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Analysis of short-term efficacy as defined by RECIST and pathological response of neoadjuvant chemotherapy comprised paclitaxel and cisplatin followed by radical surgery in patients with locally advanced cervical cancer

A prospective observational study

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Abstract

The purpose of this study is to investigate short-term efficacy as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) and pathological response of neoadjuvant chemotherapy (NACT) comprised of paclitaxel and cisplatin (TP) followed by radical surgery in patients with locally advanced cervical cancer (LACC).

This is a prospective study involving 61 women with histologically confirmed LACC referred for NACT following radical surgery at Beijing Obstetrics and Gynecology Hospital between April 2013 and January 2015.

The efficacy of NACT was evaluated by the RECIST. The total short-term efficacy of NACT was 91.8% (complete remission and partial remission). The cervical invasion ≤1/2 was 82.4% in the complete remission (CR) group, 46.2% in the partial remission (PR) group, and 20% in the stable disease (SD) group. The difference between groups was statistically significant (P = .012). The slides of all surgical specimens were reviewed and classified according to the Tumor Regression Grade (TRG). The good response was defined by good short-term efficacy (RECIST) and the difference between groups was statistically significant (P = .042). The route of administration of NACT is a factor predicting response to NACT. A significant higher response rate (P = .011) and lower chemotherapy-related adverse events (P < .05) were observed in the artery intervention (AI) group compared to those received NACT via intravenous (IV) route. All patients were followed-up to the last day of 2015 with the median follow-up time of 21.5 months for NACT. For the 61 patients referred for NACT in LACC, 2 patients had relapsed and 1 patient died from the disease.

The study showed that the NACT comprised TP for LACC treatment had a significant local effect. It could reduce tumor myometrial invasion and regress tumor. The route of administrating NACT is a predicting factor to the NACT response; 2 cycles of NACT of AI treatment to LACC patients would obtain a desired response with low chemotherapy adverse events.

Abbreviations: AC = adenocarcinoma, AI = artery intervention, ASC = adeno-squamous cell carcinoma, CR = complete remission, CTCAE v4 = Criteria for Adverse Events version 4, IV = intravenous infusion, LACC = locally advanced cervical cancer, LNI = lymph nodes involvement, LVSI = lymph vascular space invasion, NACT = neoadjuvant chemotherapy, PR = partial remission, RECIST = Response Evaluation Criteria in Solid Tumors, SCC = squamous cell carcinoma, SCCA = squamous cell carcinoma antigen, SD = stable disease, TP = paclitaxel plus platinum, TRG = tumor regression grade.

Keywords: locally advanced cervical cancer, neoadjuvant chemotherapy, paclitaxel, pathology outcome, platinum, short-term efficacy

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1. Introduction

Worldwide, cervical cancer is the fourth most common and lethal cancer worldwide. It is the second most commonly diagnosed cancer and third leading cause of cancer death among females in less-developed countries. According to the World Health Statistics 2012, it was estimated that there were 527,600 new cervical cancer cases and 265,700 deaths worldwide in 2012.[1] Although the incidence of cervical cancer decreases in countries with screening program, a large proportion of those diagnosed with invasive cancer have locally advanced disease at presentation. The concept of locally advanced cervical cancer (LACC) was established and defined in the 90s of the 20th century, especially for stage Ib2 in general and bulky stage Ib2 to IIa2 in particular (the local tumor diameter >4 cm). After radical hysterectomy, although the 5-year survival rate for patient with early stage (stage Ia–Ib1) cervical cancer may become as high as 80%–90%,[2,3] the 5-year survival rate was decreased to about 60% for stage Ib2 to IIa.[4] However, the radical surgery is limited to patients with International Federation of Gynecology and Obstetrics (FIGO) IIa or earlier stage. Patients with advanced disease (FIGO stage Ib2 and above) usually undergo traditional treatment such as radiation therapy instead of primary surgery due to bulky lesion foci, local hemorrhage, inflammatory necrosis, and parametrial invasion. Although radiation therapy can have similar efficacy as surgery, the damage to surrounding tissues caused by radiation may lead to loss of ovarian function and sexual capacity, which can significantly impact the quality of life.

At present, there is still a controversy on the treatment of LACC. Most patients with LACC are treated with radiotherapy and/or chemotherapy. Neoadjuvant chemotherapy (NACT) prior to primary surgical intervention is also being used increasingly in the management of LACC in many countries. The 2015 NCCN Guideline suggested the chemoradiation (CRT) to be the standard treatment in LACC (Category 1). The results of 18 trials from 11 countries showed clear evidence that adding chemotherapy to radiotherapy improves both overall and disease-free survival. For the trials in which CRT alone was used, there was a 6% absolute survival benefit and an 8% disease-free survival benefit at 5 years.[5,6] Recently, NACT has been reported useful in the control of LACC. Early or prechemotherapy NACT has been used to reduce tumor volume prior to surgery or radiotherapy. For patients with advanced cervical cancer, 2 to 3 cycles, NACT can improve the success rate of resection. Previous studies show that NACT can inhibit tumor micrometastases and enhance the resection rate by shrinking tumor volume.[7,8] A meta-analysis showed that NACT followed by radical hysterectomy can improve the survival rate.[9] However, a recent phase III GOG trial failed to demonstrate any survival benefit. It may be due to a variety of clinical and biological factors, and the use of different chemotherapeutic regimens based on cisplatin.[8] Currently there is no standard neoadjuvant chemotherapy regimen. The regimens often used include:[10] TP (TAX+DDP), VAC (VCR+ADM+CTX), and GP (GEM+DDP). The safety and efficacy of paclitaxel plus platinum (TP) as NACT have been demonstrated in many literatures.[11]

This prospective study enrolled 61 patients with stage Ib2 and IIa2 LACC (tumor diameter >4 cm). The efficacy and safety of NACT in treatment of LACC had been demonstrated in our preliminary study.[12] We also found that the TP used for treating NACT following radical hysterectomy had a better short-term efficacy than the direct radical hysterectomy alone. The short-term efficacy of TP regimen treatment of LACC had significant

variations and the prognosis was closely related to the short-term efficacy and the follow-up treatment. This intention of this study is to find factors that may be able predict response to the NACT treatment of LACC by further analyzing the clinical and pathological data.

2. Materials and methods

2.1. Participants

This prospective study enrolled 61 patients. All the subjects had histologically confirmed cervical cancer (including squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma) undergoing paclitaxel plus platinum as NACT followed by radical hysterectomy. The treatment was performed at the Department of Gynecological Oncology, Beijing Obstetrics and Gynecology Hospital, Capital Medical University. All the participants signed informed consents before the chemotherapy initiation. The enrolled patients also satisfied the following additional criteria: age ≤65 years; FIGO Stage Ib2 and IIa2; tumor diameter > 4 cm (by vaginal pelvic examination and CT or MRI); and scheduled to have 2 to 3 cycles of chemotherapy. The stage of each patient was determined according to the cervical cancer clinical stage criteria set by the FIGO. The exclusion criteria were: patients with severe complications cannot tolerate surgery or chemotherapy; there are clear distant metastasis (CT or MRI was performed before and after chemotherapy to evaluation); patients with cardiovascular, cerebrovascular, liver, kidney, hematopoietic system, and other serious diseases which affect the 5 years survival; there is uncontrolled epilepsy, central nervous system disorders, or a history of mental disorders; patients with a history of other malignant diseases; patients who have received cytotoxic chemotherapy, radiotherapy, or immune therapy. Evaluation of the clinical response was performed after 2 to 3 cycles of chemotherapy followed radical hysterectomy.

2.2. Chemotherapy

The NACT regimen is a platinum-based combined chemotherapy. The patients triaged to receive the TP regimen were randomly assigned into 2 groups: artery intervention (AI) group and intravenous (IV) group. The TP regimen for the AI group is: 60 mg/m^2 of paclitaxel and 60 mg/m^2 of cisplatin on day 1, every 10 to 14 days for 1 to 3 cycles. Using a standard Seldinger technique, the left femoral arteries were punctured under local anesthesia, and the bilateral internal iliac arteries were selectively catheterized by a contralateral approach. Once the access to both internal iliac arteries was gained, 5-French catheters (Roberts uterine catheter, COOK) were positioned with the tip in the 0.5 cm before the upper and lower branch of uterine artery. The bilateral branches of uterine artery were displayed by digital subtraction angiography (DSA). The average dose of chemotherapy drugs was injected into the bilateral uterine artery, respectively, embolization with PVA particles as appropriate.

The TP regimen for the IV group is: 135 to 175 mg/m^2 of median paclitaxel on day 1, AUC5 of carboplatin calculated according to creatinine clearance, every 21 to 28 days for 1 to 3 cycles. The operation was performed 10 to 14 days after the last chemotherapy. Piver III surgery was performed for all the patients after chemotherapy (radical hysterectomy and pelvic lymphadenectomy + double salpingectomy ± double ovariectomy, ovary biopsy was performed to rule out ovarian metastasis

before ovary reservation). Evaluation of the chemotherapy response was performed by 2 gynecological oncologists to evaluate the size of each patient's cervical tumor and the lymph nodes before the initial chemotherapy and at 10–14 days after the completion of the final cycle of chemotherapy. The tumor size was assessed as the product of the transverse diameter and anterior-posterior diameter measured by pelvic examination and colposcopy. The short axis of the node was measured by CT or MRI.

2.3. Observation standard
2.3.1. Clinical data.
The data collected include the general medical information (age, menopause, childbirth, family history of cancer, and the surgical methods), tumor stage, tumor type, chemotherapy ways, the cycles of chemotherapy, the prechemotherapy SCCA values, and the chemotherapy-related adverse events. Two CTs were performed, 1 before and 1 after the chemotherapy to exclude distant metastasis or indeed nodal involvement.

2.3.2. Pathological results.
The pathological data collected include histopathologic result, cell differentiation, cervical invasion, vascular invasion, lymph node involvement (LNI), parametrial infiltration, and margin status. The results were checked by 2 pathologists in our hospital together.

2.3.3. Histological response.
Histological response was evaluated according to the criteria defined by the Japan Society for Cancer Therapy.[13] The responses were classified into 4 levels: Level 0, almost no treatment-induced tumor degeneration or necrosis; Level 1, degeneration, necrosis, or liquefaction of fewer than two-thirds of the cancer cells; Level 2, marked degeneration, necrosis, liquefaction, or disappearance of more than two-thirds of the cancer cells; and Level 3, necrosis, liquefaction, disappearance or replacement by granulation tissues or fibrosis of the entire tumor. In this study, all the patients were classified into 2 groups: histological responders, including patients with Level 2 and Level 3 response, and histological nonresponders, including patients with Level 0 and Level 1 response. All pathological paraffin sections were examined. The consensus was reached by the same 2 senior pathologists after hysterectomy and before chemotherapy.

2.4. The short-term efficacy as defined by RECIST

The clinical remission was evaluated according to the World Health Organization (WHO) criteria—The Response Evaluation Criteria in Solid Tumors (RECIST).[14] The complete response (CR) is defined as disappearance of all target lesions, and any pathological lymph nodes (whether target or nontarget) must have reduction in the short axis to < 10 mm. The partial remission (PR) is defined as at least 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. The progressive disease (PD) is defined as at least 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (including the baseline sum if that is the smallest on study). In addition, the relative increase of more or new lesion is also considered as progression). The stable disease (SD) is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, in reference to the smallest sum diameters during the study. The patients with CR or PR are classified as clinical responders, and the patients with stable disease and progression of disease are defined as clinical

nonresponders. If the 2 oncologists reached different conclusions, the results will be rechecked and discussed to reach a consensus.

2.5. Follow-up

All the patients were followed-up to December 31, 2015. All the recurrence and death data were recorded (see following Figure 1 Study Flow-Chart; http://links.lww.com/MD/C264).

2.6. Statistical methods

SPSS version 18.0[15] was used for statistical analysis. Categorical variables were compared using the Chi-square and Fisher's exact tests. Descriptive analysis is presented for median age, clinical stage, tumor size at diagnosis, and the number of chemotherapy cycles. A P-value of $<.05$ was considered as significant.

3. Result

3.1. General characteristics of NACT in treatment of LACC

During the follow-up, no patient existed in PD (disease progression) group in our study. There was no significant difference between other short-term efficacy groups (CR, PR and SD) for patients' age, menopause, childbirth and oncology history ($P>.05$) (see Table 1).

3.2. The short-term efficacy of NACT in treatment of LACC

NACT in treatment of LACC has local effect. The total efficacy of NACT was 91.8% (CR plus PR). The cervical invasion (≤½) was 82.4% in the CR group, 46.2% in the PR group, and 20.0% in the SD group. The difference was statistically significant ($P=.012$). The percentage of tumor regression level 3 (TRG3) in CR group was 29.4%, which was higher than in the PR (2.5%) and in the SD (20.0%) groups. The percentage of tumor regression level 0 (TRG0) in CR group was 41.2%, which was lower than in the PR (82.1%) and in the SD (80.0%) groups. All

Table 1

The patients' general characteristic of NACT in the treatment of LACC.

	CR	PR	SD	P value
Age				
≤40	5 (29.4%)	7 (17.9%)	1 (20.0%)	.627
>40	12 (70.6%)	32 (82.1)	4 (80.0%)	
Menopause				
Yes	6 (35.3%)	14 (35.9%)	0	.265
No	11 (64.7%)	25 (54.1%)	5 (100.0%)	
Childbirth times				
No	1 (5.9%)	1 (2.6%)	1 (20.0%)	.471
1–2 times	14 (82.3%)	34 (87.2%)	3 (60.0%)	
≥3 times	2 (11.8%)	4 (10.2%)	1 (20.0%)	
Oncology history				
Yes	3 (17.6%)	7 (17.9%)	2 (40.0%)	.490
No	14 (82.4%)	32 (82.1%)	3 (60.0%)	
Operation method				
Laparoscopy	4 (23.5%)	9 (23.1%)	3 (60.0%)	.201
Laparotomy	13 (76.5%)	30 (76.9%)	2 (40.0%)	
Total	17 (27.9%)	39 (63.9%)	5 (8.2%)	61

CR = complete remission, LACC = locally advanced cervical cancer, NACT = neoadjuvant chemotherapy, PR = partial remission, SD = stable disease.

Table 2

The primary outcomes of NACT in the treatment of LACC.

	CR	PR	SD	*P* value
Cervical invasion				
≤1/2	14 (82.4%)	18 (46.2%)	1 (20.0%)	.012*
>1/2	3 (17.6%)	21 (53.8%)	4 (80.0%)	
Parametrium invasion				
Yes	0	2 (5.1%)	0	.558
No	17 (100.0%)	37 (94.9%)	5 (100.0%)	
Margin status				
Positive	0	0	0	1.000
Negative	17 (100%)	39 (100%)	5 (100%)	
LVSI				
Yes	4 (23.5%)	18 (46.2%)	1 (20.0%)	.191
No	13 (76.5%)	21 (53.8%)	4 (80.0%)	
Lymph node involvement				
Yes	2 (11.8%)	5 (12.8%)	1 (20.0%)	.888
No	15 (88.2%)	34 (87.2%)	4 (80.0%)	
TRG				
TRG3	5 (29.4%)	1 (2.5%)	1 (20.0%)	.042*
TRG2	3 (17.6%)	3 (7.7%)	0	
TRG1	2 (11.8%)	3 (7.7%)	0	
TRG0	7 (41.2%)	32 (82.1%)	4 (80.0%)	
Total	17 (27.9%)	39 (63.9%)	5 (8.2%)	61

CR = complete remission, LVSI = lymph vascular space invasion, PR = partial remission, SD = stable disease, TRG = tumor regression grade.
* *P* < .05, there is significant differences.

the slides of surgical specimens were reviewed and classified according to the Tumor Regression Grade (TRG). The good response represents the good short-term efficacy, the difference was statistically significant (*P* = .042). In the different short-term efficacy groups (CR, PR and SD), There was no significant difference between parametrium invasion, margin status, LNI and Lymph vascular space invasion (LVSI) (*P* > .05) (see Table 2).

3.3. Predictors of response to NACT in LACC

The route of administration NACT delivery affected its efficacy in the short-term LACC treatment. The AI (97.8%) was significantly more effective than IV (75.1%, *P* = .011). However, no significant different efficacy was found between different tumor stage, tumor size, cell differentiation, tumor type, pathology type, prechemotherapy SCCA values, and chemotherapy cycles (*P* > .05). (See Table 3)

3.4. Adverse events and follow-up

Gastrointestinal reaction, myelosuppression, and alopecia were mainly NACT chemotherapy-related adverse events in accordance with the Common Terminology Criteria for Adverse Events version 4 (CTCAE v4).[16] The adverse events were rare in AI compared to IV NACT chemotherapy in treatment of LACC, The difference was significant (see Table 4). Gastrointestinal reaction, Myelosuppression and Alopecia above degree 3 was 0% (0/15), 2/15 (13.3%), 2/15 (13.3%), respectively, in 3 cycles chemotherapy compared to 0% (0/34), 0% (0/34), 8.8% (3/34), respectively, in 2 cycles chemotherapy and 0% (0/12), 0% (0/12), 0% (0/12), respectively, in 1 cycle chemotherapy. So multiple cycles chemotherapy may increase the side effects. All patients were followed-up to the last day of 2015. The median follow-up time was 21.5 months. Out of the 61 patients referred for NACT in LACC, 2 patients were relapse (3.3% recurrence) and 1 patient died from the disease (1.6% mortality).

Table 3

The predictors of response to NACT in the treatment of LACC.

	CR	PR	SD	Total	*P* value
Pretreatment tumor stage					
Stage Ib2	8 (27.6%)	18 (62.1%)	3 (10.3%)	29	.842
Stage IIa2	9 (28.1%)	21 (65.6%)	2 (6.3%)	32	
Tumor diameter					
>5 cm	5 (21.7%)	15 (65.2%)	3 (13.1%)	23	.457
≤5 cm†	12 (31.6%)	24 (63.2%)	2 (5.2%)	38	
Cell differentiation					
G1	2 (100%)	0 (0.0%)	0 (0.0%)	2	.138
G2	13 (28.9%)	29 (64.4%)	3 (6.7%)	45	
G3	2 (14.3%)	10 (71.4%)	2 (14.3%)	14	
Tumor type					
Exogenous type	12 (26.1%)	29 (63.0%)	5 (10.9%)	46	.509
Endogenous type	4 (44.4%)	5 (55.6%)	0 (0.0%)	9	
Ulcerative type	1 (16.7%)	5 (83.3%)	0 (0.0%)	6	
Pathology type					
SCC	12 (26.7%)	30 (66.7%)	3 (6.6%)	45	.386
AC	2 (25.0%)	4 (50.0%)	2 (25.0%)	8	
ASC	3 (37.5%)	5 (62.5%)	0 (0.0%)	8	
Chemotherapy routes					
AI	12 (26.7%)	32 (71.1%)	1 (2.2%)	45	.011*
IV	5 (31.3%)	7 (43.8%)	4 (24.9%)	16	
Prechemotherapy SCCA values					
>50	1 (50.0%)	1 (50.0%)	0 (0.0%)	2	.681
1.5–50	8 (25.9%)	19 (61.3%)	4 (12.8%)	31	
<1.5	8 (28.6%)	19 (67.9%)	1 (3.5%)	28	
Chemotherapy cycles					
1 cycle	3 (25.0%)	6 (50.0%)	3 (25.0%)	12	.122
2 cycles	8 (23.5%)	24 (70.6%)	2 (5.9%)	34	
3 cycles	6 (40.0%)	9 (60.0%)	0 (0.0%)	15	
Total	17 (27.9%)	39 (63.9%)	5 (8.2%)	61	

AC = adenocarcinoma, AI = atery intervention, ASC = adeno-squamous cell carcinoma, G = grade, IV = intravenous infusion, NACT = neoadjuvant chemotherapy, SCC = squamous cell carcinoma, SCCA = squamous cell carcinoma antigen.
* *P* < .05, there is significant differences.
† Diameter of locally advanced cervical cancer (LACC) is larger than 4 cm.

Table 4

NACT treatment-related adverse events.

Adverse events	Degree	AI	IV	Total	*P* value
Gastrointestinal reaction†	0	22	2	24	.012*
	1	13	11	24	
	2	10	3	13	
	3	0	0	0	
	4	0	0	0	
Myelosuppression	0	42	1	43	.000*
	1	3	8	11	
	2	0	6	6	
	3	0	1	1	
	4	0	0	0	
Alopecia	0	45	1	46	.000*
	1	0	0	0	
	2	0	10	10	
	3	0	5	5	
	4	0	0	0	
Total		45	16	61	

AI = atery intervention, IV = intravenous infusion, NACT = neoadjuvant chemotherapy.
* *P* < .05, there is significant differences.
† Gastrointestinal reaction, Myelosuppression and Alopecia above degree 3 was 0% (0/15), 1/15 (6.6%), 1/15 (6.6%), respectively, in 3 cycles chemotherapy compare to 0% (0/49), 0% (0/49), 10.2% (5/49), respectively, in 2 cycles chemotherapy.

4. Discussion

The treatment of stage Ib2 and IIa2 LACC (tumor diameter > 4 cm) is controversial. The 2009 FIGO[17] guideline indicated that treatment of LACC include: directly radiotherapy concurrent chemotherapy (Level A evidence); radical hysterectomy and bilateral pelvic lymph node dissection, plus adjuvant radiotherapy postoperative (Level C evidence); radical hysterectomy after NACT, and supplementary radiotherapy post-operation (Level B evidence). In 2015, the NCCN guidelines[18] indicated that treatment of LACC including: radical radiotherapy and chemotherapy (Level 1 evidence); (ii) radical hysterectomy and bilateral pelvic lymph node dissection, plus adjuvant radiotherapy postoperation (Level 2B evidence); concurrent chemoradiotherapy supplementary hysterectomy (Level 3 evidence). Some report[10] showed that the efficacy of radical operation and radiotherapy were the same in the treatment of LACC, while others[19] showed that the efficiency of NACT was as high as 53% to 94%. The TRG1 was 10% to 13.8%. In our preliminary retrospective study, with more than 140 LAAC patients enrolled, it clearly showed the high efficacy and safety of paclitaxel plus platinum as NACT following radical surgery in treatment of LACC with low incidence of adverse reactions when compared to direct operation.[12] After the NACT preoperation, the tumor size, the metastasis rate of lymph node, the rates of LVSI, and parametrial infiltration decreased.[20,21] In order to create a good condition to eliminate subclinical lesions, the dissemination intraoperation and metastasis after operation was reduced. This led to the observation of the lower tumor recurrence and higher survival rate, which were consistent with other literature report.[22,23] Preoperation NACT can be easily observed and evaluated for the sensitivity of the tumor to chemotherapeutic drugs and can be used to guide the next stage treatment. According to the sensitivity of the preoperation therapy, the postoperation chemotherapy may not need to be adjusted or even required. But clinical efficacy is only a superficial observation. It can reflect the progression of the disease in some instance. The pathological outcomes are the main risk factors to the prognosis of the NACT treatment for the LACC. The main pathological outcomes include LVSI, LNI, depth of tumor invasion, parametrial invasion, resection margin, etc. The lager and deeper of the tumor, the more number and higher layer of LNI, the higher incidence rate of LVSI. These risk factors for the prognosis of cervical cancer could be used to directly predict the prognosis and efficacy of NACT in treatment of LACC.[8]

For the 61 patients with NACT preoperation in the study, the short-term efficacy is 91.8%, including 27.9% in CR, 63.9% in PR, and 8.2% remained in SD. There was no patient in the progression (PD) group. The Observed pathologic outcomes of NACT showed that the number of tumor invasion depth ≤1/2 and the tumor regression in the efficacy groups (CR and PR) were obviously higher than that in the SD group ($P = .012$ and .042). In terms of resection status and parametrial infiltration, there were no significant differences for LVSI and LNI between the different short-term efficacy groups ($P > .05$). Considering the effect of NACT in the treatment of LACC was mainly local that can significantly reduce the size, the myometrial invasion, and the local regression of the tumor for the NACT sensitive patients. However, the significant tumor regression may not indicate the improved potential risk in metastasis, including LNI, LVSI and parametrial infiltration that might be caused by the differences of pathogenesis between the primary tumor and the metastasis.

It has been reported that the therapeutic effect of chemotherapy was closely related to the blood supply to the tumor. The efficacy of chemotherapy was better for multi-blood supply tumor with high drug concentration in local area than that for less-blood supply tumor with low drug concentration in the local area.[24] Adachi et al[25] comparing the AI with IV NACT in the treatment of LACC and found that the drug concentration of local area in AI group was 2.8 times higher than that in IV group. This stronger tumor killing ability was mainly because the drugs were injected directly into the surrounding area of the tumors via AI, avoiding the chemotherapy first pass through the kidney and liver that can reduce the probability of drug plasma protein binding. It could also because that the arterial embolization can be used to reduce the blood supply to the tumor, promoting the tumor tissue ischemia, hypoxia and necrosis, and then reduce the spread of the tumor through blood. Our study showed that how the chemotherapy was given had major influence to the short-term NACT efficacy. The clinical effective rate in the AI group (97.8%) was significantly higher than that in the IV group (75.1%), ($P = .011$), regardless of the tumor stage, differentiation degree, tumor type, pathological type, chemotherapy cycles, tumor diameter and pre-operation SCCA values. However multi-cycle chemotherapy showed higher optimal short-term efficacy for the patients with tumor diameter ≤ 5 cm. Two and 3 cycles of chemotherapy had the optimal efficacy of up to 90% (94.1% in 2 cycles and 100% in 3 cycles), which was higher than that of one cycle chemotherapy about 70% (9/12). However, multiple cycles of chemotherapy may increase the side effects. This study showed that for patients with LACC treated with 2-cycles AI treatment NACT can achieve the desired local therapeutic efficacy. Chemotherapy-related adverse events including gastrointestinal reaction, myelosuppression and alopecia in the AI group were significantly rarer than that in the IV group.

In our study, the median follow-up time was 21.5 months. Out of the 61 patients referred for NACT in LACC, 2 patients were relapse (3.3% recurrence) and 1 patient died from the disease (1.6% mortality). For patients with malignant tumor, tumor free survival (DFS) and overall survival (OS) are important indicators of the efficacy. There was a large sample NACT treatment study[23] that compared the long-term survival rate of neo-adjuvant chemotherapy followed by radical hysterectomy to the radical surgery only and concurrent chemoradiotherapy. For the 476 patients enrolled with cervical cancer stage Ib2~IIb, the 3 years disease-free survival rates were 85.0%, 77.4%, and 52.9%, respectively, and the 5 year survival rates were 88.7%, 80.2% and 64.4%, respectively. It showed that NACT can significantly improve the long-term survival rate of LACC.

5. Conclusion and limitation

In conclusion, this study showed that NACT comprised TP for LACC treatment has significant local effect. The NACT could reduce tumor myometrial invasion and regress tumor, but had little effect to reduce the potential tumor metastasis. Around 91.8% of participants had either CR or PR by RECIST after undergoing NACT. A significantly higher response rate and lower adverse event rate were observed in the AI group than that in the IV group. Patients with tumor diameter ≤ 5 cm that received multiple cycles of chemotherapy had better short-term efficacy. It was found that 2 cycles of NACT by AI treatment to the LACC can get the desired short-term efficacy with low chemotherapy adverse events. Due to the short follow-up time of this study, it cannot answer the questions of OS and DFS. Further

study with larger sample size (in order to find more events) is needed to answer the long-term survival questions

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References

[1] Lindsey A, Torre , Freddie Bray , et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.
[2] Quinn MA, Benedet JL, Odicino F, et al. Carcinoma of the cervix uteri, FIGO 26th annual report on the results of treatment in gynecological cancer. Int J Gynaecol Obstet 2016;95:S43–103.
[3] Landoni F, Maneo A, Colombo A, et al. Randomised study of radical surgery versus radiotherapy for stage Ib–IIa cervical cancer. Lancet 1997;350:535–40.
[4] Perez CA, Grigsby PW, Nene SM, et al. Effect of tumor size on the prognosis of carcinoma of the uterine cervix treated with irradiation alone. Cancer 1992;69:2796–806.
[5] Vale CL, Tierney JF, Davidson SE, et al. Substantial improvement in UK cervical cancer survival with chemoradiotherapy: results of a Royal College of Radiologists' Audit. Clin Oncol 2010;22:590–601.
[6] CCCMAC–Chemoradiotherapy for Cervical Cancer Meta-analysis CollaborationReducing uncertainties about the effects of chemoradio-therapy for cervical cancer: A systematic review and meta-analysis of individual patient data from 18 randomised trials. J Clin Oncol 2008;26:5802–12.
[7] Hwang YY, Moon H, Cho SH, et al. Ten-year survival of patients with locally advanced, stage Ib-IIb cervical cancer after neoadjuvant chemo-therapy and radical hysterectomy. Gynecol Oncol 2001;82:88–93.
[8] Cho YH, Kim DY, Kim JH, et al. Comparative study of neoadjuvant chemotherapy before radical hysterectomy and radical surgery alone in stage IB2-IIA bulky cervical cancer. J Gynecol Oncol 2009;20:22–7.
[9] Eddy GL, Bundy BN, Creasman WT, et al. Treatment of ("bulky") stage IB cervical cancer with or without neoadjuvant vincristine and cisplatin prior to radical hysterectomy and pelvic/para-aortic lymphadenectomy: a

phase III trial of the gynecologic oncology group. Gynecol Oncol 2007;106:362–9.
[10] Wang Y, Wang G, Wei LH, et al. Neoadjucvant chemotherapy for locally advanced cervical cancer reduces surgical risks and lymph-vascular space involvement. Chin J Cancer 2011;30:645–53.
[11] Yang Z, Chen D, Zhang J. The efficacy and safety of neoadjuvant chemotherapy in the treatment of locally advanced cervical cancer: a randomized multicenter study. Gynecol Oncol 2016;141:231–9.
[12] Xing Y, Wu YM. Clinical research of Paclitaxel plus platinum neoadjuvant chemotherapy in the treatment of locally advanced cervical cancer. Chin Med Herald 2015;12:17–22. (in Chinese) (reference can be searchable on Wanfangdata).
[13] Dworak O, Keilholz L, Hoffmann A. Pathological features of rectal cancer after preoperative radiochemotherapy. Int J Colorectal Dis 1997;12:19–23.
[14] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version1.1). Eur J Cancer 2009;45:228–47.
[15] PASW Statistics for Windows, version 18.0; SPSS Inc.: Chicago, IL, USA, 2009.
[16] Chen AP, Setser A, Anadkat MJ, et al. Grading dermatologic adverse events of cancer treatments: the Common Terminology Criteria for Adverse Events Version 4.0. J Am Acad Dermatol 2012;67:1025–39.
[17] Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet 2009;105:103–4.
[18] Koh WJ, Greer BE, Abu-Rustum NR, et al. Cervical cancer, version 2.2015. J Natl Compr Canc Netw 2015;13:395–404.
[19] Modarress M, Maghami FQ, Golnavaz M, et al. Comparative study of chemoradiation and neo-adjuvant chemotherapy effects before radical hysterectomy in stage IB-IIB bulky cervical cancer and with tumor diameter greater than 4 cm. Int J Gynecol Cancer 2005;15:483–8.
[20] Zhao Q, Xing Y, Geng YN, et al. Analysis of clinical pathology of local advanced cervical cancer after neoadjuvant chemotherapy. Beijing Med J 2015;37:637–40.
[21] Benedetti Panici P, Palaia I, Marchetti C, et al. Dose-dense neoadjuvant chemotherapy plus radical surgery in locally advanced cervical cancer: a phase II study. Oncology 2015;89:103–10.
[22] Angioli R, Plotti F, Luvero D, et al. Feasibility and safety of carboplatin plus paclitaxel as neoadjuvant chemotherapy for locally advanced cervical cancer: a pilot study. Tumor Biology 2014;35:2741–6.
[23] Yin M, Zhao F, Lou G, et al. The long term efficacy of neoadjuvant chemotherapy followed by radical hysterectomy compared with radical surgery alone or concurrent chemoradiotherapy on locally advanced stage cervical cancer. Int J Gynecol Cancer 2011;21:92–9.
[24] Qin J, Cheng X, Chen X, et al. Value of three-dimensional power Doppler to predict clinical and histological response to neoadjuvant chemotherapy in locally advanced cervical carcinoma. Ultrasound Obstet Gynecol 2012;39:226–34.
[25] Adachi S, Ogasawara T, Tsubamoto H, et al. Intravenous nedaplatin and intraarterial cisplatin with transcatheter arterial embolization for patients with locally advanced uterine cervical cancer. Int J Clin Pharmaeol Res 2011;21:105–10.