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Locoregional extension and patterns of failure for nasopharyngeal carcinoma with intracranial extension

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ABSTRACT

Objective: To evaluate the locoregional extension and patterns of failure for nasopharyngeal carcinoma (NPC) with intracranial extension to improve clinical target volume (CTV) delineation.

Patients and methods: A total of 205 NPC patients with intracranial extension by magnetic resonance imaging (MRI) were retrospectively reviewed.

Results: According to the cumulative incidence rates of tumor invasion, we initially classified anatomic sites surrounding the nasopharynx into three risk grades: high risk (≥35%), medium risk (≥10–35%), and low risk (< 10%). It was concluded that the anatomic sites at high risk of tumor invasion were the middle/posterior skull base and the anatomic sites adjacent to the nasopharynx. The rate of lymph node (LN) metastasis was 90.2% (185/205). Retropharyngeal region (RP) and level IIb were the most frequently involved regions. Skip metastasis occurred in only 1.6% (3/185). At their last follow-up visit, 53 patients (25.9%) had developed treatment failure. Of the 18 local failures, 12 were considered in-field failure; the other 5 were marginal; one of the patients had outside-field failure. Among the 5 patients with marginal failures, 4 occurred mainly intracranially, and 1 occurred in the floor and the left lateral wall of the nasopharynx. Of the 11 regional failures, 10 were considered in-field failures and most of them (8/10) occurred in the unilateral upper neck.

Conclusion: For NPC with intracranial extension, primary disease and regional LN spread follow an orderly pattern and LN skipping was unusual. Clinical target volume reduction may be feasible for selected patients.

Introduction

IMRT has been accepted as the standard treatment technique of nasopharyngeal carcinoma (NPC) [1]. Clinical target volume (CTV) delineation is the key point in local tumor control and normal tissue protection. Although the CTV definitions are different in different centers, the 5-year local recurrence-free survival (LFFS) for NPC after IMRT is about 90% and the late toxicities are well tolerable [2–4]. However, radiotherapy of NPC with intracranial extension is technically challenging. In the study of 70 patients with T4 classification NPC after IMRT, 16 patients developed local failure, the images of 2 patients with only local failure were lost, 7 were in-field failure; the other 7 were marginal failure. Of these patients with marginal failure, 6 had intracranial extension on presentation [5].

Ma et al. evaluated the locoregional extension patterns of NPC by magnetic resonance imaging (MRI) [6,7]. The results indicated that primary disease of NPC spreaded stepwise from proximal sites to more distal sites and lymph node metastasis spreads from the upper neck to the lower neck. Recently, a guideline for the delineation of the CTV for NPC has been developed [8]. However, which was limited for guiding CTV delineation of NPC with intracranial extension. Thus, in this study, we evaluated the locoregional extension and patterns of failure for NPC with intracranial extension to improve CTV delineation.

Material and methods

Patient selection

Between March 2007 and February 2012, 205 non-metastatic NPC patients with intracranial extension by MRI were included in this study. All patients underwent a pretreatment evaluation that included a complete history and physical examination, hematology, and biochemistry profiles, fiber-optic nasopharyngoscopy, MRI of the head and neck, bone scintigraphy, computed tomography (CT) scan of the chest

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Table 1
Patient characteristics.

Characteristic	No. (%)
Sex	
Male	154 (75.1)
Female	51 (24.9)
Age (yr)	
Median	48
Range	15–79
Pathology classification	
Keratinizing	3 (1.5)
Non-keratinizing	202 (98.5)
N classification	
N0	20 (9.8)
N1	104 (50.7)
N2	61 (29.8)
N3	20 (9.8)
Metastasis to retropharyngeal lymph nodes	139 (67.8)
Involvement of cranial nerves	46 (22.4)
Chemotherapy	
Neoadjuvant	2 (1.0)
Neoadjuvant plus concurrent	138 (67.3)
Concurrent	4 (2.0)
Concurrent plus adjuvant	1 (0.5)
Neoadjuvant plus concurrent plus adjuvant	49 (23.9)
Neoadjuvant plus adjuvant	8 (3.9)
Radiotherapy alone	3 (1.5)
Cetuximab	2 (1.0)
Nimotuzumab	33 (16.1)

Data in parentheses are percentages.

and abdominal region, and dental check. All patients were restaged according to the 8th edition of the AJCC staging system. The characteristics of the patients are shown in Table 1.

Imaging protocol and diagnostic criteria

All patients underwent MRI on a 1.5- or 3.0-T system (Magnetom Symphony/Verio, Siemens Healthcare, Erlangen, Germany) with a head-and-neck combined coil. The scan range covered from the suprasellar cistern to the inferior margin of the sternoclavicular joint. All patients underwent T1 weighted and fat-suppressed T2 weighted sequences. After bolus injection of 0.2 ml/kg gadopentetate dimeglumine, contrast-enhanced T1-weighted images were obtained. The thickness/slice gap was 5 mm/1mm for axial plane and 5 mm/0.5 mm for sagittal and coronal plane, respectively. Two radiologists independently evaluated all scans, and any disagreements were resolved by consensus.

Skull-base invasion was diagnosed using the following criteria: (a) a defect in the low signal intensity of the bone cortex on T1-weighted image and (b) high signal intensity marrow replacement by low signal intensity tissue on T1-weighted image (an obvious enhancement in the enhanced scan). The criterion for MRI involvement of the cavernous sinus was a change in contour or enlargement of the sinus [9,10].Lymph node (LN) involvement diagnosis was based on one or more of the following radiological criteria [11]: (a) lateral retropharyngeal lymph node with a minimal axial diameter (MID) in the largest plane of an individual node at least 5 mm and any node seen in the median retropharyngeal group, lymph nodes with a MID of at least 11 mm in the jugulodigastric region and 10 mm for all other cervical nodes, excluding the retropharyngeal group; (b) lymph nodes of any size with central necrosis or a contrast-enhancing rim; (c) the presence of three or more contiguous and confluent lymph nodes, each of which should have a MID of 8 or more; and (d) lymph nodes of any size with extracapsular spread, including the presence of indistinct nodal margins, irregular nodal capsular enhancement or infiltration into the adjacent fat or muscle. retropharyngeal node (RPN) and cervical LN location were assigned according to the Radiation Therapy Oncology Group (RTOG) guidelines [12,13]. Ten LN groups were assessed: RPNs, Level Ia, Ib, II, III, IV, Va, Vb, VI and supraclavicular fossa (SCF).

Treatment

All patients received definitive radiotherapy using IMRT techniques. A detailed description of IMRT has been previously reported (CTV1 encompassed the primary tumor and positive node regions. When the primary tumor was adjacent to critical normal tissue such as the brain stem or the spinal cord, at least a 1-mm margin between the primary tumor and the brainstem or the spinal cord was planned for CTV1.) [14,15]. Briefly, the dose prescribed was 69–70.4 Gy, 63–67.2 Gy, 60–60.8 Gy and 54–54.4 Gy in 30–32 fractions delivered over 6 weeks at the periphery of the PTVg, PTVnd, PTV1 and PTV2, respectively, using the simultaneous integrated boost technique. Most patients (n = 202, 98.5%) underwent platinum-based neoadjuvant, concurrent, or adjuvant chemotherapy.

Follow-up and statistical analysis

Follow-up was calculated from the day of radiation therapy completion to the date of the event or the last follow-up visit. All patients were followed up after the completion of radiotherapy: 1 month after the completion of radiotherapy, every 3 months in the first 2 years, every 6 months from Year 3 to Year 5, and annually thereafter.

The Statistical Package for Social Sciences, version 17.0 (SPSS Inc., Chicago, IL, USA), software was used for statistical analysis. The local failure-free survival (LFFS), regional failure-free survival (RFFS), distant failure-free survival (DFFS), and overall survival (OS) were estimated by use of the Kaplan–Meier method. LFFS, RFFS, DFFS, and OS were measured from Day 1 of treatment to the date of the event. Multivariate analysis were performed by using the Cox proportional hazards model to assess the prognostic significance of selected variables [age, sex, involvement of masticator space, involvement of cranial nerves (ICN), involvement of orbital wall, N classification, metastasis to retropharyngeal lymph nodes, targeted therapy]. All statistical tests were two sided, and $P < 0.05$ was considered to be statistically significant.

Results

The risk of tumor invasion into various anatomic sites

Cumulative incidence rates of tumor invasion into the anatomic sites surrounding the nasopharynx ranged from 8.8% to 97.6% (Table 2). According to the cumulative incidence rates of tumor invasion, we initially classified anatomic sites surrounding the nasopharynx into three risk grades: high risk (≥35%), medium risk (≥10–35%), and low risk (< 10%). It was concluded that the anatomic sites at high risk of tumor invasion were the middle/posterior skull base and the anatomic sites adjacent to the nasopharynx.

Skull-base invasion

To demonstrate characteristics of privileged pathways in nasopharyngeal carcinoma with intracranial extension, skull-base invasion was analyzed. Cumulative incidence rates of tumor invasion into the anatomic sites of skull base ranged from 24.4% to 97.6%, among which the most common route was through the foramen lacerum (Table 3). No significant difference was observed in terms of cumulative incidence rates between right and left skull-base invasion.

Tumor invasion into bilateral anatomical sites

With the exception of anatomic sites on or adjacent to the midline, such as the prevertebral muscle, foramen lacerum, petrous apex, base of