

## Original Article

# Long-term survival of nasopharyngeal carcinoma patients with Stage II in intensity-modulated radiation therapy era

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## Abstract

**Objectives:** To evaluate the long-term survival and the role of chemotherapy in nasopharyngeal carcinoma (NPC) patients in Stage II treated by intensity-modulated radiation therapy (IMRT).

**Methods:** Three hundred and eleven NPC patients in Stage II were reviewed. All were treated with IMRT with or without chemotherapy, with 191, 20 and 100 patients being defined as T1N1M0, T2N0M0 and T2N1M0 stage, respectively.

**Results:** At a median follow-up of 57 months, the 5-year overall survival, disease-specific survival, distant metastasis-free survival, loco-regional relapse-free survival (LRRFS) and progression-free survival were 91.1, 93.5, 90.6, 95.9 and 87.6%, respectively. T2N1 patients had significant poorer survival outcomes than T1N1 patients, with T2N0 patients in between. Further analysis showed that the addition of chemotherapy could only improve LRRFS [hazard ratio (HR) 0.263, 95% confidence interval (CI) 0.083–0.839,  $P=0.024$ ], especially for T1N1 patients (HR 0.209, 95% CI 0.046–0.954,  $P=0.043$ ). For those in the T2N1M0 group, chemotherapy, as used in our series, added no benefit to any end-point.

**Conclusions:** IMRT in NPC patients in Stage II was quite therapeutic; however, different subgroups have distinct survival outcomes. Distant metastasis was the main failure pattern, especially for those with T2N1 disease, and the chemotherapy currently in use failed to treat subclinical metastatic foci effectively. Further prospective study is warranted to find out the role and the optimal schedule of chemotherapy in this subgroup of patients.

**Key words:** nasopharyngeal carcinoma, intensity-modulated radiation therapy, chemotherapy, Stage II, long-term outcome

## Introduction

Nasopharyngeal carcinoma (NPC) is an endemic disease in southern China (1). As has been recommended by the National Comprehensive Cancer Network and European Society for Medical Oncology clinical practice guidelines, the combination of chemo-radiotherapy (CRT) is

the standard treatment for loco-regionally advanced NPC (Stage II–IVb), while radiotherapy (RT) alone is regarded as the treatment of choice for Stage I NPC (2,3). However, there have been controversies regarding the treatment of Stage II NPC; the question remains whether chemotherapy is essential for all the patients in Stage II.

Treatment outcomes of Stage II NPC patients being treated with 2D-RT alone have been demonstrated to be far from satisfactory; most of them indicated that systemic treatment is needed because of the relatively high incidence of distant metastases and poor long-term survival after RT alone, and the addition of chemotherapy to RT may be translated into substantial improvements in long-term survival (4–11). Data from the most recent publications have shown that intensity-modulated radiation therapy (IMRT) can greatly increase the treatment outcomes and improve the quality of life of NPC patients when compared with 2D-RT (12). With the superb outcome of NPC treated with IMRT, it is reasonable to question the additive benefit of chemotherapy used with IMRT in Stage II. Lee et al. (13) reported their results of patients in Stage II (7th edition of American Joint Committee on Cancer, AJCC) treated by 3D-RT/IMRT can have a superb outcome, with the 5-year disease-specific survival (DSS) to be 95%. Our previous study also demonstrated that good 3-year outcomes may be obtained with IMRT without concurrent chemo-radiotherapy (CCRT) for most patients, and suggested that IMRT alone may be sufficient for Stage IIb (1997 AJCC) patients (14). However, Su et al. (15) indicated that although satisfactory survival outcomes could be achieved by IMRT alone for early-stage patients, those with T2bN1 (2002 AJCC) disease might have a greater risk of distant metastasis. Similarly, Luo et al. (16) showed that T2N1 disease (2002 AJCC) was a unique subgroup with higher risk of distant metastasis and the addition of chemotherapy is necessary to improve the treatment outcomes.

Thus, it is still a question that whether IMRT alone is sufficient for all patients in Stage II (7th AJCC)? Do different subgroups show different survival outcomes? The aim of this retrospective study is to report the long-term survival of a relatively large group of NPC patients in Stage II (7th AJCC) treated by IMRT in endemic area, and investigate whether different subgroups in Stage II had different prognosis. The potential effects of chemotherapy on treatment outcomes were addressed as well.

## Methods and materials

### Ethical statement

This retrospective study was conducted in compliance with the policy of our institution to protect the private information of patients enrolled and was approved by the institutional ethical committee. Informed consent was obtained from the subjects and/or guardians.

### Patients' characteristics

Between October 2005 and December 2010, a total of 311 histologically diagnosed NPC patients in Stage II were treated with IMRT in our institution. Of them, 191, 20 and 100 patients were staged as T1N1, T2N0 and T2N1 disease, respectively, as have been re-staged according to the 7th AJCC staging system (17). All patients completed a pretreatment evaluation according to our institutional protocol (18), and were pathologically confirmed, with 293, 14 and 4 patients being classified as World Health Organization (WHO) type III, II and I, respectively. Other clinical characteristics are listed in Table 1.

### Radiotherapy

A detailed description of the IMRT had been published previously (18). At the completion of the RT, a total of 81 patients were clinically diagnosed with persistent disease by physical examination (including endoscopic examination) and magnetic resonance imaging, including 32 in the primary site, 42 in the cervical lymph node regions and 7 in

**Table 1.** Clinical characteristics of Stage II patients

Characteristic	T1N1		T2N0		T2N1		P value
	N	%	N	%	N	%	
Age (years)							0.450
<47	100	52.4	9	45.0	45	45.0	
≥47	91	47.6	11	55.0	55	55.0	
Gender							0.805
Male	137	71.7	13	75.0	70	70.0	
Female	54	28.3	7	35.0	30	30.0	
Chemotherapy							<0.001
Yes	151	79.1	9	45.0	85	85.0	
No	40	20.9	11	55.0	15	15.0	

both. For these patients with persistent disease, all received boost treatment, either by IMRT or brachytherapy. The median dose (dose of boost treatment was included) of the primary tumour and regional lymph node were 69.75 Gy (range, 66.0–82.5 Gy) and 68.2 Gy (range, 55.8–79.2 Gy), respectively.

### Chemotherapy

Of the whole cohort, 245 patients received platinum-based chemotherapy. To be more specific, 108 patients (71 in T1 and 37 in T2 disease) received concurrent chemotherapy (CCT) with or without neo-adjuvant chemotherapy (NACT) and/or adjuvant chemotherapy (ACT), 132 patients (77 in T1 and 55 in T2 disease) received NACT with or without ACT, the remaining 5 patients underwent ACT alone. The chemotherapy ranged from one to six cycles. The most commonly used regimen for NACT and ACT was cisplatin (80 mg/m<sup>2</sup> intravenously in three daily doses) plus paclitaxel (135 mg/m<sup>2</sup> intravenously on Day 1), and a few patients received gemcitabine (1000 mg/m<sup>2</sup> intravenously on Days 1 and 8). Of the 108 patients who underwent CCT, 97 received cisplatin only (80 mg/m<sup>2</sup> intravenously in three daily doses); the remaining 11 received cisplatin plus paclitaxel.

### Follow-up and statistical analyses

Each patient was assessed weekly for treatment response and toxicity during treatment. After the completion of RT, the patients were required to be followed-up every 3 months for the first 2 years and every 3–6 months during Years 3–5. Data were analysed using SPSS version 19.0. The overall survival (OS), DSS, distant metastasis-free survival (DMFS), loco-regional relapse-free survival (LRRFS) and progression-free survival (PFS) rates were measured and calculated from the first day of diagnosis to death, death due to NPC, distant failure, the first loco-regional failure and disease progression, respectively. Univariate and multivariate analyses were performed to define independent predictors among various potential prognostic factors. A two-sided *P* value of ≤0.05 was considered statistically significant.

Major late toxicities including subcutaneous fibrosis, xerostomia, hearing loss, trismus, temporal lobe injury, cranial neuropathy and nasopharyngeal ulceration were recorded and graded according to the Radiation Therapy Oncology Group radiation morbidity scoring criteria and the Common Terminology Criteria for Adverse Events (Version 3.0).

## Results

### Survival and prognostic analysis

The median follow-up time was 57 months (range 5–105 months). Twenty-six patients died at the time of censorship; the causes of

**Table 2.** Univariate analysis of variables for Stage II patients

	N	OS	P value	DSS	P value	DMFS	P value	LRRFS	P value	PFS	P value
Gender			0.261		0.511		0.353		0.355		0.750
Male	220	90.0		92.7		89.3		95.6		86.9	
Female	91	94.5		95.6		93.4		92.6		87.3	
Age (years)			0.377		0.979		0.720		0.910		0.660
<47	154	92.9		93.5		89.9		95.2		85.9	
≥47	157	89.5		93.5		90.6		94.4		87.5	
Chemotherapy			0.801		0.665		0.366		0.014		0.619
No	66	89.6		95.3		93.5		89.4		84.7	
Yes	245	91.1		93.1		89.7		97.1		87.9	
N classification			0.897		0.834		0.925		0.877		0.740
N0	20	88.3		95.0		89.7		95.0		85.0	
N1	291	90.8		94.1		90.6		95.7		88.1	
T classification			0.056		0.016		0.014		0.941		0.051
T1	191	93.4		96.2		93.7		96.0		90.1	
T2	120	86.7		89.4		85.3		95.1		82.8	

OS, overall survival; DSS, disease-specific survival; DMFS, distant metastasis-free survival; LRRFS, loco-regional relapse-free survival; PFS, progression-free survival.

death included metastasis (13 patients), recurrence (2 patients), severe complications (3 patients), other diseases (4 patients) and unknown reasons (4 patients).

The 5-year OS, DSS, DMFS, LRRFS and PFS were 91.1, 93.5, 90.6, 95.9 and 87.6%, respectively. Potential prognostic factors, including gender, age, T classification, N classification and the use of chemotherapy were analysed by the log-rank test. As detailed in Tables 2 and 3, both log-rank test and multivariate analysis indicated that T classification was a significant prognostic factor for OS, DSS, DMFS and PFS, with the *P* value in multivariate analysis being 0.048, 0.013, 0.012 and 0.042, respectively. The addition of chemotherapy was only indicated to be a significant factor of LRRFS (*P* = 0.024).

### Subgroup analyses

There were 7 (3.7%), 1 (5%) and 4 (4%) patients appeared to have loco-regional recurrence in T1N1, T2N0 and T2N2 disease, respectively. A total of 28 patients had distant metastasis, with 11 (5.8%), 2 (10%) and 15 (15%) patients in T1N1, T2N0 and T2N1 disease, respectively. T1N1M0 stage had significantly better prognosis than T2N1M0 stage regarding OS (93.4 vs. 85.7%, *P* = 0.044) (Fig. 1A), DSS (96.2 vs. 88.2%, *P* = 0.009) (Fig. 1B), DMFS (93.7 vs. 84.3%, *P* = 0.010) and PFS (90.3 vs. 82.4%, *P* = 0.049) (Fig. 1D and 1E), with the 5-year LRRFS of both subgroups to be comparable (96.0 vs. 94.2%, *P* = 0.993) (Fig. 1C). The treatment outcomes of patients with T2N0 were indicated as intermediate, and the reported 5-year OS, DSS, DMFS, LRRFS and PFS were 87.1, 95.0, 89.7, 95.0 and 85.0, respectively. However, their difference between both T1N1 and T2N1 disease had no statistically significant (Fig. 1).

Considering the difference of prognosis among the three subgroups, further work was done to identify whether different subgroups had different predicting factors. Of the 191 patients in T1N1M0 stage, Cox model suggested that chemotherapy could only improve LRRFS (*P* = 0.043) as well (Table 4). For patients with T2N1M0 stage, 85 (85.0%) and 15 (15.0%) patients received CRT and radiation alone, respectively. As detailed in Table 5, treatment outcomes of those underwent CRT had comparable OS, DSS, DMFS, LRRFS and PFS for those who received radiation alone. For the 20 patients in T2N0M0 stage, further analysis was not performed since it was too difficult to get a meaningful conclusion from such a small sample.

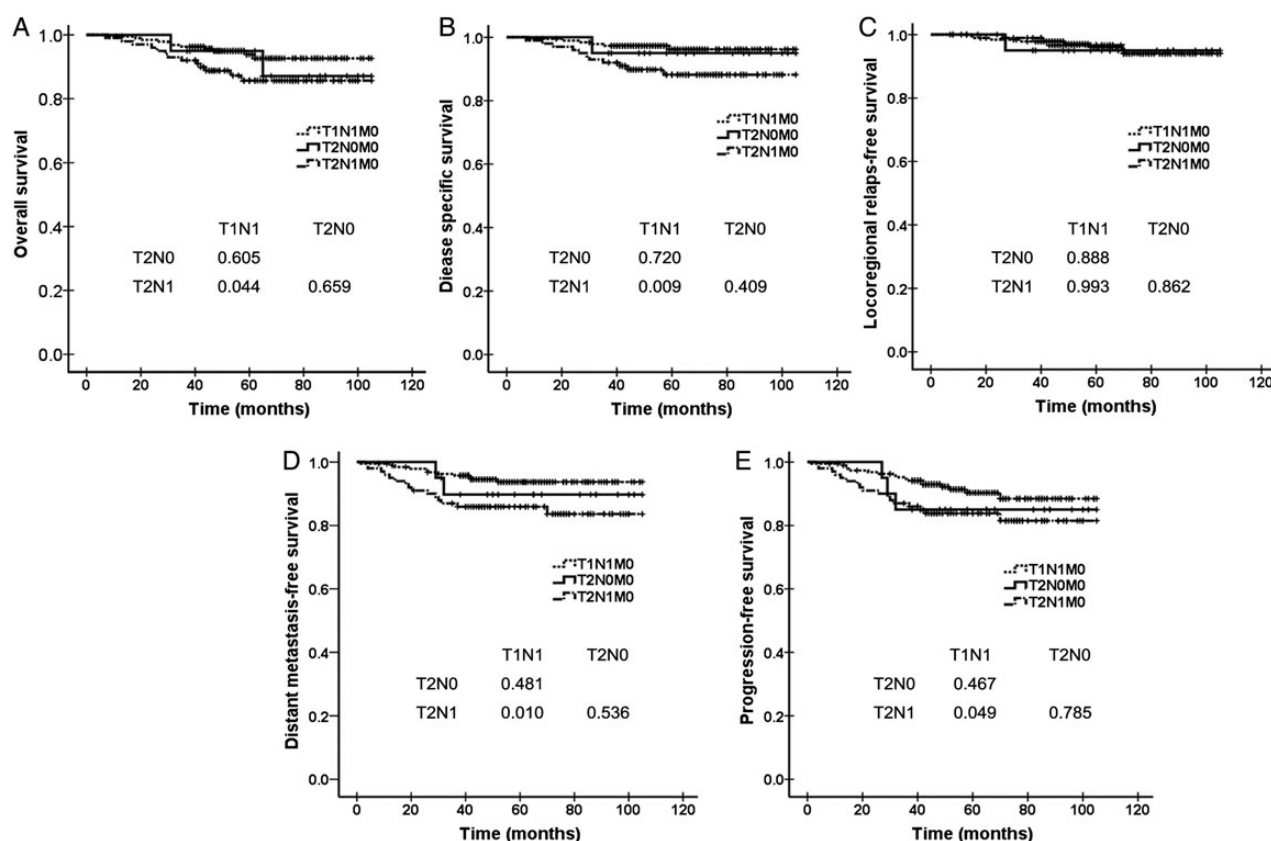
**Table 3.** Multivariate Cox proportional hazards analysis of Stage II patients

Parameters	HR	95% CI	P value
OS			
Age	1.317	0.602–2.883	0.490
Gender	0.549	0.206–1.461	0.230
RT vs. CRT	0.848	0.329–2.186	0.733
N0 vs. N1	1.474	0.316–6.872	0.614
T1 vs. T2	2.255	1.006–5.056	0.048
DSS			
Age	0.928	0.336–2.353	0.928
Gender	0.667	0.219–2.031	0.667
RT vs. CRT	1.540	0.513–4.623	0.442
N0 vs. N1	2.153	0.261–17.735	0.476
T1 vs. T2	3.530	1.300–9.590	0.013
DMFS			
Age	0.631	0.255–1.561	0.319
Gender	0.667	0.269–1.652	0.382
RT vs. CRT	1.401	0.465–4.223	0.549
N0 vs. N1	1.313	0.284–6.078	0.728
T1 vs. T2	2.725	1.246–5.959	0.012
LRRFS			
Age	0.966	0.307–3.041	0.953
Gender	1.571	0.494–4.990	0.444
RT vs. CRT	0.263	0.083–0.839	0.024
N0 vs. N1	1.357	0.145–12.681	0.789
T1 vs. T2	1.077	0.309–3.753	0.908
PFS			
Age	0.858	0.447–1.648	0.646
Gender	0.801	0.409–1.753	0.655
RT vs. CRT	0.792	0.364–1.724	0.556
N0 vs. N1	1.316	0.370–4.682	0.671
T1 vs. T2	2.020	1.025–3.978	0.042

HR, hazard ratio; confidence interval; OS, overall survival; DSS, disease-specific survival; DMFS, distant metastasis-free survival; LRRFS, loco-regional relapse-free survival; PFS, progression-free survival; RT, radiotherapy; CRT, chemo-radiotherapy.

### Late toxicities

Of the 290 patients with evaluable data of late complications, 73 (25.2%) patients suffered one or more major late complications.



**Figure 1.** Survival outcomes of T2N0M0, T1N1M0 and T2N1M0 stage: (A) overall survival, (B) disease-specific survival, (C) loco-regional relapse-free survival, (D) distant metastasis-free survival, (E) progression-free survival.

**Table 4.** Multivariate Cox proportional hazards analysis of T1N1 subgroup

Parameters	HR	95% CI	P value
OS			
Age	1.354	0.413–4.444	0.617
Gender	0.632	0.135–2.947	0.559
RT vs. CRT	1.124	0.242–5.223	0.881
DSS			
Age	1.658	0.276–9.964	0.580
Gender	0.652	0.072–5.867	0.703
RT vs. CRT	1.009	0.112–9.055	0.994
DMFS			
Age	1.417	0.431–4.655	0.566
Gender	0.994	0.262–3.768	0.994
RT vs. CRT	1.146	0.247–5.5316	0.862
LRRFS			
Age	0.846	0.189–3.796	0.827
Gender	1.818	0.399–8.272	0.439
RT vs. CRT	0.209	0.046–0.954	0.043
PFS			
Age	1.032	0.397–2.681	0.948
Gender	1.099	0.384–3.147	0.860
RT vs. CRT	0.613	0.215–1.751	0.361

HR, hazard ratio; confidence interval; OS, overall survival; DSS, disease-specific survival; DMFS, distant metastasis-free survival; LRRFS, loco-regional relapse-free survival; PFS, progression-free survival; RT, radiotherapy; CRT, chemo-radiotherapy.

**Table 5.** Multivariate Cox proportional hazards analysis of T2N1 subgroup

Parameters	HR	95% CI	P value
OS			
Age	1.000	0.332–3.010	0.999
Gender	0.397	0.087–1.804	0.231
RT vs. CRT	0.937	0.204–4.309	0.933
DSS			
Age	0.726	0.219–2.403	0.600
Gender	0.516	0.111–2.401	0.399
RT vs. CRT	1.604	0.202–12.795	0.655
DMFS			
Age	0.549	0.194–2.552	0.258
Gender	0.692	0.167–2.104	0.418
RT vs. CRT	2.228	0.290–17.108	0.441
LRRFS			
Age	0.914	0.122–6.826	0.930
Gender	0.619	0.063–6.112	0.681
RT vs. CRT	0.534	0.053–5.361	0.594
PFS			
Age	0.560	0.211–1.486	0.244
Gender	0.705	0.229–2.171	0.543
RT vs. CRT	0.784	0.278–5.456	0.784

HR, hazard ratio; confidence interval; OS, overall survival; DSS, disease-specific survival; DMFS, distant metastasis-free survival; LRRFS, loco-regional relapse-free survival; PFS, progression-free survival; RT, radiotherapy; CRT, chemo-radiotherapy.

Among them, 27 (9.3%), 11 (3.8%) and 33 (11.4%) patients had subcutaneous fibrosis, xerostomia and hearing loss of not less than Grade 2, respectively. Eight (2.8%) patients experienced trismus during follow-up (one with Grade 2 and seven with Grade 1). Sixteen patients developed central nervous system complications, including 4 (1.4%) with temporal lobe injury and 12 (4.1%) with cranial neuropathy. Of the 12 patients with cranial nerve injury, 3 died of pulmonary infection caused by deglutition barrier and bucking. Only one patient developed nasopharyngeal ulceration in our series.

## Discussion

IMRT for the treatment of NPC has been reported in numerous studies to be more effective (12). Whether the benefit gained with chemotherapy in Stage II NPC could be reduced by IMRT is unknown. The series presented here showed excellent treatment outcomes of IMRT in NPC patients in Stage II. However, T2N1M0 disease had significant poorer treatment outcomes than T1N1M0 disease, in terms of OS, DSS, DMFS and PFS. Subgroups analysis indicated that CRT could only significantly improve LRRFS for T1N1M0 patients ( $P = 0.043$ ), while survival benefits of chemotherapy for T2N1M0 disease could not be found. Treatment outcomes of T2N0 disease were indicated as an intermediate between T1N1 and T2N1 disease, but the small samples prevented us from doing further meaningful analysis. However, our results are of particular importance that we represented the first study that reported the largest cohort of patients in Stage II (7th AJCC) treated by IMRT with or without chemotherapy, and indicated that survival outcomes varied among different subgroups. T2N1M0 stage is still a unique subgroup in IMRT era, with treatment outcomes indicated to be far from satisfactory, and more aggressive systematic treatment might be needed.

To date, published data of IMRT for Stage II NPC with long-term survival have been limited. Lee et al. (13) from Hong Kong demonstrated excellent treatment outcomes of NPC patients treated by three-dimensional conformal radiotherapy (3D-CRT)/IMRT alone. In their series, 12% of the 985 patients enrolled were defined as Stage II (7th AJCC), the 5-year DSS and disease free survival (DFS) for Stage II were 95 and 90%, respectively. Su et al. (15) from Sun Yet-Sen University also reported their experience of 198 patients in Stage I–II treated with IMRT alone, among whom, 141 (71.2%) patients had Stage IIb (2002 AJCC). They reported the 5-year estimated DSS, LRFS and DMFS to be 97.3, 97.7 and 97.8%, respectively.

The effect of chemotherapy on Stage II patients in IMRT era has been reported in only three studies. The one published recently was a series of 138 patients with (AJCC 2002) Stage II treated with curative RT in 12 hospitals in South Korea, among whom, 50 (36.2%) and 78 (56.6%) patients were treated with 3D-CRT and IMRT, respectively (19). Chemotherapy was used in NACT, CCT and ACT settings, in 17.4% (24/138), 70.3% (97/138) and 30.4% (42/138) patients, respectively. The 5-year OS, PFS, LRRFS and DMFS of their study were 88.2, 74.4, 86.2 and 85.5%, respectively. They indicated that CCT significantly improved 5-year LRRFS and PFS (19). Luo et al. (16) reported a series of 69 patients with early stage (2002 AJCC) in non-endemic area; of them, 17, 22 and 31 patients were defined as Stage I, IIa and IIb, respectively. They demonstrated that the 3-year OS of NPC treated by CRT was significantly higher than that treated by IMRT alone (100 vs. 81.4%;  $P = 0.04$ ), and chemotherapy and RT were significant predictors for DMFS, local control and OS ( $P < 0.05$ ). However, our previous study showed that the comparisons between IMRT combined with chemotherapy versus IMRT alone and between CCRT versus without

showed no significant differences in the survival outcomes (14). In that study, 109 patients with Stage IIb (1997 AJCC) were enrolled, the 3-year estimated DMFS, DFS and OS reported were 94.9, 91.1 and 96.2%, respectively. With a larger cohort and a longer follow-up period, the series presented here also showed excellent treatment outcomes, with the 5-year OS, DSS, DMFS, LRRFS and DFS reported to be 91.1, 93.5, 90.6, 95.9 and 87.6%, respectively. In line with the conclusions of the Korea study (19), the addition of chemotherapy was only found to improve LRRFS ( $P = 0.024$ ). Of note, the LRRFS of the Korea study is significantly worse than that reported by Lee et al. (13), Su et al. (15) and current series; we considered its suboptimal loco-regional control may be one of the reasons that make chemotherapy significant.

Several studies have demonstrated that different subgroups had distinct survival outcomes when treated by 2D-RT (5,8). Considering the excellent results achieved by IMRT, we may question whether IMRT could narrow the gap of survival outcomes between different subgroups. Su et al. (15) indicated that IMRT alone for Stage T1N0 (2002 AJCC), T1N1, T2N0 and T2N1 yield satisfactory survival outcomes, and no differences were found in survival outcomes among these four subgroups. However, patients with Stage T2b lesions might have a relatively greater risk of local recurrence and those with T2bN1 (T2N1 in 7th AJCC) disease might have a greater risk of distant metastasis (15). Luo et al. (16) also indicated that the 3-year OS rate of the T2N1 group was significantly poorer than that of the other three groups (T1N0, T2N0 and T1N1; 74.5 vs. 100.0%;  $P = 0.01$ ), and all the 10 patients who developed treatment failure had T2N1 disease. In line with the conclusions of Su et al. (15) and Luo et al. (16), the series presented here indicated that patients in T2N1 (7th AJCC) disease still appeared as a unique subgroup in IMRT era, with most of the end-points censorship below 90%, except for LRRFS. T2N1 (15%) had the highest incidence of distant failure, followed by T2N0 (10%) and then T1N1 (5.8%). T classification was found to be a significant predicting factor for OS, DSS, DMFS and PFS. Our study may suggest that parapharyngeal space venous plexus invasion could be a potential route for haematogenous spread. Thus, it seems that the involvement of this anatomic site might be more important than that of the cervical lymph nodes regarding distant metastasis. Though, of course, the distant metastasis rate would increase further when parapharyngeal extension occurred concurrently with positive lymph node metastasis (i.e. T2N1M0 disease), as has been reported by Tang et al. (20).

The addition of chemotherapy was only found to improve LRRFS, especially for those in T1N1M0 stage. The LRRFS of those received CRT and IMRT alone in T1N1M0 stage was 97.0 and 91.3%, respectively ( $P = 0.017$ ). Considering the benefit achieved by chemotherapy for loco-regional control, it may be inappropriate to remove chemotherapy from T1N1M0 patients, since the toxicities associated with salvage treatments for loco-regional recurrence after RT alone may be greater than those related to chemotherapy. Further prospective studies should be performed to confirm the role of chemotherapy and its optimal schedule in T1N1 disease. For those with T2N1 disease, although the addition of chemotherapy could not further increase the survival rate, the treatment outcomes for this subgroup were far from satisfactory, suggesting that chemotherapy is still needed in this subgroup of patients; the main issue now is how chemotherapy should be given. A well-designed, prospective, randomized and multi-centre trial is required to investigate the optimal way to give chemotherapy in T2N1 patients, in terms of timing of chemotherapy and use of chemotherapy agents.

We do agree that applying a uniform treatment strategy to all the patients in Stage II is inappropriate. The main point to debate now is whether it is necessary to deliver chemotherapy to all patients in Stage II, and how to find out the unique subset that would benefit from the addition of chemotherapy and how chemotherapy should be given to different subgroups in Stage II. All these uncertainties highlighted the necessity of additional investigation in prospective setting. With further research into other predicting factors of NPC, such as tumour volume (21), serum lactate dehydrogenase (22), comorbidity (23) and Epstein-Barr virus Deoxyribonucleic acid (EBV-DNA) (24–26) and other molecular prognostic markers, it is likely that these will be taken in conjunction with stage classification in grouping patients into different prognostic groups, each with different recommended treatment. This kind of approach has been adopted for patients with human papillomavirus-related oropharyngeal carcinoma, as have been reported by Huang et al. (27) from Canada. Nomograms, which emerged as a simple and yet advanced method to generate an individual probability of a clinical event, such as recurrence and distant metastasis, by integrating diverse prognostic and determinant variables might assist these patients and physicians alike in all aspects of decision-making (28).

Several limitations should be addressed in our series. Firstly, the retrospective nature of the study certainly served as an inherited and fundamental pitfall; prospective randomized control clinical trials should be conducted. Secondly, chest computed tomography (CT) scans were not performed in all patients; only some of them received chest X-ray as the pretreatment evaluation. This may lead to omissions of some distant metastases at diagnoses since the sensitivity of chest X-ray is comparatively low in detecting lung metastases when compared with that of CT scan. Finally, the chemotherapy was not protocolized and used at discretion of the attending physician of individual cases, in terms of the indications, timing of chemotherapy and chemotherapy agents to use. This limited our ability to perform any meaningful and scientific analysis, and further well-designed prospective study by multicentre collaboration is warranted.

## Conclusions

IMRT in NPC patients with Stage II was quite therapeutic. However, different subgroups of early-stage NPC have distinct survival outcomes. Distant metastasis was the main failure pattern, especially for those with the T2N1 disease. Chemotherapy currently in use failed to treat subclinical metastatic foci effectively. Further prospective study is warranted to confirm the role of chemotherapy in every subgroup of Stage II, and find out the optimal sequence and regimen of chemotherapy to be used with IMRT.

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## Conflict of interest statement

None declared.

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