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Comparison of the eighth and ninth editions of American Joint Committee on Cancer/Union for International Cancer Control staging for non-metastatic nasopharyngeal carcinoma

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ABSTRACT:

Introduction: The ninth edition of the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) tumor-node-metastasis (TNM) system for patients with non-metastatic nasopharyngeal carcinoma (NPC) was based on data from endemic regions, and it required validation for application to non-endemic regions.

Aim: The aim of this study was to compare the performance of the 8th and the 9th editions of the AJCC/UICC TNM system for patients with non-metastatic NPC from non-endemic regions.

Materials and methods: Using the Surveillance, Epidemiology, and End Results (SEER) database, 2004–2021, we re-classified NPC patients using 8th and the 9th edition staging based on surrogate markers of advanced radiological extranodal extension (nodes described as "fixed") and compared the prediction performance of both staging editions for overall survival (OS) and cancer specific survival (CSS).

Results: Our analysis included 4981 patients with a median follow-up of 99.0 months. Comparing the 9th version of AJCC/UICC (TNM-9) with TNM-8, only 29 (1.8%) patients with N1 and 47 (3.3%) patients with N2 were upstaged to N3 in TNM-9. In comparisons based on OS, TNM-9 did not outperform TNM-8 with regard to hazard consistency (2.2326 *vs* 1.9160), hazard discrimination (1.4092 *vs* 1.0947), sample size balance (0.3476 *vs* 0.3398), and percent variance explained (0.2704 *vs* 0.2704). The area under the receiver operating characteristic curve (AUC) values of TNM-9 and TNM-8 were 0.5299 and 0.5330 for OS (P = 0.549), respectively. The AUC values of TNM-9 and TNM-8 were 0.5332 and 0.5357 for CSS (P = 0.345), respectively.

Conclusions: Restaging according to TNM-9 criteria involved only minor changes in the distribution of nodal (N) categories. Neither the TNM-9 nor the TNM-8 staging system demonstrated adequate overall discrimination between each stage group classification in terms of OS and CSS for patients with non-metastatic NPC from a non-endemic region.

KEYWORDS: AJCC, nasopharyngeal carcinoma, overall survival., SEER, staging, TNM

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COMPETING INTERESTS:
The authors declare that they have no competing interests.

STRESZCZENIE:

Wprowadzenie: Dziewiąta edycja klasyfikacji TNM (ang. *tumor-node-metastasis*) opracowanej przez AJCC/UICC (ang. *American Joint Committee on Cancer/Union for International Cancer Control*) dla pacjentów z nieprzerzutowym rakiem jamy nosowo-gardłowej (ang. *nasopharyngeal carcinoma*; NPC) została oparta na danych z regionów endemicznych i wymagała walidacji w celu zastosowania w regionach nieendemicznych.

Cel: Celem niniejszego badania było porównanie wyników zastosowania ósmej i dziewiątej edycji klasyfikacji TNM AJCC/UICC u pacjentów z nieprzerzutowym NPC z regionu nieendemicznego.

Materiały i metody: Na podstawie zgromadzonych w bazie SEER (ang. *Surveillance, Epidemiology, and End Results*) danych z lat 2004–2021 dokonano ponownej klasyfikacji pacjentów z NPC przy użyciu ósmej i dziewiątej edycji klasyfikacji TNM z wykorzystaniem zastępczych markerów zaawansowanego radiologicznego rozszerzenia pozawęzłowego (węzły opisane jako „zespolone" [ang. *fixed*]) i porównano skuteczność obu wersji klasyfikacji w zakresie przewidywania całkowitego przeżycia (OS) i przeżycia swoistego dla raka (CSS).

Wyniki: Analizą objęto 4981 pacjentów z medianą obserwacji wynoszącą 99,0 miesięcy. W porównaniu dziewiątej wersji klasyfikacji AJCC/UICC (TNM-9) z wersją poprzednią (TNM-8), tylko 29 (1,8%) pacjentów z klasyfikacją N1 i 47 (3,3%) pacjentów z klasyfikacją N2 zostało przekwalifikowanych do kategorii N3 w ramach TNM-9. W porównaniach opartych na OS, klasyfikacja TNM-9 nie wykazała wyższości nad klasyfikacją TNM-8 pod względem zgodności z ryzykiem, (2,2326 *vs* 1,9160), dyskryminacji ryzyka (1,4092 *vs* 1,0947), równowagi wielkości próby (0,3476 *vs* 0,3398) oraz procenta wyjaśnionej wariancji (0,2704 *vs* 0,2704). Pole powierzchni pod krzywą charakterystyki operacyjnej odbiornika (AUC) w odniesieniu do OS wynosiło dla TNM-9 i TNM-8 odpowiednio 0,5299 i 0,5330 (P = 0,549). Wartość AUC dla CSS wynosiła dla TNM-9 i TNM-8 odpowiednio 0,5332 i 0,5357 (P = 0,345).

Wnioski: Przypadki restagingu na postawie kryteriów TNM-9 obejmowały jedynie niewielkie zmiany w rozkładzie klasyfikacji N. Ani TNM-9, ani TNM-8 nie wykazywały dobrej ogólnej zdolności dyskryminacji między grupami zaawansowania w oparciu na OS i CSS w przypadkach nieprzerzutowego NPC z regionu nieendemicznego.

SŁOWA KLUCZOWE: AJCC, przeżycie całkowite, rak jamy nosowo-gardłowej, SEER, staging, TNM

ABBREVIATIONS

AJCC/UICC – American Joint Committee on Cancer/Union for International Cancer Control
AUC – area under the receiver-operator characteristic curve
CI – confidence interval
CSS – cancer-specific survival
DAHANCA – Danish Head and Neck Cancer Study Group
HR – hazard ratio
ICD-O – International Classification of Diseases for Oncology
NOS – not otherwise specified
NPC – nasopharyngeal carcinoma
OS – overall survival
SEER – Surveillance, Epidemiology, and End Results
SPSS – Statistical Package for Social Sciences
TNM – tumor-node-metastasis

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is an aggressive malignancy arising from the nasopharyngeal epithelium. This cancer is highly prevalent in Southeast Asia, but remains incredibly rare in Western countries [1]. Histologically, NPC includes non-keratinizing squamous cell carcinoma, keratinizing squamous cell carcinoma, and basal-like squamous cell carcinoma. In fact, non-keratinizing squamous cell carcinoma comprises up to 95% of incidence in the endemic areas, while keratinizing squamous cell carcinoma is more common in non-endemic regions, such as the United States and Europe. Non-keratinizing squamous cell carcinoma of the nasopharynx is more likely to develop distant metastases, albeit with better therapeutic response, whereas the keratinizing squamous cell carcinoma tends to be a locally advanced disease with poorer prognosis [1, 2].

The American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) tumor-node-metastasis (TNM) system is crucial for evaluating the progression and providing information for cancer care. Advanced radiological extranodal extension was added as a criterion for N3, and patients were regrouped into stages I to III instead of the 8th version of the AJCC/UICC (TNM-8) stages I to IVA in TNM-9 for non-metastatic NPC [3]. However, the TNM-9 was based on data from endemic regions; it required validation for application to non-endemic regions.

Therefore, we aim to address this evidence gap by validating the TNM-9 in a large-scale cohort of NPC from a non-endemic region. The Surveillance, Epidemiology, and End Results (SEER) program includes stage and survival data of cancer patients in the United States. We take NPC patients from the SEER database as the study cohort.

MATERIALS AND METHODS

Patient selection

The study collected 8936 NPC patients in the SEER database from 2004 to 2021. The International Classification of Diseases for Oncology (ICD-O) site recode was nasopharynx (C11) with histology codes 8070, 8071, 8072, 8073, 8020, 8021, 8082, and 8010. In addition, we used the following exclusion criteria: (1) not the 1st primary cancer; (2) distant metastases; (3) missing essential variables; (4) follow-up time of 0 or unknown; (5) age <18 years; (6) no radiation therapy (Fig. 1.).

Variables selection

Based on previous studies and clinical experience, we used age, sex, race, marital status, histologic subtype, and chemotherapy as study variables. The histological subtypes were classified according to the keratinizing squamous cell carcinoma (ICD-O-3: 8070 and 8071), non-keratinizing carcinoma (ICD-O-3: 8072, 8073, 8020, 8021, and 8082), and carcinoma not otherwise specified (NOS) (ICD-O-3: 8010) [4].

Advanced radiological extranodal extension and staging

Given that advanced radiological extranodal extension status was not available in the SEER database, a surrogate marker (nodes described as "fixed") was used as a clinical surrogate for advanced radiological extranodal extension. While this approach cannot perfectly substitute for the radiological assessment of advanced extranodal extension, the presence of soft tissue invasion with deep fixation is classified as clinical extranodal extension for the head and neck cancer TNM-8 staging system [5, 6].

The SEER database used the 6th edition of the AJCC/UICC TNM staging system from 2004 to 2015, version 7 in 2016 and 2017, and version 8 from 2018 onward. Based on the definitions for each edition and the description of the Collaborative Stage Site-Specific Factors 2, 3, and 4 in the SEER program, we recoded the T classification, N classification, and overall stage into TNM-8 and TNM-9.

Statistical analysis

Overall survival (OS) was calculated from the date of diagnosis to death for any cause or to the last date of follow-up. Cancer-specific survival (CSS) was calculated from the date of diagnosis to death specific to NPC or to the last date of follow-up. Comparison of TNM-9 and TNM-8 was conducted according to the Groome PA et al. criteria [7] – hazard consistency, hazard discrimination, sample size balance, and outcome prediction, using an online tool (http://rpa.renlab.org/) [8]. The results were validated by 1,000 bootstrap replicates for the two-stage systems to strengthen the reliability of verification [9]. All statistical data in this study were analyzed using Statistical Package for Social Sciences, version 22.0 (SPSS IBM Corp) software. Two-sided tests with P values < 0.05 were considered statistically significant.

RESULTS

Clinicopathological characteristics

A total of 4981 patients with non-metastatic NPC from 2004 to 2021 were included from the SEER database. The median age was 55 years (25th–75th percentile, 45–63 years), of which 43.3% (2157/4981) were white patients, 10.9% (542/4981) were black patients, and 45.8% (2282/4981) represented other racial groups, including American Indian, Alaska Native, Asian, or Pacific Islander. Keratinizing squamous cell carcinoma, non-keratinizing carcinoma, and carcinoma NOS accounted for 34.5% (1717/4981), 46.0% (2290/4981), and 19.6% (974/4981), respectively. Demographics, risk factors for non-metastatic NPC, and treatment are described in Tab. I.

Tab. I. Clinicopathological characteristics of non-metastatic nasopharyngeal carcinoma patients receiving radiotherapy (N = 4981).

CHARACTERISTIC	N (%)
Age (yr)	
≤55	2622 (52.6)
>55	2359 (47.4)
Gender	
Male	3545 (71.2)
Female	1436 (28.8)
Marital status	
Unmarried	1023 (20.5)
Married	3958 (79.5)
Race	
White	2157 (43.3)
Black	542 (10.9)
Other	2282 (45.8)
Pathology classification	
Non-keratinizing	2290 (46.0)
Keratinizing	1717 (34.5)
Carcinoma, NOS	974 (19.6)
Chemotherapy	
No/unknown	528 (10.6)
Yes	4453 (89.4)
Status	
Alive	3093 (62.1)
Dead	1888 (37.9)

NOS – not otherwise specified.

Major differences between 8th and 9th edition staging

Only 29 (1.8%) patients with N1 and 47 (3.3%) patients with N2 were upstaged to N3 in the 9th edition, due to the advanced radiological extranodal extension. A summary of the distribution of non-metastatic NPC staging based on TNM-8 and TNM-9 is shown in Tab. II. After applying the TNM-9 criteria, a significant proportion of patients were down-staged to Stage I (9.2% *vs* 32.6%). Stage I was sub-classified as Stage IA and IB in TNM-9. Overall, the stage changed for 90.8% of patients, and Stage IVA in TNM-8 was deleted for patients with non-metastatic disease in TNM-9.

Survival analysis

The median follow-up time was 99.0 months (25th–75th percentile, 50.0–153.0 months). The 5y-OS and CSS rates were 69.5% and 74.9%. The 5y-OS rates of patients with T1, T2, T3, and T4 were 69.9%, 70.7%, 67.4%, and 69.4%, respectively (p = 0.057). Based on TNM-8, the 5y-OS rates of patients with Stage I, II, III, and IVA were 70.1%, 70.2%, 67.2%, and 70.8%, respectively (p = 0.015). The 5y-OS rates of patients with N0, N1, N2, and N3 were 69.4%, 71.1%, 65.8%, and 77.0%, respectively (p = 0.003). The 5y-CSS

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Tab. II. Differences in staging based on the eighth and ninth editions of AJCC/UICC for non-metastatic nasopharyngeal carcinoma.

STAGE STATUS	PERCENT OF TNM-8 (N)	PERCENT OF TNM-9 (N)
Stage I	9.2 (456)	
Stage IA		12.1 (603)
Stage IB		20.5 (1022)
Stage II	23.9 (1188)	31.2 (1554)
Stage III	32.1 (1601)	36.2 (1802)
Stage IVA	34.9 (1736)	
TOTAL	100.0 (4981)	100.0 (4981)

AJCC/UICC – American Joint Committee on Cancer/Union for International Cancer Control; TNM – tumor-node-metastasis.

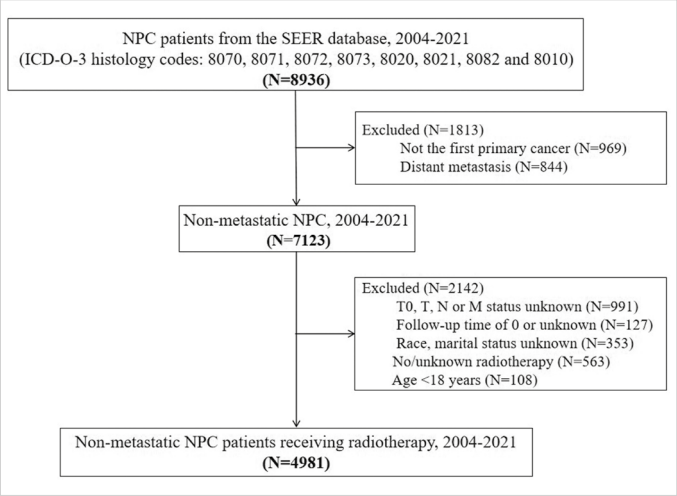

Fig. 1. Flow chart for screening patients with non-metastatic nasopharyngeal carcinoma (NPC).

SEER – the surveillance, epidemiology, and end results.

rates of patients with Stage I, II, III, and IVA were 77.0%, 75.2%, 72.6%, and 76.2%, respectively (p = 0.064). Based on TNM-9, the 5y-OS rates of patients with Stage IA, IB, II, and III were 68.1%, 71.3%, 67.6%, and 70.4%, respectively (p = 0.007). The 5y-OS rates of patients with N0, N1, N2, and N3 were 69.4%, 71.1%, 66.3%, and 70.8%, respectively (p = 0.058). The 5y-CSS rates of patients with Stage IA, IB, II, and III were 74.8%, 76.2%, 73.1%, and 75.9%, respectively (p = 0.226) (Fig. 2.).

For patients with non-keratinizing carcinoma, the 5y-OS rates of patients with Stage I, II, III, and IV based on TNM-8 were 68.3%, 70.7%, 67.2%, and 72.6%, respectively (p = 0.164). The 5y-OS rates of patients with Stage IA, IB, II, and III based on TNM-9 were 66.3%, 71.9%, 67.3%, and 72.7%, respectively (p = 0.063). No significant difference was observed in terms of TNM-8 and TNM-9 for OS in patients with keratinizing squamous cell carcinoma and carcinoma, NOS (Tab. III.).

Staging performance evaluation

In comparisons based on OS, TNM-9 did not outperform TNM-8 with regard to hazard consistency (2.2326 *vs* 1.9160), hazard discrimination (1.4092 *vs* 1.0947), sample size balance (0.3476 *vs* 0.3398), and percent variance explained (0.2704 *vs* 0.2704) (Tab. IV., Fig. 3A.). In addition, the area under the receiver-operator characteristic curve (AUC) values of TNM-9 and TNM-8 were 0.5299 and 0.5330 for OS (P = 0.549), respectively (Fig. 3B.). In comparisons based on CSS, TNM-9 did not outperform TNM-8 (Tab. IV., Fig. 3A.) and the AUC values of TNM-9 and TNM-8 were 0.5332 and 0.5357 for CSS (P = 0.345), respectively (Fig. 3B.).

DISCUSSION

In this series, restaging according to TNM-9 criteria involved only minor changes in the distribution of nodal (N) categories. Neither TNM-9 nor TNM-8 demonstrated adequate overall discrimination between each stage group in terms of OS and CSS of a non--metastatic NPC from a non-endemic region. For patients with non-keratinizing carcinoma from a non-endemic region, TNM-9 did not outperform TNM-8 between each stage group classification OS and CSS. This raises an interesting question of whether it would be better to include data from non-endemic regions in the next revision of the AJCC/UICC TNM system for NPC.

In the Danish Head and Neck Cancer Study Group (DAHANCA) database from 2000 to 2018, NPC was identified in 394 patients. The 5-year OS for the whole group was 56% (TNM-8, I: 77%, II: 78%, III: 56%, IVa: 45%) [10]. However, in the study including 1609 patients with non-metastatic endemic NPC from 2005 to 2010, higher 5y-OS rates were observed (TNM-8, I: 98%, II: 92%, III: 83%, IVa: 71%) [11]. However, the challenges of comparing treatment results across populations are highlighted by different clinicopathological characteristics and treatment.

In another non-endemic study, including 113 patients with NPC between 2009 and 2019, 5-year OS rates of Stage I, II, III, and IV (including 12 patients with distant metastasis) based on TNM-8 were 100%, 81.3%, 85.4%, and 51.4%, respectively (p = 0.01). The TNM-8 was unable to prognostically differentiate Stage II and III non-endemic NPC [12]. In the SEER database based on the study of oropharyngeal squamous cell carcinoma, TNM-8 was unable to differentiate OS and disease-specific survival between Stages I and II of the disease [13]. For lower OS rates of some subgroups, a low prognostic discrimination was observed with TNM-8 and TNM-9.

While virtually all NPCs in high-incidence regions are of the nonkeratinizing subtype [14], the histological presentation is more varied in low-incidence populations. In Finland, Ruuskanen et al. found 78% of NPCs to be of the nonkeratinizing subtype, and 22% – keratinizing squamous cell carcinoma [15]. In the present study, non-keratinizing carcinoma accounted for 46.0%. While TNM-9 outperformed TNM-8 in predicting OS across stage groups within endemic cohorts [3], the present study observed no significant difference in the prognostic utility of either system for patients with non-keratinizing carcinoma.

The limitations of our study include its retrospective design, incomplete demographic data, and the lack of comprehensive information regarding treatment and advanced radiological extranodal extension status. In Pan JJ et al.'s study, 131 patients (4.1%) who were initially classified as N1–2 in the training set were upstaged to N3 under the

Tab. III. Impact of TNM-8 and TNM-9 on OS and CSS by univariate analysis.

		5Y-OS	8Y-OS	OS HR (95% CI)	P-VALUE	5Y-CSS	8Y-CSS	CSS HR (95% CI)	P-VALUE
Whole group (N = 4981)									
TNM-8					0.016				0.066
	Stage I	70.1	61.4	1		77.0	73.4	1	
	Stage II	70.2	61.2	0.967 (0.816–1.146)	0.701	75.2	69.8	1.086 (0.882–1.336)	0.437
	Stage III	67.2	57.4	1.072 (0.910–1.263)	0.405	72.6	65.7	1.203 (0.985–1.470)	0.071
	Stage IVA	70.8	62.9	0.888 (0.747–1.054)	0.175	76.2	70.8	1.020 (0.828–1.257)	0.852
TNM-9					0.007				0.229
	Stage IA	68.1	59.2	1		74.8	71.1	1	
	Stage IB	71.3	62.3	0.841 (0.721–0.981)	0.028	76.2	70.5	0.922 (0.766–1.111)	0.393
	Stage II	67.6	57.6	0.973 (0.843–1.123)	0.705	73.1	66.2	1.048 (0.881–1.247)	0.596
	Stage III	70.4	62.6	0.831 (0.715–0.965)	0.016	75.6	70.3	0.933 (0.780–1.116)	0.447
Non-keratinizing group (N = 2290)									
TNM-8					0.167				0.302
	Stage I	68.3	62.7	1		76.5	74.2	1	
	Stage II	70.7	61.1	0.961 (0.750–1.230)	0.750	75.4	69.3	1.114 (0.821–1.513)	0.488
	Stage III	67.2	57.5	1.073 (0.846–1.362)	0.560	73.0	65.8	1.208 (0.898–1.624)	0.212
	Stage IVA	72.6	62.5	0.884 (0.686–1.138)	0.338	77.0	70.6	1.009 (0.739–1.376)	0.957
TNM-9					0.065				0.315
	Stage IA	66.3	61.0	1		73.8	71.6	1	
	Stage IB	71.9	61.7	0.841 (0.671–1.055)	0.134	76.5	69.9	0.911 (0.695–1.196)	0.502
	Stage II	67.3	57.6	0.993 (0.806–1.224)	0.951	73.1	65.9	1.040 (0.808–1.339)	0.762
	Stage III	72.7	62.5	0.820 (0.657–1.024)	0.079	77.0	70.7	0.870 (0.667–1.134)	0.303
Keratinizing group (N = 1717)									
TNM-8					0.404				0.466
	Stage I	70.6	56.0	1		76.2	68.7	1	
	Stage II	69.2	60.4	0.944 (0.691–1.290)	0.716	75.2	69.9	1.006 (0.690–1.465)	0.977
	Stage III	66.4	56.2	1.082 (0.800–1.464)	0.610	72.4	65.5	1.192 (0.829–1.713)	0.344
	Stage IVA	68.1	61.3	0.936 (0.687–1.276)	0.676	73.9	68.8	1.066 (0.737–1.543)	0.733
TNM-9					0.248				0.977
	Stage IA	67.9	54.7	1		74.1	67.0	1	
	Stage IB	70.2	61.4	0.814 (0.620–1.070)	0.140	75.7	70.4	1.011 (0.673–1.518)	0.958
	Stage II	66.7	56.2	0.961 (0.745–1.239)	0.758	73.0	65.8	1.053 (0.716–1.550)	0.793
	Stage III	68.0	61.6	0.846 (0.652–1.096)	0.206	73.7	68.9	0.980 (0.655–1.466)	0.921
Carcinoma, NOS group (N = 974)									
TNM-8					0.242				0.395
	Stage I	72.7	64.1	1		78.8	76.9	1	
	Stage II	70.6	63.0	1.019 (0.717–1.450)	0.915	74.9	70.6	1.132 (0.737–1.738)	0.572
	Stage III	68.7	59.2	1.039 (0.738–1.465)	0.825	71.9	66.0	1.187 (0.782–1.801)	0.421
	Stage IVA	72.0	67.1	0.782 (0.537–1.139)	0.200	78.9	75.6	0.899 (0.573–1.411)	0.644
TNM-9					0.628				0.977
	Stage IA	72.1	61.4	1		77.9	75.2	1	
	Stage IB	71.9	65.1	0.877 (0.627–1.225)	0.441	76.5	72.1	1.011 (0.673–1.518)	0.958
	Stage II	69.7	60.3	0.928 (0.676–1.273)	0.643	73.1	67.4	1.053 (0.716–1.550)	0.793
	Stage III	69.6	64.5	0.809 (0.578–1.133)	0.218	75.9	72.1	0.980 (0.655–1.466)	0.921

CI – confidence interval; CSS – cancer-specific survival; HR – hazard ratio; OS – overall survival; AJCC/UICC – American Joint Committee on Cancer/Union for International Cancer Control; TNM – tumor-node-metastasis.

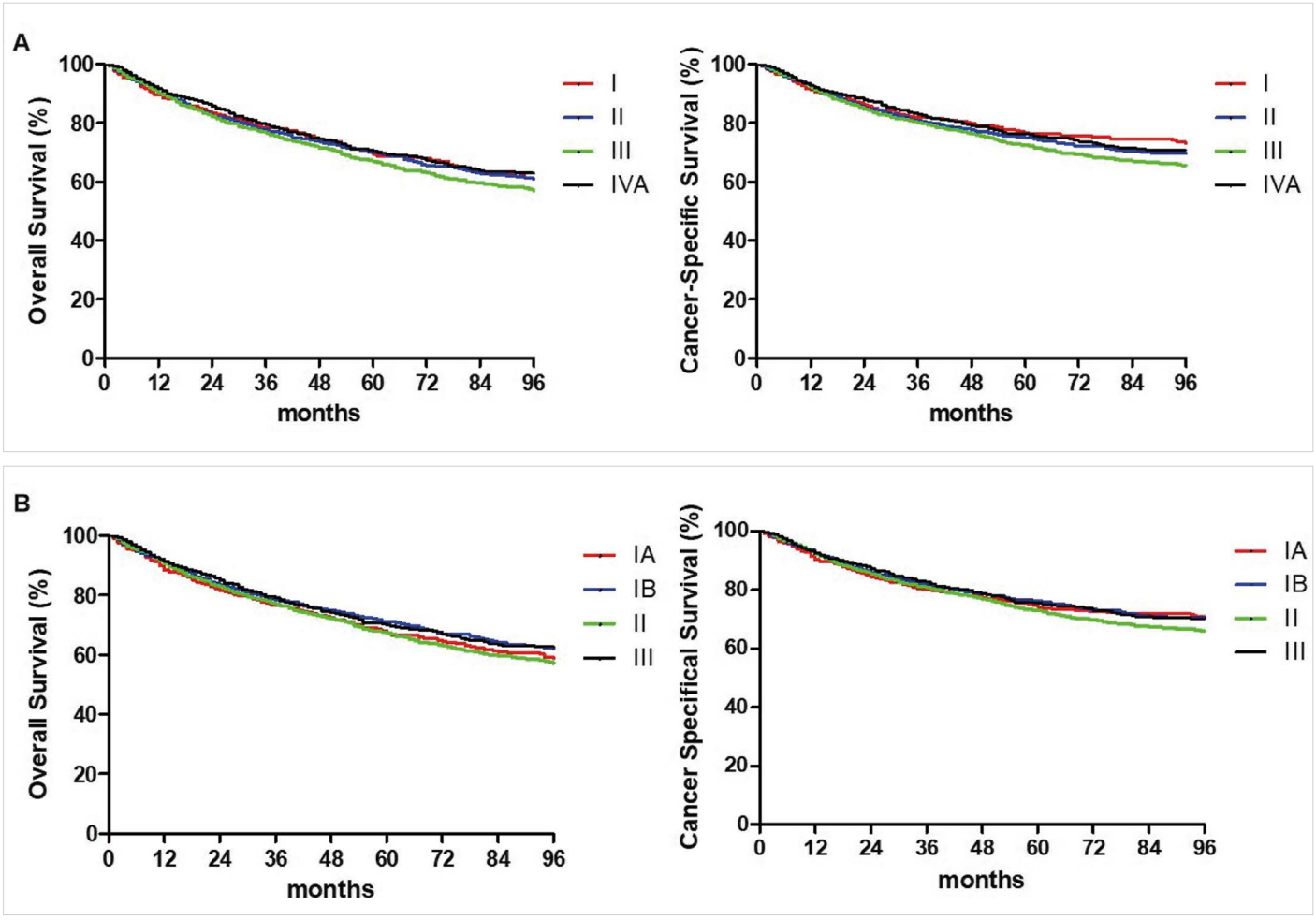

Fig. 2. Kaplan-Meier curves for overall survival and cancer-specific survival by different stages based on the 8th (A) and 9th (B) editions of American Joint Committee on Cancer/Union for International Cancer Control for non-metastatic nasopharyngeal carcinoma.

TNM – tumor-node-metastasis.

Tab. IV. Performance evaluation of TNM-8 and TNM-9 for OS and CSS in non-metastatic nasopharyngeal carcinoma.

	OS		CSS	
Evaluation criteria	TNM-8	TNM-9	TNM-8	TNM-9
% Hazard consistency	1.9160 ±0.2181	2.2326 ±0.2387	1.6542 ±0.1983	1.9327 ±0.2195
Score	0.1640 ±0.3703	0.8360 ±0.3703	0.1860 ±0.3891	0.8140 ±0.3891
Rank	1.1640	1.8360	1.1860	1.8140
Hazard discrimination	1.0947 ±0.5092	1.4092 ±0.6574	1.0577 ±0.5389	1.2970 ±0.6067
Score	0.6530 ±0.4760	0.3470 ±0.4760	0.6420 ±0.4794	0.3580 ±0.4794
Rank	1.6530	1.3470	1.6420	1.3580
Balance	0.3398 ±0.0131	0.3476 ±0.0133	0.3396 ±0.0125	0.3475 ±0.0132
Score	0.3420 ±0.4744	0.6530 ±0.4760	0.3260 ±0.4687	0.6720 ±0.4695
Rank	1.3420	1.6530	1.3260	1.6720
Percent variance explained	0.2704 ±0.0019	0.2704 ±0.0018	0.2524 ±0.0019	0.2522 ±0.0019
Score	0.4800 ±0.4996	0.5200 ±0.4996	0.4700 ±0.4991	0.5300 ±0.4991
Rank	1.4800	1.5200	1.4700	1.5300
Overall score	1.6390 ±0.8926	2.3560 ±0.8918	1.6240 ±0.9179	2.3740 ±0.9177
Overall rank	1.1570	1.4470	1.1590	1.4450
% Rank = 1	843.0	553.0	841.0	555.0

CSS – cancer-specific survival; OS – overall survival; AJCC/UICC – American Joint Committee on Cancer/Union for International Cancer Control; TNM – tumor-node-metastasis.

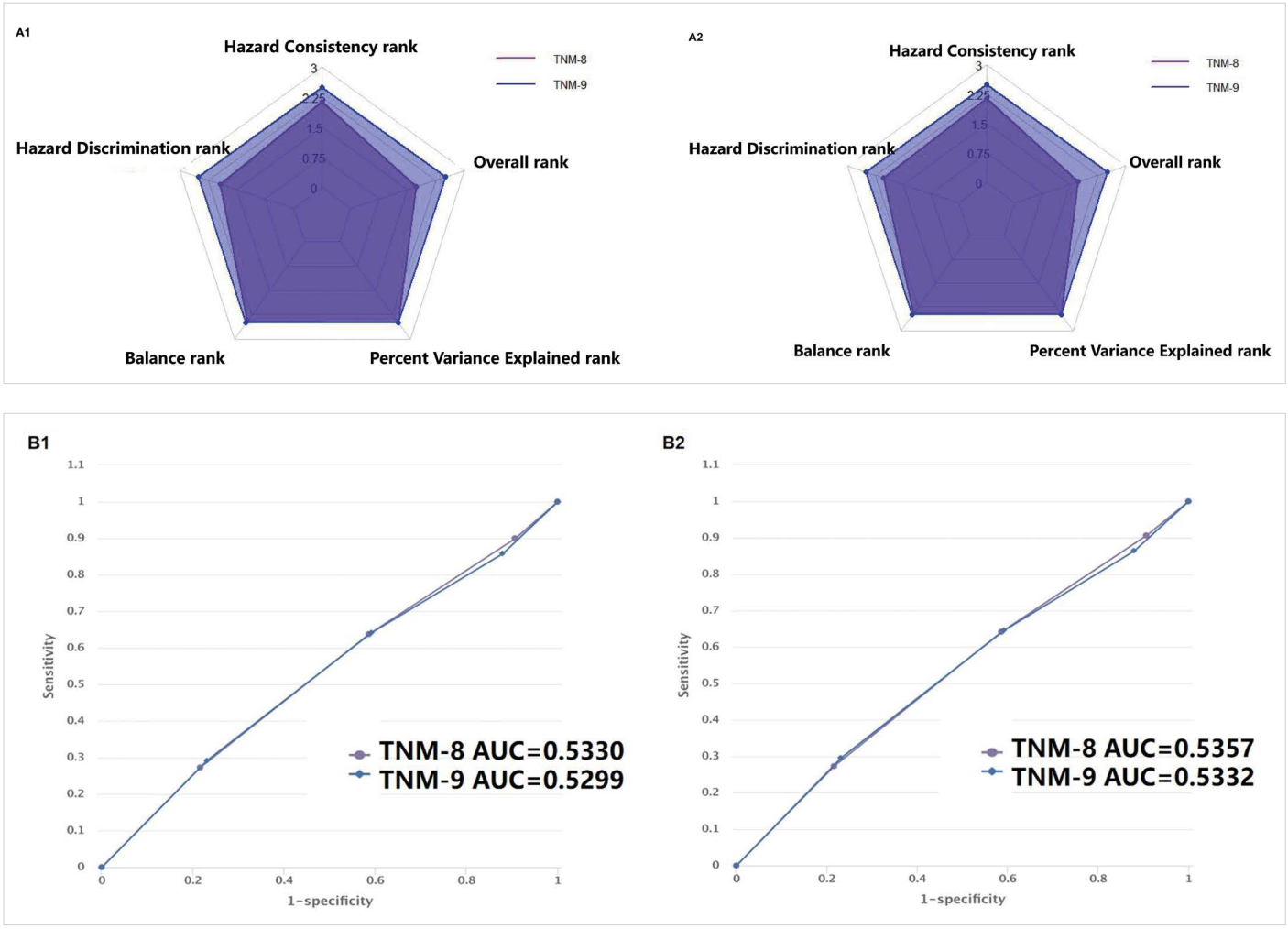

Fig. 3. The comparison of the 8th and 9th editions of American Joint Committee on Cancer/Union for International Cancer Control for non-metastatic nasopharyngeal carcinoma. (A) Radar charts for comparison of the 5 axes representing hazard consistency, hazard discrimination, sample size balance, percent variance explained, and overall properties between the 8th and 9th editions of American Joint Committee on Cancer/Union for International Cancer Control regarding OS (A1) and CSS (A2). The closer a point is to 1, the better the corresponding score; similarly, the larger the area surrounded by the points on all axes, the better the performance of the edition. (B) Comparison of receiver-operator characteristic curves between the 8th and 9th editions of American Joint Committee on Cancer/Union for International Cancer Control for OS (B1) and CSS (B2). P-value shows the AUC of the 8th edition AJCC vs the AUC of the 9th edition.

AUC – area under the receiver-operator characteristic curve; CSS – cancer-specific survival; OS – overall survival.

TNM-9 system [3]. In the present study, only 29 (1.8%) patients with N1 and 47 (3.3%) patients with N2 were upstaged to N3. This study utilized the designation of "fixed" nodes as surrogate markers for advanced radiological extranodal extension, a proxy that may not fully capture the complexity of this condition in the selected cohort. Furthermore, we harmonized tumor staging across the AJCC 6th to 9th editions, though the potential lack of homogeneity between these staging systems remains an unresolved issue.

CONCLUSIONS

Restaging according to the TNM-9 criteria involved only minor changes in the distribution of nodal (N) categories. Neither TNM-9 nor TNM-8 demonstrated adequate overall discrimination between each stage group classification in terms of OS and CSS of non-metastatic NPC from a non-endemic region.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Data analysis from the SEER database is considered to be non-human subjects by the Office for Human Research Protection as part of the US Department of Health and Human Services because patient data was anonymized and publicly available. For these reasons, the need for ethics approval was waived by the Zhejiang Cancer Hospital Ethics Committee.

DATA AVAILABILITY STATEMENT

The original data analyzed in this study are publicly available through the SEER Program of the U.S. National Cancer Institute (https://seer.cancer.gov). Access to the SEER*Stat software and datasets was obtained after submitting a data use agreement.

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