

Squamous cell carcinoma of the lip: assessment of prognostic factors

Marilda A. M. M. Abreu¹, Dalva R. N. Pimentel¹,
Olga M. P. Silva², Isaac T. Blachman³,
Nilceo S. Michalany⁴, Cleonice H. Hirata⁵,
Luc L. M. Weckx⁶, Mauricio M. A. Alchorne⁷

Key words: espinocelular carcinoma of the lips,
prognostic factors, metastasis, local recurrence,
features histopathological.

Summary

Among lip cancers, 90% to 95% of them affect the lower lip and squamous cell carcinoma is the most frequent type. The TNM classification synthesizes the clinical characteristics of the tumor that allows prognosis and makes possible the comparisons of the results. Three parameters have to be considered: size of the tumor (T), propagation to regional lymphatic ganglion (N) and metastasis (M); however, patterns starting from 2cm are established by the TNM classification. In the case of squamous cell carcinoma of the lips, 2cm lesions are considered extremely large. Aim: The objective of this study was to verify the correlation among epidemiologic, clinical, evolutionary and histopathological characteristics of squamous cell carcinoma of the lips, having as parameter lesions as small as 0.5cm. Material and Method: In the period 1993-2000 in Sao Paulo, Brazil, a transversal retrospective study was performed with patients exhibiting squamous cell carcinoma of the lips. The characteristics of the tumor were investigated through the analysis of patients' medical charts, original reports of the histopathological exams and tumors' samples. The tumors were classified from 0.5 to 2.5cm. In addition, type, grade of histologic differentiation, the presence of desmoplasia, muscular, neural and vascular infiltration, and type of inflammatory infiltrate were investigated. Results: The statistical analyses indicated that metastasis and recurrences do not depend on patients' gender and race. The independence of the tumor's localization, either in the upper or lower lip, and the incidence of metastasis and recurrence were demonstrated. A correlation between lesions as large as 0.5cm and the occurrence of metastasis and recurrence was verified. Furthermore, it was observed that the size of lesion determines the infiltration in other tissues. Lymphoplasmocytarian is the type of inflammatory infiltrate that was found in each and every lesion. On the other hand, in some of the lesions, the inflammatory infiltrate was associated with eosinophils without correlation to size of tumor. Conclusion: Smaller tumors than 2cm, from a histopathological and clinical point of view, may present a distinct evolution behavior. Most of the lesions are ulcerative, though the ulcerative-vegetative is the one that presents the most metastasis and recurrence. The ulcerative-vegetative and vegetative types are associated with the largest lesions. The size of the tumor is related, in a Yesilar way, to grades II and III, in which higher rates of metastasis and recurrence were observed. In decreasing order of frequency, the tumor invades muscles, nerves and blood vessels, which can be related to the size of the lesion. Thus, in order to have metastasis, it is necessary to have infiltration of muscles. Yet, blood vessels can only be involved when there is concomitant infiltration of nerves. As a result, desmoplasia is directly related to size of the lesion as well as to occurrence of metastasis.

¹Master in Dermatology, UNIFESP-EPM.

²Pos-graduation in Public Health, FSP-USP.

³Stomathologist and Bucco-maxillo-facial Surgeon. Master studies in Otorhinolaryngology under course, UNIFESP-EPM.

⁴Joint Professor, UNIFESP-EPM.

⁵Master in Dermatology, UNIFESP/EPM.

⁶Head of the Division of Stomathology, UNIFESP-EPM.

⁷Faculty Professor, Department of Dermatology, UNIFESP-EPM.

Departments of Pathology, Dermatology, Otorhinolaryngology and Human Communication Disorders - Federal University of Sao Paulo-Escola Paulista de Medicina.

Address correspondence to: Olga Maria Panhoca da Silva - Rua Angelo Ricchiutti 55 Sao Paulo Capital 02417-220

Tel (55 11) 6203 3364/ 9658 0342 - E-mail: ompanhocas@yahoo.com.br

Article submitted on February 11, 2004. Article accepted on September 24, 2004.

INTRODUCTION

Among the cases of lip cancer, the literature has reported that 90% to 95% of the cases affect the lower lip and squamous cell carcinoma is the most frequent type ^{2,11,13,16,17,24,25}.

Considering the type of tumor, vegetative is the most prevalent, verrucous is the rarest, least aggressive and with higher rates of cure, and the ulcerative type is the most likely to cause deep invasions ¹⁴.

TNM classification, defined by International Union Against Cancer (UICC)¹⁵, summarizes the clinical characteristics of the tumor and serves as a therapeutic guide. It allows the definition of prognosis and comparison of results, given that they have a common language. It relates three significant parameters: size of tumor (T), propagation of regional lymphatic ganglia (N), and distance metastases (M). Concerning size, TNM classification defined standards in tumors larger than 2cm. Lip lesions smaller than 2cm have good prognosis, present slow evolution, low grade malignancy and late regional ganglionic dissemination, exception of prognosis for other oral cancer types ^{2,10,15,26}.

The average rate of metastases in lesions smaller than 2cm is 13.7% ²⁰ and even though the presence of metastases in neck ganglion is the most important factor in determining the clinical course of the disease, other factors in addition to the ones provided by TNM classification are predictors of prognosis, among which we can include: degree of histological differentiation, tumor extension to other anatomical lip structures, local recurrence, level of perineural invasion, venous or lymphatic vascular embolization, desmoplasia, thickness, cell proliferation rate, and analysis of DNA ^{1,3,4,6,8,9,18,19,21,22,26}.

According to the histological grade, squamous cell carcinoma was classified by Broders (1920)⁵ as well differentiated, moderately differentiated and undifferentiated or grades I, II and III, respectively, and it has been defined that undifferentiated tumors normally have metastases ⁵. Tumors that present desmoplasia are less differentiated, and this criterion, therefore, is indicative of worse prognosis. Recurrence and metastases are, respectively, 10 times and 6 times more frequent among desmoplastic tumors ⁴.

There is high rate of metastases proportional to depth of invasion ⁸. In the lower lip, the risk of metastases is absent in tumors less than 2mm thick, low in tumors 2mm to 6mm thick and high in tumors thicker than 6mm ^{3,18}.

The correlation between size of tumor and incidence of metastases is not uniform in the literature ^{3,9}. As clinical experience has shown, most tumors are smaller than 2cm, but they may develop metastases ^{3,10,12}, questioning whether the criteria adopted by TNM classification would be reliable concerning tumor size to predict metastases in the course of lip squamous cell carcinoma.

Considering the relevance of this issue, we decided

to study squamous cell carcinoma of the lip to check the correlation between epidemiological, clinical, evolution and histopathological characteristics, based on the parameters of lesions larger than 0.5cm.

MATERIAL AND METHOD

We prepared a transversal retrospective study with patients with lip squamous cells carcinoma identified among the medical charts of the Department of Pathology, Federal University of Sao Paulo - Escola Paulista de Medicina, in the period between 1993 and 2000.

Medical charts of patients and the original reports of histopathology exams of tumors were reviewed. Slides from surgical excision of each case were examined under common optical microscope with the support of a pathologist, member of the institution.

The medical charts of patients guided the collection of information concerning metastases and recurrences and from the original histopathological reports of the lesions we gathered information on location of lesion, gender, age and race of patients. Tumor characteristics were checked in the description of macroscopic findings in the reports and the review of histological sections of the lesions.

Size of tumor obtained by the description of the macroscopic exam considered the measure of the longest axis of the lesion, and tumors were classified into five categories, according to the standard created by the authors: up to 0.5cm, from 0.5cm to 1cm; from 1cm to 1.5cm; from 1.5cm to 2cm and above 2cm. The type of tumor was obtained in the description of the macroscopic exam and confirmed by histological sections and they were classified into infiltrative, ulcerative, vegetative and ulcerative-vegetative. In the review of histological sections, we analyzed degree of histological differentiation, presence or absence of muscle tissue invasion, neural and vascular invasion, presence or absence of desmoplasia, and type of inflammatory infiltration.

Data obtained were confronted and statistically analyzed through Fisher test, Anova and Correlation test.

RESULTS

After collection of data, the sample amounted to 57 patients, 12 women and 45 men. Concerning age, we studied women aged 40 to 91 years and men aged 21 to 82 years. As to race, 46 were Caucasians, 10 were native Brazilians and 1 was African descendent. Lesions were located in 51 cases in the lower lip, in 3 cases in the upper lip, in 1 case in the lip commissure, and in 2 cases there was no information available. The medical charts showed reference to metastases in 15 patients (26.31%) and recurrence in 9 patients (15.78%).

Statistical analysis showed that metastases and

Table 1. Prevalence of recurrence and metastases in lip squamous cell carcinoma according to gender and race.

Recurrence	Female	Male	Total patients
No	9	39	48
Yes	3	6	9
Total	12	45	57

Metastases	Female	Male	Total patients
No	7	35	42
Yes	5	10	15
Total patients	12	45	57

Recurrence	Caucasian	Non-Caucasian	Total patients
No	36	8	44
Yes	6	3	9
Total patients	42	11	53

Metastases	Caucasian	Non-Caucasian	Total patients
No	32	6	38
Yes	10	5	15
Total patients	42	11	53

Fisher exact test: $p=0.27$ gender and metastases; $p=0.38$ gender and recurrences; $p=0.37$ recurrences and race; $p=0.26$ metastases and race.

recurrences do not depend on gender, race or location of upper or lower lip or commissure (Tables 1 and 2).

As to size, lesions were up to 0.5cm in 3 patients, between 0.5 and 1cm in 12 patients; between 1cm and 1.5cm in 8 patients, between 1.5cm and 2cm in 10 patients, and larger than 2cm in 24 patients. That is, among the patients, 42.1% presented lesions larger than 2cm and 57.89% presented lesions smaller than 2cm, which demonstrated predominance of smaller lesions than 2cm in this study.

We noticed there was correlation between size of lesion and occurrence of recurrences and metastases (Table 3), which means that we can statistically expect that recurrence be determined by lesion size in 70% of the cases and metastases in 69% of the cases.

As to type of lesion (Table 4), the most prevalent was ulcerative type in 27 cases, followed by vegetative in 14 cases, ulcerated-vegetative in 10 cases and infiltrative in 6 cases. The infiltrative and ulcerative cases proved to be independent from size of lesion, that is, they were present at all lesion sizes. Ulcerative-vegetative and vegetative types, in turn, were preferentially detected in larger lesions, and ulcerative-vegetative seemed to be connected with lesions larger than 1.5cm.

Metastases occurred in ulcerative-vegetative tumors in 6 cases (60%), among ulcerative type in 5 (18.51%),

among vegetative in 3 (21.42%), and among infiltrative in 1 case (16.66%). Recurrences occurred among ulcerative tumors in 4 cases (14.81%), among ulcerative-vegetative in 3 (30%), among vegetative in 1 (7.14%) and in infiltrative in 1 case (16.66%).

Size of lesion (Table 3) influenced the occurrence of histological grades II and III, but it was indifferent for histological grade I. Grades II and III showed Yesilar behaviors concerning increase of lesion size, but it was not observed for grade I. Metastases occurred, among grade I tumors, in 7 cases (18.42%), among grade II in 6 (46.15%) cases and among grades III in 2 (33.33%) cases. Among grades I, II and III there were recurrences in 5 (13.15%), 1 (7.69%) and 3 (50%) cases, respectively.

It was detected that tissue invasion by tumor occurred more in muscles, with 40 cases. In nerves, there was invasion in 10 cases and in only 3 cases there was vessel invasion. There was statistical correlation between size of lesion and invasion of the three tissues by tumor, managing to show that size of lesion determined invasion in 78% for vessels, in 73% for muscles, and in 66% for nerves. We can state that muscle invasion is detected in lesions of 1cm, in nerves in lesions larger than 1.5cm, and in vessels in lesions larger than 2cm (Table 5). As to cases with metastases, 7 (46.66%) lesions invaded only the muscles, 5 (33.33%) invaded muscles and nerves, and 3 (20%) invaded muscles, nerves and vessels. In cases with recurrence, 3 (20%) invaded only the muscles, 3 (20%) muscles and nerves, 1 (6.66%) the muscles, nerves and vessels and 2 (13.33%) none of the three tissues.

In 13 tumors, we detected the presence of desmoplasia, and out of this total 61.53% had metastases. Out of 44 non-desmoplastic tumors, only 4.54% had metastases. We noticed that there was dependence between occurrence of metastases and presence of desmoplasia, whereas recurrences were independent from presence of desmoplasia. We observed correlation between size of lesion and presence of desmoplasia ($r=0.788$).

In all tumors, inflammatory infiltrate was lymphoplasmocytarian (Table 6). In 6 cases, there was large amount of eosinophils. We did not detect correlation between size of lesion and presence of eosinophils ($r=0.48$), to which we can state that presence of eosinophils is not determined by size of lesion. None of the tumors that presented eosinophils in the inflammatory infiltrate had metastases and only one case had recurrence.

DISCUSSION

Prognosis of lip squamous cell carcinoma is directly related to development of local recurrence and metastases, which depends on many different factors. Among them, we can highlight size of lesion^{3,9-12,14,15,20,26}; however, we realized that more detailed studies with lesions sized below 2cm would be required.

Table 2. Prevalence of recurrence and metastases of lip squamous cell carcinoma according to lip location.

Recurrence	Location				Total of patients
	Commissure	Lower lip	Upper lip	No information	
No	1	42	3	2	48
Yes		9			9
Total of patients	1	51	3	2	57
Metastases					
No	1	37	2	2	42
Yes		14	1		15
Total of patients	1	51	3	2	57

Fisher exact test: $p=1$ recurrences and location; $p=0.98$ metastasis and location.

Table 3. Occurrence of recurrences, metastases and grade of differentiation of lip squamous cell carcinoma according to lesion size (cm).

Recurrence	Size of lesion (cm)					Total of patients
	Up to 0.5	0.5 - 1	1 - 1.5	1.5 - 2	Over 2	
No	3	12	8	8	17	48
Yes				2	7	9
Total of patients	3	12	8	10	24	57
Metastases						
No	3	12	6	8	13	42
Yes			2	2	11	15
Total of patients	3	12	8	10	24	57
Grade of lesion						
I	2	11	5	6	14	38
II	1		3	3	6	13
III		1		1	4	6
Total of patients	3	12	8	10	24	57

ANOVA - size of lesion and grades II and III $p<0.05$ and grade I $p>0.05$.

Table 4. Type of lesions in lip squamous cell carcinoma according to size of lesion (cm).

Type	Size of lesion					Total of patients
	Up to 0.5	0.5 - 1	1 - 1.5	1.5 - 2	Over 2	
Infiltrative	1	2		3		6
Ulcerative	2	6	7	2	10	27
Ulcerative-vegetative		1		2	7	10
Vegetative		3	1	3	7	14
Total of patients	3	12	8	10	24	57

Table 5. Occurrence of tissue invasion by the tumor and size of lesions (cm) in lip squamous cell carcinoma.

Invasion	Size of lesions (cm)					Total
	Up to 0.5	0.5 - 1	1 - 1.5	1.5 - 2	Over 2	
Vessels						
No	3	12	8	9	22	53
Yes				1	2	3
Total	3	12	8	10	24	57
Muscles						
No	3	6	1	4	3	17
Yes		6	7	6	21	40
Total	3	12	8	10	24	57
Nerves						
No	3	12	6	9	17	47
Yes			2	1	7	10
Total	3	12	8	10	24	57

Table 6. Type of inflammatory infiltrate and size of lesion (cm) in lip squamous cell carcinoma.

Type of infiltrate	Size of lesion (cm)					Total
	Up to 0.5	0.5 - 1	1 - 1.5	1.5 - 2	Over 2	
Lymphoplasmocytarian	3	10	7	10	21	51
Lymphoplasmocytarian with eosinophils		2	1		3	6
Total	3	12	8	10	24	57

Confirming the literature findings^{1,2,7,13,16,24,25}, we detected that for the studied sample, lip squamous cell carcinoma was more frequent in men. Even though they presented average age higher than women, they started to have the tumor in earlier ages than women. The higher frequency in Caucasians was confirmed^{1,2,7,13,24} and the preference for lower lip, with index of 89.47% of the cases, a rate close to that reported in the literature^{1,13,16,25,26}. The index of metastases was twice more frequent than what had been observed by Rowe et al. in 1992²⁰.

Statistical analysis, through Fisher exact test, demonstrated that metastases and recurrences did not depend on gender or race of patients and also did not depend on location of lower or upper lip, contradicting the literature that stated that upper lip cancer had worse prognosis, with more metastases and recurrence episodes^{2,26}.

Through statistical analysis of correlation and determination, we could emphasize the literature data in which recurrences and metastases are determined by size of lesion^{1,2,9-12,14,15,19,20,26}.

Contradicting the literature^{2,14}, in which the vegetative type is the most prevalent one, the highest number of cases was ulcerative, followed in decreasing order of frequency by vegetative, ulcerative-vegetative, and infiltrative. Most metastases and recurrences occurred in ulcerative-vegetative tumors, which seemed to be correlated with lesions larger than 1.5cm. This fact is in accordance with the literature that emphasized the higher occurrence of metastases in larger tumors^{1,2,9-12,14,15,20,26} and in the presence of ulcerations²³.

The analysis confirmed the correlation between size of tumor and grade of histological differentiation only in grades II and III, evidencing Yesilar behaviors in relation to increase in lesion size. However, regardless of size, many tumors were grade I.

Metastases occurred more frequently in tumors grade II followed by grade III, but grade I tumors, in smaller proportion, also developed metastases, in agreement with the report by Breuninger et al. (1990)³. Despite the reduced number of cases, grade III tumors were proportionally the ones with most recurrences, followed by grades I and II. It demonstrated that the classification by Broders (1920)⁵, even though useful, may not be used isolated as criterion for prognosis of lesions.

The tumor invaded muscles in 40 cases, nerves in 10

cases and vessels in only 3 cases. It was more frequent in muscle tissue, which started to be detected in lesions larger than 1 cm. In lesions larger than 1.5cm, there was invasion of nerves, and in lesions larger than 2cm, there was invasion of blood vessels. Therefore, lesion size seems to specifically point to which tissues are the most affected.

According to the literature^{3,8,22,23}, there was increase in the rate of metastases proportional to depth of tumor. It was observed that for metastases to occur, muscle invasion seemed to be necessary, either isolated or concomitant to the invasion of nerves or vessels, in practically the same proportion in all cases with metastases. In such cases, nerves and vessels were not invaded without concomitant invasion of muscles, as well as vessel invasion also depended on invasion of nerves. Recurrences, however, did not depend on invasion of other tissues; they occurred even in tumors that invaded the corium, demonstrating that other factors, such as inappropriate treatment techniques, are implied.

The higher frequency of metastases in desmoplastic tumors compared to non-desmoplastic ones confirmed the data reported by Breuninger et al. (1997)⁴, but in the present study, metastases in desmoplastic tumors occurred more frequently than what had been reported by other authors. However, there was no literature reference concerning correlation between desmoplasia and size of lesion in lip squamous cell carcinoma, as observed here.

All tumors presented lymphoplasmocytarian inflammatory infiltrate. The large amount of eosinophils, observed in 6 tumors, did not show correlation with size of lesion ($r=0.48$) nor with metastases or recurrences. Therefore, we can state that presence of eosinophils in the inflammatory infiltrate is a marker of good prognosis.

CONCLUSION

Based on the studied sample, we concluded that for lip squamous cell carcinoma:

1. Tumors smaller than 2cm may present different progressive behavior, from a clinical and histopathological perspective;
2. There is no difference between location of squamous cell carcinoma in the upper or lower lip and occurrence of more or less recurrences and/or metastases;

3. Size of tumor, larger than 0.5cm, is directly related with occurrence of metastases and recurrence of the disease;
4. The most prevalent type was ulcerative and the one that had most metastases and recurrence was the ulcerative-vegetative one;
5. Types ulcerative-vegetative and vegetative are related to larger lesions;
6. Yesilarly, size of tumor is related to grades II and III in which there were the highest rates of metastases and recurrences;
7. The tumor invades, in decreasing order of frequency, muscles, nerves and blood vessels, and the specific invasion in each of these tissues may be predicted by size of lesion;
8. To have metastasis, the muscle must have been invaded, and blood vessels are only involved if there is concomitant invasion of nerves;
9. Desmoplasia is directly related with size of lesion and occurrence of metastases.

REFERENCES

1. Antoniadis DZ, Styanidis K, Papanayotou P, Trigonidis G. Squamous cell carcinoma of the lips in a Northern Greek population. Evaluation of prognostic factors on 5-year survival rate-I. *Eur J Cancer B Oral Oncol* 1995; 31B(5):333-9.
2. Baker SR. Malignant neoplasms of the oral cavity. In: Cummings CW, Fredrickson JM, Harker LA, Krause CJ, Schuller DE. *Otolaryngology Head and Neck Surgery*. 2ª ed. St. Louis: Mosby Year Book; 1993. p.1248-305.
3. Breuninger H, Schaumburg-Lever G, Holzschuh J, Horny HP. Desmoplastic squamous cell carcinoma of skin and vermilion surface. A highly malignant subtype of skin cancer. *Cancer* 1997; 79(5):915-9.
4. Breuninger H, Schaumburg-Lever G, Holzschuh J, Horny HP. Desmoplastic squamous cell carcinoma of skin and vermilion surface. A highly malignant subtype of skin cancer. *Cancer* 1997; 79(5):915-9.
5. Broders AC. Squamous-cell epithelioma of the lip. A study of 537 cases. *JAMA* 1920; 74:656-64.
6. Bryne M. Prognostic value of various molecular and cellular features in oral squamous cell carcinoma: a review. *J Oral Pathol Med* 1991; 20:413-20.
7. Castro JFL, Arcoverde L, Silva AAR, Godoy GP. Carcinoma epidemóide de lábio inferior: estudo de 135 casos registrados no Hospital do Câncer de Pernambuco no período compreendido entre 1992 e 1997. *Rev. Odontol Univ St Amaro* 1999; 4(1):43-9.
8. Daniele E, Rodolico V, Leonardi V, Tralongo V. Prognosis in lower lip squamous cell carcinoma: assessment of tumor factors. *Pathol Res Pract* 1998; 194:319-24.
9. Frierson HF, Cooper PH. Prognostic factors in squamous cell carcinoma of the lower lip. *Hum Pathol* 1986; 17:346-54.
10. Gonzáles-Guerra HE, Calderaro-di-Ruggiero FJ, Troconis-Elorga JR, Castro-Garcia J. Carcinoma epidemóide del labio inferior: consideraciones prognósticas. *Centro Med* 1991; 37(2):53-8.
11. Hjortdal O, Naess A, Berner A. Squamous cell carcinomas of the lower lip. *J Craniomaxillofac Surg* 1995; 23:34-7.
12. Hosal IN, Onerci M, Kaya S, Turan T. Squamous cell carcinoma of the lower lip. *Am J Otolaryngol* 1992; 13 (6):363-5.
13. Jovanovich A, Schulten EAJM, Kostense PJ, Snow GB, van der Waall I. Squamous cell carcinoma of the lip and oral cavity in the Netherlands; an epidemiological study of 740 patients. *J Craniomaxillofac Surg* 1993; 21:149-52.
14. Luce EA. Carcinoma of the lower lip. *Surg Clin North Am*. 1986; 66(1):3-11.
15. Manual for Staging of Cancer American Joint Commiktee on Cancer. 3ª edición. Philadelphia: JB Lippincott Company; 1988. p.27-32.
16. Ochsenius G, Ormeño A, Godoy L, Rojas R. A retrospective study of 232 cases of lip cancer and pre cancer in Chilean patients. Clinical-histological correlation. *Rev Med Chil* 2003; 131(1):60-6.
17. Ogura I, Amagasa T, Iwaki H, Kijima T, Kurabayashi T, Yoshimasu H. Clinicopathological study of carcinomas of the lip and the mucosa of the upper and lower lips. *Int J Clin Oncol* 2001; 6(3):123-7.
18. Onerci M, Yilmaz T, Gedikoglu G. Tumor thickness as a predictor of cervical lymph node metastasis in squamous cell carcinoma of the lower lip. *Otolaryngol Head Neck Surg* 2000; 122(1):139-42.
19. Rodolico V, Barresi E, Di Lorenzo R, Leonardi V, Napoli P, Rappa F, Di Bernardo C. Lymph node metastasis in lower lip squamous cell carcinoma in relation to tumour size, histologic variables and p27Kip1 protein expression. *Oral Oncol* 2004; 40(1):92-8.
20. Rowe DE, Carroll RJ, Day CL. Prognostic factors for local recurrence, metastasis and survival rates in squamous cell carcinoma of the skin, ear and lip. *J Am Acad Dermatol* 1992; 26:976-90.
21. Santos LR, Cernea CR, Kowalski LP, Carneiro PC, Soto MN, Nishio S, Hojaij FC, Dutra Júnior A, Britto e Silva Filho G, Ferraz AR. Squamous-cell carcinoma of the lower lip: a retrospective study of 58 patients. *Rev Paul Med* 1996; 114(2):1117-26.
22. Saywell MS, Weedon D. Histological correlates of metastasis in primary invasive squamous cell carcinoma of the lip. *Australas J Dermatol* 1996; 37(4):193-5.
23. Stein AL, Tahan SR. Histologic correlates of metastasis in primary invasive squamous cell carcinoma of the lip. *J Cutan Pathol* 1994; 21(1):16-21.
24. Visscher JG, Grond AJ, Otter R, van der Waal I. Lip carcinoma. A review. *Ned Tijdschr Tandheelkd* 2002; 109(10):391-5.
25. Visscher JG, Schaapveld M, Otter R, Visser O, van der Waal I.