EJGO European Journal of Gynaecological Oncology

Comparison of the curative effect and safety of consolidation chemotherapy after concurrent chemoradiotherapy with concurrent chemoradiotherapy alone for locally advanced cervical cancer

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Summary

Purpose: This study investigated the curative effect and safety of consolidation chemotherapy in locally advanced cervical cancer. *Materials and Methods:* Eighty-four patients with locally advanced cervical cancer, treated in the Department of Gynaecological Oncology at JiangXi Maternal and Child Health Hospital of China between January 2011 and January 2013, were retrospectively enrolled. Forty-six patients underwent three courses of platinum-based consolidation chemotherapy following concurrent chemoradiotherapy (consolidation group), and 38 patients underwent concurrent chemoradiotherapy only (control group). Effectiveness, feasibility, survival rates, and toxicity were evaluated. *Results:* Follow-up was 15 to 54 months. Treatment strategy (HR=0.322, 95% CI: 0.123-0.843, p = 0.021) and cancer stage (HR=2.333, 95% CI: 1.043-5.218, p = 0.039) were associated with overall survival rate. Severe myelosuppression in the consolidation group was 36.96% and 18.42% in the control group, (p = 0.19), serious adverse events of the rectum were 10.87%, and 13.16%, respectively (p = 0.749). *Conclusion:* Consolidation chemotherapy increased patient survival but not the incidence of severe adverse events.

Key words: Locally advanced cervical cancer; Consolidation chemotherapy; Survival rate.

Introduction

Cervical cancer is the second leading cause of cancer-related death for young women worldwide [1]. In cases of adenocarcinoma and adenosquamous carcinoma, the prognosis is worse than squamous carcinoma [2, 3]. In less developed countries, fewer prevention programs result in higher tumor stages at diagnosis and higher incidence and lethality than in western countries [4].

At present, early stage cervical cancer is usually treated surgically, whereas intermediate and advanced stage cervical cancer is treated surgically with concurrent chemoradiotherapy. Concurrent platinum based chemoradiotherapy results in a 30% to 50% decrease in risk of death compared to radiotherapy alone for locally advanced cervical cancer [5-9]. The improved efficacy may be due to direct cytotoxicity, radiosensitization of tumor cells, and control of subclinical metastases [10]. Although this strategy has achieved a high survival rate, local metastasis of advanced cervical cancer can occur, leading to relapse and 35% of patients experience disease progression after chemoradiotherapy [11]. Such metastasis can present with specific pathologic features, including poor tumor differentiation, lymphatic vascular space invasion (LVSI), and tumor insensitivity to radiation and chemotherapy.

Although radiotherapy technology and equipment have greatly improved over the recent years, the current radiation dose used for cervical cancer (80-85 Gy) cannot be further increased. Therefore, alternative methods for reducing cervical cancer recurrence are needed. Adjuvant chemotherapy may be beneficial because five-year overall survival improves with additional chemotherapy following chemoradiotherapy [10, 11]. Consolidation chemotherapy after potentially successful standard chemoradiotherapy aims to eradicate any residual disease and improve outcomes. The potential of consolidation chemotherapy has been investigated in clinical trials and this method may improve survival and reduce distant recurrence [12-14]. In this study the authors aimed to compare the effects of consolidation chemotherapy versus concurrent chemoradiotherapy. Patients who received consolidation chemotherapy after chemoradiotherapy were compared with those who received only chemoradiotherapy. Then, the side effects and prognoses associated with the chemotherapy were evaluated. This will provide useful evidence for clinicians on whether consolidation chemotherapy is beneficial for patients with locally advanced cervical cancer.

Revised manuscript accepted for publication February 28, 2017

Eur. J. Gynaecol. Oncol. - ISSN: 0392-2936
XXXIX, n. 4, 2018
doi: 10.12892/ejgo4132.2018

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Materials and Methods

A total of 84 participants were consecutively enrolled in this retrospective cohort study aged between 28 and 69 years (average, 46 years). The patients were treatment-naive and received primary treatment in the Department of Gynaecological Oncology at JiangXi Maternal and Child Health Hospital of China between April 2010 and April 2013.

All enrolled patients met the following inclusion criteria: 1) younger than 70 years of age, and without severe complications (such as severe cerebrovascular and cardiovascular diseases, diabetes, and severe anemia), 2) the cervical cancer was confirmed by the pathological examination in the present hospital, and the pathological types were squamous carcinoma (poorly differentiated cancer or with carcinoma embolus in interstitial vascular), adenocarcinoma, and adenosquamous carcinoma, 3) clinical diagnosis was Stages Ib2, IIb, and III cancer (FIGO 2009), which was also termed locally advanced cervical carcinoma, and CT scanning ruled out multiple pelvic lymph node metastasis and para-aortic lymph node metastasis, and 4) with the KPS score ≥ 70. Exclusion criteria: 1) did not meet the inclusion criteria, 2) not treatment-naive patients in the present hospital, and 3) with severe side-effects during the treatment, and did not complete the concurrent chemoradiotherapy. The patients all provided signed informed consent for inclusion in the study. The present study was approved by the Ethics Committee of the hospital.

Based on the evidence in favor of consolidation chemotherapy [10-14], the clinicians informed the patients of the advantages and disadvantages of the treatment regimens, and every patient was referred to the cervical cancer NCCN (2015) guidelines. The patients then selected their preferred treatment regimen and were grouped accordingly. Therefore, the patients were assigned to either the consolidation chemotherapy group or the control group according to the treatment they received. None of the patients received surgery. All of the patients in both groups underwent concurrent chemoradiotherapy.

For the patients in the consolidation chemotherapy group, three cycles of chemotherapy were performed after the concurrent chemoradiotherapy, and the strategy was the same as the concurrent chemotherapy. Side-effects of chemoradiotherapy were treated in a timely manner with symptomatic treatments during the chemoradiotherapy.

External beam radiotherapy was applied to the pelvis in addition to brachytherapy. The external beam radiotherapy used cobalt 60 external irradiation, a partition dose of 200 cGy five times a week for a total dose of 3,000 cGy of whole pelvic irradiation, after that a total dose of 2,000 cGy radiotherapy was conducted using a central block of lead irradiation (lead width: 4 cm), and point B (reference point), the measuring point for pelvic lymph nodes, received a total dose of 5,000 cGy (200 cGy/25f). After three weeks of external irradiation intracavity irradiation was implemented with CT-guided brachytherapy which was executed by an Ir192 radiation therapy machine. Brachytherapy was applied for a total of six times, five times through a uterine tube applicator with point A (reference point) prescription dose of 7 Gy once a week, and once through a vaginal double-box applicator with a prescription dose of 10 Gy applied 1.0 cm next to the source once a week. When performing the brachytherapy or external beam radiotherapy, if greater than phase III myelosuppression or gastrointestinal reaction occurred, the radiation and chemotherapy were stopped to allow for symptomatic treatment. After the symptoms were actively controlled, the radiation and chemotherapy were completed as soon as possible

For patients in consolidation chemotherapy group, three cycles of chemotherapy were performed after concurrent chemoradiotherapy, and the strategy was same to the strategy of consolidation chemotherapy. If grade IV myelosuppression occurred, the dose of the next chemotherapy was reduced by 25%.

During concurrent chemoradiotherapy, an intravenously administered chemotherapy regimen of 135 mg/m^2 liposomal paclitaxel on day 1 plus carboplatin (area under the plasma drug concentration versus time curve (AUC)=4) on day 2 was used with a break every three to four weeks. In total, three courses of therapy were applied. In the consolidation chemotherapy group, the three courses of consolidation chemotherapy were applied after concurrent chemoradiotherapy. During both radiation and chemotherapy, the side effects associated with the treatment were actively monitored.

The NCI-RECIST standards were used to evaluate curative effect, including disease-free survival (DFS) time and overall survival (OS) time. Toxicity and side effects, including myelosuppression and radiation proctitis were evaluated using World Health Organization (WHO) standards and NCI CTCAE 3.0 toxic effect grading criteria [15]. Each patient underwent three or four gynecologic examinations: one before treatment, one after the pelvic external irradiation was complete, one after the synchronous radiation was complete, and one after the consolidation chemotherapy (consolidation group only) was complete. Additionally, CT of the pelvic cavity, abdominal ultrasonography, chest X-ray, biochemical evaluation, and routine blood tests were used to monitor changes in tumor properties and adverse reactions, and assisted the clinicians in dealing with complications.

For the first year after treatment, the patients were followed up every one to three months; for the second year, they were followed up every three to six months; for the third year, they were followed up every six months; and thereafter they were followed up annually. The primary method used for follow-up included a combination of inviting the patient back to the hospital for review, mailed correspondence and telephone interviews. Gynecologic examinations, pelvic CT scanning, abdominal color ultrasound, plain chest X-ray imaging, biochemical test, and routine blood examinations were performed for all the patients before the treatment and after whole pelvic irradiation (before the after-loading therapy), after concurrent radiotherapy, and after consolidation chemotherapy. Changes in the tumor and adverse responses were recorded. Out of the 84 enrolled patients, at the final date for follow-up, which was June 6, 2015, three patients (one from the study group and two from the control group) were lost to follow-up. The follow-up rate was 96.3%, the range of follow-up was 15 to 54 months, and the median follow-up time was 34 months.

SPSS 16.0 was used for statistical analysis. The measurement or count data are presented as mean ± standard deviation (SD), frequency, percentile, and the range. For the normally distributed continuous variables, the independent sample *t*-test was used; for the non-normally distributed continuous variables, the rank sum test was used. Variables in the contingency table were analyzed by the χ^2 test (or the Fisher exact test). Kaplan-Meier method was used to estimate the overall survival rate and disease free survival, and log-rank test was used for the comparison of the difference between the two groups. Multivariate Cox logistic regression analysis was used to identify the factors associated with three-year overall survival. $P < 0.05$ was considered statistically significant.

Results

The general data collected from the two study groups are shown in Table 1. There were no significant inter-group differences with respect to age, pathological pattern, or cancer stage between the two groups ($p > 0.05$). All patients in the

Table 1. — *General patient data.*

Variable		Consolidation group (n=46)	Control group (n=38)	*p*
Age		45.87±7.59	46.79±8.41	0.419
Pathology	SC G3	14	11	0.989
	SC (LVSI)	11	9	
	AC	13	12	
	ASC	8	6	
Hemoglobin		101.63±10.36	101.58±9.06	0.799
KPS		88.27±4.21	88.39±4.21	0.236
Stages	Ib2	5	4	0.962
	IIb	18	16	
	III	23	18	

SC: squamous carcinoma; AC: adenocarcinoma; ASC: adenosquamous carcinoma

Table 2. — *Cox proportional hazard analysis of factors related to overall survival (OS).*

Factors	HR	95%CI	*p*
Stage	2.333	1.043-5.218	0.039
Age	0.974	0.920-1.031	0.362
Patient treatment strategy (Consolidation or control)	0.322	0.123-0.843	0.021

HR: hazards ratio, CI: confidence interval

Table 3. — *Side effects in the consolidation group and the control group.*

Group		Consolidation	Control	*p*
Case number		46	38	
Myelosuppression	III degree	11	8	0.19
	IV degree	6	1	
Radiation proctitis	moderate	4	4	0.749
	severe	1 (rectal ulcer)	1 (rectal fistula)	

consolidation group completed three courses of consolidation therapy.

The short-term outcomes were assessed at one month after the treatment course was completed. The majority of patients in the consolidation chemotherapy group achieved complete remission after treatment. The only exception was a single patient who presented with a Stage IIIb adenocarcinoma 4th lumbar vertebra metastasis during the third course of consolidation chemotherapy. All of the control group patients achieved complete remission within one month after treatment. The DFS and local control rate was (46-1)/46 = 97.83% and 100% in the consolidation group, while the PFS and local control rate in the control group were both 100%.

The patients were followed up through June 2015, resulting in a follow-up range of 15 to 54 months with a median follow-up of 34 months. The DFS rates in the consolidation group and the control group were 82.61%

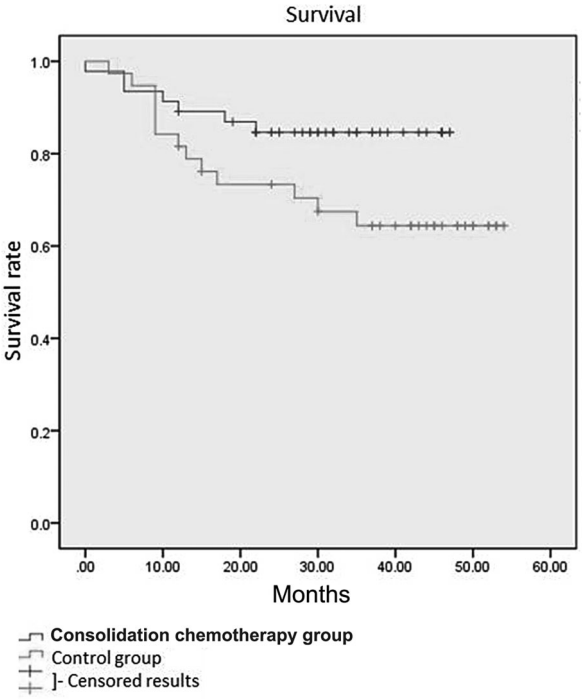

Figure 1. — Comparison of disease free survival (DFS) in the consolidation chemotherapy group and control group. χ^2 =3.450, p = 0.063.

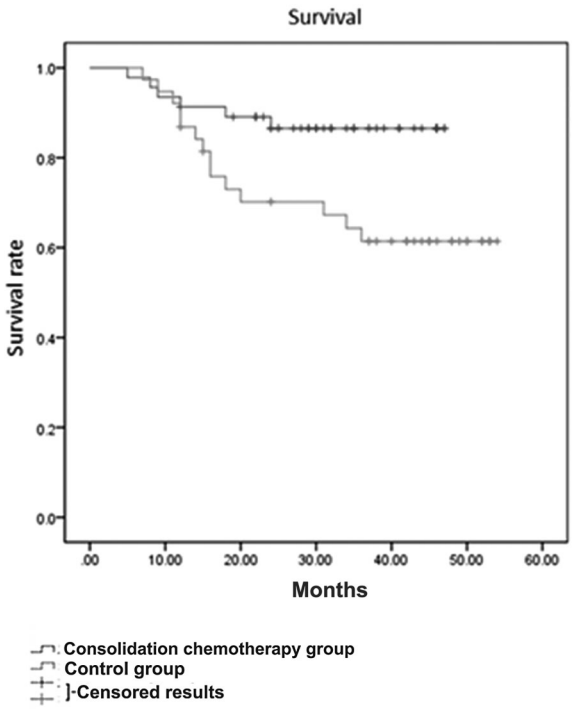

Figure 2. — Comparison of overall survival (OS) in the consolidation chemotherapy group and control group. χ^2 =5.187, p = 0.023.

(38/46) and 57.89% (22/38), respectively, and the OS rates were 84.79% (37/46) and 57.89% (22/38), respectively. The DFS curve of the consolidation group was higher than control group, but the difference was not statistically significant ($p = 0.063$, Figure 1), while the OS was significantly higher in the consolidation group than in the control group ($p = 0.023$, Figure 2).

In the consolidation chemotherapy group, there were seven cases of recurrence or metastasis. This included one case of rib metastasis 22 months after treatment completion; the affected patient is currently undergoing treatment at another hospital. There were also five deaths (one patient died from local recurrence of cervical cancer 18 months after treatment, two patients died from clavicle lymph node metastasis five months after treatment, and two patients died from pulmonary metastasis at ten and 12 months after treatment). Additionally, there was one case of L4 metastases during treatment and one case lost to follow-up at 12 months. In the control group, 14 patients died due to cancer recurrence and metastasis (three cases of pulmonary metastasis at nine, nine, and 12 months after treatment, two cases of supraclavicular lymph node metastasis at nine and 17 months after treatment, two cases of rectal metastasis at nine and 13 months after treatment, two cases of hepatic metastases at three and 30 months after treatment, one case of hip bone metastasis at 13 months after treatment, one case of local recurrence at 27 months after treatment, one case of multiple metastases at six months after treatment, and two cases of metastasis of unknown origin at 15 and 35 months after treatment), and two patients were lost to follow-up (at 12 and 24 months after treatment).

According to the criteria of α=0.05, the factors that were possibly associated with prognosis (such as age, stage [Stage Ib2, IIb, and III], patient group [consolidation chemotherapy group and control group]) were included in the Cox proportional hazard model, and the results showed that the treatment strategy and tumor stage were both associated with the OS rate (Table 2).

The adverse events in both groups were mostly mild and easily treated with symptomatic treatment. In terms of the more severe adverse events in the consolidation group, there were 11 cases of III degree myelosuppression (23.91%) and six cases of IV degree myelosuppression (13.04%). In the control group, there were eight cases of III degree myelosuppression (21.05%) and one case of IV degree myelosuppression (2.63%) (Table 3). All patients recovered after treatment. Although the severe myelosuppression ratio of the consolidation chemotherapy group seemed high, there was no significant difference between the two groups ($p = 0.190$). There were four cases of moderate radiation proctitis in the two groups (consolidation chemotherapy group: 8.70%; control group: 10.52%) and one case of severe radiation proctitis (consolidation chemotherapy group: 2.17%; control group: 2.63%). The differences in these ratios were not significant ($p = 0.749$) (Table 3).

Discussion

The aim of this study was to compare outcomes of patients treated with consolidation chemotherapy alongside concurrent chemoradiotherapy, with patients treated with concurrent chemoradiotherapy alone, and to assess the safety of the consolidation treatment. The results showed that the DFS rates were higher in the consolidation group than the control group but not significantly, and the OS was significantly higher in the consolidation group. The Cox proportional hazard model showed that the patient group and cancer stage were both associated with the OS rate. The rates of severe adverse events were slightly higher in the consolidation group, but this was not significantly different from the control group. These results suggest that consolidation chemotherapy significantly increased patient survival and did not increase the incidence of severe adverse events.

Consolidation chemotherapy has been considered by other studies and they also found similar positive outcomes [12-14]. In a study reported by Zhang *et al.* [14], 28 patients were administered 35 mg/m^2 paclitaxel and 20 mg/m^2 cisplatin weekly for a total of six weeks. Following this, the patients underwent four cycles of consolidation chemotherapy with 135 mg/m^2 paclitaxel and 60 mg/m^2 nedaplatin once every three weeks after concurrent chemoradiotherapy. The median follow-up was 23 months (range, 14-30 months). The two-year local PFS and OS rates were 82% and 93%, respectively. The rate of III degree myelosuppression and severe toxic reaction during chemotherapy was 9%. These results demonstrate that consolidation chemotherapy is effective and well-tolerated. However, some scholars believe that consolidation chemotherapy can increase the side effects of radiation and chemotherapy without improving general PFS and OS [16]. A study that assessed the long term eight-year outcomes of patients treated with consolidation chemotherapy four weeks after concurrent chemoradiotherapy with cisplatin with ifosfamide for four cycles three times a week showed that OS was 74.6% [4]. Therefore that study suggests that consolidation chemotherapy is beneficial long-term; however, like most of the studies, it did not compare results between patients treated with and without consolidation chemotherapy. Therefore, further studies are needed to determine whether patients benefit from consolidation chemotherapy. This is also important because the referenced studies did not evaluate pathologic patterns of cervical cancer or features such as tumor differentiation or LVSI, all of which affect prognosis.

In the current study, the average patient age was 46 years. This is younger than the peak incidence of cervical cancer, which occurs at an age of 50 to 55 years. This difference may explain the high number of patients (46.43% (39/84)) who presented with adenocarcinoma and adenosquamous carcinoma in the present study. Indeed, this rate is higher

than in the general population and is concordant with reports that adenocarcinoma patients are being diagnosed at a younger and younger age compared to squamous carcinoma patients [17, 18]. Among the patients in the current study who experienced recurrence, there were only two cases of local recurrence. There were also two cases of rectal metastasis, which may have resulted from local tumor recurrence that penetrated into the rectum. The remainder of the recurrence cases involved distant metastasis, a phenomenon that may be related to the specific pathological condition of the patient cohort, in which a high proportion of adenocarcinoma and squamous cell carcinoma patients with poor tumor differentiation and LVSI was present. These pathological features result in easy metastasis and recurrence. In the consolidation group, the OS was 82.61%, whereas in the control group it was 57.89%. This difference was significant and although there was a higher rate of severe adverse events in the consolidation group than the control group in this study the differences were not significant, consistent with the results presented in a study conducted by Vale *et al.* [11], who reported that severe myelosuppression was present in 36.96% (17/46) of patients undergoing consolidation chemotherapy and only 23.68% (9/38) of control patients; however, this difference was not statistically significant ($p > 0.05$).

This study has some limitations. Being a study based in a single center, the sample size was relatively small; a multicenter study would add more weight to these results. As a retrospective study the patients were not randomly selected to receive treatment so this may have introduced some bias in the results.

Conclusion

Based on the results of this study, it appears that consolidation chemotherapy can improve survival rate without causing additional side effects. However, additional studies with larger cohorts are necessary, as well as studies analyzing how pathological pattern and cancer stage together influence the outcome of analysis.

Acknowledgements

The authors thank their colleagues Wan-xia Wei, Dongxing Liu, Li-ming Mei, Mei-hong Ao and Jun Lei, and the Department of Science and Education of Maternal and Child Health Care Hospital of Jiangxi of China. This study was supported by Health department of Jiangxi province of China, project number: 20123118.

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