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THE SIGNIFICANCE OF CLINICAL AND PATHOLOGICAL FACTORS FOR DIAGNOSIS AND PROGNOSIS OF EARLY STAGES SQUAMOUS CELL CARCINOMA OF THE MOUTH

ZNAČAJ KLINIČKIH I PATOLOŠKIH FAKTORA ZA DIJAGNOZU I PROGNOZU U RANIM STADIJUMIMA PLANOCELULARNOG KARCINOMA USTA

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Abstract

This review is based on main clinical and pathological factors of the patients with squamous cell carcinoma (SCC) of the mouth (tongue and floor of the mouth predominately) in the province of Canary Islands, Spain, regarding their prognosis.

A retrospective study was made of 40 patients with early (clinical stages I/II) SCC of the tongue and floor of the mouth. The protocol designed for this study was used to record the clinical and histopathological data, which were subjected to descriptive and comparative bi- and multivariate statistical analysis of survival.

There were 34 males and 6 females, with a mean age of 55.7 years (range 33-81). In 23 cases the SCC was located in the tongue, and in 17 cases in the floor of the mouth. The average tumor diameter was 2.6 cm; 65% of the tumors were ulcerated. The mean clinical course was 3.4 months, with an average tumor growth rate of 268 (Evans formula). Thirty-four patients were smokers and 33 alcohol consumers. All SCC of the floor of the mouth, and all regional recurrences, were diagnosed as smokers and drinkers. Survival at 5 years was 65%. Well differentiated SCC was diagnosed in 52.5% of cases. The average histological malignancy grade was 1.96, and was higher in males, tongue malignancies, T2 lesions, tumors with bigger growth velocities and in recurrent neoplasms.

Early SCC of the tongue and floor of the mouth affects mainly male smokers and drinkers of alcohol under the age of 60 years. A relationship is observed between the histopathological findings (particularly invasion mode and stage) and patient prognosis.

Key words
 Squamous Cell Carcinoma, early stage, mouth.

Ključne reči
 skvuamocelularni karcinom, rani stadijum, usna duplja

INTRODUCTION

Oral cancer is common at the Canary Islands, Spain, with a gross incidence of 13.24 cases per 100,000 inhabitants; these statistics correspond to the Calvados region in France being among the highest in Europe [1]. The most frequently affected intraoral regions in our setting are the tongue (25.1%) and floor of the mouth (10.2%)[1].

The prognosis of oral malignancies remains discouraging, with global survival rates of less than 50% at 5 years, associated to important morbidity [2,3]. In this context, correct staging of the lesions at the time of diagnosis is a decisive factor in defining patient prognosis. Small lesions (ie., those in clinical stage I/II) present a relatively favorable prognosis [2-4].

With the aim of predicting the clinical course and prognosis of the disease, and thereby facilitating more effective treatment, attempts have been made to define clinical, histological, morphometric, diagnostic and other para-meters that may serve as prognostic and therapeutic indicators. No single methodological approach has yet been standardized, however [2-14].

No studies have been carried out in our setting to identify valid prognostic data in relation to this common illness, and little such work has been done elsewhere in Spain [15,16]. The present study thus investigates the main clinicopathological factors in squamous cell carcinoma (SCC) of the tongue and floor of the mouth in relation to patient prognosis, with the purpose of establishing appropriate diagnostic and therapeutic guidelines.

PATIENTS, MATERIALS AND METHODS

A prospective study was made of 40 patients with squamous cell carcinoma (SCC) of the oral cavity in University Hospital Insular of Gran Canaria, Las Palmas, between 2000 and 2008. The including selection criteria were: (a) the presence of SCC of the tongue or floor of the mouth; (b) a neoplastic lesion diameter of less than 4 cm; (c) the absence of lymph node or distant metastases at the time of diagnosis (ie., clinical stages I and II); (d) initial treatment in the form of surgery; and (e) the absence of prior radiotherapy or chemotherapy.

The malignancies studied accounted for 18.1% of all carcinomas of the floor of the mouth and 25.8% of all lingual carcinomas. There were 34 males and 6 females, with a mean age of 55.7years (range 33-81).

A previously designed protocol was used to record the most relevant clinical Information from the prognostic perspective, and the corresponding histopathological findings. In addition to patient age and sex, the following parameters were registered: tumor location and size, clinical course, growth rate [8], tobacco smoking, alcohol consumption, occupational activity, the development of other neoplastic processes, clinical appearance, treatment, occurrence and type of recurrences, and survival at 5 years. The tumor growth rate or velocity was calculated from the Evans formula by dividing the tumor area at the time of presentation by the time elapsed from appearance of the first symptoms to actual diagnosis [8].

The surgical resection pieces were processed for conventional histological study under the light microscope. The sections were stained with hematoxylin-eosin, Masson trichromic stain and periodic acid-Schiff (PAS). All cases were evaluated by two pathologists, assessing the degree of differentiation, the data relating to the multifactor system proposed by Jakobsson et al. [6] modified by Aenneroth et al. [7], and vascular and perineural invasion.

The data obtained were subjected to descriptive and comparative bi- and multivariate statistical and survival analyses based on the Kaplan-Meier curves and Cox regression test.

RESULTS

The malignancy was located in the tongue in 23 cases (57.5%), and in the floor of the mouth in 17 (42.5%) - yielding a proportion of 1.35:1. In males and females the proportion was respectively 1.12:1 and 5:1 in favor of the tongue. Tumor recurrence was recorded in 10 lingual tumors (43.5%) and in 6 cancers of the floor of the mouth (35.3%).

The mean tumor diameter was 2.62 cm (2.67 cm in males and 2.28 cm in females); patients with tumor growth velocities of over 200 (based on the Evans formula)[8] had larger tumors (mean diameter 3.32 cm).

The mean clinical course to diagnosis spanned 3.4 months. This interval was shorter in T2 lesions (measuring 2-4 cm) and in those with slower growth velocities. The mean course in those cases without recurrences was 4.1 months versus 2.6 months in the lesions that recurred. The mean course was significantly related to the mitotic index (p = 0.005).

The mean tumor growth rate or velocity was 268.02 (296.6 in males and 106.03 in females). Patients with recurrences showed a mean higher growth velocity of versus similar but something lower, among those without recurrent lesions.

Thirty-four patients (85%) were smokers, and 33 consumed alcohol (82.5%). Among the men, 97% were smokers and 94% were drinkers. In contrast, only one woman smoked and consumed alcohol - the difference being highly significant (p< 0.000). All patients with tumors of the floor of the mouth were smokers and drinkers (p = 0.02), while 94% of the patients with growth velocities of over 200 had these same toxic habits. Likewise, all patients with regional recurrences were smokers and drinkers.

Twenty-one patients were manual workers; while 7 were office workers and 6 (all the women) were housewives. Most patients (35 cases) resided in urban areas and 5 in rural zones; among the latter, 80% of the tumors were located in the tongue.

Two patients (5%) developed another aero-digestive tract cancer (bronchial carcinoma in one case and lip cancer in the other).

An exophytic clinical appearance was recorded in 5 cases (12.5%), with ulceration in 26 (65%) and mixed presentations in 9 (22.5%).

Treatment was limited to surgery in 20 patients, while in 20 cases postoperative radiotherapy (50 Grays) was added.

Tumor recurrence was documented in 18 cases (45%) - local in 10 patients, regional, and loco regional in 5 patients. Survival at 5 years was 65% (22 cases); in 14 cases (35%) the tumor caused patient death within an average of two years (13 males and 1 female). The tongue was involved in 10 of these cases and the floor of the mouth in four. Three tumors were in stage T1 at the time of diagnosis and 11 in stage T2.

As regards the histopathological findings, 21 cases (52.5%) corresponded to well differentiated SCC, 11 (27.5%) were moderately differentiated and 8 (20%) were poorly differentiated lesions. In turn, 24.1% of the stage T2 lesions and 29.4% of the tumors with high growth velocities were poorly differentiated (figs. 1,2).

The mean histological malignancy grade was 1.96 (standard deviation (s.d.) 0.49; range 1.29-3.14). The mean grade in women was 1.88, versus 1.97 in males. The tongue lesions presented an average malignancy grade of 2.02, versus 1.87for SCC of the floor of the mouth. The stage TI and T2 tumors respectively showed malignancy grades ofl.74 and 2.04. In neoplasms with lower growth velocities 200 the malignancy grade was 1.84 on average, versus 2.12 among the lesions with higher growth velocities according to the Evans formula. In turn, the tumors among patients who did not suffer recurrence presented a malignancy grade of 1.86, versus 2.08 in those who presented recurrence. The degree of malignancy was significantly correlated to tumor structure ($p < 0.000$), keratinization ($p < 0.000$), nuclear atypia ($p < 0.000$), mitosis ($p < 0.000$), invasion mode ($p < 0.000$), infiltration stage ($p < 0.000$), differentiation ($p < 0.000$), and perineural invasion ($p < 0.05$).

A relationship was observed between marked invasion (ie., greater tumor aggressiveness) and increased tumor recurrence ($p = 0.042$), and between advanced invasion stages and T2 neoplasms ($p = 0.0027$), and recurrent lesions ($p < 0.05$).

Vascular infiltration was identified in 11 cases globally (27.5%), and in 30.4% of the tongue cancers. Vascular invasion was also seen in 35.3% of the SCC with high growth velocities and in 33.3% of the recurrent malignancies.

Perineural invasion was present in 12 cases globally (30%), and in 34.8% of the tongue cancers. None of the stage T1 lesions showed perineural invasion, though 52.9%
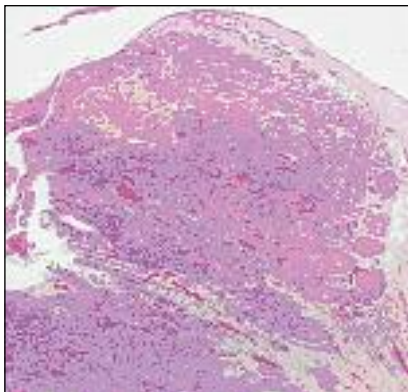

Fig. 1. *Edge of tumor with infiltrating squamous carcinomatous ulcer nests. H&E, 4 X.*
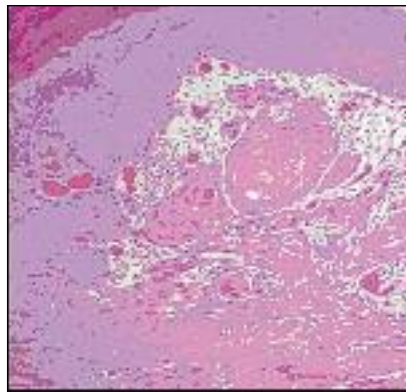

Fig. 2. *Part of the mucosa with distinct carcinomatous keratinous nests, H&E, 10 X.*

of the SCC with higher growth velocities and 38.9% of the recurrent malignancies, did present perineural invasion. The latter was significantly correlated to tumor size ($p = 0.009$).

Cox regression survival analysis yielded no statistical significance for histological malignancy grading or its related parameters.

DISCUSSION

The small size malignancies evaluated in this study accounted for only a small proportion of the global squamous cell carcinomas (SCC) of the tongue and floor of the mouth diagnosed in our center in the same study period. This fact points to the need for improved detection of early tumors in our setting, incrementing awareness of the impor-

tance of an early diagnosis among both the general population and health care professionals [17]. González-Moles et al. [16] found tumor size at the time of diagnosis to be the most decisive factor in relation to patient prognosis. Consequently, these authors suggested that an early diagnosis of oral cancer remains the best way to reduce associated mortality.

In agreement with the literature consulted [18-22], a clear relation is seen in our setting between oral cancer and tobacco smoking and alcohol consumption. This association is particularly important in relation to tumors of the tongue and floor of the mouth, and to male patients. In turn, such toxic ha-bits are associated to increased recurrence and thus to a poorer patient prognosis.

Of interest is the fact that our patients were an average of 10 years younger than those described in most other series [3, 23, 24]. The reason for this is not clear, though it may be related to the observation that many of our patients started to smoke and drink at a comparatively early age - thereby conditioning an earlier development of oral malignancies - and to the fact that the present study focused on early stage SCC.

The male/female proportion observed in our series is quite different to that reported elsewhere in other western countries, with ratios ranging from 1.3:1 to 3:1 in favor of males [3, 24-26]. Epidemiological surveys in our community [1] have revealed a high incidence of this pathology among males, with proportions of 33:1 and 15:1 for carcinomas of the floor of the mouth and tongue, respectively. We believe that these values are mainly attributable to the low incidence of the principal underlying carcinogens (tobacco and alcohol) among women in this age range, in our setting. Another contributing influence could be the fact that we only investigated two concrete locations (tongue and floor of the mouth), obviating other sites such as the jugal zone, where malignancies are more frequently seen in women.

In agreement with Langdon [11], we observed no differences of the disease between sexes for the incidence of recurrences was similar in both. This is in contrast to other studies [27-30], however, where women are seen to have a better prognosis. In our opinion, the small tumors that characterize the present study are decisive in this aspect.

In coincidence with the general epidemiological findings in our setting[1], the tongue was the most frequently affected region in the present: study. Of note is the fact that only one woman presented SCC of the floor of the mouth - an observation again accounted for by the lesser pathogenic influence of tobacco and alcohol among women, in contraposition to men where smoking and drinking constitute a fundamental factor in tumors of this particular location [31].

Unlike other authors [13, 32], we observed no significant relation between tumor size and the appearance of regional recurrences. In contrast we did observe a relation between local recurrences and growing lesion size attributable to the increasing difficulty of securing surgical removal with suffi-

cient disease-free margins as the malignancy increases in size.

In coincidence with other authors [33], the mean course of the disease up to the time of diagnosis was over three months. In our opinion, this figure again points to the need for establishing an early diagnosis of such tumors which in many cases only develop clinical manifestations in later stages. On the other hand, we observed an increased tumor growth rate or velocity among the older patients, presumably due to the larger lesions found in these subjects. The growth velocity was in turn higher among lingual SCC than in lingual malignancies - a fact that could be explained by local anatomical factors that prevent further tumor progression[34].

The tumor recurrence rate was found to be slightly higher than reported elsewhere [13, 35]. The global survival rate at 5 years was 65%, this figure being similar to that reported in the literature [31, 35-37], and women showed a comparatively greater survival - as has also been observed by other authors [11, 27-30].

In agreement with Evans [8], SCC growth velocity had a certain influence upon patient prognosis. However, as expected, on including subjective parameters such as the duration of the clinical course in the multivariate analysis, this association was seen to weaken.

Unlike other series [38, 39], no significant differences were observed in relation to histological differentiation and the clinical and prognostic parameters. We believe that this is because more radical and aggressive treatments were initially targeted against tumors diagnosed as poorly differentiated in the prior biopsy. Although increased keratinization has been described in lingual tumors [7], we observed no significant differences versus malignancies of the floor of the mouth. Nevertheless, we recorded a less aggressive biological behavior among more keratinized malignancies, with lower growth velocities and fewer recurrences.

Unlike some authors [7], and in agreement with others [40, 41], most of our cases corresponded to solid neoplastic structures (grades 1 and 2). On the other hand, and in coincidence with Woolgar and Scott [42], the presence of nuclear atypical aberrations was of no prognostic significance in these carcinomas. In agreement with Crissman [43], we found the number of mitoses to increase in direct proportion to tumor size and exhibit a relation to growth velocity.

An association between infiltration stage and tumor size was established in our series, though to a lesser degree than reported by Crissman [43]; nevertheless, recurrent tumors more often presented advanced infiltration, as expected.

Inflammatory response was of no evident prognostic significance, though in agreement with other authors [7] we consider that the intensity of inflammation may be related to the tumor ulceration frequently seen in our cases. However, a certain association was observed to local recurrences - possibly because of the increased difficulty of surgical removal in cases with a more intense inflammatory reaction. Although certain authors [41] consider that the presence of peritumoral eosinophils may constitute a good prognostic marker in oral carcinoma, we found no significant differences in this sense.

The average histological malignancy grade in our series was somewhat lower than that reported by other authors [7], and was correlated to all the histological parameters analyzed, with the exception of inflammatory response - an observation that coincides with the findings of Aenneroth et al. [7]. Although malignancy grade exhibited no prognostic significance, patients with tumor recurrences had higher malignancy grades than those without recurrences. The malignancy grade was related to tumor size, in agreement with the observations of Woolgar and Scott [42].

Authors such as Martínez-Gimeno et al. [12] consider microvascular infiltration to be one of the most important prognostic factors in oral carcinoma. We observed no significant differences in this sense in the present series - probably because of the small size of the lesions involved.

Perineural invasion was directly related to tumor size, in coincidence with the findings of Curter and Clifford [44]. It has been described [45] that this type of invasion is common in oral carcinomas - a notion that would reduce its prognostic utility.

In coincidence with Jakobsson et al. [6], we consider that although all parameters relating to malignancy grade receive the same score, some are undoubtedly more important than others. In this context, Crissman et al. [43] showed that the most influential prognostic factor is the depth of invasion followed by the frequency of mitoses and, to a lesser degree, keratinization and nuclear pleomorphism. In the same way, Yamamoto et al. [9] showed such a correlation for invasion mode, while Ambrosch et al. [46] considered that the only risk factor for the development of micro metastases is invasion depth. In view of the results of the present study, we consider tumor infiltration to be the most important factor in histologically assessing small size carcinomas of the tongue and floor of the mouth.

Unlike in other series [38, 39], no significant differences were observed in relation to histological differentiation and the clinical and prognostic parameters. We believe that this is because more radical and aggressive treatments were initially targeted against tumors diagnosed as poorly differentiated in the prior biopsy. Although increased keratinization has been described in lingual tumors [7], we observed no significant differences versus malignancies of the floor of the mouth. Nevertheless, we recorded a less aggressive biologically behavior among more keratinized malignancies, with lower growth velocities and fewer recurrences.

Sažetak

Ovaj revijski rad se zasniva na glavnim kliničkim i patološkim faktorima koji karakterišu obolele od skvamocelularnog karcinoma (SCC) usne duplje (uglavnom jezika i poda usta) sa Kanarskih ostrva (Španija), a odnose se na prognozu ovih bolesnika.

Urađena je retrospektivna studija 40 pacijenata sa ranim stadijumima SCC jezika i poda usta (I i II stadijum). Protokol dizajniran za ovu studiju je napravljen tako da zabeleži sve kliničke i patohistološke podatke koji su podvrgnuti deskriptivnoj i komparativnoj bi- i multivarijansnoj statističkoj analizi preživljavanja.

Grupu pacijenata čine 34 muškarca i 6 žena prosečne starosti 55.7 godina (opseg od 33-81). Kod 23 pacijenta karcinom je lociran na jeziku, a kod 17 na podu usta. Prosečan dijametar tumora je 2.6 cm; 65% tumora su bili ulcerisani. Srednje vreme kliničkog praćenja je bilo 3.4 meseca, a prosečna brzina rasta tumora 268 (po Evansovoj formuli). Pušači su činili grupu od 34 pacijenta, a konzumenti alkoholnih pića su bila 33 pacijenta. Svi pacijenti sa SCC poda usta i lokoregionalnim recidivima su bili pušači i konzumenti alkoholnih pića. Petogodišnje preživljavanje je bilo 65%. Dobro diferenciran SCC je dijagnostikovan kod 52.5% pacijenata. Prosečan histološki gradus tumora je bio 1.96, veću vrednost su imali muškarci, pacijenti sa tumorom na jeziku, veličine T2, tumori sa većom brzinom rasta i recidivirajuće neoplazme.

Rani stadijumi SCC jezika i poda usta se javljaju uglavnom kod muškaraca koji konzumiraju duvan i alkoholna pića i mlađi su od 60 godina. Postoji veza između patohistološkog nalaza (posebno načina invazije i stadijuma) i prognoze pacijenta

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