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Setting the stage: Contemporary staging of non-melanomatous skin cancer and implementation of the new American Joint Committee on cancer eighth edition staging manual

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ABSTRACT

Non-melanomatous skin cancer (NMSC) generally refers to basal cell and squamous cell carcinoma of the skin. The majority of patients are curatively treated with simple excision. Only few present with locally advanced disease or have evidence of high-risk features, placing them at an elevated risk of relapse. In such cases, further investigations may guide the multidisciplinary management plan. There are no universally agreed on indications for recommending additional staging investigations, due to a lack of prospective data reporting their impact on patient outcomes. Some generally agreed upon indications are discussed in this review article. Most commonly, computed tomography (CT) and magnetic resonance imaging (MR) are used in cases of locally advanced NMSC for staging purposes and surgical planning. While Positron Emission Tomography (PET)/CT and sentinel lymph node biopsy have shown utility, data is lacking to establish their roles in the staging algorithm. An updated NMSC system was included in The American Joint Committee for Cancer eighth edition staging manual (AJCC8). Under AJCC8 the majority of patients with regional disease are upstaged by the presence of extranodal extension, however, this updated system appears to provide limited prognostic discrimination between the nodal categories and the overall TNM stages. This review article will explore the contemporary role of staging investigations, including evolving technologies, and review the changes implemented in AJCC8. It will also discuss the implications of the AJCC8 decision to assign patients with p16-positive cervical nodal SCC with an unknown primary to the oropharyngeal staging system, with particular relevance to clinicians working in areas of high NMSC incidence.

Introduction

The term non-melanomatous skin cancer (NMSC) includes a range of skin neoplasias, but generally refers to the most common malignancies worldwide; cutaneous basal cell (BCC) and squamous cell carcinomas (cSCC) [1]. Worldwide, Australia has the highest incidence of NMSC as a consequence of high ultraviolet exposure to a predominantly fair-skinned population [2,3]. BCC's account for the vast majority, with approximate rates of 884/100,000 and 387/100,000 person years for BCC and cSCC in Australia, respectively [4]. There, the incidence and mortality rates from NMSC have increased over recent decades [5,6], although this could possibly represent improved reporting in an aging population. The vast majority of NMSC's occur in the sun-exposed areas of the head and neck region [7,8]. The standard treatment of localized NMSC is simple surgical excision while obtaining clear surgical margins, which on its own is often curative. Approximately 5% of all cSCC

Abbreviations: AJCC8, American Joint Committee for Cancer 8th edition staging manual; AJCC7, American Joint Committee for Cancer 7th edition staging manual; cSCC, Cutaneous squamous cell carcinomas; cHNSCC, cSCC of the head and neck; mHNSCC, mucosal head and neck SCC; PNI, perineural invasion; ECE, extranodal extension; CUP-SCC, SCC in cervical lymph nodes with an unknown primary; OPC, oropharyngeal cancer; BWH, Brigham and Women's Hospital; FNA, fine needle aspiration (FNA)

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of the head and neck (cHNSCC), will spread to regional lymph nodes, heralding a significant shift in prognosis and treatment-related morbidity [9–12].

The work-up and staging of patients with NMSC is evolving, although strong evidence is generally lacking. Most NMSC are staged primarily by pathological means at curative excision, and only patients with a suspicion of local extension or nodal disease require further investigation with cross-sectional imaging, for example, where there is suspicion of deep soft tissue or bone involvement or where there are symptoms of perineural spread (PNS) detected [13]. While the term perineural invasion (PNI) typically refers to histopathological evidence of tumour cells within a nerve sheath, radiological evidence is more commonly referred to as PNS, and magnetic resonance imaging (MR) is considered the optimal imaging modality for assessment, while additionally providing the most accurate determination of soft tissue invasion. Computed-tomography (CT) is often utilised where there is suspicion of bone invasion or there is a clinically-positive neck. Emerging staging modalities in cSCC staging include positron-emission tomography/computed-tomography (PET/CT) and sentinel lymph node biopsy (SLNB), although their exact place in the staging schema requires further research [13,14].

The eight edition of the American Joint Committee for Cancer (AJCC8) manual was released in 2016, with significant changes to the NMSC staging system (Table 1). The most significant changes were to the risk factors used to upstage the T-category of small skin lesions and, for the first time, extranodal extension (ENE) was included, resulting in the vast majority of node-positive cases being upstaged from the 7th edition [1]. A further recommendation was that where there is pathological confirmation of p16-positive SCC in cervical lymph nodes with an unknown primary (CUP-SCC), that patients be staged according to the HPV-associated oropharyngeal cancer (OPC) system. This particular directive poses challenges to clinicians working in areas with a high NMSC prevalence.

The objectives of this article are to review:

- The indications and utility of contemporary staging investigations in NMSC
- AJCC8 changes to NMSC staging and its effectiveness in prognostication
- Challenges in the staging system to clinicians working in areas with a high prevalence of NMSC

Contemporary Work-up and investigation of NMSC

Any lesions suspicious for NMSC should be assessed with a full history and physical examination, including a comprehensive skin examination. A biopsy should be performed on all suspicious lesions to characterise the histological subtype and identify adverse features for risk-stratification. Further investigations can be used more judiciously in advanced cases of NMSC, based on history, examination and pathological findings. These investigations include ultrasound (US), CT, MR, PET/CT and SLNB.

Further staging investigations may assist the treating clinician in treatment planning by establishing:

- Tumour size, depth and involvement of underlying structures such as muscle and bone
- The presence of nodal disease, including radiological features suggesting ENE
- PNS
- Metastatic disease

Initial utilization of cross-sectional imaging in NMSC

Although though there are consensus guidelines for the use of staging investigations in NMSC [13,14], imaging protocols are not uniformly agreed on. In selected cases, staging imaging may alter management and should be considered in the following circumstances:

- Tumour diameter ≥ 2 cm
- Poorly differentiated histology
- Tumors with deep soft tissue (beyond subcutaneous fat) [15] or bone invasion [16].
- Possible orbital involvement [17]
- Clinical symptoms of PNI [18]
- Recurrent tumors
- Clinical lymph node involvement
- Suspicion of metastatic disease

While the AJCC manual is the most common staging system used, alternatives including the Brigham and Women's Hospital (BWH) risk stratification for primary cSCC are also in clinical use (Table 2) [19–21]. In a series of 98 patients from their institution, imaging (mostly CT) altered management in 33% (16/45) of cases [16]. Imaged patients were at lower risk of developing nodal metastases and of any disease-related event, including local or nodal relapse or death from disease.

Standard Cross-Sectional Imaging: CT, MR and US

In the ideal world, high-quality CT and MR imaging would be performed for all cases of advanced NMSC [22]. CT is quick (1–2 minutes), available and effective. Acquisition of contrast-enhanced thin slices (0.6–1 mm) with 3-D reconstruction and soft tissue and bone windowing allows for high spatial resolution with precise anatomic detail, including nodal and bone involvement (Fig. 1) [23]. CT has less utility in detecting PNS but can be used in patients who cannot undergo MR [16]. MR, in contrast, takes longer, usually 30 minutes per study, but provides superior soft-tissue resolution, more capably defining muscle and bone marrow invasion [24] and is considered the gold standard in detecting PNS (Fig. 2). Tailored MR, known to some as 'MR neurography', uses a small FOV with thin slices and a high-resolution matrix, with short acquisition times to reduce patient motion; post contrast T1 fat suppressed sequences provide the highest accuracy to detect PNS [25]. Indirect features of nerve involvement, such as muscle denervation, seen as a hyperintense T2 signal may also be seen [26]. When PNS or skull base invasion is suspected, tailored MR/MR neurography is essential for both surgical and adjuvant radiation treatment planning, including utilization of the perineural zonal classification system [27].

Providing relevant clinical history to the head and neck radiologist is critical. This was highlighted by Baulch et al. who reported a sensitivity and specificity for detecting PNI on MR at 95% and 84% when the clinical history was provided, compared to 87% and 79% when the radiologist was blinded to clinical history [28]. MR also has its limitations; its accuracy may be limited by large air-filled paranasal sinuses and flow and motion artefacts. MR may also be contraindicated in patients with metallic implants and some patients may require sedation if anxious or claustrophobic.

US can be useful for fine needle aspiration (FNA) of equivocal lymph nodes. Dabirmoghaddam et al. reported US guided FNA as superior to US alone or palpation in detecting metastases in clinically negative lymph nodes; 96% versus 68% and 70%, respectively [29]. US has varying utility in the clinic setting with the possibility of helping to define margins but may be limited by operator dependence.

Role and evidence for use of PET/CT

FDG PET/CT has a well-established role in mucosal head and neck SCC (mHNSCC), allowing for identification of occult primaries [30], nodal and systemic staging [31], therapy response [32] and detection of second primary malignancies. While cSCC is also highly FDG avid [33] (Fig. 1), the evidence base in the NMSC setting is sparse, and its

Table 1
AJCC TNM pathological staging cutaneous squamous cell carcinoma, 8th ed [55].

Primary Tumour	
T category	**T criteria**
TX	Primary tumour cannot be identified
T1	≤2 cm in diameter
T2	Tumour > 2 cm, but ≤ 4 cm in diameter
T3	Tumour > 4 cm in diameter or minor bone erosion, perineural invasion or deep invasion*
T4	
T4a	Tumour with gross cortical bone/marrow invasion
T4b	Tumour with skull base invasion and/or skull base foramen involvement
Regional Disease	
N category	**Clinical N criteria**
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤3 cm ,no ENE
N2	
N2a	Metastases in a single ipsilateral node > 3 cm but ≤ 6 cm and no ENE
N2b	Metastases in multiple ipsilateral nodes, none > 6 cm and no ENE
N2c	Metastases in bilateral or contralateral lymph node(s), < 6 cm and no ENE
N3	
N3a	Metastasis in a lymph node > 6 cm and no ENE
N3b	Metastasis with ENE in any at one lymph node or more
	Pathological N criteria
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤3 cm ,no ENE
N2	
N2a	Metastasis in a single ipsilateral lymph node ≤ 3 and ENE ; **or**A single ipsilateral node > 3 cm but ≤ 6 cm and no ENE
N2b	Metastases in multiple ipsilateral nodes, none > 6 cm and no ENE
N2c	Metastases in bilateral or contralateral lymph node(s), < 6 cm and no ENE
N3	
N3a	Metastasis in a lymph node > 6 cm and no ENE
N3b	Metastasis in a single ipsilateral node > 3 cm and ENE; **or**
	Multiple ipsilateral, contralateral, or bilateral nodes, any with ENE; **or**
	A single contralateral node of any size and ENE

Prognostic Staging Groups			
T stage	N stage	M stage	Stage Group
Tis	N0	M0	0
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T1	N1	M0	III
T2	N1	M0	III
T3	N1	M0	III
T1	N2	M0	IV
T2	N2	M0	IV
T3	N2	M0	IV
Any T	N3	M0	IV
T4	Any N	M0	IV
Any T	Any N	M1	IV

ENE – extranodal extension.

* Deep invasion = beyond subcutaneous fat or > 6 mm; perineural invasion = tumour cells within the nerve sheath deeper than the dermis or ≥0.1 mm calibre, or clinical/radiological involvement of named nerves without skull base invasion or transgression.

Table 2
Summary of Brigham and Women's Hospital (BWH) Tumour (T) Staging System [20].

T1	0 high-risk factors[#]
T2a	1 high-risk factor
T2b	2–3 high-risk factors
T3	≥4 high-risk factors or bone invasion

[#] High risk factors include
- Tumour diameter ≥ 2 cm
- Poorly differentiated histology
- PNI ≥ 0.1 mm
- Tumour invasion beyond fat (excluding bone invasion which automatically upgrades tumours to BWH stage T3)
- Location on the ear, temple or anogenital region

application has largely been extrapolated from the mHNSCC experience [17,34].

A Japanese group recently reported the utility of FDG PET/CT in 26 patients with cSCC at high risk of regional nodal involvement [35]. SUVmax ≥ 2.5 was considered positive, with lymphoscintigraphy and sentinel node biopsy taken as the gold standard. All three patients (12%) with pathological nodal disease had moderate to high FDG avidity (SUVmax > 7). All the 'false positive' nodes (5/30; 16.7%) had SUVmax 2.5–4.0. In an Australian study of 31 patients from the Peter MacCallum Cancer Centre, FDG PET/CT changed management in eight (23%) cases [36]. The impact was considered high in three of those cases (10%); in two cases a second primary was identified and in a further case nodal metastases were identified. False positive findings resulted in two of four patients undergoing more extensive surgery based on the FDG PET/CT findings. FDG PET/CT scans did not identify FNA proven malignant nodes in three cases. The same Australian centre recently published a surgical series of 64 patients who underwent neck

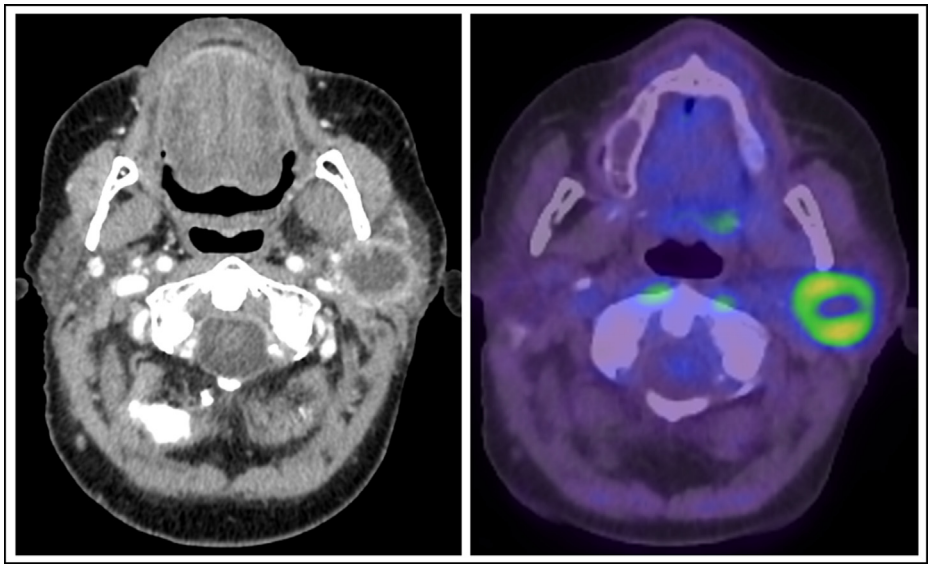

Fig. 1. Cross-sectional imaging of a cutaneous SCC metastatic to parotid. (A) Contrast enhanced CT scan. (B) PET/CT.

dissection and/or parotidectomy for cSCC [37]. FDG PET/CT had a positive and negative predictive value of 91% and 60%, respectively. The false negative cases were not explained by either small nodal size or necrosis.

FDG PET/CT may be useful in patients with chronic lymphocytic leukaemia, who are also at particular risk for developing metastatic cSCC. In this cohort of patients, PET/CT can help to distinguish cSCC nodal metastases from those with CLL infiltration with high specificity [38,39].

Role of SLNB in the clinically N0 neck

SLNB an emerging modality in cSCC [40]. The sentinel lymph node (SLN) is theoretically the most likely location for occult metastases in the cN0 neck [41], and identification of subclinical metastases by SLNB may help to guide management. However, the anatomy of the head and

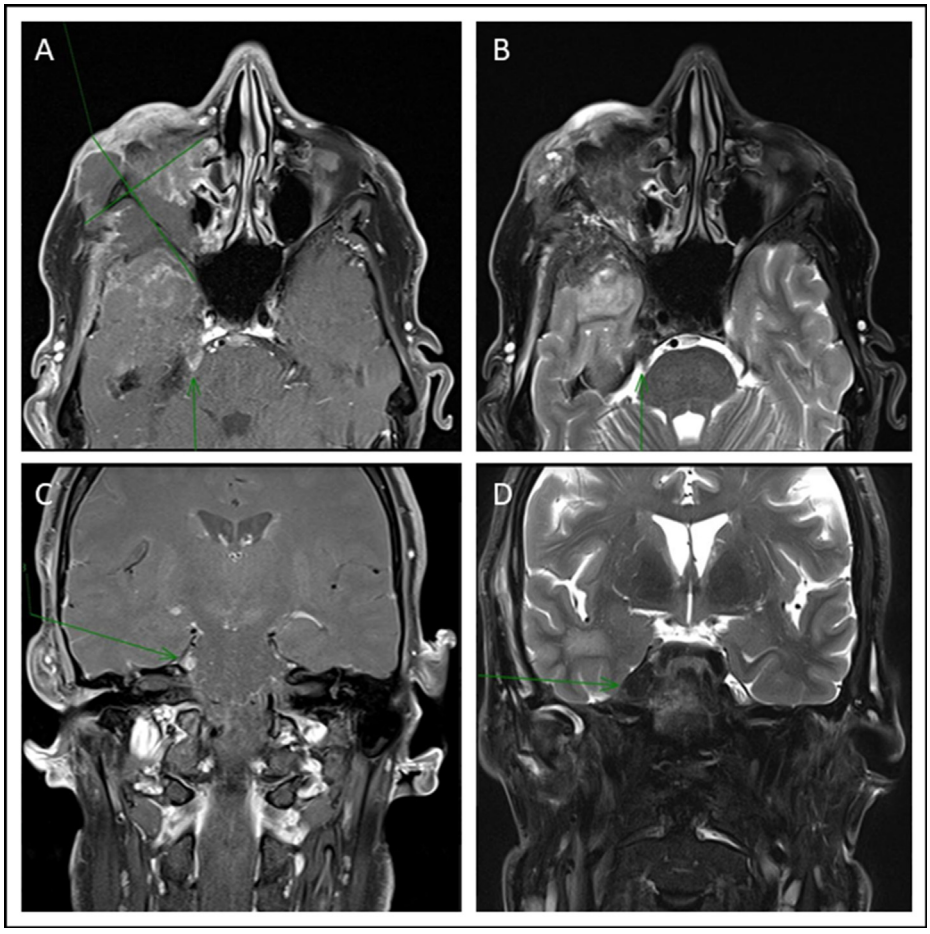

Fig. 2. MR images demonstrating extensive cutaneous SCC extending to the middle cranial fossa with V3 involvement and enhancement to the nerve root exit at the right pons. (A) Axial post contrast T1 fat saturation image. (B) Axial T2 fat saturation image. (C) Coronal post contrast T1 fat saturation image. (D) Coronal T2 fat saturation image.

neck region, with its unpredictable superficial lymphatic drainage, variable watershed lymphatics, multiple lymph node basins and complex neurovascular structures, creates challenges for the use of SLNB in this region [42,43]. A standardised technique for SLNB has not been established, and although most studies recommend preoperative lymphoscintigraphy plus the use of a hand-held gamma probe for intraoperative SLN localisation [42–45], other techniques include intraoperative blue dye injection [42,44,46] and preoperative single photon emission computed tomography [44,45].

A three-year prospective study assessed the utility of SLNB in high-risk cSCC at the time of wide local excision [40]. Of 57 patients, eight (14%) had occult LN metastases; and only one was not detected on SLNB. Three-year disease-specific survival was 82%, and a higher mortality was observed in patients where a positive SLNB was identified. A systematic review of SLNB in cSCC of the head and neck, included 73 patients from 11 studies, reported a positive SLNB in 13.7%, with sensitivity of 77%, specificity of 100% and a NPV of 95.2% [46]. A quantitative review of 260 cases of SLNB in cSCC reported a positive SLNB in 14.6% [42]. A literature review of high risk cSCC of the head and neck included 173 patients and reported SLNB to be 79% sensitive and 100% specific with a NPV of 96.1% [47].

Preliminary data confirms that SLNB may be a reliable technique in high-risk NMSC of the head and neck. Where the SLNB is positive, neck dissection may be performed, and guide recommendations for adjuvant treatment. The Australian SNIC trial will randomize patients to traditional surgery with observation versus SLNB with neck dissection and radiotherapy if positive. It is currently recruiting for a pilot phase to assess feasibility and morbidity [48].

Imaging to assess treatment response

There are no standardised imaging surveillance protocols following treatment. The NCCN for example suggest simply history and examination following definitive management of both cSCC and BCC [13,14]. A baseline MRI three months after treatment may be useful for follow up in cases of PNI treated with curative intent. Depending on the level of concern for recurrence (surgical margins, zonal classification of disease at surgery), MRI scans can then be performed at six monthly intervals for three years and then continued annually until year five [27], however there is a lack of research evidence to suggest that such a schedule improves patient outcomes. FDG PET/CT has proven utility in therapy response assessment in mHNSCC [32], but there are no studies specifically in cSCC, as the majority of patients are treated in the adjuvant setting.

Changes in the American Joint Committee on cancer 8th edition staging system for cutaneous squamous cell carcinoma

Although there are a number of staging systems in use for cSCC, including the BWH system, the most commonly used is the AJCC TNM classification. The recently revised AJCC8 cSCC staging system, which applies to all NMSC lesions of the head and neck (only Merkel cell carcinoma has its own staging system), incorporated a number of changes to both the T- and N-categories (Table 1) [18]. The prognostic value of these changes has been questioned in a number of recent publications. A major drawback in AJCC8 is the failure to incorporate immunosuppression in patients with NMSC, a factor consistently linked with higher rates of relapse and lower rates of survival [49–52]. Other staging systems such as the BWH include immune status, as well as lymphovascular invasion, anatomical site, poor differentiation, association with a scar or chronic inflammatory disease and recurrence [53].

T-category changes

The 7th edition of the AJCC TNM staging system (AJCC7) defined all primary tumours ≤ 2 cm with < 2 risk factors as T1, where the risk factors were: (1) depth > 2 mm or Clark level ≥ 4; (2) any identifiable perineural invasion; (3) location on the ear or lip; and (4) poor differentiation. All lesions with ≥ 2 risk factors or increasing size to > 2 cm were staged as T2. Locally advanced disease in AJCC7 required invasion of either the maxilla, mandible, orbit, or temporal bone (T3) or the bones of the skull base (T4). AJCC8 (Table 1) has seen a modification to this risk-stratification system, removing location and differentiation, further refining size criteria, more clearly defining PNI and upstaging patients with any risk factor to T3, rather than T2. In summary, the AJCC8 T-category changes are:

- Size: T1 < 2 cm; T2 ≥ 2 cm but < 4 cm; and T3 ≥ 4 cm
- Adverse features for upstaging to T3
  - deep invasion beyond the subcutaneous fat or > 6 mm Breslow thickness
  - "minor" bone erosion
  - PNI; now defined as tumour cells in a nerve within the dermis or ≥ 0.1 mm caliber, or the presence of clinical/radiological involvement of named nerves without skull base invasion.
- T4 category is subcategorized into:
  - gross cortical bone/marrow invasion (T4a) or
  - those with skull base invasion and/or skull base foramen involvement (T4b).

As a consequence, there may be significant T-category migration from the AJCC7 system, resulting in lesions previously categorized as T2 being upstaged to T3, or downstaged to T1 [51,54]. Karia et al. reported that AJCC8 performed much better than AJCC7 with respect to identifying primary lesions with poor outcomes based on T-category alone [54]. A smaller series by Cañueto et al. reported a similar finding, and found the risk factors used in AJCC8 independently predicted a poorer outcome, as did histological differentiation which had been previously included in AJCC7.

N-Category changes

The AJCC8 nodal-category has incorporated ENE for the first time (Table 1), as a reflection of the poor outcomes seen in patients with mHNSCC [55]. ENE upstages all patients, the majority to N3b, excepting cases of a solitary node ≤ 3 cm and ENE who migrate from AJCC7 N1 to AJCC8 N2a. ENE is seen in more than half of node-positive cHNSCC [56], and recent publications have called into question its incorporation in AJCC8, owing to poor prognostication.

Sood et al. retrospectively compared the prognostic performance of the AJCC7 and AJCC8 systems in 96 patients with node-positive cHNSCC. ECE was common (77%), resulting in upstaging of the majority from AJCC7 stage III to AJCC8 stage IV. AJCC8 was inferior to AJCC7 in predicting DSS, when analysing both nodal-category and overall TNM stage. Similarly, in the series of regionally metastatic cHNSCC reported by Liu et al., the majority had ECE (78%) [56], resulting in upstaging of 285/382 (75%); 110 (67%) migrated from AJCC7 N1 to AJCC8 pN2a, while the majority of AJCC7 N2 (175/203) were upstaged to AJCC8 N3b. While AJCC7 was able to differentiate DSS and OS between pN1 and pN3, it discriminately poorly between the pN1 and pN2 categories. AJCC8 performed even more poorly, unable to provide risk stratification between any of the nodal categories. Moeckelmann et al. have also reported that AJCC8 performed poorly when stratifying survival by N-category [57].

Other staging systems for regionally metastatic cHNSCC have been proposed from Australian centres including O'Brien's parotid and neck system [58], the N1S3 system proposed by Forest et al. [59] and the ITEM prognostic score [60]. The staging approach suggested by O'Brien et al., which separated parotid and cervical node involvement, was based on their finding that metastatic cHNSCC involving both the parotid and neck had a significantly poorer outcome than those with

isolated parotid disease [58]. This staging system was validated in a larger multi-institutional study [61], but did not hold up in all validation cohorts [62].

Overall these findings would suggest that the current AJCC8 staging system is inadequate for risk-stratification in cHNSCC where regional metastatic disease is concerned. A robust and usable staging system for cHNSCC is desperately required to provide accurate risk-stratification and counselling for patients.

Implications of the new staging system for p16 + carcinoma unknown primary cancers in regions with a high prevalence of NMSC

With contemporary diagnostic protocols, patients with true squamous cell carcinoma of unknown primary in the head and neck (CUP-HNSCC) are an infrequent occurrence, accounting for approximately 1–3% of all new head and neck presentations [63]. Determination of the putative candidate sites may be aided by consideration of clinical (age, sun exposure, smoking history, other dermatologic history), radiological (nodal location) and pathological factors (basaloid histology) [64]. Although spontaneous regression of cHNSCC has been reported only as a rare phenomenon, in regions with high rates of NMSC, a cutaneous primary remains an important differential in the presentation of CUP-HNSCC [65].

Although a number of series have reported “unknown primaries” in patients with cHNSCC, [66–68], the majority are usually cases where multiple potential lesions make the determination of the index lesion impossible [10,11,69]. In AJCC8, it is recommended that where pathological findings are suspicious of a HPV-driven cancer (i.e. p16-positivity) that CUP-HNSCC be staged in accordance with the HPV-mediated oropharyngeal carcinoma staging system. This seems a rational approach in regions of low NMSC prevalence, given retrospective pathological series have shown that approximately 90% of CUP-HNSCC are also HPV-positive, suggesting an oropharyngeal primary[70,71].

In areas with high cHNSCC prevalence, such as Australia, which has the highest rate of cHNSCC in the world, caution should be used in interpreting p16+ status alone [2]. From the Peter MacCallum Cancer Center in Australia, McDowell et al. reported that 31% (44/143) of node-positive parotid cHNSCC expressed strong p16+ positivity according to the accepted histological criteria (strong and diffuse staining in at least 70% of cells), however the mechanism was independent of latent high-risk HPV infection as HPV RNA-ISH was negative in all cases (18 high risk subtypes tested) [72]. These findings were almost identical to the 32% (53/166) p16-positive rate in a series of cHNSCC from Sydney, Australia, which also demonstrated that all cSCC specimens were negative for HPV ISH [73].

Hence, relying on isolated p16 status to determine an occult oropharyngeal primary is problematic in areas of high NMSC prevalence. Direct HPV testing would provide additional value in cases of CUP-HNSCC, but may not be routinely available in all centers, and cautious interpretation of p16 status alone in such settings is warranted.

Summary/conclusion

Although high quality data is lacking, staging investigations in high-risk NMSC may aid the multidisciplinary team in treatment planning. The introduction of the new AJCC8 staging system for NMSC has not improved prognostication, particularly where the nodal category is concerned. Further research to assess the utility of staging investigations and to improve risk stratification is needed. cHNSCC regional metastases are p16-positive in approximately one-third of cases, and in settings of high NMSC prevalence, assuming an occult oropharyngeal primary should be done with caution.

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Declaration of Competing Interest

The authors declared that there is no conflict of interest.

References

[1] Karia PS, Morgan FC, Ruiz ES, Schmults CD. Clinical and Incidental perineural invasion of cutaneous squamous cell carcinoma: a systematic review and pooled analysis of outcomes data. JAMA Dermatol 2017;153:781–8.
[2] Staples MP, Elwood M, Burton RC, Williams JL, Marks R, Giles GG. Non-melanoma skin cancer in Australia: the 2002 national survey and trends since 1985. Med J Australia 2006;184:6–10.
[3] Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. British J Dermatol 2012;166:1069–80.
[4] Albert MR, Weinstock MA. Keratinocyte carcinoma. CA Cancer J Clin 2003;53:292–302.
[5] AIHW. Cancer Data in Australia; Australian Cancer Incidence and Mortality (ACIM) books: non-melanoma skin cancer. Canberra: Australian Institute of Health and Welfare (AIHW); 2018.
[6] Olsen CM, Williams PF, Whiteman DC. Turning the tide? Changes in treatment rates for keratinocyte cancers in Australia 2000 through 2011. J Am Acad Dermatol 2014;71. 21–6e1.
[7] Leibovitch I, Huilgol SC, Selva D, Hill D, Richards S, Paver R. Cutaneous squamous cell carcinoma treated with Mohs micrographic surgery in Australia I. Experience over 10 years. J Am Acad Dermatol 2005;53:253–60.
[8] Brewster DH, Bhatti LA, Inglis JH, Nairn ER, Doherty VR. Recent trends in incidence of nonmelanoma skin cancers in the East of Scotland, 1992–2003. British J Dermatol 2007;156:1295–300.
[9] Khurana VG, Mentis DH, O'Brien CJ, Hurst TL, Stevens GN, Packham NA. Parotid and neck metastases from cutaneous squamous cell carcinoma of the head and neck. Am J Surg 1995;170:446–50.
[10] Ch'ng S, Maitra A, Allison RS, Chaplin JM, Gregor RT, Lea R, et al. Parotid and cervical nodal status predict prognosis for patients with head and neck metastatic cutaneous squamous cell carcinoma. J Surg Oncol 2008;98:101–5.
[11] Schmidt C, Martin JM, Khoo E, Plank A, Grigg R. Outcomes of nodal metastatic cutaneous squamous cell carcinoma of the head and neck treated in a regional center. Head Neck 2015;37:1808–15.
[12] Kelder W, Ebrahimi A, Forest V-I, Gao K, Murali R, Clark JR. Cutaneous head and neck squamous cell carcinoma with regional metastases: the prognostic importance of soft tissue metastases and extranodal spread. Ann Surg Oncol 2011;19:274–9.
[13] National Comprehensive Cancer Network. Squamous Cell Skin Cancer. Version 2. 2019 ed2019.
[14] National Comprehensive Cancer Network. Basal Cell Skin Cancer. Version 1.2019 ed2019.
[15] Jambusaria-Pahlajani A, Kanetsky PA, Karia PS, Hwang WT, Gelfand JM, Whalen FM, et al. Evaluation of AJCC tumor staging for cutaneous squamous cell carcinoma and a proposed alternative tumor staging system. JAMA Dermatol 2013;149:402–10.
[16] Ruiz ES, Karia PS, Morgan FC, Schmults CD. The positive impact of radiologic imaging on high-stage cutaneous squamous cell carcinoma management. J Am Acad Dermatol 2017;76:217–25.
[17] Humphreys TR, Shah K, Wysong A, Lexa F, MacFarlane D. The role of imaging in the management of patients with nonmelanoma skin cancer: when is imaging necessary? J Am Acad Dermatol 2017;76:591–607.
[18] Amin MBES, Greene FL, et al. AJCC cancer staging manual. 8th ed. New York: Springer; 2017.
[19] Blechman AB, Carucci JA, Stevenson ML. Stratification of Poor Outcomes for Cutaneous Squamous Cell Carcinoma in Immunosuppressed Patients Using the American Joint Committee on Cancer Eighth Edition and Brigham and Women's Hospital Staging Systems. Dermatologic surgery: official publication for American Society for Dermatologic Surgery [et al]; 2019.
[20] Gonzalez JL, Cunningham K, Silverman R, Madan E, Nguyen BM. Comparison of the American Joint Committee on Cancer Seventh Edition and Brigham and Women's Hospital Cutaneous Squamous Cell Carcinoma Tumor Staging in Immunosuppressed Patients. Dermatologic surgery: official publication for American Society for Dermatologic Surgery [et al]. 2017;43:784–91.
[21] Baum CL, Wright AC, Martinez J-C, Arpey CJ, Brewer JD, Roenigk RK, et al. A new evidence-based risk stratification system for cutaneous squamous cell carcinoma into low, intermediate, and high risk groups with implications for management. J Am Acad Dermatol 2018;78:141–7.
[22] Vogl TJ, Harth M, Siebenhandl P. Different imaging techniques in the head and neck: assets and drawbacks. World J Radiol 2010;2:224–9.
[23] MacFarlane D, Shah K, Wysong A, Wortsman X, Humphreys TR. The role of imaging in the management of patients with nonmelanoma skin cancer. J Am Acad Dermatol 2017;76:579–88.
[24] Millare GG, Guha-Thakurta N, Sturgis EM, El-Naggar AK, Debnam JM. Imaging findings of head and neck dermatofibrosarcoma protuberans. AJNR Am J

Neuroradiol 2014;35:373–8.
[25] Sommerville J, Gandhi M. Postoperative imaging and surveillance in large nerve perineural spread. J Neurol Surgery Part B, Skull Base 2016;77:182–92.
[26] Chandra P, Purandare N, Shah S, Agrawal A, Rangarajan V. Common patterns of perineural spread in head-neck squamous cell carcinoma identified on fluorodeoxy-glucose positron emission tomography/computed tomography. Indian J Nucl Med: IJNM: Off J Soc Nucl Med India 2016;31:274–9.
[27] Warren TA, Panizza B, Porceddu SV, Gandhi M, Patel P, Wood M, et al. Outcomes after surgery and postoperative radiotherapy for perineural spread of head and neck cutaneous squamous cell carcinoma. Head Neck 2016;38:824–31.
[28] Baulch J, Gandhi M, Sommerville J, Panizza B. 3T MRI evaluation of large nerve perineural spread of head and neck cancers. J Med Imaging Radiat Oncol 2015;59:578–85.
[29] Dabirmoghaddam PSS, Mashali L. Ultrasound-guided fine needle aspiration cytology in the assessment of cervical metastasis in patients undergoing elective neck dissection. Iran J Radiol 2014;11:e7928.
[30] Zhu L, Wang N. 18F-fluorodeoxyglucose positron emission tomography-computed tomography as a diagnostic tool in patients with cervical nodal metastases of unknown primary site: a meta-analysis. Surg Oncol 2013;22:190–4.
[31] Seeburg DP, Baer AH, Aygun N. Imaging of patients with head and neck cancer: from staging to surveillance. Oral Maxillofac Surg Clin North Am 2018;30:421–33.
[32] Mehanna H, Wong WL, McConkey CC, Rahman JK, Robinson M, Hartley AG, et al. PET-CT surveillance versus neck dissection in advanced head and neck cancer. N Engl J Med 2016;374:1444–54.
[33] Cho SB, Chung WG, Yun M, Lee JD, Lee MG, Chung KY. Fluorodeoxyglucose positron emission tomography in cutaneous squamous cell carcinoma: retrospective analysis of 12 patients. Dermatol Surg 2005;31:442–6. discussion 6–7.
[34] MacFarlane D, Shah K, Wysong A, Wortsman X, Humphreys TR. The role of imaging in the management of patients with nonmelanoma skin cancer: diagnostic modalities and applications. J Am Acad Dermatol 2017;76:579–88.
[35] Fujiwara M, Suzuki T, Takiguchi T, Fukamizu H, Tokura Y. Evaluation of positron emission tomography imaging to detect lymph node metastases in patients with high-risk cutaneous squamous cell carcinoma. J Dermatol 2016;43:1314–20.
[36] Supriya M, Suat-Chin N, Sizeland A. Use of positron emission tomography scanning in metastatic head and neck cutaneous squamous cell cancer: does it add to patient management? Am J Otolaryngol 2014;35:347–52.
[37] Hirshoren N, Olayos E, Herschtal A, Ravi Kumar AS, Gyorki DE. Preoperative positron emission tomography for node-positive head and neck cutaneous squamous cell carcinoma. Otolaryngol Head Neck Surg 2018;158:122–6.
[38] Ozturk K, Ustun C, Khaja S, Li F, Rischall M, Cayci Z. Concomitant cutaneous squamous cell carcinoma and chronic lymphocytic leukemia in a patient: the utility of (18) F-FDG PET/CT in differentiation of nodal metastasis. Am J Hematol 2018;93:597–8.
[39] Tomaszewski JM, Corry J. Utility of positron emission tomography/computed tomography for nodal staging of cutaneous squamous cell carcinoma in patients with chronic lymphocytic leukemia. Am J Otolaryngol 2014:66–9.
[40] Gore SM, Shaw D, Martin RC, Kelder W, Roth K, Uren R, et al. Prospective study of sentinel node biopsy for high-risk cutaneous squamous cell carcinoma of the head and neck. Head Neck 2016;38(Suppl 1):E884–9.
[41] Karunaratne YG, Gunaratne DA, Veness MJ. Systematic review of sentinel lymph node biopsy in Merkel cell carcinoma of the head and neck. Head Neck 2018;40:2704–13.
[42] Ahadiat O, Higgins S, Sutton A, Ly A, Wysong A. SLNB in cutaneous SCC: a review of the current state of literature and the direction for the future. J Surg Oncol 2017;116:344–50.
[43] Foy JP, Kolb F, Routier E, Cavalcanti A, Lumbroso J, Tomasic G, et al. Sentinel lymph node biopsy in 33 non-melanoma skin cancers of the head and neck: A twelve-year experience with long-term follow-up. Clin Otolaryngol 2018.
[44] Seim NB, Wright CL, Agrawal A. Contemporary use of sentinel lymph node biopsy in the head and neck. World J Otorhinolaryngol Head Neck Surg 2016;2:117–25.
[45] Dwojak S, Emerick KS. Sentinel lymph node biopsy for cutaneous head and neck malignancies. Expert Rev Anticancer Ther 2015;15:305–15.
[46] Ahmed MM, Moore BA, Schmalbach CE. Utility of head and neck cutaneous squamous cell carcinoma sentinel node biopsy: a systematic review. Otolaryngol Head Neck Surg 2014;150:180–7.
[47] Allen JE, Stolle LB. Utility of sentinel node biopsy in patients with high-risk cutaneous squamous cell carcinoma. Eur J Surg Oncol 2015;41:197–200.
[48] Australian New Zealand Clinical Trials Registry. A phase III Multicenter Randomised Trial in High Risk Non Melanoma Skin Cancer of Sentinel Lymph Node Biopsy and Lymphadenectomy versus Nodal Observation on Disease Free and Overall Survival. 11/07/3011 ed. Sydney2011.
[49] Arbab M, Margalit DN, Tishler RB, Rabinowits G, Pashtan IM, Borgelt BB, et al. Outcomes following radiation for cutaneous squamous cell carcinoma of the head and neck: associations between immune suppression and recurrence. Head Neck 2019.
[50] Manyam BV, Garsa AA, Chin RI, Reddy CA, Gastman B, Thorstad W, et al. A multi-institutional comparison of outcomes of immunosuppressed and immunocompetent patients treated with surgery and radiation therapy for cutaneous squamous cell carcinoma of the head and neck. Cancer 2017;123:2054–60.
[51] Xu MJ, Lazar AA, Garsa AA, Arron ST, Ryan WR, El-Sayed IH, et al. Major prognostic factors for recurrence and survival independent of the American Joint Committee on Cancer eighth edition staging system in patients with cutaneous squamous cell carcinoma treated with multimodality therapy. Head & Neck 2018;40:1406–14.
[52] McDowell LJ, Tan TJ, Bressel M, Estall V, Kleid S, Corry J, et al. Outcomes of cutaneous squamous cell carcinoma of the head and neck with parotid metastases. J Med Imaging Radiat Oncol 2016;60:668–76.
[53] Que SKT, Zwald FO, Schmults CD. Cutaneous squamous cell carcinoma: Management of advanced and high-stage tumors. J Am Acad Dermatol 2018;78:249–61.
[54] Karia PS, Morgan FC, Califano JA, Schmults CD. Comparison of tumor classifications for cutaneous squamous cell carcinoma of the head and neck in the 7th vs 8th edition of the AJCC cancer staging manual. JAMA Dermatol 2018;154:175–81.
[55] Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, et al. American Joint Committee on Cancer. AJCC cancer staging manual. 8th ed. New York: Springer International Publishing; 2016.
[56] Liu J, Ebrahimi A, Low TH, Gao K, Palme CE, Sydney C, et al. Predictive value of the 8th edition American Joint Commission Cancer (AJCC) nodal staging system for patients with cutaneous squamous cell carcinoma of the head and neck. J Surg Oncol 2018;117:765–72.
[57] Moeckelmann N, Ebrahimi A, Dirven R, Liu J, Low TH, Gupta R, et al. Analysis and comparison of the 8th Edition American Joint Committee on Cancer (AJCC) nodal staging system in cutaneous and oral squamous cell cancer of the head and neck. Ann Surg Oncol 2018;25:1730–6.
[58] O'Brien CJ, McNeil EB, McMahon JD, Pathak I, Lauer CS, Jackson MA. Significance of clinical stage, extent of surgery, and pathologic findings in metastatic cutaneous squamous carcinoma of the parotid gland. Head Neck 2002;24:417–22.
[59] Forest VI, Clark JJ, Veness MJ, Milross C. N1S3: a revised staging system for head and neck cutaneous squamous cell carcinoma with lymph node metastases: results of 2 Australian Cancer Centers. Cancer 2010;116:1298–304.
[60] Oddone N, Morgan GJ, Palme CE, Perera L, Shannon J, Wong E, et al. Metastatic cutaneous squamous cell carcinoma of the head and neck: the immunosuppression, treatment, Extranodal spread, and Margin status (ITEM) prognostic score to predict outcome and the need to improve survival. Cancer 2009;115:1883–91.
[61] Andruchow JL, Veness MJ, Morgan GJ, Gao K, Clifford A, Shannon KF, et al. Implications for clinical staging of metastatic cutaneous squamous carcinoma of the head and neck based on a multicenter study of treatment outcomes. Cancer 2006;106:1078–83.
[62] Palme CE, O'Brien CJ, Veness MJ, McNeil EB, Bron LP, Morgan GJ. Extent of parotid disease influences outcome in patients with metastatic cutaneous squamous cell carcinoma. Arch Otolaryngol–Head Neck Surgery 2003;129:750–3.
[63] Syrjanen S. Human papillomaviruses in head and neck carcinomas. New Engl. J. Med 2007;356:1993–5.
[64] Huo M, Panizza B, Bernard A, Porceddu SV. Head and neck squamous cell carcinoma of unknown primary: outcomes of a pre-defined institutional treatment policy in a region with a high prevalence of skin cancer. Oral Oncol 2018;77:43–8.
[65] Sengupta S, Arocho J, Christopher Windham T. Spontaneous regression of a histologically proven cutaneous squamous cell carcinoma; 2013.
[66] Hinerman RW, Indelicato DJ, Amdur RJ, Morris CG, Werning JW, Vaysberg M, et al. Cutaneous squamous cell carcinoma metastatic to parotid-area lymph nodes. Laryngoscope 2008;118:1989–96.
[67] Martinez JC, Otley CC, Stasko T, Euvrard S, Brown C, Schanbacher CF, et al. Defining the clinical course of metastatic skin cancer in organ transplant recipients: a multicenter collaborative study. Arch Dermato. 2003;139:301–6.
[68] Ch'ng S, Maitra A, Lea R, Brasch H, Tan ST. Parotid metastasis–an independent prognostic factor for head and neck cutaneous squamous cell carcinoma. J Plastic, Reconstruct Aesthetic Surgery: JPRAS 2006;59:1288–93.
[69] Ebrahimi A, Moncrieff MD, Clark JR, Shannon KF, Gao K, Milross CG, et al. Predicting the pattern of regional metastases from cutaneous squamous cell carcinoma of the head and neck based on location of the primary. Head Neck 2010;32:1288–94.
[70] Mirzamani N, Salehian P, Farhadi M, Tehran EA. Detection of EBV and HPV in nasopharyngeal carcinoma by in situ hybridization. Exp Mol Pathol 2006;81:231–4.
[71] Motz K, Qualliotine JR, Rettig E, Richmon JD, Eisele DW, Fakhry C. Changes in unknown primary squamous cell carcinoma of the head and neck at initial presentation in the era of human papillomavirus. JAMA Otolaryngol–Head Neck Surgery 2016;142:223–8.
[72] McDowell LJ, Young RJ, Johnston ML, Tan TJ, Kleid S, Liu CS, et al. p16-positive lymph node metastases from cutaneous head and neck squamous cell carcinoma: No association with high-risk human papillomavirus or prognosis and implications for the workup of the unknown primary. Cancer 2016;122:1201–8.
[73] Satgunaseelan L, Chia N, Suh H, Virk S, Ashford B, Lum T, et al. p16 expression in cutaneous squamous cell carcinoma of the head and neck is not associated with integration of high risk HPV DNA or prognosis. Pathology 2017;49:494–8.