

Comparison of oncology outcome between laparotomy and laparoscopy in early cervical squamous cell carcinoma without any high risk pathological factors

Xiaolin Chen¹, lu yijia², Hongwei Zhao¹, Lixin Sun¹, Shan Kang³, Zhumei Cui¹, Biliang Chen¹, Mei Ji⁴, Weidong Zhao¹, Ping Liu¹, and Chunlin Chen¹

¹Affiliation not available

²southern medical university

³Fourth HospitalHebei Medical University

⁴The First Affiliated Hospital of Zhengzhou University

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Abstract

Objective Explore the difference of oncology outcome of laparotomy and laparoscopy in the new FIGO2018 stage of early cervical squamous cell carcinoma without any high risk pathological factors. **Methods** The 5-years OS and DFS of cervical squamous cell carcinoma undergoing laparotomy and laparoscopy from 2004 to 2018 were compared by the total study population and propensity score from China. **Result** There was no difference in 5-year OS between laparotomy (2,478 cases) and laparoscopy (1,504 cases), but the 5-year DFS of laparotomy was higher (92.2 %vs. 90.4%, P=0.022). Cox analysis showed that laparoscopy was not an independent risk factor for the death of cervical squamous cell carcinoma (OS: P=0.598), but it was an independent risk factor for the recurrence/death (HR = 1.468,95% CI 1.131 ~ 1.906, P=0.004). There was no difference in 5-year OS between laparotomy (2,391 cases) and laparoscopy (1,495 cases) after 1:2 PSM, but the 5-year DFS of laparotomy was higher (92.7% vs. 90.8%, P = 0.006), Cox analysis showed that laparoscopy was not an independent risk factor for the death of cervical squamous cell carcinoma (OS: P=0.521), but it was an independent risk factor for the recurrence/death (HR=1.512, 95%CI 1.151~1.971, P=0.002). **Conclusion** There is no difference in 5-year OS between these groups for early cervical squamous cell carcinoma in new stage of FIGO2018 without any high-risk pathological factors, the 5-year DFS of laparotomy is higher than that of laparoscopy group, and laparoscopy is an independent risk factor for recurrence/death, so laparoscopy has a higher risk of recurrence.

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Xiaolin Chen^{1*}, Yijia Lu^{1*}, Hongwei Zhao^{2*}, Lixin Sun^{3*}, Shan Kang⁴, Zhumei Cui⁵, Biliang Chen⁶, Mei Ji⁷, Weidong Zhao⁸, Pin Liu^{1#}, Chunlin Chen^{1#}

¹Department of Obstetrics and Gynecology, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China;

^{2,3}Department of Gynecologic Oncology, Shanxi Provincial Cancer Hospital, Taiyuan 030000, China;

⁴Department of Gynecology, Fourth Hospital Hebei Medical University, Shijiazhuang 050019, China;

⁵Department of Gynecology, The Affiliated Hospital of Qingdao University, No. 16 Jiangsu Road, Shinan District, Qingdao, Shandong Province 266000, China;

⁶Department of Obstetrics and Gynecology , Xijing Hospital of Airforce Medical University 710000, China;

⁷Department of Obstetrics and Gynecology , The First Affiliated Hospital of Zhengzhou University 450000, China;

⁸Department of Gynaecology Anhui Cancer Hospital, No. 17 Lujiang Avenue, HeFei 230001,China

***These authors contributed equally to this work.**

Correspondence : Pin Liu; Chunlin Chen; Department of Obstetrics and Gynecology, Nanfang Hospital, Southern Medical University, No.1838, Guangzhou Avenue, Guangzhou 510515, People's Republic of China

Tel/Fax +86 206 278 7562

Email : lpivy@126.com; ccl1 @ smu.edu.cn

Abstract

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Methods The 5-years OS and DFS of cervical squamous cell carcinoma undergoing laparotomy and laparoscopy from 2004 to 2018 were compared by the total study population and propensity score from China.

Result There was no difference in 5-year OS between laparotomy (2,478 cases) and laparoscopy (1,504 cases), but the 5-year DFS of laparotomy was higher (92.2 %vs. 90.4%, $P=0.022$). Cox analysis showed that laparoscopy was not an independent risk factor for the death of cervical squamous cell carcinoma (OS: $P=0.598$), but it was an independent risk factor for the recurrence/death ($HR = 1.468, 95\% CI 1.131 \sim 1.906, P=0.004$). There was no difference in 5-year OS between laparotomy (2,391 cases) and laparoscopy (1,495 cases) after 1:2 PSM, but the 5-year DFS of laparotomy was higher (92.7% vs. 90.8%, $P = 0.006$), Cox analysis showed that laparoscopy was not an independent risk factor for the death of cervical squamous cell carcinoma (OS: $P=0.521$), but it was an independent risk factor for the recurrence/death ($HR=1.512, 95\%CI 1.151 \sim 1.971, P=0.002$).

Conclusion There is no difference in 5-year OS between these groups for early cervical squamous cell carcinoma in new stage of FIGO2018 without any high-risk pathological factors, the 5-year DFS of laparotomy is higher than that of laparoscopy group, and laparoscopy is an independent risk factor for recurrence/death, so laparoscopy has a higher risk of recurrence.

Key words : Cervical cancer; Laparotomy; Laparoscopy; Tumor outcome; no high-risk factors after surgery.

- 1. Introduction** A multicenter laparoscopic cervical cancer surgery (LACC) study published in New England Journal of Medicine in October, 2018 pointed out that the overall survival rate (OS) and disease-free survival rate (DFS) of cervical cancer patients who underwent laparoscopic surgery in stage IA1(LVSI+)~IB1 were lower than those who underwent open surgery, and had a higher local recurrence rate^[1]. A real-world study published in the same period further confirmed this conclusion. Minimally invasive surgery is associated with a worse oncology prognosis^[2]. This is contrary to previous related research and has caused widespread international controversy. In 2020, national comprehensive cancer network (NCCN) cervical cancer guideline^[3] changed open surgery to the standard surgical approach. Later, many studies thought that there was no difference in oncology outcome between laparotomy and laparoscopic surgery for some cervical cancer staging ^[4-5]. In the limitations of LACC research, it was mentioned that this research failed to further analyze the differences of oncology outcomes between the two surgical approaches possibly caused by pathological factors, and the conclusion could not be extended to the oncology outcomes of low-risk cervical cancer patients. The cases included in this study include squamous cell carcinoma, adenocarcinoma and adenosquamous carcinoma. However, in recent years, the research results on the oncological outcome and prognosis of cervical squamous cell carcinoma and adenocarcinoma are inconsistent. Some studies think that there is no difference between them ^[6-8], and some studies think that adenocarcinoma has a worse oncological outcome and a higher

recurrence rate than squamous cell carcinoma^[9-10]. Noh et al. ^[6]found that histological type was the only independent risk factor for cervical cancer in IB1~IIA stage. The staging of LACC study is limited to FIGO2009 staging i A1 (LVSI+) ~ i B1 cervical cancer cases, and NCCN guidelines indicate that cervical adenocarcinoma may be a new "medium risk factor". Then, whether the conclusion of this study is equally applicable to the new stage early cervical squamous cell carcinoma of FIGO2018 without any high-risk pathological factors, and what is the oncological prognosis of such patients undergoing laparotomy/laparoscopy? At present, there is still a lack of multi-center large sample research. Therefore, this study is based on the clinical diagnosis and treatment for cervical cancer in China (Four C) to screen out the cases of early cervical squamous cell carcinoma in the new stage of FIGO2018 who underwent laparotomy/laparoscopy, and compare the oncology outcomes of the patients who underwent laparotomy and laparoscopy by the total study population and propensity score matching.

2. Methods

3. **Data Collection**Four C adopted a multicenter, retrospective cohort study, which was approved by the ethics committee of Nanfang Hospital, Southern Medical University (ethics No. NFEC-2017-135) and international clinical trial registration No. ChiCTR1800017778 International Clinical Trials Registry Platform Search Port,<http://apps.who.int/trialsearch/>). See the published articles of our team for data collection methods ^[11-14]. Due to the long time span of entering cases, the cases before 2009 in this database are staged according to FIGO1994, and the cases after 2009 are staged according to FIGO2009. After all cases are put into storage, the staging shall be corrected again according to the revised version of FIGO2018.

4. **Inclusion and Exclusion Criteria**Inclusion criteria: (1) age [?] 18 years old; (2) Pathological diagnosis of cervical cancer by cervical biopsy; (3) Postoperative histopathological type of squamous cell carcinom; (4) There was no adjuvant treatment before operation; (5) FIGO stage (2018): IA2, IB1, IB2, IIA1; (6) Surgical approach: laparotomy / laparoscopy; (7) QM-B or QM-C hysterectomy, pelvic lymphadenectomy±para-aortic lymphadenectomy/biopsy; (8) The postoperative pathological report was complete, with lymph node status and negative; (9) No other high-risk pathological factors; (10) No adjuvant treatment after operation; (11) Follow-up. Exclusion criteria: (1) do not meet the above inclusion criteria; (2) Pregnancy complicated with cervical cancer, stump cancer or other malignant tumors.

5. **Propensity Score Matching**In order to eliminate the influence of baseline differences, this paper will include the following variables for propensity score matching (PSM): age and FIGO stage (2018) make the baseline balance between groups and reduce the influence of possible bias and confounding factors.

6. **Observation Indicators**The main long-term oncological outcome indicators were OS and DFS. The fifth year after the operation was taken as the cut-off point. OS was defined as the date of diagnosis to death of any cause or the last effective follow-up; DFS was defined as death/recurrence of any cause or the last effective follow-up from the date of diagnosis to the occurrence of any cause.

7. **Statistical Analysis**SPSS 23.0 software (IBM Corporation, Armonk, NY, USA) was used for statistical analysis. The measurement data are expressed as the mean $\pm$ standard deviation, Student's t-test was used for inter-group comparisons, the counting data are expressed as percentages (%), and the inter-group rates were compared by the chi-square test or Fisher's exact probability method. The follow-up time was expressed as the median; survival curves for the two groups were generated by the Kaplan-Meier (K-M) method and compared by the log-rank test; the independent risk factors were analysed by a multi-factor Cox regression model, and the related hazard ratios and confidence intervals were calculated. The PSM score was determined by a logical regression model. Differences with $P < 0.05$ were considered statistically significant. The specific statistical methods can be found in the articles published by our team^[7-10].

3. Results 3.1 Study PopulationData for a total of 63926 patients with cervical cancer in 47 hospitals in China from 2004 to 2018 were collected. Among them, 2478 patients aged 47.72 ± 10.090 years underwent laparotomy, and 1504 patiens aged 47.92 ± 9.743 years underwent laparoscopy. The median follow-up time was 49 months (laparotomy group vs laparoscopy

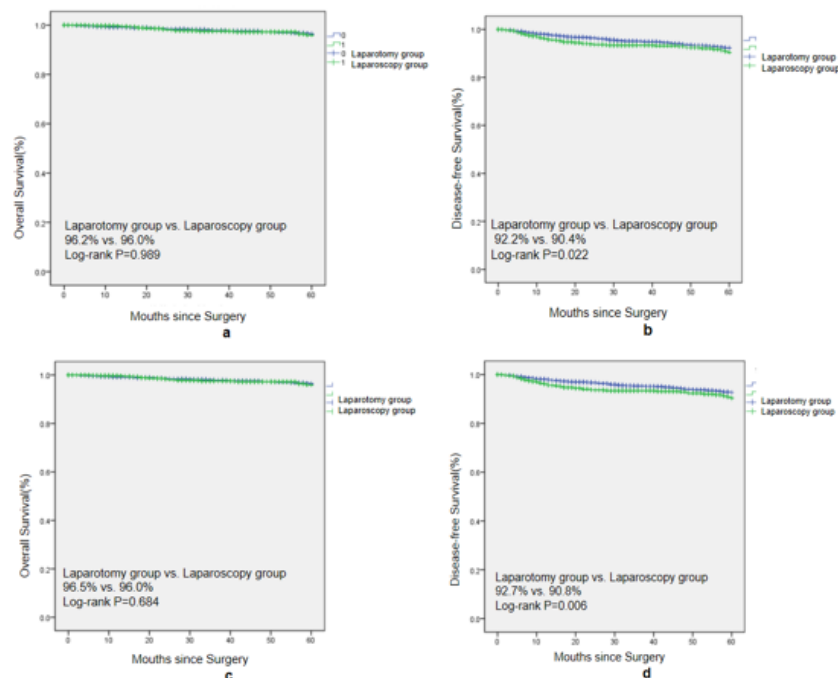
group: 57 months vs 36 months). The data filtering process is shown in figure1. According to the results of the baseline analysis between the two groups, there was a significant difference in FIGO stage (2018) between the two groups. An additional 1:2 PSM step was performed between the two groups, and a total of 3886 patients were included after matching. A total of 2391 patients aged 47.59 ± 10.054 years were included in the laparotomy group. 1495 patients aged 47.93 ± 9.757 years were included in the laparoscopy group. The median follow-up time was 49 months (laparotomy group vs laparoscopy group: 57 months vs 36 months). The baseline between the two groups was balanced. (Table 1). **Figure 1. Data Screening Flow Chart** **Table 1 Characteristics of Patients with FIGO 2018 early Stage Cervical Cancer Before and After 1:2 PSM**

Variables	The total study population Laparotomy group(N=2478)	The total study population Laparoscopy group(N=1504)	P value	1:2PSM Laparotomy group(N=2391)	1:2PSM Laparoscopy group(N=1495)
Age, years	47.72 $\pm$ 10.090	47.92 $\pm$ 9.743	0.063	47.59 $\pm$ 10.054	47.93 $\pm$ 9.757
FIGO2018			0.004		
IA2	165(6.7%)	117(7.8%)		165(6.9%)	108(7.2%)
IB1	954(38.5%)	645(42.9%)		954(39.9%)	645(43.2%)
IB2	883(35.6%)	504(33.5%)		856(35.8%)	504(33.7%)
IIA1	476(19.2%)	238(15.8%)		416(17.4%)	238(15.9%)

3.2 Comparison of Oncology Outcomes Between the total study population and 1:4 PSM in the early FIGO2018 stage of laparotomy group and laparoscopy group

In the total study population, K-M survival analysis showed that there was no significant difference in the 5-year OS between the laparotomy group and laparoscopy group (96.2% vs. 96.0%, $P = 0.989$) (Table 2 and figure 2A). The 5-year DFS in laparotomy group was higher than that in laparoscopy group (92.2% vs. 90.4%, $P = 0.022$). (Table 2 and figure 2B). Cox analysis showed that laparoscopic surgery was not an independent risk factor for death in patients with cervical squamous cell carcinoma (OS: $P = 0.598$), but it was an independent risk factor for recurrence / death in patients with cervical squamous cell carcinoma (HR = 1.468, 95% CI 1.131 ~ 1.906, $P = 0.004$). (Table 2).

The results of K-M survival analysis after 1:2 PSM showed that there was no significant difference in 5-year OS between the laparotomy group (2391 cases) and laparoscopy group (1495 cases) (96.5% vs. 96.0%, $P = 0.684$). (Table 2 and figure 2C). The 5-year DFS in laparotomy group was higher than that in laparoscopy group (92.7% vs. 90.8%, $P = 0.006$). See Table 2 and figure 2D. Cox multivariate analysis showed that laparoscopic surgery was not an independent risk factor for death in patients with cervical squamous cell carcinoma (OS: $P = 0.521$), but it was an independent risk factor for recurrence / death in patients with cervical squamous cell carcinoma (HR = 1.512, 95% CI 1.151 ~ 1.971, $P = 0.002$). (Table 2).



*Figure2 a, b The 5-year OS and DFS of the total study population; Figure2 c, d the 5-year OS and DFS after 1:2 PSM

Figure 2. FIGO2018 new stage early cervical squamous cell carcinoma: comparison of overall study population and 1:2PSM survival analysis between laparotomy group and laparoscopy group

Table 2 Survival analysis of figo2018 new stage early cervical squamous cell carcinoma in laparotomy group and laparoscopy group

	Group	Number of cases	Number of cases	Number of cases
Unadjusted OS DFS	laparotomy vs. laparoscopy	laparotomy vs. laparoscopy	2478 vs.1504	71 vs.31
Adjusted OS DFS	laparotomy vs. laparoscopy	laparotomy vs. laparoscopy	2391 vs.1495	63 vs.31

4. Discussion

The results of a multicenter and retrospective study showed that there were no high-risk and high-risk pathological factors in Four C. There was no significant difference in 5-year OS between the laparotomy group and the laparoscopy group, but the 5-year DFS in the laparotomy group was higher than that in the laparoscopy group; Cox multivariate analysis showed that laparoscopic surgery was an independent risk factor for recurrence / death in patients with early cervical squamous cell carcinoma without high and medium risk factors. In order to further reduce bias and confounding factors, 1:2PMS was carried out and the same conclusion was reached.

The results of this study found that there was no difference in 5-year OS between open surgery and laparoscopic surgery, which was different from the LACC study of Ramirez et al^[1], which believed that laparoscopic surgery was 4.5% for patients with stage IA1(LVSI+)~IB1 cervical cancer the 5-year OS was lower than that in the laparotomy group (86.0% vs. 96.5%). Considering the different stages of cervical cancer included,

there were about 91.5% in the LACC study of Ramirez et al 9% of cervical cancer patients are in stage IB1. The stage included in this study also includes stage IIA1 cervical cancer cases. The survival analysis before and after matching in Uppal et al. [15] research showed that there was no difference in the overall survival rate of patients with stage IA1(LVSI+)~IB1 cervical cancer undergoing laparoscopic surgery and laparotomy.

In terms of DFS, it is consistent with the results of LACC. It is found that the DFS of laparoscopic surgery is lower than that of laparotomy surgery. Cox multivariate analysis suggests that laparoscopic surgery is an independent risk factor for recurrence / death of cervical cancer patients. Chenx et al. [16] found that there was no difference between the 5-year OS of laparoscopic surgery and laparotomy surgery for cervical cancer patients with stage IB1 in FIGO 2009, but the 5-year DFS was significantly lower than that of laparotomy group. Cox multivariate analysis showed that laparoscopic surgery was associated with lower tumor-free survival rate, which was consistent with the results of this research, but the study did not conduct postoperative pathological review of surgical specimens and the sample size was limited, This may cause selection bias and confounding factors.

Different from the results of this study, Ratiud et al.[17] analyzed the cervical cancer patients who underwent laparotomy surgery or laparoscopic surgery in figo2009 stage IA1 ~ IIB and found that there was no significant difference in 5-year OS between the laparoscopic group and the laparotomy group (94.1% vs 85.4% $P = 0.311$), but found that the 5-year DFS in the laparoscopic group was higher than that in the laparotomy group (94.1% vs 75.6% $P = 0.049$), It is considered that minimally invasive surgery for patients with stage IA1 ~ IIB cervical cancer can improve the tumor-free survival rate. This is different from the results of this study. The reasons are as follows: first, this study does not strictly limit the presence or absence of adjuvant therapy and the number of times before operation. Second: the difference between the two groups was statistically significant in terms of baseline lymphatic vascular infiltration. However, due to the small number of cases included in the study, a total of 75 cases were not controlled by PSM. Third: the histological types of the study are different. In addition to squamous cell carcinoma, the study also includes adenocarcinoma and adenosquamous cell carcinoma. Fourth: the study stage is figo2009 stage IA1 ~ IIB, which is not specifically for early cervical cancer cases.

At present, the conclusions of oncological prognosis of laparotomy and laparoscopy are different in patients with different histological types of cervical cancer. Kimsi [18] found that when the histological type is cervical squamous cell carcinoma, the 5-year PFS of laparoscopic surgery is lower than that of laparotomy surgery, but there is no difference between the two groups in non cervical squamous cell carcinoma, while other studies found no difference in oncological outcomes between the two subtypes [6-8,19]. Leeyy[10] included 775 cases of stage IB ~ IIA cervical cancer in FIGO2009, including 636 cases of squamous cell carcinoma and 139 cases of adenocarcinoma. The results showed that compared with squamous cell carcinoma, adenocarcinoma before and after matching was associated with worse survival outcome and higher distant recurrence rate. Mabuchis et al. [20] found that the prognosis of cervical adenocarcinoma is worse than that of cervical squamous cell carcinoma when there are any high and medium risk pathological factors. When the histological type is adenocarcinoma, it may affect the oncological outcome of laparotomy surgery and laparoscopic surgery. In order to make this study more convincing, the histological type is limited to cervical squamous cell carcinoma, and whether the postoperative adjuvant treatment is standardized due to high-risk pathological factors will lead to the difference of oncological outcome between the two groups. Therefore, this study limits the pathological factors and carries out PSM to control the confounding factors, The results before and after matching showed that laparoscopic surgery had worse oncological outcomes.

Patients with cervical cancer undergoing laparoscopic surgery have a high recurrence rate, which may be related to the failure to strictly implement the tumor free principle during the operation, the promotion of inflammation and tumor metastasis by CO2 pneumoperitoneum during the operation, the use of uterine lifting device during the operation, the gasification of electrical equipment, the way of vaginal disconnection and suture [21-24]. Vaginal uterine lifter is related to direct contact with tumor lesions and long-term compression, resulting in rupture of tumor cells and artificial diffusion of tumor cells.

This study has some limitations. Firstly, the case data of 47 hospitals in China are included in this study, which will lack some clinical data. Secondly, there are some deviations in the surgical level and experience of surgeons. Third, the time span of case inclusion is long, and the surgeon's learning curve should also be one of the factors to be considered. Although there are some defects in our study, based on the multi center large sample study, it can effectively reflect the practical value of FIGO2018 new stage in the diagnosis and treatment of cervical cancer in China. PSM is used to strictly control the confounding factors. At the same time, the included pathological factors are postoperative pathology, which is more accurate. Therefore, we believe that the results of this study have high reliability. This study is also a more detailed supplement to the results of previous laparoscopic and open studies, and also provides evidence support for the recommended laparoscopic surgical approach in NCCN guidelines.

In conclusion, for patients with FIGO2018 new stage early cervical squamous cell carcinoma with any high-risk pathological factors, there was no significant difference between 5-year OS of laparotomy surgery and laparoscopic surgery. 5-year DFS of laparoscopic surgery was lower than that of laparotomy surgery. Laparoscopic surgery was an independent risk factor for recurrence / death of patients with cervical cancer.

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Ethical Statement

This study was approved by the Ethics Committee of Nanfang Hospital, Southern Medical University (ethics approval number NFEC-2017-135).

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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