Turkish Archives of Otorhinolaryngology
Turk Arch Otorhinolaryngol

Union for International Cancer Control 9th Edition TNM Classification for Head and Neck Malignancies: What is New?

Commentary

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Keywords: Head and neck neoplasms, neoplasm staging, TNM classification, squamous cell carcinoma, prognosis

The 9th edition of the Union for International Cancer Control (UICC) tumor-node-metastasis (TNM) classification of malignant tumors implements substantial, evidence-based revisions to the staging protocols for head and neck malignancies. Driven by the expanding evidence base and the imperative for refined prognostic stratification, these modifications ultimately aim to enhance the accuracy and clinical utility of the staging system within this complex anatomical region.

Building on the major innovations introduced in the 8th edition—notably, the incorporation of depth of invasion for oral cavity cancers, extranodal extension (ENE) in nodal staging, and the establishment of distinct staging for human papillomavirus (HPV)-associated oropharyngeal carcinoma (OPC), the 9th edition further advances disease stratification across multiple key subsites (1,2). Collectively, these updates represent a deliberate and strategic evolution from a purely anatomical descriptive framework toward a hybrid prognostic model that integrates robust biological and morphological variables while rigorously maintaining global applicability.

Despite anticipated implementation challenges, including variability in imaging quality, molecular testing availability, and interobserver reliability—the 9th edition provides a meaningful advancement in head and neck cancer staging. Its widespread adoption is expected to strengthen prognostic precision, improve treatment alignment, and enhance the comparability of clinical research across institutions. This commentary summarizes the notable modifications introduced in the 9th edition of the TNM classification for head and neck malignancies.

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Cite this article as: *Bayram A, Çelebi Erdivanlı Ö; Society for Head and Neck Surgery Scientific Group. Union for international cancer control 9th edition TNM classification for head and neck malignancies: what is new? Turk Arch Otorhinolaryngol. [Epub Ahead of Print]*

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Received Date: 25.11.2025
Accepted Date: 16.12.2025
Epub: 23.12.2025

DOI: 10.4274/tao.2025.2025-11-14

Nasopharyngeal Carcinoma

A multicenter study of 4,900 patients by Pan et al. (3) demonstrated that advanced image-identified ENE (iENE) is a critical prognostic determinant in nasopharyngeal carcinoma (NPC). Accordingly, the 9th edition designates advanced iENE, defined as tumor invasion into adjacent structures such as the skin, the muscle, the salivary glands, and/or neurovascular bundles-as a criterion for N3 classification, reflecting its association with markedly poorer survival.

Additionally, patients presenting with distant metastasis (M1) are now stratified into M1a (≤3 lesions) and M1b (>3 lesions). This subdivision directly addresses the considerable heterogeneity within the M1 category, significantly improving prognostic discrimination among metastatic cases (3,4). Stage grouping has also undergone major restructuring for NPC. While the T1-T2 N0-N1 subgroups demonstrated comparable five-year overall survival, they were consolidated into stage I but further subdivided into IA (T1-T2N0) and IB (T1-T2N1) to retain distinction based on adjusted hazard ratios, particularly following adjustment for chemotherapy use. To optimize hazard differentiation, former stages III and IVA are down-classified to II and III, respectively. Critically, M1 disease is now exclusively assigned to stage IV, eliminating the former conflation of advanced locoregional disease with distant metastatic disease. Prognostication within this final category is further refined by its subdivision into IVA (M1a, ≤3 lesions) and IVB (M1b, >3 lesions).

HPV-Associated OPC

A separate staging system for HPV-associated OPC was first introduced in the 8th edition due to its distinct biological behavior and significantly more favorable prognosis compared to HPV-negative OPC. However, a subset of patients previously classified as stage I or II experienced poorer outcomes than expected. The 9th edition addresses this gap by refining stage groups to improve prognostic performance and better align with contemporary treatment strategies.

One of the most significant updates for HPV-positive OPC is the incorporation of iENE into the clinical regional lymph node involvement (N category). Image-iENE has been demonstrated to be an independent, adverse prognostic factor for HPV-positive OPC (5). In the 9th edition, the presence of iENE on pretreatment imaging results is an upstaging of the N category, even if lymph node sizes or laterality criteria are unchanged. Lymph nodes demonstrating clinical or imaging-defined ENE are assigned a minimum nodal category of clinical N2, irrespective of nodal size or number. In the pathological classification, while the 8th edition relied solely on the number of metastatic lymph nodes, the 9th edition recognizes pathological ENE (pENE), defined as tumor unequivocally extending through the lymph node capsule into the surrounding connective tissue, as a critical prognostic determinant. The revised pathological N categories therefore incorporate both the number of metastatic lymph nodes and the presence of pENE, yielding improved stratification and more prognostically informative stage groups for surgically treated HPV-associated OPC.

Salivary Glands

In the 9th edition, carcinomas originating from the minor salivary glands of the upper aerodigestive tract are classified according to the rules for the tumors of the salivary glands. The principal updates focus on refining the N category to improve prognostic discrimination through the formalized incorporation of both metastatic lymph node count and ENE status into both clinical and pathological staging. Patients with one to three metastatic nodes and no ENE are classified as clinical N1, whereas those with more than three nodes or any node demonstrating ENE are categorized as clinical N2.

The primary tumor (T category) remains largely consistent with the 8th edition, maintaining size-based criteria. Importantly, extraparenchymal extension, which elevates the T stage to T3, is strictly defined as clinical or macroscopic evidence of soft tissue or nerve invasion, excluding structures specified under T4a and T4b. This distinction underscores the requirement for gross or imaging-defined invasion, not merely microscopic extension.

Future Directions and Practical Limitations

The revisions in the 9th edition represent a cautious but deliberate transition toward integrating critical prognostic determinants, such as viral status [HPV, Epstein-Barr virus (EBV)], iENE, and metastatic burden into the final stage grouping. For salivary gland and nasopharyngeal cancers, the new system is predicated on revised criteria leveraging updated imaging and anatomical characteristics; similarly, for HPV-associated oropharyngeal cancers, the staging has been specifically developed to better reflect their distinct biological behavior and prognosis. This unified approach judiciously balances contemporary evidence with the necessary constraint of global applicability, consciously avoiding reliance on molecular markers not yet feasible in all resource settings.

Notwithstanding these advancements, several practical challenges remain inherent to the implementation of the 9th edition:

• **Imaging Standardization:** Global variability in the availability and quality of high-resolution imaging modalities may compromise the reliability of staging, particularly the assessment of iENE.

• **Testing Heterogeneity:** Differences in HPV/EBV testing methods and availability may reduce inter-institutional comparability and accuracy of stage assignment.

• **Resource Intensity:** Retrospective re-staging for clinical audits or research purposes will likely require substantial resource allocation and effort.

• **System Complexity:** The increased incorporation of sophisticated prognostic variables risks heightening system complexity and, consequently, increasing interobserver variability in staging decisions.

These limitations collectively underscore the critical importance of continued professional education and the urgent need for standardization of imaging protocols and pathological assessment to ensure the system's intended benefits are fully realized.

Conclusion

The 9th edition of the UICC TNM classification for malignant tumors signifies a pivotal and necessary shift in the staging philosophy for head and neck malignancies by moving decisively toward a hybrid prognostic model. By successfully integrating contemporary evidence, specifically viral status (HPV/EBV), iENE, and metastatic burden-into the final stage groupings for key subsites (NPC, HPV-OPC, and salivary glands), the system achieves superior prognostic stratification. While the new system introduces complexity and highlights ongoing challenges related to global standardization of high-resolution imaging and testing methods, these limitations do not diminish the value of the revisions. The UICC TNM 9th edition represents a significant and pragmatic leap forward, reinforcing its status as the global standard for cancer classification. Ultimately, its successful implementation hinges on continued professional education and the sustained drive toward standardized pathological and radiological assessment worldwide.

Acknowledgement: The author utilized ChatGPT (version 5.1; OpenAI Inc., San Francisco, CA, USA) exclusively for grammar and language editing to improve clarity and readability. The tool was employed solely for linguistic refinement and did not contribute to the generation or interpretation of scientific content.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.B., Ö.Ç.E., Society for Head and Neck Surgery Scientific Group, Concept: A.B., Ö.Ç.E., Society for Head and Neck Surgery Scientific Group, Design: A.B., Ö.Ç.E., Society for Head and Neck Surgery Scientific Group, Data Collection and/or Processing: A.B., Ö.Ç.E., Society for Head and Neck Surgery Scientific Group, Analysis or Interpretation: A.B., Ö.Ç.E., Society for Head and Neck Surgery Scientific Group, Literature Search: A.B., Ö.Ç.E., Society for Head and Neck Surgery Scientific Group, Writing: A.B., Ö.Ç.E., Society for Head and Neck Surgery Scientific Group.

Conflict of Interest: The authors declare that they have no conflict of interest.

Financial Disclosure: The author declares that this study has received no financial support.

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