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The new 8th edition of TNM staging and its implications for skin cancer

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The new 8th edition of TNM staging and its implications for skin cancer: a review by the British Association of Dermatologists and the Royal College of Pathologists, United Kingdom.

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Short title: New 8th edition of TNM staging and implications for skin cancer

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SUMMARY

The 8th edition of TNM (Tumour, Node and Metastasis) has numerous and important changes compared to the 7th edition. Public Health England (PHE) and the Royal College of Pathologists, United Kingdom (RCPATH) have adopted the 8th edition of TNM (TNM8) published by the Union for International Cancer Control (UICC) for skin cancer staging. These changes will have an impact on the management of both non-melanoma and melanoma skin cancer by all members of the skin cancer multidisciplinary team. These will also need to be highlighted to commissioners and managers for appropriate service planning.

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T1 to T3 categories for non-melanoma skin cancer (NMSC) staging require the clinician to measure the maximum dimension (usually diameter) of every potential invasive cancer. This measurement must be recorded in the patient record *and* entered on the histopathology specimen request form. The clinical measurement should be expressed in whole millimetres and a standardised national request form would promote this overall aim.

For squamous, basal and adnexal carcinomas, but not Merkel cell carcinoma (MCC), the T1 to T3 categories are defined by new 20 and 40 mm divisions based on the maximum dimension of the lesion. In addition, new risk factors upstage T1 or T2 to T3. These include deep invasion (a tumour depth greater than 6 mm and/or invasion beyond the subcutaneous fat), or specifically defined perineural invasion. Unlike TNM7, tumour site and histological differentiation are not included in TNM8 staging.

For melanoma, although ulceration still remains, mitotic index no longer influences separation of pT1 into pT1a and pT1b subdivisions. Instead there is a new additional stratification level at 0.8 mm Breslow thickness. Subdivision pT1b, with a *negative sentinel lymph node biopsy* (pN0), is now stage IA compared to the previous IB and therefore now has a NICE recommendation for a 1-year rather than 5-year follow-up. The pN subdivisions require information on whether involved lymph nodes are clinically occult or detectable; information that must be recorded clinically and conveyed to the reporting pathologist.

For MCC, sentinel lymph node biopsy (SLNB) is now included specifically in the pN staging system. The pT1 subdivision requires clinical information as to whether histologically involved nodes were clinically occult or detectable. This, like the maximum tumour diameter for other NMSC, is clinical information which must be recorded and made available to the reporting pathologist for staging purposes.

Eyelid carcinoma continues to have a staging system different from general skin and the system is substantially revised in TNM8.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- Knowledge of cancer stage is essential for optimal patient management.
- Cancer stage includes tumour characteristics, regional extension to lymph node(s) and the presence of any distant metastasis (termed TNM stage or stage group)
- TNM7, published in 2010, formed the basis of the professional datasets to handle and report skin cancer specimens, published online by the RCPATH (www.rcpath.org).

WHAT DOES THIS STUDY ADD?

- The new 8th edition of TNM was published in late 2016. Both PHE and RCPATH have adopted the UICC TNM8 version, because the AJCC8 staging system for cutaneous squamous cell carcinoma (cSCC) only relates to primary tumours on the head and neck. Otherwise, for other skin cancers, UICC8 and AJCC8 are very similar.
- TNM8 displays significant changes in the staging of skin cancers, including cutaneous melanoma, cSCC, basal cell carcinoma (BCC), MCC and adnexal carcinomas. These changes have important clinical implications.

- For NMSC, there is a new responsibility for every clinician to measure and record the maximum clinical dimension (usually diameter) of every lesion to establish its T category. It is imperative that this measurement is conveyed to the histopathologist on the pathology request form.
- For melanoma and MCC, the pN staging requires information on whether involved lymph nodes (LNs) are clinically detectable (by palpation and/or imaging) or clinically occult (detected histologically or cytologically by LN sampling). The referring clinician now has an additional responsibility to convey information on the presence or absence of clinically or radiologically suspicious LNs to the histopathologist.
- pT1b melanoma, *with a negative sentinel lymph node biopsy*, is now stage IA and not IB, with a consequent NICE recommendation of a 1-year and not 5-year follow-up.
- For SCC, anatomical site and tumour differentiation no longer influence pathological staging.
- TNM8 highlights important differences between the staging systems of eyelid non-melanoma skin cancer compared to other cutaneous sites. Both clinicians and pathologists need to be aware that eyelid tumours are staged using a different system in TNM8.
- pT1a vs. pT1b melanoma continues to be stratified by ulceration. A mitotic index, however, of $\geq 1/\text{mm}^2$ is no longer a criterion and instead, 0.8 mm Breslow thickness becomes a new criterion for the subdivision. It should be emphasised that pT1b N0 M0 now falls into pathological stage 1A.

BACKGROUND

The previous 7th edition of the TNM (Tumour, Node and Metastasis) staging system, published by the American Joint Committee on Cancer (AJCC), failed to give the degree of discrimination required in cSCC risk stratification, with the T2 group emerging as too large and too few cases being staged as T3 and T4. The Brigham and Women's Hospital tumour staging system constituted a proposed alternative, but failed to contain a major staging criterion for cSCC; namely, measured tumour depth/thickness.²

Accordingly, the publication of the 8th edition of TNM (TNM8) was awaited with interest. TNM8 was published in late 2016, with a version from both the AJCC and the Union for International Cancer Control (UICC).^{3,4} In the United Kingdom (UK), TNM8 was implemented from 1st January 2018. The transition into practical use, by histopathologists and skin cancer multidisciplinary teams (MDTs), will follow shortly after. Full revision by Public Health England and the National Cancer Registration and Analysis Service (NCRAS), to include site-specific skin data, will follow in 2020 with the next edition (version 9) of the Cancer Outcomes and Services Dataset (COSD). The current COSD (version 8), however, has a core section which permits the use of different editions of TNM staging, although the edition being used in pathology reports and MDTs must be recorded at the time of data entry.⁵ During 2018, an important part of the UK transition to TNM8 will be on-line publication by the RCPATH of new TNM8 datasets for the histopathological reporting of skin cancers (www.rcpath.org). To assist this, the TNM8 Appendices of the draft datasets were published on-line in December 2017. These are based on the original UICC TNM8 publication, subsequent online errata (www.uicc.org) and professional interpretation of some UICC terms.³ **It should also be emphasised that the UICC is effectively the international custodian for TNM7 and in the UK, UICC is generally regarded as the most appropriate version for cancer staging.** AJCC is published primarily for use in the United States of America. Although AJCC7 was used in the UK for skin cancer TNM7, this was because of

publication errors in UICC7. UICC and AJCC work closely together and, in most instances, the TNM version of each organisation is the same or very similar. Unlike UICC, however, AJCC operates by a licence model for usage, with the requirement of payment of an institutional annual fee. Unexpectedly, AJCC was wanting in its TNM8 edition, by limiting the staging system for cSCC to the head and neck. In contrast to TNM7, a staging system for cSCC of trunk and limbs was not provided. By comparison, UICC TNM8 provides two chapters for skin carcinoma; one covering primary sites of the head and neck (titled *Skin Carcinoma of the Head and Neck*) and one covering trunk and limbs (titled *Carcinoma of the Skin*). The UICC terms skin carcinoma or carcinoma of the skin, in common with the AJCC cSCC chapter, incorporate not only cSCC but also basal cell and adnexal carcinoma. It must be noted however, as previously, that carcinoma of the vulva, penis, perianal skin within 5 cm of the perianal margin and eyelid have their own separate TNM8 staging systems. Genital and perianal carcinomas are not considered in this review in view of their specialist nature. Some eyelid carcinomas are managed by ophthalmic surgeons and reported by ophthalmic pathologists. Many, however, are managed by dermatologists, maxillofacial or general plastic surgeons and reported by non-ophthalmic histopathologists. Accordingly, eyelid carcinoma is covered in this review. This appears particularly appropriate because, whereas AJCC lists eyelid tumours under an ophthalmic heading, UICC places eyelid tumours under the general heading of *Skin Tumours* and specifically uses the subheading *Carcinoma of Skin of the Eyelid*. In addition, as some pathologists and MDTs have inappropriately staged eyelid carcinoma under general cSCC or BCC (NCRAS personal communication to DNS), the inclusion of eyelid heightens awareness of its separate staging system. This may partly have resulted from COSD not having an ophthalmic site-specific entry. Additionally, separate staging systems/chapters are provided in TNM8 for cutaneous melanoma and Merkel cell carcinoma (MCC). MCC of the vulva, penis and eyelid are staged using the MCC and not their own system. UICC8, unlike AJCC8, has continued, in common with UICC and AJCC TNM7, to place NMSC of the vermilion (non-hair bearing) lip in the staging chapter for lip and oral cavity and not skin carcinoma.

Overall, the two chapters in UICC8 and AJCC8 for cSCC TNM8 of the head and neck are essentially identical. In addition, the main difference in TNM8 chapters between UICC8 skin carcinoma of the head and neck and carcinoma of the skin (i.e. trunk and limbs) is in the pN (node) category. Unlike the carcinoma of the skin, skin carcinoma of the head and neck incorporates extranodal extension and laterality into its staging criteria. This matches the TNM8 nodal staging system for mucosal head and neck cancer.

These observations on TNM8 provided support for PHE and the RCPATH to jointly adopt UICC8 and not AJCC8, for skin cancer staging in the UK. **Hence, it should be emphasized that UICC8 will be used in the following sections and tables of this article unless clearly stated otherwise.**

The main changes for the T, N and M categories and TNM stage/stage group are given below. Primarily, these have used the pathological (p) TNM classification rather than the clinical (c) classification. This is because MDTs use the pTNM classification for final staging / stage grouping when all pathological information is available. In practice T (i.e. cT) is often identical to pT.

The main changes between UICC/AJCC TNM7 and UICC8 TNM8 are summarised in Table 1.

SQUAMOUS CELL, BASAL CELL AND ADNEXAL CARCINOMA

pT (tumour) category

Compared to TNM7, the pT1 to pT3 categories are now defined by stratification using new numerical divisions of maximum lesion dimensions. In addition, there are new risk factor criteria to upstage pT1 or pT2 to pT3. In addition, and unlike TNM7, clinical site (ear and lip) and

a poorly differentiated tumour grade no longer have a role in pT upstaging. The evidence base for the removal of poor differentiation grade is not stated, although it has long been acknowledged to be of strong prognostic importance.

The pT categories of T1 and T2 are now defined by stratification of the maximum tumour dimension (usually diameter) at 20 or 40 mm divisions. T1 and T2 can be upstaged to T3 by the presence of one or more risk factors comprising specifically defined perineural invasion or deep invasion, representing either a tumour depth greater than 6 mm and/or invasion beyond the subcutaneous fat; the latter includes any type of tissue excluding bone. T3 is also defined by minor bone erosion, T4a is defined by gross cortical or marrow invasion and T4b by axial skeleton/skull base or foraminal invasion. If perineural invasion is present, it must be assessed whether it conforms to the specified type required to upstage to T3. UICC8 states this is in a named nerve, which may be detected clinically or by imaging. Unfortunately, UICC8 does not contain a pathological definition for upstaging perineural invasion. Named nerves, however, are larger calibre in nature, ≥ 0.1 mm in diameter and located beyond the dermis. UICC are aware of the omission and it is under consideration to be adopted. This would also be consistent with other staging systems and publications that have used these criteria in the same way.²

UICC and AJCC versions of TNM8 are very similar but currently not identical. The UICC version appears preferable. UICC8 stratifies T1, T2 and T3 at ≤ 20 mm, >20 mm to ≤ 40 mm and >40 mm, respectively. This format of stratification is identical to that used for Merkel cell carcinoma, tumours of the lip and oral cavity, and NMSC in TNM7.

AJCC8 states that the maximum lesion dimension (usually diameter) to define a T1-T3 category should now be obtained by clinical measurement. Pathological measurement is, however, permitted if the clinical one is not available. UICC8 is less specific on this point but states that it should be by physical examination. It is logical that any pathological data used, if required, should be the macroscopic measurement as this is most comparable, unless in a particular case use of a microscopic one is unavoidable.

The macroscopic maximum diameter of a lesion has always been a core item in the RCPATH skin cancer datasets. TNM8, however, now places a new responsibility on all clinicians to record the measured maximum clinical dimension of a lesion in the patient record and to always supply this information to the pathologist on the histopathology request form that accompanies the specimen. This must apply to every lesion as, unless there has been a previous biopsy, there will always be a degree of diagnostic uncertainty clinically. The opportunity to measure a lesion in an unfixed state is lost once the specimen is placed in formalin and undergoes shrinkage. It is recommended that the measurement is made in whole millimetres to parallel other histopathological measurements and the staging of eyelid carcinoma. A standardised national request form would help to achieve this aim.

pN (node) category

As with TNM7, UICC TNM8 still bases nodal staging on the size, number and location of positive nodes, although minor differences exist between TNM7 and TNM8. Similarly, UICC TNM8 carcinoma of the skin and skin carcinoma of the head and neck display minor differences. The pN categories of UICC TNM8 carcinoma of the skin (trunk and limbs) are based purely on ipsilateral nodes, whereas contralateral involved nodes are regarded as distant metastases. For single positive nodes, pN stratification for pN1, pN2 and pN3 is still ≤ 30 mm, >30 mm to 60 mm and >60 mm, respectively. Multiple nodes that are ≤ 60 mm are also pN2. The pN categories of

UICC TNM8 skin carcinoma of the head and neck and carcinoma of the skin are similar with regard to the size of nodes and number, although for the former single and multiple nodes ≤ 60 mm in pN2 are defined as pN2a and pN2b, respectively. A bilateral or contralateral node that is ≤ 60 mm for head and neck is defined as pN2c and a positive node >60 mm is defined as pN3a.

A major development in pN3 in UICC TNM8 head and neck is the recognition of extranodal extension/spread/invasion (ENE). ENE was not part of staging in TNM7 but is a major adverse prognostic factor. ENE can be detected clinically or pathologically and its presence with an involved node defines pN3b. If clinical and/or imaging evidence of ENE is identified, this information must be conveyed to the pathologist on the specimen request form, to be incorporated in the nodal staging system.

Currently, the role of sentinel lymph node biopsy (SLNB) in cSCC remains uncertain and is not included in TNM8.

pTNM8 stage/ stage group

The pTNM8 stage group is largely similar to that in TNM7. UICC TNM8, however, divides Stage IV into Stage IVA and Stage IVB depending on the absence or presence of a distant metastasis.

CUTANEOUS MALIGNANT MELANOMA

It must be noted that the originally published book version of UICC TNM8 for melanoma contained errors in pT1. These have now been corrected under UICC website errata and both UICC8 and AJCC8 versions for melanoma are now the same. Eyelid melanoma may arise from the eyelid skin (anterior eyelid lamella) or from the conjunctiva (posterior eyelid lamella). These should be staged as cutaneous or conjunctival melanoma respectively.

pT (tumour) category

In pT1, mitotic index no longer has a role in defining pT1a and pT1b subdivisions although it remains a major prognostic indicator. As in TNM7, ulceration still remains a criterion for a and b subdivision for pT1-4. With or without ulceration, however, pT1a and pT1b subdivision is now additionally achieved by stratification at 0.8 mm Breslow thickness. The AJCC Melanoma Expert Panel, using the International Melanoma Database, has shown that ulceration and stratification at 0.8 mm were stronger predictors of melanoma-specific survival than mitotic rate.⁶ For the first time, melanoma Breslow thickness is now measured to one decimal point and not two. The majority of pathologists will support this modification.

pN (node) category

Involved lymph nodes are now defined as clinically occult (e.g. positive on SLNB) or clinically detected, rather than microscopic or macroscopic as in TNM7.

New N1, N2 and N3 categories are defined, with N1c, N2c, N3c representing satellite, microsattellite or in-transit metastases with either 0, 1 or ≥ 2 associated positive nodes, respectively.

It is vital that clinicians inform the reporting pathologist on the specimen request form, whether involved lymph nodes are clinically occult or detectable, so that the information can be incorporated into pN category staging.

M category

M1d is a new subdivision representing involvement of the central nervous system.

When known, lactic dehydrogenase receives a (0) or (1) M suffix (for non-elevated and elevated, respectively) for each M subdivision.

pTNM stage/stage group

Stage IA, with a negative sentinel lymph node biopsy (pN0), now includes pT1b. This is clinically relevant as NICE recommends a 1-year follow-up, and not a 5-year follow-up as previously the case when categorized under stage IB in TNM7.⁷ The UICC TNM8 stage for pT1b, with no clinical nodal enlargement and *when no sentinel lymph node biopsy has been undertaken*, is not stated clearly in the TNM publications, although this is expected to be clarified in a forthcoming publication of the UICC TNM8 Supplement (personal communication, D.N. Slater). In the interim, the BAD and RCPATH consider it appropriate to interpret this situation as clinical stage IB and for the patient to have a 5-year and not 1-year follow-up. It should be noted that the pT1 changes in TNM8 staging have no effect on the choice of sentinel lymph biopsy, as this is qualified by the additional requirement of a Breslow thickness over 1 mm. Stage IIID is new to incorporate pT4b and N3. It should be observed, however, that the NICE guideline on melanoma was based on TNM7 and this therefore may necessitate a review of its recommendations in the context of TNM8.

MERKEL CELL CARCINOMA

pT (tumour) category

The pT1 to pT4 categories remain the same as in TNM7. As with squamous cell, basal cell and adnexal carcinoma, however, the maximum dimension (usually diameter) of the lesion, on which the categories are based, should be a clinical measurement, although a pathological measurement can be used if a clinical one is not available.

pN (node) category

pN1 is now divided into pN1a (sn) and pN1a, representing positive clinically occult node(s) on SLNB and lymphadenectomy, respectively. This implies a possible new role for SLNB in the staging and management of MCC.

pT1a and pT1b subdivisions all require clinical information as to whether the nodes were clinically occult or clinically detectable and this information must be conveyed to the reporting histopathologist. In-transit metastasis is now staged as pN2 or pN3 according to whether lymph node(s) are microscopically negative or positive.

pTNM stage /stage group

Stages I, II and III in UICC TNM8 are all new. Stage IIIA now incorporates the specific clinical situation of no primary cutaneous tumour (T0) but clinically detectable and microscopically confirmed nodal involvement (pNb).

EYELID CARCINOMA

pT (tumour) category

For the greatest lesion dimension, pT1, pT2 and pT3 have new stratification divisions of ≤ 10 mm, >10 to ≤ 20 mm and >20 to ≤ 30 mm, respectively. Neither UICC8 or AJCC8, perplexingly, include a measurement for > 30 mm.

a, b and c subdivisions, respectively, now represent no involvement of the tarsal plate or eyelid margin, involvement of the tarsal plate or eyelid margin and involvement of full thickness of eyelid.

pN (node) category

N1 and N2 are new and represent involvement by node(s) ≤ 30 mm and >30 mm, respectively.

pTNM stage/stage group

Stages II and III are both new.

CONCLUSIONS

The changes in TNM8 for skin cancer will have a significant impact on clinical practice.

For NMSC, the principal effect will be the necessity for the maximum clinical dimension (usually the diameter) of every potential case to be entered in the patient record. This information must also be entered on the specimen request form, to enable TNM staging by the pathologist and skin cancer MDT.

For both NMSC and melanoma, nodal staging will place an additional obligation on clinicians to inform pathologists whether nodal disease is occult or clinically detectable.

For MCC, a new nodal staging category for a positive SLNB implies a possible greater role for SLNB in the management of MCC.

For eyelid carcinoma, a substantially revised tumour and nodal staging system has been introduced. It is desirable that the separate staging system for eyelid carcinoma is better recognised and is better used by pathologists and skin cancer MDTs.

It appears highly likely that TNM8 staging will have major role in the risk stratification and clinical follow-up of cSCC and it is expected that these areas will be covered in the next edition of the BAD guidelines on cSCC. It should be noted, however, that UICC8 introduces the concept of risk stratification using prognostic grids, incorporating stage, tumour parameters, host factors, environment and other significant factors.

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Table 1. A summary of the main changes in skin cancer, comparing the previous UICC/AJCC TNM7 with the new UICC TNM8

	TNM7	TNM8
MELANOMA		
T category <i>T1a or T1b</i>	Subdivision based on ulceration or mitotic index $\geq 1/\text{mm}^2$	Subdivision based on ulceration or stratification at 0.8 mm Breslow thickness
N category <i>Positive node terminology</i> <i>Satellite or in-transit metastasis</i>	a or b subdivision indicating micrometastasis or macrometastasis, respectively N2c or N3 when nil or involved node, respectively	a or b subdivision indicating clinically occult or detected, respectively N1c or N2c or N3c when nil or 1 or ≥ 2 involved nodes, respectively
M category <i>Central nervous system involvement</i> <i>Serum LDH</i>	M1c M1c if elevated	M1d New (0) or (1) suffix for each M division if non-elevated or elevated, respectively
pTNM stage <i>pT1b</i>	IB (5-yr recommended follow-up by NICE)	IA <i>with negative sentinel node</i> (1-yr recommended follow-up by NICE)
NON-MELANOMA SKIN CANCER		
T category <i>Maximum lesion dimension (usually diameter)</i>	Based on pathological measurement N.B. Measurements in whole millimetres	Based on clinical measurement
SQUAMOUS CELL, BASAL CELL AND ADNEXAL CARCINOMA		
T category <i>Stratification of greatest lesion dimension</i> <i>Upstaging</i>	T1/2 division at 20 mm T1 to T2 if two or more >2 mm thickness, invasion at or below reticular dermis, perineural invasion, poorly differentiated or ear or hair-bearing lip location	T1, T2 and T3 at ≤ 20 mm, >20 mm to ≤ 40 mm and >40 mm, respectively T1 or T2 to T3 if one or more of deep invasion (>6 mm thickness and/or beyond subcutaneous fat) or specified perineural invasion (invasion of a named nerve clinically or by imaging or histologically in a nerve of diameter

		≥0.1 mm or below the dermis)
N category <i>Extranodal extension (head and neck only)</i>	Not included in staging	N3b. Present clinically or pathologically with an involved node.
	N.B. Additional minor differences exist between TNM7 and TNM8 and between carcinoma of the skin and skin carcinoma of the head and neck	
MERKEL CELL CARCINOMA		
N category <i>Positive node terminology</i>	a or b subdivision indicating micrometastasis or macrometastasis, respectively	a or b subdivision indicating clinically occult or detected, respectively
<i>Positive clinically occult node</i>	N1a micrometastasis	N1a (sn) (with SLNB) N1a (with lymphadenectomy)
<i>In-transit metastasis</i>	N2	N2 or N3 if nodes microscopically negative or positive, respectively
pTNM stage	Stage groupings as published	Stages I, II and III in UICC TNM8 are all new. Stage IIIA now incorporates the specific clinical situation of no primary cutaneous tumour (T0) but clinically detectable and microscopically confirmed nodal involvement (pNb).
EYELID CARCINOMA		
T category <i>Stratification of greatest lesion dimension</i>	T1, T2 and T3 divisions by ≤5 mm, >5 to ≤20 mm and >20 mm or perineural invasion, respectively	T1, T2 and T3 divisions by ≤10 mm, >10 mm to ≤20 mm and >20 mm to ≤30 mm, respectively
	N.B. a and b subdivisions of T2 by either stratification at 10 mm or tarsal plate, margin or full thickness involvement, respectively	N.B. a, b, c subdivisions of the T1, T2 and T3 divisions by no involvement of tarsal plate or eyelid margin, involvement of tarsal plate or eyelid margin and involvement of full thickness, respectively
N category <i>Stage</i>	N1 positive node	N1 positive node ≤30 mm; N2 positive node >30 mm

This table is based on the online RCPATH TNM8 Appendices for skin cancer (www.rcpath.org). These are based on the original UICC TNM8 publication, subsequent online errata (www.uicc.org) and professional interpretation of some UICC terms.³