

Original Article

A new T staging system for nasopharyngeal carcinoma based on intensity-modulated radiation therapy: results from a prospective multicentric clinical study

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Abstract: Purpose: This prospective multicentric study aimed to establish a new clinical T staging standard for nasopharyngeal carcinoma (NPC) based on intensity-modulated radiotherapy (IMRT). Methods and materials: Between January 2006 and December 2009, four hundred and ninety-two NPC patients undergoing IMRT were staged according to the seventh edition of the UICC/AJCC staging system. The Kaplan-Meier method was used to calculate survival rates, and the log-rank test was used to compare survival differences. Results: The 5-year overall survival (OS), disease-free survival (DFS), recurrence-free survival (RFS), and distant metastasis-free survival (DMSF) rates were 80.5%, 78.6%, 94.1%, and 84.3%, respectively. Univariate and multivariate analyses showed that the invasion of the nasal cavity, parapharyngeal space, oropharynx, skull base, internal pterygoid muscle, external pterygoid muscle, paranasal sinus, infratemporal fossa, orbit, cranial nerves, cavernous sinus, and intracalvarium were independent prognostic factors ($P < 0.05$). According to the results of risk variety and survival curves, we suggest that the new T staging system for NPC based on magnetic resonance imaging and intensity modulated radiation therapy can be classified as T1 (nasopharynx, nasal cavity, parapharyngeal space, oropharynx, skull base and internal pterygoid muscle) and T2 (external pterygoid muscle, paranasal sinus, infratemporal fossa, orbit, cranial nerves, cavernous sinus and intracalvarium). Compared to the seventh edition of UICC/AJCC staging system, our new recommended staging system performs better in risk difference and distribution balance. Furthermore, the differences between the substages of 5-year curves of LRFS, DMFS and OS were all statistically significant in our new recommended staging system. Conclusions: Our new recommended staging system is more adaptable to IMRT and can predict the prognosis of NPC patient in a more objective and accurate manner.

Keywords: Nasopharyngeal carcinoma, intensity modulated radiation therapy, T staging, prognosis, magnetic resonance imaging

Introduction

In the past 10 years, diagnosis and treatment of nasopharyngeal carcinoma (NPC) have dramatically improved. Magnetic resonance imaging (MRI) has become the preferred imaging tool for detecting NPC. It has been proven by many researchers that, compared to computed tomography (CT), MRI can more clearly display

the invasion area of lesions and lead to a change in staging [1, 2]. Additionally, intensity-modulated radiotherapy (IMRT) has gradually replaced regular two-dimensional radiotherapy (2D-RT) as the mainstream therapy for NPC [3-5]. Combination therapy, with IMRT as the principle component, has dramatically improved the prognosis for NPC patients, with 5-year overall survival (OS) rates of over 80% [6-12].

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While significantly improving the local control rate, this technology also reduces the RT-related side effects [13].

The improved outcomes may be attributed to the following factors: (1) compared to 2D-RT, IMRT, with a capacity to provide highly conformal and precise coverage with sharp dose gradients, has been accepted as the standard treatment technique for NPC [14], with regional control rates for stages T1-T3 and stage T4 of 94%-99%, and 83%, respectively [15]; (2) coverage of parapharyngeal space and skull base provided by IMRT can avoid the problem of low radiation doses to these regions, which commonly exists in conventional field arrangement of regular 2D-RT, and improve the regional control rate for T2 and T3 stages [16]; (3) the application of conformal radiation therapy and chemoradiotherapy dramatically increases the regional control rate for locoregional advanced NPC and thus makes differences between T substages statistically insignificant [17-19]. However, the seventh edition of the UICC/AJCC staging standard, published in 2009, is based on results from conventional 2D-RT techniques and fails to reflect the influence on staging of innovations in diagnosis and therapy. At present, there is still a lack of a clinical staging standard that is adaptable to IMRT. Therefore, it is imperative to establish such a new T system to make accurate predictions for prognosis and to better guide the treatment of NPC patients.

In this study, we performed a prospective multicenter clinical trial enrolling 492 NPC patients to analyze the outcomes affected by a variety of involved sites, including the nasopharynx, nasal cavity, parapharyngeal space, oropharynx, skull base, internal pterygoid muscle, external pterygoid muscle, paranasal sinus, infratemporal fossa, orbit, cranial nerves, cavernous sinus, and intracalvarium, in an attempt to establish a new clinical T staging system for NPC based on MRI and the results of IMRT.

Materials and methods

Eligibility criteria

Four hundred ninety-two (492) NPC patients treated with IMRT between January 2006 and December 2009 were selected from six hospitals in the Guangxi Zhuang Autonomous Region. Three hundred thirty-eight (338) were male and

154 were female. The median age of the group was 45 years old (range 18-81 years old). Patients who met criteria for blood counts and other tests (i.e. Karnofsky Performance Status score ≥ 70 ; serum creatinine ≤ 1.6 mg/dl and serum bilirubin ≤ 1.5 mg/dl; white blood cell $\geq 3600/\text{mm}^3$, platelet $\geq 100,000/\text{mm}^3$, and hemoglobin ≥ 12.0 g/dl for male, ≥ 11.0 g/dl for female) were eligible for the study.

Workup and staging

Before treatment, all patients were required to undergo a detailed physical examination, routine blood examination, nasopharyngeal fiberoptic examination, chest X-ray or CT, abdominal ultrasound, and MRI of the nasopharynx and neck. Patients at N2-N3 stage received additional bone scanning. All patients were staged according to the criteria of the 2009 AJCC/UICC Staging System. Written informed consent was obtained from all patients and the study was approved by the Institutional Review Board (IRB) of Guangxi Medical University.

MRI was performed with a GE Signa 1.5 T Magnetic Resonance Scanner. All patients received both plain and contrast-enhanced scanning with cross, sagittal, and coronal sections. The scanning conditions were as follows: T2WI (TR 3000~4000 ms, TE 102~110 ms), T1WI (TR 2200~2400 ms, TE 77~109 ms, TI 750 ms), and T1WI enhanced scan with position and parameters the same as those of the T1WI plain scan. The quadrature head coil was adopted with a slice thickness of 6 mm, a slice gap of 1 mm, and a matrix of 256 \times 192. The cross-section scan field ranged from the suprasellar cistern to the bottom edge of the clavicle. Gd-DTPA was used as the contrast agent.

The MRI images for each patient were independently reviewed on the PACS system by two physicians. If consensus could not be reached, the research team then defined the stage according to the staging system and other information such as cranial nerve palsy and size of lymph nodes. The locations of lymph nodes were identified according to the Radiation Therapy Oncology Group (RTOG) nodal classification criteria (2013 edition).

Target delineation and IMRT planning

Contrast-enhanced CT scanning was performed from the skull base to 3 cm below the clavicle,

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with a layer distance of 3 mm and a layer thickness of 3 mm. The target delineation was in accordance with the International Commission on Radiation Units and Measurements Reports 50 and 62. The gross tumor volume (GTV) included the primary tumor site (GTVnx), metastatic retropharyngeal lymph node (GTVrpn), and metastatic cervical lymph node (GTVnd). The clinical target volume (CTV) was adjusted according to tumor invasion. For example, CTV1 should include GTVnx, GTVrpn, the entire nasopharyngeal mucosa, and 5-mm submucosal volume; CTV2 should include CTV1, as well as some of the following: posterior nasal cavity, pterygopalatine fossa, posterior maxillary sinus, part of the posterior ethmoid sinus, lateral pharyngeal space, skull base, part of cervical vertebra, and slope. The planning target volume (PTV) was generated by adding a 3-5 mm margin to GTVs or CTVs. The prescription doses were as follows: PGTVnx and PTVrpn (68-74 Gy), PTVnd (66-70 Gy), PTV1 (60-66 Gy), and PTV2 (50-56 Gy). All targets were treated once daily, 5 times weekly, for a total fraction of 30-33. Dose constraints were within the tolerance according to the published recommendations [20, 21].

Primary sites and the neck were irradiated with coplanar radiation fields. The dose distribution on the target volumes and organs at risk was appraised slice by slice according to the dose volume histogram (DVH) and CT film. PTV required that the volume percentage relevant to 100% prescription dose curve be equal to or greater than 95%, the PTV volume percentage relevant to not less than a 110% prescription dose curve be less than 20%, the PTV volume percentage relevant to not less than a 115% prescription dose curve be less than 5%, and the PTV volume percentage relevant to less than a 93% prescription dose curve be less than 1%.

All stages were defined according to the 7th Edition of the UICC/AJCC staging standards. Of the 477 patients with Stage II-IVB disease, 93.70% (461/492) received platinum-based chemotherapy. All centers used identical chemotherapy protocols. Of these cases, 51.0% (235/461) received concurrent chemotherapy, 37.09% (171/461) received induction-concurrent chemotherapy, 7.59% (35/461) received concurrent-adjuvant chemotherapy, 4.12% (19/461) received induction-concurrent-adju-

vant chemotherapy, and 0.22% (1/461) received induction chemotherapy. Inspection of the nasopharyngeal size and neck neoplasms of patients was performed weekly during the course of treatment. The MRI data were reviewed after treatment and every six months during the follow-up.

Statistical analysis

The follow-up time was calculated from the date of treatment completion to the date of last contact or death. Time to failure was calculated from the date of treatment completion to the date of the relevant event. SPSS18.0 software (SPSS, Chicago, IL, USA) was used for statistical analysis. Kappa analysis, Kaplan-Meier method, and Long-rank test were applied to compare the distribution consistency of patients in different stages, to estimate the survival rates, and to test the differences in survival rates, respectively. The endpoints included overall survival (OS), disease-free survival (DFS), relapse-free survival (RFS), and distant metastasis-free survival (DMFS). A *p* value of <0.05 was considered statistically significant.

Results

Patient characteristics

Of the 492 patients, 3.0% (15/492), 14.4% (71/492), 35.8% (176/492), 38.0% (187/492), and 8.7% (43/492) were classified as stages I, II, III, Iva, and IVb, respectively. The patients were distributed as 6.7% in stage T1 (33/492), 18.5% in stage T2 (91/492), 33.7% in stage T3 (166/492) and 41.1% in stage T4 (202/492). There were 13.0% of patients with N0 disease, 32.3% with N1 disease, 45.9% with N2 disease, 2.2% with N3a disease, and 6.5% with N3b disease.

Treatment outcome

The median follow-up period was 64.1 months (range, 6-92 months). The 5-year OS, DFS, RFS, and DMSF for the entire group were 80.5%, 78.6%, 94.1%, and 84.3%, respectively.

Extent of primary disease invasion

In all 492 patients, the extents of primary disease invasion were in the nasopharynx (100%, 492/492), nasal cavity (25.6%, 126/492), par-

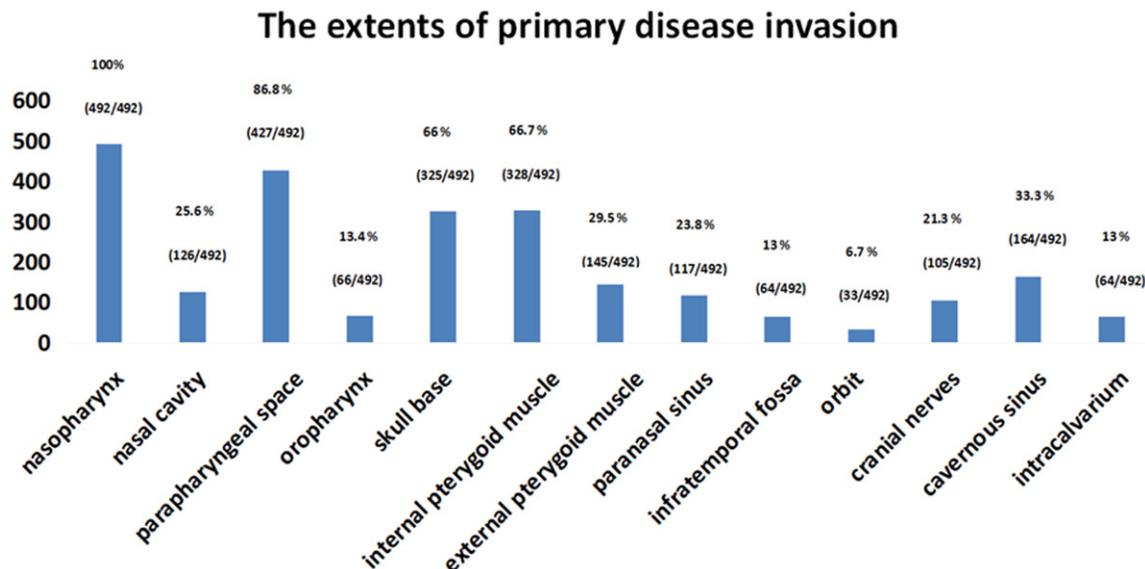


Figure 1. Extent of primary disease invasion. The number of patients and the percentage of the entire patient cohort are shown, grouped by location of primary disease invasion.

Table 1. Significance of invasion regions on univariate analysis

Region	OS	X ²	P	DFS	X ²	P	RFS	X ²	P	DMFS	X ²	P
Nasopharynx	83.7			83.4			88.2			84.7		
Nasal cavity	70.0	3.951	0.047	63.8	0.479	0.489	74.1	5.912	0.015	72.4	5.162	0.023
Parapharyngeal space	80.5	4.935	0.026	81.3	4.306	0.038	87.7	0.845	0.358	83.9	1.532	0.216
Oropharynx	71.4	10.358	0.001	67.6	0.888	0.346	73.1	7.532	0.006	75.4	5.499	0.019
Skull base	78.3	7.361	0.006	80.3	10.888	0.001	83.6	1.835	0.176	77.9	6.096	0.014
Internal pterygoid muscle	75.7	9.535	0.002	78.7	11.828	0.001	83.7	5.030	0.025	79.1	7.460	0.006
External pterygoid muscle	52.6	11.648	0.001	54.5	10.712	0.001	70.7	5.162	0.023	63.2	7.777	0.005
Paranasal sinus	53.5	11.160	0.001	63.4	8.620	0.003	73.0	8.074	0.004	55.6	9.641	0.002
Infratemporal fossa	35.4	12.811	<0.001	32.7	14.623	<0.001	25.3	6.490	0.011	59.0	17.867	<0.001
Orbit	29.2	13.496	<0.001	26.1	4.164	0.041	37.6	9.945	0.002	42.3	19.334	<0.001
Cranial nerves	32.0	10.771	0.001	47.4	28.501	<0.001	34.9	8.559	0.003	58.8	18.882	<0.001
Cavernous sinus	43.3	17.466	<0.001	54.8	23.053	<0.001	77.5	15.065	<0.001	69.5	26.253	<0.001
Intracalvarium	22.1	10.022	0.001	29.5	22.135	<0.001	67.8	14.192	<0.001	52.5	21.145	<0.001

apharyngeal space (86.8%, 427/492), oropharynx (13.4%, 66/492), skull base (66.0%, 325/492), internal pterygoid muscle (66.7%, 328/492), external pterygoid muscle (29.5%, 145/492), paranasal sinus (23.8%, 117/492), infratemporal fossa (13.0%, 64/492), orbit (6.7%, 33/492), cranial nerves (21.3%, 105/492), cavernous sinus (33.3%, 164/492), and intracalvarium (13.0%, 64/492) (**Figure 1**).

Univariate analysis according to involved sites

A univariate analysis was performed to evaluate the effect of the different involved sites on

the treatment outcome. As shown in **Table 1**, the invasions of the nasal cavity, parapharyngeal space, oropharynx, skull base, internal pterygoid muscle, external pterygoid muscle, paranasal sinus, infratemporal fossa, orbit, cranial nerves, cavernous sinus, and intracalvarium affected the survival ratios of patients (P<0.05).

Multivariate analysis according to involved sites

A multivariate analysis was also performed to evaluate the effect of the different involved

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Table 2. Significance of invasion regions on multivariate analysis (*P* value as shown)

Region	OS	DFS	RFS	DMFS
Nasal cavity	0.030	0.001	0.025	0.035
Parapharyngeal space	0.045	0.064	0.058	0.030
Oropharynx	0.031	0.002	0.043	0.040
Skull base	0.025	0.094	0.058	0.020
Internal pterygoid muscle	0.014	0.004	0.032	0.002
External pterygoid muscle	0.024	0.033	0.024	0.072
Paranasal sinus	0.001	0.106	0.003	0.025
Infratemporal fossa	0.003	0.048	0.079	0.028
Orbit	0.003	0.046	0.007	0.001
Cranial nerves	0.001	0.001	0.001	0.002
Cavernous sinus	0.031	0.051	0.011	0.027
Intracalvarium	0.014	0.042	0.009	0.083

Table 3. COX multivariate analysis of invasion regions of NPC

Region	P	β	Exp(B)	95.0% CI for Exp(B)
Nasal cavity	0.030	0.579	1.785	1.057-3.012
Parapharyngeal space	0.045	0.589	1.802	1.014-3.203
Oropharynx	0.031	0.517	1.678	1.050-2.681
Skull base	0.025	0.685	1.984	1.088-3.617
Internal pterygoid muscle	0.014	0.767	2.153	1.170-3.960
External pterygoid muscle	0.024	1.230	3.422	1.175-9.962
Paranasal sinus	0.001	1.184	3.269	1.623-6.583
Infratemporal fossa	0.003	1.426	4.161	1.610-10.754
Orbit	0.003	1.577	4.843	1.716-13.665
Cranial nerves	0.001	1.634	5.126	2.933-8.960
Cavernous sinus	0.031	1.119	3.063	1.110-8.499
Intracalvarium	0.014	1.476	4.374	1.342-14.254

sites on the treatment outcome. As shown in **Table 2**, the invasions of the nasal cavity, parapharyngeal space, oropharynx, skull base, internal pterygoid muscle, external pterygoid muscle, paranasal sinus, infratemporal fossa, orbit, cranial nerves, cavernous sinus and intracalvarium were independent prognostic factors in patients ($P < 0.05$).

New recommended T staging standard

According to the above results of the univariate and multivariate analyses, the risks of invasions of nasal cavity, parapharyngeal space, oropharynx, skull base, internal pterygoid muscle are low ($P < 0.05$), while the risks of invasions of external pterygoid muscle, paranasal sinus,

infratemporal fossa, orbit, cranial nerves, cavernous sinus and intracalvarium are high ($P < 0.05$) (**Table 3**). As shown in **Figure 2**, the survival curve of NPC patients with invasions of the parapharyngeal space ($HR=1$) is not statistically different than those of the nasal cavity, oropharynx, skull base, internal pterygoid muscle ($P > 0.05$), but is statistically different than those of external pterygoid muscle, paranasal sinus, infratemporal fossa, orbit, cranial nerves, cavernous sinus and intracalvarium ($P < 0.05$). Therefore, the new clinical NPC T staging standard based on MRI and adaptable to IMRT is recommended as T1 (nasopharynx, nasal cavity, parapharyngeal space, oropharynx, skull base and internal pterygoid muscle) and T2 (external pterygoid muscle, paranasal sinus, infratemporal fossa, orbit, cranial nerves, cavernous sinus and intracalvarium).

The survival predictive value of new recommended t staging standard

In our new recommended T stage standard, there were significant differences between the OS curves ($\chi^2=82.348$, $P < 0.05$) and RFS curves ($\chi^2=46.527$, $P < 0.05$) of T1 and T2 (**Figure 3A, 3B**). However, in the UICC/AJCC staging standard, the OS curves of T1, T2 and T3 overlap, and there are no statistical differences between T1 and T2 ($\chi^2=0.379$, $P > 0.05$), T1 and T3 ($\chi^2=0.687$, $P > 0.05$), or T2 and T3 ($\chi^2=0.285$, $P > 0.05$). The differences of the LRFS curves between T4 and the other 3 stages are statistically significant: T1 and T4 ($\chi^2=4.381$, $P < 0.05$); T2 and T4 ($\chi^2=9.629$, $P < 0.01$); T3 and T4 ($\chi^2=13.759$, $P < 0.01$) (**Figure 3C, 3D**). This suggests that our proposed T staging system provides greater stratification than the UICC/AJCC staging system.

Distribution balance

The cases numbers and ratios of our new recommended staging system and those of the UICC/AJCC staging system are listed in **Table 4**. In the UICC/AJCC staging system, the proportions of each T stage were T1 (6.7%), T2 (18.5%),

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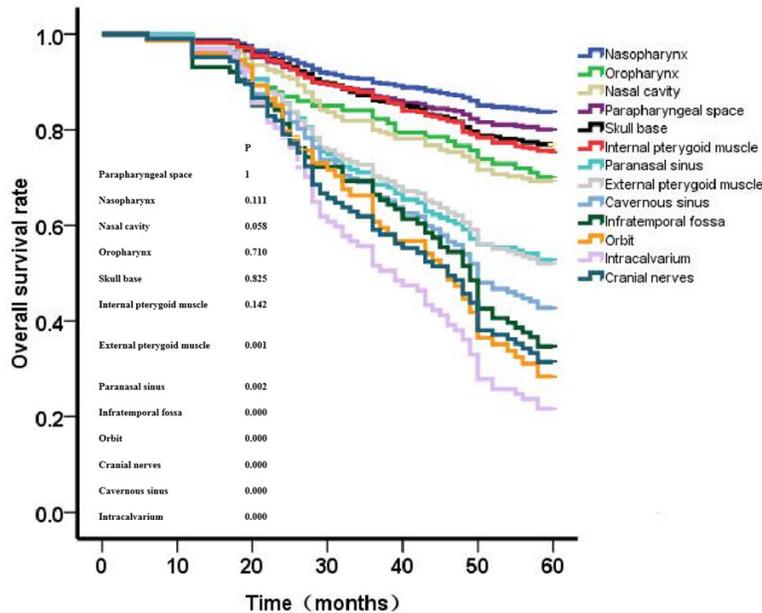


Figure 2. The OS Curves of invasion regions of NPC in UICC/AJCC. Invasions of the parapharyngeal space (HR=1) were not statistically different with those of the nasal cavity, oropharynx, skull base, and internal pterygoid muscle ($P>0.05$), but were statistically different with those of the external pterygoid muscle, paranasal sinus, infratemporal fossa, orbit, cranial nerves, cavernous sinus and intracalvarium ($P<0.05$).

T3 (33.7%) and T4 (41.1%), while in our new recommended staging system T1 and T2 are 40.9% and 59.1%, respectively, indicating the distribution balance of our recommended T staging system is more functional than that of UICC/AJCC staging system.

Risk difference

The risk difference and overall survival hazard ratios between our proposed new staging system and UICC/AJCC staging system are listed in **Table 4**, where stage T1 is chosen as the benchmark (HR=1). The risk differentials between each stage of our proposed staging system are significantly different ($P<0.05$). However, in UICC/AJCC staging system, there are no statistical differences among the risk differences of T1, T2 and T3. Together, the risk differentiation of our proposed T staging system is better than that of UICC/AJCC staging system.

Discussion

In the past 10 years, diagnosis and therapy for NPC have dramatically improved. Intensity modulated radiotherapy (IMRT) has gradually

replaced two-dimensional radiotherapy (2D-RT) as the mainstream therapy for NPC [22]. Combination therapy, with IMRT as the lead therapy, has dramatically improved the prognosis of NPC patients and the 5-year overall survival has reached 80% [6-12]. Zong et al. [23] surveyed 1241 nasopharyngeal carcinoma (NPC) patients treated with IMRT, of whom 88.7% of patients received concurrent platinum-based chemotherapy. The 5-year rates of OS, DSS, DMFS, RRFs and LRFs were 81.1%, 82.6%, 82.6%, 95.4%, and 92.9% respectively. In the present study, the 5-year OS, DFS, RFS and DMSF of the entire cohort group are 80.5%, 78.6%, 94.1% and 84.3%, respectively. This is consistent with other reports.

In this study, we observed 492 NPC patients for initial treatment and analyzed the relationship between prognosis and staging. The results of univariate and multivariate analysis show that invasions of the nasal cavity, parapharyngeal space, oropharynx, skull base, internal pterygoid muscle, external pterygoid muscle, paranasal sinus, infratemporal fossa, orbit, cranial nerves, cavernous sinus and intracalvarium are independent prognostic factors ($P<0.05$). Among them, the ratio of the invasions of the paranasal sinus is 23.8%, which is similar with several other reports. In a report based on the CT and MRI findings of 114 patients with NPC, 21%, 9% and 4% of those patients were detected with sphenoid sinus, maxillary sinus and ethmoid sinus invasion, respectively [24]. King et al. showed that the incidence rates of sphenoid sinus, maxillary sinus and ethmoid sinus invasion were 27%, 5% and 14%, respectively [25]. According to the 7th Edition of the UICC/AJCC staging system, the masticator space consists primarily of the mastication muscles, which are the medial and lateral pterygoid, masseter, and temporalis muscles. In the present study, the ratios of the

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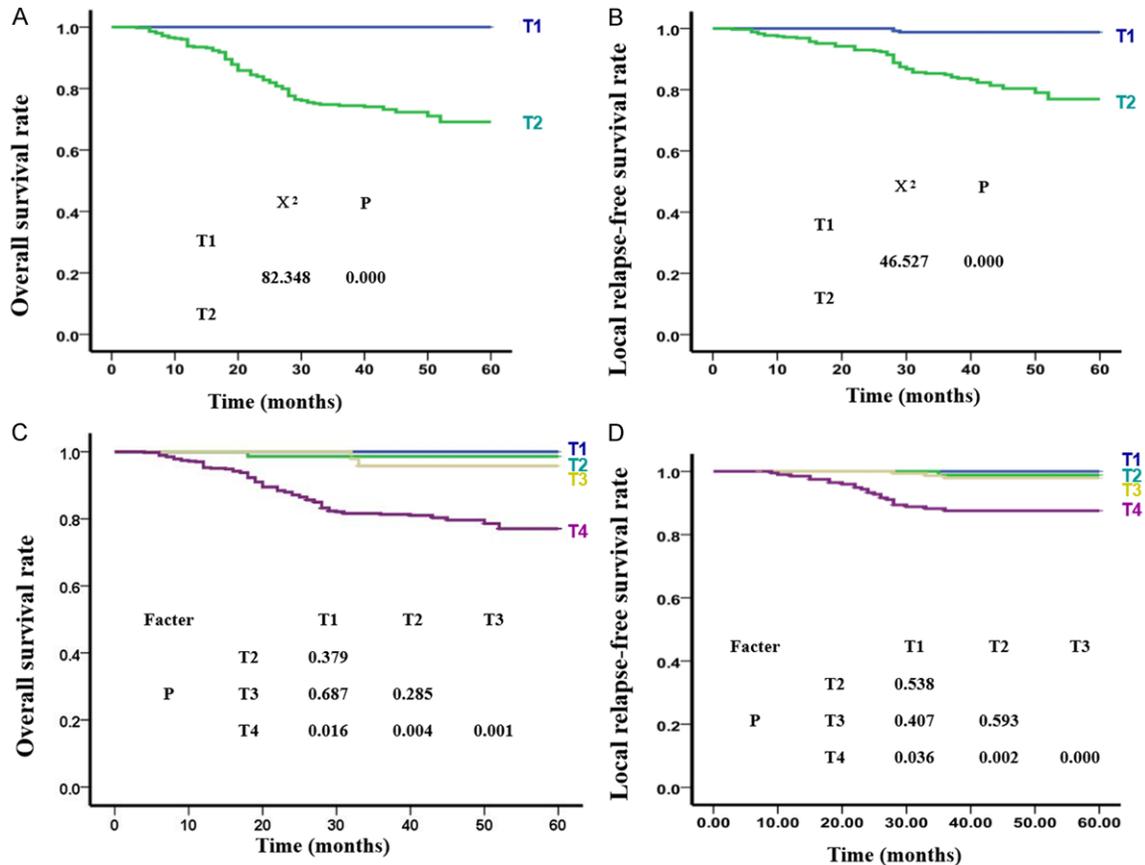


Figure 3. Comparison of OS and LRFS curves between the proposed staging system and the current UICC/AJCC staging system. A: The OS Curves of T stage of our proposed staging system. B: The LRFS Curves of the T stages of our proposed staging system. C: The OS Curves of the T stages of the UICC/AJCC Staging System. D: The LRFS Curves of the T stages of the UICC/AJCC staging system.

Table 4. Comparison of the distribution balance and risk differentiation between the two staging systems

N stage	N	Relapse-free survival Hazard ratio (95% CI)	Overall survival Hazard ratio (95% CI)
Proposed system			
T1	201 (40.9)	1	1
T2	291 (59.1)	18.072 (5.678-57.518)*	54.453 (10.753-275.732)*
UICC system			
T1	33 (6.7)	1	1
T2	91 (18.5)	0.077 (0.011-0.551)	0.041 (0.002-1.122)
T3	166 (33.7)	0.044 (0.001-1.121)	0.044 (0.001-2.375)
T4	202 (41.1)	28.470 (3.970-204.185)*	30.100 (2.509-361.137)*

*P<0.05.

invasions of the internal pterygoid muscle, external pterygoid muscle and infratemporal fossa are 66.7%, 29.5% and 3.0%, respectively, which is similar with another report showing that the ratios of the invasions of internal pterygoid muscle and external pterygoid muscle are

34.97% and 15.3% respectively [26]. In addition, compared with concurrent involvement of the medial and lateral pterygoid muscle, the medial pterygoid muscle involvement correlated with a higher OS and LRFS. NPC involving the lateral pterygoid muscle presents a worse

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survival outcome than that involving the medial pterygoid muscle. Any cancer involving the lateral pterygoid muscle should be classified in a higher T-stage subclassification. In our study, the incidence of skull base invasion is 66.0%, which is a little higher than multiple reports showing that skull base erosion could be detected in 25-63% of NPC patients [25, 27-31]. The incidence of cranial nerve invasion is 21.3%, which is consistent with previous data 2.9-36% [32-34]. The incidence of cavernous sinus invasion is 33.3%, which is a little higher than two other groups [33, 35]. NPC always invades the intracranial region and orbit through the skull base and neural foramina. Liu et al. demonstrated that intracranial and orbit extension are frequently associated with MRI-detected intracranial nerve involvement, including invasion of the cavernous sinus segment of cranial nerves III and VI, the trigeminal ganglion, cranial nerves in the cistern, the inferior orbital fissure, orbital apex, and the superior orbital fissure [36]. This is consistent with our results showing that the occurrence of invasions of the orbit and intracalvarium are 6.7% and 13.0% respectively.

The TNM staging system is the comprehensive manifestation of all manners of prognostic factors proven by research in clinical epidemiology, and the identification of new prognostic factors depends on the improvement of diagnosis and therapy. Due to the continuous improvement in diagnostic and therapeutic technologies, prognostic factors are also changing and the clinical system should also be continuously improved. The staging standard of the Seventh Edition of the UICC/AJCC is primarily based on the data and results of two-dimensional radiotherapy. As a progression of accurate radiotherapy, IMRT has been more frequently applied in the treatment of NPC than traditional two-dimensional radiotherapy. Many studies have indicated that the UICC/AJCC staging system is inappropriate for the staging of patients who have received IMRT [37]. Han et al. performed a retrospective analysis on 305 patients who had received IMRT and found that T stage was no longer the influential factor for local regional control rate and overall survival rate [38]. Lin et al. also indicated that T stage was no longer the prognostic factor that influences clinical treatment effect, but that N stage was a prominent prognostic factor that influences distant metas-

tasis-free survival and overall survival [13]. The results of one group indicated that differences in local relapse risk ratios between T2b and T1, T2b and T2a and T2b and T3 were not statistically significant [17]. Studies have shown that the differences in overall survival between T1 and T2a/T2b substages were not statistically significant [39-41], and the prognosis of T2N0 and T1N1 of stage II was similar to that of T1N0 of stage I [16, 41]. The Seventh Edition of the UICC/AJCC staging standard is based on the data of regular 2D-RT and fails to reflect the influence of innovations in diagnosis and therapies on staging. At present, there remains a lack of a clinical staging standard that is adaptable to IMRT. Therefore, it is imperative to establish such a new T standard to make accurate predictions for prognoses and provide better guidance for the treatment of NPC patients. In this study, we performed a prospective multicenter clinical trial including 492 NPC patients to analyze the NPC invasion of the surrounding tissues, including the nasopharynx, nasal cavity, parapharyngeal space, oropharynx, skull base, internal pterygoid muscle, external pterygoid muscle, paranasal sinus, infratemporal fossa, orbit, cranial nerves, cavernous sinus and intracalvarium, with the aim to establish a new clinical T staging standard for NPC based on MRI and IMRT. The results of univariate and multivariate analyses showed that invasions of the nasal cavity, parapharyngeal space, oropharynx, skull base, internal pterygoid muscle, external pterygoid muscle, paranasal sinus, infratemporal fossa, orbit, cranial nerves, cavernous sinus and intracalvarium are independent prognostic factors ($P < 0.05$). According to the results of risk variety and survival curves, we suggest that the new T staging system for NPC, based on magnetic resonance imaging and intensity modulated radiation therapy, can be classified as T1 (nasopharynx, nasal cavity, parapharyngeal space, oropharynx, skull base and internal pterygoid muscle) and T2 (external pterygoid muscle, paranasal sinus, infratemporal fossa, orbit, cranial nerves, cavernous sinus and intracalvarium). Compared to the 2009 seventh edition of the UICC/AJCC staging system, our new recommended staging system more accurately characterizes risk differentiation and distribution balance. Furthermore, the differences between the sub-stages of 5-year curves of LRFS, DMFS and OS were all statistically significant in our new recommended stag-

ing system. In conclusion, our new recommended staging system is more adaptable to IMRT and can predict the prognoses of NPC patients in a more objective and accurate way.

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Disclosure of conflict of interest

None.

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