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EDITORIAL

Dissection of the TNM staging classification for nasopharyngeal cancer – past, present, and future

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Accurate cancer staging is the foundation of precision oncology and guides prognosis prediction and therapeutic decision-making. The conjoint TNM System by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) has served as the global standard for tumor classification since inception. However, this approach was initially not universally accepted for nasopharyngeal carcinoma (NPC) because the 1st–4th editions adopted a generic system for all head and neck cancers without accounting for unique NPC characteristics. Growing evidence highlights NPC as a distinct malignancy with unique epidemiology, viral etiology, clinical behavior, treatment considerations, and responsiveness. This growing recognition necessitates a customized disease-specific staging system for NPC. Consequently, endemic regions developed their own classification system, most notably the Ho's system in Hong Kong and Chinese Systems in the Chinese mainland. While these regional systems address local needs, the discrepancies create barriers to international collaboration and knowledge sharing.

Over the past three decades the staging system for NPC has undergone significant transformations, reflecting advances in diagnostic imaging, treatment paradigms, and our understanding of tumor biology. The global incidence of NPC is approximately 120,000 new cases annually with nearly 80% of cases occurring in South, East, and Southeast Asia[1]. Indeed, China alone accounts for nearly 50% of the worldwide burden with age-standardized incidence rates > 20 per 100,000 in Southern China, compared to < 0.5 per 100,000 in Western countries[2-4]. Hence, TNM staging development for NPC relies heavily on data from the Chinese mainland and Hong Kong.

The past – evolution of NPC staging

The AJCC/UICC 5th edition (released in 1997) was the first milestone toward global unification. We demonstrated that prognostication could be significantly improved by merging the strengths of the AJCC/UICC 4th edition and the Ho's system based on a retrospective analysis of > 4,500 patients from Hong Kong[5]. Among the key changes introduced was acknowledgement of the the importance of extension in addition to size and laterality at the nodal level, leading to inclusion of supraclavicular fossa involvement as an N3 criterion. This marked a major paradigm shift in NPC staging and was the first time that the AJCC/UICC adopted a customized system for NPC.

The AJCC/UICC 6th edition did not involve extensive review. The only change was the addition of the term, masticator space (as a synonym for infratemporal fossa), as a T4 criterion, which is aligned with radiology terminology. However, this change led to confusion regarding the inclusion of pterygoid muscles in T4. Furthermore, a study reported insignificant prognostic differences between stage II and stage I patients[6]. The AJCC/UICC 7th edition addressed the significance of the parapharyngeal space and provided clarification on the categorization of retropharyngeal nodes.

Although the AJCC/UICC 5th–7th editions were accepted as the global standard for NPC staging, parallel development continued in China. Given the high NPC burden in China, Chinese researchers continued to refine staging systems through successive iterations; specifically, the new iterations included the palpation-based Tianjin (1959) and

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Shanghai (1965) systems, the imaging-driven Fuzhou (1992) computed tomography (CT)-based system, and the Chinese (2008) system, which introduced magnetic resonance imaging (MRI)-stratified cervical lymph node N descriptors. These parallel developments highlighted the need for a revision of NPC staging and laid the groundwork for future international harmonization.

The AJCC/UICC 8th edition (released in 2017) was the second milestone in NPC staging evolution. This revision was driven by adaptation of advanced imaging modalities (especially MRI), the implementation of 3D conformal and intensity-modulated radiation therapy, and the use of combination chemotherapy. We demonstrated significant improvement in prognostication by integrating the strengths of the AJCC/UICC 7th edition and the Chinese 2008 staging system based on a literature review and analysis of 1,609 patients from the Chinese mainland and Hong Kong, and by formalizing MRI-based anatomic criteria[7]. Several critical modifications were implemented in the AJCC/UICC 8th edition. First, pterygoid muscle involvement was down-classified from T4 to T2. Second, prevertebral muscle involvement was included as a T2 criterion. Third, the N3 criterion of supraclavicular fossa involvement was replaced with lower neck extension, which was specifically defined as extension below the caudal border of the cricoid cartilage. Finally, the staging system consolidated T4 and N3 classifications under stage IVA. These anatomic classifications reflect imaging technology advances and the improved local infiltration control achieved through concurrent chemoradiation during this period. These evidence-based revisions successfully harmonized the AJCC/UICC and Chinese systems, leading to true global unification in NPC classification.

The present – AJCC/UICC TNM version 9

The current AJCC/UICC version 9 (TNM-9) is the third milestone, representing the most intensive internal analysis and extensive review by international multidisciplinary experts[8]. Notably, among all head and neck cancers, NPC has become the first head and neck cancer to progress to version 9 of the TNM classification system.

The development of TNM-9 was driven by three key developments: (1) paradigm shifts in treatment strategies; (2) emerging evidence on prognostic stratification; and (3) methodologic improvements in staging validation. The standard of care for non-metastatic NPC has transitioned toward combined modality therapy, particularly with the use of induction chemotherapy followed by concurrent chemoradiation for patients with locoregionally advanced disease[9]. These therapeutic advances, coupled with significant improvements in radiologic imaging, radiotherapy planning, and precision treatment delivery, have substantially improved clinical outcomes. Furthermore, the therapeutic value of locoregional radiotherapy for *de novo* metastatic cases has gained recognition[10]. In our multicenter study 80% of M1 patients received locoregional radiotherapy for the primary tumor and 48% received local treatment for the metastatic lesions in addition to systemic therapy[8]. These evolving treatment paradigms have necessitated a comprehensive reassessment and revision of the TNM-8 staging to better align with contemporary clinical practice and outcomes.

The development of TNM-9 underwent unprecedented methodologic rigor through five critical phases conducted through collaboration between initiating investigators and leaders of the Core Head and Neck Committee from the AJCC and UICC. The process began with comprehensive evidence synthesis, in which a systematic review of literature from 2013–2019 identified potential key prognostic factors[11]. This process was followed by robust internal validation using a primary cohort of 4,914 cases from 8 centers in the Chinese mainland and Hong Kong[8]. In addition to an internal validation designed within the core study, the findings underwent external validation with an independent cohort of 8,834 cases[12]. Only those findings supported by the core and external validation studies were advanced for consideration by a multidisciplinary panel of international experts comprised of oncologists (surgical, radiation, and medical), radiologists, and pathologists. Repeated iterative review and consensus building took into consideration the statistical evidence of benefit, clinical practicability, and reproducibility. Finally, all proposed changes underwent meticulous review by the AJCC Evidence-based Medicine Committee to ensure scientific validity before final endorsement by the AJCC and UICC. This multi-phase approach ensured that TNM-9 reflects robust scientific evidence and global clinical relevance, while meeting the highest standards of oncologic staging classification. This stringent process is an exemplary model for the development of new staging systems.

The newly developed TNM-9 was released for global application on 1 January 2025. The following key changes were

Table 1 Classification criteria and stage grouping by different systems

	AJCC/UICC 5th & 6th editions	AJCC/UICC 7th edition	AJCC/UICC 8th edition	AJCC/UICC TNM 9th version
T-category				
T1	Nasopharynx	Nasopharynx, oropharynx, nasal fossa	Nasopharynx, oropharynx, nasal fossa	Tumor confined to nasopharynx or extension to any of the following without parapharyngeal involvement: oropharynx, nasal cavity (including nasal septum)
T2	Oropharynx or nasal fossa T2a: without parapharynx T2b: with parapharynx	Parapharyngeal extension	Parapharyngeal extension, adjacent soft tissue involvement (medial pterygoid, lateral pterygoid, prevertebral muscles)	Tumor with extension to any of the following: parapharyngeal space, adjacent soft tissue involvement (medial pterygoid, lateral pterygoid, prevertebral muscles)
T3	Bony structure, paranasal sinuses	Bony structure, paranasal sinuses	Bony structure (skull base, cervical vertebra), paranasal sinuses	Tumor with unequivocal infiltration into any of the following bony structures: skull base (including pterygoid structures), paranasal sinuses, cervical vertebrae
T4	Intracranial extension, cranial nerve, hypopharynx, orbit, infratemporal fossa (masticatory space)	Intracranial extension, cranial nerve, hypopharynx, orbit, infratemporal fossa (masticatory space)	Intracranial extension, cranial nerve, hypopharynx, orbit, extensive soft tissue involvement (beyond the lateral surface of the lateral pterygoid muscle, parotid gland)	Tumor with any of the following extension/involvement: • intracranial extension • unequivocal radiological and/or clinical involvement of cranial nerves • hypopharynx • orbit (including inferior orbital fissure) • parotid gland • extensive soft tissue infiltration beyond the anterolateral surface of the lateral pterygoid muscle
N-category				
N0	None	None	None	No tumor involvement of regional lymph node(s)
N1	Unilateral cervical node, ≤ 6 cm, above supraclavicular fossa	Retropharyngeal (regardless of laterality); unilateral cervical, ≤ 6 cm, above supraclavicular fossa	Retropharyngeal (regardless of laterality); unilateral cervical, ≤ 6 cm, above supraclavicular fossa	Tumor involvement of any of the following: • unilateral cervical lymph node(s) • unilateral or bilateral retropharyngeal lymph node(s) AND all of the following: • ≤ 6 cm in greatest dimension • above the caudal border of cricoid cartilage • without advanced extranodal extension
N2	Bilateral node, ≤ 6 cm, above supraclavicular fossa	Bilateral cervical node, ≤ 6 cm, and above supraclavicular fossa	Bilateral cervical node, ≤ 6 cm, and above caudal border of cricoid cartilage	Tumor involvement of bilateral cervical lymph nodes AND all of the following: • ≤ 6 cm in greatest dimension • above the caudal border of cricoid cartilage • without advanced extranodal extension
N3	N3a: > 6 cm N3b: in supraclavicular fossa	N3a: > 6 cm N3b: in supraclavicular fossa	> 6 cm and/or below caudal border of cricoid cartilage (regardless of laterality)	Tumor involvement of unilateral or bilateral cervical lymph node(s), AND any of the following: • > 6 cm in greatest dimension • extension below the caudal border of cricoid cartilage • advanced radiologic extranodal extension with involvement of adjacent muscles, skin, and/or neurovascular bundle

Table 1 Continued

	AJCC/UICC 5th & 6th editions	AJCC/UICC 7th edition	AJCC/UICC 8th edition	AJCC/UICC TNM 9th version
M-category				
M0	No distant metastasis	No distant metastasis	No distant metastasis	No distant metastasis
M1	Distant metastasis	Distant metastasis	Distant metastasis	Distant metastasis M1a: ≤ 3 metastatic lesions in one or more organs/sites M1b: > 3 metastatic lesions in one or more organs/sites
Stage groups				
I	T1 N0 M0	T1 N0 M0	T1 N0 M0	IA: T1-2 N0 M0 IB: T1-2 N1 M0
II	IIA: T2a N0 M0 IIB: T1-2a N1 M0 T2b N0-1 M0	T1 N1 M0 T2 N0-1 M0	T1 N1 M0 T2 N0-N1 M0	T1-2 N2 M0 T3 N0-2 M0
III	T1-2b N2 M0 T3 N0-2 M0	T1-2 N2 M0 T3 N0-2 M0	T1-2 N2 M0 T3 N0-2 M0	T4 Any N M0 Any T N3 M0
IV	IVA: T4 N0-2 M0 IVB: Any T N3 M0 IVC: Any T Any N M1	IVA. T4 N0-2 M0 IVB. Any T N3 M0 IVC. Any T Any N M1	IVA. T4 or N3 M0 IVB. Any T Any N M1	IVA: Any T Any N M1a IVB: Any T Any N M1b

introduced (**Table 1**): N-category (addition of advanced extranodal extension [ENE] as an N3 criterion has important clinical implications); M-category (subdivision of M1 into M1a and M1b); and stage group (merging I and II, down-classifying III and IVA to II and III, respectively, exclusive inclusion of M1 into IV, and subdivision of stages I and IV).

This is the first time that ENE is incorporated as an N3-category criterion. Our defining criterion for advanced ENE is "unequivocal involvement of adjacent muscle, skin, and/or neurovascular structures", because this is an independent adverse factor for all endpoints (including overall survival (OS), nodal control, and distant control)[8]. Similarly, N1 disease with advanced ENE and N3 disease showed no significant differences in outcomes in the external validation cohort[12]. Hence, patients with advanced ENE should be managed as locoregionally advanced disease independent of size and level of extension, and consequently require treatment intensification strategies.

Imaging-detected ENE is defined by the presence of clearly irregular or ill-defined nodal margins, extension into perinodal fat, invasion through two or more inseparable adjoining nodes, or infiltration into adjacent structures, such as muscle, skin, salivary glands, or the neurovascular bundle, according to the recently published criteria by the Head and Neck Cancer International Group (HNCIG)[13]. However, it should be noted that ENE limited to perinodal fat or coalescent lymph nodes is not associated with significant prognostic implications for NPC[8,12]. Therefore, the "advanced ENE" criterion should be used for NPC staging because this criterion more accurately reflects outcomes under current standard-of-care therapy.

This is the first time that non-metastatic patients are grouped into stages I-III, while stage IV is used exclusively for patients with metastatic disease. This is also the first time that stage I is expanded to include T1–2N0–1M0 diseases based on survival analysis demonstrating comparable outcomes across these subgroups. Although T1–2N0 and T1–2N1 diseases demonstrate similar survival outcomes, our analysis revealed significant differences in treatment patterns and underlying prognosis between these subgroups. A substantially higher proportion of N1 patients received multi-modality treatment and multivariate analysis incorporating chemotherapy as a co-variable revealed significantly worse outcomes in the N1 subgroup[8]. De-escalated treatment approaches (e.g., radiotherapy alone) are sufficient for low-risk disease, whereas patients with high-risk features, such as bulky primary tumors and nodes or elevated pretreatment plasma EBV-DNA levels,

require more intensive treatment strategies. Hence, stage I is subdivided into stage IA (T1–2N0) and stage IB (T1–2N1) to provide better guidance for therapeutic decision-making. While the down-classification of previous stage III to current stage II reflects improved outcomes achieved through modern therapies, clinicians should note that this revision assumes adherence to current treatment standards until further evidence becomes available[14-16].

The TNM-9 also introduces major modifications to the staging of metastatic disease. Stage IV (and corresponding M1) is subdivided into IVA and IVB to reflect the different prognoses. The criteria of ≤ 3 metastatic lesions *vs.* > 3 lesions are adopted as the cut-off for subdividing M1 into M1a and M1b. The 5-year OS for the corresponding stages IVA and IVB demonstrates significant prognostic discrimination with rates of 61% *vs.* 44%, respectively ($P = 0.01$)[8]. This specific cut-off was selected based on three key considerations: value as a pragmatic clinical criterion; ability to provide clear prognostic discrimination; and confirmation through external validation studies[12].

A randomized controlled trial (Registration No. NCT02111460) demonstrated that consolidative locoregional radiotherapy added to first-line chemotherapy significantly improved outcomes for patients with *de novo* metastatic NPC with 2-year OS rates of 76% *vs.* 55%[17]. Radiotherapy directed at metastatic lesions further enhanced survival benefits[18,19]. Current treatment guidelines recommend induction chemotherapy followed by locoregional chemoradiation for oligometastatic disease[14,16]. In our cohort > 75% of M1a patients underwent aggressive multimodal therapy, including systemic treatment and locoregional radiotherapy with or without metastasis-directed ablation[8]. However, further research is needed to define the role of consolidative radiation, especially now that immunotherapy has become the standard first-line treatment for metastatic disease. Ongoing research, including the NCT04944914 phase III trial evaluating the combination of immunotherapy with stereotactic body radiotherapy for patients with controlled primary tumors, aims to further optimize treatment approaches for oligometastatic NPC. However, it is important to carefully select patients who potentially benefit from aggressive treatment against futile attempts with additional treatment-related toxicities.

The TNM-9 system marks a transformative advance in NPC staging, which has progressed from palpation, CT-based Chinese classification and the Ho's system through the initial adaptation of MRI-based N descriptors in the Chinese 2008 and TNM-7 to TNM-8 formalization of MRI-based anatomic criteria. TNM-9 now refines this framework through ENE classification and metastatic subclassification and delivers diagnostic precision tailored for contemporary precision oncology paradigms.

The future

This evolutionary process demonstrates the dynamic nature of cancer staging systems, which must balance anatomic precision with clinical utility, while accommodating diagnostic and therapeutic advances. The transition from generic head and neck staging to increasingly refined NPC-specific classifications has significantly improved prognostic accuracy and therapeutic decision-making. TNM staging, which is based on anatomic extent of disease, is a robust prognostic factor that is applicable globally. However, as we enter the era of molecular oncology, future iterations will aim for further refinement by incorporating non-anatomic factors.

Plasma EBV-DNA has demonstrated strong prognostic value across multiple studies[11]. However, several challenges currently limit universal incorporation into standard staging systems. First, EBV-DNA testing is not available worldwide. Second, the lack of standardized quantification methodologies has resulted in significant variability in proposed cut-off values for risk stratification. Furthermore, not all patients with non-keratinizing NPC, including patients with advanced disease, have detectable circulating EBV-DNA. A pragmatic solution has yet to be implemented before EBV-DNA testing can become widely applicable. Future research priorities include establishing standardized EBV-DNA cut-offs for risk stratification and developing frameworks for EBV-DNA testing integration into TNM staging systems. While plasma EBV-DNA remains a promising biomarker for integration, other prognostic factors identified by our systematic review[11], including gross tumor volume, serum lactate dehydrogenase activity, hemoglobin concentration, neutrophil:lymphocyte ratio, platelet count, C-reactive protein level, albumin level, and body mass index, also warrant further evaluation.

Looking ahead, research opportunities emerge from the implementation of TNM-9 staging. First, the integration of biological markers with anatomic staging requires prospective validation, particularly for circulating EBV DNA levels when combined with TNM-9 categories to enhance prognostic precision. Second, therapeutic optimization studies are needed, such as randomized controlled trials investigating treatment

modulation strategies based on the newly established M1a *vs.* M1b metastatic subclassifications. Third, the definition of advanced ENE in TNM-9 staging requires MRI evaluation due to superior soft-tissue visualization, which is essential for detecting nodal capsular invasion and adjacent tissue infiltration. However, MRI evaluation presents significant challenges in areas where MRI accessibility is constrained by infrastructure limitations, workforce shortages, and high costs. These disparities arise from interconnected technologic, economic, and social barriers, which create implementation gaps for precise TNM-9 staging. To ensure global applicability, research must systematically evaluate these challenges in resource-limited settings by developing scalable solutions that maintain prognostic accuracy while improving equitable access. Finally, prospective trials with global participation are essential for future TNM staging development, offering three key advantages: (1) ensuring generalizability across diverse populations and healthcare systems; (2) capturing regional variations in disease biology and treatment responses; and (3) facilitating rapid validation of staging modifications through large, representative datasets. These research priorities will be critical for maximizing the clinical utility of the updated staging system across diverse practice environments.

Conclusions

Version 9 of the TNM staging system for NPC represents a significant step forward in refining prognostic stratification and guiding treatment decisions. By incorporating critical updates, such as the formal recognition of ENE and subclassification of metastatic disease, TNM-9 better aligns with contemporary diagnostic and therapeutic advances. These changes reflect a rigorous, evidence-based development process involving multicenter validation and international consensus, addressing key limitations of prior editions while maintaining global applicability. As NPC management evolves toward precision medicine, the TNM system must continue adapting to incorporate emerging biomarkers and advanced imaging features. Collaborative international efforts will be essential to ensure future staging development, ultimately improving patient outcomes worldwide. The TNM-9 marks important progress, but the journey toward optimal risk stratification and treatment guidance continues.

Author contribution

Conceived and designed the paper: AL.
Collected the data: QL.
Wrote the paper: QL.
Reviewed and revised the paper: AL.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

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