Recommendation for Cranial Upper Border of Level IIb in Clinical Target Volumes (CTV) for Nasopharyngeal Carcinoma

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Research

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Abstract

Purpose: To recommend the cranial side of level IIb in clinical target volumes (CTV) for nasopharyngeal carcinoma (NPC) patients receiving intensity-modulated radiotherapy, to help reach a consensus on contouring level IIb in CTV.

Methods: From 2012 to 2016, 331 non-metastatic NPC patients treated with IMRT were retrospectively enrolled. According to the AJCC 8th staging system of NPC, there were 15 patients with stage I, 76 stage II, 103 stage III, and 137 stage IV. Distribution of cervical lymph nodes in NPC was assessed based on imaging results. Comparison of the safety and the parotid dose parameters between patients with or without a reduction in the range of level IIb was taken by SPSS 25.0 and R 2.14.2 software.

Results: Metastasis rates of the most common diseased lymph nodes, lateral retropharyngeal lymph node and IIb lymph node, were 82.8% and 64.0%, respectively. Among patients with level IIb involvement, the upper borders of metastatic nodes in 13.7% of cases were beyond the caudal edge of C1. The D50 and V26 values for parotid glands were significantly reduced after modified the upper bound of level IIb in CTV ($P = 0.000$).

Conclusions: The upper bound of level IIb should reach the lateral skull base during the delineation of the cervical CTV for NPC. To protect the parotid glands, however, individualized reduction in the upper bound of level IIb is recommended for patients who meet the formulated standard.

Introduction

Compared to other head and neck squamous cell carcinomas, nasopharyngeal carcinoma (NPC) has a distinct epidemiology, etiology, and clinical manifestation[1]. Since NPC has the highest preponderance for regional lymph node metastasis among head and neck cancer (HNC), the contouring of clinical target volume (CTV) in the bilateral neck lymphatic drainage area is very important in the intensity-modulated radiation therapy (IMRT) for NPC[2, 3]. CT-based international consensus guidelines for a delineation of neck CTV in node-negative patients were proposed in 2003 [4], and the new guideline was updated in 2013 [5].

However, these guidelines were primarily derived from patients with head and neck squamous cell carcinomas. Considering the specific biological behavior of NPC, there are still some controversies in the delineation of the neck CTV for NPC. Intending to provide more suitable cranial boundaries for level IIb in neck CTV for NPC, we carried out this retrospective study and investigated the distribution and metastasis of high-seated lymph nodes in level IIb.

Methods And Materials

Patients and pretreatment evaluations
We performed a retrospective study of 331 patients that fulfilled the following criteria in our hospital between February 2012 and December 2016. Inclusion criteria were pathologically confirmed NPC, previously untreated, no evidence of distant metastases, receiving the whole course of radical IMRT, and full treatment plan data was available, including the isodose distribution and dose-volume histogram (DVH). Exclusion criteria included: prior or other current malignancy; prior RT, chemotherapy or surgery (except for diagnostic procedures) to the primary tumor or nodes.

Routine workup comprised complete medical history, physical and neurologic examinations, hematology and biochemistry profiles. MRI scans of the head and neck were performed to evaluate the extent of the locoregional disease. Chest and abdominal CT, as well as bone scintigraphy were performed to exclude distant metastasis. Medical records and imaging studies were analyzed retrospectively. All patients were restaged according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system for NPC.

**MR scanning protocol**

All MR images were acquired with the same 1.5 Tesla unit (Achieva, Philips, Best, Netherlands) using a head and neck coil. The plain scanning examination was performed with the following sequences:
- axial/coronal view: T1-weighted, short-term inversion recovery with T2-weighted fat suppression; sagittal view: T1- and T2-weighted imaging; slice thickness = 5mm; and spacing = 1mm. Enhanced scanning was performed as follows: axial, coronal, and sagittal fat-suppressed T1-weighted imaging after intravenous injection of 0.1mmol/kg Gd-DTPA (Bayer Pharma AG, Leverkusen, Germany).

**Image assessment**

All MR scans were evaluated by a multi-disciplinary treatment group of NPC, which included three radiation oncologists and two diagnostic radiologists; all disagreements were resolved by consensus. Radiologic criteria for the diagnosis of lymph node metastasis were based on the literature.

The diagnostic criteria for retropharyngeal lymph node (RPLN) and cervical lymph node (CLN) involvement included:[6-10] (1) any visible LN in the median RPLNs, a shortest axial dimension $\geq$ 5mm in the lateral RPLNs, $\geq$ 11mm for the jugulodigastric region and $\geq$ 10mm in other cervical regions, or a group of three LNs that were borderline in size; or (2) LNs of any size in the presence of necrosis or extracapsular spread (ES). The definition of central necrosis on MRI was a focal area of high signal intensity on T2-weighted images or a focal area of low signal intensity on T1-weighted images with or without a surrounding rim of enhancement. The criteria for ES were the presence of indistinct LN margins, irregular LN capsular enhancement, or infiltration into the adjacent fat or muscle. Lymph node locations were based on the International Consensus Guidelines for neck level delineation [5].

**Treatment**

All patients received IMRT. Patients were immobilized in the supine position with a thermoplastic mask. Target volumes were defined by ICRU50 and 62 (International Commission on Radiation Units and
Measurements) [11, 12]. The gross tumor volume (GTV) included the primary tumor (GTV-T) and metastatic lymph nodes (GTV-N). CTV-1 (defined as the high-risk clinical target volume) should include GTV plus 5- to 10-mm margin and also cover the entire nasopharynx, parapharyngeal space, and retropharyngeal nodal regions. CTV-2 (defined as the low-risk clinical target volume) included CTV-1 plus 5 mm margin and also encompassed the maxillary sinus (limited to 5 mm anterior to the posterior nasal aperture and maxillary mucosa), pterygopalatine fossa, posterior ethmoid sinus, parapharyngeal space, skull base, the anterior third of clivus and cervical vertebra, inferior sphenoid sinus, and cavernous sinus. CTV-N-the clinical target volume of the neck nodal regions included bilateral coverage of levels 1, 2, 3, and 4, which were outlined according to the recommendation by the Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer (EORTC) delineation consensus for head and neck malignancies [3, 5]. The selection of level b contouring methods was detailed below.

Radiation was delivered using a simultaneous integrated boost-IMRT technique. The radiation dose prescribed evolved: a total dose of 66~70 Gy in fractions at 2.18 Gy/fraction to GTV-P and GTV-N, 60 Gy at 1.875 Gy/fraction to CTV-1, 50.4 Gy at 1.8 Gy/fraction to CTV-2, and 50.4~60 Gy to CTV-N in 28~32 fractions. The normal tissue constraints and plan evaluation were following the RTOG 0225 protocol [13]. A total of 282 patients received 1~2 cycles of cisplatin-based chemotherapy and 26 received 3~4 cycles. Whenever possible, salvage treatments (including boost irradiation, re-IMRT, surgery, and chemotherapy) were provided for patients who developed relapse or persistent disease.

**Selection of level b contouring methods**

Two methods were used to contour the level b. The first delineated the cranial border of level b to the skull base, according to the guideline of RTOG 0615 (control group) [14]. The other method contoured the cranial border of level b to the lateral process of atlas for patients who meet the following criteria (modified group): the primary tumor has no expanded tendency to posterior and lateral direction on the ipsilateral side; no positive retropharyngeal LNs (LN\(_{RP}\)) on the ipsilateral side; on the ipsilateral side, the primary tumor do not invade the carotid sheath area, or invade the carotid sheath area but invasion <90° (the degree of contact arch between the tumor and carotid artery is less than 90°); there is no positive lymph node in the level b above the cranial edge of the second cervical vertebra (C2); there is no visible lymph node in level b from the skull base to the upper edge of C2.

**Follow up**

Follow-up was measured from the first day of treatment to the day of last examination or death. Patients underwent weekly physical and hematolog related examinations during the radiotherapy process. The follow-ups were conducted every 3 to 4 months during the first 2 years, then 6 to 12 months from year 3 to year 5 after radiotherapy. Follow-up examinations included a complete physical examination, blood tests, standard nasopharyngeal MRI scan, chest and upper abdominal enhanced CT scan (or chest radiography and abdominal ultrasound), bone scan, and fiber nasopharyngoscopy.

**Statistical analysis**
SPSS version 25.0 (SPSS Inc., Chicago, IL) and R version 3.0.2 (www.r-project.org) were used for data analysis. The Kaplan-Meier method was used for survival analysis, and the Log-rank test was applied to compare the difference. The $\chi^2$ test was used for comparing categorical variables, and the independent t-test was used for comparing the means of continuous variables.

To balance the distribution of baseline characteristics, we used propensity score matching (PSM). PSM was performed by logistic regression analysis and included age, gender, AJCC staging, AJCC T classification, AJCC N classification and chemotherapy. Patients were matched 1:1 based on their propensity scores. All statistical tests were 2-tailed, with a level for significance set at <0.05.

**Results**

**Incidence and distribution of nodal metastasis**

A total of 295 (89.12%) cases had involved lymph nodes, and 135 (40.79%) cases had bilateral lymph node metastasis. Retropharyngeal LNs and level $b$ LNs were the most commonly involved lymph nodes, with metastasis rates of 82.8% and 64%, respectively. The distribution is detailed in Table 1.

**Distribution of nodal in perch of level $b$**

Of the 212 patients with level $b$ node involvement, the upper border of metastatic lymphadenopathies relative to the cervical vertebra was assessed. It was founded that the most superior edge in 58.02% (123/212) of the patients was reaching the cephalic edge of the second cervical vertebra (C2), 13.2% (28/212) exceeding the caudal edge of the lateral process of the first vertebra (C1), the suggested upper border of level $b$ in the 2013 updated international consensus guidelines, and 2.83% (6/212) reaching the skull base (Fig. 1). The distribution of nodal in perch of level $b$ was shown in Table 2.

However, all the 135 cases with level $a$ node involvement were below the caudal edge of the lateral process of C1.

**Optimization of level $b$ contouring method**

As mentioned above, two methods were used to contour the level $b$ based on the different imaging characteristics of tumors displayed by MR. A total of 124 patients were included in the control group, which delineated the cranial border of level $b$ to the skull base, according to the guideline of RTOG 0615. The other 207 cases, who met the optimization criteria mentioned above, were included in the modified group. In the modified group, the upper border of level $b$ in cervical CTV was contoured to the lateral process of C1.

**Propensity score-based survival analysis**

Baseline patient characteristics between the control group and the modified group were significantly different (Table 3). To balance the distribution of baseline characteristics, we used propensity score
matching (PSM). After PSM, baseline characteristics between the two groups were similar (Table 3). We collected 103 matched pairs and compared the 5-year overall survival (OS) 5-year local control rate (LCR) 5-year distance metastasis-free survival (DMFS) and 5-year disease-free survival (DFS) between two case-control groups.

Kaplan-Meier curves displayed OS, LC, DMFS and DFS rate for NPC patients in the modified group and control group (Fig. 2). The 5-year OS, LC, DMFS and DFS rate for the modified group vs control group were 85.3% vs 87.8%, 92.73% vs 92.71%, 86.33% vs 82.19%, and 76.86% vs 79.32, respectively. As shown in Fig.2, there were no significant differences between the two groups.

**Comparison of radiation dose parameters of parotid glands**

The level b is adjacent to the deep lobe of the parotid gland. In the modified group, the optimized cervical CTV contouring method will inevitably reduce the radiation dose of the parotid gland. We compared the D50 (dose of 50% volume) and V26 (volume of 26Gy) of the parotid gland between the two groups. The parotid D50 and V26 were significantly lower in the modified group than in the control group (Table 4).

**Discussion**

Since cervical node metastasis is very common in patients with NPC, the bilateral neck lymphatic drainage area is always recommended to be irradiated for a higher locoregional control rate, regardless of the stage at presentation [3]. Lymph node metastasis of NPC follows an orderly pattern. In this study, we retrospectively analyzed the distribution of involved lymph nodes in 331 patients with NPC and confirmed that the most commonly involved regions include retropharyngeal and level IIb lymph nodes, with metastasis rates were 82.8% and 64.0%, respectively.

In the past two decades, recommendations for selection and delineation of the neck node CTV have been proposed by several researchers [2, 3, 15]. The recently updated guidelines defined in 2013 were proved to be comprehensive enough and boundaries described are applicable for most levels for NPC under routine circumstances [2, 16]. However, there is a paucity of knowledge on the patterns of nodal metastasis from NPC based on this guideline. Moreover, there is no evidence that this guideline fully covers the lymphatic drainage pathway of NPC. Our study reported the distribution of cervical metastatic lymph nodes, and we investigated whether the upper border of level IIb suggested in the new guidelines are comprehensive enough. The caudal edge of the lateral process of C1 is still proposed being the upper border of level II in the new guideline. Our study showed that among the 212 cases with level IIb node involvement, the uppermost border in 28 cases (13.2%) was beyond the proposed boundary, with 123 cases (58.02%) exceeding the upper margin of C2, and 6 cases (2.83%) reaching the skull base. However, all the 135 cases with level a node involvement were within the proposed boundaries. Zhang et al. [17] and Wang et al. [16, 18] reported that the cranial edge of level II did not fully cover all level II involvement. Hence, some researchers proposed that the upper border of level II should be extended up to the skull base for NPC cases, regardless of the nodal status. But the consensus of this suggestion is low to 64% [3].
Based on our data, since the cranial edge of level IIb proposed in updated guideline could not fully cover all level IIb involvement in a part of patients, we agree with the suggestion that the upper border of level IIb should be extended up to the skull base for NPC cases in principle. However, the upper border of level IIb could be reduced to the caudal edge of the lateral process of C1 for patients who meet the optimization criteria mentioned above. In the modified group, our CTV was based on the following: (1) high-resolution planning CT, high-quality MRI, and PET-CT (for some patients), (2) the individual tumor extent, (3) the distinctive orderly and stepwise pattern of spread of NPC. In this study, after case-control by PSM, we did not observe significant differences between the two groups with regard to 5-year OS, LC, DMFS and DFS rate. Importantly, with a median follow-up of 35 months in the whole group, there was no marginal or out-of-field recurrence with our optimized contouring method of level IIb in neck CTV.

Once the upper border of level II in neck CTV extended to the skull base, the surrounding normal tissues are exposed to increased radiation. In the long term, decreased radiation therapy dose to the parotid glands should decrease the incidence of xerostomia, whose incidence remains high in the IMRT era [19, 20]. Eisbruch et al. [21] and Pointreau Y et al. [19] proposed that when the radiation dose of the parotid gland is less than 26 Gy, the function could be gradually restored after radiotherapy. Chao et al. [22] predicted that the dose threshold of salivary flow reduction (<25% of pretreatment level of parotid stimulated secretion) was 32Gy. We estimated the parotid 50% volume dose D50 and the volume percentage dose V26 at 26Gy in two groups. Our results show that the parotid D50 and V26 were markedly lower in the modified group than in the control group.

There are several important limitations to our study. Although all patients were treated with a protocolized target volume, the study was retrospective research. Additionally, there was variation in treatment modality, radiation therapy dosing, and the cycles of chemotherapy among our cohort. We overcame this shortcoming by including consecutive patients who were treated at a single center, performing an in-depth review of imaging studies and medical records, and providing continuous, long-term follow-up.

**Conclusions**

In summary, based on our data about the distribution of involved lymph nodes of NPC patients, we agree with the suggestion that the upper bound of level IIb in principle should reach the lateral skull base during the delineation of the neck CTV. In order to protect the parotid glands, however, individualized reduction in the upper bound of level IIb is recommended for patients who meet the formulated standard: the primary tumor has no expanded tendency to posterior and lateral direction on the ipsilateral side; no positive retropharyngeal LNs (LN_RP) on the ipsilateral side; on the ipsilateral side, the primary tumor do not invade the carotid sheath area, or invade the carotid sheath area but invasion <90° (the degree of contact arch between the tumor and carotid artery is less than 90°); there is no positive lymph node in the level above the cranial edge of the second cervical vertebra (C2); there is no visible lymph node in level from the skull base to the upper edge of C2.
We did not observe an increase in the rate of local or regional recurrence. The selective reduced CTV might effectively avoid unnecessary radiation to parotid glands. Thereby decreasing the incidence of xerostomia.

**Abbreviations In This Article**

CTV: Clinical Target Volumes

NPC: Nasopharyngeal Carcinoma

D50: Dose Received by 50% of volume

V26: Volume Percentage of Received 26Gy

HNC: Head and Neck Cancer

IMRT: Intensity-modulated Radiation Therapy

DVH: Dose-volume Histogram

MRI/MR: Magnetic Resonance Imaging

CT: Computed Tomography

AJCC: the American Joint Committee on Cancer

RPLN: Retropharyngeal Lymph Node

CLN: Cervical Lymph Node

ES: Extracapsular Spread

GTV: Gross Tumor Volume

RTOG: the Radiation Therapy Oncology Group

EORTC: European Organisation for Research and Treatment of Cancer

C2: the Second Cervical Vertebra

PSM: Propensity Score Matching

OS: Overall Survival

LCR: Local Control Rate

DMFS: Distance Metastasis-free Survival
DFS: Disease-free Survival

LNc2: level b LNs Located above the C2 Vertebra

LNab: LNs above the Upper Border of Level b

Declarations

Ethical Approval and Consent to participate

This study was approved by the institutional ethical committee (Ethics Committee of Nanjing Medical University).

Consent for publication

Not applicable.

Availability of supporting data

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

Lijun Wang and Shengfu Huang designed the study. Lijun Wang made study design, data acquisition, and wrote the manuscript. Shengfu Huang made the Quality control of data and algorithms. Lanfang Zhang made data analysis and interpretation. Yatian Liu did the statistical analysis. Xia He and Yiqing Zhang revised critically the manuscript for important intellectual content. All authors have read and approved the final manuscript.

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Not applicable.

Conflict of Interest Statement
The authors declare no potential conflicts of interest.

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Tables

Table 1. Detailed distribution of the 331 cases with involved lymph nodes
| LN Group                  | Unilateral | Bilateral | Total Percentage(%) |
|---------------------------|------------|-----------|---------------------|
| Rouviere's LN             | 125        | 149       | 82.8                |
| Medial group of pharynx LN| 1          | 0         | 0.3                 |
| Level b                   | 2          | 5         | 2.1                 |
| Level a                   | 105        | 30        | 40.8                |
| Level b                   | 144        | 68        | 64.0                |
| Level c                   | 101        | 14        | 34.7                |
| Level a                   | 33         | 1         | 10.3                |
| Level b                   | 1          | 0         | 0.3                 |
| Level a                   | 35         | 2         | 11.2                |
| Level b                   | 7          | 2         | 2.7                 |
| Level c                   | 3          | 0         | 0.9                 |
| Parotid LN                | 12         | 0         | 3.6                 |

**Table 2. Distribution of upper lymph nodes in level b**

| Level b | Number (percentage) of patients | LNc2 | LNab |
|---------|---------------------------------|------|------|
|         | Unilateral | Bilateral | Unilateral | Bilateral |
| Positive LNs | 99 29.9 | 24 7.25  | 26 7.85  | 2 0.60  |
| LN \(\geq\) 5mm | 24 7.25 | 13 3.93  | 1 0.30  | 0 0.00  |

abbr: LNc2: level b LNs located above the C2 vertebra

LNab: LNs above the upper border of level b

**Table 3. Characteristics of patients included in the study**
| Characteristic                | Before Matching | Case-Control |
|------------------------------|-----------------|--------------|
|                              | Modified Group  | Control Group| P value | Modified Group | Control Group | P value |
| N=207                        | N=124           | N=103        |         | N=103         |               |         |
| Age, mean(SD), y             | 49.9(11.48)     | 45.7(14.57)  | 0.007   | 48.25(13.24)  | 47.79(13.58)  | 0.803 |
| Age, No(%)                   | 0.003           |              |         |               | 0.385         |         |
| ≥ 46y                        | 146(70.5)       | 68(54.8)     |         | 69(67.0)      | 62(60.2)      |         |
| <46y                         | 61(29.5)        | 56(45.2)     |         | 34(33.0)      | 41(39.8)      |         |
| Gender, No(%)                | 0.030           |              |         |               | 1.000         |         |
| Male                         | 161(77.8)       | 84(67.7)     |         | 73(70.9)      | 73(70.9)      |         |
| Female                       | 46(22.2)        | 40(32.3)     |         | 30(29.1)      | 30(29.1)      |         |
| AJCC Staging*, No(%)         | 0.014           |              |         |               | 1.000         |         |
| I-II                         | 66(31.9)        | 25(20.2)     |         | 21(20.4)      | 21(20.4)      |         |
| III-IV                       | 141(68.1)       | 99(79.8)     |         | 82(79.6)      | 82(79.6)      |         |
| AJCC T classification*, No(%)| 0.777           |              |         |               | 0.843         |         |
| T1                           | 59(28.5)        | 35(28.2)     |         | 23(22.3)      | 28(27.2)      |         |
| T2                           | 35(16.9)        | 18(14.5)     |         | 14(13.6)      | 14(13.6)      |         |
| T3                           | 49(23.7)        | 31(25.0)     |         | 26(25.2)      | 26(25.2)      |         |
| T4                           | 64(30.9)        | 40(32.3)     |         | 40(38.8)      | 35(34.0)      |         |
| AJCC N classification*, No(%)| 0.000           |              |         |               | 0.107         |         |
| N0                           | 31(15.0)        | 5(4.0)       |         | 9(8.7)        | 4(3.9)        |         |
| N1                           | 111(53.6)       | 58(46.8)     |         | 56(54.4)      | 50(48.5)      |         |
| N2                           | 49(23.7)        | 34(27.4)     |         | 28(27.2)      | 28(27.2)      |         |
| N3                           | 16(7.7)         | 27(21.8)     |         | 10(9.7)       | 21(20.4)      |         |
| Chemotherapy, No(%)          | 0.013           |              |         |               | 1.000         |         |
| No                           | 5(4.0)          | 18(8.7)      |         | 4(3.9)        | 4(3.9)        |         |
| Yes, 1-2 cycles              | 103(83.1)       | 179(86.5)    |         | 90(87.4)      | 90(87.4)      |         |
| Yes, 3-4 cycles              | 16(12.9)        | 10(4.8)      |         | 9(8.7)        | 9(8.7)        |         |

* Defined by the criteria of the AJCC 8th staging system
Table 4 Comparison of radiation dosimetric parameters of parotid glands in the 331 cases

| Group          | Modified group | Control group | P-value |
|----------------|----------------|---------------|---------|
| Parotid's D50 (Gy) |                |               |         |
| Left           | 26.88±5.32     | 31.77±8.18    | 0.000   |
| Right          | 25.99±5.13     | 31.42±7.54    | 0.000   |
| Parotid's V26 (%) |                |               |         |
| Left           | 52.42±15.94    | 64.21±17.45   | 0.000   |
| Right          | 49.41±14.51    | 63.79±16.41   | 0.000   |

Figures
Figure 1

A case with involved lymph node exceeding the upper border of level b: a: MRI (T1-weighted, T2-weighted, T1 C+ and DWI) b: planning CT with 3 successive slides
Figure 2

PSM-based survival curves of overall survival (a), Local control (b), distance metastasis-free survival (c), and disease-free survival (d) between modified group and control for the 206 patients with NPC.