Int J Clin Exp Pathol 2021;14(6):713-719
www.ijcep.com /ISSN:1936-2625/IJCEP0129665

Original Article

Survival analysis of recurrent squamous cell carcinoma of the lower oral cavity treated by surgery

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Received January 6, 2021; Accepted May 10, 2021; Epub June 15, 2021; Published June 30, 2021

Abstract: The aim of the present study was to investigate the survival of individuals with squamous cell carcinoma of the lower oral cavity who underwent surgical treatment and experienced recurrence, considering the site of the recurrent disease. A retrospective longitudinal study was conducted, comparing the survival rates of patients with and without recurrence and considering the site of recurrence (local, regional, distant). Statistical analysis was performed with SPSS and a *p*-value ≤ 0.05 was considered significant. The sample comprised 150 patients, 59 (39.3%) of whom experienced recurrence. Local recurrence occurred in 35 patients (23.4%), regional recurrence in 17 (11.3%), and distant recurrence in seven (4.6%). The average survival of participants with local, regional, and distant recurrence was 12, five, and two months, respectively. Patients with recurrent disease had worse survival than those who did not (P < 0.001). Patients with local recurrence had better survival than those with regional/distant recurrence (P = 0.011). All patients with regional and distant recurrence had deceased by the last follow-up. In conclusion, patients with local recurrence of squamous cell carcinoma of the lower oral cavity treated by surgery have a better survival rate than those with regional and distant recurrence. Local recurrence poses the possibility of curative salvage therapy.

Keywords: Mouth neoplasms, squamous cell carcinoma, recurrence, survival analysis, salvage therapy

Introduction

Squamous cell carcinoma (SCC) is the most common type of cancer of the lip and oral cavity and is among the fifteen most common types of cancer [1]. It has been associated with low socioeconomic status [1-3], occupying the fourth position among men living in countries with a low or medium Human Development Index [1].

Treatment for SCC of the oral cavity is essentially surgical [4, 5]. In some advanced cases, adjuvant radiotherapy is indicated in combination or not with chemotherapy [4, 6, 7]. Oncological control depends on the extent and location of the primary tumor as well as the involvement of cervical lymph nodes [6, 8].

Oral SCC recurs in around 20% of early-stage cases [4, 5, 9] and up to 70% of patients with advanced forms of the disease, and is mainly represented by local and/or regional failures [10]. Tumor recurrence as well as regional and distant metastasis are related to characteristics of the patient, tumor, and treatment performed [4, 11, 12]. Other predictors of recurrence are bone invasion, positive surgical margins by the tumor, perineural invasion, lymphovascular invasion, and extranodal extension [7, 8, 10, 13]. Salvage surgery, although important as the main salvage therapy, can lead to significant morbidity [7, 14, 15].

While survival rates for early-stage oral SCC without recurrence can reach 90% [4], rates for advanced tumors and patients having undergone salvage surgery are only 30% to 50% [4, 5, 7, 9, 10, 14]. Locoregional recurrence is a significant indicator of a poor prognosis in oral SCC [5, 11, 16]. Some histopathologic features

Table 1. Tumor location and clinical stage† of 150 squamous cell carcinomas of the lower oral cavity treated with surgery

Variable	n	%
Tumor Site		
Floor of mouth	59	39.3
Tongue	56	37.4
Retromolar region	21	14.0
Lower gum	11	7.3
Buccal mucosa	3	2.0
T stage		
T1	4	2.7
T2	54	36.0
T3	31	20.6
T4	61	40.7
N stage		
N0	84	56.0
N1	34	22.6
N2a	12	8.0
N2b	10	6.7
N2c	7	4.7
N3	3	2.0
Clinical stage		
I	4	2.7
II	36	24.0
III	37	24.6
IV	73	48.7

†Based on American Joint Committee on Cancer Staging Manual, Eighth Edition[19].

of tumors, such as the depth of invasion and tumor budding status, also exert an influence on the prognosis [8, 17, 18].

The major aim of the present study was to investigate the survival of individuals diagnosed with SCC of the lower oral cavity who underwent surgical treatment and experienced recurrence, considering the site of the recurrent disease (local, regional, distant). The rationale is to determine whether the site of recurrence affects survival of patients surgically treated for SCC of the lower oral cavity.

Materials and methods

This study was performed in accordance with the Declaration of Helsinki and received approval from the institutional review board of *Universidade Federal de Minas Gerais* (certificate number: 63411616.9.0000.5149).

A retrospective longitudinal study was conducted. The inclusion criteria were patients who underwent surgical treatment for SCC of the lower oral cavity (tongue, floor of the mouth, lower gum, retromolar area, and buccal mucosa) from January 2005 to June 2009. The medical records of these patients were analyzed. All patients were treated by the Head and Neck Surgery Group, which comprises three institutions: Alpha Institute of Gastroenterology of the *Hospital das Clínicas* of the *Universidade Federal de Minas Gerais* (city of Belo Horizonte, Brazil), *Baleia* Hospital (Belo Horizonte, Brazil), and *São João de Deus* Hospital (city and not City of Divinópolis, Brazil). The included patients were followed up for at least five years or until recurrence. The exclusion criteria were patients who had undergone previous treatment and those with lip tumors.

Preoperative staging was performed using the criteria formulated by the American Joint Committee on Cancer and updated according to the last publication [19]. All patients underwent surgical resection of the primary tumor as well as neck dissection. Radiotherapy was indicated for T3/T4 tumors, neck metastases or positive surgical margins.

Statistical analysis was performed with the aid of the SPSS® software, version 13.0. First, the survival of patients with and without recurrence was determined and comparisons were made of the survival of individuals with local, regional, and distant recurrence. Survival analysis was performed using the Kaplan-Meier method and the curves were compared using *log-rank* test. The chi-square test was used to compare the frequency of recurrence according to tumor size ("T") and lymph node status ("N"). *P*-values ≤ 0.05 were considered significant.

Results

One hundred fifty patients were included. One hundred eleven were men (74.0%) and 39 were women (26.0%). Average age was 57 years (range: 26 to 90). The data on tumor site and stage are described in **Table 1**.

Figure 1 displays the flowchart of patients included in the study. Fifty-nine (39.3%) participants experienced recurrence during the follow-up period. Local recurrence occurred in 35 cases (23.4%), regional recurrence occurred in 17 cases (11.3%), and distant recurrence oc-

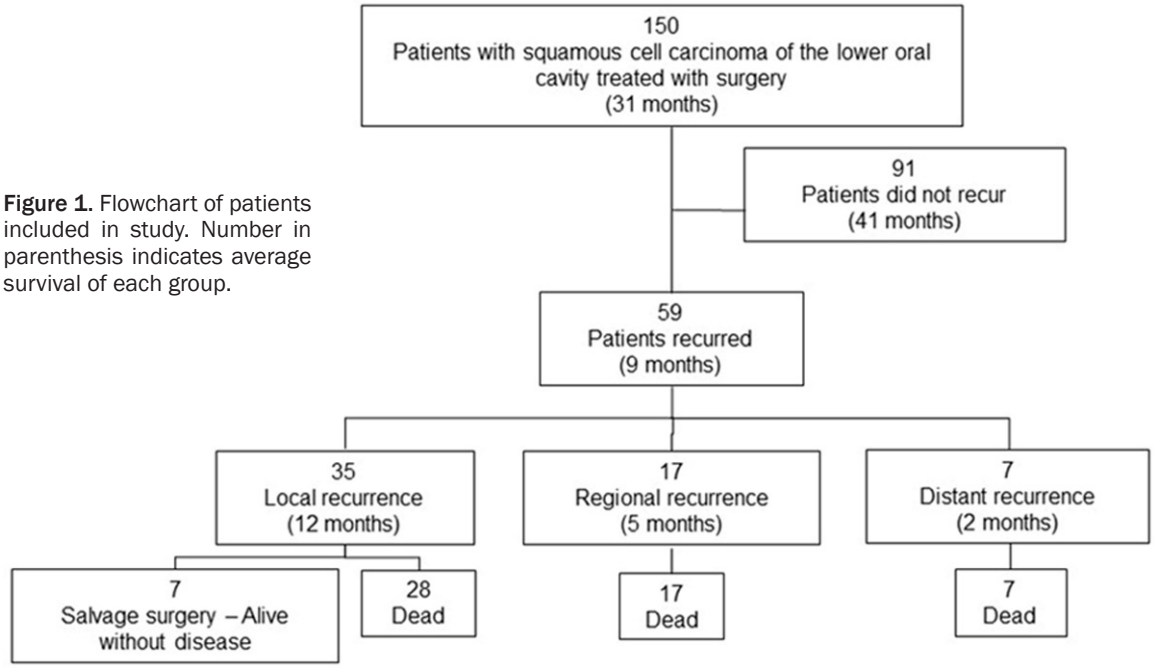

Figure 1. Flowchart of patients included in study. Number in parenthesis indicates average survival of each group.

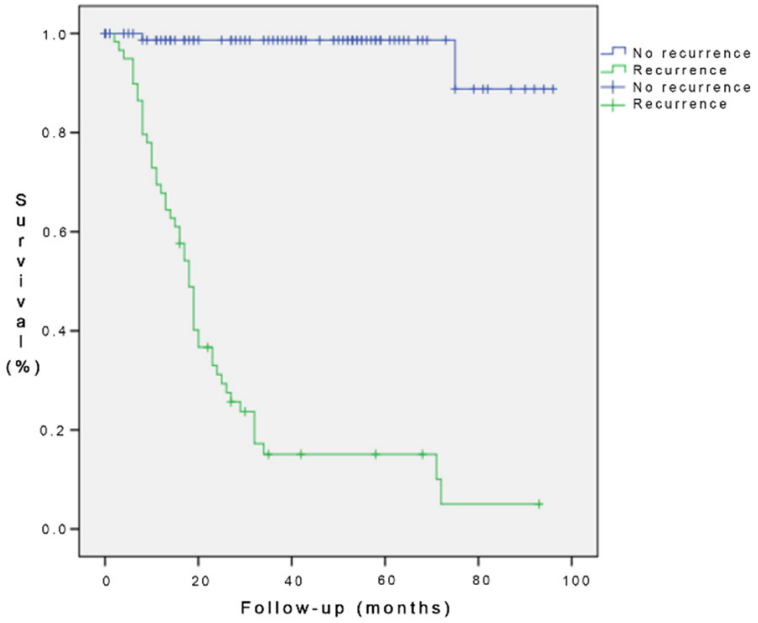

Figure 2. Survival curves of patients with (n = 59) and without (n = 91) recurrence of squamous cell carcinoma of lower oral cavity treated with surgery (*p*-value < 0.001).

curred in seven cases (4.6%). The average length of follow-up was 41 months (range: one to 96 months). The average time from surgery to local, regional, and distant recurrence was 12, 14, and six months, respectively.

The average overall survival of the sample (n = 150) was 31 months. The average survival of patients with recurrence (n = 59) was nine months, while average survival of those without recurrence (n = 91) was 41 months (**Figure 2**, P < 0.001). The average survival of the participants with local, regional, and distant recurrence was 12, five, and two months, respectively (**Figure 3**, P < 0.001). Patients with local recurrence had better survival than those with regional and distant recurrence (**Figure 4**, P = 0.011).

Among the participants with local recurrence (n = 35), seven (20.0%) underwent salvage surgery, all of whom were alive and without any evidence of disease at the last follow-up. Despite having undergone salvage therapy, no patients with regional (n = 17) or distant (n = 7) recurrence were alive at the end of the follow-up period. Thus, among all the patients who experienced recurrence (n = 59), 52 (88.1%) died of their disease.

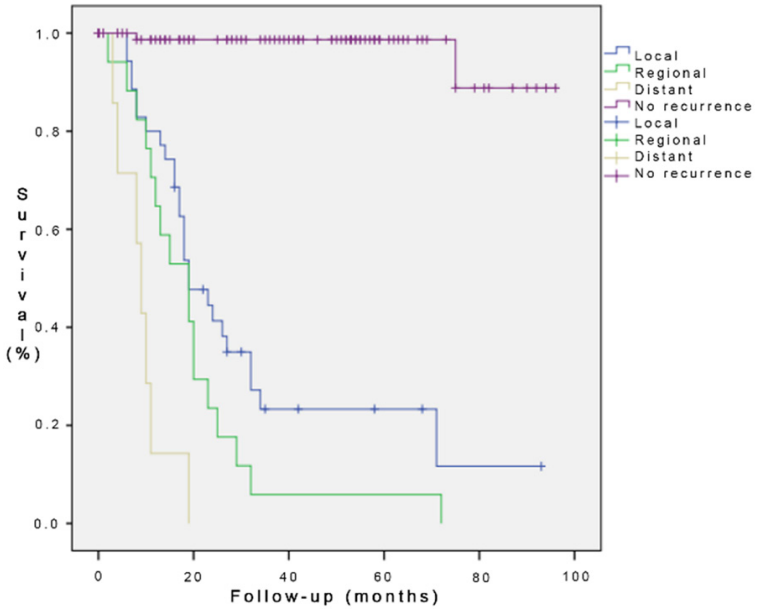

Figure 3. Survival curves of patients without recurrence (n = 91) and those with local (n = 35), regional (n = 17), and distant (n = 7) recurrence of squamous cell carcinoma of lower oral cavity treated with surgery (*p*-value < 0.001).

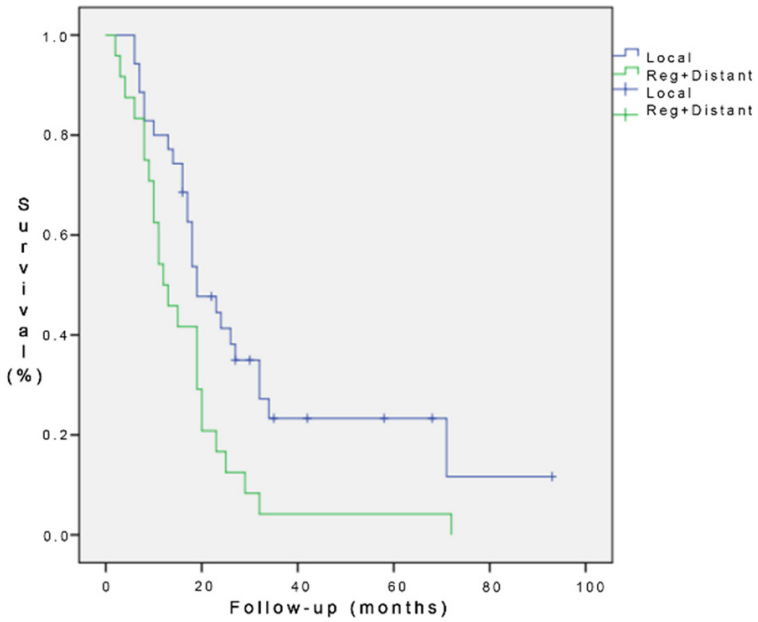

Figure 4. Survival curves of patients with local (n = 35) and regional (reg) + distant (n = 24) recurrence of squamous cell carcinoma of lower oral cavity treated with surgery (*p*-value = 0.011).

The frequency of overall recurrence was 50.0% (2/4) of cases in stage T1, 33.3% (18/54) of those in stage T2, 38.7% (12/31) of those in stage T3, and 44.3% (27/61) of those in stage T4 (P = 0.828). When the analysis was based on lymph node status, the rates of recurrence were as follows: N0, 34.5% (29/84); N1, 45.0% (15/34); N2, 45.0% (13/29); and N3, 66.0% (2/3) (P = 0.345).

Discussion

In the present study, patients with local recurrence had better survival than those with regional/distant recurrence. Twenty percent of those with local recurrence underwent a salvage surgical procedure and were alive without any evidence of disease at the last follow-up. In contrast, no patients with regional or distant recurrence were cured, despite the use of salvage therapy. Most therapeutic options for relapsed cases are surgical combined or not with chemoradiation, but, in some cases, palliative management is the only recourse [5, 9, 20]. The literature shows a decrease in survival rates over the years for both patients treated surgically and those undergoing palliative treatment, although the rate is better for the former group [5, 9]. Local recurrence usually presents as large tumors, making resection more difficult, more disfiguring, and usually followed by additional morbidity [4, 5]. However, salvage surgery can be curative for such cases. Deaths related to the local recurrence of oral cavity cancer can be twofold higher in cases for which salvage surgery is not performed [9]. When recurrence appears in the neck, failure is usually associated with multifocal lymph node disease and capsular rupture, making management difficult and resulting in a poorer prognosis [5, 13].

For SCC of the oral cavity, local and regional recurrence are the most common patterns of failure and depend on the primary site, clinical stage, histologic characteristics of the tumor, and the treatment performed [4, 5, 8, 11, 17, 18]. Distant metastases are infrequent, but strongly associated with death [5]. The rates of local (23.3%), regional (11.3%), and distant (4.6%) recurrence found herein corroborate the different frequency of sites affected by recurrent disease.

Notwithstanding the use of surgery and adjuvant radiotherapy, SCC of the oral cavity recurs in one-quarter to two-thirds of cases, depending on the tumor stage [5, 9, 10]. In the present study, the overall recurrence rate was 39.3%, which may have been due to the high proportion (73.3%) of individuals with advanced disease (stages III and IV) [10].

The primary tumor site is considered a critical factor for the local control of the disease. Data in the literature indicate that tumors originating in the floor of the mouth, tongue, and buccal mucosa have characteristics that make their control more difficult compared to other sites in the oral cavity [5, 6, 9, 21]. In this study, more than 2/3 of the sample had tumors in floor of the mouth or tongue. Therefore, the recurrence rate of nearly 40% is compatible with reports in the literature on SCC affecting these sites.

The findings on recurrence by nodal status revealed increasing rates from N0 to N3 stages, although without statistical significance. The prognostic relevance of the involvement of cervical lymph nodes in oral cavity SCC is largely accepted [5, 6, 14]. Chung et al. [14] showed a relationship between a worse prognosis in patients submitted to salvage surgery and advanced initial N stage, loco-regional recurrence, advanced recurrent T stage, disease-free survival less than eight months prior to salvage, and recurrence in a previously treated field.

Recurrence occurred predominantly within the first two years of follow-up. This is compatible with findings described in the literature, which also reports this short time associated with poor survival [5, 14]. Weckx et al. [5] found an association between the timing of recurrence and the lymph node ratio (ratio of positive lymph nodes to the total number of lymph nodes removed), margin status, and grade of the primary tumor.

Despite advances in oncological treatment modalities, the surgical approach for SCC of the lower oral cavity remains the gold standard and adequate initial treatment provides the best odds of a cure, with surgery, radiotherapy, and chemotherapy as the main therapeutic resources. Among these modalities, surgery is the most efficacious for tumors in both early and advanced stage [4, 5]. Therefore, surgeons should make every effort to achieve clean margins during the first surgical resection of a tumor. Moreover, the histopathologic report should provide detailed information to aid in the correct and precise indication of adjuvant therapy.

The major limitation of this study is the absence of histopathologic data of the tumors. Future studies should try to establish criteria to identify patients with early-stage tumors carrying a higher risk of recurrence, who would benefit from a more aggressive initial treatment.

In conclusion, patients with local recurrence of SCC of the lower oral cavity treated by surgery have better survival than those with regional and distant recurrence. Local recurrence poses the possibility of curative salvage therapy.

Acknowledgements

This work was supported by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) under grant number #405585/2018-7; and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) under Financial Code 001.

Disclosure of conflict of interest

None.

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