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Concomitant chemoradiotherapy versus pure radiotherapy in locally advanced cervical cancer: a retrospective analysis of complications and clinical outcome

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Summary

Purpose: To assess the complications and clinical outcomes of concurrent chemoradiotherapy (CCRT) or pure radiotherapy (RT) in local advanced cervical carcinoma (LACC) patients. *Materials and Methods:* A retrospective study was carried out in 113 consecutive LACC (FIGO Stage IB2-IIIB) patients, of whom 68 received CCRT; the others received pure RT. Five-year overall survival (OS) and the incidence, type, and severity of postoperative complications were analyzed. *Results:* The five-year survival rate for CCRT and pure RT were 67.7% and 46.8%, respectively ($p = 0.018$). The incidences of bone marrow suppression and gastrointestinal reaction for CCRT and pure RT were 100% *vs.* 88.89% ($p < 0.001$) and 70.6% *vs.* 33.33% ($p < 0.001$). Only 16.18% patients received CCRT developed chronic radiation enteritis, and 4.35% developed chronic radiation cystitis. While 11.11% patients received pure RT experienced chronic radiation enteritis ($p = 0.449$), 4.44% experienced chronic radiation cystitis ($p = 0.312$). *Conclusions:* This retrospective study demonstrated that CCRT followed by radical surgery achieved a better outcome compared with pure RT in LACC patients, but could apparently rise the incidence and severity of hematologic and gastrointestinal toxicity.

Key words: Local advanced cervical carcinoma; Concurrent chemoradiotherapy; pure radiotherapy; Complications; Clinical outcome.

Introduction

Cervical carcinoma is the second most common cancer affecting women's health worldwide, and more than 80% of all cervical cancers occur in women in developing countries [1]. Cervical cancer remains an important public health problem in mainland China. In 2005, there were approximately 58,000 new cervical cancer cases (National Office for Cancer Prevention and Control *et al.*, 2009) and about 20,000 deaths [2].

The treatment strategy of cervical carcinoma has been improved significantly in the past two decades. On the basis of numerous notable studies in the late 1990s, concurrent irradiation with cisplatinum-based chemotherapy (CCRT) has been recommended as standard treatment for local advanced cervical carcinoma (LACC) in most developed counties in the world [3, 4]. Cisplatin added to radiation could reduce the relative risk of death from cervical carcinoma by approximately 50% by decreasing local failure and distant metastasis, and improve overall survival (OS) by 9%–18% as well [5, 6]. However, the five-year OS of LACC patients still remains around 70% [7], and in elderly patients, patients with co-morbid medical conditions, poor performance status (PS), and those who refused chemotherapy cannot be administered, for which a different strategy is required to enhance the effects of radiotherapy given as a single modality of treatment [8]. Moreover, one of the major criticisms raised against CCRT is the potentially higher risk of complications, such as hematologic and gastrointestinal toxicities. Thus, it is still critical to explore a more effective therapeutic strategy for further OS improvement of LACC.

Until now, it is still not clear whether CCRT can provide a significant advantage for LACCs, eg, Stages III–IVA, in comparison with pure radiotherapy (RT) or in combination following radical surgery [9]. A meta-analysis study demonstrated that survival benefit of CCRT might be restricted to lower stage patients with International Federation of Obstetricians and Gynaecologists (FIGO) Stage IB–IIA, IIB having an increase in OS of 10% and 7%, respectively, by CCRT [10]. A retrospective study carried out in 174 Chinese patients with LACC reported that preoperative CCRT achieved outcomes superior to RT alone, but depending on the pathologic response, tumor size and lymph-node involvement as major prognostic factors [11]. However, previous studies did not define the incidence, type, and severity of postoperative complications and long term efficacy of CCRT in a large series of Chinese LACC patients. Therefore, the aim of this study was to determine

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Table 1. — *Comparison of baseline clinical characteristics between the two groups.*

Clinical variables	Group A (n=68)	Group B (n=45)	*p*
Median age (range)	47.5 (29.3-64.2)	48.6 (31.6-67.8)	0.674
Histotype			
Squamous	58	41	
Adenocarcinoma	8	4	0.602
Adenosquamous carcinoma	2	0	
FIGO Staging			
IB2	21	16	
IIB	30	22	0.705
IIIB	17	7	

Group A: concomitant chemoradiotherapy; Group B: pure radiotherapy. FIGO: The International Federation of Gynecology and Obstetrics.

whether CCRT offered a lower incidence of toxic reactions and better long-term efficacy in comparison with pure RT in a five-year follow-up retrospective cohort.

Materials and Methods

Patients

LACC patients who were treated in The Second Hospital of Tianjin Medical between January 2007 and January 2009 were recruited in this study. Inclusion criteria were: (1) Biopsy proven cases of advanced squamous cell carcinoma of uterine cervix, Stage IB2–IIIB (as per FIGO 2009 staging); (2) age between 25 and 75 years; (3) Karnofsky Performance Status (KPS) ≥ 70; (4) adequate bone marrow, liver, and renal function (Hb ≥ 10 g/dl; WBC ≥ 3,000/mm^3, platelets ≥ 120,000/mm^3; bilirubin < 2 mg/dl; blood urea nitrogen < 25 mg/dl, creatinine < 1.5 mg/dl); (5) no obvious mental abnormalities, psychological disorder and cognitive impairment; (6) with complete basic medical records and follow-up information. Exclusion criteria were: (1) age > 75 years or < 25 years; (2) KPS < 70; (3) pregnancy; (4) history of pelvic surgery, malignancy, exposure to cytotoxic chemotherapy or radiation; (5) combination of other tumor or sever chronic illness, such as chronic obstructive pulmonary disease, coronary heart disease, diabetes; (6) with distant metastasis. The study was approved by the Institutional Review Board of the present hospital. Written informed consent was obtained from all of the patients according to the committee's regulations.

One hundred thirteen LACC cases who met the eligibility criteria were divided into two groups according to the treatment arm: 68 patients in group A received CCRT, and 45 patients in group B received pure RT. Baseline patient characteristics were similar and well-balanced in both groups (Table 1).

Treatment

Both groups received combination of external beam radiation therapy (EBRT) and intracavitary brachytherapy (ICBT). EBRT included 6~15 MV of linear accelerator therapy apparatus, and ICBT included a WD- HDR18 close after installed with Iridium 192 radioactive sources. EBRT included DT 46~50 Gy, 2.0 Gy/times, five times a week, and the radiation field included the upper bound on the edge between the lumbar spine, lower obturator under two cm, and with the vaginal invaded scope changes, the lateral reach derma pelvic most outside diameter 1~2 cm wide, common iliac, external iliac, and iliac and sacral front and obturator lymph nodes were involved. All patients received ICBT immediately after completion of EBRT, DT 36~42 Gy, six Gy/week,once a week to point A (a point two cm lateral to the center of the uterine canal and two cm above the mucous membrane of the lateral fornix of the vagina in the plane of the uterus). The CCRT group received RT. Chemotherapy began from the first day of RT using PF scheme: cisplatin (DDP) 50~70 mg/m^2 1~2 days, 5 fluorouracil (5-Fu) 750 mg/m^2, 2~5 days, intravenous drip, three weeks/times, a total of three times.

Follow-up and toxicity evaluation

Patients were followed up by both the radiation oncologist and the gynecologist with detailed physical and gynecological examinations. Patients were followed up every six months from June 2009 to June 2014. The incidence of bone marrow suppression, gastrointestinal reaction, chronic radiation enteritis, and chronic radiation cystitis were assessed and recorded. Toxicity assessment was performed according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment for Cancer late-radiation morbidity-scoring scheme [12].

Statistical analysis

Statistical analysis was performed with SPSS 18.0, χ^2 test were used for categorical variables, and Mann-Whitney U test was used to for continuous values. OS was calculated from the date of diagnosis to the date of death or the date of the last follow-up. Survival curves were plotted using the Kaplan-Meier product-limit method, and differences between survival curves were tested using the log-rank test. All tests were two-tailed and a p-value < 0.05 was considered significant.

Table 2. — *Comparison of the incidence of bone marrow suppression between the two groups (n / %).*

Groups	Cases	Grade 0	Grade I	Grade II	Grade III	Grade IV	Total	Z	p^*
Groups A	68	0 (0.00)	12 (17.65)	37 (54.41)	15 (22.06)	4 (5.89)	68 (100)	-4.879	0.000
Groups B	45	54 (11.11)	21 (46.67)	17 (37.78)	2 (4.44)	0 (0.00)	40 (88.89)		

Group A: concomitant chemoradiotherapy; Group B: pure radiotherapy. *Mann-Whitney U test.

Table 3. — *Comparison of the incidence of gastrointestinal reaction between the two groups (n / %).*

Groups	Cases	Grade 0	Grade I	Grade II	Grade III	Grade IV	Total	Z	p^*
Groups A	68	20 (29.4)	20 (29.4)	12 (17.6)	10 (14.7)	6 (8.82)	48 (70.6)	-3.788	0.000
Groups B	45	30 (66.67)	7 (15.56)	5 (11.11)	2 (4.44)	1 (2.22)	15 (33.33)		

Group A: concomitant chemoradiotherapy; Group B: pure radiotherapy. *Mann-Whitney U test.

Table 4. — *Comparison of the incidence of chronic radiation enteritis between the two groups (n / %).*

Groups	Cases	Grade 0	Grade I	Grade II	Grade III	Grade IV	Total	Z	p^*
Groups A	68	57 (83.82)	4 (5.89)	5 (7.35)	2 (2.94)	0 (0.00)	11 (16.18)	-0.799	0.449
Groups B	45	40 (88.89)	3 (6.67)	1 (2.22)	1 (2.22)	0 (0.00)	5(11.11)		

Group A: concomitant chemoradiotherapy; Group B: pure radiotherapy. *Mann-Whitney U test.

Table 5. — *Comparison of the incidence of chronic radiation cystitis between the two groups (n / %).*

Groups	Cases	Grade 0	Grade I	Grade II	Grade III	Grade IV	Total	Z	p^*
Groups A	68	63 (92.65)	3 (4.41)	1 (1.47)	1 (1.47)	0 (0.00)	5 (4.35)	-0.625	0.612
Groups B	45	43 (95.56)	1 (2.22)	1 (2.22)	0 (0.00)	0 (0.00)	2 (4.44)		

Group A: concomitant chemoradiotherapy; Group B: pure radiotherapy. *Mann-Whitney U test.

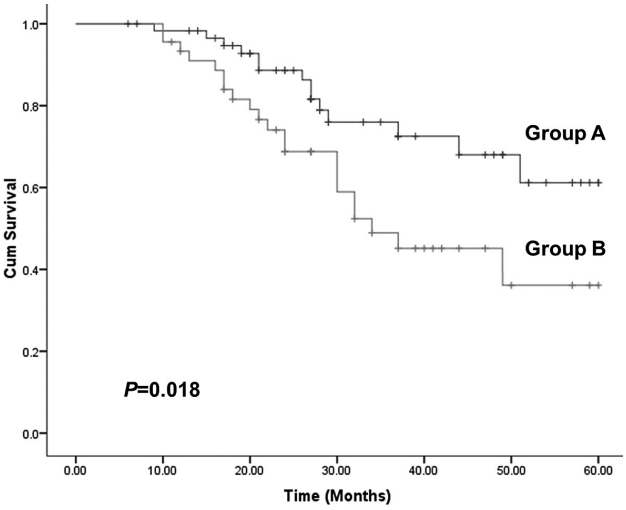

Figure 1. — Overall survival by means of the Kaplan–Meier survival analysis using the Log rank test. The overall survival time was 48.8 months for group A and 39.2 months for group B. The five-year survival rate of the group A was significantly higher than the group B (76.7% *vs.* 53.3%; $\chi^2 = 5.629$, $p = 0.018$).

Results

Hematologic, gastrointestinal, nephrotoxic. and urinary complications were the most common types of toxicity. During the observation period, as shown in Table 2, 68 (100%) patients in group A experienced no grade bone marrow suppression complications, and 19 (27.94%) of them had ≥ grade 3 complications. In Group B, the bone marrow suppression complications occurred in 40 (88.89%) patients, significantly lower than that of group A (Z = - 4.579, $p < 0.000$), and two (4.44%) of them had ≥ grade 3 complications, significantly lower than that of group A ($\chi^2 = 8.389$, $p = 0.004$).

As shown in Table 3, the incidence rate of gastrointestinal reaction in group A was 70.6% (48/68), significantly higher than that of group B [33.33% (15/45), Z = - 3.788, $p < 0.000$]. The III-IV grade gastrointestinal reaction in group A was 23.53% (16/68), significantly higher than that of group B [6.67% (3/45), $\chi^2 = 4.336$, $p = 0.037$].

Of the 68 patients in group A, only 11 (16.18%) patients developed early-grade chronic radiation enteritis, and five (4.35%) patients developed early-grade chronic radiation cystitis. While in group B, five (11.11%) patients developed early-grade chronic radiation enteritis, and two (4.44%) patients developed early-grade chronic radiation cystitis. No significantly differences were observed between two groups (Z=-0.799, $p = 0.449$; Z = - 0.625, $p = 0.312$, respectively) (Tables 4 and 5).

No patients were lost during the follow-up; the median follow-up was 52 months in both groups. The overall survival time was 48.8 months for group A and 39.2 months for group B. The five-year survival rate of the group A was significantly higher than the group B (67.7% *vs.* 46.8%; $\chi^2 = 5.629$, $p = 0.018$) (Figure 1).

Discussion

This retrospective study evaluated the prevalence of complications and long term-efficacy of CCRT in a relatively large sample of Chinese LACC patients. The results demonstrated that CCRT achieved an outcome superior to pure RT in 113 Chinese patients with LACC, which was consistent with previous studies [11]. However, the present study found that preoperative CCRT was associated with significantly higher incidence of bone marrow suppression and gastrointestinal reaction, compared with RT alone, suggesting that CCRT could increase the hematologic and gastrointestinal toxicity.

CCRT is now the standard treatment in LACC and cisplatin appears to be the ideal chemotherapeutic agent. Green *et al.* [13] analyzed data from 19 randomized trials comprising 4,580 patients and concluded that concomitant chemotherapy results in improved overall survival and progression-free survival. However, the absolute survival benefit was 12% maximum in early-stage (I and II) disease, and the three-year overall survival (74%) or five-year overall survival or progression-free survival (50%–63%) of the standard CCRT alone were still not satisfactory [14]. In the present study, the five-year OS rates for patients undergoing CCRT and pure RT were 67.7% and 46.8%, respectively, suggesting that preoperative CCRT achieved better outcome in comparison to RT alone for LACC with acceptable low nephrotoxic and uri-

nary toxicity and complications. This study together with previous studies suggest that a combination of preoperative CCRT and radical surgery may provide a feasible and effective treatment for patients with LACC.

In the present study, patients receiving CCRT all experienced bone marrow suppression complications, and 27.94% had grades 3 and 4 in comparison to RT alone (4.44%, p = 0.004). Morris *et al.* found that 44% patients receiving pelvic radiation with concurrent chemotherapy experienced grades 3 and 4 bone marrow suppression complications, while this only occurred in 3% patients treated with RT alone [15]. In addition, 70.6% patients receiving CCRT experienced gastrointestinal reaction, and 23.53% had grades 3 and 4 in comparison to RT alone (6.67%, p = 0.037). Green *et al.* also reported that the incidence of gastrointestinal reaction was significantly higher in CCRT patients compared with RT patients [16]. Several large cohort and phase-III studies on exclusive CCRT have also described severe late toxicity ranging from 10% to 18.3 % with a predominant pattern of intestinal toxicity (13% grades 3–4 complications) and vaginal toxicity (20% grades 3–4 complications) [17, 18]. Interestingly, CCRT treatment showed similar toxicities compared with the RT treatment in chronic radiation enteritis and cystitis. The chronic radiation enteritis rates following radiation therapy range from 10-20%, and 1-10% for chronic radiation enteritis, depending on the bias of the reports. In the present study, 16.18% patients receiving CCRT developed chronic radiation enteritis, and 4.35% patients developed chronic radiation cystitis, and the results were in agreement with the above reported. Altogether, these studies suggest that CCRT could apparently rise the incidence and severity of hematologic and gastrointestinal toxicity, thus emphasizing the need of a close clinical and radiological monitoring of patients in postoperative period.

In conclusion, this retrospective study demonstrated that CCRT followed by radical surgery achieved a better outcome compared with pure RT in LACC patients, but could apparently increase the incidence and severity of hematologic and gastrointestinal toxicities. However, this finding is not conclusive due to the small sample size and lack of correlation analysis of clinical variables with complications, which are major drawbacks of this study. Moreover, the present authors indicate that this observation is still a retrospective study, which might be a limitation along with a lack of sufficiently balanced numbers of patients. However, these findings warrant further multicenter investigation in a randomized clinical trial.

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