Received: 27 July 2019 | Revised: 23 April 2020 | Accepted: 30 May 2020

DOI: 10.1002/hed.26344

WILEY

CLINICAL REVIEW

Risk stratification in oral squamous cell carcinoma using staging of the eighth American Joint Committee on Cancer: Systematic review and meta-analysis

Alhadi Almangush DDS, PhD[1,2,3,4] | **Matti Pirinen MSc, PhD**[5,6,7] | **Omar Youssef MD, PhD**[1,2] | **Antti A. Mäkitie MD, PhD**[2,8,9] | **Ilmo Leivo MD, PhD**[3]

[1]Department of Pathology, University of Helsinki, Helsinki, Finland

[2]Research Program in Systems Oncology, Faculty of Medicine, University of Helsinki, Helsinki, Finland

[3]Institute of Biomedicine, Pathology, University of Turku, Turku, Finland

[4]Faculty of Dentistry, University of Misurata, Libya

[5]Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Helsinki, Finland

[6]Department of Public Health, University of Helsinki, Helsinki, Finland

[7]Department of Mathematics and Statistics, University of Helsinki, Helsinki, Finland

[8]Department of Otorhinolaryngology—Head and Neck Surgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

[9]Division of Ear, Nose and Throat Diseases, Department of Clinical Sciences, Intervention and Technology, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden

Correspondence
Alhadi Almangush, DDS, PhD, Department of Pathology, University of Helsinki, Haartmaninkatu 3, P.O. Box 21, 00014 Helsinki, Finland.
Email: alhadi.almangush@helsinki.fi, alhadi.almangush@gmail.com

Abstract

The eighth edition of the American Joint Committee on Cancer (AJCC8) staging manual has major changes in oral squamous cell carcinoma (OSCC). We searched PubMed, OvidMedline, Scopus, and Web of Science for studies that examined the performance of AJCC8 in OSCC. A total of 40 808 patients were included in the studies of our meta-analysis. A hazard ratio (HR) of 1.87 (95% CI 1.78-1.96) was seen for stage II, 2.65 (95%CI 2.51-2.80) for stage III, 3.46 (95%CI 3.31-3.61) for stage IVa, and 7.09 (95%CI 4.85-10.36) for stage IVb. A similar gradual increase in risk was noted for the N classification. For the T classification, however, there was a less clear variation in risk between T3 and T4. AJCC8 provides a good risk stratification for OSCC. Future research should examine the proposals introduced in the published studies to further improve the performance of AJCC8.

KEYWORDS

eighth edition American Joint Committee on Cancer (AJCC 8), depth of invasion (DOI), extranodal extension, N classification, oral squamous cell carcinoma (OSCC), prognosis, T classification, TNM stage

Funding information
Finnish Cancer Society; Finnish Dental Society (Apollonia); Finska Läkaresällskapet; Helsinki University Hospital; Maritza and Reino Salonen Foundation; Turku University Hospital Fund

1 | INTRODUCTION

Oral cancer constitutes a life-threatening disease with a high mortality rate. According to Global Cancer Statistics, GLOBOCAN, there were 354 864 new cases of oral cavity cancer causing 177 384 deaths during 2018.[1] Smoking, in addition to chewing habits, is the main risk factor for oral cavity cancer. Other risk factors that might associate with the occurrence of oral cancer include, for example, alcohol consumption and poor oral hygiene.[2,3] In many countries, there is an increase in the incidence of oral cancer in young people.[4] Oral squamous cell carcinoma (OSCC) is the most common histologic type of oral cavity cancer. OSCC is usually treated with surgical resection of the tumor and with consequent neck dissection when there is evidence of neck disease or the risk for regional metastases is high. Adjuvant treatment (radiotherapy with or without chemotherapy) is used in cases with high-risk of poor prognosis. Indeed, patients eligible for such an aggressive treatment should be selected carefully on case-by-case basis.

A proper cancer staging is an important step toward individualized treatment approach. Current staging of cancer is based on evaluation of extension of tumor (T), involvement of lymph nodes (N) and distant metastasis (M). Together, these three categories form the TNM staging system that was released in a collaboration between the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC). This system is internationally accepted as the universal system for staging and it strongly influences treatment planning. According to the publishing history of AJCC (http://cancerstaging.org), the first edition of AJCC Manual was published in 1977 and since then new editions were published to update the staging of different cancers. For OSCC, the eighth edition of AJCC staging manual (AJCC 8) that has been recently released includes the most significant changes in the classification for over 30 years. These changes include the incorporation of depth of invasion into T classification, and extranodal extension into N classification.[5] Such changes will influence the staging of many cases of OSCC and that indeed will influence the clinical decision making. Therefore, the impact of the AJCC 8 staging system is an important topic of research and its prognostic performance has recently been evaluated in several studies. We sought to review these studies systematically and to carry out meta-analysis of the accumulated evidence to conclude about the utility of AJCC 8 in OSCC. We also discuss further improvements of AJCC 8 based on proposals by the published studies.

2 | METHODS

2.1 | Data search

We searched the databases of PubMed, OvidMedline, Scopus, and Web of Science using the following search terms: ("oral squamous cell carcinoma" OR "oral cancer") AND ("American Joint Committee on Cancer" OR "AJCC"). Two independent researchers (AA & OY) screened the retrieved studies, excluding duplicates and irrelevant studies. A study was considered relevant and eligible for inclusion if it analyzed prognostic performance of AJCC 8 in OSCC. The references of relevant studies were searched manually.

According to the website of AJCC, the eighth edition was published in 2016, and therefore we limited our database searching to the period from January 2016 until the date we conducted the literature search (25 February 2019). Non-English articles and conference abstracts were excluded. From the relevant studies (Table 1), the following items were extracted: name of first author, country, year of publication, number of cases, stage of cases, category of TNM analyzed, main treatment, percentage of cases that were upstaged due to AJCC 8, main findings about AJCC 8, survival outcome analyzed, and statistical values reported. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) were followed to ensure proper search of literature.[6]

2.2 | Quality assessment

We used Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK)[7] to evaluate the quality of all eligible studies as previously described.[8,9]

TABLE 1 Summary of studies that evaluated the prognostic significance of the 8th edition of the American Joint Committee on Cancer (AJCC 8) staging in oral squamous cell carcinoma (OSCC)

First Author et al, year (Country)	No. of cases	Stage	8th AJCC analyzed	Main treatment	% of cases upstaged	Main findings regarding prognostic performance of AJCC 8	Outcome	HR (95% CI)	*P* value
Dirven et al, 2017 (Australia)[a]	456	I-IV	T classification	Surgery	21.9%	Prognostic significance of T classification of AJCC 8 is same whether depth of invasion or tumor thickness was used.	OS DSS	HR: NA C-index: 0.64 HR: NA C-index: 0.63	NA NA
Ho et al, 2017 (USA)	14 554	T1-4 N0-3	T classification N classification	Surgery, Neck dissection	% NA	The AJCC 8 showed good prognostic value that improved by incorporation of number of metastatic nodes to N classification.	OS	**2.96 (2.23-3.92)*** **3.68 (3.25-4.16)****	**<.001*** **<.001****
Matos et al, 2017 (Brazil)	298	pT1-3 pN1-3	pT classification, pN classification	Surgical resection and neck dissection (all cases)	22.8% in pT, 29.2% in pN	AJCC 8 allows a better stratification of OSCC cases. Cases that received upstaging in pT and/or pN classification have a worse OS and DFS.	OS DSS DFS	NA **NA**	.017* <.001** .007* .001** .002*
Almangush et al, 2018 (Finland & Brazil)	311	T1-3	cT classification	Surgery	16.7%	AJCC 8 provides better prognostication than AJCC 7 and can be further optimized.	DSS DFS	2.21 (1.05-4.64) **2.37 (1.12-4.99)** 2.08 (1.07-4.01) **2.12 (1.09-4.08)**	.036 **.023** .03 **.027**
Amit et al, 2018 (USA)	244	I-IV	Overall stage, pT classification, pN classification	Surgery	25%	AJCC 8 allows for better risk stratification of OTSCC than AJCC 7.	OS DSS	**13.72 (2.39-105.3)** **14.41 (4.18-145.2)**	**<.05** **<.05**
Cramer et al, 2018 (USA)	39 361	I-IV	T classification, N classification	Surgery, RT, CT, CRT	10%	AJCC 8 upstaged a substantial number of cases and that slightly improved the prognostication in OSCC.	OS (T classification) OS (N classification)	5.34 (4.77–5.98) **3.86 (3.44-4.33)** 3.31 (2.90-3.78) **2.48 (2.16-2.84)**	NA NA
Kano et al, 2018 (Japan)	112	T1-4	T classification	Surgery, CRT (n = 3), BT (n = 2)	23.2%	T3 of AJCC 8 is reasonable in prognostication; while T2 represents a heterogenous group of cases.	DSS Nodal metastasis	NA NA	<.01 <.01
Liao et al, 2018 (Taiwan)	1933	pN0-N3b	pN classification	Surgery	% NA	pN classification of AJCC 8 showed good risk stratification of OS, DDS and DFS; but less useful stratification for distant metastasis.	OS DSS DFS	NA NA NA	<.001 <.001 <.001
Mascitti et al, 2018 (Italy)	73	I-IV	Overall stage, pT classification, pN classification	Surgery; Neck dissection (all cases)	23.3%	AJCC 8 allows for better risk stratification for TSCC cases.	OS DFS	NA NA	<.05 <.05
Moeckelmann et al, 2018 (Australia)[a]	663	I-IV	Overall stage	Surgery	35.6%	AJCC 8 performs better stratification for survival of OSCC.	OS DSS	6.91 (3.80-12.56) 10.22 (4.57-22.84)	.000 .000
Moeckelmann et al, 2018 (Australia)[a]	325	III-IV	N classification	Surgical resection and neck dissection (all cases)	45.8%	Risk stratification of AJCC 8 is better in OSCC than in cutaneous SCC. However, performance was relatively poor in both cancers.	OS DSS	3.6 (2.07-6.22) 4.4 (2.21-8.60)	.000 .000

(Continues)

TABLE 1 (Continued)

First Author et al, year (Country)	No. of cases	Stage	8th AJCC analyzed	Main treatment	% of cases upstaged	Main findings regarding prognostic performance of AJCC 8	Outcome	HR (95% CI)	*P* value
Pollaers et al, 2018 (Australia)	118	I-IV	Overall stage, T classification	Surgery	27.1%	AJCC 8 provides improved stratification for DFS in OSCC.	OS DFS DFS (T classification)	 	.0002 .0002 .019
Subramaniam et al, 2018 (India)[b]	441	T1-2	T classification	Surgical resection (with or without RT or CRT)	51.7%	AJCC achieved a better prognostication of OS in early OSCC.	OS (OR)	2.34 (1.53-1.58) **2.46 (1.15-5.26)**	<.001 **.021**
Tirelli et al, 2018 (Italy)	174	pT1-4 N0-3	pT classification pN classification	Surgery	31% for pT, 14% for pN	AJCC 8 improved discrimination of T classification for analysis of DSS	DSS	**NA**	.01 (for pN, .001)
Vuity et al, 2018 (UK)	449	pT1-4 pN0-3	pT classification	Surgery	% NA	AJCC 8 provided a better distribution than that in AJCC 7. However, AJCC 8 did not discriminate between patients with T3 and T4.	OS DSS	**NA** **NA**	<.0001 <.0001
Weimar et al, 2018 (Canada)[c]	335	T1-4	T classification	Surgery	% NA	AJCC 8T classification can be classified using radiologic thickness/depth and showed incremental HR with higher T classification.	OS	4.2 (1.77-9.95)	<.001
Jain et al, 2019 (India)	342	I-IV	pT classification pN classification	Surgery with neck dissection	38.8% for pT; 37.3% for pN	pN was the most powerful prognosticator for OSCC.	OS DFS	4.24 (2.20-8.14) 7.63 (4.30-13.56)	<.001 <.001
Lee et al, 2019 (Republic of Korea)	345	I-IV	Overall stage, N classification	Surgery and neck dissection	% NA	AJCC 8 overall stage (I-IV) showed good risk stratification. Incorporation of number of positive LN with N classification improved the prognostication of AJCC 8.	OS DSS DFS	**11.13 (5.41-22.89)** **22.87 (7.99-65.49)** **11.50 (5.15-25.68)**	**<.001** **<.001** **<.001**
Murthy et al, 2019 (India)[b]	441	I-II	T classification	Wide excision and neck dissection	51.7%	In early OSCC, AJCC 8 provides better survival prediction than AJCC 7.	OS DSS DFS	NA NA NA	<.017 <.016 <.05
Rajappaa et al, 2019 (India)	1431	T1-4 N0-3	T classification N classification	Surgery	% NA	Both T classification and N classification showed good risk stratification, and authors recommended incorporation of number of positive LN in the staging system.	OS DFS	**3.60 (2.34-5.53)*** 3.25 (2.47-4.28)**	**<.001*** <.001**

Notes: Statistical values from each study were for the highest overall stage, T classification and/or N classification. Values in bold are from multivariable analysis. * values for T-classification. ** values for N-classification.

Abbreviations: BT, brachytherapy; CI, confidence interval; CRT, chemoradiation therapy; CT, chemotherapy; DFS, disease-free survival; DSS, disease-specific survival; HR, hazard ratio; LN, lymph node; NA, not available; OS, overall survival; OR, Odds ratio; RT, radiation therapy.

[a]Dirven et al (2017) and Moeckelmann et al (2018) are overlapped.

[b]Subramaniam et al (2018) and Murthy et al (2019) are overlapped.

[c]Weimar et al (2018) used radiologic measurement of tumor depth/thickness to re-stage T classification according to criteria of AJCC 8.

2.3 | Statistical analysis

The meta-analysis of hazard ratios (HR) was performed by the "meta" package (version 4.8-1) in statistical software R (version 3.4.0). For each analysis, we carried out an inverse variance-weighted fixed-effects analysis and a DerSimonian-Laird random effects analysis.[10] We considered the random effects analysis as our main result to account for heterogeneity between the studies. In addition to the meta-analyzed effect sizes, our results also included the estimated proportion of variation in effect sizes due to heterogeneity (I^2)[11] and the DerSimonian-Laird estimate of the variance of the effect sizes (t^2).[10] The confidence intervals reported by "meta" package are based on the estimated SE and therefore can show a slight numerical difference from the confidence intervals reported in the original studies.

The reference group in HR calculation was stage I for the overall stages II-IV, T1 for the T-classifications T2-T4, and N0 for the N-classifications N1-N3. We excluded from the meta-analysis a single study[12] that reported HR for N-classification with respect to category N1. Because many studies had analyzed the advanced stage as one category (eg, IV) and other studies provided detailed analyses of the subcategories (ie, IVa, IVb, IVc), we conducted separate meta-analyses for each subcategory for which HR and 95%CI were reported in two or more studies. In addition, we combined the subcategories into a single category by using inverse-variance weighting within each study as follows: stage IVa, IVb, and IVc were combined as stage IV; T4a and T4b were combined as T4; N2a, N2b, and N2c were combined as N2; while N3a and N3b were combined as N3. For those studies of the overall stage (I-IV) that reported only Kaplan-Meier curves without an HR estimate, we estimated the HR manually following the approach presented by Tierney et al.[13] In Table 2, these estimates are highlighted by Italic font. In detail, we extracted numerical information from the Kaplan-Meier curves by using GraphClick 3.0.3 software. When both the curve coordinates and the censoring information were visible in the original figure, we used the Cox proportional hazards model as implemented in "coxph" function of the R package "survival" (version 2.43-3) to estimate the HR and its SE. When no censoring information was available, we assumed that censoring was non-informative and that patients were censored at a constant rate within any given time interval.[13] As the study by Cramer et al[14] analyzed stages I-IV including a large number of samples compared to other studies, we conducted an additional meta-analysis for stages I-IV excluding this large cohort. We used funnel plot to visually assess possible publication bias.

3 | RESULTS

3.1 | Search results

A total of 337 articles were retrieved, and there were 53 duplicates. A total of 284 hits were screened and 261 of these were excluded as being irrelevant. Of the 23 studies that were relevant, three studies[15-17] were excluded because they included different subsites of head and neck cancer. Therefore, 20 studies were eligible as they evaluated the prognostic performance of AJCC 8 in OSCC (Figure 1). Of these, seven studies were from Asia,[18-24] four were from *Australia*,[12,25-27] four from Europe,[28-31] four from North America,[14,32-34] and one from South America.[35] In addition, a Brazilian cohort was analyzed in one of the published studies combined with a Finnish cohort.[28] Most studies included different subsites of OSCC, and only four studies included oral tongue SCC without any other subsite.[18,28,29,33] Overlapping studies were from Australia[12,25,26] and India[20,21]; and they were not included together in the present meta-analysis.

3.2 | Meta-analysis results

There were seven studies (40 808 patients) eligible for pooled analysis of overall stage (I-IV). This analysis (Figure 2A-C) showed that risk of mortality continued to increase with each higher stage. Stage I was the reference point for our pooled analysis (as in the original studies), and a HR of 1.87 with 95% confidence interval (95%CI) of 1.78 to 1.96 was reported for stage II, HR 2.65 (95%CI 2.51-2.80) for stage III, and HR 4.94 (95%CI 3.61-6.76) for stage IV. The study with an exceptionally large number of cases[14] was then excluded from the meta-analysis of overall stage (I-IV) and the remaining six studies (1447 patients) were included in the second analysis (Figure 3A-C). Consistently with the previous analysis, an increased risk of mortality with each higher stage was observed with HR 1.77 (95%CI 1.15-2.73) for stage II, 2.86 (95%CI 1.85-4.42) for stage III, and 5.75 (4.27-7.75) for stage IV.

Out of the three subclasses of stage IV, we were able to carry out meta-analyses (Figure 4 A, B) for stage IVa with a HR of 3.46 (95%CI 3.31-3.61), and for stage IVb with a HR of 7.09 (95%CI 4.85-10.36). We were not able to conduct a meta-analysis for stage IVc because only one study[14] reported it.

In the meta-analysis for T classification (Figure S1A-C), HR 1.98 (95%CI 1.51-2.59) was observed for T2, HR 3.12 (95%CI 2.19-4.45) for T3, and HR 3.71 (95%CI 3.28-4.20) for T4, as compared to the reference category T1. We were not able to conduct meta-analyses for T4a and T4b subclasses separately because almost all published

TABLE 2 Studies (with their statistical values) that were included in the meta-analyses

Overall stage (I-IV)				
Study	**Total No.**	**Stage**	**HR (95%CI)**	**Subclass: HR (CI)**
Amit et al, 2018	244	Stage I	1.00	NA
		Stage II	2.64 (0.43-17.98)	
		Stage III	5.86 (1.51-52.69)	
		Stage IV	13.72 (2.39–105.3)	
Cramer et al, 2018	39 361	Stage I	*1.00*	
		Stage II	*1.87 (1.78-1.97)*	
		Stage III	*2.65 (2.51-2.80)*	
		Stage IV	*3.79 (3.63-3.95)*	IVa 3.45 (3.31-3.61)
				IVb 5.28 (4.88-5.71)
				IVc 9.14 (8.39-9.94)
Mascitti et al, 2018	73	Stage I	*1.00*	NA
		Stage II	*1.90 (0.21-16.81)*	
		Stage III	*2.87 (0.35-23.24)*	
		Stage IV	*9.28 (1.25-68.97)*	
Moeckelmann et al, 2018	663	Stage I	1.00	
		Stage II	1.67 (0.88-3.16)	
		Stage III	1.57 (0.81-3.04)	
		Stage IV	4.51 (2.94-6.93)	IVa 2.86 (1.54-5.31)
				IVb 6.91 (3.80-12.56)
Pollaers et al, 2018	118	Stage I	*1.00*	
		Stage II	*2.52 (0.68-9.40)*	
		Stage III	*3.23 (1.01-10.32)*	
		Stage IV	*4.43 (1.50-13.03)*	IVa *3.45 (1.13-10.59)*
				IVa *12.75 (3.46-46.98)*
Jain et al, 2019	342	Stage I	*1.00*	
		Stage II	*0.72 (0.14-3.68)*	
		Stage III	*3.97 (0.91-17.26)*	
		Stage IV	*5.33 (1.29-21.95)*	IVa *4.30 (1.03-18.041)*
				IVb *10.79 (2.45-47.63)*
Lee et al, 2019	345	Stage I	1.00	
		Stage II	1.97 (0.87-4.50)	
		Stage III	4.37 (2.12-8.99)	
		Stage IV	7.84 (4.74-12.99)	IVa 5.61 (2.77-11.37)
				IVa 11.13 (5.41-22.89)
T classification (T1-T4)				
Ho et al, 2017	14 554	T1	1.00	NA
		T2	1.54 (1.12-2.11)	
		T3	2.12 (1.59-2.81)	
		T4	2.96 (2.23-3.92)	
Cramer et al, 2018	39 361	T1	1.00	
		T2	2.00 (1.91-2.09)	
		T3	3.32 (3.14-3.51)	
		T4	3.84 (3.68-4.00)	T4a 3.64 (3.48-3.81)
				T4b 5.34 (4.77-5.98)
Weimar et al, 2018	335	T1	1.00	NA
		T2	1.67 (0.72-3.88)	
		T3	2.88 (1.26-6.58)	
		T4	4.2 (1.77-9.95)	
Rajappaa et al, 2019	1431	T1	1.00	NA
		T2	4.06 (2.03-8.10)	
		T3	6.23 (3.11-12.5)	
		T4	4.71 (2.24-9.89)	

TABLE 2 (Continued)

Overall stage (I-IV)				
Study	**Total No.**	**Stage**	**HR (95%CI)**	**Subclass: HR (CI)**
N classification (N0-N3)				
Ho et al, 2017	14 554	N0	1.00	
		N1	1.59 (1.37-1.84)	
		N2	2.62 (2.36-2.91)	N2a 2.27 (1.84-2.81)
				N2b 2.70 (2.35-3.10)
				N2c 2.91 (2.25-3.75)
		N3	3.65 (3.23-4.13)	N3a 2.04 (0.65-6.36)
				N3b 3.68 (3.25-4.16)
Cramer et al, 2018	39 361	N0	1.00	
		N1	1.95 (1.86-2.05)	
		N2	2.68 (2.59-2.78)	N2a 2.25 (1.98-2.57)
				N2b 2.54 (2.43-2.66)
				N2c 3.1 (2.91-3.3)
		N3	3.69 (3.35-4.06)	N3a 4.18 (3.63-4.83)
				N3b 3.31 (2.9-3.78)
Jain et al, 2019	342	N0	1.00	NA
		N1	1.82 (0.83-4.04)	
		N2	2.48 (1.34-4.60)	
		N3	4.24 (2.20-8.14)	

Notes: Hazard ratio (HR) and 95% confidence interval (CI) that in Italic font were calculated from Kaplan-Meier curves. Underlined values refer to combination of the subclassifications into a single class to make them comparable to other studies.
Abbreviation: NA: not available.

studies reported HR and 95%CI for T4 classification as one category. Cramer et al[14] was the only study that provided detailed analysis for T4a and T4b as explained in Table 2.

For N classification (Figure S2A-C), an increased risk with each higher N classification was observed with HR 1.79 (95%CI 1.50-2.13) for N1, 2.67 (95%CI 2.59-2.77) for N2 and 3.68 (95%CI 3.41-3.97) for N3, as compared to the reference of N0. Only two studies[14,32] were eligible for the meta-analyses of the subclasses of N2 and N3 classifications. The meta-analyses showed a HR of 1.91 (95%CI 1.83-2.00) for N2a, 2.26 (95%CI 2.02-2.52) for N2b, 2.55 (95%CI 2.45-2.67) for N2c, 3.09 (95%CI 2.91-3.28) for N3a, and a HR of 4.13 (95%CI 3.59-4.76) for N3b subclassification.

Out of all meta-analyses, the heterogeneity measure I^2 showed high heterogeneity ($I^2 > 75\%$)[11] only for T3 classification (Figure S1B) where I^2 was 76%.

3.3 | Publication bias

Funnel plots were created for each pooled analysis of stages II-IV (Figures S3 and S4) as well as for stage IVa and IVb (Figure S5). In Figure S3C, the funnel plot showed asymmetry with the smaller studies showing higher effects compared to the meta-analysis result. When the largest study by Cramer et al[14] was excluded (Figure S4C), the asymmetry disappeared. Hence, it seems likely that the asymmetry in Figure S3C was due to a relatively small effect size estimate in the single large study of Cramer et al[14] rather than due to a publication bias among the smaller studies. Other funnel plots than that in Figure S3C did not show asymmetry.

4 | DISCUSSION

Staging of OSCC is the cornerstone to proper treatment planning to avoid overtreatment or undertreatment. The AJCC staging system (ie, TNM) has been used for decades as a universal system for risk stratification. However, AJCC has been criticized during the last decade due to suboptimal performance in prognostication of OSCC.[36-38] Recently, the AJCC has released the eighth edition with major changes in staging of some cancers (including OSCC) to improve risk stratification.[5] Our current study meta-analyzed the relevant studies of OSCC and found a good risk stratification based on the new criteria of AJCC 8. However, further adjustment of AJCC 8 is discussed based on the published studies.

The new criteria of AJCC 8 incorporate depth of invasion into the T classification. The approach of including depth of cancer infiltration into the TNM staging system

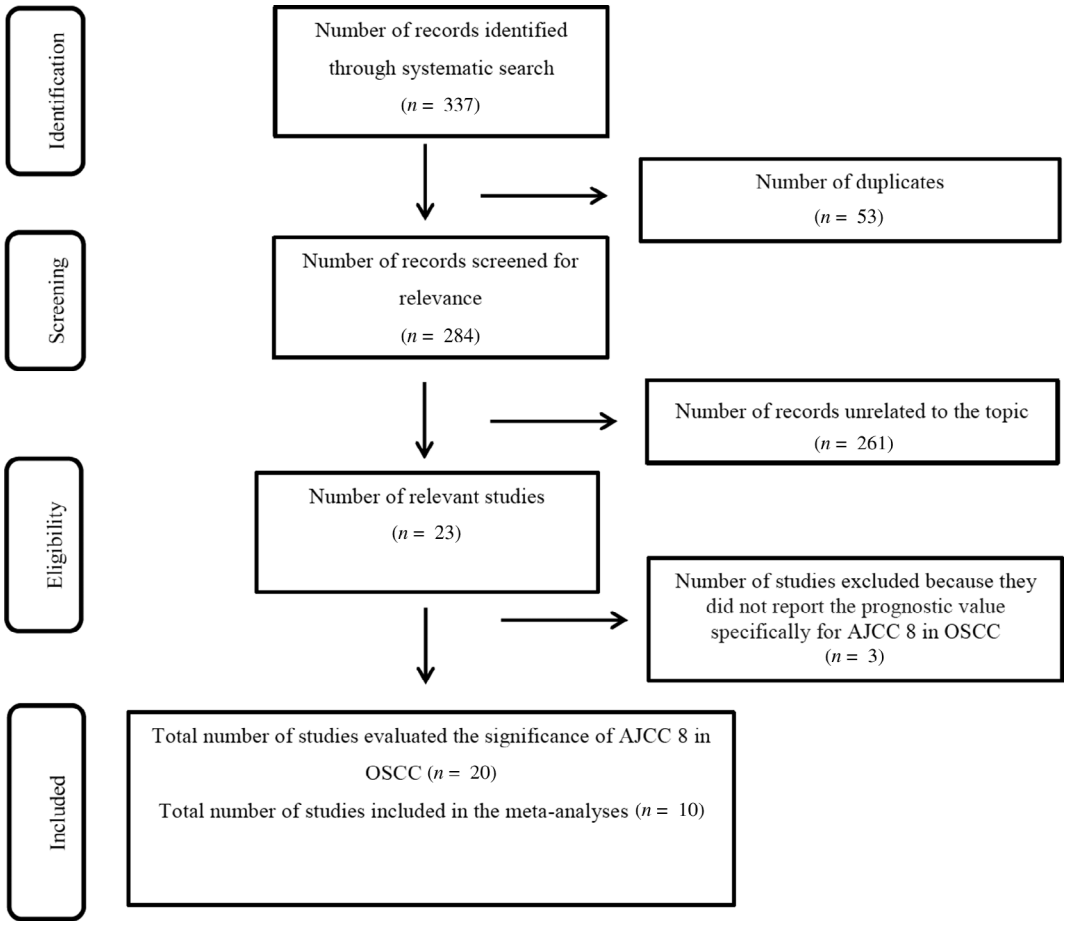

FIGURE 1 PRISMA Flowchart of our literature search and selection of studies

is routinely used in some malignancies such as melanoma and colorectal cancer.[38] In OSCC, the incorporation of depth of invasion (DOI) into T-classification was proposed by Ebrahimi et al[39] in 2014 based on a large cohort from 11 cancer centers worldwide. In addition, the significance of DOI has also been underlined in other studies.[40-43] The AJCC 8 has defined DOI as measurement from the basement membrane of the adjacent normal mucosa to the deepest point of tumor invasion. AJCC emphasized that depth of invasion and not tumor thickness should be incorporated into the T classification. Of note, Dirven et al[25] in their recent analysis of a large cohort of OSCC found almost the same performance for the T classification (AJCC 8) while using depth or thickness. Moreover, another recent study[34] reported that the T classification of AJCC 8 can be classified using radiologic (preoperative CT or MR imaging) measurements of tumor thickness. This is an important finding for preoperative staging based on AJCC 8 and requires further validation.

In another proposal, Subramaniam et al[21] proposed incorporating adverse histopathologic features such as perineural invasion into the T classification. Furthermore, Ebrahimi et al[44] showed that patients with medullary bone invasion have widely disparate prognoses based on the size of the primary tumor and not all of these patients should be classified as T4. For instance, tumors with bone invasion limited to the cortex would have a similar prognosis to those without bone invasion. They thus proposed upstaging by one T classification in case of medullary bone invasion.[44] Validation of the independent predictive impact of cortical vs medullary invasion will be needed before de-staging of a subgroup of T4 tumors can be performed and treatment protocols de-escalated.

It is noteworthy that only a very small risk difference between T3 (HR 3.32, 95%CI 3.14-3.51) and T4a (HR 3.64, 95%CI 3.48-3.81) was observed by Cramer et al[14] who included a large cohort in their analysis. However, the reported HR for T4b (5.34, 95% 4.77-5.98) showed a considerable difference from T3 or T4a classifications. In our meta-analysis, we noted a very close risk between T3 classification (HR 3.12, 95%CI 2.19-4.45) and T4 classification (HR 3.71, 95%CI 3.28-4.20). This was also noted in two of the included studies with the largest cohorts.[14,32] However, because other studies (Table 2) did not analyze

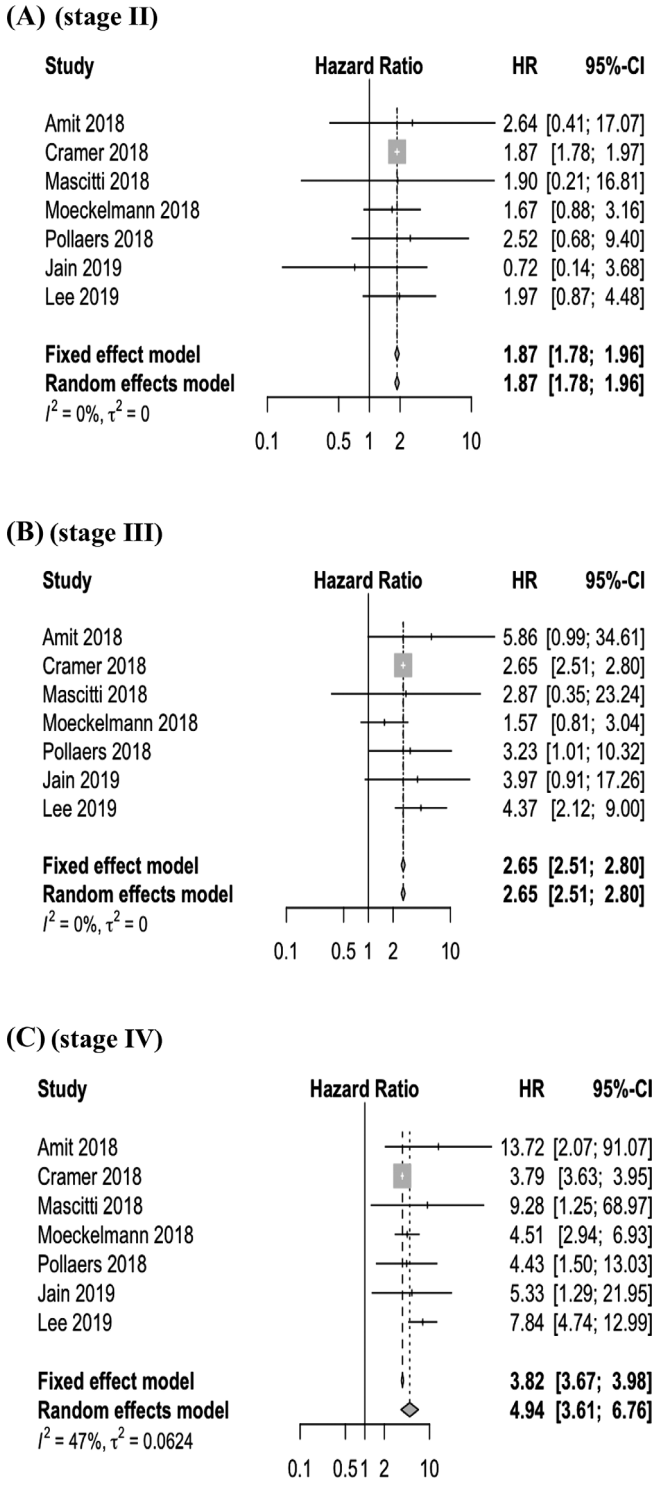

FIGURE 2 Forest plots of the pooled analysis of all eligible studies for stage II (panel A), stage III (panel B) and stage IV (panel C)

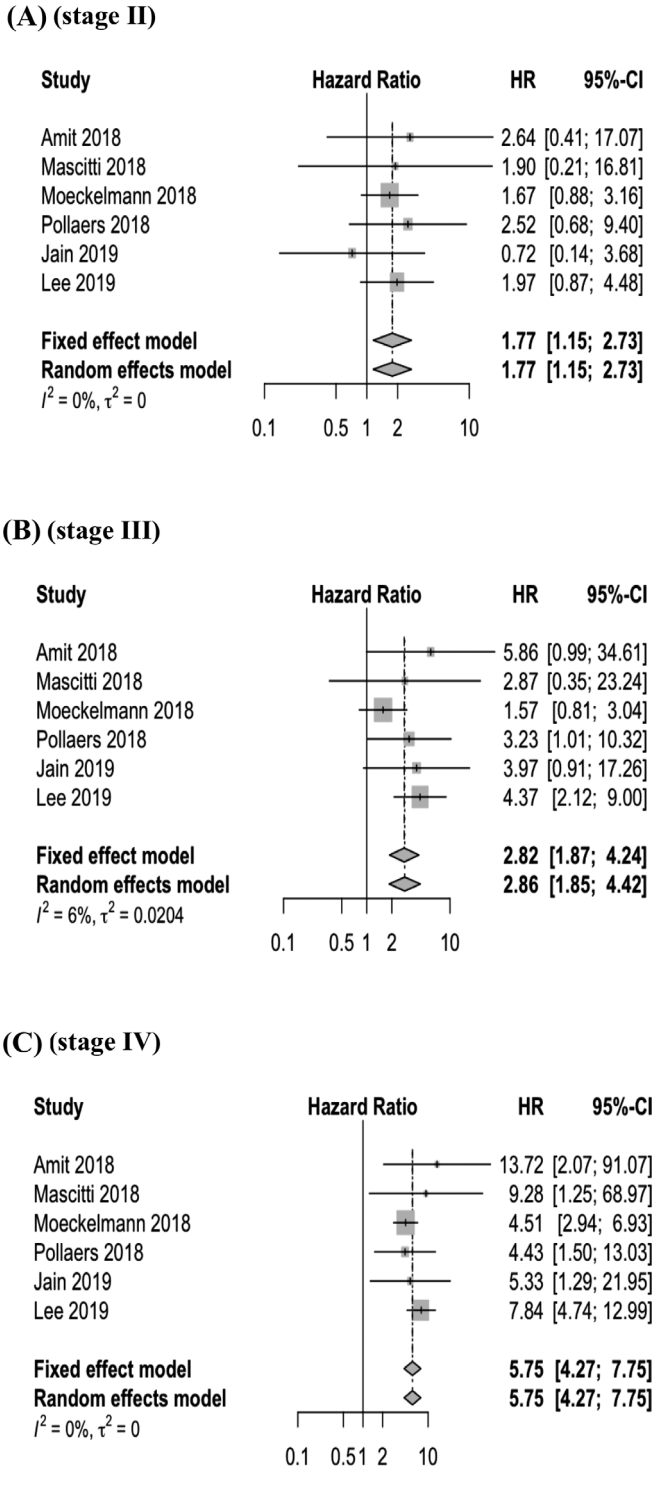

FIGURE 3 Forest plots of the pooled analysis of 6 eligible studies for stage II (panel A), stage III (panel B) and stage IV (panel C) after excluding Cramer et al that included an extremely large number of cases compared to these 6 studies

T classification in large cohorts, we should interpret the result of our meta-analysis regarding advanced T classification (ie, T3 and T4) with caution. This issue requires future research based on large cohorts to reach a definitive conclusion about risk differences between T3 and T4.

Of note, Liao et al[45] recommended to maintain extrinsic muscle invasion for classification of pT4 tumors as the outcome of such tumors was poorer than that of pT3 tumors. On the other hand, Barrett et al[46] supported the removal of invasion of extrinsic muscles of the tongue

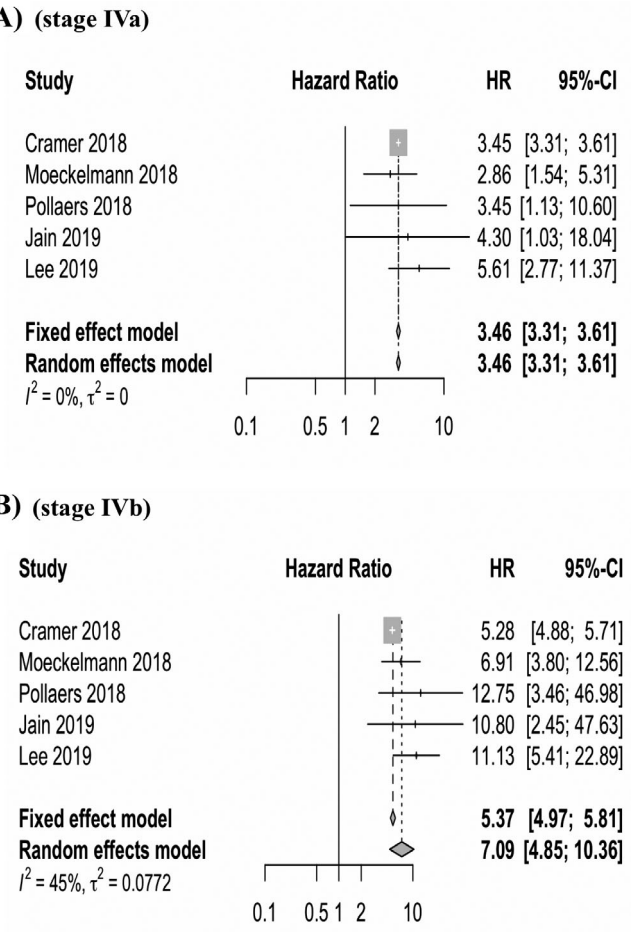

FIGURE 4 Forest plots of the pooled analysis of all eligible studies that reported stage IVa (panel A) and stage IVb (panel B)

from pT4a. Also another recent study[47] has accepted the removal of the involvement of extrinsic muscles from T4 because the lingual extrinsic muscles are not deep and sometimes superficial cancers involve them. It seems that this issue about exclusion of extrinsic muscle involvement requires further studies as the published papers on AJCC 8 did not widely focus on it.

For nodal staging, AJCC 8 incorporated extranodal extension into the N classification to improve the prognostic performance of the TNM system. In patients with OSCC, as well as in those with other cancers of head and neck, extranodal extension is a common microscopic feature and it was widely reported as a promising prognostic factor to identify cases at high-risk of worse prognosis.[16,48] The impact of including extranodal extension into the N classification of AJCC 8 has been analyzed in many studies (Table 1). Our meta-analysis showed an incremental increase in risk of worse survival with each higher N classification of AJCC 8 (Figure S2). It is speculated that a case of OSCC with numerous ipsilateral positive lymph nodes will have a worse survival compared with a case with only one or two positive nodes.[32] Interestingly, Ebrahimi et al[49] based on an international multicenter cohort have reported on promising significance of the number of metastatic lymph nodes in OSCC. Therefore, some of the studies that assessed the performance of AJCC 8 showed that the number of positive metastatic nodes can be a good modifier for the N classification.[23,24,32] Findings of these studies should be considered for future research as they might be useful for further improvement of TNM staging.

Of note, upstaging of several cases was a common phenomenon in the published studies (Table 1) when the patient cohorts were re-staged according to AJCC 8. For example, re-staging of our multicenter cohort according to AJCC 8[50] showed upstaging of many "early-stage" cases (ie, T1 or T2) to T3 which would be considered as an "advanced-stage". Dirven et al[25] reported that 20.7% of T1 tumors (based on AJCC 7) were upstaged to T2 and 6.7% upstaged to T3 when AJCC 8 was applied; in addition, 39.9% of T2 (based on AJCC 7) were upstaged to T3. In another study, Matos et al[35] reported on upstaging of 22.8% of cases based on pT classification, and upstaging of 29.2% based on the pN classification criteria of AJCC 8. In the study by Amit et al,[33] 25% of all cases were upstaged, and 12% of them were considered as early stage (I-II) according to AJCC 7 but advanced stage (III-IV) according to AJCC 8. In Mascitti et al[29] study, 20.5% were upstaged when DOI was included in the pT classification, and 13.7% were upstaged when ENE was included in the pN classification. In general, the proportion of upstaged cases (when re-classified according to AJCC 8) ranged in the published cohorts from 10%[14] to 51.7%[20] depending on how many deep tumors and/or ENE-positive cases were included in these cohorts (Table 1). Moreover, a "two-step" upstaging (eg, from stage I to stage III) was noted in the published studies.[21,28]

The above-mentioned upstaging will indeed influence treatment planning. For example, an early stage T1 tumor without nodal involvement is usually treated by surgical excision only, while a T3 tumor is considered as a locally advanced case requiring both surgical resection and adjuvant therapy. In the current era of upstaging caused by AJCC 8, a case with a small T1 or T2 tumor based on AJCC 7 will be upstaged to T3 if the depth of invasion is more than 10 mm. The role of adjuvant therapy in such cases is still not clear.[51] However, Ebrahimi et al[52] have recently emphasized that depth alone (ie, in absence of other risk factors such as nodal metastasis or close margin) should not be used as an indication of postoperative radiotherapy in patients with a small OSCC. This is supported by the finding from another recent study[53] concluding that in case of a small oral tongue cancer ($\leq$2 cm) with DOI > 4 mm, the presence of at

least two adverse features (eg, perineural invasion and lymphovascular invasion) will warrant the consideration of adjuvant therapy. Indeed, multimodality treatment based on multiple adverse prognostic indicators is practically safer than a treatment decision based on a single parameter. In general, any proposed change in the treatment protocol based on AJCC 8 should be considered with caution because the current evidence is based on data of retrospective nature. Future research should ideally consider prospective trials to analyze the treatment implications caused by AJCC 8.

The endpoints of survival analyses (overall survival, disease-specific survival or disease-free survival) and the examined classification/stage (T classification, N classification, or overall stage) were not similar between some of the published studies (Table 1). We considered overall survival when we conducted our meta-analyses because this endpoint was the most commonly reported in the published studies. Of note, the findings of our meta-analysis were consistent with almost all of the publications indicating a good prognostic performance of AJCC 8 (I-IV). We also noted that studies examining the significance of AJCC 8 in cohorts of mucosal squamous cell carcinoma from different subsites of the head and neck, including the oral cavity, have shown a good prognostic performance of AJCC 8.[15-17] Even though some authors have criticized the complexity of AJCC 8 due to the inclusion of depth of invasion and extranodal extension, they have, however, also reported a useful performance of AJCC 8.[26] The published studies have cohorts from different geographic regions (Asia, Australia, Europe, North America, and South America) with different ethnic groups and with variable socioeconomic status. This might indicate that AJCC 8 can be used worldwide for staging of OSCC.

Many studies compared the prognostic ability of both staging systems (ie, AJCC 7 and AJCC 8) using concordance index (C-index). For example, Cramer et al[14] reported an improvement in the survival concordance index from 0.714 (AJCC 7) to 0.715 (AJCC 8) for clinical staging, and an improvement from 0.699 (AJCC 7) to 0.704 (AJCC 8) for pathologic staging. In the study by Moeckelmann et al,[26] AJCC 8 showed a better prognostic performance (0.70) than AJCC 7 (0.65) for overall survival, and for disease-specific survival (0.74 vs 0.69). Similar superior prognostic performance for AJCC 8 in analysis of overall and disease-specific survival was reported by Amit et al[33]; and a modest predictive performance (C-index 0.66) was found in two other studies.[12,22] In addition, the promising performance of AJCC 8 has also been reported using Akaike information criterion (AIC) in some studies of OSCC.[26,33] Moreover, many other studies that did not report the C-index or AIC have reported that AJCC 8 allows for better risk stratification (than AJCC 7) for OSCC cases as indicated by the prognostic values and survival curves.[20,21,27-30] Interestingly, AJCC 8 has demonstrated a good prognostic performance in recent studies on gastric cancer,[54,55] breast cancer[56,57] and lung cancer.[58] In cutaneous squamous cell carcinoma of the head and neck, a weaker prognostic performance (C-index 0.58 for overall survival and 0.61 for disease-specific survival) has been reported.[12]

The distribution of patients between risk categories of T classification, N classification, and overall TNM stage (I-IV) for all studies analyzed AJCC 8 is summarized in Table 3. We noted that there were small percentages of cases in some advanced subclasses (IVb, IVc, T4b, N2a, N2b, N2c, or N3a). Specifically for N3a, there were no cases or a very small population in the relevant studies[19,32,33,35] that reported the subclasses of N classification (Table 3). A possible explanation for the lack of N3a cases is that it is rare for a nodal metastasis of more than 6 cm in diameter not to have ENE, and therefore, cases with such advanced nodal classification were all categorized as N3b in the published studies.[19,26,32,33,35] Future studies should analyze this issue of advanced nodal staging in larger cohorts to find out whether missing ENE (due to for example sampling error) cannot influence the classification in cases of nodal metastasis of more than 6 cm in diameter.

In addition to lack of clear evidence for the difference between the reported T classification (T3 vs T4), also other limitations should be acknowledged. Firstly, majority of the published studies included patients with different oral cavity subsites. It is important to examine the AJCC 8 in separate cohorts of oral subsites as the clinical behavior and survival outcome do vary between the subsites. Secondly, majority of studies that reported the hazard ratio for T classification have considered T4 as one group without identifying the difference between T4a (which is curable) and T4b (which is often incurable). Only the study by Cramer et al[14] reported the hazard ratio for T4a separately from T4b with a little higher risk of the latter one in multivariate analysis. Due to this shortcoming in majority of the published studies, we were not able to show the difference in risk between T4a and T4b in our meta-analysis. The third limitation is that the analyses of the advanced subclasses of N classification (ie, N2a, N2b, N2c; N3a, N3b) have been reported in only a few studies,[14,32] and therefore our meta-analyses of these subclasses should be interpreted with caution. Fourthly, the inappropriate grouping of some cases (that may be due to overlapping between some risk categories) should be acknowledged. Finally, individual cohorts were relatively small (except for Cramer et al[14]). These shortcomings should be avoided in future studies.

TABLE 3 The distribution of cases between risk categories of T classification, N classification and overall TNM stage (I-IV) for studies applying AJCC 8

First Author et al, year (Country)	No. of cases	T classification	N classification	Overall TNM
Dirven et al, 2017 (Australia)	456	**pT1** 18.6% **pT2** 30.3% **pT3** 34.0% **pT4** 17.1%	NA	NA
Ho et al, 2017 (USA)	14 554	NA	**N0** 64.1% **N1** 9.4% **N2a** 3.2% **N2b** 8.1% **N2c** 1.9% **N3a** 0.1% **N3b** 13.3%	NA
Matos et al, 2017 (Brazil)	298	**pT1** 11.7% **pT2** 14.4% **pT3** 29.9% **pT4** 44.4%	**pN0** 45.4% **pN1** 8.9% **pN2a** 6.5% **pN2b** 10.1% **pN2c** 4.8% **pN3a** 0.0% **pN3b** 24.3%	NA
Almangush et al, 2018 (Finland & Brazil)	311	**cT1** 28.9% **cT2** 64.6% **cT3** 6.4%	All cases included were cN0	NA
Amit et al, 2018 (USA)	244	**pT1** 32.4% **pT2** 49.6% **pT3** 18.0%	**pN0** 70.1% **pN1** 11.9% **pN2a** 3.3% **pN2b** 6.1% **pN2c** 0.4% **pN3b** 8.2%	NA
Cramer et al, 2018 (USA)	39 361	NA	NA	**0** 4.8% **I** 35.5% **II** 19.1% **III** 10.8% **IV** 29.8% IVa 25.1% IVb 2.7% IVc 2.0%
Kano et al, 2018 (Japan)	112	**T1** 17.86% **T2** 37.5% **T3** 42.86% **T4a** 0.89% **T4b** 0.89%	NA	NA
Liao et al, 2018 (Taiwan)	1933	NA	**pN0** 61.7% **pN1** 9.3% **pN2** 10.2% **pN3a** 0.0% **pN3b** 18.9%	NA
Mascitti et al, 2018 (Italy)	73	**pT1** 17.81% **pT2** 38.36% **pT3** 21.92% **pT4a** 21.92%	**pN0** 46.58% **pN1** 23.29% **pN2** 17.81% **pN3** 12.33%	**I** 6.85% **II** 23.29% **III** 23.29% **IVa** 34.25% **IVb** 12.33%

TABLE 3 (Continued)

First Author et al, year (Country)	No. of cases	T classification	N classification	Overall TNM
Moeckelmann et al, 2018 (Australia)	663	NA	NA	**I** 18.8% **II** 22.5% **III** 20.9% **IVa** 21.6% **IVb** 16.2%
Moeckelmann et al, 2018 (Australia)	325	NA	**N0** was not included **N1** 23.4% **N2a** 8.6% **N2b** 22.5% **N2c** 5.2% **N3a** 0.0% **N3b** 40.3%	**I, II** were not included **III** 16.6% **IV** 83.4
Pollaers et al, 2018 (Australia)	118	NA	NA	**I** 25.4% **II** 15.3% **III** 24.6% **IVa** 28.0% **IVb** 6.8%
Subramaniam et al, 2018 (India)	441	**T1** 26.4% **T2** 41.7% **T3** 31.9%	NA	NA
Tirelli et al, 2018 (Italy)	174	**pT1** 27.54% **pT2** 24.55% **pT3** 32.93% **pT4** 14.97%	**pN0** 63.47% **pN1** 10.18% **pN2** 13.77% **pN3** 12.57%	NA
Vuity et al, 2018 (UK)	449	**pT1** 32% **pT2** 30% **pT3** 22% **pT4** 16%	NA	NA
Weimar et al, 2018 (Canada)	335	—	—	—
Jain et al, 2019 (India)	342	**pT1** 10.6% **pT2** 35.1% **pT3** 28.9% **pT4** 25.4%	**pN0** 55.0% **pN1** 11.4% **pN2** 20.2% **pN3** 13.4%	**I** 9.1% **II** 22.8% **III** 20.5% **IV** 47.6%
Lee et al, 2019 (Republic of Korea)	345	NA	NA	NA
Murthy et al, 2019 (India)	441	**pT1** 28.28% **pT2** 40.27% **pT3** 31.45%	NA	NA
Rajappa et al, 2019 (India)	1431	NA	**N0** 67.4% **N1** 11.1% **N2** 11.0% **N3** 10.5%	NA
Summary of all studies in a weighted manner[a]		**pT1** 20.12% **pT2** 28.27% **pT3** 28.74% **pT4** 22.94%	**pN0** 59.78% **pN1** 10.09% **pN2** 12.76% **pN3** 17.44%	**I** 15.95% **II** 21.92% **III** 21.30% **IV** 40.84%

Note: Almangush et al (2018), Subramaniam et al (2018), and Murthy et al (2019) were designed for early-stage of OSCC.
[a]Summary was computed for all possible studies to provide % distribution of pT classification, pN classification, and TNM stage.

With all these limitations in mind, however, the overall stage (I-IV) as recently described in the AJCC 8 staging manual provides a good risk stratification for OSCC. Upstaging of cases was a common observation in the published studies, and this reflects changes in treatment planning. Further research should implement prospective studies and multi-institutional collaboration when evaluating AJCC 8 and examining its proposed modifications

for T and N classifications. Meanwhile, it can be recommended to use AJCC 8 in daily practice as it provides successful risk stratification of OSCC cases.

ACKNOWLEDGMENT

This study is funded by Turku University Hospital Fund, Helsinki University Hospital Research Fund, Finnish Cancer Society, Finnish Dental Society (Apollonia), Finska Läkaresällskapet, and the Maritza and Reino Salonen Foundation.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

ORCID

Alhadi Almangush https://orcid.org/0000-0003-4106-314X

Antti A. Mäkitie https://orcid.org/0000-0002-0451-2404

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394-424.
2. Oji C, Chukwuneke F. Poor oral hygiene may be the sole cause of oral cancer. *J Maxillofac Oral Surg*. 2012;11:379-383.
3. Tsai ST, Wong TY, Ou CY, et al. The interplay between alcohol consumption, oral hygiene, ALDH2 and ADH1B in the risk of head and neck cancer. *Int J Cancer*. 2014;135:2424-2436.
4. Hussein AA, Helder MN, de Visscher JG, et al. Global incidence of oral and oropharynx cancer in patients younger than 45 years versus older patients: a systematic review. *Eur J Cancer*. 2017;82:115-127.
5. Amin MB, Edge S, Greene F, et al. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017.
6. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
7. Altman DG, McShane LM, Sauerbrei W, Taube SE. Reporting recommendations for tumor marker prognostic studies (REMARK): explanation and elaboration. *BMC Med*. 2012;10:51.
8. Almangush A, Heikkinen I, Makitie AA, et al. Prognostic biomarkers for oral tongue squamous cell carcinoma: a systematic review and meta-analysis. *Br J Cancer*. 2017;117:856-866.
9. Almangush A, Pirinen M, Heikkinen I, Makitie AA, Salo T, Leivo I. Tumour budding in oral squamous cell carcinoma: a meta-analysis. *Br J Cancer*. 2018;118:577-586.
10. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177-188.
11. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539-1558.
12. Moeckelmann N, Ebrahimi A, Dirven 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;25:1730-1736.
13. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials*. 2007;8:16.
14. Cramer JD, Reddy A, Ferris RL, Duvvuri U, Samant S. Comparison of the seventh and eighth edition american joint committee on cancer oral cavity staging systems. *Laryngoscope*. 2018;128:2351-2360.
15. Garcia J, Lopez M, Lopez L, et al. Validation of the pathological classification of lymph node metastasis for head and neck tumors according to the 8th edition of the TNM classification of malignant tumors. *Oral Oncol*. 2017;70:29-33.
16. Lop J, Rigo A, Codina A, de Juan J, Quer M, Leon X. Prognostic significance of extranodal extension in head and neck squamous cell carcinoma cN0 patients with occult metastatic neck nodes. *Acta Otorrinolaringol Esp*. 2018;69:156-164.
17. Majercakova K, Valero C, Lopez M, et al. Postoperative staging of the neck dissection using extracapsular spread and lymph node ratio as prognostic factors in HPV-negative head and neck squamous cell carcinoma patients. *Oral Oncol*. 2018;77:37-42.
18. Kano S, Sakashita T, Tsushima N, et al. Validation of the 8th edition of the AJCC/UICC TNM staging system for tongue squamous cell carcinoma. *Int J Clin Oncol*. 2018;23:844-850.
19. Liao CT, Lee LY, Hsueh C, et al. Pathological risk factors stratification in pN3b oral cavity squamous cell carcinoma: Focus on the number of positive nodes and extranodal extension. *Oral Oncol*. 2018;86:188-194.
20. Murthy S, Low TH, Subramaniam N, et al. Validation of the eighth edition AJCC staging system in early T1 to T2 oral squamous cell carcinoma. *J Surg Oncol*. 2019;119:449-454.
21. Subramaniam N, Murthy S, Balasubramanian D, et al. Adverse pathologic features in T1/2 oral squamous cell carcinoma classified by the American Joint Committee on Cancer eighth edition and implications for treatment. *Head Neck*. 2018;40:2123-2128.
22. Jain D, Dravid C, Singla A, Kumari S, Grover RK. Comparison of the seventh and eighth editions of the American Joint Committee on cancer pT and pN classifications as predictors of survival in patients with oral squamous cell carcinoma. *Am J Clin Pathol*. 2019;151:292-301.
23. Lee H, Roh JL, Cho KJ, Choi SH, Nam SY, Kim SY. Number of positive lymph nodes better predicts survival for oral cavity cancer. *J Surg Oncol*. 2019;119(6):675–682. https://doi.org/10.1002/jso.25386.
24. Rajappa SK, Maheshwari U, Jaipuria J, et al. Number of positive nodes—current relevance in determining prognosis of oral cavity cancer after the recent AJCC staging update. *Oral Oncol*. 2019;90:1-5.
25. Dirven R, Ebrahimi A, Moeckelmann N, Palme CE, Gupta R, Clark J. Tumor thickness versus depth of invasion—analysis of the 8th edition American Joint Committee on Cancer Staging for oral cancer. *Oral Oncol*. 2017;74:30-33.
26. Moeckelmann N, Ebrahimi A, Tou YK, et al. Prognostic implications of the 8th edition American Joint Committee on Cancer (AJCC) staging system in oral cavity squamous cell carcinoma. *Oral Oncol*. 2018;85:82-86.
27. Pollaers K, Hinton-Bayre A, Friedland PL, Farah CS. AJCC 8th Edition oral cavity squamous cell carcinoma staging—is it an improvement on the AJCC 7th Edition? *Oral Oncol*. 2018;82:23-28.

28. Almangush A, Makitie AA, Makinen LK, et al. Small oral tongue cancers (</= 4 cm in diameter) with clinically negative neck: from the 7th to the 8th edition of the American Joint Committee on Cancer. *Virchows Arch*. 2018;473:481-487.
29. Mascitti M, Rubini C, De Michele F, et al. American Joint Committee on Cancer staging system 7th edition versus 8th edition: any improvement for patients with squamous cell carcinoma of the tongue? *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2018;126:415-423.
30. Tirelli G, Gatto A, Boscolo Nata F, et al. Prognosis of oral cancer: a comparison of the staging systems given in the 7th and 8th editions of the American Joint Committee on Cancer Staging Manual. *Br J Oral Maxillofac Surg*. 2018;56:8-13.
31. Vuity D, McMahon J, Takhiuddin S, et al. Is the 8th edition of the Union for International Cancer Control staging of oral cancer good enough? *Br J Oral Maxillofac Surg*. 2018; 56:272-277.
32. Ho AS, Kim S, Tighiouart M, et al. Metastatic lymph node burden and survival in oral cavity cancer. *J Clin Oncol*. 2017;35: 3601-3609.
33. Amit M, Tam S, Takahashi H, et al. Prognostic performance of the American Joint Committee on Cancer 8th edition of the TNM staging system in patients with early oral tongue cancer. *Head Neck*. 2019;41:1270-1276.
34. Weimar EAM, Huang SH, Lu L, et al. Radiologic-pathologic correlation of tumor thickness and its prognostic importance in squamous cell carcinoma of the oral cavity: implications for the eighth edition tumor, node, metastasis classification. *AJNR Am J Neuroradiol*. 2018;39:1896-1902.
35. Matos LL, Dedivitis RA, Kulcsar MAV, de Mello ES, Alves VAF, Cernea CR. External validation of the AJCC Cancer Staging Manual, 8th edition, in an independent cohort of oral cancer patients. *Oral Oncol*. 2017;71:47-53.
36. Rusthoven K, Ballonoff A, Raben D, Chen C. Poor prognosis in patients with stage I and II oral tongue squamous cell carcinoma. *Cancer*. 2008;112:345-351.
37. Almangush A, Bello IO, Coletta RD, et al. For early-stage oral tongue cancer, depth of invasion and worst pattern of invasion are the strongest pathological predictors for locoregional recurrence and mortality. *Virchows Arch*. 2015;467:39-46.
38. Piazza C, Montalto N, Paderno A, Taglietti V, Nicolai P. Is it time to incorporate 'depth of infiltration' in the T staging of oral tongue and floor of mouth cancer? *Curr Opin Otolaryngol Head Neck Surg*. 2014;22:81-89.
39. International Consortium for Outcome Research in H, Neck C, Ebrahimi A, et al. Primary tumor staging for oral cancer and a proposed modification incorporating depth of invasion: an international multicenter retrospective study. *JAMA Otolaryngol Head Neck Surg*. 2014;140:1138-1148.
40. Almangush A, Bello IO, Keski-Santti H, et al. Depth of invasion, tumor budding, and worst pattern of invasion: prognostic indicators in early-stage oral tongue cancer. *Head Neck*. 2014; 36:811-818.
41. Caldeira PC, Soto AML, de Aguiar MCF, Martins CC. Tumor depth of invasion and prognosis of early-stage oral squamous cell carcinoma: a meta-analysis. *Oral Dis*. 2019. https://doi.org/10.1111/odi.13194.
42. Arora A, Husain N, Bansal A, et al. Development of a new outcome prediction model in early-stage squamous cell carcinoma of the oral cavity based on histopathologic parameters with multivariate analysis: the Aditi-Nuzhat Lymph-node Prediction Score (ANLPS) system. *Am J Surg Pathol*. 2017;41:950-960.
43. Tam S, Amit M, Zafereo M, Bell D, Weber RS. Depth of invasion as a predictor of nodal disease and survival in patients with oral tongue squamous cell carcinoma. *Head Neck*. 2019; 41:177-184.
44. Ebrahimi A, Murali R, Gao K, Elliott MS, Clark JR. The prognostic and staging implications of bone invasion in oral squamous cell carcinoma. *Cancer*. 2011;117:4460-4467.
45. Liao CT, Lee LY, Hsueh C, et al. Clinical outcomes in pT4 tongue carcinoma are worse than in pT3 disease: how extrinsic muscle invasion should be considered? *Ann Surg Oncol*. 2017; 24:2570-2579.
46. Barrett AW, Tighe JV, Gulati A, et al. Staging of squamous cell carcinoma of the tongue: extrinsic lingual muscles and the 8th editions of the American Joint Committee on Cancer/Union for International Cancer Control staging manuals. *Br J Oral Maxillofac Surg*. 2017;55:921-926.
47. Murthy SP, Thankappan K, Jayasankaran SC, et al. Deep extrinsic muscle involvement is a fallacy in the American Joint Committee on Cancer's seventh edition of tumor staging of oral cavity cancers. *J Oral Maxillofac Surg*. 2018;76:206-212.
48. Almulla A, Noel CW, Lu L, et al. Radiologic-pathologic correlation of extranodal extension in patients with squamous cell carcinoma of the oral cavity: implications for future editions of the TNM classification. *Int J Radiat Oncol Biol Phys*. 2018;102: 698-708.
49. Ebrahimi A, Gil Z, Amit M, et al. The prognosis of N2b and N2c lymph node disease in oral squamous cell carcinoma is determined by the number of metastatic lymph nodes rather than laterality: evidence to support a revision of the American Joint Committee on Cancer staging system. *Cancer*. 2014;120: 1968-1974.
50. Almangush A, Makitie AA, Makinen LK, et al. Small oral tongue cancers (</= 4 cm in diameter) with clinically negative neck: from the 7th to the 8th edition of the American Joint Committee on Cancer. *Virchows Arch*. 2018;473: 481-487.
51. Rajappa SK, Ram D, Bhakuni YS, Jain A, Kumar R, Dewan AK. Survival benefits of adjuvant radiation in the management of early tongue cancer with depth of invasion as the indication. *Head Neck*. 2018;40:2263-2270.
52. Ebrahimi A, Gil Z, Amit M, et al. Depth of invasion alone as an indication for postoperative radiotherapy in small oral squamous cell carcinomas: an International Collaborative Study. *Head Neck*. 2019;41:1935-1942.
53. Larson AR, Kemmer J, Formeister E, et al. Beyond depth of invasion: adverse pathologic tumor features in early oral tongue squamous cell carcinoma. *Laryngoscope*. 2019;130(7): 1715–1720.
54. Zhu MH, Zhang KC, Yang ZL, Qiao Z, Chen L. Comparing prognostic values of the 7th and 8th editions of the American Joint Committee on Cancer TNM staging system for gastric cancer. *Int J Biol Markers*. 2020;35:26-32.
55. Jeong O, Jung MR, Kang JH, Ryu SY. Prognostic performance of preoperative staging: assessed by using multidetector computed tomography-between the new clinical classification and the pathological classification in the eighth American Joint

Committee on Cancer classification for gastric carcinoma. *Ann Surg Oncol*. 2020;27:545-551.
56. Savage P, Yu N, Dumitra S, Meterissian S. The effect of the American Joint Committee on Cancer eighth edition on breast cancer staging and prognostication. *Eur J Surg Oncol*. 2019;45:1817-1820.
57. Weiss A, Chavez-MacGregor M, Lichtensztajn DY, et al. Validation study of the American Joint Committee on Cancer eighth edition prognostic stage compared with the anatomic stage in breast cancer. *JAMA Oncol*. 2018;4:203-209.
58. Koul R, Rathod S, Dubey A, Bashir B, Chowdhury A. Comparison of 7th and 8th editions of the UICC/AJCC TNM staging for non-small cell lung cancer in a non-metastatic North American cohort undergoing primary radiation treatment. *Lung Cancer*. 2018;123:116-120.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Almangush A, Pirinen M, Youssef O, Mäkitie AA, Leivo I. Risk stratification in oral squamous cell carcinoma using staging of the eighth American Joint Committee on Cancer: Systematic review and meta-analysis. *Head & Neck*. 2020;1–16. https://doi.org/10.1002/hed.26344