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Review article

Assessing the role of minimally invasive radical hysterectomy for early-stage cervical cancer

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ABSTRACT

Surgery is the mainstay of treatment in the management of early-stage cervical cancer. Until the publication of the Laparoscopic Approach to Cervical Cancer (LACC) trial, minimally invasive radical hysterectomy was the recommended approach to treat patients with early-stage disease. The results of the LACC trial questioned the adoption of minimally invasive surgery in cervical cancer. In comparison with the open approach, minimally invasive surgery correlated with worse disease-free and cancer-specific survival. Similarly, other retrospective studies highlighted this correlation, thus corroborating the results of the LACC trials. In the present review, we evaluated current evidence and further prospective of the adoption of minimally invasive radical hysterectomy in cervical cancer. Moreover, we sought to assess some unsolved issues regarding the role of minimally invasive surgery in early-stage cervical cancer patients.

Introduction

In the last two decades, minimally invasive surgery has replaced the open approach for the management of several benign and malignant diseases. Thanks to technical and technological improvements, minimally invasive surgery allows the management of challenging conditions, including cancers [1]. Accumulating evidence highlighted that minimally invasive surgery correlated with better short-term perioperative outcomes than open surgery [2,3]. In particular, robust evidence suggested that laparoscopic hysterectomy includes a more rapid recovery, fewer febrile episodes, and lower surgical site infection rates in comparison to open abdominal hysterectomy [2,3]. Moreover, data support the adoption of minimally invasive surgery in patients with endometrial cancer and other malignancies [2–5]. In patients with endometrial cancer, a minimally invasive approach correlated with better short-term results and similar long-term oncologic outcomes, in comparison to open surgery [2]. Prospective randomized controlled trials supported the safety of minimally invasive surgery in patients with cancers arising into hollow organs, such as the esophagus, stomach, and colon [6–8]. These previous trials have shown that, in comparison to conventional procedures, a minimally invasive approach reduces surgical trauma and results in reduced blood loss, fewer complications,

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	Minimally invasive surgery N=319	Open surgery N=312
Operative time, min	216 (75, 441)	187 (61, 425)
Estimated blood loss, ml	101 (10, 1500)	209 (10, 2200)
Conversions to open surgery	3%	-
Lenght of stay, days	3 (0-72)	5 (0-69)
Intraoperative adverse event	12%	10%
Postoperative adverse event	54%	48%
Major adverse event	18%	16%
Serious adverse event	14%	12%
Quality of Life, FACT-Cx at 6 wks	130 (19.8)	128.7 (19.9)
Disease-free survival rates at 3 yrs	91.2%	97.1%
Overall survival rates at 3 yrs	93.8%	99.0%

Fig. 1. Main findings reported in the LACC trial.

shorter length of hospital stay, and a faster recovery to normal activity [6–8].

Similarly, several retrospective experiences highlighted that minimally invasive surgery was a safe and effective approach to managing cervical cancer patients, especially in the early stage of disease [9,11]. This retrospective evidence supported the adoption of laparoscopic and robotic-assisted surgery in women with early-stage cervical cancer [9–11]. However, the level of evidence is low and there are limited data regarding whether survival outcomes after minimally invasive surgery are comparable to those after open surgery. The Laparoscopic Approach to Cervical Cancer (LACC) trial, tested the hypothesis that minimally invasive radical hysterectomy was not inferior to open radical hysterectomy in terms of the disease-free survival rate [12]. The study was conducted between 2008 and 2017, and it was stopped early by the data and safety monitoring committee after enrolling 631 of a planned 740 patients [12]. Fig. 1 shows the main findings reported in the LACC trial. The LACC trial randomized 319 and 312 patients to minimally invasive and open radical hysterectomy, respectively. Among patients who had a minimally invasive radical hysterectomy, 84.4% and 15.6% had a laparoscopy and robot-assisted surgery, respectively. The rate of disease-free survival at 4.5 years was 86.0% and 96.5% after minimally invasive and open surgery, respectively. The unexpected results of the LACC trial underlined that minimally invasive radical hysterectomy was associated with a lower rate of overall survival than open surgery (3-year rate, 93.8% vs. 99.0%), and a higher rate of locoregional recurrence (3-year rate of locoregional recurrence-free survival, 94.3% vs. 98.3%) [12]. Recently, the update results of the LACC trial, after the completion of 4.5 years of follow-up, corroborated these findings [13]. Minimally invasive hysterectomy correlated with a high risk of developing loco/regional recurrences as well as worse progression-free and overall survival than open approach. The hazard ratio (HR) for cumulative local/regional recurrence was 4.70 (95% CI, 1.95–11.37; $P = 0.001$). The HR for progression-free survival was 3.99 (95% CI, 2.12–7.51; $P < 0.0001$), and the HR for overall survival was 2.71 (95% CI, 1.32–5.59; $P = 0.007$) [13].

The LACC trial has some weaknesses (mostly due to the lack of central pathology review, the large amount of missing data regarding pathological characteristics, and the unequal distribution between laparoscopic (84%) and robotic-assisted (16%) cases [14]. However, the strength of the LACC trail is related to the prospective randomized controlled study design and the surgeon proficiency requirements. On the light of these points, the LACC trial was a game-changer.

Interestingly, in the same issue of the New England Journal of Medicine, Melamed et al., published a cohort study evaluating the role of surgical approach in women undergoing radical hysterectomy at Commission on Cancer-accredited hospitals in the United States (since 2010 to 2013) [15]. They also evaluated outcomes of patients undergoing surgery from 2000 to 2010, using the Surveillance, Epidemiology, and End Results (SEER) program database [15]. They observed that the implementation of minimally invasive radical hysterectomy was associated with worse overall survival. The 4-year mortality was 9.1% and 5.3% after minimally invasive and open surgery, respectively [15]. After the publication of these two studies, other retrospective investigations highlighted the detrimental role of adopting minimally invasive surgery in patients with early-stage cervical cancer [16–18]. Those emerging evidence triggered the scientific community, thus promoting a paradigm shift in the treatment of cervical cancer. Even the new NCCN and ESGO guidelines supported the adoption of open instead of minimally invasive radical hysterectomy [19,20]. Here, in the present paper, we aimed to review the possible explanations of these findings, the current pattern of utilization of minimally invasive surgery, and to assess some unsolved issues regarding the role of minimally invasive surgery in early-stage cervical cancer patients.

Why minimally invasive surgery is correlating with worse outcomes?

The real reasons why minimally invasive surgery is correlating with worse outcomes in comparison to open surgery are still unknown and controversial. Possible explanations include: (i) the steep learning curve of minimally invasive radical hysterectomy; (ii) the non-standardized technique and radicality of hysterectomies; (iii) mesothelial cell hypoxia due to CO2 pneumoperitoneum; (iv) tumor contamination at the time of colpotomy, directly worsened by the flow of CO2 [21–23]. Possibly it is a multifactorial phenomenon. The contamination at the time of intra-corporeal colpotomy might determine tumor spread into the peritoneal cavity. Moreover, the severity and the duration of acute inflammation and mesothelial cell damage (given by surgery plus CO2-related hypoxia) is postulated to promote the implantation of cancer cells into the peritoneal cavity as observed in several animal models [21–23]. Recently, prospective proof-of-principle study was performed to try to assess this issue. Indocyanine green was applied to the cervical surface before performing the hysterectomies [24]. The authors observed that contamination of the peritoneal cavity and laparoscopic instruments occurred in 75% and 60% of cases, respectively [24]. These data supported that at the time of colpotomy tumor cells might exfoliate into the abdominal cavity. Interestingly, a previous study of our working group observed that patients undergoing minimally invasive radical

hysterectomy are characterized by different patterns of recurrence in comparison to patients undergoing open radical hysterectomy [25]. The minimally invasive approach correlated with a high risk of developing carcinomatosis and intra-pelvic recurrences, thus supporting a multifactorial phenomenon based on intra-abdominal contamination and peritoneal damage. Further models investigating this issue are needed.

Why did previous studies fail to demonstrate the detrimental effect of minimally invasive surgery?

Although in absence of high-level evidence, minimally invasive surgery was the preferred treatment modality for cervical cancer patients, until November 2018. Interestingly, guidelines defined a minimally invasive approach as the preferred technique to perform a radical hysterectomy. In 2019, after the publication of the LACC trial, other retrospective experiences started to corroborate its results. They suggested that minimally invasive surgery had a detrimental effect on patient outcomes [12,13]. However, no other retrospective investigations noted these findings, before November 2018. Some reasons might explain why these studies failed to identify the effect of minimally invasive surgery: (i) few studies are focused on surgical outcomes; (ii) there was a high risk of selection biases in most studies; (iii) they did not include consecutive series of patients and (iv) compared low-risk patients having minimally invasive surgery vs. high-risk patients having open surgery; (v) the number of months of follow-up differed greatly between the two groups in some retrospective study; and more importantly (vi) the majority of studies are underpowered to assess differences in survival outcomes [26]. Of note, a systematic review and *meta*-analysis of 15 observational studies (all published before April 2020), reported pooled data of 9,499 patients who underwent radical hysterectomy (49% (n = 4684) had minimally invasive surgery). 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, 1.36–2.15; $p < 0.001$), and the hazard of death was 56% higher (HR: 1.56; 95%CI, 1.16–2.11; $p = 0.004$) [26].

The pattern of utilization of minimally invasive surgery after the publication of the LACC trial

The publication of the LACC trial impacted clinical practice, dramatically. Even the New England Journal of Medicine classified the LACC trial as one of the most impacting studies for the year 2018. Subsequently, a substantial decrease in the use of minimally invasive surgery occurred [12]. Few studies assessed the use of minimally invasive surgery as compared with open radical hysterectomy for cervical cancer before and after the publication of the LACC Trial [27,28]. In one study on this issue, the authors evaluated data from the Premier Healthcare Database, a large, US national sample from providers with diverse demographic characteristics [27]. The study included records of 2,437 patients who received care at 283 medical centers between November 2015 and March 2020. Around 61 percent of these patients were treated at academic centers and about 39 percent at nonacademic centers. The minimally invasive approach was used in 58.0% vs 42.9% of hysterectomies before vs after publication of the LACC trial. Interestingly, the use of minimally invasive surgery decreased by 73% in academic centers and by 19% in nonacademic centers ($p = 0.004$) [27]. Similarly, another study evaluated how the publication of the LACC trial influenced the minimally invasive radical hysterectomy use and perioperative complications for cervical cancer surgery [28]. The authors performed a retrospective study using a population-based register, querying National Inpatient Sample from October 2015 to December 2018 [28]. Comparing 5120 and 1645 patients having surgery before and after LACC, the authors observed that in the post LACC period women were less likely to have minimally invasive surgery (-63%), but more likely to develop perioperative complications (+23%) and longer length of hospital stay (3 vs. 2 days) [28]. Although in the randomized LACC trial open surgery was not correlated with increased morbidity, these data. should be taken into account [28]. Possibly, the rapid shift from minimally invasive to open surgery might explain these findings. Further attempts are needed to improve the quality of care of patients with cervical cancer, regardless type of surgical approach.

The impact of surgical approach on morbidity and quality of life (QoL)

Before November 2018, accumulating retrospective and prospective evidence highlighted that the adoption of minimally invasive surgery correlated with a shorter length of hospital stay, improved perioperative outcomes, and lower morbidity rate in comparison to open surgery [9–11]. Those data are corroborating previous level A evidence supporting the utilization of minimally invasive surgery in patients with endometrial cancer [2,3]. Data on morbidity and QoL were well addressed by two secondary analyses of the LACC trial. One of the most interesting findings of the LACC trial was that the adoption of minimally invasive surgery did not reduce the risk of developing postoperative morbidity. Obermair et al., reported that the rate of intraoperative events was similar between groups (12% and 10% in the minimally invasive and open group, respectively). Similarly, the overall incidence of postoperative grade ≥ 2 adverse events was 54% and 48%in the minimally invasive and open group, respectively (difference, 6.2%; 95% CI: −2.2, 14.7%; $p = 0.14$) [28]. Frumovitz et al., reported data about QoL [29]. Eligible patients included in the LACC trial filled validated QoL and symptom assessments (12-item Short-Form Health Survey [SF-12], Functional Assessment of Cancer Therapy-Cervical [FACT-Cx], EuroQoL-5D [EQ-5D], and MD Anderson Symptom Inventory [MDASI]) before surgery and at 1 and 6 weeks and 3 and 6 months after surgery (FACT-Cx was also completed at additional time points up to 54 months after surgery). The authors observed that QoL was similar between groups at 6 weeks and 3 months after surgery, thus suggesting that minimally invasive surgery did not improve short-term outcomes in comparison to open surgery [30]. Further studies testing the impact of minimally invasive radical hysterectomy are needed. However, based on the available (level A) evidence, we can conclude that minimally invasive and open radical hysterectomies are characterized by similar safety profiles [29,30]. The surgical approach did not influence morbidity rates and QoL.

The impact of tumor volume on patients' outcomes (FIGO stage IB1, tumor < 2 cm)

The LACC trial was designed to test the non-inferiority of minimally invasive in comparison to open surgery [12]. A sub-group analysis of the LACC trial highlighted that the detrimental effect of minimally invasive surgery was evident for patients with tumor volume >2 cm (FIGO stage IB2). While this detrimental association was not demonstrated for patients with tumor diameter <2 cm (FIGO stage IB1). This is corroborated also by the updated results of the LACC trial (at 4.5-year follow-up), presented at the SGO 2022 [13]. Although not statistically relevant, we have to point out that 7 and 0 events occurred in 75 and 65 patients with tumor <2 cm, having minimally invasive and open radical hysterectomy, respectively. The relative low risk of recurrence in patients with tumor <2 cm is making this difference less evident. Moreover, it is important to highlight that the study was not powered to test this correlation in this subgroup population [12,13]. Accumulating retrospective experiences were published to verify wheatear the surgical approach influenced the outcomes of low-volume cervical cancer patients [18,31]. A population-based retrospective study was carried out to assess outcomes of cervical cancer patients who had a primary radical hysterectomy by a gynecologic oncologist from 2006 to 2017 in Ontario, Canada [18]. This study included 958 patients (minimally invasive radical hysterectomy = 475; open radical hysterectomy = 483) [18].

Table 1
Ongoing prospective studies evaluating the role of minimally invasive surgery in early-stage cervical cancer.

Study identifier	Study design	Participants	Procedures	Disease characteristics	Procedures to avoid contamination	Estimated study completion date
RWS-01 NCT03955185	Prospective non-randomized study	2000	Laparoscopic and robotic-assisted vs. open radical hysterectomy	Patients with FIGO stage (2018) IA1 (with lymph vascular space invasion), IA2, IB1, IB2 or IIA1 disease	1) Uterine manipulator type Cup-shaped uterine manipulator is prohibited, uterus hanging wire is allowed. 2) Avoid tumor cells shedding into the pelvis: A. Cut the vagina with the transvaginal method, B. Cut the vagina after closed loop ligation of the vagina.	2024
RACC NCT03719547	Prospective randomized study	800	Robotic-assisted vs. open radical hysterectomy	Patients with FIGO stage (2018) IB1, IB2 or IIA1 disease	Not specified*	2027
SOLUTION NCT04370496	Single arm prospective study	124	Laparoscopic and robotic-assisted radical hysterectomy	Patients with FIGO stage (2018) IB disease	Radical hysterectomy through minimally invasive surgery using an endoscopic stapler which both cuts and simultaneously sutures the open vaginal stump	2028
MITOR NCT04999696	Prospective randomized study	820	Laparoscopic vs. open radical hysterectomy	Patients with FIGO stage (2018) IA1 (with lymph vascular space invasion), IA2, IB1, IB2 or IIA1 disease	Not specified*	2031

Abbreviation: FIGO, International Federation of Obstetrics and Gynecology; *, not specified in clinicaltrials.gov.

This study reported that minimally invasive radical hysterectomy was associated with increased rates of recurrence and death in patients with stage IB cervical cancer, regardless of tumor volume [18]. However, we have to point out that other retrospective experience seems to support the safety of minimally invasive hysterectomy in patients with tumor <2 cm. An Italian retrospective study reported that while laparoscopy correlated with worse disease-free survival in patients with stage IB2 disease, in stage with IB1 disease laparoscopy correlated with superimposable outcomes [31]. However, the number of events (i.e., recurrence) according to stage of the disease is highly impacting these results. Although the relatively high number of patients with tumors <2 cm included (114 and 137 in the open and laparoscopic group, respectively), the low prevalence of events in the stage IB1 group, made the analysis underpowered to demonstrate a statistically significant difference between the study groups [31]. Further studies have to address the point. Possibly the increase in tumor diameter is directly related to the increased risk of peritoneal contamination at the surgery. From a theoretical point of view, minimally invasive radical hysterectomy should be avoided in any patient with macroscopic cervical disease. Another point deserving attention in this cluster of patients is radicality. Level of radical is probably not influencing outcomes of patients with tumor <2 cm. Interestingly, in the prospective, single-arm, multicenter study ConCerv Trial patients with "low-risk early-stage cervical cancer" (i.e., those with FIGO grade 1 and 2 cervical cancer with tumor <2 cm, tumor stromal invasion <10 mm, and no lymphovascular space invasion) were offered to have conservative surgery and/or simple hysterectomy (with nodal assessment) [32]. Other studies highlighted that level of radicality is not impacting outcomes of patients with tumor <2 cm [33]. Hence, we can postulate that in this setting type of surgical approach is more impacting than level of radicality.

The impact of tumor volume on patients' outcomes (FIGO stage IA, no-macroscopic tumor)

Most patients included in the LACC trial were affected by stage IB1 disease, while only 51 (25 in the open group vs. 26 in the minimally invasive group) patients were affected by stage IA disease. In an aforementioned population-based study from the Ontario Cancer Registry, the authors evaluated the impact of surgical approach in patients with cervical cancer (stages: IA (n = 244), IB (n = 543), II+ (n = 124), and unknown (n = 56)) [18]. In this study, the surgical route did not impact the survival outcomes of patients affected by stage IA disease [18]. Similarly, other authors observed that minimally invasive surgery had no impact on stage IA cervical cancer [34]. However, we have to point out that two aspects might have influenced these results: (i) most patients with stage IA had no residual tumor at the surgery since they had had preoperative conization; (ii) a very large sample size would be necessary, due to the low risk of recurrence in stage IA, to show any difference. Therefore, even in the setting of stage IA cervical cancer, the adoption of minimally invasive surgery should be adopted with caution. Counseling about available evidence is necessary. Moreover, protective maneuvers are needed and patients would be enrolled into prospective registers.

Methods to reduce the risk of contamination during minimally invasive surgery

Recently, several researchers have attempted to identify maneuvers that would reduce the risk of contamination during minimally invasive radical hysterectomy [20]. These studies observed that methods aiming to reduce the risk of tumor fragmentation and intra-abdominal spread correlated with improved outcomes. Growing evidence highlighted that tumor removal with preoperative conization is associated with similar outcomes to open surgery removing the primary tumor before surgery avoids any source of spillover [35]. The European, multicenter, retrospective, observational cohort SUCCOR study was designed to evaluate disease-free survival in patients with stage IB1 cervical cancer undergoing open and minimally invasive radical hysterectomy. But more interestingly, as a secondary objective, the SUCCOR study aimed to investigate the association between protective surgical maneuvers and the risk of relapse. This study suggested that avoiding the uterine manipulator and using maneuvers to avoid tumor spread at the time of colpotomy in minimally invasive surgery was associated with similar outcomes to open surgery [18]. In particular, patients who had minimally invasive radical hysterectomy using a uterine manipulator experienced a 2.76-times higher hazard of recurrence; while patients who had a minimally invasive radical hysterectomy without a uterine manipulator experienced similar disease-free survival in comparison to patients who had an open radical hysterectomy. Similarly, the adoption of protective vaginal closure had similar rates of relapse to those who underwent open surgery (HR: 0.63; 95%CI: 0.15, 2.59; p < 0.52). Interestingly, other studies suggested the importance of avoiding

spillage during colpotomy. In particular, a recently published paper suggested that patients undergoing laparoscopy-assisted radical vaginal hysterectomy experienced similar outcomes than patients undergoing open surgery, thus highlighting the need to avoid the contact of the cervical tumor with the peritoneal cavity [36].

Ongoing trials

Three large studies are ongoing to assess the impact of minimally invasive techniques in managing cervical cancer [37]. The Robot-assisted Approach to Cervical Cancer (RACC) trial is focusing on the role of robotic-assisted surgery. The RACC study is randomizing patients to robotic-assisted and open surgery. The estimated enrollment is 800 patients. The estimated study completion date is February 2027 [37]. The RWS-01 trial is a multicenter, prospective, non-randomized study aiming to enroll 2000 participants having minimally invasive and open abdominal radical hysterectomy in China. The estimated study completion date is May 2024. The Minimally Invasive Therapy Versus Open Radical Hysterectomy (MITOR) for the management of early-stage cervical cancer aims to compare laparoscopic and open radical hysterectomy. The MITOR study is a prospective, randomized controlled trial. The estimated enrollment is 820 participants. The estimated study completion date is July 2033 [37]. Table 1 reports main details of the prospective studies investigating the role of minimally invasive surgery in cervical cancer.

Conclusions

Up to now, level A evidence suggested that the adoption of minimally invasive radical hysterectomy correlates with an increased risk of recurrence and cancer-specific death in comparison to open radical hysterectomy. Moreover, these data highlighted that the surgical approach (minimally invasive vs. open surgery) did not impact morbidity rates and QoL. Evidence corroborating the results of the LACC trial is needed. Further attention is necessary to identify the best way to avoid contamination at the time of radical hysterectomy [38]. At this point, in the light of the available evidence minimally invasive radical hysterectomy (for stage IB disease) should be proposed only in the setting of clinical trials or after a comprehensive discussion of the data available with patients demanding minimally invasive surgery.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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