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Original Article

Treatment outcomes for different subgroups of nasopharyngeal carcinoma patients treated with intensity-modulated radiation therapy

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Abstract

Although many studies have investigated intensity-modulated radiation therapy (IMRT) for nasopharyngeal carcinoma (NPC), sample sizes in the reported studies are usually small and different in outcomes in different T and N subgroups are seldom analyzed. Herein, we evaluated the outcomes of NPC patients treated with IMRT and further explored treatment strategy to improve such outcome. We collected clinical data of 865 NPC patients treated with IMRT alone or in combination with chemotherapy, and classified all cases into the following prognostic categories according to different TNM stages: early stage group (T1–2N0–1M0), advanced local disease group (T3–4N0–1M0), advanced nodal disease group (T1–2N2–3M0), and advanced locoregional disease group (T3–4N2–3M0). The 5-year overall survival (OS), local relapse-free survival (LRFS), and distant metastases-free survival (DMFS) were 83.0%, 90.4%, and 84.0%, respectively. The early disease group had the lowest treatment failure rate, with a 5-year OS of 95.6%. The advanced local disease group and advanced nodal disease group had similar failure pattern and treatment outcomes as well as similar hazard ratios for death (4.230 and 4.625, respectively). The advanced locoregional disease group had the highest incidence of relapse and death, with a 5-year DMFS and OS of 62.3% and 62.2%, respectively, and a hazard ratio for death of 10.402. Comparing with IMRT alone, IMRT in combination with chemotherapy provided no significant benefit to locoregionally advanced NPC. Our results suggest that the decision of treatment strategy for NPC patients should consider combinations of T and N stages, and that IMRT alone for early stage NPC patients can produce satisfactory results. However, for advanced local, nodal, and locoregional disease groups, a combination of chemotherapy and radiotherapy is recommended.

Key words Nasopharyngeal carcinoma, intensity-modulated radiation therapy, stratification treatment

Nasopharyngeal carcinoma (NPC) is one of the most common malignant tumors in China with the highest incidence in the south Chinese province of Guangdong[1,2]. For patients without distant metastatic lesions, radiotherapy is the principal treatment for NPC. In early stage diseases, overall survival is 84%–90% after receiving two-dimensional conventional radiotherapy (2D-CRT) alone[3-5]. After 2D-CRT alone, the treatment outcomes of locoregionally advanced disease is poor, with a 5-year survival of 66%–70%[6,7]. Different survival outcomes and failure patterns have been observed in different subgroups of early stage and locoregionally advanced NPC treated with 2D-CRT technique alone[3,6]. Xiao *et al.*[3] divided 362 early-stage NPC patients treated with 2D-CRT alone into four subgroups (T1N0M0, T2N0M0, T1N1M0, and

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T2N1M0) and found that the treatment outcome of the T2N1M0 subgroup was a unique group with the poorest prognosis because of distant metastasis. Thus, this group may benefit from chemotherapeutic intervention. Moreover, in the analysis of Chen *et al*.[6] on 556 patients with locoregionally advanced NPC who received 2D-CRT alone, the N stage was considered the primary factor determining the treatment outcome, with T stage as the secondary factor. As a result, they recommended stratified chemoradiotherapy should be used for locoregionally advanced NPC patients, basing on their N and T stages.

With the development of radiotherapeutic equipment and computer technology, intensity-modulated radiation therapy (IMRT) has been used for NPC and has improved outcome and reduced toxicity in the treatment of NPC[8-10]. Zhao *et al*.[11] have reported 419 cases of NPC receiving full course IMRT: the 5-year local recurrence-free survival (LRFS), regional relapse-free survival (RRFS), distant metastasis-free survival (DMFS), and overall survival (OS) were 92.7%, 95.8%, 85.5%, and 83.3%, respectively; no grade 4 acute or late toxicity was observed in the whole group; among 243 patients who were followed up for more than 3 years, the incidence of grade 3 late toxicity was only 2.8%. Compared with 2D-CRT, IMRT could improve the treatment outcomes of NPC in stages I, II, III, and IV: the 5-year OS of stage I was improved by about 3%, and the OS of stages II, III, and IV were improved by 14%, 12%, and 19%, respectively[11,12]. Zhang *et al*.[13] chose 190 patients treated with primary NPC treated with IMRT and another 190 patients treated with 2D-CRT according to the matched ratio of 1:1 to compare treatment effect and toxicity, and found the 4-year DMFS, LRFS, progression-free survival (PFS), and OS of patients treated with IMRT were improved by approximately 5%, 12%, 15%, and 13%, respectively. Meanwhile, IMRT can reduce some radiation-related complications in NPC patients compared with 2D-CRT. Previous studies have confirmed that IMRT changed the failure pattern of NPC from local recurrence and distant metastasis to predominantly distant metastasis in patients treated with 2D-CRT[9-11,13]. Phase III clinical trials based on 2D-CRT have confirmed that concurrent chemoradiotherapy can improve treatment outcomes and has been regard as standard treatment modality for locoregionally advanced NPC[14-16]. Chemotherapy provided no significant benefit to IMRT in locoregionally advanced NPC, but increased toxicities[17,18].

Previous results have demonstrated that in comparing with 2D-CRT, both the clinical outcomes and failure patterns have changed in NPC patients treated with IMRT. Thus, further investigation of treatment modality is warranted. Although there are many reports on IMRT for NPC, sample size is relatively small and the difference of treatment outcomes among different T and N combination subgroups was rarely analyzed. Therefore, we retrospectively analyzed the long-term clinical outcomes of 865 patients with NPC treated with IMRT, and performed the analysis of treatment outcomes stratified by different combination of T and N classification to explore the treatment strategy for patients with different T and N stage diseases.

Patients and Methods

Clinical data

Clinical data of 865 NPC patients treated at the Sun Yat-sen University Cancer Center between May 2001 and January 2008 were collected and analyzed. Cases met the following criteria were eligible for this study: pathologically proven NPC with no distant metastasis, nasopharynx computed tomography (CT) or magnetic resonance imaging (MRI) performed before primary treatment, and receiving radical IMRT at initial diagnosis. Of 865 patients with NPC, 673 were males and 192 were females, with a sex ratio of 3.5:1. Their age range was 13 to 78 years, with a median age of 43 years. According to the UICC 2002 staging criteria, there were 452, 210, 410, and 164 patients with stage I, II, III, and IVa disease, respectively, as shown in Table 1.

Radiotherapy

Primary nasopharyngeal tumor and the upper neck were treated with IMRT, whereas the lower neck and the supraclavicular fossae were treated with a single anterior split field by conventional RT with a dose of 50 Gy in 2-Gy daily fractions. All patients were immobilized in the supine position with a head, neck, and shoulder thermoplastic mask. Two set images, with and without contrast, were obtained from the CT simulator for treatment planning purposes. All patients were scanned with serial 3-mm slices from the vertex through the clavicles. Inverse IMRT planning was performed using the Corvus system, version 3.0 (Peacock, Nomos, Deer Park, IL), and a MiMi multileaf collimator (Nomos, Sewickly, PA) was used for planning and treatment. The delineation of target volumes and adjacent critical organs, and the doses to these target volumes and organs referred to a previously described institutional treatment protocol[19]. The prescribed doses and

distribution of each target volume are shown in Table 2.

Chemotherapy

Of patients with early stage NPC (T1–2N0–1M0), 198 patients were treated with IMRT alone, 43 with concurrent chemotherapy, and 21 with induction plus concurrent chemotherapy. Of patients with locoregionally advanced disease (T3–4N0–3M0 or T1–4N2–3M0), 101 were treated with IMRT alone, 222 with concurrent chemotherapy, 207 with induction plus concurrent chemotherapy, 35 with concurrent chemotherapy plus adjuvant chemotherapy, and 38 with induction chemotherapy or adjuvant chemotherapy.

Follow-up and statistical methods

Follow-up duration was calculated since completion of treatment. Median follow-up duration for the whole group was 40 months (range, 6 to 104 months). Data was analyzed employing SPSS13.0 statistic soft package. Survival rates were estimated using the Kaplan-Meier method. Differences between subgroups of patients were analyzed using the log-rank test. Risk ratio of death was calculated using the Cox regression risk model. A value of $P < 0.05$ was considered to be significantly different.

Results

Clinical treatment outcomes

Of 865 patients, 170 (19.5%) developed failure after treatment, with 5-year OS, LRFS, and DMFS at 83.0%, 90.4%, and 84.0%, respectively. Locoregional relapse mostly (68.6%) occurred within 1 to 3 years after treatment, fewer (25.7%) occurred during the fourth and fifth years, and quite rare (5.7%) occurred after 5 years. Most distant metastases (87.8%) occurred within 1–3 years. Distant metastasis was the major failure pattern after treatment, local relapse was the secondary pattern with cervical lymph node relapse occurring rarely (Table 3). With T stage elevation, the 5-year LRFS of patients gradually decreased. LRFS were significantly different between subgroups of patients with different T stage disease, except for subgroups with stages T1 and T2 disease, indicating T stage was still effective in predicting risk of local relapse (Table 4). DMFS was significantly different between subgroups of patients with different N stage disease; N stage was directly related to the risk of distant metastasis. No significant differences in OS were found between stages I and II or between stages IVa and IVb. However, significant differences were observed between other groups. With clinical stage increase, OS decreased (Table 4). In a certain T stage, as N stage increased, DMFS, PFS, and OS showed a tendency to decrease. In a certain N stage, as T stage increased, the OS also showed a tendency to decrease (Table 5).

Comparison on treatment outcomes among different treatment modalities for locoregionally advanced NPC

Most patients with locoregionally advanced NPC (T3–4N0–3M0 or T1–2N2–3M0) were treated with combined treatment modalities based on concurrent chemotherapy. Patients with poor liver or renal function and in poor condition were treated with radiotherapy alone, whereas patients with stage T3–4N0–1 disease were treated with concurrent chemotherapy, patients with

Table 1. Distribution of T and N stages of 865 patients with nasopharyngeal carcinoma (NPC)

Stage	N0	N1	N2	N3	Total
T1	52 (6.0)	16 (1.8)	9 (0.2)	2 (0.1)	79 (9.1)
T2	84 (9.7)	110 (12.7)	83 (9.6)	13 (1.5)	290 (33.5)
T3	84 (9.7)	125 (14.5)	109 (12.6)	11 (1.3)	329 (38.0)
T4	43 (5.0)	71 (8.2)	50 (5.8)	3 (0.3)	167 (19.3)
Total	263 (30.4)	322 (37.2)	251 (29.0)	29 (3.4)	865 (100.0)

Data are presented as numbers of patients, with percentages in parentheses.

Table 2. The prescription doses to target volumes and dose-volume statistics

Target	Mean volume (cm^3)	Goal dose (Gy)	Fractions	Maximum mean dose (Gy)	Minimum mean dose (Gy)	Mean dose (Gy)
GTV	33.93	68	30	80.59	64.33	74.45
CTV1	58.89	60	30	79.57	54.54	69.85
CTV2	247.00	54	30	77.66	38.71	62.37

Table 3. Patterns of failures in 170 NPC patients after treatment

Patterns of failure	No. of patients (%)
Primary recurrence	38 (22.4)
Nodal recurrence	10 (5.9)
Primary, nodal recurrence	7 (4.1)
Distant metastasis	
Lung metastasis	16 (9.4)
Liver metastasis	23 (13.5)
Bone metastasis	24 (14.1)
Mediastinal metastasis	2 (1.2)
Multiple metastasis	35 (20.6)
Distant metastasis, primary and/or nodal recurrence	15 (8.8)

Table 4. Five-year survival rate of patients with different stage NPC

T stage	No. of patients	LRFS[a] (%)	N stage	No. of patients	DMFS[b] (%)	Clinical stage	No. of patients	OS[c] (%)
T1	79	100.0	N0	263	96.8	I	52	98.1
T2	290	95.3	N1	322	85.0	II	210	95.8
T3	329	88.6	N2	251	73.5	III	410	80.3
T4	167	80.5	N3	29	62.1	IVa–b	193	68.9

LRFS, local recurrence-free survival; DMFS, distant metastasis-free survival; OS, overall survival.
[a] $\chi^2 = 27.74$, $P < 0.01$; [b] $\chi^2 = 67.44$, $P < 0.01$; [c] $\chi^2 = 2.81$, $P = 0.59$.

Table 5. Five-year survival rate of patients with different T and N stage NPC

Group	No. of patients	DMFS	PFS	OS	Group	No. of patients	DMFS	PFS	OS
T1N0	52	100.0	100.0	93.8	T3N1	125	85.0	72.2	80.9
T1N1	16	100.0	100.0	100.0	T3N2	109	72.1	63.4	63.1
T1N2	9	100.0	100.0	100.0	T4N0	43	90.6	59.1	68.2
T2N0	84	98.8	97.6	96.3	T4N1	71	66.8	63.5	74.2
T2N1	110	94.2	84.1	94.6	T4N2	50	51.0	43.9	66.0
T2N2	83	83.4	72.6	84.5	T1–2N3	15	73.3	73.3	80.0
T3N0	84	96.6	88.2	98.8	T3–4N3	14	50.0	50.0	45.7

PFS, progression-free survival; other abbreviations as in Table 4.

stage T1–4N2–3 disease were treated with induction chemotherapy plus concurrent chemotherapy for their higher risk of distant metastasis, and patients failing to achieve complete remission after radiotherapy were treated with adjuvant chemotherapy. When employing IMRT for locoregionally advanced NPC, the treatment outcomes of radiotherapy alone, induction chemotherapy plus radiotherapy or radiotherapy plus adjuvant chemotherapy, concurrent chemoradiotherapy, induction chemotherapy plus concurrent chemoradiotherapy, and concurrent chemoradiotherapy plus adjuvant chemotherapy were similar. Comparing with those treated with IMRT alone, patients failed to benefit from various combined treatment modalities of radiotherapy and chemotherapy, as shown in Table 6.

Death risk of NPC patients in various T and N combination subgroups

Based on T1–2N0 (risk ratio = 1), with death being the endpoint, sex, age and combined with chemotherapy or not being the covariates, the Cox regression model was used to calculate risk ratios of death in various T and N combination subgroups (Figure 1). T1N0 was analyzed together with T2N0 due to limited case fold; similarly, T1N1 and T2N1, T1N2 and T2N2, T1N3 and T2N3, and T3N3 and T4N3 were combined and analyzed. As T and N stage combination increased,

Table 6. Comparison of 5-year survival rates in patients with stage T3–4N2–3 NPC treated with different treatment strategies

Treatment strategy	No. of patients	LRFS[a] (%)	DMFS[b] (%)	OS[c] (%)	RRFS[d] (%)	PFS[e] (%)
RT alone	101	86.7	82.3	77.2	94.2	66.8
IChe + RT or Ach + RT	38	86.3	83.0	82.3	97.3	70.6
CCRT	222	91.6	80.7	78.7	96.6	71.4
IChe + CCRT	207	85.6	71.5	73.4	95.5	61.3
CCRT + ACh	35	95.2	73.9	80.6	100	69.8

RT, radiotherapy; IChe, induction chemotherapy; Ach, adjuvant chemotherapy; CCRT, concurrent chemoradiotherapy; RRFS, regional relapse-free survival; other abbreviations as in Tables 4 and 5.
[a] $\chi^2 = 5.06$, $P = 0.28$; [b] $\chi^2 = 1.27$, $P = 0.87$; [c] $\chi^2 = 2.81$, $P = 0.59$; [d] $\chi^2 = 4.18$, $P = 0.38$; [e] $\chi^2 = 1.32$, $P = 0.86$, among different groups.

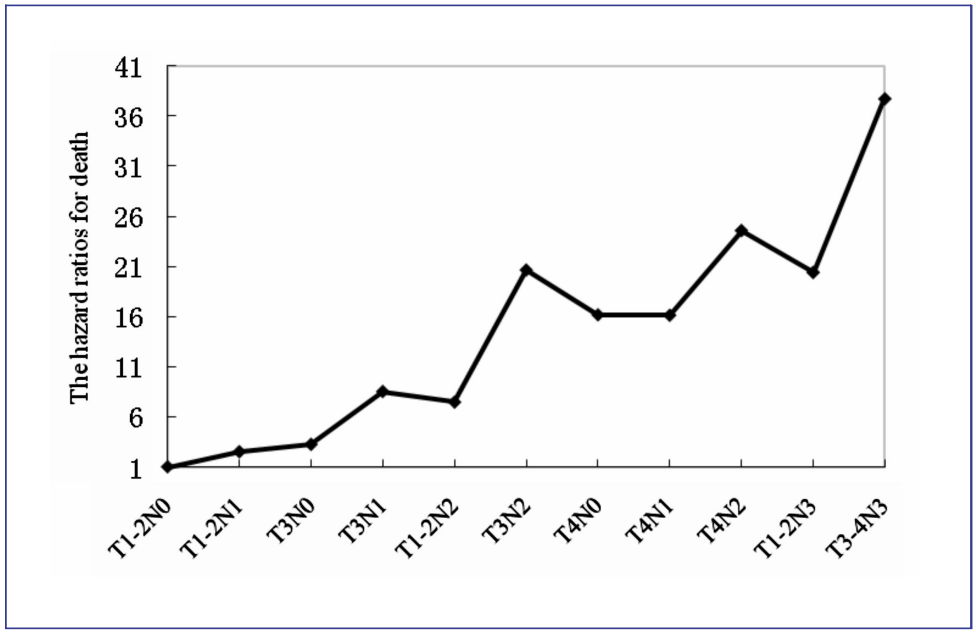

Figure 1. Risk ratios of death in patients with different T and N stage nasopharyngeal careinoma (NPC).

death risk ratio showed a tendency to gradually increase. Death risk ratio of T3N2 disease was similar to that of T4N2 disease.

Prognosis of NPC patients in various subgroups

The survival rates of NPC patients in locally advanced group (T3–4N0–1M0, 323 cases) and regionally advanced stage group (T1–2N2–3M0, 107 cases) were similar and the survival curves of the two groups were similar or interlaced. Treatment outcomes of NPC patients in early stage group (T1–2N0–1M0, 262 cases) were best, with a survival rate above 90% (Table 7). Treatment outcomes of NPC patients in locoregionally advanced stage group (T3–4N2–3M0, 173 cases) were worst, with a 5-year OS of 62.2% (Figure 2). Based on locoregionally early stage group (risk ratio = 1), belonging to low death risk group, the death risk ratio of NPC patients in various T and N subgroups gradually increased. Death risk ratios of NPC patients in locally advanced group (4.230) and regionally advanced group (4.625) were similar, belonging to media death risk group. Death risk of NPC patients in locoregionally advanced group, up to 10.402, was the highest and thus, belonged to a high death risk group.

Discussion

Radiotherapy is the principal treatment modality for non-metastatic NPC. In the present study, 865 primary NPC patients were treated with IMRT with 5-year LRFS, DMFS, and OS of 90.4%, 84.0%, and 83.0%, respectively. Treatment outcome of IMRT was improved compared with that of conventional radiotherapy[6,7,20]. Wong *et al.*[10]

Table 7. Five-year survival rates of 865 patients with different TN stage NPC

Group	No. of patients	LRFS[a] (%)	DMFS[b] (%)	OS[c] (%)	RRFS[d] (%)	PFS[e] (%)
T1–2N0–1	262	97.1	96.3	95.6	97.3	91.9
T3–4N0–1	323	87.2	84.4	80.1	98.1	72.4
T1–2N2–3	107	94.7	83.3	84.8	94.2	72.3
T3–4N2–3	173	83.0	62.3	62.2	94.0	54.8

[a] χ^2 = 18.88, P < 0.01; [b] χ^2 = 69.33, P < 0.01; [c] χ^2 = 55.90, P < 0.01 ; [d] χ^2 = 7.61, P = 0.55; [e] χ^2 = 68.13, P < 0.01, among different groups.

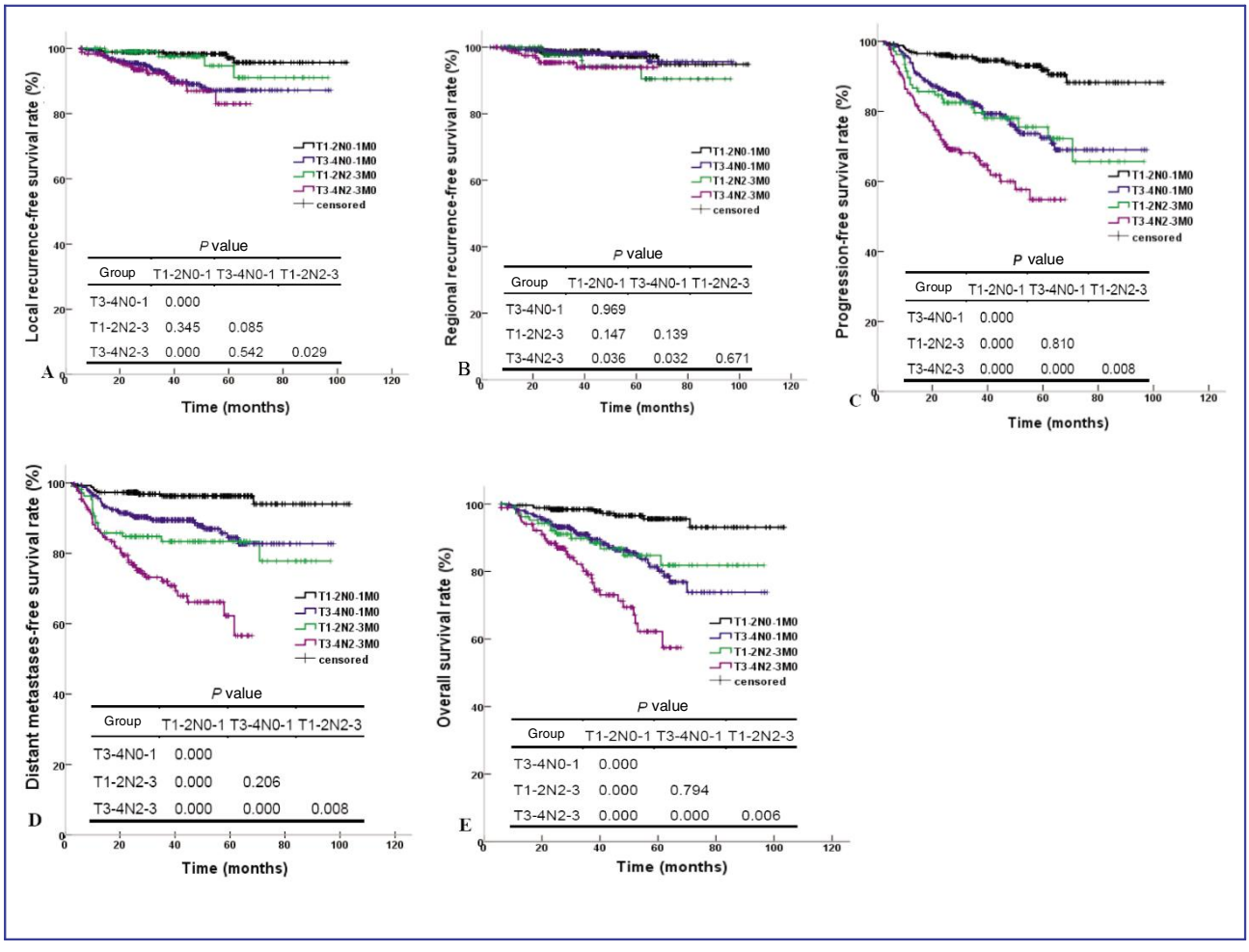

Figure 2. **Local recurrence-free survival curves (A), regional recurrence-free survival curves (B), progression-free survival curves (C), distant metastasis-free survival curves (D), and overall survival curves (E) of NPC patients in different subgroups.**

reported that the 3-year LRFS rate in patients with stage T1, T2a, T2b, T3, and T4 disease were 93.4%, 100%, 93.4%, 94.4%, and 87.8%, respectively, after IMRT, without significant differences among the three groups. Results by Tham *et al.*[21] indicated local relapsed rates of patients with stage T1–T3 NPC were similar, which is lower than that of patients with stage T4 NPC. Both studies showed when IMRT was used for NPC, the T stage failed to satisfactorily predict the local relapse rate. However, present results showed the 5-year local control rate of the nasopharynx of patients with stages T1, T2, T3 and T4 NPC gradually decreased with an increase of T stage, there were significant differences among the groups except between stages T1 and T2. Comparing with the results by Wong *et al.*[10] and Tham *et al.*[21], our results showed that T stage was effective in predicting local relapse in patients treated with IMRT, likely due to a larger case size and longer

follow-up time in the present research. In the present series, significant differences of DMFS were detected among different N stage groups. The N stage may perfectly predict distant metastasis. Most of the recurrence and metastasis of the present research occurred within 3 years after treatment, which is similar to the result of 2D-CRT[6,12]. This finding suggests a close follow-up examination should be strengthened in the former 3 years after treatment to detect early relapse or metastasis and deliver salvage treatment in time. In the present research, although the 5-year survival of patients with stages I, II, III, IVa and IVb NPC were better than that of patients with the same stage diseases treated with 2D-CRT [3,7,20,22], the 5-year survival of advanced stages (stages III and IV) was still worse than that of early stages (stages I and II).

Our results showed a direct relationship between an increased death risk and a higher TN combination stage. The treatment outcome of early stage group (T1–2N0–1M0) was the best, with a 5-year OS of up to 95.6%. Studies of NPC patients treated with 2D-CRT showed the distant metastasis rate of the N1 group was higher than that of the N0 group in early stage diseases. Therefore, combined treatment modality of radiotherapy and chemotherapy for patients with N1 stage disease was recommended [5,23,24]. We previously used IMRT for patients with early stage NPC, the 5-year tumor specific survival rate reached 97.3%, and observed similar treatment outcomes among T1N0, T2N0, T1N1, and T2N1 groups[25]. As a result, we recommend IMRT alone for the early stage group.

In general, T stage is related to local control, whereas N stage is related to distant metastasis. Present data, however, showed the advanced local disease group (T3–4N0–1M0) had a similar local control rate, distant metastasis rate, PFS, and OS with the advanced nodal disease group (T1–2N2–3M0). In addition, with the survival curves interlacing and being close to each other, the death risks of the two groups, 4.230 and 4.625, respectively, were at the same level. Zong *et al.*[23] also found advanced local disease group and advanced nodal disease group have similar treatment outcomes when employing 2D-CRT techniques for NPC patients. Compared with the advanced local disease group (T3–4N0–1M0), the LRFS, DMFS, and PFS of early stage group (T1–2N0–1M0) were improved by about 10.0%, 12.0%, and 9.5%, respectively, and its OS was improved by about 15.0%. These results indicate for patients with early N stage disease, as T stage increased, not only the risk of local failure but also the risk of distant metastasis increased. Compared with early stage group, advanced local disease group had a poorer LRFS and DMFS, considered to be related for the following reason: although IMRT could improve the target coverage of the nasopharyngeal tumor, in patients with stage T3–4 disease, doses of some targets were insufficient because of the tolerance dose constraint of organs at risk such as brain stem and temporal lobe, which led to the reduced local control. Extensive bone erosion was usually seen in patients with stage T3–4 disease. Cheng *et al.*[26] reported the distant metastasis rate increased when the bone marrow of the skull base was invaded and that invasion of the parapharyngeal venous plexus could increase the distant metastasis rate. In addition, distant metastasis may increase in some patients with T4 disease combined with invasion to the cavernous sinus, which communicates with the ophthalmic and facial veins and with the pterygoid venous plexus branching through the foramen ovale. In our study, the treatment outcome of advanced locoregional disease group (T3–4N2–3M0) was the worst, with the 5-year DMFS of only 62.3% and the highest death risk up to 10.402, which decreased by about 20.0% as compared with the advanced nodal disease group (T1–2N2–3M0) at the same N stage level, indicating that distant metastasis was related to N and T stages.

According to the results of phase III clinical trials and meta-analysis previously reported, concurrent chemoradiotherapy had the most definite survival benefit for locoregionally advanced NPC and had become a standard treatment regimen [14-16]. In these phase III clinical trials and meta-analysis, 2D-CRT technique was adopted for radiotherapy, and survival mainly benefited from the increase of local control rate. Present results show when compared with IMRT alone, IMRT combined with concurrent chemotherapy reaps no benefit for local control and survival. In addition, Lin *et al.*[18] also reported that when IMRT was used for NPC patients, the application of concurrent chemotherapy failed to improve the treatment outcome or prognosis. The 5-year RFS of the present study was as high as 90%, whereas the 3-year local control rate previously reported was up to 93%–95% [10,18,21,27]. We thought the application of IMRT improves the local control rate, which may "counteract" the effect of concurrent chemoradiotherapy on improving the local control rate and survival rate. However, there are no phase III clinical trials to identify the value of concurrent chemotherapy on locoregionally advanced NPC treated with IMRT. As a result, we recommend further investigation on the value of concurrent chemotherapy combined with IMRT on locoregionally advanced NPC.

The relapse rate and distant metastasis rate in advanced local disease group (T3–4N0–1M0), advanced nodal disease group (T1–2N2–3M0), and advanced locoregional disease group (T3–4N2–3M0) were quite high. Unfortunately, existing chemotherapeutic regimens (cisplatin plus fluorouracil) in induction chemotherapy and adjuvant chemotherapy failed to reduce distant

metastasis or improve survival[22,28-30]. In recent years, the application of new chemotherapeutic regimens and molecular target agents on head and neck cancer and NPC show great promise [31-35]. Meanwhile, the application of IMRT has improved the treatment outcome of NPC and reduced the toxicity of radiotherapy, facilitating the intensification of systemic chemotherapy. Further randomized clinical trials on the application of IMRT combined with different systemic treatment methods are necessary for the development of an effective treatment regimen to improve the prognosis of NPC patients.

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