Oral Oncology 98 (2019) 141–146

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Validation of the 8th edition of AJCC/UICC staging system for nasopharyngeal carcinoma: Results from a non-endemic cohort with 10-year follow-up

Li-Rong Wu[a], Xiu-Ming Zhang[b], Xiao-Dong Xie[b], Yue Lu[a], Jian-Feng Wu[a], Xia He[a,*]

[a] Department of Radiation Oncology, Jiangsu Cancer Hospital, Jiangsu Institute of Cancer Research and Nanjing Medical University Affiliated Cancer Hospital, Nanjing 210009, China

[b] Department of Radiology, Jiangsu Cancer Hospital, Jiangsu Institute of Cancer Research and Nanjing Medical University Affiliated Cancer Hospital, Nanjing 210009, China

ARTICLE INFO

Keywords:
Nasopharyngeal carcinoma
AJCC/UICC
TNM staging system
Radiotherapy
Prognosis

ABSTRACT

Objectives: This study aimed to validate the 8th edition of American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) TNM staging system for nasopharyngeal carcinoma (NPC) in non-endemic region.

Materials and methods: We recruited 607 patients with histology-proven, previously untreated, non-metastatic NPC treated by intensity-modulated radiotherapy (IMRT) at our center. Harrell's concordance index (c-index) and Akaike information criterion (AIC) were applied to compare the prognostic discrimination between the 7th and 8th edition staging system.

Results: For T category, the local recurrence-free survival (LRFS) Kaplan-Meier curves of T1, T2 and T3 were well separated in the 8th edition; however, LRFS did not significantly differ between T3 and T4 ($P = 0.166$). Moreover, the 7th edition achieved higher c-index (0.702 [95% CI, 0.618–0.787] vs. 0.685 [95% CI, 0.604–0.767]) and lower AIC (766.1 vs. 770.8) than 8th edition for LRFS. With regard to N category, the 8th edition achieved higher c-index (0.796 [95% CI, 0.749–0.843] vs. 0.751 [95% CI, 0.696–0.805]) and lower AIC (1439.4 vs. 1471.9) for distant metastasis-free survival. In terms of overall stage, the 8th edition also had higher c-index (0.798 [95% CI, 0.753–0.844] vs. 0.721 [95% CI, 0.672–0.770]) and lower AIC (1963.9 vs. 2007.2) compared with the 7th edition for overall survival. Furthermore, interval validation by bootstrapping the sample randomly for ~100–1000 times also validated above findings.

Conclusion: The 8th edition of AJCC/UICC TNM staging system achieved significantly better prognostic discrimination than the 7th edition with regard to N category and overall stage but not T category.

Introduction

Nasopharyngeal carcinoma (NPC), a malignancy arising from the nasopharynx epithelial, has the highest incidence among all head and neck cancers in China [1]. Also, the newly diagnosed cases of NPC in China accounted for nearly 50% of all cases around the world in 2018 [2]. Radiotherapy has remained the only curative therapy for non-disseminated NPC for its nature of high radiosensitivity and anatomical constrain. Early disease is usually treated by radiotherapy alone while concurrent chemoradiotherapy (CCRT) with or without induction chemotherapy or adjuvant chemotherapy is the preferable care for advanced disease [3–8].

Currently, risk stratification, prognosis prediction, treatment selection and follow-up strategies making for patients with malignancies mainly refer to the TNM staging system. Thus, an accurate TNM staging system is crucial for clinical practice. The present widely used staging stratification for NPC is the 8th edition of staging system which is developed by the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC). Compared to the 7th edition, the 8th edition made some modifications such as altering medial and lateral pterygoid muscle invasion from T4 to T2, and adding the item of parotid gland involvement as T4 [9]. These adjustments were mainly proposed by Pan et al. [10] who applied two large cohorts from endemic area. Subsequently, several studies were reported to validate

* Corresponding author at: Department of Radiation Oncology, Jiangsu Cancer Hospital, Jiangsu Institute of Cancer Research and Nanjing Medical University Affiliated Cancer Hospital, 42 Baiziting Road, Xuanwu District, Nanjing 210009, China.
E-mail address: hexia206@yeah.net (X. He).

https://doi.org/10.1016/j.oraloncology.2019.09.029
Received 4 June 2019; Received in revised form 24 September 2019; Accepted 29 September 2019
Available online 04 October 2019
1368-8375/

the 8th edition of staging system [11–13]. Generally, the conclusions from these studies revealed the current 8th edition performed better than the 7th edition. Of note, these validation cohorts were all from endemic regions and had relatively insufficient follow-up duration. Undoubtedly, a reliable and stable staging system should achieve excellent performance among patients from different areas and treated by different modalities. Therefore, we conducted this study to further validate the 8th edition of AJCC/UICC staging system using a cohort from non-endemic area and with a median follow-up duration of 122.7 months.

Materials and methods

Study participant

Medical records on patients diagnosed and treated between April 2004 and December 2008 at Nanjing Medical University Affiliated Cancer Hospital/Jiangsu Cancer Hospital of China were retrospectively reviewed. Patients meeting the following criteria were included for this study: (1) newly diagnosed, previously untreated NPC; (2) non-disseminated disease; (3) treated by intensity-modulated radiotherapy (IMRT); (4) receiving magnetic resonance imaging (MRI) of head and neck as staging workup; (5) did not combined with other malignancies. This study was approved by the Research Ethics Committee of our hospital, and written informed consent was obtained from all the patients before treatment.

Pre-treatment evaluation

Comprehensive pre-treatment evaluation for tumor stage including history obtainment, physical examination, routine radiological workups (magnetic resonance imaging [MRI] of head and neck, chest radiography or contrast-CT, abdominal ultrasonography or CT scan, whole body bone single-photon emission CT scan) and laboratory profiles was performed for every patient. 18F- fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)-CT would also be recommended if conventional staging workup could not determine distant metastasis. Two radiologists with more than 10 years of experience in MRI diagnosis of head and neck cancers reviewed the radiological data and regrouped all patients according to the 7th and 8th edition of AJCC/UICC staging system (Table S1). Discrepancies were solved by consensus.

Radiotherapy and chemotherapy

Radical IMRT was delivered to all patients using simultaneous integrated boost (SIB) at our center as previously described [14]. Target tumor volumes were delineated on planning CT according to the protocol of International Commission on Radiation Units and Measurements Reports 50 and 62. The prescribed radiation doses were 66–75 Gy/31–35 fractions to the planning target volume (PTV) of nasopharynx tumor and metastatic retropharyngeal lymph nodes, 65–75 Gy/32–35 fractions to the PTV of metastatic cervical lymph nodes, 56–60 Gy/30 fractions to the PTV of high-risk regions including whole nasopharynx cavity and levels II and III cervical lymphatic drainage regions, and 50 Gy/30 fractions to the PTV of low-risk regions which encompassed high-risk regions with a margin of 3 to 5 mm, the lower neck, and the supraclavicular lymphatic drainage region. All patients were irradiated with 1 fraction daily, 5 days per week.

According to our institutional treatment protocol, patients with stage I disease received IMRT alone. For patients with stage II-IVA disease, platinum-based chemotherapy regimens were administered before, concurrent with or after radiotherapy every three weeks. The cumulative chemotherapy cycle during the whole treatment period was limited to no more than six.

Follow-up

Patients were followed by conventional assessment methods including a complete patient history, physical examination, MRI of head and neck, chest radiography or contrast-CT and abdominal ultrasonography or CT scan every 3–6 months during the first 2 years after treatment, every 6–12 months during 3th-5th years and annually thereafter. Whole body bone single-photon emission CT scan was performed once a year. Local and regional relapse were diagnosed by histological pathology. Distant metastasis, where biopsy was difficult or not available, was diagnosed by imaging methods including MRI, CT or 18F-FDG PET/CT. Follow-up was measured from pathological diagnosis to last visit or death.

Given the significant association between T category and local control (Chi-square test, $P = 0.001$ for 7th and $P = 0.014$ for 8th), between N category and distant metastasis ($P < 0.001$), between overall stage and overall survival ($P < 0.001$) and between overall stage and disease-free survival (DFS, $P < 0.001$), We therefore set locoregional relapse-free survival (LRFS, time interval between pathological diagnosis and local relapse) as the primary endpoint for T category comparison and distant metastasis-free survival (DMFS, time interval between pathological diagnosis and distant failure) as the primary endpoint for N category comparison. For overall stage comparison, overall survival (OS, time interval between pathological diagnosis and treatment failure or death) is the primary endpoint and disease-free survival (DFS, time interval between pathological diagnosis and treatment failure or death) as the second endpoint.

Statistical method

Kaplan-Meier method was applied to calculate the actuarial survival rates of OS, DFS, DMFS and LRFS between different T categories, N categories and overall stages, and the difference was compared using log-rank test. Multivariate analysis with Cox Proportional hazard model was used to establish independent prognostic variables by backward elimination method. To quantify the discrimination performance of the 7th and 8th edition of AJCC/UICC staging system, Harrell's concordance indices (c-index) [15] and Akaike information criterion (AIC) [16] were applied. C-index = 0.5 indicates that the model is not better than random chance, and c-index = 1 indicates that the model has perfect predictive accuracy. Statistical analysis was conducted with R software (version 3.5.1; http://www.Rproject.org) and Stata Statistical Package 12 (StataCorp LP, College Station, TX, USA). A two-sided p value < 0.05 was considered statistically significant difference.

Result

Patient baseline information

Between February 2, 2004 and December 23, 2008, a total of 607 patients were eligible and recruited for our current study, and baseline characteristics of these patients were summarized in Table S2. The whole cohort had a median age of 46 years (range, 9–85 years) and a male-to-female ratio of 2.6:1. The median radiation dose was 70 Gy (range, 66–80 Gy), and 448 (73.8%) patients received chemotherapy. By the database lock (December 30, 2016), the median follow-up duration for the whole cohort was 112.7 months (range, 7.6–156.8 months) and 122.7 months (range, 97.7–156.8 months) for patients alive.

Tumor stage modification

Overall, 57 (9.4%) patients experienced T category modification, 37 (6.1%) had N category modification and 110 (18.1%) patients suffered overall stage modification when re-grouped by 8th edition of AJCC/UICC staging system (Table 1). For T category, 3 (0.5%) patients

Table 1
Distribution of tumor stage according to the 7th and 8th Edition of AJCC/UICC staging system.

7th Edition AJCC Staging System	8th Edition AJCC Staging System				Total
T category	T1	T2	T3	T4	
T1	101 (16.6)	3 (0.5%)			104 (16.9%)
T2	10 (1.6%)	115 (19.0%)			125 (20.6%)
T3			216 (35.6%)		216 (35.6%)
T4		4 (0.7%)	40 (6.6%)	118 (19.4%)	162 (26.7%)
Total	111 (18.3%)	122 (20.1%)	256 (42.2%)	118 (19.4%)	607 (100%)
N category	N0	N1	N2	N3	
N0	85 (14.0%)				85 (14.0%)
N1		279 (46.0%)		26 (4.3%)	305 (50.3%)
N2			167 (27.5%)	11 (1.8%)	178 (29.3%)
N3a				27 (4.4%)	27 (4.4%)
N3b				12 (2.0%)	12 (2.0%)
Total	85 (14.0%)	279 (46.0%)	167 (27.5%)	76 (12.5%)	607 (100%)
Overall stage	I	II	III	IVA	
I	17 (2.8%)				17 (2.8%)
II	6 (1.0%)	115 (18.9%)		11 (1.8%)	132 (21.7%)
III			251 (41.4%)	16 (2.6%)	267 (44.0%)
IVA		4 (0.7%)	34 (5.6%)	114 (18.8%)	152 (25.0%)
IVB				39 (6.4%)	39 (6.4%)
Total	23 (3.8%)	119 (19.6%)	285 (47.0%)	180 (29.6%)	607 (100%)

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

upgraded from T1 to T2, 10 (1.6%) patients downgraded from T2 to T1, 4 (0.7%) from T4 to 2 and 40 (6.6%) from T4 to T3, respectively. For N category, 26 (4.3%) patients upgraded from N1 to N3 and 11 (1.8%) from N2 to N3. With regard to overall stage, 27 (4.4%) patients achieved upgrade (11 [1.8%] from II to IVA, 16 [2.6%] from III to IVA) and 84 (13.7%) had downgrade (6 [1.0%] from II to I, 4 [0.7%] from IVA to II, 34 [5.6%] from IVA to III and 39 [6.4%] from IVB to IVA).

T category comparison

The 10-year LRFS rates for patients with T1 vs. T2 vs. T3 vs. T4 stratified by the 7th edition of AJCC/UICC staging system were 94.2% vs. 92.4% vs. 91.3% vs. 79.2% (Table S3, Fig. 1A). After stratified by 8th edition staging system, the corresponding 10-year LRFS rates were 95.6%, 91.2%, 87.7% and 82.7%, respectively (Table S3, Fig. 1B). Generally, the survival curves of T1-T3 stratified by 8th edition were separated better than that of 7th edition; however, no significant difference was found between T3 and T4 ($P = 0.166$). The c-indexes of LRFS were 0.702 (95% confidence interval [CI], 0.618–0.787) for 7th edition and 0.685 (95% CI, 0.604–0.767) for the 8th edition (Table 2). The AICs of LRFS were 766.1 for the 7th edition and 770.8 for the 8th edition (Table 2). These results validated that the 7th edition achieved significantly better prognostic ability for LRFS than the 8th edition.

N category comparison

The 10-year DMFS rates for patients with N0 vs. N1 vs. N2 vs. N3a vs. N3b stratified by 7th edition and 8th edition AJCC/UICC staging system were 97.6% vs. 83.7% vs. 70.4% vs. 48.1% vs. 71.4% (Table S3, Fig. 2A), and 97.6% vs. 88.0% vs. 72.7% vs. 44.6% (Table S3, Fig. 2B), respectively. The c-indexes of DMFS were 0.751 (95% CI, 0.696–0.805) for 7th edition and 0.796 (95% CI, 0.749–0.843) for the 8th edition. The AICs of DMFS were 1471.9 for 7th edition and 1439.4 for the 8th edition (Table 2). Together, these findings showed that the 8th edition achieved significantly better prognostic ability for DMFS than the 7th edition.

Overall stage comparison

The 10-year OS and DFS survival rates for patients with stage I vs. II vs. III vs. IVA vs. IVB stratified by 7th edition staging system were 100% vs. 86.9% vs. 75.5% vs. 60.8% vs. 38.7% (Table S3, Fig. 3A), and 92.9% vs. 86.3% vs. 75.5% vs. 54.2% vs. 38.0% (Table S3, Fig. 3B), respectively. The corresponding OS and DFS rates stratified by 8th edition were 100% vs. 91.5% vs. 78.7% vs. 46.7% (Table S3, Fig. 3C) and 94.7% vs. 91.7% vs. 76.2% vs. 44.3% (Table 2, Fig. 3D), respectively. The c-indexes of OS and DFS were 0.721 (95% CI, 0.672–0.770) and

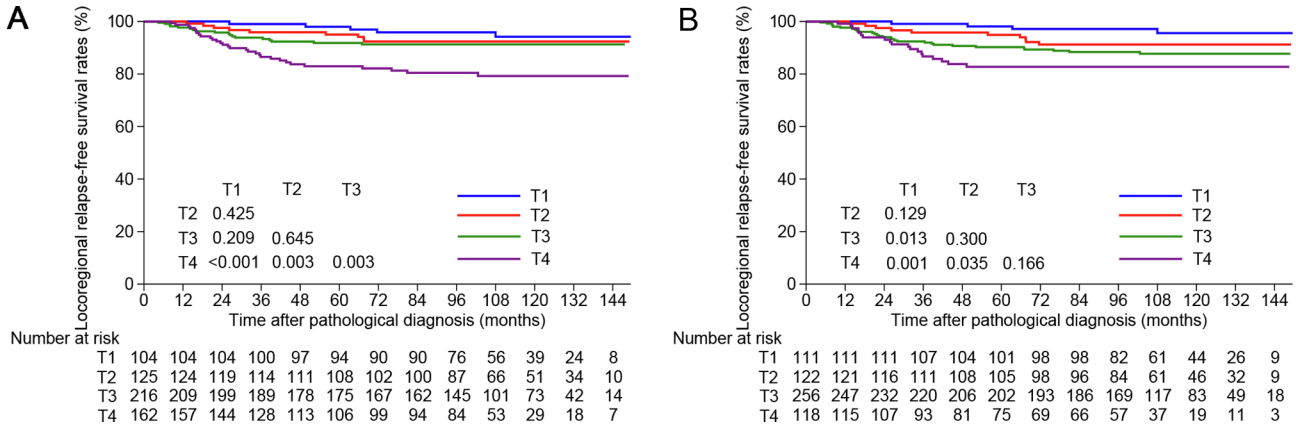

Fig. 1. Kaplan-Meier local relapse-free survival curves stratified by 7th (A) and 8th (B) edition of T category (American Joint Committee on Cancer/Union for International Cancer Control staging system).

Table 2
C-index of different tumor stage according to 7th and 8th edition staging system.

Tumor stage	Edition	C-index (95% CI)			
		OS	DFS	DMFS	LRFS
T category	7th	0.654 (0.599–0.709)	0.671 (0.620–0.721)	0.661 (0.598–0.725)	0.702 (0.618–0.787)
	8th	0.670 (0.615–0.724)	0.677 (0.626–0.727)	0.673 (0.610–0.736)	0.685 (0.604–0.767)
N category	7th	0.707 (0.653–0.761)	0.717 (0.666–0.768)	0.751 (0.696–0.805)	0.590 (0.488–0.691)
	8th	0.750 (0.701–0.798)	0.750 (0.705–0.796)	0.796 (0.749–0.843)	0.591 (0.494–0.688)
Overall stage	7th	0.721 (0.672–0.770)	0.735 (0.690–0.780)	0.728 (0.672–0.784)	0.714 (0.633–0.794)
	8th	0.799 (0.753–0.844)	0.800 (0.757–0.843)	0.809 (0.758–0.861)	0.730 (0.645–0.815)
		AIC			
		OS	DFS	DMFS	LRFS
T category	7th	2036.9	2173.1	1502.7	766.1
	8th	2029.3	2172.1	1498.2	770.8
N category	7th	2017.2	2159.0	1471.9	780.5
	8th	1975.1	2122.3	1439.4	779.7
Overall stage	7th	2007.2	2144.7	1482.4	766.4
	8th	1963.9	2108.5	1448.0	766.2

Abbreviations: OS, overall survival; DFS, disease-free survival; DMFS, distant metastasis-free survival; LRFS, locoregional relapse-free survival. AIC, Akaike information criterion; CI, confidence interval.

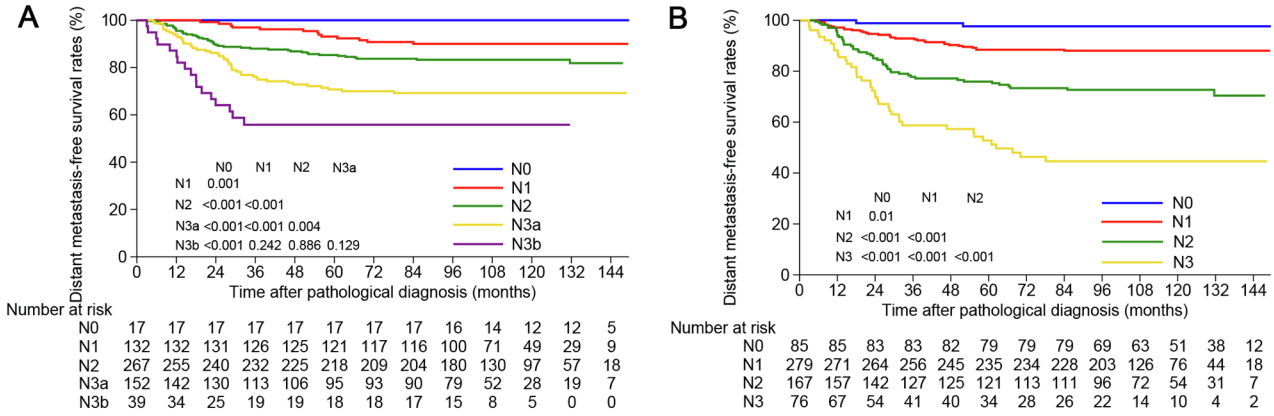

Fig. 2. Kaplan-Meier distant metastasis-free survival curves of different N categories stratified by 7th (A) and 8th (B) edition of N category (American Joint Committee on Cancer/Union for International Cancer Control staging system).

0.735 (95% CI, 0.690–0.780) for the 7th edition, and 0.798 (95% CI, 0.753–0.844) and 0.800 (95% CI, 0.757–0.843), respectively. The AICs of OS and DFS were 2007.2 and 2144.7 for 7th edition, and were 1963.9 and 2108.5 for the 8th edition (Table 2). Obviously, the 8th edition achieved significantly better prognostic ability in terms of both OS and DFS.

Internal validation

Further, we conducted internal validation by bootstrapping the sample randomly for ~100–1000 times. The c-indexes and AIC of LRFS were 0.701 (95% CI, 0.609–0.794) and 764.8 for 7th edition T category, and 0.685 (95% CI, 0.605–0.765) and 766.3 for 8th edition T category. Accordingly, they were 0.751 (95% CI, 0.691–0.806) and 1468.2 for 7th edition N category, and 0.795 (95% CI, 0.746–0.839) and 1436 for 8th edition N category. For overall stage comparison, the corresponding c-indexes and AICs of OS were 0.722 (95% CI, 0.672–0.771) and 1999.6, and 0.799 (95% CI, 0.751–0.843) and 1962.4; that of DFS were 0.733 (95% CI, 0.692–0.777) and 2141.6, and 0.799 (95% CI, 0.752–0.841) and 2110.8 for 7th and 8th edition, respectively. This analysis further validated that the 7th edition achieved significantly better prognostic ability for LRFS while the 8th edition achieved better prognostic power for DMFS and OS.

Discussion

Our current study conducted a comparison between the 7th and 8th edition of AJCC/UICC staging system for NPC, and found that the 8th edition achieved better prognostic discrimination than the 7th edition in terms of N category and overall stage; however, the 7th edition had stronger power in T category. To date, this is the first study conducted in non-endemic region with the longest follow-up duration.

An accurate and reliable staging system is essential in cancer management for prognosis prediction, treatment consideration, follow-up strategies making and experience sharing across different centers around the world. With the application of advanced imaging diagnosis methods like 18F-FDG PET/CT [17,18] and effective treatment interventions such as induction chemotherapy [7,8,19,20], periodic update of the staging system is necessary to ensure continual suitability and exploration for further improvement. The current 8th edition of AJCC/UICC staging system made its update in 2017 [9] by incorporating several revisions proposed by Pan et al. [10] into the 7th edition staging system [21]. Subsequently, three reports from Guangzhou (China) validated it [11–13,21]. However, these cohorts were all from endemic area. Moreover, the relatively insufficient follow-up duration may limit their power.

Generally, our findings were consistent with previous results [11–13,21] that the 8th edition of AJCC/UICC staging system showed prognostic ability improvement in N category and overall stage but not T category. The main modification of T category is downgrading medial

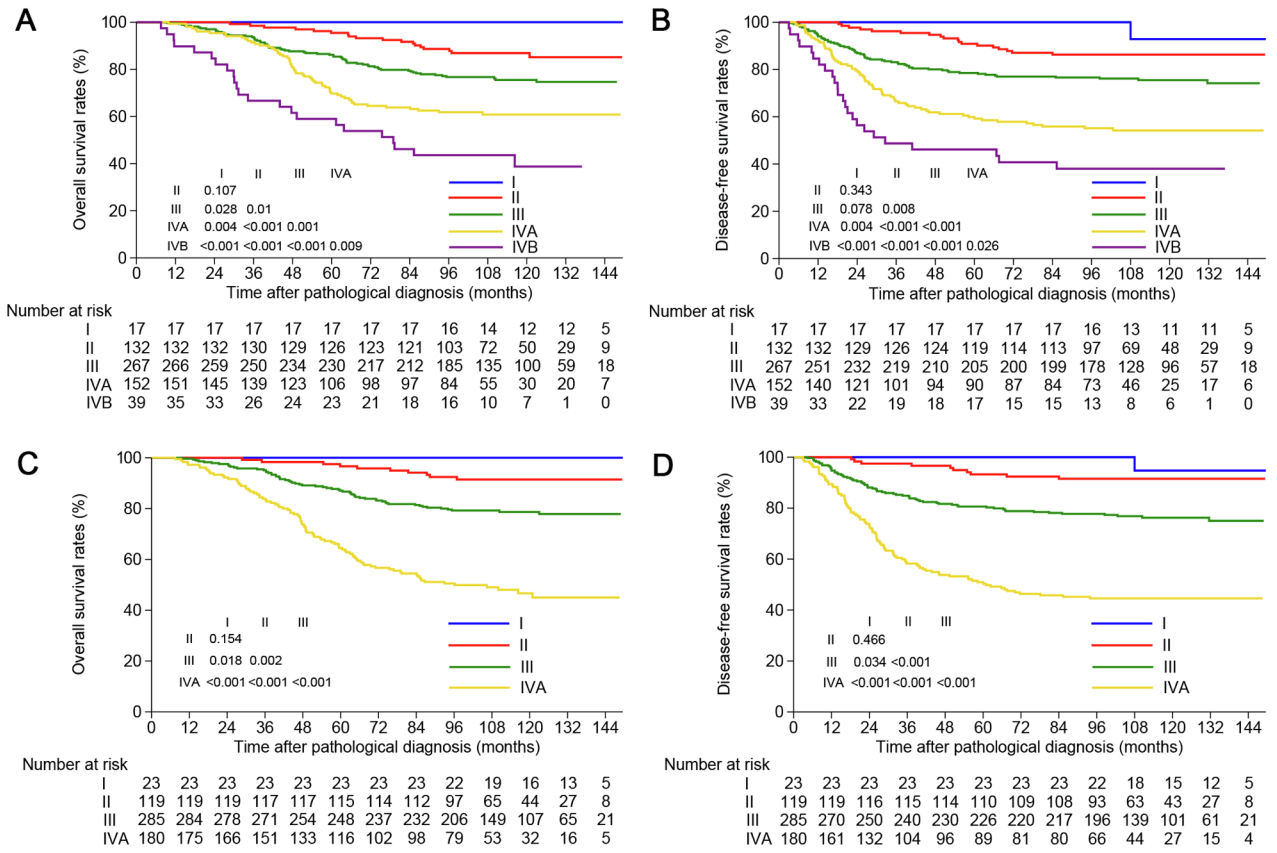

Fig. 3. Kaplan-Meier overall survival (OS) and disease-free survival (DFS) curves of different overall stages stratified by 7th and 8th edition of American Joint Committee on Cancer/Union for International Cancer Control staging system. (A) OS curves of 7th edition; (B) DFS curves of 7th edition; (C) OS curves of 8th edition; (D) DFS curves of 8th edition.

and lateral pterygoid involvement from T4 to T2. The prognostic value of medial and lateral pterygoid involvement as T4 was established by Tang et al. [22] which was adopted by the 7th edition staging system. Of the 45 patients with T4 downgrade in our study, 41 (91.1%) were from T4 to T3 which resulted in the no significant difference of LRFS between T3 and T4 (Fig. 1B) although the curves of T1, T2 and T3 were separated better than that of 7th edition. Moreover, the prognostic discrimination power of 8th edition for LRFS significantly decreased compared with that of 7th edition. The shrinkage of LRFS difference between T3 and T4 stratified by 8th edition suggested that patients with medial and lateral pterygoid involvement should have worse LRFS than patients with T3 but not medial and lateral pterygoid involvement. Thus, it may be better to classify medial and lateral pterygoid involvement as T4. Another point to note is that no significant LRFS difference was found between T2 and T3 category stratified by both 7th and 8th edition not only in our study but also in previous reports [10,12,23]. This may yield the need for merging T2 and T3 which was proposed by Tang et al [23].

Compared to the modifications of T category, the adjustments of N category and overall stage were small which mainly merged two subgroups to form one stage. This change simplified the staging system and improved the prognostic power at the same time, facilitating clinical application. Of note, the DMFS curve of N3b were closed to that of N2 but above that of N3a in the 7th edition, and this should be attributed to the small sample size of N3b (N = 12).

As we all know, the AJCC/UICC TNM staging system only taking anatomical invasion into consideration which was found to be insufficient for prognosis prediction [24–27]. NPC is highly correlated with Epstein-Barr virus (EBV) infection and numerous studies have validated plasma EBV DNA as a powerful prognostic biomarker [28–33]. Recently, two studies were carried out to provide a new insight into adding pretreatment plasma EBV DNA into the TNM staging system [34,35]. Therefore, future perspectives should focus on the combination of prognostic biomarkers with TNM staging system to develop a more precise and individualized staging system.

As abovementioned, one of the main advantages of our study is the long follow-up duration (median: 122 months) which could provide the 10-year survival outcomes. Undoubtedly, validation using such long follow-up time would provide stronger power. The limitations of our study should also be pointed out. First, the data were retrospectively corrected from a single institution, meaning potential bias may exist. Second, the sample size may be small. Therefore, we did not divide the whole cohort into test and validation sets, and internal validation was done in the cohort of randomly selected four fifths of patients.

After employing a cohort from non-endemic region with long follow-up duration, our study validated that the 8th edition of AJCC/UICC staging system achieved significantly better prognostic discrimination than the 7th edition with regard to N category and overall stage; however, T category did not show improvement. Future work on T category simplification and the combination of prognostic biomarkers with TNM staging system should be implemented.

Role of the funding source

This work receives funding support from the National Natural Science Foundation of China (No. 81672989), Jiangsu Clinical medicine Science and Technology Special Fund (BL2014091) and Jiangsu Provincial Commission of Health and Family Planning Youth Research Project (Q201601).

Declaration of Competing Interest

The authors declare no competing interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.09.029.

References

[1] Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016;66:115–32.

[2] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.

[3] Al-Sarraf M, LeBlanc M, Giri PG, Fu KK, Cooper J, Vuong T, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. J Clin Oncol 1998;16:1310–7.

[4] Lee AW, Lau WH, Tung SY, Chua DT, Chappell R, Xu L, et al. Preliminary results of a randomized study on therapeutic gain by concurrent chemotherapy for regionally-advanced nasopharyngeal carcinoma: NPC-9901 Trial by the Hong Kong Nasopharyngeal Cancer Study Group. J Clin Oncol 2005;23:6966–75.

[5] Wee J, Tan EH, Tai BC, Wong HB, Leong SS, Tan T, et al. Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union against cancer stage III and IV nasopharyngeal cancer of the endemic variety. J Clin Oncol 2005;23:6730–8.

[6] Chen Y, Liu MZ, Liang SB, Zong JF, Mao YP, Tang LL, et al. Preliminary results of a prospective randomized trial comparing concurrent chemoradiotherapy plus adjuvant chemotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma in endemic regions of china. Int J Radiat Oncol Biol Phys 2008;71:1356–64.

[7] 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;17:1509–20.

[8] Li WF, Chen NY, Zhang N, Hu GQ, Xie FY, Sun Y, et al. Concurrent chemoradiotherapy with/without induction chemotherapy in locoregionally advanced nasopharyngeal carcinoma: long-term results of phase 3 randomized controlled trial. Int J Cancer 2019;145:295–305.

[9] Amin MB, Edge S, Greene F, et al. AJCC Cancer Staging Mannual. 8th ed. New York, NY: Springer; 2016.

[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: staging of Nasopharyngeal Cancer. Cancer 2016;122(4):546–58. https://doi.org/10.1002/cncr.v122.410.1002/cncr.29795.

[11] OuYang PY, Xiao Y, You KY, Zhang LN, Lan XW, Zhang XM, et al. Validation and comparison of the 7th and 8th edition of AJCC staging systems for non-metastatic nasopharyngeal carcinoma, and proposed staging systems from Hong Kong, Guangzhou, and Guangxi. Oral Oncol 2017;72:65–72. https://doi.org/10.1016/j.oraloncology.2017.07.011.

[12] 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(7):913–9. https://doi.org/10.6004/jnccn.2017.0121.

[13] Yang XL, Wang Y, Liang SB, He SS, Chen DM, Chen HY, et al. Comparison of the seventh and eighth editions of the UICC/AJCC staging system for nasopharyngeal carcinoma: analysis of 1317 patients treated with intensity-modulated radiotherapy at two centers. BMC Cancer 2018;18:606.

[14] Wu LR, Liu YT, Jiang N, Fan YX, Wen J, Huang SF, et al. Ten-year survival outcomes for patients with nasopharyngeal carcinoma receiving intensity-modulated radiotherapy: An analysis of 614 patients from a single center. Oral Oncol 2017;69:26–32.

[15] Harrell Jr. FE, Califf RM, Pryor DB, Lee KL, Rosati RA. Evaluating the yield of medical tests. JAMA 1982;247:2543–6.

[16] Akaike H. A new look at the statistical model identification. IEEE Trans Automat Contr 1974;19:716–23.

[17] Comoretto M, Balestreri L, Borsatti E, Cimitan M, Franchin G, Lise M. Detection and restaging of residual and/or recurrent nasopharyngeal carcinoma after chemotherapy and radiation therapy: comparison of MR imaging and FDG PET/CT. Radiology 2008;249:203–11.

[18] Peng H, Chen L, Tang LL, Li WF, Mao YP, Guo R, et al. Significant value of (18)F-FDG-PET/CT in diagnosing small cervical lymph node metastases in patients with nasopharyngeal carcinoma treated with intensity-modulated radiotherapy. Chin J Cancer 2017;36:95.

[19] Hui EP, Ma BB, Leung SF, King AD, Mo F, Kam MK, et al. Randomized phase II trial of concurrent cisplatin-radiotherapy with or without neoadjuvant docetaxel and cisplatin in advanced nasopharyngeal carcinoma. J Clin Oncol 2009;27:242–9.

[20] Frikha M, Auperin A, Tao Y, Elloumi F, Toumi N, Blanchard P, et al. A randomized trial of induction docetaxel-cisplatin-5FU followed by concomitant cisplatin-RT versus concomitant cisplatin-RT in nasopharyngeal carcinoma (GORTEC 2006–02). Ann Oncol 2018;29:731–6.

[21] Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th Edition of the AJCC Cancer Staging Manual and the Future of TNM. Ann Surg Oncol 2010;17(6):1471–4. https://doi.org/10.1245/s10434-010-0985-4.

[22] Tang LL, Li WF, Chen L, Sun Y, Chen Y, Liu LZ, et al. Prognostic value and staging categories of anatomic masticator space involvement in nasopharyngeal carcinoma: a study of 924 cases with MR imaging. Radiology 2010;257:151–7.

[23] 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.

[24] 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;13:633–41.

[25] Tang LQ, Li CF, Li J, Chen WH, Chen QY, Yuan LX, et al. Establishment and Validation of Prognostic Nomograms for Endemic Nasopharyngeal Carcinoma. J Natl Cancer Inst 2016;108.

[26] Tang XR, Li YQ, Liang SB, Jiang W, Liu F, Ge WX, et al. Development and validation of a gene expression-based signature to predict distant metastasis in locoregionally advanced nasopharyngeal carcinoma: a retrospective, multicentre, cohort study. Lancet Oncol 2018;19:382–93.

[27] Peng H, Dong D, Fang MJ, Li L, Tang LL, Chen L, et al. Prognostic Value of Deep Learning PET/CT-Based Radiomics: Potential Role for Future Individual Induction Chemotherapy in Advanced Nasopharyngeal Carcinoma. Clin Cancer Res 2019;25:4271–9.

[28] Lo YM, Chan AT, Chan LY, Leung SF, Lam CW, Huang DP, et al. Molecular prognostication of nasopharyngeal carcinoma by quantitative analysis of circulating Epstein-Barr virus DNA. Cancer Res 2000;60:6878–81.

[29] Lin JC, Chen KY, Wang WY, Jan JS, Liang WM, Tsai CS, et al. Detection of Epstein-Barr virus DNA in the peripheral-blood cells of patients with nasopharyngeal carcinoma: relationship to distant metastasis and survival. J Clin Oncol 2001;19:2607–15.

[30] Chan AT, Lo YM, Zee B, Chan LY, Ma BB, Leung SF, et al. Plasma Epstein-Barr virus DNA and residual disease after radiotherapy for undifferentiated nasopharyngeal carcinoma. J Natl Cancer Inst 2002;94:1614–9.

[31] Lin JC, Wang WY, Chen KY, Wei YH, Liang WM, Jan JS, et al. Quantification of plasma Epstein-Barr virus DNA in patients with advanced nasopharyngeal carcinoma. New Engl J Med 2004;350:2461–70.

[32] Leung SF, Zee B, Ma BB, Hui EP, Mo F, Lai M, et al. Plasma Epstein-Barr viral deoxyribonucleic acid quantitation complements tumor-node-metastasis staging prognostication in nasopharyngeal carcinoma. J Clin Oncol 2006;24:5414–8.

[33] Peng H, Guo R, Chen L, Zhang Y, Li WF, Mao YP, et al. Prognostic impact of plasma epstein-barr virus DNA in patients with nasopharyngeal carcinoma treated using intensity-modulated radiation therapy. Sci Rep 2016;6:22000.

[34] Guo R, Tang LL, Mao YP, Du XJ, Chen L, Zhang ZC, et al. Proposed modifications and incorporation of plasma Epstein-Barr virus DNA improve the TNM staging system for Epstein-Barr virus-related nasopharyngeal carcinoma. Cancer 2019;125:79–89.

[35] Lee VH, Kwong DL, Leung TW, Choi CW, O'Sullivan B, Lam KO, et al. The addition of pretreatment plasma Epstein–Barr virus DNA into the eighth edition of nasopharyngeal cancer TNM stage classification. Int J Cancer 2019;144(7):1713–22. https://doi.org/10.1002/ijc.v144.710.1002/ijc.31856.