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Research Article

Stage I Squamous Cell Carcinomas of the Tongue and Floor of the Mouth: Which Factors can Predict Occult Cervical Lymph Node Metastases?

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Abstract

Background: The prognostic assessment and the therapeutic planning of oral cavity carcinomas are based on TNM classification which makes no reference to certain aspects of tumoral biology. Identification of factors related to aggressive biological behavior would enable a better selection of patients who would benefit from more radical or multidisciplinary treatment.

Patients and Methods: This was a retrospective analysis of the impact of various demographic, clinical, and histopathological factors, as well as a molecular factor (p53 expression) in the biological behavior of 49 squamous cell carcinomas of the tongue and floor of the mouth, stage I, treated at the Cancer Hospital I-Brazilian National Cancer Institute, Rio de Janeiro, Brazil. The association of these factors with the development of cervical metastases were evaluated by univariate and multivariate analysis.

Results: Twelve patients (24.5%) developed neck metastases: 5 (10.2%) had micro metastases identified during elective neck dissection and 7 (14%) developed Lymph Node Metastases (LNM) during the follow-up period. At univariate analysis, the number of mitoses per HPF (p=.029), mode of invasion (p=.025), stage of invasion (p=.017), lymphoplasmocytic infiltration (p=.025), malignancy grading score (p=.040), tumoral thickness (p=.035), perineural invasion (p=.010) and microvascular invasion (p=.001), presented statistical significance for the occurrence of lymph node metastases. The multivariate analysis identified the presence of microvascular invasion (p=.002) as independent predictor of cervical metastases.

Conclusions: The most important predictive factor for occult LNM in stage I SCC of the tongue and floor of the mouth was microvascular invasion. The 24.5% rate of occult cervical metastases suggests the need for elective treatment of the neck in this group of patients.

Introduction

The prognostic assessment and therapeutic planning of oral cavity carcinomas are based on TNM classification. However, this system is based upon clinical information and makes no reference to certain aspects of tumoral biology which ultimately could explain differences in the biological behavior of tumors having the same histology and stages. In fact, a significant fraction of patients with stage I disease, usually presenting unfavorable histologic features, may have a relatively poor prognosis despite the small size of the tumor [1]. Identification of factors related to aggressive biological behavior could provide a better selection of those patients for whom more radical or multidisciplinary treatment would be recommended.

The biological aggressiveness of Oral Squamous Cell Carcinoma (OSCC), particularly in its initial stages (stages I and II) is reflected in its ability to metastasize to the regional lymphatic chains. Micrometastases can be found in up to 42% of patients with early T1-2 oral tongue carcinoma, and locoregional recurrences are considered the main cause of treatment failures of oral tongue carcinoma [2-3]. If regional metastases are present in a patient's initial evaluation or appears subsequently to a primary therapy, the 5-year survival rate can decrease to lower than 20% [3].

It is important to emphasize that micrometastases are not detectable by the best contemporary diagnostic technology making nodal recurrence, as result of undetectable subclinical nodal metastases, the main cause of treatment failure of early stage I OSCC [4-7]. The question of whether the patient with N0 neck should undergo Elective Neck Dissection (END), versus observation remains unanswered, particularly in stage I OSCC.

In this study, our aim was principally to make a retrospective analysis of the impact of various epidemiological, clinical, and histopatological factors, and a molecular factor in the presence of occult LNM in a series of 49 squamous carcinomas of the tongue and Floor of the Mouth (FOM), stage I, treated in a single institution.

Patients and Methods

This is a retrospective cohort study including 49 patients stage I SCC of the Tongue and FOM, treated at the Cancer Hospital I of the Brazilian National Cancer Institute, Rio de Janeiro, between

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Table 1: Distribution and Univariate Analysis of Epidemological and Clinical Variables for the Occurrence of Regional Lymph Node Metastases.

		Metastases					
Variable	Category		No		Yes	Total	P
		n	%	n	%		
Age	≤50	10	83.3	2	16.7	12	0.703 (*)
	>50	27	73	10	27	37	
Gender	Male	22	71	9	29	31	0.494 (*)
	Female	15	83.3	3	16.7	18	
Race	Caucasian	24	70.6	10	29.4	34	0.298 (*)
	Non Caucasian	13	86.7	2	13.3	15	
Morphologic	Exophytic	11	68.8	5	31.3	16	0.492 (*)
Aspect	Infiltrative	26	78.8	7	21.2	33	
Site	Tongue	22	75.9	7	24.1	29	1.000 (*)
	Floor of Mouth	15	75	5	25	20	

(*) The values of p were obtained by means of the Fischer's exact test.

Table 2: Distribution and Univariate Analysis of histopatological and molecular variables for the occurrence of regional lymph node metastases.

Varible	Category	Metastases			Yes	Total	P
			No				
		N	%	n	%		
Tumor lenght	≤10mm	21	77.78	6	22.22	27	0.683 (1)
	>10 ≤20mm	16	72.73	6	27.27	22	
Tumor	≤4mm	19	90.48	2	9.52	21	0.035 (1)
Thickness	>4mm	18	64,29	10	35.71	28	
Depth of	≤4mm	21	87,50	3	12.5	24	0.056 (1)
Invasion	>4mm	16	64	9	36	25	
Tu Lenght vs	TL ≤10 vs TT ≤4	16	88.89	2	11.11	18	0.179 (1)
Thickness	TL >10 vs TT ≤4	3	100	0	0	3	
(TT)	TL ≤10 vs TT >4	5	55.56	4	44.44	9	
	TL >10 vs TT >4	13	68.42	6	31.58	19	
Tu Lenght *vs*	TL ≤10 vs DOI ≤4	15	88.24	2	11.76	17	0.290 (2)
Depth (DOI)	TL >10 vs DOI ≤4	6	85.71	1	14.69	7	
	TL ≤10 vs DOI >4	6	60	4	40	10	
	TL >10 vs DOI >4	10	66.67	5	33.33	15	
Microvasc.	No	29	90.63	3	9.38	32	<0.001 (2)
Invasion	Yes	8	47.06	9	52.94	17	
Perineural	No	25	89.29	3	10.71	28	0.010 (1)
Invasion	Yes	12	57.14	9	42.86	21	
Degree of	Well Diff.	9	64.29	5	35.71	14	0.467 (2)
Different.	Mod. Diff.	27	79.41	7	20.59	34	
	Poorly Diff.	1	100	0	0	1	
p53	No	21	77.78	6	22.22	27	0.683 (1)
	Yes	16	72.73	6	27.27	22	

- The values of p were obtained by means of the Pearson's chi square test.
- The values of p were obtained by means of the Fischer's exact test.

January 1985 and December 1995. Several factors were evaluated: demographic (gender, race, and race), clinical (primary site, and morphological aspect); and histopathological factors classified according the malignancy grading system proposed by Anneroth et al [8]. This classification details the following six items: 1) grade of keratinization, 2) number of mitoses per high powered field [HPF], 3)

nuclear polymorphism, 4) mode of invasion, 5) stage of invasion, 6) lymphoplasmocytic infiltration, with the addition of one parameter; degree of differentiation at deep margins. Each tumor was scored on individual items in the classification system using a 4-point rating scale. A composite score also was considered for each tumor as the sum of the individual scores called total malignancy grading score.

In addition to the degree of tumor differentiation, tumor thickness (measured from the surface of the tumor to the deepest point of invasion) and depth (meaning the extent of cancer growth into the tissue beneath an epithelial surface) measured in millimeters, as stated by Moore et al [9], a two-dimensional measurement (> diameter *vs*. thickness, and > diameter *vs*. depth of invasion) as well as the presence of microvascular and perineural invasion were also analyzed. Perineural Invasion (PNI) was defined as infiltration of the perineural space by tumor cells while Microvascular Invasion (MVI) was defined as the presence of aggregates of tumor cells within endothelial-lined channels or invasion of the media of vessel with ulceration of the overlying intima. A molecular factor, p53 expression tested by immunostaining and scored according to the percentage of positivity (incubated with a monoclonal antibody p53-Dako A/S-Denmark cod. M7001) was also evaluated. All slides were reviewed by a single pathologist (RAA) and a senior research fellow (A.F.L.), blinded to the clinical outcomes.

The staging classification used in this study was in accordance with that proposed by the Union Internationale Contre le Cancer, 7th Edition, 2009, for Cancer Staging and End Results Reporting.

All patients were followed for a minimum of 24 months or until the time of death. No patient was lost for follow-up in this series. The follow-up period ranged from 24 to 153 months, with a median of 57 months.

Univariate and multivariate analysis evaluated the association between the factors and cervical metastases as primary outcome. For the univariate analysis, the following methods were employed: Pearson's chi-square test [10] with Yate's correction for continuity. The Fischer's exact test [11] was used when bias existed in chi-square analysis. To evaluate the probability of the development of regional metastases identified at the univariate analysis, a multivariate analysis was employed [12]. Survival curves were calculated using the Kaplan-Meyer life-table method [13].

Results

Of the 49 untreated stage I, 25 patients underwent resection of the primary tumor alone (RA) and 24 had resection of the primary tumor with elective neck dissection (R+END).

The study included 32 (65%) men and 17 (35%) women. The ages varied from 37 to 92 years, with a median of 59 years. There were 34 (69%) white patients and 15 (31%) non-white patients. Twenty-eight (57%) patients had oral tongue cancers and 21 (43%) had FOM cancers. Based on the gross appearance of the tumors, 30 (61%) patients had exophytic lesions and 19 (39%) had endophytic lesions (Table 1).

Of the 25 patients who underwent RA, 8 (32%) had FOM tumors and 17 (68%) had tongue tumors in comparison with 13 (54%) FOM and 11 (46%) tongue tumors in the R+END group. Eighty-four percent (21) of patients in the RA group had exophytic types of tumors and 16% (4) had endophytic tumors, in comparison with 37.5% (9) of exophytic tumors and 62.5% (15) of endophytic tumors in the R+END group. Thirty-five patients (71.5%) had moderately differentiated SCC, 13 (26.5%) had well-differentiated SCC, and only 1 patient (2%) had poorly differentiated SCC.

Tumor thickness varied from 0.7 to 16.7 mm, with a median of 5.36 mm, while DOI varied from 0.7 to 16.7 mm too, with a median of 5.34 mm. Microvascular invasion was found in 32 (65.3%) patients; PNI was found in 28 (57%). With regard to the two-dimensional measurements between highest tumor diameter (HD) and TT, 18 (36.5%) patients had HD < 10 mm *vs*. T < 4mm, 3 (6%) had HD> 10 mm *vs*. T < 4 mm, 9 (18.5%) had HD < 10 mm *vs*. T > 4 mm, and 19 (39%) had HD > 10 mm *vs*. T > 4 mm. Two-dimensional measurements between HD and DOI, however showed 17 (34.5%) patients with HD < 10mm *vs*. DOI < 4 mm, 7 (14.5%) with HD > 10 mm *vs*. DOI< 4 mm, 10 (20.5%) with HD < 10 mm *vs*. DOI > 4 mm, and 15 (30.5%) with HD > 10 mm *vs*. DOI > 4 mm (Table 2).

Malignancy tumor grading (according to Anneroth's 6 items scale) plus the analysis of the degree of differentiation at deep margins (7o item) and the results are shown in Table 3.

The quantification of p53 expression, evaluated by immunohistochemical analysis (positive staining > 20% of the nuclei of tumor cells), revealed 22 positive tumors and 27 negative tumors, respectively 45% and 55% of all patients tumor samples.

Twelve patients (24.5%) developed LNM. Lymphatic metastases were identified in five patients (10.2%) during the elective treatment of the neck (micrometastases) at the time of the treatment of their primary tumors. Micrometastases occurred at level I in 2 cases (40%), at level III in 2 cases (40%), and at levels I and II in 1 case (20%).

Metastases were ipsilateral in all 5 cases. In one patient with anterior FOM cancer, metastases developed in both sides of the neck. All but one metastases involved only one lymph node. None had extra-capsular spread at histopathologic examination.

Seven patients (14%) developed LNM during the follow-up after the treatment of the primary tumor. Metastases occurred at level I in 3 cases (42%), at levels I and II in 1 case (14.5%), at levels II and III in 1 case (14.5%), at levels II, III, and IV in 1 case (14.5%), and at levels I, II, III, IV, and V in 1 case (14.5%). Metastases were ipsilateral in 5 cases and bilateral in 2 cases with primaries located in the lateral aspect of the oral tongue. Extra-capsular spread was found in 3 patients (42.8%).

Of the 5 patients (10.2%) who died of oral cancer, 4 died of regional recurrence and 1 died of both regional and systemic diseases despite salvage therapy attempted by means of radical surgery and postoperative radiotherapy in 3 cases (60%), radical surgery in one case (20%), and radiotherapy in 1 case (20%).

Overall Survival (OS) calculated by the Kaplan-Meyer method was 83% and 68% for periods of 36 and 60 months, respectively. Disease-Free Survival (DFS) was 83% for periods of 36 and 60 months. Uncensored survival, defined as the time from diagnosis to death from oral cancer for 36 and 60 months was, respectively, 91% and 89%. The DFS for RA and R+END were 74% and 97%, respectively.

Table 3: Distribution and univariate analysis of histopatological Variables for the occurrence of regional lymph node metastases.

			Metastases				
Variable	Category		No		Yes	Total	P
		n	%	n	%		
Degree of Keratinization	1	11	73.33	4	26.7	15	0.343 (*)
	2	9	90	1	10	10	
	3	10	83.33	2	16.7	12	
	4	7	58.33	5	41.7	12	
Degree of Differentiation at Deep Margins	1	2	66.67	1	33.3	3	0.776 (*)
	2	20	76.92	6	23.1	26	
	3	12	80	3	20	15	
	4	3	60	2	40	5	
Nuclear Polymorphism	1	7	87.5	1	12.5	8	0.622 (*)
	2	10	71.43	4	28.6	14	
	3	13	81.25	3	18.8	16	
	4	7	63.64	4	36.4	11	
Number of Mitoses	1	25	83.33	5	16.7	30	0.027 (*)
	2	8	80	2	20	10	
	3	2	28.57	5	71.4	7	
	4	2	100	0	0	2	
Pattern of Invasion	1	4	100	0	0	14	< 0.001 (*)
	2	9	75,00	3	25	12	
	3	9	81.82	2	18.2	11	
	4	5		7	58.3	12	
Stage of Invasion	1	3	100	0	0	3	0.048 (8)
	2	15	93.75	1	6.25	16	
	3	19	63.33	11	36.7	30	
Linfoplasmocytic Infiltration	1	6	75	2	25	8	0.039 (*)
	2	17	94.44	1	5.56	18	
	3	13	59.09	9	40.9	22	
	4	1	100	0	0	1	
Malignancy Grading Score	≤2,5	28	84.85	5	15.2	33	0.040 (*)
	>2,5	9	56.25	7	43.8	16	

(*) The values of p were obtained by means of the Fischer's exact test.

The 23% difference between the two groups, analyzed by Wilcoxon signed-rank test, was statistically significant (p=.03).

In the univariate analysis, variables found to be strongly associated with the occurrence of neck metastases were: TT (p=.035, number of mitoses per HPF (p=.029), mode of invasion (P=.025), stage of invasion (p=.017), lymphoplasmocitic infiltration (p=.025), total malignancy grading score (p=.040), PNI (p=.010), and MVI (p<.001) (Table 4).

At multivariate analysis, MVI was the only variable independently and significantly associated with the risk of neck metastases (p=.002; Odds ratio=10.875, 95% CI 2.37 to 49.87) (Table 5).

Discussion

The incidence of occult LNM in early stages of OSCC ranges from 21% to 42% [2,3,7,8,14]. For those individuals who undergo close observation of the neck and develop lymphatic metastases, 77% may develop either N2 or extra-capsular extension requiring radical neck dissection as surgical salvage procedure [15].

Overall salvage in our study, by means of surgery, radiotherapy or a combination of these two methods was 37.5% (3/8 recurrences), including 1 patient with local recurrence (12.5%). These results are comparable with the 35% salvage rates found in most series published [3,6,7,14,17-19].

Neither age, gender, or race seemed to be significant predictors of biological behavior in our study (p=.703, p=.494, and p=.298). Although some authors have found an aggressive behavior in young patients with oral cancer [22,23], male sex [22,23], and non-white patients [22,28,29], our results are similar to others published in the

Table 4: Variables selected at univariate analysis for the occurrence of regional lymph node metastases.

Variables	P
Tumor Thickness	0.035
Number of Mitoses	0.029
Pattern of Invasion	0.025
Stage of InvasIon	0.017
Lymphoplasmocytic Infiltrataion	0.025
Malignancy Grading Score	0.04
Microvascular Invasion	<0.001
Perineural Invasion	0.01

Table 5: Interpretation of the variables selected at the logistic regression model for the risk of regional lymph node metastases.

		Metastases			
Variable	Estimate	Default errors	P	Odds Ratio	CI
Intercepto	-2.67	0.61	<0.001		
Microvascular	2.39	0.78	0.002	10.875	2.371; 49.879
Invasion					

p: Descriptive level associated with the null parameter test. IC: Confidence Interval with 95% for Odds Ratio.

literature [16,17,24,25].

We were also unable to identify any significant statistic difference when we evaluated the impact of the clinical factors (primary site, and morphological aspect) in the development of LNM in our study (p=.1 and p=.492).

The anatomic location of the lesion could also be considered as a prognostic indicator, since the tumors behave differently depending on anatomic location. Shaw et al, in 2009 [30] examined 482 consecutive OSCC patients and concluded that the primary site had little influence on prognosis. Chen et al [22] and Ulrist et al. [31], on the other hand, found that SCC of the tongue and FOM generally have poor prognosis due to the frequent presence of LNM, which has an impact in survival rates. Regarding the morphologic aspect of the primary tumor, our results are conflicting with the majority of the reports in the literature. Authors also consider that predominantly infiltrative or endophytic tumors carry a higher risk of the involvement of lymphovascular micro-channels and of the development of LNM [3,19,20,32,33]. The fact that our series included only stage I tumors, with limited depth of invasion (median of 5.34 mm) may explain our results.

Tumor Thickness (TT) and DOI have been studied extensively as a predictor of occult cervical metastases. Most studies support a cut-off value of 2-6 mm for TT and 4-5 mm for DOI [3,9,14,17,18,32-35].

Mohit-Tabatabai et al [36] and Spiro et al [18] were the first authors to apply Breslow's hypothesis of the relationship between nodal involvement and TT to OSCC. They found that a TT of 1.5mm and 2.0mm should be utilized as cut-off points to indicate the elective treatment of the neck in early OSCC.

In this study we considered the cut-off value of 4mm, because Kligerman et al [18] had already used it in a prospective study published from our Institution. They used the median of the TT of all T1-2 OSCC accrued as the cut-off value in their analysis.

Huang et al, in 2009, [34] published a meta-analysis from 16 studies and a pooled total of 1136 patients with the aim of evaluated the optimal cut-off for TT in OSCC. They were able to find a metastases rate of 4.5% for a TT of 4 mm, rising rapidly to 16.6% for a TT of 5 mm. They concluded that TT was a strong predictor for cervical LNM and that the optimal TT cut-off point was 4 mm.

We found similar results with metastases found in 9.52% of patients with TT < 4mm in comparison with 35.71% of patients with TT > 4 mm (p=.035). Interestingly, results were marginal when we analyzed the same aspect utilizing DOI, with metastases found in 12.5% of patients with DOI < 4 mm in comparison with 36% of patients with DOI > 4 mm (p=.056). This is in line with the results of Moore et al (1986) [9], Ambrosch et al (1995) [32], Asakage et al (1998) [37], and Mücke et al (2016) [39]. Only a few authors failed to find an association between TT and LNM [38,40,41].

Several authors suggested that association of Tumor length and thickness (or depth) could offer a better evaluation of the biological behavior of OSCC in comparison with TNM stage in the past [42-44]. Recent data published by van der Schroeff et al [45], and Mücke et al [46] also suggested that Tu Volume (TV) is an important factor to predict the biologic aggressiveness of OSCC. Others also found MRI-measured TV as a predictor of 2 year DSS and DFS, as well as occult cervical LNM in lingual cancer [27,47].

In the present study, the two-dimensional measurements utilizing Tumor Length *vs.* TT and DOI did not show statistical significance (p=.179, and p=.290, respectively) with the development of LNM.

There has been an ongoing debate about the predictive value of histopathological parameters in OSCC. In the past decades, the most commonly used histopathological grading system is the one introduced by Broders and modified by the World Health Organization (WHO) [48]. In 1973, Jakobsson et al. developed a multi-factorial malignancy grading system to obtain a more precise morphologic evaluation of the growth potential of SCC's in the head and neck region [49]. To make the morphologic criteria more precise, Anneroth and Hansen modified the grading system Jakobsson et al. developed for application to SCCs in the tongue FOM [50].

In our study we evaluated the six parameters of Anneroth's classification [16,50] due to various reasons: it is a standard method for OSCC, is easy to understand by a lab technician, gives more specific result, predicts the prognosis and guides the surgeon about the proper treatment plan.

Among the parameters evaluated at the univariate analysis, with predictive value for the development of LNM, we found: the number of mitosis per HPF (p=.029), pattern of invasion (p=.025), stage of invasion (p=.017), lymphoplasmocytic infiltration (p=.025), and the composite score of malignancy grading (p=.040). These results reflecting the evaluation of the tumor/host interaction are, partly, in line with the results of several authors in the literature [16,17,19,33,37,48]. More recently, Li et al, in 2013 [51] utilized the Risk Model originally proposed in 2005 by Brandwein-Gensler et al [52], found that the risk model was significantly predictive of LRR (p=.001), and DSS (P=.0005).

Tumor invasion into lymphatic and/or blood vessels has long been postulated to be an important pathologic factor [17]. However, its impact on the development of lymph node metastases remains to be elucidated [49,53-55].

Poleksic et al first linked MVI to aggressive tumor characteristics in head and neck SCC.

Other studies reported the association of MVI with tumor site, thickness, PNI, and status of resection margin [17,54]. Additionally, many previous studies also found an association between MVI and cervical LNM [17,54-57]. The reported incidence of MVI/ lymphovascular involvement in Head and Neck (H&N) cancer varies with histopathology, and it has been reported in 8-35% of head and neck SCC [17,58,59]. MVI in OSCC series can be remarkably variable, ranging from 3% to 81% [53,55,60]. This wide range of percentage of MVI may be explained by the heterogeneity of the study populations (all intraoral sites and T stages) as well as by the criteria utilized for the definition of MVI. Close et al [55] classified vascular invasion in: small vessel invasion and venous invasion, observing different correlations with LNM rates. Adel et al [60] suggested that the use of immunohistochemistry techniques could increase the rates of identification of MVI. In this study, microvascular invasion was evaluated only with H&E staining, based on Woolgar et al criteria [23].

In the present study, MVI appeared to be strongly associated with metastases to the lymphatic chains in early OSCC (p<.001), at univariate analysis.

Perineural Invasion (PNI) describes a malignant tumor's affinity for neural tissue and is associated with adverse outcome in many types of cancer. It is well known that PNI in oral carcinoma is associated with poor outcomes [39]. Remarkably, not only the risk of local recurrence, but also the risk of regional recurrence is increased [61,62]. According to the protocol of the College of American Pathologists (CAP), PNI status is a required feature of the pathology report for OSCC [63]. The incidence of PNI in H&N cancer varies with histopathology, and it has been reported in 27-82% of H&N SCC [58,59,61,62]. We found that 57% (28/49) of our patients had PNI associated with their tumors. Tai et al [62], in 2013, found that, not only the presence of PNI correlated with the T stage (17.1% in T1 and 36.6% in T2, p<.001), but also independently predicted cervical LNM (p<.001), neck recurrence and poor DSS. Binmadi and Basile, in 2011 [64], performed a review of the literature with the aim of reviewing the relationship of PNI with patient's outcome. They found that the preponderance of evidence in the literature suggests that PNI is a significant prognostic indicator in the ability of OSCC to spread to cervical lymph nodes, in addition to other factors such as TT and other histopathological factors.

In our study, we found that PNI was present in 28 (57%) patients. PNI was significantly associated with the development of LNM in our population of T1 OSCC (P=.01), at univariate analysis.

Several studies have focused on the p53 protein. The expression of p53 protein in OSCC varies from 27%-61%, according to the international literature [65-67]. Significant association between p53 expression and poor patient outcome in OSCC patients was found as an indication of impending malignant development in oral premalignant lesions [65], and with a correlation with LNM and survival in a few studies [66,67]. A few reports have dedicated their analysis to the correlation between p53 protein expression and LNM in OSCC.

Tatemoto et al, in 1998 [68] found that of 62 patients with regional LNM, 45 (72.6%) were positive for p53 while 45 (52.9%) of 88 without metastasis expressed p53 protein (p <0.02). Lymph node and distant metastasis were also comparatively studied in 225 OSCC using clinical and immunohistopathological approaches by Osaki et al, in 2000 [69]. They found that the expression of p53 protein was correlated with LNM. De Vicente et al, in 2004 [70] found strong relationship between p53 immunoexpression and poor prognosis in patients with OSCC without LNM. Baltaziak et al, in 2006 [71], found a statistically significant relationship between p53 expression in primary oral cancers and its expression in LNM (P<0.02) as well as an increased expression of Bcl-xL, Bax, and p53 in metastatic sites compared with primary tumors.

We were unable to find a statistically significance association between the expression of p53 protein and LNM in our patients with stage I SCC of the tongue and floor of the mouth (p=.683) at univariate analysis.

The multivariate analysis identified the presence of MVI (p=.002) as the only independent factor significantly associated with increased risk of LNM in our study.

In conclusion, this study has confirmed the predictive value of MVI in the development of lymph node metastases in our group of patients, as demonstrated by multivariate analysis (p=.002). Additionally the 24.5% rate of LNM emphasizes the need for elective treatment of the neck in stage I SCC of the Tongue and FOM.

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