Prognostic classification for patients with nasopharyngeal carcinoma based on American Joint Committee on cancer staging system T and N categories

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Background: This study examined the current American Joint Committee on Cancer (AJCC) 8th edition staging system and proposes a new classification for nasopharyngeal carcinoma (NPC).
Methods: One thousand four hundred eighteen newly diagnosed patients with NPC without distant metastasis from 1995 through 2010 were identified. Patients treated with three-dimensional conformal radiotherapy (3D-CRT) were used as the training cohort. Based on the T and N categories of the AJCC 7th edition staging system, recursive partitioning analysis (RPA) was used to derive a new grouping system for NPC. This system was validated in patients who received intensity-modulated radiation therapy (IMRT) and compared to the current AJCC staging system.
Results: The RPA algorithm divided the 643 patients in the training cohort (3D-CRT group) into 3 groups. Group I included T1–3N0–1 and T1N2 diseases, group II included T2–3N2 diseases, and group III included T4 or N3 diseases. In the validation cohort (IMRT group, n=775), the 5-year overall survival rate using the AJCC 8th edition staging system were 94.0% for stage I, 93.9% for stage II, 89.2% for stage III, and 73.7% for stage IVA. With our RPA classification, the 5-year survival rate were 92.2% for group I, 86.5% for group II, and 72.7% for group III.
Conclusions: Our new grouping system more accurately reflects survival outcomes for patients with NPC than the current AJCC staging system. Based on this grouping system, more patients were considered to have early-stage disease with favorable prognosis.

Keywords: American Joint Committee on Cancer (AJCC); chemoradiotherapy (CRT); nasopharyngeal carcinoma (NPC); prognosis; staging system

Introduction

Nasopharyngeal carcinoma (NPC) is an uncommon disease worldwide, with high prevalence in endemic regions such as South China and Southeast Asia. Nearly all cases in endemic areas are non-keratinizing subtypes and are related to the Epstein-Barr virus (EBV). Radiotherapy is the preferred treatment modality for NPC because of its high radiosensitivity; moreover, its anatomical location is unsuitable for surgery, except in cases requiring salvage therapy. The Intergroup 0099 study first showed that concurrent, adjuvant chemotherapy improved the outcomes of patients with NPC (1). Further studies from endemic
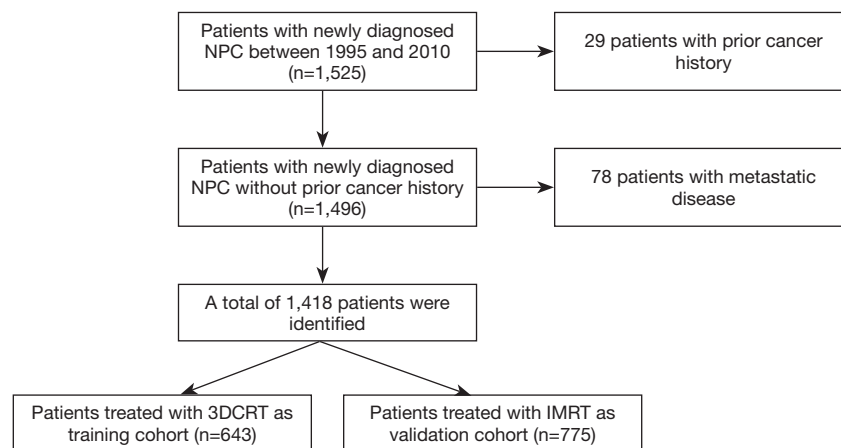
Figure 1 Flow chart showing patient selection. Patients who received three-dimensional conformal radiotherapy (3D-CRT) were used as the training cohort and patients who received intensity-modulated radiation therapy (IMRT) were used as the validation cohort.

areas have also demonstrated the efficacy of concurrent chemoradiotherapy (CRT) (2-5). Several other factors, including advanced conformal radiotherapy techniques, progress in diagnostic imaging, novel systemic agents, and improved medical care, have also improved the prognosis of NPC. A novel staging system is warranted to reflect these improved outcomes.

The American Joint Committee on Cancer (AJCC) TNM staging system is one of the most commonly used staging systems that provides a strategy for grouping patients with respect to their prognosis. Compared to the previous edition, the current 8th edition staging system has been validated to provide more accurate prognostic information (6). However, our previous studies have demonstrated that selected patients with stage III NPC treated with CRT without adjuvant chemotherapy had a 10-year overall survival (OS) rate of 90% (7,8). Given the good prognosis in selected patients with stage III disease, this study examined the current staging system and attempted to allocate patients into more homogeneous groups that reflect their favorable prognosis.

Methods

Study population and data collection

With institutional review board (IRB) approval, we retrospectively analyzed newly diagnosed patients with histological confirmation of NPC treated at our institution from 1995 to 2010. The Consolidated Standards of Reporting Trials (CONSORT) flow diagram is presented in *Figure 1*. One thousand five hundred twenty five newly diagnosed patients with NPC were identified in our NPC database. Patients with prior cancer history or metastatic disease were excluded. Finally, 1,418 patients remained for the training and validation analyses. Patients who received three-dimensional conformal radiotherapy (3D-CRT) were used as the training cohort. Patients who received intensity-modulated radiation therapy (IMRT) were used as the validation cohort. IMRT was first implemented in our department in the third quarter of 2003.

According to IRB guidelines, we collected the clinical information of all patients prospectively. The comprehensive data of all patients are organized and stored in the NPC database as reported previously (9). SAS programs were used to manage quality control and data input (10). Pretreatment evaluation included detailed medical history, physical and neurological examination, nasopharyngoscopy, complete blood counts, and serum chemistry panels. Magnetic resonance imaging (MRI) and/ or computerized tomography (CT) of the head and neck region was used to evaluate the extent of the disease. Chest X-ray, bone scintigraphy or positron emission tomography CT (PET-CT), and liver sonography were used to assess whether there was any distant metastases.

Treatment and surveillance

Diagnostic images of individual patients were reviewed by a multidisciplinary team. The anatomical structures invaded by the primary tumor and the regions of metastatic lymph nodes were recorded. The criteria for diagnosing lymph

node metastases included >5 mm for retropharyngeal lymph nodes, >10 mm in the shortest axis for cervical lymph nodes, lymph nodes with contrast-enhanced rims or central necrosis, suspicious contiguous and confluent lymph nodes near significant lymph nodes, and lymph nodes with fluorodeoxyglucose (FDG) uptake if ^{18}F-FDG PET-CT was performed.

The treatment strategy for each patient involved a multidisciplinary approach and followed institutional guidelines. Generally, stage I (T1N0M0, AJCC 7th edition) patients were treated solely with radiation therapy. Patients with low-risk stage II–III NPC (T1–T2a disease) were treated with CRT without adjuvant chemotherapy. Patients with intermediate-risk stage II–III NPC (T2b–T3 disease) underwent CRT and adjuvant chemotherapy. Stage IVA–B patients were treated with CRT followed by adjuvant chemotherapy and weekly maintenance fluorouracil (5-FU) and leucovorin for 6 months (11).

All patients were followed-up at intervals of 3 months for the first 2 years, intervals of 6 months for the third through fifth years, and 1-year intervals thereafter. Nasopharyngoscopy was performed at each clinic visit. MRI of the head and neck region was performed 3 months after the completion of radiotherapy to evaluate the treatment response.

Statistical analysis

We compared the differences between the training and validation cohorts using Fisher's exact test for categorical variables. The Kruskal-Wallis test was used to compare the differences between continuous variables. The primary outcome was OS, which was defined as the time from treatment to death from any cause and was calculated using the Kaplan-Meier method (12). A log-rank test was used to evaluate statistical significance in specific patient subsets (13). Hazard ratios (HRs) for risk of death were calculated using multivariable Cox regression (14). We treated the T (T1–T4) and N (N0–N3) categories of the AJCC 7th edition staging system for NPC as ordinal variables. Factors included in the multivariate analysis were age, sex, and the use of concurrent chemotherapy. We calculated the Harrell concordance index (C-index) by using the Survival package in R (15). The C-index assesses the discrimination power of a model (16). The range of the C-index was between 0.5 and 1, and better predictive performance is indicated by a higher C-index. To compare the goodness of the fit of the model, we also calculated the Akaike information criterion (AIC) (17). AIC can estimate the relative amount of information lost by a model. A lower AIC indicates better performance of a model.

We assumed that our new staging system could be universally applied regardless of radiation technique (e.g., 3D-CRT or IMRT). Patients treated with 3D-CRT were used as the training cohort, and those treated with IMRT were used as the validation cohort. Recursive partitioning analysis (RPA) was used to reclassify the combinations of the AJCC 7th edition T and N categories according to the similarity of their outcomes in the training cohort. The HRs for the risks of death for the 7th edition T category, N category, and each T and N combination were calculated and adjusted by age, sex, and the use of concurrent chemotherapy. After RPA classification, we compared the performance of the RPA-derived model with that of the AJCC 8th edition staging system in the validation cohort. All analyses were performed using R version 3.5.2 (R Foundation for Statistical Computing).

Results

The median follow-up period was 84.6 months (range, 2–175 months). Clinical and demographic characteristics are provided in *Table 1*. Among all patients, 71.4% were men. The median age was 45 years (range, 10–86 years). Stage distribution according to the 8th edition staging system was as follows: 95 patients in stage I (6.7%); 226 patients in stage II (15.9%); 609 patients in stage III (42.9%) and 488 patients in stage IVA (34.4%)

For the entire cohort, the 5-year OS rate was 92.6% [95% confidence interval (CI), 87.4–98.0] for the AJCC 8th edition stage I patients, 94.1% (95% CI, 91.0–97.3%) for stage II patients, 86.9% (95% CI, 84.3–89.7%) for stage III patients, and 72.0% (95% CI, 68.0–76.1%) for stage IVA patients (*Figure 2A*). The 5-year OS for patients with AJCC 8th edition T1, T2, T3, and T4 NPC were 90.2% (95% CI, 87.6–92.9%), 85.8% (95% CI, 81.2–90.6%), 82.6% (95% CI, 79.1–86.4%), and 70.5% (95% CI, 65.4–76.1%). The 5-year OS rate for patients with 8th edition N0, N1, N2, or N3 NPC were 88.8% (95% CI, 84.1–93.7%), 90.2% (95% CI, 87.1–93.5%), 82.8% (95% CI, 79.9–85.8%), and 71.8% (95% CI, 66.5–77.5%) (*Figure 2B,C*). In the multivariate Cox regression analyses adjusted by age, sex, and the use of concurrent chemotherapy, the 8th edition stage II disease did not differ significantly from stage I disease (HR, 1.5; 95% CI, 0.8–2.9; P=0.198). Age and sex (males had lower survival rate) affected the OS in patients with NPC (*Table 2*).

Table 1 Patient characteristics

Characters	Total (n=1,418)	3D-CRT (n=643)	IMRT (n=775)	P value
Sex, n (%)				0.516
Male	1,012 (71.4)	453 (70.5)	559 (72.1)	
Female	406 (28.6)	190 (29.5)	216 (27.9)	
Age, median [range], years	45 [10–86]	44 [10–86]	45 [14–78]	0.62
The 7th edition T category, n (%)				<0.001
T1	491 (34.6)	212 (33.0)	279 (36.0)	
T2	214 (15.1)	133 (20.7)	81 (10.5)	
T3	375 (26.4)	136 (21.2)	239 (30.8)	
T4	338 (23.8)	162 (25.2)	176 (22.7)	
The 7th edition N category, n (%)				0.0851
N0	171 (12.1)	76 (11.8)	95 (12.3)	
N1	361 (25.5)	152 (23.6)	209 (27.0)	
N2	731 (51.6)	354 (55.1)	377 (48.6)	
N3	155 (10.9)	61 (9.5)	94 (12.1)	
Treatment, n (%)				0.00817
CRT	1,357 (95.7)	605 (94.1)	752 (97.0)	
RT	61 (4.3)	38 (5.9)	23 (3.0)	
The 7th edition stage, n (%)				0.41
I	95 (6.7)	45 (7.0)	50 (6.5)	
II	232 (16.4)	108 (16.8)	124 (16.0)	
III	644 (45.4)	287 (44.6)	357 (46.1)	
IVA	292 (20.6)	142 (22.1)	150 (19.4)	
IVB	155 (10.9)	61 (9.5)	94 (12.1)	
The 8th edition stage, n (%)				0.95
I	95 (6.7)	45 (7.0)	50 (6.5)	
II	226 (15.9)	105 (16.3)	121 (15.6)	
III	609 (42.9)	273 (42.5)	336 (43.4)	
IV	488 (34.4)	220 (34.2)	268 (34.6)	

Fisher's exact test for categorical variables was used to compare the differences between the training and validation cohorts. The Kruskal-Wallis test was used to compare continuous variables. T and N categories were analyzed based on the AJCC 7th edition staging system. AJCC, American Joint Committee on Cancer; 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiation therapy; CRT, concurrent chemoradiotherapy; RT, radiotherapy.
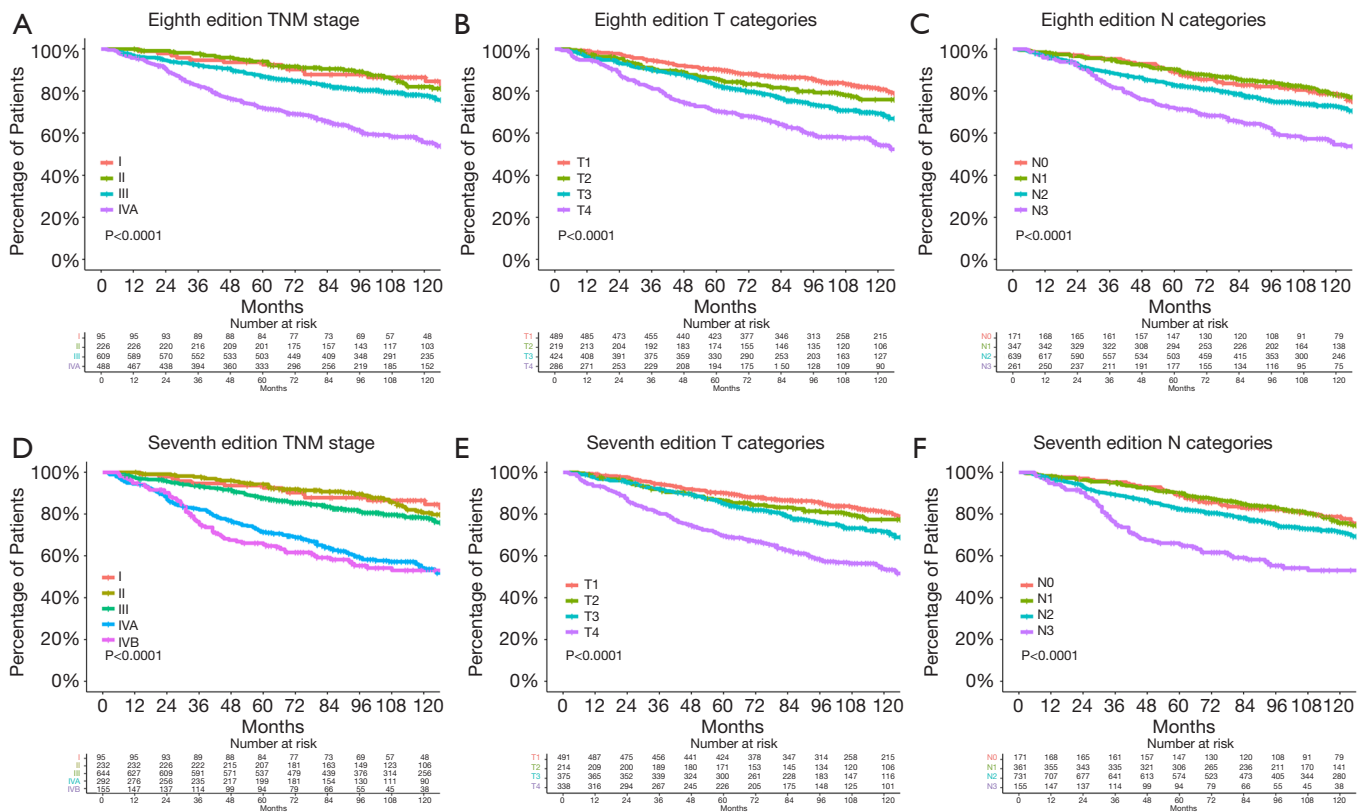
A Eighth edition TNM stage

Percentage of Patients — Months

I, II, III, IVA — P<0.0001

Number at risk
	0	12	24	36	48	60	72	84	96	108	120
I	95	95	93	89	88	84	77	73	69	57	48
II	226	226	220	216	209	201	175	157	143	117	103
III	609	589	570	552	533	503	449	409	348	291	235
IVA	488	467	438	394	360	333	296	256	219	185	152

B Eighth edition T categories

Percentage of Patients — Months

T1, T2, T3, T4 — P<0.0001

Number at risk
	0	12	24	36	48	60	72	84	96	108	120
T1	489	485	473	455	440	423	377	346	313	258	215
T2	219	213	204	192	183	174	155	146	135	120	106
T3	424	408	391	375	359	330	290	253	203	163	127
T4	286	271	253	229	208	194	175	150	128	109	90

C Eighth edition N categories

Percentage of Patients — Months

N0, N1, N2, N3 — P<0.0001

Number at risk
	0	12	24	36	48	60	72	84	96	108	120
N0	171	168	165	161	157	147	130	120	108	91	79
N1	347	342	329	322	308	294	253	226	202	164	138
N2	639	617	590	557	534	503	459	415	353	300	246
N3	261	250	237	211	191	177	155	134	116	95	75

D Seventh edition TNM stage

Percentage of Patients — Months

I, II, III, IVA, IVB — P<0.0001

Number at risk
	0	12	24	36	48	60	72	84	96	108	120
I	95	95	93	89	88	84	77	73	69	57	48
II	232	232	226	222	215	207	181	163	149	123	106
III	644	627	609	591	571	537	479	439	376	314	256
IVA	292	276	256	235	217	199	181	154	130	111	90
IVB	155	147	137	114	99	94	79	66	55	45	38

E Seventh edition T categories

Percentage of Patients — Months

T1, T2, T3, T4 — P<0.0001

Number at risk
	0	12	24	36	48	60	72	84	96	108	120
T1	491	487	475	456	441	424	378	347	314	258	215
T2	214	209	200	189	180	171	153	145	134	120	106
T3	375	365	352	339	324	300	261	228	183	147	116
T4	338	316	294	267	245	226	205	175	148	125	101

F Seventh edition N categories

Percentage of Patients — Months

N0, N1, N2, N3 — P<0.0001

Number at risk
	0	12	24	36	48	60	72	84	96	108	120
N0	171	168	165	161	157	147	130	120	108	91	79
N1	361	355	343	336	321	306	265	236	211	170	141
N2	731	707	677	641	613	574	523	473	405	344	280
N3	155	147	137	114	99	94	79	66	55	45	38

Figure 2 Overall survival for the whole cohort by (A) the 8th edition TNM stage, (B) the 8th edition T categories, (C) the 8th edition N categories; (D) the 7th edition TNM stage, (E) the 7th edition T categories, and (F) the 7th edition N categories.

Table 2 Multivariable Cox analysis of the risk of death according to the AJCC 8th edition TNM stage

Variable	Hazard ratio (95% CI)	P value
AJCC stage I	1 (reference)	–
AJCC stage II	1.53 (0.8–2.9)	0.195
AJCC stage III	2.38 (1.29–4.4)	0.005
AJCC stage IVA	4.87 (2.69–8.8)	<0.001
Age	1.046 (1.04–1.1)	<0.001
Sex (male vs. female)	1.28 (1.02–1.6)	0.03
RT vs. CRT	1.73 (0.99–3.0)	0.053

AJCC, American Joint Committee on Cancer; CI, confidence interval; CRT, concurrent chemoradiotherapy; RT, radiotherapy.

The 5-year OS rate was 92.6% (95% CI, 87.4–98.0%) for the AJCC 7th edition stage I patients, 94.2% (95% CI, 91.2–97.3%) for stage II patients, 87.6% (95% CI, 85.1–90.2%) for stage III patients, 71.4% (95% CI, 66.4–76.9%) for stage IVA patients, and 65.5% (95% CI, 58.3–73.6%) for stage IVB patients (*Figure 2D*). The 5-year OS for patients with AJCC 7th edition T1, T2, T3, and T4 NPC were 90.1% (95% CI, 87.4–92.8%), 86.4% (95% CI, 81.9–91.2%), 85.0% (95% CI, 81.4–88.7%), and 69.7% (95% CI, 64.9–74.8%). The 5-year OS rate for patients with 7th edition N0, N1, N2, or N3 NPC were 88.8% (95% CI, 84.1–93.7%), 90.0% (95% CI, 87.0–93.2%), 82.5% (95% CI, 79.7–85.3%), and 65.5% (95% CI, 58.3–73.6%)

(*Figure 2E,F*). Multivariate analyses using Cox regression models adjusted by age, sex, and the use of concurrent chemotherapy revealed no significant differences between the 7th edition T1, T2, and T3 categories and no significant differences between the N0 and N1 categories (*Table 3*).

Table 4 shows the HRs for the risks of mortality

according to combinations of the 7th edition T and N categories adjusted by age, sex, and the use of concurrent chemotherapy. In the validation dataset, patients with T2N2 and T3N2 disease had significantly higher HRs [4.37 (95% CI, 1.07–17.8) and 4.03 (95% CI, 1.19–13.6), respectively] than did patients with T1N0 disease. The HRs for the risks of mortality are higher in patients with T4 or N3 disease, which are 6.62 (95% CI, 1.41–31.0), 5.69 (95% CI, 1.56–20.7), 8.02 (95% CI, 2.33–27.6), 7.72 (95% CI, 1.98–30.1), 13.22 (95% CI, 3.52–49.6), 7.33 (95% CI, 1.56–34.4), 7.91 (95% CI, 2.09–29.9) for patients with T4N0, T4N1, T4N2, T4N3, T1N3, T2N3 and T3N3 NPC, respectively.

Among the 643 patients with NPC treated with 3D-CRT, the RPA algorithm divided the patients into 3 groups. Group I included patients with T1–3N0–1 and T1N2 disease, group II included those with T2–3N2 disease, and group III included those with T4 or N3 disease. The 5-year OS rate were 92.3%, 82.5%, and 65.4% for each group, respectively (*Figure 3*, *Figure 4A,B*).

For the validation cohort (IMRT group, n=775), the 5-year OS rate according to the AJCC 8th edition staging system were 94.0% for stage I (n=50), 93.9% for stage II (n=121), 89.2% for stage III (n=336), and 73.7% for stage IVA (n=268). After RPA classification, the 5-year OS rate in the validation cohort were 92.2% for group I (n=357), 86.5% for group II (n=174), and 72.7% for group III (n=244) (*Figure 3*, *Figure 4C,D*). *Table 5* shows the HRs for the risks of death using the RPA-derived grouping system, adjusted for age, sex, and the use of concurrent chemotherapy for

Table 3 Multivariable Cox analysis of the risk of death according to AJCC 7th edition T and N categories

Variable	Hazard ratio (95% CI)	P value
T category (the 7th edition)		
T1	1 (reference)	–
T2	1.00 (0.72–1.4)	0.977
T3	1.25 (0.94–1.6)	0.12
T4	2.35 (1.83–3.0)	<0.001
N category (the 7th edition)		
N0	1 (reference)	–
N1	1.10 (0.74–1.6)	0.637
N2	1.58 (1.10–2.3)	0.014
N3	2.90 (1.91–4.4)	<0.001
Age	1.048 (1.04–1.1)	<0.001
Sex (male *vs.* female)	1.29 (1.04–1.6)	0.023
RT *vs.* CRT	1.33 (0.8–2.2)	0.267

AJCC, American Joint Committee on Cancer; CI, confidence interval; CRT, concurrent chemoradiotherapy; RT, radiotherapy.

Table 4 Hazard ratios (95% confidence intervals) for the risk of death according to each combination of AJCC 7th edition T and N categories adjusted by age, sex, and the use of concurrent chemotherapy

AJCC 7th edition T-N categories	T1	T2	T3	T4
Training cohort				
N0	1, n=45	1.03 (0.29–3.7), n=11	0.89 (0.11–7.1), n=6	3.71 (1.52–9.1), n=14
N1	1.58 (0.71–3.5), n=54	1.09 (0.44–2.7), n=43	1.27 (0.47–3.5), n=26	2.97 (1.31–6.7), n=29
N2	1.39 (0.64–3.0), n=100	1.65 (0.74–3.6), n=66	2.73 (1.29–5.8), n=89	3.60 (1.78–7.3), n=99
N3	4.29 (1.57–11.7), n=13	2.94 (1.08–8.0), n=13	2.35 (0.86–6.4), n=15	8.49 (3.66–19.7), n=20
Validation cohort				
N0	1, n=50	2.06 (0.33–12.9), n=10	2.94 (0.67–12.9), n=26	6.62 (1.41–31.0), n=9
N1	1.84 (0.49–7.0), n=93	0.82 (0.08–8.1), n=21	2.02 (0.48–8.5), n=48	5.69 (1.56–20.7), n=47
N2	2.81 (0.78–10.1), n=109	4.37 (1.07–17.8), n=36	4.03 (1.19–13.6), n=138	8.02 (2.33–27.6), n=94
N3	13.22 (3.52–49.6), n=27	7.33 (1.56–34.4), n=14	7.91 (2.09–29.9), n=27	7.72 (1.98–30.1), n=26

AJCC, American Joint Committee on Cancer.

the training, validation, and entire cohorts.

The C-index for the validation cohort was 0.6934 for the RPA-derived group and 0.6930 for the 8th edition staging system after adjusting for age, sex, and the use of concurrent chemotherapy. The AIC was 2,142.96 for the RPA-derived group and 2,141.33 for the 8th edition staging system. Therefore, the performances were similar between the two models.

Compared with the current staging system, more patients were considered to have early-stage disease in the entire cohort according to the RPA-derived grouping system (group I vs. the 8th edition stage I and II: 45.3% vs. 22.6%, P<0.001). *Figure 5* shows that the survival curves of the RPA-group I patients from the entire cohort and the 8th edition stage I and II patients were not significantly different (P=0.79). The 5-year OS rate were 92.3% for group I patients and 93.6% for the 8th edition stage I and II patients.

Discussion

Using our institutional prospective NPC database, we were able to demonstrate that patients with NPC treated using modern techniques have excellent outcomes. Patients with the 8th edition stage I and II disease achieved equally good outcomes. The 5-year OS rate of patients with stage II disease was higher than that of patients with stage I disease in the entire cohort (94.1% vs. 92.6%). In addition, our data showed that selected patients with stage III disease (T3N0–1 and T1N2) had good prognosis with 5-year survival rate of more than 90%. Therefore, it is not necessary to divide these patients into different prognostic groups; the current staging system still lacks the power of prognostic discrimination (*Table 2*).

Our proposed RPA grouping system better reflects the favorable prognosis of NPC in the modern era, and more patients are considered to have early disease. Classified as group I by RPA, T1N2 and T3N0 disease would be classified as stage III disease according to the current AJCC 8th edition staging system. The diagnosis of "stage III" disease may cause unnecessary panic in patients, even if the treatment outcomes are excellent. Our findings are valuable as they have the potential to reduce emotional distress in these patients.

We also found that N0 and N1 categories had similar risks of death in our cohort. Limited lymph node metastasis does not seem to affect the survival outcomes of patients with NPC in the modern era. Moreover, the risk of death

in the AJCC 7th edition T1–3 categories did not differ significantly (*Table 3*). The 5-year OS rate were similar for patients with T2 and T3 disease; however, the survival curves diverged after 5 years which may be attributed to mortality related to late toxicities from treatment rather than a difference in the prognosis of T2 and T3 disease (*Figure 2B,C,D,E*). Tang *et al.* also demonstrated that there was no significant difference in locoregional failure-free survival, disease-free survival, and OS between T2 and T3 disease in the era of IMRT (6). Another study showed that T3 patients with pterygoid process or sphenoid bone base invasion had better prognosis than those with invasion in other sites in the base of the skull (18).

The T category of the current staging system is primarily based on the treatment outcomes of 2-dimensional radiotherapy (2D-RT) using opposed bilateral portals without CT simulation. It is challenging to achieve sufficient target coverage without harming normal tissues in advanced disease with this outdated technique. With advancements in radiotherapy techniques, the survival outcomes for NPC have improved substantially due to improvements in target volume coverage and normal tissue sparing. The use of systemic agents and progress in diagnostic imaging have also contributed to improved prognosis. Lee *et al.* demonstrated improved survival in patients with NPC treated with 3D-CRT and IMRT compared to those treated with 2D-RT (19). The main differences occurred in patients with stage III–IV disease; the 5-year survival rate of these patients was 60% in the 2D-RT era and 79% in the IMRT era. The late toxicity rate has also improved in the IMRT era. However, more advanced T and N categories are associated with increased volumes in high-dose areas which could lead to more treatment-related toxicities.

One meta-analysis demonstrated an increased risk of carotid artery stenosis in patients with NPC treated with radiotherapy (20), which can lead to stroke or even death. Radiation-associated dysphagia is caused by damage to the anatomic structures associated with swallowing, such as the pharyngeal constrictor muscles, and may lead to aspiration pneumonia. Although damage to normal tissues caused by radiation decreased with the advent of IMRT, late treatment-related toxicities may become more severe over time and become a competing risk of death. Efforts should be made to reduce the incidence of radiation-associated late toxicities by reducing treatment intensity, especially for patients with a life expectancy of more than 5 years.

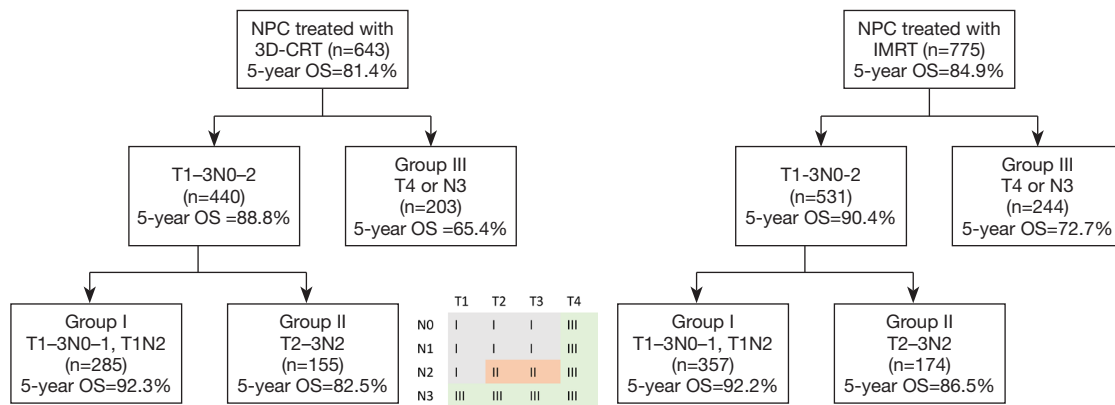Several ongoing trials are designed to test the feasibility

Figure 3 Recursive partitioning analysis-derived grouping system based on the 7th edition T–N combinations and hazard ratios for the risk of death in the training cohort (patients who received 3D-CRT) and validation cohort (patients who received IMRT). NPC, nasopharyngeal carcinoma; 3D-CRT, three-dimensional conformal radiotherapy; OS, overall survival; IMRT, intensity-modulated radiation therapy; AJCC, American Joint Committee on Cancer 8th edition.
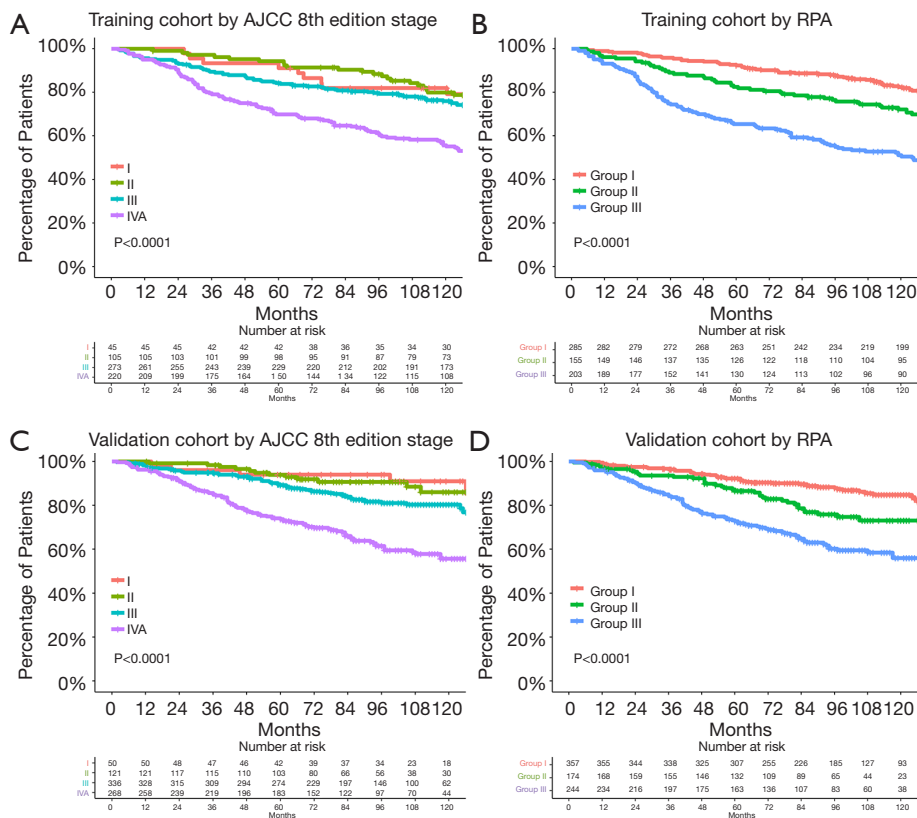

Figure 4 Overall survival by (A) the 8th edition TNM stage in the training cohort, (B) RPA grouping system in the training cohort, (C) the 8th edition TNM stage in the validation cohort, and (D) RPA grouping system in the validation cohort. AJCC, American Joint Committee on Cancer; RPA, recursive partitioning analysis.

Table 5 Hazard ratios for the risk of death according to the RPA-derived grouping system adjusted by age, sex, and the use of concurrent chemotherapy for the training cohort, validation cohort, and entire cohort

RPA group	Hazard ratio (95% CI)	P value
Training cohort		
Group I	1 (reference)	–
Group II	1.67 (1.18–2.4)	0.004
Group III	2.84 (2.13–3.8)	<0.001
Validation cohort		
Group I	1 (reference)	–
Group II	1.95 (1.27–3.0)	0.002
Group III	3.66 (2.55–5.3)	<0.001
Total		
Group I	1 (reference)	–
Group II	1.80 (1.37–2.4)	<0.001
Group III	3.22 (2.57–4.0)	<0.001

RPA, recursive partitioning analysis; CI, confidence interval.
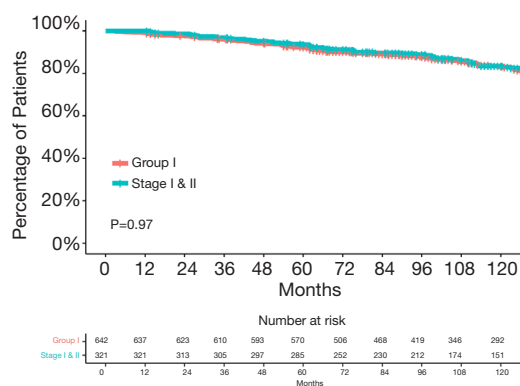
Figure 5 Survival curves of the entire cohort for the RPA-group I patients and the AJCC 8th edition stage I and II patients. RPA, recursive partitioning analysis; AJCC, American Joint Committee on Cancer.

of treatment de-escalation for patients with human papillomavirus-related oropharyngeal cancer. Given good outcomes in the modern era, treatment de-escalation may also be considered for patients with early-stage NPC to reduce the incidence of late treatment-related toxicities. A meta-analysis demonstrated that, for patients with stage II NPC, concurrent chemotherapy did not improve OS, but increased acute grade 3 or 4 toxicities compared to radiation

therapy alone in the IMRT era (21). The lack of a survival benefit may be due to improved locoregional control with IMRT. A combined analysis of the NPC-9901 and NPC-9902 trials demonstrated that, for patients with stage III–IV NPC, there was no significant difference in disease control between patients receiving either two or three concurrent cycles of cisplatin (100 mg/m^2) (22). Decreasing the intensity of chemotherapy may be considered as a strategy for treatment de-escalation in patients with good prognosis. Another prospective randomized study revealed that reducing the target volume after induction chemotherapy subsequently reduced the radiation dose received by healthy tissues and did not compromise the 3-year outcome for patients with stage III–IV NPC (23). The quality of life was also improved. More phase III studies are necessary to demonstrate the feasibility of treatment de-escalation for patients with NPC.

Even with modern treatment, the prognosis of patients with T4 or N3 NPC remains suboptimal. The 5-year OS rate of the patients in group III in our study was only 69.4% (65.4% in the 3D-CRT group and 72.7% in the IMRT group). Treatment intensification may be considered for these patients, and strategies to intensify treatments in the current practice include induction and/or adjuvant systemic therapy. Recently, several studies have shown the benefits of induction chemotherapy prior to concurrent CRT for patients with locally-advanced NPC. A randomized controlled phase 3 study from China has demonstrated that, for patients with locally-advanced NPC, induction gemcitabine and cisplatin (GC) followed by cisplatin-based CRT improved OS and recurrence-free survival compared to those of patients treated with CRT alone (24). The main benefit of induction GC was the improvement in 3-year distant-metastasis recurrence-free survival (HR, 0.43; 91.1% in the induction GC followed by CRT group *vs.* 84.4% in the CRT alone group). There was no significant difference in 3-year locoregional recurrence-free survival. The benefits were more pronounced for patients with N2–3 diseases compared to patients with N1 disease. According to the results of this study, for patients with advanced N-category NPC, induction GC should be considered as a treatment strategy.

Another randomized control study from Taiwan revealed that, for patients with stage IVA–IVB NPC (AJCC 7th edition), induction chemotherapy with three cycles of cisplatin, epirubicin, mitomycin C, and 5-FU/leucovorin (MEPFL) prior to CRT improved disease-free survival compared to that of patients treated with CRT alone (25).

The 5-year disease-free survival rate were 61% in the induction arm and 50% in the CRT alone arm. In contrast to induction GC, the main benefit of induction MEPFL was the improvement in locoregional failure-free survival (HR, 0.664; 5-year rate 80% in the induction MEPFL followed by CRT group *vs.* 70% in the CRT alone group). There was no difference in OS or distant failure-free survival between the two arms. Further research is necessary to determine the optimal treatment for these patients. Novel agents including immune checkpoint inhibitors may have the potential to improve prognosis for patients with locally advanced NPC.

One strength of our study is that it was based on a large cohort of patients in a prospective database. We also demonstrated that our RPA-derived model was applicable to patients treated with 3D-CRT and IMRT. However, there are several limitations to our study. The first is the retrospective design of the analysis, which may have led to several forms of bias. The second is that the data were from a single institution with its own protocol; further external validation is needed to test its generalizability. Moreover, some known prognostic factors for NPC, including World Health Organization classification, lactate dehydrogenase level, performance status, and plasma EBV DNA level, were not considered in the survival analysis. Furthermore, we analyzed survival outcomes but did not analyze other important endpoints, including locoregional-free survival, distant metastasis-free survival, and non-cancer-related death. An analysis based on these endpoints may help optimize treatment strategies for NPC. However, we demonstrated more favorable outcomes for patients with NPC. Therefore, a new staging system for NPC based on modern treatment methodologies is urgently needed.

In this single-center retrospective cohort study, we demonstrated that the current staging system does not reflect the favorable survival outcomes of patients with NPC in the modern era. By using RPA, we propose a novel grouping system for NPC as follows: group I (AJCC 7th edition T1–3N0–1 and T1N2), group II (T2–3N2), and group III (T4 or N3). Patients with metastatic disease can be classified into group IV and have the worst prognosis. Based on this grouping system, more patients with NPC are considered to have early-stage disease with favorable outcomes. Further external validation is warranted to confirm the performance of this grouping system.

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