Oral Oncology 91 (2019) 113–120

Contents lists available at ScienceDirect

Oral Oncology

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

Depicting distant metastatic risk by refined subgroups derived from the 8th edition nasopharyngeal carcinoma TNM

Qiaojuan Guo[a,b,1], Tianzhu Lu[c,1], Shao Hui Huang[d], Brian O'Sullivan[d], Jingfeng Zong[a], Youping Xiao[e], Wei Xu[f], Chuanben Chen[a], Sufang Qiu[a], Luying Xu[a], Wei Zheng[a], Yunbin Chen[d], Shaojun Lin[a,*], Jianji Pan[a,*]

[a] Department of Radiation Oncology, Fujian Medical University Cancer Hospital & Fujian Cancer Hospital, Fuzhou, China
[b] Key Laboratory of Systems Biomedicine (Ministry of Education), Shanghai Center for Systems Biomedicine, Shanghai Jiao Tong University, Shanghai, China
[c] Department of Radiation Oncology, Fujian Medical University Cancer Hospital, Fuzhou, China
[d] Department of Radiation Oncology, Princess Margaret Cancer Centre/University of Toronto, Toronto, Canada
[e] Department of Radiology, Fujian Medical University Cancer Hospital & Fujian Cancer Hospital, Fuzhou, China
[f] Department of Biostatistics, Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada

ARTICLE INFO

Keywords:
Nasopharyngeal carcinoma
Intensity-modulated radiation therapy
Chemotherapy
Prognostication
Distant metastasis
Recursive partitioning analysis

ABSTRACT

Background: Tumor-nodal-metastasis (TNM) is the most important survival predictor in nasopharyngeal carcinoma (NPC). Distant metastasis (DM) is the predominant failure pattern of NPC in the intensity-modulated radiotherapy (IMRT) era. The DM risk appears to be different for T-N subsets within the same clinical stage. Appropriately depicting DM risk has emerged as an important issue in tailoring individualized treatment and underpins the reason for this study.

Methods: A total of 1616 non-metastatic (M0) NPC patients treated with IMRT were included. All were re-staged according to the 8th edition AJCC/UICC TNM (TNM-8). DM-free survival (DMFS) was calculated and compared among T-N subsets within each stage and DM risk groups were derived by Recursive-partitioning analysis (RPA) based on ordinal T and N categories.

Results: Significant heterogeneity in DM risk was evident among T-N subsets within cTNM-8 stages II-IV. The RPA algorithm classified patients into four DM risk groups: RPA-I (T1N0-1 and T2-3N0), RPA-II (T2-3N1), RPA-III (T4N0-1 and T1-3N2) and RPA-IV (T4N2 and T1-4N3), with 5-year DMFS of 93.4% (95% CI: 91.3–96.1), 84.3% (80.8–87.8), 78.9% (75.4–82.4) and 63.6% (56.3–70.9), respectively ($p < 0.001$). Compared to cTNM-8 stage grouping, RPA grouping had a lower Akaike information criterion (AIC) and higher Harrell's concordance index (c-index) for DMFS.

Conclusions: Significant heterogeneity in DM risk exists among T-N subsets within cTNM-8 stages. The RPA groups demonstrated improved intra-group hazard consistency compared to cTNM-8 stage groups. While further validation is warranted, these RPA prognostic groupings provide a strong anatomic foundation to augment DM prediction for optimal targeting in future clinical trials.

Introduction

The application of intensity-modulated radiotherapy (IMRT) has significantly improved loco-regional control (LRC) of nasopharyngeal carcinoma (NPC); however, about 15% to 30% patients experience failure at distant sites [1]. In fact, distant metastasis (DM) has become the principal form of failure and main cause of death for NPC patients following IMRT [1,2]. Therefore, precise evaluation of DM risk and appropriate stratification is an important first step to tailoring more individualized treatment and improving survival.

The anatomic tumor-node-metastasis (TNM) staging system has long been recognized as the most important survival indicator for NPC patients, and is critical in facilitating treatment planning. While invaluable for cancer treatment, and with additional advantages from simplicity and ease of use worldwide, the TNM classification was recognized at its genesis as having limitations. Thus, it has always been

* Corresponding authors at: Department of Radiation Oncology, Fujian Medical University Cancer Hospital & Fujian Cancer Hospital, No. 420 Fuma Road, Fuzhou 350014, China.
E-mail addresses: linshaojun@yeah.net (S. Lin), panjianji@126.com (J. Pan).
[1] Both Qiaojuan Guo and Tianzhu Lu contributed equally to this study.

https://doi.org/10.1016/j.oraloncology.2019.02.021
Received 25 November 2018; Received in revised form 12 February 2019; Accepted 21 February 2019
Available online 12 March 2019
1368-8375/

appreciated that many factors in addition to TNM contribute to prognosis (including age, sex, social determinants of health and numerous pathological factors) [3]. Moreover, other outcomes may be governed by separate prognostic factors compared to overall survival (OS), the usual end-point used in cancer staging[4,5]. For this reason, the UICC and AJCC have attempted to refine knowledge and processes to address important prognostic factors relevant to outcomes following specific treatments [6]. To date for NPC, there has not been a comprehensive process to address the prediction of DM, potentially the most important outcome that governs survival in this disease. This may largely be a consequence of the traditional concern about achieving local control in the protected sanctuary of the skull base; however, this emphasis has diminished with the contemporary high LRC rates due to IMRT, high quality imaging, and cisplatin chemotherapy as a potential radiotherapy sensitizer. Effectively the challenge has shifted to the risk of DM, which may have its own unique characteristics and may be receptive to new approaches that may target DM separately.

Although many biomarkers, such as blood EBV-DNA [7,8], and serum lactate dehydrogenase (LDH) [9,10], have been identified as DM predictors, TNM categories and stage groups represent the basic anatomic building blocks needed to explore incorporation of these biomarkers. Unfortunately, significant heterogeneity in risk of DM is often observed for different T-N subgroups of patients within apparently equivalent clinical TNM stage [11–16]. The UICC/AJCC staging system was updated to the 8th version (TNM-8)[17], in which both T and N categories were modified. Whether the heterogeneity of DM risk still exists within the updated stage groupings remains unknown. Hence, we conducted this retrospective analysis of a series of non-metastatic NPC patients treated with IMRT in our institution to evaluate the predictability of DM risk within each TNM-8 stage. We used recursive-partitioning analysis (RPA) to construct a framework intended to provide high sensitivity to predict DM risk using the anatomic components of the 8th edition T and N. It is envisioned that additional biomarkers factors could subsequently be employed to refine the risk and determine with precision subgroups of patients with the greatest need for novel systemic treatments to reduce DM. Such factors could comprise tissue-based factors such as microRNA signatures [18,19] or circulating blood indices such as EBV copy number or LDH levels.

Materials and methods

Patients and treatment

Patients with histologically-proven NPC who received definitive IMRT with or without chemotherapy at our institution between June 2005 and December 2011 were candidates for this retrospectively study. Other eligible criteria included: (1) no history of previous treatment or prior malignancy; (2) a completed pretreatment evaluation according to our institutional protocol [20], (3) availability of imaging data that permitted re-staging according to the TNM-8 [17]. With these criteria, 1616 patients from our database were eligible for this analysis, of whom 1197 were previously included, together with a cohort from Hong Kong, in the original study that proposed the TNM-8 classification [17]. Imaging data were reviewed, and T and N categories were reclassified according to the TNM-8 criteria. This retrospective study was conducted in compliance with the policy of our institution to protect the private information of patients enrolled, and was approved by the Institutional Review Board of our hospital.

All patients received IMRT with or without chemotherapy. A detailed description of the IMRT planning and dose prescription has previously been published [20]. Additional treatment with platinum-based chemotherapy (various schedules) was administered to 91.2% of patients with stage II-IVA (Table 1 and supplementary table). The most commonly used regimens for neoadjuvant and adjuvant were paclitaxel or gemcitabine plus cisplatinum; however, the specific regimen of chemotherapy was chosen at the discretion of the attending physician according to individual case features and patient perference.The chemotherapy schedules ranged from 1 to 6 cycles.

Table 1
Patient characteristics at baseline based on the 8th edition of AJCC/UICC stage classification.

Covariate	N (%)
Gender	
Male	1211 (74.9%)
Female	405 (25.1%)
Age (years)	
Median (Min, Max)	46 (11–84)
LDH ((IU/L)	
Median (Min, Max)	147 (71–586)
Missing	4
Chemotherapy	
No	191 (11.8)
Yes	1425 (88.2)
Chemotherapy cycles	
≤3	901 (55.8)
> 3	715 (44.2%)
Pathology	
Keratinizing squamous cell	17 (1.0)
Nonkeratinizing, differentiated	116 (7.2)
Nonkeratinizing, undifferentiated	1483 (91.8)
T classification	
T1	413 (25.6)
T2	288 (17.8)
T3	591 (36.6)
T4	324 (20.0)
N classification	
N0	226 (14.0)
N1	884 (54.7)
N2	346 (21.4)
N3	160 (9.9)
Clinical stage	
I	77 (4.8)
II	397 (24.6)
III	678 (42.0)
IV	464 (28.7)

Abbreviation: LDH = lactate dehydrogenase

Statistical analyses

The primary endpoint was DMFS (time to DM) where death without DM was censored. An additional endpoint was OS (time to death due to any causes). Descriptive statistics were provided with median and ranges for continuous variables, and frequency and percentages for categorical variables. Survival curves were created with the Kaplan–Meier method and compared by log-rank test. Multivariate analyses (MVA) by Cox proportional hazards model were performed to evaluate the stage prognosis on DMFS and OS, adjusting by clinical factors; the latter included age, gender, LDH, and treatment (chemotherapy yes vs. no). Hazard ratio (HR) with corresponding 95% confidence intervals were provided.

To derive new groupings for patients with different risks of DM, RPA using the STREE program (http://masal.med.yale.edu/stree/) was performed to construct RPA groups objectively with ordinal T (T1/T2/T3/T4) and N (N0/N1/N2/N3) categories. This algorithm was based on the optimized binary partitions of T or N categories. It resulted in subgroups with relatively homogeneous DMFS performance. The performance of the RPA groups and TNM-8 stages in predicting DMFS were then compared with the Akaike information criterion (AIC)[21] and Harrell's concordance index (c-index)[22]. The AIC and c-index were both calculated for the Cox proportional hazards regression model. The prognostic performance of the RPA groups on OS was also evaluated. All statistical analyses were conducted with SPSS 22.0 and R3.13, and two-tailed P values < 0.05 were considered statistically significant.

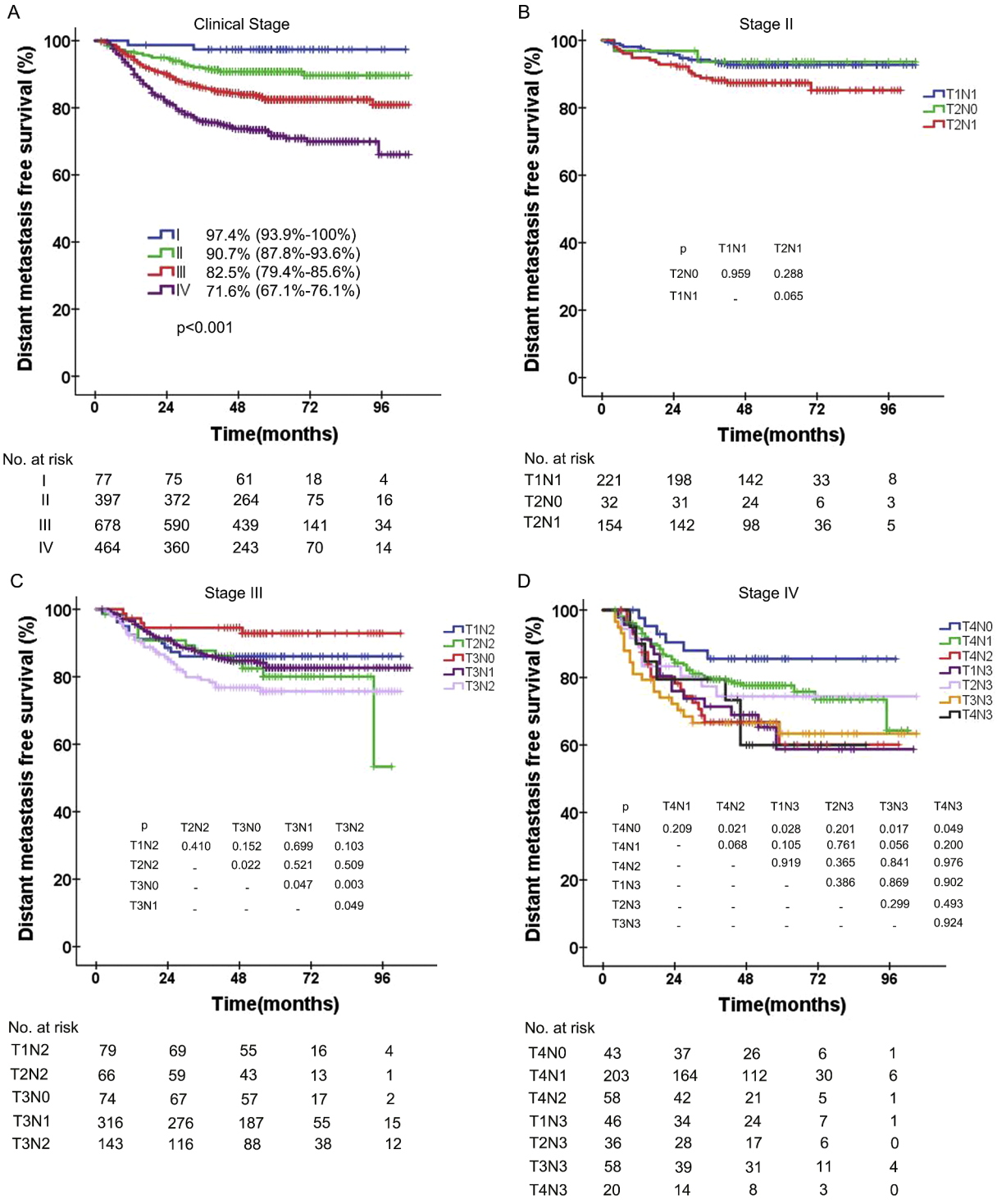


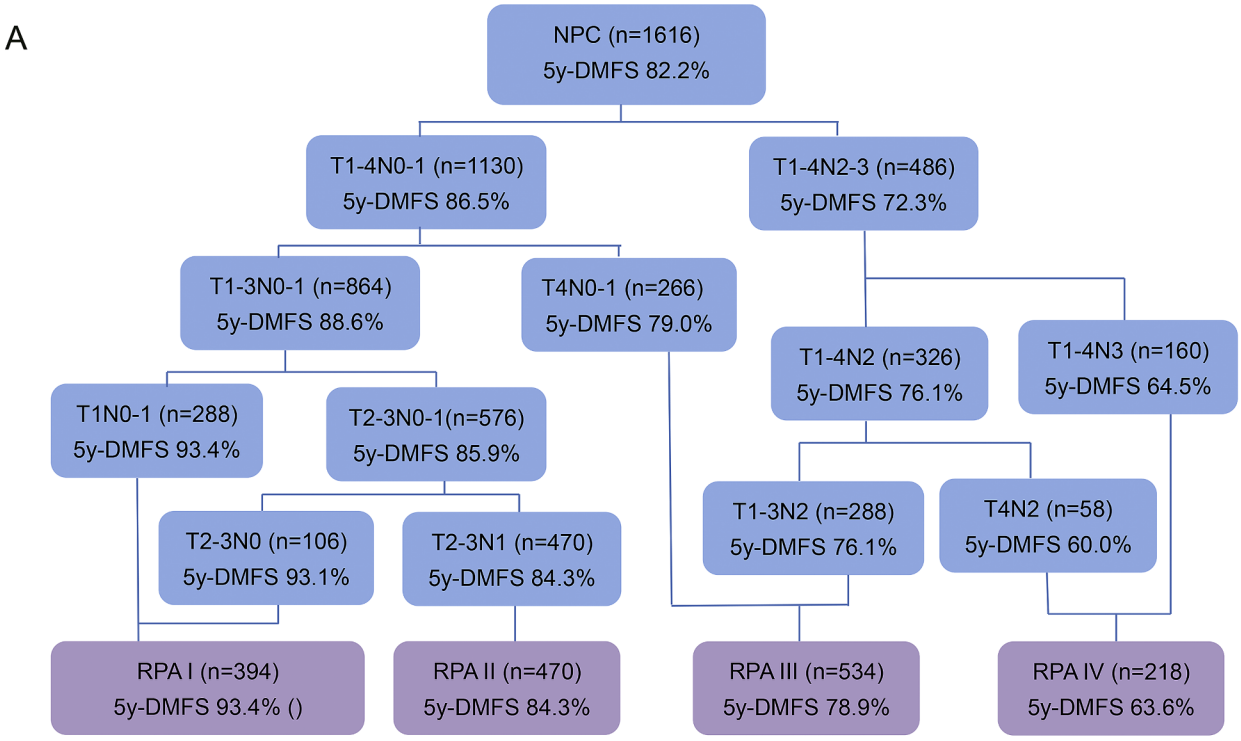
Fig. 1. Kaplan-Meier curves of DMFS in NPC patients with the 8th edition clinical TNM stage (A), T-N subsets within stage II (B), stage III (C), and stage IV (D).

Results

Patients' characteristics and performance of the TNM-8 in predicting risk of DM

The clinical characteristics of the 1616 eligible patients are listed in Table 1. The majority were nonkeratinizing (undifferentiated) carcinoma (1483, 91.8%) according to the World Health Organization (WHO) classification. Median follow-up time was 53 months. A total of 93 (5.8%) local, 72 (4.5%) regional, and 273 (16.9%) distant failures were identified. The 5-year DMFS for TNM-8 stage I, II, III and IV were 97.4% (95% CI: 93.9–100), 90.7% (87.8–93.6), 82.5% (79.4–85.6) and 71.6% (67.1–76.1), respectively (Fig. 1A). Although a relatively monotonic reduction in 5-year DMFS according to higher clinical stages was evident and the difference was statistically distinguishable between adjacent clinical stages, subgroups within the same clinical stage demonstrated poor consistency of metastatic hazard, as indicated in Figure 1.

For patients with TNM-8 stage II, the T2N1 subset (n = 154) had a lower DMFS compared to other stage II patients (92.9% vs. 86.0%,



B

RPA	T1	T2	T3	T4
N0	RPA I (n=77) AHR=1.0 (REF)	RPA I (n-32) AHR=2.5	RPA I (n-74) AHR=2.7	RPA III (n=43) AHR=6.0
N1	RPA I (n=211) AHR=2.9	RPA II (n=154) AHR=5.4	RPA II (n=316) AHR=6.7	RPA III (n=203) AHR=10.3
N2	RPA III (n=79) AHR=5.9	RPA III (n=66) AHR=8.2	RPA III (n=143) AHR=10.2	RPA IV (n=58) AHR=16.7
N3	RPA IV (n=46) AHR=16.3	RPA IV (n=36) AHR=11.5	RPA IV (n=58) AHR=17.3	RPA IV (n=20) AHR=16.8

C

TNM-8	T1	T2	T3	T4
N0	Stage I	Stage II	Stage III	Stage IVA
N1	Stage II	Stage II	Stage III	Stage IVA
N2	Stage III	Stage III	Stage III	Stage IVA
N3	Stage IVA	Stage IVA	Stage IVA	Stage IVA

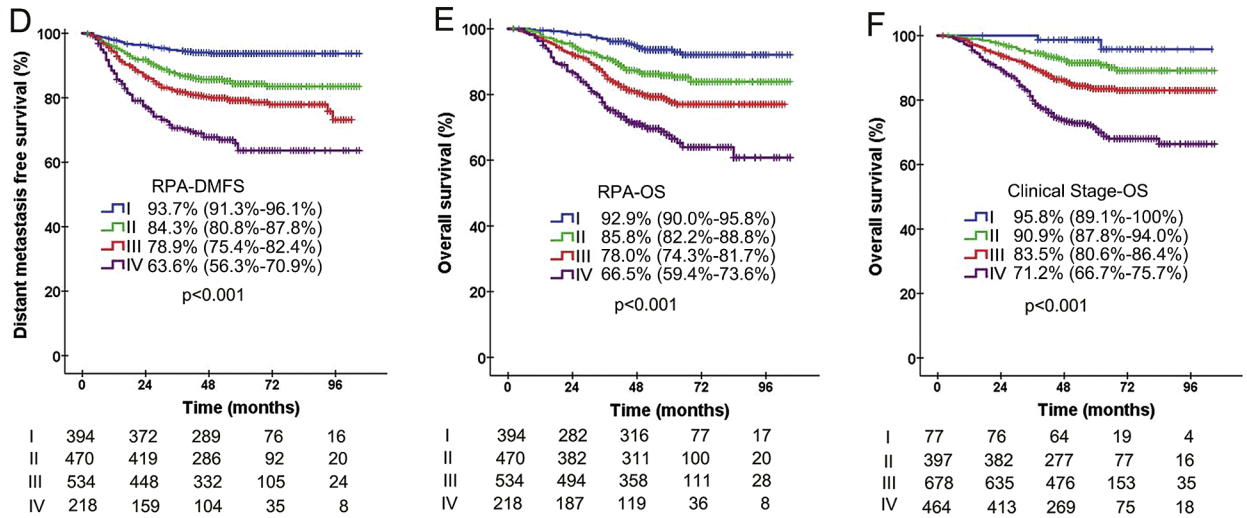


Fig. 2. The proposed risk grouping derived by recursive partitioning analysis (RPA) (A and B); T-N grouping of the 8th edition TNM staging system(C); Kaplan-Meier curves for RPA-DMFS (D), RPA-OS (E) and 8th edition Clinical TNM stage - OS (F).

$p = 0.049$). For stage III, the 5-year DMFS was significantly different between T3N0 and T2N2 (92.9% vs. 80.0%, $p = 0.022$), T3N0 and T3N1 (92.9% vs. 84.1%, $p = 0.047$), T3N0 and T3N2 (92.9% vs. 75.7%, $p = 0.003$), and T3N1 vs T3N2 (84.1% vs. 75.7%, $p = 0.049$) (Fig. 1C). For patients with stage IVA, the risk of DM was also significantly different between T4N0 and T4N2 (85.8% vs. 60.1%, $p = 0.021$), T4N0 and T1N3 (85.8% vs. 58.7%, $p = 0.028$), T4N0 and T3N3 (85.8% vs. 63.4%, $p = 0.017$), and T4N0 vs. T4N3 (85.8% vs. 60.0%, $p = 0.049$) (Fig. 1D)

Table 2
Multivariate analysis of risk of distant metastasis by Clinical stage and RPA groups adjusting for other potential predictors.

Covariate	Clinical stage			RPA group		
	HR	95% CI	*p*	HR	95% CI	*p*
Gender						
Male	reference			reference		
Female	0.734	(0.538, 1.001)	0.051	0.743	(0.544, 1.016)	0.063
Age (years)	1.012	(1.002, 1.022)	**0.021**	1.012	(1.002, 1.023)	**0.018**
LDH (IU/L)	1.005	(1.002, 1.008)	**0.001**	1.005	(1.002, 1.008)	**0.003**
Chemotherapy						
≤3 cycles	reference			reference		
>3 cycles	1.038	(0.807, 1.334)	0.772	0.996	(0.773, 1.283)	0.977
Clinical stage						
Stage I	reference					
Stage II	3.977	(0.957, 16.530)	0.058			
Stage III	7.014	(1.726, 28.503)	**0.006**			
Stage IV	11.702	(2.879, 47.562)	< **0.001**			
RPA group						
RPA-I				reference		
RPA-II				2.560	(1.606, 4.080)	< **0.001**
RPA-III				3.437	(2.200, 5.370)	< **0.001**
RPA-IV				6.054	(3.773, 9.716)	< **0.001**

Abbreviation: LDH = lactate dehydrogenase; RPA = Recursive-partitioning analysis; HR = hazard ratio for distant metastasis; CI: confidence interval

Refined RPA-based anatomic stage groupings for different DM risk strata

RPA classified patients into four distinct DM risk groups: RPA-I (T1-3 N0 and T1N1, n = 394), RPA-II (T2-3 N1, n = 470), RPA-III (T4N0-1 and T1-3 N2, n = 534) and RPA-IV (T4N2 and T1-4 N3, n = 218), with 5-year DMFS of 93.4% (95% CI: 91.3–96.1), 84.3% (80.8–87.8), 78.9% (75.4–82.4) and 63.6% (56.3–70.9), respectively ($p < 0.001$) (Fig. 2A–D). The Cox regression model, adjusting for age, gender, treatment modality and LDH, confirmed that higher RPA groupings conferred a higher risk of DM (Table 2).

As shown in Fig. 3, the RPA model showed better intra-group consistency, when compared with clinical TNM-8 stage with a lower AIC (3845.2 vs. 3860.5) and higher c-index (0.665 vs. 0.657) for DMFS (Table 3).

It is worth mentioning that the RPA groupings also showed better performance in predicting risk of death versus TNM-8 stages, with a lower AIC (3713.6 vs. 3714.2) and higher c-index (0.721 vs. 0.719) (Table 3). Five-year OS of RPA-I, RPA-II, RPA-III and RPA-IV were 92.9% (95% CI: 90.0–95.8), 85.8% (82.2–88.8), 78.0% (74.3–81.7) and 66.5% (59.4–73.6), respectively ($p < 0.001$) (Figure 2E).

Discussion

This large single institution cohort of non-metastatic NPC treated with IMRT showed that, similar to the 6th and 7th edition UICC/AJCC staging system, TNM-8 has limitations in portraying the risk of DM consistently within each stage. Using an RPA algorithm, we generated the following four distinctly different DM risk groups: RPA-I (T1-3N0 and T1N1), RPA-II (T2-3N1), RPA-III (T4N0-1 and T1-3N2) and RPA-IV (T4N2 and T1-4N3) [Fig. 2]. This RPA risk grouping performed better in depicting risk of DM compared to TNM-8 stage grouping with improved homogeneity in DM risk among T-N subsets within each group.

Earlier we indicated that the AJCC and UICC have traditionally recommended OS as the preferred end-point to use in staging and prognostic studies since it has the fewest methodological issues in determining outcome reliably; however the AJCC has also acknowledged that disease-specific survival may provide additional benefit through censoring and adjustment for competing risk. In addition, greater granularity addressing other outcomes (e.g. recurrence) might need to be considered in realizing the goals for individualizing prognosis in the practice of precision oncology [4]. With advances in radiotherapy and imaging techniques (e.g. IMRT and MRI), as well as the addition of chemotherapy, the pattern of failure for NPC has changed. LRC is no longer a major challenge of this disease. DM has emerged as the major form of failure and cause of death for this patient population. Appropriately depicting DM risk is an important initial step in contemporary risk tailored approaches. Several RPA prognostic models relying on EBV DNA combined with TNM-8 have been proposed to depict risk of disease progression or death, but not DM specifically[23,24]. However, such models face other practical challenges since large inter-laboratory variability exists[25] and a proportion (20–30%) of NPC patients have undetectable EBV DNA even in advanced presentations, including in endemic regions [26]. In addition, due to inter-laboratory variability, the optimal cutoff value of EBV DNA also remains elusive [27–29]. In contrast our anatomic-based RPA risk stratification for DMFS serves a practical advantage in the current environment and provides a framework for future essential biomarkers to be incorporated using the strongest initial predictive partitions.

The RPA-I group comprised T1-3N0 and T1N1 subsets and was classified as the low-risk of DM group with both DMFS and OS exceeding 90%. It is intuitive that DM risk appears strongly linked to nodal disease burden while primary disease extent plays a lesser role. These results are consistent with several other IMRT series. Similarly high DMFS and OS in the T1-3N0 subsets was also observed by Sun et al. [30] while high DMFS in T1N1 subset was reported by Su et al. [31], although both reports were based on TNM-7. Notably, the current study identifies the majority of stage II (with the exception of T2N1) and a small subset of stage III (T3N0) as having a low risk of DM (RPA-I). However there are clinical implications for this finding since current treatment guidelines advocate routine chemo-radiotherapy for stage II and III. Whether chemotherapy is needed in stage II NPC has been a subject of debate. The indication for chemotherapy in stage II disease is based on a single randomized trial undertaken before the advent of IMRT and the definition of 'stage II' in the trial used the Chinese 1992 NPC stage classification where a small proportion [11% RT alone and 16% concurrent chemoradiotherapy (CCRT) arm] had bilateral upper neck nodal disease (representing N2/stage III by TNM-7/TNM-8 definition) [32]. Several retrospective reports[12,33–35] suggest that TNM-7 Stage II disease managed with IMRT alone could achieve comparable outcomes to CCRT. Two recently completed phase II trials both confirmed similarly high 5-year DMFS (> 90%) and OS (> 85%) in stage II NPC patients treated with IMRT without vs with concurrent [36]or concurrent-adjuvant chemotherapy [37]. It should be noted that T3N0, a subset of RPA-I belonging to TNM-8 stage III disease, also shows a low

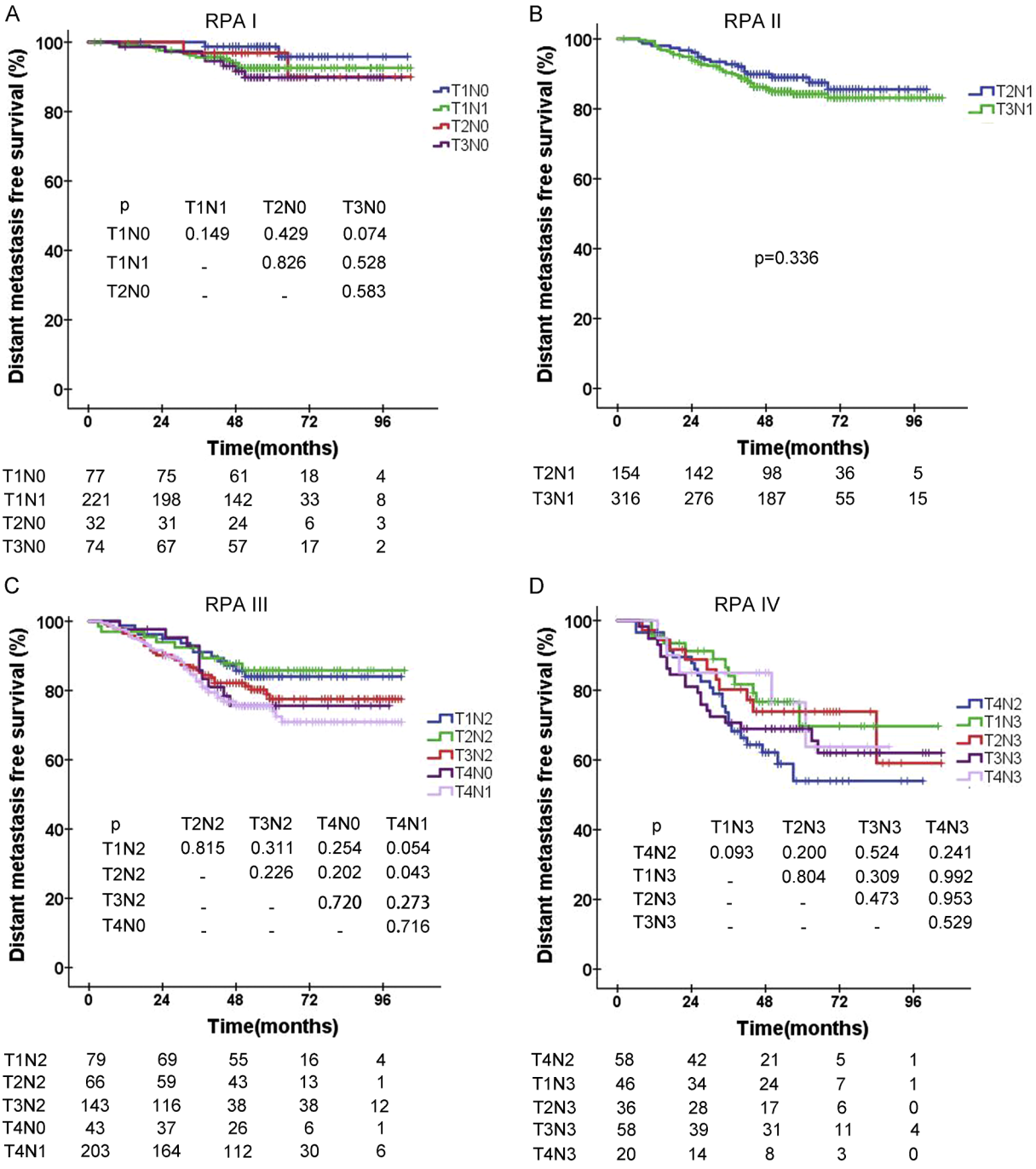


Fig. 3. Kaplan-Meier curves for DMFS of T-N subsets in NPC patients within each RPA groups: (A) RPA-I, (B) RPA-II, (C) RPA-III and (D) RPA-IV.

risk of DM, which is supported by several observational studies [13,30,38] implying that CCRT may have limited survival advantages over IMRT alone in this subset as well. In the present study very few T1N1 and T2-3 N0 patients received IMRT alone and we are unable to evaluate whether the high DMFS would be maintained if chemotherapy was omitted in these subsets. Notwithstanding these favorable results in observational studies, we must maintain a cautious and evidence-based approach to the omission of chemotherapy in RPA-I until more data from randomized trials are available.

RPA-II, represented by T2N1 and T3N1 disease, is a group of patients with low-intermediate risk of DM. In the 2D-RT era, T2N1 disease was a unique subgroup of stage II characterized by worse survival [39–41], and our results and published evidence suggest that this situation has not changed in the IMRT era [11,16,31,42,43]. Su et al. [31] argued that, although LRC was equivalent in patients with stages IIb and I NPC, T2bN1 disease might have a greater DM risk when treated with RT alone. Our previous data indicated that T2N1M0 disease (TNM-7) experience significantly poorer OS (85.7% vs. 93.4%, $p = 0.044$) and DMFS (84.3% vs. 93.7%, $p = 0.010$) compared to those with T1N1M0 disease[11]. Luo et al [42] also demonstrated that 3-year OS (74.5% vs 100.0%, $p = 0.01$) and DMFS (86.7% vs. 100.0%, $p = 0.04$) were significantly poorer in T2N1 (all were T2bN1 in TNM-6) compared to T1-2N0 and T1N1 patients. Another candidate included in RPA-II is T3N1 disease, a long recognized low-risk subgroup of "advanced" stage, and one that has been frequently excluded from clinical trials addressing loco-regionally advanced NPC (LA-NPC). Based on the evidence presented herein, RT alone for RPA-II seems less suitable for de-intensification strategies that omit chemotherapy. The most optimal

Table 3
Performance of RPA model and clinical stage in predicting risk of distant metastasis and overall survival.

	Stage group	RPA group
Distribution		
I	77 (4.8)	394 (24.4)
II	397 (24.6)	470 (29.1)
III	678 (42.0)	534 (33.0)
IV	464 (28.7)	218 (13.5)
5-y DMFS		
I	97.4%	93.4%
II	90.7%	84.3%
III	82.5%	78.9%
IV	71.6%	63.6%
C-index of DMFS (95%CI)	0.657 (0.622–0.692)	0.665 (0.630–0.700)
AIC of DMFS	3860.5	3845.2
5-y OS		
I	95.8%	92.9%
II	90.9%	85.5%
III	83.5%	78.0%
IV	71.2%	66.5%
c-index of OS (95%CI)	0.719 (0.684–0.754)	0.721 (0.686–0.756)
AIC of OS	3714.2	3713.6

Abbreviation: DMFS = distant metastasis-free survival; OS = overall survival: AIC = Akaike information criterion; 5y = 5-year

combination of chemotherapy is unclear. Well-designed RCTs are needed to assist in establishing the best use of chemotherapy in RPA-II.

RPA-III (T4N0-1 and T1-3N2) is an intermediate-high risk group, with a 5-year DMFS rates of 78.9%. T4N0-1 are stage IV candidates, but are generally considered to have a relatively lower risk of DM compared to other stage IV patients [44–46]. A study from Turkey included 90 patients staged as T4N0 using the 5th edition TNM (TNM-5), and only 6 patients (6/90, 6.6%) developed DM at a median follow-up time of 38 months following definitive radiotherapy using 2D-RT techniques [44]. Cao et al. [46] analyzed a series of 335 non-metastatic T4 classification (TNM-7) NPC patients treated by IMRT, and found that patients with T4N0-1 had significantly better DMFS compared to T4N2-3 disease (84.0% vs. 68.3%, p = 0.003). It maybe hypothesized that T4N0-1, especially T4N0 patients, represent biologically different diseases with different clinical behavior and gene expression patterns [47], and may potentially require different treatment approaches, when compared with other stage IV disease. Some investigators have even indicated that T4N0-1 should be classified as stage III [16]. Whether these suggestions are appropriate remains to be explored, preferably in trials.

Besides N3 disease, T4N2 patients were also classified as the highest DM risk subset (RPA-IV) with a 5-year DMFS of only 63.6% although almost all of them received intensified treatment, thereby mirroring results reported by Li et al. [16]. This suggests that novel treatment strategies, such as immunotherapy or novel chemotherapy agents and sequencing, for this subset of patients are needed. Accurate means to identify these subgroups is also warranted, as provided by the current study (i.e. RPA-IV), to facilitate clinical trial design exploring more effective systemic agents and/or sequences.

Several limitations should be noted when interpreting our results. Firstly, this is retrospective study of a relatively unselected large NPC population that includes the entire spectrum of disease (stage I-IV). Although we have adjusted major confounders including chemotherapy cycles for DMFS, other factors, such as chemotherapy regimens, number and type of chemotherapy agents, and treatment compliance, might still influence results. Secondly, the data were derived from an academic cancer center in an endemic jurisdiction. Whether the findings can be reproduced and are generalizable to other patient populations remains to be determined. External validation in independent datasets is warranted. Thirdly, some may argue that non-anatomical factor, such as EBV-DNA [23,24,48], should be integrated into the model; however, routine detection of plasma EBV-DNA is not widely used in secondary/tertiary hospitals, and the methodology has not been standardized so far. Finally, the observed improvement in AIC and C-index RPA DM risk grouping vs TNM-8 is modest. While statistically different DM risk seemed be present among some T-N subsets within TNM-8 stage grouping, they no longer exist within the RPA risk grouping (p value were all > 0.05 between T-N subsets within each RPA risk group). It is conceivable that including other parameters, such as tumor volume, might further improve depiction of DM risk. Primary gross tumor volume (GTV) has been shown to be prognostic for NPC in several studies and has been proposed for inclusion in the T classification [49–51]. However, this factor was not included in the 8th edition due to lack of consensus about who should determine this component (radiology vs radiation oncology), uncertainty about optimal cutoffs, and which imaging modality (CT, MRI, or PET) should be used as a basis for evaluation, as well as concerns about inter-rater variation and applicability on a worldwide basis. In this situation, our model presents a practical way for evaluating risk of DM, and provides a relatively stable anatomic framework that partitions according to a DM risk hierarchy that may permit EBV DNA to be most optimally incorporated in the future, when testing methods become more standardized and available widely.

Conclusions

This large single institution study of a contemporary treated NPC cohort shows that DM risk increases with higher TNM-8 stage, although significant heterogeneity exists for DMFS within each stage. Deriving relatively homogeneous DM risk groups would help refine treatment strategies. Using an RPA algorithm, we generated four groups based on TNM-8T and N definitions, namely RPA-I (T1N0-1 and T2-3N0), RPA-II (T2-3N1), RPA-III (T4N0-1 and T1-3N2) and RPA-IV (T4N2 and T1-4N3). These RPA risk groupings performed better in stratifying DM risk compared to the TNM-8 stage grouping. If these results can be validated with independent datasets, it should be useful in guiding future therapeutic trials for the best utilization of chemotherapy (i.e. regimens and courses) with IMRT. It also provides an anatomic framework to permit incorporation of biomarkers to further enhance prediction of risk of DM.

Conflict of interest statement

None declared

Acknowledgement

This work was sponsored by National Clinical Key Specialty Construction Program and Key Clinical Specialty Discipline Construction Program of Fujian, China. This research is also supported by grant from the Fujian Provincial Natural Science Foundation of China (grant No. 2018 J01275). We acknowledge the Bartley-Smith Wharton Fund and the O. Warwick Prize of the Canadian Cancer Society for supporting BO'S academic activities.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.02.021.

References

[1] Lee AW, Ma BB, Ng WT, Chan AT. Management of nasopharyngeal carcinoma: current practice and future perspective. J Clinical Oncol : Official J Amer Soc Clin Oncol 2015;33:3356–64.
[2] Zhang MX, Li J, Shen GP, Zou X, Xu JJ, Jiang R, et al. Intensity-modulated radiotherapy prolongs the survival of patients with nasopharyngeal carcinoma compared with conventional two-dimensional radiotherapy: a 10-year experience with a large

cohort and long follow-up. European J Cancer (Oxford, England) 1990;2015(51):2587–95.
[3] O'Sullivan B, Brierley J, Byrd D, Bosman F, Kehoe S, Kossary C, et al. The TNM classification of malignant tumours-towards common understanding and reasonable expectations. Lancet Oncol 2017;18:849–51.
[4] Compton CC, Hess KR, Halabi S, Balis UGJ, Gershenwald JE, Gimotty PA, et al. Risk Models for Individualized Prognosis in the Practice of Precision Oncology. In: Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Wahington MK, editors. AJCC Cancer Staging Manual. 8th Ed.Switzerland: Springer International Publishing AG; 2017. p. 47–52.
[5] O'Sullivan B. Introduction. In: Brierley J, Gospodarowicz M, O'Sullivan B, Ch W, editors. UICC TNM Classification of Malignant Tumours. 8th Ed.Chichester, West Sussex: UK: John Wiley & Sons, Ltd; 2017. p. 1–15.
[6] O'Sullivan B, Brierley J, Gospodarowicz M. Chapter 3: Prognosis and classification of cancer. In: O'Sullivan B, Brierley J, D'Cruz A, Fey M, Pollock R, Vermorken J, editors. UICC Manual of Clinical Oncology. 9th Ed.Chichester, UK: John Wiley & Sons, Ltd.; 2015. p. 23–33.
[7] Kim KY, Le QT, Yom SS, Ng RHW, Chan KCA, Bratman SV, et al. Clinical utility of epstein-barr virus DNA testing in the treatment of nasopharyngeal carcinoma patients. Int J Radiat Oncol Biol Phys 2017;98:996–1001.
[8] Zhang J, Shu C, Song Y, Li Q, Huang J, Ma X. Epstein-Barr virus DNA level as a novel prognostic factor in nasopharyngeal carcinoma: a meta-analysis. Medicine 2016;95:e5130.
[9] Pan JJ, Ng WT, Zong JF, Lee SW, Choi HC, Chan LL, et al. Prognostic nomogram for refining the prognostication of the proposed 8th edition of the AJCC/UICC staging system for nasopharyngeal cancer in the era of intensity-modulated radiotherapy. Cancer 2016;122:3307–15.
[10] Wan XB, Wei L, Li H, Dong M, Lin Q, Ma XK, et al. High pretreatment serum lactate dehydrogenase level correlates with disease relapse and predicts an inferior outcome in locally advanced nasopharyngeal carcinoma. European J Cancer (Oxford, England) 1990;2013(49):2356–64.
[11] Guo Q, Lu T, Lin S, Zong J, Chen Z, Cui X, et al. Long-term survival of nasopharyngeal carcinoma patients with stage II in intensity-modulated radiation therapy era. Jpn J Clin Oncol 2016;46:241–7.
[12] Chen KH, Zhu XD, Li L, Qu S, Liang ZQ, Liang X, et al. Comparison of the efficacy between concurrent chemoradiotherapy with or without adjuvant chemotherapy and intensity-modulated radiotherapy alone for stage II nasopharyngeal carcinoma. Oncotarget 2016;7:69041–50.
[13] Lan XW, Xiao Y, Zou XB, Zhang XM, OuYang PY, Xie FY. Outcomes of adding induction chemotherapy to concurrent chemoradiotherapy for stage T3N0-1 nasopharyngeal carcinoma: a propensity-matched study. OncoTargets Therapy 2017;10:3853–60.
[14] Chua DT, Sham JS, Wei WI, Ho WK, Au GK. The predictive value of the 1997 american joint committee on cancer stage classification in determining failure patterns in nasopharyngeal carcinoma. Cancer 2001;92:2845–55.
[15] Chua DT, Ma J, Sham JS, Mai HQ, Choy DT, Hong MH, et al. Improvement of survival after addition of induction chemotherapy to radiotherapy in patients with early-stage nasopharyngeal carcinoma: subgroup analysis of two Phase III trials. Int J Radiat Oncol Biol Phys 2006;65:1300–6.
[16] Li AC, Xiao WW, Shen GZ, Wang L, Xu AA, Cao YQ, et al. Distant metastasis risk and patterns of nasopharyngeal carcinoma in the era of IMRT: long-term results and benefits of chemotherapy. Oncotarget. 2015;6:24511–21.
[17] Pan JJ, Ng WT, Zong JF, Chan LL, O'Sullivan B, Lin SJ, et al. Proposal for the 8th edition of the AJCC/UICC staging system for nasopharyngeal cancer in the era of intensity-modulated radiotherapy. Cancer 2016;122:546–58.
[18] Bruce JP, Hui AB, Shi W, Perez-Ordonez B, Weinreb I, Xu W, et al. Identification of a microRNA signature associated with risk of distant metastasis in nasopharyngeal carcinoma. Oncotarget 2015;6:4537–50.
[19] Liu X, Luo HN, Tian WD, Lu J, Li G, Wang L, et al. Diagnostic and prognostic value of plasma microRNA deregulation in nasopharyngeal carcinoma. Cancer Biol Ther. 2013;14:1133–42.
[20] Lin S, Pan J, Han L, Zhang X, Liao X, Lu JJ. Nasopharyngeal carcinoma treated with reduced-volume intensity-modulated radiation therapy: report on the 3-year outcome of a prospective series. Int J Radiat Oncol Biol Phys 2009;75:1071–8.
[21] A. H. A new look at the statistical model identification. IEEE Trans Automat Contr 1974;19:716–23.
[22] Harrell Jr. FE, Califf RM, Pryor DB, Lee KL, Rosati RA. Evaluating the yield of medical tests. JAMA 1982;247:2543–6.
[23] 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 8th edition of nasopharyngeal cancer TNM stage classification. Int J Cancer. 2018.
[24] 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 2018.
[25] Yip TT, Ngan RK, Fong AH, Law SC. Application of circulating plasma/serum EBV DNA in the clinical management of nasopharyngeal carcinoma. Oral Oncol 2014;50:527–38.
[26] 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.
[27] Wang WY, Twu CW, Chen HH, Jiang RS, Wu CT, Liang KL, et al. Long-term survival analysis of nasopharyngeal carcinoma by plasma epstein-barr virus DNA levels. Cancer 2013;119:963–70.
[28] Lu L, Li J, Zhao C, Xue W, Han F, Tao T, et al. Prognostic efficacy of combining tumor volume with Epstein-Barr virus DNA in patients treated with intensity-modulated radiotherapy for nasopharyngeal carcinoma. Oral Oncol 2016;60:18–24.
[29] Li WF, Zhang Y, Huang XB, Du XJ, Tang LL, Chen L, et al. Prognostic value of plasma Epstein-Barr virus DNA level during posttreatment follow-up in the patients with nasopharyngeal carcinoma having undergone intensity-modulated radiotherapy. Chinese J Cancer 2017;36:87.
[30] Sun Y, Tang LL, Chen L, Li WF, Mao YP, Liu LZ, Lin AH, Li L, Ma J. Promising treatment outcomes of intensity-modulated radiation therapy for nasopharyngeal carcinoma patients with N0 disease according to the seventh edition of the AJCC staging system. BMC Cancer 2012;12(1):68.
[31] Su SF, Han F, Zhao C, Chen CY, Xiao WW, Li JX, et al. Long-term outcomes of early-stage nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy alone. Int J Radiation Oncol Biol Phys 2012;82:327–33.
[32] Chen QY, Wen YF, Guo L, Liu H, Huang PY, Mo HY, et al. Concurrent chemoradiotherapy vs radiotherapy alone in stage II nasopharyngeal carcinoma: phase III randomized trial. J Natl Cancer Inst 2011;103:1761–70.
[33] Pan XB, Huang ST, Chen KH, Zhu XD. Chemotherapy use and survival in stage II nasopharyngeal carcinoma. Oncotarget 2017;8:102573–80.
[34] Fangzheng W, Chuner J, Quanquan S, Zhimin Y, Tongxin L, Jiping L, et al. Addition of chemotherapy to intensity-modulated radiotherapy does not improve survival in stage II nasopharyngeal carcinoma patients. J Cancer 2018;9:2030–7.
[35] Xu C, Zhang LH, Chen YP, Liu X, Zhou GQ, Lin AH, et al. Chemoradiotherapy versus radiotherapy alone in stage ii nasopharyngeal carcinoma: a systemic review and meta-analysis of 2138 patients. J Cancer 2017;8:287–97.
[36] Yi JZC, Chen X, Gao L. The long term results of adding chemotherapy to intensity-modulated radiation therapy in the treatment of stage II nasopharyngeal carcinoma - a multicenter phase 2 study. Int J Radiat Oncol Biol Phys 2018;102:S125.
[37] Chen SMY, Shen Y, Ning X, Xiong C, Lin Z. Chemotherapy may not be necessary in stage II nasopharyngeal carcinoma treated with intensity-modulated radiation therapy. Int J Radiat Oncol Biol Phys 2018;102:S125–6.
[38] Zhang LN, Gao YH, Lan XW, Tang J, Su Z, Ma J, et al. Propensity score matching analysis of cisplatin-based concurrent chemotherapy in low risk nasopharyngeal carcinoma in the intensity-modulated radiotherapy era. Oncotarget 2015;6:44019–29.
[39] Chua DT, Sham JS, Kwong DL, Choy DT, Au GK, Wu PM. Prognostic value of paranasopharyngeal extension of nasopharyngeal carcinoma. A significant factor in local control and distant metastasis. Cancer 1996;78:202–10.
[40] Teo P, Lee WY, Yu P. The prognostic significance of parapharyngeal tumour involvement in nasopharyngeal carcinoma. Radiotherapy Oncol : J European Soc Therapeutic Radiol Oncol 1996;39:209–21.
[41] Xiao GL, Gao L, Xu GZ. Prognostic influence of parapharyngeal space involvement in nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2002;52:957–63.
[42] Luo S, Zhao L, Wang J, Xu M, Li J, Zhou B, et al. Clinical outcomes for early-stage nasopharyngeal carcinoma with predominantly WHO II histology treated by intensity-modulated radiation therapy with or without chemotherapy in nonendemic region of China. Head Neck 2014;36:841–7.
[43] Tang LL, Sun Y, Mao YP, Chen Y, Li WF, Chen L, et al. Prognostic value of parapharyngeal extension in nasopharyngeal carcinoma treated with intensity modulated radiotherapy. Radiotherapy Oncol : J European Soc Therapeutic Radiol Oncol 2014;110:404–8.
[44] Atasoy BM, Ozyar E, Akman F, Esassolak M, Abacioglu U. T4N0M0 nasopharyngeal carcinoma patients: do they have a distinct tumor biology? Kulak burun bogaz ihtisas dergisi : KBB =. J Ear, Nose, Throat 2010;20:89–96.
[45] Maalej M, Daoud J, Bouaouina N, Benna F, Frikha H, Jallouli M, et al. Clinical and evolutive aspects of nasopharyngeal T4 N0 neoplasms. Bull Cancer 1995;82:728–31.
[46] Cao CN, Luo JW, Gao L, Yi JL, Huang XD, Wang K, et al. Update report of T4 classification nasopharyngeal carcinoma after intensity-modulated radiotherapy: an analysis of survival and treatment toxicities. Oral Oncol 2015;51:190–4.
[47] Liang WJ, Qiu F, Hong MH, Guo L, Qin HD, Liu QC, et al. Differentially expressed genes between upward and downward progressing types of nasopharyngeal carcinoma. Ai zheng = Aizheng =. Chinese J Cancer 2008;27:460–5.
[48] Leung SF, Chan KC, Ma BB, Hui EP, Mo F, Chow KC, et al. Plasma Epstein-Barr viral DNA load at midpoint of radiotherapy course predicts outcome in advanced-stage nasopharyngeal carcinoma. Annals Oncol : Official J European Soc Medi Oncol 2014;25:1204–8.
[49] Qin L, Wu F, Lu H, Wei B, Li G, Wang R. Tumor Volume Predicts survival rate of advanced nasopharyngeal carcinoma treated with concurrent chemoradiotherapy. otolaryngology–head and neck surgery : official journal of american academy of otolaryngology-head and neck. Surgery 2016;155:598–605.
[50] Peng H, Chen L, Tang LL, Zhang Y, Li WF, Mao YP, et al. Primary tumor inflammation in gross tumor volume as a prognostic factor for nasopharyngeal carcinoma patients. Oncotarget 2016;7:14963–72.
[51] Chen C, Fei Z, Pan J, Bai P, Chen L. Significance of primary tumor volume and T-stage on prognosis in nasopharyngeal carcinoma treated with intensity-modulated radiation therapy. Jpn J Clin Oncol 2011;41:537–42.