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Consolidation chemotherapy in early-stage cervical cancer patients with lymph node metastasis after radical hysterectomy

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HIGHLIGHTS

- The clinical value of consolidation chemotherapy is limited for patients with only one positive lymph node after radical hysterectomy
- Consolidation chemotherapy may provide a benefit for patients with >3 positive lymph nodes or those with >2 positive lymph nodes, lymphovascular space invasion, and greater than 1/3 stromal invasion after radical hysterectomy
- Consolidation chemotherapy increased the rate of grade 3/4 myelosuppression

ABSTRACT

Objective Post-operative concurrent chemoradiotherapy has become the standard treatment for patients with positive lymph nodes after radical surgery. The aim of this study was to explore the efficiency and safety of consolidation chemotherapy in early-stage cervical cancer patients with lymph node metastasis after radical hysterectomy.

Method We reviewed the medical records of patients with early-stage cervical cancer with lymph node metastasis after radical hysterectomy from January 2010 to January 2017. All patients underwent adjuvant concurrent chemoradiotherapy (n=49) or three cycles of platinum-based consolidation chemotherapy following concurrent chemoradiotherapy (n=89). The primary end points of the study were disease-free survival and overall survival.

Results The median follow-up time was 51 months (range 10–109). No significant difference was noted in disease-free survival, overall survival, or grade 3/4 gastrointestinal disorder between the consolidation chemotherapy group (78.1% vs 83.1% vs 6.7%) and the concurrent chemoradiotherapy alone group (75.4% vs 75.3% vs 4.1%), (p=0.42, 0.26, 0.80, respectively). However, the grade 3/4 myelosuppression rate in the consolidation group was higher than in the concurrent chemoradiotherapy alone group (40.4% vs 22.4%, p=0.03). For patients with >3 positive lymph nodes or patients with >2 positive lymph nodes+lymphovascular space invasion/≥1/3 stromal invasion, disease-free survival and overall survival were superior in the consolidation chemotherapy group compared with the concurrent chemoradiotherapy alone group (p<0.05).

Conclusion In patients with >3 positive lymph nodes or patients with >2 positive lymph nodes, lymphovascular space invasion, and greater than 1/3 stromal invasion, disease-free survival and overall survival were superior with consolidation chemotherapy. However, consolidation chemotherapy was also associated with an increased grade 3/4 myelosuppression rate.

INTRODUCTION

Surgery is the main treatment for early-stage cervical cancer and lymph node metastasis is an independent factor for its prognosis. The 5-year overall survival of early-stage patients is approximately 90%, while for patients with positive lymph nodes this is reduced by 20–50%.[1] Post-operative concurrent chemoradiotherapy has become the standard treatment for patients with positive lymph nodes and this has been associated with an improvement in overall survival. However, 20–30% of patients still suffer local recurrence and 18–25% of patients develop distant metastasis.[2–4]

A search for other treatments to improve the clinical outcome for this group of patients is important. Consolidation chemotherapy might be an option.[5 6] A number of trials have been performed to study the efficiency and feasibility of consolidation chemotherapy in patients with early-stage cervical cancer with high-risk factors; however, their results are inconsistent.[7 8] This study aims to evaluate the role of consolidation chemotherapy after concurrent chemoradiotherapy in early-stage cervical cancer patients with lymph node metastasis and/or other high-risk factors after radical hysterectomy.

METHODS

We reviewed the medical records of Jiangxi Maternal and Child Health Hospital from January 2010 to January 2017 to identify eligible patients. The qualifying criteria were as follows: (1) women who were 18–70 years old with histologically-confirmed invasive cervical cancer (squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma); (2) International Federation of Gynecology and Obstetrics (FIGO, 2018) stage IB1, IB2, or IIA1; (3) initially treated with radical surgery including a type III radical

hysterectomy with pelvic lymphadenectomy, with or without para-aortic lymphadenectomy; (4) with pelvic and/or para-aortic lymph nodes metastasis; (5) post-operative concurrent chemoradiotherapy given with or without consolidation chemotherapy (there are six oncology wards in our hospital and different physicians take charge of different wards; consolidation chemotherapy was therefore not administered to every patient with positive lymph nodes due to differences in management strategies); (6) Eastern Cooperative Oncology Group (ECOG) performance status 0–2, adequate cardiac, hepatic and renal functions, normal white blood cell and platelet count, hemoglobin level ≥10.0 g/dL; (7) complete follow-up data.

Distant metastasis was excluded by chest radiography, abdominal and pelvic computed tomography. Those who underwent chemotherapy or radiation before surgery were also not included in this study. From January 2010 to January 2017, 1985 patients with early-stage cervical cancer underwent a radical hysterectomy in our hospital. Patients were divided into two groups: group A (consolidation chemotherapy group) and group B (concurrent chemoradiotherapy alone). The characteristics of these patients are listed in Table 1.

All patients received external beam radiotherapy at a daily fraction of 1.8–2.0 Gy for a total dose of 45–50 Gy. The clinical target volume included tumor bed, the parametria, upper 3.0 cm of vagina, paravaginal soft tissue lateral to the vagina, and adjacent nodal basins (common iliac, external iliac, internal iliac, obturator, and presacral nodal basins). In patients with common iliac lymph node/para-aortic lymph node involvement, extended field radiotherapy was administered up to the level of the renal vessels. The clinical target volume was drawn according to the consensus guidelines of the Radiation Therapy Oncology Group 0418.[9] Pelvic external beam radiotherapy was delivered mainly by a two-field technique or intensity modulated radiation therapy at 6 MV on a linear accelerator.

Concurrent chemotherapy was administered once a week and the regimen included paclitaxel liposome (60 mg/m^2)/docetaxel (25 mg/m^2) and carboplatin (area under the curve (AUC)=2.0)/nedaplatin (30 mg/m^2). Consolidation chemotherapy started 3 weeks after the completion of radiation. Three cycles of paclitaxel liposome (150 mg/m^2)/docetaxel (65 mg/m^2) and carboplatin (AUC=5.0)/nedaplatin (80 mg/m^2) were infused every 3–4 weeks. Chemotherapy regimens are listed in Table 2.

Complications that occurred within 90 days after the start of the primary treatment were considered to be acute complications. The severity of acute complications was evaluated by the Common Terminology Criteria for Adverse Events Version 4.0.[10] Complete blood count was tested every 3 days and liver/renal functions were tested every 2 weeks to assess the toxicities.

The primary end points of the study were disease-free survival and overall survival. Disease-free survival was defined as the interval between the beginning of treatment and the first recurrence or the last follow-up visit and overall survival was that from the start of treatment to the death of any cause or the last follow-up visit. The surveillance was as follows: history, physical examination, and other auxiliary examinations every 3–6 months for the first 2 years, every 6–12 months for another 3 years, and then annually. Patients with high-risk disease could be evaluated more frequently.

Frequency distributions among these groups were performed by the χ^2 test. The Kaplan–Meier method was used to calculate the survival rate and the log-rank test was applied to determine the significance of differences in survival distribution. A p value <0.05 was defined as statistically significant.

Table 1 Characteristics of patients

Characteristics	Group A* (n=89)	Group B† (n=49)	P value
Age (years), median (range)	45 (31–66)	43 (25–64)	0.80
ECOG status			
0	72 (80.9%)	37 (75.5%)	
1	15 (16.9%)	10 (20.4%)	0.71
2	2 (2.2%)	2 (4.1%)	
Histology			
SCC	66 (74.2%)	40 (81.6%)	0.32
Non-SCC	23 (25.8%)	9 (18.4%)	
FIGO stage			
IB1, IB2	74 (83.1%)	42 (85.7%)	0.69
IIA1	15 (16.9%)	7 (14.3%)	
Number of positive lymph nodes			
1	39 (43.8%)	26 (53.1%)	0.30
≥2	50 (56.2%)	23 (46.9%)	
Lymphovascular space invasion			
Yes	74 (83.1%)	35 (71.4%)	0.11
No	15 (16.9%)	14 (28.6%)	
Stromal invasion depth			
≥1/3	80 (89.9%)	39 (79.6%)	0.09
<1/3	9 (10.1%)	10 (20.4%)	
Positive CILN/PALN			
Yes	14 (15.7%)	6 (12.2%)	0.56
No	75 (84.3%)	43 (87.8%)	

*Group A: consolidation chemotherapy group.
†Group B: concurrent chemoradiotherapy alone group.
CILN, common iliac lymph node; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion; PALN, para-aortic lymph node; SCC, squamous cell carcinoma.

RESULTS

Overall, 1985 patients with early-stage cervical cancer underwent a radical hysterectomy. A total of 212 patients had metastatic lymph nodes and 40 patients underwent chemotherapy before surgery, 21 patients did not receive radiotherapy, and 13 patients lost contact during follow-up. Finally, 138 patients were enrolled, 89 in group A (consolidation chemotherapy group) and 49 in group B (concurrent chemoradiotherapy alone group). The median follow-up time was 51 months (range 10–109). A total of 24 patients died during the follow-up period, 13 patients in group A and 11 patients in group B. The disease-free survival of patients in groups A and B was 78.1%

Table 2 Chemotherapy regimens

Chemotherapy regimens	Group A* (n=89)	Group B† (n=49)	P value
Paclitaxel liposome + nedaplatin	27 (30.3%)	15 (30.6%)	0.93
Paclitaxel liposome + carboplatin	8 (9.0%)	4 (8.1%)	
Docetaxel + nedaplatin	18 (20.2%)	8 (16.4%)	
Docetaxel + carboplatin	36 (40.5%)	22 (44.9%)	

*Group A: consolidation chemotherapy group.
†Group B: concurrent chemoradiotherapy alone group.

and 75.4%, respectively (p=0.42) and the overall survival for the respective groups was 83.1% and 75.3% (p=0.26) (Figure 1).

The incidence of grade 3/4 gastrointestinal toxicity in groups A and B was 6.7% and 4.1%, respectively (p=0.80). However, overall rates of grade 3/4 myelosuppression in group A was higher than that of group B (40.4% vs 22.4%, p=0.03). The incidence and categories of adverse events are shown in Table 3.

Pathological factors evaluated in this study included lymphovascular space invasion, stromal invasion depth, number of positive lymph nodes, histology, and para-aortic lymph node status. Positive margins and positive parametrium were not included in this analysis due to the scarcity of these patients (there was only one patient with a positive margin and one patient with a positive parametrium). A comparison of survival of patients with different pathological factors between the consolidation chemotherapy group and the concurrent chemoradiotherapy alone group is shown in Table 4. Consolidation chemotherapy was beneficial to the disease-free survival and overall survival of those patients with >3 positive lymph nodes or with >2 positive lymph nodes+lymphovascular space invasion/≥1/3 stromal invasion (p<0.05). Disease-free survival and overall survival of patients with other pathological factors were not statistically different between the two groups.

DISCUSSION

The current standard for adjuvant treatment for patients with cervical cancer with risk factors for recurrence is cisplatin-based chemoradiotherapy,[2 11] but further survival improvements have not yet been observed when consolidation doublet chemotherapy is applied.[12] A search for other treatments to improve the clinical outcome for this group of patients is important. Consolidation chemotherapy may offer a benefit to such patients; however, there is a paucity of data concerning this subject.[5 6] A number of studies have been performed evaluating the feasibility of consolidation chemotherapy in patients with early-stage cervical cancer with high-risk factors, but the results are inconsistent[7 8]

Lee et al[7] evaluated the role of consolidation chemotherapy after concurrent chemoradiotherapy in 40 patients with early-stage cervical carcinoma with high-risk factors (25 patients underwent concurrent chemoradiotherapy alone and 15 patients underwent consolidation chemotherapy). However, a worse 2-year disease-free survival was observed by adding consolidation chemotherapy (87.7% vs 67.0%, p=0.17). Zhao et al[8] performed a phase III randomized trial comparing consolidation chemotherapy with concurrent chemoradiotherapy alone in 136 post-surgical patients with high-risk factors. The study showed that the distant metastasis

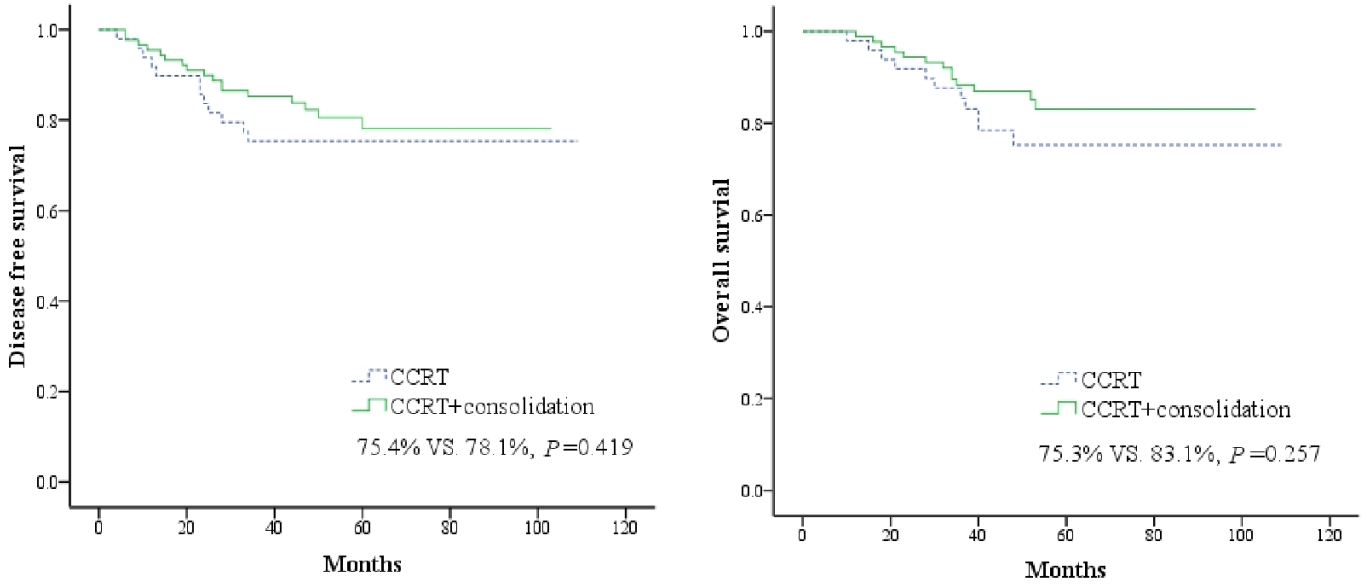

Figure 1 Disease-free survival and overall survival of patients in the concurrent chemoradiotherapy alone group (CCRT) and the CCRT+consolidation chemotherapy group.

Table 3 Comparison of toxicities between group A and group B

Group/ toxicities	Gastrointestinal			Myelosuppression		
	III	IV	Rate (%)	III	IV	Rate (%)
Group A*	6	0	6.74%	26	10	40.45%
Group B†	2	0	4.08%	8	3	22.45%
P value	0.80			0.03		

*Group A: consolidation chemotherapy group.
†Group B: concurrent chemoradiotherapy alone group.

rate of patients in the consolidation chemotherapy group was reduced by 11.0% (2.8% vs 13.8%, p=0.048). The 3-year disease-free survival rate (82.0% vs 74.3%, p=0.55) and the overall survival rate (86.6% vs 78.3%, p=0.38) was not improved in the consolidation chemotherapy group when compared with the concurrent chemoradiotherapy alone group.

Our result was different from the trial by JW Leet al.[7] First, in the study by Lee et al[7] 17.5% of patients (7/40) only had high-risk factors such as a positive parametrium or positive vaginal margin but not positive lymph nodes, and consolidation chemotherapy may not be necessary for these patients. Second, 30% of patients (12/40) with stage IB2 cervical cancer were also included in the study by Lee et al while, in our hospital, initially radical hysterectomy was not a routine practice for this stage of disease.

In patients with lymph node involvement there was a positive correlation between the number of positive nodes and the risk of relapse,[13] perhaps suggesting that different treatments should be administered depending on the number of metastatic lymph nodes. The potential clinical value of consolidation chemotherapy is very limited for early-stage patients with only one positive lymph node. In our study there were 65 patients with only one metastatic lymph node, 39 in the consolidation chemotherapy group and 26 in the concurrent chemoradiotherapy alone group. There was no difference in disease-free survival or overall survival. The study by Lee and colleagues[14] also revealed that little improvement was achieved by adding consolidation chemotherapy for patients with only one positive lymph node (HR=1.0). However, for those patients with more than three positive lymph nodes or patients with more than two positive lymph nodes+lymphovascular space invasion/≥1/3 stromal invasion, the disease-free survival and overall survival was superior in the consolidation chemotherapy group compared with the concurrent chemoradiotherapy alone group (p value for disease-free survival was 0.03, 0.01, 0.015 and p value for overall survival was 0.048, 0.02, 0.016, respectively).

In this study the incidence of grade 3/4 gastrointestinal toxicity in the consolidation chemotherapy group and the concurrent chemoradiotherapy alone group was 6.74% and 4.08%, respectively, and this difference was not statistically significant. However, overall rates of grade 3/4 myelosuppression in the consolidation chemotherapy group was much higher than in the concurrent chemoradiotherapy alone group, and there was a statistical difference between the two groups (40.45% vs 22.45%, p=0.03). In a recent meta-analysis[15] comparing the toxicities of consolidation chemotherapy (120 patients) with concurrent chemoradiotherapy alone (128 patients) the rate of grade 3/4 myelosuppression was higher in the consolidation chemotherapy than in the concurrent chemoradiotherapy alone group (HR=2.42, 95% CI 1.24 to 4.77, p=0.01). However, Zhao et al[8] found that the incidence of grade 3/4 myelosuppression in the consolidation chemotherapy group was only slightly higher than that in the concurrent chemoradiotherapy alone group (25.3% vs 12.3%, p=0.053). In another retrospective trial,[16] no difference was observed for grade 3/4 myelosuppression in the consolidation chemotherapy and concurrent chemoradiotherapy groups (p=0.07). The reason may be due to different chemotherapy regimens. In some trials, cisplatin was used and the main toxicity of cisplatin was kidney damage while, in our study, carboplatin or nedaplatin was used and the major adverse effects of these is myelosuppression.

Table 4 Survival according to different factors between the consolidation chemotherapy group and the concurrent chemoradiotherapy alone group

Pathologic factors/group	N	Disease-free survival			Overall survival		
		Group A*	Group B†	P value	Group A*	Group B†	P value
One positive LN	65	88.9%	92.3%	0.74	90.2%	92.3%	0.99
One positive LN+LVSI	50	86.8%	94.1%	0.49	90.9%	91.7%	0.67
One positive LN+≥1/3 stromal invasion	53	87.6%	95.0%	0.43	91.4%	92.9%	0.64
One positive LN+non-SCC	11	71.4%	100.0%	0.27	71.4%	100.0%	0.27
One positive LN+LVSI+≥1/3 stromal invasion	46	84.9%	94.1%	0.41	89.7%	91.7%	0.61
≥2 positive LN	73	68.0%	55.9%	0.10	73.9%	58.0%	0.08
≥2 positive LN+LVSI	59	65.7%	43.2%	0.01	70.7%	44.4%	0.02
≥2 positive LN+≥1/3 stromal invasion	62	64.2%	39.7%	0.015	70.4%	42.5%	0.016
≥2 positive LN+positive PALN	19	51.9%	16.7%	0.08	57.1%	22.2%	0.11
≥2 positive LN+non-SCC	20	66.7%	40.0%	0.21	62.9%	30.0%	0.26
≥3 positive LN	49	69.7%	40.0%	0.03	70.8%	43.2%	0.048

*Group A: consolidation chemotherapy group.
†Group B: concurrent chemoradiotherapy alone group.
CILN, common iliac lymph node; LN, lymph nodes; LVSI, lymphovascular space invasion; PALN, para-aortic lymph node; SCC, squamous cell carcinoma.

Our study has some limitations. First, the sample size was insufficient to obtain a confirmative conclusion. The heterogeneous population and selection bias from the retrospective design was also a limitation of our study and, lastly, the chemotherapy regimen was not the same for all patients enrolled, which might influence the results of the trial.

We conclude that consolidation chemotherapy may be of benefit in patients with >3 positive lymph nodes or those with >2 positive lymph nodes, lymphovascular space invasion, and greater than 1/3 stromal invasion after radical hysterectomy.

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