Clinical and histopathologic independent prognostic factors in oral squamous cell carcinoma: a retrospective study of 334 cases

Clinical and Histopathologic Independent Prognostic Factors in Oral Squamous Cell Carcinoma: A Retrospective Study of 334 Cases

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Purpose: This retrospective hospital-based study reviewed and evaluated the outcome of patients with oral squamous cell carcinoma (OSCC) with the aim of identifying factors affecting the clinical course and survival rate.

Patients and Methods: Patients with a follow-up of at least 12 months were included. The data collected were statistically analyzed for the presence of factors valuable for prognosis; survival curves were processed in accordance with the Kaplan-Meier method. Differences in the expression of variables in different grading levels were investigated. Cox's proportional hazard model for Z_i covariates (grading, age, T, N) also was calculated.

Results: Mean patient age was 67.7 years in women (n = 152) and 62.4 years in men (n = 182). A total of 98 patients were identified with Broder's/World Health Organization grade 1 histology, 176 with grade 2, and 55 with grade 3; 5 patients were identified as grade 4 (carcinoma in situ). Gender and risk factors seemed to be unrelated to prognosis, whereas a significant increase in mortality was seen in patients over age 70. Histological grading, tumor size, and neck involvement were related, as independent factors, in predicting survival in patients with OSCC (QM-H > 3.9). Gender, age, and risk factors had no statistical relationship with cancer histological differentiation.

Conclusions: Our analysis reveals a statistically significant relationship among histological Broder's grading of malignancy, tumor size, locoregional involvement, and survival rates, underscoring the utility of tumor differentiation in predicting the clinical course and outcome of OSCC.

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Oral squamous cell carcinoma (OSCC) is the most common head and neck cancer, accounting for greater than 90% of total cases. Despite considerable advances in the diagnostic and therapeutic techniques, OSCC continues to portend a poor prognosis, with an estimated 5-year overall survival rate of only 56% in the United States and Western Europe.[1] The incidence of OSCC has increased over the past decades, as has mortality.[2-4] Knowledge of the prognostic factors at the start of treatment can be crucial in

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determining the appropriate therapy for each individual patient.

Although various biological and molecular factors have been proposed as prognostic factors in OSCC, so far these factors have had no impact on routine clinical care; comprehensive histopathologic staging of pathological specimens is still an important determinant of postoperative management and prognosis prediction.[5] TNM stage, grade, and depth of tumor invasion remain important factors in predicting the course of disease. Based on a survey of the available literature data, however, it may be stated that the prognostic value of these classical clinicopathologic parameters is often uncertain and controversial.[6]

Although many risk factors associated with OSCC have been well-documented, few related clinical studies have been conducted in northern Italy. The present study was conducted to analyze the outcome of patients with OSCC treated by different modalities, with the aim of identifying factors that may affect survival rate.

Patients and Methods

From a standardized computerized database,[7] the case records of 347 patients diagnosed with OSCC at the Oral Medicine Section, University of Turin over a 10-year period (June 1, 1994, to June 1, 2004) were retrospectively reviewed. The study cohort included patients with histologically confirmed diagnosis of OSCC, a minimum follow-up of 12 months, and a computerized digital file.

The data evaluated for each patient included demographic information, agreement of histological diagnosis between the first biopsy specimen and the surgical specimen, age at the time of diagnosis, gender, smoking (current or former smoker vs nonsmoker), alcohol consumption (current or former drinker vs nondrinker), tumor site, T classification and neck node involvement at the time of diagnosis,[8] treatment received, and outcome. Patient survival was evaluated as of December 31, 2005; all cases for which patient survival could not be confirmed or for which recall checks could not be performed were excluded. After the data-trimming process, 334 cases of OSCC were selected. Characteristics of these patients and the tumors are summarized in Tables 1 and 2. All subjects were residents of the Piedmont region in northwestern Italy.

Tumor grade according to the World Health Organization (WHO) classification system (ie, well, moderately, or poorly differentiated),[9] as determined by the pathologist from paraffin sections of pretreatment biopsy specimens, was blindly and retrospectively reexamined by an expert oral pathologist. Ages were divided into different groups (Table 1). Tumor locations were categorized as occurring in the alveolar mucosa, lateral border of the tongue and dorsum, mouth floor, palate, buccal mucosa, lips, retromolar area, or anterior tonsillar pillar. The cases were also classified according to treatment modality: surgery alone, radiotherapy alone, surgery in combination with radiotherapy, or no treatment. Ablative surgical resection was the main treatment modality. Patients who presented with node-positive neck disease also underwent elective neck dissection in the same manner as those in whom tumor invasion of the midline structure was observed. Adjuvant radiotherapy with a local dose field of 50 to 66 Gy was administered to those patients with positive or close margins, vascular or perineural invasion, and extracapsular spread.

Table 1. PATIENT CHARACTERISTICS

Variable	Number	%
Age, yrs		
<31	11	3.3
31 to 40	29	8.7
41 to 50	72	21.5
51 to 60	86	25.8
61 to 70	90	26.9
>70	46	13.8
Gender		
Female	152	45.5
Male	182	54.5
Smoking		
Nonsmoker	169	50.6
Some or every day	165	49.4
Alcohol consumption		
None	169	50.6
Some or every day	165	49.4
Site		
Alveolar mucosa	50	14.9
Lateral border of the tongue	111	33.3
Dorsum of the tongue	9	2.7
Mouth floor	58	17.4
Palate	13	3.9
Buccal mucosa	60	17.9
Lips	11	3.3
Retromolar area	13	3.9
Anterior tonsillar pillar	9	2.7

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The typical follow-up schedule was 1, 2, 3, 6, 9, and 12 months postoperatively in the first year, followed by every 6 months through the fifth year, and yearly thereafter. Computed tomography scanning or magnetic resonance imaging of the head and neck region were performed 6 months postoperatively and yearly thereafter.

Based on the digital files, the evolution of OSCC was characterized as healing (H) if, during the follow-up period, new lesions did not appear in the same location as the primary disease, or as an oncologic event (OE) if, during the follow-up period, an-

Table 2. ESTIMATED MORTALITY RATES TO 60 TO 120 MONTHS AND COMPARISON OF DIFFERENT DATA ACCORDING TO THE SAME CATEGORY

	Number of Events	Number of Deaths	λ of Outcomes	Dead at 5 years	Dead at 10 years	Mortality of Outcome A Versus Outcome B H_0: $\lambda_A = \theta_{M\text{-}H} \cdot \lambda_B$, $\theta_{M\text{-}H} = 1$ H_a: $\lambda_A = \theta_{M\text{-}H} \cdot \lambda_B$, $\theta_{M\text{-}H} < 1$	P	$\theta_{M\text{-}H}$	inf ($\theta_{M\text{-}H}$)	Sup ($\theta_{M\text{-}H}$)	Significantly Lower Mortality of A Versus B: $P < .01$ (**); $P < .5$ (*); NS
Dead										
OSCC	334	80	0.00439	23.2%	41.0%					
Other causes	334	119	0.00653	32.4%	54.3%					
Grading										
1	98	9	0.00164	9.3%	17.8%	1 vs 2	.001	0.3	0.2	0.6	**
2	176	47	0.00482	25.1%	43.9%	1 vs 3	.000	0.2	0.1	0.4	**
3	55	23	0.00874	40.8%	64.9%	2 vs 3	.042	0.6	0.4	1.0	*
Gender										
F	152	30	0.00356	19.2%	34.7%	M vs F	.133	0.7	0.4	1.1	NS
M	182	50	0.00511	26.4%	45.9%					
Age, yrs										
< 70	288	60	0.00359	19.4%	35.0%	< 70 vs > 70	.000	0.4	0.2	0.6	**
> 70	46	20	0.01334	55.1%	79.8%					
Smoke										
Yes	165	44	0.00532	27.3%	47.2%	Yes vs no	.156	1.4	0.9	2.1	NS
No	169	36	0.00362	19.5%	35.3%					
Alcohol										
Yes	165	39	0.00454	23.9%	42.0%	Yes vs no	.977	1.0	0.6	1.5	NS
No	169	41	0.00426	22.5%	40.0%					
T						1 vs 2	.013	0.4	0.2	0.8	*
1	144	14	0.00163	9.3%	17.7%	1 vs 3	.000	0.2	0.1	0.4	**
2	85	19	0.00372	20.0%	36.0%	1 vs 4	.000	0.2	0.1	0.3	**
3	26	11	0.00882	41.1%	65.3%	2 vs 3	.050	0.5	0.2	1.0	*
4	79	36	0.01107	48.5%	73.5%	2 vs 4	.001	0.4	0.2	0.7	**
N						3 vs 4	.772	0.9	0.5	1.8	NS
$N_0 + N_4$	228	31	0.00230	12.9%	24.1%	N_0+N_4 vs N_1	.003	0.4	0.2	0.8	**
N_1	62	19	0.00574	29.1%	49.8%	N_0+N_4 vs $N_2 + N_3$	.000	0.1	0.1	0.2	**
$N_2 + N_3$	44	30	0.02078	71.3%	91.7%	N_1 vs $N_2 + N_3$	.000	0.3	0.2	0.5	**
Surgery										
Yes	294	55	0.00317	17.3%	31.6%	Yes vs no	.000	0.2	0.1	0.3	**
No	40	25	0.02955	83.0%	97.1%					
RT										
Yes	136	48	0.00663	32.8%	54.9%	No vs yes	.000	0.4	0.3	0.7	**
No	198	32	0.00291	16.0%	29.5%					
OE										
Yes	99	47	0.00916	42.3%	66.7%	No vs yes	.000	0.3	0.2	0.4	**
No	235	33	0.00252	14.0%	26.1%					

Abbreviation: NS, not significant.

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other dysplastic or neoplastic lesion was diagnosed in the oral cavity.

Statistical Analysis

A descriptive analysis was performed on age, gender, risk factor exposure, localization of lesions, T stage, histopathologic grading, therapy, and follow-up. Continuous variables are expressed as mean ± standard deviation. Kaplan-Meier analysis was performed to determine the probability of survival. Estimated mortality rates, λ, and survival to 60 to 120 months were computed; survival curves were constructed using product limit estimation (Table 2). Survival curves A and B (with $\lambda A = \theta \cdot \lambda B$, with the null hypothesis H0: $\theta = 1$ and the alternative hypothesis

Table 3. ANALYSIS OF DICHOTOMOUS (D) AND POLICHOTOMOUS (P) CATEGORICAL VARIATES VERSUS INCREASING GRADING PERFORMED USING THE LIKELIHOOD RATIO TEST (*G* TEST) AND ARMITAGE ANALYSIS OF TREND

	G Test With Williams' Correction	p_G	$p_G < .01$ (**); $p_G < .5$ (*); NS	Armitage Trend for Categorical Variates # p_{trend}	Armitage Trend for Categorical Variates # $p_{trend\ linearity}$
Gender (D)	0.061	0.970	NS		
Smoke (D)	1.467	0.480	NS		
Alcohol (D)	0.487	0.784	NS		
Surgery (D)	2.583	0.275	NS		
RT (D)	6.156	0.046	*	0.036	0.435
Dead of cancer (D)	23.402	0.000	**	0.000	0.160
Survived (D)	10.177	0.006	**	0.007	0.181
OE (D)	1.976	0.372	NS		
Age (D)	0.387	0.824	NS		
T (P)	18.551	0.005	**		
N (P)	12.706	0.,013	*		

Abbreviation: NS, not significant.

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Ha: $\theta > 1$; where θ is the relative hazard rate) were compared with a family of 2-sample rank tests, especially the Mantel-Haenszel QM-H (Table 3). Strata also were included in the Mantel-Haenszel test.[10] Variables were compared for different grading values by nonparametric log-likelihood ratio test, adjusted with Williams' correction.[11] In addition, dichotomous categorical variables versus increased grading were studied by Armitage linear trend analysis,[12] and correlation of polychotomous ordinal variables, with significant *G* (log-likelihood ratio) values, and increasing grading was studied using nonparametric Spearman's rank test.[13] A Cox regression model was used to analyze censored survival data for identifying differences in survival due to prognostic factors. All of the statistical analyses were performed using Statistica 6.0 software (StatSoft, Inc, Tulsa, OK).

Results

PATIENT CHARACTERISTICS

A total of 334 cases of OSCC were studied in 182 men and 152 women (mean age, 66.90 ± 11.72 years). Average age at diagnosis was 67.7 ± 13.9 years in the women and 62.4 ± 13.3 years in the men. The TNM staging system identified the following lesion categories: T1 (n = 144), T2 (n = 85), T3 (n = 26), and T4 (n = 79). N stage also was recorded (Table 2, in which N4 means N_X).[8] Histological analysis of the biopsy specimens revealed 98 well-differentiated, 176 moderately differentiated, and 55 poorly differentiated tumors. Five patients were identified as grade 4 (carcinoma in situ). The most common tumor location was the lateral border of the tongue (33.2%), followed by the buccal mucosa (17.9%) and the floor of the mouth (17.3%). In the study group, 49.4% of the patients were tobacco smokers and alcohol drinkers; 70.8% of the men were smokers and 66.7% were drinkers, compared with 23.9% and 29% of the women, respectively.

Surgery was the primary treatment modality (Table 2). Postoperative radiation therapy was administered to 136 patients selected on clinicopathologic basis.

Follow-up ranged from 12 to 132 months (median, 54 months). Only 3 patients were followed for just 12 months.

Outcome

During the study period, 80 patients (23.9%) died due to tumor. No recurrence was seen in 235 patients (70.3%). Recurrence developed in 99 patients (29.7%), of whom 39 had been treated by surgery, 8 by radiotherapy, and 53 by surgery plus radiotherapy. The overall cumulative survival rate was 76.8% at 5 years after the initial diagnosis, and 59% at 10 years (Table 2).

Survival curves for OSCC according to gender ($P = .13$) and risk factors (smoking, $P = .16$; alcohol use, $P = .98$) exhibited no significant differences. Moreover, univariate analysis demonstrated that age affected survival rate only when considering patients over age 70 years ($P < .01$) (Table 2; Fig 1).

Patients with tumors with high T and N values had a less favorable prognosis than those with lower T and N values (Table 2; Fig 2); specifically, 10-year mortality rates were 17.7% for T1, 36% for T2, 65.3% for T3, and 73.5% for T4. The finding of an oncologic event implicated an increase in the 5-year mortality rate from 14% to 42.3% and in the 10-year mortality rate

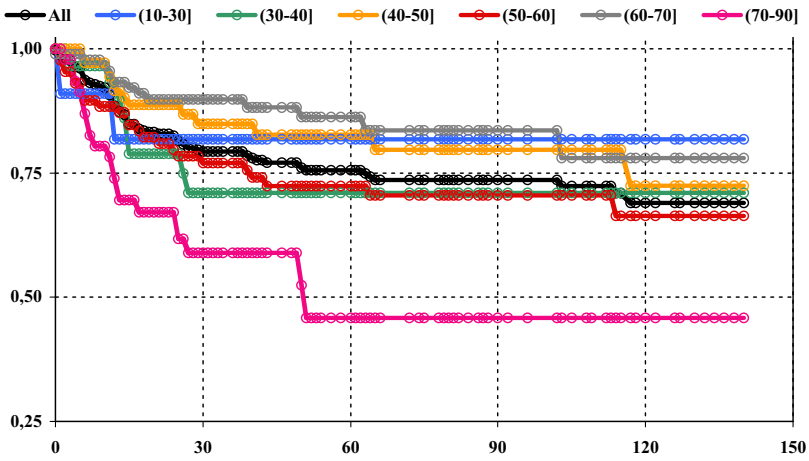

FIGURE 1. Survival curves according to age.

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from 26.1% to 66.7% compared with patients who did not have a recurrence (Table 2).

A gradual drop in the survival rate for more posteriorly located tumors also was found only in comparison with tumors located on the tongue (data not shown) ($P < .5$). The survival rates for patients treated by surgery or radiotherapy (considered separately) revealed statistical differences only for patients treated by surgery and patients not treated ($P < .01$).

An attempt was made to distinguish different survival curves depending on the histopathologic grade of the primary tumor (Table 2; Fig 3). Mean 5-year and 10-year mortality, respectively, were 9.3% and 17.8% for grade 1 tumors, 25.1% and 43.9% for grade 2 tumors, and 40.8% and 64.9% for grade 3 tumors. There is a clear overlap of these regions, and significant differences were found when comparing grade 1 tumors versus grade 2 and grade 3 tumors, and also grade 2 tumors versus grade 3 tumors (Table 2).

The data also were analyzed for differences in histopathologic grading with respect to host factors (age, gender, smoking, alcohol use), tumor factors (T and N stage), and treatment outcome (survival and oncologic events) (Table 3). The host factors did not influence the grading (gender, $P = .68$; age, $P = .60$; smoking, $P = .32$; alcohol use, $P = .06$). Lower histological differentiation revealed a higher incidence of oncologic events (25.5% for grade 1, 29.1% for grade 2, and 38.2% for grade 3), with no significant differences. Significant differences were found in the grade of differentiation and the various T stages ($P = .01$) and the cervical lymph node involvement ($P = .02$) at the time of initial diagnosis; the lower the histological differentiation, the larger the size of the tumor and the greater the N involvement (Table 4).

Finally, a Cox proportional hazard model was used to calculate survival rates for each prognostic variable. The model assumed that the underlying hazard rate was a function of the independent variables (covariates). The model is expressed as $h(t,\mathbf{z}) = h_0(t)^*\exp(b^x\mathbf{z})$, where $h(t,\mathbf{z})$ is the hazard rate, contingent on a particular covariate vector $\mathbf{z}$; $h_0(t)$ is the baseline hazard (eg, the hazard rate when the values for all independent variables [ie, in $\mathbf{z}$] are equal to their minimum value); b is the vector of regression coefficients; and ^{x} indicates the inner product. To estimate the survival function, S, contingent on a particular covariate vector $\mathbf{z}$, the algorithm uses the simple relationship $S(t,\mathbf{z}) = S_0(t)\exp(b^x\mathbf{z})$, where S_0 is the baseline survival function, when the values for all independent variables (ie, in $\mathbf{z}$) are equal to their minimum value, independent of the covariates; all covariates are assumed to be independent (Table 5; Fig 4). Table 6 gives predicted overall 5-year and 10-year survival rates using our Cox proportional hazard model.

Discussion

OSCC is one of the most complex malignancies to control, and only slight improvement in the survival rate has been achieved over the last several decades. The present study was conducted to analyze certain factors that apparently exert some influence on survival.

The clinical course of a patient with OSCC is determined by specific primary tumor factors, host characteristics, and, naturally, the type of treatment applied. One important tumor factor to take into consideration is histopathologic grade, which can provide a possible indication of the tumor's biological behavior. Several studies have analyzed the influence of Broder's/WHO tumor grade in foretelling the clinical course of OSCC; the results have demonstrated some significant

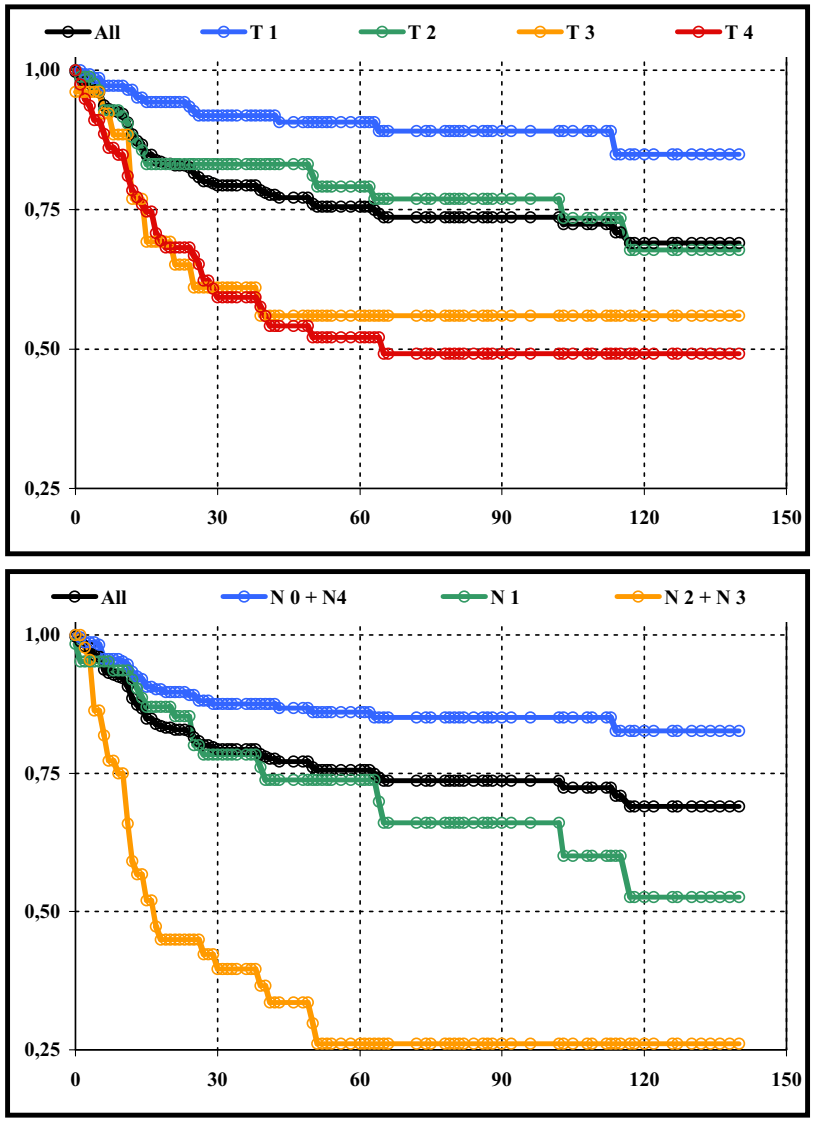

FIGURE 2. Survival curves according to size and node involvement of OSCC.

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discrepancies. According to some authors, the appraisal of grading can provide valid information for predicting the course of the disease and determining the optimum treatment; however, today most authorities recognize that Broder's/WHO grade is poorly correlated with outcome and response to treatment in individual patients.[5] The subjective nature of the measurement, small biopsy specimens from histologically heterogeneic tumors, and reliance on structural characteristics have led to new systems of grading that allow better prediction of the clinical outcome of the disease.

Most of the general characteristics of our patient population were consistent with those in previous studies. OSCC is generally a disease of the elderly, with a peak incidence in the sixth and seventh decades of life. The median age of our study group was almost 67 years, similar to previous studies. The females presented at a significantly older age than males ($P < .05$).[14-20] The ratio of male-to-female incidence is typically reported as greater than 2:1. Our gender ratio was 1.19:1, apparently disagreeing with the literature. However, a few reports have shown this ratio to be decreasing, especially in the last 20 years, possibly reflecting the increased number of women using tobacco products during this period.[19,21] Historically, the floor of the mouth and the lateral border of the tongue, followed by the soft palate, anterior tonsillar pillar, the retromolar trigone, and the buccal mucosa, are the most common sites of OSCC.[14,18,22-24] In our series, the tongue, the buccal mucosa, and the floor of the mouth were the most commonly involved sites, likely because (as reported previously), these sites are more vulnerable and more exposed to chemical and

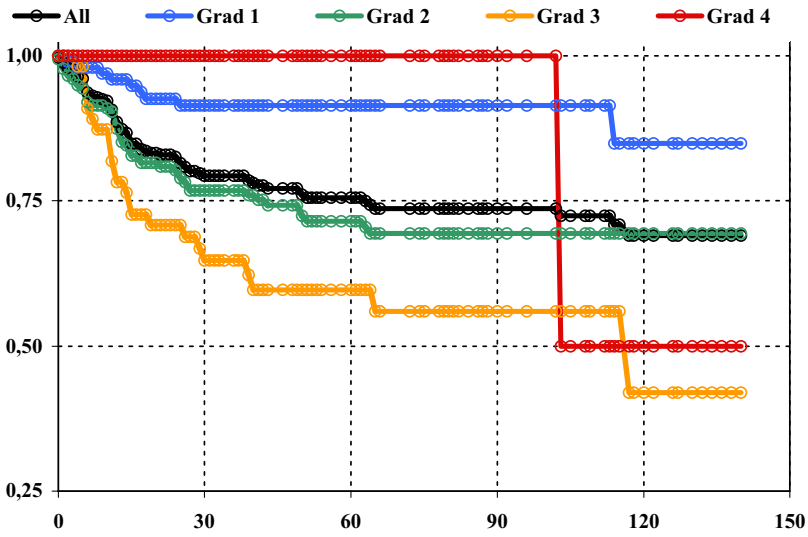

FIGURE 3. Survival curves according to histological grade.

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physical aggression and to the carcinogenic effects of tobacco.

The size of the primary tumor usually affects both the choice of treatment and the outcome; indeed, it is critical in evaluating the surgeon's ability to gain tumor-free margins and in determining the radiation dose in patients treated by radiotherapy.[5] In our series, 43.1% of the tumors were T1, probably reflecting the peculiar nature of our institution, in which prevention is emphasized and many patients are constantly followed-up for different reasons; moreover, our department is one of the largest reference centers in the region. In our study group, 98 tumors (29.3%) were identified as well-differentiated, 176 (52.6%) as moderately differentiated, and 55 (16.4%) as poorly differentiated, similar to previously reported findings.[14,15,25]

OSCC of the head and neck is commonly associated with the use of alcohol and tobacco. Almost half of our patients were tobacco smokers and alcohol drinkers; 70.8% of the men were smokers and 66.7% were drinkers, compared with only 23.9% and 29%, respectively, of the women. These data, which apparently differ from earlier published findings, are similar to those recent studies indicating that most female patients are neither smokers nor drinkers.[18,26]

Treatment of OSCC remains mainly surgical, with adjuvant radiotherapy added for advanced-stage disease or in patients at increased risk of locoregional failure. Because of the predominance of T1 tumors, most of our patients were treated exclusively with surgery.[19] In particular, 73.2% of the T1 tumors and 62.3% of the T2 tumors were treated with surgery only, whereas greater than 60% of the T3 and T4 tumors were treated with surgery plus adjuvant radiotherapy.

Recurrence developed in almost 30% of our patients. This percentage agrees with the literature, which reports recurrence between 16% and 42%.[14,19,21,27-29] In our sample, tumor size and histopathologic grading contributed to this difference in prognosis; recurrence was 26.9% in patients with T1

Table 4. CORRELATION ANALYSIS BETWEEN SIGNIFICANT POLICHOTOMOUS VARIATES, PERFORMED WITH SPEARMAN'S RANK ANALYSIS

	Grading	T	N
Grading		0.18	0.17
T	0.18		0.47
N	0.17	0.47	

NOTE. All R's of correlation are highly significant: $P < .001$.

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Table 5. COX'S PROPORTIONAL HAZARD MODEL FOR Z_i COVARIATES (GRADING, AGE, T, N)

	b_i	P
Grading (1, 2, 3)	0.57	.001**
Age (≤ 70 = 0; > 70 = 1)	0.87	.001**
T (1, 2, 3, 4)	0.32	.005*
N (1, 2, 3)	0.58	.001**

NOTE. Censoring variate: dead from cancer.

$S(t,z) = S_0(t)^{e^{(0.57 \cdot G + 0.87 \cdot A + 0.32 \cdot T + 0.58 \cdot N - 1.47)}}$

*$P < .001$;

**$P < .01$.

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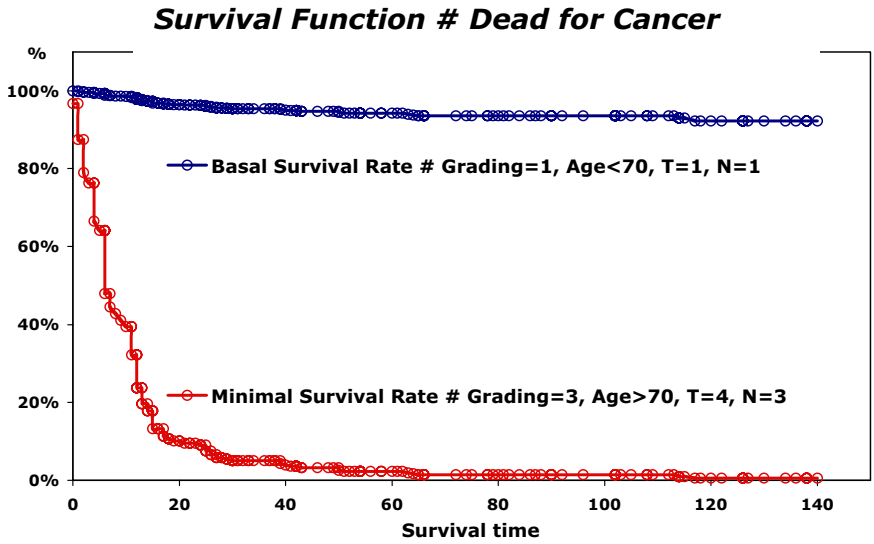

FIGURE 4. Survival curves according to Cox's proportional hazard model for **Z**i covariates [grading, age, T, N] # Censoring variate: "Dead for Cancer" [survival time in months].

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and T2 tumors and 38.9% in those with T3 and T4 tumors; moreover, recurrence occurred in 16.7% of in situ carcinomas, 25.5% of grade 1 tumors, 29.1% of grade 2 tumors, and 38.2% of grade 3 tumors.

The overall survival for our patients with OSCC was within the range reported in the recent literature,[14,19,20] although slightly higher because of the numerous T1 cases reported. There were no apparent

Table 6. SURVIVAL RATES AT 5 AND 10 YEARS, USING COX'S PROPORTIONAL HAZARD MODEL FOR ZI COVARIATES (GRADING, AGE, T, N)

				Survival Rate						Survival Rate						Survival Rate	
G	T	N	Age	5-Year	10-Year	G	T	N	Age	5-Year	10-Year	G	T	N	Age	5-Year	10-Year
1	1	1	<70	94%	92%	2	1	1	<70	90%	87%	3	1	1	<70	83%	77%
1	1	1	>70	87%	82%	2	1	1	>70	78%	71%	3	1	1	>70	64%	54%
1	1	2	<70	90%	87%	2	1	2	<70	83%	77%	3	1	2	<70	72%	63%
1	1	2	>70	78%	71%	2	1	2	>70	64%	54%	3	1	2	>70	45%	34%
1	1	3	<70	83%	77%	2	1	3	<70	71%	63%	3	1	3	<70	55%	44%
1	1	3	>70	64%	54%	2	1	3	>70	45%	33%	3	1	3	>70	24%	14%
1	2	1	<70	92%	89%	2	2	1	<70	86%	82%	3	2	1	<70	77%	70%
1	2	1	>70	82%	76%	2	2	1	>70	70%	62%	3	2	1	>70	54%	43%
1	2	2	<70	86%	82%	2	2	2	<70	77%	70%	3	2	2	<70	63%	53%
1	2	2	>70	70%	62%	2	2	2	>70	54%	43%	3	2	2	>70	33%	22%
1	2	3	<70	77%	70%	2	2	3	<70	63%	53%	3	2	3	<70	44%	32%
1	2	3	>70	53%	43%	2	2	3	>70	33%	22%	3	2	3	>70	14%	7%
1	3	1	<70	89%	86%	2	3	1	<70	82%	76%	3	3	1	<70	70%	61%
1	3	1	>70	76%	69%	2	3	1	>70	62%	52%	3	3	1	>70	42%	31%
1	3	2	<70	82%	76%	2	3	2	<70	70%	61%	3	3	2	<70	53%	42%
1	3	2	>70	61%	52%	2	3	2	>70	42%	31%	3	3	2	>70	22%	12%
1	3	3	<70	70%	61%	2	3	3	<70	53%	42%	3	3	3	<70	32%	21%
1	3	3	>70	42%	31%	2	3	3	>70	21%	12%	3	3	3	>70	6%	2%
1	4	1	<70	85%	81%	2	4	1	<70	76%	68%	3	4	1	<70	61%	51%
1	4	1	>70	69%	60%	2	4	1	>70	51%	40%	3	4	1	>70	30%	20%
1	4	2	<70	76%	68%	2	4	2	<70	61%	51%	3	4	2	<70	41%	30%
1	4	2	>70	51%	40%	2	4	2	>70	30%	20%	3	4	2	>70	12%	6%
1	4	3	<70	61%	51%	2	4	3	<70	41%	30%	3	4	3	<70	21%	12%
1	4	3	>70	30%	20%	2	4	3	>70	12%	5%	3	4	3	>70	2%	1%

NOTE. Censoring variate: dead of cancer.

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prognostic differences between males and females, in agreement with previous findings.[19,21,30]

The correlation of prognosis with age apparently is controversial. Some authors have reported no correlation, whereas others have demonstrated worse prognosis in older patients.[19,31] In our series, the survival curves established poor prognosis for patients over age 70 years.

We found no relationship between survival and the amount of tobacco or alcohol use, similar to some previous studies[19,30,32] but in disagreement with others that have reported higher mortality in smokers and alcohol drinkers.

The gradual drop in the survival rate of more posteriorly located tumors has been widely recognized and is likely explained by the influence of tumor location on nodal metastasis.[5] Our findings seem to confirm this correlation. As reported previously, the site of origin of OSCC is a chief prognostic factor[14]; our findings indicate that the posterior sites of the oral cavity had a worse prognosis only when compared with that of the tongue.

Cancer staging based on the TNM system is considered imperfect for prognostic purposes. However, the vast majority of authors accept that disease staging has a crucial influence on the outcome; in particular, tumor size at presentation has been associated with an increased risk of local recurrence and poor survival.[5,20,21,24,31] In the TNM staging classification system, the greatest surface dimension is used to determine tumor size, although tumor thickness is currently recognized to be a better histological prognostic factor. However, in our series, the size of the tumor at the time of initial diagnosis can be considered a prognostic factor affecting treatment outcome and survival.

The presence of cervical lymph node metastases is a widely accepted major prognostic factor in patients with OSCC.[33,34] Our findings demonstrate the prognostic importance of lymph node involvement; their occurrence has been linked to a decrease in worldwide survival rates, with up to a 91.7% 10-year mortality rate in patients with N2 and N3 disease.

Finally, our findings also reveal a correlation between lower histological differentiation and poor prognosis, in agreement with some authors[15,32,35-39] but not others.[19,21,23,40,41] Only T and N seem closely correlated with tumor grading, logically justifying our view that tumor size, neck involvement, and histological grade are high-quality biological factors that remain useful prognostic indicators in OSCC.[15,35] Other variables studied (ie, age, gender, and risk factors) demonstrated no association with histological grading.

In conclusion, our findings demonstrate the value of tumor grade, size, and node involvement as autonomous prognostic factors in predicting survival in patients with OSCC. Accordingly, histological grade, as originally described by Broders, remains a useful prognostic indicator, especially because it is simple and well known by pathologists. However, it remains essential for pathologists and surgeons to communicate efficiently regarding the histological *feel* of tumors, using a grading system as a device to aid in standardizing diagnosis. Future work should analyze the influence of these prognostic factors and the results of therapy in a selective manner for each subsite of the oral cavity. It is possible that the findings will indicate that no sole prognostic factor is the key, but that management should be based on a wide-ranging consideration of multiple combined factors.

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