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Squamous cell carcinoma of the oral cavity: a follow up study of 85 cases and analysis of prognostic variables

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SUMMARY

We have studied clinical and morphological variables of 85 patients with squamous cell carcinoma of the oral cavity. After a follow up which varied between 2 months and 6 years, we carried out an analysis of the survival rate, and obtained significant differences ($p < 0.05$) for the Breslow and Mantel-Cox tests in relation to the clinical stage, size and presence of lymphadenopathy. Furthermore we have carried out a predictive-prognostic statistical analysis through a multiple regression study, from which we have concluded that the size of the lesion and the number of peritumoral eosinophils were the variables with prognostic significance with respect to the survival rate of the patients. Furthermore, once the variables in relation to the incidence of relapse were analyzed, we found that the size, the presence of lymphadenopathy, the number of peritumoral eosinophils and the number of mitoses were those variables considered to be of the greatest prognostic value.

KEY WORDS:

Oral cancer, squamous cell carcinoma, pathology.

RÉSUMÉ

Nous avons étudié les caractères cliniques et morphologiques de 85 cas de carcinome épidermoide de la cavité orale. Après un suivi de 2 mois à 6 ans, nous avons réalisé une analyse du taux de survie. Nous avons constaté des différences significatives ($p < 0,05$) concernant les tests de Breslow et Mantel Cox, en relation avec le stade clinique, la taille de la tumeur et l'existence d'adénopathies.
Ensuite nous avons effectué une analyse statistique à l'aide d'une étude de régression multiple, qui nous a permis de conclure que la taille de la lésion et le nombre d'oesinophiles péritumoraux sont des variables dont le pronostic significatif est en rapport avec le pourcentage de survie des patients.

Une fois analysées les variables en relation avec les incidences de rechute, nous avons observé que la taille de la tumeur, l'existence d'adénopathies et le nombre de mitoses sont les variables de plus grande valeur pour le pronostique.

MOTS CLEFS:

Cancer oral, carcinome épidermoïde, pathologie.

INTRODUCTION

Squamous cell carcinoma is the most common cancer found in the oral cavity, representing approximately 90% of all malignant tumours in this location (Cann et al., 1985). The survival rate of the patients with this neoplasm is not very high, with percentages in the order of 50% in a post-treatment period of 5 years (Conte et al., 1989), with this rate being even lower when there is invasion of the lymph nodes. The fact that many patients sought treatment when the disease was well-advanced, and moreover, the high percentage of relapse or lymphatic metastases implies that the patient prognosis is very uncertain.

This rather high mortality rate has several researchers to undertake investigations to determine if there is any parameter which may serve to establish a prognosis (Will & Nathanson, 1973; Crissman et al., 1984; Shingaki et al., 1988; Ildstad et al., 1989).

The classification of the tumours according to the clinical stage has proven to be related to the patient survival rate (Ildstad et al., 1989), this being higher in the initial stages than in the advanced stages. Furthermore, recent studies have investigated the possibility that certain morphological characteristics of carcinoma can in some way be involved in the prognosis of the patient (Willén & Nathanson, 1973; Shingaki et al., 1988).

Hence, in this present study we have analyzed a group of squamous cell carcinomas to determine if there were any clinical or histopathological characteristic that, due to their relation to the survival rate could be considered useful in establishing the prognosis of the patient. Another objective was to investigate if any of the variables influenced the incidence of relapse.

MATERIAL AND METHODS

In the Oral Medicine Department of the Faculty of Medicine and Odontology in Valencia, 85 patients with squamous cell carcinoma of the oral cavity were studied; 48 cases had been referred by other centres for diagnosis, investigation and treatment and 37 came from I.V.O. (Valencian Cancer Institue). Sixty-nine were male and 16 female, with ages between 33 and 85 years. With the exception of two patients who had no treatment, all patients were treated by standard surgical procedures (with or without neck dissection) and radiotherapy.

We carried out a clinical history in which the following data were collected: age, sex, possible aetiological factors (tobacco, alcohol), follow-up period, localization, size of tumour, clinical appearance, the presence of lymphadenopathy, general state (according to Karnofsky's index) (Karnofsky et al., 1948), and clinical stage (according to TNM classification) (U.I.C.C., 1978).

We examined some morphological characteristics such as the structural growth pattern, keratinization, the number of mitoses, and the number of intra and peritumoral eosinophils (Table 1).

Table 1
Morphological characteristics in 85 cases of S.C.C.
Caractéristiques morphologiques de 85 cas de carcinome épidermoide.

Structural growth pattern

1. Solid (the neoplastic cells are grouped forming masses or solids).
2. Cord-like (the cells are distributed in bands or cords).
3. Small groups (a number of neoplastic cell elements form small groups).
4. Dissociated (the cells are arranged in a diffuse or disperse manner).

Keratinization

1. Maximum (3 or more keratin pearls/field at 4×, or 7 or more dyskeratotic cells/field at 10×).
2. Moderate (2 keratin pearls/field at 4×, or 5-7 dyskeratotic cells/field at 10×).
3. Minimum (1 keratin pearl/field at 4×, or 3-5 dyskeratotic cells/field at 10×).
4. Absent (no keratin pearl/field at 4×, or <3 dyskeratotic cells/field at 10×).

Mitoses

1. 0-1 mitoses/8 fields
2. 1-3 mitoses/8 fields
3. 3-5 mitoses/8 fields
4. >5 mitoses/8 fields

Intratumoral Eosinophils: a recount of their number in 5 fields at 40×.

Peritumoral Eosinophils: a recount of their number in 5 fields at 40×.

We determined the time which had elapsed from the diagnosis until the last time the patient was seen or died. Furthermore we noted if there had been any relapse and the date it occurred.

Through analysis programmes of survival rates we developed the Kaplan-Meier survival curves, and with the Cox multiple regression curve of the BMDP statistical package, we investigated if there was any prognostic variable in relation to survival and tumoural relapse. The programme 2L of the BMDP package analyzes survival data for which the time-to-response is influenced by other measured variables. The goal of this analysis is to quantify the relationship between survival and a set of explanatory variables (often called covariables or prognostic factors). Through a stepwise selection option a subset of variables related to survival are selected, and it is assumed that the death rates may be modelled as log-linear functions of the covariates.

RESULTS

Analysis of survival

Fig. 1 shows survival as a function of the follow up in months. Of the 85 patients studied, 2 were eliminated due to lack of data. Of the 83 remaining cases, 47 died during the follow up period. The period of survival after diagnosis varied greatly (between 2 months and 6 years) (Table 2).

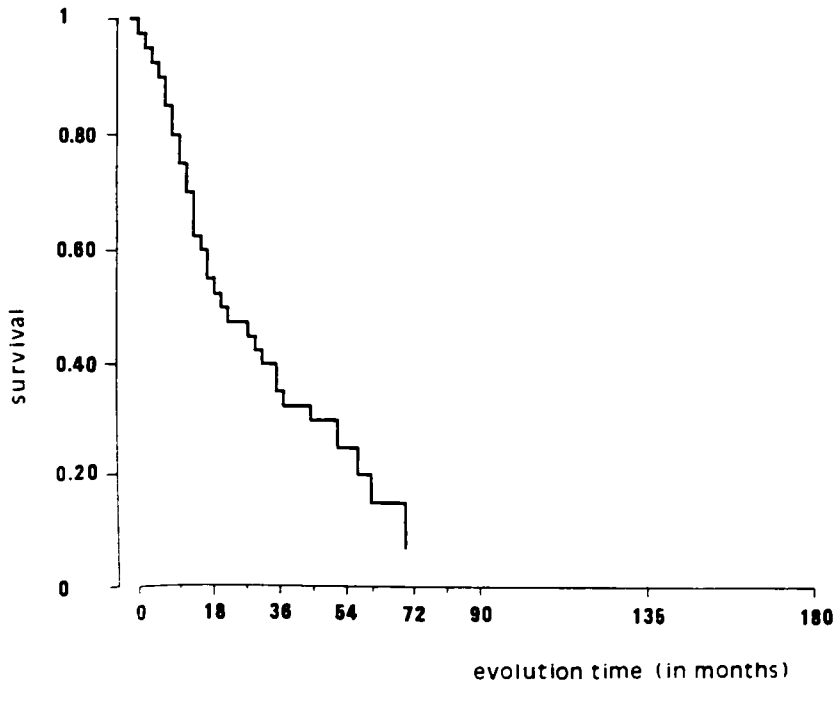

Fig. 1: Overall survival curve.
Courbe de survie générale.

Table 2
Number of patients dead or alive in relation to the years of follow up. Two cases were excluded, and seven cases died because of other diseases.
Nombre de patients décédés ou vivants en relation avec les années du suivi. 2 cas furent exclus, et 7 cas décidèrent d'autres affections.

Follow up	Alive	Dead	Total	% Alive
1 year	47	29	76	62
2 years	25	10	35	71
3 years	16	5	21	76
4 years	9	2	11	82
5 years	3	1	4	75
6 or more	3	0	3	100

Cumulative survival was 73% in the first year, 48% in the second and 36% in the third (Table 3). Fig. 2 shows the different survival curves for each clinical stage. Of the 23 patients in stage I, 7 died (31%); of the 20 patients in stage II, 11 died (55%); 16 died in stage III (64%); and 13 died in stage IV (87%).

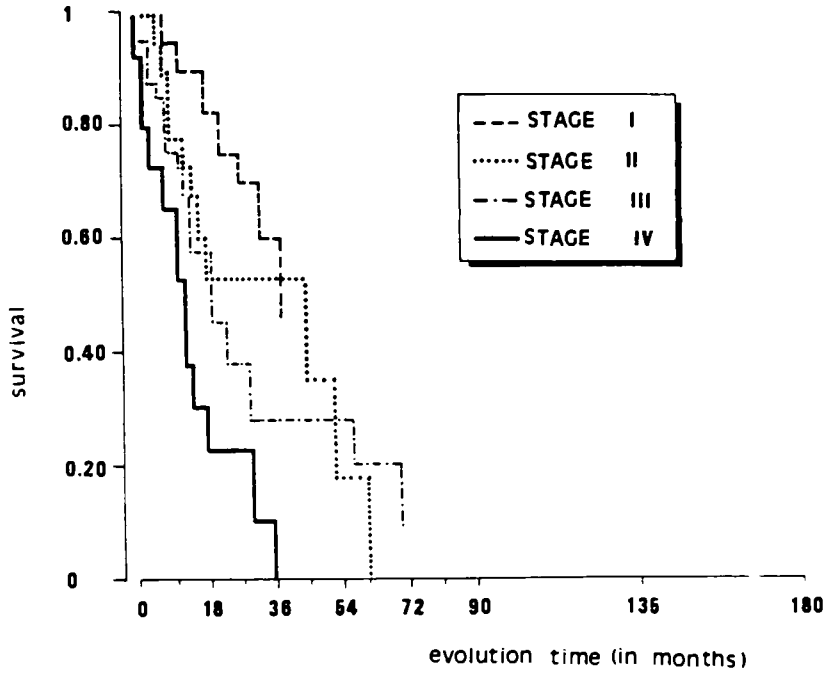

Fig. 2: Survival according to the patient's clinical stage.
Fig. 2: Survie en rapport avec le stade clinique.

Table 3
Cumulative survival rate per years elapsed.
Taux de survie cumulatif par nombre d'années écoulées.

1 year	73 %
2 years	48 %
3 years	36 %
4 years	30 %
5 years	15 %
6 years	7 %

By comparing the survival rate curves in Fig. 2, we can observe the different percentages of survival for any given moment. So at 18 months, in stage I, this percentage was 83%, in stage II, it was 53%, in stage III, 50%, and in stage IV, 22%. The Breslow and Mantel-Cox tests were significant with a value of $p = 0.0015$ and 0.0008 respectively, indicating significant differences in survival rate between the different clinical stages.

By comparing the stages in pairs we observed that between I and III, I and IV, and II and IV the differences were significant ($p < 0.05$ for Breslow and Mantel-Cox tests); while III and IV, and I and II were significant although to a lesser degree ($p < 0.05$). Contrary to this, the differences between stages II and III were not significant ($p > 0.5$).

Analysis of survival rates according to the size of the lesion (Fig. 3) showed big differences between small sized neoplasms of less than 2 cm. (T1), those between 2 and 4 cm. (T2) and the large ones of over 4 cm (T3), with very significant values for the Breslow and the Mantel-Cox ($p = 0.00001$). The percentage of survivors at 18 months was 84% among T1 tumours, 53% among T2 and 26% among T3, with the total percentage of mortality at the end of the study being 30% for T1, 65% for T2 and 88% for T3.

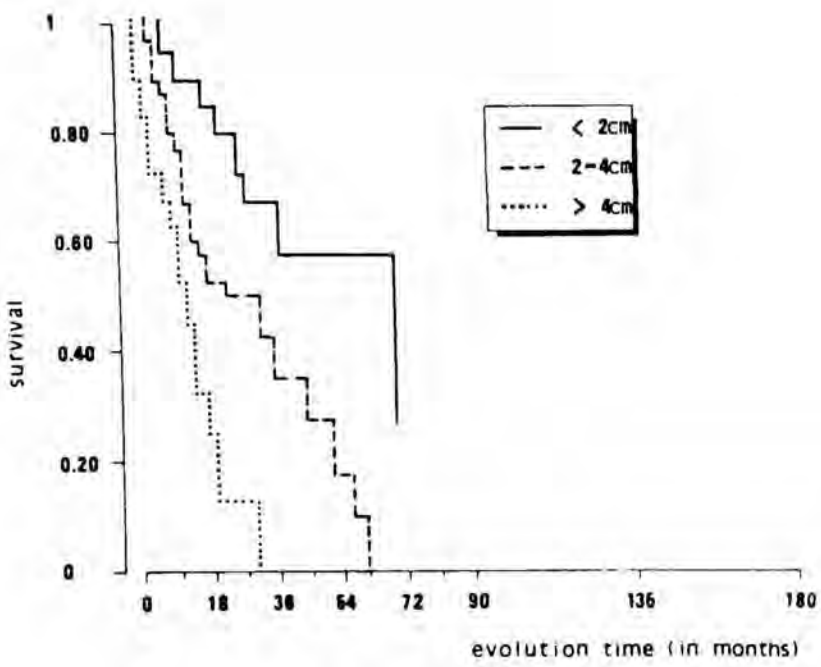

Fig. 3: Survival according to size of lesion.
Fig. 3: Survie en rapport avec la taille de la tumeur.

The survival rate curves in Fig. 4 were produced by grouping together patients according to whether or not palpable nodes were present at the time of baseline data colleciton. We classified the patients into two categories; NOA (non palpable nodes), SIA (palpable lymphadenopathy present) (in this category both fixed and moveable, small and large ones were included), always keeping in mind that the palpability of a node did not necessarily signify that there was neoplastic invasion, since it could have been an inflammatory or reactive lymphadenopathy. Analyzed globally (Fig. 4) we observed that at 18 months, 70% of the patients without palpable lymphadenopathies survived, compared with only 40% of those that had palpable lymphadenopathies. The percentage of mortality at the end of the study was 45% for NOA's and 74% for SIA's. These differences were significant with a value of $p = 0.0056$ and 0.0212 for the Breslow and Mantel-Cox statistic tests, respectively.

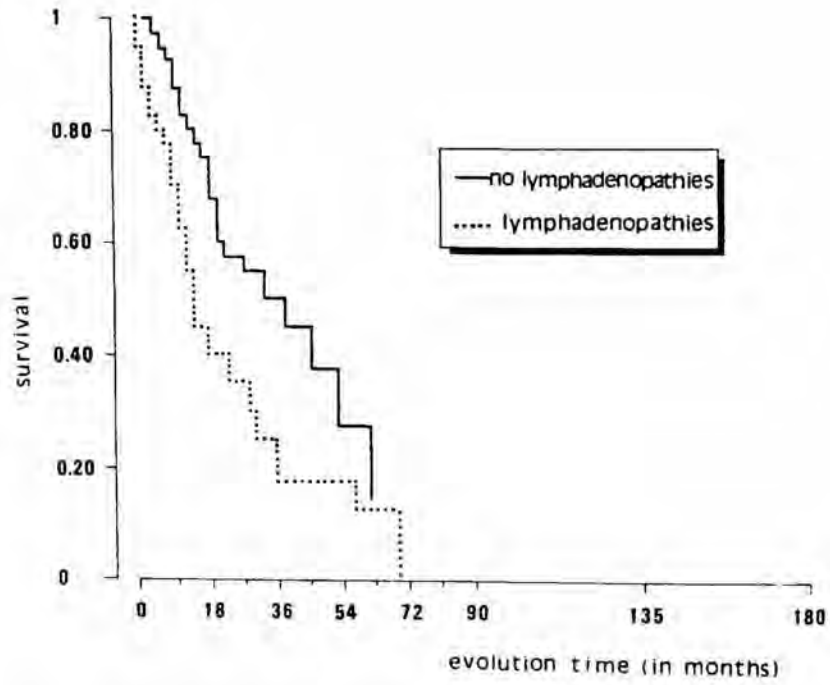

Fig. 4: Survival according to the presence or not of palpable nodes.
Fig. 4: Survie en rapport avec l'existence ou non de ganglions palpables.

We did not obtain significant differences when we analyzed survival rate in relation to age (we grouped the patients into two groups, those under 60 years of age, and those aged 60 and over), sex, and the different histological variables analyzed (structural growth pattern, keratinization, number of mitoses, intra- peritumoral eosinophils).

Regression Analysis: Study of prognostic variables

By applying programme 2L of the BMDP statistical package we have investigated the existence of some variable which could influence the survival of the patient and that could therefore be considered as a prognostic variable. Furthermore, we have carried out the same process in order to investigate the possibility that some variable could be related to the incidence of relapse.

Of the clinical and morphological variables (clinical stage, size, the presence of lymphadenopathy, structural pattern, keratinization, mitoses, intra and peritumoral eosinophils) with which we carried out the regression study, only the size and the number of peritumoral eosinophils presented significant values with $p < 0.05$.

By analyzing the same variables that we used to establish survival rates in those cases where relapse occurred (Table 4), with the aim of proving if any of them could be related to the last, we obtained the following results: global investigation of all cases showed that firstly size ($p = 0.00001$) and the presence of lymphadenopathy ($p = 0.0017$), followed in decreasing order by EOE (peritumoral eosinophils) ($p = 0.0047$), the number of mitoses ($p = 0.0068$), and the structural pattern ($p = 0.04$) were the variables considered to have the greatest prognostic value.

Table 4
Number of cases with repapse according to the years of follow-up.
Nombre de cas avec rechute en rapport avec le nombre d'années du suivi.

Relapse	Evolution time
28 cases	1 year
4 cases	2 years
2 cases	3 years
2 cases	4 years

DISCUSSION

There are numerous studies which have analysed the evolution and survival of patients with squamous cell carcinoma in different locations in the head and neck focusing on them from different points of view, either in relation to morphological parameters (Holm et al., 1982; Aneroth & Hansen, 1984), or clinical (Hibbert et al., 1983); in relation to survival and mortality; or in relation to the incidence of relapse or lymphatic metastases.

Hibbert et al. (1983) carried out an investigation aimed at determining the clinical factors that affected survival and did not observe significant differences between the clinical stages, except between stages III and IV. These authors did not detect significant differences in the survival of the different groups of patients in relation to size but did find significant differences according to nodal state; survival rates decreased from 65% among N0 to 0% among N3. According to Hibbert, the nodal stage would probably be the decisive factor influencing survival, while tumoral size would influence the presence of lymphatic metastases.

As far as lymphatic metastases are concerned, Kalnins et al. (1977), studied the survival rates of 340 patients in advanced stages followed up for a minimum of 5 years. The survival of patients with histologically negative nodes was 75%, while it was 29% for those with positive nodes. Histologically proven lymphatic metastases were revealed as a very important factor for the prognosis of patients.

In relation to tumoral size, Moore et al. (1986) found that in neoplasms under 2 cm, there was a correlation between size and prognosis, but in tumours larger than 2 cm, the size was not a predictive factor (there was no correlation). Brown et al. (1989) also found differences in the survival rates of patients with regards to size, with significance between T1 and T2, but not between T2 and T3.

In the multiple regression study we found that among the clinical variables, size had the highest predictive-prognostic value in relation to the overall survival rate and the development of relapses. It is interesting to note that we did not find that the clinical stage was a prognostic variable as might be expected. Hence for a given clinical stage, size provides us with additional information in relation to survival but for tumours of a particular size, the clinical stage did not influence the prognosis.

Ildstad et al. (1989) however, found that the clinical stage was the variable that exercised the greatest influence upon the suvival rate; nevertheless they did not include the parameters of size of tumour and the presence of lymphadenopathy in the statistical analysis, which could have possibly modified their results. When these parameters were exluded by us from the regression study, we found that the clinical stage was one of the variables selected as prognostic ($p < 0.05$).

We have found significant differences in our patients in relation to survival rates; these being 84% for T1 tumours, 53% for T2 and 26% for T3. Furthermore we found significant differences in relation to clinical stage and presence of palpable lymphadenopathies. We did not find any differences on comparing the survival rate with age, sex, and the morphological variables that were studied.

When we carried out the multiple regression analysis, we found that after size, the number of EOE (peritumoral eosinophils) was the second most important variable considered to be prognostic. Thus, the survival rate diminished with increasing size, while an increase in the number of peritumoral eosinophils corresponded with greater survival levels. The fact that we did not find any differences when we analyzed the patient survival curves, grouped according to the number of peritumoral eosinophils, was due to the fact that tumours of different dimensions were included in each group and these variations in size veiled the possible results. In the multiple regression study we analyzed the influence of EOE on the survival rate for a given size along with the other variables (that is for tumours of equivalent size), obtaining in this case significant values for this EOE variable.

Some controversy exists in relation to the influence of eosinophils, since some authors have found a relation between the number of them in the stroma and survival rate, while others writers deny it (Bostrom & Hart, 1981). Lowe and Fletcher (1984) studied 275 carcinomas of which 121 were located in the oral cavity, classifying the eosinophilia as moderate or severe according to the number of eosinophils in 10 fields (greater than 10 or greater than 100). Seven cases with severe eosinophilia and eight cases with mild eosinophilia demonstrated a higher survival rate in those patients with greater numbers of eosinophils.

Pastrñak and Jansa (1984) studied 93 oral carcinomas and analyzed the eosinophils and could not find a positive correlation between the number of these and the survival rate of the patient. Nor did Bostrom and Hart (1981) find that the presence of eosinophils bore any prognostic significance although 5 of the 6 patients with intense eosinophilia examined by them were alive after a follow up of more than 10 years.

It would appear that eosinophilia is site-related or is related to a particular tumour cell type, but the observation of eosinophilic infiltrate in the lymph nodes by Lowe 8 Fletcher (1984) excludes the pathogenetic importance of the site-specific reaction. Therefore it is possible that a particular pattern of squamous differentiation or dedifferentiation is linked in some way with a tissue eosinophil response. It was observed by Lowe & Fletcher (1984) that all the tumours with massive esosinophilic infiltrate were large cell, poorly keratinizing, moderately differentiated carcinomas. Then the process of dedifferentiation of squamous cells may be associated with the production or release of eosinophilotactic agents (Looi, 1987). Furthermore it is thought that the stromal eosinophilia may appear because the carcinoma cells produce eosinotactic and eosinopoietic factors (Wasserman et al., 1974; Slungaard et al., 1983) or from immunologic interactions of inflammatory lymphoid cells and mast cells with antigens of the cacinoma cells (Bostrom & Hart, 1981). And there is evidence that eosinophils may have cytotoxic properties (Looi, 1987).

With regards to the relationship between morphological variables and survival rate, Willén and Nathanson (1973) found that nuclear pleomorphism and the mode of invasion were the parameters that exercised the greatest influence; in our statistical study. We found that apart from size the presence of peritumoral eosinophils was the variable of prognostic significance.

Our results coincide in some respect with those of Crissman et al. (1984) since their conclusions showed that the morphological variable with prognostic significance was the pattern of invasion (with 4 grades: pushing borders, solid cords, thin irregular cords and single cells) that, as they stated, described comparable characteristics with regards to the tumoral structure. In considering the histological and clinical parameters, the variables selected as predictive by the programme, apart from invasion pattern, were size, nodal stage and sex. We however did not obtain significant results with respect to sex; this variable was processed with the rest of the variables in the regression study but was not selected as a prognostic variable.

As far as the relapse study is concerned, the results showed that relapse depends on size, the lymphadenopathies, the EOE, the number of mitoses and the structural pattern.

The separate study of clinical stages is of little value since the number of patients was low and the difference between the values of the variables was very small for which the variance was 0. As Aneroth and Hansen (1984) have stated, it would be necessary to have a larger number of patients in comparable

groups or stratified according to clinical stage and similarity of treatment in order to obtain more precise data.

In conclusion, our results agree with others in confirming that size is one of the significant prognostic variables for oral cancer, but they also suggest the possible significance of local eosinophilia.

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