ORIGINAL PAPER

The place of the histopathologic exam for establishing the profile of the squamous cell carcinoma of the lower lip with a high degree of malignity

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Abstract

The squamous cell carcinoma of the lip has a metastasizing potential by lymphatic or/and sanguine ways. *Objective*. Knowing the profile of the squamous cell carcinoma of the lip with a high degree of metastasizing. *Patients and method*. We have analyzed on a group of 322 patients the influence of the degree of the histological differentiation of the tumor and the influence of the seriousness of the invasion over the metastasized potential. The biopsic fragments have been processed according to the usual histological technique paraffin embedding, and the sections have been colored with Hematoxylin–Eosin. Some of the cases have been immunomarked, to confirm the diagnosis, with antibody anti-cytokeratins, anti-vimentin, anti-protein S100 and anti-alpha actin. *Results*. 12.24% of the patients with tumors with Broders II degree, 28.5% of those with Broders III degree and 52.94% of those patients with Broders IV degree presented metastasis, that show that the incidence of the regional ganglionary metastasis is higher in the case of the tumors with a low histological differentiation (test χ^2, $p<0.001$). 1.88% of the patients with an invasive squamous cell carcinoma under 6 mm and 38.60% of those with tumors of over 6 mm presented metastasis, that show that the risk of metastasizing is higher when the profoundness of the invasion is over 6 mm (test χ^2, $p<0.001$). In two cases we *faced the changing of the malignity degree*, meaning that it got worse passing from the Broders III degree (primary tumor) to Broders IV degree (relapse of the tumor). *Conclusions*. The histological differential degree of the tumor and the profoundness of the invasion are two important parameters when shaping the profile of the squamous cell carcinoma of the lip with a high degree of metastasis. The degree of malignity of the tumor may worsen during the evolution of the lip cancer, raising the risk of metastasizing as well.

Keywords: squamos cell carcinoma, lower lip, malignity.

Introduction

The squamous cell carcinoma (SCC) of the lip is a malign tumor of epithelial origin, infiltrated and destructive, with a potential of metastasis by lymphatic or/and sanguine way. It represents 15–30% from the squamous cell carcinoma of the cephalic extremity and 1/5 from tumors of superior digestive tract [1, 2].

It is mostly situated at the lower lip (75–95% of cases) and it affects the men who are over 60 years old, with light skin, who stay a lot in the sun and who also smoke [3–5].

Still, in a lot of cases is about the action of a group of external factors (HPV, ionizing radiations, traumatisms) and internal factors (immunosuppression), with various share of participation [6–10].

The squamous cell carcinoma of the lip has a tendency to extension either on the surface, in deepness or in both dimensions depending on various factors, some of them being related to the tumor and others being related to the patient's structure.

In the first phase, the evolution of the squamous cell carcinoma of the lip is strictly localized, and it is only then that we can encounter metastasis in the regional lymphatic ganglions, the affecting of neighborhood bones and rarely distant metastasis. We have researched the influence of the histological differentiation degree of the tumor and the influence of the profoundness of the invasion over the metastasized potential having as main objective to find out the profile of the squamous cell carcinoma of the lip with a high risk of metastasizing.

Patients and methods

Study group: 322 patients with squamous cell carcinoma of the lip (Figure 1) – 280 males and 42 females, with an average age of 63.3 years old (28–79 years) from whom 27 patients (8.38%) developed regional ganglionary metastasis, one of them presenting pulmonary metastasis.

The study period was of five years (1996–2000), having the possibility to examine the post-therapeutically state of the patients during the next five years (2001–2005).

There have been processed biopsic fragments according to the usual histological technique paraffin embedding for ***the histological study***, and the sections have been colored with Hematoxylin–Eosin.

The histological study comprised:

- Lightening the malignity degrees (Broders).

▪ The histologic aspect of the squamous cell carcinoma of the lip at different stages, at cases with various turn backs.

▪ The correlation of the intratumoral and peritumoral infiltration with the clinical form of the squamous cell carcinoma of the lip.

▪ The profoundness of the invasion of the squamous cell carcinoma of the lip.

In seven cases of squamous cell carcinoma with fusiformal cells Broders IV degree has required differential diagnosis with lesions with mesenchymal origin: malignant melanoma with fusiformal cells, fibrosarcoma, leiomyosarcoma or atypical fibro-xantoma. This cases have been processed immuno-histochemical with LSAB/HRP method and antibodies (made by DakoCytomation) anti-cytokeratins AE1/AE3 (clone AE1/AE3, dilution 1 : 50), anti-vimentin (clone V9, dilution 1 : 50), anti-protein S-100 (polyclonal, dilution 1 : 500) and anti-alpha actin clone 1A4, dilution 1 : 150), seeing the confirmation of the epithelial origin.

The study took place at the Emergency County Hospital and Immunohistochemical Laboratory of University of Medicine and Pharmacy of Craiova.

Results

From all the patients with squamous cell carcinoma **males** have represented 86.96% and **females** only 13.4%.

The most of the cases (40.37%) it was in the group of age 61–70 years old; the **average age** was 63.3 years old.

From all the patients 69.86% were **smokers** and 19.25% **alcoholics**. All the chronic alcohol consumers have been smokers.

From **rural medium** proceeded 90.37% of cases and 79.50% of patients were farmers who stay a lot in the sun.

The tumor is situated at:

▪ the lower lip – 85.40% of patients;

▪ the upper lip – 9.94% of patients;

▪ juxto-commisural – 4.66% of patients.

Concerning the **clinical forms**, the most of the patients have presented squamous cell carcinoma ulcero-vegetant (41.30% of cases), vegetant (17.39% of cases) and keratosic, verrucous form (17.08% of cases). The rest of the patients 24.23% was represented of squamous cell carcinoma ulcerate (26 patients), nodular (21 patients), fisurar (11 patients), endofitic (ten patients), terebrant (nine patients), one patient presented bifocal squamous cell carcinoma at the lower lip.

The most of the patients had tumors $\mathbf{T_1}$ (190 cases) and $\mathbf{T_2}$ (106 cases), while only 26 patients (8.07%) have presented tumors $\mathbf{T_3}$ (17 cases) and $\mathbf{T_4}$ (9 cases).

Regional ganglionary metastasis presented 8.32% of cases, one of whom had a visceral (pulmonary) metastasis.

Taking into consideration the Broders classification which divides squamous cell carcinoma in four degrees of malignity (Figures 2–5), the distribution of the 322 patients is rendered in Table 1.

Table 1 – The patient's distribution according to the malignity level

Malignity level	No. of patients (%)
I. Over 75 % from the cells are differentiated. The corn-like globes are in large numbers and have a completely keratinized center (Figure 2)	186 (57.76%)
II. Between 50–75% from the cells are differentiated. The corn-like globes are rare and incompletely keratinized (Figure 3)	98 (30.44%)
III. Between 25–50% of the tumoral cells are differentiated. The corn-like globes do not exist and there can be noticed many atypical elements (nuclear) many divisions and rare keratinized cells, isolated with a small nucleus and hypercrome (Figure 4)	21 (6.52%)
IV. Under 25% of the cells are differentiated The keratinized tendency is difficult to be observed and the anaplasic cells, without cellular bounds become fusiformal and tend to isolate themselves looking like a sarcoma (Figure 5)	17 (5.28%)

In seven cases of squamous cell carcinoma with fusiformal cells Broders IV degree was necessary to confirm immunohistochemical the diagnosis that was suggest by the usual histological technique, we established the followings:

▪ positive immunomarking for cytokeratin AE1/AE3 in tumoral cells in all the cases analyzed (Figures 6 and 7);

▪ negative immunomark at vimentin, alpha-actin and protein S-100 in tumoral cells in all the cases analyzed.

These results have confirmed the presence of the markers of intermediary filaments at tumoral cells and the negativity at the mesenchimal markers in tumoral cells have excluded the possibility of fibrohistiocitary, melanocytary and muscularly differentiation in the cases hard to diagnose.

In our group the most of the patients with squamous cell carcinoma of the lip had presented *Broders I degree* of malignity (186 cases) and *Broders II degree* of malignity (98 cases) while *Broders III and IV degree* of malignity in 21 cases, respectively 17 cases.

In what the ***situation of the patients with a metastasizing squamous cell carcinoma*** regards the results are the followings:

▪ From 98 patients with the *Broders II degree* of malignity (between 50–75% from the cells are differentiated; the corn-like globes are rare and incompletely keratinized), 12 presented metastasis (12.24%).

▪ From 21 patients with *Broders III degree* of malignity (between 25–50% of the tumoral cells are differentiated; the corn-like globes do not exist and there can be noticed many atypical elements (nuclear) many divisions and rare keratinized cells, isolated with a small nucleus and hypercrom), six presented metastasis (28.5%).

▪ From 17 patients with *Broders IV degree* of malignity (under 25% of the cells are differentiated; the keratinized tendency is difficult to be observed and the anaplasic cells, without cellular bounds become fusiformal and tend to isolate themselves looking like a sarcoma), nine presented metastasis (52.94%).

Figure 1 – ***Squamous cell carcinoma of the lower lip***

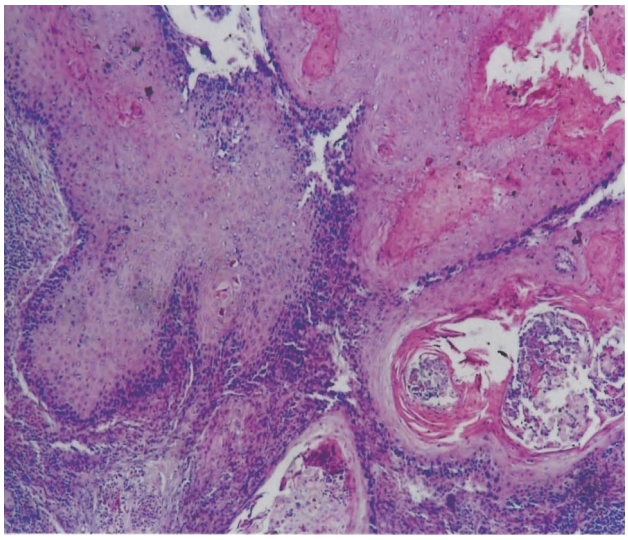

Figure 2 – ***Squamous cell carcinoma Broders I degree (HE stain, ob. ×10)***

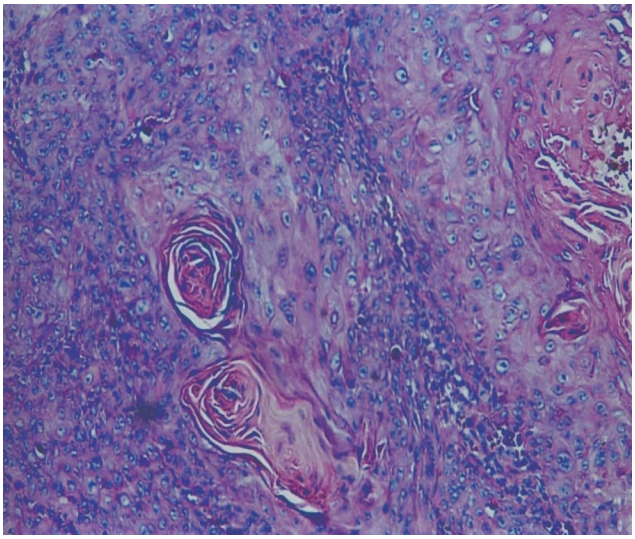

Figure 3 – ***Squamous cell carcinoma Broders II degree (HE stain, ob. ×10)***

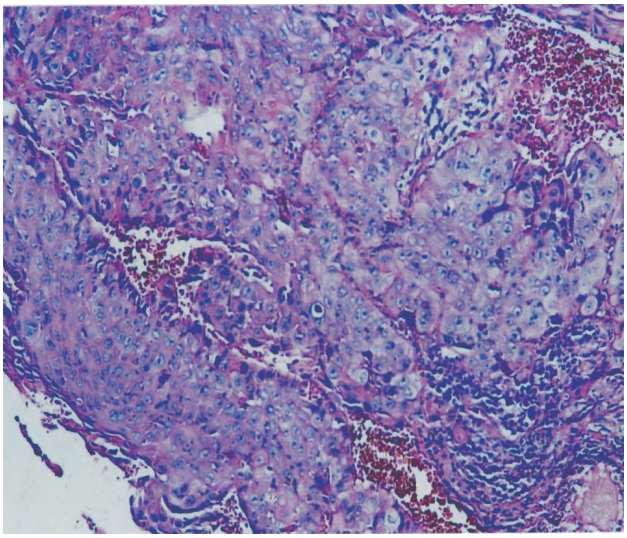

Figure 4 – ***Squamous cell carcinoma Broders III degree (HE stain, ob. ×10)***

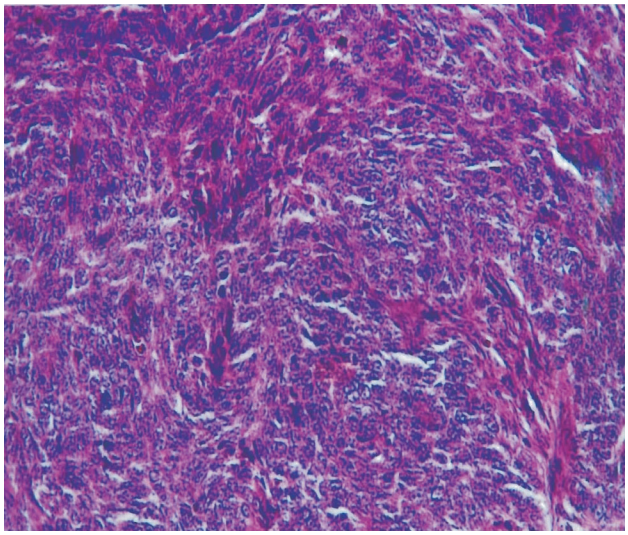

Figure 5 – ***Squamous cell carcinoma Broders IV degree (HE stain, ob. ×10)***

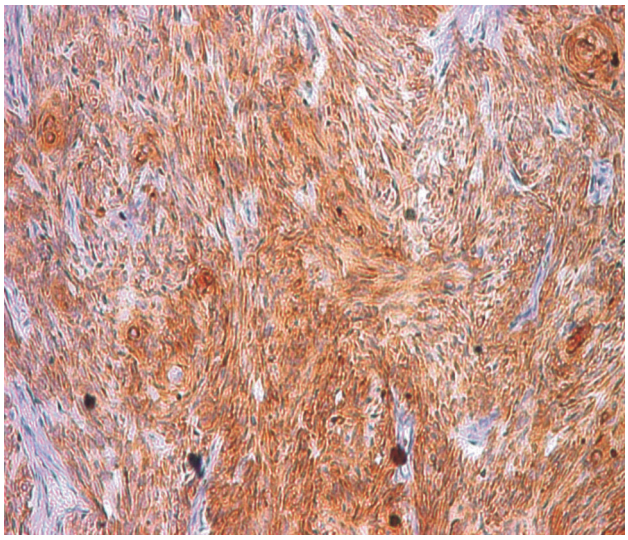

Figure 6 – ***Squamous cell carcinoma G IV with fusiform cells (immunomarking AE1/AE3, ob. ×10)***

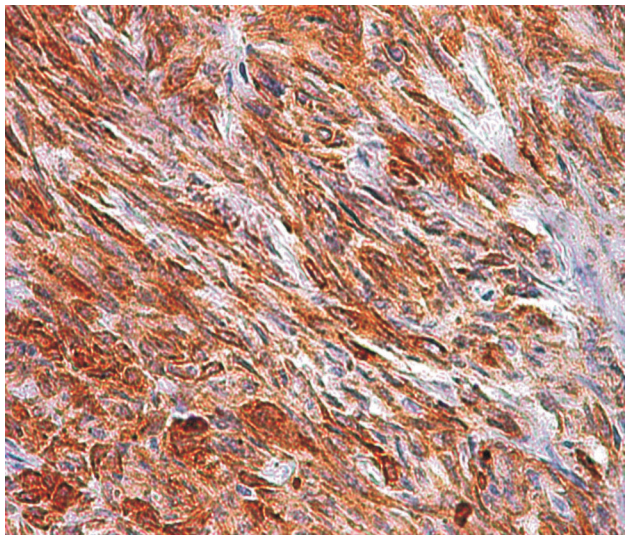

Figure 7 – ***Squamous cell carcinoma G IV with fusiform cells (immunomarking AE1/AE3, ob. ×10)***

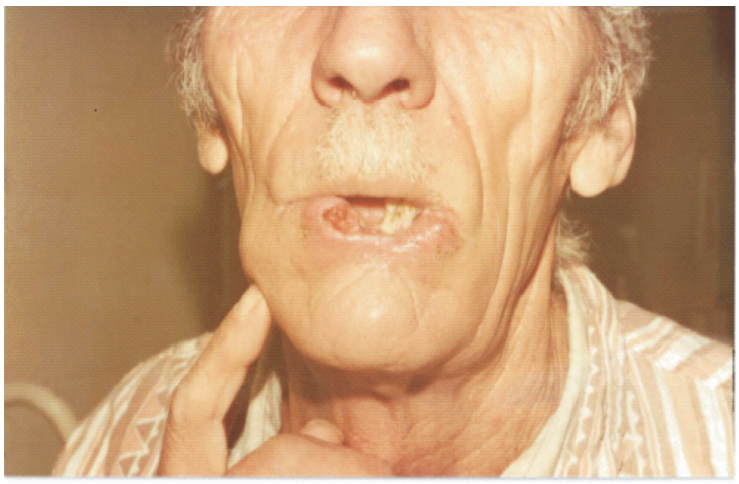

Figure 8 – ***Squamous cell carcinoma ulcero-infiltrative with submandibular metastatic ganglion***

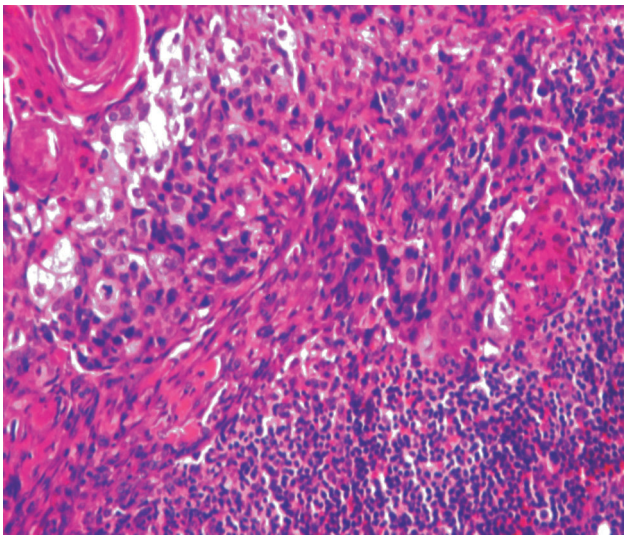

Figure 9 – ***Ganglionary metastasis of squamous cell carcinoma Broders II degree***

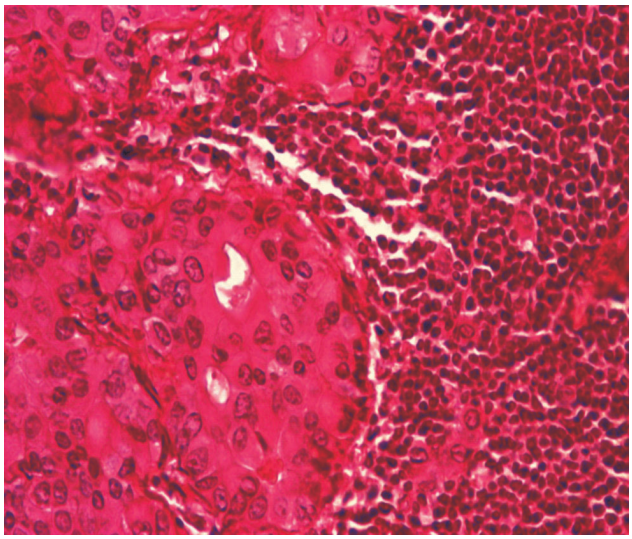

Figure 10 – ***Ganglionary metastasis of squamous cell carcinoma Broders III degree***

No patient from those with *Broders I degree* of malignity (over 75% from the cells are differentiated; the corn-like globes are in large numbers and have a completely keratinized center) presented metastasis.

In two cases (the male patients aged 48 and 52) who presented multiple turn backs (two turn backs the first patient, three turn backs the second one) we ***faced the changing of the malignity degree***, meaning that it got worse passing from the Broders III degree to Broders IV degree.

We have assisted, in all the cases, to a rich reactional infiltrate containing lymphocytes, plasmocytes and rare eosinophiles. In ulcerate and ulcero-infiltrative tumors (50.05% of cases) it was present an important granulocyte infiltrate.

As a result to the study of ***the invasion profoundness*** the situation of the patients was the following:

- *Invasion under 6 mm*: 265 patients (82.30% of cases), from whom five presented metastasis.
- *Invasion over 6 mm*: 57 patients (17.90% of cases), from whom 22 presented metastasis.

After the correlation of the influence of the profoundness of the invasion with the metastasized potential situation was the following:

- From 265 patients with tumors with invasion *under 6 mm* have presented metastasis five cases (1.89%);
- From 57 patients with tumors with *invasion over 6 mm* have presented metastasis 22 cases (38.60%).

Discussions

The squamous cell carcinoma of the lip diagnosis is based on the clinical presence of the tumor and it can be certified through a histological exam, analyzing the structure as well as the cytology of that lesion. The deep invasion, the infiltration of the pod of the nerves and/or of the adventitia of the vascular axes can also be evidenced, through a histological exam [11]. Tumor embolisms are rare as far as the cutaneous epidermoid carcinoma.

We have studied the 322 lip squamous cell carcinoma cases after having the histological differential diagnosis with a keratoacanthoma, with an extended keratinized squamous cell carcinoma from the cutaneous part of the lip and with a pseudocarcinomatous epidermis hyperplasia.

The most difficult differential diagnosis is with the keratoacanthoma. There are authors who consider keratoacanthoma as a very well differentiated form of an epidermoid carcinoma [11].

Cribier B *et al.* having as main objective optimizing the diagnosis criteria for the two tumors (squamous cell carcinoma squamous cell carcinoma, keratoacanthoma), as the result of the study [12] got the following conclusions:

- the presence of the spur and the brutal transition between the healthy epiderm and the tumor pleads for the keratoacanthoma (sensitivity 81%, specificity 91%);
- the absence of the ulceration and that of the pleiomorphism pleads for the keratoacanthoma (sensitivity 82.3%, specificity 86.7%).

The distinction of a pseudocarcinomatous epidermic hyperplasia is delicate especially for the veruccous carcinomas. A lot of biopsies are also necessary. We did not have any veruccous carcinoma in the studied group.

Malignity Broders IV degree epidermoid tumors have to be differentiated from a sarcoma, from a melanoma with fusiform cells and from the atypical fibroxanthoma. The presence of the centre of contagion with epidermoid carcinoma or with signs of keratinized differentiation, such as dyskeratic cells, allows the diagnosis. The expression of cytokeratines at the level of tumor cells and the negativity at the mesenchimal markers solves the diagnosis. But there can be confirmed some cases of squamous carcinoma with fusiform cells only ultra structurally (ME) because it does not present aspects of epithelial differentiation even in the case of using a large immunohistochemical panel [13].

From the total of 322 patients we have studied, 27 (8.32%) presented regional ganglionary metastasis, one having a pulmonary metastasis. The frequency of metastasis at our patients was relatively close to that reported by Fitzpatrick (7%) and others (10%).

After decentralizing numerous studies, with a total of 11 094 lip cancer cases, Descamps V *et al.* [14]. found metastasis in five years time at 13.7% of patients.

About the profile of the tumor with a high risk of metastasis there have been many articles [11, 14–17], taking in consideration more parameters:

- diameter of the lesion of the squamous cell carcinoma of the lip;
- turn back of the squamous cell carcinoma of the lip;
- localization of the lip cancer;
- histological differentiation degree of the tumor;
- profoundness of the invasion of the cancer;
- neurotropism;
- immunosuppresion.

In an elaborated study [14] concerning the unfavorable prognosis factors for squamous cell carcinoma in general (including lip cancers as well) the authors found metastasis in five years time at 30.3% from the tumors with the diameter over 2 cm and at 9.1% from those with the diameter under 2 cm. Important differences concerning the behavior of the cancer have been found compared with the profoundness of the invasion. For those tumors with an invasion larger than 4 mm (over 6 mm for those with a local localization) – Clark IV; V – metastasis came up in 45.7% of the cases in 5 years time, while for the invasion tumors under these Clark I–III markers, metastasis has been found in 6.7% of the cases.

Ortonne N [11] includes among the criteria that allow the appreciation of the malignity potential of the epidermoid carcinomas: the degree of the invasion of the tumor in profoundness; the presence of the perivenous interest; the differentiation degree; the histological type of cancer. When referring to the last criteria, we consider that the acantholytic and pseudovascular forms have an important local aggressiveness.

Kanitakis J [17] studying the prognosis value of some cellular proliferation markers [Ki67, PCNA],

he got to the conclusion that the proliferation degree does not seem directly related to the pejorative evolution of the squamous cell carcinoma. It may be possible that the intervention of other factors such as the adhesion cells to be at the origin of the aggressive evolution of some epidermoid carcinomas.

The recidivisms of the primary lesions have been related with the high degree cancers and with a low histological differentiation of the tumor [18, 19].

Kyzas PA *et al.* investigating the role of the immunohistochemical expression of the vascular endothelial growth factor (VEGF), they found an interesting association of the high expression of this factor and the growing incidence of the local recidivisms ($p<0.001$) [20].

Somma P *et al.* researched the immuno-histochemical expression of FAS/FASL in neoplasic cells and in the inflammatory infiltrate for 32-squamous cell carcinoma of the lip cases. They noticed that the patients with FAS/FASL supraexpression in neoplasic cells and FAS^+ in T cell had cancers with a more aggressive clinical behavior [21].

In a recent study [22], on a group of 95 patients with squamous cell carcinoma of the lip the authors found the conclusion that the patients with high risk of metastasis in regional ganglions are those with squamous cell carcinoma over 2 cm, with a low histological differentiation, tumors with profoundness over 6 mm and in the cases with perineural invasion and low expression of protein P27 kip 1.

Most doctors accept the fact that the probability of the metastasis of the squamous cell carcinoma of the lip rises once with the tumor's diameter, with its ulcerated aspect and the metastasizing potential is higher in the case of turns back rather in the case of the primary tumors. The tumors with a juxta-commissural localization or on the side of the mucous part of the lip are considered as having a high degree of metastasizing.

The quality of the surgical excision is the most important criteria in time at the patients with squamous cell carcinoma.

Analyzing **the distribution of our patients with squamous cell carcinoma of the lip on the Broders degrees** we have remarked that 88.20% of the patients presented tumors with I and II degree of malignity. In a study of 250 cases the proportion (83%) is close to that found by us. There are authors who group the squamous cell carcinoma of the lip in well, medium and low differentiated. Chen J *et al.* studying 2 291 cases of lip SCC discovered well differentiated forms at 44.2% of the patients and medium differentiated at 48.5% of cases [23].

From our patients with metastasizing squamous cell carcinoma of the lip (Figure 8) 12 presented Broders II degree (12.24% from the tumors with II degree), six patients had Broders III degree (28.5% from the III degree tumors) and nine had Broders IV degree (52.94% from the tumors with IV degree). Our data, highlight the fact that the incidence of the regional ganglionary metastasis is higher in the case of the tumors with a low histological differentiation (test χ^2, $p<0.001$).

In Figures 9 and 10 we present two cases of squamous cell carcinoma metastazed in regional lymph nodes (submandibular).

The profoundness of the invasion of the squamous cell carcinoma of the lip has been less investigated as compared to the histological differentiation degree of the tumor. But, Stein Al and Tahan SR, studying 44 cases of invasive squamous cell carcinoma of the lip noticed the correlation of the profoundness with the metastasizing rate, in the way that all the patients with invasive tumors larger than 6 mm presented ganglionary metastasis [24].

Some authors say that this cancer can give early ganglionary metastasis if the profoundness is over 6 mm.

In what we are concerned, analyzing **the distribution of the patients as compared to the profoundness of the invasion of the cancer** it is stated that only five patients from 265 (1.88%) with an invasive tumor of under 6 mm presented metastasis, while the metastasis took place at 22 from 57 patients (38.60%) with the cancer invasion of over 6 mm. The results have a highly statistical signification (test χ^2, $p = 0.001$).

There are authors [14] who adopting, according to the melanoma model, the Clark level of invasion can appreciate the fact that the metastasizing risk rises once with the invasion of the profoundness of the tumor (IV and V Clark levels).

Finally, the data from the specialty literature show that distant metastasis is rare in the squamous cell carcinoma of the lip.

In some studies it was observed three metastases on 827 cases, in the lungs, liver and suprarenal glands.

Other authors found 12 metastases on 438 cases, 17 on 387 cases, and from 256 patients with a lip squamous cell carcinoma three developed distant metastasis – a case with pulmonary metastasis and two with cerebral metastasis.

It is worth underlining the fact that in our case with three local turn backs and multiple pulmonary metastasis we have faced the changing of the malignity degree in a period of six months (from Broders III and IV degree).

Conclusions

The histological differentiation degree and the profoundness of the invasion are two parameters which are worth taking into consideration for the contour of the squamous cell carcinoma of the lip profile with a high degree of metastasizing.

The malignity level of the tumor may worsen during the evolution of the lip cancer raising the risk of metastasizing.

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