing, and more stringent criteria for surgical candidacy,[21] fewer radical hysterectomies are being performed in the United States, and cytoreductive surgery for advanced ovarian cancer is now regarded as the operation that distinguishes the subspecialty. A prospective, nonrandomized trial in the United States may have results similar to the LACC trial, with the recent generation of gynecologic oncologists (less-experienced with performance of radical hysterectomy) more likely to have adopted robotic surgery, whereas earlier generations (better trained in radical surgery for cervical cancer) less inclined to have incorporated robotics into their practices.

Some have argued that another randomized trial is needed, but consensus regarding study design and feasibility have thus far been difficult to achieve. Should a trial with a 7% threshold to declare noninferiority have two arms (ie, open *v* robotics), or should there be a third adaptive arm for laparoscopy? Although approximately 92% of patients in LACC had FIGO 2014 stage IB_1 disease and just over 40% of lesions in each arm were 2 cm or larger, as discussed earlier, tumor size is missing for a substantial number of patients. Is it even ethical to study MIS radical hysterectomy in women with lesions larger than 2 cm? Some gynecologic oncologists acknowledge that tactile feedback afforded by the open approach (Table 2) is invaluable in determining tumor clearance when operating around large lesions. If a new study were restricted to lesions 2 cm or smaller, then extended follow-up and international participation (with the inherent shortcomings discussed earlier) would be required to optimize accrual because events will be fewer, given a population with better prognosis.

Patients must be counseled regarding the potential risks of MIS radical hysterectomy. However, with a high-profile publication and an FDA warning, many MIS surgeons are uncomfortable waiting for another trial and have preferentially moved back to the open approach. This increases the risk of prolonged hospitalization and convalescence, as well as delay in initiation of adjuvant therapy and subsequent radiation-associated complications if indicated by surgical-pathologic findings. Despite these unanticipated consequences, the LACC study team needs to be commended for having made an important contribution with practice-changing ramifications concerning patient safety for women diagnosed with early-stage cervical cancer.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the author and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.19.02024.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Honoraria: Tesaro, Clovis Oncology
Consulting or Advisory Role: Genentech
Speakers' Bureau: Genentech, AstraZeneca, Merck
Research Funding: AbbVie (Inst), Genentech (Inst), Morphotek (Inst), Merck (Inst), Regeneron (Inst)
Travel, Accommodations, Expenses: Genentech

No other potential conflicts of interest were reported.