

Distribution pattern and prognosis of metastatic lymph nodes in cervical posterior to level V in nasopharyngeal carcinoma patients

Chaoyang Jiang

the general hospital of western theater command

Ji Ma

west china hospital

Hui Gao

the general hospital of western theater command

Ling Zhang

the general hospital of western theater command

Hua Li

the general hospital of western theater command

Tao Zhang

the general hospital of western theater command

Bisheng Liu (✉ lbs402889873@163.com)

Sichuan University West China Hospital <https://orcid.org/0000-0002-9630-5188>

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Abstract

Background:Lymph node metastasis in the cervical region posterior to level V (PLV) often occurs in patients with nasopharyngeal carcinoma (NPC), but the significance of lymph node metastasis in this region and the delineation of the radiotherapy target area have not been reported. We aimed to explore the distribution pattern and prognosis of metastatic lymph nodes in the PLV region in patients with NPC.

Methods:We retrospectively studied 605 cases of NPC diagnosed by pathology from December 2011 to November 2017. All patients were subjected to an enhanced CT scan from the cranial apex to 2 cm below the sternoclavicular joints. The nodal distribution at each level was assessed in accordance with the Radiation Therapy Oncology Group (RTOG) guidelines proposed in 2013. The central points of the metastatic lymph nodes of the PLV region in the patients were recreated proportionally on the CT images of a standard patient with N0 NPC in reference to the normal anatomy of the PLV area. The correlation between the PLV region and the other levels, the nodal location, and the characteristics and prognosis of the PLV region were analyzed.

Results:Lymph node metastasis occurred in 557 (92.06%) of 605 patients, and the top four areas with the highest probability of metastasis were level IIb (77.85%), level VIIa (73.05%), level IIa (60.0%), and level III (41.48%). There were 30 patients (4.95%) with lymph node metastasis in the PLV region. A total of 49 metastatic lymph nodes from the PLV region were counted, and the mean distance of the central point of each lymph node from the leading edge of the trapezius muscle was 14 mm. Linear regression correlation analysis suggested that lymph node metastasis in the PLV region was associated with ipsilateral level IVa ($P=0.018$), level Va, level Vb, and level Vc lymph node metastasis (all $P<0.001$). The 5-year OS, PFS, LRFS, and DMFS of 29 patients with lymph node metastasis in the PLV region were 41.6%, 27.7%, 89.1%, and 47.3%, respectively. The 5-year OS, PFS, LRFS, and DMFS of patients with N3 NPC with or without lymph node metastasis in the PLV region were 41.8% vs 67.3% ($P=0.007$), 27.8% vs 48.5% ($P=0.005$), 92.3% vs 80.5% ($P=0.521$), 40.6% vs 78.4% ($P<0.001$), respectively. Multivariate analysis showed that lymph node metastasis in the PLV region was an independent prognostic factor for DMFS ($P<0.05$).

Conclusion:NPC patients with lymph node metastasis in the PLV region had a poor prognosis and a high risk of distant metastasis. When patients have lymph node metastasis in levels IVa and V, the posterior boundary of the radiotherapy target in ipsilateral level V should be appropriately moved backward. We recommend that the margin of the PLV region may be a new cervical lymph node segment for head and neck tumors.

Background

Nasopharyngeal carcinoma (NPC) is a malignant tumor of the head and neck. Approximately 80% of NPCs occur in Southeast Asia and South China, including Guangdong, Guangxi, and Hunan Provinces^[1]. Since the early symptoms of NPC are not obvious, many patients reach the advanced stage of the

disease, and the clinical treatment effect is very poor^[2]. Despite improvements in its detection, surgical resection, and radiotherapy, the mortality of NPC is still very high. Currently, radiotherapy is the main treatment for NPC. Radiotherapy combined with chemotherapy or surgery can effectively improve the survival rate of patients with NPC^[3]. Importantly, accurate delineation of the radiotherapy target area is key to delivering precise treatment and reducing the side effects for patients with NPC.

The lymph node metastasis rate of NPC is approximately 80%, which not only affects the clinical stage and radiotherapy plan of NPC but is also one of the main influencing factors of prognosis^[4, 5]. In 2013, the new European version of the "National Head and Neck Cancer Cervical Lymph Node Division Guide" (referred to as the 2013 Guideline) not only elaborated the boundaries of each subarea but also further standardized the delineation of radiotherapy target areas of head and neck tumors^[6]. In the 2013 Guideline, level V nodes were refined into levels Va, Vb, and Vc, where the anterior border of the trapezius and 1 cm anterior to the serratus anterior muscles were defined as the posterior border of levels Va, Vb and Vc^[6]. However, the 2013 Guideline does not describe the cervical region posterior to level V (PLV) (the region between the trapezius muscle and the scapular levator). There are many patients with lymph node metastasis in the PLV region. Existing studies do not suggest a reference for the delineation of the radiotherapy target area of the PLV region for NPC patients, and the prognosis of NPC patients with lymph node metastasis in the PLV region is unclear^[7-10].

In this study, we retrospectively studied the clinical data of 605 patients with NPC, analyzed the extent of cervical lymph node metastasis, and explored the distribution pattern and prognosis of metastatic lymph nodes in the PLV region. Our study provides a useful reference for the delineation of the radiotherapy target area of the PLV region as well as a further revision of the head and neck lymph node division and N stage.

Methods

Patient population

This study was approved by the Ethics Committee of The General Hospital of Western Theater Command and Sichuan Cancer Hospital and Institute. We retrospectively reviewed the records of 605 patients with NPC from December 2011 to November 2017 in two hospitals. All patients had been pathobiologically confirmed as having NPC. Tumor stages and disease grades were classified according to the 2017 edition for the staging of NPC in China^[11]. All patients underwent a CT cross-sectional enhanced scan before treatment. The scan range was 2 cm below the cranial crest to the thoracic joint, and the thickness of each slice was 3 mm.

Diagnostic criteria for cervical lymph node metastasis

All patient CT images were reviewed and interpreted by two experienced radiological experts. The criteria for neck lymph node levels are based on the 2013 updated consensus guidelines for neck lymph node

levels [12]. The diagnostic criteria for cervical lymph node metastasis were as follows: 1) maximum diameter of lymph nodes on the largest cross-sectional image ≥ 10 mm; 2) central necrosis or ring enhancement; 3) ≥ 3 lymph nodes in one high-risk area, and a minimum diameter of the largest cross-section of ≥ 8 mm; 4) lymph node extracapsular invasion, including irregular enhancement of the edge of the lymph node, partial or total disappearance of the peripheral fat space, and lymph node fusion; 5) a minimum diameter of the largest cross-section of the posterior pharyngeal lymph node of ≥ 5 mm; 6) a shrunken lymph node after radiotherapy and chemotherapy. One of the above criteria can be judged as an eligibility criterion.

Delineation of the center point of the lymph node at the PLV

A case of N0 NPC was selected as the standard for a CT simulation scan. According to its anatomical structure and proportion, the central points of the metastatic lymph nodes in the PLV region were outlined on a CT image from the standard case. The central point is defined as the geometric center of the metastatic lymph node. When an individual fused lymph node could not be distinguished, the common geometric center of the observed fused lymph nodes was drawn. The epicenter of every node was contoured by marking the geometric center with a pen tip with a diameter of 5 mm. A horizontal line was drawn on the leading edge of the trapezius to measure the vertical distance between the center point of each metastatic lymph node in the PLV region and the horizontal line, and the vertical distance of the fusion lymph nodes in the PLV region was measured between the common geometric center of the lymph nodes and the horizontal line.

Treatment strategy and follow-up

Patients with stage I cancer received radiotherapy alone. Patients with stage II~IVa cancer received radiotherapy and chemotherapy with a cisplatin-based regimen. The primary nasopharyngeal tumor and metastatic retropharyngeal lymph nodes were defined as GTVnx. Cervical metastatic lymph nodes were defined as GTVnd. The clinical target volume (CTV1) was defined as a high-risk area that included the GTVnx with a 5-10 mm margin, the whole nasopharynx, GTVnd and the level II and III cervical lymphatic drainage regions. CTV2 was defined as a low-risk area that encompassed CTV1 and the retropharyngeal lymph nodal regions, the base of skull, the anterior half of clivus, the parapharyngeal space, the pterygoid fossa, the inferior sphenoid sinus, the posterior edge of the nasal cavity, the maxillary sinuses and the lower neck. The prescribed radiation doses of each target volume were as follows: 66-72 Gy for GTVnx, 64-70 Gy for GTVnd, 56-64 Gy for CTV1, and 50-56 Gy for CTV2. All patients were irradiated with 1 fraction per day, 5 days per week, for a total of 30-33 fractions. The radiation dose limits for critical structures were within the tolerance recommended by the RTOG 0225 protocol. All patients were followed up by hospitalization, outpatient visits, and telephone enquiries until December 2018. Follow-up examinations included the following: nasopharyngeal and cervical MRI, fiber nasopharyngoscopy, abdominal ultrasound, and chest CT.

Statistical analysis

All data were analyzed using the SPSS 20.0 software. Linear regression was performed to identify the correlation between the PLV region and the remaining lymph node levels. The Kaplan-Meier method was employed to calculate the survival rate, and the log-rank method was used to compare survival curves between groups. A Cox hazard model with stepwise selection was used to perform multivariate analyses. Overall survival (OS), progression-free survival (PFS), no local recurrence (LRFS), and no distant metastasis (DMFS) were analyzed. *P* values of less than 0.05 were considered statistically significant.

Results

Patient characteristics and prognosis

Of the 605 patients with pathologically confirmed NPC, 433 were males and 172 were females. The median age of the patients was 48 years old (12-81 years old), 97.52% of the pathological types were WHO II-III, and 2.47% of the pathological types were WHO type I. The counts and percentages of patients with T1, T2, T3, and T4 NPC were 156 (25.8%), 120 (19.8%), 161 (26.6%), and 168 (27.8%), respectively; and the counts and percentages of patients with N0, N1, N2, and N3 NPC were 48 (7.9%), 165 (27.3%), 303 (50.1%), 89 (14.7%), respectively. The number and percentages of patients in stages I, II, III, IVa and IVb were 22 (3.63%), 86 (14.21%), 250 (41.32%), 237 (39.17%) and 10 (1.65%), respectively (Table 1). In all patients, 10 patients were in stage IVb, and 4 patients gave up treatment during radiotherapy. A total of 591 patients were followed up for 8-81 months with a median of 37 months, and the 5-year OS, PFS, LRFS, and DMFS were 80.1%, 69.4%, 88.4%, and 83.9%, respectively. Seventy-four patients died, and the main cause of death was distant metastasis, followed by local recurrence and hemorrhage of the nasopharynx. Forty-two cases had local recurrence, mainly in the nasopharyngeal cavity, skull base bone, carotid sheath area, intracranial cavernous sinus area, etc. Seventy-five cases had distant metastasis, most commonly in the liver, lungs and bones. Patients with a single metastasis site were rare, and most patients had two or three sites with simultaneous metastasis.

Cervical lymph node metastasis

In the 605 patients, 557 patients (92.06%) had cervical lymph node metastasis (Table 2). The top four levels with the highest probability of lymph node metastasis were IIb (77.85%), VIIa (73.05%), IIa (60.0%), and III (41.48%). The levels with less than a 5% probability of the lymph node metastasis was IVb (1.98%), Vc (1.48%), VIIb (0.82%), and VIII (0.49%), and no lymph node metastasis was found in levels Ia, VI, IX and X. There were 12 patients with lymph node metastases in level IVb, and these patients also had lymph node metastasis in the level IVa. Nine patients had lymph node metastasis in level Vc, and these patients were also accompanied by lymph node metastasis in level Vb. Three patients with lymph node metastasis in level VIII were associated with lymph node metastasis in levels Ib, II, and III, and one patient with lymph node metastasis in level II showed local necrosis and lymph node fusion.

Distribution characteristics of metastatic lymph nodes in the PLV region

In the whole group of 605 patients, 30 patients (4.95%) showed lymph node metastasis in the PLV region (Table 3). There was a total of 49 metastatic lymph nodes, including 25 metastatic lymph nodes in the left neck and 24 metastatic lymph nodes in the right neck. In one patient, lymph node metastasis in the PLV region occurred simultaneously on both sides of the neck. There were 23 metastatic lymph nodes with a short diameter of less than 10 mm, 22 metastatic lymph nodes with a short diameter of 11-20 mm, and 4 metastatic lymph nodes with a short diameter of 21-30 mm. The median vertical distance of the center point of each metastatic lymph node from the leading edge of the trapezius muscle in the standard NPC patient was 14 mm (3-37 mm). There were 25 lymph nodes with a diameter of less than 10 mm, 14 lymph nodes with a diameter between 11 and 20 mm, 7 lymph nodes with a diameter between 21 and 30 mm, and 3 lymph nodes with a distance of more than 31 mm. The centers of 93.87% (46/49) of the metastatic lymph nodes in the PLV region were located less than 25 mm from the leading edge of the trapezius muscle. The distribution of the metastatic lymph nodes in the PLV region is shown in Table 4. The location of the corresponding CT layer of the standard NPC patient is shown in Figure 2.

Correlation analysis of lymph node metastasis in the PLV region

To analyze the relationship between lymph node metastasis in the PLV region and other cervical lymph node metastases, linear regression analysis was used. The lymph node metastasis in the PLV region was used as the dependent variable, and the remaining lymph node regions were included as independent variables in the analysis. The results showed that the lymph node metastasis of the PLV region was associated with the ipsilateral IVa ($P=0.018$), Va, Vb and Vc levels (all $P<0.001$), and no correlations were found for the other variables (Table 5).

Prognosis of patients with lymph node metastasis in the PLV region

A total of 29 patients with lymph node metastasis in PLV were followed up for a median of 21 (4 to 60) months. Fourteen patients had distant metastases, 11 patients died during the follow-up period (death overlapped with distant metastases), and 2 patients relapsed. The 5-year OS, PFS, LRFs, and DMFS were 41.6%, 27.7%, 89.1%, and 47.3%, respectively.

Prognosis of patients with N3 NPC with or without lymph node metastasis in the PLV region

The number of patients with N3 NPC with or without lymph node metastasis in the PLV region was 26 and 60, respectively. The 5-year OS, PFS, LRFs, and DMFS of the two groups were 41.8% and 67.3% ($P=0.007$), 27.8%, and 48.5% ($P=0.005$), 92.3%, and 80.5% ($P=0.521$), and 40.6% and 78.4% ($P < 0.001$), respectively (Table 6, Figure 3).

Univariate and multivariate analysis

The results showed that gender was a prognostic factor for 5-year OS, age was a prognostic factor for 5-year OS and PFS, T-stage was a prognostic factor for 5-year LRFs, and N-stage and lymph node metastasis in the lower neck were prognostic factors for 5-year OS, PFS, LRFs, and DMFS (Table 7). Lymph node metastasis in the lower neck was refined into levels IVa, IVb, Vb, and Vc and the PLV region

in multivariate analysis, and the parameters were designed as two categorical variables. Analysis showed that lymph node metastasis in the PLV region was an independent prognostic factor for DMFS ($P=0.035$).

Discussion

N Nasopharyngeal carcinoma (NPC) is very prone to lymph node metastasis [13]. Some studies have reported that approximately 40% of patients with NPC have a first symptom of cervical lymphadenopathy [14]. Approximately 60–90% of patients with newly diagnosed NPC have lymph node metastasis [15]. Therefore, the segmentation and metastatic characteristics of cervical lymph nodes are of great importance for the delineation of target areas of radiotherapy. In the 2013 Guideline, level V of cervical lymph nodes is refined into levels Va, Vb, and Vc [6]. However, the 2013 Guideline do not describe the PLV gap (the gap between the trapezius muscle and the scapular levator). In the PLV region, metastatic lymph nodes are frequently found. Unfortunately, this PLV region is often overlooked. The delineation of the radiotherapy target area for the PLV region and the prognosis of NPC patients with lymph node metastasis in the PLV region are still unknown.

Previous studies have shown that the rate of lymph node metastasis is not high in the PLV region; the metastasis rates in the studies [16–18] were 1.1%, 2.4% and 2.5%, respectively. In this study, we found that in the whole group of 605 patients, there were 30 patients with lymph node metastasis in the PLV region, and the metastasis rate was 4.95%, slightly higher than in the abovementioned studies, which may be related to the relatively low level of awareness of the disease in patients in western China. In this study, we also found 49 metastatic lymph nodes in the PLV region. The central points of these metastatic lymph nodes were located 25 mm from the leading edge of the trapezius muscle, and metastatic lymph nodes were located in both the trapezius and scapular levator muscles. Further analysis showed that 132 patients had lymph node metastasis in level Va, including 30 patients with lymph node metastasis in the PLV region. At the same time, we also found that all lymph node metastases in the PLV region were associated with ipsilateral lymph node metastasis in level Va. Correlation analysis suggested that the lymph node metastasis in the PLV region was also associated with lymph node metastasis in levels IVa, Va, Vb and Vc. Therefore, when NPC patients present with lymph node metastasis in level Va, Vb, and Vc but not in the PLV region, it is recommended that the posterior boundary of the ipsilateral V region be appropriately moved back to 25 mm behind the leading edge of the trapezius muscle to prevent lymph node metastasis in the gap between the trapezius muscle and the scapular levator; when NPC patients present without lymph node metastasis in these areas, the posterior border of the level V region can be outlined to the leading edge of the trapezius muscle.

A previous study showed that 5-year OS, PFS, LRFS, and DMFS rates in NPC patients were 77.1%, 69.6%, 89.8%, and 74.1%, respectively [19]. Another study showed 5-year OS, PFS, LRFS, and DMFS rates in NPC patients of 83.3%, 76.3%, 92.7%, 85.5%, respectively [20]. This finding is similar to that of our study, which also showed that the 5-year OS, PFS, LRFS, and DMFS of patients with lymph node metastasis in the PLV were 41.6%, 27.7%, 89.1%, and 47.3%, respectively. Moreover, patients with N3 NPC accompanied by

lymph node metastasis in the PLV region have a worse prognosis. Multivariate analysis showed that lymph node metastasis in the PLV region was an independent prognostic factor for DMFS. This further indicates that the prognosis of NPC patients with PLV-region lymph node metastasis is poor, and lymph node metastasis in this region indicates a high risk of distant metastasis.

This study has the following limitations: first, a pathological diagnosis of metastatic lymph nodes is lacking, especially in the deep fat gap of the PLV region, and performing histopathology in this region is difficult. Second, since the measurement of the vertical distance was performed on a standard patient, the position of the frontal area of the trapezius muscle may be different depending on the weight, age, and body type of different patients. To minimize these variations, we tried to recreate the position of the central point of each lymph node on the CT images of the standard patient. Third, there is a difference in the fat space between the trapezius muscle and the levator scapulae of in different patients. To clearly show the fat gap between the trapezius muscle and the scapular levator muscle, we selected a patient with a wide gap as the standard patient.

Conclusion

The PLV region mainly refers to the gap between the trapezius muscle and the levator scapulae. Few detailed reports have been published on lymph node metastasis in the PLV region. To the best of our knowledge, in this study, we report for the first time the distribution and metastasis of lymph nodes in the PLV region of NPC patients and provide a reference for the delineation of the lymph node area in the PLV region. In addition, we found that the metastasis rate of lymph nodes in the PLV region was 4.95%, which was close to or even exceeded the metastasis rate in the Ib, IVb, Vb, and Vc regions. However, the 2013 Guideline describes the posterior boundary of the V region as the leading edge of the trapezius muscle and the front 10 mm of the anterior serratus. This also indicates that it may fail to fully consider the PLV region, which may be a missing neck segment. Therefore, we propose to use the PLV region as a new cervical lymph node partition as follows: upper boundary: the lower edge of the annular cartilage; lower boundary, the level of the clavicle or anterior serratus; the anterior boundary: the leading edge of the trapezius muscle; posterior boundary: the intersection of the trapezius muscle and the scapula levator; medial boundary: the lateral edge of the scapular levator; and lateral boundary: the medial edge of the trapezius muscle.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of The General Hospital of Western Theatre Command and Sichuan Cancer Hospital and Institute. The written informed consent was obtained from a parent or guardian for participants under 16 years old.

Consent for publication

Not Applicable.

Availability of data and materials

The datasets used and/or analysed 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

CYJ, JM and BSL, study concept and design, acquisition of data, analysis and interpretation of data, statistical analysis and project funding. JM, drafting of the manuscript. HG, LZ, TZ and HL, acquisition of data and material support. All authors read and approved the final manuscript.

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None.

Abbreviations

PLV: posterior to level V; NPC: nasopharyngeal carcinoma; RTOG: Radiation Therapy Oncology Group; CTV: clinical target volume; OS: overall survival; PFS: progression-free survival; LRFS: no local recurrence; DMFS: no distant metastasis.

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Tables

Table 1: Patient characteristics

Characteristic	Number of patients (<i>n</i>)
Gender	
Male	433(71.57%)
Female	172(28.42%)
Age(years)	
<45	209(34.54%)
≥45	396(65.45%)
Histology	
WHO I	15(2.47)
WHO II- III	590(97.52)
T stage	
T1	156(25.78%)
T2	120(19.83%)
T3	161(26.61%)
T4	168(27.76%)
N stage	
N0	48(7.93%)
N1	165(27.27%)
N2	303(50.08%)
N3	89(14.71%)
UICC/AJCC stage	
I	22(3.63%)
II	86(14.21%)
III	250(41.32%)
IVa	237(39.17%)
IVb	10(1.65%)

Table 2 : Patterns of cervical nodal metastasis of nasopharyngeal carcinoma

Neck node level	Number(%)
Ia	0(0.0)
Ib	25(6.17)
IIa	363(60.0)
IIb	471(77.85)
III	251(41.48)
IVa	77(12.72)
IVb	12(1.98)
Va	132(21.81)
Vb	35(5.78)
Vc	9(1.48)
VI	0(0.0)
VIIa	442(73.05)
VIIb	5(0.82)
VIII	3(0.49)
IX	0(0.0)
X	0(0.0)

Table 3: Baseline characteristics of patients with metastasis of posterior to level V

Gender	Number (%)
Male	28(93.33)
Female	2(6.66)
T stage	
T1	7(23.33)
T2	7(23.33)
T3	8(26.66)
T4	8(26.66)
N stage	
N2	3(10.00)
N3	27(90.00)
TNM stage	
I	3(10.00)
Ia	26(86.66)
Ib	1(3.33)

Table 4: Patterns of cervical nodal metastasis of posterior to level V

Short diameter of lymph nodes (mm)	Left (%)	Right (%)
£10	12(24.48)	11(22.44)
11-20	9(18.36)	13(26.53)
21-30	4(8.16)	0(0)
The vertical distance from the anterior border of trapezius (mm)	Left (%)	Right (%)
£10	11(22.44)	14(28.57)
11-20	8(16.32)	6(12.24)
21-30	4(8.16)	3(6.12)
£31	2(4.08)	1(2.04)
sum	25(51.02)	24(48.97)

Table5: The data of linear-regression analysis for neck node

Variable	B	Std.Error	t	p	95% CI for B
β _b	0.014	0.036	0.374	0.708	-0.057-0.085
β _a	-0.004	0.016	-0.228	0.820	-0.035-0.028
β _b	-0.004	0.019	-0.224	0.823	-0.042-0.034
β	-0.012	0.018	0.669	0.504	-0.047-0.023
β _a	0.062	0.026	2.366	0.018	0.011-0.114
β _b	0.106	0.059	1.776	0.076	-0.011-0.222
V _a	0.118	0.021	5.729	0.000	0.078-0.159
V _b	0.243	0.038	6.391	0.000	0.168-0.318
V _c	0.435	0.071	6.112	0.000	0.295-0.574
β _a	0.017	0.016	1.041	0.298	-0.015-0.048
β _b	0.001	0.077	0.017	0.987	-0.151-0.153
β	-0.162	0.101	-1.597	0.111	-0.360-0.037

Abbreviations: B=regression coefficient, t=t test, Dependent Variable: PLV

Table6: The survival data of N3 patients with or without node metastasis of PLV

Variable	5-year OS			5-year PFS			5-year LRFS			5-year DMFS		
	%	c ²	P	%	c ²	P	%	c ²	P	%	c ²	P
PLV (+) (n=26)	41.8			27.8			92.3			40.6		
		7.240			7.818			0.412			14.438	
PLV (-) (n=60)	67.3			48.5			80.5			78.4		
		0.007			0.005			0.521			<0.001	

Abbreviations: PLV (+): node metastasis with posterior to level V; PLV (-): node metastasis without posterior to level V

Table 7: Univariate analysis of prognosis in 591 NPC patients

Variable	N	5-year OS (%) <i>p</i>	5-year PFS (%) <i>p</i>	5-year LRFS (%) <i>p</i>	5-year DMFS (%) <i>p</i>
Gender		0.04	0.194	0.619	0.328
Male	423	78.0	67.5	89.0	82.2
Female	168	85.6	74.1	87.2	87.8
Age (years)		0.039	0.463	0.744	0.846
<45	205	86.3	72.0	87.3	84.9
≥45	386	76.8	67.9	89.0	83.2
T stage		0.28	0.096	0.003	0.802
T ₁ +T ₂	271	82.4	72.8	93.1	85.2
T ₃ +T ₄	320	77.2	62.4	82.9	81.7
N stage		0.004	< 0.001	0.025	0.002
N ₀ +N ₁	211	86.6	79.8	91.7	90.4
N ₂ +N ₃	380	73.9	58.8	86.0	78.9
TNM stage		0.006	< 0.001	0.014	0.015
I+II	108	89.6	84.4	94.9	92.3
III+IVa	483	76.7	64.6	86.3	81.1
Involvement of lower neck levels		< 0.001	< 0.001	0.07	< 0.001
Yes	90	57.6	41.7	82.3	68.7
No	501	83.5	74.2	89.3	86.7

Table 8: Multivariate analysis of prognosis in 591 NPC patients

Variable	B	SE	<i>P</i>	HR	95%CI
Involvement of lower neck levels (yes vs. no)					
level IVa					
level IVb	0.392	0.356	0.271	1.480	0.736-2.976
level Vb	0.908	0.565	0.108	2.479	0.819-7.503
level Vc	0.708	0.469	0.131	2.030	0.809-5.092
PLV	0.030	0.646	0.963	1.030	0.290-3.656
	0.985	0.468	0.035	2.678	1.069-6.705

Figures

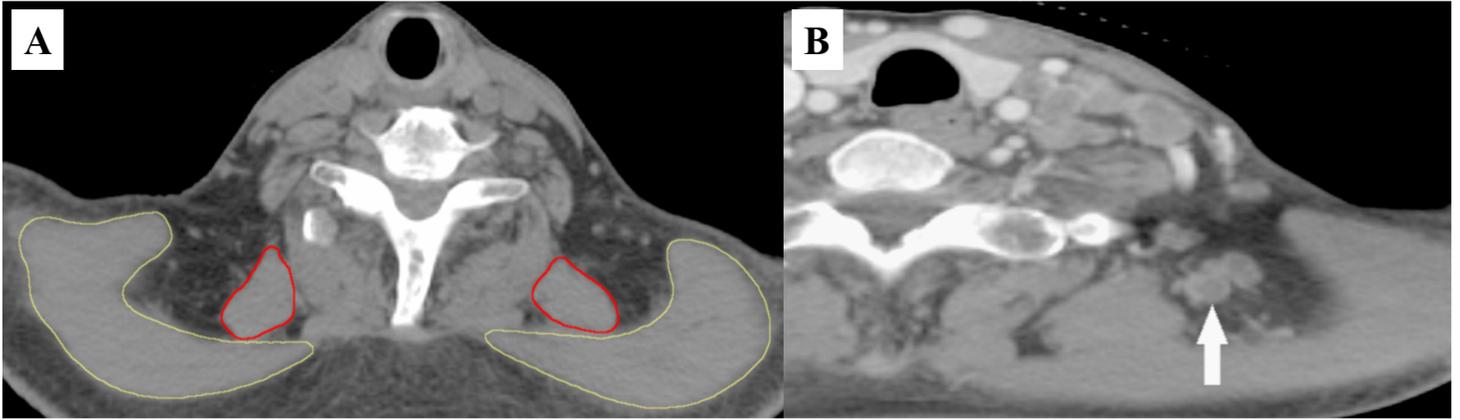


Figure 1

A. The PLV region in the CT scan. The PLV region is between the trapezius muscle and the scapular levator. The yellow line presents the trapezius, and the red line presents the levator scapulae. B. Metastatic lymph nodes in the PLV region. A typical picture of the metastatic lymph nodes in the PLV region is shown. The white arrows indicate the metastatic lymph nodes.

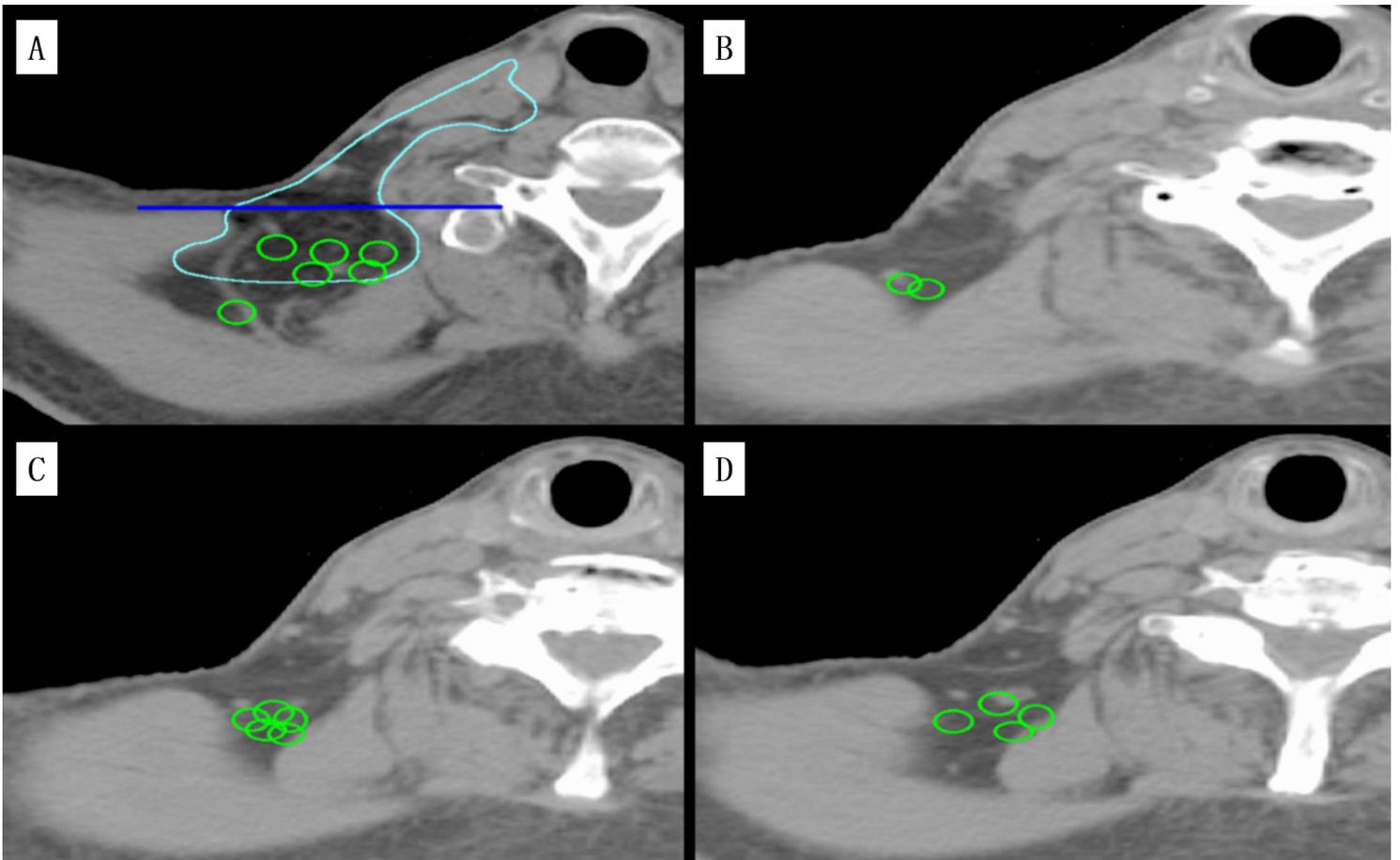


Figure 2

Schematic diagram of the distribution of metastatic lymph nodes in the PLV region. The blue line is the horizontal line through the anterior surface of the trapezius, which was used to calculate the vertical

distance between the central points of the metastatic lymph nodes in the PLV region and the horizontal line. The light blue line is the delineation of the PLV region with the ipsilateral metastatic lymph nodes of levels Va, Vb, and Vc. The green circle indicates the metastatic lymph nodes of the PLV region that were recreated proportionally on the CT images of a standard patient to further understand the location of their distribution.

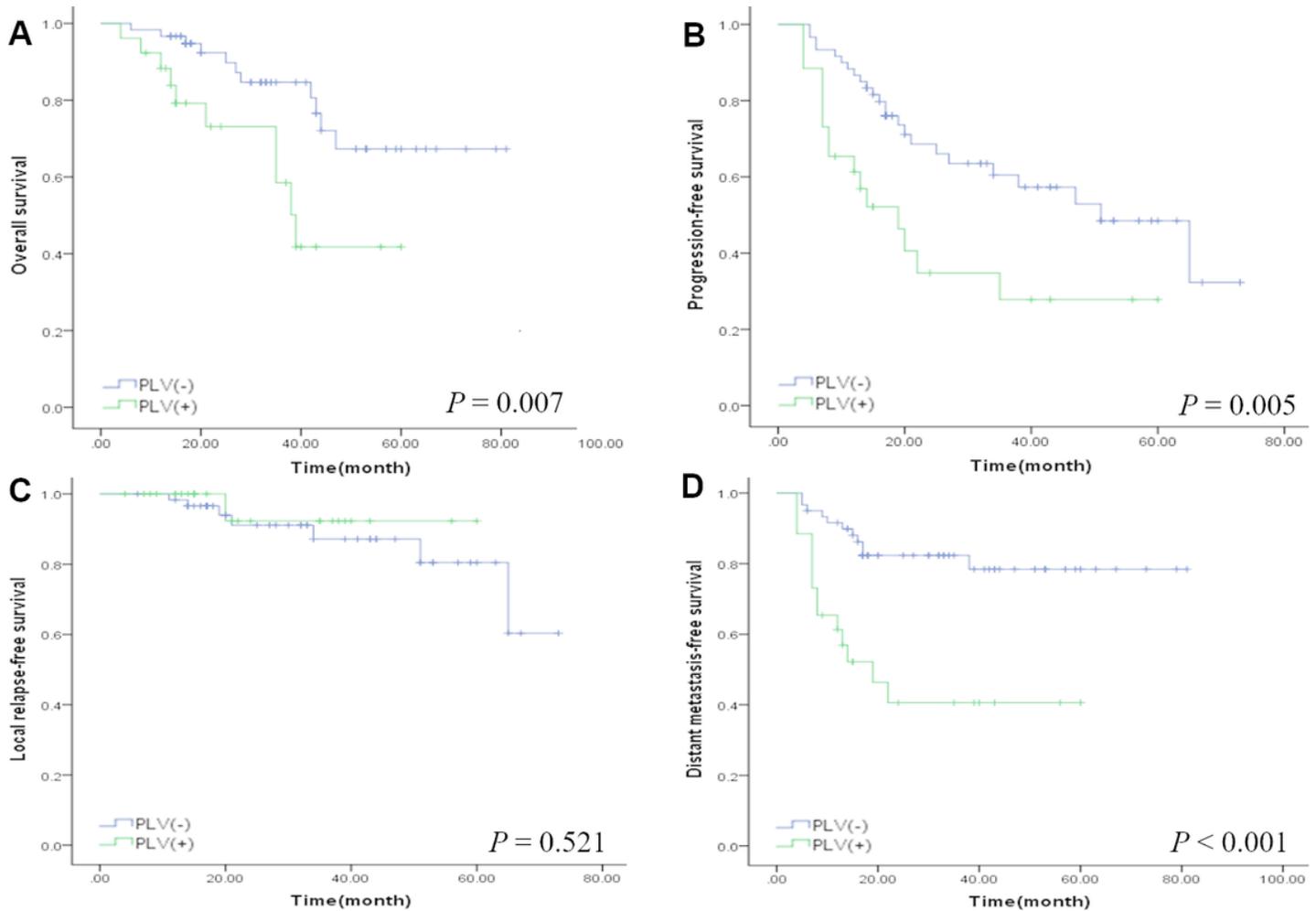


Figure 3

The 5-year survival curve of patients with N3 NPC with or without lymph node metastasis in the PLV region. A. OS ($P=0.007$), B. PFS ($P=0.005$), C. LRFS ($P=0.521$), D. DMFS ($P < 0.001$).

Supplementary Files

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