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Neoadjuvant chemotherapy does not improve the prognosis and lymph node metastasis rate of locally advanced cervical squamous cell carcinoma

A retrospective cohort study in China

Wenxing Yan, MD[a], Lihui Si, MD[b], Yaming Ding, MD[a], Shuang Qiu, MD[c], Qi Zhang, MD[a], Linlin Liu, MD[a,*]

Abstract

Locally advanced cervical carcinoma has a poor prognosis. Neoadjuvant chemotherapy (NACT) can reduce tumor size and improve tumor resection rate, but its use in large locally advanced cervical carcinoma is controversial. This study aimed to evaluate the treatment and prognosis of NACT in patients with cervical carcinoma stage IB2 or IIA2.

This was a retrospective cohort study of patients who underwent type-C radical surgery and pelvic lymphadenectomy due to cervical carcinoma stage IB2/IIA2 between 2/2014 and 12/2016 at the Second Hospital of Jilin University. The patients were grouped according to whether they received NACT (paclitaxel and a platinum salt) or not. Overall survival (OS) and progression-free survival (PFS) were compared between the 2 groups.

Of the 144 patients, 60 (41.7%) received NACT. A total of 119 patients underwent postoperative radiation therapy, of which 97 received radiation therapy alone and 22 received concurrent chemoradiotherapy. The adverse reactions in the NACT group were mainly hematologic toxic reactions, but were tolerated. No grade ≥III adverse reactions were observed. NACT did not significantly affect the PFS ($P = .453$) and OS ($P = .933$) between the 2 groups. No factor was found to be independently associated with OS or PFS (all $P > .05$).

Compared with patients who underwent surgery with/without radiotherapy and/or chemotherapy, NACT using paclitaxel and a platinum salt does not improve the prognosis and lymph node metastasis rate of locally advanced cervical carcinoma in Chinese patients.

Abbreviations: CT = computed tomography, DFS = disease-free survival, NACT = neoadjuvant chemotherapy, NCCN = National Comprehensive Cancer Network, OS = overall survival, PFS = progression-free survival.

Keywords: cervical carcinoma, disease-free survival, lymph node metastasis, lymphatic space infiltration, neoadjuvant chemotherapy, overall survival

1. Introduction

Cervical carcinoma is a serious disease threatening many women and its incidence is the highest among the malignancies of the female reproductive system.[1] Annually, there are about 529,000 new cases and 200,000 deaths from cervical carcinoma in the world and 80% of the deaths occur in developing countries. There are about 132,000 new cases and 30,000 deaths each year in China due to cervical carcinoma.[2] Early cervical carcinoma is mainly treated with surgery and the 5-year survival rate is over 90%. Locally advanced cervical carcinoma is mainly treated with radiation therapy, but the prognosis is relatively poor with a 5-year survival rate of 50% to 60%.[3]

Locally advanced cervical carcinoma refers to cervical carcinoma >4 cm and stage IB2 or IIA2. Surgery for these patients is difficult because of the large tumor, tumor invasion, and no clear boundary between the tumor and the surrounding tissues. Neoadjuvant chemotherapy (NACT) may improve the surgical resection rate for these patients. NACT is thought to inhibit tumor viability, reduce the surgical difficulty, improve the tumor resection rate, improve prognosis, and reduce metastasis.[4] Cai et al[5] found in a controlled study of 100 patients with locally advanced cervical carcinoma that the 5-year disease-free survival (DFS) of the surgery group was significantly shorter than that of the patients who underwent NACT and surgery. The overall tumor-free survival was significantly improved in the NACT + surgery group, but there was no significant difference between the 2 groups in patients with tumors <4 cm. A meta-analysis by Kim et al[6] indicated that NACT can reduce the

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[a] Department of Radiotherapy, [b] Department of Obstetrics and Gynecology, The Second Hospital of Jilin University, [c] School of Public Health Jilin University, Changchun, Jilin, China.

[*] Correspondence: Linlin Liu, Department of Radiotherapy, The Second Hospital of Jilin University, Changchun, Jilin, China (e-mail: chinawtj218@163.com).

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incidence of high-risk pathologic results in patients with locally advanced cervical carcinoma, but did not affect long-term survival. In addition, NACT can complicate the pathologic examination of the specimen and staging.[4]

Therefore, considering the controversy about the advantages of NACT in patients with massive cervical carcinoma combined with the health care issues of developing countries and patients' wishes, the practical significance of NACT still need further exploration in these patients. Therefore, the present study reviewed the treatment and prognosis of NACT in Chinese patients with cervical carcinoma stage IB2 or IIA2. The results should provide direction for the diagnosis and treatment of cervical carcinoma in developing countries.

2. Material and methods

2.1. Study design and patients

This was a retrospective cohort study of patients who underwent type-C radical surgery and pelvic lymphadenectomy due to cervical carcinoma at stage IB2 or IIA2 between February 2014 and December 2016 at the Second Hospital of Jilin University. This study has been approved by the ethics committee of the Second Hospital of Jilin University. The need for individual consent was waived by the committee.

The diagnostic and staging criteria were based on the 2017 FIGO staging criteria.[4] The staging of all patients was determined by 2 or more senior gynecologists. If there were disagreements, staging would be determined by consultation with senior physicians. The indications for NACT referred to the 2015 version of the FIGO Guideline (Class C Evidence).[7]

The inclusion criteria were: cervical carcinoma at stage IB2 or IIA2; squamous cell carcinoma; tumor diameter >4 cm; 18 to 75 years of age; and type-C radical surgery and pelvic lymphadenectomy for cervical carcinoma were performed. The exclusion criteria were: preoperative radiotherapy; or positive parauterine tissues, positive margin, or positive para-aortic lymph nodes.

The patients were grouped according to whether the patients received NACT or not before surgery.

2.2. Neoadjuvant chemotherapy

All patients received TP regimens, namely paclitaxel (175 mg/m^2 D1) + cisplatin (75 mg/m^2 D1); paclitaxel (175 mg/m^2 D1) + nedaplatin (80 mg/m^2 D1); or paclitaxel (175 mg/m^2 D1) + lobaplatin (30 mg/m^2 D1); all based on 3-week cycles. NACT was generally performed for 1 to 3 cycles and the response was determined according to the objective remission rate (ORR) and the adverse reactions. Surgical treatment was usually performed 3 to 4 weeks after NACT.

2.3. Surgery

Surgery was performed by 2 or 3 senior associate chief surgeons (with >10 years of clinical experience). Type-C radical surgery for cervical carcinoma was performed routinely. Bilateral pelvic lymphadenectomy was performed. The range of lymphadenectomy included the internal iliac lymph nodes, external iliac lymph nodes, common iliac lymph nodes, obturator lymph nodes, and anterior sacral lymph node. All patients underwent pathologic examination after surgery, and the results were determined by the independent diagnoses of 2 senior pathologists. Tumor differentiation, vascular cancer emboli, tumor size, infiltration depth (>50%), and number of metastatic lymph nodes were recorded.

2.4. Postoperative treatment

The postoperative treatment regimen was based on the 2017 National Comprehensive Cancer Network (NCCN) guidelines.[8] Patients with positive lymph nodes and tumor >4 cm were recommended for postoperative adjuvant radiation therapy combined with chemotherapy. Patients with high risk factors such as poor differentiation, lymphatic space infiltration, and invasion depth >50% were recommended to undergo adjuvant radiation therapy and/or chemotherapy after surgery. The postoperative treatment regimen was determined by the comprehensive consideration of the wishes of the patients and their family members, and by their economic condition.

The postoperative radiation therapy was either intensity modulated radiation therapy or rotary volume modulated radiation therapy. The dose of external irradiation was 45 to 50.4 Gy/1.8 to 2.0 Gy/25 to 28 f. The synchronous sensitization chemotherapy regimen was cisplatin (40 mg/m^2) once a week for 5 weeks. The postoperative chemotherapy regimen was the same as the preoperative NACT regimen.

2.5. Follow-up

All patients were followed up every 6 months after surgery. Follow-up was censored on July 31, 2018. Follow-up was performed by reexamination at the outpatient department. The patients underwent gynecologic physical examination, thinprep cytology test, pelvic magnetic resonance imaging, chest computed tomography, and abdominal color Doppler ultrasound. The time for relapse, metastasis, and death were recorded. Patients who were unable to return to the hospital for reexaminations were followed by telephone and the results of examinations at local hospitals were recorded. The diagnosis of postoperative local relapse and metastasis was based on physical examinations, imaging, and pathologic findings. The treatments after relapse were not included in this study.

2.6. Statistical analysis

Categorical data are presented as frequencies and were analyzed using the Chi-squared test. Continuous data are presented as mean ± standard deviation and were analyzed using the Student *t* test. Survival curves were plotted by the Kaplan–Meier method and analyzed using the log-rank test. The risk factors were assessed by Cox regression analysis. All analyses were performed using SPSS 19.0 (IBM Corp, Armonk, NY). Two-sided *P*-values <.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics of patients

The characteristics of the 144 patients with locally advanced cervical carcinoma are shown in Table 1. The follow-up duration was 28 to 55 months (median of 36.4 months). Of the 144 patients, 60 (41.7%) received NACT. The incidence of lymphatic space infiltration was lower in the NACT group (35.0% vs 58.3%, $P=.006$). The pathologic differentiation of

Table 1

Baseline characteristics of the patients.

Variable	NACT + surgery (n = 60)	Surgery (n = 84)	P
Age, yrs	52.4 ± 8.8	49.9 ± 10.8	.135
FIGO stage, n (%)			<.001
IB2	25 (41.7)	63 (75.0)	
IIA2	35 (52.3)	21 (25.0)	
LNM, n (%)			.818
Negative	46 (76.7)	63 (75.0)	
Positive	14 (23.3)	21 (25.0)	
Stromal invasion, n (%)			.041
<One-half	12 (20.0)	30 (35.7)	
>One-half	48 (80.0)	54 (64.3)	
LVSI, n (%)			.006
Negative	39 (65.0)	35 (41.7)	
Positive	21 (35.0)	49 (58.3)	
Pathology, n (%)			<.001
Moderately differentiated	41 (68.3)	74 (88.1)	
Poorly differentiated	4 (6.7)	8 (9.5)	
Others	1 (1.7)	2 (2.4)	
None	14 (23.3)	0	
Postoperative treatment, n (%)			.037
RT	20 (33.3)	13 (15.5)	
CT	3 (5.0)	7 (8.3)	
RT + CT	34 (56.7)	52 (61.9)	
NFT	3 (5.0)	12 (14.3)	

CT = chemotherapy, LVSI = lymphovascular space invasion, NACT = neoadjuvant chemotherapy, NFT = no further therapy, RT = radiation therapy.

patients in the NACT group was higher ($P < .001$). A total of 119 patients underwent postoperative radiation therapy, of which 97 received radiation therapy alone and 22 received radiation therapy combined with chemotherapy. The adverse reactions in the NACT group were mainly hematologic toxic reactions, but were tolerated. No grade ≥III adverse reactions were observed.

3.2. Survival

Figure 1 shows that NACT did not significantly affect the progression-free survival (PFS; $P = .453$) and overall survival (OS; $P = .933$) between the 2 groups. The 1-, 2-, and 3-year PFS in the NACT and surgery groups were 93.3% vs 95.2%, 90.0% vs 92.9%, and 86.7% vs 90.5%, respectively (all $P > .05$). The 1-, 2-, and 3-year OS in the NACT and surgery groups were 96.7% vs 98.8%, 91.7% vs 96.4%, and 90.0% vs 89.3%, respectively (all $P > .05$).

3.3. Multivariable analyses for OS and PFS

Table 2 presents the univariable and multivariable analyses of the factors associated with OS and PFS. The results showed that age, FIGO stage, positive lymph nodes, stromal invasion, lymphovascular space invasion, histologic grade, NACT, and postoperative treatments were not independently associated with OS or PFS (all $P > .05$).

4. Discussion

Locally advanced cervical carcinoma has a poor prognosis.[3] NACT can reduce tumor size and improve tumor resection rate, but its use in large locally advanced cervical carcinoma is controversial.[6] Therefore, this study aimed to review the treatment and prognosis of NACT in patients with cervical carcinoma stage IB2 or IIA2. The results suggest that compared with patients who underwent surgery with/without radiotherapy and/or chemotherapy, NACT using paclitaxel and a platinum salt does not improve the prognosis and lymph node metastasis rate of locally advanced cervical carcinoma in Chinese patients.

In 2017, the cancer survey report in China showed that the incidence of cervical carcinoma ranked first among gynecologic malignancies around the country.[2] Currently, cervical squamous cell carcinoma accounts for 80% to 85% of cervical carcinoma in China.[2] Squamous cell carcinoma has a better

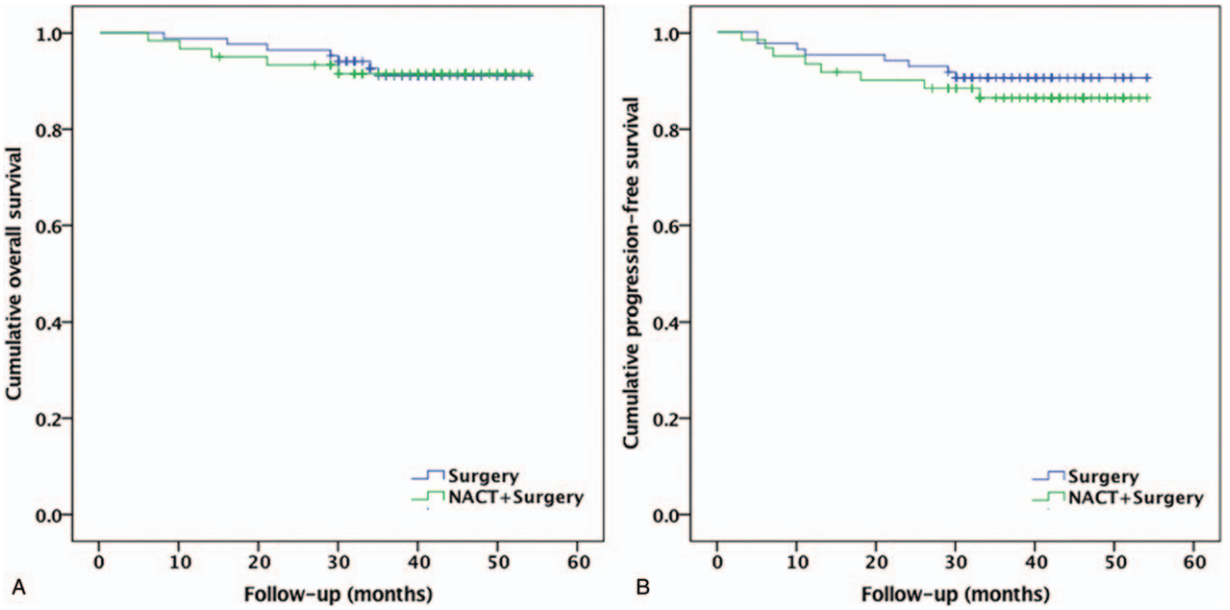

Figure 1. Overall survival (OS) and progression-free survival (PFS) based on neoadjuvant chemotherapy vs no neoadjuvant chemotherapy before surgery. (A) OS ($P = .933$). (B) PFS ($P = .450$).

Table 2

Univariable and multivariable analyses of OS and PFS.

	Univariable			Multivariable		
	HR	95% CI	*P*	HR	95% CI	*P*
OS						
Age (>50 vs ≤50 yrs)	0.485	0.146–1.610	.226			
FIGO stage (IB2 vs IIA2)	1.897	0.514–7.008	.328			
LNM (negative vs positive)	0.313	0.101–0.972	.033	0.433	0.129–1.457	.176
Stromal invasion (<1/2 vs ≥1/2)	0.215	0.028–1.668	.105			
LVSI (negative vs positive)	0.310	0.084–1.145	.063	0.422	0.104–1.714	.228
Pathology (G2 vs others)	0.455	0.137–1.512	.187			
NACT (yes vs no)	1.051	0.333–3.311	.933			
Postoperative treatment (CT or RT vs NFT)	1.250	0.161–9.679	.831			
PFS						
Age (>50 vs ≤50 yrs)	0.562	0.204–1.548	.258			
FIGO stage (IB2 vs IIA2)	1.406	0.488–4.047	.525			
LNM (negative vs positive)	0.504	0.183–1.386	.175			
Stromal invasion (<1/2 vs ≥1/2)	0.151	0.020–1.146	.035	0.267	0.034–2.100	.209
LVSI (negative vs positive)	0.413	0.144–1.190	.09	0.368	0.099–1.372	.137
Pathology (G2 vs others)	0.510	0.177–1.467	.203			
NACT (yes vs no)	1.456	0.546–3.879	.45			
Postoperative treatment (CT or RT vs NFT)	1.733	0.229–13.118	.59			

CT = chemotherapy, LNM = lymph node metastasis, LVSI = lymphovascular space invasion, NACT = neoadjuvant chemotherapy, NFT = no further therapy, OS = overall survival, PFS = progression-free survival, RT = radiation therapy.

prognosis than the other pathologic types of cervical cancer.[8] Most cervical squamous cell carcinomas are highly sensitive to platinum and paclitaxel.[8] Nevertheless, the prognosis of locally advanced cervical carcinoma is relatively poor.[3]

The results of this study suggest that NACT did not reduce the lymph node metastasis rate in patients with cervical carcinoma ($P = .818$). In addition, NACT did not influence the PFS ($P = .184$) and OS ($P = .176$) in patients with cervical carcinoma at stages IB2 and IIA2. Notwithstanding, the incidence of lymphatic space invasion was decreased in patients after NACT ($P = .006$), and the degree of pathologic differentiation was better ($P < .001$). NACT reduced the rate of postoperative radiation therapy and chemotherapy in patients. Over the past 3 years, the patients treated at our hospital were characterized by a relatively large number of patients with cervical carcinoma treated over a short period of time with relatively uniform treatment regimens. The current chemotherapy for cervical carcinoma is based on platinum combined with taxanes. The chemotherapy regimens were in line with standard treatment.[8] DNA-modifying agents such as platinum salts have been shown to slow down or impair the action of various DNA polymerases.[9] On the contrary, taxanes disrupt the cytoskeleton and prevent cell division.[10]

Lee et al[11] showed that in patients with stage IB2 or IIB, the OS and PFS of patients in the NACT + surgery group were better than those in the group with radiation therapy alone, and that NACT can increase resectability. A meta-analysis by Kim et al[6] showed that NACT can reduce the size of the lesion and reduce lymph node metastasis and distant metastasis in patients with cervical carcinoma stages IB1 to IIA. GOG-141 compared the effects of surgery after NACT and direct surgery in patients with cervical carcinoma. The results showed that the relapse and mortality rates were similar in the 2 groups, suggesting that NACT did not bring additional benefits for patients with IB2 cervical carcinoma.[12] There are currently no clear indication for NACT in the NCCN guidelines.[8] Many authors believe that NACT for locally advanced cervical carcinoma should be repositioned in the strategies for future research.[13]

The results of the present study are supported by previous studies. Yang et al[14] analyzed 219 patients with cervical carcinoma, and found that vascular invasion and deep muscle invasion in the NACT + surgery group was less important than in the direct surgery group. The meta-analysis by Peng et al[15] about comparison between NACT + surgery vs direct surgery suggested that the lymph node metastasis and deep myometrial invasion in the direct surgery group was more extensive than in the NACT + surgery group. Gong et al[16] showed that NACT reduced the complications associated with radical surgery in patients with locally advanced cervical cancer. On the contrary, de Azevedo et al[4] showed that NACT did not influence the ORR.

In the present study, NACT did not bring advantages in OS and PFS. Harsh et al[17] showed that the 3- and 5-year OS and disease-free survival (DFS) in 332 patients who received NACT combined with concurrent chemoradiotherapy were significantly longer than in those who received concurrent chemoradiotherapy alone, as supported by Marita et al.[18] Narayan et al[19] analyzed 612 patients with locally advanced cervical carcinoma, and compared NACT combined with concurrent chemoradiotherapy vs chemotherapy alone, and similar results were obtained. For these patients, it is possible that giving NACT and then performing sequential concurrent chemoradiotherapy may achieve better clinical outcomes. Gong et al[16] showed that NACT did not influence OS and PFS in patients with locally advanced cervical cancer. Gupta et al[20] showed that cisplatin-based concomitant radiochemotherapy was superior to NACT. Taken together, there remain important conflicting results among studies. The evidence for improved survival with NACT for locally advanced cervical squamous cell carcinoma is still insufficient, and it is also still unknown whether the benefits of chemoradiotherapy come from the radiation part alone or a combinatorial effect is achieved.[21–23] For example, Shrivastava et al[23] showed that cisplatin-based chemoradiotherapy achieved better survival than radiotherapy alone, while Hu et al[22] showed that patients with squamous cell carcinoma of the cervix had poor survival, regardless of chemoradiotherapy vs

radiotherapy alone. In the present study, the multivariable analyses in the present study were not able to identify risk factors for OS and PFS. Novel chemotherapy strategies could be needed, for example, dose-dense chemotherapy before and after surgery.[24] In addition, the chemotherapy alone, radiotherapy alone, and different combination regimens should be examined in relation to NACT.[22]

This study has limitations. The number of patients was relatively small, the follow-up time was relatively short, and the combination of surgery and radiotherapy was relatively simple. For the value of NACT and the mode of treatment for patients with locally advanced cervical carcinoma, further large-scale, randomized clinical trials are needed.

5. Conclusion

Compared with patients who underwent surgery with/without radiotherapy and/or chemotherapy, NACT using paclitaxel and a platinum salt (cisplatin, nedaplatin, or lobaplatin) does not improve the prognosis and lymph node metastasis rate of locally advanced cervical carcinoma in Chinese patients.

Author contributions

Conceptualization: Linlin Liu.
Investigation: Wenxing Yan, Lihui Si, Yaming Ding, Shuang Qiu, Qi Zhang.
Methodology: Wenxing Yan, Lihui Si, Yaming Ding, Shuang Qiu, Qi Zhang.
Writing – original draft: Wenxing Yan.
Writing – review & editing: Linlin Liu.

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