What Do Risks Exist After Minimally Invasive Surgery in Patients With Stage IA1-IIA1 Cervical Cancer

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Research

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Abstract

**Objective:** To investigate the risks of patients with stage IA1-IIA1 cervical cancer after laparoscopic hysterectomy, and whether adjuvant radiotherapy is necessary.

**Patients and Methods:** From January 2013 to December 2016, we retrospectively analyzed 221 patients with cervical cancer of stage IA1-IIA1. Sixty-two patients were treated with laparoscopic hysterectomy and adjuvant radiotherapy (group A), 115 patients only underwent open surgery (group B) and 44 patients received laparoscopic hysterectomy alone (group C). Local recurrence-free survival (LRFS) was the primary outcome, distant metastasis free survival (DMFS) and overall survival (OS) rates were secondary outcomes in the study.

**Results:** The median follow-up time was 58.33 months (range, 56.91-59.76 months) for all the patients. Three groups were balanced in terms of baseline characteristics. The 3-year LRFS rates were 98.4% in group A, 97.4% in group B, and 86.4% in group C, respectively. The LRFS rates of group A and B surpassed group C (group A vs. B, p=0.634; group A vs. C, p=0.011; group B vs. C, p=0.006). In subgroup analysis of stage IB1-IB3 disease, the 3-year LRFS was 100% in group A, 98.8% in group B and 83.1% in group C, the 3-year OS rates were 100% in group A, 98.9% in group B, 91.5% in group C. The 3-year LRFS and OS rates on group A and B were significantly superior to group C (p<0.05). No benefits of adjuvant radiotherapy were observed in patients with stage IA and IIA1 cervical cancer.

**Conclusions:** There is a risk of local failure in laparoscopic hysterectomy for early stage cervical cancer. Adjuvant radiotherapy can reduce the risk of recurrence and improve local control for women with early cervical cancer and bring survival benefits for patients with stage IB disease after minimally invasive hysterectomy.

Introduction

According to National Comprehensive Cancer Network (NCCN) clinical guidelines, postoperative adjuvant radiotherapy is generally not required for stage IA1 ~ IB cervical cancer patients if there are no risk factors (such as lymph-node involvement, nerve invasion, and large tumor). Recently, A recent study by Ramirez, a highly noteworthy phase III study, was published in the October 2018 New England journal of medicine, which found that the 4.5-year disease-free survival and 3-year tumor-free survival in the minimally invasive surgery group were significantly lower than those in the open surgery group, and the risk of death or recurrence in the minimally invasive group was 3.74 times higher than that in the open surgery group(1). A retrospective study by Melame et al. had similar results. It can be speculated that minimally invasive surgery may bring the risk of local recurrence(2). Therefore, We speculate that minimally invasive hysterectomy for early cervical cancer carries a risk of local failure, it is worth studying whether additional postoperative radiotherapy is needed for these patients with minimally invasive surgery.

Methods
From January 2013 to December 2016, a total of 221 patients with early-stage squamous-cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of cervical cancer admitted to our institution. The clinical data of eligible patients with stage IA1-IIA1 cervical cancer were retrospectively analyzed. All patients had an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1. Exclusion criteria included a history or contraindication to radiotherapy; the advanced stage cervical cancer; absence of severe mental disorders or severe diseases of heart, liver, lung, kidney; the existence of high-risk factors (lymph-node involvement, parauterine invasion, and positive vaginal resection margin). Patients were also excluded if the postoperative pathologic risk factors meet the Sedlis Criteria of the latest version of NCCN Guidelines (Version 1.2020). According to different treatment approaches, patients were assigned to different groups. The first group underwent laparoscopic hysterectomy combined with postoperative radiotherapy (group A, n = 61), the second group only received open surgery (group B, n = 115), and the third group received laparoscopic hysterectomy alone (group C, n = 44). The median age was 47 years (24–69). Patients were re-staged based upon International Federation of Gynecology and Obstetrics (2018 FIGO) Surgical Staging of Cancer of the Cervix Uteri(2018). Enrolled patients underwent open surgery or laparoscopic hysterectomy. The patients who received post-operative radiotherapy were treated with 45 to 50 Gy in 95% PTV of expansion based on the tumor bed and high-risk lymph node drainage area delivered over 4 to 5 weeks at 1.8 to 2 Gy per fraction in 4 weeks following the surgical resection, which were carried out by intensity modulated radiotherapy (IMRT). SPSS 24.0 statistical software was used for data analysis. The primary outcome was 3-year LRFS. The secondary endpoints were 3-year OS and 3-year DMFS. Survival rates were used to calculate by the Kaplan-Meier method. Cox regression analysis was used to estimate prognostic factors. And the statistically significant P value was a two-tailed P value less than 0.05.

Results

Demographic and baseline variables and treatment characteristics of patients

The clinical baseline characteristics of the three groups including age, tumor size, histologic subtypes, stage of disease and ECOG performance-status score were not statistically different (Table 1). The median age was 47 years (range, 24–69 years). All patients were restaged according to FIGO 2018. In group A, there were 6 (9.7%) patients with stage IA, 34 (54.8%) with stage IB1, 14 (22.6%) with stage IB2, 2 (3.2%) with stage IB3 and 6 (9.7%) patients with stage IIA1. In group B, the number of patients with stage IA was 16 (14%), IB1 was 79 (68.7%), IB2 was 10 (8.7%), IB3 were 2 (3.2%), IB3 was 5 (4.3%) and IIA1 was 5 (4.3%). In group C, patients with stage IA was 2 (4.5%), IB1 3 (6.8%), IB2 was 35 (79.5%), IB3 was 1 (2.3%) and IIA1 was 1 (2.3%). No statistical difference existed between groups (p > 0.05). The percentage of lymphovascular invasion was 6.5% (n = 4) in group A, 1.7% (n = 2) in group B and 2.3% (n = 1) in group C. There was no significant difference in the rate of lymphovascular invasion between-groups.
Table 1
baseline characteristics of patients

|                               | No.of patients (%) | P-value |
|-------------------------------|--------------------|---------|
|                               | Group A(n = 62)    | Group B(n = 115) | Group C(n = 44) |
| Age (years)                   |                    |                     |                   |
| Median (range)                | 50(27–64)          | 47(24–64)          | 49(24–69)         | 0.277 |
| ≤ 47                          | 30(48.4)           | 63(54.8)           | 18(40.9)          |       |
| > 47                          | 32(51.6)           | 52(45.2)           | 26(59.1)          |       |
| Tumor size (cm)               |                    |                     |                   | 0.810 |
| ≤ 2                           | 16(25.8)           | 28(24.3)           | 9(20.5)           |       |
| > 2                           | 46(74.2)           | 87(75.7)           | 35(79.5)          |       |
| Stage of disease              |                    |                     |                   | 0.106 |
| IA1                           | 4(6.5)             | 8(7.0)             | 2(4.5)            |       |
| IA2                           | 2(3.2)             | 8(7.0)             | 3(6.8)            |       |
| IB1                           | 34(54.8)           | 79(68.7)           | 35(79.5)          |       |
| IB2                           | 14(22.6)           | 10(8.7)            | 2(4.5)            |       |
| IB3                           | 2(3.2)             | 5(4.3)             | 1(2.3)            |       |
| IIA1                          | 6(9.7)             | 5(4.3)             | 1(2.3)            |       |
| Histologic subtype - no. (%)  |                    |                     |                   | 0.150 |
| Squamous-cell carcinoma       | 50(80.6)           | 90(78.3)           | 34(77.3)          |       |
| Adenocarcinoma                | 10(16.1)           | 25(21.7)           | 8(18.2)           |       |
| Adenosquamous carcinoma       | 2(3.2)             | 0(0)               | 2(4.5)            |       |
| ECOG performance-status score |                    |                     |                   | 0.840 |
| 0                             | 58(93.5)           | 106(93.0)          | 42(95.5)          |       |
| 1                             | 4(6.5)             | 8(7.0)             | 2(4.5)            |       |
Table 2
Incidence and pattern of CC failures in the three groups

| Pattern of failures       | Group A (n = 62) | Group B (n = 115) | Group C (n = 44) |
|---------------------------|------------------|-------------------|-------------------|
| Total failures            | 4 (6.5)          | 5 (4.3)           | 6 (13.6)          |
| Pelvis recurrence         | 0                | 2 (1.7)           | 2 (4.5)           |
| Vaginal vault             | 0                | 1 (0.8)           | 3 (6.8)           |
| Distant metastasis        | 3 (4.8)          | 2 (1.7)           |                   |
| Pelvic recurrence + distant metastasis | 1 (1.6) |                   | 1 (2.3)           |

**Primary outcome**

With a median follow-up time of 58.33 months (range, 56.90 to 59.76 months), the 3-year LRFS, DMFS and OS rates for all patients were 95.5%, 96.4% and 96.4%, respectively. A total of 10 relapses occurred in 3 years for all patients. In group A, local failure occurred in only one patient. The 3-year LRFS rates were 98.4%. In group B, three patients encountered pelvic or vaginal recurrences, the 3-year LRFS rates were 97.4%. In group C, there were 5 patients suffered from the local recurrences. The 3-year LRFS rate was 86.4%, which was significantly lower than that in group A and B (A vs. B, p = 0.634, A vs. C, p = 0.011, B vs. C, p = 0.006) (Fig. 1).

**Secondary outcomes**

A total of 7 patients developed lung or bone metastases during 3 years. Four of them were in group A, 2 were in group B, 1 was in group C. The 3-year DMFS rates were 93.5% in group A, 98.3% in group B, 97.7% in group C, respectively. There was no statistically significant between-group difference (A vs. B, p = 0.123, A vs. C, p = 0.381, B vs. C, p = 0.810) (Fig. 2).

Of the 221 patients, 8 patients died within 3 years, all of whom were tumor-related deaths. The 3-year OS rates were 96.8% in group A, 97.4% in group B, and 93.2% in group C, respectively. The inter-group differences were not statistically significant (A vs. B, p = 0.872, A vs. C, p = 0.341, B vs. C, p = 0.206) (Fig. 3).

**Subgroups analysis**

In exploratory subgroup analysis of the different stages, we compared the LRFS, DMFS and OS rates across the subgroup of stage IA disease, the subgroup of stage IB1-IB3 disease and the subgroup of stage IIA1 disease, respectively.

In subgroup of stage IA disease, there was one patients (6.2%) encountered recurrence and death from cervical cancer in group B, the 3-year LRFS and OS rates were both 93.8%. There were not any recurrences
and death occurred in group A and group C. There was no statistically significant between-group difference on 3-year LRFS and OS (group A vs. B, \( p = 0.540 \), group B vs. C, \( p = 0.576 \)). No patients with stage IA disease had distant metastasis.

In subgroup of stage IB1-IB3 disease, no recurrences and death occurred in group A. Recurrence occurred in one patients in group B and six in group C. The 3-year LRFS was 98.8% in group B and 83.1% in group C, respectively. The rates of LRFS significantly differed between the three groups. (group A vs. B, \( p = 0.446 \); group A vs. C, \( p = 0.003 \); group B vs. C, \( p = 0.000 \)) (Fig. 4). The 3-year DMFS rates were 96.0% in group A, 98.9% in group B, 97.0% in group C. The inter-group differences of DMFS were not different from each other (group A vs. B, \( p = 0.276 \), group A vs. C, \( p = 0.829 \), group B vs. C, \( p = 0.483 \)). The 3-year OS rates were 100% in group A, 98.9% in group B, 91.5% in group C. The significant differences existed between groups (group A vs. B, \( p = 0.448 \), group A vs. C, \( p = 0.037 \), group B vs. C, \( p = 0.037 \))(Fig. 5). The LRFS and OS benefits were observed in patients with cervical cancer stage IB1-IB3.

In subgroup of stage IIA1 disease, two patients relapsed, one in group A (1/6), another in group B (1/5). Two women had distant metastasis, one of them in group A (1/6) and another in group B (1/5). In terms of OS, a total of three patients died for the disease, two patients in group A, and one in group C. However, the only one patients with stage IIA1 cervical cancer in group C did not had distant metastasis or recurrence. The 3-year LRFS, DMFS and OS rates did not differ significantly between the three approaches (\( p > 0.05 \)).

**Prognostic factors**

Patients underwent laparoscopic hysterectomy alone had a higher rate of local recurrence than patients received laparoscopic hysterectomy combined with adjuvant radiotherapy or open surgery (hazard ratio for local recurrence, 11.39; 95% CI, 1.36 to 95.50), a difference remained after the adjustment for, ECOG performance-status score, stage of disease, age, and lymphovascular invasion (LVSI) (hazard ratio for disease local recurrence from cervical cancer, 12.27; 95% CI, 1.34 to 112.58). Deep stromal invasion (DSI) was an independent risk factor for local recurrence (hazard ratio, 3.48; 95% CI, 1.17 to 10.37), a difference remained with the adjustment for ECOG performance-status score, stage of disease, age, and different approaches (hazard ratio for local recurrence, 4.00; 95% CI, 1.07 to 14.99).

**Discussion**

In the retrospective analysis, women receiving laparoscopic hysterectomy combined with adjuvant radiotherapy or open surgery for early-stage cervical cancer had lower 3-year LRFS rates than patients who received laparoscopic hysterectomy alone. In subgroup analysis, patients with stage IB cervical cancer who underwent laparoscopic hysterectomy benefited from adjuvant radiotherapy on LRFS and OS. The results revealed that post-operative radiotherapy can decrease the local recurrence rate of the women with early-stage cervical cancer and improve the survival of women with stage IB disease after laparoscopy hysterectomy.
Laparoscopic hysterectomy has the advantages of a decrease in operative blood loss, a shorter hospital stay, and a lower rate of postoperative complications than open radical hysterectomy in previous studies (3–5). And the recurrence and survival rates do not differ significantly between the two approaches (6, 7). Therefore, National Comprehensive Cancer Network (National Comprehensive Cancer Network, NCCN) guidelines recommend that minimally invasive surgery is an acceptable approach to radical hysterectomy in patients with early-stage cervical cancer (8, 9). However, the main limitations was a paucity of adequately powered, prospective, randomized trials. Postoperative adjuvant treatment was indicated depending on surgical findings and disease stage. For patients with early stage cervical cancer who have high-risk disease (positive pelvic nodes, positive surgical margin, and/or positive parametrium) after radical hysterectomy, postoperative pelvic external beam radiotherapy with concurrent platinum-containing chemotherapy (category 1) with (or without) vaginal brachytherapy is recommended (10–12).

In patients with intermediate risk factors (large tumor diameter (LTD), DSI and LVSI), Sedlis criteria is recommended (13–18). For patients without any high-risk factors or that the intermediate risk factors that do not meet the Sedlis criteria, there is currently no clear indication for adjuvant therapy.

In 1980s, Gynecologic Oncology Group (GOG) study of clinical and pathologic predictors of surgically treated stage carcinoma of the cervix confirmed that LTD, DSI, and LVSI could increase the probability of cancer recurrence at 3 years from 2–31% (19). The result indicated a statistically significant (47%) reduction in risk of recurrence (relative risk = 0.53, P = 0.008, one-tail) among the pelvic radiotherapy group. The recurrence-free rates were 88% for adjuvant radiotherapy versus 79% for the no-adjuvant-treatment group at 2 years (20). The updated analysis showed that adjuvant pelvic radiotherapy increased progression free survival; a clear trend towards improved overall survival was noted (HR = 0.70, 90%CI = 0.45 to 1.05, p = 0.074) after a long-term follow-up (12 years) (21). These results proposed the establishment of Sedlis criteria. However, laparoscopic hysterectomy for cervical cancer has not been fully carried out at that time, whether this standard is applicable to patients undergoing laparoscopic hysterectomy requires a further investigation. In a comparative study initiated by Eun-Ju Lee et al. (22), disease-free survival were compared between patients underwent laparoscopic radical hysterectomy (LRH) and radical abdominal hysterectomy (RAH). With a median follow-up time of 78 months for the LRH group and 75 months for the RAH group. There was no significant difference in the 5-year disease-free survival rates between the groups (90.5% and 93.3% for LRH and RAH, respectively, p = 0.918). However, only 24 patients were enrolled and two people relapsed, the size was too small to make a meaningful statistical analysis of the failure modes of local or distant recurrences. In the trial of H. Steed et al. (23), a total of 71 and 205 patients have undergone laparoscopic-assisted radical vaginal hystectomy (LARVH) and RAH, there have been 4 recurrences in the LARVH group and 13 in the RAH (P = NS). But the median follow-up time was 17 and 21 months, respectively. The overall 2-year recurrence-free survival was 94% and 94% in the LARVH and RAH groups (P = NS). Both of the studies were retrospective studies, the short follow-up time and the small sample size were still the main limitations. As a result, the value of radiotherapy post laparoscopic hysterectomy has not been further explored.

In 2018, the results of Laparoscopic Approach to Cervical Cancer (LACC) Trial published in The Lancet(1), A total of 319 patients were assigned to minimally invasive surgery and 312 to open surgery.
The rate of disease-free survival at 4.5 years was 86.0% with minimally invasive surgery and 96.5% with open surgery, a difference of -10.6 percentage points (95% confidence interval [CI], −16.4 to −4.7). Minimally invasive radical hysterectomy was associated with lower PFS and OS rates. However, part of enrolled patients were found to have the diseases of parametrial involvement (6.5% in the minimally invasive surgery group and 3.9% in the open-surgery group), or lymph-node involvement (12.4% in the minimally invasive surgery group and 13.1% in the open-surgery group) in postoperative histopathological assessment. And the scholars noted that this study cannot be generalized to women with “low-risk” factors (tumor size less than 2 cm; no lymphovascular invasion; depth of invasion less than 10 mm; and negative lymph-node), because it was not powered to evaluate the oncologic outcomes of the two surgical approaches in that context. Similarity, another study was conducted by Melamed et al. (2), focusing on the long-term survival of patients with minimally invasive surgery and open surgery. The results showed that the 4-year annual mortality rate was 9.1% in patients undergoing minimally invasive surgery and 5.3% in patients undergoing laparotomy (HR = 1.65, 95% CI: 1.22 to 2.22). The relative survival rate decreased by 0.8% annually during the four years since the start of minimally invasive surgery in 2006, though the tumors were relatively small, and the stage were earlier in patients undergoing minimally invasive surgery. Both trials lack of further exploration of subgroups with different stages or different risk factors, and noted that the value of adjuvant radiotherapy after laparoscopic radical hysterectomy in patients with “low-risk” cervical cancer remained unknown.

To explore the value of adjuvant radiotherapy, we conducted this study to compared the survival outcomes of three groups. In order to better rule out the impact of risk factors on the results, we used FIGO 2018 to re-stage and excluded patients with high-risk factors or intermediate-risk factors that met the Sedlis criteria. In our analysis, we were surprised to find that even for “low-risk” patients with early cervical cancer, the recurrence rate after laparoscopic hysterectomy was still higher than that of patients undergoing open surgery, and postoperative radiotherapy could decrease the recurrence rate of patients who had underwent laparoscopic hysterectomy. This results also confirms from the side that laparoscopic hysterectomy is negatively related to survival outcomes, the conclusion of LACC that minimally invasive radical hysterectomy was associated with lower rates of disease-free survival and overall survival than open abdominal radical hysterectomy may be still applicable to “low-risk” patients with early stage cervical cancer.

In terms of 3-year DMFS rates, laparoscopic hysterectomy combined with radiotherapy group did not show advantages over the others. The patients received laparoscopic hysterectomy alone were not inferior to the open surgery. The results were similar to some previous studies (22, 24, 25). Postoperative radiotherapy did not reduce the rate of distant metastasis, which may be related to the biological characteristics of the tumor. Williams et al. (26) found that lymphatic vessel density was an important indicator of the prognosis of stage I cervical cancer and a low podo-planin immunoreactivity was associated with lymphatic invasion and lymph node metastasis of cervical cancer. (27). Krishnan J et al. (28) found that VEGF-C and VEGF-D were involved in mediating the direction of tumor cell migration. In subgroup analysis, patients with stage IB cervical cancer had a higher rate of local control and overall survival after postoperative radiotherapy, which revealed that patients with IB stage may be the part of
population who benefited from postoperative radiotherapy after laparoscopic hysterectomy. However, no benefits existed in patients with stage IA and IIA1 disease. The possible reasons may be: There was only one patient with stage IIA1 in Group C, and the sample size was too small to assess the overall survival benefit. The follow-up time of some patients was not long enough to show the differences on OS or DMFS. The 3-year overall survival is already too high to show a between-group difference in subgroup of stage IA disease.

There were several limitations in our study. Firstly, robot-assisted radical hysterectomy was not carried out in our institution, it can not be inferred that this conclusion is applicable to early-stage cervical cancer patients assisted by robot. Secondly, the sample size needs to be further expanded for further exploration and analysis. Furthermore, the study is a retrospective study and patients may still have bias in the choice of treatment due to some reasons that could not be traced.

In conclusion, there is a risk of local failure in laparoscopic hysterectomy for early stage cervical cancer. Adjuvant radiotherapy can reduce the risk of recurrence and improve local control for women with early cervical cancer and bring survival benefits for patients with stage IB disease after minimally invasive hysterectomy.

Declarations

Ethics approval and consent to participate

This study was approved by our Institutional Review Board.

Consent for publication
Not applicable.

Conflict of interest: all Authors have nothing to disclose.

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Availability of data and materials
All data generated and analyzed during this study are included in this published article.

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Author contributions
Wenqi Liu and Yeping Wei designed this study. Xu-wei Jiang, Xue-mei Xu, Hai-ying Yue, Xiang-de Li, Hui-jun Zhu, Xue Ou, Qiu-lu Zhong collected data and followed the patients. Dan-jing Luo, Qian-fu Liang, Yi-ting Xie performed the data analyses. Li Jiang, Qinghua Du and Yixiu Gan wrote the paper. Wenqi Liu and Jian Li inspected the manuscript critically and took part in the revision of
manuscript. Yixiu Gan and Qinghua Du contributed equally to this study and are the co-first authors of this paper. All authors have read and approved the final manuscript.

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**Figures**

Group A, laparoscopic hysterectomy and adjuvant radiotherapy; Group B, open surgery; Group C, laparoscopic hysterectomy alone.
Figure 1

Local recurrence-free survival (LRFS) stratified by three groups.

Figure 2

Distant metastasis free survival (DMFS) stratified by three groups.
Figure 3

Overall survival (OS) stratified by three groups.
Figure 4

Local recurrence-free survival (LRFS) stratified by three groups for patients with stage IB1-IB3 disease.

Figure 5

OS stratified by three groups for patients with stage IB1-IB3 disease.