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Prognostic implications of the 8th edition American Joint Committee on Cancer (AJCC) staging system in oral cavity squamous cell carcinoma

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ABSTRACT

Background: The American Joint Committee on Cancer (AJCC) has changed the staging system of oral squamous cell carcinoma (OSCC) in the 8th edition of its staging manual to include depth of invasion (DOI) of the primary tumor as a modifier to the T category and extranodal extension (ENE) to upstage node positive OSCC. This study aims to evaluate the performance of the AJCC 8 pathologic staging system in OSCC and compare it to its predecessor (AJCC 7).

Methods: Analysis of 663 patients with OSCC from a prospective database was performed using the Cox proportional hazards competing risk model. The prognostic performance of the pathologic staging system was assessed using the Akaike Information Criterion (AIC) and Harrell's concordance index (C-index).

Results: AJCC 8 led to upstaging of 35.6% (N = 235) of patients in this cohort. Both AJCC 7 and 8 show limited monotonicity and poor stratification between stage groups I to III. The estimates for model performance reveal that AJCC 8 has modest predictive capacity for overall survival (OS) and disease specific survival (DSS) (Harrell's C of 0.70 and 0.74, respectively) but is superior to AJCC 7 (Harrell's C of 0.65 and 0.69, respectively).

Conclusions: The AJCC 8 staging system is more complex than its former version due to the inclusion of DOI and ENE. Compared with AJCC 7, it performs better in stratifying survival of OSCC patients by stage.

Introduction

Squamous cell carcinoma of the oral cavity and the lip (OSCC) contributes a significant burden of disease throughout the world [1]. The clinical benefit of the 8th Edition of the American Joint Committee on Cancer staging system (AJCC 8) is enhanced by its uniformity across the sites of the head and neck region. Nevertheless, it is well known that the prognostic performance for selected subgroups is suboptimal [2–4]. Ideally, a staging system distinguishes prognostic categories that are internally homogeneous. Recently AJCC 8 has been released. It makes two major changes for the staging of OSCC as shown in Table 1. One is the inclusion of depth of invasion (DOI) of the primary tumor as a modifier to the T category [5]. This is based on studies showing that tumors with a larger DOI or thickness are associated with an increased risk of nodal metastasis and worse survival outcomes [6–8]. The new staging manual emphasizes that it is important to use DOI instead of tumor thickness for staging purposes. At the same time, extrinsic tongue muscle involvement was excluded as an attributor for the T4a category. Second, the inclusion of extranodal extension (ENE) is used to upstage nodal positive OSCC. In AJCC 8, a distinction was made between seven

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Table 1
AJCC 7 and AJCC 8 staging system.

AJCC 7	T-category	AJCC 8
Tumor ≤ 2 cm	**T1**	Tumor ≤ 2 cm, ≤5 mm DOI
Tumor > 2 cm but ≤4 cm	**T2**	Tumor ≤ 2 cm, DOI > 5 mm and ≤ 10 mm or tumor > 2 cm but ≤ 4 cm, and ≤ 10 mm DOI
Tumor > 4 cm	**T3**	Tumor > 4 cm or any tumor > 10 mm DOI
	T4	
(lip) Tumor invades through cortical bone or involves the inferior alveolar nerve, floor of mouth, or skin of face (i.e., chine or nose) (oral cavity) Tumor invades adjacent structures (e.g., through cortical bone [mandible or maxilla] into deep[extrinsic] muscle of tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, skin of face)	**T4a**	(lip) Tumor invades through cortical bone or involves the inferior alveolar nerve, floor of mouth, or skin of face (i.e., chine or nose) (oral cavity) Tumor invades adjacent structures only (e.g., through cortical bone of the mandible or maxilla, or involves the maxillary sinus or skin of the face).
Tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery	**T4b**	Tumor invades masticator space, pterygoid plates or skull base and/ or encases the internal carotid artery
	N-category	
Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension	**N1**	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension and ENE-negative
Metastasis in single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension	**N2a**	Metastasis in a single ipsilateral or contralateral lymph node 3 cm or less in greatest dimension and ENE-positive; or metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension and ENE-negative
Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension	**N2b**	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension and ENE-negative
Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension	**N2c**	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension and ENE-negative
Metastasis in a lymph node more than 6 cm in greatest dimension	**N3**	
	N3a	Metastasis in a lymph node more than 6 cm in greatest dimension and ENE-negative
	N3b	Metastasis in a single ipsilateral node more than 3 cm in greatest dimension and ENE-positive; or metastasis in multiple ipsilateral, contralateral, or bilateral lymph nodes, with any ENE-positive

Abbreviations: AJCC = American Joint Committee on Cancer, DOI = depth of invasion, ENE = Extranodal Extension.

different categories (N0, N1, N2a, N2b, N2c, N3a and N3b), hence adding one more N category. The aim of this study was to determine the utility of the recent staging system (AJCC 8) to distribute and stratify patients into prognostic groups, and compare it with its predecessor (AJCC 7). The model performance of the current as well as the former staging system will be investigated in terms of their ability to stratify OSCC patients into prognostic groups

Material and Methods

Study population

Clinicopathological data were extracted from a prospectively maintained database from patients treated at the Sydney Head and Neck Cancer Institute (SHNCI) between the years 1987 to 2016. The included patients were treated with curative intent for oral cavity and lip squamous cell carcinoma. The database includes demographic data, clinical and pathological staging, as well as treatment and follow-up details. All patients were restaged according to AJCC 8 [9]. Institutional ethics committee approval has been obtained for collection of data within the database (Protocol X16-0367 &HREC/16/RPA/510).

Statistical analysis

Statistical analysis was performed using Stata version 12.0 (StataCorp, College Station, TX). All statistics were 2-sided, and $P < 0.05$ was considered statistically significant. The end points for this analysis included overall survival (OS) and disease-specific survival (DSS). Overall survival was calculated from the date of surgery to the date of death or last follow-up. For DSS, patients who died from other causes than OSCC were censored at time of death. Univariate analysis was carried out using the Cox proportional hazard method to assess the impact of each category and stage for AJCC 7 and 8. Survival curves were generated using the Kaplan- Meier method. The prognostic performance of each model was evaluated using the Akaike Information Criterion (AIC), Harrel's concordance index (C-index), and visual inspection of the Kaplan- Meier curves for stratification into distinct prognostic categories.

Results

Patient characteristics and treatment

There were 927 patients with OSCC who fulfilled the inclusion criteria. Complete follow up and data on pathological staging was available for 663 patients. There were 380 patients (57%) who underwent surgery alone, 241 patients (36%) had surgery and adjuvant radiotherapy (RT) and 42 patients (6%) received surgery and adjuvant chemoradiotherapy (CRT). A neck dissection was performed in 510 patients (77%) in addition to the primary tumor resection. Relevant demographic, clinicopathological and treatment data are presented in Table 2.

Clinical outcome

Within the study population 153 deaths were observed, 94 of which were due to OSCC accounting for a 5-year OS rate of 70% and 5-year DSS rate of 81%. The median time to death from OSCC was 1.1 years (range 2 months to 5 years).

Redistribution of stage in AJCC 8th Edition

There were 661 patients restaged according to AJCC 8 (Table 1). In total, 235 patients (35.6%) were upstaged and 30 patients (4.5%) were down-staged. The distribution of patients by stage is summarized in Table 3. This demonstrates a shift away from stage IVA category towards stage IVB due to a major increase in stage IVB patients, from 4 to 107 patients, as well a reduction of IVA patients from 263 to 143, comparing AJCC 8 to AJCC 7. Within the upstaged patient group (N = 235), approximately half (50.6%) were reclassified due to a