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Squamous Cell Carcinoma of the Lips in a Northern Greek Population. Evaluation of Prognostic Factors on 5-year Survival Rate—I

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The purpose of this study was to determine the clinical features of squamous cell carcinoma (SCC) of the lips, along with its prognostic factors, in order to extend and update the information related to lip cancer in northern Greece and to provide a basis for international comparison. Records of 1510 patients with SCC of the oral cavity presented at the Theagenion Anticancer Institute of Thessaloniki, Greece from 1979 and 1989 were reviewed. The most common site for oral squamous cell carcinoma (OSCC) was found to be the lips (59.4%) as compared to 40.5% of intra-oral SCC. Males were affected more frequently, presenting a ratio of 9.2:1. The peak age of incidence was found to be the 6th decade for men and the 8th for women. Rural residents and outdoor workers were affected more than urban residents (79.9% versus 28.1%). Most of the patients were diagnosed in early categories and early clinical stages of the disease. Almost all (98.5%) were classified into T1 and T2 categories, and 92.9% into stages I and II. A total of 7.59% of patients presented with clinically-positive lymph-node involvement. Most of them were classified as an advanced stage of the disease.

Primary surgical excision was performed on 60.14%, radiotherapy on 35.14%, a combination of these on 2.47%, and chemotherapy alone or in combination with the above regimens in 2.22% of the cases. The outcome was adequate for surgery, radiotherapy, and the combination of the two, since 91.3, 74, and 90%, respectively, survived for more than 5 years.

An overall 5-year survival rate of 83.3% was found. Our findings showed that the survival rate was significantly influenced by the main prognostic factors, such as the size of the tumour, the lymph-node involvement, the clinical stage of the disease and the histologic differentiation.

SCC of the lips continues to be the most common site of oral cancer development amongst the Greek population. The aetiologic significance of actinic radiation for SCC of the lips is confirmed by our findings. The main prognostic factors proved to significantly influence the survival of our patients. Our results support the fundamental principal of head and neck cancer, i.e. that early detection of the primary tumour is the best prognostic factor for increasing survival rates. Therefore, public awareness concerning the disease, and better education for health care workers which will provide a thorough knowledge for the prognosis of oral cancer and the factors influencing it, is necessary.

Keywords: oral cancer, squamous cell carcinoma (SCC), lip cancer, prognostic factors, survival rates

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INTRODUCTION

ORAL CANCER is one of the 10 most common cancers in the world [1]. Epidemiological studies have shown that the incidence of oral cancer varies significantly between the continents and within developed and developing countries [1, 2]. In western countries, oral cancer accounts for 3–6%, whereas in some countries, such as Sri Lanka, India, Pakistan and Bangladesh, it is the most frequent form of cancer, and accounts for over 30% [1, 3–7]. Epidemiological studies have also shown that the sites of occurrence for oral cancer widely differ. In some studies the tongue is referred to as the most common site of cancer development [2, 4, 6], while in other studies, the lips are found to be the most common site [5, 8]. Similar studies performed in our country also show that the lips are the most common site of oral cancer development [9–11] with the exception of one study in which the most common site is the tongue [12].

Although in the last 30 years advances have been achieved in oral cancer treatment regimens [13], it is discouraging that

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about half of all oral cancer patients die due to their disease [14–16]. An exception to this pessimistic situation is lip cancer. Studies show that 5-year survival rates range from 85 to 95% [17, 18]. Studies have also shown that the 5-year survival rate for oral cancer and the prognosis of lip cancer are influenced by several prognostic variables. Clinical (TNM) classification, staging, the site of the primary tumour, and the primary treatment regimens, are referred to as the main prognostic factors [16, 17, 19, 20]. The TNM classification of oral cancer and the need for supplementary prognostic factors suggested by Bryne have been implied to be a severe shortcoming in the prognostic differentiation [21]. Thus, Bryne [21], in his extended review of recent literature, concludes that histological malignancy grading, tumour thickness, and DNA content have been shown to be of independent prognostic value. Also, cell features at the invasive tumour margins have been found to be of greater importance for prognostic evaluation than other parts of the tumour. In our country, similar studies have not been performed and therefore we were unaware of the above data.

The present study has been conducted in an attempt to determine some features of lip cancer (site of occurrence, sex, age and stage of the disease) and particularly to evaluate the degree of influence of some of the clinico-pathological factors (TNM classification, staging of the disease, histological differentiation of the lesion) and treatment used on the 5-year survival rates.

MATERIALS AND METHODS

The materials used for this survey originated from the files of the Theagenion Anticancer Institute of Thessaloniki, Greece. This anticancer institute is one of the better known institutes in Greece in which most cancer patients were and continue to be admitted.

We found that over the 10-year period from 1 January 1979 to 1 January 1989, 1510 patients with oral cancer had been treated. The records of 897 patients presenting histologically-confirmed squamous cell carcinoma of the lips (SCCLs) were reviewed in detail. We only found adequate data for analysis in the records of 408 patients. The TNM classification and staging, along with the age, sex, place of residence, occupation, location site of the primary tumour, degree of histological differentiation and primary treatment regimens used were tabulated. The N stages were grouped into clinically-positive and clinically-negative neck node(s) only. The analysis was carried out using the stat graphics program for PC. Z tests were used for statistical analysis of association residence on SCCL development and the influence of the primary treatment regimens used, lymph-node involvement (N) and histological differentiation on the 5-year survival rate. Linear regression was used for the statistical analysis of the association size (T) and the TNM stage had on the 5-year survival rate. The results would be considered statistically significant if the P value was less than 0.05. Information about the survival period of patients who had died was collected from the official registry of deaths.

RESULTS

Evaluation of the data from this study revealed a dramatic predominance of SCC of the lips compared to intra-oral cancer (59.4% versus 40.59%) because the findings showed that in more than half of the patients (59%), the oral cancer was located on the lips (Fig. 1).

From the 897 patients' records, the only evaluative finding was the site location of the tumour. Eight hundred and thirty-two lesions (93%) were located on the lower lip and 65 (7%) on the upper lip (Fig. 1). Of the 408 patients in which we found complete data for evaluation, the male:female ratio was 9.2:1 (368:40), whereas for SCC of the upper lip a slight predominance was observed in females (M:F = 1:1.4 (5:7) (Table 1).

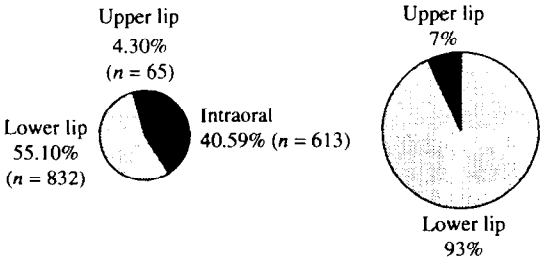

Fig. 1. Oral squamous cell carcinoma registrations by site.

Table 1. *Age and sex distribution of patients with squamous cell carcinoma of the lips (SCCLs)*

	SCCLs				SCC of the lower lip				SCC of the upper lip			
Age	M	%	F	%	M	%	F	%	M	%	F	%
20–29	2	0.49		0.00	2	0.51		0.00		0.00		0.00
30–39	12	2.94		0.00	12	3.03		0.00		0.00		0.00
40–49	37	9.07	6	1.47	36	9.09	5	1.26	1	8.33	1	8.33
50–59	146	35.78	9	2.21	146	36.87	8	2.02		0.00	1	8.33
60–69	86	21.08	8	1.96	84	21.21	8	2.02	2	16.67		0.00
70–79	55	13.48	13	3.19	55	13.89	9	2.27		0.00	4	33.33
80–89	27	6.62	4	0.98	25	6.31	3	0.76	2	16.67	1	8.33
90–99	3	0.74		0.00	3	0.76		0.00		0.00		0.00
	368	90.20	40	9.80	363	91.67	33	8.33	5	41.67	7	58.33
	408				396				12			
M:F		9.2:1				11:1				1:1.4		

Mean age 64 years. Male mean age 61.6 years. Female mean age 78.2 years.

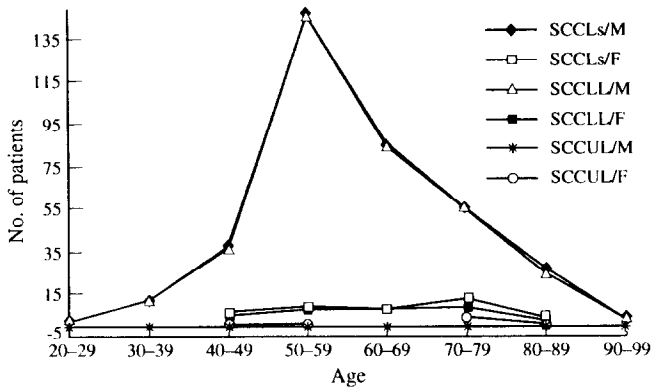

Fig. 2. Distribution of SCCLs patients by age, location and sex.

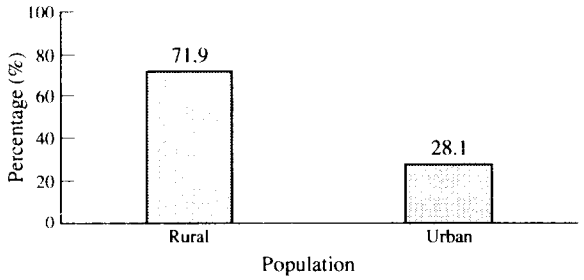

Fig. 3. Distribution of patients manifesting SCCL according to residence and occupations.

This finding showed a significant difference in the incidence of SCC of the lips between the sexes ($P<0.001$).

Table 1 also shows the age and sex distribution of patients with SCC of the lips and specifically the distribution between the lower and upper lip, and also percentage rates. Significant differences were observed between sexes concerning the age group with the highest incidence of SCCL. In the males an abrupt increase appeared before the highest incidence, reached in the 6th decade, followed by a gradual decline until the 9th decade, whereas in females a more gradual rise with advancing age was observed until a peak in the 8th decade (Fig. 2). Another noteworthy observation was the small number of patients presenting SCCL under the age of 40 years (14 male patients, 3.5%).

Figure 3 illustrates patient distribution according to their residence and occupation. A significant predominance of SCC occurrence of the lip is evident in rural populations (labourers, fisherman, woodcutters and shepherds) as compared to urban populations, as 293 out of 408 (71.9%) patients were rural residents versus 115 (28.1%) urban residents ($P<0.0001$).

According to the AJCC classification system 1988 [22], 330 out of 408 (80.90%) patients were classified as category T1, 72 (17.60%) as category T2 and 6 (1.50%) as category T3 (Table 2). These figures showed that almost all (98.50%) patients with SCC of the lips were diagnosed in the early stages. Table 2 also shows that lymph-node involvement was clinically proven in 31 (7.59%) patients. It was found that lymph-node involvement was influenced dramatically by the stage of the disease. Thus, we found that the rate of lymph-node involvement in the T1 category was only 2.72% (9 out of 330 patients), whereas it was 25.00% and 66.70% in categories T2 and T3, respectively ($P<0.001$).

Since tumour size (T), lymph-node involvement (N) and metastases (M) are the main prognotic factors, the AJCC defined the tumour stages I–IV where the T, N and M categories are combined. In this study we found that 321 patients belonged to stage I, 54 to stage II, 15 to stage III and 6 to stage IV (Table 2). This finding further confirmed the possibility of the early diagnosis of lip cancer.

The patho-histological patient records revealed that SCC of the lips was well differentiated in 262 out of 408 patients (64.21%), moderately differentiated in 118 patients (28.90%) and poorly differentiated in only 28 patients (6.90%) (Fig. 4).

The 5-year survival rate assessment was performed only for patients whose data was completely available for evaluation at the time of the study. Table 3 demonstrates patients' 5-year survival rate in relation to size (T), lymph-node involvement (N) and to the stage (TNM) of the disease. The overall 5-year survival rate was found to be 83.3% (340 out of 408 patients were still alive after 5 years). Taking into account the tumour size (T) as the prognostic factor, a 5-year survival rate of 89.70% was found for category T1 and 59.70% and 16.60% for categories T2 and T3, respectively (Fig. 5). Evaluating stages I–IV as prognostic factors, a very high 5-year survival rate (91.90%) for patients of stage I was found. For stages II, III and IV the 5-year survival rate was 68.51%, 40.00% and 11.20%, respectively (Fig. 6). Finally, in patients presenting lymph-node involvement, a 5-year survival rate of 19.4% was found. However, in patients without lymph nodes, clinical findings showed a 5-year survival rate of 88.6% (Fig. 7). These observations demonstrated that all factors of clinical TNM

Table 2. Patient distribution according to tumour size (T), lymph-node involvement and TNM stage

	Size: T		Lymph-node involvement in relation to size of the tumour						
			No		N+				
	%	*n*	%	*n*	%	*n*	TNM Stage	%	*n*
T1	80.90	330	97.20	321	2.72	9	I (T1NoMo)	78.67	321
T2	17.60	72	75.00	54	25.00	18	II (T2NoMo)	13.23	54
T3	1.50	6	33.30	2	66.66	4	III (T3NoMo) (T1-3N1Mo)	3.67	15
							IV (T4NoMo) (AnyTN2-3Mo) (AnyTAnyNM1)	4.41	18

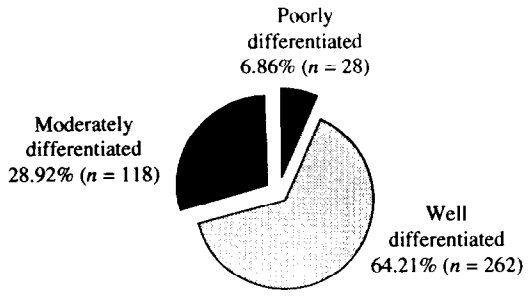

Fig. 4. Distribution of patients by histological grading.

classification and staging of SCCLs significantly influenced the 5-year survival rate ($P<0.001$). As the primary tumour size increased, on the one hand, the possibility of lymph-node involvement increased, and on the other hand, the 5-year survival rate decreased. In addition, the advanced stages of the disease were accompanied by a decline in the 5-year survival rate.

Figure 8 shows that the 5-year survival rate is significantly ($P<0.001$) influenced by the grade of histological differentiation of the primary tumour. Therefore, we found that 91.6% of patients presenting well-differentiated tumours survived for more than 5 years. For those with moderate- and poorly-differentiated tumours, the survival percentage beyond 5 years was 75.4% and 39.3%, respectively.

A special interest was also taken in the results of the applied forms of initial treatment regimens. Figure 9 shows that surgical excision was applied as an initial treatment in 243 patients, radiotherapy in 142, the combination of the two in 10 patients and chemotherapy alone or in combination with the above in 9 patients. From this data, a preference for surgical excision is obvious, compared to other forms of treatment regimens.

In addition, the outcomes of applied treatment regimens are presented in Fig. 9. The efficacy of surgery alone and the combination of the latter with radiation was equal, since 91.35% and 90%, respectively, of the patients who underwent these treatment regimens remained alive for longer than the 5-year period. Radiotherapy alone produced less sufficient results. Those patients who were irradiated showed a 5-year survival rate of 73.9%. These findings show that there exists no significant difference in therapeutic results from the performance of the above treatment regimens ($P<0.02$). However, a statistically significant difference ($P=0.001$) was found between the therapeutic results from the application of surgery, radiotherapy or their combination, and from chemotherapy alone or the combination of the latter with one of the other treatment regimens. Thus, those patients who underwent this form of treatment showed a 5-year survival rate of 22.2%.

DISCUSSION

In the present study we found that squamous cell carcinoma of the lips (SCCLs) was the most common site, presenting a very high frequency of 59.40%. As mentioned previously, similar studies in Greece also showed that SCCL was the most common [9–11]. However, differences were observed concerning the frequency of appearance. For example, a study performed by Marmarinou-Nomikou in a similar anticancer institute (St. Sabbas in Athens) in a series of 1965 patients, found an 81.78% frequency of SCC of the lips [10]. Respectively, in a previous study [11], performed in the Oral Medicine Department of our university, SCC of the lips was also the most common site, but the frequency rate was lower (48.22%) compared to the previously mentioned studies. It should be pointed out though, that in a single study, tongue cancer was referred to as the most common site [12]. As the study in question consisted of a large number of patients, the observed predominance of SCCLs should be considered representative of the Greek population. Therefore, Greece ought to be classified among the countries showing a high frequency of SCCLs, along with Canada [23, 24], Israel [25], Finland [26], Hungary, Romania and regions of Italy and Spain [7, 24].

In our study, the occurrence of SCCLs is predominant, although in other reports the tongue and the floor of the mouth were the sites most frequently affected by oral cancer [19, 27–29]. The observed high frequency of SCC in this study confirms the significance and association of actinic radiation as an aetiologic factor. This issue may be particularly true for Greece, where continuous sunshine is a natural phenomenon. Furthermore, the implication of actinic radiation with SCCLs is also confirmed by the fact that a high percentage of the patients in this study (79.1%), as well as in the previous one [11] (88.4%), are rural residents and/or outdoor workers. However, Spitzer *et al.* [30] and Szpak *et al.* [31] fail to support the implication of actinic radiation as a primary aetiologic factor in the incidence of SCCLs.

In the present study, the observed downward trend of SCCL occurrence is in accordance with most reports on the decline of SCCL in many white populations [6, 19, 29]. Silverman [19] attributes this reduction to public awareness about the dangers of sunlight exposure and to the use of lip protective agents. Also, Hindle and Nally [29] suggest that the decrease in pipe smoking and decreases in the number of

Table 3. Five-year survival rate in relation to the size (T) of the tumour, clinical lymph-node findings and TNM stage

Size (T)			Lymph-node involvement			Stage (TNM)		
T	%	*n*	N	%	*n*	Stage	%	*n*
T1	89.70	296/330	No	88.60	334/377	I	91.90	295/321
T2	59.70	43/72	N+	19.40	6/31	II	68.51	37/54
T3	16.60	1/6				III	40.00	6/15
T4						IV	11.20	

Overall 5-year survival rate ($n=340/408$).

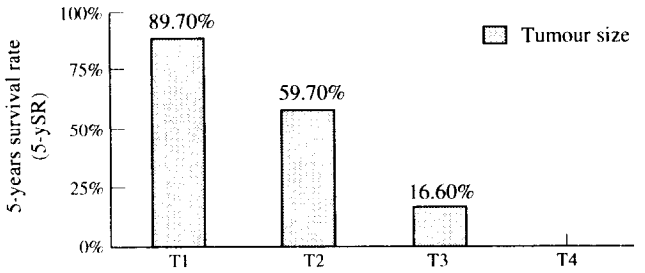

Fig. 5. Correlation of tumour size (T) and 5-year survival rate.

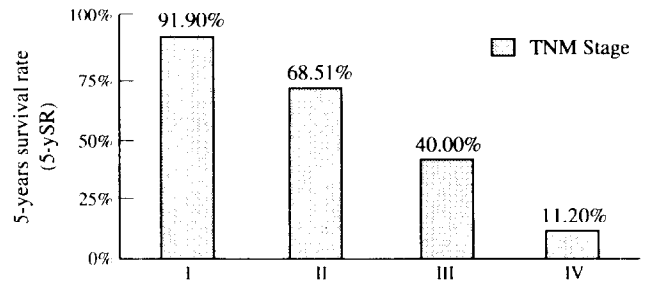

Fig. 6. Correlation of TNM Stage and 5-year survival rate.

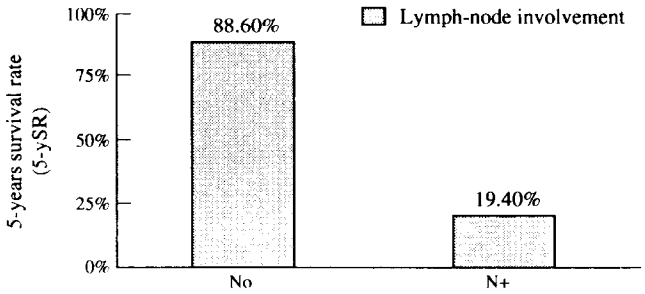

Fig. 7. Correlation of lymph-node involvement and 5-year survival rate.

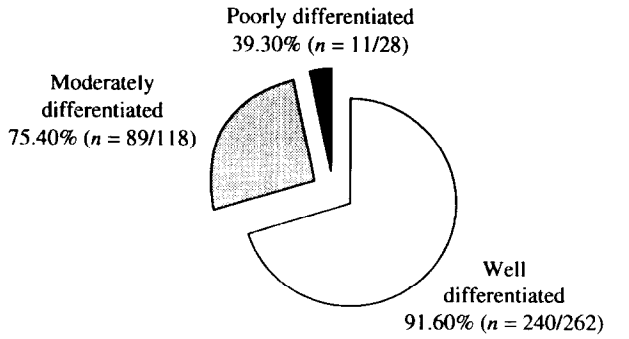

Fig. 8. Correlation of histological grading and 5-year survival rate.

outdoor workers and fishing fleets during the last 3–4 decades account for the decrease of SCCLs. Indeed, the same decrease in the number of outdoor workers has also been observed in Greece since the 1960s, due to a massive migration of the population from rural to urban areas.

In this study, the male to female ratio is 9.2:1 for both lips, whereas it was 11:1 for the squamous cell carcinoma of the lower lip (SCCLL). This observed higher ratio in men is in agreement with that reported by Hindle and Nally [29] and Jovanovich *et al.* [2] (8.3:1 and 7.8:1, respectively). This high male:female ratio could be attributed to the fact that in Greece most outdoor workers have been, and continue to be, men. Furthermore, this finding might demonstrate the aetiologic association of actinic radiation in combination with other climatic factors, such as dust, wind, low air humidity, and smoking and alcohol consumption.

The mean age of all patients in the present study was 64 years, a figure similar to other reports [1, 29, 32]. It is interesting, however, that females, in accordance with other reports [29, 33], appear to develop SCCLs, on average, 11.2 years older than men. Furthermore, SCCLs are found to be very rare under the age of 40, and are encountered exclusively in men, which is in accordance with our previous study [11]. This finding enhances the view that SCCLs may be an age- or a time-dependent process [34]. Rich and Radden [32] suggest that the greater longevity of females should be considered as a factor for the later development of oral cancer in females, whereas Jovanovich *et al.* [2] attributes the phenomenon to the later exposure of women to carcinogens, such as social habits and other unknown factors. These suggestions do not seem to hold true for the Greek population, since Greek women began to smoke and abuse alcohol only a few years ago, and Greek men may have been heavy smokers but they did not smoke a pipe nor did they abuse alcohol. Greater female longevity should not be considered such an important factor, for the life span differs by only 2–3 years in males and females. However, we might suggest that SCCL develops later in females because of later exposure to sunlight due to the fact that most female labourers at a young age (<40 years) covered their faces during their outdoor work, whereas males did not protect themselves from sun exposure. This suggestion is confirmed from the high frequency of SCCL observed in the 6th decade in men and in the 8th in women, respectively, and this is in accordance with other reports in the literature [2, 5, 17]. Unfortunately, we cannot speculate about the observed abrupt increase in the high frequency of SCCL in males compared to the gradual rise in females until the 8th decade.

Regarding the size of the lesions, at presentation we found that approximately all (98.5%) were diagnosed in early categories. A relatively high percentage of early diagnosed (T1 and T2) SCCL patients is reported in the literature and is explained by the fact that lesions of the lips are easily detected due to their visibility and the patients' trend to seek medical advice soon after noticing the symptoms [32].

A significant association has been found between the clinically palpable lymph node and tumour size. The clinically-positive lymph nodes exhibit a statistically significant association with increasing tumour size ($P<0.001$). A similar positive correlation has been reported in the literature by several authors [2, 35–38]. However, Hosal and his colleagues [18] have not found a close relationship between the tumour size and lymph-node metastasis. However, despite that, they have also found a low incidence of lymph-node metastases.

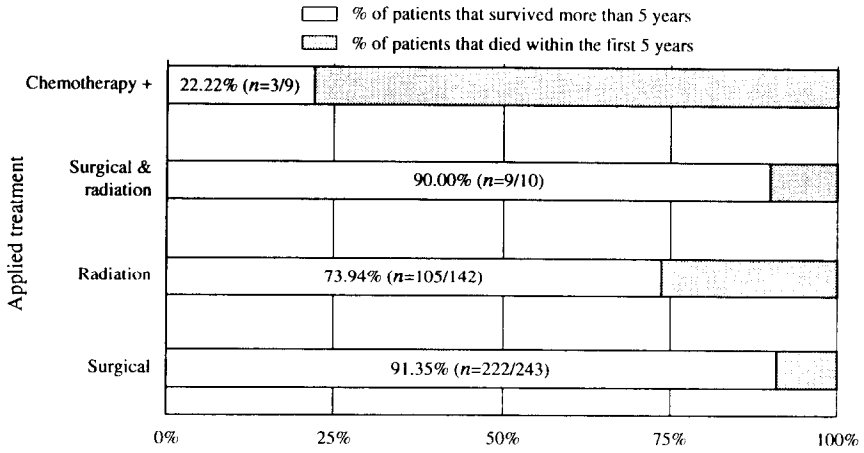

Fig. 9. Forms of treatment and the influence on the 5-year survival rate.

Since the stage of the disease is defined as the combination of TNM categories, it was expected that most of the patients were classified in the early stage of the disease. Percentages of 91.9% and 78.67% were classified in stages I and II, respectively, and only 3.67% in stage III.

As mentioned previously, the main purpose of this study was to evaluate the prognostic significance of some of the clinico-pathological factors on the 5-year survival rate. Unfortunately, in our prognostic assessment, we were restricted to the analysis of clinical TNM classification and staging and the differentiation grade of the tumours. However, this should not be considered a minus, since these are the prognostic factors mainly used by clinicians even though other factors have recently been mentioned to be of independent prognostic value [19, 21, 22].

In our series of patients, an overall 5-year survival rate of 83.3% was found. This is in accordance with the findings of several other authors and is considered to be the result of the early detection of lip cancer [17, 18, 35]. It should be noted that Hemprich and Muller [14] reported a percentage of 69.4%, whereas a higher percentage of 5-year survival rate was reported by MacKay and Sellers [39].

In agreement with other reports in the literature [17, 18, 35, 37, 40], we found that the size of the tumour is a significant prognostic factor ($P<0.001$), since the 5-year survival rate decreases as the size of the tumour increases. The percentages of survival rates were 81.7, 59.7, and 16.6%, respectively, for T1, T2, and T3 categories. The stage of the disease was also found to be a significant prognostic factor ($P<0.001$). According to the ASCC staging, the 5-year survival rate was 91.9% for stage I, 68.51% for stage II, 40.8% for stage III, and 11.2% for stage IV. None of the patients of stage IV survived for more than 3 years. Similar figures were found by Hemprich and Muller [14].

Our findings also revealed that the presence of clinically-positive lymph-node involvement substantially lowers the chances of survival. Thus, a statistically significant difference concerning the 5-year survival rate of patients with or without lymph-node involvement (88.6% versus 19.4%) was observed ($P<0.001$). This finding is in partial agreement with other reports in the literature in which higher percentages of 5-year survival rate were mentioned [39, 41, 42].

The importance of the differentiation grade in determining the prognosis for squamous cell carcinoma was introduced by Broders in his study of SCC of the lips [43, 44]. Subsequent studies that included grade evaluation showed that prognosis for patients with SCCLs varied according to that parameter [41, 45, 46]. The present study confirmed the prognostic value of the grade of histological differentiation, since 91.6% of the patients with well-differentiated lesions survived more than 5 years, compared to 39.3% of the patients with poorly-differentiated or anaplastic lesions ($P<0.001$).

Finally, evaluating the influence of the treatment regimens used on the 5-year survival rate in our series of patients, we found that surgery, radiotherapy, and the combination of the two showed favourable results of SCCLs (91.35, 73.94, and 90%, respectively, of patients surviving for more than 5 years). The effectiveness of chemotherapy conducted alone or in combination with surgery and radiotherapy, cannot be compared with the results stated above since it was used as a treatment regimen in patients of stage IV or in cases where other treatment regimens were shown to be ineffective.

Indeed, most of the authors have reported that the therapeutic outcomes of SCC of the lip are almost equivalent to surgery and radiotherapy or to the combination of both. Despite this, surgery is suggested as the method of choice for providing disease eradication, along with lip reconstruction in a single session, as well as information about margin status and histological grade of differentiation. In addition, the complications of radiotherapy are avoided by surgery and the case of local recurrence is best managed surgically [35, 37, 40, 47].

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