The evolution of the nasopharyngeal carcinoma staging system over a 10-year period: implications for future revisions

Si-Qi Tang, Yan-Ping Mao, Cheng Xu, Rui Guo, Wen-Fei Li, Ling-Long Tang, Ying Sun, Jun Ma

Department of Radiation Oncology, Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine; Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangzhou, Guangdong 510060, China.

Abstract

Background: The classification criteria and staging groups for nasopharyngeal carcinoma described in the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) staging system have been revised over time. This study assessed the proportion of patients whose staging and treatment strategy have changed due to revisions of the UICC/AJCC staging system over the past 10 years (ie, from the sixth edition to the eighth edition), to provide information for further refinement.

Methods: We retrospectively reviewed 1901 patients with non-metastatic nasopharyngeal carcinoma treated in our cancer center between November 2009 and June 2012. The Akaike information criterion and Harrell concordance index were applied to evaluate the performance of the staging system.

Results: In total, 25 (1.3%) of the 1901 patients who were staged as T2a according to the sixth edition system were downgraded to T1 in the eighth edition; 430 (22.6%) staged as N0 in the sixth edition were upgraded to N1 in the eighth edition; 106 (5.6%) staged as N1/2 in the sixth edition were upgraded to N3 in the eighth edition. In addition, 51 (2.7%) and 25 (1.3%) of the study population were upstaged from stage I to stage II and stage II to stage IVa, respectively; 10 (0.5%) was downgraded from stage II to stage I. The survival curves of adjacent N categories and staging groups defined by eighth classification system were well-separated. However, there was no significant difference in the locoregional failure-free survival ($P = 0.730$) and disease-free survival ($P = 0.690$) rates between the T2 and T3 categories in the eighth edition classification system.

Conclusions: Modifications to the tumor-node-metastasis staging system over the past 10 years have resulted in N classification changes in numerous cases. Although the eighth edition tumor-node-metastasis staging system better predicts survival outcomes, the T classification could be simplified in future revisions.

Keywords: Nasopharyngeal carcinoma; Tumor-node metastasis staging system; Prognosis

Introduction

The tumor-node-metastasis (TNM) staging system for nasopharyngeal carcinoma (NPC) is crucial for predicting prognosis, planning treatment strategies, facilitating treatment stratification, and uniformly exchanging clinical data.[1] However, given the advances in detection and therapeutic techniques, the TNM staging system must be routinely modified to remain clinically useful worldwide. In particular, the use of magnetic resonance imaging (MRI) has allowed more accurate evaluation of local tumor extension and lymph node status than computed tomography (CT),[2] and positron-emission tomography/CT (PET/CT) has improved the detection of small nodal lesions as well as distant metastases.[3-5] Moreover, the introduction of new radiation modalities, such as intensity-modulated radiotherapy (IMRT), has improved the targeting of tumor tissues, allowing sufficient dose escalations to the gross tumor volume.[6,7] Indeed, the most recent (eighth) edition of the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) staging system released in 2016 is mainly based on studies from the IMRT era.[8]

In the past, the staging systems for NPC were different in Western and Eastern countries.[9] In particular, the AJCC staging manual was mainly modified in response to studies from European and American countries. However, since the sixth edition staging system, data from the mainland of China have been included in the revisions. Indeed, the eighth edition staging system was refined in light of the

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000000978

Correspondence to: Prof. Jun Ma, Department of Radiation Oncology, Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine; Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, 651 Dongfeng Road East, Guangzhou, Guangdong 510060, China
E-Mail: majun2@mail.sysu.edu.cn

Copyright © 2020 The Chinese Medical Association, produced by Wolters Kluwer, Inc. under the CC-BY-NC-ND license. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Chinese Medical Journal 2020;133(17)

Received: 01-04-2020 **Edited by:** Ning-Ning Wang

Table 1: Comparison of the sixth, seventh, and eighth editions of the UICC/AJCC staging system for nasopharyngeal carcinoma.

Stage	Sixth Edition	Seventh Edition	Eighth Edition
T category			
T0	-	-	No tumor identified, but EBV-positive cervical node(s) involvement
T1	Nasopharynx		
	Nasopharynx, oropharynx or nasal cavity without parapharyngeal extension	Nasopharynx, oropharynx or nasal cavity without parapharyngeal extension	
T2		Parapharyngeal extension	Parapharyngeal extension, adjacent soft tissue involvement (medial pterygoid, lateral pterygoid, prevertebral muscles)
T2a	Oropharynx and/or nasal cavity without parapharyngeal extension	-	-
T2b	Parapharyngeal extension	-	-
T3	Bony structures and/or paranasal sinuses	Bony structures of skull base and/or paranasal sinuses	Bony structures (skull base, cervical vertebra) and/or paranasal sinuses
T4	Intracranial extension, involvement of cranial nerves, hypopharynx, orbit, or with extension to the infratemporal fossa/masticator space	Intracranial extension, involvement of cranial nerves, hypopharynx, orbit, or with extension to the infratemporal fossa/masticator space	Intracranial extension, involvement of cranial nerves, hypopharynx, orbit, parotid gland, or extensive soft tissue involvement (beyond the lateral surface of the lateral pterygoid muscle)
N category			
N0	No regional lymph node metastasis	No regional lymph node metastasis	No regional lymph node metastasis
N1	Unilateral cervical lymph node (s), ≤6 cm, above supraclavicular fossa	Unilateral cervical, unilateral or bilateral retropharyngeal lymph node(s), ≤6 cm, above supraclavicular fossa	Unilateral cervical, unilateral or bilateral retropharyngeal lymph node(s), ≤6 cm, above the caudal border of cricoid cartilage
N2	Bilateral lymph node(s), ≤6 cm, above supraclavicular fossa	Bilateral lymph node(s), ≤6 cm, above the supraclavicular fossa	Bilateral lymph node(s), ≤6 cm, above the caudal border of cricoid cartilage
N3			>6 cm and/or below caudal border of cricoid cartilage (regardless of laterality)
N3a	>6 cm	>6 cm	-
N3b	Extension to supraclavicular fossa	Extension to supraclavicular fossa	-
M category			
M0	No distant metastasis	No distant metastasis	No distant metastasis
M1	Distant metastasis	Distant metastasis	Distant metastasis
Stage/Group			
I	T1 N0 M0	T1 N0 M0	T1 N0 M0
II		T2 N0-1 M0, T1 N1 M0	T2 N0-1 M0, T0-1 N1 M0
IIA	T2a N0 M0	-	-
IIB	T2b N0 M0, T1-2 N1 M0	-	-
III	T1-3 N2 M0, T3 N0-1 M0	T1-3 N2 M0, T3 N0-1 M0	T3 N0-2 M0, T0-2 N2 M0
IV			
IVA	T4 N0-2 M0	T4 N0-2 M0	T4 or N3 M0
IVB	Any T N3 M0	Any T N3 M0	Any T, any N M1
IVC	Any T, any N M1	Any T, any N M1	-

EBV: Epstein-Barr virus; UICC/AJCC: Union for International Cancer Control/American Joint Committee on Cancer.

data from high-risk areas in China, thus synthesizing both domestic and foreign experiences.[10]

Table 1 describes the classification criteria and stage groupings among the sixth, seventh, and eighth editions of the UICC/AJCC staging systems.[8,11,12] There were two major revisions from the sixth to the seventh editions[12]: one was the involvement of the oropharynx and nasal cavity to the T1 category and the second was adding retropharyngeal lymph node metastases into the N classification system. From the seventh to the eighth edition, four revisions were made as follows: addition of

Epstein-Barr virus (EBV)-positive cervical lymph node involvement of unknown primary tumors into the T0 group; alteration of medial and lateral pterygoid muscle involvement from T4 to T2, and addition of prevertebral muscle involvement as T2; replacement of the ambiguous "masticator space" and "infratemporal fossa" in the previous T4 criteria, with a specific description of soft-tissue involvement; and a change from the previous N3b criterion of supraclavicular fossa to the lower neck (as defined by nodal extension below the caudal border of the cricoid cartilage).[8]

Previous studies have compared two adjacent editions of the UICC/AJJC staging systems for NPC;[13,14] however, the difference between the sixth and eighth editions has not been examined to date. Such analyses would help us determine the improvement of the staging system over a 10-year period and provide information for further refinement. Therefore, in this study, we performed a large-scale retrospective comparison between the sixth and eighth editions of the UICC/AJCC staging systems in patients evaluated with MRI and treated by IMRT in the endemic area of NPC.

Methods

Patient characteristics

A total of 1901 consecutive patients with newly diagnosed, non-metastatic, and histologically proven NPC treated with IMRT in our Sun Yat-Sen University Cancer Center between November 2009 and June 2012 were retrospectively reviewed. The median age was 45 years (range, 14–79 years). Of the 1901 patients included, 74.7% were males and 25.3% were females. According to the World Health Organization classification, 1890 (99.4%) of patients had NPC type II or III, and the rest 11[0.6%] had type I.

All patients underwent the following pretreatment evaluation: a complete patient history, physical examination, hematology and biochemistry profiles, MRI of both neck and nasopharynx, chest radiography, abdominal sonography, and single-photon emission CT for the whole-body bone scan. Additionally, a ^{18}F-fluorodeoxyglucose PET/CT examination was performed in 538 (28.3%) patients. All patients were restaged according to the sixth and eighth editions of the UICC/AJCC staging system.

This study was reviewed and approved by the Institutional Review Board at the Sun Yat-sen University Cancer Center. All original raw data have been uploaded to the Research Data Deposit, a public platform to file research data that ensures authenticity (http://www.researchdata.org.cn), with the identifier RDDA2020001509.

Treatment

All patients were treated by IMRT for the entire course. Target volumes were delineated following an individualized delineation protocol, which is consistent with the International Commission on Radiation Units and Measurements Reports 50 and 62. The prescribed radiation doses were 66 to 72 Gy to the planning target volume (PTV) of the gross tumor volume of the primary tumor (GTVnx), 64 to 70 Gy to the PTV of the GTV of the involved lymph nodes, 60 to 63 Gy to the PTV of the high-risk clinical target volume (CTV1), and 54 to 56 Gy to the PTV of the low-risk clinical target volume (CTV2) in 28 to 33 fractions. The mean dose delivered was 68.93 ± 1.28 Gy to the PTV of the GTVnx. All targets were treated simultaneously using the simultaneous integrated boost technique.

As for the treatment scheme, institutional guidelines recommended IMRT alone for patients with stage I disease and concurrent chemoradiotherapy with or without additional chemotherapy for those in stage II to stage IVB according to the seventh edition of the UICC/AJCC staging system. Neoadjuvant or adjuvant chemotherapy was cisplatin-based combination regimens. Concurrent chemotherapy was delivered with a platinum-based agent given weekly for two to three cycles. Deviation from institutional guidelines occurred due to the intolerance to the radiotherapy or chemotherapy. Moreover, salvage treatments such as intra-cavitary brachytherapy were provided for patients with relapsed or persistent disease. In this cohort, 242 patients were treated with IMRT only. Concurrent chemotherapy only was delivered to 689 patients. Induction and adjuvant chemotherapies, followed by concurrent chemotherapy were given to 707 and 25 patients, respectively.

Follow-up

The follow-up duration was measured from the day of initial therapy to the day of the last examination visit or death. Patients were examined every 3 months during the first 2 years, then every 6 months for 3 years thereafter, or until death. A biopsy was ordered for the patients with any clinical symptoms or imaging indicating residual or recurrent disease. The endpoints were disease-free survival (DFS), overall survival (OS), locoregional failure-free survival (LRFFS), and distant metastasis-free survival (DMFS), which were measured from the start of treatment to the first defining event.

Statistical analysis

All analyses were performed in R version 3.6.2 (www.r-project.org) and SPSS version 23.0 (IBM Corporation, Armonk, NY, USA). The actuarial rates were estimated by the Kaplan-Meier method and compared using the log-rank test.[15] The Cox proportional hazards model was used in multivariate analyses for assessing independent significance by backward elimination of insignificant explanatory variables.[16] Age, gender, and chemotherapy application were included as covariates in all tests. The Akaike information criterion (AIC) and Harrell concordance index (c-index) were applied to evaluate the performance of each staging system and calculated based on the Cox proportional hazards model.[17,18] The AIC measures how well the statistical model fits; a superior model generates a lower AIC value. Harrell c-index assesses how well the model performs; a more accurate

Table 2: Distribution of the T/N categories and stage as defined by the sixth and eighth editions of the UICC/AJCC staging system in our study population ($n = 1901$, n [%]).

Sixth edition	Eighth Edition				
	T1	T2	T3	T4	Total
T1	286 (15.0)				286 (15.0)
T2a	25 (1.3)	70 (3.7)			95 (5.0)
T2b		238 (12.5)			238 (12.5)
T3			904 (47.6)		904 (47.6)
T4				378 (19.9	378 (19.9)
Total	311 (16.4	308 (16.2)	904 (47.6)	378 (19.9)	1901 (100.0)
	N0	N1	N2	N3	Total
N0	311 (16.4)	430 (22.6)			741 (39.0)
N1		675 (35.5)		53 (2.8)	728 (38.3)
N2			299 (15.7)	54 (2.8)	353 (18.6)
N3a/b				79 (4.2)	79 (4.2)
Total	311 (16.4)	1105 (58.1)	299 (15.7)	186 (9.8)	1901 (100.0)
	Stage I	Stage II	Stage III	Stage Iva	Total
Stage I	94 (4.9)	52 (2.7)			146 (7.7)
Stage IIa/b	9 (0.5)	324 (17.0)		24 (1.3)	357 (18.8)
Stage III			890 (46.8)	61 (3.2)	951 (50.0)
Stage IVa/b				447 (23.5)	447 (23.5)
Total	103 (5.4)	376 (19.8)	890 (46.8)	532 (28.0)	1901 (100.0)

UICC/AJCC: Union for International Cancer Control/American Joint Committee on Cancer.

model has a higher c-index value. Two-tailed P values <0.05 were considered statistically significant.

Results

Patterns of treatment failure and survival

The median follow-up time in this study was 95.2 months (range, 3.4–120.4 months). In total, 219 (11.5%) patients experienced disease recurrence, 280 (14.7%) developed distant metastases, and 410 (21.6%) died. The 5-year LRFFS, DMFS, DFS, and OS were 90.1%, 86.8%, 77.6%, and 85.6%, respectively.

Distribution of T category, N category, and staging groups

The distribution agreement and discrepancies between T categories, N categories, and stage groupings defined by the sixth and eighth editions of the UICC/AJCC staging systems are shown in Table 2. Of the 1901 patients included, 25 (1.3%) who were staged as T2a according to the sixth edition system were subsequently classified as T1 in the eighth edition (ie, as oropharyngeal and/or nasal cavity extended disease). A total of 430 (22.6%) patients with N0 disease in the sixth edition system were classified N1 in the eighth edition, owing to retropharyngeal lymph node disease extension; 107 (5.6%) patients staged as N1/2 disease in the sixth edition were reclassified as N3 in the eighth edition, as they had lymphopathy below the caudal border of cricoid cartilage. Overall, 52 (2.7%) and 24 (1.3%) patients were upstaged from stage I to stage II and from stage II to stage IVa, respectively; nine (0.5%) patients were downgraded from stage II to stage I.

T classification

The LRFFS and DFS curves for the T classifications are presented in Figure 1. Regardless of the editions of the staging system, the LRFFS was generally high for all patients in all T categories. The DFS for patients classified T1 and T2a in the sixth edition system did not differ significantly ($P = 0.509$). Meanwhile, the DFS for patients classified T1 and T2 using the eighth edition system was significantly different ($P = 0.002$). For the T2 and T3 population, the LRFFS and DFS curves did not differ significantly in the eighth edition ($P = 0.730$ and $P = 0.690$). The AIC and c-index values for OS and LRFFS were similar for the sixth and eighth editions [Table 3].

N classification

The DMFS and DFS curves for the N classifications are presented in Figure 2. In both editions, the patterns of DMFS were similar to that of DFS. The DMFS for patients classified N2 and N3 in the sixth edition were not significantly different ($P = 0.056$). However, the DMFS and DFS for patients classified in adjacent N categories defined by the eighth edition system were significantly different, and there was an improved separation between N0 and N3 using the eighth edition system compared to the sixth edition. Therefore, the eighth edition was associated with superior AIC and c-index values for DFS, OS, and DMFS than the sixth edition [Table 3].

Stage grouping

The OS and DFS curves for the stage groupings are presented in Figure 3. According to the sixth edition

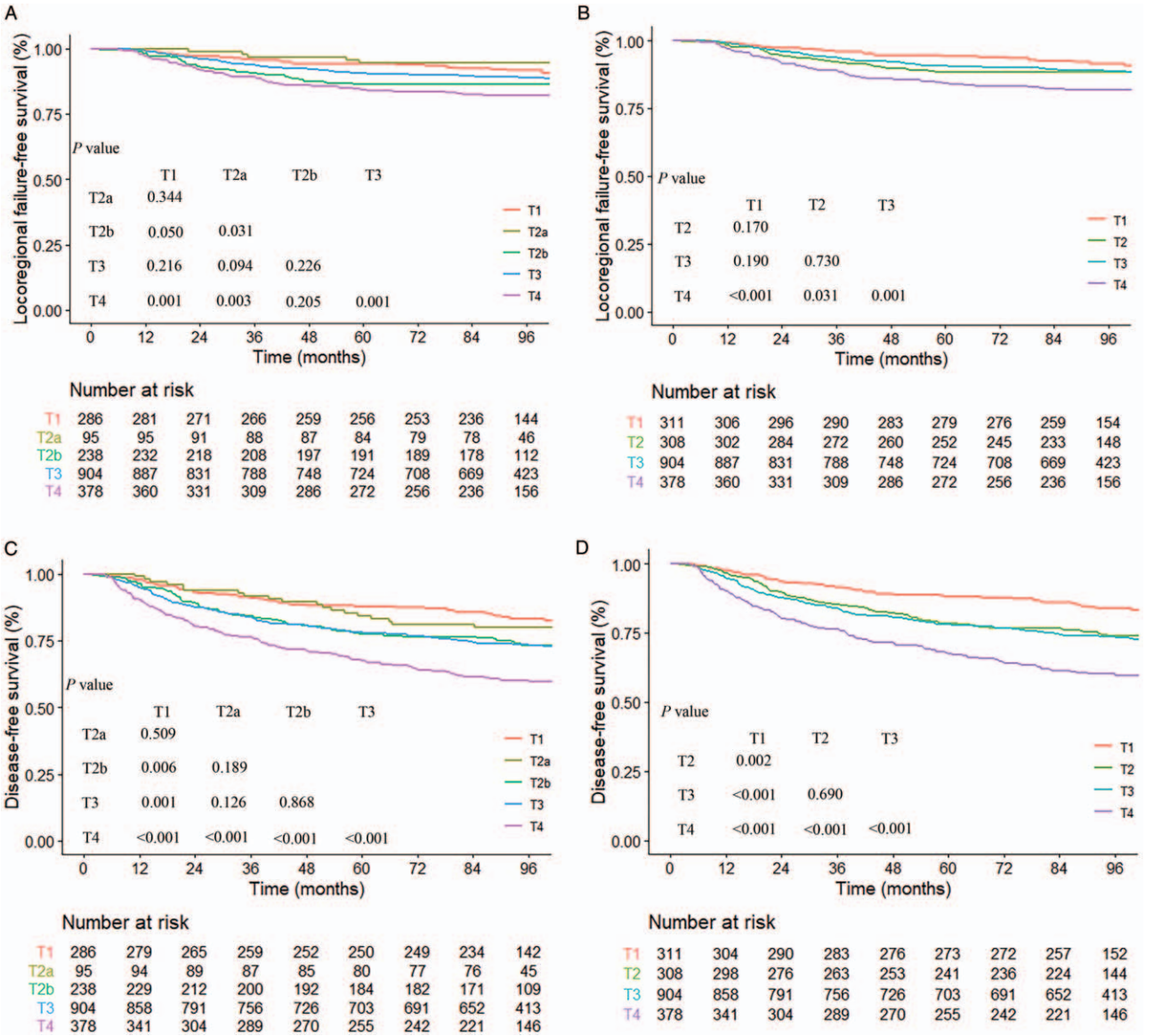

Figure 1: Locoregional failure-free survival (A, B) and disease-free survival (C, D) for each T category as defined by the sixth (A, C) and eighth (B, D) editions of the Union for International Cancer Control/American Joint Committee on Cancer staging system.

Table 3: Performance of the the sixth and eighth editions of the UICC/AJCC staging system for nasopharyngeal carcinoma.

Items	Sixth edition				Eighth edition			
	DFS	OS	LRFFS	DMFS	DFS	OS	LRFFS	DMFS
T category								
AIC*	7676.2	5989.6	3236.5	4136.3	7674.6	5987.2	3236.4	4134.9
c-index*	0.60	0.63	0.59	0.60	0.61	0.63	0.59	0.61
N category								
AIC*	7644.5	5961.5	3233.4	4094.5	7620.4	5941.0	3234.2	4052.8
c-index*	0.63	0.65	0.60	0.65	0.64	0.66	0.60	0.68
Stage								
AIC*	7640.1	5950.0	3230.5	4109.6	7610.4	5921.8	3228.8	4069.8
c-index*	0.63	0.65	0.60	0.63	0.64	0.67	0.60	0.67

* The AIC and c-index values were calculated using a Cox proportional hazards regression model that included age (≤45 *vs.* > 45 years), sex (male *vs.* female), and chemotherapy (yes *vs.* no). AIC: Akaike information criterion; c-index: Harrell concordance index; DFS: Disease-free survival; OS: Overall survival; LRFFS: Locoregional failure-free survival; DMFS: Distant metastasis-free survival; UICC/AJCC: Union for International Cancer Control/American Joint Committee on Cancer.

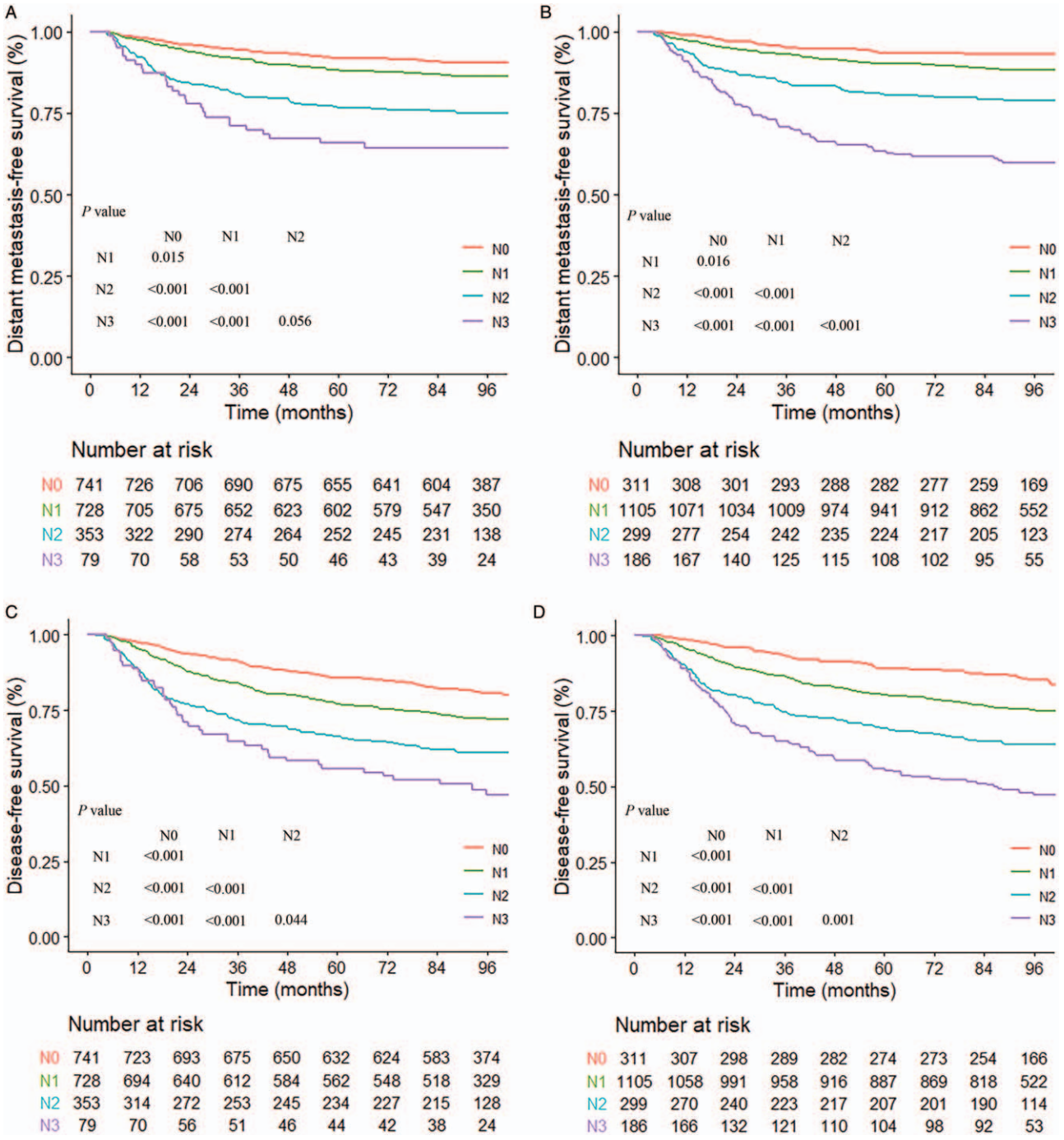

Figure 2: Distant metastasis-free survival (A, B) and disease-free survival (C, D) for each N category as defined by the sixth (A, C) and eighth (B, D) editions of the Union for International Cancer Control/American Joint Committee on Cancer staging system.

classification system, the OS and DFS curves for patients with stages I and IIa were similar ($P = 0.226$ and $P = 0.513$), as were the DFS for patients with stage IIB and stage III ($P = 0.148$). However, the OS and DFS curves were significantly different for patients with adjacent stages according to the eighth edition classification system. Thus, the eighth edition classification system produced superior AIC and c-index values for DFS, OS, and DMFS compared with the sixth edition [Table 3].

Discussion

According to the latest two revisions of staging systems, we found that 1.3% and 28.2% of patients changed their T category and N category, respectively. Moreover, despite the improvement in prognosis prediction with the eighth edition classification system over the sixth edition, mainly in terms of the N category and overall stage, the unsatisfactory separation of survival curves between T2 and T3 disease remains an issue.

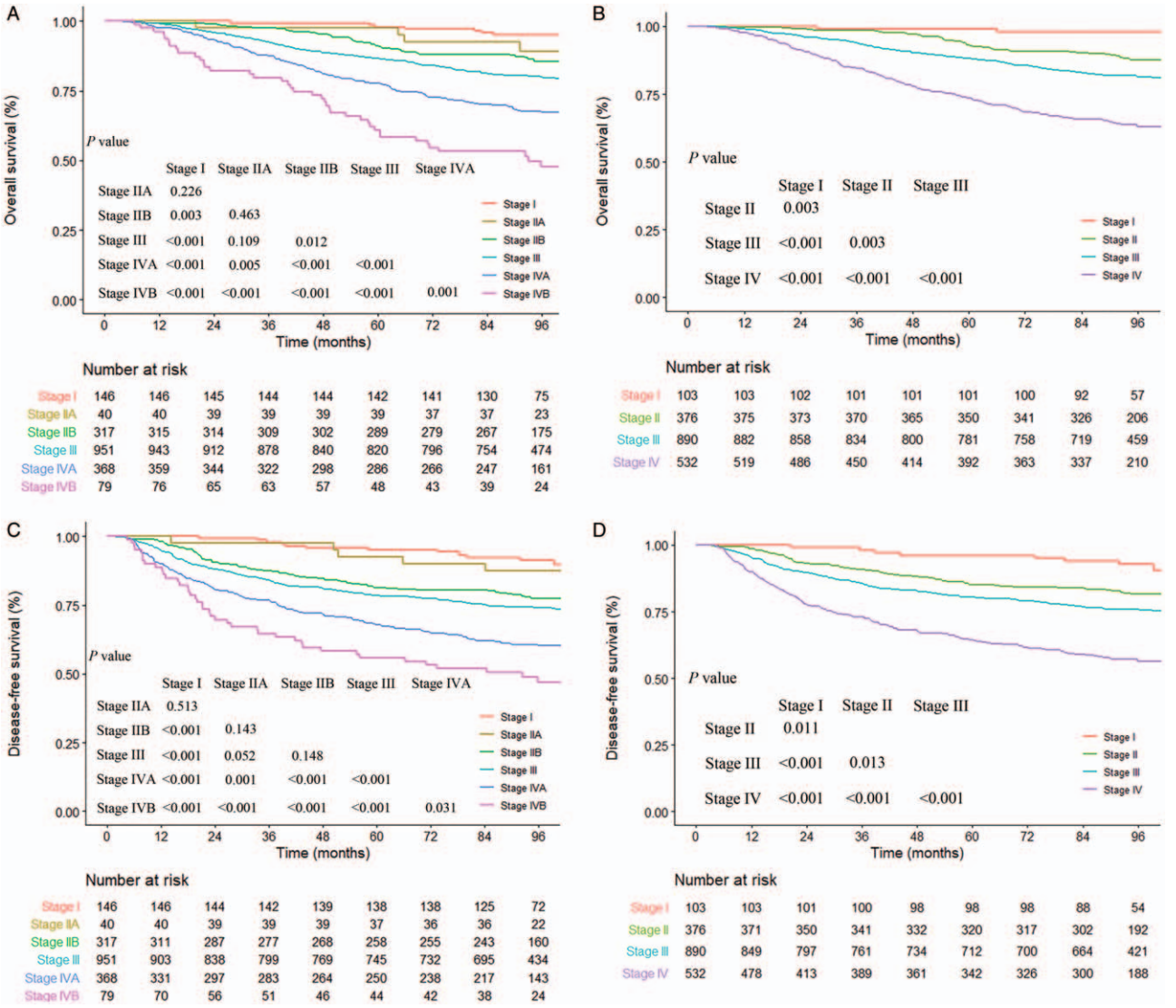

Figure 3: Overall survival (A, B) and disease-free survival (C, D) for each stage group as defined by the sixth (A, C) and eighth (B, D) editions of the Union for International Cancer Control/American Joint Committee on Cancer staging system.

Changes in treatment strategy

According to the National Comprehensive Cancer Network guideline and the randomized clinical trials evaluating treatment strategies for NPC, definitive radiotherapy was delivered to patients with stage I disease, concurrent chemotherapy and radiotherapy were suggested to patients with stage II disease, and induction or adjuvant chemotherapy followed by concurrent chemoradiotherapy was recommended for stage III and stage IVA patients.[19-22] In our study, 52 (2.7%) and 24 (1.3%) patients were upstaged from stage I to stage II and stage II to stage IVa, respectively. Thus, 76 (4.1%) patients needed more intensive treatment with the addition of chemotherapy. On the contrary, nine (0.5%) patients were downgraded from stage II to stage I; thus, a less intense therapeutic strategy would be beneficial to these patients.

Simplification of the T category

We found minimal differences in survival among patients classified T2 and T3 as defined by the sixth and eighth editions of the staging system, which indicates the T category could be simplified in the future. Similarly, Tang *et al* and Chen *et al* found no significant difference in LRFFS and DFS for T2 and T3 disease defined by the sixth, seventh, and eighth editions of the staging system.[13,14] Generally, the advanced T category is associated with poor locoregional control and poor OS. However, with the advent of MRI, IMRT, and concurrent chemotherapy, a locoregional control rate 90% to 95% has been achieved.[7,23,24] Therefore, the prognostic value of the T category may have become weaker. Indeed, Tang *et al* proposed a simplified T classification (ie, merging T2 and T3 into T2), and confirmed that significant differences in OS, LRFFS, and DFS could be found using the new

T categories both in a training set and an external validation cohort.[25] Moreover, the new stages generated by regrouping the T and N classifications showed significant differences in OS and DFS.[25]

Definition of the T0

Cervical lymph node (CLN) metastasis from EBV-related NPC is associated with a poorer prognosis than those from head and neck carcinoma unrelated to oncogenic viruses. Therefore, a T0 classification was added to the eighth edition system, referring to EBV-positive CLN involvement with unknown primary tumors.[8] However, the level of evidence for this revision is suboptimal, as EBV is not only related to NPC but is also a causative factor in other tumors, such as lymphoidepithelioma-like cancer (LELC).[26] LELC occurs in the mucosa outside the nasopharynx and manifests as lymphoid tissue infiltration, which is morphologically similar to undifferentiated NPC; moreover, the involvement of CLN is also common in LELC.[26-28] Therefore, it is difficult to differentiate LELC from NPC when the initial feature is EBV-positive CLN. Indeed, Luo *et al* revealed that among the cases of EBV-positive CLNs, the most common primary site was nasopharynx (51.7%), followed by the salivary gland (24.5%), lung (7.8%), oropharynx (3.3%), nasal cavity/maxillary (3.3%), oral cavity (2.2%), orbit (1.1%), and liver (0.4%).[29] Additionally, some primary sites also showed specific patterns of CLN metastases. Thus, the NPC T0 classification should be assigned with caution, and the consideration of lymph node metastasis patterns and other molecular biomarkers may be useful.

Unsettled issues of the N classification

The N classification of the UICC/AJCC staging system is currently based on the nodal level, laterality, and size. However, the point at which distant metastasis occurs, which is mainly determined by the N classification, is now recognized as the major cause of failure in patients with NPC. Therefore, further refinement of the N classification is warranted.

The inclusion of nodal necrosis and extranodal extension in the N classification system remains controversial. In the IMRT era, Zhang *et al* found nodal necrosis was a significant prognostic factor for poor OS, local relapse-free survival, regional relapse-free survival, DMFS, and DFS.[30] Similarly, a recent study by Feng *et al* suggested that patients should be reclassified as a higher N category if nodal necrosis is present.[31] Indeed, compared to the eighth edition staging system, the N classification system proposed by Feng *et al* substantially improved the difference in OS and DMFS between the N1 and N3 categories.[31] Another refined N classification incorporating extranodal spread was proposed based on a retrospective study of 1,616 patients in the IMRT era, which also improved prognostication of DMFS and mortality risk versus the eighth edition system.[32] The addition of extranodal extension to N1 and N2 disease showed similar poor OS, regional relapse-free survival, and DMFS to N3 disease in the eighth edition of the staging system; therefore, extranodal extension was suggested as a new criterion for N3 nodal disease.[33] In contrast, several studies demonstrate that nodal necrosis and extracapsular spread are not significant in predicting DMFS, and are found to be strongly correlated with nodal level.[34-36] However, the cut-off values of the maximal axial dimension of the lymph node varied in these studies, and they were partly based on evidence from the seventh edition system.[30,31,34-38] Therefore, improvements to the N classification system require further investigation, including unified criteria for measuring nodal size.

Limitations and future directions

This study was a retrospective review of patients treated in a single institution in south China, an endemic area where World Health Organization type II or III disease accounts for 97% of all NPC cases.[39] Therefore, large-scale studies from multiple institutions are necessary to confirm the impact and applicability of the eighth edition system and validate the modifications discussed in this study. Additionally, PET/CT was only performed on 538 (28.3%) patients in our cohort due to the high cost. As PET/CT imaging carries a higher diagnostic accuracy than CT or MRI in the evaluation of nodal and distant metastasis, staging accuracy would be improved with PET/CT.[3,40]

The eighth edition system is limited to elements describing the anatomical extent of the tumor, as determined by clinical and pathological methods. However, many studies have been conducted to identify prognostic factors beyond the TNM system and evaluate their predictive value in combination with the TNM staging system. Indeed, several factors (such as primary tumor volume, EBV DNA level in plasma, and miRNAs) can be used to predict prognosis in NPC.[41-44] Therefore, a more individualized survival assessment taking into account multiple parameters (ranging from clinical factors to molecular biomarkers) may help improve patient outcomes in the future.

Conclusion

Modifications to the TNM staging system over time have resulted in N classification changes in many cases. The eighth edition of the TNM staging system can better predict survival outcomes for patients with NPC, mainly in terms of their N category and stage grouping. However, the T classification could be simplified in future revisions.

Funding

This study was supported by the grants from the National Natural Science Foundation of China (No. 81930072), the Key-Area Research and Development Program of Guangdong Province (No. 2019B020230002), the Natural Science Foundation of Guangdong Province (No. 2017A030312003), Health & Medical Collaborative Innovation Project of Guangzhou City, China (No. 201803040003), the Innovation Team Development Plan of the Ministry of Education (No. IRT_17R110), and Overseas Expertise Introduction Project for Discipline Innovation (111 Project, No. B14035).

Conflicts of interest

None.

References

1. Lo KW, To KF, Huang DP. Focus on nasopharyngeal carcinoma. Cancer Cell 2004;5:423–428. doi: 10.1016/s1535-6108(04)00119-9.
2. King AD, Vlantis AC, Bhatia KS, Zee BC, Woo JK, Tse GM, *et al*. Primary nasopharyngeal carcinoma: diagnostic accuracy of MR imaging versus that of endoscopy and endoscopic biopsy. Radiology 2011;258:531–537. doi: 10.1148/radiol.10101241.
3. Gordin A, Golz A, Daitzchman M, Keidar Z, Bar-Shalom R, Kuten A, *et al*. Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography imaging in patients with carcinoma of the nasopharynx: diagnostic accuracy and impact on clinical management. Int J Radiat Oncol Biol Phys 2007;68:370–376. doi: 10.1016/j.ijrobp.2006.12.028.
4. Adams S, Baum RP, Stuckensen T, Bitter K, Hor G. Prospective comparison of 18F-FDG PET with conventional imaging modalities (CT, MRI, US) in lymph node staging of head and neck cancer. Eur J Nucl Med 1998;25:1255–1260. doi: 10.1007/s002590050293.
5. Kim MR, Roh JL, Kim JS, Lee JH, Cho KJ, Choi SH, *et al*. Utility of 18F-fluorodeoxyglucose positron emission tomography in the preoperative staging of squamous cell carcinoma of the oropharynx. Eur J Surg Oncol 2007;33:633–638. doi: 10.1016/j.ejso.2007.02.016.
6. Lee N, Xia P, Quivey JM, Sultanem K, Poon I, Akazawa C, *et al*. Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience. Int J Radiat Oncol Biol Phys 2002;53:12–22. doi: 10.1016/s0360-3016 (02)02724-4.
7. Tham IW, Hee SW, Yeo RM, Salleh PB, Lee J, Tan TW, *et al*. Treatment of nasopharyngeal carcinoma using intensity-modulated radiotherapy-the national cancer centre Singapore experience. Int J Radiat Oncol Biol Phys 2009;75:1481–1486. doi: 10.1016/j.ijrobp.2009.01.018.
8. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, *et al*. AJCC Cancer Staging Manual. New York: Springer; 2016.
9. Lee AW, Foo W, Poon YF, Law CK, Chan DK, O SK, *et al*. Staging of nasopharyngeal carcinoma: evaluation of N-staging by Ho and UICC/AJCC systems. Union Internationale Contre le Cancer. American Joint Committee for Cancer. Clin Oncol (R Coll Radiol) 1996;8:146–154. doi: 10.1016/s0936-6555(96)80038-0.
10. Pan JJ, Ng WT, Zong JF, Chan LL, O'Sullivan B, Lin SJ, *et al*. Proposal for the 8th edition of the AJCC/UICC staging system for nasopharyngeal cancer in the era of intensity-modulated radiotherapy. Cancer 2016;122:546–558. doi: 10.1002/cncr.29795.
11. Greene FL, Page DL, Fleming ID, Fritz AG, Balch CM, Haller DG, *et al*. AJCC Cancer Staging Manual. New York: Springer; 2002.
12. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC Cancer Staging Manual. Philadelphia, PA: Lippincott-Raven; 2009.
13. Chen L, Mao YP, Xie FY, Liu LZ, Sun Y, Tian L, *et al*. The seventh edition of the UICC/AJCC staging system for nasopharyngeal carcinoma is prognostically useful for patients treated with intensity-modulated radiotherapy from an endemic area in China. Radiother Oncol 2012;104:331–337. doi: 10.1016/j.radonc.2011.10.009.
14. Tang LL, Chen YP, Mao YP, Wang ZX, Guo R, Chen L, *et al*. Validation of the 8th edition of the UICC/AJCC staging system for nasopharyngeal carcinoma from endemic areas in the intensity-modulated radiotherapy era. J Natl Compr Canc Netw 2017;15:913–919. doi: 10.6004/jnccn.2017.0121.
15. Kaplan EL, Meier P. Nonparametric estimation from incomplete observation. J Am Stat Assoc 1958;53:457–481. doi: 10.1007/978-1-4612-4380-9_25.
16. Cox DR. Regression models and life tables. J R Stat Soc 1972;34:187–220. doi: 10.1007/978-1-4612-4380-9_37.
17. Akaike H. A new look at the statistical model identification. IEEE Trans Auto Control 1974;19:716–723. doi: 10.1007/978-1-4612-1694-0_16.
18. Harrell FE Jr, Califf RM, Pryor DB, Lee KL, Rosati RA. Evaluating the yield of medical tests. JAMA 1982;247:2543–2546. doi: 10.1001/jama.1982.03320430047030.
19. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Version 1. 2020. Available from: https://www.nccn.org/professionals/physician_gls/default.aspx. [Accessed February 10, 2020]
20. Zhang Y, Chen L, Hu GQ, Zhang N, Zhu XD, Yang KY, *et al*. Gemcitabine and cisplatin induction chemotherapy in nasopharyngeal carcinoma. N Engl J Med 2019;381:1124–1135. doi: 10.1056/NEJMoa1905287.
21. Sun Y, Li WF, Chen NY, Zhang N, Hu GQ, Xie FY, *et al*. Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial. Lancet Oncol 2016;17:1509–1520. doi: 10.1016/s1470-2045(16)30410-7.
22. Chen QY, Wen YF, Guo L, Liu H, Huang PY, Mo HY, *et al*. Concurrent chemoradiotherapy vs radiotherapy alone in stage II nasopharyngeal carcinoma: phase III randomized trial. J Natl Cancer Inst 2011;103:1761–1770. doi: 10.1093/jnci/djr432.
23. Lai SZ, Li WF, Chen L, Luo W, Chen YY, Liu LZ, *et al*. How does intensity-modulated radiotherapy versus conventional two-dimensional radiotherapy influence the treatment results in nasopharyngeal carcinoma patients? Int J Radiat Oncol Biol Phys 2011;80:661–668. doi: 10.1016/j.ijrobp.2010.03.024.
24. Haberer-Guillerm S, Touboul E, Huguet F. Intensity modulated radiation therapy in nasopharyngeal carcinoma. Eur Ann Otorhinolaryngol Head Neck Dis 2015;132:147–151. doi: 10.1016/j.anorl.2014.02.008.
25. Tang LL, Liang SB, Huang CL, Zhang F, Xu C, Mao YP, *et al*. The development and external validation of simplified T category classification for nasopharyngeal carcinoma to improve the prognostic value in the intensity-modulated radiotherapy era. Cancer Med 2019;8:2213–2222. doi: 10.1002/cam4.2131.
26. Weiss LM, Movahed LA, Butler AE, Swanson SA, Frierson HF Jr, Cooper PH, *et al*. Analysis of lymphoepithelioma and lymphoepithelioma-like carcinomas for Epstein-Barr viral genomes by in situ hybridization. Am J Surg Pathol 1989;13:625–631. doi: 10.1097/00000478-198908000-00001.
27. Chan JY, Wong EW, Ng SK, Vlantis AC. Non-nasopharyngeal head and neck lymphoepithelioma-like carcinoma in the United States: a population-based study. Head Neck 2016;38 (Suppl 1):E1294–E1300. doi: 10.1002/hed.24215.
28. Wenig BM. Lymphoepithelial-like carcinomas of the head and neck. Semin Diagn Pathol 2015;32:74–86. doi: 10.1053/j.semdp.2014.12.004.
29. Luo WJ, Feng YF, Guo R, Tang LL, Chen L, Zhou GQ, *et al*. Patterns of EBV-positive cervical lymph node involvement in head and neck cancer and implications for the management of nasopharyngeal carcinoma T0 classification. Oral Oncol 2019;91:7–12. doi: 10.1016/j.oraloncology.2019.01.012.
30. Zhang LL, Li JX, Zhou GQ, Tang LL, Ma J, Lin AH, *et al*. Influence of cervical node necrosis of different grades on the prognosis of nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy. J Cancer 2017;8:959–966. doi: 10.7150/jca.17998.
31. Feng Y, Cao C, Hu Q, Chen X. Prognostic value and staging classification of lymph nodal necrosis in nasopharyngeal carcinoma after intensity-modulated radiotherapy. Cancer Res Treat 2019;51:1222–1230. doi: 10.4143/crt.2018.595.
32. Lu T, Hu Y, Xiao Y, Guo Q, Huang SH, O'Sullivan B, *et al*. Prognostic value of radiologic extranodal extension and its potential role in future N classification for nasopharyngeal carcinoma. Oral Oncol 2019;99:104438. doi: 10.1016/j.oraloncology.2019.09.030.
33. Ai QY, King AD, Poon DMC, Mo FKF, Hui EP, Tong M, *et al*. Extranodal extension is a criterion for poor outcome in patients with metastatic nodes from cancer of the nasopharynx. Oral Oncol 2019;88:124–130. doi: 10.1016/j.oraloncology.2018.11.007.
34. Li WF, Sun Y, Mao YP, Chen L, Chen YY, Chen M, *et al*. Proposed lymph node staging system using the International Consensus Guidelines for lymph node levels is predictive for nasopharyngeal carcinoma patients from endemic areas treated with intensity modulated radiation therapy. Int J Radiat Oncol Biol Phys 2013;86:249–256. doi: 10.1016/j.ijrobp.2012.09.003.
35. Guo Q, Pan J, Zong J, Zheng W, Zhang C, Tang L, *et al*. Suggestions for lymph node classification of UICC/AJCC staging system: a retrospective study based on 1197 nasopharyngeal carcinoma patients treated with intensity-modulated radiation therapy. Medicine (Baltimore) 2015;94:e808. doi: 10.1097/md.0000000000000808.

36. Zhou X, Ou X, Yang Y, Xu T, Shen C, Ding J, *et al*. Quantitative metastatic lymph node regions on magnetic resonance imaging are superior to AJCC N classification for the prognosis of nasopharyngeal carcinoma. J Oncol 2018;2018:9172585. doi: 10.1155/2018/9172585.
37. Lan M, Huang Y, Chen CY, Han F, Wu SX, Tian L, *et al*. Prognostic value of cervical nodal necrosis in nasopharyngeal carcinoma: analysis of 1800 patients with positive cervical nodal metastasis at MR imaging. Radiology 2015;276:536–544. doi: 10.1148/radiol.15141251.
38. Luo Y, Ren J, Zhou P, Gao Y, Yang G, Lang J. Cervical nodal necrosis is an independent survival predictor in nasopharyngeal carcinoma: an observational cohort study. Onco Targets Ther 2016;9:6775–6783. doi: 10.2147/ott.S110558.
39. Marks JE, Phillips JL, Menck HR. The National Cancer Data Base report on the relationship of race and national origin to the histology of nasopharyngeal carcinoma. Cancer 1998;83:582–588. doi: 10.1002/(sici)1097-0142(19980801)83:3<582::aid-cncr29>3.0.co;2-r.
40. Ng SH, Chan SC, Yen TC, Chang JT, Liao CT, Ko SF, *et al*. Staging of untreated nasopharyngeal carcinoma with PET/CT: comparison with conventional imaging work-up. Eur J Nucl Med Mol Imaging 2009;36:12–22. doi: 10.1007/s00259-008-0918-7.
41. Guo R, Sun Y, Yu XL, Yin WJ, Li WF, Chen YY, *et al*. Is primary tumor volume still a prognostic factor in intensity modulated radiation therapy for nasopharyngeal carcinoma? Radiother Oncol 2012;104:294–299. doi: 10.1016/j.radonc.2012.09.001.
42. Leung SF, Chan KC, Ma BB, Hui EP, Mo F, Chow KC, *et al*. Plasma Epstein-Barr viral DNA load at midpoint of radiotherapy course predicts outcome in advanced-stage nasopharyngeal carcinoma. Ann Oncol 2014;25:1204–1208. doi: 10.1093/annonc/mdu117.
43. Li WF, Zhang Y, Huang XB, Du XJ, Tang LL, Chen L, *et al*. Prognostic value of plasma Epstein-Barr virus DNA level during posttreatment follow-up in the patients with nasopharyngeal carcinoma having undergone intensity-modulated radiotherapy. Chin J Cancer 2017;36:87. doi: 10.1186/s40880-017-0256-x.
44. Liu N, Chen NY, Cui RX, Li WF, Li Y, Wei RR, *et al*. Prognostic value of a microRNA signature in nasopharyngeal carcinoma: a microRNA expression analysis. Lancet Oncol 2012;13:633–641. doi: 10.1016/s1470-2045(12)70102-x.

How to cite this article: Tang SQ, Mao YP, Xu C, Guo R, Li WF, Tang LL, Sun Y, Ma J. The evolution of the nasopharyngeal carcinoma staging system over a 10-year period: implications for future revisions. Chin Med J 2020;133:2044–2053. doi: 10.1097/CM9.0000000000000978