Survival after minimally invasive surgery in early cervical cancer: is the intra-uterine manipulator to blame?

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HIGHLIGHTS

• Use of an intra-uterine manipulator in patients with early cervical cancer was not an independent factor associated with recurrence.
• Tumor size is a significant predictor of recurrence in patients who undergo minimally invasive radical hysterectomy.
• Eliminating intra-uterine manipulator use does not mitigate the higher recurrence rate with minimally invasive radical hysterectomy.

ABSTRACT

Objectives Minimally invasive radical hysterectomy is associated with decreased survival in patients with early cervical cancer. The objective of this study was to determine whether the use of an intra-uterine manipulator at the time of laparoscopic or robotic radical hysterectomy is associated with inferior oncologic outcomes.

Methods A retrospective cohort study was carried out of all patients with cervical cancer (squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma) International Federation of Gynecology and Obstetrics 2009 stages IA1 (with positive lymphovascular space invasion) to IIA who underwent minimally invasive radical hysterectomy at two academic centers between January 2007 and December 2017. Treatment, tumor characteristics, and survival data were retrieved from hospital records.

Results A total of 224 patients were identified at the two centers; 115 had surgery with the use of an intra-uterine manipulator while 109 did not; 53 were robotic and 171 were laparoscopic. Median age was 44 years (range 38–54) and median body mass index was 25.8 kg/m² (range 16.6–51.5). Patients in whom an intra-uterine manipulator was not used at the time of minimally invasive radical hysterectomy were more likely to have residual disease at hysterectomy (p<0.001), positive lymphovascular space invasion (p=0.02), positive margins (p=0.008), and positive lymph node metastasis (p=0.003). Recurrence-free survival at 5 years was 80% in the no intra-uterine manipulator group and 94% in the intra-uterine manipulator group. After controlling for the presence of residual cancer at hysterectomy, tumor size and high-risk pathologic criteria (positive margins, parametria or lymph nodes), the use of an intra-uterine manipulator was no longer significantly associated with worse recurrence-free survival (HR 0.4, 95% CI 0.2 to 1.0, p=0.05). The only factor which was consistently associated with recurrence-free survival was tumor size (HR 2.1, 95% CI 1.5 to 3.0, for every 10 mm increase, p<0.001).

Conclusion After controlling for adverse pathological factors, the use of an intra-uterine manipulator in patients with early cervical cancer who underwent minimally invasive radical hysterectomy was not an independent factor associated with rate of recurrence.

INTRODUCTION

Cervical cancer is the most common gynecologic malignancy,1 and the third most common cause of cancer-related death in women2 in the developing world. In North America, more than 70% of cervical cancer cases are diagnosed at an early stage through routine screening.3–5 Prognosis for early stage cervical cancer after radical hysterectomy and pelvic lymphadenectomy is excellent, with over 90% recurrence-free survival in randomized and long-term follow-up studies.6 7

Retrospective studies and a meta-analysis showing excellent short-term morbidity and equivalent oncologic outcomes with a minimally invasive approach led to the adoption of laparoscopic and robotic surgery around the world.7–10 However, the results of the Laparoscopic Approach to Cervical Cancer (LACC) trial, a randomized controlled trial, as well as several population-based studies8 7 9 have raised concerns about the oncologic safety of minimal invasive surgery compared with laparotomy in the treatment of early cervical cancer, showing increased recurrence of disease and mortality with laparoscopic and robotic approaches. Several hypotheses have been proposed to explain these observations, including low volumes and insufficient surgeon experience with minimally invasive radical hysterectomy, tumor exposure to the abdominal cavity, and tumor dissemination with the use of an intra-uterine manipulator or carbon dioxide gas.10–12

The use of an intra-uterine manipulator is not obligatory at radical hysterectomy, but it can improve the...
ability to mobilize the uterus and increase visualization. However, there are concerns about its oncologic safety in gynecologic malignancies, especially cervical cancer, as the device is inserted through the cervical canal. 13–15 Currently, two randomized trials are accruing patients with the goal of evaluating survival and recurrence rates after open and minimally invasive radical hysterectomy for early cervical cancer. A secondary objective of the study by Chao et al is to test the association between intra-uterine manipulator use and survival in the minimally invasive radical hysterectomy group. 16,17 Our study was designed to determine if use of an intra-uterine manipulator during minimally invasive radical hysterectomy for early cervical cancer is associated with increased rates of cancer recurrence.

**METHODS**

**Patient selection**

This was a retrospective cohort study at two academic cancer centers in Toronto, Canada. The Research Ethics Boards at both centers provided approval. Patients treated with a radical hysterectomy between January 2007 and December 2017 with a minimally invasive approach (laparoscopic or robotic) for a diagnosis of cervical cancer were identified using validated Canadian Classification of Health Interventions (CCI) procedure codes in hospital medical records. All International Federation of Gynecology and Obstetrics (FIGO) 2009 18 stages IA1 (with positive lymphovascular space invasion) to IIA and the following histologies were included: squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma. Patient demographics, pathological data, surgical and peri-operative details, as well as follow-up information were retrospectively collected from electronic medical records.

**Surgical procedure**

The primary treatment protocol for patients with early cervical cancer at both institutions was radical hysterectomy if the tumor was <40 mm in size and primary chemo-radiation for tumors >40 mm. However, for young patients with tumors >40 mm, radical hysterectomy was considered if the tumor was exophytic with superficial (<1/3) stromal involvement on magnetic resonance imaging. All patients included in this study underwent a minimally invasive radical hysterectomy and lymph node assessment with sentinel lymph node biopsy or bilateral pelvic lymphadenectomy. When the sentinel lymph node was positive, surgeons either completed ipsilateral pelvic lymphadenectomy with or without assessment of the para-aortic lymph nodes or abandoned the hysterectomy in favor of primary chemo-radiation. Only patients who underwent hysterectomy were included in this study. The protocols for the sentinel lymph node procedure using technetium sulfur colloid or indocyanine green have been published independently by the two centers. 19,20

The main exposure was use of an intra-uterine manipulator (VCare, ConMed Endosurgery, Utica, New York, USA) at the time of minimally invasive radical hysterectomy, ascertained from surgical reports. The decision of whether to use an intra-uterine manipulator was at the discretion of the surgeon, but due to institution-specific convention, surgeons at one center all used an intra-uterine manipulator while surgeons at the second center did not.

**Outcome assessment**

Our primary objective was to study the impact of using an intra-uterine manipulator at the time of minimally invasive radical hysterectomy on recurrence-free survival in patients with early cervical cancer. The primary outcome was recurrence-free survival, and this was calculated from time of hysterectomy to time of recurrence. Recurrence was defined as the date of radiologic or histopathologic confirmation.

**Statistical analysis**

We compared patient and tumor characteristics between the two groups. Means of continuous normally distributed variables were compared using the Student’s t-test, while medians of continuous variables that were not normally distributed were compared using the Wilcoxon rank-sum test. Categorical data were compared using the $\chi^2$ or the Fisher exact test. Statistical significance was defined as a p value of <0.05 (two-tailed comparison). Missing data were assumed to be missing at random. Kaplan–Meier survival curves for recurrence-free survival were generated and compared using the log-rank test between patients who had minimally invasive radical hysterectomy with the use of an intra-uterine manipulator and those in whom one was not used. A multivariable Cox proportional hazards model was constructed for recurrence-free survival. Included variables were chosen a priori based on clinical relevance and previous literature, and these included the presence of residual tumor in the hysterectomy specimen, pathologic tumor size (operationalized as continuous variable for every 10 mm increase in size), and a composite of high-risk prognostic criteria (positive surgical margins, positive lymph node metastasis, or positive parametria). Multicollinearity was assessed and model assumptions were tested, including the proportional hazards assumption. The decision to perform subgroup analysis for the lowest risk patients with tumors <20 mm was made a priori. A multivariable model was not constructed due to the lack of events in one of the two groups.

Statistical analysis was completed using SAS 9.4.

**RESULTS**

**Cohort characteristics**

We identified 224 patients with early cervical cancer treated with minimally invasive radical hysterectomy. An intra-uterine manipulator was used in 115 (51%) and no intra-uterine manipulator was used in 109 (49%). Patient and treatment characteristics are detailed in Table 1. Median age was 42 years (IQR 38–54) and median pathologic tumor size was 15 mm (IQR 7–25). The majority of patients had FIGO 2014 stage IB1 (78%) and squamous cell (47%) or adenocarcinoma (44%) histology. There was no statistically significant difference between the two groups (manipulator and no manipulator, respectively) with respect to patients’ age (median 44 vs 42 years, p=0.11), year of surgery (46% vs 35% after 2013, p=0.15), pathologic tumor size (median 13 mm vs 17 mm, p=0.31), proportion of patients who received adjuvant treatment (16.5% vs 22.9%, p=0.23). Stage distribution between the two groups was similar with <5% of cases categorized as 2009 FIGO stage >IB1. The no intra-uterine manipulator group had a significantly higher proportion of patients with residual tumor in the hysterectomy specimen (84%...
Original research

Table 1  Patient and tumor characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total n=224</th>
<th>Intra-uterine manipulator n=115</th>
<th>No intra-uterine manipulator n=109</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (IQR)</td>
<td>44 (38–54)</td>
<td>44.5 (40–55)</td>
<td>42 (37–54)</td>
<td>0.11</td>
</tr>
<tr>
<td>Year of surgery, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td>2007–2012</td>
<td>135 (60%)</td>
<td>64 (56%)</td>
<td>71 (65%)</td>
<td></td>
</tr>
<tr>
<td>2013–2017</td>
<td>89 (40%)</td>
<td>51 (46%)</td>
<td>38 (35%)</td>
<td></td>
</tr>
<tr>
<td>FIGO stage, n (%)*</td>
<td></td>
<td></td>
<td></td>
<td>0.026</td>
</tr>
<tr>
<td>IA1</td>
<td>15 (6.9%)</td>
<td>3 (2.7%)</td>
<td>12 (11%)</td>
<td></td>
</tr>
<tr>
<td>IA2</td>
<td>28 (12.8%)</td>
<td>17 (15.5%)</td>
<td>11 (10.1%)</td>
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</tr>
<tr>
<td>IB1</td>
<td>170 (77.6%)</td>
<td>89 (80.9%)</td>
<td>81 (74.3%)</td>
<td></td>
</tr>
<tr>
<td>IB2</td>
<td>4 (1.8%)</td>
<td>0 (0%)</td>
<td>4 (3.7%)</td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>2 (0.9%)</td>
<td>1 (0.9%)</td>
<td>1 (0.9%)</td>
<td></td>
</tr>
<tr>
<td>Histology, n (%)*</td>
<td></td>
<td></td>
<td></td>
<td>0.046</td>
</tr>
<tr>
<td>Squamous</td>
<td>104 (46.9%)</td>
<td>51 (45.1%)</td>
<td>53 (48.6%)</td>
<td></td>
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<td>Adenocarcinoma</td>
<td>97 (43.7%)</td>
<td>56 (49.6%)</td>
<td>41 (37.6%)</td>
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<tr>
<td>Adenosquamous</td>
<td>21 (9.4%)</td>
<td>6 (5.3%)</td>
<td>15 (13.8%)</td>
<td></td>
</tr>
<tr>
<td>Adjuvant, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.23</td>
</tr>
<tr>
<td>Yes</td>
<td>44 (19.6%)</td>
<td>19 (16.5%)</td>
<td>25 (22.9%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>180 (80.4%)</td>
<td>96 (83.5%)</td>
<td>84 (77.1%)</td>
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<tr>
<td>Residual, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
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<tr>
<td>Yes</td>
<td>153 (68.3%)</td>
<td>61 (53%)</td>
<td>92 (84.4%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>71 (31.7%)</td>
<td>54 (47%)</td>
<td>17 (15.6%)</td>
<td></td>
</tr>
<tr>
<td>Size (mm),* median (IQR)</td>
<td>15 (7–25)</td>
<td>13 (6.7–24)</td>
<td>17 (9–25)</td>
<td>0.31</td>
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<tr>
<td>LVSI, n (%)*</td>
<td></td>
<td></td>
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<td>0.02</td>
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<tr>
<td>Positive</td>
<td>77 (38.3%)</td>
<td>28 (29.8%)</td>
<td>49 (45.8%)</td>
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<tr>
<td>Negative</td>
<td>124 (61.7%)</td>
<td>66 (70.2%)</td>
<td>58 (54.2%)</td>
<td></td>
</tr>
<tr>
<td>Margins, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.0038</td>
</tr>
<tr>
<td>Positive</td>
<td>17 (7.6%)</td>
<td>3 (2.6%)</td>
<td>14 (12.8%)</td>
<td></td>
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<tr>
<td>Negative</td>
<td>207 (92.4%)</td>
<td>112 (97.4%)</td>
<td>95 (87.2%)</td>
<td></td>
</tr>
<tr>
<td>Parametria, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.65</td>
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<tr>
<td>Positive</td>
<td>7 (3.1%)</td>
<td>3 (2.6%)</td>
<td>4 (3.7%)</td>
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<tr>
<td>Negative</td>
<td>217 (96.9%)</td>
<td>112 (97.4%)</td>
<td>103 (96.3%)</td>
<td></td>
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<tr>
<td>Nodes, n (%)</td>
<td></td>
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<td>0.0081</td>
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<tr>
<td>Positive</td>
<td>26 (11.6%)</td>
<td>7 (6.1%)</td>
<td>19 (17.4%)</td>
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<tr>
<td>Negative</td>
<td>198 (88.4%)</td>
<td>108 (93.9%)</td>
<td>90 (82.6%)</td>
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<td>Recurrence, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.0029</td>
</tr>
<tr>
<td>Yes</td>
<td>28 (12.5%)</td>
<td>7 (6.1%)</td>
<td>21 (19.3%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>196 (87.5%)</td>
<td>108 (93.9%)</td>
<td>88 (80.7%)</td>
<td></td>
</tr>
</tbody>
</table>

*Missing 5 for stage, 2 for histology, 5 for size, 23 for LVSI.
FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion.

vs 53%, p<0.0001), a higher proportion with lymphovascular space invasion (46% vs 30%, p=0.02), positive margins (13% vs 3%, p=0.004), and positive lymph node metastases (17% vs 6%, p=0.008).

Recurrence-free survival
Median follow-up was 50 months (IQR 27–63 months). There were a total of 28 recurrences, 7 (6%) in the intra-uterine manipulator group and 21 (19%) in the no intra-uterine manipulator group.
significant differences with respect to patients’ age (median 45.7 in 69 patients. Within this subgroup there were no statistically and were inc


characteristics are shown in Table 3. An intra-

A total of 140 patients (62.5%) had small tumors ≤20

Subgroup analysis: ≤20 mm tumors

was the only variable predictive of recurrence (HR 2.1 for every 10

Median time to recurrence was 21 months (IQR 10–34 months). We observed no recurrences in patients with tumors <7 mm in size. Median survival was not reached in this low-risk cohort of early stage disease. Five-year recurrence-free survival was 94% in the intra-uterine manipulator group and 80% in the no intra-uterine manipulator group. The unadjusted analysis for recurrence found that the use of an intra-uterine manipulator was associated with significantly improved recurrence-free survival (p=0.0085) (Figure 1).

On multivariable analysis, after adjusting for confounders there was a trend for improved survival in the intra-uterine manipulator group (HR 0.4, 95% CI 0.2 to 1.0, p=0.05). Pathologic tumor size was the only variable predictive of recurrence (HR 2.1 for every 10 mm increase in tumor size, 95% CI 1.5 to 3.0, p<0.001), while residual disease at hysterectomy (HR 2.0, 95% CI 0.4 to 9.3, p=0.4) and high-risk pathologic criteria (HR 0.7, 95% CI 0.3 to 2.0, p=0.40) were not significantly associated with recurrence (Table 2).

Subgroup analysis: ≤20 mm tumors

A total of 140 patients (62.5%) had small tumors ≤20 mm in size and were included in our subgroup analysis. Patient and tumor characteristics are shown in Table 3. An intra-uterine manipulator was used in 71 patients and no intra-uterine manipulator was used in 69 patients. Within this subgroup there were no statistically significant differences with respect to patients’ age (median 45.7 vs 44.4 years, p=0.45), tumor size (median 8.7 mm and 10 mm, p=0.64), proportion of patients with lymphovascular space invasion (20% vs 29.9%, p=0.21), positive margins (1.4% vs 5.8%, p=0.16), or receiving adjuvant treatment (8.5% vs 14.5%, p=0.26) between patients who had surgery with an intra-uterine manipulator and those who did not. The no intra-uterine manipulator group had a higher proportion of patients with residual tumor at hysterectomy (78% vs 44%, p=0.0001) and with positive lymph node metastases (12% vs 1%, p=0.01). Eight patients (12%) experienced a recurrence at 5-year follow-up, all in the no intra-uterine manipulator group; there were no recurrences in the group of patients in which an intra-uterine manipulator was used. Tumor characteristics of the eight patients who recurred are shown in Table 4. One of these patients had positive margins, three had positive lymph node metastasis and five had lymphovascular space invasion; three of the eight were treated with adjuvant chemo-radiation based on the presence of high-risk pathologic criteria.

DISCUSSION

The results of the LACC trial have had an overwhelming effect on the gynecologic oncology community and have led us to reassess and radically change the standard treatment of early cervical cancer. Despite not knowing the mechanism by which a minimally invasive approach to radical hysterectomy in the treatment of early cervical cancer negatively impacts the survival of patients, most surgeons have abandoned the practice in favor of laparotomy and some have tried to modify the technique or to restrict the patients to whom it is offered. We observed a 5-year recurrence-free survival of 94% and 100% in the entire intra-uterine manipulator group and in the subgroup with tumors ≤20 mm in size, respectively.

The use of an intra-uterine manipulator is a well-established and accepted practice in gynecology, but its use in gynecologic malignancies has been questioned. A recent large multicenter retrospective study found that, in patients with FIGO stage I–II endometrial cancer, the use of an intra-uterine manipulator at minimally invasive surgery was associated with worse oncological outcomes, while several other retrospective studies did not find that intra-uterine manipulator use increased the risk of recurrence or affected patient survival. Results are also mixed in recent cervical cancer literature; a recent large multi-institutional retrospective study only included 26 patients who had minimally invasive radical hysterectomy without an intra-uterine manipulator and observed no recurrences. The SUCCOR study, a large cohort study from Europe comparing outcomes of minimally invasive radical

Table 2 Results of Cox proportional hazards analysis adjusting for tumor size (as continuous variable for every 10 mm increase), residual disease in hysterectomy specimen, and high-risk pathologic criteria (positive margins, parametria, lymph nodes)

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% confidence limits</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-uterine manipulator</td>
<td>0.4</td>
<td>0.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Residual disease on hysterectomy specimen</td>
<td>2.0</td>
<td>0.4</td>
<td>9.3</td>
</tr>
<tr>
<td>Tumor size (for every 10 mm increase)</td>
<td>2.1</td>
<td>1.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Meets high-risk pathologic criteria</td>
<td>0.7</td>
<td>0.3</td>
<td>2.0</td>
</tr>
</tbody>
</table>

A total of 219 observations included in the model (five missing data for tumor size).
hysterectomy with laparotomy, showed that the use of an intra-uterine manipulator was associated with a 2.76 times increase in the hazard of recurrence.33

The goal of our study is not to advocate for the continued use of minimally invasive surgery or the use of intra-uterine manipulators in cervical cancer; our aim was to single out the effect of intra-uterine manipulator use in laparoscopic and robotic surgery in order to test if this may contribute to the observed decreased survival. Our study did not find any evidence of harm associated with the use of an intra-uterine manipulator, and we speculate that it is likely that another mechanism yet to be determined also contributes to the increased rate of recurrence in the minimally invasive group of the LACC trial. Nevertheless, our intra-uterine manipulator group was a low-risk group, and these findings are thus not generalizable to a general population with larger tumors or with additional high-risk pathologic factors. Compared with the SUCCOR study,33 where all patients had FIGO stage IB1 disease and patients with previous conization were excluded, our cohort included 32% of patients with no residual disease and 20% of patients with FIGO stage IA who have a lower risk of recurrence. In the SUCCOR study, disease-free survival at 4.5 years in the minimally invasive radical hysterectomy group was 79%; at a median follow-up of 50 months,

### Table 3  Patient and tumor characteristics for those with tumors ≤20 mm

<table>
<thead>
<tr>
<th></th>
<th>Total n=140</th>
<th>Intra-uterine manipulator n=71</th>
<th>No intra-uterine manipulator n=69</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (IQR)</td>
<td>44.4 (38–55)</td>
<td>45.7 (48.9–55.8)</td>
<td>44.4 (38–55)</td>
<td>0.45</td>
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<tr>
<td>FIGO stage, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1A1</td>
<td>14 (10.1%)</td>
<td>2 (2.9%)</td>
<td>12 (17.4%)</td>
<td>0.01</td>
</tr>
<tr>
<td>1A2</td>
<td>25 (18.1%)</td>
<td>15 (21.7%)</td>
<td>10 (14.5%)</td>
<td></td>
</tr>
<tr>
<td>1B1</td>
<td>99 (71.7%)</td>
<td>52 (75.4)*</td>
<td>47 (68.1%)</td>
<td></td>
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<tr>
<td>Histology, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.23</td>
</tr>
<tr>
<td>Squamous</td>
<td>62 (44.3%)</td>
<td>29 (40.9%)</td>
<td>33 (47.8%)</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>64 (45.7%)</td>
<td>37 (52.1%)</td>
<td>27 (39.1%)</td>
<td></td>
</tr>
<tr>
<td>Adenosquamous</td>
<td>14 (10%)</td>
<td>5 (7%)</td>
<td>9 (13.1%)</td>
<td></td>
</tr>
<tr>
<td>Adjuvant, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.26</td>
</tr>
<tr>
<td>Yes</td>
<td>16 (11.4%)</td>
<td>6 (8.5%)</td>
<td>10 (14.5%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>124 (88.6%)</td>
<td>65 (91.5%)</td>
<td>59 (85.5%)</td>
<td></td>
</tr>
<tr>
<td>Residual, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Yes</td>
<td>85 (60.7%)</td>
<td>31 (43.7%)</td>
<td>54 (78.3%)</td>
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</tr>
<tr>
<td>No</td>
<td>55 (39.3%)</td>
<td>40 (56.3%)</td>
<td>15 (21.7%)</td>
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</tr>
<tr>
<td>Size (mm), median (IQR)</td>
<td>9.3 (5–14)*</td>
<td>8.7 (5.5–13)</td>
<td>10 (3.5–14.8)</td>
<td>0.64</td>
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<tr>
<td>LVSI, n (%)</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Positive</td>
<td>31 (25.4%)</td>
<td>11 (20%)</td>
<td>20 (29.9%)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>91 (74.6%)*</td>
<td>44 (80%)</td>
<td>47 (70.1%)</td>
<td></td>
</tr>
<tr>
<td>Margins, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.16</td>
</tr>
<tr>
<td>Positive</td>
<td>5 (3.6%)</td>
<td>1 (1.4%)</td>
<td>4 (5.8%)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>135 (96.4%)</td>
<td>70 (98.6%)</td>
<td>65 (94.2%)</td>
<td></td>
</tr>
<tr>
<td>Parametria, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>140 (100%)</td>
<td>71 (100%)</td>
<td>69 (100%)</td>
<td></td>
</tr>
<tr>
<td>Nodes, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Positive</td>
<td>9 (6.4%)</td>
<td>1 (1.4%)</td>
<td>8 (11.6%)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>131 (93.6%)</td>
<td>70 (98.6%)</td>
<td>61 (88.4%)</td>
<td></td>
</tr>
<tr>
<td>Recurrence, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Yes</td>
<td>8 (5.7%)</td>
<td>0 (0%)</td>
<td>8 (11.6%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>132 (94.3%)</td>
<td>71 (100%)</td>
<td>61 (88.4%)</td>
<td></td>
</tr>
</tbody>
</table>

*Missing two for stage, two for size, 18 for LVSI.

FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion.
disease-free survival in our cohort was 87%. We propose that perhaps uterine manipulator use has a more significant negative impact in patients with larger tumors such as in the SUCCOR study (60% of patients with >20 mm tumors), and that this effect is mitigated in our lower risk cohort of patients with smaller tumors (63% of patients with <20 mm tumors). We found that tumor size was a statistically significant predictor for recurrence in our study. This finding may give insight to the possible mechanism of recurrence, with larger tumors having an increased risk of tumor spillage into the peritoneal cavity at colpotomy. In a large retrospective multicenter study the authors showed that patients who had conization before surgery had a lower rate of recurrence, and patients with no residual tumor at hysterectomy had no recurrences.\(^{34}\) Similarly, we noted no recurrences in patients with microscopic (<7 mm) tumors, which are less likely to have spillage and dissemination in the peritoneal cavity. Moreover, we showed in this study that the rate of recurrence in the <20 mm group is not insignificant; thus, the 20 mm cut-off for tumor size, which now differentiates FIGO stage IB1 from IB2 based on new staging criteria,\(^{35}\) is not sensitive enough to differentiate between patients who may still benefit from a minimally invasive approach. Uppal et al also observed increased recurrence in patients with cervical tumors <20 mm who underwent minimally invasive radical hysterectomy compared with those who had a laparotomy.\(^{34}\) Tumor size is a continuous variable, and while survival has been shown to be superior with tumors <20 mm, likely due to a lower risk of parametrial and nodal involvement which is proportional to tumor size,\(^{36}\) this cut-off should not be extrapolated and applied to the debate regarding surgical approach.

In the post-LACC trial climate, various groups have devised modifications to the standard minimally invasive radical hysterectomy with the goal of containing the cervical tumor, preventing dissemination, and preventing recurrence.\(^{14}\) These employ a combination of not using an intra-uterine manipulator, performing a portion of the surgery vaginally, and preventing intra-abdominal exposure of the cervical tumor. A recent report from Germany describes a combined laparoscopic-vaginal technique in a large sample of patients, yielding over 95% disease-free and overall survival in long-term follow-up, similar to the laparotomy arm of the LACC trial.\(^{39}\) This was a retrospective study of a low-risk group, with the majority of tumors <20 mm and only 27% lymphovascular space invasion, 1% parametrial involvement, and 3% lymph node metastasis. This is similar to our intra-uterine manipulator group with respect to tumor characteristics, while the characteristics of the patients in our no intra-uterine manipulator group are more similar to those of patients in the LACC trial, who had a higher proportion of parametrial and lymph node involvement. Minimally invasive radical hysterectomy may then yield similar oncologic outcomes to an open approach in a low-risk group irrespective of intra-uterine manipulator use; however, none of these studies were designed or powered to answer this question.

Our study does have its limitations, the most evident being the retrospective non-randomized study design which makes it prone to selection, measurement, and attrition bias. Selection bias is evident in the differences we noted between the two groups with respect to patient and tumor characteristics. The no manipulator group included a higher proportion of patients with high-risk factors (residual disease at hysterectomy, positive lymph nodes, parametria and margins), and thus more patients in this group experienced recurrence irrespective of intra-uterine manipulator use. We chose to mitigate this in our multivariable analysis by controlling for the abovementioned confounders, as well as for tumor size. The relatively small sample size and low event rate allowed for inclusion of only a few co-variables in order to avoid model overspecification.\(^{40}\) Even after adjusting for a number of variables in our recurrence analysis there is residual confounding, with the intra-uterine manipulator group having a trend towards less recurrence (HR 0.4, 95% CI 0.2 to 1.0). We attribute this to the substantial heterogeneity of the two groups being compared at two different institutions, which is a limitation of this study.

Despite these limitations, our results add important information to the existing literature. Eliminating the use of an intra-uterine manipulator is not likely to constitute enough change from the minimally invasive radical hysterectomy techniques routinely employed before the LACC trial to improve oncologic outcomes. Despite undergoing minimally invasive radical hysterectomy with an intra-uterine manipulator, we showed that patients with low-risk features have very good long-term oncologic outcomes. Finally, we found that tumor size is a significant predictor of disease recurrence in patients who underwent minimally invasive radical hysterectomy, indicating perhaps that a key mechanism at play is intra-abdominal dissemination of malignant cells during minimally invasive colpotomy.

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**Table 4** Tumor characteristics of patients with tumors ≤20 mm who recurred

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Histology</th>
<th>Size (mm)</th>
<th>Margins</th>
<th>Nodes</th>
<th>LVSI</th>
<th>Chemo-radiation</th>
<th>Recurrence-free survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Adenocarcinoma</td>
<td>7</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>Adenosquamous</td>
<td>18</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>Adenosquamous</td>
<td>8</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>Squamous</td>
<td>13</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>27</td>
</tr>
<tr>
<td>5</td>
<td>Adenosquamous</td>
<td>20</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>36</td>
</tr>
<tr>
<td>6</td>
<td>Squamous</td>
<td>18</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>36</td>
</tr>
<tr>
<td>7</td>
<td>Adenocarcinoma</td>
<td>14.5</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>Squamous</td>
<td>15</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>10</td>
</tr>
</tbody>
</table>

An intra-uterine manipulator was not used in any of these patients. They were all stage IB1 and none had parametrial invasion. LVSI, lymphovascular space invasion.
REFERENCES


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