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

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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 reviewed 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. 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), and positron-emission tomography/CT (PET/CT) has improved the detection of small nodal lesions as well as distant metastases. 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. 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.

In the past, the staging systems for NPC were different in Western and Eastern countries. 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...
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/AJCC 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 18F-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
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 subsequently classified as 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...
Table 3: Performance of 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.
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.
**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 \textit{et al} and Chen \textit{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 \textit{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. Moreover, the new stages generated by regrouping the T and N classifications showed significant differences in OS and DFS. 

**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. 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 lymphoepithelioma-like cancer (LELC). 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. 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%). 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. Similarly, a recent study by Feng et al suggested that patients should be reclassified as a higher N category if nodal necrosis is present. 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. 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. 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. 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. 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. 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. 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.

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. 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.

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Conclusions

None.

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