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Prognosis and staging of parotid lymph node metastasis in nasopharyngeal carcinoma: An analysis in 10,126 patients

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ABSTRACT

Objective: In nasopharyngeal carcinoma (NPC), the staging category of parotid lymph node (PLN) metastasis is not explicitly defined, resulting in varied classifications and treatment strategies in clinical practice. This study aimed to determine the prognostic value and optimal staging category of PLN metastasis in NPC.
Materials and methods: With the NPC database from a big-data platform, 10,126 patients with primarily diagnosed, non-metastatic NPC and treated with intensity modulated radiotherapy at our center from 2009 to 2015 were analyzed in this study.
Results: In total, 43/10126 patients (0.4%) were diagnosed with histologically verified PLN metastasis at initial diagnosis. Of these, 88.4% (38/43) had enlarged lymph nodes in level II and 34.9% (15/43) in level Ib. Compared with patients without PLN metastasis, those with PLN metastasis had higher risk of disease failure (adjusted hazard ratio [HR], 1.770), distant metastasis (HR, 1.907), and regional recurrence (HR, 3.649), with similar 3-year disease-free survival (70.0% vs. 71.1%) and distant metastasis-free survival (74.8% vs. 77.4%) with patients with N3 disease. Of note, 10/43 patients had regional recurrence: six had recurrent lymph nodes in level Ib; and four of these six patients had no identifiable level Ib lymph nodes on pretreatment imaging.
Conclusion: PLN metastasis was associated with high risk of distant metastasis and regional recurrence, and patients with PLN metastasis had similar outcome compared with patients with N3 disease. Regional recurrences in rare levels, such as level Ib, were common in patients with PLN metastasis at initial diagnosis.

Introduction

Nasopharyngeal carcinoma (NPC) is prevalent in southern China, Southeast Asia, North Africa, the Middle East and Alaska [1]. Compared with other head and neck cancers, NPC has a higher incidence of cervical lymph node metastasis: up to 85% of cases present with lymphadenopathy at diagnosis [2,3]. Cervical lymph node metastases appear to occur in an orderly fashion with infrequent skip metastasis, with the retropharyngeal space and the upper neck most commonly involved [3–5].

The parotid lymph nodes (PLNs), classified as level VIII in the latest International Consensus Guidelines for nodal levels [6], are also at risk of harboring metastases from the nasopharynx [3]. However, in the universally used tumor-node-metastasis staging system published by the International Union Against Cancer/American Joint Committee on Cancer (UICC/AJCC), the staging category of PLN metastasis is not explicitly defined [7]. Due to the low incidence and scarcity of report in the literature, suspicious PLN metastasis might be overlooked by radiologists and treating physician, which would result in misdiagnosis and inadequate treatment. Moreover, some physicians might see the PLN metastasis as distant metastasis and give patients palliative instead of curative treatment.

Two previous small-cohort studies explored the prognosis of NPC patients with PLN metastasis and recommended that this be considered an N3 disease [8,9]. However, both studies used magnetic resonance imaging (MRI) as the diagnostic method. As a wide range of benign or malignant, primary or metastatic neoplasms can present as masses in the parotid gland, misdiagnosis is inevitable when using imaging to diagnose PLN metastasis. In one previous study, only one out of four patients with suspicious PLN on imaging was proved to have NPC

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metastasis by pathology [8]. Therefore, this study aimed to determine the prognostic value and optimal staging category of PLN metastasis in NPC, using data of patients with histologically verified PLN metastasis derived from a big-data platform.

Materials and methods

Data extraction and study population

This retrospective study has been approved by the institutional review board at our center and the patient consent was waived. The NPC-specific database from the well-established big-data intelligence platform at our cancer center was used to identify patients with histologically proven NPC. This novel 'big-data' research system enables the automatic organization, integration, re-structuring, and updating of real-time data from a number of clinical systems, based on a well-designed data model and algorithm. A detailed description of this intelligence platform has been reported in previous studies [10–14].

Patient demographics and diagnostic and therapeutic information were obtained from the intelligence platform using search terms including 'diagnosis', 'histology', 'age at first diagnosis', 'sex', 'disease stage', 'radiotherapy method', 'chemotherapy regimen', and 'EBV DNA'. First, we restricted our sample to histologically confirmed, non-disseminated NPC patients who were diagnosed between April 2009 and December 2015, using "diagnosis" variable provided by the platform. Second, we only included patients treated by intensity-modulated radiotherapy (IMRT). Third, by searching keyword "parotid" in pathological reports of above selected patients, we finally identified patients with histologically proven metastatic PLN at initial diagnosis.

In total, 10,126 patients were identified on this platform who had been diagnosed with non-disseminated NPC (M0) between April 2009 and December 2015 and underwent IMRT (Table 1). Of these patients, a total of 63 patients underwent pathologic examination of parotid nodules before treatment, among which 43 (67.2%) were confirmed to have PLN metastasis of NPC (Table 2). Typical magnetic resonance image of parotid lymph node metastasis was shown in Fig. 1. The key raw data have been uploaded onto the Research Data Deposit public platform (RDD), with the approval number RDDA2018000778.

Table 1
Clinicopathological characteristics of 10,126 nasopharyngeal carcinoma patients with or without metastatic parotid lymph nodes.

Characteristic	n = 10083 (%)	n = 43 (%)	*P*
Sex			0.24
Male	7405 (73.4)	35 (81.4)	
Female	2678 (26.6)	8 (18.6)	
Age (years)			
< 45	5204 (51.6)	28 (65.1%)	0.08
≥45	4879 (48.4)	15 (34.9%)	
T category‡			0.23
T1	1671 (16.6)	3 (7.0)	
T2	1626 (16.1)	6 (14.0)	
T3	4682 (46.4)	21 (48.8)	
T4	2104 (20.9)	13 (30.2)	
N category‡			< 0.001
N0	1585 (15.7)	1 (2.3)	
N1	5120 (50.8)	12 (27.9)	
N2	2157 (21.4)	15 (34.9)	
N3	1221 (12.1)	15 (34.9)	
Stage‡			0.005
I	558 (5.5)	0	
II	1783 (17.7)	3 (7.0)	
III	4656 (46.2)	17 (39.5)	
IV	3086 (30.6)	23 (53.5)	
Pretreatment EBV DNA (copies/ml)			0.003
< 2000	4742 (47.0)	12 (27.9)	
≥2000	4685 (46.5)	31 (72.1)	
Not available	656 (6.5)		
Chemotherapy			0.07
Yes	8970 (89.0)	42 (97.7)	
No	1113 (11.0)	1 (2.3)	

EBV, Epstein–Barr virus; N, node; T, tumor.
‡ According to the eighth edition of the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) staging system. Parotid lymph node metastasis was disregarded in the staging.

Table 2
Pathological findings of parotid nodules biopsy.

Pathological findings	Number (%) (n = 63)
Nasopharyngeal carcinoma metastasis	43 (67.2)
Lymphoid tissue	9 (14.1)
Adipose connective tissue	3 (4.7)
Lymphopapillary cystadenocarcinoma	2 (3.1)
Mucoepidermoid carcinoma	2 (3.1)
Basal cell adenoma	1 (1.6)
Myoepithelioma	1 (1.6)
Benign tumor not specified	1 (1.6)
Parotid issues	1 (1.6)
Pleomorphic adenoma	1 (1.6)

Diagnosis and treatment

Patients underwent complete pretreatment evaluation, including physical examination, hematology and biochemistry profiling, fiberoptic nasopharyngoscopy, MRI scanning of the suprasellar cistern to the collarbone, chest radiography, abdominal ultrasonography, and whole-body bone scan, or ^{18}F-fluorodeoxyglucose positron emission tomography and computed tomography (PET-CT). According to our institutional guidelines, biopsy was recommended whenever possible for nasopharyngeal carcinoma patients with suspicious parotid nodules on pretreatment imaging. Patients with metastatic PLN in pathologic examination were diagnosed with histologically proven PLN metastasis; and those with direct tumor extension to the parotid gland were not included. In this study, all patients were restaged based on pretreatment imaging by two radiation oncologists specializing in head and neck cancer, according to the eighth edition of the AJCC/UICC staging system [7]. PLN metastasis was disregarded in the restaging.

The nasopharyngeal and neck tumor volumes of the patients were treated for the entire treatment course with radical radiotherapy based on intensity-modulated radiotherapy (IMRT) with the simultaneous integrated boost technique. Further details of the radiotherapy techniques used during the study period have been previously reported [15]. The prescribed doses were 66–72 Gy/28–33 fractions to the planning target volume (PTV) of the primary gross tumor volume (GTVnx), 64–70 Gy/28–33 fractions to the PTV of the GTV of the involved lymph nodes (GTVnd, including metastatic PLNs), 60–63 Gy/28–33 fractions to the PTV of the high-risk clinical target volume (CTV1), and 54–56 Gy/28–33 fractions to the PTV of the low-risk clinical target volume (CTV2). All confirmed metastatic PLNs received curative doses (≥66 Gy) and the PLNs plus an 8–10 mm margin were included in CTV2 and received 54–56 Gy.

During the study period, radiation alone was the standard of care for stage I disease and concurrent chemoradiotherapy with or without induction/adjuvant chemotherapy was recommended for stages II to IVB disease according to institutional guidelines. In total, out of 7782 patients with locoregionally advanced disease (stage III–IVB), 7414 (95.3%) received chemotherapy. Salvage treatments, including re-radiation, chemotherapy, and surgery, were provided for persistent or recurrent disease.

Follow-up

In general, patients returned for follow-up approximately every three months in the first two years, every six months during years 3–5,

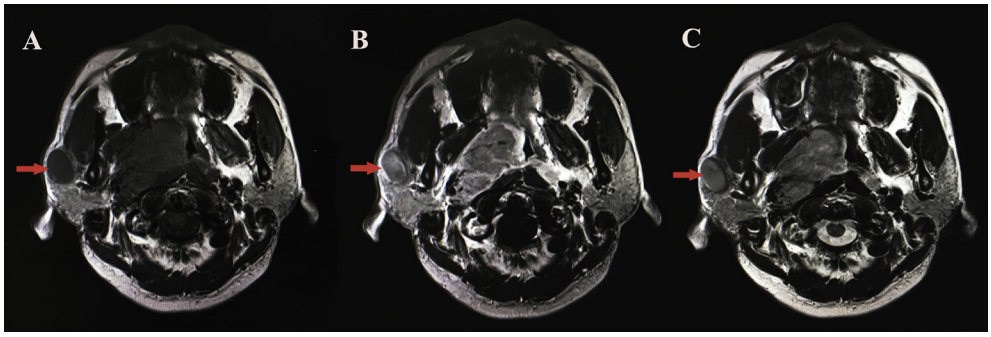

Fig. 1. Axial T1 (A), T1 + C (B) and T2 (C)-weighted magnetic resonance image of parotid lymph node metastasis as shown by red arrow in a 44-year-old man with NPC. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

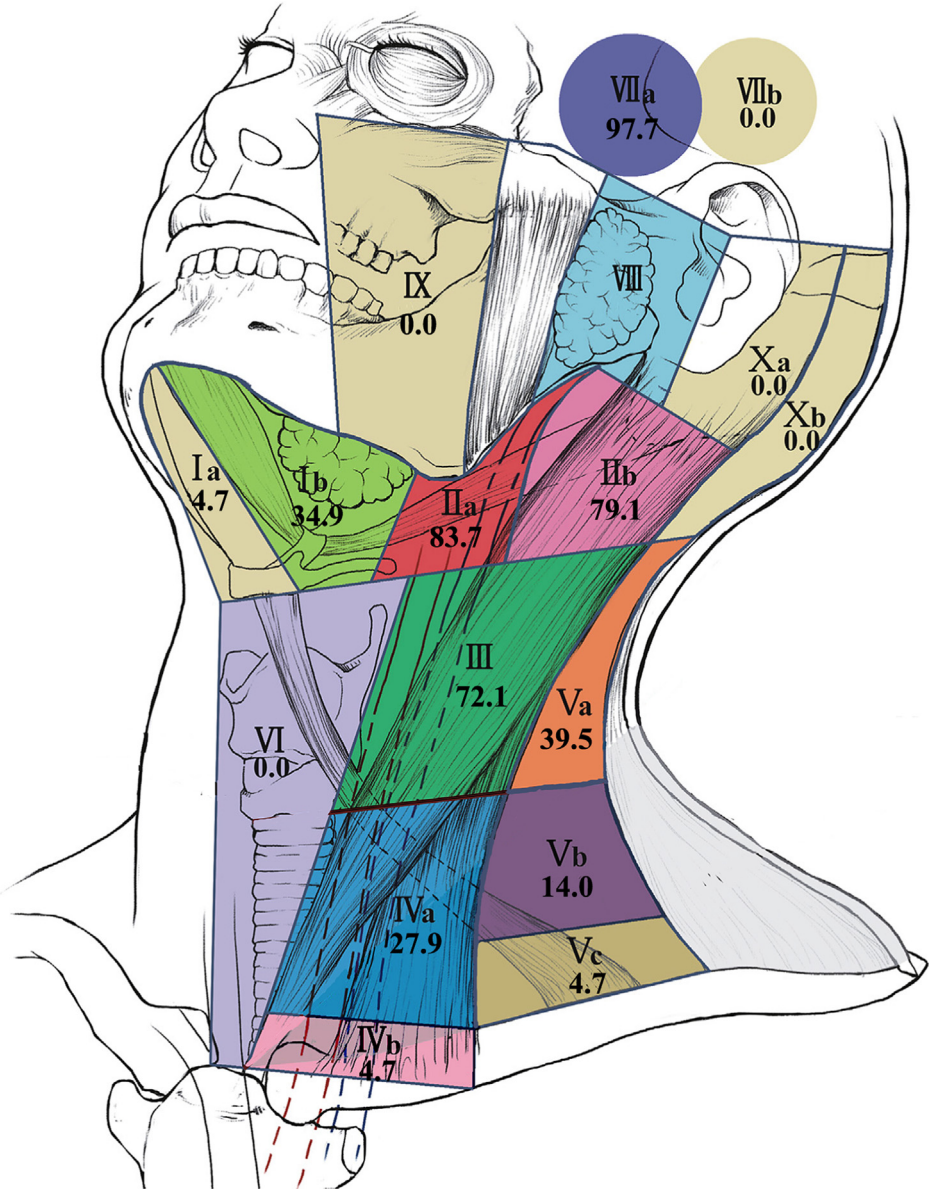

Fig. 2. Distribution of lymphadenopathy according to the levels defined by the 2013 International Consensus Guidelines in patients with nasopharyngeal carcinoma and parotid lymph node metastasis. The numbers represent the percentage of patients presenting with positive lymph node metastasis to each nodal station.

and every year thereafter. Whenever possible, locoregional or distant recurrences were confirmed by fine needle aspiration or biopsy. Clinical diagnosis was accepted for sites that were not accessible if classic changes were present (with or without clinical symptoms) on at least two imaging methods, such as ^{18}F-fluorodeoxyglucose PET-CT, MRI, CT of the chest or abdomen, and bone scan; however, if imaging findings were equivocal, subsequent follow-up (e.g., disease progression) would be used to ascertain the diagnosis [16].

Table 3
Univariate and multivariate analyses of prognostic factors in 10,126 patients with nasopharyngeal carcinoma.

		Univariate	Multivariate analysis	
Endpoint	Variable	*P*-value	HR (95% CI)	*P*-value
DFS	Age (< 45 vs. ≥45 years)	< 0.001	1.204 (1.095–1.323)	< 0.001
	Sex	< 0.001	0.784 (0.699–0.880)	< 0.001
	T classification (T4 vs. T1–3)	< 0.001	1.571 (1.416–1.743)	< 0.001
	N classification (N2–3 vs. N0–1)	< 0.001	1.797 (1.629–1.982)	< 0.001
	Parotid lymph node metastasis	< 0.001	1.770 (1.081–2.899)	0.023
	EBV DNA (> 2000 vs. < 2000 copies/ml)	< 0.001	1.950 (1.752–2.171)	< 0.001
	Chemotherapy (with vs. without)	< 0.001		0.181
DMFS	Age (< 45 vs. ≥ 45)	0.034		0.198
	Sex	< 0.001	0.693 (0.596–0.806)	< 0.001
	T classification (T4 vs. T1–3)	< 0.001	1.524 (1.336–1.738)	< 0.001
	N classification (N2–3 vs. N0–1)	< 0.001	2.192 (1.933–2.486)	< 0.001
	Parotid lymph node metastasis	< 0.001	1.907(1.078–3.372	0.026
	EBV DNA (> 2000 vs. < 2000 copies/ml)	< 0.001	2.328 (2.018–2.686)	< 0.001
	Chemotherapy (with vs. without)	< 0.001	0.816 (0.646–1.030)	0.087
RRFS	Age (< 45 vs. ≥45 years)	0.404		0.503
	Sex	0.026	0.790 (0.621–1.004)	0.054
	T classification (T4 vs. T1–3)	0.903		0.371
	N classification (N2–3 vs. N0–1)	< 0.001	2.185 (1.778–2.684)	< 0.001
	Parotid lymph node metastasis	< 0.001	3.649 (1.808–7.364)	< 0.001
	EBV DNA (> 2000 vs. < 2000 copies/ml)	< 0.001	2.058 (1.643–2.578)	< 0.001
	Chemotherapy (with vs. without)	< 0.001		0.310

DFS, disease-free survival; DMFS, distant metastasis-free survival; RRFS, regional recurrence-free survival; EBV, Epstein–Barr virus; T, tumour; N, node.

Statistical analysis

The analyses included following endpoints: disease-free survival (DFS), distant metastasis-free survival (DMFS), local relapse-free survival (LRFS), and regional relapse-free survival (RRFS). We calculated DFS from the first day of treatment to the date of distant metastasis, local or regional persistence/relapse, or death from any cause, whichever occurred first. DMFS, LRFS, and RRFS were defined as latency to the first distant metastasis, local or regional persistence/relapse, respectively. Actuarial rates were estimated using the Kaplan–Meier method, and the differences were compared with the log-rank test. [17] Patients who were lost to follow-up were censored in analysis. We also carried out a multivariate Cox regression analysis using backward selection to test the independent significance of different factors [18]. Covariates included in multivariate analyses were sex, age (> 45 vs. ≤45 years), T (T4 vs. T1–3) and N (N2–3 vs. N0–1) classification, pretreatment EBV DNA load (pre-DNA, > 2000 vs. ≤2000 copies/ml), and chemotherapy (yes vs. no). 656 patients, whose pretreatment plasma EBV DNA assay was not available, were not included in multivariate analysis. All statistical tests were two-sided, and *P* values of < 0.05 were deemed significant. SPSS version 22.0 was used for analyses (IBM Corporation, Armonk, NY, USA).

Results

The median age of the 10,126 patients was 45 years (range, 6.0–85.0 years) and the male to female ratio was 2.8:1. (Table 1) The median follow-up time of the entire cohort (10126 patients) was 45.2 months (range, 1.7–108.7 months). A total of 1823/10126 (18.0%) patients experienced disease failure: 480/10126 (4.7%) and 419/10126 (4.1%) patients developed local and regional recurrence, respectively, and 1142/10126 (11.3%) patients had distant metastasis. Three-year DFS, DMFS, RRFS, and LRFS for the entire cohort were 84.1%, 89.7%, 96.4%, and 95.8%, respectively.

Incidence of PLN metastasis

A total of 54 metastatic PLNs were detected in 43 (0.4%) patients. 8 patients had ≥2 metastatic PLNs- the PLNs were in unilateral side in 6/8 patients and were in bilateral sides in 2/8 patients. The median value of the minimal axial diameter was 8 mm (range, 4–18 mm; interquartile range, 6–8 mm). In 43 patients with PLN metastasis, 97.7% (42/43) had metastatic retropharyngeal lymph nodes and 88.4% (38/43) had level II nodes. The median value of the minimal and maximal axial diameter of the lymph nodes in level II was 20 mm (interquartile range, 15–26 mm) and 27 mm (interquartile range, 22–36 mm), respectively. In addition, 34.9% (15/43) patients had metastatic lymph nodes in level Ib. Detailed information regarding the landscape of cervical lymph node metastasis in patients with metastatic PLN can be seen in Fig. 2.

The incidence of PLN metastasis in patients with N0, N1, N2, and N3 disease was 0.06% (1/1586), 0.2% (12/5132), 0.7% (15/2172), and 1.2% (15/1236), respectively. (Table 1) A higher incidence of metastatic PLNs was found when cervical lymph node metastasis was present (0.5% vs. 0.06%; $P < 0.001$). Moreover, the more advanced the N category, the higher the incidence of metastatic PLNs.

The prognostic value of PLN metastasis

In univariate analysis, PLN metastasis was correlated with significantly poorer 3-year DFS (70.0% vs. 84.3%; $P < 0.001$), DMFS (74.8% vs. 89.8%; $P < 0.001$), and RRFS (87.1% vs. 96.5%; $P < 0.001$). In multivariate analysis incorporating sex, age (> 45 vs. ≤ 45 years), tumor (T4 vs. T1–3) and node (N2–3 vs. N0–1) classification, pretreatment EBV DNA load (> 2000 vs. ≤ 2000 copies/ml), and chemotherapy (with vs. without) as covariates, PLN metastasis was an independent prognostic factor for DFS (HR, 1.770; 95% CI, 1.181–2.899; $P = 0.023$), DMFS (HR, 1.907; 95% CI, 1.078–3.372; $P = 0.026$) and RRFS (HR, 3.649; 95% CI, 1.808–7.364; $P < 0.001$, Table 3).

Staging category for PLN metastasis

The 3-year DFS of patients with N0 & PLN (-), N1 & PLN (-), N2 & PLN (-), N3 & PLN (-), and PLN (+) were 93.2%, 87.0%, 78.5%, 71.1%, and 70.0%, respectively (Fig. 3A). Patients with PLN metastasis had similar 3-year DFS with those with N3 disease ($P = 0.488$), but significantly poorer DFS than those with N0, N1, or N2 disease (all *P* values < 0.03). The 3-year DMFS in patients with N0, N1, N2, N3, and PLN (+) was 96.8%, 92.5%, 85.2%, 77.4%, and 74.8%, respectively (Fig. 3B). Again, patients with PLN metastasis had similar 3-year DMFS

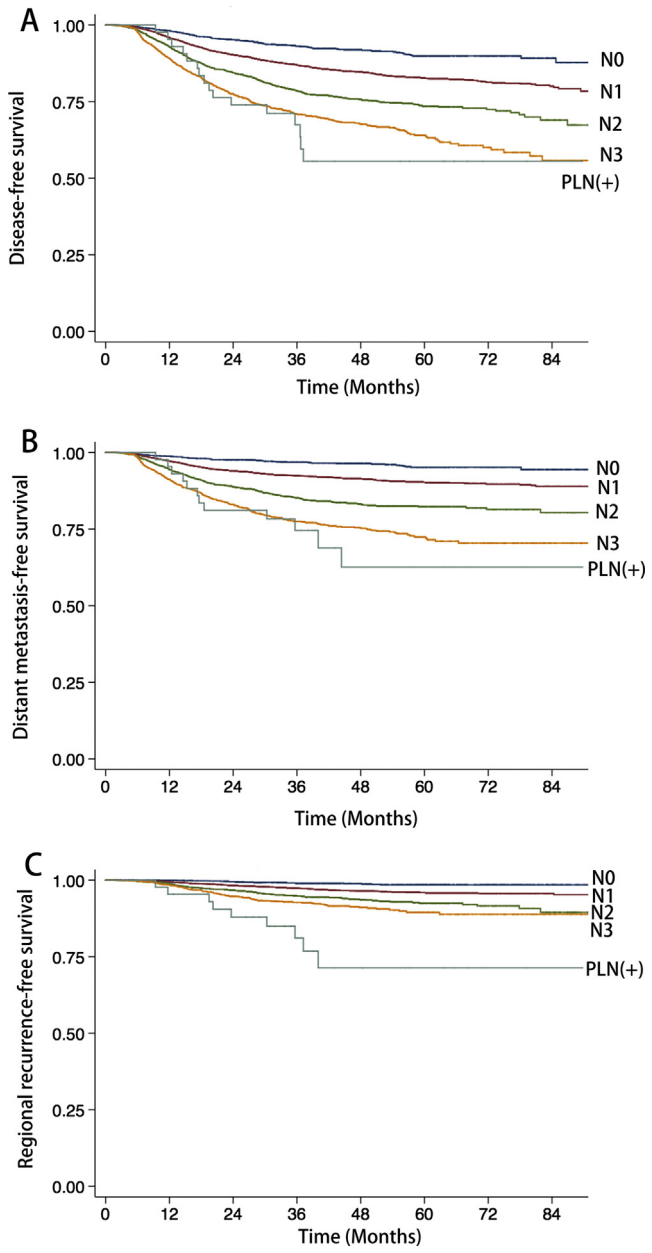

Fig. 3. Kaplan–Meier curves of disease-free survival (A), distant metastasis-free survival (B), and regional recurrence-free survival (C) for patients with N0, N1, N2, and N3 disease and parotid lymph node (PLN) metastasis, respectively. N was categorized according to the eighth edition of the American Joint Commission on Cancer (AJCC) staging system. PLN metastasis was disregarded in the staging.

with those with N3 disease ($P = 0.542$), but significantly poorer survival than those with N0, N1, or N2 disease (all P values < 0.025).

Patients with PLN metastasis had the poorest RRFS compared with N0, N1, N2 (all P values < 0.001) and N3 categories ($P = 0.012$), with 3-year RRFS of 87.1%, 99.0%, 97.3%, 94.8%, and 92.8%, respectively; Fig. 3C). In detail, 10 (23.3%) of 43 patients with PLN had regional lymph node failure. Notably, six of these 10 patients had level Ib lymph node recurrence, including two patients who had level Ib nodes present before treatment and received a curative dose. The remaining four patients had no identifiable level Ib lymph nodes on imaging before treatment and only one patient received prophylactic radiation of level Ib. (Fig. 4) Compared with patients without PLN metastasis, those with PLN metastasis had a higher risk of lymph node recurrence in level Ib. (0.2% vs. 14.0%, $P < 0.001$)

Discussion

To our knowledge, this is the first study to investigate the prognosis of NPC patients with PLN metastasis confirmed by pathology. PLN metastasis was associated with higher risk of disease failure, distant metastasis, and regional recurrence. Moreover, patients with PLN metastasis had similar DFS and DMFS with those with N3 disease, supporting the categorization of PLN metastasis as N3 in future staging.

A major strength of the current study is that all metastatic PLNs were diagnosed by pathology. Though imaging is noninvasive and can provide important information for discrimination between benign and malignant parotid masses, misdiagnoses are inevitable, as a wide range of benign or malignant, primary or metastatic neoplasms can present as masses in the parotid gland. In this study, only 67.2% (43/63) of patients with suspicious parotid nodules were confirmed to have PLN metastasis of NPC Therefore, compared with previous studies, which have all used MRI as the diagnostic method, the data we have presented here provide a more solid basis for the evaluation of risk and prognosis.

The PLNs receive efferent lymphatic drainage from the frontal and temporal skin, eyelids, conjunctiva, auricle, external acoustic meatus, tympanum, nasal cavities, root of the nose, nasopharynx and Eustachian tubes [6]. In NPC, PLN metastasis is relatively rare, with reported incidences ranging from 1% to 3.4% [3–5,8,9,19]. In the study by Wang et al., large lymph nodes in level II might be potential high risk factors for PLN metastasis in NPC [20]. In our study, those with advanced N category had higher risk of PLN metastasis. Enlarged lymph nodes in level II were common in patients with PLN metastasis, with incidence up to 85%. Moreover, these patients had heavy disease burden in level II, with the median value of the minimal and maximal diameter of the enlarged lymph nodes of 20 and 27 mm, respectively. Anatomically, lymphatics from the parotid drain along the retromandibular vein to superficial nodes along the outer surface of the sternocleidomastoid muscle, and then partially drain into upper nodes of the deep cervical chain. The enlarged cervical nodes in level II may cause blockage of the normal routes of lymphatic drainage and induce retrograde tumor spread to the PLNs. This might also explain the high prevalence of level Ib involvement in patients with PLN metastasis.

In the previous conventional radiotherapy era, lateral opposing fields encompassed the parotids in the irradiation volume. In the last decade, IMRT has replaced conventional radiotherapy as the preferred method for NPC treatment [21,22]. IMRT caters for delivery of tumoricidal doses to gross tumor and subclinical disease, while minimizing doses to adjacent normal tissues [23,24]. In order to reduce xerostomia and thus improve quality of life, the parotid gland area is spared and receives low radiation doses. Therefore, PLN metastasis has garnered attention in the IMRT era, as missed diagnose of PLN metastasis could lead to overprotection of the parotid and thus increase the risk of disease recurrence [19]. Suspicion of PLN metastasis, especially in patients with advanced nodal disease, should be raised on pretreatment imaging.

In NPC, the prognosis of PLN metastasis has rarely been studied and the staging category of PLN metastasis in NPC is controversial. Our results showed that PLN metastasis was associated with higher risk of distant metastasis and regional recurrence, and survival of these patients was similar to those with N3 disease, which supports PLN metastasis categorized as N3 disease. Similar results have previously been reported [8,9]. There are two possible reasons for this. Firstly, in patients with PLN metastasis, lymph might drain in a retrograde fashion, which might account for the high risk of distant metastasis. Secondly, patients with PLN metastasis had a larger volume of cervical lymph nodes, which has been shown to be correlated with higher risk of distant metastasis and cervical lymph node recurrence in previous studies [25].

Notably, we found that regional recurrence in rare levels, such as level Ib, were more common in patients with PLN metastasis compared with those without PLN metastasis. Of the six patients who had level Ib

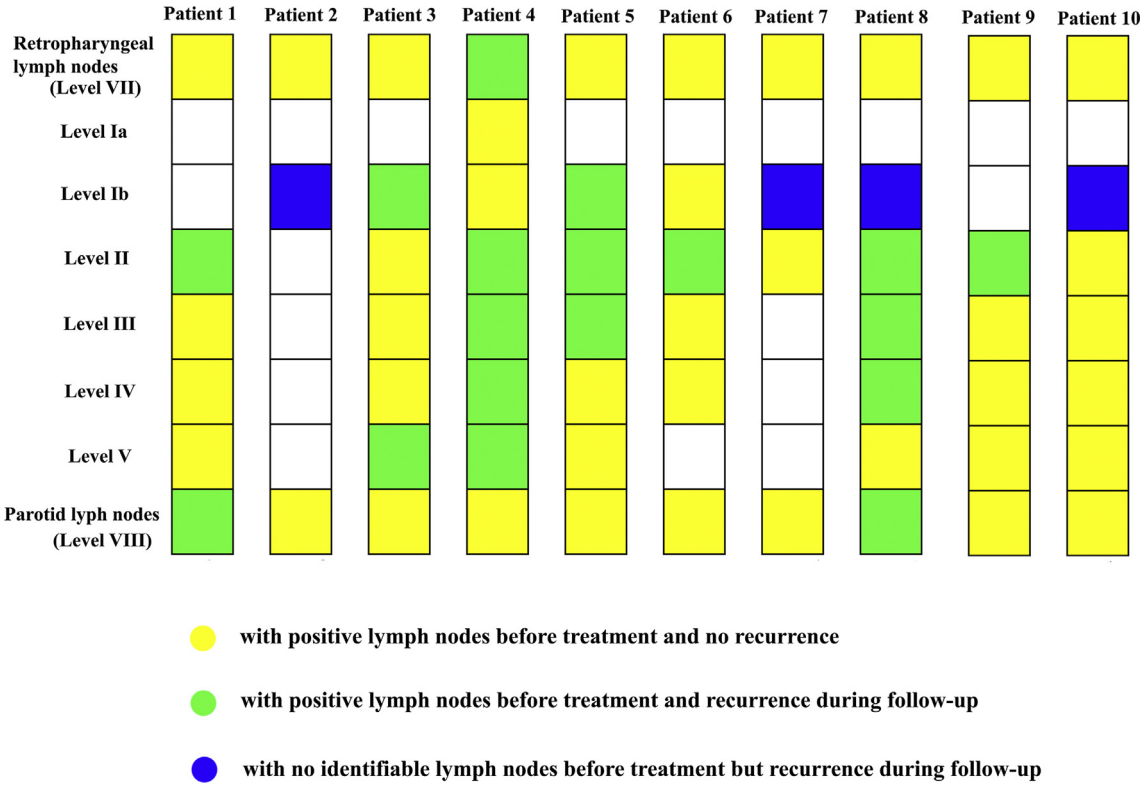

Fig. 4. Distribution of recurrent lymph nodes among patients with parotid lymph node (PLN) metastasis according to the levels defined by the 2013 International Consensus Guidelines. A total of 10 patients with PLN metastasis had regional failure.

recurrence, four had no level Ib lymph nodes that were identifiable on imaging before treatment. In China, prophylactic radiation of level Ib is only recommended for patients with positive lymph nodes in level Ib, minimal diameter of a level II lymph node > 20 mm, or oropharynx involvement [26]. Therefore, in patients with PLN metastasis, it may be necessary to include level Ib in prophylactic clinical target volumes. Moreover, close follow-up, especially monitoring of regional recurrence and distant metastasis, might be beneficial in these patients.

This study has some limitations. Firstly, we only included patients at a single center in an NPC-endemic area, and > 98% of the enrolled patients had WHO type II or III disease. Multicenter studies are needed to confirm the findings of this study. Secondly, we couldn't rule out selection bias concerning choosing patients for parotid node biopsy due to the retrospective nature of current study. However, it might be infeasible to conduct a prospective study of PLN metastasis given its low incidence. Moreover, according to our institutional guidelines, biopsy was recommended whenever possible for nasopharyngeal carcinoma patients with suspicious parotid nodules on pretreatment imaging.

In conclusion, PLN metastasis was associated with high risk of distant metastasis and regional recurrence, and patients with PLN metastasis had similar outcome compared with patients with N3 disease. Regional recurrences in rare levels, such as level Ib, were common in these patients. These results may provide important information for clinical practice and refining the staging system in the future.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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