Title: **Practice patterns and 90-day treatment-related morbidity in early-stage cervical cancer**

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Highlights:

- The publication of the LACC trial determined a shift from the use of minimally invasive to open surgery.
- Overall and severe 90-day complication rates were not influenced by the surgical approach
- The paradigm shift from minimally invasive to open radical hysterectomy does not increase the complication rate.

Abstract

Background: To evaluate the impact of the Laparoscopic Approach to Cervical Cancer (LACC) Trial on patterns of care and surgery-related morbidity in early-stage cervical cancer.

Methods: This is a retrospective, a multi-institutional study evaluating 90-day surgery-related outcomes of patients undergoing treatment for early-stage cervical cancer before (period I: 01/01/2016-06/01/2018) and after (period II: 01/01/2019-06/01/2021) the publication of the results of the LACC trial.

Results: Charts of 1,295 patients were evaluated: 581 (44.9%) and 714 (55.1%) before and after the publication of the LACC trial, respectively. After the publication of the LACC trial, the number of patients treated with minimally invasive radical hysterectomy decreased from 64.9% to 30.4% ($p<0.001$). Overall, 90-day complications occurred in 110 (18.9%) and 119 (16.6%) patients in the period I and period II, respectively ($p=0.795$). Similarly, the number of severe (grade 3 or worse) complications did not differ between the two periods (38 (6.5%) vs. 37 (5.1%); $p=0.297$). Overall and severe 90-day complications were consistent between periods even evaluating stage IA ($p=0.471$), IB1 ($p=0.929$), and IB2 ($p=0.074$), separately.

Conclusions: The present investigation highlighted that in referral centers the shift from minimally invasive to open radical hysterectomy does not influence 90-day surgery-related morbidity.

Keywords: Laparoscopy; Radical hysterectomy; Morbidity; Complications

Introduction

Over recent years, the minimally invasive approach has revolutionized surgical care [1]. Accumulating evidence highlighted that minimally invasive surgery correlated with better perioperative outcomes than open surgery [2, 3]. In comparison to open surgery, minimally-invasive surgery is associated with lower postoperative pain, recovery time, hospital stays, and marked improvements in cosmetic outcome and overall cost-effectiveness either in benign or malignant disease. Level A evidence supports the adoption of minimally invasive surgery in endometrial cancer [2]. Minimally invasive approach correlates with improved short-term postoperative course and morbidity than open surgery without affecting oncologic outcomes. Similarly, retrospective data highlighted the feasibility of laparoscopic radical hysterectomy in patients with early-stage cervical cancer [4-6].

The Laparoscopic Approach to Cervical Cancer (LACC) Trial was designed to assess the non-inferiority of a minimally invasive approach in comparison to open surgery [7]. However, the unexpected results of the LACC trial showed that a minimally invasive approach is associated with lower rates of disease-free survival and overall survival than open abdominal radical hysterectomy among women with early-stage cervical cancer [7]. Moreover, two secondary analyses of the randomized LACC trial suggested that minimally invasive and open approaches correlated with similar morbidity rates and postoperative quality of life (QoL) [8, 9]. The publication of the LACC trial impacted clinical practice, dramatically. We assisted in a rapid paradigm shift, with a decrease in the adoption of minimally invasive radical hysterectomy [10, 11]. Lewicki PJ et al., 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. Using data from the Premier Healthcare Database, the authors highlighted that the minimally invasive approach decreased from 58.0% (pre-LACC) to. 42.9% (post-LACC) [10]. Other studies reported similar findings [11]. Interestingly, they observed that the increased adoption of open radical hysterectomy resulted in an increased surgery-related

morbidity rate. In order to assess patterns of utilization of minimally invasive and open radical hysterectomy as well as surgery-related morbidity, we designed the present investigation.

Methods:

This is a multi-institutional retrospective study coordinated by the Fondazione IRCCS Istituto Nazionale dei Tumori. As coordinator center the Institutional Review Board of the Fondazione IRCCS Istituto Nazionale dei Tumori approved this investigation (#572020). Charts of patients affected by early-stage cervical cancer (stage IA- IB2) were collected in 24 referral centers in Italy. The primary endpoint measure was to evaluate how the publication of the LACC trial impacted patterns of care and surgery-related morbidity of patients affected by early-stage cervical cancer. For the purpose present study, we collected medical records of consecutive patients with newly diagnosed early-stage cervical cancer treated in Italy before (period I: 01/01/2016-06/01/2018) and after (period II: 01/01/2019-06/01/2021) the publication of the results of the LACC trial [7]. Supplemental material 1 displays the centers participating in the study.

We included consecutive patients receiving treatment (i.e., conservative approach, radical hysterectomy, and radiotherapy) in period I and period II. We included patients aged ≥ 18 years old, with a confirmed histological diagnosis of early-stage cervical cancer. In all included centers, data concerning surgical procedures, peri-operative details, as well as 90-day follow-up evaluations were recorded in computerized databases, updated by trained residents and nurses on a regular basis.

Exclusion criteria were: (i) stage II endometrial cancer receiving radical hysterectomy; (ii) administration of neoadjuvant chemotherapy; (iii) lack of data of 90-day postoperative course; (iv) consent withdrawal. During the two study periods, there were no significant differences in the facilities available for patient care and in the referral patterns of our services. Other features of patient management remained consistent in the two periods. The TNM classification was applied in order to categorize patients *per* stage [12]. Postoperative complications included any deviation of normal postoperative course, within 90 days. To improve quality of complication reporting complications

were graded per a severity system [13, 14]. The Clavien-Dindo classification was adopted to grade postoperative complications [13]. For the purpose of this study only severe complications, occurring within 90-day, are reported. They included events requiring surgical, endoscopic, or radiological intervention (with or without general anesthesia). Additionally, life threatening complications (including intensive care unit (ICU) admission as well as single or multi organ dysfunction) and postoperative death are registered [13]. Martin criteria were applied to improve quality of complications reporting [14]. Intraoperative complications were abstracted as well.

Statistical methods:

Basic descriptive statistics were used to describe the study populations. Differences in categorical variables were analyzed using the Fisher exact and Chi-square test when comparing two and three (or more) groups, respectively. When indicated odds ratio (OR) and 95% confidence intervals (95%CI) were calculated. T-test and Mann-Whitney tests were used to compare continuous variables as appropriate. P values <0.05 were considered statistically significant. Statistical analysis was performed with GraphPad Prism version 6.0 (GraphPad Software, San Diego CA) and IBM-Microsoft SPSS version 20.0 (SPSS Statistics. International Business Machines Corporation IBM 2013 Armonk, USA) for Mac.

Results:

Charts of 1,327 patients were retrieved. Data of 32 patients were excluded since they did not match the inclusion criteria. The study included 1,295 patients: 581 (44.9%) and 714 (55.1%) before and after the publication of the LACC trial, respectively. The study population included 199 (34.2%), 211 (36.3%), and 171 (29.4%) patients with stage IA, stage IB1, and stage IB2 treated in the period I and 293 (41.1%), 219 (30.6%), and 202 (28.3%) patients with stage IA, stage IB1, and stage IB2 treated in the period II (p=0.028; p-for trend <0.001). The proportion of patients receiving conservative treatments increase over the study period (13.6% vs. 20.6%; p-for trend <0.001); while the proportion

of patients receiving radiotherapy (with or without chemotherapy) remained stable in the two periods (5.8% vs. 7.3%; p=0.303). Figure 1 shows the flow of patients through the study design. Table 1 reports data of patients treated in the period I and period II. Data for patients affected by stage IA, IB1, and IB2 are reported in Supplemental material 2, 3, and 4, respectively. After the publication of the LACC trial, the number of patients treated with minimally-invasive radical hysterectomy decreased from 64.9% (304 out of 468 radical hysterectomies) to 30.4% (157 out of 515 radical hysterectomies) (p<0.001).The decrease of minimally-invasive radical hysterectomy rates was observed for patients with stage IA (81.8% vs. 58.2% (-23.6%); p<0.001), stage IB1 (68.8% vs. 20.3% (-48.5%); p<0.001), and stage IB2 (45.3% vs. 14.5% (-30.8%); p<0.001). All participating centers suggested that they adopted protective maneuvers with the aim to reduce the risk of disease dissemination at the time of minimally invasive radical hysterectomy. Those maneuvers included: (i) preoperative tumor removal thorough conization (n=130), the avoidance of the use of uterine manipulator (n=87), vaginal closure before colpotomy (n=37). In most cases, surgeons adopted more than one technique to reduce possible contamination of the abdominal cavity. These maneuvers were used in 86% of patients with tumors <2 cm and 100% of tumors larger than 2 cm. Intraoperative complication rates were similar between period I and period II (2.4% vs. 1.4%; p=0.215). Overall, 90-day complications occurred in 110 (18.9%) and 119 (16.6%) patients in the period I and period II, respectively (p=0.795). Similarly, the number of severe (grade 3 or worse) complications were not influenced by the publication of the LACC trial (38 (6.5%) vs. 37 (5.1%); p=0.297). Supplement material 5 reports details of overall and severe complications in period I and period II. Overall and severe 90-day complications were consistent between periods even evaluating stage IA, IB1, and IB2, separately (p>0.20). Table 2 shows overall and severe complications that occurred in period I and period II.

Considering available data on perioperative data, we observed that minimally invasive radical hysterectomy correlated with similar operative time (235 vs. 244 minutes; p=0.261) and lower blood

loss (100 vs. 200; p<0.001) in comparison to open surgery. The mean (SD) postoperative recovery time was 2 (1.1) and 4 (2.4) days after minimally-invasive and open radical hysterectomy (p<0.001).

Discussion

The present study evaluated changes in patterns of care and treatment-related morbidity in early-stage cervical cancer patients after the publication of the LACC trial [7]. The present study reported a number of noteworthy findings. First, we observed that the prevalence of minimally invasive radical hysterectomy significantly decreased after the publication of the LACC trial [7]. Second, the burden of intraoperative, 90-day postoperative complications, and 90-day severe postoperative complications remained stable over the periods. This finding was confirmed after stratification per stage of the disease. Third, we assisted an increased number of patients undergoing treatments in period II.

The LACC trial was designed to test the non-inferiority of minimally invasive radical hysterectomy in comparison to open radical hysterectomy in early-stage cervical cancer [7]. The trial planned to enroll 740 patients. However, the trial was suspended earlier (after the enrollment of 631 patients) since the imbalance in deaths between the two groups [7]. Ramirez et al., observed that patients undergoing minimally invasive radical hysterectomy had lower disease-free (91.2% vs. 97.1%) and overall (93.8% vs. 99%) survival rates and a higher rate of locoregional recurrence (94.3% vs. 98.3%) than patients who underwent open abdominal radical hysterectomy [7]. These findings were corroborated by an epidemiological study published in the same issue of the NEJM [15]. Melamed et al., reported data of patients with early-stage cervical cancer treated during the 2010-2013 period at Commission on Cancer-accredited hospitals in the United States. They also conducted an interrupted time-series analysis involving patients undergoing radical hysterectomy during the 2000-2010 period, using the Surveillance, Epidemiology, and End Results (SEER) program database [15]. In this paper, the authors observed that after a median follow-up of 45 months, the mortality rate was 9.1% and 5.3% after minimally invasive and open radical hysterectomy, respectively [15]. After the publication of those two studies, accumulating evidence suggested the detrimental role of minimally invasive

radical hysterectomy [16, 17]. Reasons, why the execution of minimally invasive hysterectomy correlates with poor outcomes, are still unknown. The most imputable reasons are the possible contamination of the pelvic cavity at the time of colpotomy and the flow of CO2 that might spread the cells into the abdominal cavity [16, 18]. We must note that the CO2 pressure might cause the penetration of the cells into the superficial mesothelial layer of the peritoneum. Moreover, the CO2 might promote the spread of the cells in mechanical and biochemical ways. Interestingly, research from our study group evaluated patterns of recurrence in patients undergoing laparoscopic and open radical hysterectomy [19]. Applying a propensity-matched comparison, the findings of this study highlighted that patients undergoing laparoscopic radical hysterectomy are at higher risk of developing intrapelvic recurrences and peritoneal carcinomatosis in comparison to patients undergoing open radical hysterectomy [19]. We assisted in a paradigm shift from minimally invasive to open radical hysterectomy [20].

The LACC trial is one of the most impacting studies in the field of gynecologic oncology, being a game-changer. Even the NEJM classified the LACC trial as one of the most impacting studies for the year 2018 [7]. Accumulating data from the U.S. suggested that after the publication of the LACC trial, a dramatic decrease in the adoption of minimally invasive radical hysterectomy was observed [10, 11]. Interestingly, Matsuo K et al., evaluating the National Inpatient Sample from October 2015 to December 2018, evaluated data of 5,120 and 1,645 patients undergoing surgery before and after the publication of the LACC. In the post LACC period patients were less likely to have a minimally invasive radical hysterectomy (-63%), but more likely to develop perioperative complications (+23%) and longer length of hospital stay (3 vs. 2 days) [11]. The present study provides similar findings, we observed an important (statistically significant) decrease in the adoption of minimally invasive radical hysterectomy that was more evident in patients with stage IB1 (-48.5%), than for stage IB2 (-30.8%), and stage IA (-23.6%). However, we have to highlight that the reduction of minimally invasive radical hysterectomy rates was less pronounced than those expected. In our series, the shift from minimally invasive to open hysterectomy did not correlate with an increased morbidity rate. This data

corroborated the secondary analysis of the LACC trial suggesting that surgery-related morbidity does not differ significantly between the two approaches [8]. The inherent biases related to the retrospective nature of the study design are the main weaknesses of the present paper. Additionally, four points of the present paper have to be addressed: (i) due to the absence of follow-up, we are not able to evaluate the impact of this paradigm shift on oncologic outcomes of early-stage cervical cancer patients involved in this study. (ii) we observed an increased number of patients treated in period II; this feature might be related both to the improvement in patients' workflow and due to COVID-19. After the onset of the COVID-19 outbreak, we assisted to centralization of oncologic cases in referral - highly specialized centers (like those included in our series) [21]. (iii) We collected a huge amount of data (more than 1,300 patients) from the whole Italian territory, with a potential missing of cervical cancer cases diagnosed and treated in low volume centers. (iv) We were not able to correct our results on the basis of patients demographic characteristics. The main merit of the present study is the inclusion of a large sample size of consecutive patients treated before and after the publication of the LACC trial [7]. Moreover, this paper investigated the impact of the LACC trial in a European country for the first time. Interestingly, the inclusion of patients who had not radical surgery (i.e., conservative treatment and radiotherapy) would help to avoid possible allocation biases and to better understand the changes in patterns of care in cervical cancer management.

In conclusion, the present study evaluated changes in the pattern of care in patients treated before and after the publication of the LACC trial [7]. We assisted in an important decrease in minimally invasive radical hysterectomy, over time. The increased prevalence of open surgery did not correlate with worse perioperative outcomes. Intraoperative, postoperative, and severe postoperative complication rates were similar between groups. Further evidence is warranted to assess peri-operative and long-term changes in early-stage cervical cancer, provided by the LACC trial [7].

Authors contribution:

Conceptualization: All authors., Methodology: All authors.; Data extraction: All authors; Project administration: GB, VDD.; Supervision: GS, FR.; writing – original draft: All authors; writing – review & editing: All authors.

Conflicts of interest:

The Authors declare no conflicts of interest.

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Legend to Figure:

Figure 1: Study design

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