Maximal lymph nodal diameter in staging system of nasopharyngeal carcinoma

Xin-Bin Pan

Guangxi Medical University Cancer Hospital

Song Qu

Guangxi Medical University Cancer Hospital

Ling Li

Guangxi Medical University Cancer Hospital

Long Chen

Guangxi Medical University Cancer Hospital

Shi-Xiong Liang

Guangxi Medical University Cancer Hospital

Xiao-Dong Zhu (✉ zhuxiaodonggx@163.com)

Guangxi Medical University Cancer Hospital

Research

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Abstract

Background: The value of maximal lymph nodal diameter in staging system of nasopharyngeal carcinoma (NPC) is not well established.

Methods: NPC patients were extracted from SEER database between 2004 and 2016. Overall survival (OS) and cancer-specific survival (CSS) were compared among three groups based on the maximal lymph nodal diameter: ≤ 3.0 cm, >3.0 - 6.0 cm, and >6.0 cm. Included patients were randomly divided into training set and validated set with 1:1 ratio. In training set, X-tile plots were created by dividing maximal lymph nodal diameter into three populations. All possible divisions of the maximal lymph nodal diameter were assessed. Two cut-off values were calculated by the X-tile plots in training set. The two cut-off values were evaluated in validated set.

Results: The 10-year OS and CSS were different between the three groups. Multivariate regression analysis revealed that maximal lymph nodal diameter >6.0 cm was an independent risk prognostic factor for OS (hazard ratio [HR]=1.91, 95% confidence interval [CI]: 1.51-2.43; $P<0.001$) and CSS (HR=1.99, 95% CI: 1.51-2.61; $P<0.001$). The cut-off values of maximal lymph nodal diameter were 1.3 cm and 5.0 cm using X-tile plots in the training set. In the validated set, the maximal lymph nodal diameter >5.0 cm was a risk prognostic factor for OS and CSS.

Conclusions: The maximal lymph nodal diameter of 5.0 cm may be a reasonable cut-off value for N stage.

Background

The tumor-node-metastasis (TNM) staging system is crucial for making treatment for nasopharyngeal carcinoma (NPC), which is also one of the most important predictive prognostic factors(1). N stage of NPC was reported to be a crucial predictive factor for distant metastasis, which was the main failure pattern of NPC(2, 3). However, the maximal lymph nodal diameter in N stage was not well established. Although the maximal lymph nodal diameter > 6 cm is classified as N3 in the 8th edition of the American Joint Committee on Cancer (AJCC) staging system(1), it was suggested to be downstaged from N3 to N2 or rejected from the N category based on survival analysis(4–7). On the other hand, the maximal lymph nodal diameter > 3 – 6 cm was excluded in the 8th AJCC edition(1), which was defined as N2 stage in the 2008 Chinese edition staging system. Until now, the value of the maximal lymph nodal diameter in survivals of NPC remains unclear. Thus, this retrospective cohort study was conducted to investigate the prognostic value of the maximal lymph nodal diameter and further identify optimal cut-off values.

Methods

Patients

The Surveillance, Epidemiology, and End Results (SEER) database from 2004 to 2016 was queried to extract NPC patients. Pathologic confirmed NPC patients with complete data of maximal lymph nodal diameter were included in this study. Clinical variables including age, sex, race, tumor grade, tumor histology, radiotherapy, and chemotherapy were extracted. Included patients were divided into three groups based on the maximal lymph nodal diameter values: ≤ 3.0 cm, $> 3.0-6.0$ cm, and > 6.0 cm according to the 2008 Chinese edition and the 8th AJCC edition for NPC(1, 8).

Endpoints

Overall survival (OS) was the primary endpoint. OS was defined as the time until death as a result of any cause in the SEER database. Cancer-specific survival (CSS) was the secondary endpoint. CSS was defined as the time until death attributed to NPC in the SEER database.

Statistical analysis

The continuous variable of age was transformed to a categorical variable(9). Categorical variables, including sex, race, tumor grade, tumor histology, radiotherapy, and chemotherapy were analyzed using Fisher test and were presented as percentages.

The Kaplan-Meier method was used to calculate 10-year OS and CSS between ≤ 3.0 cm, $> 3.0-6.0$ cm, and > 6.0 cm groups. The log-rank test was used to assess differences between survival curves. Multivariable proportional hazards models adjusted for age, sex, race, tumor grade, tumor histology, radiotherapy, and chemotherapy were performed to assess independent prognostic factors. The results are reported as hazard ratios (HRs) with 95% confidence intervals (CIs).

The data of maximal lymph nodal diameter was randomly divided into training set and validated set with 1:1 ratio. In training set, X-tile plots were created by dividing maximal nodal diameter data into three populations(10). All possible divisions of the maximal nodal diameter data were assessed. Two optimal cut-off values were calculated by the X-tile plots. The cut-off values were evaluated in validated set.

SPSS Statistics Version 23.0 software (IBM Co., Armonk, NY, USA) and R software (version 3.4.4) were used to perform statistical analyses. Two-tailed $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

Patient selection is showed in Fig. 1. A total of 2928 patients were included: 1873 (63.97%) patients in the ≤ 3.0 cm group, 894 (30.53%) patients in the $> 3.0-6.0$ cm group, and 161 (5.50%) patients in the > 6.0 cm group. The patient characteristics are showed in Table 1. The median follow-up times were 34 (interquartile range [IQR]: 12–73) months for the ≤ 3.0 cm group, 35 (IQR: 12–70) months for the $> 3.0-6.0$ cm group, 21 (IQR: 8–52) months for the > 6.0 cm group, respectively.

Table 1
Patient characteristics.

	≤ 3.0 cm (n = 1873)	> 3.0–6.0 cm (n = 894)	> 6.0 cm (n = 161)	<i>P</i>
Diameter (cm)				
Median (IQR)	2.0 (1.5–2.5)	4.0 (3.6-5.0)	7.1 (7.0-8.6)	< 0.001
Age				
≤ 19	50 (2.67%)	23 (2.57%)	9 (5.59%)	0.011
20–39	243 (12.97%)	128 (14.32%)	34 (21.12%)	
40–59	927 (49.49%)	460 (51.45%)	78 (48.45%)	
60–79	594 (31.71%)	251 (28.08%)	36 (22.36%)	
≥ 80	59 (3.15%)	32 (3.58%)	4 (2.48%)	
Race				
Asian	783 (41.80%)	387 (43.29%)	78 (48.45%)	0.001
Black	204 (10.89%)	100 (11.19%)	35 (21.74%)	
White	848 (45.27%)	389 (43.51%)	47 (29.19%)	
other	38 (2.03%)	18 (2.01%)	1 (0.62%)	
Sex				
female	577 (30.81%)	212 (23.71%)	30 (18.63%)	< 0.001
male	1296 (69.19%)	682 (76.29%)	131 (81.37%)	
Grade				
unknown	25 (1.33%)	11 (1.23%)	2 (1.24%)	0.054
I	144 (7.69%)	42 (4.70%)	6 (3.73%)	
II	548 (29.26%)	256 (28.64%)	41 (25.47%)	
III	569 (30.38%)	271 (30.31%)	55 (34.16%)	
IV	587 (31.34%)	314 (35.12%)	57 (35.40%)	
Pathology				
WHO I	600 (32.03%)	289 (32.33%)	42 (26.09%)	0.675
WHO II	476 (25.41%)	218 (24.38%)	39 (24.22%)	
WHO III	340 (18.15%)	162 (18.12%)	33 (20.50%)	

	≤ 3.0 cm (n = 1873)	> 3.0–6.0 cm (n = 894)	> 6.0 cm (n = 161)	<i>P</i>
other	457 (24.40%)	225 (25.17%)	47 (29.19%)	
Radiotherapy				
no	209 (11.16%)	121 (13.53%)	22 (13.66%)	0.149
yes	1664 (88.84%)	773 (86.47%)	139 (86.34%)	
Chemotherapy				
no	199 (10.62%)	103 (11.52%)	20 (12.42%)	0.615
yes	1674 (89.38%)	791 (88.48%)	141 (87.58%)	
IQR: interquartile range. WHO: World Health Organization.				

Survival analysis

The 10-year OS was 48.12%, 42.89%, and 35.12% for ≤ 3.0 cm, > 3.0–6.0 cm, and > 6.0 cm groups, respectively (Fig. 2A). The 10-year OS of the three groups was significantly different in pairwise comparisons ($P = 0.047$ for ≤ 3.0 cm and > 3.0–6.0 cm groups, $P < 0.001$ for ≤ 3.0 cm and > 6.0 cm groups, and $P < 0.001$ for > 3.0–6.0 cm and > 6.0 cm groups). Multivariate regression analysis revealed that maximal lymph nodal diameter > 6.0 cm was an independent risk prognostic factor for OS (HR = 1.91, 95% CI: 1.51–2.43; $P < 0.001$) setting maximal nodal diameter ≤ 3.0 cm as a reference (Fig. 3).

The 10-year CSS was 63.13%, 57.19%, and 45.76% for ≤ 3.0 cm, > 3.0–6.0 cm, and > 6.0 cm groups, respectively (Fig. 2B). The 10-year CSS of the three groups was significantly different in pairwise comparisons ($P = 0.007$ for ≤ 3.0 cm and > 3.0–6.0 cm groups, $P < 0.001$ for ≤ 3.0 cm and > 6.0 cm groups, and $P < 0.001$ for > 3.0–6.0 cm and > 6 cm groups). Multivariate regression analysis revealed that maximal lymph nodal diameter > 3.0–6.0 cm (HR = 1.18, 95% CI: 1.01–1.37; $P = 0.037$) and > 6.0 cm (HR = 1.99, 95% CI: 1.51–2.61; $P < 0.001$) were independent risk prognostic factors for CSS setting maximal nodal diameter ≤ 3.0 cm as a reference (Fig. 4).

Identification of cut-off values

In the training set, associations were calculated by the log-rank test for OS (Fig. 5A) and CSS (Fig. 5B). The data of maximal lymph nodal diameter were represented graphically in a right-triangular grid where each point represented the data from a given set of divisions. Data points away from the hypotenuse of right-triangular grid up or to the left represented results from two cut-off values. The cut-off values divided the data of maximal lymph nodal diameter into three groups. Specifically, the cut-off values were calculated and were showed on the grid using a color code. The cut-off values for OS were 1.3 cm and 5.0 cm. The cut-off values for CSS were also 1.3 cm and 5.0 cm.

Survival in training set

The 10-year OS was 48.27%, 46.39%, and 34.97% for ≤ 1.3 cm, > 1.3 -5.0 cm, and > 5.0 cm groups, respectively (Fig. 6A). The 10-year OS of > 5.0 cm group differed significantly from ≤ 1.3 cm ($P < 0.001$) and > 1.3 -5.0 cm ($P < 0.001$) groups in pairwise comparisons. However, no difference was observed between the ≤ 1.3 cm and > 1.3 -5.0 cm groups ($P = 0.181$).

The 10-year CSS was 68.83%, 60.41%, and 49.22% for ≤ 1.3 cm, > 1.3 -5.0 cm, and > 5.0 cm groups, respectively (Fig. 6B). In pairwise comparisons, the 10-year CSS of > 5.0 cm group was different from ≤ 1.3 cm ($P < 0.001$) and > 1.3 -5.0 cm ($P < 0.001$) groups. In contrast, there was not different between the ≤ 1.3 cm and > 1.3 -5.0 cm groups ($P = 0.052$).

Survival in validated set

In the validated set, the 10-year OS of ≤ 1.3 cm, > 1.3 -5.0 cm, and > 5.0 cm groups were 54.01%, 47.51%, and 30.68%, respectively (Fig. 7A). The 10-year CSS was 74.39%, 60.90%, and 45.41%, respectively (Fig. 7B). Pairwise comparisons revealed that > 5.0 cm group was different from ≤ 1.3 cm ($P < 0.001$) and > 1.3 -5.0 cm ($P < 0.001$) groups for both OS and CSS. However, OS ($P = 0.407$) and CSS ($P = 0.115$) were not different between the ≤ 1.3 cm and > 1.3 -5.0 cm groups.

Discussion

This study evaluated the prognostic value of the maximal lymph nodal diameter for NPC. The results revealed that NPC patients with the maximal lymph nodal diameter > 5.0 cm had worse OS and CSS compared to patients with the maximal lymph nodal diameter ≤ 5.0 cm. The results indicated that the maximal nodal diameter > 5.0 cm might be a reasonable cut-off value for N3 stage.

It is reasonable that the maximal lymph nodal diameter > 3.0 –6.0 cm is not classified as N2 in the 8th AJCC edition according to the current study. The multivariate regression analysis of our study revealed that the maximal lymph nodal diameter > 3.0 –6.0 cm was not an independent prognostic factor for OS, although it was an independent prognostic factor for CSS. Moreover, the results of training set and validated set both indicated that OS and CSS among patients with the maximal lymph nodal diameter ≤ 5.0 cm were not significant different. Our study suggested that the maximal lymph nodal diameter = 3.0 cm was not a reasonable cut-off value. Patients with the maximal lymph nodal diameter ≤ 5.0 cm should be treated as a whole group. Similarly, previous studies revealed that cut-off value set at 3.0 cm failed to show any independent prognostic value in survivals(1, 6, 7, 11).

The maximal lymph nodal diameter > 6.0 cm is still classified as N3 in the 8th AJCC edition. However, it might not be a reasonable cut-off value. The reasonable cut-off value still needs further investigation. Pan et al.(1) reported that differences in OS and distant metastasis-free survival were significant between all N categories setting the cut-off value = 6.0 cm. In contrast, several studies reported that the maximal lymph nodal diameter > 6.0 cm was not an independent prognostic factor(6, 7, 11–13). Moreover, the proportion of the maximal lymph nodal diameter > 6.0 cm is small, which was less than 4.5%(1, 6, 7, 11). Our study revealed the proportion of the maximal lymph nodal diameter > 6.0 cm was 5.50%, while the

proportion of the maximal lymph nodal diameter > 5.0 cm was 10.3%. In future, the incidence of patients with the maximal lymph nodal diameter > 6.0 cm will greatly decrease due to improvements in diagnosis. Thus, our study proposed the cut-off value = 5.0 cm might be more reasonable.

Assessment of the maximal lymph nodal diameter is crucial. The maximal lymph nodal diameter was assessed by palpation in the last decade(14). However, palpation-determined nodal size differs among clinicians. The maximal lymph nodal diameter measured on images was more accurate than palpation-based greatest dimension. Because palpation might involve subcutaneous tissue and aggregated nodes(6). According to the 2008 Chinese edition staging system, the maximal lymph nodal diameter was measured in axial plot. It was reported that no measurements of longitudinal maximal lymph nodal diameter were made in the coronal or sagittal planes may lead to negative results(6). In contrast, Guo et al.(7) found that the maximal lymph nodal diameter measured in all the longitudinal, sagittal, and coronal planes was not a useful indicator in predicting the spread potential of NPC patients. It was suggested that the maximal lymph nodal diameter might not represent the tumor burden, which could be replaced by the tumor volume(15, 16) and metabolic tumor volume(17–20).

Distant metastasis is the main failure pattern of NPC(2, 3). Due to the limitations of SEER database, data of distant failure were not available. Thus, this study could not assess the association between the maximal lymph nodal diameter and distant-metastasis free survival. It was unknown whether the unfavorable OS and CSS of patients with maximal lymph nodal diameter > 5.0 cm were due to distant failure or not. Further studies should be conducted to assess the correlation.

In conclusion, this study proposed that the maximal lymph nodal diameter > 5.0 cm was a cut-off value for nodal staging. However, the prognostic significance of size criteria (> 5.0 cm vs $\leq$ 5.0 cm) still needs further evaluation in prospective multi-center cohort studies.

List Of Abbreviations

NPC: nasopharyngeal carcinoma

OS: Overall survival

CSS: cancer-specific survival

HR: hazard ratio

CI: confidence interval

TNM: tumor-node-metastasis

AJCC: American Joint Committee on Cancer

SEER: Surveillance, Epidemiology, and End Results

IQR: interquartile range

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Guangxi Medical University Cancer Hospital.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

PXB and ZXD contributed to the conception of the study. QS and LL performed the data analyses. CL and LSX contributed to manuscript preparation and helped to perform the analysis with constructive discussions. All authors read and approved the final manuscript.

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Not applicable

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Figures

Figure 1

Flowchart depicting patient selection.

Figure 2

Survivals between the maximal lymph nodal diameter ≤ 3.0 cm, >3.0 - 6.0 cm, and >6.0 cm groups. (A) Overall survival. (B) Cancer-specific survival.

Figure 3

Multivariate regression analysis of prognostic factors for overall survival.

Figure 4

Multivariate regression analysis of prognostic factors for cancer-specific survival.

Figure 5

Identification of cut-off values using X-tile plots. (A) Overall survival. (B) Cancer-specific survival. The vertical axis represents all possible “high” populations, with the size of the high population increasing from top to bottom. The horizontal axis represents all possible “low” populations, with the size of the low population increasing from left to right. Data along the hypotenuse represent results from a single cut-point that divides the data into high or low subsets. Data points away from the hypotenuse of right-triangular grid up or to the left represent results from two cut-off values.

Figure 6

Survivals between the maximal lymph nodal diameter ≤ 1.3 cm, >1.3 - 5.0 cm, and >5.0 cm groups in training set. (A) Overall survival. (B) Cancer-specific survival.

Figure 7

Survivals the maximal lymph nodal diameter ≤ 1.3 cm, >1.3 - 5.0 cm, and >5.0 cm groups in validated set. (A) Overall survival. (B) Cancer-specific survival.