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

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26

27 **Highlights:**

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

33 **Abstract**

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

36 **Methods:** This is a retrospective, a multi-institutional study evaluating 90-day surgery-related
37 outcomes of patients undergoing treatment for early-stage cervical cancer before (period I:
38 01/01/2016-06/01/2018) and after (period II: 01/01/2019-06/01/2021) the publication of the results
39 of the LACC trial.

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

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

50

51 **Keywords:** Laparoscopy; Radical hysterectomy; Morbidity; Complications

52 **Introduction**

53 Over recent years, the minimally invasive approach has revolutionized surgical care [1].
54 Accumulating evidence highlighted that minimally invasive surgery correlated with better
55 perioperative outcomes than open surgery [2, 3]. In comparison to open surgery, minimally-invasive
56 surgery is associated with lower postoperative pain, recovery time, hospital stays, and marked
57 improvements in cosmetic outcome and overall cost-effectiveness either in benign or malignant
58 disease. Level A evidence supports the adoption of minimally invasive surgery in endometrial cancer
59 [2]. Minimally invasive approach correlates with improved short-term postoperative course and
60 morbidity than open surgery without affecting oncologic outcomes. Similarly, retrospective data
61 highlighted the feasibility of laparoscopic radical hysterectomy in patients with early-stage cervical
62 cancer [4-6].

63 The Laparoscopic Approach to Cervical Cancer (LACC) Trial was designed to assess the non-
64 inferiority of a minimally invasive approach in comparison to open surgery [7]. However, the
65 unexpected results of the LACC trial showed that a minimally invasive approach is associated with
66 lower rates of disease-free survival and overall survival than open abdominal radical hysterectomy
67 among women with early-stage cervical cancer [7]. Moreover, two secondary analyses of the
68 randomized LACC trial suggested that minimally invasive and open approaches correlated with
69 similar morbidity rates and postoperative quality of life (QoL) [8, 9]. The publication of the LACC
70 trial impacted clinical practice, dramatically. We assisted in a rapid paradigm shift, with a decrease
71 in the adoption of minimally invasive radical hysterectomy [10, 11]. Lewicki PJ et al., assessed the
72 use of minimally invasive surgery as compared with open radical hysterectomy for cervical cancer
73 before and after the publication of the LACC Trial. Using data from the Premier Healthcare Database,
74 the authors highlighted that the minimally invasive approach decreased from 58.0% (pre-LACC) to
75 42.9% (post-LACC) [10]. Other studies reported similar findings [11]. Interestingly, they observed
76 that the increased adoption of open radical hysterectomy resulted in an increased surgery-related

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

79

80 **Methods:**

81 This is a multi-institutional retrospective study coordinated by the Fondazione IRCCS Istituto
82 Nazionale dei Tumori. As coordinator center the Institutional Review Board of the Fondazione
83 IRCCS Istituto Nazionale dei Tumori approved this investigation (#572020). Charts of patients
84 affected by early-stage cervical cancer (stage IA- IB2) were collected in 24 referral centers in Italy.
85 The primary endpoint measure was to evaluate how the publication of the LACC trial impacted
86 patterns of care and surgery-related morbidity of patients affected by early-stage cervical cancer. For
87 the purpose present study, we collected medical records of consecutive patients with newly diagnosed
88 early-stage cervical cancer treated in Italy before (period I: 01/01/2016-06/01/2018) and after (period
89 II: 01/01/2019-06/01/2021) the publication of the results of the LACC trial [7]. Supplemental material
90 1 displays the centers participating in the study.

91 We included consecutive patients receiving treatment (i.e., conservative approach, radical
92 hysterectomy, and radiotherapy) in period I and period II. We included patients aged ≥ 18 years old,
93 with a confirmed histological diagnosis of early-stage cervical cancer. In all included centers, data
94 concerning surgical procedures, peri-operative details, as well as 90-day follow-up evaluations were
95 recorded in computerized databases, updated by trained residents and nurses on a regular basis.
96 Exclusion criteria were: (i) stage II endometrial cancer receiving radical hysterectomy; (ii)
97 administration of neoadjuvant chemotherapy; (iii) lack of data of 90-day postoperative course; (iv)
98 consent withdrawal. During the two study periods, there were no significant differences in the
99 facilities available for patient care and in the referral patterns of our services. Other features of patient
100 management remained consistent in the two periods. The TNM classification was applied in order to
101 categorize patients *per* stage [12]. Postoperative complications included any deviation of normal
102 postoperative course, within 90 days. To improve quality of complication reporting complications

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

110

111 **Statistical methods:**

112 Basic descriptive statistics were used to describe the study populations. Differences in categorical
113 variables were analyzed using the Fisher exact and Chi-square test when comparing two and three (or
114 more) groups, respectively. When indicated odds ratio (OR) and 95% confidence intervals (95%CI)
115 were calculated. T-test and Mann-Whitney tests were used to compare continuous variables as
116 appropriate. P values <0.05 were considered statistically significant. Statistical analysis was
117 performed with GraphPad Prism version 6.0 (GraphPad Software, San Diego CA) and IBM-
118 Microsoft SPSS version 20.0 (SPSS Statistics. International Business Machines Corporation IBM
119 2013 Armonk, USA) for Mac.

120

121 **Results:**

122 Charts of 1,327 patients were retrieved. Data of 32 patients were excluded since they did not match
123 the inclusion criteria. The study included 1,295 patients: 581 (44.9%) and 714 (55.1%) before and
124 after the publication of the LACC trial, respectively. The study population included 199 (34.2%), 211
125 (36.3%), and 171 (29.4%) patients with stage IA, stage IB1, and stage IB2 treated in the period I and
126 293 (41.1%), 219 (30.6%), and 202 (28.3%) patients with stage IA, stage IB1, and stage IB2 treated
127 in the period II ($p=0.028$; p -for trend <0.001). The proportion of patients receiving conservative
128 treatments increase over the study period (13.6% vs. 20.6%; p -for trend <0.001); while the proportion

129 of patients receiving radiotherapy (with or without chemotherapy) remained stable in the two periods
130 (5.8% vs. 7.3%; $p=0.303$). Figure 1 shows the flow of patients through the study design. Table 1
131 reports data of patients treated in the period I and period II. Data for patients affected by stage IA,
132 IB1, and IB2 are reported in Supplemental material 2, 3, and 4, respectively. After the publication of
133 the LACC trial, the number of patients treated with minimally-invasive radical hysterectomy
134 decreased from 64.9% (304 out of 468 radical hysterectomies) to 30.4% (157 out of 515 radical
135 hysterectomies) ($p<0.001$). The decrease of minimally-invasive radical hysterectomy rates was
136 observed for patients with stage IA (81.8% vs. 58.2% (-23.6%); $p<0.001$), stage IB1 (68.8% vs.
137 20.3% (-48.5%); $p<0.001$), and stage IB2 (45.3% vs. 14.5% (-30.8%); $p<0.001$). All participating
138 centers suggested that they adopted protective maneuvers with the aim to reduce the risk of disease
139 dissemination at the time of minimally invasive radical hysterectomy. Those maneuvers included: (i)
140 preoperative tumor removal thorough conization ($n=130$), the avoidance of the use of uterine
141 manipulator ($n=87$), vaginal closure before colpotomy ($n=37$). In most cases, surgeons adopted more
142 than one technique to reduce possible contamination of the abdominal cavity. These maneuvers were
143 used in 86% of patients with tumors <2 cm and 100% of tumors larger than 2 cm. Intraoperative
144 complication rates were similar between period I and period II (2.4% vs. 1.4%; $p=0.215$). Overall,
145 90-day complications occurred in 110 (18.9%) and 119 (16.6%) patients in the period I and period II,
146 respectively ($p=0.795$). Similarly, the number of severe (grade 3 or worse) complications were not
147 influenced by the publication of the LACC trial (38 (6.5%) vs. 37 (5.1%); $p=0.297$). Supplement
148 material 5 reports details of overall and severe complications in period I and period II. Overall and
149 severe 90-day complications were consistent between periods even evaluating stage IA, IB1, and IB2,
150 separately ($p>0.20$). Table 2 shows overall and severe complications that occurred in period I and
151 period II.

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

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

156

157 **Discussion**

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

165 The LACC trial was designed to test the non-inferiority of minimally invasive radical hysterectomy
166 in comparison to open radical hysterectomy in early-stage cervical cancer [7]. The trial planned to
167 enroll 740 patients. However, the trial was suspended earlier (after the enrollment of 631 patients)
168 since the imbalance in deaths between the two groups [7]. Ramirez et al., observed that patients
169 undergoing minimally invasive radical hysterectomy had lower disease-free (91.2% vs. 97.1%) and
170 overall (93.8% vs. 99%) survival rates and a higher rate of locoregional recurrence (94.3% vs. 98.3%)
171 than patients who underwent open abdominal radical hysterectomy [7]. These findings were
172 corroborated by an epidemiological study published in the same issue of the NEJM [15]. Melamed et
173 al., reported data of patients with early-stage cervical cancer treated during the 2010-2013 period at
174 Commission on Cancer-accredited hospitals in the United States. They also conducted an interrupted
175 time-series analysis involving patients undergoing radical hysterectomy during the 2000-2010 period,
176 using the Surveillance, Epidemiology, and End Results (SEER) program database [15]. In this paper,
177 the authors observed that after a median follow-up of 45 months, the mortality rate was 9.1% and
178 5.3% after minimally invasive and open radical hysterectomy, respectively [15]. After the publication
179 of those two studies, accumulating evidence suggested the detrimental role of minimally invasive

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

192 The LACC trial is one of the most impacting studies in the field of gynecologic oncology, being a
193 game-changer. Even the NEJM classified the LACC trial as one of the most impacting studies for the
194 year 2018 [7]. Accumulating data from the U.S. suggested that after the publication of the LACC
195 trial, a dramatic decrease in the adoption of minimally invasive radical hysterectomy was observed
196 [10, 11]. Interestingly, Matsuo K et al., evaluating the National Inpatient Sample from October 2015
197 to December 2018, evaluated data of 5,120 and 1,645 patients undergoing surgery before and after
198 the publication of the LACC. In the post LACC period patients were less likely to have a minimally
199 invasive radical hysterectomy (-63%), but more likely to develop perioperative complications (+23%)
200 and longer length of hospital stay (3 vs. 2 days) [11]. The present study provides similar findings, we
201 observed an important (statistically significant) decrease in the adoption of minimally invasive radical
202 hysterectomy that was more evident in patients with stage IB1 (-48.5%), than for stage IB2 (-30.8%),
203 and stage IA (-23.6%). However, we have to highlight that the reduction of minimally invasive radical
204 hysterectomy rates was less pronounced than those expected. In our series, the shift from minimally
205 invasive to open hysterectomy did not correlate with an increased morbidity rate. This data

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

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

229

230 **Authors contribution:**

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

234

235 **Conflicts of interest:**

236 The Authors declare no conflicts of interest.

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238

239 **Legend to Figure:**

240 Figure 1: Study design

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