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A Prospective Study on Therapeutic Gain by Concurrent Chemoradiotherapy for Stage Ⅱ-Ⅳa Nasopharyngeal Carcinoma*

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Summary: The benefit achieved by concurrent chemoradiotherapy (CCR) and sequential chemoradiotherapy (SCR) *vs* radiotherapy (RT) alone for patients with stage Ⅱ-Ⅳa nasopharyngeal carcinoma (NPC) was compared. A total of 113 patients with stage Ⅱ-Ⅳa NPC were allotted into CCR group (*n*=38), SCR group (*n*=36) and RT alone group (*n*=39). All patients were irradiated with the same RT technique to ≥66 Gy at 2 Gy per fraction, conventional 5 fractions/week in all groups. The CCR group received concurrent chemotherapy of weekly cisplatin for 7 weeks, and the SCR group received neoadjuvant and (or) adjuvant chemotherapy. The results showed that the 3- and 5-year overall survival rate was significantly higher in CCR group than in RT alone group (92.16% *vs* 61.54%, 81.58% *vs* 51.28%, *P*<0.005). The median survival time was significantly longer in CCR group than in RT alone group (67.8 months *vs* 52.7 months, *P*<0.005). It was concluded that CCR could significantly improve overall survival rate, progression-free survival rate, and median survival time when compared with RT alone.
Key words: nasopharyngeal carcinoma; radiotherapy; concurrent chemotherapy; sequential chemotherapy; long-term survival

Nasopharyngeal carcinoma (NPC) is of high prevalence in southern part of China, Southeast Asia and Northern part of Africa. Histologically, WHO-2 and WHO-3 types of NPC are seen most frequently[1]. NPC is sensitive to radiotherapy and chemotherapy, but regional lymph nodes and distant cancer metastasis also easily happens, which is lethal to patients. Especially, the poorly differentiated cancer takes a very important part in the metastasis trend. Up to now, with regard to stage Ⅰ NPC, 10-year survival rate of NPC is up to 98% if using merely radiotherapy. But the status of chemotherapy in the early metaphase patients, is still controversial in the initial treatment of NPC[2]. In recent years, the survival rate of NPC has been elevated to some extent, which is contributed to the application of concurrent chemotherapy (random-co ntrolled study and meta analysis showing the effect of chemotherapy). Many scholars carry out the clinical studies of NPC with radiotherapy and chemotherapy, but the results are discordant. This study emphatically explored the influence of two different treatment modes of radiotherapy and chemotherapy on the long-term efficacy of stage Ⅱ-Ⅳa NPC.

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1 PATIENTS AND METHODS

1.1 Pretreatment Evaluation

Eligibility criteria were as follows: (1) The initial patients being diagnosed as NPC pathologically; (2) Age <75 years; (3) To be confirmed having no distant metastasis by CT, chest X-ray, bone ECT screening, etc; (4) No severe heart and lung function disorders, and normal liver and renal functions; (5) Karnofsky score ≥70; (6) Stage Ⅱ-Ⅳa patients by AJCC staging. This study was performed after approval from the institutional ethics committee. From October 2001 to March 2003, there were 113 cases of stage Ⅱ-Ⅳa NPC with poor differentiation and undifferentiation to bring into this study, 38 cases into concurrent chemoradiotherapy (CCR) group, 36 cases into sequential chemoradiotherapy (SCR) group, and 39 cases into radiotherapy (RT) alone group. There were 85 males and 28 females with age ranging from 13 to 72 years old (mean 47.13 years). The number of patients in stage Ⅱ, Ⅲ and Ⅳa was 36, 54 and 23, respectively (table 1).

1.2 Treatment Protocols

In CCR group, following RT protocols were done as follows: (1) Conventional fractionation (2 Gy/fra ction, once every day, 5 times each week); (2) All patients were treated in the supine position, usually through bilateral parallel opposed fields to the primary tumor and upper neck and a single anterior field to the lower neck, 36 Gy. Then a three-field combination technique was administered; (3) The total planned dose was 66 to 74 Gy every 7 to 8 weeks to the primary tumor and positive neck region, and 50 to 60 Gy every 5 to 6 weeks to the negative

neck region; (4) Seven-week concurrent chemotherapy was done during the period of radiotherapy (cisplatin, 30 mg/m^2, day 1, repeat every week). In SCR group, the chemotherapy was the same as that in CCR group. Sequential chemotherapy of 2 to 4 cycles before and after radiotherapy was performed (scheme: cisplatin, 80—100 mg/m^2, day 1+5-FU, 800—1000 mg/m^2, continuous intravenous infusion CI×5 days; repeat every 3 weeks). In RT alone group, the radiotherapy was the same as that in CCR and SCR groups, but no chemotherapy was given.

Table 1 Clinical characteristics of the patients with NPC

Characteristics	CCR group	SCR group	RT alone group	χ^2	*P*
n	38	36	39		
Sex				0.396	0.82
Male	29	28	28		
Female	9	8	11		
Age (years)	48	49	49		
Clinical staging				0.756	0.944
Ⅱ	13	11	12		
Ⅲ	19	17	18		
Ⅳa	6	8	9		
Karnofsky score				0.083	0.959
≥90	27	26	27		
70—80	11	10	12		

1.3 Follow-up

The patients in 3 groups were followed up from the beginning of the treatments to December, 2008.

1.4 Statistical Analysis

SPSS 13.0 statistical software was used for statistical analysis, and $P<0.05$ was considered statistically significant. Descriptive statistics, then with Kaplan-Meier method was adopted to draw survival curve diagram, and by using Log-Rank test, the difference in survival time among the groups was compared. Acute toxicity was assessed according to the RTOG acute radiation morbidity scoring criteria during the treatment period, and the acute toxicity was compared between CCR and RT alone groups by Chi-square test.

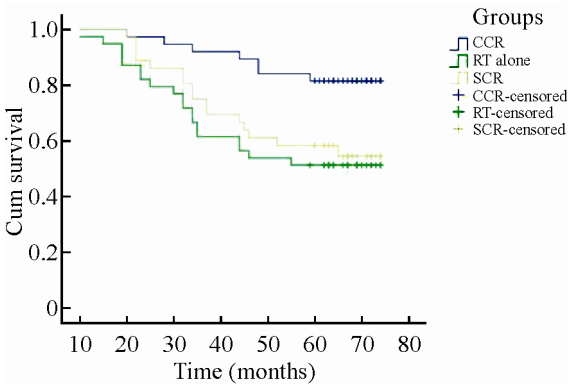

Fig. 1 Survival curve diagram in three groups

2 RESULTS

2.1 Overall Survival Rate

The 5-year overall survival rate in the three groups was 63.72%. One-year survival rate in CCR, SCR and RT alone groups was 100%, 100% and 97.44% ($P>0.05$), 3- year survival rate was 92.16%, 75.00%, and 61.54% ($P<0.01$), and 5-year survival rate was 81.58%, 58.33% and 51.28% ($P<0.025$) respectively (fig. 1).

There was statistically significant difference in 3- and 5-year overall survival rate among three groups. There was significant difference in 3- and 5-year overall survival rate between CCR and RT alone groups ($P<0.005$), but there was no significant difference in 3- and 5-year overall survival rate between SCR and RT alone groups ($P>0.05$, table 2).

Table 2 Overall survival rate in each group

Groups	1-year			3-year			5-year		
	Alive cases	*n*	OS (%)	Alive cases	*n*	OS (%)	Alive cases	*n*	OS (%)
CCR	38	38	100	35	38	92.16	31	38	81.58
SCR	36	36	100	27	36	75.00	21	36	58.33
RT alone	38	39	97.44	24	39	61.54	20	39	51.28

OS: overall survival

2.2 Progression-free Survival Rate

The total group's progression-free survival (PFS) rate was 59.29%. The one-year PFS rate in CCR, SCR and RT along groups was 94.74%, 94.44%, and 92.31% ($P>0.05$), 3-year PFS rate was 86.84%, 66.67%, and 53.85% ($P<0.01$), and 5-year PFS rate was 76.32%, 55.56%, and 46.15% ($P<0.025$), respectively. There was significant difference in 3- and 5-PFS rate between CCR and RT alone groups ($P<0.005$), but no significant difference was found between SCR and RT alone groups ($P>0.05$, table 3).

2.3 Median Survival Time

The median survival time in CCR, SCR and RT alone groups was 67.8, 56.8, and 52.7 months, respectively. Log-Rank test revealed there was significant difference in median survival time between CCR and RT alone groups ($\chi^2=7.899$, $P<0.005$), or between SCR and CCR groups ($\chi^2=4.782$, $P<0.05$), but no significant dif-

ference was found between SCR and RT alone groups (χ^2=0.376, P>0.05). It was suggested that the curative effectiveness of CCR group was better than that of RT alone group (P<0.005), but no significant difference in curative effectiveness between SCR and RT alone groups.

Table 3 Progression-free survival rate in each group

Groups	1-year			3-year			5-year		
	Disease-free cases	*n*	DFS (%)	Disease-free cases	*n*	DFS (%)	Disease-free cases	*n*	DFS (%)
CCR	36	38	94.74	33	38	86.84	29	38	76.32
SCR	34	36	94.44	24	36	66.67	20	36	55.56
RT alone	36	39	92.31	21	39	53.85	18	39	46.15

2.4 Acute Toxicity

Chi-square test demonstrated that the incidence of nausea and vomiting of Ⅰ-Ⅱ degrees, and marrow toxicity of Ⅱ-Ⅲ degrees in CCR group was higher than in RT alone group, but other acute toxicities had no significant difference between CCR and RT alone groups. In CCR group, no severe complications such as febrific neutrocytopenia were found, and if support treatment was enhanced, patients could tolerate chemotherapy (table 4).

Table 4 Comparison of acute toxicity between CCR and RT alone groups

Acute toxicity	CCR group			RT alone group			χ^2	*P*
	Cases	*n*	Incidence (%)	Cases	*n*	Incidence (%)		
Dry mouth (Grade Ⅰ-Ⅱ)	23	38	60.5	22	39	56.4	0.13	>0.05
Mucocitis	21	38	55.3	19	39	48.7	0.33	>0.05
Grade Ⅱ	16	38	42.1	15	39	38.5	0.11	>0.05
Grade Ⅲ	5	38	13.2	4	39	10.3	1.72	>0.05
Vomiting (Grade Ⅰ-Ⅱ)	16	38	42.1	6	39	15.4	6.73	<0.01
Anemia (Grade Ⅰ-Ⅱ)	8	38	21.1	8	39	20.5	3.41	>0.05
Skin reaction (Grade Ⅱ-Ⅲ)	24	38	63.2	26	39	66.7	0.10	>0.05
Bone marrow depression (Grade Ⅱ-Ⅲ)	18	38	47.4	4	39	10.3	12.9	<0.01

3 DISCUSSION

Radical radiotherapy of NPC has been generally considered as the most effective therapeutic method from 1960s. The 5-year survival rate was reported from 37%—57%, but 50%—78% in recent years[3]. The 5-year survival rate in this study was 63.72%, which matched the report of recent years, but patients with stage Ⅲ and Ⅳ in this group took up a higher ratio (65.1%).

Radiotherapy is the main treatment for NPC. The patients with NPC in early stage can advance survival rate and regional control rate through simple radiotherapy, but intermediate and advanced stages of NPC still have much higher regional relapse rate and distant metastasis rate. In order to elevate the survival rate, many clinical studies have reported radiotherapy in combination with chemotherapy to treat NPC. Some researches consider that induction chemotherapy before radiotherapy fails to raise the survival rate of intermediate and advanced stages of NPC, and adjuvant chemotherapy after radiotherapy whether raising the survival rate still is controversial[4].

The results from some prospective studies indicates that induction chemotherapy fails to raise the progression-free and overall survival rate of intermediate and advanced stages of NPC[5-7], which may be related with the fact that induction chemotherapy reduces the tolerance of patients to chemotherapy and induces the accelerating repopulation of tumor cells[8]. And many prospective clinical studies hint that concurrent chemotherapy may raise the curative effect of intermediate and advanced stages of NPC. Ma's Meta analysis result (6 clinical randomized trials) indicates that CCR increases the survival rate of advanced stage of NPC as compared with radiotherapy alone[9]. In 10 clinical randomized studies with 2450 cases, Langendijk *et al* reported that concurrent chemotherapy obtained a survival rate of 20% after 5 years in locally advanced NPC[10]. The results from Kwong's research indicated that concurrent chemotherapy significantly reduced distant metastasis rate as compared with radiotherapy alone[11].

The theory of concurrent chemotherapy raising curative effect takes as follows: (1) sensitization effect of chemotherapy drugs to radiotherapy; (2) direct killing effect of chemotherapy drugs to tumor cells; (3) chemotherapy drugs reducing repair of injured tumor cells; (4) growing downwards the volume of tumor and increasing re-oxygen saturation of tumor cells; (5) synergism effect of cytokinetics; (6) selectivity effect to anoxic cells; (7) mutual independence of toxicity[12]. The purpose of adjuvant chemotherapy after radiotherapy is to kill residual and subclinical focus. There are still existing disputes about whether adjuvant chemotherapy raises the curative effect of locally advanced stage of NPC. Prasad *et al*, who used cisplatin and fluorouracil to carry out adjuvant chemotherapy three times after radiotherapy, found that adjuvant chemotherapy after radiotherapy could further raise the curative effect of NPC[13]. Kwrong *et al*[14], who took 6 times adjuvant chemotherapy after radiotherapy to locally advanced stage of NPC, reported that adjuvant chemotherapy could raise 3-year survival rate (80.4% vs 83.1%, P=0.69).

This center enforced a prospective study on 113

cases of Ⅱ-Ⅳa stages NPC with CCR, SCR, or RT alone, and the results indicated that CCR raised 3- and 5-year survival rate and PFS rate in comparison to radiotherapy alone, and prolonged the survival time of the patients. The 1-, 3-, and 5-year survival rate in CCR group was 100%, 92.16%, 81.58%, and 1-, 3-, and 5-year PFS rate was 94.74%, 86.84%, and 76.32% respectively, but there was no significant difference in survival rate and survival time between SCR and RT alone groups. The findings were consistent with those from most clinical studies and Meta analysis published recently.

Chi-square test demonstrated that the incidence of nausea and vomiting of Ⅰ-Ⅱ degrees, and marrow toxicity of Ⅱ-Ⅲ degrees in CCR group was higher than in RT alone group, but other acute toxicities had no significant difference between CCR and RT alone groups. In CCR group, no severe complications such as febrific neutrocytopenia were found, and if support treatment was enhanced, patients could tolerate chemotherapy.

This study fails to embody survival predominance of induction chemotherapy, which may be related with no concurrent chemotherapy after induction chemotherapy. At present, related studies on concurrent chemotherapy after induction chemotherapy is under investigation. Some Ⅱ stage clinical trials indicate that the treatment strategy is feasible but must need to select suitable patients[15]. In American clinical oncology organization, a report about recent clinical research result indicates induction chemotherapy of docetaxel combined with cisplatin is feasible, and it doesn't affect the cisplatin-based concurrent chemotherapy thereafter[16]. The primary results are inspiring. Reassuming concurrent chemotherapy after induction chemotherapy may be the best choice of high risk patients[17].

To sum up, radical radiotherapy combined with concurrent chemotherapy can raise overall survival rate and PFS rate of NPC patients, and prolong survival time. But radiotherapy combined with sequential radiotherapy doesn't show the dominance.

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