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ORIGINAL ARTICLE – HEAD AND NECK ONCOLOGY

Prognostic Performance of Current Stage III Oral Cancer Patients After Curative Intent Resection: Evidence to Support a Revision of the American Joint Committee on Cancer Staging System

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ABSTRACT

Background. The American Joint Committee on Cancer (AJCC) stage III classification of oral cavity squamous cell carcinoma (OCSCC) represents a heterogeneous group of patients with early local disease with regional metastases (T1N1 and T2N1) and advanced local disease with or without regional metastasis (T3N0 and T3N1).

Objective. The aim of this study was to evaluate prognostic heterogeneity in the stage III category.

Methods and Patients. An international retrospective multicenter study of 1815 patients who were treated for OCSCC from 2003 to 2011.

Results. Kaplan–Meier survival analysis and multivariate models of stage III patients revealed better overall survival (OS; HR 2.12, 95 % CI 1.03–4.15; $p = 0.01$) and disease-specific survival (DSS; HR 1.7, 95 % CI 1.16–4.12; $p = 0.04$) rates for patients with T1–2N1/T3N0 disease than for patients with T3N1 disease. The outcomes of patients with T3N1 and stage IVa disease were similar ($p = 0.89$ and $p = 0.78$ for OS and DSS, respectively). Modifying stage classification by transferring the T3N1 category to the stage VIa group resulted in a better prognostic performance [Harrell's concordance index, C index 0.76; Akaike's Information Criterion (AIC) 4131.6] compared with the AJCC 7th edition staging system (C index 0.65; AIC 4144.9) for OS. When DSS was assessed, the suggested staging system remained the best performing model (C index 0.71; AIC 1061.3) compared with the current AJCC 7th edition staging (C index 0.64; AIC 1066.2).

Conclusions. The prognosis of T3N1 and stage IVa disease are similar in OCSCC, suggesting that these categories

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could be combined in future revisions of the nodal staging system to enhance prognostic accuracy.

Oral cavity squamous cell carcinoma (OCSCC) is the eighth most common cancer worldwide.[1] The American Joint Committee on Cancer (AJCC) Staging Manual categorizes early OCSCC disease as stage I or II, and locally advanced disease or distance metastasis as stage IV. Stage III disease represents a heterogeneous group, composed of patients with early local disease with regional metastases (T1N1 and T2N1) and patients with T3 disease with (N1) or without (N0) regional metastasis.[2] Although the simplicity and consistency across subsites of the current AJCC staging for head and neck cancer promotes clinical utility, it is widely acknowledged that the prognostic performance is suboptimal in selected subgroups.[3–6] Ideally, a staging system distinguishes prognostic categories that are internally homogeneous; however, our clinical experience suggests that the stage III classification for oral cancer encompasses a wide spectrum of disease severity with variable prognoses.

In this international, multicenter, pooled study, we aimed to evaluate prognostic heterogeneity in the stage III category of OCSCC. We show an improvement in patient outcome stratification based on a novel categorization of stage III compared with the previous one.

MATERIALS AND METHODS

Patient Population

Our study cohort comprised 1815 patients who were treated for OCSCC from 2003 to 2011 in seven cancer centers worldwide; patients with oropharyngeal disease were excluded. Relevant demographic and clinicopathological details are summarized in Table 1. The study was approved by the local Institutional Review Board (IRB) committees. Patients ranged in age from 15 to 93 years, with a median of 54 years, and follow-up ranged from 6 to 116 months, with a median of 35 months.

Treatment

Treatment modalities included surgery alone (61 patients, 26 %), surgery and adjuvant radiotherapy (101 patients, 43 %), or surgery followed by chemoradiotherapy (74 patients, 31 %). Adjuvant cetuximab was administered to 28 patients (11 %). All patients underwent a standardized neck dissection involving levels I–III, I–IV, or I–V, as described by the American Head and Neck Society.[7] The type of neck dissection was prespecified in all patients prior to the operation. Elective neck dissection was performed in 147 patients (62 %), while 89 patients (38 %) underwent therapeutic neck dissection.

TABLE 1 Baseline clinicopathological data ($N = 1810$)

Variable	*N*	%
Age (years)		
Mean ± SD	55 ± 13	
Median (range)	54 (15–93)	
Sex		
Male	1158	64
Female	652	36
Pathological T stage		
T1	341	19
T2	564	31
T3	205	12
T4	700	38
Pathological N stage		
N0	1001	55
N1	259	14
N2a	35	2
N2b	404	22
N2c	99	6
N3	12	1
TNM stage		
I	268	15
II	333	18
III	236	13
IV	973	54
Adjuvant treatment		
No	504	28
Radiotherapy	795	44
Chemoradiotherapy	370	20
Chemoradiotherapy and cetuximab	141	8
Extent of neck dissection		
Selective (I–III or I–IV)	1093	62
Comprehensive (I–V)	253	14
Bilateral	434	24
Follow up (months)		
Median (range)	35 (6–116)	

Data Entry, Patient Exclusions, and Statistical Methods

Data were entered into a commercially available spreadsheet (Microsoft Excel 2000, Microsoft Corporation, Seattle, WA, USA), and statistical analysis was performed using a computerized software package (JMP version 4.0, SAS Institute Inc., Cary, NC, USA; and SPSS, SPSS Inc. Chicago, IL, USA). The follow-up interval was calculated in months from the date of surgery to the date of last follow-up or death. Overall survival (OS) and disease-specific survival (DSS) rates were calculated using the Kaplan–Meier method, and univariate comparisons between groups were performed using

TABLE 2 Demographics and clinical characteristics of 236 patients with stage III OCSCC

Variable	No. of patients (%)				*p* value
	T1N1 [29 (12)]	T2N1 [80 (34)]	T3N0 [91 (39)]	T3N1 [36 (15)]	
Age (years)					
<65	20 (69)	66 (83)	66 (73)	31 (86)	0.15
≥65	9 (31)	14 (17)	25 (27)	5 (14)	
Sex					
Male	17 (58)	54 (67)	75 (82)	29 (80)	0.02
Female	12 (42)	26 (33)	16 (18)	7 (20)	
Clinical N classification					
N0	15 (51)	41 (51)	76 (84)	15 (41)	<0.001
N+	14 (49)	39 (49)	15 (16)	21 (59)	
Extent of neck dissection					
I–III or I–IV	26 (89)	70 (88)	71 (78)	26 (72)	0.04
I–V	0	1 (1)	2 (2)	0	
Bilateral	3 (11)	9 (11)	18 (20)	10 (28)	
Nodal yield					
<18	6 (21)	11 (14)	13 (14)	3 (8)	0.55
≥18	23 (79)	69 (86)	78 (86)	33 (92)	
Surgical margins					
Negative	23 (79)	61 (76)	74 (81)	25 (69)	0.67
Close (<5 mm)	5 (17)	13 (16)	10 (11)	6 (17)	
Positive	1 (4)	6 (8)	7 (8)	5 (14)	
Depth of invasion					
<5	7 (24)	8 (10)	17 (19)	1 (2)	0.12
≥5	22 (76)	72 (90)	74 (81)	35 (98)	
Extracapsular spread					
Yes	6 (21)	22 (27)	0	12 (33)	<0.001
No	23 (79)	59 (73)	81 (100)	24 (67)	
Treatment					
Surgery	8 (28)	16 (20)	36 (40)	1 (2)	<0.001
Surgery + RT	15 (51)	34 (42)	36 (40)	16 (44)	
Surgery + CRT	6 (21)	30 (38)	19 (20)	19 (52)	

RT radiotherapy, *CRT* chemoradiation, *OCSCC* oral cavity squamous cell carcinoma

the log-rank test. OS was calculated from the date of surgery to the date of death or last follow-up. For DSS, patients who died from causes other than OCSCC were censored at the time of death. Patients not experiencing these endpoints were censored at last follow-up. Other covariates of interest included age, clinical nodal status, surgical margin status [clear, close (<5 mm), involved], extracapsular nodal spread (ECS; absent, present), depth of invasion (<5 mm), and treatment group (surgery alone, postoperative radiotherapy, or postoperative chemoradiotherapy). Multivariable analyses were performed using Cox proportional hazards regression, stratified by study center. The additional prognostic value of covariates of interest was determined by:

(i) Tests of statistical significance in multivariable analyses.

(ii) Akaike's Information Criterion (AIC) and Harrell's concordance index (*c* statistic), a generalization of the area under the receiver operating characteristic curve that quantifies the proportion of all patient pairs for whom the predicted and observed survival outcomes are concordant.[8] A value of $c = 0.5$ indicates no predictive ability compared with chance alone, and a value of 1 indicates perfect discrimination. In general, a predictive model with a low AIC indicates a better model fit, and a high *c* statistic represents a better discrimination ability.[9]

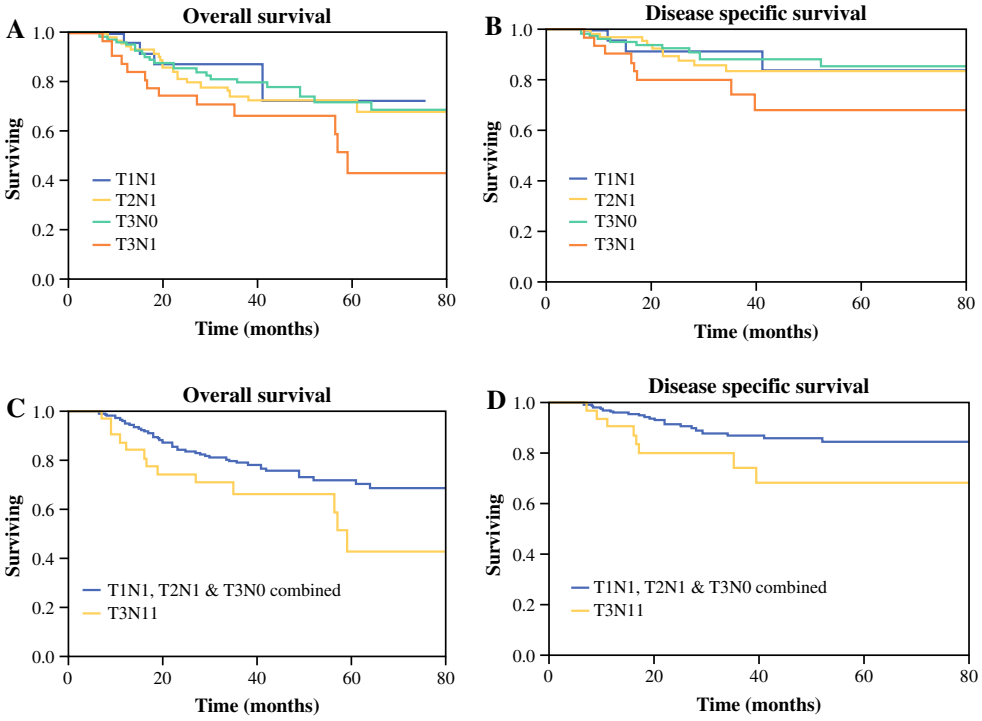

FIG. 1 Kaplan–Meier analysis of stage III patients according to TNM groups (T1N1, T2N1, T3N0, and T3N1). Five-year (**a**) OS and (**b**) DSS. Five-year OS (**c**) and (**d**) DSS of patients with T1–2N1/T3N0 (*blue line*) and T3N1 (*yellow line*) disease. *OS* overall survival, *DSS* disease-specific survival

(iii) Comparison with multivariable models with and without the covariate of interest, using a likelihood ratio test to determine whether model fit was significantly improved. A p value ≤ 0.05 was considered significant, and significant factors were entered into multivariate analysis using the Cox proportional hazards model.

RESULTS

To assess differences in outcome, patients with stage III OCSCC were divided into four groups according to the primary tumor (T) and regional lymph node (N) classification: T1N1 ($n = 29$ patients, 12 %), T2N1 ($n = 80$ patients, 34 %), T3N0 ($n = 91$ patients, 39 %), and T3N1 ($n = 36$ patients, 15 %). Table 2 presents the clinical and demographical data of patients with OCSCC stage III ($n = 236$). We first investigated the differences in demographic and clinical characteristics between the four groups. Male sex was more prevalent in patients with T3 than combined T1 and T2 classification (82 vs. 65 %; $p = 0.02$). Patients in the T2N1 group were younger (mean age 50.8 ± 1.4 vs. 55.8 ± 2.3 years; $p = 0.03$) than in the other classification groups combined. No differences between the groups in the rates of depth of invasion or positive surgical margins were observed.

We identified differences in treatment regimens between classification groups: T3N1 patients underwent postoperative radiotherapy with or without chemotherapy more frequently than patients in the other stage III groups combined (98 and 70 %, respectively; $p < 0.001$).

Kaplan–Meier analysis of patients with stage III disease according to TNM groups is shown in Fig. 1. The curves show better 5-year OS for patients with T1N1, T2N1, and T3N0 disease (71, 67, and 73 %, respectively) than for those with T3N1 disease (52 %). Similarly, stratifying stage III disease by T3N1 and T1–2N1/T3N0 revealed significantly worse outcomes for T3N1 patients: DSS ($p = 0.037$) and OS ($p = 0.036$). Most importantly, multivariable models for stage III patients show significantly worse outcomes for T3N1 patients than for patients in the other stage III groups combined: DSS (HR 1.7, 95 % CI 1.16–4.12; $p = 0.04$) and OS (HR 2.12, 95 % CI 1.03–4.15; $p = 0.01$), as shown in Table 3.

Next, we assessed whether T3N1 patients have similar prognosis as those in stage IVa (T4aN0–2, T1–3N2). Figure 2a and b compare OS and DSS of stage IVa patients with rates of the T3N1 group. Five-year OS and DSS for T3N1 patients were comparable with rates for the stage IVa subgroups (Fig. 2a, $p = 0.89$; and Fig. 2b, $p = 0.78$). Similarly, multivariate analysis showed no significant differences between stage IVa and T3N1 patients. Furthermore, removal of T3N1 patients from the stage III category preserved the differences in prognosis between stages II and III (OS, $p = 0.01$; DSS, $p = 0.04$) (Fig. 2c, d).

Through regression modeling, the staging system with the best prognostic discriminatory ability was then assessed through iterative statistical models and comparison of AIC

TABLE 3 Multivariable analysis of disease-specific and overall survival to determine prognostic value of stage III stratification

	Overall survival		Disease-specific survival	
	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Stage III stratification		0.01		0.04
T1N1	Referent		Referent	
T2N1	1.11 (0.6–1.84)		1.16 (0.7–1.56)	
T3N0	1.42 (0.8–2.14)		1.43 (0.72–1.99)	
T3N1	2.12 (1.03–4.15)		1.7 (1.16–4.12)	
Age (years)	0.99 (0.23–3.93)	0.9	0.69 (0.09–4.44)	0.7
Clinical nodal status		0.03		0.08
N0	Referent		Referent	
N+	1.96 (1.05–3.78)		2.17 (0.94–5.33)	
Nodal yield		0.04		0.01
<18			Referent	
≥18			3.79 (1.33–9.89)	
ECS		0.06		0.05
Absent	Referent		Referent	
Present	2.15 (0.94–4.7)		2.74 (0.99–7.2)	
Excision margin		0.06		0.1
Clear	Referent		Referent	
Close (<5 mm)	1.1 (0.41–2.5)		1.07 (0.16–8.08)	
Involved	3.00 (1.19–6.89)[a]		1.26 (0.16–4.06)	
Adjuvant therapy		0.53		0.44
Nil	Referent		Referent	
Adjuvant RT	1.6 (0.69–3.90)		0.84 (0.36–2.04)	
Adjuvant CRT	1.56 (0.60–4.21)		1.18 (0.48–2.96)	
Depth of invasion (mm)		0.15		0.92
<5	Referent		Referent	
≥5	1.98 (0.75–4.64)		1.07 (0.16–4.12)	

HR hazard ratio, *CI* confidence interval, *ECS* extracapsular spread, *RT* radiotherapy, *CRT* chemoradiation

[a] $p < 0.05$

and *c*-statistic values. For OS, the suggested staging was noted to have a better prognostic performance (C index 0.76; AIC 4131.6) than the AJCC 7th edition (C index 0.65; AIC 4144.9). When DSS was assessed, the suggested staging system remained the best performing model (C index 0.71; AIC 1061.3) compared with the current AJCC 7th edition staging (C index 0.64; AIC 1066.2).

To confirm our results, we repeated the multivariate analysis on an independent cohort of 255 pathologically staged III–IV patients who were treated in a single institution (National Cancer Center of Singapore, Singapore). Statistical analyses of this single-institution cohort showed that T3N1 patients had worse OS and DSS than other stage III patients ($p = 0.002$ and $p = 0.001$, respectively). Similar to the results of the current, larger cohort, we did not find significant differences in outcomes between T3N1 and stage IV patients.

DISCUSSION

The mainstay of treatment in oral cavity cancer is surgery.[10] Adjuvant treatment is administered to patients with early disease (staged as I–II) only in the presence of adverse pathological features. In contrast, in patients with advanced disease (staged as III–IV), or in the presence of positive lymph nodes, adjuvant treatment is usually indicated. Early disease is well-defined by limited local disease or the absence of metastatic lymph nodes (T1–2, N0). Nevertheless, stages III and IV entail heterogeneous groups, which may be characterized by limited local disease with extensive nodal metastases, locally advanced disease and no lymph node metastases, or locally advanced disease with nodal metastases.[11]

Improvements in the sensitivity of imaging techniques, computerized tomography (CT), positron emission

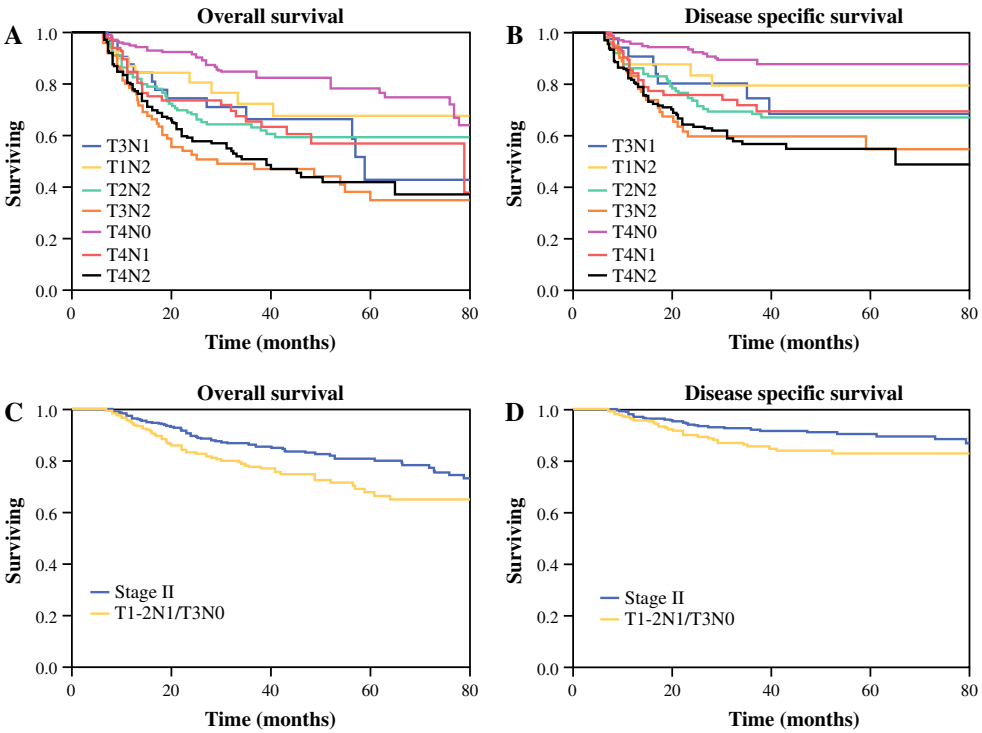

FIG. 2 Kaplan–Meier analysis of 5-year (**a**) OS and (**b**) DSS of patients with T3N1 and different stage IV groups (T1N2, T2N2, T3N2, T4N0, T4N1, and T4N2) disease. Five-year (**c**) OS and (**d**) DSS of patients with stage II (*blue line*) and stage III after removal of T3N1 (*yellow line*) disease. *OS* overall survival, *DSS* disease-specific survival

tomography (PET), and ultrasound have augmented our ability to identify metastatic lymph nodes as small as 3 mm in size.[12–14] The result is an increase in the number of patients presenting with a single nodal metastasis. The presence of single lymph node metastases in patients with early local disease (T1–2) has been associated with poor outcome.[15–19] In the current study, we show for the first time that the presence of both single lymph node metastasis and a tumor larger than 4 cm (i.e., T3N1) predicts worse outcome than the other risk groups within the stage III category. Furthermore, our multivariate analysis shows that this group of patients has similar prognosis to that of patients staged as IVa, and that removal of T3N1 patients from the stage III category improved the statistical coherence of this group, while preserving the prognostic characteristics of stages II and IV.

Current National Comprehensive Cancer Network (NCCN) guidelines indicate adjuvant radiotherapy in patients with pT3, regardless of their nodal status. The addition of concurrent chemotherapy in such cases, in the absence of extracapsular spread or positive margins, is still equivocal and not under uniform consensus. Compared with radiotherapy alone, slight improvement in 5-year survival rates have been demonstrated after adjuvant concurrent chemoradiation therapy for advanced head and neck SCC.[20] However, due to the significant morbidity associated with intensification of adjuvant treatment, i.e., adding chemotherapy to radiotherapy, there is still considerable controversy over the pathological characteristics of the tumor that predict the need for more aggressive adjuvant treatment.[19]

Re-stratifying patients with T3N1 classification to stage IVa can potentially assist in identifying patients with poor outcomes, and for whom concomitant adjuvant treatment may be needed. Further studies are required to determine whether these patients will benefit from concurrent chemoradiation therapy.

This study has some limitations of this study, i.e., the potential inconsistencies in surgical techniques and in the processing of pathological specimens, and the differences in treatment regimens. To address the matter of heterogeneity we performed an external validation using data from a single institute not included in our cohort. In that analysis we found that T3N1 classification remained a significant independent predictor of outcome and that T3N1 patients had worse OS and DSS compared with other stage III patients. Conversely, the significance of our heterogeneous cohort across multiple countries assures the broad applicability of our research findings worldwide and might facilitate the upstaging of T3N1 into stage IVa in diverse patient populations.[21] Due to the retrospective nature of the study, data regarding primary tumor site, smoking status, and alcohol exposure were not consistently available, and were therefore not included in the analysis.

CONCLUSIONS

Our data, derived from a multi-institutional international study that represents the largest and most detailed cohort of

OSCC to date, suggest the reclassification of T3N1 patients as stage IVa. We show that T3N1 classification represents patients at high risk of treatment failure similar to those in stage IVa, and therefore for whom concurrent adjuvant treatment may be considered.

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CONFLICT OF INTEREST The authors have no conflicts of interest to declare.

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