Submitted: 08 June, 2022 Accepted: 02 August, 2022 Published: 15 February, 2023 DOI:10.22514/ejgo.2023.003

ORIGINAL RESEARCH

European Journal of Gynaecological Oncology

Effectiveness of neoadjuvant chemotherapy followed by radical surgery in young patients with locally advanced cervical cancer

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Abstract

To investigate the efficacy and survival benefit of neoadjuvant chemotherapy (NACT) followed by type C radical surgery in patients with locally advanced cervical cancer (LACC) and moderate risk factors for recurrence. The clinical and pathological data of 338 cases with stage IB3 and IIA2 cervical carcinoma who received NACT followed by radical surgery from January 2008 to December 2018 were collected. In line with the clinical response, the patients were divided into a chemotherapy-effective group (n = 309) and a chemotherapy-ineffective group (n = 29), and the clinical and pathological characteristics of the two groups were compared. Survival was analyzed using the Kaplan-eier method. After NACT and surgical resection, 309 (91.4%, 309/338) patients experienced a clinical response. Fewer patients had a maximum tumor diameter $\geq$5 cm in the chemotherapy-effective group compared with the chemotherapy-ineffective ($p = 0.021$). The 5-year progression-free survival (PFS) and overall survival (OS) rates were higher in the chemotherapy-effective group (86.29% and 85.75%, respectively) than in the chemotherapy-ineffective group (77.64% and 75.56%, respectively; $p < 0.001$). Among patients with high-risk and moderate-risk factors, the 5-year PFS and OS rates were higher in the patients who received chemotherapy (95.90% and 94.81%) than in those who received CCRT (78.06% and 77.25%, respectively; $p < 0.001$). NACT followed by surgical resection may be an appropriate treatment strategy for young patients with LACC, allowing them to avoid radiochemotherapy and the resultant damage to ovarian and vaginal function. A future prospective study of this treatment strategy is warranted.

Keywords

Locally advanced cervical cancer; Neoadjuvant chemotherapy; Young patients; Risk factors

1. Introduction

Cervical cancer is the most common gynecological malignancy. According to the 2018 Global Cancer Report published by the International Agency for Research on Cancer, China has the second highest incidence of cervical cancer in the world, and the age at onset tends to be younger than in western countries [1, 2]. Concurrent chemoradiotherapy (CCRT) is standard treatment for locally advanced cervical cancer (LACC), which causes irreversible damage to the ovaries and vagina and seriously affects patients' ovarian function and sexual life. Therefore, developing individualized and comprehensive treatments based on the Clinical Practice Guidelines for Cervical Cancer Developed by the National Comprehensive Cancer Network to improve the quality of life of LACC patients is an urgent problem for clinicians. NACT combined with radical surgery has been used in some countries and regions and offers the advantage of preserving ovarian and vaginal functions [3–6]. However, with the degradation of pathological results after NACT, lymph nodes with tumor metastasis may appear negative, masking the true risk after surgery and obfuscating the choice of adjuvant therapy after NACT followed by radical surgery. For this reason, this present study analyzed the clinicopathologic data of young patients with LACC to investigate the effect of NACT on outcomes in patients with moderate risk factors.

2. Materials and methods

2.1 Patient selection

For this retrospective study, we collected the data for 338 patients with LACC treated in our hospital between January 2008 and December 2018. The inclusion criteria were as follows: (1) stage IB3 or IIA2 cervical cancer according to the 2018 Federation International of Gynecology and Obstetrics (FIGO) classification; (2) age $\leq$45 years and treatment with

1–3 courses of preoperative NACT; (3) ability to tolerate type C radical hysterectomy according to Querleu-Morrow classification based partly on a preoperative white blood cell count $\geq 3 \times 10^9$/L, hemoglobin ≥ 80 g/L, platelet count $\geq 100 \times 10^9$/L, normal kidney and liver function, and normal chest radiograph; and (4) provision of informed consent for treatment. Patients were excluded if they met any of the following criteria: (1) metastasis of cervical cancer or presence of other malignant neoplasms; (2) pregnancy or lactation; (3) prior hysterectomy; (4) incomplete clinical case data; and (5) failure to complete the protocol described in this study for any reason. The patients were examined by two or more clinical gynecologic oncologists before treatment.

2.2 Treatment plan

Before surgical treatment, patients underwent transvaginal ultrasonographic measurements as well as chest and urinary B-ultrasound. If necessary, further imaging analyses were also performed, such as magnetic resonance imaging (MRI), abdominopelvic computed tomography (CT) scanning, intravenous pyelography, and colonoscopy.

The patients received 1–3 cycles of intravenous chemotherapy every 10–21 days and then within 7–14 days underwent type C radical open surgery involving radical hysterectomy, pelvic lymphadenectomy. Only the common iliac lymph nodes were sent for freezing pathology during the operation. If any of these nodes were positive, lymphadenectomy below the inferior mesenteric artery (low para-aortic) was performed. One or both ovaries were shifted to the paracolic sulcus in cervical squamous cell carcinoma patients with normal ovarian function.

2.3 NACT assessment

In the early stage before 2016, there was no relevant guideline for neoadjuvant chemotherapy, and thus, the chemotherapy regimen was not standardized but followed the recommendations of postoperative chemotherapy guidelines. Informed consent was obtained before treatment with systemic intravenous platinum-based combination chemotherapy in patients without contraindications to chemotherapy. The major chemotherapy regimens applied for each pathologic type are described in Table 1. At 2 weeks after chemotherapy, a gynecological examination was performed combined with B ultrasound, CT, or MRI to evaluate tumor size and pelvic conditions. Treatment efficacy was evaluated in reference to the World Health Organization (WHO) standards for solid tumors, with outcomes categorized as complete response (complete disappearance of the tumor), partial response (>50% reduction in tumor volume), stable disease (<50% reduction or <25% increase in tumor volume with no appearance of new lesions), or progressive disease (>25% increase in tumor volume or formation of new lesions) [7]. Complete response and partial response were considered a clinical response. Adverse side effects attributed to NACT were evaluated according to the WHO standard for toxicity [8]. According to the efficacy of chemotherapy, the patients were divided into a chemotherapy-effective group and a chemotherapy-ineffective group. The clinicopathological characteristics of the two groups were compared.

2.4 Postoperative adjuvant therapy and survival

Indications for postoperative supplementary treatment included pelvic lymph node metastasis, parametric infiltration, or a positive surgical margin. These cases were treated with supplementary radiotherapy and chemotherapy, which was formulated according to National Comprehensive Cancer Network (NCCN) guidelines. Patients with lymph-vascular space invasion (LVSI) or deep cervical stromal invasion were given 2–4 cycles of platinum-based chemotherapy upon giving informed consent. All patients were followed up regularly after treatment every 3 months for 2 years, every 6 months from the 3rd to the 5th year, and annually from the 6th year. Follow-up evaluations included gynecological examination, vaginal exfoliative cytology, pelvic b-ultrasound or pelvic CT, squamous cell carcinoma antigen measurement, *etc*. The date of last follow-up was 31 May 2019. Survival curves were constructed by the Kaplan-Meier method. The progression-free survival (PFS) and overall survival (OS) of the patients were analyzed to evaluate the efficacy and survival benefit of NACT in patients with risk factors for cervical cancer recurrence.

2.5 Statistical analysis

Statistical Package Service Solution (SPSS) 22.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for all data analysis. Measurement data that did not follow a normal distribution were represented as median and percentile, and classification data were represented as rate. The measurement data for the two groups were compared by Wilcoxon rank test. Rates or compositions of the two groups were compared by χ^2 test. Differences for which $p < 0.05$ were considered statistically significant.

3. Results

3.1 Distribution of clinical features and evaluation of NACT

The present study analyzed the data for 338 patients with stage IB3 or IIA2 cervical cancer treated in our hospital from January 2008 to December 2018. The patients received different NACT regimens according to the pathological type of cervical cancer (Table 1). The overall mean patient age was 39 years, and the age group with the most patients in both the chemotherapy-effective and -ineffective groups was 36–45 years (Table 2). Different degrees of tumor reduction were observed after NACT, with 16 patients achieving a complete response (4.7%, 16/338). Overall, 309 patients achieved a clinical response (91.4%, 309/338; chemotherapy-effective group), and the clinical response rate specifically among cases of squamous cell carcinoma was 91.46% (257/281). The 29 cases those did not achieve a clinical response and were assigned to the chemotherapy-ineffective group all showed stable disease. The main side effects of chemotherapy were grade I–II myelosuppression (*e.g.*, leukopenia, thrombocytopenia, and

TABLE 1. NACT regimens administered according to pathological type of cervical cancer (n).

Regimen	Squamous n = 281	Adenocarcinoma n = 32	Adenosquamous n = 20	Special* n = 5
BP	182	0	8	2
5-Fu + BP/BVP	33	2	3	2
FIP	0	9	2	0
TP/TC	66	21	7	1

**Special: neuroendocrine small cell carcinoma or combined type.*
BP: cisplatin (50 mg/m^2, day 1), plus bleomycin (15 mg) or pingyangmycin (16 mg, days 1–2); BVP: BP plus vincristine (1 mg/m^2, day 1); FBP: 5-fluorouracil (500 mg, days 1–3), plus cisplatin (50 mg/m^2, day 1), plus bleomycin (15 mg) or pingyangmycin (16 mg, days 1–2); FIP: 5-fluorouracil (1000 mg, days 1–3), plus cisplatin (50 mg/m^2, day 1), plus ifosfamide (1 g/m^2) and mesna (200 mg/m^2, at 0, 4, and 8 h); TP/TC, paclitaxel (135–175 mg/m^2, day 1), plus cisplatin (50 mg/m^2) or carboplatin (area under the concentration time curve, 5.0–7.5, day 1).

TABLE 2. Age distributions and clinical characteristics in the chemotherapy-effective and -ineffective groups.

Characteristics	Chemotherapy-effective group (n = 309)		Chemotherapy-ineffective group (n = 29)		χ^2	p
	n	%	n	%		
Age (years)						
≤25	3	0.97	0	0.00		
26–35	66	21.36	8	27.59	0.846	0.655
36–45	240	77.67	21	72.41		
Stage						
IB3	83	26.86	3	10.34	3.812	0.051
IIA2	226	73.14	26	89.66		
Pathological type						
Squamous	257	83.17	24	82.76	0.003	0.955
Non-squamous	52	16.83	5	17.24		
Grade						
G3	244	78.96	25	86.21	0.856	0.355
G1, G2	65	21.04	4	13.79		
Tumor diameter before chemotherapy						
<5 cm	66	21.36	1	3.45	5.351	0.021
≥5 cm	243	78.64	28	96.55		

hemoglobinemia), digestive reaction (*e.g.*, nausea, vomiting, temporary diarrhea), and alopecia. None of the patients experienced severe side effects (WHO grades III–IV). No significant differences were shown in clinical stage, pathological type, and tissue differentiation between the two groups. However, the number of patients with tumor diameter over 5 cm in the chemotherapy-effective group was significantly less than that in the ineffective group ($p = 0.021$; Table 2).

3.2 Analysis of risk factors for postoperative recurrence of cervical cancer

Although there were no obvious differences between the chemotherapy-effective and -ineffective groups in pelvic lymphatic metastasis, parametric infiltration, positive surgical margin, cervical stromal infiltration more than 1/2, and LVSI, the results of postoperative pathological reports showed trends of lower rates of lymph node metastasis (20.7% *vs.* 34.5%), positive surgical margin (1.6% *vs.* 6.9%), parametric infiltration (5.8% *vs.* 10.3%), and deep cervical stromal invasion (60.2% *vs.* 75.9%) in the chemotherapy-effective group compared with the chemotherapy-ineffective group (Table 3).

3.3 Patient prognosis after NACT

Of the 338 cases included in this study, 313 cases were followed up successfully and 25 cases were lost (23 cases in the chemotherapy-effective group and 2 cases in the chemotherapy-ineffective group), for a follow-up rate of 92.6%. The follow-up period ranged from 5–142 months (median, 32 months). The respective 5-year PFS and OS rates were 86.29% and 85.75% in the chemotherapy-effective group

TABLE 3. Analysis of risk factors for postoperative recurrence of cervical cancer.

Risk factors	Chemotherapy-effective group (n = 309)		Chemotherapy-ineffective group (n = 29)		χ^2	p
	n	%	n	%		
Lymph node						
Positive	64	20.71	10	34.48	2.940	0.086
Negative	245	79.29	19	65.52		
Surgical margin						
Positive	5	1.62	2	6.90	3.642	0.056
Negative	304	98.38	27	93.10		
Parametric infiltration						
Positive	18	5.83	3	10.34	0.929	0.335
Negative	291	94.17	26	89.66		
Deep cervical stromal						
≥1/2	186	60.19	22	75.86	2.750	0.097
≤1/2	123	39.81	7	24.14		
Lympho-vascular invasion						
Positive	133	43.04	11	37.93	0.283	0.595
Negative	176	56.96	18	62.07		

versus 77.64% and 75.56% in the chemotherapy-ineffective group. The PFS and OS rates in the chemotherapy-effective group were higher than those of the chemotherapy-ineffective group (both $p < 0.001$; Fig. 1 and Table 4). The postoperative pathological reports showed a complete pathological response in 11 cases, micro-infiltration in 5 cases, and no case of recurrence; however, the results for 2 cases were lost. Pathological examination revealed high-risk factors (*e.g.*, lymph node metastasis, parametric infiltration, and positive surgical margin) in 178 cases that received supplemental CCRT. Among them, 31 patients experience cervical cancer recurrence, and 27 patients died. For these 178 cases, the 2-year PFS and OS rates were 82.92% and 87.75%, respectively, and the 5-year PFS and OS rates were 78.06% and 77.25%, respectively. A total of 107 cases had moderate risk factors (cervical stromal infiltration more than 1/2 or LVSI) that needed supplementary chemotherapy, among which 3 cases experienced recurrence. For these 107 cases, the 2-year PFS and OS rates were 95.9% and 99%. respectively, and the 5-year PFS and OS rates were 95.90% and 94.81%, respectively. Among the patients with moderate risk factors, 85 patients with squamous cell carcinoma retained unilateral or bilateral ovaries during the operation. These patients were followed up regularly after the operation, and none showed obvious signs of menopause. The 2-year and 5-year PFS and OS rates among patients who received supplemental chemotherapy after surgery were higher than those among patients who received supplemental CCRT (both $p < 0.001$; Fig. 2 and Table 5).

4. Discussion

The comparison of survival rates in our study demonstrated that sensitivity to chemotherapy is an important prognostic factor in patients with stage IB3 and IIA2 cervical cancer treated with NACT, as other studies have found [9]. Patients with LACC had more local recurrence and distant metastasis than other patients with earlier stages of cervical cancer. Young patients, like the 338 patients in our study, should be treated with full consideration of protecting their ovarian and vaginal functions and thereby improving their quality of life. Some research has indicated that patients with LACC more often experience local recurrence and distant metastasis than patients diagnosed with earlier stages of cervical cancer after therapy [10, 11]. In considering the tumor diameter distribution before NACT in the present study, 5 cm was used as the cutoff, and the results showed that the effect of chemotherapy was relatively poor in patients with lesions larger than 5 cm in diameter, confirming the relationship between the efficacy of NACT and tumor size in cervical cancer. The reason may be that with increasing tumor size, the tumor contains more anoxic cells, and the anoxic microenvironment makes the tumor less sensitive to chemotherapy [12]. In this study, chemotherapy drugs were selected according to tumor type to improve the effectiveness. The chemotherapy regimens for different types of cervical cancer were not unified until 2013. Thus, the BP program was mainly used in squamous cell cancer, and the clinical response rate of squamous cell cancer was 91.46% (257/281). Moreover, the tumor volumes were significantly reduced after NACT with no patients experiencing serious side effects (grades III–IV), demonstrating that BP was an effective regimen for preoperative chemotherapy.

After NACT, the tumor volume decreased significantly,

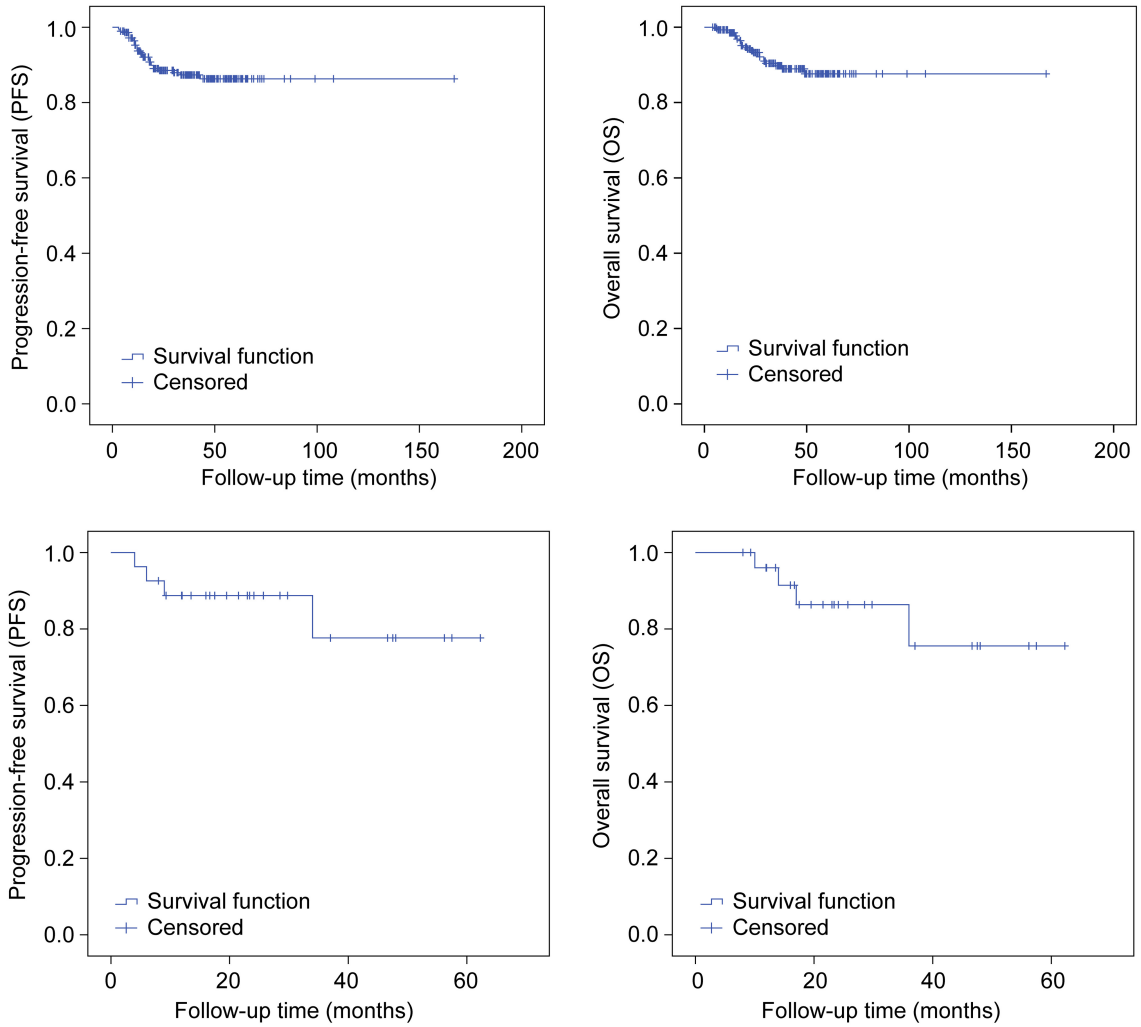

FIGURE 1. PFS and OS according to the effectiveness of chemotherapy. (A) PFS and (B) OS in the chemotherapy-effective group. The 5-year PFS and OS rates in this group were 86.29% and 85.75%, respectively. (C) PFS and (D) OS in the chemotherapy-ineffective group. The 5-year PFS and OS rates in this group were 77.64% and 75.56%, respectively.

TABLE 4. Comparison of postoperative survival rates between the chemotherapy -effective and -ineffective groups.

Survival rate	Chemotherapy-effective group (n = 309)	Chemotherapy-ineffective group (n = 29)	Z	*p*
2-year PFS	88.53%	88.73%	0.031	>0.050
2-year OS	92.92%	86.35%	0.866	>0.050
5-year PFS	86.29%	77.64%	7.119	<0.001
5-year OS	85.75%	75.56%	4.762	<0.001

PFS: progression-free survival; OS: overall survival.

TABLE 5. Comparison of survival rates between patients who received chemotherapy and patients who received CCRT after operation.

Survival rate	Postoperative chemotherapy (n = 107)	Postoperative CCRT (n = 178)	Z	*p*
2-year PFS	95.90%	82.92%	3.564	<0.001
2-year OS	99.00%	87.75%	3.882	<0.001
5-year PFS	95.90%	78.06%	4.197	<0.001
5-year OS	94.81%	77.25%	3.552	<0.001

PFS: progression-free survival; OS: overall survival.

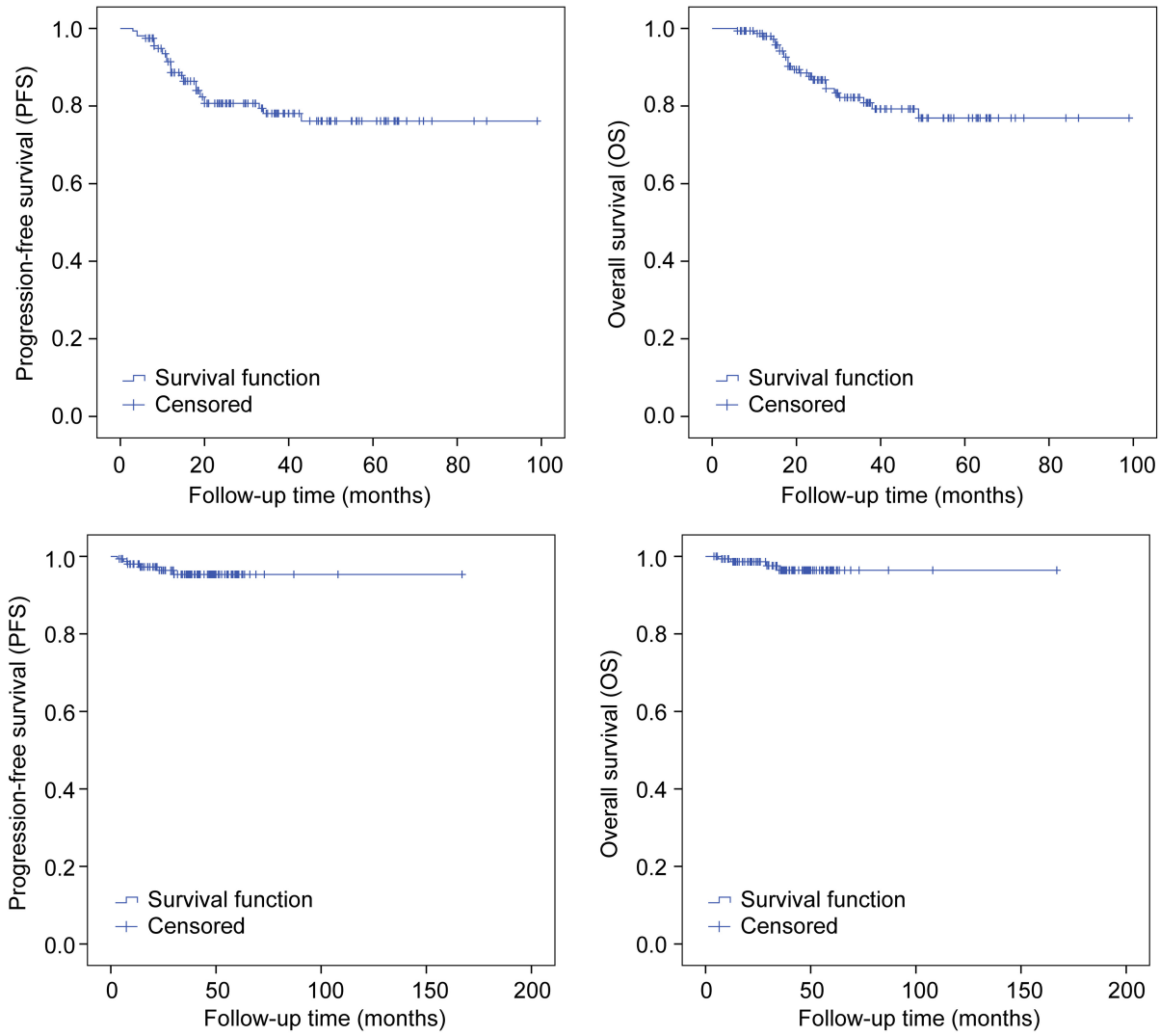

FIGURE 2. PFS and OS of cervical cancer patients with different categories of risk factors and different treatment strategies. (A) PFS and (B) OS of the 178 cases with high-risk factors who received supplemental CCRT. The 5-year PFS and OS rates for these patients were 78.06% and 77.25%, respectively. (C) PFS and (D) OS of the 107 cases with moderate-risk factors (deep cervical stromal invasion >1/2 or LVSI) who received supplementary chemotherapy. The 5-year PFS and OS rates for these patients were 95.90% and 94.81%, respectively.

creating opportunities for surgery. The rates of lymphatic metastasis and cervical stromal infiltration were reduced by more than 1/2 in those who responded to chemotherapy, lessening the need for postoperative radiotherapy, and thus protecting the ovarian and vaginal functions of young patients [13–16].

The major currently recognized risk factors include pelvic lymphatic metastasis, parametric infiltration, positive surgical margin, lymphatic metastasis, LVSI, tumor diameter greater than 4 cm, and adenocarcinoma, and pelvic lymph node metastasis, parametric infiltration, and positive surgical margin are considered high-risk factors. Once these occur, the patient's chance of survival rate decreases [16]. Deep cervical stromal invasion, LVSI, and tumor diameter greater than 4 cm are considered moderate risk factors. Patients with only one moderate risk factor can be followed up temporarily to avoid complications caused by postoperative radiochemotherapy [17]. Although there were no significant differences in these risk factors between the chemotherapy-effective and -ineffective groups in our study, except for tumor volume, the rates of lymph node metastasis (20.7% *vs.* 34.5%), positive surgical margin (1.6% *vs.* 6.9%), parametric infiltration (5.8% *vs.* 10.3%), and deep cervical stromal invasion (60.2% *vs.* 75.9%) tended to be lower in the chemotherapy-effective group than in the -ineffective group. Several explanations for these results are as follows. First, all patients in the chemotherapy-ineffective group had stable disease after treatment, and their tumors were reduced to varying degrees. Second, the course of preoperative chemotherapy included 1–2 cycles in most cases, and thus, the dose and course may not have been sufficient to significantly improve the postoperative risk factors in the chemotherapy-effective group. Also, the proportion of patients with a tumor exceeding 5 cm in diameter before chemotherapy in the chemotherapy-ineffective group was significantly higher than that in the chemotherapy-effective group (p = 0.021). If the patients in the chemotherapy-ineffective group with larger tumors had undergone surgical resection directly, the

difficulty of operation would have been greater, increasing the risk of recurrence and worsening their prognosis. Moreover, if radiotherapy had been given directly, the patients' vaginal and ovarian functions would have been seriously damaged, which is not ideal for young patients. In the study, 178 cases with high-risk factors received supplemental CCRT after surgery. Although this proportion was high, due to the intraoperative ovarian transposition of these squamous cell carcinoma patients, compared with direct CCRT, this treatment protects the patients' ovarian function to the greatest extent and improves their quality of life after treatment. In summary, these results suggest that NACT may have an effect on risk factors for recurrence independent of the clinical effectiveness of the chemotherapy.

The prognosis achieved with different treatment modes is the focus of cancer research. There is no doubt about the effect of CCRT in LACC, but the radiotherapy-related complications cannot be ignored. For young patients with moderate risk factors, the possibility that postoperative chemotherapy alone can replace traditional radiotherapy is worth discussing. Our study confirmed that the 5-year PFS and OS rates in the chemotherapy-effective group were significantly higher than those in the chemotherapy-ineffective group. A previous meta-analysis of seven phase III clinical trials showed that the 5-year PFS of patients with LACC who underwent radical surgery after NACT was 62%, which was higher than that of the radical radiotherapy group (45.5%), suggesting that NACT is a more reasonable choice for patients with LACC [18]. Another analysis of the clinical data of 633 LACC patients showed that the 5-year PFS of patients who underwent radical surgery after NACT or CCRT were 69.3% and 76.7%, respectively, and these differences in survival rates were statistically significant (p = 0.038). However, the 5-year OS rates did not differ significantly at 75.4% and 74.7%, respectively (p = 0.87) [19]. Another study analyzed the PFS and OS of 476 patients with LACC after NACT + RS, RS and CCRT. The results showed that the 5-year tumor free survival rates of NACT + RS, RS and CCRT groups were 85.00%, 77.44%, and 52.94%, respectively, and the 5-year overall survival rates were 88.67%, 80.21% and 64.37%, respectively ($p < 0.0001$). Compared with RS and CCRT, NACT + RS can improve the PFS and OS of LACC [20]. A randomized controlled trial compared the efficacy of NACT + RS and CCRT in 633 patients with stage IB2, IIA or IIB squamous cervical cancer and showed that the 5-year PFS rate increased in the CCRT group, but the main benefit was observed for stage IIB cases and no difference in OS was detected between the two groups [19]. A recent report retrospectively analyzed 609 cervical cancer patients with stage IIA2 disease from 2004 to 2018 who underwent abdominal radical hysterectomy (ARH) or radiochemotherapy. The results showed ARH provided higher 5-year OS and DFS rates than radiochemotherapy; however, due to the limitations of retrospective research, we need randomized controlled studies to confirm our findings [21]. Therefore, according to a patient's age, physical condition, desire to maintain vaginal and ovarian functions, and economic situation, NACT followed by surgical resection may be an appropriate treatment strategy for young patients with LACC [19, 22, 23]. The study lays a foundation for a future prospective study of young patients with LACC who have risk factors for recurrence after NACT followed by surgical resection.

5. Conclusions

NACT followed by surgical resection may be an appropriate treatment strategy for young patients with LACC. For stage IB3 and IIA2 patients who are effective in NACT, if there are only moderate risk factors for recurrence after operation, postoperative chemotherapy can be selected after full communication and informed notification, so as to avoid radiochemotherapy and the resultant damage to ovarian and vaginal function. A future prospective study of this treatment strategy is warranted.

AUTHOR CONTRIBUTIONS

LG, RTY, QLL, CB and ZLP—conceived and designed research; LG—collected data and conducted research, analyzed and interpreted data and wrote the initial paper; ZLP—revised the paper and had primary responsibility for final content. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee of West China Second Hospital (approval number: 2021-095). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Written informed consent was obtained from all individual participants included in this study.

ACKNOWLEDGMENT

Thanks to all the peer reviewers for their comments and suggestions.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Lin Gong, Ru-Tie Yin, Qing-Li Li, Ce Bian, Zhi-Lan Peng. Effectiveness of neoadjuvant chemotherapy followed by radical surgery in young patients with locally advanced cervical cancer. European Journal of Gynaecological Oncology. 2023; 44(1): 26-33. doi: 10.22514/ejgo.2023.003.