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ORIGINAL RESEARCH

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# Neoadjuvant chemotherapy followed by radical surgery versus primary surgery in stage IB2–IIB cervical adenocarcinoma: a retrospective study

Feitianzhi Zeng[1], Peng Guo[1], Meng Xia[1], Mian He[1,*]

[1]Department of Obstetrics and Gynecology, the First Affiliated Hospital of Sun Yat-sen University, 510080 Guangzhou, Guangdong, China

***Correspondence**
hemian@mail.sysu.edu.cn
(Mian He)

## Abstract

This retrospective study was conducted to compare the survival outcomes of patients with cervical adenocarcinoma treated with neoadjuvant chemotherapy followed by radical surgery (NACT + RS) compared to those treated with primary surgery (PS) only. The data of stage IB2–IIB cervical adenocarcinoma patients treated with NACT + RS or PS at our institution were retrieved and assessed. Kaplan-Meier analysis was conducted to compare the survival differences between the investigated treatment groups. Cox proportional hazards model was used to identify potential prognostic factors. A total of 45 patients were eligible for this study, with 20 patients in the NACT + RS group and 25 in the PS group. The 3-year overall survival (OS) of patients from the NACT + RS group was 79.7%, while it was 84.0% for those in the PS group, but the difference was not statistically significant ($p = 0.974$). In addition, their corresponding 3-year progression-free survival (PFS) was also comparable, at 70.0% and 80.0%, respectively ($p = 0.716$). Of the responders and non-responders to neoadjuvant therapy who underwent NACT + RS, their corresponding 3-year OS was 100.0% versus 53.3% ($p = 0.013$), and their 3-year PFS was 90.9% versus 44.4% ($p = 0.016$), respectively. The incidences of lymph node metastasis, parametrial invasion, surgical margin involvement, lymphovascular space invasion and deep stromal invasion were comparable between the two treatment groups. Multivariate analysis showed that lymph node metastasis was an independent prognostic factor for PFS. In conclusion, neoadjuvant chemotherapy followed by radical surgery was not associated with improved survival prognosis or reduced pathological risk factors in patients with stage IB2–IIB cervical adenocarcinoma, but response to neoadjuvant chemotherapy could be a potential indicator of better prognosis.

## Keywords

Cervical adenocarcinoma; Neoadjuvant chemotherapy; Radical hysterectomy

## 1. Introduction

Cervical cancer is the most common gynecologic malignancy worldwide [1], of which cervical adenocarcinoma accounts for approximately 20% of all cervical cancer and its incidence has been increasing over the past decades [2]. Although the current management of cervical adenocarcinoma is similar to squamous cell cancer, which is the most common histological type of cervical cancer, a growing number of studies have revealed that cervical adenocarcinoma differs from squamous cell cancer in numerous aspects, including epidemiology, molecular profile, response to treatment and survival outcomes [3–8].

Radical hysterectomy with pelvic lymphadenectomy is a classic treatment option for stage IB2–IIB cervical cancer patients classified with the International Federation of Gynecology and Obstetrics (FIGO) [9–11]. The main surgical approach to radical surgery in patients with cervical cancer includes open surgery and minimally invasive surgery. They were considered to yield comparable survival outcome based on previous retrospective studies, until the Laparoscopic Approach to Cervical Cancer (LACC) trial has demonstrated that minimally invasive surgery is associated with higher incidence of recurrence and death [12–15]. In some areas and countries of the world, neoadjuvant chemotherapy (NACT) is administered to selected patients with locally advanced cervical cancer before radical surgery. Previous studies showed that NACT could shrink the initial size of the tumor and decrease the risk of parametrial infiltration, as well as lymph node and distant metastasis; thus, increasing the feasibility of radical surgery and reducing the need for adjuvant radiotherapy after surgery [16–19]. However, there is no consensus on whether NACT followed by radical surgery (NACT + RS) could improve the survival outcomes of patients with cervical cancer [17–22].

Previous studies comparing the efficacy of NACT + RS and other treatment options mainly focused on squamous cervical cancer, and of the few studies on cervical adenocarcinoma,


  

most were single-arm and retrospective studies. In previous studies, the response rate of cervical adenocarcinoma to platinum-based NACT was reported to range between 41% to 82%, and the 5-year progression-free survival (PFS) and overall survival (OS) of those who underwent NACT + RS were approximately 73–77% and 84–87% respectively [23–26]. Presently, it remains unclear whether NACT + RS could impact the prognosis of patients with cervical adenocarcinoma. Therefore, we conducted this retrospective study to determine the clinical outcome of NACT + RS versus primary surgery (PS) in patients with FIGO stage IB2–IIB cervical adenocarcinoma.

## 2. Patients and methods

### 2.1 Patient selection

Medical records of cervical adenocarcinoma patients treated with surgery at the First Affiliated Hospital of Sun Yat-sen University between January 2001 and December 2018 were retrieved and reviewed. The inclusion criteria were: histologically confirmed adenocarcinoma of the uterine cervix; FIGO 2009 stage IB2–IIB; age $\geq$18 years; Eastern Cooperative Oncology Group performance status 0–2; and underwent radical hysterectomy. The exclusion criteria were: other histological types contained in the tumor, such as neuroendocrine carcinoma, adenosquamous carcinoma, *etc.*; treated with radiotherapy before surgery; the presence of secondary or multiple malignancies; incomplete medical records; and incomplete follow-up data.

### 2.2 Treatments

Patients who underwent NACT + RS received the physician's choice of platinum-based regimen. The NACT regimens used in this study were as follows: (1) taxane and platinum based (TP) regimen: paclitaxel 135–175 mg/m$^2$ or docetaxel 75 mg/m$^2$ administered on day 1, cisplatin 70–75 mg/m$^2$ or carboplatin with an area under the curve (AUC) 5 mg/mL/min or nedaplatin 80–100 mg/m$^2$ administered on day 2, repeated at 3 weeks interval; (2) carboplatin and 5-fluorouracil (C/F) regimen: carboplatin with an AUC 5 mg/mL/min and 5-fluorouracil 1000 mg/m$^2$ administered on day 1, repeated at 3 weeks interval; (3) bleomycin, carboplatin and cyclophosphamide (BLM/C/CTX) regimen: bleomycin 45 U and carboplatin with an AUC 5 mg/mL/min administered on day 1, cyclophosphamide 600 mg/m$^2$ on day 2, repeated at 3 weeks interval. After NACT, the patients underwent radical hysterectomy with pelvic lymphadenectomy. The rest of the enrolled patients underwent radical surgery as primary treatment. All patients underwent type C radical hysterectomy (Querleu-Morrow classification), *via* open or laparoscopic approach selected based on the physician's discretion [27]. The extent of pelvic lymphadenectomy included bilateral common iliac, external iliac, internal iliac, deep inguinal and obturator lymph nodes. After surgery, adjuvant radiotherapy was performed according to each patient's pathological risk factors, general condition and multidisciplinary discussion results.

### 2.3 Evaluation of response and outcomes

The clinical response to neoadjuvant chemotherapy was evaluated using the Response Evaluation Criteria in Solid Tumors guideline version 1.1. Complete response was defined as the disappearance of all lesions. Partial response was defined as a more than 30% decrease in the longest diameter of the cervical lesion. Objective response rate was determined as the sum of complete and partial response rates. OS was defined as the time interval between the start of treatment and death, and PFS as the time interval between the start of treatment and the first documented recurrence or death, whichever came first.

### 2.4 Statistical analysis

The differences in baseline characteristics between treatment groups and post-surgery pathological risk factors were assessed by *t*-test for continuous variables and $\chi^2$ test or Fisher's exact test for categorical variables. OS and PFS curves were drawn using the Kaplan-Meier method. The significance of the survival differences between treatment groups was tested by the Log-rank test. Hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated by univariate Cox analysis. The Cox proportional hazards model was used to perform multivariate analysis estimating the effect of potential prognostic factors. A $p$-value $< 0.05$ was considered statistically significant. The IBM SPSS Statistics for Windows, version 26.0 (IBM Corp, Armonk, NY, USA) and GraphPad Prism version 5.0 for Windows (GraphPad Software, San Diego, CA, USA) were used for data analysis.

## 3. Results

### 3.1 Baseline characteristics of patients

Medical records of 317 patients diagnosed with cervical adenocarcinoma and underwent surgical resection at the First Affiliated Hospital of Sun Yat-sen University from 2001 to 2018 were reviewed (Fig. 1). Of the 45 patients eligible for this study, 20 underwent NACT + RS and 25 underwent PS. As shown in Table 1, the baseline characteristics, including age, FIGO stage, histological differentiation and tumor size, were comparable between patients in the NACT + RS group and the PS group.

### 3.2 Treatment and response

The treatment details of both groups are summarized in Table 2. A combination of platinum and taxane was the most common NACT regimen in this study, which was administered to 90.0% of patients (18/20) in the NACT + RS group. The objective response rate to NACT was 55.0% (11/20). All patients underwent radical hysterectomy with pelvic lymphadenectomy *via* open surgery (21/45, 46.7%) or laparoscopic surgery (24/45, 53.3%). After surgery, 70.0% of patients (14/20) in the NACT + RS group and 40.0% (10/25) in the PS group underwent adjuvant radiotherapy. The median follow-up time was 62 months (range 8–179 months) in the NACT + RS group and 83 months (range 15–167 months) in the PS group.

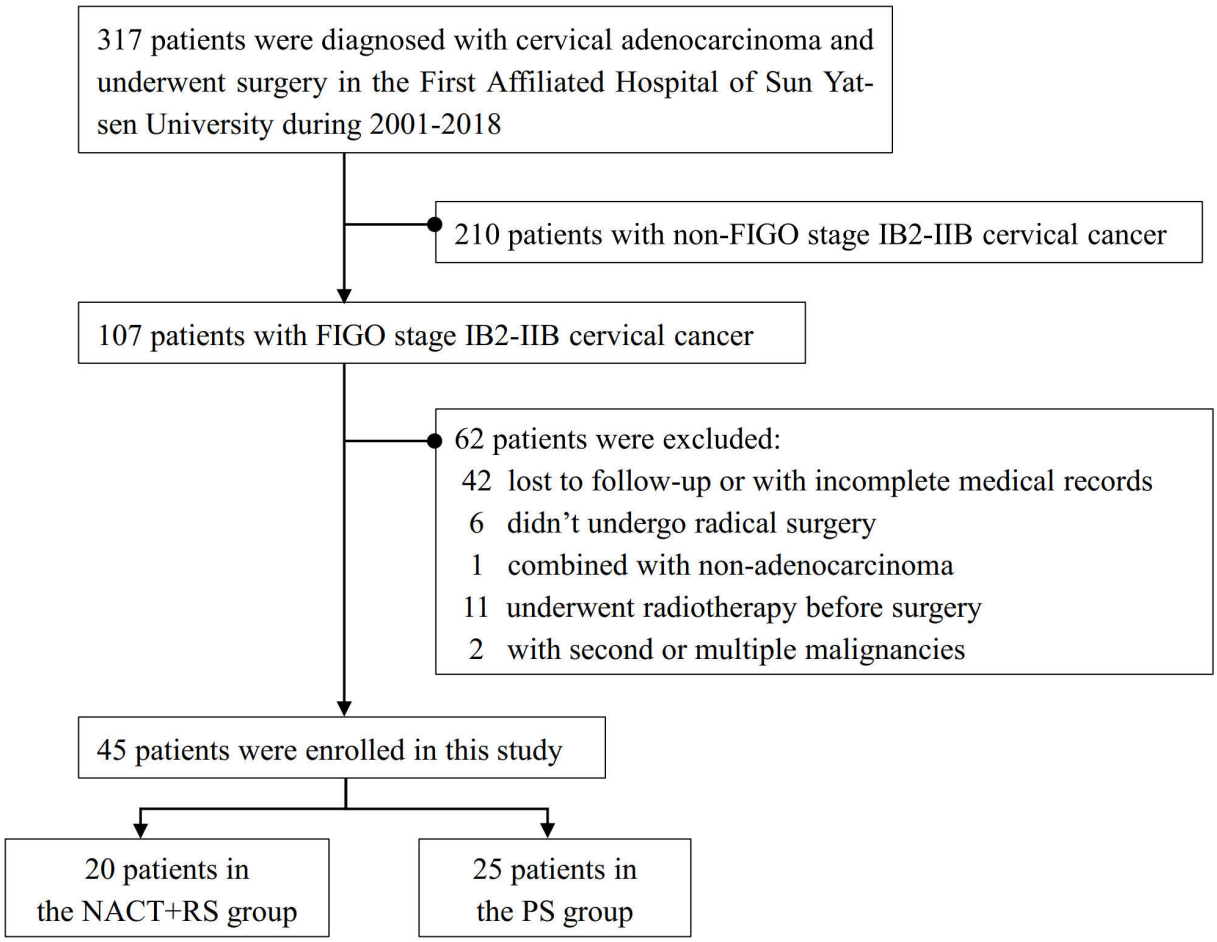


**FIGURE 1. Flow chart of patient selection.** FIGO, International Federation of Gynecology and Obstetrics; NACT + RS, neoadjuvant chemotherapy followed by radical surgery; PS, primary surgery.

**TABLE 1. Baseline characteristics of patients.**

| Characteristics | NACT + RS (n = 20) | PS (n = 25) | *p* |
|---|---|---|---|
| Median age (range) | 43 (24–67) | 46 (32–64) | 0.604 |
| FIGO stage (%) | | | |
| IB2 | 9 (45.0) | 9 (36.0) | |
| IIA | 5 (25.0) | 12 (48.0) | 0.274 |
| IIB | 6 (30.0) | 4 (16.0) | |
| Histological differentiation (%) | | | |
| Well-differentiated | 1 (5.0) | 2 (8.0) | |
| Moderately differentiated | 10 (50.0) | 14 (56.0) | 0.788 |
| Poorly differentiated | 6 (30.0) | 4 (16.0) | |
| Undefined | 3 (15.0) | 5 (20.0) | |
| Tumor size (%) | | | |
| ≤2 cm | 1 (5.0) | 5 (20.0) | |
| 2–4 cm | 6 (30.0) | 8 (32.0) | 0.310 |
| >4 cm | 13 (65.0) | 12 (48.0) | |

*NACT + RS, neoadjuvant chemotherapy followed by radical surgery; PS, primary surgery; FIGO, International Federation of Gynaecology and Obstetrics.*

**TABLE 2. Treatment details of the NACT + RS group and the PS group.**

| Treatment details | NACT + RS (n = 20) | PS (n = 25) | *p* |
|---|---|---|---|
| NACT cycles (%) | | | |
| 1 | 9 (45.0) | NA | |
| 2 | 11 (55.0) | | |
| NACT regimens (%) | | | |
| TP | 18 (90.0) | | |
| BLM/C/CTX | 1 (5.0) | NA | |
| C/F | 1 (5.0) | | |
| Response to NACT (%) | | | |
| No | 9 (45.0) | NA | |
| Yes | 11 (55.0) | | |
| Surgical approach (%) | | | |
| Open surgery | 9 (45.0) | 12 (48.0) | 1.000 |
| Laparoscopic surgery | 11 (55.0) | 13 (52.0) | |
| Adjuvant radiotherapy (%) | | | |
| No | 6 (30.0) | 15 (60.0) | 0.071 |
| Yes | 14 (70.0) | 10 (40.0) | |

*NACT + RS, neoadjuvant chemotherapy followed by radical surgery; PS, primary surgery; TP, taxane and platinum-based chemotherapy; BLM, bleomycin; C, carboplatin; CTX, cyclophosphamide; F, 5-fluorouracil; NA, not applicable.*

### 3.3 Survival

The 3-year OS was 79.7% in the NACT + RS group and 84.0% in the PS group (Fig. 2A. HR, 1.021; 95% CI, 0.286 to 3.647; $p = 0.974$). Additionally, the corresponding 3-year PFS was 70.0% and 80.0%, respectively (Fig. 2B. HR, 1.225; 95% CI, 0.410 to 3.656; $p = 0.716$). No significant difference was observed in the 3-year OS and PFS between the NACT + RS and PS groups.

We also compared the survival outcomes between responders (11/20) and non-responders (9/20) to neoadjuvant therapy in patients from the NACT + RS group. We found that both the OS and PFS of responders were significantly superior to non-responders (Fig. 2C,D), with a 3-year OS of 100.0% versus 53.3% ($p = 0.013$) and a 3-year PFS of 90.9% versus 44.4% ($p = 0.016$), respectively. Moreover, the survival outcomes of non-responders were also inferior to patients in the PS group (Fig. 2E,F), although only significant differences in PFS were reached ($p = 0.042$).

*Post-hoc* subgroup analysis was performed to investigate the impact of baseline factors, such as FIGO stage, lymph node status, surgical approach, tumor size and histological differentiation, on the survival of the patients. However, the results identified no subgroup of patients whose OS or PFS in the NACT + RS group significantly differed from the PS group (**Supplementary Tables 1 and 2**).

### 3.4 Prognostic factors

The incidences of pathological risk factors, including lymph node metastasis, parametrial invasion, surgical margin involvement, lymphovascular space invasion (LVSI) and deep stromal invasion, were comparable between the NACT + RS group and the PS group (Table 3). Univariate analysis identified age ≥45, lymph node metastasis, parametrial involvement, LVSI and deep stromal invasion as potential prognostic factors for both OS and PFS. However, multivariate analysis showed that only lymph node metastasis was an independent risk factor for PFS (**Supplementary Table 3**).

## 4. Discussion

In this study, we compared the survival outcomes of patients with FIGO stage IB2–IIB cervical adenocarcinoma treated with NACT + RS or PS and found that the 3-year OS and PFS of patients in the NACT + RS group and the PS group were statistically comparable.

The results of previous studies investigating the role of NACT before surgery in the treatment of cervical cancer have been inconsistent in regard to whether NACT + RS could improve patients' outcomes. The Cochrane review by Rydzewska *et al.* [17] comprising six trials involving 1078 patients of early or locally advanced cervical cancer demonstrated that both OS (HR, 0.77, 95% CI, 0.62 to 0.96, $p = 0.02$) and PFS (HR, 0.75, 95% CI, 0.61 to 0.93, $p = 0.008$) were significantly improved in the NACT + RS group compared with the PS group. However, the phase III Japan Clinical

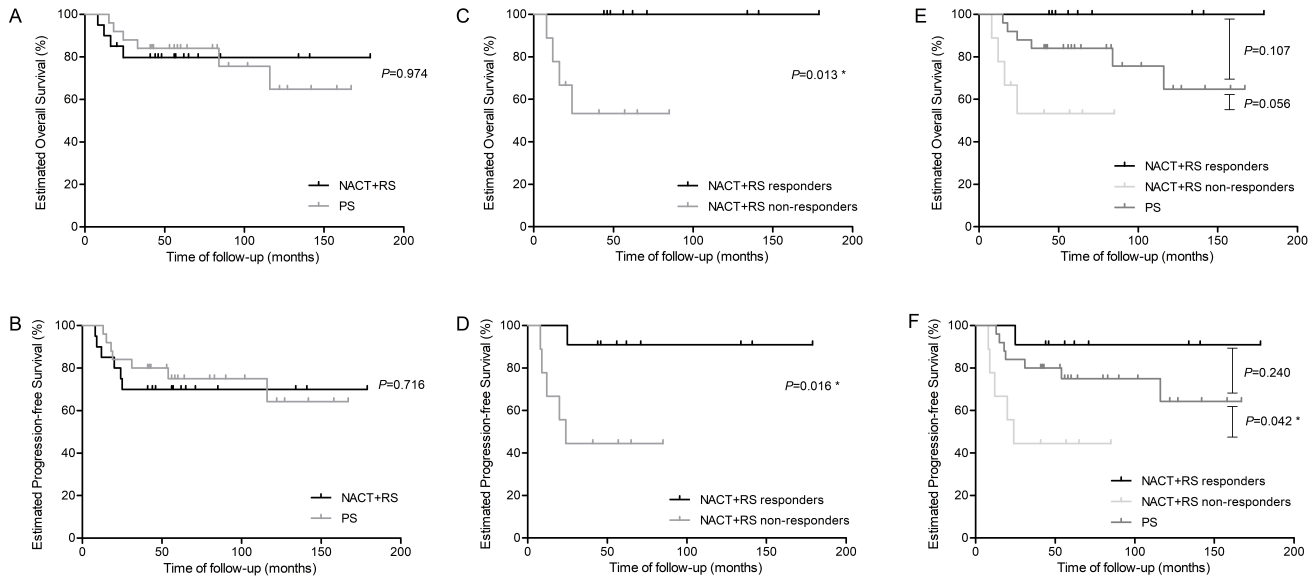


**FIGURE 2. The OS and PFS of cervical adenocarcinoma patients.** (A,B) Survival curves for OS (A) and PFS (B) in patients treated with NACT + RS and PS. (C,D) Survival curves for OS (C) and PFS (D) of responders and non-responders from the NACT + RS group. (E,F) Survival curves of OS (E) and PFS (F) in responders and non-responders from the NACT + RS group and patients in the PS group. The tick marks indicate censored data. NACT + RS, neoadjuvant chemotherapy followed by radical surgery; PS, primary surgery.

**TABLE 3. Pathological risk factors in the NACT + RS group and the PS group.**

| Pathological risk factors | NACT + RS (n = 20) | PS (n = 25) | *p* |
|---|---|---|---|
| Lymph node status (%) | | | |
| Negative | 13 (65.0) | 18 (72.0) | 0.749 |
| Positive | 7 (35.0) | 7 (28.0) | |
| Parametrial involvement (%) | | | |
| Negative | 17 (85.0) | 23 (92.0) | 0.642 |
| Positive | 3 (15.0) | 2 (8.0) | |
| Surgical margin invasion (%) | | | |
| Negative | 19 (95.0) | 25 (100.0) | 0.444 |
| Positive | 1 (15.0) | 0 | |
| LVSI (%) | | | |
| Negative | 13 (65.0) | 23 (92.0) | 0.057 |
| Positive | 7 (35.0) | 2 (8.0) | |
| Stromal Invasion (%) | | | |
| <2/3 | 13 (65.0) | 14 (56.0) | 0.760 |
| ≥2/3 | 7 (35.0) | 11 (44.0) | |

*NACT + RS, neoadjuvant chemotherapy followed by radical surgery; PS, primary surgery; LVSI, lymphovascular space invasion.*

Oncology Group (JCOG) 0102 randomized controlled trial that compared the efficacy of NACT + RS versus PS in patients with locally advanced squamous cervical cancer reported no significant differences in both 5-year OS (70% versus 74.4%, $p = 0.85$) and PFS (59.9% versus 62.7%, $p = 0.85$) between the two treatment groups [21]. Additionally, in a retrospective study by Zhang *et al.* [18] the authors reported that NACT + RS could significantly prolong the 5-year PFS in cervical cancer patients with a tumor larger than 5 cm (94.8% versus 83.7%, $p = 0.016$) or serum squamous cell carcinoma antigen level higher than 5ng/ml (90.6% versus 70.5%, $p = 0.007$) compared with patients who underwent PS. However, no significant difference between the treatment groups was observed in 5-year OS.

Nevertheless, most patients included in previous studies were diagnosed with cervical squamous cell cancer. Due to the intrinsic differences between squamous cell cancer and adenocarcinoma of the cervix, it might not be appropriate to extrapolate these findings to patients with cervical adenocarcinoma. Regarding studies that focused on cervical adenocarcinoma, the retrospective study of Ouyang *et al.* [23] found no significant difference in both 5-year PFS (73.7% versus 91.8%, $p = 0.222$) and OS (86.8% versus 100%, $p = 0.120$) between the NACT + RS group and the PS group in patients with FIGO stage IB2 and IIA2 cervical adenocarcinoma, which was consistent with our present study.

Platinum combined with taxane is the preferred chemotherapy regimen for cervical cancer currently. Previous studies showed that cervical adenocarcinoma was less sensitive to chemotherapy than squamous cell cancer. The clinical response rate to platinum-based NACT was reported to be 75–83% in patients with squamous cervical cancer [18–20, 28], while that of patients with cervical adenocarcinoma was 41–82% [23–26]. In our present study, the objective response rate to NACT was 55%. Aside from the characteristic that cervical adenocarcinoma might be less sensitive to chemotherapy, another possible explanation for the relatively low response rate is that patients in our study received fewer cycles of NACT before surgery than those in previous studies.

Even though only 1–2 cycles of NACT were administered in our study, we surprisingly found that the subgroup of patients who responded to NACT before surgery had excellent survival outcomes. On the other hand, the survival of non-respondents to NACT was not only worse than responders but also inferior to patients in the PS group. Previous studies also reported similar findings in cervical cancer with other histological types. For instance, in the retrospective study performed by Huang *et al.* [32] on patients with FIGO stage IB2–IIA2 cervical cancer, the authors reported that NACT responders had improved 5-year OS (85.4% versus 63.3%, $p = 0.002$) and PFS (71.4% versus 52.4%, $p = 0.002$) compared to non-responders [26, 29–32]. Therefore, similar findings in our study suggested that response to NACT could be a potential indicator of a favorable prognosis for patients with cervical adenocarcinoma.

Previous studies on cervical squamous cancer found that NACT before surgery was associated with a lower incidence of pathological risk factors, including LVSI, deep stromal invasion, and parametrial and lymph node metastasis, leading to the reduced need for adjuvant radiotherapy after surgery [17, 21, 33]. As shown in the JCOG 0102 study, the proportion of patients in the NACT + RS group who met the criteria for adjuvant radiotherapy after radical surgery was significantly lower than that of the PS group (72% versus 89%, $p = 0.015$) [21]. However, the cervical adenocarcinoma patients in this present study showed no significant decrease in the incidence of pathological risk factors in the NACT + RS group compared with the PS group. Besides, the criteria for adjuvant radiotherapy in cervical cancer were mainly based on pathological risk factors. In our study, the proportion of patients who received adjuvant radiotherapy after surgery in the NACT + RS group was numerically greater than that in the PS group, though the difference was not statistically significant. This indicated that the efficacy of chemotherapy in reducing the risk of micro-metastasis might be probably weaker in cervical adenocarcinoma, and the benefit of NACT + RS in reducing the need for radiotherapy might be limited. However, further studies with a larger sample size are needed to validate these observations.

Open surgery is the standard and classic approach for radical hysterectomy in patients with early-stage cervical cancer. Nevertheless, the use of laparoscopic and robotic-assisted radical hysterectomy has become increasingly popular in recent decades because of their inherent advantages of less intraoperative blood loss, shorter hospital stay and lower risk of postoperative complications, without increasing the risk of recurrence or death, as shown in several retrospective studies [12–14]. However, the LACC trial, a randomized control trial comparing the efficacy of minimally invasive surgery and open surgery in patients with early-stage cervical cancer, showed that minimally invasive radical hysterectomy was unexpectedly associated with lower rates of both disease-free and overall survival [15]. As a result, the selection of surgical approaches in clinical practice has shifted from minimally invasive surgeries to open surgery [34]. Despite this, selected patients may still benefit from the minimally invasive approach, as the LACC trial also showed that minimally invasive surgery was not associated with worse clinical outcome in the subgroup of patients with a tumor smaller than 2 cm [15]. In this study focusing on patients with cervical adenocarcinoma, our data showed that the choice of surgical approach was not associated with statistically different clinical outcomes. In the subgroup of patients who underwent either laparoscopic or open surgery, the survival prognosis of patients in the NACT + RS group and PS group remained comparable. In addition, the LACC trial found that patients underwent minimally invasive surgery have higher risk of locoregional recurrence than those with open surgery [15]. The use of uterine manipulator and the procedure of colpotomy are main factors which are possible to encourage locoregional tumor spread in minimally invasive surgery [35]. Hence, the technique of manipulator-free radical hysterectomy and enclosed colpotomy might help improve the clinical outcome of patients with minimally invasive surgery, but further studies are necessary to substantiate these hypothesis [36].

Apart from radical surgery, concurrent chemoradiotherapy (CCRT) is also a recommended treatment for locally advanced cervical cancer. In the study by Gupta *et al.* [20] who evaluated the efficacy of NACT + RS and CCRT in patients

with FIGO stage IB2–IIB cervical squamous cell cancer, the authors showed that the 5-year PFS in the CCRT was superior to the NACT + RS group (76.7% versus 69.3%, $p$ = 0.038), while the 5-year OS was comparable between the two treatment groups (74.7% versus 75.4%, $p$ = 0.87). However, cervical adenocarcinoma was reported to be less sensitive to radiotherapy compared with squamous cell cancer, as shown in Katanyoo *et al.* [4]'s study, whereby patients with cervical adenocarcinoma had significantly lower complete response rate to radical radiotherapy than patients with squamous cell cancer (86.5% versus 94.7%, $p$ = 0.004). These results suggest that surgery might be more important in managing cervical adenocarcinoma. Further work comparing the efficacy of NACT + RS and CCRT with more focus on cervical adenocarcinoma is therefore suggested.

There were several limitations in our study. First, the sample size was small due to the scarcity of cervical adenocarcinoma cases. Second, given the retrospective study design, there might have been a certain level of bias in the selection process of patients to receive NACT + RS or PS, and the NACT regimens were not standardized. Thus, further randomized control studies on cervical adenocarcinoma with larger sample sizes are needed to provide more definitive evidence.

## 5. Conclusions

In conclusion, our study found that NACT + RS did not improve the survival outcomes of patients with FIGO stage IB–IIB cervical adenocarcinoma compared to those who underwent PS. In addition, we found that response to NACT might be a potential indicator of a favorable prognosis for patients with cervical adenocarcinoma. In contrast to previous findings in cervical squamous cell cancer, we found that NACT + RS was not associated with a lower rate of pathological risk factors or a reduction in the need for adjuvant radiotherapy in patients with cervical adenocarcinoma. Therefore, careful consideration and evaluation are suggested before referring cervical adenocarcinoma patients to undergo NACT + RS.

### AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

### AUTHOR CONTRIBUTIONS

FTZZ—designed the study, collected and analyzed the clinical data, and wrote the original manuscript. PG and MX—collected and analyzed the clinical data, revised the manuscript. MH—designed and supervised the study, and revised the manuscript. All authors read and approved the final manuscript.

### ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was carried out in line with the principles of the Declaration of Helsinki and approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University (No. 2022-512). Informed consent for this retrospective study was waived, and the anonymity of all patients' data was preserved.

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### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.ejgo.net/files/article/1735530058378821632/attachment/Supplementary%20material.docx.

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