Laparoscopic Versus Open Abdominal Radical Hysterectomy for Patients with Endometrial Cancer Involving Cervix

Ming Wang  
Beijing Obstetrics and Gynecology hospital

Ziyi Zhao  
Beijing Obstetrics and Gynecology Hospital

Xiaohong Xu  
Beijing Obstetrics and Gynecology Hospital

Jinwei Miao  
Beijing Obstetrics and Gynecology Hospital

Weimin Kong  
Beijing Obstetrics and Gynecology Hospital

Wei Duan  
Beijing Obstetrics and Gynecology Hospital

Li Su  
Beijing Obstetrics and Gynecology Hospital

Ziran Yin  
Beijing Obstetrics and Gynecology Hospital

Yumei Wu (✉️ wym597118@163.com)  
Capital Medical University Beijing Obstetrics and Gynecology Hospital

Research article

Keywords: Minimally invasive surgery, Endometrial cancer, Laparoscopy, Survival

DOI: https://doi.org/10.21203/rs.3.rs-25259/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

BACKGROUND: Data on the survival outcome between laparoscopic and open abdominal radical hysterectomy is limited in patients with endometrial cancer involving cervix.

METHODS: We performed a retrospective 1:1 matched observational study in patients who had their cervix involved by endometrial cancer during the 2010–2018 period in Beijing Obstetrics and Gynecology Hospital in China. All enrolled patients underwent cancer-directed radical hysterectomy through laparoscopic approach or open abdominal surgery and followed until 3 years after the surgery. The primary outcome was the rates of disease-free survival and overall survival.

RESULTS: A total of 142 patients were included in the study, 54 patients received laparoscopic surgery and 54 of the remaining 88 patients who received open surgery were selected as control. Overall, the median follow-up duration was 54.22 ± 31.14 months (95%CI: 48.71–59.89 months). There was no difference on the baseline information between two groups, including ages, rates of histologic subtypes, rates of deep myometrial invasion, rates of lymph-node involvement, and postoperative stage. There was no significant difference between the three-year disease-free rates between two groups (3-year rate, 94.3% vs. 92.2%; hazard ratio, 1.36; 95% CI, 0.40 to 4.61). The 3-years rate of overall survival in patients of the laparoscopic group was comparable to patients in the open surgery group (3-year rate, 89.87% vs. 92.14%; hazard ratio for death from any cause, 1.87; 95% CI, 0.60 to5.86).

CONCLUSIONS: This study revealed that laparoscopic approach surgery was not associated with shorter disease-free survival and overall survival than open abdominal radical hysterectomy in patients with endometrial cancer involving cervix.

Background

The incidence and mortality rate of endometrial cancer remains high in developed countries and is increasing among women in developing countries\(^\text{[1]}\)\(^\text{[2]}\). An estimated 382069 new cases of endometrial cancer were diagnosed around the world in 2018, and 89929 people died of the disease.

Previous studies involving patients with endometrial cancer have shown that laparoscopic hysterectomy is associated with less intraoperative blood loss, a shorter length of hospital stay and a lower risk of postoperative complications than open abdominal surgery\(^\text{[3]}\)\(^\text{[4]}\). In addition, it has been suggested that overall survival (OS) and disease-free survival (DFS) is comparable to laparotomy in several meta analysis\(^\text{[5]}\)\(^\text{[6]}\). For patients with suspected cervical involvement, total hysterectomy or radical hysterectomy is recommended along with bilateral salpingo-oophorectomy, and dissection of lymph nodes if indicated. However, most patients mentioned in these studies were in stage I and very few data is available in the selected population of patients with cervix involved. Besides, recent studies showed that minimally invasive radical hysterectomy was associated with lower rates of disease-free survival and
overall survival than open abdominal radical hysterectomy among women with early-stage cervical cancer\[7\][8].

This study aims to evaluate the recurrence and survival of different approaches of radical hysterectomy in patients with endometrial cancer involving cervix.

**Methods**

**Patient Selection**

This was a retrospective, case-controlled study that recruited patients from a single tertiary care university medical center, Beijing Obstetrics and Gynecology Hospital in Beijing, China, from January 2009 to February 2018. The trial was approved by the institutional ethics review committee. The Subjects were screened for the following eligibility criteria: diagnosed with endometrial cancer; confirmed with cervix involved by endometrial cancer through MRI or cervical biopsy; received radical hysterectomy and standard cancer-directed surgery as primary treatment. We also excluded the women who had distant metastasis or other malignant diseases.

**Study Procedures and Data Collections**

Patients fulfilling the inclusion and exclusion criteria were enrolled in the study. The electronic medical record system and hospital paper charts, pertinent data from the clinic and inpatient services in the Department of Gynecological Oncology in Beijing Obstetrics and Gynecology Hospital were retrospectively reviewed. The surgical route was chosen depending on the experience of the surgeons and patients’ preference.

**Preoperative phase.** The preoperative study indicated that the cervix of the patients were involved by endometrial cancer through cervical biopsy or magnetic resonance imaging.

**Operative technique.** The patient who selected the laparoscopic route was in a 25–30° Trendelenburg position. The laparoscope is introduced into the patients’ cavity through a 10 mm supra-umbilical trocar. Three 5-mm trocars are placed under direct visualization in both iliac fossae and at the midline between the umbilicus and the subcostal margin. A uterine manipulator and colpo-occluder balloon is used\[10\]. Laparotomy was performed with a vertical paramedian incision in a horizontal position. The surgical steps resembled those of laparoscopic surgery.

All patients underwent Piver II-III radical hysterectomy or class B or C hysterectomy according to Q-M classification\[9\] and bilateral salpingo-oophorectomy. Pelvic and aortic lymphadenectomy was performed at the same time. In selected cases, suspension of the sigmoid and cecum was accomplished to obtain better exposure of the operative field.

**Postoperative phase.** The staging was performed according to the 2009 International Federation of Gynecology and Obstetrics (FIGO)’s classification 5. Adjuvant chemotherapy, radiotherapy or both were
delivered according to the practice of high risk factors of age, pathology subtype, grades, and tumor extension.

For subjects who were eligible for enrollment, the pertinent patients’ data were collected as follows: medical history, clinical characteristics, blood tests, and imaging scan. In case of recurrence, further examinations and consultations were requested such as MRI or CT scan.

**Outcome Measurements and Endpoints**

Disease-free survival was defined as the length of time that the women remained disease-free. Overall survival was defined as the time interval between the initial diagnosis of endometrial cancer and the date of death for any reason. The primary outcome was the rate of disease-free survival and overall survival through the end of February, 2020.

**Statistical Analysis**

For endpoint measurements, we performed the Intention to treat (ITT) analysis, which was defined as analysis included all enrolled patients, including those with protocol deviations. In the primary intention-to-treat analysis, all the patients whose surgical procedure was initiated by a laparoscopic approach were categorized as having undergone minimally invasive surgery, even when conversion to open surgery occurred. Patients lost follow-up during the study were counted as treatment failures in ITT analyses.

Baseline characteristics and laboratory results were summarized for the three groups utilizing descriptive statistics, including percentage, means ± standard deviation (SD), and 95% CI. For the quantitative variable, the t-test was used to compare group differences. For categorical variables, the chi-square test was used for group comparisons. The significance level was set at P < 0.05; all data were analyzed by SPSS 17.0 (SPSS, Inc., Chicago, IL).

**Results**

**Study Population**

A total of 2506 patients were screened and 142 patients were enrolled in the study from January 2010 to February 2017 (Fig. 1). All patients were found with cervical invasion by cervical biopsy or MRI and received radical or modified radical hysterectomy. 54 patients received laparoscopic approach surgery and 88 patients received open surgery. 54 of 88 patients who received open surgery were selected as the control for the laparoscopic group. No patients had conversion from laparoscopic approach surgery to laparotomy. The baseline characteristics of the patients are summarized in Table 1. The mean age of the patients in the laparoscopic group was comparable to the patients in the open surgery group (51.57 ± 9.43 vs. 53.26 ± 7.14 years, p = 0.30). There were no significant differences between the two groups with respect to high risk histologic subtype assessed postoperatively (Endometiod G1/G2, endometrioid G3, other high risk types: 61.1%, 27.8% and 11.1% vs. 64.8%, 29.6% and 5.6%, p = 0.58), deep myometrial
invasion (51.9% and 55.6%, p = 0.70), lymphovascular invasion positive (31.5% and 35.2%, p = 0.68), or lymph-node involvement (16.7% and 16.7%, p = 1).

| Table 1 | The Baseline Values between patients received laparoscopic or laparotomy surgery (n = 155) |
|-----------------|-----------------------------------|-----------------|
| N.(Ratio)       | GroupA (n = 54)                    | Group B (n = 54) | p-value  |
| Age (X ± SD)    | 51.57 ± 9.43                      | 53.26 ± 7.14    | t = 1.05, p = 0.30  |
| Histologic type |                                   |                 |           |
| Endometiod G1/G2| 33(61.1)                          | 35(64.8)        | X² = 1.09, p = 0.58 |
| Endometiod G3   | 15(27.8)                          | 16(29.6)        |           |
| Other high risk types | 6(11.1)                          | 3(5.6)          |           |
| Deep myometrial invasion | 28(51.9)                        | 30(55.6)       | X² = 0.15, p = 0.70 |
| LVSI (+)        | 17(31.5)                          | 19(35.2)        | X² = 0.17, p = 0.68 |
| Lymph node positive |                                 |                 |           |
| Pelvic lymph node | 7(13.0)                           | 7(13.0)         | Z = 0, p = 1   |
| Paraaortic lymph node | 2(3.7)                           | 2(3.7)          |           |
| Adnexa/serous invasion | 3(5.6)                           | 3(5.6)          | X² = 0, p = 1   |
| Postoperative stage |                                 |                 |           |
| I               | 4(7.4)                            | 7(13.0)         | Z = 0.10, p = 0.92 |
| II              | 38(70.4)                          | 33(61.1)        |           |
| IIIA/IIB       | 12(22.2)                          | 14(25.9)        |           |

*Note:

Survival Analysis

The median follow-up time was 54.22 ± 31.14 months (95%CI: 48.71–59.89 months). At the time of the analysis, the rate of available survival information on the primary outcome at 3 years was 72.2%, which provided 85% power for the primary outcome given design assumptions[11]. At the time of the analysis, 2 patients (laparoscopic group/open surgery group = 1/1) were lost to follow-up. 9 patients had a recurrence (4 in the laparoscopic group and 5 in the open surgery group). The distribution of tumors among patients who had a recurrence was similar in the two groups. Of the 5 recurrences in open surgery group, 2 occurred in the pelvis, 1 in the right supraclavicular lymph node, 1 in lung and 1 in the abdominal
incision and inguinal region. Of the 4 recurrences in the laparoscopic group, 1 occurred in the pelvis, 1 in brain, 1 in lung and 1 in left trocar incision. The rate of disease-free survival at 3 years was 94.3% (95% CI, 83.3 to 98.1) in the laparoscopic surgery group which was comparable to 92.2% (95% CI, 80.4 to 97.0) in the open surgery group. No differences were found on the rates of recurrence between two groups (hazard ratio for recurrence, 1.36; 95% CI, 0.40 to 4.61; Log-rank test, p = 0.59 ) (Fig. 2A).

A total of 10 deaths were noted, 6 in the laparoscopic approach surgery group and 4 in the open surgery group. Of 4 death in open surgery group, 1 died of hemorrhagic stroke and 3 died of recurrence of endometrial cancer. Of 6 death in laparoscopic group, 3 died of recurrence of endometrial cancer, 1 died of endometrial cancer progression, and 2 died of other reasons. The rate of overall survival at 3 years was 89.87% (95% CI, 77.0 to 95.7) in the laparoscopic surgery group and 92.14% (95% CI, 80.3 to 97.0) in the open surgery group. Compared with the open surgery group, the laparoscopic approach was not associated with a lower rate of survival (hazard ratio for any reason death, 1.87; 95% CI, 0.60 to 5.87; Log-rank test, p = 0.26 ) (Fig. 2B).

**Discussion**

Our findings suggest that laparoscopic approach surgery was not associated with a higher risk of recurrence or death than open surgery among women who underwent radical hysterectomy for endometrial cancer with cervix invasion.

Total hysterectomy, bilateral salpingo-oophorectomy, and lymph node assessment is the primary treatment of apparent uterine-confined endometrial carcinoma, unless patients desire (and are candidates) for fertility-sparing options\[12\],[13],[14]. The surgery can be performed by any surgical route, such as laparoscopic and abdominal. Randomized trials, a cochrane database systematic review, and population-based surgical studies support that minimally invasive techniques are preferred in this setting due to a lower rate of surgical site infection, transfusion, venous thromboembolism, decreased hospital stay, and lower cost of care\[5],[15],[16],[17],[18]. In the largest Cochrane database of systematic reviews on the comparison of laparoscopic surgery compared with laparotomy for presumed early stage endometrial cancer\[5]. No significant differences were found in the ris of recurrence and death between the laparoscopy and laparotomy groups. Another systematic review compared the minimally invasive surgery and laparotomic approach in the treatment of high risk endometrial cancer\[6]. Similar results about recurrence and survival outcomes were found.

However, no study focus on patients with cervix involvement in endometrial cancer who need the radical or modified radical hysterectomy. Recent studies showed that minimally invasive radical hysterectomy was associated with lower rates of disease-free survival and overall survival than open abdominal radical hysterectomy among women with early-stage cervical cancer\[7],[8]. We found there were no difference in 3-year rate of overall survival and disease free survival between laparoscopic surgery and open surgery. Our study supports the use of laparoscopic approach in patients with the cervix involved. Obesity and age are the two epidemiological risk factors that are most associated with endometrial cancer\[19]. Minimal
invasive surgical staging in obese women with endometrial cancer could represent the surgical route of choice because it decreases operative bleeding, hospital admission length and the early postoperative complication rate without compromising recurrence-free survival or overall survival.

Some limitations of the current study include its sample size and a relatively short follow-up interval, especially for the laparoscopic group. Based on the HR of the study, a significance level of 0.05 (two-tailed) and detection power of 0.80 need 811 patients for the equal entry and follow up interval of disease free survival. A larger sample size multicenter trials are needed for the further verification of laparoscopic radical hysterectomy in this population.

**Conclusions**

This study revealed that in patients with endometrial cancer involving cervix, laparoscopic approach surgery was not associated with shorter disease-free survival and overall survival than open abdominal radical hysterectomy.

**Abbreviations**

OS, overall survival; DFS, Disease free survival; PFS, progression-free survival; FIGO, International Federation of Gynecology and Obstetrics; ITT, intention to treat analysis; LVSI, lymph-vascular space invasion.

**Declarations**

**Ethics approval and consent to participate**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The institutional ethics review committee of Beijing Obstetrics and Gynecology Hospital, Capital Medical University approved the trial and the need for informed consent was waived.

**Consent for publication**

Not applicable.

**Availability of data and material**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.
Competing Interest:
The authors declare that they have no conflict of interest.

Funding:
This study was supported by Beijing Hospitals Authority Talent Training Plan (grant number: QMS20191706) and sailing plan (grant number: Capital Development ZYLX201705).

Acknowledgement
All authors have no conflict of interest to be disclosed.

Author Contributions:
Drs Yumei Wu and Ming Wang proposed the concept and designed the study. Dr. Yu mei Wu obtained the research funding. Drs Ming Wang, Ziyi Zhao, Xiaohong Xu, Jinwei Miao, Weimin Kong, Wei Duan, Li Su and Ziyan Yin contributed to the acquisition of data. Dr. Wu supervised the data collection. Drs. Wang performed the statistics, interpreted the data and wrote the manuscript with assistance from Dr. Wu. Dr. Zhao assisted data analyses and editorial work. All authors provided inputs for the manuscript. Dr. Wu performed critical revisions of the manuscript and addressed the comments from the journal.

References
1. Siegel R L, Miller K D, Jemal A. Cancer statistics, 2018. CA: a cancer journal for clinicians, 2018,68(1):7.
2. Chen W, Sun K, Zheng R, et al. Cancer incidence and mortality in China, 2014. Chinese journal of cancer research, 2018;30:1-12.
3. Obermair A, Manolitsas T P, Leung Y, et al. Total laparoscopic hysterectomy versus total abdominal hysterectomy for obese women with endometrial cancer. International Journal of Gynecological Cancer, 2005;15:319–24.
4. Smits A, Lopes A, Das N, et al. The impact of BMI on quality of life in obese endometrial cancer survivors: does size matter? Gynecologic oncology, 2013;132(1):137–41.
5. Galaal K, Donkers H, Bryant A, et al. Laparoscopy versus laparotomy for the management of early stage endometrial cancer. The Cochrane database of systematic reviews, 2018,10; 10CD006655.
6. Scaletta G, Dinoi G, Capozzi V, et al. Comparison of minimally invasive surgery with laparotomic approach in the treatment of high risk endometrial cancer: A systematic review, European journal of
surgical oncology. the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology,2020,46:782-788.

7. Melamed A, Margul DJ, Chen L, et al. Survival after Minimally Invasive Radical Hysterectomy for Early-Stage Cervical Cancer. The New England journal of medicine,2018,379:1905-1914.

8. Carsten H, Ohlmann, Boris H. Minimally Invasive Versus Abdominal Radical Hysterectomy for Cervical Cancer. European Urology,2019,75:875-875.

9. Querleu D, Cibula D, Abu-Rustum N R. 2017 Update on the Querleu-Morrow Classification of Radical Hysterectomy. Annals of surgical oncology,2017,24:3406-3412.

10. Uccella S, Bonzini M, Malzoni M, et al. The effect of a uterine manipulator on the recurrence and mortality of endometrial cancer: a multi-centric study by the Italian Society of Gynecological Endoscopy. American journal of obstetrics and gynecology,2017,216:e1-592.e11.

11. Gebski V, Garès V, Gibbs E, et al. Data maturity and follow-up in time-to-event analyses. International journal of epidemiology,2018,47:850-859.

12. ACOG practice bulletin, clinical management guidelines for obstetrician-gynecologists, number 65, August 2005: management of endometrial cancer. Obstetrics and gynecology,2005;106:413-42.

13. Bakkum-Gamez JN, Gonzalez-Bosquet J, Laack NN, et al. Current issues in the management of endometrial cancer. Mayo Clinic Proceedings,2008,83:97-112.

14. Edge SB, Byrd DR, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Annals of surgical oncology, 2010, 17(6):1471-1474.

15. Walker JL, Piedmonte MR, Spirtos NM, et al. Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group Study LAP2. Journal of clinical oncology: official journal of the American Society of Clinical Oncology,2009;27(32):5331-6.

16. Kornblith AB, Huang HQ, Walker JL, et al. Quality of life of patients with endometrial cancer undergoing laparoscopic international federation of gynecology and obstetrics staging compared with laparotomy: a Gynecologic Oncology Group study. Journal of clinical oncology: official journal of the American Society of Clinical Oncology,2009;27:5337-5342.

17. Scalici J, Laughlin BB, Finan MA, et al. The trend towards minimally invasive surgery (MIS) for endometrial cancer: an ACS-NSQIP evaluation of surgical outcomes. Gynecologic oncology,2015;136:512-5.

18. Fader AN, Weise RM, Sinno AK, et al. Utilization of Minimally Invasive Surgery in Endometrial Cancer Care: A Quality and Cost Disparity. Obstetrics and gynecology,2016,127(1):91-100.

19. Lachance JA, Everett EN, Greer B et al. The effect of age on clinical/pathologic features, surgical morbidity, and outcome in patients with endometrial cancer. Gynecologic oncology,2006; 101: 470-475.

Figures
Figure 1. Patients selections and study design

2506 patients were screened for the eligibility

2364 patients with the following conditions were excluded:
- No evidence of cervix involvement: 2025
- Received total hysterectomy: 145
- Uterine sarcoma: 151
- Suspected parametrial involvement or distant metastasis: 43

142 patients were enrolled

Group A (n=54)
Patients received laparoscopic surgery

Group B (n=54)
54 of 88 Patients who received open surgery were selected as control

53/54 patients were under follow-up

53/54 patients were under follow-up
Figure 2

Kaplan–Meier Estimates of Overall Survival and Disease-free Survival. A: shows the Kaplan–Meier plot for overall survival, measured from the date of surgery to the date of death or the date that the patient was last known to be alive.
Figure 3

Kaplan–Meier Estimates of Overall Survival and Disease-free Survival. B: shows the cumulative incidence curves for disease-free survival, measured from the date of surgery to the date of death or the date that the patient was last known without recurrence. A Cox proportional-hazards model was used to determine the hazard ratio and 95% confidence interval. Tick marks indicate censored data.