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ORIGINAL RESEARCH

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# Comparison of pathological outcomes of neoadjuvant chemotherapy before surgery versus radical hysterectomy alone in stage IB3 and IIA2 cervical cancer

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## Abstract

As an alternative treatment strategy, the efficacy of neoadjuvant chemotherapy (NAC) for patients with stage IB3 and IIA2 cervical carcinoma remains uncertain. To address this limitation, this evaluates the pathological outcomes of patients with locally advanced cervical cancer (LACC) treated with NAC before surgery compared with those who underwent radical hysterectomy (RH) alone. A total of 592 patients with stage IB3 and IIA2 cervical cancer were eligible for this study. They were divided into a NAC group (NAC before surgery, n = 259) and a RH group (radical hysterectomy alone, n = 333). Propensity score matching (PSM) was used to eliminate confounding intergroup factors, leading to 233 cases being finally included in the two groups. Patients in the NAC group received 1–3 cycles of nedaplatin plus paclitaxel/docetaxel/irinotecan regimens, followed by surgery 3–5 weeks post-NAC. Patients in the RH group underwent radical hysterectomy after the diagnosis of cervical cancer. Intermediate-risk factors (*i.e.*, lymphovascular space invasion and deep stromal infiltration) and high-risk factors (*i.e.*, lymph node metastasis, positive parametria and positive surgical margin) for the recurrence of LACC were compared between the two groups before and after PSM. The results showed no significant difference in high-risk factors between the NAC and RH groups before and after PSM ($p > 0.05$). In regard to intermediate-risk factors, a significant difference was observed before PSM in inter-group analysis (lymphovascular space invasion, $p = 0.028$; deep stromal infiltration, $p = 0.011$). After PSM, only deep stromal infiltration remained significant, with a decreased incidence observed in the NAC group ($p = 0.004$). In conclusion, NAC before surgery had minimal impact on high-risk factors and lymphovascular space invasion compared to the RH group. However, we did observe a decrease in deep one-third stromal invasion. These results may be relevant to the decision-making process for postoperative radiotherapy.

## Keywords

Uterine cervical neoplasms; Risk factors; Neoadjuvant therapy; Hysterectomy

## 1. Introduction

Cervical cancer is the fourth most common cancer among females, with approximately 604,000 new cases and 342,000 deaths recorded annually worldwide [1, 2]. Locally advanced cervical cancer (LACC) is defined as stage IB3 and IIA2 invasive cervical carcinoma having a largest dimension >4 cm, according to the 2018 International Federation of Gynecology and Obstetrics (FIGO) [2]. Given the particularity of LACC, whose tumor size outrides that which can be treated successfully with surgery alone, comprehensive treatment is presently the main treatment strategy [3, 4].

Although concurrent platinum-based chemoradiation therapy (CCRT) is the preferred treatment option for LACC, therapeutic methods vary greatly in different areas. Preoperative neoadjuvant chemotherapy (NAC) has some advantages, including tumor shrinkage for improving resectability and surgical safety, and reducing the risk of metastasis as well as disease recurrence [5–9]. However, NAC may interfere with the evaluation of postoperative adjuvant chemotherapy or CCRT by masking the pathologic findings [10–13]. An alternative to this treatment approach is radical hysterectomy (RH), which can improve patients' survival outcomes and maintain primitive postoperative pathological state [14]. Intermediate-risk factors, including large tumor diameter >4 cm, lymphovascular space invasion (LVSI) and deep stromal infiltration, and high-risk factors, such as lymph node metastasis (LNM), positive parametria and positive surgical margin, have a significant impact on the recurrence of LACC [15].

In this study, we aimed to investigate the effects of NAC before surgery on the incidence of high- and intermediate-risk factors of LACC, which is essential for determining the


  

appropriate postoperative adjuvant therapy and estimating the prognosis of patients with stage IB3 and IIA2 cervical cancer.

## 2. Materials and methods

### 2.1 Data collection

In this retrospective study, the medical records of 739 stage IB3 or IIA2 cervical cancer patients treated at the Tongji Hospital (Wuhan, China) from 2002 to 2019 were extracted.

Based on physical examination and ultrasound or magnetic resonance imaging scans, all patients were classified according to the 2018 FIGO staging system [2]. Previously defined stage IB2 by 2014 FIGO staging system was revised to stage IB3 according to the up-to-date 2018 FIGO staging system. The exclusion criteria were coexisting malignancies and incomplete medical records. The inclusion criteria were: (1) pathologically confirmed cervical cancer; (2) stage IB3 or IIA2 with the largest tumor diameter >4 cm according to the 2018 FIGO staging system; (3) the age at surgery ranged from 18 to 80 years; (4) treatment naïve cases without previous chemotherapy history.

After filtering the data, 592 patients were found eligible for this study and assigned into two groups. Patients (n = 259) who received NAC before surgery were classified as the NAC group, and those who underwent RH without preoperative chemotherapy were classified as the RH group (n = 333). Their demographic information, including age at surgery, disease stage, histological type and pathology degree, and pathological findings, including lymph nodes, surgical margin, parametria, LVSI and stromal infiltration, were evaluated.

### 2.2 Neoadjuvant chemotherapy regimens followed by surgical procedure

The widely adopted NAC procedure included 1–3 cycles of 80 mg/m$^2$ nedaplatin and 175 mg/m$^2$ paclitaxel at 3–5 weeks' intervals. Few patients who were candidates for NAC received 1–2 cycles of chemotherapy with nedaplatin 80 mg/m$^2$ and docetaxel 80 mg/m$^2$ or nedaplatin 60 mg/m$^2$ and irinotecan 165 mg/m$^2$. The cycles and drugs were determined by patients' response and tolerance degree. All patients tolerated the chemotherapy regimen without any severe complications. Then, 3–5 weeks after the final chemotherapy cycle, the patients were evaluated by physical, biochemistry and imaging examinations to assess their eligibility for surgical resection. After their laboratory tests returned to normal, the patients underwent surgery. Querleu and Morrow (QM) type C radical hysterectomy with pelvic lymphadenectomy (with or without para-aortic lymphadenectomy) were performed by experienced gynecologists. Vaginal stump, bilateral adnexa, parametrium, round ligament, broad ligament and lymph nodes were inspected intraoperatively.

### 2.3 Radical hysterectomy procedure

Patients in the RH group underwent QM type C radical hysterectomy with pelvic lymphadenectomy (with or without para-aortic lymphadenectomy). The aforementioned resected tissues were also inspected intraoperatively.

### 2.4 Propensity score matching (PSM)

To eliminate differences in the clinical characteristics (*i.e.*, age at surgery, FIGO stage, histological type and pathology degree) between the NAC and RH groups, we used the PSM method to balance the patients' factors to ensure intergroup comparability. After 1: 1 PSM, there were 233 cases included in each group, following which a logistic regression analysis was performed using the following risk factors: LNM, surgical margin, parametria, LVSI and deep stromal invasion.

### 2.5 Statistical analysis

Data analysis was performed using the IBM SPSS Statistics v26.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as the mean ± standard deviation (SD). Categorical variables are expressed as the absolute number (percentage). An Independent sample *t*-test was used for numerical data. For the data dissatisfying normal distribution, the Kruskal-Wallis H test was used. The chi-square test was used for categorical data. Fisher's exact test was used instead for the data with theoretical frequency <5. Besides, logistic regression analysis was used to adjust the influence on the pathological results between the NAC and RH groups. $p$-value $< 0.05$ was considered statistically significant.

## 3. Results

### 3.1 Baseline characteristics

In this study, 592 cervical cancer patients with a median age of 48.30 (23–76) years were investigated, of whom 259 were in the NAC group, and 333 were in the RH group. The study screening process is illustrated in Fig. 1, and the patients' baseline characteristics are shown in Table 1. The results showed an unbalanced proportion of patients with stage IB3 and IIA2 between the two groups ($p < 0.001$). After 1: 1 PSM, 233 cases were included in each group attaining comparability in regard to the baseline data ($p > 0.05$). In the NAC group, our results showed that different neoadjuvant chemotherapy cycles had no significant impact on the high- and intermediate-risk factors (**Supplementary Table 1**).

### 3.2 Comparison of pathological outcomes between NAC and RH groups

As shown in Table 1, the high-risk factors for LACC recurrence between the two groups were not statistically significant regardless of PSM (before matching: LNM, 48 (18.5%) *vs.* 83 (24.9%), $p = 0.063$; surgical margin, 7 (2.7%) *vs.* 6 (1.8%), $p = 0.458$; and parametria, 4 (1.5%) *vs.* 6 (1.8%), $p = 1.000$; after matching: LNM, 47 (20.2%) *vs.* 53 (22.7%), $p = 0.498$; surgical margin, 6 (2.6%) *vs.* 6 (2.6%), $p = 1.000$; and parametria, 4 (1.7%) *vs.* 4 (1.7%), $p = 1.000$, respectively). However, the NAC group had a significantly lower rate of detection of the two intermediate-risk factors, but the difference in LVSI was eliminated after PSM (before matching: LVSI, 23 (8.9%) *vs.* 47 (14.1%), $p = 0.028$; deep one-third stromal invasion, 126 (48.6%) *vs.* 199 (59.8%), $p = 0.011$; after matching: LVSI, 22 (9.4%) *vs.* 34 (14.6%), $p = 0.103$; and deep one-third stromal invasion, 111 (47.6%) *vs.*

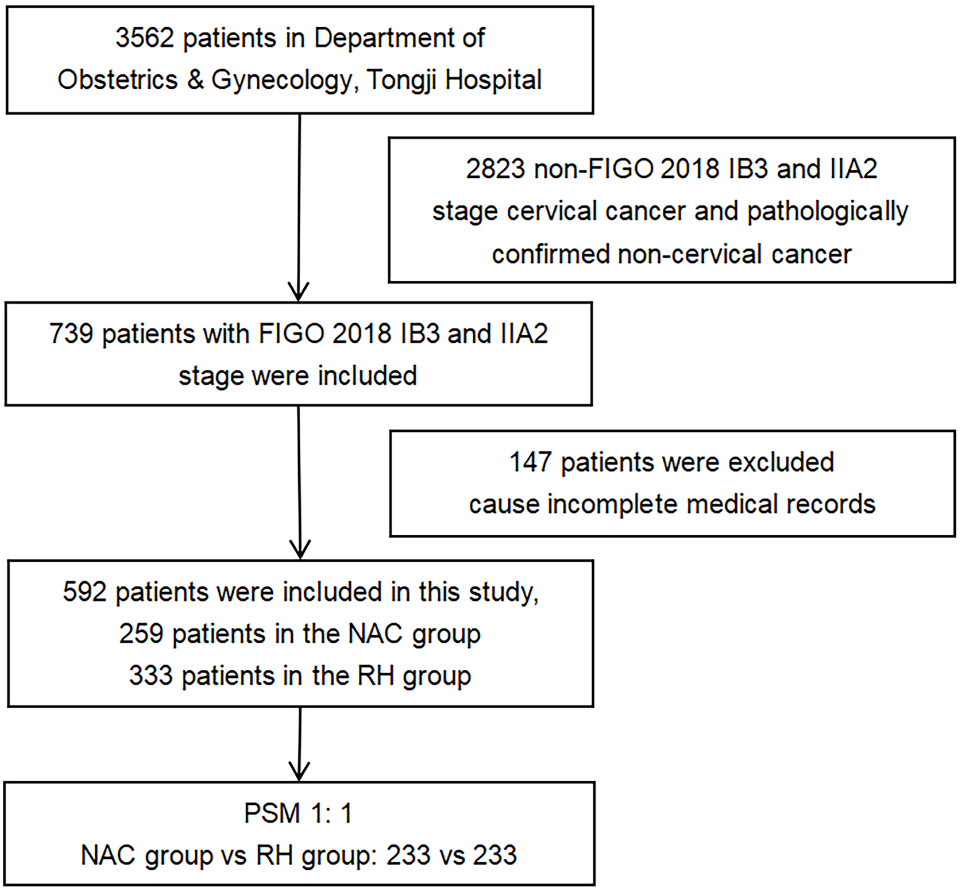


**FIGURE 1. Flowchart of patients included in the analysis.** FIGO, International Federation of Gynecology and Obstetrics; NAC, neoadjuvant chemotherapy; RH, radical hysterectomy; PSM, propensity score matching.

146 (62.7%), $p = 0.004$, respectively). Furthermore, logistic regression analysis showed that NAC was an independent protective factor for cervical deep stromal invasion ($p = 0.003$).

## 4. Discussion

In this clinical retrospective study on the effects of NAC for patients diagnosed with stage IB3 and IIA2 cervical cancer, we observed that NAC had no influence on the high-risk factors and LVSI in regard to LACC recurrence compared with the RH group after PSM, except for deep one-third stromal invasion, which remained the only affected intermediate-risk factor for the LACC recurrence ($p = 0.004$).

The effects of NAC in LACC, especially on patients' survival and prognosis, have been debatable, and there has been a lack of research on pathological outcomes associated with the influence of postoperative adjuvant therapy and prognosis. Previous literature indicated that NAC might attenuate the effects of the high- and/or intermediate-risk factors, although the conclusions remain controversial. Li *et al.* [16] reported that LACC patients responding to NAC had a lower rate of LVSI, deep stromal infiltration, LNM and postoperative radiotherapy, consequently benefitting from higher 5-year disease-free survival (DFS) and overall survival (OS). Similar results were obtained by Hu *et al.* [17], who reported no significant influence on high-risk factors. Although there are reports showing that NAC may lower the rate of intermediate- and high-risk factors and reduce the need for postoperative radiotherapy, no difference in survival was obtained following comparison with their respective RH group [13, 18] and opposite conclusions were reported in some other studies [19, 20]. Kim *et al.* [20] found that NAC reduced the rate of intermediate-risk factors and positive parametria in patients with stage IIA. Further, a meta-analysis showed that NAC lowered tumor diameter, LNM and postoperative radiotherapy, but the patients had a worse OS.

The possible reasons for the contradicting observations in literature could be as follows: (1) a wide range of included cervical cancer stages covering IB1–IIB stages; (2) low-powered study with small samples; (3) non-comprehensive limited studies on intermediate- and high-risk factors for LACC recurrence. Hence, the novelty of our study was the focus on LACC (stage IB3 and IIA2) rather than including other distinct stages to eliminate confounding factors. A local tumor with the largest diameter >4 cm is considered an intermediate-risk factor for recurrence. However, IB1, IB2 and IIA1 stages of cervical cancer often have a diameter <4 cm, which is intrinsically inconsistent with the characteristic of LACC. It also differs from stage IIB LACC with parametrial invasion, which is already a positive high-risk factor. Furthermore, our study was committed to covering all high- and intermediate-risk factors associated with LACC recurrence due to the large included study cohort. The latest National Comprehensive Cancer Network (NCCN) guidelines recommend different postoperative adjuvant treatments for "intermediate-risk" and "high-risk"

**TABLE 1. Clinicopathologic characteristics of patients with locally advanced cervical cancer between the NAC and RH groups.**

| | Before PSM | | | After PSM | | |
|---|---|---|---|---|---|---|
| | NAC (n = 259) | RH (n = 333) | *p* value | NAC (n = 233) | RH (n = 233) | *p* value |
| Age at surgery[1] (yr) | 48.43 ± 8.41 | 48.19 ± 9.04 | 0.737 | 48.52 ± 8.49 | 49.10 ± 9.11 | 0.479 |
| FIGO stage, n (%) | | | | | | |
| IB3 | 124 (47.9) | 222 (66.7) | <0.001 | 123 (52.8) | 125 (53.6) | 0.853 |
| IIA2 | 135 (52.1) | 111 (33.3) | | 110 (47.2) | 108 (46.4) | |
| Histology type, n (%) | | | | | | |
| SCC | 234 (90.3) | 282 (84.7) | 0.125 | 209 (89.7) | 208 (89.3) | 0.754 |
| AC | 23 (8.9) | 45 (13.5) | | 23 (9.9) | 22 (9.4) | |
| ASC | 2 (0.8) | 3 (0.9) | | 1 (0.4) | 3 (1.3) | |
| Others | 0 | 3 (0.9) | | 0 | 0 | |
| Pathology, n (%) | | | | | | |
| High differentiated | 11 (4.2) | 10 (3.0) | 0.593 | 7 (3.0) | 10 (4.3) | 0.597 |
| Middle differentiated | 146 (56.4) | 182 (54.7) | | 133 (57.1) | 124 (53.2) | |
| Low differentiated | 102 (39.4) | 139 (41.7) | | 93 (39.9) | 99 (42.5) | |
| Undifferentiated | 0 | 2 (0.6) | | 0 | 0 | |
| LNM, n (%) | | | | | | |
| Negative | 211 (81.5) | 250 (75.1) | 0.063 | 186 (79.8) | 180 (77.3) | 0.498 |
| Positive | 48 (18.5) | 83 (24.9) | | 47 (20.2) | 53 (22.7) | |
| Surgical margin, n (%) | | | | | | |
| Negative | 252 (97.3) | 327 (98.2) | 0.458 | 227 (97.4) | 227 (97.4) | 1.000 |
| Positive | 7 (2.7) | 6 (1.8) | | 6 (2.6) | 6 (2.6) | |
| Parametria, n (%) | | | | | | |
| Negative | 255 (98.5) | 327 (98.2) | 1.000 | 229 (98.3) | 229 (98.3) | 1.000 |
| Positive | 4 (1.5) | 6 (1.8) | | 4 (1.7) | 4 (1.7) | |
| LVSI, n (%) | | | | | | |
| Negative | 2 (0.8) | 9 (2.7) | 0.028 | 2 (0.9) | 5 (2.1) | 0.103 |
| Positive | 23 (8.9) | 47 (14.1) | | 22 (9.4) | 34 (14.6) | |
| Unknown | 234 (90.3) | 277 (83.2) | | 209 (89.7) | 194 (83.3) | |
| Stromal invasion, n (%) | | | | | | |
| Inner 1/3 | 68 (26.3) | 58 (17.4) | 0.011 | 63 (27.0) | 41 (17.6) | 0.004 |
| Middle 1/3 | 65 (25.1) | 76 (22.8) | | 59 (25.3) | 46 (19.7) | |
| Outer 1/3 | 126 (48.6) | 199 (59.8) | | 111 (47.6) | 146 (62.7) | |

[1]*Age at surgery (yr) data are mean ± SD.*

*NAC, neoadjuvant chemotherapy; RH, radical hysterectomy; PSM, propensity score matching; FIGO, International Federation of Gynecology and Obstetrics; SCC, squamous cell carcinoma; AC, adenocarcinoma; ASC, adenosquamous carcinoma; LNM, lymph node metastasis; LVSI, lymphovascular space invasion.*

diseases due to their associated divergent survival rates [21]. Given the importance of postoperative adjuvant therapy for cervical cancer, we investigated the discrepancy of risk factors between the NAC and RH groups to systematically explore their possible impact.

Positive high-risk factors play an essential role in postoperative adjuvant therapy, such as postoperative pelvic external-beam radiotherapy with concurrent platinum-containing chemotherapy with (or without) vaginal brachytherapy [21]. Unlike previous studies, our study found that NAC did not affect LNM, surgical margin and parametrium compared with the RH group. Without concealing the potential adverse effects of NAC on pathological outcomes, patients in each group could undergo comparable adjuvant radiotherapy regimens to avoid escaping postoperative adjuvant therapy. A similar result was observed in the study by Hu *et al.* [17], who reported non-significant difference in LNM between the two groups, and an increased 5-year DFS and OS in the NAC group. A possible reason could be the different responses to the chemotherapy agents, leading to obstruction of the lymph node deactivation in the non-responders.

Likewise, the intermediate-risk factors are also important for adopting postoperative adjuvant therapy. The findings of our study suggest that NAC decreased the incidence of deep one-third stromal infiltration ($p = 0.004$). This result remains significant after logistic regression analysis, confirming the protective effect on deep stromal invasion of NAC ($p = 0.003$). Intermediate-risk factors are used to guide postoperative adjuvant treatment decisions, including greater than one-third stromal invasion, LVSI and cervical tumor greatest dimension >4 cm (Sedlis Criteria) [22]. Given the nature of LACC and intergroup LVSI with no significance, invasion of the outer one-third cervical stroma is the only factor in deciding whether to implement adjuvant pelvic radiotherapy alone versus no further therapy, which played a minor role in the choice of postoperative adjuvant therapy. Similar to previous studies, NAC was found to positively affect stromal invasion compared with the RH group in this current study [13, 16, 17]. Notwithstanding, there are still inconsistent trends in the survival rate of LACC patients. The administration of NAC in LACC may hinder the detection of risk factors for adjuvant radiotherapy after surgery, or it may reduce tumor volume and disease recurrence, thereby improving patients' prognosis [19]. Further survival analysis is necessary to investigate the impact of NAC on survival rates and prognosis of LACC patients.

Some reports have found that histological types of cervical cancer affected NAC efficacy and LNM, especially between squamous cell carcinoma and endocervical adenocarcinoma [21, 23]. Therefore, it is a limitation that lacks analysis for the neoadjuvant chemotherapy responses of different histological subtypes. However, we eliminated the interference of baseline characteristics (*i.e.*, age at surgery, disease stage, histological type and pathology degree) using the implemented PSM method to ensure intergroup comparability.

The other limitations of our study were its retrospective nature, incomplete medical records and revision from stage IB2 to stage IB3 according to the FIGO 2018 staging system. Although the data were meticulously verified, there may still be insufficiency due to the lack of immediateness to measurements. Additionally, patients with incomplete information were excluded from the subsequent analysis resulting in data loss. However, we obtained the required information by checking the associated clinicians and tracing the included patients. Also, the re-assignment of stages was strictly conducted according to the 2018 FIGO staging system. The potential bias was minimized by rechecking the tumor diameter and invasion sites.

## 5. Conclusions

This study showed that NAC before surgery had little influence on the high- and intermediate-risk factors of stage IB3 and IIA2 cervical cancer patients compared with RH treatment, except for deep stromal invasion, which was the only affected intermediate-risk factor. Future follow-up studies are needed to clarify the prognosis and survival of LACC patients treated with NAC or RH.

### ABBREVIATIONS

NAC, neoadjuvant chemotherapy; RH, radical hysterectomy; PSM, propensity score matching; LACC, locally advanced cervical cancer; FIGO, International Federation of Gynecology and Obstetrics; CCRT, concurrent platinum-based chemoradiation therapy; LVSI, lymphovascular space invasion; LNM, lymph node metastasis; QM, Querleu and Morrow; SD, standard deviation; DFS, disease-free survival; OS, overall survival; NCCN, National Comprehensive Cancer Network.

### AVAILABILITY OF DATA AND MATERIALS

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

### AUTHOR CONTRIBUTIONS

JL and SFL—designed the research study, collected the data from medical records and analyzed the data. YQY—searched the literature. JL, SFL and YQY—wrote the manuscript. JCW—contributed to the conception of the study. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

### ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study received ethical approval from the institutional review board of the local ethics committee of Tongji Hospital (TJ-IRB20220925). The ethics committee approved exemption from informed consent.

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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/1669261377739341824/attachment/Supplementary%20material.docx.

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