·Original Article·

Efficacy of concurrent chemoradiotherapy plus adjuvant chemotherapy on advanced cervical cancer

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[Abstract] Background and Objective: Concurrent chemoradiotherapy for cervical carcinoma develops rapidly and has become a common and standard therapy in recent years. Both the local control rate and survival rate of patients were increased and the risk of death fell by 30%–50%. This study aimed to explore the efficacy of concurrent chemoradiotherapy plus adjuvant chemotherapy on and the treatment compliance of the patients with advanced cervical squamous cell carcinoma. **Methods:** A total of 156 patients with stage IIa–IIIb cervical squamous cell carcinoma were randomly divided into the concurrent chemoradiotherapy group (experimental group) and radiotherapy group (control group). Intracavity and external beam radiation therapy were administered. At point A, 40–48 Gy were given by 10–12 fractions; at point B, 46–50 Gy were given by 23–25 fractions. In the same time, experimental group was treated by cisplatin (DDP, 40 mg) on day 1, repeated every week. Ten days after radiation therapy, TP regimen was administered as adjuvant chemotherapy. **Results:** For the experimental and control groups, the objective response rates were 88.61% and 75.32%, 1-year survival rates were 88.57% and 70.77%, 1-year local control rates were 81.43% and 64.62%, 3-year survival rates were 82.14% and 57.69%, and 3-year local control rates were 75.00% and 46.15%, with significant differences ($P < 0.05$). Quality of life of all patients were significantly improved after treatment ($P < 0.05$). **Conclusion:** Concurrent chemoradiotherapy plus adjuvant chemotherapy for advanced cervical cancer can improve short-term and long-term survival and local control rates of patients, improve the quality of life, and the toxicity can be tolerated.

Key words: Cervical neoplasm, concurrent chemoradiotherapy, short-term efficacy, local control rate

Cervical cancer is a kind of common malignant tumor that seriously threatens female health. At present, surgery or radiotherapy is the main treatment modality for cervical cancer. Radiotherapy applies to all of the stage I–IV patients. It is confirmed by clinical practice that radical radiotherapy could achieve similar efficacy to surgery, but about 30%–40% of the patients had treatment failure because of local failure or distant metastasis. Local failure is probably relevant to large tumor size, more hypoxic calls, parametrial infiltration which is insensitive to local radiotherapy, sub-infiltration focus which is beyond radiation filed and could not be controlled by radiotherapy, and limitations of radiation dose. Distant metastasis is relevant to intravascular tumor thrombus, fusion of metastatic lymph nodes, and late tumor stage. For the patients with locoregional advanced disease, improving local control rate and preventing distant metastasis are the keys to balance the treatment benefits. Chemotherapy agents could inhibit the repair of cells damaged by radiation, and concurrently synchronize tumor cells to the radiosensitive cycle. It is confirmed that cisplatin-based (DDP 40 mg/m^2) concurrent chemoradiotherapy could significantly reduce local treatment failure, improve the overall and disease-free survival of patients with cervical cancer, decrease the risk of death by 30%–50%[1,2], and improve the prognosis. Eifel *et al.*[2] reported the results of the RTOG (9001) prospective randomized controlled clinical trial which enrolled 388 patients with cervical cancer of more than 5 cm in diameter or infiltrated pelvic lymph nodes. The patients in the

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concurrent chemoradiotherapy group were given 45 Gy with pelvic plus para-aortic external beam radiotherapy, 2 cycles of adjuvant chemotherapy with DDP + 5-fluorouracil (5-FU) regimen, followed by intracavity radiotherapy. Compared with the radiotherapy alone group, with a median follow-up of 43 months, the 5-year survival rates were 73% and 58% (P = 0.004), and the 5-year progression-free survival rates were 67% and 40% (P < 0.001), respectively. The radiotherapy alone group had higher local recurrent rate, higher distant metastasis rate, and fewer acute adverse events than the concurrent chemoradiotherapy group (P < 0.001). In 2004, the US National Cancer Institute published the GOG90-01 clinical report and suggested that for the patients with cervical cancer, DDP-based chemotherapy should be given concurrently with radiotherapy. This report represents the change of treatment pattern for cervical cancer, and DDP-based concurrent chemoradiotherapy has become the standard treatment for patients with cervical cancer who have received surgery and / or radical radiotherapy. On the basis of concurrent chemoradiotherapy, we gave the enrolled patients docetaxel (the third generation chemotherapy agent) based adjuvant chemotherapy regimen to control and reduce the risk of cervical lymph node metastasis at high position and / or distant metastasis, hence further improve long-term survival. However, the adverse events such as hematological toxicity and gastrointestinal reaction increased during concurrent chemoradiotherapy and adjuvant chemotherapy, and have partially become the main factors that influencing whether patients could complete the entire treatment. The present paper explored the treatment efficacy and compliance of concurrent radiotherapy plus adjuvant chemotherapy using TP regimen, and how to deal with them during treatment in order to reduce the influence of adverse events on treatment procedure.

Patients and Methods

Inclusive criteria

All enrolled patients had pathologically confirmed cervical squamous cell carcinoma. The FIGO 2003 staging criteria was adopted basing on the results of CT or MRI scan and vagino-recto-abdominal examination: stage II, the cancer has grown beyond the cervix, with parametrial invasion not spreading to the walls of the pelvis, or with vaginal invasion not spreading to the lower 1/3 part; stage III, the cancer has spread to the walls of the pelvis or the lower 1/3 of the vagina, or patients with hydronephrosis or non-functioning kidney caused by tumor. Karnofsky scores of all patients were all ⩾ 70. Written informed consent was signed by each patient.

Enrolled patients and grouping

The 156 patients with stage II and III cervical squamous cell carcinoma were enrolled between June 2005 and October 2009: 81 at stage II and 75 at stage III. The median age was 52.4 years (range, 42-65 years). After tumor stage stratification (stage II or III), the patients were allocated by lot to control group (77 cases) and experimental group (79 cases). Till April 2010, 135 patients were followed up for over 1 year after treatment and 54 were followed up for over 3 years. The clinical data of the two groups were comparable as confirmed by the χ^2 test.

Treatment methods

The patients in the control group received radiotherapy combined with 3 cycles of adjuvant chemotherapy using TP regimen, whereas those in the experimental group received concurrent chemoradiotherapy combined with 3 cycles of adjuvant chemotherapy using TP regimen. Cisplatin 40 mg/d1 was used in concurrent chemoradiotherapy, repeated every week. TP regimen adjuvant chemotherapy began at the tenth day after the completion of radiotherapy: docetaxel 60 mg/m^2 was used on day 1, cisplatin 40 mg on days 1–3, repeated every 21 days.

Radiotherapy was administered by external beam radiation and intracavity after-loading therapy. Conventional box-like radiation or conformal fields by 46–50 Gy/23–25f was used in external beam radiotherapy. Dose of 40–48 Gy/10–12f, 2 f/w was given to point A in intracavity after-loading therapy. External beam radiotherapy was delivered during and on the same day of after-loading therapy, and the whole radiotherapy finished in 5–6 weeks.

During radiotherapy and 1 month after radiotherapy, all patients received vaginal irrigation and uterus unblocking to keep the cervical canals open.

Evaluation criteria

Evaluation contents: (1) the WHO short-term standard of therapeutic efficacy was adopted to evaluate short-term treatment efficacy; (2) the 1- and 3-year survival rates and local control rates were evaluated according to the results of vaginal examination and pelvic CT/MRI scan during follow-up; (3) the patients' quality of life before and after treatment were evaluated according to the quality of life in patients with tumor criteria (QOL, 1990, China); (4) the incidence of adverse events during treatment was evaluated according to the common terminology criteria for adverse events (V3.0) established by the U.S. National Institutes of Health, and all the adverse events were graded I–V. In clinical practice, the occurrence of grade II adverse events

was acceptable, so only adverse events over grade III were evaluated, mainly including diarrhea of ⩾ 7 stools which required intravenous fluids, nausea which required intravenous fluids, vomiting of ⩾ 6 episodes per day over baseline which required intravenous fluids, and blood/bone marrow adverse events. The patients were followed up by hospital visits, phone calls, and letters, and the follow-up rate was 100%.

Statistical analysis

The SPSS13.0 software was used in statistical analysis. The χ^2 test was used to compare inter-group clinical data such as patients' age and physical condition, and to compare clinical treatment efficacy and adverse events over grade III during treatment. The *t* test was used to compare quality of life before and after treatment.

Results

Comparison of short-term efficacy

The short-term response rate was significantly higher in the experimental group than in the control group (88.61% vs. 75.32%, $P = 0.031$) (Table 1). Stage-based stratified analysis showed that the response rate of stage III patients was significantly higher in the experimental group than in the control group ($P = 0.003$), and the number of patients with PD decreased, indicating that the concurrent chemoradiotherapy had certain short-term treatment effects on patients at advanced stage.

Table 1 Short-term outcomes of control group and experimental group

Group	Cases	CR (%)	PR (%)	SD (%)	PD (%)	CR+PR (%)	χ^2	*P*
Control	77	42(54.55)	16(20.78)	13(16.88)	6(7.79)	58(75.32)		
II	39	31(79.49)	2(5.13)	4(10.25)	2(5.13)	33(84.62)		
III	38	11(28.95)	14(36.84)	9(23.68)	4(10.53)	25(65.79)		
Experimental	79	55(69.62)	15(18.99)	6(7.59)	3(3.80)	70(88.61)	4.672	0.031
II	42	35(83.33)	3(7.14)	3(7.14)	1(2.38)	38(90.48)	0.642	0.423
III	37	20(54.05)	12(32.43)	3(8.11)	2(5.41)	32(86.49)	8.731	0.003

CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease.

Comparison of 1- and 3-year survival rate and local control rate

The 1- and 3- year survival and local control rates were significantly higher in the experimental group than in the control group ($P < 0.05$) (Table 2). For the stage II patients, the 3-year survival rate and local control rate in experimental group were significantly improved when compared with the control group ($P < 0.05$). For the stage III patients, the 1-year survival rate and local control rate in experimental group were significantly improved when compared with control group ($P < 0.05$).

Comparison of quality of life before and after treatment

The quality of life of patients in both the control group and the experimental group was significantly improved after treatment ($P < 0.05$) (Table 3). However, the difference between the two goups was not significant ($t = -1.34$, $P = 0.183$).

Table 2 The 1- and 3-year overall survival (OS) rates and local control rates (LCR) of the control group and experimental group

Group	Cases	1-year OS (%)	1-year LCR (%)	Cases	3-year OS (%)	3-year LCR (%)
Control	65	46(70.77)	42(64.62)	26	15(57.69)	12(46.15)
II	32	31(96.88)	30(93.75)	14	9(64.29)	9(64.29)
III	33	15(45.45)	12(36.36)	12	6(50.00)	3(25.00)
Experimental	70	62(88.57)[a]	57(81.43)[b]	28	23(82.14)[c]	21(75.00)[d]
II	36	36(100.00)	36(100.00)	16	15(93.75)	15(93.75)
III	34	26(76.47)	21(61.76)	12	8(66.67)	6(50.00)

Up to now, 135 patients were followed up for no less than 1 year: 65 in the control group and 70 in the experimental group. Fifty-four patients were followed up for no less than 3 years: 26 in the control group and 28 in the experimental group. a: $\chi^2 = 6.61$, $P = 0.010$; b: $\chi^2 = 4.87$, $P = 0.027$; c: $\chi^2 = 3.87$, $P = 0.049$; d: $\chi^2 = 4.72$, $P = 0.030$.

Table 3 Quality of life of the experimental group and control group before and after treatment

Group	Cases	Before treatment	After treatment	*t* value	*P*
Control	77	38.74 ± 6.15	45.72 ± 5.88	−7.20	< 0.01
Experimental	79	39.73 ± 5.74	48.63 ± 3.75	−11.53	< 0.01

Comparison of adverse events between experimental group and control group

More grade III–IV diarrhea, nausea, and blood/bone marrow adverse events were seen in then experimental group than in the control group ($P < 0.05$) (Table 4).

Table 4 Adverse events in the control group and experimental group during treatment

Adverse event (III–IV)	Control group (n = 77)	Experimental group (n = 79)	χ^2	*P*
Diarrhea	31(40.26%)	50(63.29%)	8.29	0.004
Lack of appetite	43(58.44%)	59(74.68%)	6.12	0.013
White blood cell	31(40.26%)	46(58.23%)	5.04	0.025
Hemoglobin	22(28.57%)	38(48.10%)	6.28	0.012
Platelet	14(18.18%)	20(25.32%)	1.17	0.281

Discussion

Cervical cancer has a high occurrence in female, and the incidence has presented a trend of increasing and toward younger age in recent years. In China, surgery (Ia–Ib) and radiotherapy are mainly used to treat cervical cancer, and the 5-year survival rate of patients with early stage cervical cancer was around 80% –90% [3]. However, because locally advanced cervical cancer is usually accompanied by high risk factors such as surrounding tissue infiltration, vessel cancerous embolus, and lymph node metastasis, the efficacy of radiotherapy alone has not further improved for years. The reason might relate to tumor pathologic type, size, more hypoxic cells, radiation dose, and limitation of normal tissue tolerance. As a result, the current treatment modality lays emphasis on the improvement of treatment intensity and combined treatment which consists of radiotherapy, chemotherapy, and biological therapy. During the past 10 years, the GOG, RTOG and SWOG groups have published plenty of prospective randomized controlled clinical trials with large sample size on platinum-based concurrent chemoradiotherapy. Their reports showed that concurrent chemoradiotherapy have improved the response rate and reduced modality of the patients with advanced/recurrent cervical cancer.

Concurrent chemoradiotherapy has distinct significance for the improvement of local control rate. It also demonstrates the importance of controlling cervical lymph node metastasis at high position and distant metastasis, recurrence and reducing the death. Therefore, selecting proper adjuvant chemotherapy regimen and developing characteristic targeted therapy agents are the key to improve the efficacy. Docetaxel combines with the free globular protein, promotes globular protein to assemble to stable microtubules, inhibits its disaggregation, helps to form and fix microtubule bundles, and consequently inhibits the mitosis[4,5]. At the same time, it could synchronize cells to M phase, which is the most sensitive to radiation, and thus enhances the cytotoxic effect of radioactive rays. In vitro experiment has confirmed that both docetaxel and cisplatin are cell cycle-specific radiosensitizers. In addition, they can also promote the reoxygenation of anoxic cells and induce the apoptosis of tumor cells. The efficiency of docetaxel combined with cisplatin was 30% –50% in treating locally advanced cervical cancer[6]. The efficacy of paclitaxel plus carboplatin on recurrent or persistent cervical cancer has been evaluated by a trial, and the results showed that 4 out of the 15 patients got complete remission and 5 got partial remission with a response rate of 60%, and median survival time was 17 months (4–39 months) [5]. Because the hematopoiesis volume of the pelvis accounts for around 25% of the total hematopoiesis volume of human body, and carboplatin could cause relatively severer hematological toxicity, the US National Cancer Institute has classified cisplatin as the standard treatment for cervical cancer. The present study took the regimen of docetaxel plus cisplatin to cooperate with concurrent chemoradiotherapy, expecting to improve the long-term treatment outcome and reduce metastasis for the patients with locally advanced cervical cancer.

Our results showed that compared with control group, the overall short-term outcomes, 1- and 3-year survival rates

of experimental group were significantly higher ($P < 0.05$), which was similar to the results from Green *et al*.[7] Stage-based stratified analysis showed that in stage III patients, the differences in short-term efficacy, 1-year survival and local control rates between experimental group and control group were significant ($P < 0.05$), whereas the differences in 3-year survival and local control rates were not significant. There was no significant difference on short-term efficacy in stage II patients between experimental group and control group, showing that concurrent chemoradiotherapy could achieve good overall treatment responses in these patients, and the difference of treatment outcome awaits longer follow-up and observation. For the 30 stage II patients who had been followed up for over 3 years, the difference of 3-year survival and local control rates between experimental group and control group were significant ($P < 0.05$). The improvement of long-term survival rate by concurrent chemoradiotherapy might more depend on the condition of local control.

Our results showed that the quality of life of all enrolled patients was significantly improved after treatment ($P < 0.05$) mainly because of the improvement of local symptoms. The patients' diet after treatment, degree of comfort, recognition of disease, heightened confidence on disease treatment and rehabilitation took large proportions in the improvement of quality of life.

It was proved that concurrent chemoradiotherapy plus adjuvant chemotherapy is a relatively better treatment modality for cervical cancer[8,9], and helped to achieve satisfactory long-term survival rate and improved physical strength and quality of life. The shortcoming of this treatment modality is the high incidence of adverse events such as diarrhea, vomiting, and hematological toxicity[10]. Our results showed that the acute toxicity was more and severer in the experimental group than in the control group. It was observed that part of the adverse events related closer to the treatment method and procedure. For example, the number of patients who suffered from grade III–IV diarrhea during concurrent chemoradiotherapy and grade III–IV vomiting and hematological toxicity during adjuvant chemotherapy was significantly higher in experimental group than in control group ($P < 0.05$), and the time needed for patients' recovery was longer. Clinically, intravenous fluids should be given to the patients to maintain the electrolytes stable and guarantee the requirements for calorie and vitamins, biological preparation should be given to maintain the immune status and reduce the hematological toxicity, vaginal irrigation should be given every day until one month after treatment, and uterus unblocking should be given weekly for four times. With the measures mentioned above, patients could endure treatment, and the quality of life after treatment is guaranteed.

In short, concurrent chemoradiotherapy plus adjuvant chemotherapy using TP regimen could improve the short-term efficacy, 3-year survival rate and quality of life for patients with locally advanced cervical cancer, and is a satisfactory treatment modality.

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