

Lip Squamous Carcinoma - Epidemiologic, Clinical, Evolutive and Therapeutical Aspects

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ABSTRACT: Purpose. Squamous carcinoma (SC) of the lip is an infiltrating and destructive malignant epithelial tumor, with high potential for lymphatic and/or blood metastasizes. Lip SC is 15-30% of all SC the cephalic extremity and 1/5 of the upper aerodigestive tract cancers We conducted a prospective study in Dermatology Clinic from Craiova, between 2004-2010, with the aim of highlighting the epidemiological aspects, clinical and therapeutically evolution of patients with lip SC. **Material and methods.** Study group: 152 patients with lip SC, stages T0, T1N0M0. For each patient we filled an analytical card, including: identification data (name, first name, gender, age), area of residence, risk factors (occupation, smoking, alcohol consumption), the site of cancer, disease history, clinical form, the histopathological result, treatment and therapeutic response. All patients undergone surgery. **Results.** Most of the patients were male (78,95%), from rural environment (85,53%) and they were smokers (84,21%). The tumor site was predominantly on the lower lip (98,03%) and it was preceded by precursor lesions in 67,10% of the cases. We noticed a clinical polymorphism, and histopathological prevailed the well differentiated form (64,47%). **Conclusions.** Lip SC affects with predisposition men past 60 years, with prolonged exposure to the sun and who smoke. Lip SC onset occurs frequently on premalignant lesions, especially on chronic keratozic cheilitis, pointing out the importance of early diagnosis and appropriate treatment for preblastomatous cheilitis. Early establishment of treatment of lip SC offers the safety of therapeutic accomplishment. Option for surgical treatment of T0, T1N0M0 lip SC is justified by the very good oncological, aesthetic and functional results in most cases. Surgical treatment of primary T0, T1 lesions, respecting the oncological surgery principles makes it not recommended to "filling in" the results with other therapeutic methods. Patients should be regularly examined for a period of at least three years to capture the moment of occurrence of metastases, or a possible relapse of a lip SC. Actions are needed to educate the population about the risk factors and to detect precancerous lesions and SC of rim in early stage.

KEYWORDS: lip squamous carcinoma, risk factor. prognostic factor

Introduction

Squamous carcinoma (SC) of the lip is a infiltrating and destructive malignant epithelial tumor, with high potential for lymphatic and/or blood metastasize. Metastasis rate is about 10%. Most of the lymph node metastases appear in the first 2 years of evolution and are more common in cases T 2(tumor > 2 cm) and T3 (tumor > 4 cm), compared with T1 (tumor≤2 cm).

Lip SC is 15-30% of all SC the cephalic extremity and 1/5 of the upper aerodigestive tract cancers [1,2]. It is estimated that in the U.S. annually occur approximately 40,000 new cases of oral squamous cell carcinomas and about 500,000 new cases worldwide. In the U.S.A. are diagnosed each year 3500-4000 new cases of cancer of the lip, and the incidence is 2% 000 [3].

In Romania lip cancer accounts for about 1% of the nearly 60,000 new cases of malignant tumors detected annually [4]. In Dolj county 1,5% of cancers are lip cancers. Lip cancer is about 40% of oral squamous carcinomas in this geographical area.,

Although it is easy to detect, patients often presents T2-T3-T4 lip SC or metastasized, situations involving multimodal treatment, including surgical excision followed by laborious reconstructive lip defect after surgery. Regrettably, some of the those patients dies due to this disease, lip SC occupying seventh place in the pecking order of deaths caused by malignant tumors.

We conducted a prospective study in Dermatology Clinic from Craiova, between 2004-2010, with the aim of highlighting the epidemiological aspects, clinical and therapeutically evolution of patients with lip SC.

Material and methods

Study group: 152 patients with lip SC, stages T0, T1N0M0.

For each patient I've drawn an analytical card, including: identification data (name, first name, gender, age), environment of origin, risk factors (occupation, smoking, alcohol consumption), the site of cancer,

disease history, clinical form, the histopathological result, treatment and therapeutic response.

Epidemiological study followed the patients' distribution by age, sex, occupation, environment of origin.

Clinical-evolutionary study was based on disease history, previous treatment history and specifies the site and clinical form of the lip SC at the time of hospitalization.

For histopathological study we had in mind the degree of differentiation of the lip SC and the association of cancer with the dysplastic lesions.

Based on the traditions of the dermatology school from Craiova, we performed surgical treatment to all 152 cases of lip SC hospitalized in our clinic. We practiced: vermillionectomy in 7 patients with SC in situ and keratotic cheilitis; vermillionectomy plus "V" excision in 6 patients with cancers accompanied by leucoplastic or keratotic cheilitis; excision in „ V", „W", „U" depending on the tumor diameter, for the other 139 cases. The surgical margins were of minimum 5 mm. We evaluated therapeutic outcomes (oncological, functional and aesthetic) at the end of the time of hospitalization and after 2 years of periodic checks.

In assessing the results of the surgery we had in mind the following criteria:

- very good aesthetic results: invisible scar and normal aspect of the lip;

- good aesthetic results: scar visible up close (20 cm), but without observing it from the normal distance of communication; the lip has the normal appearance;

- moderate aesthetic results: visible scar from one meter and/or anatomical aspect of an less well defined structure;

- unsatisfactory aesthetic results: we see that the patient underwent surgery; the anatomy of the lip is changed.

Results

The distribution by sex was M-78,95%; F-21,05%. The distribution by area of residence: rural 85,53%; urban-14,47%. Average age was 67,79 years (29-84 years).

Regarding their profession, most were farmers (76,32%), mechanics (10,53%), constructors (9,21%), the rest having other professions.

84,21% of them were smokers and 42,10% of them have recognized chronic consumption of alcohol.

The disease history was between 6 and 14 months.

The site of cancer prevailed at the lower lip: 97,37% of cases.

I encountered the following clinical forms: ulcerative and vegetant (42,10%), nodular (21,05%), keratotic (15,79%), ulcerative and infiltrating (9,72%), vegetant (5,92%), in situ carcinoma (4,60%) and fissuring form (1,32%).

The frequency of chronic keratotic cheilitis was 49,34% and smoke leucoplastic cheilitis is about 17,76%.

In terms of histopathological exam, the situation was the following: well differentiated SC(64,47%), moderately differentiated SC (28,95%), poorly differentiated SC(6,58%).

Evaluating therapeutic results, at the end of the time of hospitalization and after 2 years of periodic checks, allowed us to notice healing at 98,03% of the cases. Aesthetic and functional results were very good at 92,76% of patients.

Discussion

Lip SC affects with predilection men past 60 years (except Africa, where age is 36-40 years old) with white skin, with long-standing exposure to the sun and who smoke. The lower lip is the site for about 90% of cases. In our study the tumor was located on lower lip in 97,37% of cases, and the average age of the patients was 67,79 years.

Pathogenesis. Many studies in the field have revealed several risk factors for inducing lip SC:

- *Actinic radiation.* Alongside the action of photons on DNA (pyrimidinic dimers formation with possible activation of protooncogenes), UV may occur through:

- ornitinecarboxylase increased activity (the enzyme that participates in the synthesis

of polyamines: putresceine, spermine, spermidine) which has action of promotion and progression;

production by ion irradiation phaeomelanin, superoxide and other radicals with high-powered carcinogen;

lipidic peroxidation with the generation of aldehydes mutagens;

Oxygenated sterols, especially action of 1α -dehydrocholesterol produced by UV irradiation of cholesterol. It is carcinogenic and immunosuppressive strong;

Cellular immunity depression. Both UVA and UVB entail a reduction of functional immunological markers and histochemical markers of Langerhans cells.

Also, at the skin chronically exposed to solar radiation was observed a decrease in the order of 50% in the number of Langerhans cells, which makes the appearance of malignant cell clones that are at the origin of skin cancers.

The action of the UV on the genome is a subject of ongoing interest to researchers. They have proven that repairs of the damages of DNA produced by sun are possible due to, the action of the protein p53 (p53 gene-encoded protein that belongs to the family of suppressor genes). This protein stops cell proliferation, and resume their cells after the repair cycle. If damages are very important then p53 provoke apoptosis through bax gene induction and diminishing bcl2 gene expression. So that explains the name given to p53 gene – the guardian of the genome. It was found that the p53 gene is inactive in 20-50% of cases of cutaneous carcinomas. Interesting is that mutations of the p53 gene were found in precancerous lesions and skin irradiated with UV, chronic data that can be viewed as a signal of alarm for a solar capital already dangerous. In all skin carcinomas we found mutations of H protooncogene, but with a lower frequency.

Locating in the CS to the lower lip, disadvantaged its position relative to the Sun, is another argument to support the involvement of UV radiation in the appearance of this tumor;

§ *Smoking* is a major risk factor for lip cancer; over 80% of the patients were

smokers. The oncogenic effect of the smoking is the result of double action, thermal and chemical properties, the latter particularly through carcinogenic aromatic polycyclic hydrocarbons contained in the cigarette smoke. After almost half a century of study for identification of toxic and carcinogenic substances (over 480) contained in cigarette smoke, the list remains open. In recent times, research in the field has revealed tobacco association with mutations in the p53 gene, which reveals a different way of engaging in the process of carcinogenesis.

§ *Biological factor* represented by certain oncogene HPV, in particular potential types 16, 18. In one study [5] conducted on 27 cases of lip SC, 20 patients were present at the level of DNA tumor virus, of which HPV DNA at 17, most 16, 18. The authors concluded that HPV (primarily 16,18) may be involved in the genesis of the SC of the lip. Regarding the mechanism of HPV E6 protein, remember that which belongs to HPV 16 and 18 combines with the protein that inactivates p53, resulting in an effect similar to p53 gene mutations. Also HPV E7 protein with the tropism which leads on mucous binds with the strong affinity of retinoblastoma protein pRb and thus it cannot impound E2F transcription factor on the issue. Through these mechanisms contribute to genomic instability propagation HPV induced by UV.

§ *Ionizing radiation* – through sub-lethal damage and mutations on irradiated cells, initiates cancer. The use of ionizing radiation in the treatment of diseases of the lips, first CS, due to massive irradiation, may lead to a chronic radiodermatitis, important by its ability of malignant transformation. The coexistence of an actinic cheilitis hurries the occurrence of cancer of the upper lip;

§ *Alcohol*. The risk of developing cancer is 10 times more raised to the great alcohol consumptions, reaching up to 15 times if you add smoking. Between the mechanisms by which alcohol consumption may be carried out: suppression of immune system of cellular hypersensitivity; the growth

action of dimethyl-benzanthracen present in the cigarette smoke; toxicity over enzymatic systems of epithelia; the production of liver injuries, enabling enzymatic activation of certain carcinogens; metabolic disorders by deficiency of B vitamins;

§ *Chemical carcinogens*. Arsenic causes both cancers of the skin, but also about aerodigestive tract, lung, bone, liver. The latency period is 25-30 years. The integument may appear arsenical keratosis, Bowen's disease, squamous carcinoma. Coal tars are involved in etiopathogenesis of rim and skin cancers, being discussed more carcinogenetic mechanisms: mutations in the p53 gene and the H-ras protooncogene; the generation of free radicals; Langerhans cells inhibition presenting function and reducing response T lymphocytes;

§ *Immunosupression*. The risk for the occurrence of cancer, including on the lip, is increased in people with grafts [6,7] or those with AIDS. In these categories of patients, cancers occur early and often are more aggressive. SC represents 2/3 of skin cancers developed in patients with grafts. To patients with kidney graft, skin cancer development risk is 3-20 times higher than the rest of the population;

§ *Mechanical trauma*. The importance of this factor is further observations concerning the existence of cases of cancer of the lip to the glass blowers, trumpeters, people who used to smoke with heavy pipe, as well as the existence of CS lip with starting point from a trauma chronic dental prostheses or inappropriate;

§ *Genetic factor* – determines the sensitivity of the individual to the solar radiation, and in the context of genodermatoses, skin and lip cancers are much more common and early [8].

Even if the actinic radiation and smoking have a predominant role in the etiopathogenesis of CS rim, however in many cases this tumor is the result of the action of external and internal factors with different participation rates.

In regards to the study of new patients, we believe that contributed substantially to the development of RIM CS following

factors: actinic radiation, smoking, chronic consumption of alcohol.

Lip SC can develop on one of the following injuries: chronic actinic preblastomatous keilitis; circumscribed thermal keratosis of lip; smoke leukoplasic cheilitis; cutaneous horn; keratoacantoma of the lip; postradiotherapy cheilitis; labial eritroplazia; oral florid papilomatosis; lip lesions in the context of genodermatosis (xeroderma Pigmentosum, Bloom syndrome, Rothmund Thomson syndrome).

In our study, precancerous lesions were identified in 67,10% of cases of chronic keratotic cheilitis (fig1.) being present at 49,34% of patients, while smoke leukoplasic cheilitis was highlighted to 17,76%. They proceeded with one to two years and cancer was highlighted through peritumoral dermatological exam at the time of hospitalization of patients.



Fig. 1 Nodular SC and keratotic cheilitis, lower lip

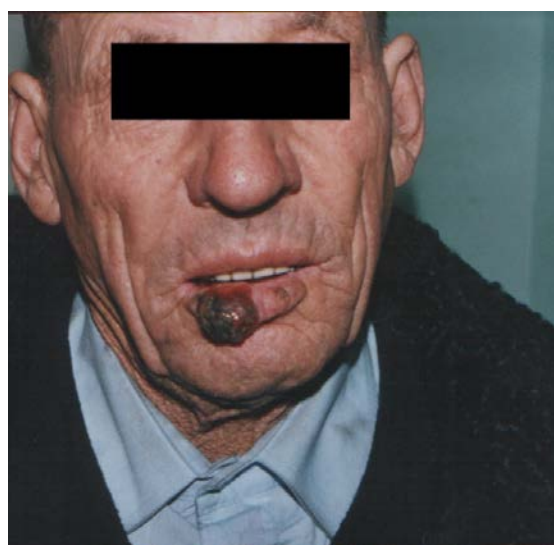


Fig.2 SC, ulcerative and vegetant form

The stage of the tumor lodged CS lip dress up clinical polymorphism: keratotic, ulcerative-vegetant, nodular, nodular ulcerated area, ulcer, tenebrant, fissured, infiltrative with radial expansion, multifocal. In order of frequency, we met the first three places following rim CS: ulcerative - vegetant (fig.2), nodular (fig3.) and keratotic (fig4.)

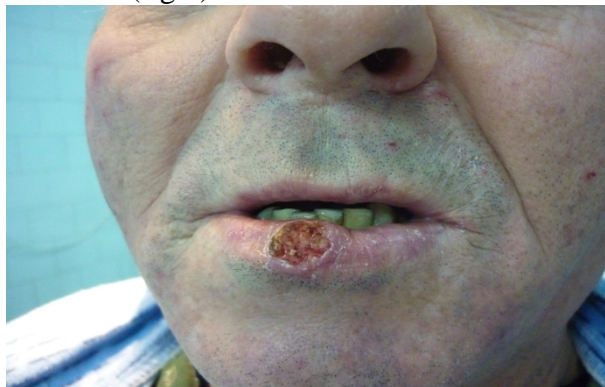


Fig. 3 SC, nodular and ulcerative form



Fig.4 SC, keratotic form and keratotic cheilitis

Evolution. Prognostic factors Expansion tendency characterizes the lip SC and manifests itself in either surface or depth or both dimensions. This process is in relation to several factors, some related to the tumor, others from the patient. In the first phase it is strictly localized evolution CS lip, after which we can meet metastases in regional lymph nodes, affecting the bones of neighborhood and rarely metastasize.

An important factor involved in the process of malignization of squamous epithelium and in progression of the acinar from the head and neck is the adhesion molecules, especially the V6 variant CD44 thereof (CD44varV6). This molecule has a

tendency of disappearing in premalignant and malignant lesions. Also, there is the existence of a good correlation between the molecules level expression and the survival rate of patients with cancer of the lip. So these patients as expressing a lower level of CD44 the prognosis will be more reserved [9].

EGFR is a proto-oncogene which once enabled at the cell surface via growth factor TGF Alpha helps promote cell proliferation. Otherwise it is known that inactivation of tumor suppressor genes such as p53 and activation of protooncogenes, as cyclin D1 and EGFR, leading to disturbances of cell cycle and promote cervical.

High expression of EGFR is associated with oral cancers with increased risk of recurrences\metastasis, low rate of survival and resistance to chemotherapy\ radiotherapy [10]. This is the reason why oral cancers constitute the object of study of some clinical trials both with monoclonal antibodies (Panitumumab) directed against EGFR and tirozinkinase inhibitors (Cetuximab, Gefitinib, Erlotinib) [11- 13].

Another factor that can influence tumour the aggressiveness is the vascular endothelial growth factor (VEGF), a protein whose production is stimulated under conditions of hypoxia and promoting in particular vascular permeability and proliferation of endothelial cells. In squamous carcinoma of the head and neck, the increased level of VEGF is associated with an increased rate of local relapse, distance metastasize and a shorter survival. Such researches open new therapeutic perspectives, alongside the classics, in a challenge to improve the survival rate of patients with oral cancers, including those of the lip [14].

It was hypothesized that the metastases potential results from a well-established genetic program, with the intervention of metalloproteinase gene, degrading cellular matrix [15]. Researchers have shown that MMP2 and MMP9 are capable of degrading collagen IV, the major component of the basal membrane. The data in a study on patients with oral cancer [16] indicates as

MMP2 and MMP9 can be useful to identify the phenotype of metastases as well as to monitor the treatment of cancers with this location.

In the wake of another research carried out in 2008 on a lot of patients with oral melanomas and sino-nasal, the authors [17] have concluded that MMP2 and MMP9, MMP14, can represent prognostic markers for these cases. Patel BP and Cooper studied MMP2 and MMP9 at 39 patients with oral squamous carcinoma (28 cases had no metastases; 11 cases with metastases) [18] and noted that the work of these metalloproteinase is more increased in malignant tissues, compared to adjacent normal tissue. Interesting is the fact that the activity of MMP2 was significantly higher in patients with lymph metastasis. Proven if activity remains elevated MMP2 and MMP9 in cases without metastasis at the time of treatment represent a prognostic factor for squamous oral cancer, including one at the level of the lip. Although it is quite a different localization of cancer, the authors [19], after the study conducted on 125 patients, concluded that predictive MMP9 is independent of disease recurrence for cancer. MMP2 and MMP9 that have a role in the complex mechanisms of prostate esophagus, larynx, oral-labial and colon cancers to metastasize, made to become a key target in cancer disease therapeutic strategy using synthetic inhibitors of matrix-metalloproteinase.

In lip SC, the regional lymph node metastases are the most common secondary injuries. Frequency reported from literature data, vary within limits large enough, at 2.7% (Breuninger) at 37% (Stoll). Media lies around the values of 8-10%. Figures are provided by studies on patients belonging to maxillo-facial surgery services [20]. After centralization of many studies including 11094 cases of lip cancers, Descamps and Cooper found metastases of oversight at 13.7% of patients after 5 years. Most lymph node metastases appear in the first two years of evolution of lip SC. These are more common in cases with T2 and T3, compared with patients with T1.

In another study [21] on a lot of 95 patients with lip SC authors have concluded that the present increased risk of development of regional lymph node metastasis patients with tumors over 2 cm, those with poor histological differentiation, tumor with the maximum depth exceeding 6 mm and in cases with perineural invasion and low expression of p27 protein kip 1.

In our study all patients presenting with tumors less than 2 cm, cases that can be handled by dermatologist and the histopathological exam concluded that prevailed well differentiated form (64,47% of cases) (fig.5). The moderately differentiated form (fig.6) we met at 28,95% of cases, while poorly differentiated form (fig.7) was present at 10 patients (6,58%). It is thus a very good evolution due to post-with therapeutic healing on 98,3% of cases.

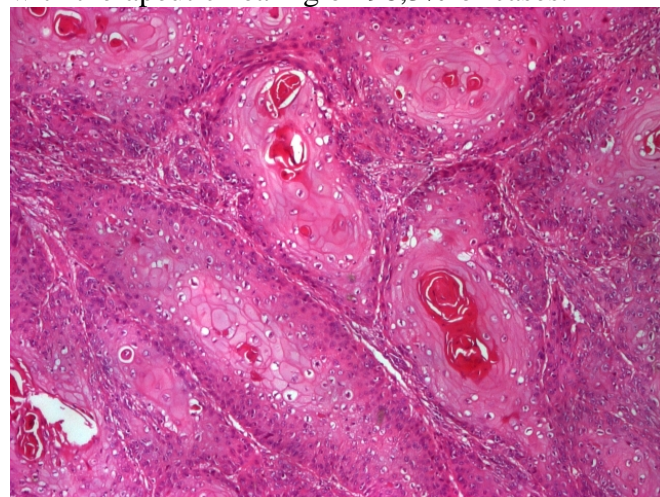


Fig.5 Well differentiated squamous carcinoma, col HE, Ob. x4

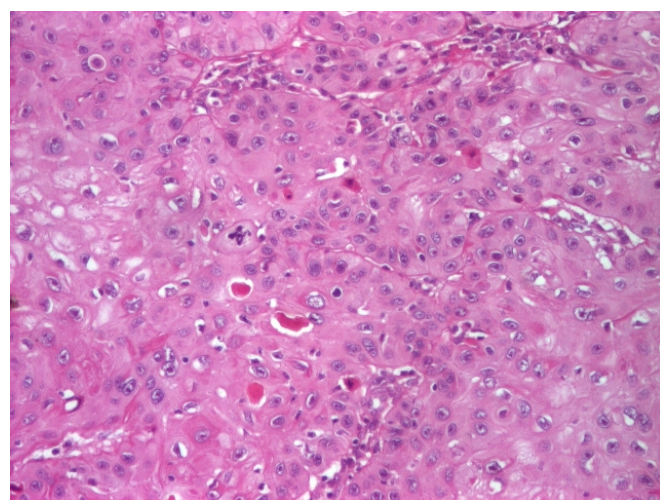


Fig.6 Moderately differentiated squamous carcinoma, col HE, Ob. x4

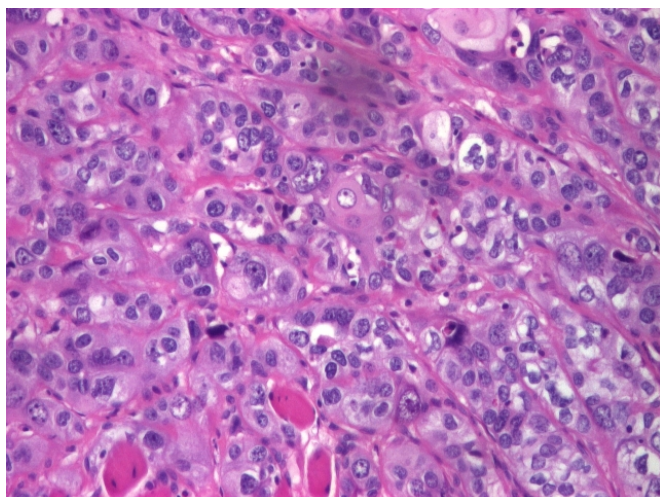


Fig.7. Poorly differentiated squamous carcinoma, col HE, Ob. x4

The site, the size of the tumor, infiltrating in in-depth, the appearance of neurological signs of perineural invasion and immunosuppression represent factors of clinical prognostic. Shape, degree of histopathological differentiation, tumor thickness and depth of invasion, perineural invasion are value prognostic factors for lip SC. [22].

Systemic metastases are very rare in the lip SC (<1% of cases) and impaired bone during cancer evolution keeps the first delay in the presentation to the physician, then the aggressiveness of the tumor. Bone metastases occur either directly, through the invasion of almost close, either on the mandibular canal. At other times, impairment of mandibular bone and periosteum root disease is a secondary lymph node metastases were neglected. In some cases participates in all three ways.

In terms of recurrences of the primary tumor after treatment, these were correlated with large cancers and with poor histological differentiation of the primary lesion. Frequency is 11.3% (Korenvs e. et al – study on 189 patients) [23] values (10.8%) being entered in another study on 223 patients [21].

The average survival rate of patients with RIM CS is 2 years of about 90%, and 5 years of 83%. Patients with T3 or T4 and those with distant metastases have poor prognosis. After treatment, patients should be examined periodically, at least 5 years for

the surprise of relapses and eventual regional metastases. Almost 75% of the metastases occur in the first year after the operation, during which checks must be rigorous.

Treatment involves satisfying lip SC has at least two imperatives: to be curative therapy; the treatment entails a minimal functional repercussion and aesthetics. You can call the classical surgery, radiotherapy, cryotherapy, surgery plus electro cauterization. For cases with in situ carcinoma we can resort to Photodynamic therapy or local application of 5-Fluorouracil, the original. Chemotherapy and treatments combined (multimodal) are reserved mainly for cases with those metastasize.



Fig 8a. Vermillionectomy



Fig.8b. Excision in "V" and Vermillionectomy

Depending on the outcome of the examination, we performed clinical vermillionectomy in patients with in situ carcinoma and keratotic cheilitis (fig.8a) and excision in "V" plus vermillionectomy to those with cancers accompanied by leucoplazic or keratotic cheilitis. In other cases we performed excision in "V" (fig.8b), "W", "U", in relation to the diameter of the tumor. The safety zone was of minimum 5 mm. Evaluation of therapeutic results, at the end of the period of hospitalization and after 2 years of periodic checks, permitted us to notice healing to 98,03% of the cases. I registered in the first year after surgery two recurrences of the tumor, and a sick has developed the early submandibular lymph node metastases. Aesthetic and functional results, evaluated by the patients and treating doctor, were very good at 92,76% of the cases.

Conclusions

- Lip SC affects with predisposition men past 60 years, with prolonged exposure to the sun and who smoke;
- Lip SC onset occurs frequently on premalignant lesions, especially on chronic keratotic cheilitis, pointing out the importance of early diagnosis and appropriate treatment for preblastomatous cheilitis;
- Early establishment of treatment of lip SC, offers the safety of therapeutic accomplishment
- Option for surgical treatment of T0, T1N0M0 lip SC is justified by the very good oncological, aesthetic and functional results in most cases;
- Surgical treatment of primary T0, T1 lesions, respecting the oncological surgery principles makes it not recommended to "filling in" the results with other therapeutic methods;
- Patients should be regularly examined for a period of at least three years to capture the moment of occurrence of metastases, or a possible relapse of a lip SC;
- Actions are needed to educate the population for the knowledge of risk factors

and to detect precancerous lesions and CS of rim in early stage.

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