Grading of MRI–detected skull-base invasion in nasopharyngeal carcinoma with skull-base invasion after intensity-modulated radiotherapy

Yanru Feng, Caineng Cao, Qiaoying Hu and Xiaozhong Chen*

Abstract

Background: The aim of this study is to evaluate the prognostic value of grading MRI–detected skull-base invasion in nasopharyngeal carcinoma (NPC) with skull-base invasion after intensity-modulated radiotherapy (IMRT).

Methods: This study is a retrospective chart review of 469 non-metastatic NPC patients with skull-base invasion. Patients were classified as extensive skull-base invasion (ESBI) group and limited skull-base invasion (LSBI) group.

Results: Multivariate analysis showed that the skull-base invasion (LSBI vs. ESBI) was an independent prognostic predictor of progression free survival (PFS). The estimated 5-year local failure free survival (LFFS), distant metastasis free survival (DMFS), PFS, and overall survival (OS) rates for patients in the T3-LSBI and T3-ESBI group were 92.9% versus 93.5, 89.8% versus 86.1, 81.6% versus 76.4, and 93.5% versus 86.3%, respectively (P > 0.05).

Conclusion: Grading of MRI-detected skull-base invasion is an independent prognostic factor of NPC with skull-base invasion. It is scientific and reasonable for skull-base invasion as a single entity to be classified as T3 classification.

Keywords: Nasopharyngeal carcinoma, Skull-base invasion, Intensity-modulated radiotherapy, Prognostic value, American joint committee on Cancer staging system

Introduction

Nasopharyngeal carcinoma (NPC) is endemic in China and over 33,000 new patients were diagnosed in 2012 [1]. According to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system for NPC, T classification is based on the anatomical extent of the primary tumor and which has been proposed in the era of intensity-modulated radiotherapy (IMRT) [2, 3]. In the 8th edition of the AJCC staging system for NPC, skull-base invasion is classified as T3 disease [2].

With respect to the prognostic value of magnetic resonance imaging (MRI)-detected skull-base invasion for NPC, there are limited reports, especially, for patients treated by IMRT [4–6]. The aim of this study is to grade MRI–detected skull-base invasion in NPC with skull-base invasion and evaluate the prognostic value of the grading in the era of IMRT.

Materials and methods

Patients and patient workup

This study was approved by the Institutional Review Board to identify the patients diagnosed with NPC in our center. Because this study was a retrospective study, consent was not obtained and patient records were anonymized and de-identified prior to analysis. The medical records of consecutive 695 patients with previously untreated, biopsy-proven, non-metastatic NPC that was treated with IMRT between January 2007 and February 2012 in our center were retrospectively evaluated. Of these, 469 patients with skull-base invasions were included in this study. All patients wererestaged according to the 8th edition of the AJCC staging system. The pretreatment workup 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 and abdominal region, and dental check.

MR imaging
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. Two radiologists independently evaluated all scans, and any disagreements were resolved by consensus.

Skull-base invasion was diagnosed using the following criteria: (1) a defect in the low signal intensity of the bone cortex on T1-weighted image and (2) high signal intensity marrow replacement by low signal intensity tissue on T1-weighted image (an obvious enhancement in the enhanced scan) [5]. Patients were classified as limited skull-base invasion (LSBI) group if they had invasion of one or more of these sites including the pterygoid process, base of sphenoid bone, petrous apex, clivus, and foramen lacerum.

Patients were classified as extensive skull-base invasion (ESBI) group if they had invasion of one or more of these sites including the medial pterygoid plate, foramen ovale, pterygopalatin fossa, foramen rotundum, foramen magnum, hypoglossal canal, lateral pterygoid plate and jugular foramen [4, 6].

Treatment
All patients received definitive IMRT. A detailed description of IMRT has been previously reported [7]. Briefly, using the simultaneous integrated boost technique, 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 planning target volume (PTV) of primary tumor, PTV of metastatic lymph nodes, PTV of high-risk clinical target volume, and PTV of low-risk clinical target volume, respectively. Most patients (n = 459, 97.9%) received platinum-based neoadjuvant, concurrent, or adjuvant chemotherapy.

Follow-up and statistical analysis
Follow-up was calculated from the first day of treatment 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 IMRT, 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 χ², and Fisher exact t tests were used to compare the differences between the extensive skull-base invasion (ESBI) group and limited skull-base invasion (LSBI) group. The local failure free survival (LFFS), distant metastasis free survival (DMFS), progression free survival (PFS), and overall survival (OS) were estimated by use of the Kaplan–Meier method. LFFS, DMFS, PFS and OS were measured from Day 1 of treatment to the date of the event. Multivariate analysis was performed by using the Cox proportional hazards model. All statistical tests were two sided, and P < 0.05 was considered to be statistically significant.

Results
Grading of MRI-detected skull-base invasion
Incidence of skull-base invasion of each site in the 469 patients is shown in Table 1. Of the 469 patients, 185 patients were classified into the LSBI group, and 284 patients were classified into the ESBI group. The patient characteristics of the LSBI group and ESBI group are shown in Table 2.

Treatment outcomes
The median follow-up period was 61 months (range, 2–116 months). By the last follow-up, 22.8% (107/469) of patients developed treatment failure and more patients developed treatment failure in the ESBI group (26.1% vs. 17.8%, p = 0.038). The details of treatment failure are listed in Table 3. The estimated 5-year
LFFS, DMFS, PFS, and OS rates for the whole group were 91.9, 86.1, 76.6 and 87.5%, respectively. The estimated 5-year LFFS, DMFS, PFS, and OS rates for patients in the LSBI and ESBI group were 92.6% versus 90.8% (\( P = 0.296 \)), 90.0% versus 84.2% (\( P = 0.116 \)), 81.3% versus 73.6% (\( P = 0.032 \)), and 93.1% versus 84.0% (\( P = 0.024 \)), respectively (Fig. 1).

Univariate and multivariate analyses
The value of various potential prognostic factors including age, sex, skull-base invasion, T classification, N classification and concurrent chemotherapy on predicting LFFS, DMFS, PFS, and OS were evaluated. Univariate analysis by log-rank test showed that skull-base invasion (LSBI vs. ESBI) was associated with PFS (\( P = 0.042 \)), and OS (\( P = 0.024 \)) (Table 4). Multivariate analysis by Cox proportional-hazards model showed that the skull-base invasion (LSBI vs. ESBI) was an independent prognostic predictor of PFS (HR 1.523, 95%CI 1.006–2.306, \( P = 0.047 \)). (Table 5).

Discussion
In this study, we observed a high incidence of skull-base invasion in NPC and that grading of skull-base invasion is an independent prognostic factor of PFS in NPC after IMRT.

**Table 2** Patient Characteristics

| Characteristic       | LSBI group (N = 185) | ESBI group (N = 284) | \( P \)  |
|----------------------|----------------------|----------------------|----------|
| Sex                  | Male 113 (61.1)      | 209 (73.6)           | 0.004    |
|                      | Female 72 (38.9)     | 75 (26.4)            |          |
| Age (year)           | < 48 99 (53.5)       | 127 (44.7)           | 0.062    |
|                      | \( \geq 48 \) 86 (46.5) | 157 (55.3)           |          |
| Pathology classification | Keratinizing 2 (1.1) | 2 (0.7)              | 0.664    |
|                      | Non-keratinizing 183 (98.9) | 282 (99.3)           |          |
| T classification      | T3 174 (94.1)        | 83 (29.2)            | < 0.001  |
|                      | T4 11 (5.9)          | 201 (70.8)           |          |
| N classification      | N0 26 (14.1)         | 29 (10.2)            | 0.329    |
|                      | N1 74 (40.0)         | 136 (47.9)           |          |
|                      | N2 61 (33.0)         | 87 (30.6)            |          |
|                      | N3 24 (13.0)         | 32 (11.3)            |          |
| Overall stage         | III 152 (82.2)       | 73 (25.7)            | < 0.001  |
|                      | IVA 33 (17.8)        | 211 (74.3)           |          |
| Concurrent chemotherapy| Yes 176 (95.1)       | 270 (95.1)           | 0.975    |
|                      | No 9 (4.9)           | 14 (4.9)             |          |

**Table 3** Patterns of Treatment Failure for Patients with Skull-base Invasion after IMRT

| Treatment Failure Pattern | LSBI group (N = 185) | ESBI group (N = 284) | \( P \)  |
|---------------------------|----------------------|----------------------|----------|
| Distant only              | 12 (6.5)             | 34 (12.0)            | 0.051    |
| Bone                      | 3 (1.6)              | 9 (3.2)              |          |
| Liver                     | 3 (1.6)              | 9 (3.2)              |          |
| Lung                      | 5 (2.7)              | 11 (3.9)             |          |
| Bone and liver            | 0                    | 1 (0.4)              |          |
| Bone and lung             | 1 (0.5)              | 2 (0.7)              |          |
| Lung and liver            | 0                    | 1 (0.4)              |          |
| Other                     | 0                    | 1 (0.4)              |          |
| Regional and distant      | 4 (2.2)              | 4 (1.4)              |          |
| Local and distant         | 2 (1.1)              | 3 (1.1)              |          |
| Local, regional, and distant | 0          | 1 (0.4)              |          |
| Local only                | 6 (3.2)              | 18 (6.3)             |          |
| Regional only             | 6 (3.2)              | 12 (4.2)             |          |
| Local and regional        | 3 (1.6)              | 2 (0.7)              |          |
| Total                     | 33 (17.8)            | 74 (26.1)            | 0.038    |

**T-classification category of the grading in patients with T3 classification**

According to the 8th AJCC staging system, 257 patients were classified as T3 classification. Of these, 83 (32.3%) patients developed extensive skull-base invasion (T3-ESBI) and 174 (70.8%) didn’t (T3-LSBI). The estimated 5-year LFFS, DMFS, PFS, and OS rates for patients in the T3-LSBI and T3-ESBI group were 92.9% versus 93.5% (\( P = 0.997 \)), 89.8% versus 86.1% (\( P = 0.562 \)), 81.6% versus 76.4% (\( P = 0.280 \)), and 93.5% versus 86.3% (\( P = 0.299 \)), respectively. The estimated 5-year LFFS, DMFS, PFS, and OS rates for the patients with T4 classification were 89.5, 83.2, 72.6 and 83.2%, respectively (Fig. 2). No significant difference was observed in terms of LFFS, DMFS, PFS, and OS between patients with T3-ESBI and those with T4 classification (\( P > 0.05 \)). When extensive skull-base invasion was classified as T3 classification, the segregation of survival curves between the T3 and T4 classifications was clearly displayed.

---

*LSBI* limited skull-base invasion, *ESBI* extensive skull-base invasion

---

* Lung, liver, mediastinal and retroperitoneal lymph nodes, and left adrenal gland

---

---
Kaplan–Meier survival curves for patients in the ESBI and LSBI groups. (ESBI, extensive skull-base invasion; LSBI, limited skull-base invasion; LFFS, local failure free survival; DMFS, distant metastasis free survival; PFS, progression free survival; OS, overall survival)

Table 4 Univariate Analysis of Variables Correlated with Various Clinical Endpoints

| Characteristic                  | 5y-LFFS | P     | 5y-DMFS | P     | 5y-PFS | P     | 5y-OS | P     |
|--------------------------------|---------|-------|---------|-------|--------|-------|-------|-------|
| Sex                            |         |       |         |       |        |       |       |       |
| Male                           | 89.7    | 0.052 | 84.9    | 0.359 | 73.7   | 0.017 | 86.2  | 0.301 |
| Female                         | 95.2    |       | 88.6    |       | 82.7   |       | 90.1  |       |
| Age (y)                        |         |       |         |       |        |       |       |       |
| ≥ 48                           | 89.6    | 0.245 | 85.9    | 0.866 | 75.0   | 0.646 | 83.3  | 0.037 |
| <48                            | 93.2    |       | 86.3    |       | 78.0   |       | 91.5  |       |
| Skull-base invasion            |         |       |         |       |        |       |       |       |
| LSBI                           | 92.6    | 0.296 | 90.0    | 0.116 | 81.3   | 0.032 | 93.1  | 0.024 |
| ESBI                           | 90.8    |       | 84.2    |       | 73.6   |       | 84.0  |       |
| T classification               |         |       |         |       |        |       |       |       |
| T3                             | 93.1    | 0.093 | 88.5    | 0.036 | 79.9   | 0.042 | 90.9  | 0.014 |
| T4                             | 89.5    |       | 83.2    |       | 72.6   |       | 83.2  |       |
| N classification               |         |       |         |       |        |       |       |       |
| N0                             | 92.2    | 0.909 | 94.1    | < 0.001 | 84.7 | 0.066 | 87.7  | 0.879 |
| N1                             | 90.7    |       | 89.3    |       | 79.2   |       | 89.9  |       |
| N2                             | 91.5    |       | 84.3    |       | 73.6   |       | 86.3  |       |
| N3                             | 93.7    |       | 69.9    |       | 66.4   |       | 80.8  |       |
| Overall Stage (the 8th AJCC)   |         |       |         |       |        |       |       |       |
| III                            | 92.7    | 0.220 | 91.1    | 0.001 | 81.8   | 0.008 | 92.4  | 0.003 |
| IVa                            | 90.4    |       | 81.5    |       | 71.9   |       | 82.7  |       |
| Concurrent chemotherapy        |         |       |         |       |        |       |       |       |
| Yes                            | 91.3    | 0.585 | 86.4    | 0.471 | 75.8   | 0.924 | 87.7  | 0.706 |
| No                             | 94.1    |       | 80.9    |       | 76.7   |       | 84.7  |       |

ESBI, extensive skull-base invasion; LSBI, limited skull-base invasion; LFFS, local failure free survival; DMFS, distant metastasis free survival; PFS, progression free survival; OS, overall survival.
MRI is recommended as the preferred modality for NPC staging and has proven to be more sensitive in detecting early infiltration of tumor cells into the bone marrow [8–10]. Based on MRI, skull base erosion may be observed in 50–70% of NPC [4–6, 9, 10]. In this study, 469/695 (67.5%) patients with skull-base invasions were reported.

In the era of IMRT, MRI-detected skull-base invasion was not observed to be an independent prognostic factor for NPC. However, the classification of skull-base invasion (LSBI vs. ESBI) was an independent prognostic factor in T3 (according to the 7th edition of the AJCC staging system) NPC patients in terms of the 5-year OS (P = 0.028), DMFS (P = 0.032), and PFS rates (P = 0.002) [6]. The result of this study indicates that LSBI was associated with a better prognosis in terms of PFS compared to ESBI. Foramen ovale, foramen rotundum, hypoglossal canal and jugular foramen all belong to the ESBI group and are neural foramina. These areas were frequently related with MRI-detected cranial nerve involvement, which was associated with distant metastasis and poor survival [11]. As distant metastasis is the most commonly failure pattern for NPC treated by IMRT, especially, for patients with ESBI [6, 12]. Although most ESBI patients (277/284; 97.5%) in our study were treated by chemoradiotherapy, they still had an unsatisfactory survival rate. Further studies including more intensive systemic approach or newer agents are needed to improve treatment outcome for these patients.

In the 7th edition of the AJCC staging system for NPC, patients with skull-base invasion were classified as T3, and this classification remains in the 8th edition of the AJCC staging system. No significant difference was observed in terms of LFFS, DMFS, PFS, and OS between patients with T3-ESBI and those with T3-LSBI (P > 0.05), which was probably associated with the aid of IMRT, MRI, and the use of chemotheraphy [12–14]. In addition, when ESBI was classified as T3 classification, the segregation of survival curves between the T3 and T4 classifications was clearly displayed. In a sense, this study demonstrated that it was more suitable for skull-base invasion as a single entity to be classified as T3 classification.

There are several limitations in the current study, including the inclusion of patients treated at a single center and the retrospective nature of the study design. The effect of skull-base invasion on the prognosis and staging of patients with NPC should be further confirmed by other cohorts from different centers.

| Table 5 Multivariate Analysis of Variables Correlated with Various Clinical Endpoints |
|---|---|---|---|
| Endpoint | Item | HR | 95% CI | P |
| DMFS | T3 vs. T4 | 1.741 | 1.039–2.916 | 0.035 |
| N0–1 vs. N2–3 | 2.272 | 1.347–3.829 | 0.002 |
| PFS | N0–1 vs. N2–3 | 1.621 | 1.107–2.374 | 0.013 |
| Male vs. Female | 0.620 | 0.392–0.980 | 0.041 |
| LSBI vs. ESBI | 1.523 | 1.006–2.306 | 0.047 |
| OS | T3 vs. T4 | 1.910 | 1.079–3.382 | 0.026 |

HR hazard ratio, CI confidence interval, ESBI extensive skull-base invasion, LSBI limited skull-base invasion, DMFS distant metastasis free survival, PFS progression free survival, OS overall survival.

Fig. 2 Kaplan–Meier survival curves for patients in the T3-ESBI, T3-LSBI and T4 groups. (ESBI, extensive skull-base invasion; LSBI, limited skull-base invasion; LFFS, local failure free survival; DMFS, distant metastasis free survival; PFS, progression free survival; OS, overall survival)
Conclusion
Grading of MRI-detected skull base erosion is an independent prognostic factor of NPC treated by IMRT. Our results confirm that it is scientific and reasonable for skull-base invasion as a single entity to be classified as T3 classification in the AJCC staging system for NPC.

Abbreviations
AJCC: American Joint Committee on Cancer; CI: Confidence interval; CT: Computed tomography; DMFS: Distant metastasis free survival; ESBI: Extensive skull-base invasion; HR: Hazard ratio; IMRT: Intensity-modulated radiotherapy; LFFS: Local failure free survival; LSBI: Limited skull-base invasion; NPC: Nasopharyngeal carcinoma; OS: Overall survival; PFS: Progression free survival; PTV: Planning target volume

Funding
The present study was supported by Zhejiang Province Medical and Health Science and Technology Project [No. 2017182785, 2018244679].

Availability of data and materials
Our data cannot be made publicly available for ethical reasons. Data are from the present study whose authors may be contacted at chenxiaozhong2016@163.com or Department of Radiation Oncology, Zhejiang Cancer Hospital, Hangzhou, China.

Authors’ contributions
Conceived and designed the experiments: YF CC QH XC. Performed the experiments: YF CC QH XC. Analyzed the data: YF CC QH XC. Contributed reagents/materials/analysis tools: YF CC QH XC. Wrote the paper: YF CC XC. Gave many suggestions in the formation of the manuscript: CC QH XC. All authors read and approved the final manuscript.

Ethics approval and consent to participate
This study obtained approval from the Independent Ethics Committee of the Zhejiang Cancer Hospital to identify patients diagnosed with nasopharyngeal carcinoma in our center. Because this was a retrospective study, consent was not obtained and patient records were anonymized and de-identified before analysis.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References
1. IARC. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. 2012.
2. Amin MB, et al. AJCC Cancer staging manual. 8th ed. New York: Springer; 2017.
3. Pan JJ, et al. Proposal for the 8th edition of the AJCC/UICC staging system for nasopharyngeal cancer in the era of intensity-modulated radiotherapy. Cancer. 2016;122(4):546–58.
4. Chen L, et al. Grading of MRI-detected skull-base invasion in nasopharyngeal carcinoma and its prognostic value. Head Neck. 2011;33(9):1309–14.
5. Li YZ, et al. Nasopharyngeal cancer: impact of skull base invasion on patients prognosis and its potential implications on TNM staging. Eur J Radiol. 2013;82(3):107–11.
6. Cheng YK, et al. MRI-detected skull-base invasion: prognostic value and therapeutic implication in intensity-modulated radiotherapy treatment for nasopharyngeal carcinoma. Strahlenther Onkol. 2014;190(10):905–11.
7. Jin T, et al. Interim analysis of a prospective randomized non-inferiority trial of cisplatin and fluorouracil induction chemotherapy with or without docetaxel in nasopharyngeal carcinoma. Oncotarget. 2016. https://doi.org/10.18632/oncotarget.10903.
8. Chiua ML, et al. Nasopharyngeal carcinoma. Lancet. 2016;387(10022):1012–24.
9. Chong VF, Fan YF. Skull base erosion in nasopharyngeal carcinoma: detection by CT and MRI. Clin Radiol. 1996;51(9):625–31.
10. Ng SH, et al. Nasopharyngeal carcinoma: MRI and CT assessment. Neuroradiology. 1997;39(10):741–6.
11. Liu L, et al. Prognostic impact of magnetic resonance imaging-detected cranial nerve involvement in nasopharyngeal carcinoma. Cancer. 2009;115(9):1995–2003.
12. Cao CN, et al. Update report of T4 classification nasopharyngeal carcinoma after intensity-modulated radiotherapy: an analysis of survival and treatment toxicities. Oral Oncol. 2015;51(2):190–4.
13. Cao C, et al. Magnetic resonance imaging-detected intracranial extension in the T4 classification nasopharyngeal carcinoma with intensity-modulated radiotherapy. Cancer. 2017;49(2):518–25.
14. Lee AW, et al. Management of nasopharyngeal carcinoma: current practice and future perspective. J Clin Oncol. 2015;33(29):3356–64.