Improvement in Survival of Patients With Oral Cavity Squamous Cell Carcinoma

An International Collaborative Study

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BACKGROUND: An association between the survival of patients with oral cavity squamous cell carcinoma (OCSCC) and advancements in diagnosis and therapy has not been established. **METHODS:** This was a retrospective, longitudinal, international, population-based study of 2738 patients who underwent resection of OCSCC during 2 different decades. Characteristics of patients from 7 international cancer centers who received treatment between 1990 and 2000 (group A; n = 735) were compared with patients who received treatment between 2001 and 2011 (group B; n = 2003). **RESULTS:** Patients in group B had more advanced tumors and tended to develop distant metastases more frequently than patients in group A ($P = .005$). More group B patients underwent selective neck dissection and received adjuvant radiotherapy ($P < .001$). Outcome analysis revealed a significant improvement in 5-year overall survival, from 59% for group A to 70% for group B ($P < .001$). There was also a significant improvement in disease-specific survival associated with operations performed before and after 2000 (from 69% to 81%, respectively; $P < .001$). Surgery after 2000, negative margins, adjuvant treatment, and early stage disease were independent predictors of a better outcome in multivariate analysis. The decade of treatment was an independent prognostic factor for cancer-specific mortality (hazard ratio, 0.42; 95% confidence interval, 0.3-0.6). **CONCLUSIONS:** The survival rate of patients with OCSCC improved significantly during the past 2 decades despite older age, more advanced disease stage, and a higher rate of distant metastases. The current results suggest that the prognosis for patients with OCSCC has improved over time, presumably because of advances in imaging and therapy. ***Cancer* 2013;119:4242-8**. *© 2013 American Cancer Society.*

KEYWORDS: oral cavity, survival, time, trends, squamous, margins.

INTRODUCTION

Oral cavity squamous cell carcinoma (OCSCC) is the eighth most common cancer worldwide.[1] There has been a decline in the incidence of OCSCC over the last 25 years, which has been attributed by some to reductions in the use of tobacco and alcohol.[2,3] Recent reports suggest that this decline is partly related to a change in the etiology of OCSCC.[4] Recent advancements in imaging modalities and refinements in surgical and reconstructive methods have enabled an increasing number of patients with OCSCC to undergo curative surgical resections.[5,6] In addition, the implementation of adjuvant therapy regimens, including radiation therapy and chemotherapy and the use of targeted therapy directed against epidermal growth factor receptor (EGFR), have led to longer survival times in clinical trials.[7-11] However, whether these advancements have translated into improved survival in practice remains to be elucidated.

In this international, multicenter, pooled study, our objective was to evaluate the changes in patient populations and the trends in survival that occurred during the last 2 decades in several comprehensive cancer centers around the world. We demonstrate an improvement in patient outcomes despite an increase in the rate of an advanced disease in the last decade compared with the previous decade.

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TABLE 1. Number of Patients From Each Medical Center

Institute	No. of Patients (%)	Change in OS, %	Change in DSS, %
Brescia, Italy	74 (2.7)	+11	+5
Sydney, Australia	255 (9.3)	+13	+9
Camargo, Sao Paulo, Brazil	245 (8.9)	+14	+15
Cologne, Germany	230 (8.4)	+13	+11
Tata Memorial Hospital, Mumbai, India	540 (19.7)	+11	+14
MSKCC, New York, USA	218 (7.9)	+11	+10
CGMH, Taoyuan, Taiwan	1176 (42)	+12	+14
Total	2738 (100)	11	12

Abbreviations: CGMH, Chang Gung Memorial Hospital; DSS, disease-specific survival; MSKCC, Memorial Sloan-Kettering Cancer Center; OS, overall survival.

MATERIALS AND METHODS

Patient Population

Our study cohort included 2738 patients who received treatment for OCSCC from 1990 to 2011 in 7 cancer centers worldwide (Table 1). Patients with oropharyngeal disease were excluded. The study was approved by the local institutional review board committees. The patients ranged in age from 17 to 91 years (median age, 53 years). Table 1 lists their demographic data. Follow-up ranged from 12 to 187 months (median, 42 months).

Treatment

Treatment modalities included surgery alone (850 patients, 31%), surgery and adjuvant radiotherapy (1389 patients; 51%), or surgery followed by chemoradiotherapy (499 patients; 18%). Adjuvant cetuximab was received by 139 patients (5%). All patients underwent a standardized neck dissection involving levels I through III, I through IV, or I through V, as described by the American Head and Neck Society.[12] The type of neck dissection was prespecified in all patients before the operation. In total, 1643 patients (60%) underwent elective neck dissection, and 1095 patients (40%) underwent therapeutic neck dissection.

Data Entry, Patient Exclusions, and Statistical Methods

Data were entered into a commercially available spreadsheet (Microsoft Excel 2000; Microsoft Corporation, Seattle, Wash), and statistical analyses were performed using computerized software packages (JMP version 4.0 [SAS Institute Inc., Cary, NC] and SPSS [SPSS Inc., Chicago, Ill]). The follow-up interval was calculated in months from the date of surgery to the date of either last follow-up or death. Overall survival (OS), disease-specific survival (DSS), disease-free survival (DFS), and distant metastasis rates were calculated using the Kaplan-Meier method; and univariate comparisons between groups were performed using the log-rank test. A P value $\leq .05$ was considered significant, and significant factors were entered into multivariate analysis using a Cox proportional hazards model.

TABLE 2. Demographics and Clinical Characteristics of Patients With Oral Cavity Squamous Cell Carcinoma

	No. of Patients (%)		
Variable	1990-2000	2001-2011	*P*
Total	735 (27)	2003 (73)	
Age, y			
<70	670 (86)	2220 (90)	.005
≥70	111 (14)	237 (10)	
T classification			
T1	103 (15)	276 (13)	< .001
T2	278 (38)	638 (32)	
T3	167 (22)	239 (13)	
T4	187 (25)	850 (42)	
N classification			
N0	413 (56)	1114 (56)	.8
N1	119 (16)	304 (15)	
N2	202 (27)	581 (29)	
N3	1 (0.1)	4 (0.2)	
TNM staging			
I	247 (34)	553 (28)	< .001
II	185 (24)	301 (15)	
III	103 (14)	90 (5)	
IV	199 (27)	1059 (52)	
Surgical margins			
Negative	549 (76)	1649 (82)	< .001
Close	103 (14)	264 (13)	
Positive	73 (10)	90 (5)	
Depth of invasion, mm			
<4	65 (11)	247 (14)	.06
≥4	517 (89)	1494 (86)	
Extracapsular spread			
Yes	135 (24)	864 (47)	< .001
No	433 (76)	1001 (53)	
Neck dissection levels			
I-III/I-IV	343 (47)	989 (68)	< .001
I-V	194 (26)	189 (13)	
Radical	60 (8)	15 (1)	
Bilateral	138 (19)	270 (18)	
Treatment			
Surgery	319 (44)	531 (27)	< .001
Surgery +RT	393 (53)	996 (50)	
Surgery+ CRT	23 (3)	475 (23)	

Abbreviations: CRT, chemoradiation; RT, radiotherapy.

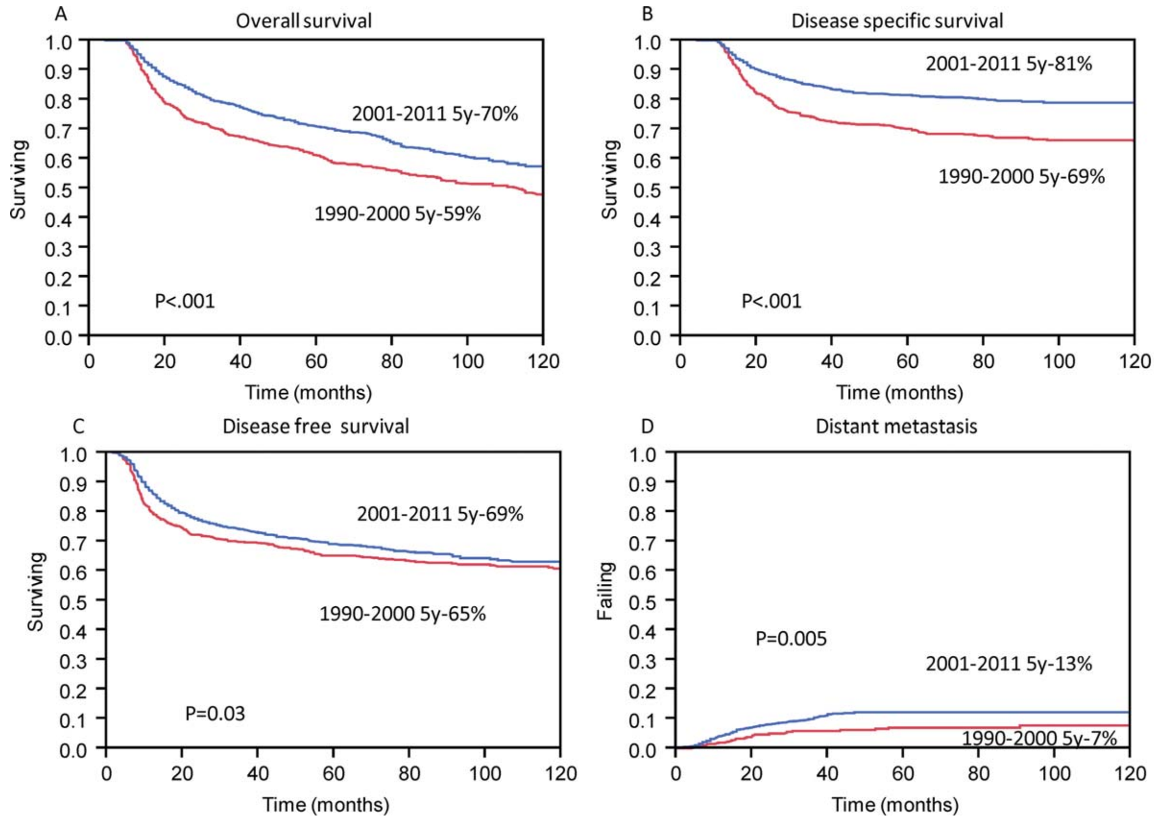

Figure 1. Kaplan-Meier 5-year (5y) curves illustrate the survival of patients who underwent surgery during the 2 periods (1990-2000 [red line] and 2001-2011 [blue line]), including (A) overall survival, (B) disease-specific survival, (C) disease-free survival, and (D) distant metastasis.

RESULTS

The patients were divided into 2 groups to assess changes in outcome between 1990 and 2000 (group A; n = 735 patients; 27%) and between 2001 and 2011 (group B; n = 2003 patients; 73%). First, we investigated the differences in demographic and clinical characteristics between the 2 groups. Table 2 indicates that the patients in group B were younger than the patients in group A (mean age ± standard deviation: ≥52.9 ± 12 years vs 55.2 ± 12 years, respectively; $P = .05$). Advanced disease (TNM stage III and IV) was more prevalent among group B patients (57% vs 41%; $P < .001$), presumably because of the higher proportion with advanced T classification (T3-T4; 55% vs 47%; $P < .001$). Conversely, the rate of positive lymph node metastasis was similar between groups ($P = .7$). The rate of positive surgical margins was higher in group A than in group B (24% and 17%, respectively; $P < .001$). There was no difference in the depth of invasion between the 2 groups ($P = .06$). The change in OS ranged from 11% to 14%, and the change in DSS ranged from 5% to 15%. Table 1 provides data from the individual institutes. To assess the role of environmental factors contributive to OCSCC, the survival of patients from different continents was calculated. We did not observe a statistically significant difference between continents in survival measures.

We also identified changing treatment trends over the duration of the study. The neck management for patients in group A was more likely to include level V (27% vs 19% in group B; $P = .03$). In contrast, limited selective neck dissection was more frequent in group B (67% vs 46% in group A; $P < .001$). Group B patients also received postoperative radiotherapy more frequently than group A patients (73% and 56%, respectively; $P < .001$). Similarly, group B patients received chemoradiation significantly more frequently than group A patients (24% and 3%, respectively; $P < .001$). The most common adjuvant treatment for advanced cancer among the group A patients was radiotherapy alone (69%), and only 4% received adjuvant chemoradiation. In contrast, 65% of group B patients received radiotherapy alone, 18% received adjuvant chemoradiotherapy for advanced

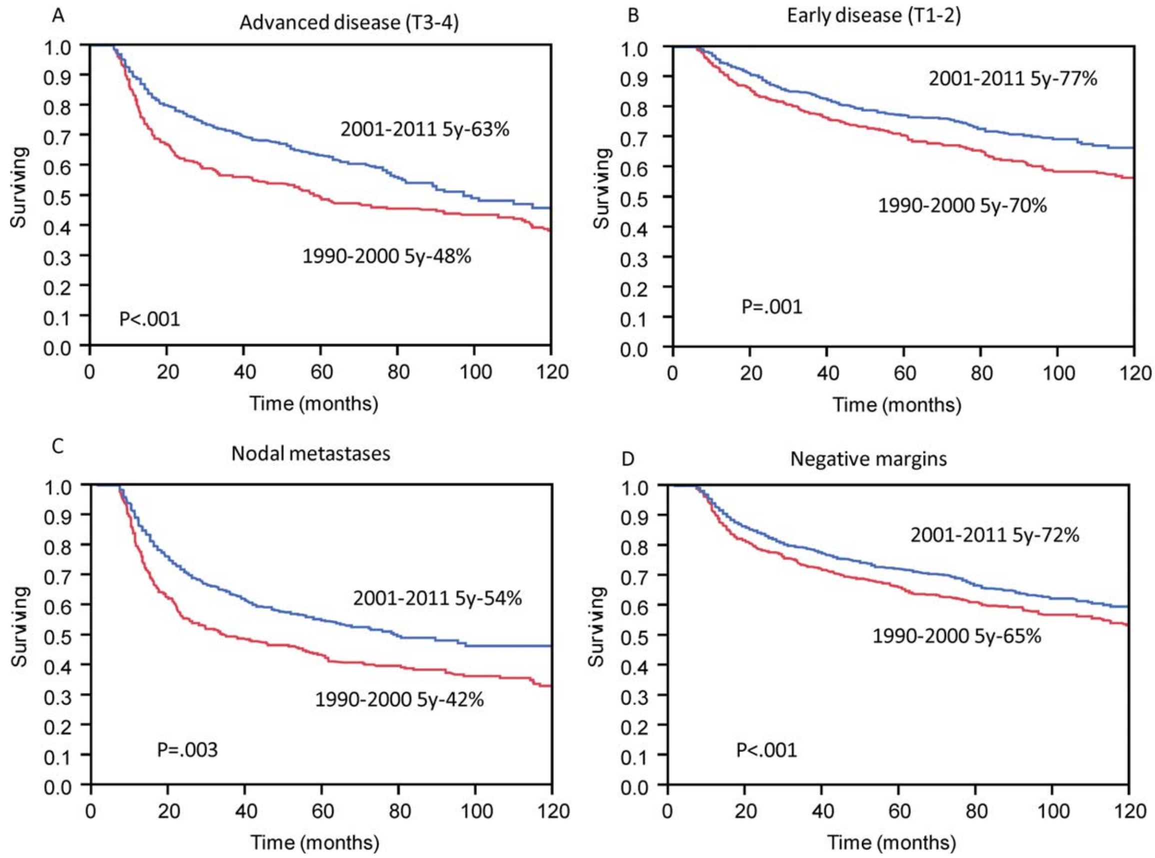

Figure 2. Kaplan-Meier 5-year (5y) curves illustrate the overall survival of selected patients who underwent surgery during the 2 periods (1990-2000 [red line] and 2001-2011 [blue line]), including patients with (A) advanced disease (T3-T4), (B) early stage disease (T1-T2), (C) lymph node metastasis, and (D) negative surgical margins.

disease, and 8% received chemoradiotherapy with cetuximab.

Next, we assessed the outcome of patients in each group. The Kaplan-Meier curves for the patients in each group are depicted in Figure 1. Survival analysis revealed a significant improvement in OS and DSS for group B compared with group A (11% and 12% improvement, respectively; $P < .01$). There was a significant improvement in DFS between groups (+4% between groups A and B; $P = .03$). In contrast, there was a statistically significant higher rate of distant metastases in group B compared with group A (13% and 7%, respectively; $P = .005$).

Univariate analysis revealed that tumor (T) and lymph node (N) classification, depth of invasion, surgical margin status, extracapsular spread, adjuvant treatment, and decade of surgery were associated significantly with OS, DSS, and DFS (Table 3). Figure 2 depicts the Kaplan-Meier curves for OS according to decade of treatment in patients with early stage disease (TNM stages I and II), advanced disease (TNM stages III and IV), positive lymph node status, and positive surgical margins.

Finally, we used multivariate analysis to test whether the decade in which patients underwent surgery had an independent impact on survival. The factors that had been identified as significant on univariate analysis were entered into a multiple regression model using log-rank analysis. Table 4 indicates that the significant predictors of OS, DSS, and DFS were decade of surgery, margin status, and T and N classification. An operation performed in the latter decade was an independent protective factor, with a hazard ratio (HR) of 0.42 (95% confidence interval [CI], 0.3-0.6) for cancer-specific death. Adjuvant treatment was an independent predictor of OS and DSS, whereas depth of invasion was significantly associated with DSS. To evaluate the potential role of adjuvant chemotherapy in high-risk patients, we performed a multivariate analysis in the subset of patients who had either

TABLE 3. Prognostic Factors for Overall and Disease-Specific Survival: Univariate Analysis

Variable	5-Year OS, %	*P**	5-Year DSS,%	*P*
Age, y				
<70	66	.03	76	.4
≥70	55		71	
T classification				
T1	84	< .001	91	< .001
T2	70		77	
T3	52		65	
T4	55		64	
N classification				
N0	80	< .001	89	< .001
N1	57		70	
N2	41		51	
N3	24		49	
TNM staging				
I	81	< .001	89	< .001
II	63		77	
III	55		67	
IV	41		41	
Surgical margins				
Negative	68	< .001	79	< .001
Close	63		75	
Positive	29		33	
Depth of invasion, mm				
<4	81	< .001	92	< .001
≥4	64		75	
Extracapsular spread				
Yes	50	< .001	83	< .001
No	74		63	
Neck dissection levels				
I-III/I-IV	71	< .001	80	< .001
I-V	71		79	
Radical	50		52	
Bilateral	57		61	
Treatment				
Surgery	80	< .001	89	< .001
Surgery + RT	61		74	
Surgery + CRT	47		54	
Decade of treatment				
1990-2000	59	< .001	69	< .001
2001-2011	70		81	

Abbreviations: CRT, chemoradiation; DSS, disease-specific survival; OCSCC, oral cavity squamous cell carcinoma; OS, overall survival; RT, radiotherapy.

positive lymph node status or positive surgical margins. Here, although significant on univariate analysis, multivariate analysis revealed no statistical significant effect of adjuvant chemotherapy on OS (HR, 1.3; 95% CI, 0.8-1.9) or DSS (HR, 1.6; 95% CI, 0.5-2.4).

DISCUSSION

Over the past decade, surgery has become the standard treatment for malignant tumors involving the oral cavity.[13] The past few years have witnessed considerable improvements in preoperative imaging assessment, technical advances in tumor resection, new reconstruction methods, effective radiotherapy, stringent case selection, and the fruitful cooperation of multidisciplinary clinical teams. These developments have contributed to our ability to safely treat tumors involving the oral cavity while providing a good quality of life for patients.[14-17] We designed the current study to examine whether these improvements were associated with temporal trends in the outcome of patients with OCSCC as recorded in pooled data from 7 international cancer centers over 2 decades. The aims of our study were to delineate 1) differences in the clinical and demographic characteristics of patient populations across 2 decades and 2) changes in survival. This retrospective, international, multicenter, pooled analysis compared the survival of patients who underwent surgery during 1990 to 2000 (group A) with those who underwent surgery during 2001 to 2011 (group B). Our analysis revealed that the group B patients were older and had more advanced T classification than the group A patients. In correlation, there was an increase in the rate of distant metastases during the last decade (the 5-year metastases rate rose from 7% to 13%). The group B patients underwent less extensive (selective) neck dissection and more frequently received adjuvant radiotherapy. Despite their advanced disease, the rate of close/positive margins was significantly lower among them. We identified a significant improvement in the 5-year OS rate, from 59% for group A patients to 70% for group B patients. A similar improvement was observed in the DSS rate (from 69% to 81%, respectively). Multivariate analysis revealed that surgery in the last decade was independently associated with improved OS, DSS, and DFS (HR: 0.69, 0.42, and 0.5, respectively). The improvement in survival measures did not differ significantly between centers or geographic regions. In agreement with previous reports, we demonstrated that TNM classification, margins status, and adjuvant treatment were significant predictors of outcome.

Mortality rates for different types of cancer decreased during the last 2 decades by 10% to 20% among females and males, respectively.[18] The reduction in mortality from cancer has been attributed mainly to prevention, early detection, and treatment. A 10% increase in survival was reported among patients with oral cavity carcinoma in the United States between 1975 to 2005.[18] Compared with that 10% improvement over 3 decades, our current results indicated a 12% improvement in OS and a 14% improvement in DSS during the last 2 decades among patients who received treatment in leading cancer centers around the world. This change was independent of demographic or clinical/biologic factors (Table 1). It was also independent of the receipt of radiotherapy, which was used more frequently in the latter period.

TABLE 4. Multivariate Analysis of Factors Associated With Survival

	OS		DSS		DFS	
Variable[a]	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age <70 y vs ≥70 y		.15		.61		.97
T classification						
T1	1.00	< .001	1.00	< .001	1.00	.01
T2	1.7 (1.2-2.86)		1.2 (0.7-1.5)		1.7 (1.2-3.8)	
T3	2.6 (1.5-4.1)		2.4 (1.4-3.4)		2 (1.3-3)	
T4	4.1 (2.7-6.2)		3.7 (2.1-6.6)		2.6 (1.9-3.3)	
N classification						
N0	1.00	.001	1.00	< .001	1.00	< .001
N1	2.2 (1.5-4.4)		2.4 (1.9-3.4)		2.1 (1.2-4.5)	
N2	2.9 (2-5.7)		3.6 (3-5.8)		3.4 (2-6.7)	
N3	3.4 (2.7-4.9)		4.2 (2.9-5.7)		3.5 (2.8-4.4)	
TNM staging		.69		.72		.94
Surgical margins						
Negative	1.00	.007	1.00	.003	1.00	< .001
Close	1.15 (0.7-1.4)		1.1 (0.6-1.4)		1.2 (0.8-1.6)	
Positive	1.9 (1.3-2.3)		2 (1.5-2.6)		1.9 (1.3-3.4)	
Depth of invasion, mm						
<4		.14	1.00	.001		.06
≥4			1.5 (1.1-2.4)			
Extracapsular spread: Yes vs no		.4		.1		.6
Neck dissection levels		.23		.96		.93
Treatment						
Surgery	1.00	.001	1.00	.007		.06
Surgery + RT	1.11 (1.03-1.5)		1.29 (1.1-1.8)			
Surgery + CRT	1.42 (1.1-1.7)		1.5 (1.06-2)			
Decade of treatment						
1990-2000	1.00	.004	1.00	< .001	1.00	.01
2001-2011	0.69 (0.56-0.89)		0.42 (0.3-0.6)		0.5 (0.27-0.65)	

Abbreviations: CI, confidence interval; CRT, chemoradiation; DFS, disease-free survival; DSS, disease-specific survival; HR, hazard ratio; OCSCC, oral cavity squamous cell carcinoma; OS, overall survival; RT, radiotherapy.

[a] The HR was calculated according to the first variable in each category.

Several studies have focused on the survival of patients with OCSCC.[19-27] The large variability in OS and DSS that was reported in those articles (ie, OS, 49%-60%; DSS, 55%-76%) can be explained largely by differences in the period during which the study was carried out, patient characteristics, the surgeon's experience, the distribution of early and advanced tumor stage, the radiotherapy quality, and the use of adjuvant treatment.[27] Our results also are in line with previous reports indicating that OS and DSS are influenced by margin status and TNM classification.[28,29] Our finding of a higher rate of metastases in group B may be explained by more advanced T classification at diagnosis compared with group A or by the different distribution of disease within oral cavity subsites. Alternatively, a higher locoregional control rate in group B also may have contributed to a longer OS and the development of distant metastases during follow-up. Another explanation may be the great availability, quality, and use of imaging for distant metastases, particularly metabolic imaging, such as positron emission tomography. The latter enabled us to identify smaller, clinically silent recurrences earlier in the latter decade. This may explain the more modest yet significant increase in DFS.

Modalities that potentially contributed to improved survival during the last decade are better preoperative imaging with later generation computerized tomography and magnetic resonance imaging studies, wider resections because of the availability of free-flap reconstructions, the greater use of adjuvant radiotherapy and combined chemoradiation therapy with or without cetuximab, the routine use of imaging modalities during follow-up, and the introduction of a multidisciplinary team approach.[13,27] Another important factor that may have contributed to better outcomes during the last decade is the volume of operations per cancer center, which reportedly can improve the perioperative mortality and long-term survival of patients undergoing complex cancer operations at high-volume hospitals.[30]

In conclusion, the results of the current study demonstrate a significant improvement in the 5-year OS and DSS rates (11%-12%) among patients with OCSCC during the past decade compared with the previous decade.

Multivariate analysis revealed that, although patients who underwent surgery during the latter period had a significantly greater risk of a poor outcome because of more advanced disease, including a higher rate of distant metastases, treatment during the last decade was independently associated with a significant improvement in outcome. In addition, we observed that the frequency of selective neck dissection among the patients in group B was significantly greater without compromising their survival.

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CONFLICT OF INTEREST DISCLOSURES

Snehal Patel has a patent pending in the United States for an endoscopic laser scalpel and receives royalties for a textbook on head and neck oncology. Ziv Gil receives royalties for textbooks on head and neck tumors.

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