RESEARCH ARTICLE

Concurrent Chemoradiotherapy Versus Radiotherapy Alone for Locoregionally Advanced Nasopharyngeal Carcinoma

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Abstract

Objective: To compare the clinical effects of concurrent radiochemotherapy with those of radiotherapy in treating locally advanced nasopharyngeal carcinoma (Stage III~IVa). Methods: A total of 95 patients suffering from nasopharyngeal carcinoma (Stage III~IVa) were divided into two groups: concurrent radiochemotherapy (Group CCRT, n=49) and radiotherapy (Group RT, n=46). The two groups were both delivered conventional fractionated radiotherapy, while Group CCRT also received three cycles of PF (DDP+5-Fu) or PLF (DDP+5-Fu+CF) chemotherapy. Results: The complete remission rate and total remission rate of Group CCRT were higher than those of Group RT (X^2=4.72~7.19, P<0.05). The one-year overall survival (OS) rate calculated by the life table method, was also higher than that of Group RT (X^2=4.24, P<0.05) as well as the 3-year OS rate, nasopharyngeal control rate and cervical lymph nodes' control rate (X^2=4.28~4.40, P<0.05). In addition, the 5-year OS and metastasis-free rates of Group CCRT were higher than those of Group RT and the differences were of statistical importance (X^2=3.96~8.26, P<0.05). However, acute toxicity was also obviously higher, the difference in gastrointestinal reactions being statistically significant (X^2=11.70, P<0.05). Conclusion: This study demonstrated that concurrent radiochemotherapy could improve the remission rate, overall survival rate and locally control rate. The toxicity of concurrent radiochemotherapy could be tolerated by the patients.

Keywords: Nasopharyngeal carcinoma - radiotherapy - chemotherapy - remission rate - survival rate - toxicity

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Introduction

In China, 90% of nasopharyngeal carcinoma s' (NPC) pathological subtype are poorly differentiated squamous cell carcinoma, often with cervical lymph nodes metastasis and are sensitive to chemotherapy. Clinical researches have demonstrated that the cure rate of early stage NPC by radiotherapy alone is higher than locally or regionally advanced ones (T3, T4 or N3, N4), which are easy to recurrent and metastasis distantly.

In recent years, many clinical researches have proven that concurrent radiochemotherapy is superior to radiotherapy alone and PF or PLF regimen is most commonly used. Despite the expected higher acute toxicities with the addition of 5-FU to cisplatin, the compliance with RT was not compromised, and the delay of RT was not increased when compared with RT alone arm. These results suggest that the combination of cisplatin and 5-FU can safely be incorporated to RT in locally advanced NPC patients. Radical external radiotherapy is the mainstay of treatment, resulting in an overall 5-year survival rate of over 80% for stage I and over 70% for stage II disease (Hara et al., 2008; Wee et al., 2008). However, in locoregionally advanced disease, despite good initial local control after radiotherapy, there is a significant rate of distant metastases and local failures resulting in a 5-year survival rate of around 50% (Hara et al., 2008; Wang et al., 2012).

Over the past two decades, attempts have been made to improve the results of radiotherapy in the treatment of patients with other head and neck cancers by incorporating some form of chemotherapy. Although overall survival has not been significantly improved, randomized studies of adjuvant chemotherapy have demonstrated a reduction in the rate of development of distant metastases (Pignon et al., 2000; Liu et al., 2008). As NPC is even more chemosensitive than head and neck cancers at other sites, and in view of the well-documented poor 5-year survival rate for locoregionally advanced NPC, the use of combination chemotherapy-radiotherapy has been investigated, with a view to decreasing the rate of distant metastasis and locoregional relapse and increasing disease-free and overall survival (Chen et al., 2008; Zhang et al., 2010; Kalaghchi et al., 2011; Shueng et al., 2011).

Early results using concurrent cisplatin-radiotherapy in head and neck cancers, including NPC, have been encouraging (Lee et al., 2008; Lee et al., 2009; Rottey et al., 2011; Xiao et al., 2011). Cisplatin acts both as a cytotoxic agent and as a radiation sensitizer. The optimal scheduling of cisplatin and radiation has not been

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established, but daily low-dose, weekly intermediate-dose, or 3-week high-dose regimens have all been used. In a randomized trial using postoperative cisplatin and radiotherapy versus radiotherapy alone in patients with high-risk head and neck cancers, cisplatin 50 mg intravenously weekly for a total of seven to nine cycles was given in the concurrent chemotherapyradiotherapy arm; 88 patients were randomized and the 2-year disease-free survival was significantly in favor of the concurrent arm (Rottey et al., 2011).

Given the early success of concurrent chemoradiation in head and neck cancers (Lee et al., 2008; Lee et al., 2009; Rottey et al., 2011) and the encouraging data in NPC (Xiao et al., 2011), we embarked on the present study in locoregionally advanced NPC comparing radiotherapy with concurrent cisplatin-radiotherapy. In recent years, many clinical researches have proven that concurrent radiochemotherapy is superior to radiotherapy alone and PF or PLF regimen is most commonly used. Since 2001, our department has treated stage III ~ IVa NPC patients with conventional radiotherapy combined with PF or PLF regimen chemotherapy, and obtained a favourable effect.

Materials and Methods

Clinical data

We performed an analysis of 95 cases treated for stage III ~ IVa NPC at our department during the period from June 2001 to June 2007. 70 cases were male and 25 cases were female; the patients were from 21 to 70 years old; all patients were poorly differentiated squamous cell carcinoma confirmed by pathology, without distant metastasis and any other treatments; 65 patients (68.4%) were with cervical lymph nodes metastasis. According to CT, MRI, or pathology and NPC with AJCC stage T3/T4 or N2/N3 and M0 disease, there were 58 stage III cases and 37 stage IVa cases. All eligible patients were required to have measurable diseases, including at least one bidimensionally measurable lesion, no previous anticancer treatment, a life expectancy of at least 3 months, ECOG performance status ≤ 1, absolute neutrophil count ≥500/μl, platelet count ≥100,000/ll, no abnormalities in the liver, kidneys, heart, and lungs (renal function: 24 h creatinine clearance ≥60 ml/min), and no double primary cancer, and to give an informed consent for treatment.

Patients were evaluated by a multidisciplinary team before treatment. Pretreatment evaluation included a medical history, physical examination, and assessment of performance status and fiberoptic examination of upper aerodigestive tract. Computerized tomography (CT) or magnetic resonance imaging (MRI) scans of nasopharynx and neck, including cervical and supraclavicular lymph node area, was used to evaluate the primary tumor and nodal status before and after the chemoradiation, and at the end of the RT. CT scan of chest or liver, and bone scan were used when any initial investigation suggested metastasis. Patients were required to have a dental examination before treatment. Individual patient consent was not required.

Treatments

Radiotherapy patients in both groups were delivered conventional fractionated radiotherapy, 6MV X-ray, external irradiation, 2Gy/F, 5F/w, scanned by CT and fixed by thermoplastic mask. Firstly, parallel opposed lateral fields (primary tumor + neck) 38Gy ~ 40Gy / 19 ~ 20F, then push total dose to 70 ~ 76Gy after sparing spinal cord. The total dose of metastatic neck lymph nodes was DT 65~70Gy. The elective neck dose was 50Gy~54Gy.

Chemotherapy group CCRT was administered Three cycles PF regimen (DDP 30 mg/m^2 d1-3 and 5-Fu 500 mg/m^2 d1-5, q3w × 3cycles) chemotherapy; or PLF regimen (DDP 30 mg/m^2 d1-3, 5-Fu 500 mg/m^2 d1-5 and CF 200 mg/m^2 d1-5, q3w × 3cycles) chemotherapy. The first cycle chemotherapy began concurrently on the first day of radiotherapy. Blood cell count was taken every week, while liver and kidney functions every 3 weeks. When WBC < 3.0 × 10^9/L, both radiotherapy and chemotherapy should be suspend, and patient was inject Recombinant Human Granulocyte Colony Stimulating Factor subcutaneously. When patients complained intolerable vomiting or mucocutaneous reactions, reduced the cycles or terminated chemotherapy.

Observation Indices

Collected information including blood cell count, relating toxicities, and the effect. Patients took nasopharynx CT 2 or 3 months after the treatments, and doctors compare it with the previous nasopharynx CT to evaluate the curative effects. The curative effects in short terms are according to response evaluation criteria in solid tumors (Cheng et al., 2000) and divided into completely remission (CR), partly remission (PR), stable disease (SD) and progressed disease (PD). The curative effects in long terms include survival rate, nasopharyngeal control rate, neck lymphatics control rate and distant metastasis-free rate. The toxicities are evaluated by RTOG standards (Shen et al., 2001).

Follow-up

Followed up the patients respectively in 1, 6 and 12 months after the radiotherapy. Followed up them every 6 months after one year, and every one year after three years. The termination time point was October 31st, 2010 (median follow-up time was 77 months), with head and neck CT, thorax CT, abdominal ultrasonography and ECT. The follow-up rate was 100%.

Data processing

The curative effects in short terms was calculated directly. The survival rate and local control rate was calculated by life table method and their significant differences are compared by Log-rank test. Compare the toxicities between two groups by X^2 test. All statistical analyses are performed with SPSS 13.0 (SPSS Inc., Chicago, IL) and PPMS1.5, using an alpha level of significance of 0.05.

Results

Treatments' compliance

All the 95 patients completed the planned radiotherapy, 47 patients (95.9%) in Group CCRT completed the

Table 1. Comparison of Two Groups' Acute Toxic Reactions

	CCRT(n=49) Grade3/4 N(%)	RT(n=46) Grade3/4 N(%)	
Mucositis	28(57.1)	19(39.1)	X^2=3.08, P>0.05
Upper gastrointestinal Tract reactions	11(22.4)	0(0)	X^2=11.7, P<0.05
Myelosuppression	8(16.3)	2(4.3)	X^2=3.16, P>0.05

Table 2. Comparison of Two Groups' Short-term Effects

Group	Cases	CR	PR	SD	PD	CR + PR	Cervical lymph nodes remission rate
CCRT	49	43(87.8%)	6(12.2%)		0	100.00%	40(81.6%)
RT	46	32(69.6%)	6(13.0%)	8(17.4%)	0	82.60%	28(60.9%)

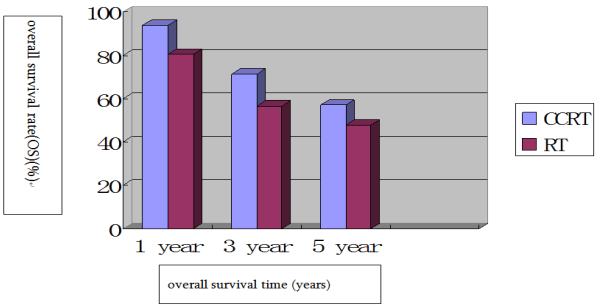

Figure 1. The 1, 3 and 5 Year Overall Survival Rate(OS) for Patients with CCRT in Comparison with RT Only Patients

concurrent radiochemotherapy, one patient stopped chemotherapy due to Grade IV myelosuppression, and one patient only accepted 2 cycles chemotherapy due to Grade III myelosuppression and Grade IIgastrointestinal reactions.

Toxic reactions

A large proportion of toxic reactions are acute ones. The mucositis (Grade III and IV) rates of Group CCRT and Group RT during the radiotherapy were respectively 57.1% (28/49) and 39.1% (18/46) (X^2=3.08, P>0.05); The rates of Grade III and IV Upper gastrointestinal tract reactions were respectively 22.4% (11/49) and 0 (0/46) (X^2=11.7, P<0.05); The rates of Grade III and IV myelosuppression were respectively 16.3% (8/49) and 4.3 (2/46) (X^2=3.16, P>0.05). (Table 1)

Survival condition

Short-term effects Group CCRT: There were 46(87.8%) patients with complete remission (CR), 6 (12.2%) with partial remission (PR) and the total remission (CR + PR) rate was 100.0%. Group RT: there were 32 (69.6%) patients with complete remission (CR), 6 (13.0%) with partial remission (PR) and the total remission (CR + PR) rate was 82.6%. The comparisons by X^2 test of complete remission (CR), total remission (CR + PR) rate and cervical lymph nodes remission were of statistical significance (X^2=4.72~7.19, P <0.05) (Table 2).

Long-term effects: The 1, 3 and 5 year OS rate of Group CCRT and Group RT were respectively 93.9% vs. 80.4% (P<0.05), 71.4% vs. 56.5% (P<0.05), and 57.1% vs. 47.8% (P<0.05) (Figure 1).

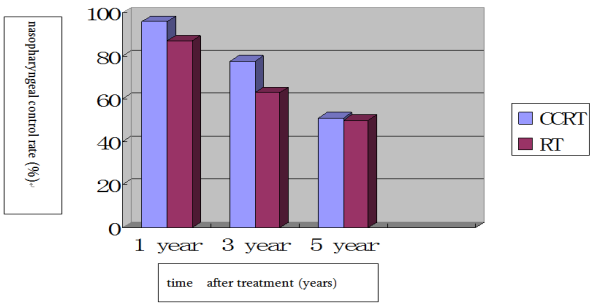

Figure 2. The 1, 3 and 5 year Nasopharyngeal Control Rate of Group CCRT and Group RT

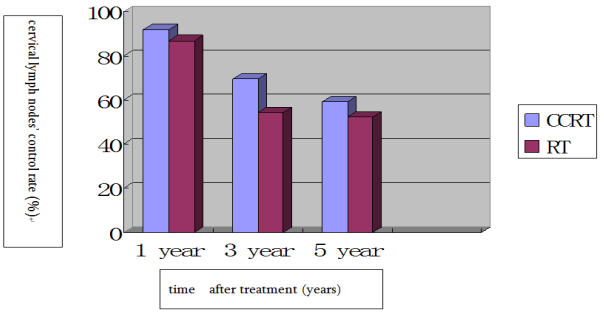

Figure 3. The 1, 3 and 5 year Cervical Lymph Nodes' Control Rate of Group CCRT and Group RT

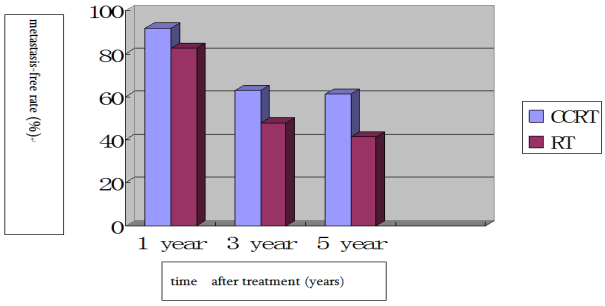

Figure 4. The 1, 3 and 5 year Metastasis-free Rate of Group CCRT and Group RT

The 1, 3 and 5 year nasopharyngeal control rate of Group CCRT and Group RT were respectively 95.9% vs. 87.0% (P>0.05), 77.6% vs. 63.0% (P<0.05), and 51.0% vs. 50.0% (P>0.05) (Figure 2). The 1, 3 and 5 year cervical lymph nodes' control rate of Group CCRT and Group RT were respectively 91.8% vs. 86.9% (P>0.05), 69.4% vs. 54.3% (P<0.05), and 59.1% vs. 52.2% (P>0.05) (Figure 3). The 1, 3 and 5 year metastasis-free rate of Group CCRT and Group RT were respectively 91.8% vs. 82.6% (P>0.05), 65.3% vs. 47.8% (P>0.05), and 61.2% vs. 41.3% (P<0.05) (Figure 4).

The median time of distant metastasis of Group CCRT and Group RT are respectively 1.83 years (22 months) and 1.33 years (16 months).

Discussion

In recent years, many clinical trials have shown that some advancements are made from radiotherapy combined with chemotherapy for locally advanced NPC. One Meta-analysis (Baujat et al., 2006) launched by French showed that radiotherapy combined with chemotherapy

could improve the 5-year overall survival rate by 6 % and event-free survival rate by 10%.

In 2009, Hui et al. (2009) from Hong Kong treated 65 stage III and IVa NPC patients with radiotherapy or radiotherapy combined with two cycles Cisplatin and Docetaxel chemotherapy, and reported that the 3-year survival rates were respectively 67.7% and 94.1% (P=0.012). Hu et al. (2007) compared the effect of inductive chemotherapy combined with radiotherapy with that of concurrent radiochemotherapy, and the difference between residual tumor rates of the two groups was of statistical significance (P=0.008). However, the differences of residual tumor rate after 3 months and the survival rate were of no statistical significance (P> 0.05).

Huang et al. (2009) from Guangzhou Cancer Laboratory randomly divided 408 cases into two groups that are inductive chemotherapy combined with concurrent radiochemotherapy group (IC/CCRT) and inductive chemotherapy combined with radiotherapy group (IC/RT). The results showed that the differences of progression-free survival rate, locally control rate and control rate of distantly metastasis were of no statistical significance. In conclusion, inductive chemotherapy combined with concurrent radiochemotherapy in their hands did not improve the overall survival rate of locally advanced nasopharyngeal cancer.

The effect of concurrent radiochemotherapy is better than other therapeutic alliances. The prognosis, local control rate, long-term survival rate and life quality of patients could be improved by concurrent chemotherapy, and the toxicities can be tolerated by patients (Lee et al., 2002). The theoretical basis and clinical advantages are as follows: a. Chemotherapy could increase the sensitivity to radiotherapy (Sun et al., 2003) and has a synergistic effect with radiotherapy. Some head and neck tumors are sensitive to agents such as Cisplatin, Fluorouracil, Paclitaxel and so on, which play a sensitized role by affecting the DNA synthesis phase of tumor cells and synchronizing them; cytotoxic drugs achieve a synergistic effect with radiotherapy on tumor cells after radiotherapy by inhibiting sublethal injury and potentially lethal damage repair; B. The cooperation of different treatments could supplement each other. The radiotherapy only kill local tumor cells, but chemotherapy can effectively control distant metastasis. Therefore, finding a suitable treatment for NPC is still an important task.

A clinical randomized study performed by Lin et al. (2003) showed that the 1, 3 and 5-year OS rate of Group concurrent radiochemotherapy were all higher than those of Group radiotherapy. 1, 6 and 12-month complete remission rates were 87.5%, 90.6% and 93.7%; 1, 6 and 12-month complete remission rates of cervical lymph nodes were 91.5%, 94.9% and 98.3%; 1, 3 and 5-year OS rates were 91.5 %, 80.4% and 62.5%. The results were similar to foreign reports. In 2006, some scientist reported the preliminary results of 9902 Study performed by Hong Kong NPC Research Group (Lee et al., 2006): compared with simple accelerated radiotherapy, AF regimen chemotherapy combined with radiotherapy could notably increase tumor control rate, but both chemotherapy groups' acute toxicities were higher (P<0.005). In 2008, Yang et al. (2008) performed a meta-analysis on 18 clinical studies (n = 1993) of patients treated for locally advanced NPC with concurrent radiochemotherapy in Chinese mainland. The results showed that compared with radiotherapy, concurrent radiochemotherapy improved 3 and 5-year survival rates by 12% and 11%, and decreased decrease distant metastasis rate by 12%.

Our 95 patients were divided into Group CCRT and Group RT, and the complete tumor regression rate of Group CCRT was higher than that of Group RT. The reasons were as follows: patients in Group CCRT were delivered chemotherapy at the same time, which reduced tumor load and the proportion of tumor anoxic cells, while eradicated tumor cells easily, which were vascular-rich because of no radiotherapy yet. Concurrent chemotherapy had a radiosensitizing effect so that the radiotherapy could kill more tumor cells and improve the local control rate. Concurrent chemotherapy can also kill residual tumor cells after radiotherapy and distant small lesions, and reduce recurrence and distant metastasis (Gu et al., 2008). However, patients in Group RT were delivered radiotherapy alone, which is less likely to make a too large tumor smaller to the size that immune system can eliminate it. So the local control rate is lower. Once the tumor is recurrent, the local drug concentration is difficult to achieve lethal dose of tumor cells for radiation-induced muscle fibrosis, local vascular lumen narrowing and blocking. So, the tumor cells could proliferate and metastasize. Therefore, the effect of Group CCRT is better than that of Group RT.

The adverse reactions were mainly caused by head and neck radiotherapy. The treatments of the acute radiation reactions to are as follows: as to oral oropharyngeal mucositis, patients should mainly maintain oral health; to oral ulcers, patients were delivered Xilei San or intravenous infusion nutrition support to reduce the oral response; to gastrointestinal reactions in the chemotherapy, we mainly delivered patients ondansetron, metoclopramide, diphenhydramine, dexamethasone and other symptomatic treatments, then patients could tolerated the reactions well; to bone marrow suppression, patients were delivered them the medications to rise blood cells; to the renal toxicity of DDP, increased intravenous fluid infusion and encouraged patients to drink more water during chemotherapy. Therefore, development of better CCRT protocol using more sophisticated RT techniques is still needed.

In summary, our study showed that concurrent radiochemotherapy with DDP +5- Fu ± CF could improve the response rate of locally advanced NPC, and had the trend to improve the local control rate and survival rate. However, since the cases were not enough, which might result in no significant differences between the data of local control rate and survival rate. We should increase the cases. Concurrent chemotherapy increased the blood and gastrointestinal toxicities, but most patients can tolerate. We should take some auxiliary measures to minimize the toxicities according to the patients' situation. In future, how to optimize the dose and chemotherapy regimens, reduce side effects and then to improve long-term survival are the focuses of studies.

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