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Markers of metastasis in lip cancer

The incidence of lip cancer in Granada, Spain, is much higher than that recorded in other countries. The natural history of the disease generally includes induction on previous actinic lesions, promotion with local growth of the tumour, and the appearance of metastasis in regional lymph node chains and, exceptionally, via the blood stream. In order to determine the risk factors for metastases, a retrospective hospital-based study was conducted of 251 cases of lower lip cancer diagnosed and treated during a 10-year period from 1985 to 1995. All patients studied had a minimum follow-up of five years. Among the metastasis risk factors considered, only localization in commissure showed statistical significance ($p < 0.001$).

Key words: Aetiology, epidemiology, lip neoplasms

Lip cancer is a form of oral cancer at the junction between the oral cavity and the skin [1] that appears predominantly in white males [2]. The lower incidence among females may be due to their frequent use of lip solar protection and lesser occupational exposure [3]. The maximum incidence of lip cancer is during the sixth and seventh decades of life, and the lower lip is more frequently affected than the upper [2, 4, 5]. More than 90% of malignant tumours of the lip are squamous cell carcinomas [6].

The highest incidence of lip cancer world-wide is recorded in the South of Australia, with 13.49 cases/100,000 inhabitants/year in males and 3.21 cases/100,000 inhabitants/year in females. In Europe, Granada (Spain) presents the highest male incidence (12.70 cases/100,000 inhabitants/year and Graubunden (Switzerland) the highest female incidence (0.83 cases/100,000 inhabitants/year) [7].

The elevated incidence in our area of lip cancer, the non-melanoma skin cancer that most commonly presents lymph node involvement, prompted us to study prognostic factors that could indicate the need for treatment of lymph node metastases.

Material and methods

A retrospective study was conducted of the 308 patients diagnosed with and treated for squamous cell carcinoma of the lower lip at our Surgical/Medical Clinic of Dermatology during a 10-year period from 1985 to 1995. Every patient in the study had a minimum follow-up of 5 years. Out of the 308 patients, 57 were excluded from the study because of missing follow-up data.

A data collection protocol was applied to all patients. The clinical parameters considered *(Table I)* were: age (in years); gender; localization of tumour on lower lip (right, left, middle, commissure, various other localizations); size (maximum and minimum diameters in centimetres); presence or absence of ulceration; and presence of lymph node metastasis, considering both the number of lymph nodes involved (in three categories: 1-3 nodes; 4-6 nodes; > 6 nodes) and their localization (chains: submaxillary, submandibular, jugular, submaxillary + sub-

Table I. *Description of clinical variables of patients in the study (n = 251).*

Variable	n (%)
Gender	
Male	227 (90.44%)
Female	24 (9.56%)
Localization of lesions	
Lower right lip	108 (43.03%)
Lower left lip	71 (28.29%)
Lower middle lip	47 (18.72%)
Lip commissure	14 (5.58%)
Various lower lip localizations	11 (4.38%)
Presence of ulceration	
Ulcerated	182 (72.51%)
Non- ulcerated	69 (27.49%)
Lymph node metastasis	
No	235 (93.62%)
Yes	16 (6.38%)
Number of nodes involved	
1-3 nodes	7 (2.78%)
4-6 nodes	7 (2.78%)
> 6 nodes	2 (0.79%)
Lymph node chain involved	
Submaxillary	3 (1.19%)
Submandibular	2 (0.79%)
Jugular	0 (0.00%)
Submaxillary + Submandibular	2 (0.79%)
Submaxillary + Jugular	5 (1.99%)
Submandibular + Jugular	4 (1.59%)

Table II. *Distribution of tumours according to clinical appearance and presence of lymph node metastasis.*

	Lymph node metastasis			
Presence of ulceration	Yes	No	**Total**	P
Ulcerated	16	166	182	< 0.05
Non-ulcerated	0	69	69	
Total	16	235	251	

P: Probability

mandibular, submaxillary + jugular, submandibular + jugular).

Statistical analysis

The data were expressed as means ± standard deviation and percentages. The chi-square test was used to compare qualitative variables and the Student's t test and Mann-Whitney test to compare quantitative variables. Bivariate and multivariate analyses were carried out, determining the cross-product Odds Ratio with a 95% confidence interval (CI). The statistical software package SPSS 9.0 for Windows was used for the data analysis.

Results

All patients in our study (n = 251) were or had been smokers and lived in rural areas; most of them had outdoor occupations (farmers, labourers or fishermen); 227 patients (90.44%) were males, with a mean age of 63.27 ± 12.62 years. Almost half the tumours (43.03%) were localized on the right lower lip, 28.29% on the left and 18.72% in the middle area; the carcinoma was localized in a commissure in only 14 patients (5.58%), while 11 (4.38%) showed involvement of more than one of these localizations.

The mean maximum diameter of the tumours was 1.41 ± 1.17 cm (range, 0.2 - 10 cm) and the mean minimum diameter was 1.03 ± 0.64 centimetres (range, 0.2 - 4 cm); 72.51% of the tumours were ulcerated.

Lymph node metastases appeared in 16 (6.38%) of the 251 tumours studied. Table I lists the number of lymph nodes with metastases and the cervical lymph node chains involved.

In the bivariate analysis, the females with lip cancer (73.75 ± 12.28 years) were found to be significantly ($p < 0.001$) older than the males (62.16 ± 12.16 years). There was a statistically significant relationship between the presence of ulceration and lymph node involvement ($p < 0.05$). All of the metastatic tumours (n = 16) were ulcerated *(Table II)*. There was also a statistically significant relationship between the presence of lymph node metastases and both the maximum ($p < 0.05$) and minimum ($p < 0.05$) diameters. Metastatic tumours presented a mean maximum diameter of 2.45 ± 1.93 cm and minimum diameter of 1.40 ± 0.73 cm, whereas non-metastatic tumours had smaller maximum and minimum diameters of 1.33 ± 1.06 cm and 1.01 ± 0.63 cm, respectively.

When the presence of lymph node metastases was considered as reference variable in the bivariate analysis *(Table III)*, the age at diagnosis was not a risk factor that influenced the appearance of lymph node metastases (OR 1.013; 95% CI = 0.97 – 1.06). However, when the presence of lymph node metastases was compared with the different tumour localizations, it was observed that 31.25% of the metastatic tumours were localized in the commissures and the relationship between tumour localization and presence of lymph node metastases was very significant ($p < 0.001$) *(Table IV)*. As a result, we divided the tumours between those of commissural localization and those at other localizations in the lower lip *(Table V)*, and found that 35.7% of the tumours in the commissure were metastatic, compared with only 4.6% of the tumours at other localizations ($p < 0.001$). Commissural localization is, therefore, a major risk factor that increases more than 11-fold the risk of lymph node metastases (OR 11.06; 95% CI = 3.17 – 38.59).

Table III. *Bivariate model. Adjusted odds ratio with 95% confidence interval for presence of lymph node metastasis according to age, localization and tumour area.*

VARIABLE	OR	95% CI
Age	1.013	(0.97 – 1.06)
Localization		
Non- commissural (Ref.)	1	1
Commissural	11.060	(3.17 – 38.59)
Tumour area	1.170	(1.03 – 1.32)

OR: Odds Ratio; *CI:* confidence interval *Ref:* Reference category

We also observed that tumours with lymph node metastases had a greater mean tumour area (3.43 cm^2) with respect to non-metastatic tumours (1.34 cm^2). The increase in tumour area was a risk factor for developing lymph node metastases (OR 1.17; 95% CI = 1.03 – 1.32). Table VI displays the multivariate model, which included the patient age and the tumour area and localization. As in the bivariate model, age was not a risk factor for the appearance of lymph node metastases (OR 1.01; 95% CI = 0.95 – 1.06), while tumour area was no longer a significant risk factor (OR 1.08; 95% CI = 0.97 – 1.24). As found in the bivariate model, localisation in commissure was a major risk factor that increased 8-fold the risk of developing lymph node metastases (OR 8.02; 95% CI = 2.05 – 31.37).

Table IV. *Distribution of tumours by tumour localization and presence of lymph node metastasis.*

	Lymph node metastasis			
Tumour localization	Yes	No	**Total**	**P**
Lower right lip	3	105	108	< 0.001
Lower left lip	4	67	71	
Lower middle lip	1	46	47	
Lip commissure	5	9	14	
Various lower lip localizations	3	8	11	
Total	16	235	251	

P: Probability.

Table V. *Distribution of tumours by commissural/other localization and presence of lymph node metastasis.*

	Lymph node metastasis		
Localization	Yes	No	% Metastatic tumours
Commissure*	5	9	35.7% $p < 0.001$
Other localizations	11	226	4.6%
Total	16	235	

**OR:* 11.06 (3.17-38.59)

Discussion

Cancer of the lip is the most frequent tumour of the orofacial area [7] and generally appears in adulthood, especially between the ages of 60 and 70 years [8]. The results of the present study are consistent with these data and showed a mean age of 63.27 years.

Most authors agree that lip cancer presents a clear predilection for the male gender. Worldwide, the male: female ratio ranges from 5.7: 1 [9] to 11: 1 [10]. We found a marked predominance of males (90.44%) with lip cancer with respect to females (9.56%), a ratio of 9.4: 1, very similar to the 9.2: 1 ratio reported by Antoniades *et al*. [11].

In our series, the mean age of lip cancer detection in the females (73.75 years) was significantly ($p < 0.001$) higher than that in the males (62.16 years). On average, this tumour appeared around ten years earlier in males. De Visscher *et al*. [9] found a smaller five-year difference in the age of lip cancer appearance in Holland (68 years in males vs. 73 years in females). This variability may be due to geographical, climatic, social and cultural differences.

There are few studies on the localization of tumours in different areas of the lower lip (left, right, middle or commissure). The only study we found, by Bouquot *et al*. [12], reported that 1-2% of lip cancers involved the commissures, somewhat lower than the 5.58% of tumours at this localization in our series.

A finding of interest, which we have been unable to compare with other published results, was that 35.71% of the tumours localized in the commissure presented lymph node metastases and, therefore, a worse prognosis. The percentage of metastatic tumours at other localizations in the lower lip was much lower, ranging from 2.2% of tumours in the middle to 5.63% of tumours on the left side. We found a highly significant association between tumour localisation and presence of lymph node metastases ($p < 0.001$), indicating a worse prognosis for commissural tumours.

The majority of tumours in our study (mean maximum diameter: 1.41 cm) were T1 tumours (of size below 2 cm), consistent with findings by numerous other studies that most of these lesions are classified in the T1 stage [11, 13-15]. The vast majority (93.62%) of our series of tumours did not have lymph node metastases (N0), whereas the remaining 6.38% presented metastasis in one of the cervical lymph node chains adjacent to the tumour. This percentage of lip cancers with metastasis is similar to other reports, which range from 7.59% [11] to 14% [14]. We have found no published study that individually analysed the cervical lymph nodes involved.

One hundred and eighty-two (72.51%) of our series of lip cancers were ulcerated, in line with the finding by most studies of a higher frequency of ulcerated forms [16-18]. An interesting hypothesis, which has been raised elsewhere [18] but has yet to be tested, is that a persistent ulcerated lesion on the lip causes patients greater concern and produces an earlier visit to a specialist. More than 8% of the ulcerated tumours in our series presented lymph node metastases, whereas none of the non-ulcerated tumours were metastatic, a statistically significant difference ($p < 0.05$).

In our series, the metastatic tumours had a significantly ($p < 0.05$) greater mean size (2.45 ± 1.93 cm) than that of the non-metastatic tumours (1.40 ± 1.07 cm.).

Lymph node involvement is widely considered [19, 20] to be one of the factors with greatest influence on the tumour prognosis. Five-year survival rates of 65% have been reported in tumours with no lymph node involvement (N0), compared with 20% in those with some lymph node involvement and 13% in tumours with two or more lymph nodes involved [21]. These observations underline the importance of the early diagnosis of any cancer and especially of lip cancer, which has an excellent 80% five-year survival rate when detected early.

Our bivariate and multivariate analyses, designed to establish the influence of different parameters on the risk of developing lymph node metastases in lip cancer, revealed that age and tumour area are not risk factors for developing lymph node metastases. However, localization at the commissure emerged as a very important risk factor that increased this risk 11-fold in the bivariate model and 8-fold in the multivariate model. We have found no other study that analyzed the influence of tumour localisation on the risk of cervical lymph node metastases.

In our view, wider research is warranted to consider other risk factors that may be implicated in lip cancer besides the aetiological factors widely studied to date.

Our results indicate that special attention should be paid to tumours on the lip that are of large size, ulcerated or localised in the commissure, which carry a worse prognosis.

Table VI. *Multivariate model. Adjusted odds ratio with 95% confidence interval for presence of lymph node metastasis according to age, localization and tumour area.*

VARIABLE	OR	95% CI
Age	1.01	(0.95 – 1.06)
Localization		
Non-commissural (Ref.)	1	1
Commissural	8.02	(2.05 – 31.37)
Tumour area	1.08	(0.97 – 1.24)

OR: Odds Ratio; *CI*: confidence interval; *Ref:* Reference category

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