

Efficacy and prognostic factors of concurrent chemoradiotherapy in patients with stage Ib3 and IIa2 cervical cancer

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ABSTRACT

Objectives: We investigated the efficacy, side effects, and prognostic factors of concurrent chemoradiotherapy for patients with stage Ib3-IIa2 cervical cancer.

Material and methods: We conducted a retrospective analysis of clinicopathologic data from 73 patients with stage Ib3-IIa2 cervical cancer who received concurrent chemoradiotherapy from January 2008 to December 2013 in our hospital. Overall response and disease control rates were used to evaluate short-term outcomes; the 3-year and 5-year disease-free survival and overall survival were used to evaluate long-term efficacy. Toxicity reactions and prognostic factors were recorded.

Results: With concurrent chemoradiotherapy, overall response and disease control rates were 91.78% and 97.26%, respectively. The 3-year disease-free and overall survival were 80.82% and 83.56%; the 5-year disease-free and overall survival were 75.34% and 79.45%, respectively. All side effects were tolerated and potentially alleviated by symptomatic treatment. Tumor pathological type, differentiated degree, primary tumor size and squamous cell carcinoma antigen levels before and after treatment were closely related to survival (univariate analysis; $p < 0.05$). Pathological type, primary tumor size and squamous cell carcinoma antigen levels one month after treatment were independent prognostic factors for long-term outcome (multivariate analysis).

Conclusions: Short- and long-term efficacy of concurrent chemoradiotherapy for stage Ib3-IIa2 cervical cancer is well-determined and tolerable. Patients with adenocarcinomas, tumor diameter ≥ 5 cm and squamous cell carcinoma antigen levels ≥ 1.5 ng/mL (one month after treatment) had poor prognosis and should be assessed further.

Key words: concurrent chemoradiotherapy; efficacy; locally advanced cervical cancer; prognostic; retrospective

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INTRODUCTION

Patients with stage Ib3 and IIa2 cervical cancer have a poorer prognosis because of the larger tumour volume and difficult control of the local lesions. The 5-year survival rate of patients was reported to be approximately 50%–60% [1, 2]. At present, there is no uniform standard therapy mentioned in the NCCN guidelines (2019). The options include pelvic external irradiation + cisplatin (concurrent chemotherapy) + vaginal brachytherapy (level 1 evidence); extensive hysterectomy + pelvic lymphadenectomy \pm para-abdominal aortic lymph node sampling (level 2B evidence); and post-radiotherapy + assisted hysterectomy (level 3 evidence) [3]. However, the best treatment is controversial. We reviewed the clinical data of 73 patients with stage Ib3 and IIa2 cervical cancer treated with concurrent chemoradiotherapy at

our hospital and evaluated the short-term and long-term efficacies and influencing factors associated with chemoradiotherapy in order to provide evidence for guiding clinical treatment.

Objectives

To explore the efficacy and adverse reactions of concurrent chemoradiotherapy for stage Ib3 and IIa2 cervical cancer and to discuss the related factors affecting prognosis, so as to provide reference for the follow-up clinical treatment.

MATERIAL AND METHODS

General information

The clinical and pathological data of 73 patients with stage Ib3 and IIa2 cervical cancer who received concurrent

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chemoradiotherapy in the Gynecological Oncology Department of our hospital (Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Beijing, China.) from January 2008 to December 2013 were collected. The entry criteria consisted of the following: 1. Cervical squamous cell carcinoma or adenocarcinoma confirmed by pathology; 2. 2018 International Federation of Gynaecology and Obstetrics (FIGO) stage Ib3 or IIa2 confirmed by at least two doctors at a level of deputy director of gynaecological oncology or above; 3. patients initially treated with concurrent chemoradiotherapy; 4. no serious heart, liver, kidney, brain or hematopoietic system diseases; no history of immune-related diseases; and no other tumours. 5. The clinical data are complete. Exclusion criteria: 1. Complicated with other tumours; 2. Cervical cancer of other pathological types, such as adenosquamous carcinoma, clear cell carcinoma; 3. History of previous radiotherapy or chemotherapy; 4. Refusal to participate in the study. General information for the patients is shown in Table 1.

Therapy

All patients were treated with concurrent chemoradiotherapy. Radiotherapy consisted of external beam radio-

therapy and intracavitary radiotherapy. The external beam radiotherapy was performed with a Cobalt-60 machine. The prescription of external beam radiotherapy for whole pelvic was 50 Gy/2.0 Gy/25 f. When the external radiation dose reaches 20–30 Gy, the intracavitary radiotherapy started. Intracavitary radiotherapy was performed with a 192-Iridium (Ir) post-installed machine, 6–7 times at point A, for a total of 36–42 Gy. Concurrent chemotherapy was given during the radiotherapy period. The chemotherapy regimen was either a single cisplatin intravenous infusion (40 mg/m²) once a week for five–six cycles or 5-fluorouracil (5-FU; 3–4 g/m², 96-hour continuous intravenous pump infusion) + cisplatin (20 mg/m², 1–4 days), once every four weeks for two–three cycles.

Efficacy and adverse reactions

All patients underwent gynaecological examinations, pelvic and abdominal computed tomography (CT) scans or magnetic resonance imaging (MRI), and chest X-ray imaging before and after treatment. The curative effect of treatment was evaluated accordingly. The adverse reactions of all patients were recorded during chemoradiotherapy and during the follow up period, including gastrointestinal reactions, nephrotoxicity and urinary system reactions, and bone marrow suppression. These adverse reactions were assessed by World Health Organization (WHO) criteria for acute and subacute toxicities [4].

Follow-up began at the end of treatment and continued until December 31, 2018. Patients were followed every 3 months for 2 years and every 6 months thereafter. Follow-up assessments included a gynecological examination, a ThinPrep cytologic test (TCT), blood squamous cell carcinoma antigen (SCC-Ag) levels, basin abdominal computed tomography (CT) or magnetic resonance imaging (MRI), and chest X-ray imaging. If no abnormality was observed, TCT was checked once a year, and CT/MRI and X-ray images were checked every six months.

During the follow-up period patients were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. The RECIST criteria comprises four categories: complete remission (CR), partial remission (PR), disease progression (PD), and disease stability (SD).

Short-term efficacy was evaluated by CR + PR and disease control rate (CR + PR + SD) three months after treatment and long-term efficacy was evaluated by the 3-year and 5-year disease-free survival (DFS) and overall survival (OS) rates.

Criteria

We defined the survival time as the period from the beginning of treatment to the last follow-up or death. Tumor-free survival time was defined as the time of recur-

Table 1. Univariate analysis of prognostic factors

Factors	N [%]	5-year survival rate	p value
Age [year]			
≤ 40	21 (28.77)	76.3%	0.709
> 40	52 (71.23)	80.8%	
Pathological Type			
Squamous	63 (86.30)	82.5%	0.034
Adenocarcinoma	10 (13.70)	60.0%	
Stages			
Ib3	50 (68.49)	80.0%	0.137
IIa2	23 (31.51)	78.3%	
Differentiation			
G1	6 (8.22)	83.3%	0.046
G2	53 (72.60)	81.1%	
G3	14 (19.18)	71.4%	
Diameter			
< 5 cm	61 (83.56)	83.6%	0.032
≥ 5 cm	12 (16.44)	58.3%	
SCCA* before treatment			
≥ 1.5 ng/mL	49 (67.12)	77.6%	0.038
< 1.5 ng/mL	24 (32.88)	83.3%	
SCCA after treatment (1 month)			
≥ 1.5 ng/mL	13 (17.81)	53.8%	0.012
< 1.5 ng/mL	60 (82.19)	85.0%	

SCCA — squamous cell carcinoma antigen

rence, metastasis, or last follow-up from the beginning of treatment of any site.

Statistical analysis

The experimental data are presented as mean ± standard deviation (SD). Kaplan-Meier method was used for survival analysis. The chi-square test was used for univariate analysis and logistic regression was used for multivariate analysis. p-values < 0.05 were considered statistically significant. Calculations were carried out using the Statistical Package for the Social Sciences (SPSS for Windows, version 19.0, SPSS Inc., Chicago, IL, USA).

RESULTS

Short-term and long-term efficacies

The average follow-up time was 68.9 months. The 3-year follow-up rate was 98.63%, and the 5-year follow-up rate was 97.26%. During the follow-up period, 18 of 73 patients relapsed (24.66%); 15 died (20.54%) after relapse, and 3 survived with tumours (4.11%). Three months after the end of treatment there were 60 cases of CR, 7 cases of PR, 4 cases of SD, and 2 cases with PD. The effective rate (CR + PR) was 91.78%, and the disease control rate (CR + PR + SD) was 97.26%. The 3-year DFS rate was 80.82%, and the total survival rate was 83.56%. The 5-year DFS rate was 75.34% and the total survival rate was 79.45%.

Adverse effects

The incidence of chemotherapy-related gastrointestinal reactions, bone marrow suppression, and nephrotoxicity were 56.16% (41/73), 58.90% (43/73), and 5.48% (4/73), respectively, all of which were grades I–II. The incidence of radiation-related proctitis and cystitis was 21.92% (16/73) and 19.18% (14/73), respectively. All adverse reactions were tolerated and remitted after symptomatic treatment. The therapy was completed as planned.

Prognostic factors

Multivariate analysis showed that pathological type, primary tumor size and SCC-Ag levels one month after treatment were independent factors affecting long-term efficacy (p < 0.05; Tab. 2). The respective survival curves are shown in Figure 1–3.

Table 2. Multivariate analysis of prognostic factors				
Factors	β	p	OR	95% CI
Pathological type	0.191	0.023	1.958	1.473–3.166
Diameter	0.096	0.040	1.716	1.304–2.316
SCCA after treatment (1 month)	0.087	0.030	1.804	1.286–2.805

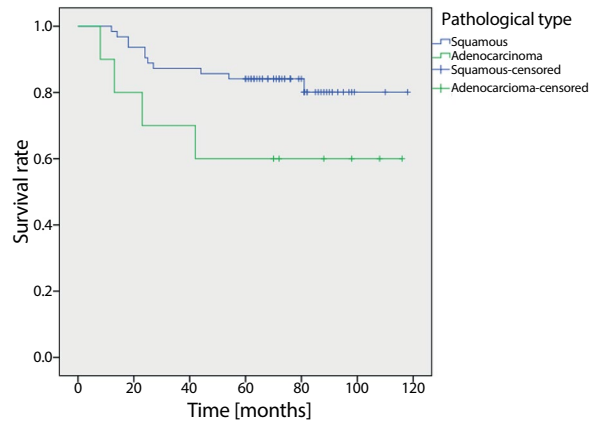


Figure 1. Survival curves of different pathological types of cervical cancer

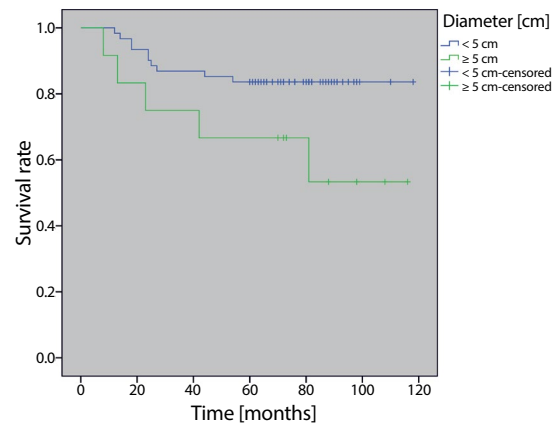


Figure 2. Survival curves of different tumor diameters

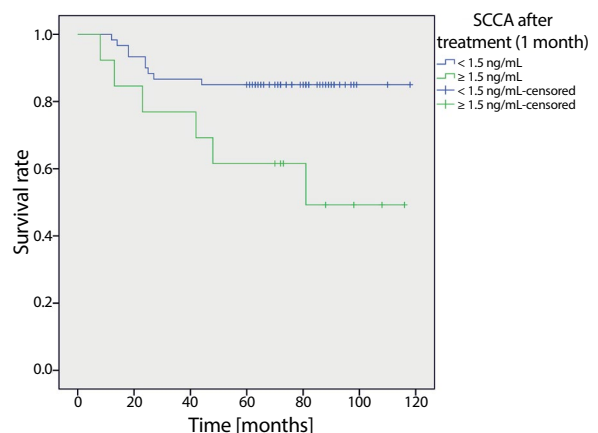


Figure 3. Survival Curves of Different SCCA Values after treatment (1 month)

DISCUSSION

According to the FIGO classification, locally advanced cervical cancer broadly refers to Ib3–IVa tumors and more

specifically to Ib3 and IIa2 tumors. Locally advanced cervical cancers have a tumor diameter larger than 4 cm. Surgery is often difficult in patients with locally advanced cervical cancer, and there are many pathological high-risk factors after surgery that can increase the risk for recurrence and metastasis [5]. At present, commonly used treatment methods are neoadjuvant chemotherapy plus surgery, post-radiotherapy supplementary surgery, and concurrent chemoradiotherapy [6].

Previous studies have shown that concurrent chemoradiotherapy can enhance the sensitivity of patients to radiotherapy [7], improve the 5-year survival rate, and increase the local control rate of tumors [8]. The mechanism may be as follows: 1. Chemotherapy is a systemic therapy, which can kill distant metastasis and local tumor cells, weaken the invasiveness of tumor; 2. Chemotherapy prevents the cell damage and repair caused by radiotherapy; 3. Chemotherapy and radiotherapy act on different phases of cell cycle and complement each other, but do not prolong the overall treatment time; 4. Chemotherapy can reduce the proportion of hypoxic cells and increase the effect of tumor cells on radiotherapy Sensitivity. Five randomized clinical trials of concurrent chemoradiotherapy for stage Ib–IVa cervical cancer reported in the United States in 1999 showed that current chemoradiotherapy reduced the risk of death by 30–50% compared with radiotherapy alone. Datta et al. [9] analyzed the curative effect of radical concurrent chemoradiotherapy, radical concurrent radiotherapy, and postoperative concurrent radiotherapy and chemotherapy in the treatment of Ib2 and IIa2 cervical cancer, and found that the curative effect of concurrent chemoradiotherapy was better than the other two groups. Currently, the National Cancer Institute recommends platinum-based concurrent chemoradiotherapy as the standard treatment for locally advanced cervical cancer [10]. Cisplatin is one of the most sensitive chemotherapeutic drugs [11]. The NCCN Guidelines® for cervical cancer in the United States in 2019 also recommend that the treatment of stage Ib3 and IIa2 cervical cancer should be the combination of pelvic radiotherapy, brachytherapy, and cisplatin-containing concurrent chemotherapy, which is the level-1 evidence.

The current study results showed that the effective rate of radical concurrent radiotherapy and chemotherapy was 91.78%. The 3-year survival rate was 83.56%, and the 5-year survival rate was 79.45%, which was similar to previous studies. Our results indicated that concurrent chemoradiotherapy was effective in the treatment of stage Ib3 and stage IIa2 cervical cancer.

Although chemoradiotherapy acts on tumor cells and coordinates and improves the therapeutic effect, it is not without adverse effects. The main reported adverse effects were radiation enteritis, radiation cystitis, digestive tract

reactions, bone marrow suppression, and damage to liver and kidney functions [12]. Compared with concurrent radiotherapy and chemotherapy, neoadjuvant chemotherapy plus surgery and post-operative supplementary radiotherapy have different complications. Fabri [13] has reported no difference in adverse reactions between neoadjuvant chemotherapy and concurrent chemoradiotherapy. Dang et al. [14] compared the complications of concurrent radiotherapy and chemotherapy with that of radiotherapy alone and found that concurrent radiotherapy and cisplatin-based chemotherapy could increase the therapeutic effect in cervical cancer patients and significantly improve the therapeutic benefit without increasing adverse reactions.

Like the above studies, the current study showed that the adverse events related to chemotherapy were all grades I–II. The incidences of radiation-related proctitis and cystitis were 21.92% and 19.18%, respectively, which were tolerable.

However, concurrent chemoradiotherapy still face many problems: 1. The lymph node metastasis rate of local advanced cervical cancer is high, concurrent chemoradiotherapy can not accurately evaluate whether the lymph node metastasis or the location of metastasis, so it's difficult to determine the radiotherapy field; 2. For young patients, they are faced with the problem of ovarian function loss; 3. In addition to radiation cystitis, radiation enteritis and other radiotherapy specific adverse reactions, there are also literature reports that the long-term adverse reaction rate of concurrent chemoradiotherapy is higher than that of radiotherapy alone, especially myelosuppression and digestive tract reaction, which seriously affects the quality of life of patients [15]; 4. In some developing countries, radiotherapy equipment and afterloading equipment are insufficient; 5. The survival rate of concurrent chemoradiotherapy for local advanced cervical cancer is still not ideal. All above these questions require further observation and research.

At present, there are few reports on the prognostic factors of Ib3 and IIa2 cervical cancer treated with radical concurrent chemoradiotherapy. Kim [16] analyzed the clinical data of 174 patients with stage Ib1–IVa cervical cancer who received radical concurrent chemoradiotherapy. Stage, size, and clinical response had significant effects on OS. PFS was also affected by the level of SCC-Ag after treatment. Patients with normal SCC-Ag levels had a longer DFS after treatment. Chen [7] performed a multivariate analysis of 125 patients with stage Ib2–III cervical cancer who received intensity-modulated radiation therapy combined with concurrent chemotherapy. Chen showed that cervical adenocarcinoma and lymph node metastasis were independent adverse prognostic factors for locally advanced cervical cancer. Endo [17] found that tumor diameter > 6 cm, lymph node enlargement, and distant metastasis were significantly and independently associated with adverse outcomes in

patients undergoing radical concurrent chemoradiotherapy. Queiroz [18] showed that in stage Ib and IIa cervical cancer, there was a poor prognosis for patients with lymph node metastasis and SCC-Ag levels that did not decrease to 1.5 mg/L one month after treatment.

Our study results supported findings of previous studies in terms of the relationship of survival rate to pathological type, differentiation degree, primary tumor size and SCC-Ag value of blood before and after treatment. Limitations of our study include the retrospective design and small number of cases. Prospective studies that include larger patient cohorts are needed for further research.

CONCLUSIONS

In conclusion, we analyzed the efficacy and adverse reactions of concurrent chemoradiotherapy for Ib3 and IIa2 cervical cancer and discussed the related factors affecting prognosis. Our findings indicate that concurrent chemoradiotherapy is an effective and tolerable treatment for this cancer. We should pay more attention to patients with adenocarcinoma, tumor diameter ≥ 5 cm and blood SCC-Ag levels ≥ 1.5 ng/mL one month after treatment and explore a more adequate treatment plan in order to improve the survival rate. A multi-center, large-sample prospective study is required to further confirm the validity of our conclusions.

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WM Kong: Critical revision of the manuscript for important intellectual content

Y Liu: Acquisition of data

D Song: Statistical analysis

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