

A simplified T classification based on the 8th edition of the UICC/AJCC staging system for nasopharyngeal carcinoma

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Objective: This study aimed to establish a simplified T classification based on the 8th edition of the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) staging system for nasopharyngeal carcinoma (NPC).

Methods: In total, 325 patients with NPC were included in this study. All patients underwent magnetic resonance imaging, and the staging criteria were recorded. These patients were subjected to staging with the 8th edition of the UICC/AJCC staging system for NPC.

Results: Involvement of the oropharynx, nasal cavity, adjacent soft tissue (medial pterygoid, lateral pterygoid, and prevertebral muscles), cervical vertebra, orbit, and hypopharynx were always accompanied by other equivalently or more advanced T-stage classifications. All cases with involvement of the paranasal sinuses showed skull base erosion. The majority of cases with involvement of the pterygoid structure showed skull base erosion.

Conclusion: According to the simplification principle, the following new T classification based on the 8th edition of the UICC/AJCC staging system was established: T1, tumor confined to nasopharynx, or beyond the nasopharynx without parapharyngeal involvement; T2, tumor with extension to the parapharyngeal space; T3, tumor with infiltration to bony structures at the skull base; T4, tumor with intracranial extension, involvement of the cranial nerves or parotid gland, and/or extensive soft tissue infiltration beyond the lateral surface of the lateral pterygoid muscle. Validation with a large series of patients is needed.

Keywords: nasopharyngeal cancer, TNM staging system, T classification

Introduction

An accurate staging system is crucial for the treatment of cancer, evaluation of therapeutic effects, and prediction of prognosis. It is also the basis for academic communication and clinical research among different centers. Since the 7th edition of the International Union against Cancer/American Joint Committee on Cancer (UICC/AJCC) staging system was internationally recommended, research on nasopharyngeal carcinoma (NPC) has increased significantly. This research has produced a positive impact on the diagnosis, treatment, and scientific understanding of NPC worldwide. However, with the development of diagnostic imaging and radiation therapy technology, especially intensity-modulated radiotherapy (IMRT), the limitations of the 7th edition staging system became obvious, and revision was clearly needed. The UICC and AJCC committee issued the 8th edition of the UICC/AJCC staging system for NPC in 2017. This edition was more comprehensive, incorporating the strengths of both the 7th edition and the Chinese 2008 staging systems. Several

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studies have confirmed that the 8th edition staging system can predict the prognosis of NPC patients more accurately than the 7th edition in the IMRT era.^{1–3}

There are four main adjustments to the T classifications in the 8th edition: 1) T0 is added for Epstein-Barr virus-positive, unknown primary lesions with cervical lymph node involvement. 2) Adjacent muscle involvement (including medial pterygoid, lateral pterygoid, and prevertebral muscles) is now designated as T2. 3) The previous T4 criteria “masticator space” and “infratemporal fossa” are now replaced by specific descriptions of soft tissue involvement to avoid ambiguity. 4) Invasion of cervical vertebra or pterygoid structures invaded is added as T3; and invasion of the parotid gland is added as a T4 criterion.⁴ However, popularization and application of the 8th edition have been greatly limited due to the complexity of its T classification, which uses 17 anatomic structures. Here, we performed a retrospective study that enrolled 325 patients with NPC who were staged by magnetic resonance imaging (MRI) according to the 8th edition of the UICC/AJCC staging system. The aim of this study was to establish a simplified T classification based on the 8th edition of the UICC/AJCC staging system for NPC.

Methods

Patients

We retrospectively reviewed the medical records of 325 patients with newly diagnosed, biopsy-proven, non-metastatic NPC at our center. Among them, 235 were male, and 90 were female. The median age was 46 years (range, 15–81 years of age). All patients were required to undergo a detailed physical examination, hematology and biochemistry profiles, nasopharyngeal fiberscope examination, chest radiography, abdominal ultrasound, whole-body bone scan, MRI of the nasopharynx and neck, and/or [18F] fluorodeoxyglucose positron emission tomography and computed tomography (PET/CT). The patient clinical characteristics are shown in Table 1.

Imaging

MRI was performed with a 1.5-T system (GE Signa Infinity Echospeed Plus 1.5T). The region from the suprasellar cistern to the inferior margin at the sternal end of the clavicle was examined with a head-and-neck combined coil. T1-weighted fast spin-echo images in the axial, coronal, and sagittal planes and T2-weighted fast spin-echo images in the axial plane were obtained before injection of contrast material. After intravenous injection, T1-weighted

Table 1 Characteristics of 325 patients with nasopharyngeal carcinoma

| Characteristics | No. of patients (%) |
|------------------|---------------------|
| Age (years) | |
| Median | 46 |
| Range | 15–81 |
| Gender | |
| Male | 235 (72.3) |
| Female | 90 (27.7) |
| Histology (WHO) | |
| I | 2 (0.6) |
| II/III | 323 (99.4) |
| T classification | |
| T1 | 45 (13.8) |
| T2 | 138 (42.5) |
| T3 | 84 (25.8) |
| T4 | 58 (17.8) |
| N classification | |
| N0 | 12 (3.7) |
| N1 | 91 (28.0) |
| N2 | 132 (40.6) |
| N3 | 90 (27.7) |
| Stage | |
| I | 10 (3.1) |
| II | 54 (16.6) |
| III | 128 (39.4) |
| IVa | 133 (40.9) |

axial and sagittal sequences and T1-weighted fat-suppressed coronal sequences were performed sequentially. All data were uploaded to the PACS system.

Image assessment and clinical staging

The MRI images for each patient were independently reviewed on the PACS system by two senior physicians. All of the staging criteria mentioned in the 8th edition of the UICC/AJCC staging system was recorded. These patients were subjected to the staging with the 8th edition of the UICC/AJCC staging system for NPC. In controversial cases, agreement was reached by consensus.

Diagnostic criteria

Nasal cavity invasion was defined as the tumor invading the bony nasal septum, turbinate, or extension to the line of bilateral pterygopalatine fossa.^{5–8} Oropharynx involvement was defined as tumor involvement below the plane of the superior surface of the soft palate or the lower margin

of C1.^{5–8} Parapharyngeal space invasion was defined as tumor involvement exceeding the pharyngobasilar fascia.⁸ Hypopharyngeal involvement was defined as tumor detection below the plane of the superior border of the hyoid bone or the lower margin of C3.^{6,7} The criterion for orbit invasion was tumor extension to the orbital apex, the inferior orbital fissure, or the superior orbital fissure.⁹ The criterion for pterygoid structure invasion included invasion of the medial/lateral pterygoid plate, pterygoid body/process, pterygomaxillary fissure, or pterygopalatine fossa.¹⁰ Bony structures at the skull base were not included in any part of the pterygoid process (eg, medial plate, lateral plate, and pterygoid base) in the 8th edition. Cranial nerve involvement was defined by imaging (MRI) and clinical examination with the observation of simultaneous cranial nerve invasion and paralysis.¹¹

Results

Incidence of the staging criteria on the T classification

According to the T classification of the 8th edition of the UICC/AJCC staging system, the distribution of T1–T4 patients was 13.8%, 42.5%, 25.8%, and 17.8%, respectively. The incidence rates for the staging criteria of the T classification in NPC patients are shown in Table 2. The nasopharynx had the highest involvement rate (100%),

followed by the parapharyngeal space (87.1%) and the medial pterygoid muscle (54.2%). The incidences of involvement of the cervical vertebra, orbit, hypopharynx, and lateral surface of the lateral pterygoid muscle were the lowest (all <5%).

Relationships among the T staging criteria

In this cohort of patients, nasal cavity or oropharynx invasion was almost always concomitant with nasopharynx invasion in the T1 category. For the T2 category, all cases of adjacent soft tissue (medial pterygoid, lateral pterygoid, prevertebral muscles) invasions showed parapharyngeal invasion. In the T3 category, all cases of involvement of the paranasal sinuses showed skull base erosion, which was also found in a majority of cases with pterygoid structure invasion. In addition, involvement of the cervical vertebra, orbit, and hypopharynx was always accompanied by other equivalently or more advanced T stage criteria. The relationships among the T staging criteria in NPC patients are shown in Table 2.

Recommendation of a simplified T classification system for NPC based on the 8th edition of the UICC/AJCC staging system

According to the simplification principle, the following staging criteria, including involvement of the oropharynx,

Table 2 Incidences of T staging criteria and the relationships among them, n (%)

| | Staging criteria | Cases | Accompanied by equivalent/higher T stage criteria | Not accompanied by equivalent/higher T stage criteria |
|----|--|--|---|---|
| T1 | Nasopharynx Oropharynx Nasal cavity | 325 (100) 32 (9.8) 61 (18.8) | 283 (87.1) 32 (100) 61 (100) | 42 (12.9) 0 0 |
| T2 | Parapharyngeal space Medial pterygoid muscle Lateral pterygoid muscle Prevertebral muscle | 283 (87.1) 176 (54.2) 51 (15.7) 92 (28.3) | 209 (73.9) 176 (100) 51 (100) 92 (100) | 74 (26.1) 0 0 0 |
| T3 | Bony structures at the skull base Cervical vertebra Pterygoid structures Paranasal sinuses | 131 (40.3) 13 (4.0) 49 (15.1) 89 (27.4) | 96 (73.3) 13 (100) 45 (98.8) 89 (100) | 35 (26.7) 0 4 (1.2) 0 |
| T4 | Intracranial Cranial nerves Hypopharynx Orbit Parotid gland Soft tissue infiltration beyond the lateral surface of the lateral pterygoid muscle | 35 (10.8) 24 (7.4) 3 (0.9) 10 (3.1) 21 (6.5) 14 (4.3) | 23 (65.7) 20 (83.3) 3 (100) 10 (100) 12 (57.1) 11 (78.6) | 12 (34.3) 4 (16.7) 0 0 9 (42.9) 3 (21.4) |

Table 3 Recommended simplified T classification based on the 8th edition of the UICC/AJCC staging system for nasopharyngeal carcinoma

| | The T classification of the 8th edition of the UICC/AJCC staging system | A simplified T classification based on the 8th edition of the UICC/AJCC staging system |
|----|---|---|
| T0 | No tumor identified, but EBV-positive cervical node(s) involvement | No tumor identified, but EBV-positive cervical node(s) involvement |
| T1 | Tumor confined to nasopharynx, or extension to oropharynx and/or nasal cavity without parapharyngeal involvement | Tumor confined to nasopharynx, or beyond the nasopharynx without parapharyngeal involvement |
| T2 | Tumor with extension to parapharyngeal space and/or adjacent soft tissue involvement (medial pterygoid, lateral pterygoid, prevertebral muscles) | Tumor with extension to parapharyngeal space |
| T3 | Tumor with infiltration of bony structures at skull base, cervical vertebra, pterygoid structures, and/or paranasal sinuses | Tumor with infiltration of bony structures at skull base |
| T4 | Tumor with intracranial extension, involvement of cranial nerves, hypopharynx, orbit, parotid gland, and/or extensive soft tissue infiltration beyond lateral surface of the lateral pterygoid muscle | Tumor with intracranial extension, involvement of cranial nerves, parotid gland, and/or extensive soft tissue infiltration beyond lateral surface of the lateral pterygoid muscle |

Abbreviations: UICC/AJCC, Union for International Cancer Control/American Joint Committee on Cancer; EBV, Epstein-Barr virus.

nasal cavity, adjacent soft tissue (medial pterygoid, lateral pterygoid, and prevertebral muscles), cervical vertebra, paranasal sinuses, hypopharynx, and orbit, can be removed from the T classification of the 8th edition. The skull base and pterygoid structures can also be merged with bony structures in T3. These results suggested that excluding the staging criteria mentioned above may not affect the constituent ratio of T classifications using the 8th edition of the UICC/AJCC staging system. Therefore, we recommended a simplified T classification based on the 8th edition of the UICC/AJCC staging system for NPC (Table 3).

Discussion

When Pan et al¹⁰ proposed the 8th edition of the UICC/AJCC staging system for NPC, the recommendations by contemporary series were validated in a large series of patients who were staged with MRI and treated with IMRT from two major centers (in Hong Kong and Fujian, China), before attaining consensus among international multidisciplinary experts. A significant improvement in the 8th edition was the optimal balance between clinical practicability and global applicability. However, the main weaknesses of the T classification in the 8th edition included the following: 1) more staging criteria while the relationship between them was ignored. 2) No significant difference between adjacent T stages.

Further simplification of T classification is suggested and acquiring information on the incidence of and relationship between the criteria is important. This study is the first to establish a simplified T classification based on the 8th edition for NPC.

In a retrospective analysis of 2,687 newly diagnosed NPC patients based on the 6th edition staging system, Lee et al¹² found that there were no significant differences between the T2a (nasal cavity/oropharynx involvement without parapharyngeal extension) and T1 categories in the risk of disease failure or survival rate and proposed that T2a should be categorized as T1. Subsequently, Low et al¹³ and Liu et al¹⁴ also reported that T2a had a similar and favorable prognosis to T1. Based on these findings, the 7th and 8th edition of the UICC/AJCC staging system classified the extension of the nasal cavity/oropharynx as T1 and the parapharyngeal space as T2. Chen et al¹⁵ retrospectively analyzed 1,573 patients staged by the Chinese system (2008 version) for NPC; they found that among the cases with nasal cavity invasion, 90.46% showed the involvement of the structures seen in the T3 or T4 stage, which was found in all cases with oropharynx invasion. Lin et al¹⁶ also reported that the involvement of oropharynx and nasal cavity was 100% accompanied with other same or more advanced T-stage classifications according to the 2008 Chinese edition. These findings were consistent with our results. Using the 8th edition, our results demonstrated that all cases of involvement of nasal cavity or oropharynx were associated with the erosion of other criteria that belonged to the same or higher T classification. Consequently, we suggested that the involvement of the nasal cavity/oropharynx can be removed from the T1 subgroup.

The ambiguous definition of the infratemporal fossa/masticator space, which was regarded as a T4 criterion in the 7th edition, has been replaced by a specific description of soft tissue involvement in the 8th edition. Zhang et al¹⁷ proposed that the masticator space involvement in NPC should be

graded as medial (stage T2 disease) or lateral (stage T4 disease). Sze et al¹⁸ reported that the involvement of the medial pterygoid and/or lateral pterygoid did not lead to poor survival as in patients with extensive infiltration beyond the lateral surface of the lateral pterygoid muscle. The authors suggested that the involvement of the medial pterygoid and/or lateral pterygoid muscle alone should be classified as T2 disease. Pan et al¹⁰ found that patients with medial pterygoid and/or lateral pterygoid muscle invaded had similar overall survival (OS) to those with parapharyngeal space and prevertebral muscle invaded. Therefore, they proposed a downstaging of adjacent soft tissue involvement (medial pterygoid, lateral pterygoid, prevertebral muscles) to T2 stage. They suggested that this would lead to better distinction of hazards between different T categories. This recommendation was accepted by the AJCC/UICC 8th edition staging system for NPC. The parapharyngeal space was the first space where the tumors extended from the pharyngeal mucosa.¹⁹ The tumors infiltrate the tough pharyngobasilar fascia into the parapharyngeal space, and then spread laterally to the adjacent soft tissue (medial pterygoid, lateral pterygoid, prevertebral muscles). In other words, extension into the parapharyngeal space is the basis of adjacent soft tissue involvement. Our study showed that all cases of involvement of the adjacent soft tissue were accompanied by parapharyngeal extension. Therefore, based on the principle of stage simplification, we recommend that the T2 category may eliminate the adjacent soft tissue involvement.

Involvement of the pterygoid structures (including the medial/lateral pterygoid plate, pterygoid body/process, pterygomaxillary fissure, and pterygopalatine fossa), mentioned for the first time in the 8th edition as a T3 criterion, is associated with a similar prognosis to that of skull base bony erosions.¹⁰ However, the pterygoid structure has not been widely accepted in clinical practice. The reason for writing an unfamiliar anatomical concept into the stage system is not enough. Our research showed that the incidence of pterygoid structure involvement was 15.1%, most of which were combined with skull base bony erosions. It is more reasonable to merge skull base and pterygoid structure to bony structures at skull base, which were regarded as T3 stage.

Involvement of the paranasal sinuses are important landmarks of local tumor extension surrounding the nasopharynx in the anterior and superior directions. Tumors with extension to the paranasal sinuses were staged as T3 in the 8th edition staging system. However, how paranasal sinus invasion should be classified remains controversial. Zhang et al²⁰ retrospectively analyzed 1,811 patients who treated with

IMRT and found that ethmoid sinus or maxillary sinus invasion had a higher risk of local failure than sphenoid sinus invasion alone. Therefore, the authors recommended that sphenoid sinus invasion alone should be classified as T3 stage and ethmoid sinus or maxillary sinus involvement as T4 stage. Other studies have examined the same issue in patients receiving IMRT. Wang et al²¹ and Cao et al²² suggested that NPC with involvement of paranasal sinus should be classified as T4 stage. MRI diagnostic criteria for the invasion of the paranasal sinuses included the following: tumors that had invaded into the sinus cavity connected with a primary nasopharyngeal lesion and with bone destruction of the wall of the sinus and presentation with the same signal intensity characteristics as revealed in the primary lesion.²³ In clinical practice, nasal sinus wall invasion is classified as skull base bone invasion, while a tumor invading the sinus wall into the sinus cavity is categorized as paranasal sinus invasion.¹⁵ Tian et al²⁴ reported that 100% of patients revealed damage of the sinus wall with paranasal sinus invasion in MRI images. That is, skull base bone destruction is the only way for paranasal sinus invasion to occur. Thus, it is rational to recommend that the paranasal sinuses should be eliminated from the staging system since both the paranasal sinuses and the skull base are staged as T3 criteria.

In the T classification of the 8th edition, cervical vertebra invasion was added as T3; and parotid gland invasion was added as T4. Pan et al¹⁰ found that the subgroup of patients with extensive soft tissue involvement (infiltration beyond the lateral surface of the lateral pterygoid, hypopharynx, orbital structures, and parotid gland) but no other T4 criteria had poor OS similar to that of the subgroup with intracranial extension and/or cranial nerve palsy. However, several studies have found that the invasion rate of the hypopharynx, orbit, and cervical vertebra of NPC were very low.^{5,16,25,26} Based on the above results, the orbit and cervical vertebra were excluded in the Chinese system (2008 version) for NPC.²⁷ Our research was consistent with the results of these studies. We found that all patients with involvement of orbit, hypopharynx, and cervical vertebra must be presented with other staging criteria in the same T classification or a higher T level in the 8th edition. These results suggested that excluding the staging criteria mentioned above in the staging system may not affect the constituent ratio of T classification. Although more anatomical structures can provide more information about involvement, it does not meet the simplified requirements of the stage system and limits the clinical application of the 8th edition. Therefore, we

propose to delete these staging criteria of cervical vertebra, orbit, and hypopharynx in the T classification of the 8th edition. Furthermore, the parotid gland invasion was first described as a T4 criterion in the 8th edition. In this study, the parotid gland invasion was identified in 21 cases. Among these 21 cases, 9 cases were considered as the T4 criteria alone. However, further studies are needed to directly confirm the prognostic role of parotid gland invasion in advanced NPC patients.

In conclusion, we suggest that the involvement of the following staging criteria can be removed from the T classification based the 8th edition of the UICC/AJCC staging system for NPC: oropharynx, nasal cavity, adjacent soft tissue (medial pterygoid, lateral pterygoid, and prevertebral muscles), cervical vertebra, paranasal sinuses, hypopharynx, and orbit. We also suggest that the skull base and pterygoid structures can be merged with bony structures as T3 criteria. According to the simplification principle, the following new T classification based on the 8th edition of the UICC/AJCC staging system was established: T1, tumor confined to nasopharynx, or beyond the nasopharynx without parapharyngeal involvement; T2, tumor with extension to the parapharyngeal space; T3, tumor with infiltration to bony structures at the skull base; T4, tumor with intracranial extension, involvement of the cranial nerves or parotid gland, or extensive soft tissue infiltration beyond the lateral surface of the lateral pterygoid muscle. However, this study has certain limitations. First, this was a retrospective study. Second, the sample size was small. Therefore, validation in a large series of patients is needed.

Ethical statement

The study was approved by the Institutional Ethnic Committee of Nanhai Hospital Affiliated to Southern Medical University (NO. 2017030). This study retrospectively analyzed the patient's MRI images, did not implement any intervention measures, and did not have any impact on the patient's outcome. Therefore, the informed consent of the patients was not required. The patient data in this study was anonymously managed in all stages, including stages of data cleaning and statistical analyses. This study was conducted in accordance with the Declaration of Helsinki.

Disclosure

The authors report no conflicts of interest in this work.

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