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Overview of the 8th Edition TNM Classification for Head and Neck Cancer

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Opinion Statement

The main purpose of the TNM system is to provide an anatomic-based classification to adequately depict cancer prognosis. Accurate cancer staging is important for treatment selection and outcome prediction, research design, and cancer control activities. To maintain clinical relevance, periodical updates to TNM are necessary. The recently published 8th edition TNM classification institutes the following changes to the staging of head and neck (excluding thyroid cancer): new stage classifications [HPV-related oropharyngeal cancer (HPV+ OPC) and soft tissue sarcoma of the head and neck (HN-STS)] and modification of T and N categories [T and N categories for nasopharyngeal cancer (NPC), T categories for oral cavity squamous cell carcinomas (OSCC), N categories for non-viral related head and neck cancer and unknown primary (CUP), and T categories for head and neck cutaneous carcinoma]. These changes reflect better understanding tumor biology and clinical behavior (e.g., HPV+ OPC and HN-STS), improved outcomes associated with technical advances in diagnosis and treatment (e.g., NPC), evolving knowledge about additional prognostic factors and risk stratification from research and observation (e.g., inclusion of depth of invasion variable for OSCC, inclusion of extranodal extension variable for all non-viral head and neck cancer, and reintroduction of size criteria for non-Merkel cell cutaneous carcinoma of the head and neck). This review summarizes the changes and potential advantages and limitations/caveats associated with them. Further evidence is needed to evaluate whether these changes would result in improvement in TNM stage performance to better serve the needs for clinical care, research, and cancer control.

Introduction

The TNM stage classification addresses anatomic tumor extent using the "tumor" (T), "lymph node" (N), and metastasis (M) attributes, where "T" describes the extent of primary tumor (T), "N" refers to absence or presence and extent of overt regional lymph node(s) [LN(s)], and "M" depicts the absence or presence of distant metastasis. The first edition of the TNM classification was published by the Union for International Cancer Control (UICC) in 1968 followed by two editions in 1974 and 1978 [1]. The American Joint Committee on Cancer (AJCC) published a similar but separate TNM classification in 1977 [2]. The two staging systems became unified in 1987 (4th edition) [1].

The TNM classification plays a pivotal role in clinical care, clinical trial eligibility and stratification, research, health services, and cancer registry activities, as well as cancer control and policy development. Since its debut, it is widely employed by multiple users including clinicians, researchers, and cancer registrars in multiple domains [3]. To maintain its clinical relevance and to keep pace with the demands of evidence-based practice, periodic updates are undertaken. These generally follow sound principles and solid data/evidence that consider both feasibility and practicality. In 2002, the UICC introduced a structured process to improve TNM staging: the annual review of relevant literature, formation of site-specific expert panels, discussion of inclusion/exclusion of changes, and proposal for change (considering clinical relevance and evidence of improved prognostic ability) for the site-specific expert panels to consider. The AJCC similarly has expert disease site committees. Both organizations promote and facilitate a system of mutual liaison to develop and refine proposals with the goal of having a uniform classification across the world. Final recommendations are reviewed critically and ultimately approved by the combined UICC/AJCC TNM committee [4].

Since the original inclusion of "buccal cavity," "pharynx," and "larynx" in the first edition of TNM, the staging of head and neck cancer (HNC) evolved in response to better understanding of tumor biology and disease behavior, emergence of new diseases, and better prognosis as a consequence of improved diagnosis and management. In recent decades, outcomes of HNC improved significantly owing to technical advances in diagnostic imaging (MR, PET-CT) and radiotherapy planning (intensity modulated radiotherapy, IMRT) as well as image-guided treatment delivery (IGRT). In addition, recognition of the rapidly emerging HPV-driven oropharyngeal cancer and its clinical behavior has necessitated a separate TNM classification specific to this disease. In the newly published 8th edition TNM [5, 6], the following changes have been made to the overall schema: (1) introduction of three new TNM classifications: HPV/p16-mediated oropharyngeal carcinoma (OPC) [7, 8], HN soft tissue sarcoma (HN-STS) [9, 10], and HN unknown primary – cervical nodes (HN-CUP) [7, 11]; (2). modification of the definition of the T and/or N categories in nasopharyngeal cancer (NPC) [7, 12]; (3) modification of the T category by inclusion of the "*depth of invasion* (DOI)" variable for oral cavity squamous cell carcinoma (OSCC) [7, 13]; (4) modification of the N category by inclusion of the "*extranodal extension* (ENE)" variable for non-viral related mucosal HNC including salivary gland malignancies [11]; and (5) reintroduction of size in the T categories for non-Merkel cell cutaneous carcinoma of the head and neck [14, 15]. This review summarizes the changes and potential advantages and limitations/caveats associated with them.

New TNM classifications

HPV-mediated (p16+) OPC

In response to an urgent need to properly depict the character and prognosis of this new disease, a new stage classification has been introduced for HPV-positive OPC in the 8th edition TNM [7, 8] (Table 1). It is also the first time that separate clinical and pathological N-definitions and T-N groupings have been introduced in the HNC classification. The clinical staging (cTNM) based on the proposal of *the International Collaboration on Oropharyngeal cancer Network* (ICON-S) group is derived from a study of 1907 HPV-positive OPC from seven

Table 1. The 8th edition clinical and pathologic TNM classification for the HPV-mediated oropharyngeal cancer

HPV+ OPC	Clinical stage				Pathologic stage				
Category	T	N		M	T	N		M	
Stage I	T1, T2	N0: no regional LNs N1: ipsilateral LNs		M0	T1, T2	N0: no regional LNs N1: 1–4 LNs		M0	
Stage II	T1, T2	N2: bilateral or contralateral LNs		M0	T1, T2	N2: ≥ 5 LNs		M0	
	T3	N0: no regional LNs N1: ipsilateral LNs N2: bilateral or contralateral LNs		M0	T3, T4	N0: no regional LNs N1: 1–4 LNs		M0	
Stage III	T4	Any N		M0	T3, T4	N2: ≥ 5 LNs		M0	
	Any T	N3: >6.0 cm LN(s)		M0					
Stage IV	Any T	Any N		M1	Any T	Any N		M1	
Stage grid for non-metastatic (M0) HPV+ OPC									
Clinical stage group					Pathologic stage group				
cTcN	T1	T2	T3	T4	pTpN	T1	T2	T3	T4
N0	I	I	II	III	N0	I	I	II	II
N1	I	I	II	III	N1	I	I	II	II
N2	II	II	II	III	N2	II	II	III	III
N3	III	III	III	III	Not applicable				

LN lymph node

institutions in four countries across two continents using *training* (PMH) *validation* (six other institutions) design [16••]. The pathologic stage classification (pTNM) was based on a study of 704 surgically managed cases from five cancer centers [17••].

The new clinical and pathological TNM classification for HPV-positive OPC was needed because of better understanding disease behavior. Many studies have demonstrated the inadequacy of 7th edition TNM for predicting outcomes of HPV-positive disease [18, 19••], especially as relates to the classification of neck disease where limitations were noted in the previous decade [20]. HPV-specific staging is necessary for several reasons: (1) relevance to discussion with patient/family, (2) clinical trials design and stratification since they are now addressing HPV-positive and HPV-negative diseases separately, and (3) practice guidelines will probably differ for both diseases in the future. Separate classifications for HPV-positive and HPV-negative OPC also seem applicable for both clinical care and cancer surveillance. While high HPV prevalent jurisdictions need an HPV-positive OPC specific TNM, low HPV prevalence regions might be able to continue to use the traditional HPV-negative TNM classification since these are unlikely to impact on surveillance strategies at the population level. In addition, despite the significant survival difference between HPV-positive vs HPV-negative diseases, tumor HPV status identifies a biologically distinct disease entity underpinned by a definable and different molecular etiologic process. In this context, it provides a biomarker with diagnostic rather than prognostic utility for clinical management once the diagnosis is confirmed. In this

way, a separate staging is needed in an anatomic region where disease would otherwise lack biological consistency and homogeneity.

The ICON-S study derived cTNM for HPV+ OPC with the same methodology as a prior "discovery study" and refined a previously proposed RPA-based clinical TNM [19••] by moving T3N0-N2b from RPA-stage I into ICON-S stage II. It also re-termed 7th edition "N1-N2b" to ICON-S "N1" due to the OS similarity of these traditional N sub-categories while "N2c" is re-termed ICON-S "N2." The ICON-S stage classification is now incorporated into the UICC/AJCC 8th edition as the clinical TNM classification for HPV-positive OPC: stage I: T1–2_N0-N1; stage II: T1–2_N2 or T3_N0-N2; stage III: T4 or N3; and stage IV: any T or N with M1 disease (Table 1). Notably, the ICON-S N classification resembles that of NPC (another viral related pharyngeal cancer) but without a lower neck LN variable.

The presence of lower neck LNs is traditionally considered an adverse variable for NPC and was empirically included in its stage classification many decades ago. The ICON-S study analyzed the influence of radiologically overt level 4 or 5B LNs on an expanded Princess Margaret Hospital (PMH) cohort (n = 702) and showed that lower neck LNs also influence survival. However, the effect lacks independence on multivariable analysis and is typically linked to more advanced disease (T4 or N3 subset). For this reason, it was not included as an N classification variable in the proposal. The performance of the ICON-S classification (i.e., current 8th edition clinical TNM) was subsequently validated in other independent datasets [21, 22] and appears to outperform another clinical staging proposal using an NPC-like N classification introduced empirically without conventional hypothesis based statistical model generation. The latter defined level 4 LNs as lower neck LNs [23]. The reporting centre and these patients were also included in the ICON-S cohort.

Surgical series, largely managed by trans-oral approaches that include robotic surgery (TORS) or laser microsurgery (TLM), have shown that traditional prognostic factors, such as higher N category and extranodal spread (ENE), were no longer prognostic; in contrast, higher number of pathologic involved LNs conveys the greatest determinant of lower disease-specific survival [24••, 25, 26]. The most relevant cutoff for the number of pN+ appeared to be at ≥5 [24••]. Therefore, a cutoff of 5 LNs were included in the pTNM for HPV-positive OPC [17••]: stages I (pT1–T2, 0–4 LNs), II (pT1-T2, > = 5 LNs, or T3, 0–4 LNs), and III (pT3–T4, > = 5 LNs) (Table 1).

The differences in N classification stage grouping between clinical and pathological TNM likely reflect differences in case selection and inherent differences in assessment tools/criteria (cN based on clinical exam and imaging vs pN based on surgical specimen). Most surgical series are limited to T1-T2 tonsil or base of tongue tumors, with less representation of T3 and T4 tumors or N3 diseases. Therefore, the true impact of these diseases subsets might not yet be reliably reflected in the studies available to date.

The 8th edition TNM mandates p16 immunostaining positive as the surrogate for tumor HPV status while the presence of high-risk HPV by in situ hybridization (ISH) is an alternative. Concerns remain about detrimental consequences due to potential false positive. The rationale for using p16 as a surrogate is because it is generally accepted as a reliable surrogate marker for oncologically relevant HPV-driven tumor in oropharynx provided stringent criteria for scoring and interpretation are followed [27–29]. It is unlikely to be

misrepresented if the proper context is considered addressing correct anatomic subsite in the tonsil, base of tongue, or vallecula and a high priority to high staining intensity in a sufficient proportion of cells. This surrogate indicator is also agnostic to HPV subtype which is an advantage compared to HPV subtype specific testing methods which may lack sensitivity. The presence of high-risk HPV by polymerase chain reaction (PCR) method may not always indicate that the tumor is driven by HPV, i.e., HPV could be the "bystander." As well, it carries a better cost profile over other testing methods. However, when p16 staining is equivocal, HPV by ISH or PCR should be performed to confirm the presence/absence of high-risk HPV in tumor. If there was no confirmation of HPV status, it should follow the HPV-negative/p16-negative OPC TNM classification.

Of note, the 8th edition has classified T1–2 with unilateral neck nodes as stage I disease. The result is based on the current treatment paradigm where many such patients have traditionally received intensified treatment. Whether all of such patients are suitable for deintensification remains to be addressed by clinical trials.

HN-Soft Tissue Sarcoma

HN-STS is another new classification introduced in the 8th edition TNM. In the previous version, HN-STS used the same TNM classification as STS of other sites. Although they are biologically similar, HN-STS present some unique characteristics. The traditional 5-cm size cut-point separating T1 and T2 soft tissue sarcomas of the extremity and trunk lacks relevance for HN-STS since the majority of patients in recent studies do not even reach the 5 cm cutoff [30, 31]. Nonetheless, despite presenting with smaller tumors than in other sites, HN-STS often carry a greater local recurrence risk that is frequently ominous from a survival perspective, since salvage may be very problematic. Their anatomic location is more in line with traditional HNC in management philosophy in terms of resectability, emphasizing esthetic and functional considerations that have profound implications on patient decision-making.

In this edition, the 2-cm and 4-cm breakpoint for T category was arbitrarily chosen based on traditional HNC size criteria: T1 ≤2 cm, T2 >2 to ≤4 cm, T3 >4 cm, and T4—for very extensive tumors [9, 10] (Table 2). Whether this cutoff is appropriate for this disease remains to be evaluated. It is conceivable that a smaller size cut-point would facilitate data capturing for future risk stratification for many HN-STS. Notably, the N category remains the same as STS of other sites (N0: no overt regional LN; N1: regional LN metastasis). Due to lack of reports that incorporate grade, no anatomic stage grouping has been derived yet for STS which requires the inclusion of tumor grade and further data for analysis in the future.

HN-CUP and modification of N categories (inclusion of the extranodal extension)

An independent chapter describing the principles for staging of CUP in HN has been introduced in the AJCC Staging Manual. T0 will be assigned for all CUPs. For EBV-positive CUP and HPV-positive CUP, the N classification follows NPC and HPV-positive OPC definitions respectively and requires these biological assessments to direct their assignations. For the remainder, a modified N classification is instituted by inclusion of the ENE variable [7, 11] since the

Table 2. Definition of the T category in the 8th edition TNM for cancer of oral cavity, soft tissue sarcoma of the head and neck and cutaneous carcinoma of the head and neck

Definition of T category	
Oral cavity	
T1	• Size ≤2 cm and DOI ≤ 0.5 cm
T2	• Size ≤2 cm and DOI >0.5 but ≤1.0 cm, or • Size 2–4 cm, and DOI ≤ 1.0 cm
T3	• Size >4 cm or >1.0 cm
T4	• Moderately advanced or very advanced disease
Soft tissue sarcoma of the head and neck	
T1	• Size ≤2 cm
T2	• Size >2 cm but ≤4 cm
T3	• Size >4 cm
T4	• Tumor invading adjacent structures
Cutaneous carcinoma of the head and neck	
T1	• Size ≤2 cm
T2	• Size >2 cm but ≤4 cm
T3	• Size >4 cm, or • Minor bone erosion, or • Peri-neural invasion, or • Depth of invasion >0.6 cm or beyond the subcutaneous fat
T4	• Gross cortical bone/marrow/skull base invasion and/or skill base foramen invasion

presence of ENE has been shown to have as an independent adverse prognostic impact for non-viral related HNC [32•, 33, 34, 35•] (Table 3).

Notably, inclusion of ENE is applicable for both clinical and pathologic ENE, not only for CUP but also for all non-viral related HNC including salivary gland malignancies, with the exception of melanoma, STS, and thyroid cancer. However, the definition of clinical and pathological ENE is different. Most data supporting adverse impact of ENE is based on pathologic ENE. Several studies have shown that CT or MRI cannot be used to reliably determine the presence of pathologic ECS for HNSCC [36]. Therefore, clinical ENE has different criteria and only refers to those with unambiguous clinical/radiological evidence of gross ENE, such as dermal involvement or soft tissue invasion with deep fixation/tethering to underlying muscle or adjacent structures or clinical signs of nerve involvement. Ongoing work is needed to assess the reliability of CT or MRI based rENE for pENE and its clinical relevance [37]. Additional subtleties may additionally emerge in subsequent analyses relative to the degree of ENE involvement recognized in pathology assessment. For example, further definition of extent of ENE is encouraged: gross ENE is defined as clinical unambiguous ENE (ENEc). For pENE, the extent of ENE is further classified as: microscopic ENE (ENEmi): ENE ≤ 0.2 cm beyond nodal capsule; major ENE (ENEma): ENE > 0.2 cm beyond nodal capsule. Soft tissue deposits in the lymphatic drainage pathways without identifiable lymph node(s) would be recorded as

Table 3. The 8th edition N classification for non-viral related head and neck cancer and stage grouping for viral and non-viral unknown primary – cervical nodes

	N category for non-viral CUP and HNC		
N	Clinical N classification	Pathologic N classification	
N1	Single ipsilateral LN, ≤3 cm, no ENE	Single ipsilateral LN, ≤3 cm, no ENE	
N2a	Single ipsilateral LN, 3–6 cm, no ENE	Single ipsilateral LN, ≤3 cm, with ENE[a], single ipsilateral LN, 3–6 cm, no ENE	
N2b	Multiple ipsilateral LNs, ≤6 cm, no ENE	Multiple ipsilateral LNs, ≤6 cm, no ENE	
N2c	Bilateral or contralateral LNs, ≤6 cm, no ENE	Bilateral or contralateral LNs, ≤6 cm, no ENE	
N3a	Any LN >6 cm, no ENE	Any LN >6 cm, no ENE	
N3b	Any LN with clinical ENE[a]	A single LN >3 cm with pathologic ENE[b] Any multiple ipsilateral/bilateral/contralateral LN(s) with ENE	
Stage grouping for viral and non-viral-related CUP			
Stage	HPV+/p16+ CUP	EBV+ CUP	Non-viral related CUP
Stage I	T0_N1_M0	Not applicable	Not applicable
Stage II	T0_N2_M0	T0_N1_M0	Not applicable
Stage III	T0_N3_M0	T0_N2_M0	T0_N1_M0
Stage IV	Clinical: T0_N1–3_M1 Pathological: T0_N1–2_M1	IVA: T0_N3_M0 IVB: T0_N1–3_M1	IVA: T0_N2_M0 IVB: T0_N3_M0 IVC: T0_N1–3_M1

HNC head and neck cancer, *LN* lymph node, *ENE* extranodal extension, *CUP* cervical nodal metastasis with unknown primary
[a]Clinical ENE refers to unambiguous clinical/radiological evidence of gross ENE, such as dermal involvement or soft tissue invasion with deep fixation/tethering to underlying muscle or adjacent structures or clinical signs of nerve involvement
[b]Pathologic ENE could be further recorded as ENEmi: microscopic ENE ≤ 0.2 cm beyond nodal capsule; ENEma: major ENE > 0.2 cm beyond nodal capsule; soft tissue deposit within lymphatic drainage without identifiable LN would be recorded as pN+ and ENE+

positive LN with ENE+ because it would represent a LN totally replaced by metastatic tumor; such a nodule should be recorded as a positive LN with ENE [ENE(+)] [11].

Modification of T and/or N categories

NPC: modification of the T and N categories

A literature review revealed four major issues in the 7th edition TNM for NPC: a. ambiguity on definition of "masticator space" and its prognostic significance, uncertainty about the significance of "pre-vertebral muscle invasion," out dated terminology for the "supraclavicular fossa" in the contemporary anatomic nodal "levels," and questionable necessity of separate N3a and N3b subgroups. In response, the NPC stage classification in the 8th edition underwent notable changes to the T category definition as follows: (1) changing masticator and LP involvement from T4 to T2, (2) adding pre-vertebral muscle involvement as T2. In the N category, the "supraclavicular fossa (SCF)" (i.e., Ho's triangle) is replaced by a more conventional "lower neck" description that recognizes the use of

contemporary cross-sectional imaging (levels 4 and/or 5B LNs) [38] and merging this lower neck attribute with maximum nodal diameter > 6 cm as N3 (formally N3a and N2b), and (4) in stage grouping, T4 and N3 have been merged as stage IVA (formally stage IVA and IVB separately) [7, 12] (Table 4). All such changes are based on data from a combined study of 1609 NPC patients from Fujian and Hong Kong [39••].

The T and N category changes for NPC result from more accurate imaging permitting better delineation of tumor extent and early detection of occult metastases linked to advances in radiotherapy with increasing conformity of tumor coverage and sparing of uninvolved structures and by the contemporary use of combination chemotherapy that improves tumor control and cure rates, especially for advanced loco-regional disease. The 8th edition TNM also eliminated the ambiguity of "masticator space" or "infratemporal fossa" and allows

Table 4. Change of the T and N categories in the 8th edition compared to 7th edition TNM classification for nasopharyngeal cancer

	7th edition TNM	8th edition TNM
T1	Tumor confined to nasopharynx, or extends to oropharynx and/or nasal cavity without parapharyngeal involvement	No change
T2	Tumor with parapharyngeal extension	Tumor with parapharyngeal extension, and/or adjacent soft tissue involvement (medial or lateral pterygoid, and/or pre-vertebral muscles) **Change: medial or lateral pterygoid extension from T4 to T2; adding pre-vertebral muscle involvement as T2*
T3	Tumor involves bony structures of skull base and/or paranasal sinuses	Tumor invades bony structures of skull base cervical vertebra, pterygoid structures, and/or paranasal sinuses
T4	Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, or with extension to the infratemporal fossa/masticator space	Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, parotid gland and/or infiltration beyond the lateral surface of the lateral pterygoid muscle **Change: eliminated the ambiguous terminology of "infratemporal fossa" and "masticator space"*
N0	No regional LN	No change
N1	• Unilateral cervical LN(s), ≤6 cm, above supraclavicular fossa, and/or • Unilateral or bilateral RPLN(s), ≤6 cm	**Change: replacing "supraclavicular fossa" with "caudal border of cricoid cartilage"*
N2	Bilateral cervical LN(s), ≤6 cm, above supraclavicular fossa	**Change: replacing "supraclavicular fossa" with "caudal border of cricoid cartilage"*
N3	N3a: metastatic LN(s) > 6 cm N3b: metastatic LN(s) extend to supraclavicular fossa	**Change:* • *Replacing "supraclavicular fossa" with "caudal border of cricoid cartilage"* • *Merging previous "N3a" and "N3b" as "N3"*

In the 8th edition, the definition of lower neck lymph nodes is defined as any lymph node below "caudal border of cricoid cartilage" (replacing previous definition of "below supraclavicular fossa"). Since there is no subdivision of N3a and N3b, the T4 and N3 M0 is merged as stage IVA while M1 disease is IVB

LN lymph node, *RPLN* retropharyngeal lymph node

a clearer description of anatomical criteria for extensive soft tissue involvement that comprises T4 diseases.

Although pre-treatment plasma or serum EBV-DNA copy number has been shown to be prognostic and reflects tumor burden in many studies [40–44], it was not incorporated in the 8th edition TNM classification. Challenges arise from both feasibility and practicality. Problems include lack of standardization and harmonization of testing methods between laboratories; most particularly, a substantial proportion (>20%) of patients seem not to have detectable viral copies [40] rendering it impossible to include it in a classification intended for the disease overall. Finally, the assay is not universally available in endemic jurisdictions.

Gross tumor volume (GTV) [45–47] is another factor proposed previously by several studies but is not included in the cTNM for NPC in the 8th edition. Paucity of data on the reliability and practicality in deriving this parameter by radiologists on diagnostic imaging on a large population based scale has hindered its inclusion in the current edition.

OSCC: modification of the T categories (inclusion of depth of invasion)

Depth of invasion (DOI) or tumor thickness is another dimension of tumor size and likely reflects the proximity to underlying lymph-vascular structure. It has been reported as a good predictor of the presence of pathologic overt LNs (LNs) [48–51]. Based on a study of 3149 patients by the *International Consortium for Outcome Research in Head Neck Cancer* [52••], the 8th edition TNM includes this parameter in the definition of T categories for oral cavity cancers using cutoffs of 0.5 and 1.0 cm for T1, T2, and T3 tumors, respectively, according to the following criteria: T1: ≤2 cm in maximum size and ≤0.5 cm in DOI; T2: ≤2 cm in maximum size with DOI between 0.5–1.0 cm, or 2–4 cm sized lesion and DOI ≤1.0 cm; and T3: >4 cm in size or any tumor with DOI >1.0 cm [7, 13] (Table 2).

The inclusion of DOI is applicable to all OSCC subsites, although it is primarily derived from studies focusing on oral tongue. Data regarding its applicability in other subsites in OSCC is lacking. In addition, it is introduced for both pTNM and cTNM. The latter may be challenging in practice because there is a paucity of data reporting the reliability of measuring DOI on radiologic imaging or clinical examination, although a few small studies have indicated some promising results of measuring this parameter on CT [53] or MRI [54]. Such studies all suffer from small sample size and lack of inter-rater and intra-rater concordance. The concordance and reliability of assessing clinical/radiologic DOI against pathologic DOI and its clinical relevance remain to be evaluated.

HN cutaneous carcinoma: modification of T category (reintroduction of tumor size criteria)

In the non-Merkel cell cutaneous carcinoma of the head and neck chapter of the 8th edition TNM, size criteria were reintroduced for T classification because many studies have shown a strong correlation between tumor size and more biologically aggressive disease [55–59]. The cutoff point for primary size is now in line with other mucosal HNSCC where a ≤ 2 cm primary is classified as T1, and a 2–4 cm primary is classified as T2, a larger tumor (>4 cm) or with other

high-risk features is classified as T3 (DOI > 0.6 cm or peri-neural invasion or minor bone erosion) or T4 (major invasion of bone or skull base) [14, 15].

Conclusion

The TNM stage classification is a universal language for cancer care. It is used by clinicians, researchers, cancer registrars, and policy makers. The evolution of treatment and continuing understanding disease behavior necessitate periodic updates to maintain relevance for contemporary cancer management. The changes introduced in the 8th edition TNM better reflect tumor biology and clinical behavior (e.g., HPV-mediated OPC, HN-STS), improved outcomes associated with technical advances in diagnosis and treatment (e.g., NPC), evolving knowledge about prognostic factors and risk stratification from research and observation (e.g., inclusion of DOI variable for OSCC, and inclusion of ENE variable for all non-viral HNC, and reintroduction of size criteria for HN cutaneous SCC). Ideally, changes should be based on reliable data with sound methodology even though not all proposals can be driven by ideal evidence but can be accepted if the classification has not previously addressed the needs of practitioners or patients (e.g., HN-STS). Improving the TNM classification frequently requires collaboration, compromise, attention to all goals of TNM, and must consider practicality, reliability, and feasibility. Collecting and generating good evidence and data is fundamental to further improve TNM to meet global needs for cancer care and cancer control.

Compliance with Ethical Standards

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

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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