·Clinical Research·

Influence of level-Ib lymphadenopathy on the prognosis of the patients with nasopharyngeal carcinoma

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[Abstract] Background and Objective: Level-Ib lymph node metastasis is rare in nasopharyngeal carcinoma (NPC). When and how this level should be irradiated with precise radiotherapy remains controversial. This study evaluated the prevalence and prognostic significance of level-Ib lymphadenopathy on the prognosis of NPC patients. **Methods:** Between January 1990 and December 1999, 933 newly diagnosed patients with NPC treated at the Sun Yat-sen University Cancer Center were randomly selected, examined with computed tomography (CT) imagining for evidence of level-Ib lymphadenopathy before treatment. All patients received radical radiotherapy with or without chemotherapy. The relationship between level-Ib lymphadenopathy and post-treatment outcomes including overall survival (OS), locoregional recurrence-free survival (LRFS), and distant metastasis-free survival (DMFS) were analyzed using Kaplan-Meier methods. The Cox proportional hazards regression model was used to adjust for other prognostic factors. **Results:** Of the 933 patients, 55 (5.9%) were found to have level-Ib lymphadenopathy, which was associated with carotid sheath involvement, oropharynx involvement and levels, and lateral cervical lymph node involvement. In the subgroup with carotid sheath involvement, with multivariate analysis accounting for all previously known prognostic factors, level-Ib lymphadenopathy was still associated with a risk of decreased OS (RR, 2.124; $P < 0.001$), DMFS (RR, 2.168; $P < 0.001$), and LRFS (RR, 1.989; $P = 0.001$). **Conclusion:** Level-Ib lymphadenopathy in the patients with carotid sheath involvement is an independent prognostic factor.

Key words: Nasopharyngeal carcinoma, level-Ib lymphadenopathy, prognosis

Nasopharyngeal carcinoma (NPC) is a common cancer in South China, especially in the Guangdong area. Most NPC patients have poorly differentiated pathologic presentation that is prone to infiltrative growth and distant metastasis. The observed rate of cervical lymph node metastasis could be as high as 78.9%.[1] The currently accepted consensus guidelines using computed tomography (CT) for delineating the cervical node levels were endorsed by major cooperative groups in Europe and North America in 2003.[2] Research based on these guidelines reported that the characteristics of cervical lymph node metastasis included progression from upper to lower levels, with a low rate of leap metastasis, levels II, III, IV, and V are the most likely to be involved, and level I, which is not in the lymph drainage path of the nasopharynx, is rarely involved. The rate of nodal involvement in level Ib in patients with primary NPC was reported to be 2.8% –8.45% .[3-5] In the conventional radiation technique in China, level Ib is always included in the radiation field of the facial-cervical field or the upper-cervical tangential field. Only a few patients were in this group, so the clinical significance of level-Ib metastasis has not gotten much attention.

In the past few decades, three-dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiotherapy (IMRT) have been widely used in clinic, and the practice of determining targets have become more refined. Finding the proper balance of radiation—not too much, not too little—helps to precisely control the field of radiation, while decreasing the dose delivered to organs at risk and reducing adverse reactions after radiotherapy without lessening the local control rate.[6-11] To relieve xerostomia after radiotherapy, the radiation dose to major salivary glands should be decreased. Yet, protecting only the parotid glands is not enough; to get a satisfactory effect, the submandibular glands should also be protected as much as possible.[12,13]

As a result, radiation to level Ib where the submandibular

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glands are located has come under clinical dispute. Lower doses, or even no dose, could be selectively given to areas radiated by high doses in the beam pathway in conventional radiotherapeutic techniques because the parotid and submandibular glands are protected. Potential metastasis in these areas would probably be precisely omitted, and hence become sources of local recurrence or further metastasis.[14] Cannon *et al.*[15] reported that in two cases of NPC receiving IMRT, the selectively reduced radiation dose to the parotid glands led to lymph-node relapse in that region. Concerning level Ⅱb, some research has asserted that it should be included in 3D-CRT and IMRT as a conventional method,[7,16-18] but others have thought that no radiation or selective radiation should be given.

For the Cancer Hospital, China Academy of Medical Science, the appropriate clinical target volume (CTV) of IMRT for level Ib should be CTV1 (a high-risk target) if ipsilateral level-Ⅱ lymph nodes ⩾ 2 cm, if the upper cervical lymph nodes invade the skin, or if the patient has a history of surgery in the upper neck.[19] For the States National Cancer Center in Singopore, the appropriate CTV of IMRT for level Ib should be CTV60 and only when ipsilateral metastasis in the cervical lymph nodes exist.[20] In addition, the RTOG0615 clinical trial has a more detailed definition of level-Ⅱb radiotherapy.[21] However, no research with a large sample size supports these rules. As a result, we conducted a series of clinical and experimental studies that included correlation factors and the influence on prognosis, as well as pathology research on level-Ib lymphadenopathy. This paper will report the first part: the correlation factors and the influence of level-Ib lymphadenopathy on prognosis by the retrospective analysis of 933 patients with NPC receiving conventional radiotherapy at the Sun Yat-sen University Cancer Center.

Materials and Methods

General clinical data

Using SAS statistical software, we randomly chose 1000 cases from 6519 patients diagnosed with NPC between January 1990 and December 1999 at the Sun Yat-sen University Cancer Center. Case selection was conducted according to the following criteria: (1) NPC was confirmed in pathologic findings; (2) a CT scan of the nasopharynx was performed before radiotherapy; and (3) radical radiotherapy was performed at our center as primary treatment. A total of 933 cases met these criteria. The male: female ratio was 3.2:1, the median age was 45 years (range, 11–80 years), and the pathologic types were mostly poorly differentiated squamous cell carcinoma. According to the 1992 Fuzhou staging criteria,[22] 52 patients had stage-Ⅰ disease, 270 had stage-Ⅱ, 414 had stage-Ⅲ, and 197 had stage-Ⅳ disease (Table 1).

Table 1 Patient characteristics and incidence of level-Ib lymphadenopathy

Patient characteristic	Patient No.	Level Ib (+)	Incidence (%)	*P*
Age (years)				0.372
< 30	61	5	8.2	
30–60	800	44	5.5	
> 60	72	6	8.3	
Sex				0.414
Male	711	45	6.3	
Female	222	10	4.5	
Clinical stage				0.013
I	52	0	0.0	
II	270	9	3.3	
III	414	29	7.0	
IV	197	17	8.6	
T stage				0.218
T1	171	6	3.5	
T2	328	17	5.2	
T3	283	23	8.1	
T4	151	9	6.0	
N stage				< 0.001
N0	256	0	0.0	
N1	341	17	5.0	
N2	286	29	10.1	
N3	50	9	18.0	
Histology				0.899
Poorly differentiated squamous-cell carcinoma	858	53	6.2	
Undifferentiated carcinoma	38	1	2.6	
Vesicular nucleus cell carcinoma	29	1	3.4	
Other	8	0	0.0	

Treatment

All patients received radiotherapy alone or radiotherapy combined with adjuvant chemotherapy.

Conventional radiation techniques with either ^{60}Co γ ray or accelerator 6–8 MV high-energy X-rays were used. First, the bilateral facial-cervical fields + the anterior tangential field were used, some with the anterior nasal field, with the dose to the nasopharynx and neck between 36 Gy and 40 Gy. Then the small bilateral facial-cervical fields shielding the spinal cord + the anterior tangential field + the bilateral posterior cervical triangle area electronic fields were radiated to 50 Gy. Finally, the bilateral anterior auricular fields to the nasopharynx were delivered a total dose of between 66 Gy and 78 Gy. Doses of between 46 Gy and 50 Gy were given if there was no metastatic cervical lymph node, and if metastatic cervical lymph nodes existed, the dose to any metastatic lesion was elevated to between 60 Gy and 70 Gy. A regimen of PF was mainly used as adjuvant chemotherapy, with cisplatin 80–100 mg/m^2 intravenous drip on day 1, and 5-fluorouracil 500–1000 mg/m^2 intravenous drip on days 2–5.

The definition of level Ib and observation index of lymphadenopathy

According to the 2003 CT-based consensus guidelines[2] for

the delineation of cervical lymph node levels, the upper bound of level Ib is delimited cranially by the mylohyoid muscle and the cranial edge of the submandibular gland, and caudally by a plane crossing the central part of the hyoid bone. Anteriorly it is delimited by the platysma muscle and the symphysis menti, posteriorly by the posterior edge of the submandibular gland, laterally by the basilar edge and the inner side of the mandible, the platysma, and the skin, and medially by the lateral edge of the anterior belly of the digastric muscle. The lymph nodes appearing in the above areas are level-Ib lymph nodes.

According to the diagnostic criteria of cervical lymph node metastasis by van den Brekel *et al.*[23] and the NPC 2008 staging criteria,[24] patients would be included in the level-Ib lymphadenopathy group if CT imaging meets each of the following criteria: (1) the short diameter of enlarged lymph nodes $\geqslant$ 1 cm; (2) the presence of a cluster accumulation of more than three lymph nodes, with the short diameter $\geqslant$ 1 cm in one of them; and (3) the presence of central necrosis, circular enhancement, or extracapsular spread in the enlarged lymph nodes.

Observation index components

(1) Incidence of lymphadenopathy in level Ib. (2) Overall survival (OS) time: observed survival time between the beginning of follow-up and either death or the time of the last follow-up. (3) Locoregional relapse-free survival (LRFS) time: observed survival time without primary lesions in the nasopharynx or regional lymph node recurrence. (4) Distant metastasis-free survival (DMFS) time: the survival time without distant metastasis.

The beginning of radiotherapy was defined as the beginning of follow-up in this research.

Follow-up

Three kinds of follow-up, including phone calls, mailings, and interviews in the outpatient department, were used. The patients were followed for between 5 months and 218 months, with a median of 83 months. The 3- and 5-year follow-up rates were 97.2% and 94.9%, respectively.

Statistical analysis

SPSS version 16.0 was used for data processing. The correlations of each clinical factor and level-Ib lymphadenopathy were compared by a χ^2 test. Single-variate analysis was calculated by Kaplan-Meier methods and a log-rank test; multivariate prognosis analysis was analyzed by the Cox proportional hazards model. A $P < 0.05$ was considered statistically significant.

Results

Correlation factors of level-Ib lymphadenopathy

Clinical characteristics of patients with level-Ib lymphadenopathy

Among the 933 patients, 55 were diagnosed with primary level-Ib lymphadenopathy, and the incidence was 5.9% . This group of patients were called the Ib (+) group for short, and the others were called the Ib (-) group. Clinical and pathologic characteristics of patients in the Ib (+) group are listed in Table 1. Analysis showed that correlation existed between level-Ib lymphadenopathy and clinical stage and N stage.

Correlation between level-Ib lymphadenopathy and primary tumor invasion We analyzed the following invasive structures: the carotid sheath, the nasal cavity, the oropharynx, accessory nasal sinuses, and the cavernous sinus. Among them, invasions of the oropharynx and the carotid sheath had close correlation with level-Ib lymphadenopathy (Table 2).

Table 2 The relationship between level-Ib lymphadenopathy and local involvement

Local involvement	Level Ib (-) (Patient No.)	Level Ib (+) (Patient No.)	Incidence (%)	*P*
Nasal cavity				0.821
Negative	787	49	5.9	
Positive	91	6	6.2	
Oropharynx				0.032
Negative	535	25	4.5	
Positive	343	30	8.0	
Carotid sheath				0.005
Negative	480	20	4.0	
Part involved	151	8	5.0	
Entirely involved	247	27	9.9	
Paranasal sinus				0.394
Negative	765	46	5.7	
Positive	105	9	7.9	
Cavernous sinus				0.766
Negative	817	53	6.1	
Positive	53	2	3.6	

Note: The paranasal sinus or cavernous sinus involvement could not be evaluated in 8 patients.

Correlation between level-Ib lymphadenopathy and lymph node involvement at other cervical levels For patients with cervical lymph node metastasis, as the involvement of levels and sides increased, the incidence of level-Ib lymphadenopathy elevated significantly ($P < 0.05$). However, although the incidence of level-Ib lymphadenopathy had the tendency to gradually increase as the major diameter of the cervical lymph nodes increased, the difference failed to reach statistical significance ($P > 0.05$) (Table 3).

Prognosis and level-Ib lymphadenopathy

All cases The 5-year OS, LRFS, and DMFS of the Ib (+) group were 44%, 36%, and 40%, respectively, which were significantly lower than the 67%, 55%, and 62%, of the Ib (-) group ($P<0.05$). The comparison of survival curves of OS and DMFS are shown in Figure 1.

We conducted further multivariate analysis using the Cox model. The prognostic factors included sex, age (divided into three groups: < 30 years, 30–60 years, > 60 years), T stage, and N stage. Our results showed that level-Ib lymphadenopathy was not an independent prognostic factor for OS, LRFS, or DMFS in NPC (Table 4).

The carotid sheath invasion subgroup Patients were divided

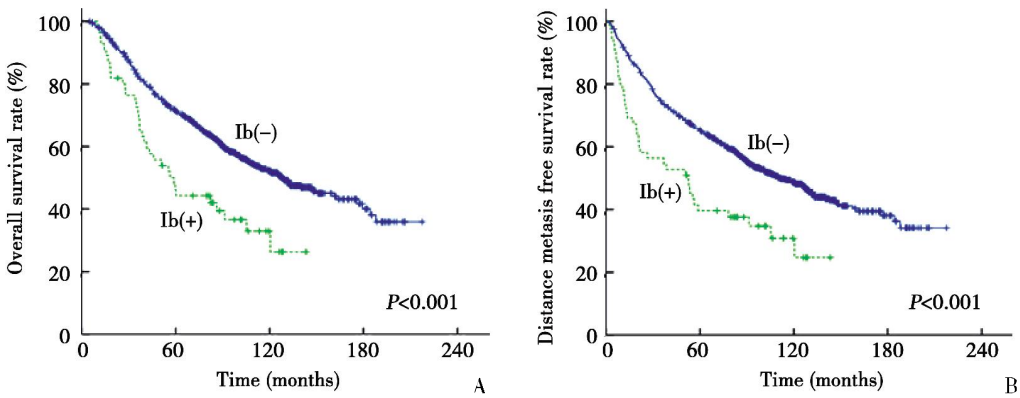
Table 3 The relationship of level-Ib lymphadenopathy and other cervical lymph node involvement

Characteristic	Level Ib (−) (No.)	Level Ib (+) (No.)	Incidence (%)	*P*
Maximal axial diameter of involved lymph nodes[a]				0.403
< 2 cm	185	12	6.1	
2–4 cm	285	27	8.7	
> 4 cm	152	16	9.5	
Involved level[a]				0.002
Upper neck	497	34	6.4	
Lower neck	99	13	11.6	
Supraclavicular	26	8	23.5	
Involved lateral of neck[a]				0.004
Unilateral	430	27	5.9	
Bilateral	192	28	12.7	

[a]Excluded patients without cervical lymph node metastasis.

into two subgroups, with or without carotid sheath invasion, and the survival differences between the Ib (+) and the Ib (-) groups in each subgroup were compared. Each survival rate of the Ib (+) and the Ib (-) groups were without significant differences in the subgroup without carotid sheath invasion, whereas OS, LRFS, and DMFS of the Ib (+) group were significantly lower than those of the Ib (-) group in the subgroup with carotid sheath invasion (P < 0.001) (Figure 2).

Multivariate analysis was conducted within the subgroup with carotid sheath invasion. Besides carotid sheath invasion, the prognostic factors included sex, age (grouped as mentioned above), nasal cavity invasion, oropharynx invasion, major diameter of metastatic cervical lymph nodes (grouped as no metastasis, < 4 cm, and ⩾ 4 cm), the involved cervical levels (grouped as no metastasis, upper neck involvement, lower neck involvement, and supraclavicular involvement), and the involved cervical sides (grouped as no metastasis, unilateral involvement, and bilateral involvement). Our result showed that the Ib (+) group had independent prognostic factors for OS, LRFS, and DMFS in NPC (P < 0.001) (Table 5).



Figue 1 The Kaplan-Meier plot of overall survival and distant metastasis-free survival of level-Ib lymphadenopathy in all studied patients

Table 4 Results of multivariate survival analysis of all studied patients

Prognostic factor	OS		LRFS		DMFS	
	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*
Age	1.898 (1.479–2.435)	<0.001	1.801 (1.434–2.262)	<0.001	1.792 (1.417–2.268)	<0.001
T stage	1.309 (1.185–1.447)	<0.001	1.278 (1.166–1.401)	<0.001	1.274 (1.159–1.400)	<0.001
N stage	1.604 (1.440–1.787)	<0.001	1.494 (1.355–1.648)	<0.001	1.650 (1.488–1.830)	<0.001
Level-Ib lymphadenopathy	1.371 (0.962–1.953)	0.080	1.213 (0.863–1.705)	0.267	1.342 (0.953–1.890)	0.092

OS, overall survival; LRFS, locoregional recurrence-free survival; DMFS, distant metastasis-free survival; RR, relative risk; CI, confidence interval.

Discussion

Conventional theories of lymphatic metastasis assert that lymph nodes in level Ib reside in the lymphoglandulae cervicales superficiales, which is not in the drainage pathway of the nasopharynx. As a result, the retrogression of superficial metastasis in the lymph nodes would happen only when cervical lymph vessels were blocked or excised after extensive metastasis in the lymphoglandulae cervicales profundae, radiotherapy, or radical resection of the lymph nodes.[25] However, anatomically, the lymphatic vessels of the anterior third of the nasal cavity interact with the nasal vestibule and the external nose, which mainly run laterally along the facial vein and flow into the lymph nodes in level Ib. Besides, nasopharyngeal lymphatic tissue and the lymph nodes in level Ib belong to the inner and outer pharyngeal

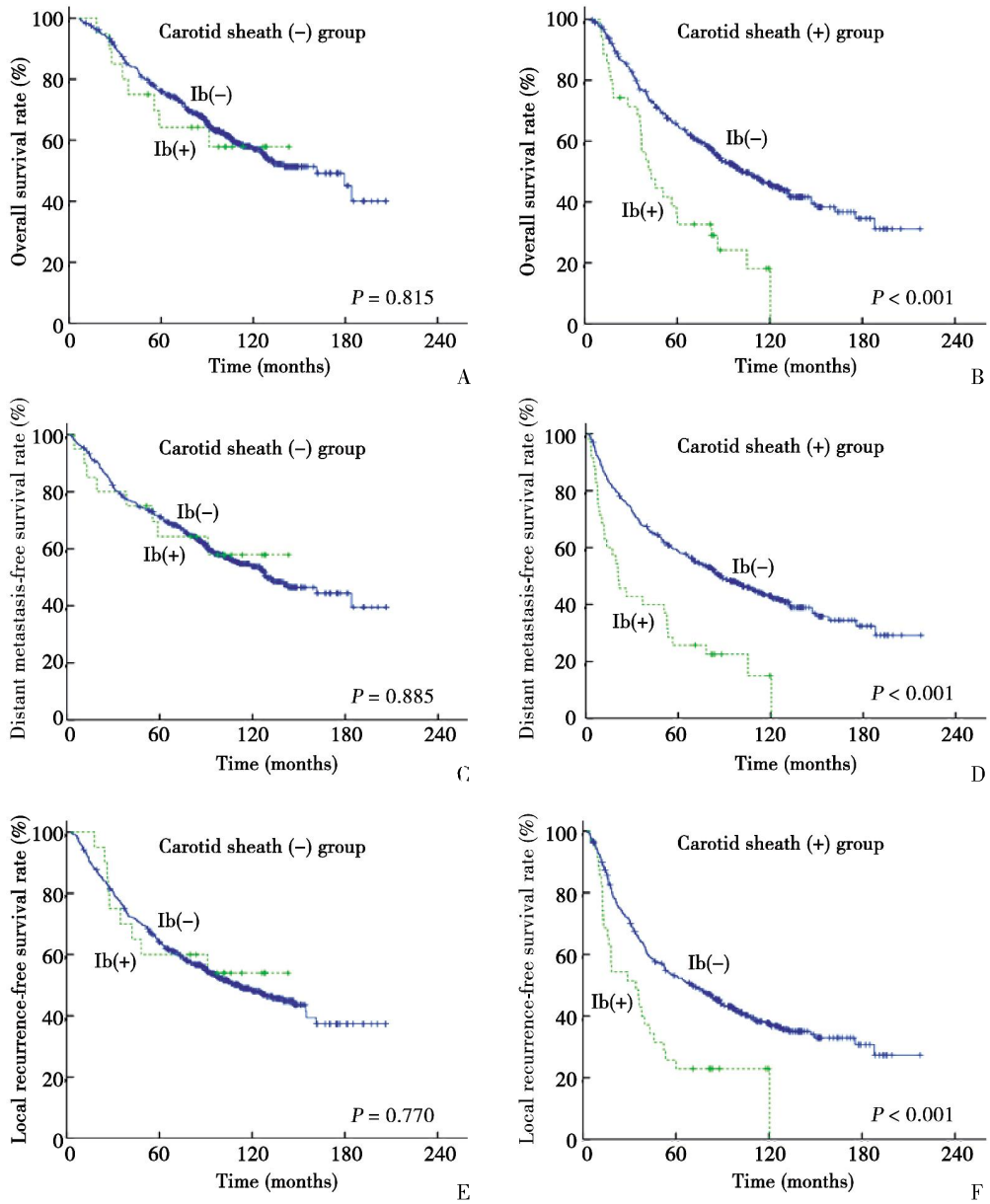


Figure 2 The Kaplan-Meier plot of overall survival, local recurrence-free survival, and distant metastasis-free survival by level-Ib lymphadenopathy in the subgroups with carotid sheath involvement

Table 5 Results of multivariate survival analysis in the patients with carotid sheath involvement

Prognostic factor	OS		LRFS		DMFS	
	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*
Age	2.083 (1.498–2.897)	<0.001	2.163 (1.603–2.917)	<0.001	1.945 (1.417–2.670)	<0.001
Nasal cavity involvement	1.662 (1.202–2.299)	0.002	1.447 (1.068–1.961)	0.017	–	–
Maximum axial diameter of involved lymph nodes	1.138 (1.068–1.213)	<0.001	–	–	–	–
Involved level	–	–	1.531 (1.241–1.888)	<0.001	1.686 (1.353–2.101)	<0.001
Level-Ib lymphadenopathy	2.124 (1.407–3.207)	<0.001	1.989 (1.335–2.965)	0.001	2.168 (1.455–3.232)	<0.001

Abbreviations as in Table 4.

lymphatic ring (Waldeyer's ring) with abundant interaction between the tissue. So theoretically, through these two lymphatic channels, direct metastasis at the level-Ib lymph nodes could cause NPC to invade the surrounding structures.[26]

Besides the direct metasta sis of NPC, another cause of level-Ib lymphadenopathy is reactive hyperplasia induced by

various metabolites of cancer cells flowing into the lymph nodes alone with lymph circulation. In addition, because lymph nodes in level-Ib drain lymph from the skin, mucous membranes, and the organs of the nasal and oral cavities, level-Ib lymphadenopathy could also be caused by inflammation in these regions.

Both of these factors could change the understanding of level-Ib lymphadenopathy. Cancer-induced level-Ib lymphadenopathy in recurrent NPC was reported at 43.3%, with the rest reported as inflammation.[27] This suggests that probably not all primary level-Ib lymphadenopathy is caused by tumor metastasis. Theoretically, only lymphadenopathy caused by cancer metastasis could influence prognosis. As a result, to eliminate the non-cancer factors for lymphadenopathy as much as possible, we consulted the CT-imaging diagnostic criteria for cervical lymph node metastasis when choosing cases.[23]

Our result found that primary level-Ib lymphadenopathy correlated closely with metastatic status of the lymph nodes in other cervical levels. Similar to other published reports,[28] as the metastatic lymph nodes increase in size and number, the probability of level-Ib lymphadenopathy gradually increases. This indicates that the conventional theory of lymphatic pathway back-streaming plays an important role in the development of level-Ib lymphadenopathy.

Primary level-Ib lymphadenopathy also correlated closely to the carotid sheath invasion in T staging. When the carotid sheath was invaded or occupied by tumor, the incidence of level-Ib lymphadenopathy increased significantly. Domestic CT-based research showed that in most cases, NPC extended and invaded the carotid sheath first, and then ipsilateral cervical lymph node metastasis developed.[29,30] Therefore, we have strong reason to believe that the area of the carotid sheath is the transfer station when NPC metastasizes to level-Ib and other cervical levels.

Invasion to the oropharynx also correlated to level-Ib lymphadenopathy, which was consistent with lymphatic anatomy. The oropharynx is adjacent to level Ib, and both belong to the inner and outer pharyngeal lymphatic ring, respectively, with abundant connections between them. Therefore, invasion of the oropharynx could increase the probability of metastasis in level-Ib lymph nodes, hence elevating the incidence of level-Ib lymphadenopathy.

Our study did not find an increased incidence of level-Ib lymphadenopathy caused by nasal cavity invasion. The reason for this phenomenon could possibly be that most patients received treatment before the tumor invaded the anterior third of the nasal cavity, and that the lymphatics of the nasopharynx are located downstream of lymphatic drainage from the nasal cavity,[31] with a low probability of retrograde metastasis.

All patients in our study received the conventional technique of radiotherapy, and the lymph nodes in level-Ib were radiated by a dose of between 50 Gy and 60 Gy, regardless of whether they were enlarged.[32] No further radiation boost was delivered to patients with level-Ib lymphadenopathy. Based on that, single-variant analysis on Ib (+) showed that the emergence of level-Ib lymphadenopathy predicted poor prognosis. However, multivariate analysis also showed that level-Ib lymphadenopathy failed to be an independent prognostic factor for NPC.

We supposed that the emergence of this phenomenon was in part because level-Ib lymphadenopathy was non-metastatic, which interfered with the influence of metastatic level-Ib lymph nodes on prognosis. So, further subgroup analysis to distinguish them is necessary. Retropharyngeal lymph nodes were the sentinel lymph nodes of NPC-lymphatic metastasis, and usually it is rare to find direct cervical lymph-node involvement without retropharyngeal lymph node metastasis.[28] However, it is difficult to distinguish retropharyngeal lymph node metastasis in the carotid sheath and direct primary-tumor invasion on CT. As a result, we listed and analyzed the carotid sheath invasion group separately in our research, trying to increase the proportion of metastatic level-Ib lymphadenopathy. Nevertheless, level-Ib lymphadenopathy failed to influence the prognosis when the carotid sheath was not invaded, while the survival prognosis became significantly worse for the level-Ib lymphadenopathy group in the carotid sheath invasion subgroup (Figure 2).

Multivariate analysis also showed that level-Ib lymphadenopathy independently influenced each survival index in this subgroup. Hence, we suggested that the probability of metastatic level-Ib lymphadenopathy was lower when the carotid sheath was not invaded. The probability significantly increased with carotid sheath invasion, and conventional radiotherapy would possibly be inadequate to eliminate its adverse influence on prognosis. To a certain extent, this conclusion could be considered when judging the character of level-Ib lymphadenopathy and determining the radiation dose.

Because of the limitations of retrospective research, none of the patients with level-Ib lymphadenopathy in our study received biopsy to identify its pathology. As a result, we will conduct pathologic research on level-Ib lymphadenopathy in our next phase of research to understand the actual status of metastatic lymphadenopathy. In addition, besides clinical factors, metastatic lymphadenopathy also correlates to various genes and proteins, such as nm-23 gene, matrix metalloproteinases (MMPs), vascular endothelial cell growth factor (VEGF), and EB virus latent membrane protein (LMP).[33] We will also conduct molecular biologic research on metastatic level-Ib lymphadenopathy to investigate its metastatic molecular mechanism. These studies would help to establish the foundation for more reasonable treatment modalities for patients with level-Ib lymph nodes in NPC.

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