Evolution of the Chinese staging system for nasopharyngeal carcinoma

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Abstract: The clinical treatment of nasopharyngeal carcinoma (NPC) in China started in 1940s is based on our own clinical staging system. In 1965, we established the first TNM staging system for NPC. Advances in technology and therapy led to continuous updates in clinical staging. Currently, the Chinese staging system of 2008 is commonly used in China. Compared with the 7th edition of the American Joint Committee on Cancer (AJCC) staging system, which is widely used internationally, the N classification was based on magnetic resonance imaging (MRI) as well as the lymph node criteria of the Radiation Therapy Oncology Group (RTOG) consensus guidelines. However, several studies showed that these two staging systems were associated with limitations. Additional international studies from different cancer centers are needed to improve and evolve a universally accepted staging system for NPC.

Keywords: Nasopharyngeal carcinoma (NPC); staging system; Chinese 2008 staging system

Introduction

In mainland China, the first case of nasopharyngeal carcinoma (NPC) was identified in 1930s. It was later found that NPC was mainly prevalent in five provinces of southern China including Guangdong, Guangxi, Hunan, Jiangxi, and Fujian. Radiotherapy (RT) is the primary treatment modality for NPC due to its complex anatomic location, biological behavior and high radiosensitivity. The RT of NPC in China has been used since 1940s. Decades of development, advances in external irradiation technology, RT software, and clinical experience, has improved survival rates up to 80% (1-3).

An accurate staging system holds the key to successful treatment strategies, prediction of clinical outcomes, and international communication (4). With advances in diagnostic imaging and radiation technology, as well as the biological features of NPC, the revised Chinese staging system for NPC evolved from experience to evidence-based practice.

History of Chinese staging system for NPC

Although China developed independent criteria for clinical staging of NPC since 1959, the first TNM staging system was established in Shanghai in 1965. It was based on the extent of tumor as an indicator of prognosis. Clinical experience suggests that NPC patients with large, fixed cervical lymph nodes or supraclavicular lymph node metastases had shorter survival time. The symptoms of cranial nerve palsy were often caused by lymphadenectasis. Thus, four posterior cranial nerves (IX, X, XI and XII) were also defined as N disease for several years. In 1979, it was

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revised into Changsha staging system in which the cranial nerves involvement was finally defined as T classification. In 1981, after reviewing the Changsha and Ho's staging system [1978] (5), the Guangzhou staging system was established. In a major update, the tumor confined to nasopharynx was assigned T1 irrespective of the involvement of the lateral. Additionally, the size of lymph node was considered as an N classification factor (6) (*Table 1*).

Chinese 1992 staging system based on computed tomography (CT)

The Chinese 1992 staging system was based on the retrospective data of Sun Yat-sen University reported by Min *et al.* (1). Four hundred and twenty-one NPC patients undergoing CT scan before primary definitive RT between 1985 and 1987 were enrolled and analyzed. All the potential prognostic factors that affect T and N classifications including physical examination, tumor involvement in CT scan and host factors at the time of the patient presentation were included in the multivariate analysis with Cox proportional hazards. The minor and major stratification risk factors were obtained to develop the new staging criteria. The implementation of this staging system established a precedent for evidence-based clinical staging system in China, and actively promoted the study of NPC.

In early 1990s, the two-dimensional conventional RT with two to three facial fields combined with an anterior-posterior whole neck field resulted in a 5-year overall survival of about 50% (1,7). Subsequently, the two bilateral facio-cervical fields were wildly accepted and resulted in a higher 5-year overall survival of 60–70% (8,9). Intensity modulated radiation therapy (IMRT) (9), chemoradiotherapy (10), and magnetic resonance imaging (MRI)-based irradiation (11) were now used across China resulting in an increased 5-year survival rate of 80%.

The limitations of the Chinese staging system [1992] were mainly two-fold: firstly, it was based on CT criteria. However, compared with CT, MRI altered the clinical stage in more than 30% of patients (11). Secondly, anatomical structures such as temporal fossa, retropharyngeal lymph nodes (RLN), cranial nerves, nasal cavity, and parapharyngeal space were not clearly defined. In addition, the N criteria primarily measured during clinical examination, were highly unreliable and dependent on physicians' experience (12).

Therefore, the Chinese staging system of 1992 no longer represented the ideal criteria under the new circumstances.

Should we just discard it and switch to the commonly used American Joint Committee on Cancer (AJCC) staging system? Following extensive discussion, the consensus in mainland China was that both the staging systems were imperfect, and additional clinical studies were needed to establish a more acceptable staging system, especially at cancer centers of Southern China, which has the highest incidence rates of NPC in the world. It was of utmost importance given that more than 95% of the newly diagnosed NPC patients in China were Epstein-Barr virus (EBV) positive for undifferentiated nonkeratinizing carcinoma (WHO III histology type).

Chinese 2008 staging system based on MRI

With the aim of building a platform for the study of the Chinese staging system and guaranteeing the continuity of the investigation into NPC, the Chinese Committee for Staging of Nasopharyngeal Carcinoma (CCSNPC) was founded in Guangzhou, China, in December 2008. After extensive evaluation and discussion, a preliminary revision of the Chinese 1992 staging system resulted in drafting the Chinese 2008 staging system for NPC, which was a consensus based on a comprehensive literature review. Changes in the staging system are as follows (*Table 2*) (12):

(I) Parapharyngeal involvement including pre-styloid space and post-styloid space were staged as T2;

(II) Any cranial nerve involvement was considered as T4;

(III) T classification was simplified; structures, such as anterior cervical vertebrae soft tissue, soft palatine, pterygopalatine fossa, orbit, and cervical vertebrae, were eliminated;

(IV) The definition of masticator space was used in place of infratemporal fossa;

(V) RLN involvement was classified as N1a, either unilateral or bilateral;

(VI) N classification was based on MRI and judged according to the criteria of the Radiation Therapy Oncology Group (RTOG), and the traditional nomenclature was no longer needed. In addition, the site, size, laterality, and extranodal neoplastic spread were enrolled in the criteria of the N category.

Further, the revised staging defined each anatomical structure including parapharyngeal space involvement described as tumor invasion across buccopharyngeal fascia, the boundary between the nasopharyngeal and the nasal cavity as the posterior of the maxillary sinus, which

Table 1 Chinese clinical staging criterion for NPC in history

Classification	Shanghai staging system [1965]	Changsha staging system [1979]	Guangzhou staging system [1981]
T-primary tumor			
T1	Tumor confined to unilateral nasopharynx	Tumor confined to unilateral nasopharynx or boundary of bilateral nasopharynx	Tumor confined to nasopharynx; T1a: minor invasive lesions; T1b: unilateral or midline of nasopharynx; T1c: bilateral nasopharynx
T2	Bilateral or more nasopharynx extension	Bilateral or more nasopharynx extension, but confined to nasopharynx	Nasal cavity, oropharyngeal extension
T3	Nasal cavity extension, bone structure, paranasal sinuses, I–VI cranial nerve extension	Skull base or cranial nerve extension,	Skull base, paranasal sinus, or cranial nerve extension
T4	Two or more extension in T3	Two or more extension in T3	T2 and T3 tumor extension, or hypopharynx, orbit, infratemporal fossa extension
N-regional lymph nodes			
N0	No regional lymph node metastasis	No regional lymph node metastasis	No regional lymph node metastasis
N1	Uni/bilateral mobile upper cervical lymph nodes, <3×3 cm in greatest dimension	Mobile upper cervical lymph nodes, <3×3 cm in greatest dimension	Upper cervical lymph nodes, mobile or fixed, <3 cm in greatest dimension
N2	Uni/bilateral fixed lymph node, <8×8 cm in greatest dimension	Lower cervical lymph nodes, restricted or fixed	Upper cervical lymph nodes, mobile or fixed, 3–8 cm in greatest dimension, lower cervical lymph nodes, mobile, >8 cm in greatest dimension
N3	Lymphadenectasis, with symptom of cranial nerve or cervical sympathetic nerve	>8×8 cm in greatest dimension, extension to the supraclavicular fossa	Lower cervical lymph nodes, fixed, >8 cm in greatest dimension, or extension to the supraclavicular fossa, or supraclavicular skin nodule
N4	>8×8 cm in greatest dimension, extension to the supraclavicular fossa		
M-distant metastasis			
M0	No distant metastasis	No distant metastasis	No distant metastasis
M1	Distant metastasis	Distant metastasis	Distant metastasis
Stage grouping			
Stage I	T1N0M0	T1N0M0	T1N0M0
Stage II	T1-2N1M0, T2N0M0	T1-2N1M0, T2N0M0	T1-2N1M0, T2N0M0
Stage III	T3N0-1M0, T1-3N2M0	T3N0-1M0, T1-3N2M0	T3N0-1M0, T1-3N2M0
Stage IV	T4N0-2M0, T1-4N3-4, T1-4N0-4M1	T4N0-2M0, T1-4N3M04, T1-4N0-3M1	T4N0-2M0, T1-4N3M04, T1-4N0-3M1

NPC, nasopharyngeal carcinoma.

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Table 2 The staging systems for NPC based on CT/MRI

Classification	The Chinese 1992 staging system	The Chinese 2008 staging system	The 7th edition of the AJCC staging system
T-primary tumor			
T1	Tumor confined to the nasopharynx	Tumor confined to nasopharynx	Nasopharynx, oropharynx, or nasal cavity extension
T2	Involvement of nasal cavity, oropharynx, soft palatine, anterior cervical vertebrae soft tissue, and parapharyngeal space extension before SO line*	Nasal cavity, oropharynx, parapharyngeal; parapharyngeal extension	Parapharyngeal extension
T3	Extension over SO line, involvement of anterior or posterior cranial nerves alone, skull base, pterygoprocess zone, and pterygopalatine fossa	Skull base, medial pterygoid muscle extension	Bone structure, paranasal sinuses extension
T4	Involvement of both anterior and posterior cranial nerves, paranasal sinus, cavernous sinus, orbit, infratemporal fossa, and direct invasion of first or second cervical vertebra	Cranial nerve, paranasal sinus, masticatory space excluding medial pterygoid muscle, intracranial (cavernous, dural meninges) extension	Intracranial extension, cranial nerve, hypopharynx, orbit, infratemporal fossa (masticatory space) extension
N-regional lymph nodes			
N0	No enlarged lymph node	No regional lymph node metastasis	No regional lymph node metastasis
N1	The diameter of upper neck lymph node <4 cm, movable	N1a RLN involvement; N1b unilateral level Ib, II, III, and Va involvement and the maximum diameter <3 cm	Unilateral metastasis in lymph node(s), uni/bilateral RLN, <6 cm in greatest dimension, above the supraclavicular fossa
N2	Lower neck lymph node or the diameter between 4 and 7 cm	Bilateral level Ib, II, III, and Va or the maximum diameter >3 cm or with extranodal neoplastic spread	Unilateral metastasis in lymph node(s), <6 cm in greatest dimension, above the supraclavicular fossa involvement
N3	Supraclavicular lymph node or the diameter >7 cm or fixed or skin infiltration	Level IV, Vb involvement	N3a >6 cm in greatest dimension; N3b extension to the supraclavicular fossa
M-distant metastasis			
M0	Absence of distant metastasis	No distant metastasis	No distant metastasis
M1	Presence distant metastasis	Distant metastasis	Distant metastasis
Stage grouping			
Stage I	T1N0M0	T1N0M0	T1N0M0
Stage II	T2N0-1M0, T1N1M0	T1N1a-1bM0,T2N0-1bM0	T2N0-1M0, T1N1M0
Stage III	T1-2N2M0, T3N0-2M0	T1-2N2M0, T3N0-2M0	T1-2N2M0, T3N0-2M0
Stage IV			
Stage IVA	T4N0-2M0, T1-4N3M0	T4N0-2M0, T1-4N3M0	T4N0-2M0
Stage IVB	Any T Any N M1	Any T Any N M1	T1-4N3M0
Stage IVC			Any T Any N M1

SO line*: the line that is connected from the styloid process to the midpoint on posterior edge of the great occipital foramen. CT, computed tomography; MRI, magnetic resonance imaging; NPC, nasopharyngeal carcinoma; AJCC, American Joint Committee on Cancer; RLN, retropharyngeal lymph nodes.

improved the interpretation and reduced subjective bias.

Most significantly, the new staging system considered MRI as the preferred imaging modality for NPC staging. The MRI criteria and report template were established. The diagnostic criteria of cervical lymph node metastasis based on imaging modality were stated as follows.

- (I) A minimum diameter of not less than 10 mm on cross-sectional images;
- (II) Central necrosis or rim enhancement;
- (III) More than three lymph nodes in a high-risk region, and at least one of the involved lymph nodes with the minimum diameter on the largest cross-sectional images not less than 8 mm. The high-risk region was described as follows: level II for N0, followed by the next level of lymph node involvement for N-positive patients;
- (IV) Extranodal neoplastic spread, such as irregular enhancement at the edge of the lymph node, with partially or completely disappearing fat space, and lymph node convergence;
- (V) RLN: minimum diameter on the largest cross-sectional images not less than 5 mm.

These criteria of lymph node measurement on MRI images redefined the lymph node clusters and extranodal neoplastic spread, and reduced the subjectivity of clinical diagnosis.

Chinese 2008 staging system *vs.* 7th edition AJCC staging system

The 6th edition AJCC staging system was commonly used in the rest of the world when the Chinese 2008 staging system was revised (13). The anatomical structures such as RLN and infratemporal fossa were poorly defined in the Chinese 1992 staging system similar to the 6th AJCC staging system. In 2010, the AJCC committee published the revised 7th edition of the staging system (14). Compared with the previous edition, the changes were as follows (*Table 2*):

- (I) Oropharynx and nasal cavity involvement was assigned T1 instead of T2a;
- (II) Parapharyngeal space involvement was classified as T2 disease;
- (III) RLN was categorized as N1 subgroup.

Compared with the Chinese staging system [2008], the controversies related to:

- (I) Whether or not masticator space involvement including the medial and lateral pterygoid muscles should be classified as T4 (15,16);
- (II) Whether or not the extranodal neoplastic spread based on MRI should be included under N classification (17).

A retrospective study of a large number of cases showed that the prognostic value of the T classification of the AJCC system was better, whereas the N classification of the Chinese 2008 was superior (18,19). However, the measurement of extranodal cervical lymph node on MRI was still controversial (20). The CCSNPC conducted a prospective multicenter study to evaluate the two staging systems of NPC, in 1,508 cases at nine different cancer centers in mainland China. A preliminary report revealed that the distribution of cases, the prognosis of clinical staging and T classification of the two staging systems were similar, while the prognostic value of N classification of the Chinese 2008 was superior. However, additional evidence was still needed (21).

Future development of staging system

The revisions in the Chinese 2008 staging system and the 7th edition of the AJCC staging system, were based on retrospective analysis of NPC patients who were treated with conventional RT. Currently, IMRT is regarded as the standard treatment modality for NPC. Local control rates improved around 10% with IMRT when compared with conventional RT (22,23), which was a huge challenge for the current staging system (24). Prospective multicenter studies may avoid the defects of the retrospective analysis and provide more accurate estimates of staging system supported by robust evidence for staging revisions.

The expression of virus EB-DNA was used to evaluate the treatment outcomes in recent studies. Leung *et al.* found that the EB-DNA had an independent prognostic value and suggested its role as a biological factor in the NPC staging system (25). However, there were significant differences in the EBV DNA expression levels detected in different studies. The cut-off value was a major issue for inclusion of EBV DNA in the current staging system (26).

A few studies indicated that the primary gross tumor volume (GTV) had a prognostic value and therefore, should be incorporated into the current staging system (27-29). However, the measurement of GTV was not based on consensus, currently. Further studies should be initiated to confirm its positive effect on staging system (30).

Recent studies found that certain biomarkers with potential prognostic value included miRNAs (31), EBV miRNAs (32), lactotransferrin (33), LDH (34), hemoglobin,

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and neutrophil-to-lymphocyte ratio and platelets (35). Additional studies are needed to establish the role of these molecular biomarkers before incorporating them into the clinical staging system.

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Footnote

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