Prognostic factors for surgically resected squamous cell carcinoma of the lower oral cavity

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Aim. The objective of this study was to evaluate the impact of clinical variables on survival rates in patients with squamous cell carcinomas in the lower oral cavity.

Methods. We conducted a retrospective study of patients who exhibited a histological diagnosis of squamous cell carcinoma of the lower oral cavity, who underwent surgery. Data on clinical, histological, and treatment variables were collected to assess the effect of these variables on global survival and disease-free curves.

Results. We studied 117 patients, 86 (73.5%) males and 31 (26.5%) females, who underwent surgery between January 2005 and June 2009. The overall survival rate was 74.4% after two years, and the disease-free rate was 67.5%. Midline invasion by the primary tumor negatively impacted overall survival (P=0.02) and disease-free survival (P=0.01). The disease-free survival rate of patients with histologically confirmed neck metastases was 76.8% versus 59% for patients without metastases (P=0.01). Disease-free survival of patients with one affected lymph node was 89.5%, and 45.2% for more than one affected lymph node (P<0.01). Patients who ended radiotherapy in less than 60 days exhibited a disease-free rate of 59.0%, and patients whose treatment lasted more than 60 days exhibited a rate of 77.1% (P=0.06).

Conclusion. In our study, primary tumor invasion of the midline, the presence of more than one affected lymph node as confirmed by histology, the delaying radiotherapy for more than 56 days and radiotherapy that lasted longer than 60 days worsen patient prognosis.

KEY WORDS: Mouth neoplasms - Head and neck neoplasms - Squamous cell carcinoma - Prognosis.

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Oral cancer is the most common neoplasia in the upper aerodigestive tract, and squamous cell carcinomas (SCCs) account for more than 95% of these lesions.[1, 2]

Diagnostic and treatment techniques have evolved in recent decades, but patient survival rates have not significantly improved.[3]

Biomolecular markers are not routinely used despite our improved understanding, and the results of studies on the use of these markers remains controversial. Therefore, factors that are related to the patient, tumor, and treatment underlie treatment program decisions and prognoses.

This study evaluated the impact of clinical variables for patients, tumors, and treatment influence on survival rates in patients with squamous cell carcinomas in the lower oral cavity.

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Materials and methods

We conducted a retrospective study from the charts of patients who underwent surgery in the Head and Neck Surgery Group of the Alpha Institute of Gastroenterology at UFMG General Hospital from January 2005 to June 2009. Operations were performed at UFMG General Hospital and Baleia Hospital in Belo Horizonte and the Hospital São João de Deus in Divinópolis, Minas Gerais, Brazil. Patients who had not undergone previous treatment but exhibited a histological diagnosis of squamous cell carcinoma of the tongue, mouth floor, lower gums, retromolar space, or the buccal mucosa were included in the study. We use the following criteria for inclusion in the study:

— patients with squamous cell carcinomas in the lower oral cavity;

— lesions located on the lower oral cavity, in the following sub-sites: tongue, mouth floor, lower gums, retromolar space or the buccal mucosa;

— patients who had not undergone previous treatment;

— patients undergoing surgery with or without adjuvant treatment;

— patients with complete clinical description of the lesion and staging well described;

— presence of histological report with the information about the variables studied;

— adequate clinical follow-up.

The exclusion criteria were:

— other malignant neoplasms of mouth than squamous cell carcinoma;

— patients undergoing non-operative treatment;

— lesions located in other subsites of the mouth as hard palate, upper gum or lesions of lip;

— lost of clinical follow-up.

Preoperative staging followed the staging system of the American Joint Committee on Cancer 2010.[4]

Patients underwent primary tumor resection with or without cervical dissection sometimes followed by radiotherapy. Radiotherapy was indicated for advanced tumors (T3 or T4), the presence of neck metastases, or compromised resection boundaries.

Data on clinical, histological, and treatment variables were collected to assess the effect of these variables on global survival and disease-free curves. The following variables were analysed: sex, age, primary lesion location, midline invasion by the primary tumor, presence of neck metastases on pathological exam, time between the operation and beginning of radiotherapy, and duration of radiotherapy.

Categories for each variable are presented in Table I.

Overall survival and disease-free survival curves were constructed for the studied variables. Patients were monitored for at least two years from the date of the operation or until death. Patients in whom clinical follow-up was not possible were excluded.

Statistical analysis

Statistical analysis was performed using SPSS version 13.0. Kaplan-Meier curves were used for survival analysis. The log-rank test was used to compare Kaplan-Meier curves between different variables. A 5% level of significance was used. Results that fell between 5% and 10% were considered marginally significant.

Results

We studied 117 patients, 86 (73.5%) males and 31 (26.5%) females, who underwent surgery between January 2005 and

TABLE I.—*Analysed variables.*

Age	<50 years	50-60 years	>60 years		
Tumor location	Tongue	Floor	Lower gums	Retromolar space	Buccal mucosa
Number of metastases	Zero	One	More than one		
Time until radiotherapy was initiated	<56 days	>56 days			
Duration of Radiotherapy	<60 days	>60 days			

June 2009. Patient ages ranged from 34 to 90 years, with an average age of 57.4 years. One hundred (85.5%) patients were smokers, and 96 (82.1%) were alcoholics.

Clinical data for the lesions are presented in Tables II-VI. The surgeries are detailed in Tables VII, VIII.

A total of 156 neck dissections were performed, including 70 (61.9%) unilateral and 43 (38.1%) bilateral.

The types of dissections are presented in Table IX.

Adjuvant radiotherapy was performed in 91 (77.8%) of the 117 patients.

TABLE II.—*Primary tumor location*.

Location in lower mouth	Tongue	Mouth floor	Retromolar space	Lower gums	Buccal mucosa	Total
N.	44	43	17	10	3	117
%	37.6%	36.8%	14.5%	8.5%	2.6%	100%

TABLE III.—*T stages*.

	T1	T2	T3	T4	Total
N.	4	43	25	45	117
%	3.4%	36.8%	21.4%	38.5%	100%

TABLE IV.—*N stages*.

	N0	N1	N2a	N2b	N2c	N3	Total
N.	62	28	10	8	6	3	117
%	53%	23.9%	8.5%	6.8%	5.1%	2.6%	100%

TABLE V.—*Stages*.

	Stage I	Stage II	Stage III	Stage IV	Total
N.	4	20	27	56	117
%	3.4%	25.6%	23.1%	47.9%	100%

TABLE VI.—*Midline invasion*.

	Present	Absent	Total
N.	37	80	117
%	31.6%	68.4%	100%

TABLE VII.—*Type of operation*.

	Mouth floor resection and glossectomy	Glossectomy	Mouth floor resection	Mouth floor resection and mandibulecto-my of the retromolar space	Buccal mucosa resection	Total
N.	62	28	10	8	6	117
%	53%	23.9%	8.5%	6.8%	5.1%	100%

TABLE VIII.—*Necessity of mandibulectomy*.

	Yes	No	Total
N.	53	64	117
%	45.3%	54.7%	100%

TABLE IX.—*Type of neck dissection*.

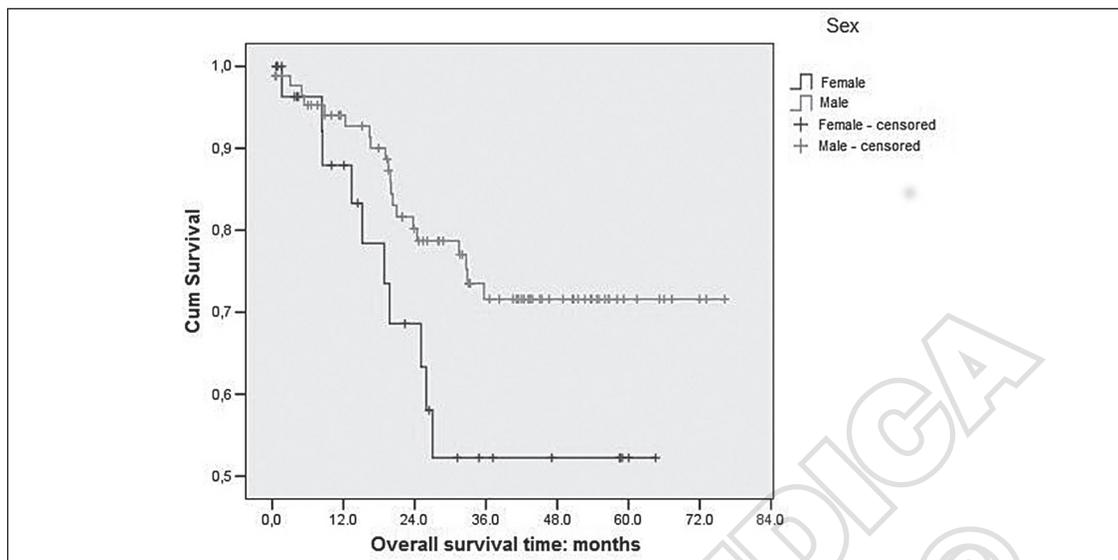|	I–III	I–IV	I–V	II–IV	Total
N.	60	17	72	7	156
%	38.4%	10.9%	46.1%	4.4%	100%

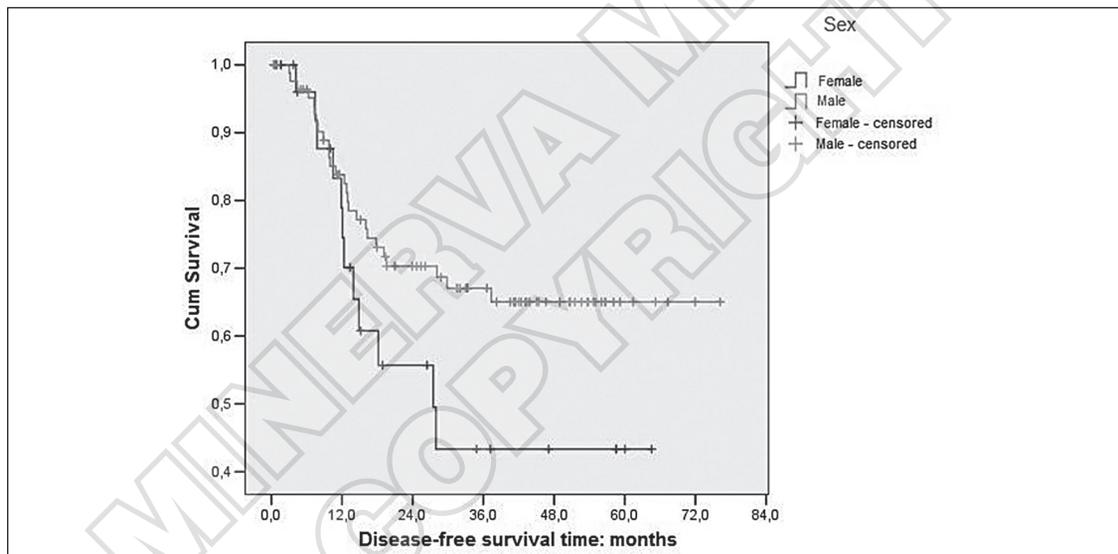Figure 1.—Overall disease survival curve by gender.

Figure 2.—Disease-free survival curve by gender.

The overall survival rate was 74.4% after two years, and the disease-free rate was 67.5%.

The overall survival rates for patients under 50 years of age, between 50 and 60 years of age, and over 60 years of age were 66.7%, 73.7% and 81.4% (P=0.71), respectively, and the disease-free rates were 58.3%, 68.4%, and 74.4% (P=0.67), respectively.

Overall survival was 76.7% in males and 67.7% in females (P=0.06). The disease-free survival rate was 69.8% for males and 61.3% for females (P=0.09).

The effect of gender on patient survival is illustrated in Figures 1 and 2.

The location of the primary lesion did not correlate with survival. The overall survival was 79.1% for mouth floor lesions, 72.7% for
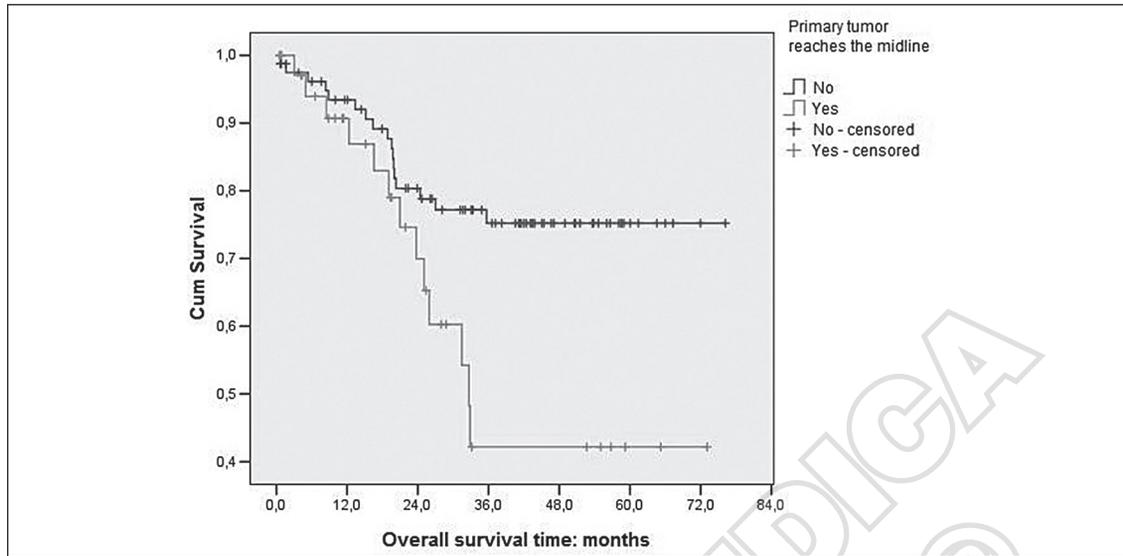
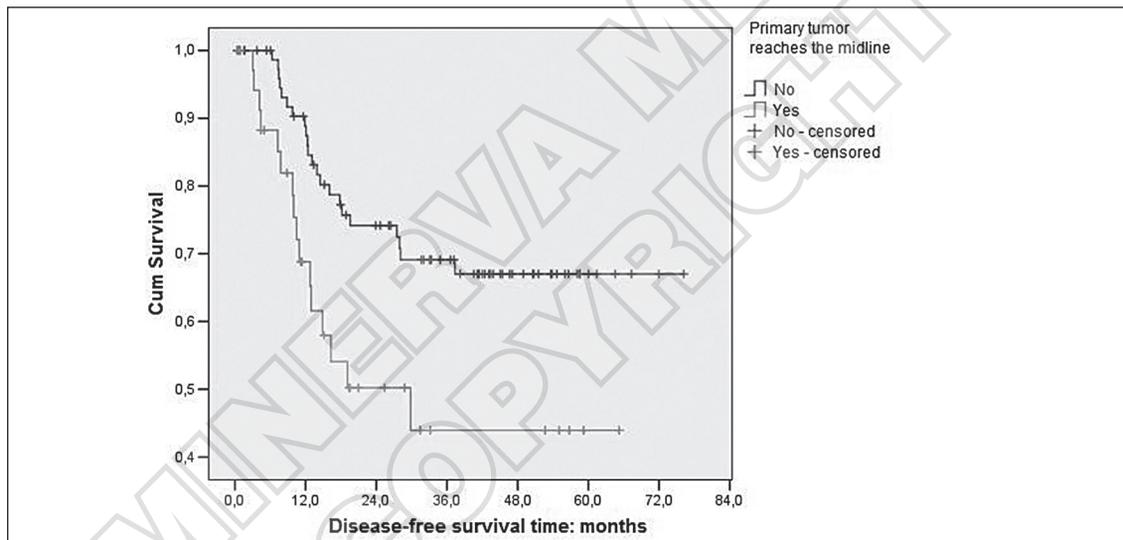Figure 3.—Overall survival curve and midline invasion.

Figure 4.—Disease-free survival curve and midline invasion.

tongue lesions, 70.6% for retromolar space lesions, 70% for lower gum lesions, and 66.7% for buccal mucosa lesions (P=0.90).

Disease-free survival was 65.1% for the mouth floor, 63.9% for the tongue, 70.6% for the retromolar space, 80% in the lower gums, and 100% in the buccal mucosa (P=0.78).

Midline invasion by the primary tumor negatively impacted patient survival. The overall survival of patients with midline invasion was 64.9% *versus* 78.8% for patients without invasion (P=0.02). Midline invasion also decreased the disease-free survival rate from 72.5% to 56.8% (P=0.01).

The effect of midline invasion on survival is illustrated in Figures 3 and 4.

The T stage and clinical stage of the lesion did not correlate with survival. The survival rates for T2, T3, and T4 lesions were 79.1%,

84%, and 64.4%, respectively (P=0.13), and the disease-free rates were 74.4%, 72%, and 60% (P=0.19), respectively. The overall survival rate after two years for stage II, III, and IV cancers were 83.3%, 74.1%, and 69.6%, respectively (P=0.30), and the respective disease-free rates were 80.0%, 66.7%, and 62.5% (P=0.19). Patients with stage I cancer were not included in the survival analysis as the total number of such patients was insufficient.

The overall survival rate of patients with histologically confirmed neck metastases was 78.6% *versus* 70.5% for patients without metastases (P=0.43). The disease-free survival rate in the absence of neck metastases was 76.8% *versus* 59% when present (P=0.01).

The effect of neck metastases on disease-free survival is presented in Figure 5.

Survival analysis of the three groups that were separated by the number of affected lymph nodes revealed that the overall survival rate of patients with zero, one, or more than one affected lymph node was 78.6%, 78.9%, and 66.7%, respectively (P=0.22). Disease-free survival of patients with no affected lymph nodes was 76.8%. Disease-free survival of patients with one affected lymph node was 89.5%, and the

rate for more than one affected lymph node was 45.2% (P<0.01).

The impact of the number of affected lymph nodes on disease-free survival is illustrated in Figure 6.

Analysis of radiotherapy initiation demonstrated that patients who initiated radiation more than 56 days after surgery experienced a two-year survival rate of 65.1%, and patients who received radiation before 56 days exhibited a survival rate of 81.3% (P=0.08). The disease-free rates were 62.8% and 71.9%, respectively (P=0.23).

Patients who ended radiotherapy in less than 60 days exhibited a survival rate of 71.4%, and patients whose treatment lasted more than 60 days exhibited a rate of 71.8% (P=0.76). The disease-free rates were 77.1% and 59%, respectively (P=0.06).

Discussion

The clinical progression of oral SCC patients depends on factors that are related to the patient, tumor and treatment. These factors remain the primary tools for the choice of treatment and the determination of the patient's prognosis.[3]

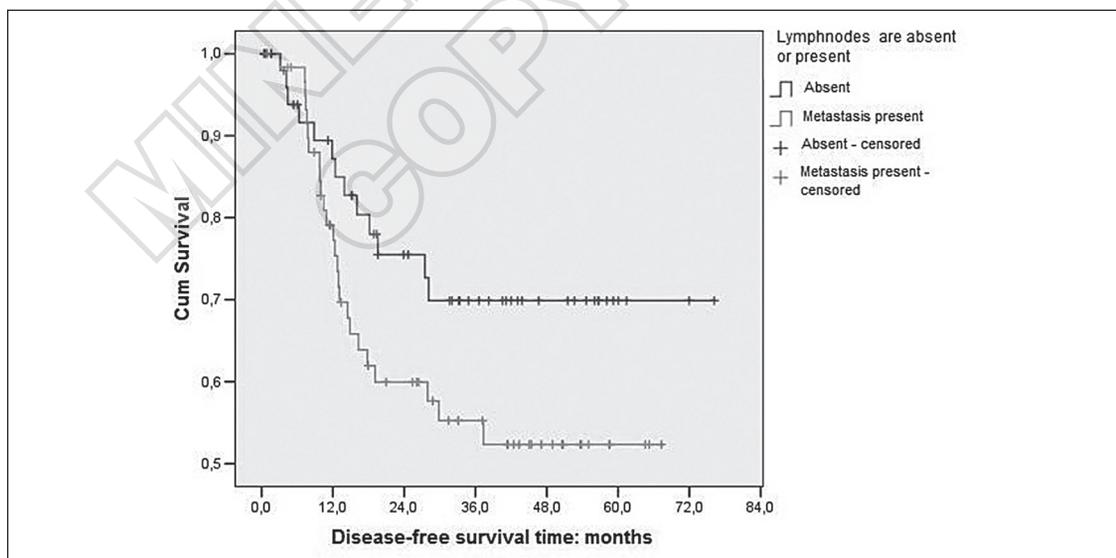The use of biomolecular markers to pre-

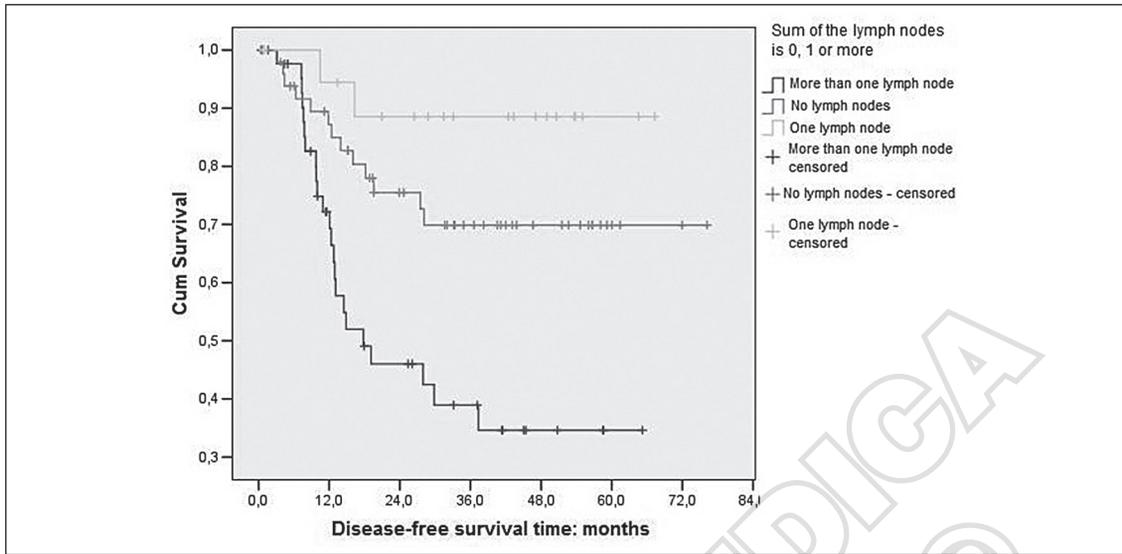Figure 5.—Disease-free survival curve and neck metastasis.

Figure 6.—Disease-free survival curve and number of affected lymph nodes.

dict malignant neoplasia behaviour and guide therapy has been investigated. However, concerns about the validity of these tested markers persist, and they are not regularly used in daily clinical practice.[2] Therefore, these markers do not affect treatment choice or accurately predict disease progression.

This study was performed in a developing country in which most SCC patients were diagnosed at an advanced clinical stage.

The overall survival rate during our follow-up period was 74.4%, and the disease-free survival rate was 67.5%. The average patient age was 57.4 years, which is slightly below the average age of 65 years in the literature.[3] The importance of age in prognosis is controversial. Several authors have demonstrated high remission rates in young patients, but other authors report no influence of age on prognosis, which corroborates our results.[3, 5, 6]

Male patients were overrepresented in our study, with a male: female ratio of 2.8:1, which is consistent with previous studies. No difference in the survival rate between sexes has been reported previously.[1, 3, 7] However, we observed marginally significant lower overall and disease-free survival rates in females. The analysis of midline invasion

rates between sexes revealed a marginally significantly higher rate in females. This result creates an overlap of midline invasion and female gender, which complicated the analysis of the influence of sex on survival.

Malignant tumors in various locations in the mouth exhibit different prognoses; tumors in the back of the mouth exhibit a worse prognosis.[3] However, this relationship is not clear because some studies include both mouth and throat lesions in survival curves analyses. We only evaluated lesions on the mouth floor, and patients with primary tumors on the lips, throat, and roof of the mouth were excluded. Lesion location exhibited no effect on survival in the present study.

TNM (Tumor, Node, Metastasis) staging is widely accepted as the primary tool for the determination of disease prognosis because patients with advanced disease exhibit worse prognoses.[6, 8] Patients in advanced stages exhibited worse prognoses than patients in the initial disease stages in our study. However, this difference was not statistically significant, perhaps due to the small number of patients in each subgroup as reported previously.[9]

The presence of neck metastases worsens patient prognosis.[8, 10] Here, 156 neck

dissections were performed; 70 (61.9%) dissections were unilateral, and 43 (38.1%) dissections were bilateral. Bilateral neck dissection was indicated when the primary lesion invaded the midline or extended to the base of the tongue, or when neck metastases contralateral to the primary legion were detected.

The presence of histologically confirmed neck metastases decreased the overall survival rate from 78.6% to 70.5% in the present study, which was not significant (P=0.43). The disease-free survival rate decreased from 76.8% to 59% in patients with and without metastases, respectively. This difference was marginally significant (P=0.09).

The disease-free survival rate was lower in the group with more than one affected lymph node, independent of the unilateral or bilateral nature, compared to the groups with zero lymph nodes affected and one lymph node affected (P<0.01). The presence of more than one affected lymph node is a risk factor for contralateral and distant metastases, which worsens patient prognosis.[9] Previous studies have also demonstrated that patients with metastases at various locations in the neck exhibit worse prognoses than patients with no metastases or a single metastasis.

Invasion of the midline by the primary tumor is not well studied. Midline invasion is a risk factor for contralateral metastases,[10] and the survival rates of patients with midline invasion of the tongue has been reported to decrease by one-half compared to patients who lack this prognostic factor.[11]

Our data demonstrated that invasion of the midline in the mouth reduced the overall survival from 78.8% to 64.9% (P=0.02) and increased the neoplasia recurrence rate from 56.8% to 72.5% (P=0.01) during the two-year follow-up period. These results demonstrate that this variable affected the prognosis of the studied population.

The best treatment for advanced oral cavity cancers is surgery and adjuvant radiotherapy. The treatment time and radiotherapy technique are also critical. The initiation of radiotherapy more than 56 days after surgery decreased the survival rate from 81.3% to 65.1% (P=0.08) in the studied population. Radiotherapy that lasted longer than 60 days decreased the disease-free survival rate from 77.1% to 59.0% (P=0.06). These marginally significant results demonstrate that delayed radiotherapy and an increase in treatment duration may worsen patient prognosis.

Conclusions

In assessing the population of patients with squamous cell carcinoma of lower oral cavity, without prior treatment, which were surgically treated at our institution, we can come to some conclusions. Based on what was considered statistically significant, we can say that primary tumor invasion of the midline or the delaying radiotherapy for more than 56 days lowered the overall survival. Additionally, a decrease in disease-free survival was correlated with invasion of the midline by the primary tumor, the presence of more than one affected lymph node as confirmed by histology, and more than 60 days of radiotherapy. We believe that greater monitoring of patients may further corroborate our findings and we can even find other clinical variables that will influence the prognosis of the patients.

Riassunto

Fattori prognostici per il carcinoma a cellule squamose della cavità orale inferiore resecato chirurgicamente

Obiettivo. Obiettivo del presente studio è stato quello di valutare l'impatto delle variabili cliniche sui tassi di sopravvivenza dei pazienti affetti da carcinomi a cellule squamose della cavità orale inferiore.

Metodi. Abbiamo condotto uno studio retrospettivo su pazienti con diagnosi istologica di carcinoma a cellule squamose della cavità orale inferiore, i quali sono stati sottoposti a chirurgia. I dati sulle variabili cliniche, istologiche e terapeutiche sono stati raccolti per valutare l'effetto di tali variabili sulle curve di sopravvivenza globale e sopravvivenza libera da malattia.

Risultati. Sono stati inclusi nello studio 117 pazienti, di cui 86 (73,5%) uomini e 31 (26,5%) donne,

i quali sono stati sottoposti a intervento chirurgico tra il gennaio 2005 e il giugno 2009. Dopo due anni, il tasso di sopravvivenza complessiva era del 74,4%, mentre il tasso di sopravvivenza libera da malattia era del 67,5%. L'invasione della linea mediana da parte del tumore primitivo ha influito negativamente sulla sopravvivenza complessiva (P=0,02) e sulla sopravvivenza libera da malattia (P=0,01). Il tasso di sopravvivenza libera da malattia nei pazienti con metastasi al collo confermate istologicamente e nei pazienti privi di metastasi era rispettivamente del 76,8% e del 59% (P=0,01). La sopravvivenza libera da malattia dei pazienti con un linfonodo interessato e dei pazienti con più di un linfonodo interessato era rispettivamente dell'89,5% e del 45,2% (P<0,01). I pazienti che hanno terminato la radioterapia in meno di 60 giorni hanno mostrato un tasso di sopravvivenza libera da malattia del 59%, mentre i pazienti il cui trattamento è durato più di 60 giorni hanno mostrato un tasso del 77,1% (P=0,06).

Conclusioni. Nel nostro studio, l'invasione della linea mediana da parte del tumore primitivo, la presenza confermata istologicamente di più di un linfonodo interessato, il rinvio della radioterapia per più di 56 giorni e una durata della radioterapia superiore ai 60 giorni sono fattori che hanno peggiorato la prognosi del paziente.

PAROLE CHIAVE: Cavo orale, neoplasie - Testa e collo, neoplasie - Carcinoma a cellule squamose - Prognosi.

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