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Prognostic value of the 8th edition American Joint Commission Cancer (AJCC) nodal staging system for patients with head and neck cutaneous squamous cell carcinoma: a multi-institutional study

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1002/hed.26512](https://doi.org/10.1002/hed.26512)

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Funding sources: No funding obtained.

Disclosures: No conflict of interest to disclose.

Running title: AJCC8 in head and neck cutaneous SCC

Key words: American Joint Committee on Cancer (AJCC), head and neck cutaneous squamous cell carcinoma, nodal metastases, staging, prognosis

Abstract

Background: The 8th edition American Joint Committee on Cancer staging manual (AJCC8) introduced a separate staging system for head and neck cutaneous squamous cell carcinoma (HNCSCC) which parallels mucosal SCC and incorporates extranodal extension (ENE). This study aims to evaluate its prognostic utility

Methods: Univariate analysis of 1146 patients with metastatic HNCSCC from four Australian cancer centers was performed according to both AJCC 7th (AJCC7) and the 8th editions.

Results: AJCC8 increased classification of 924 (80.6%) patients to either pN2a or pN3b and 341 patients (29.8%) from Stage III to IV compared to AJCC7. The disease specific survival (DSS) was not significantly different between pN1, pN2 or pN3a categories per AJCC8. Estimates of model performance for the AJCC8 pN staging revealed modest predictive capacity (Harrell's C of 0.62 for DSS).

Conclusions: The risk stratification according to pN classification of AJCC8 staging system performed poorly as a prognostic indicator.

Introduction

Cutaneous squamous cell carcinoma (cSCC) is one of the most common malignancies worldwide¹ with incidence ranging from 5 to 499 per 100,000 patients depending on geographic location.² cSCC most commonly occurs in the head and neck (HNcSCC) due to sun-exposure.³ With increasing incidence worldwide, cSCC poses a significant disease burden in the aging population and in regions with high solar ultraviolet index.⁴

The 7th edition of American joint committee on cancer staging system (AJCC7)⁵ introduced a new nodal staging system for cSCC which parallels that of head and neck mucosal SCC. In the more recent 8th edition of the AJCC staging system (AJCC8)⁶, HNcSCC was staged as a separate entity for the first time. The nodal staging system still continued to remain identical to that of head and neck mucosal SCC however extranodal extension (ENE) has been incorporated for the first time resulting in upstaging of the patients (Table 1). Approximately 5% of the patients with HNcSCC develop lymph node metastases.⁷ However, nodal metastases (pN) carry greater prognostic significance for HNcSCC as compared to the primary (pT)⁸⁻¹⁰, possibly as most of these patients show severe actinic damage and multiple skin cancers; most of which may have been treated topically by a dermatologist or a general practitioner without concurrent histopathologic examination.¹¹ Furthermore cutaneous malignancies of the head and neck frequently metastasise to the parotid and peri-parotid lymph node basin in close proximity to the facial nerve. Thus, there are significant differences in the management of primary mucosal and cutaneous squamous cell carcinomas of the head and neck, the incidence of metastases of these malignancies and their metastatic

basins. Previous studies had demonstrated that the AJCC7 nodal staging system was too complex and had limited prognostic value for cSCC.^{12,13} We recently published single institution studies of metastatic HNCSCC demonstrating that AJCC8 nodal staging system performs poorly at prognostic stratification of patients with metastatic HNCSCC.^{14,15} The current study aims to collate data from multiple Australian cancer centers with expertise in management of HNCSCC to validate our previous single institutional findings as well as identify factors that play a role in prognostication of metastatic HNCSCC.

Materials and methods

Study population

After institutional ethics approval, data on patients with parotid or neck nodal metastases from HNCSCC was obtained from four Australian cancer centers: the Sydney Head and Neck Cancer Institute (SHNCI) at Chris O'Brien Lifehouse (N=443), Westmead Head and Neck Cancer Centre (WHNCC) (N=410), Peter MacCallum Cancer Centre (PMCC) (N=197) and Liverpool Hospital (N=96). After excluding cases with peri-operative mortality and missing data on follow-up or variables necessary to determine the 7th and 8th edition AJCC pathological Nodal (pN) and TNM stage, the final study population included 1146 patients treated with curative intent between 1980 and 2017. There were 155 patients excluded from the analysis due to missing data. We compared this subgroup against the study population and found no significant difference in age ($p=0.435$), gender ($p=0.455$) or treatment period (2000 onwards versus prior to year 2000, $p=0.900$). The patients with missing data were more likely to be treated with surgery alone compared to the study population (36.8% versus

16.8%, $p < 0.001$). Patients with soft tissue deposits were classified as ENE positive for the purposes of pN classification. The demographic, histopathologic, treatment, and follow-up details were obtained.

Statistical analysis

Statistical analysis was performed using Stata version 12.0 SE (StataCorp LP, College Station, TX). All statistics were two-sided and a value of $P < 0.05$ was considered statistically significant. The clinical end points of interest were disease-specific survival (DSS) and overall survival (OS). Overall survival was calculated from the date of surgery to the date of death or last follow-up visit. For DSS, patients who died from causes other than HNCSCC were censored at the time of death. Univariate analysis was carried out using the Cox proportional hazard method to assess the impact of each pN and TNM stage sub-group for AJCC7 and 8. The proportional hazards assumption was tested using Schoenfeld residuals. Survival curves were generated using the Kaplan-Meier method. The prognostic performance of each model was evaluated using a measure of the proportion of survival time variation explained by the model (proportion of variation explained, PVE), Harrell's concordance index (C-index) and Akaike Information Criterion (AIC). The PVE ranges from 0-100% with higher values indicating better predictive ability of the model.¹⁶ The C-index provides a measure of model discrimination, with a value of 1 indicating perfect prediction, whilst 0.5 is equivalent to the toss of a coin.¹⁷ The AIC takes into account how well a model fits the data with penalties for model complexity.¹⁸

Results

Patient demographics

The study population consisted of 1146 cases of metastatic HNCSCC including 972 males and 174 females (M:F 5.6:1) with a median age of 73 years (range 18-100 years) and median follow-up of 3.4 years (mean 3.8 years). Treatment included surgery alone in 193 patients (16.8%), surgery and adjuvant radiotherapy in 879 patients (76.7%), and 74 patients (6.5%) received surgery and adjuvant chemoradiotherapy. The median number of lymph nodes removed was 26 (range 1-123), the median number of positive lymph nodes was 1 (range 1-67). The median size of largest lymph node deposit was 2.4cm (range 0.02-11cm). During the study period, there were 512 deaths (44.7%), of which 206 (18%) were due to HNCSCC. The 5-year disease-specific and overall survival were 77.1% (95% CI: 73.9-79.9%) and 53.8% (95% CI: 50.3-57.2%), respectively. A summary of relevant demographic and clinicopathologic factors is provided in Table 2.

Increase of pN classification and TNM stage following application of AJCC 8 criteria

ENE including formation of soft tissue deposits of metastatic HNCSCC was seen in 927 patients (80.9%), all of whom were upstaged by AJCC8. 342 patients (76%) classified as pN1 as per the AJCC7 criteria were increased to pN2a due to the presence of ENE with a single involved lymph node ≤ 3 cm in size as per the AJCC8. Similarly, 110 patients (81.5%) classified as pN2a, 418 patients (85.0%) classified as pN2b, 28 patients (77.8%) classified as pN2c, and 29 (87.9%) patients classified as pN3 by AJCC7 were increased to pN3b due to the presence of ENE as per the AJCC8 criteria (Table 3).

For overall TNM stage, 343 (76.1%) AJCC7 Stage III patients were upstaged to IV. This resulted in 90.6% of patients being classified as Stage IV in AJCC8 (Table 4).

Prognostic performance of the pN categories

Kaplan-Meier DSS and OS curves according to pN classification are shown in Figure 1 and the prognostic performance is shown in Table 5. For AJCC7, in comparison to pN1, patients classified as pN2b (HR 2.09; 95% CI: 1.50-2.90; $P < 0.001$), pN2c (HR 2.29; 95% CI: 1.09-4.81; $P = 0.029$) and pN3 (HR 6.63; 95% CI: 3.78-11.63; $P < 0.001$) demonstrated significantly worse DSS. Similarly, pN2b (HR 1.39; 95% CI: 1.14-1.69; $P = 0.001$) and pN3 (HR 3.38; 95% CI: 2.16-5.28; $P < 0.001$) patients demonstrated significantly worse OS compared to pN1. For both DSS and OS, whilst pN2a demonstrated worse survival, it did not reach statistical significance (HR 1.57; 95% CI: 0.96-2.59; $P = 0.074$ and HR 1.30; 95% CI: 0.97-1.74; $P = 0.081$ respectively). In contrast, AJCC 8 did not demonstrate risk stratification between pN1 and pN2a (HR 1.72; 95% CI: 0.84-3.51; $P = 0.137$), pN2b (HR 1.53; 95% CI: 0.61-3.86; $P = 0.366$), and pN2c (HR 1.75; 95% CI: 0.22-13.80; $P = 0.596$) in terms of DSS. Only pN3b (HR 3.65; 95% CI: 1.86-7.17; $P < 0.001$) demonstrated significantly worse DSS as compared to pN1. In terms of OS, pN2a (HR 1.82; 95% CI: 1.23-2.69; $P = 0.003$), pN3a (HR 4.40; 95% CI: 1.05-18.44; $P = 0.043$) and pN3b (HR 2.56; 95% CI: 1.76-3.73; $P < 0.001$) demonstrated significantly worse outcome as compared to pN1. Whilst the pN classification used by AJCC7 appeared to provide marginally better prognostic information

compared to AJCC8, there was poor risk stratification between the various pN2 subcategories in both systems.

AJCC7 showed modest predictive capacity for both DSS and OS (Harrell's C of 0.62 and 0.58, respectively) while AJCC8 showed similar predictive capacity for both DSS and OS (Harrell's C of 0.62 and 0.59, respectively). Similar results were found after adjusting for administration of adjuvant radiotherapy in both DSS and OS analysis and age in OS analysis. In addition, sensitivity analyses excluding patients treated before the year 2000 confirmed consistent results.

Prognostic performance of TNM staging

Kaplan-Meier survival curves based on TNM stages are shown in Figure 2. Stage IV patients demonstrated significantly worse DSS (HR 2.10; 95% CI: 1.55-2.86; $P < 0.001$) and OS (HR 1.41; 95% CI: 1.18-1.69; $P < 0.001$) compared with stage III patients as per AJCC7. Similarly in AJCC8, stage IV patients demonstrated significantly worse DSS (HR 2.73; 95% CI: 1.40-5.32; $P = 0.003$) and OS (HR 2.15; 95% CI: 1.49-3.11; $P < 0.001$) compared with stage III.

Similar to pN classification, AJCC7 showed modest discrimination between stage III and IV for both DSS and OS (Harrell's C of 0.59 and 0.56, respectively) while AJCC8 showed slightly worse discrimination for both DSS and OS (Harrell's C of 0.54 and 0.53, respectively). Similar results were found after adjusting for administration of adjuvant radiotherapy and age, and excluding patients treated before the year 2000.

Discussion

The current study is the largest multi-institutional analysis of the prognostic value of the AJCC8 nodal staging system for HNCSCC. This study included 1146 patients with a median follow up of 3.4 years. During the study period, there were 206 deaths due to HNCSCC from 4 centers which manage high volumes of HNCSCC in Australia, a country that has one of the highest incidence of skin cancer in the world. The results indicate that nodal staging of patients as per the AJCC8 staging system stratifies risk poorly. These findings are consistent with our previous study.¹⁴

In 2010, the AJCC7 adopted the mucosal SCC nodal staging system for metastatic cSCC, despite the differing aetiology, disease biology, differences in the nodal drainage basin and management of the two diseases.⁵ Earlier studies questioned the validity of using this staging system for cSCC and have found lack of prognostic discrimination within the pN2 classification.¹² The AJCC8 staging system further incorporated ENE into nodal staging of HNCSCC resulting in increase of pN classification in majority of cases. An earlier study from our group on HNCSCC patients with nodal metastases found lack of prognostic utility of AJCC8 in stage III and IV HNCSCC.¹⁴

ENE was present in a high proportion (80%) of the current cohort of metastatic HNCSCC, consistent with previous studies.^{13,19,20} ENE has previously been shown to be a strong independent adverse prognostic factor²¹⁻²³, however the reason for high incidence of ENE in

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HNcSCC has not been investigated previously. It is plausible that contributing factors include lack of follow up after excision of the primary lesion, metastases to deep parotid nodes which may not become clinically obvious until ENE is present and infiltrative nature of SCC capable of metastasis. Incorporation of ENE in the AJCC8 upstaged 80% of patients and resulted in the majority of the patients being assigned pN2a or pN3b. More than 50% of the cohort was classified as pN3b and 90% of the cohort was assigned Stage IV. The AJCC8 pN2a classification includes patients with small lymph node deposits with sub-millimetre ENE as well as large lymph node deposits (up to 6cm) without ENE while the N3b classification includes patients with two or more small lymph node deposits with sub-millimetre ENE as well as single large lymph node deposit (larger than 3cm) with ENE. In other words, pN2a and pN3b categories combine patients with heterogeneous disease characteristics, all of which are consolidated into Stage IV and include patients with small lymph node metastases with minimal ENE to patients with massive nodal metastases with extensive ENE, perineural invasion and skull base involvement. This negatively impacts the prognostic distinction between stage III and stage IV HNcSCC which is indicated by a Harrell's C of 0.53. Indeed the prognosis and management of these two groups of patients differ depending on the extent of involvement of adjacent structures.²⁴

It is also important to note that only 0.3% of the current cohort was classified as pN3a disease. This reflects that metastatic deposits larger than 6cm are rarely confined to the lymph node without ENE. Metastatic HNcSCC most commonly show infiltrative growth through the nodal capsule rather than distend the node with central necrosis.¹⁹ Interestingly, the DSS

curve for pN3a appear worse than pN3b, further highlighting the negative impact on the prognostic distinction due to classifying lower or moderate risk patients into pN3b based on ENE. Whilst it is difficult to be conclusive about the prognostic utility of pN3a given the limited number of patients in this classification, it appears to be biologically and clinically redundant.

Concerns have previously been raised regarding the use of mucosal SCC nodal staging system for cSCC in AJCC7.¹² Whilst using a unified system maintains simplicity and promotes acceptance through familiarity,²⁵ the validity of using the same system for mucosal SCC and cSCC is questionable given the distinct disease biology of the two diseases. In contrast to mucosal SCC, metastatic nodal HNCSCC usually do not present with the concurrent index primary, the histopathologic details of which are often unavailable or prognostically irrelevant.^{13,26,27} Therefore the nodal stage is frequently the most critical prognostic factor. Furthermore, HNCSCC often metastasise to the parotid lymph nodes which is not part of the drainage basin for mucosal SCC. ENE within parotid lymph nodes can involve excision margins or give rise to perineural invasion of the facial nerve which adversely affects the prognosis.²⁶ Indeed, the AJCC8 nodal staging system has been shown to perform better in mucosal SCC than cSCC.²⁸ The data indicate that HNCSCC would benefit from an independent staging system and alternative systems have been proposed. A system proposed by Andruchow et al.²⁴ takes into account parotid involvement, number of lymph nodes and the size. A simplified system called “N1S3” has also been proposed by Forest et al.¹⁹ and only takes into account number of lymph nodes and size. These alternative staging

systems will require validation with larger multi-institutional cohorts to determine their prognostic utility.

One of the limitations of the current study is its long timeframe of data collection which spans over 30 years. The data may be confounded by changes in treatment standards and techniques, methods of disease detection as well as variability in histopathologic sampling and documentation of pathological features, particularly the lack of structured reporting and reliable reporting of ENE in older cases. However, we recently showed that disease-specific and overall survival have been consistent since the year 2000 in this cohort of patients and sensitivity analyses excluding those treated prior to this showed consistent results.²⁹

Conclusions

This is the largest multi-institutional study assessing the prognostic performance of the AJCC8 nodal staging system for HNCSCC. The incorporation of ENE in the AJCC8 resulted in upstaging of the majority of patients. AJCC8 nodal staging system performs poorly as risk stratification therefore an appropriate nodal staging system should take into account the distinct disease biology and anatomy of the lymphatic drainage.

Figure legends

Figure 1. Kaplan-Meier disease-specific survival by N classification for (A) AJCC7 and (B) AJCC8. Overall survival by N classification for (C) AJCC7 and (D) AJCC8

Figure 2. Kaplan-Meier disease-specific survival by TNM stage for (A) AJCC7 and (B) AJCC8. Overall survival by TNM stage for (C) AJCC 7 and (D) AJCC 8

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Table 1. Comparison between AJCC7 and AJCC8 classifications for pT, pN, and TNM prognostic stage groups of HNCSCC

AJCC7		AJCC8	
T classification			
T1	Tumor ≤2 cm	T1	Tumor <2 cm
T2	Tumor >2 cm or tumor any size with two or more high-risk features	T2	Tumor ≥2 cm but <4 cm
T3	Tumor with invasion of maxilla, mandible, orbit, or temporal bone	T3	Tumor >4 cm or minor bone erosion or PNI or deep invasion
T4	Tumor with invasion of skeleton (axial or appendicular) or perineural invasion of skull base	T4a	Tumor with gross cortical bone/marrow invasion
		T4b	Tumor with skull base invasion and/or skull base foramen involvement
N classification			
N1	Metastasis in a single ipsilateral lymph node ≤3 cm	N1	Metastasis in a single ipsilateral lymph node ≤3 cm and ENE (–)
N2a	Metastasis in a single ipsilateral lymph node, >3 cm but ≤6 cm	N2a	Metastasis in a single ipsilateral or contralateral lymph node ≤3 cm and ENE (+) or a single ipsilateral node >3 cm but ≤6 cm and ENE (–)
N2b	Metastasis in multiple ipsilateral lymph nodes ≤6 cm	N2b	Metastasis in a multiple ipsilateral lymph nodes ≤6 cm and ENE (–)
N2c	Metastasis in bilateral or contralateral lymph nodes ≤6 cm	N2c	Metastasis in bilateral or contralateral lymph nodes ≤6 cm and ENE (–)
N3	Metastasis in a lymph node >6 cm	N3a	Metastasis in a single lymph node >6 cm and ENE (–)
		N3b	Metastasis in a single lymph node >3 cm and ENE (+) or multiple ipsilateral, contralateral, or bilateral nodes, any with ENE (+)
TNM stage			
I	T1, N0, M0	I	T1, N0, M0
II	T2, N0, M0	II	T2, N0, M0
III	T3 or N1, M0	III	T3 or N1, M0
IV	T4 or N ≥ 2 or M1	IV	T4 or N ≥ 2 or M1

Table 2 Patient clinicopathological data

Variable	N	%
Age (years)		
<60	192	16.8
60-80	661	57.6
>80	293	25.6
Sex		
Male	972	84.8

Female	174	15.2
Institution		
Chris O'Brien Lifehouse/RPAH	443	38.6
Westmead Hospital	410	35.8
Peter MacCallum Cancer Centre	197	17.2
Liverpool Hospital	96	8.4
Extranodal extension		
Absent	219	19.1
Present	927	80.9
Treatment		
Surgery alone	193	16.8
Surgery + radiotherapy	879	76.7
Surgery + chemoradiotherapy	74	6.5
Surgery type		
Parotidectomy alone	152	13.3
Parotidectomy + SND	478	41.7
Parotidectomy + CND	242	21.1
SND alone	166	14.5
CND alone	97	8.5
Other	11	0.9
Pathological N classification (AJCC8)		
pN1	108	9.4
pN2a	367	32.0
pN2b	74	6.5
pN2c	8	0.7
pN3a	4	0.3
pN3b	585	51.1
TNM Stage (AJCC8)		
III	108	9.4
IV	1038	90.6

Abbreviations: *SND*, selective neck dissection; *CND*, comprehensive neck dissection

Table 3. pN classification change from AJCC7 and AJCC8.

AJCC7 pN classification (No.)	AJCC8 pN classification (No.)						
	pN1	pN2a	pN2b	pN2c	pN3a	pN3b	Total
pN1	108	342	0	0	0	0	450
pN2a	0	25	0	0	0	110	135
pN2b	0	0	74	0	0	418	492
pN2c	0	0	0	8	0	28	36
pN3	0	0	0	0	4	29	33
Total	108	367	74	8	4	585	1146

Table 4. TNM stage change from AJCC7 and AJCC8.

	AJCC8 TNM (No.)		
AJCC7 TNM (No.)	Stage III	Stage IV	Total
Stage III	108	343	451
Stage IV	0	695	695
Total	108	1038	1146

Table 5. Univariate survival analysis and model performance for AJCC7 and AJCC8 staging systems

Disease-specific Survival					
	HR (95% CI)	P value	C-index	PVE (%)	AIC
AJCC7					
pN2a v pN1	1.57 (0.96-2.59)	0.074	0.62	12.3	2657
pN2b v pN1	2.09 (1.50-2.90)	<0.001			
pN2c v pN1	2.29 (1.09-4.81)	0.029			
pN3 v pN1	6.63 (3.78-11.63)	<0.001			
Stage IV v III	2.10 (1.55-2.86)	<0.001	0.59	11.4	2670
AJCC8					
pN2a v pN1	1.72 (0.84-3.51)	0.137	0.62	13.9	2663
pN2b v pN1	1.53 (0.61-3.86)	0.366			
pN2c v pN1	1.75 (0.22-13.80)	0.596			
pN3a v pN1	5.64 (0.71-44.54)	0.101			
pN3b v pN1	3.65 (1.86-7.17)	<0.001			
Stage IV v III	2.73 (1.40-5.32)	0.003	0.54	13.7	2682
Overall Survival					
	HR (95% CI)	P value	C-index	PVE (%)	AIC
AJCC7					
pN2a v pN1	1.30 (0.97-1.74)	0.081	0.58	3.4%	6262
pN2b v pN1	1.39 (1.14-1.69)	0.001			
pN2c v pN1	1.30 (0.76-2.25)	0.339			
pN3 v pN1	3.38 (2.16-5.28)	<0.001			
Stage IV v III	1.41 (1.18-1.69)	<0.001	0.56	2.7%	6270
AJCC8					
pN2a v pN1	1.82 (1.23-2.69)	0.003	0.59	6.3%	6249
pN2b v pN1	1.40 (0.84-2.32)	0.197			
pN2c v pN1	0.65 (0.09-4.74)	0.667			
pN3a v pN1	4.40 (1.05-18.44)	0.043			
pN3b v pN1	2.56 (1.76-3.73)	<0.001			
Stage IV v III	2.15 (1.49-3.11)	<0.001	0.53	8.5%	6263

Abbreviations: AJCC, American Joint Committee on Cancer; HR, hazard ratio; CI, confidence interval; v, versus; C-index, Harrell's concordance index; PVE, proportion of variation explained; AIC, Akaike information criterion.

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Title:

Prognostic value of the 8th edition American Joint Commission Cancer nodal staging system for patients with head and neck cutaneous squamous cell carcinoma: A multi-institutional study

Date:

2020-10-29

Citation:

Luk, P. P., Ebrahimi, A., Veness, M. J., McDowell, L., Magarey, M., Gao, K., Palme, C. E., Clark, J. R. & Gupta, R. (2020). Prognostic value of the 8th edition American Joint Commission Cancer nodal staging system for patients with head and neck cutaneous squamous cell carcinoma: A multi-institutional study. HEAD AND NECK-JOURNAL FOR THE SCIENCES AND SPECIALTIES OF THE HEAD AND NECK, 43 (2), pp.558-567. <https://doi.org/10.1002/hed.26512>.

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