Survival Outcomes and Patterns of Failure in Maxillary Alveolus Squamous Cell Carcinoma

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Abstract

Introduction Squamous cell carcinoma (SCC) of the maxillary alveolus is a relatively rare disease. There is lack of data on this subsite as compared with other sites. The factors that affect survival in cases of maxillary alveolar SCC are tumor stage, local and cervical metastases, histological grading, and the margin status.

Objectives To evaluate the overall survival (OS), the disease free survival (DFS), and the complex interaction and effects of margin status, histological differentiation, habits (such as smoking and the use of smokeless tobacco products), and cervical and distant metastases based on clinicopathological data.

Methods We examined the electronic database at our hospital from 2003 to 2017. We included all cases with a histopathological diagnosis of SCC of the maxillary alveolus. Tumors originating primarily from the maxillary alveolus were included, while those originating from adjacent subsites, like the hard palate, the buccal mucosa or the maxillary sinus were excluded. We also excluded all the patients who were not operated on with a curative intent.

Results More than half of the patients had stage-IV tumors at the time of presentation, while only one fourth of them had nodal metastasis. The rate of recurrence increased in cases of primary tumors in advanced stages and the degree of histological differentiation. The 2-year and 5-year OS rates were of 54.5% (18 patients) and 30.3% (10 patients) respectively.

Conclusion Primary tumors in advanced stages, histological grade, and presence of nodal metastasis are poor prognostic markers in terms of long-term survival.

Keywords
- squamous cell carcinoma
- prognosis
- maxilla
- survival

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Introduction

Squamous cell carcinomas (SCCs) account for more than 90% of all the malignant tumors in the oral cavity,[1] and their location in the maxilla is rare as compared with other subsites. They comprise around 0.5% to 5% of all SCCs in the oral cavity.[2,3] Some researchers[4] believe that cases of SCCs of the maxillary alveolus and hard palate present a low risk of developing cervical metastasis.

Neck dissection in clinically-negative necks with maxillary alveolus SCC is controversial. Weiss et al.[5] recommended neck dissection when the probability of cervical-node metastasis was greater than 20%; however, other authors[6] have recommended neck dissection in any stage of the Tumor, Node, Metastasis (TNM) Classification of Malignant Tumors. Paleri et al.[7] recommended sentinel-node biopsy in early tumors in patients with clinically-negative necks (cN0).

The paucity of data on SCC of the maxillary alveolus is due to the decreased incidence of this neoplasm in this particular site. The question of whether to address or not the neck has not been fully answered. In the absence of cervical lymphadenopathy, some surgeons like to wait until the tumor reaches stage T1, while others recommend elective neck dissection in tumor stages T2 to T4.[8] An understanding of the lymphatic drainage and regional metastasis is essential to comprehend the appropriate treatment and the extent of surgery.[9] It was once believed that maxillary SCC behaves less aggressively then SCCs in other oral subsites; however, researchers[10] have proven this assumption wrong.

The main aim of the present study was to evaluate the overall survival (OS), the disease-free survival (DFS) and the complex interaction and effects of margin status, histological differentiation, habits (such as smoking and the use of smokeless tobacco products), and cervical and distant metastases based on clinicopathological data.

Materials and Methods

We examined the electronic database at our hospital from 2003 to 2017 in search of all cases with a histopathological diagnosis of maxillary alveolus SCC. The Institutional Review Board approved the study, and the exemption the approval number EX-20–06–21–01, from July 30th, July 2021. Tumors originating from the maxillary alveolus were included, while those involving alveoli from adjacent subsites, such as the hard palate, the buccal mucosa, or the maxillary sinus, were excluded. We also excluded all the patients who were not operated on with a curative intent. The data collected included TNM stages, histological grade, local and nodal recurrence, distant metastasis, DFS and OS. We also calculated the two- and five-year OS rates and the rate of recurrence. The standard approach is neck dissection at level I-III, which can be extended to IV in rare cases, based on perioperative findings. All cases were discussed in a multidisciplinary team meetings before the decision to perform or not a surgical intervention.

All of the patients were staged according to the eight edition of the American Joint Committee on Cancer (AJCC) *Cancer Staging Manual*. We used the preoperative magnetic resonance imaging (MRI)/computed tomography (CT) scans to ascertain the site of origin of the tumor, and a thorough clinical examination to confirm it; only tumors originating in maxillary alveolus were included. In addition to the TNM stage, we also assessed the patients' age, gender, ethnicity, alcohol use, smoking, and the use of non-cigarette tobacco products, such as pan (chewing tobacco) and naswar (dipping tobacco commonly placed in the buccal/labial sulcus). We also assessed the patients regarding the performance of neck dissection (yes or no, unilateral or bilateral), the total lymph node yield and the number of nodes involved by the metastatic tumor, the margin status, perineural and lymphovascular invasion, and the follow-up and disease-free periods.

The statistical analysis was performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, United States) software, version 20.0. The log-rank test was used to assess the relationships regarding the clinical characteristics. Values of $p < 0.05$ were considered statistically significant.

Results

The sample was composed of 33 patients, 21 male (63.6%) and 12 female (36.4%), with a mean age of 54.36 ± 12.48 years, and the youngest patient being 29 years of age and the oldest, 76. All the patients with incomplete medical record or those lost to follow up were excluded. The maxillectomies were performed according to the classification by Brown and Shaw:[11] class Ib – 5 patients; class IIb – 17 patients; class IIc – 4 patients; class IId – 4 patients; and class IIIb – 3 patients.

As for the T stage, it was T1 in 6 patients (18.2%), T2 in 7 (21.2%), T3 in 4 (12.1%), and T4 in 16 (48.5%) patients (►**Table 1**). Regarding nodal metastasis, we found that 18 patients (54.5%) did not undergo neck dissection, 7 patients (21.2%) were N0, 1 patient (3%) had N1 disease, and 7 patients (21.2%) had N2 disease. The final TNM stages were: stage I – 6 (18.2%) patients; stage II – 5 (15.2%) patients; stage III – 2 (6.1%) patients; and stage IV – 20 (60.6%) patients. Most of the tumors in the present study were well differentiated (45.5%) or moderately differentiated (51.5%), except for 1 (3.0%) patient who had a poorly-differentiated SCC. Regarding the neck dissection, 18 patients (54.5%) did not undergo it, and were labeled Nx according to the National Comprehensive Cancer Network (NCCN) Guidelines (version 3.2021, April 27, 2021). In total, 12 (36.6%) patients underwent ipsilateral neck dissection, and only 1 (3.0%) patient underwent bilateral neck dissection.

As for recurrence, almost half of the patients (48.5%) did not present it, 11 had recurrence at the primary site (33.3%), 4 (12.1%) presented nodal recurrence, and 2 (6.1%) had distant metastases to the bone and liver.

The stage wise distribution is shown in ►**Table 2**. Almost half of the 18 (54.5%) Nx patients were pT4, and this was due to early bone invasion in some tumors in early T stages. Among 10 T3 and T4 Nx patients, 3 had refused dissection,

Table 1 Gender and data regarding the tumors of the study sample

	N	%
Gender		
Male	21	63.63
Female	12	36.36
Tumor, node, metastasis (TNM) stage		
I	6	18.2
II	5	15.2
III	2	6.1
IV	20	60.6
Tumor stage		
T1	6	18.2
T2	7	21.2
T3	4	12.1
T4	16	48.5
Node stage		
N1	1	3.0
N2	7	21.2
N3	0	0
N0	7	21.2
Nx	18	54.5
Differentiation		
G1	15	45.5
G2	17	51.5
G3	1	3

while 7 had comorbidities that rendered them inoperable. All the patients who did not undergo elective dissection had a clinical N0 status.

The mean OS was of 36.60 months, ranging from 2 to 86 months. Such a wide range is due to a few cases of patients lost to follow-up after surgery. The DFS was of 29.96 months. The 2- and 5-year OS rates were of 54.5% (18 patients) and 30.3% (10 patients) respectively. The Kaplan–Meir curve of the patients is shown in **figures 1** and **2**. For the purpose of the Kaplan–Meir curve, we included the poorly-differentiated group G3 in the moderately-differentiated group G2. At the end of the follow-up period, 20 (60.6%) patients were

Table 2 Tumor stage distribution of patients in whom no neck dissection was performed

Tumor stage	(n%)
T1	5/18 (27.7%)
T2	3/18 (16.6%)
T3	2/18 (11.1%)
T4	8/18 (44.4%)

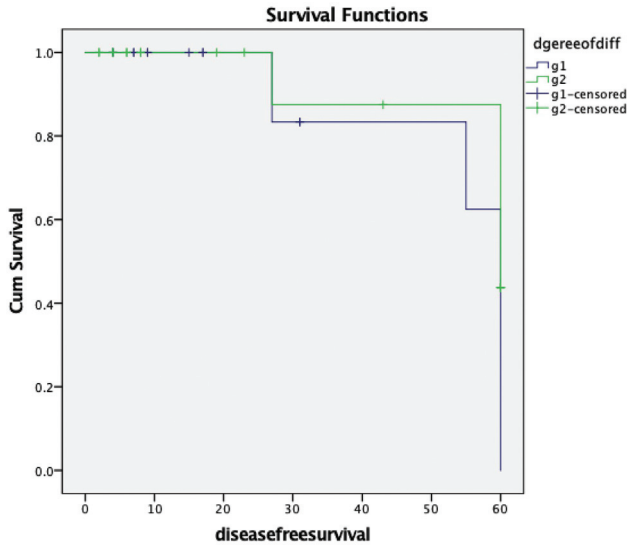

Fig. 1 Kaplan Meir graph showing the disease free survival

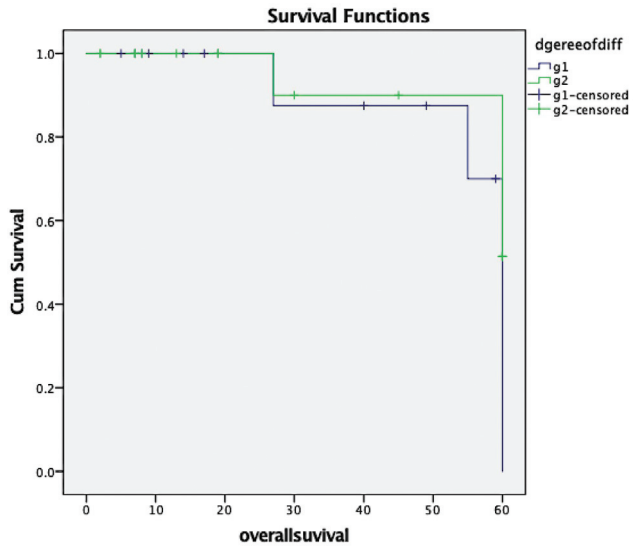

Fig. 2 Kaplan Meir graph showing overall survival

alive, 9 (27.3%) had died, and 4 (12.1%) had been lost to follow-up.

We defined clean margins as those measuring ≥ 5 mm, close margins as those measuring between 2 mm and 4 mm,

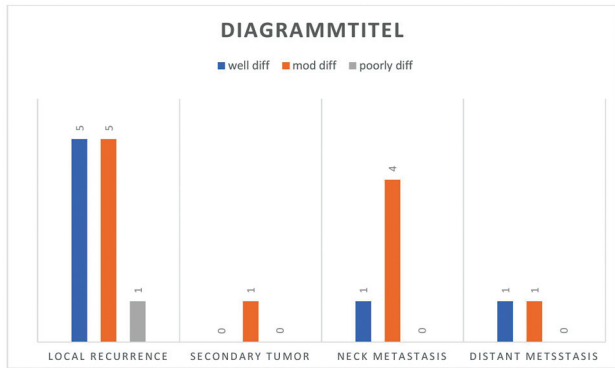

Fig. 3 Impact of histological grading, local recurrence, cervical metastasis and distant metastasis.

Table 3 Failure pattern according to primary tumor stage

Primary tumor stage	Local recurrence	Neck metastasis	Distant metastasis	n (%)
T1		1	1	2/6 (33.3)
T2	2	2		4/7 (57.14)
T3				0/4 (0)
T4	6	2	1	9/16 (56.25)
Total	8	5	2	15/33(45.4)

Table 4 Nodal metastasis according to tumor stage

Tumor stage	Nodal metastasis	n (%)
T1	1	1/6 (16.6)
T2	1	1/7 (14.2)
T3	0	0/4 (0)
T4	3	3/16 (18.7)
Total	5	33

Table 6 Nodal recurrence for patients in all node stages

Node stage	Nodal recurrence -ve: n	Nodal recurrence +ve: n (%)
N0	6	1 (14.2%)
N1	1	0 (0%)
N2	5	2 (28.5%)
Nx	16	2 (11.1%)

and involved margins as those measuring $\leq$ 1 mm. A total of 20% of our patients had clean margins, 40% had close margins, and 40% had involved margins.

We found the relationship between the margin status and OS to be statistically insignificant. ►**Table 3** shows the relationship between the stage of the primary tumor and the percentage of patients who presented with primary-site recurrence, cervical metastasis and distant metastasis. Our data showed a 33.33% recurrence rate for T1 tumors and a very similar rate for T2 and T4 tumors (of 57.14% and 56.25% respectively). None of the patients with T3 disease had recurrence during the follow-up. The 2- and 5-year recurrence rates were of 57.6% (19 patients) and 72.7% (24 patients) respectively. We can conclude that a higher T stage causes a greater chance of presenting disease recurrence.

The risk of developing nodal metastasis was similar for patients in almost all T stages, except those in T3 did not develop it. Out of 33 patients, only 5 had nodal recurrence, and 28 did not have nodal metastasis.

A slightly increased risk of developing nodal metastasis was observed among T4 patients as compared with T1 and T2 patients (►**Table 4**); however the risk of developing nodal metastasis was lower than 20% among patients in every T stage, but we cannot make a conclusion regarding the need for neck dissection based on this data due to two reasons: the size of our sample was small, and, clinically, some of our T1 cases were upstaged to T4 because of early bone involvement.

There is a strong association regarding advanced T stages and habits such as smoking and use of alcohol and naswar. A total of 18 patients (54.5%) had a history of one of the risk factors/habits, and 66.6% of the total were stage IV on presentation (►**Table 5**). The likelihood ratio was of 5.232, and the *p*-value was not significant for this association.

In N0 necks, only 1 out of 6 patients had nodal recurrence, this rate was very similar to that of the pT4 patients who did not undergo neck dissection, which was a surprising finding (►**Table 6**), that can be explained by the small sample size.

We found a direct correlation between the histological grade and local recurrence, neck metastasis, distant metastasis, and the emergence of a second primary tumor (**figure 3**). The value was statistically insignificant in all the cases ($p > 0.05$). As the degree of differentiation decreases, the percentage of patients with local and neck failures increased.

We evaluated the margin status as an independent factor in terms of tumor recurrence. We divided the patients into 3 categories regarding their margin status: clean margins – $\geq$ 5 mm away from the tumor front; close margins – between 2 mm and 4 mm; and involved margins – $\leq$ 1mm. In the present study, 7 patients had clear margins, and 13 had closed or involved margins (►**Table 7**). Margin status as an independent factor was not significant according to our study. A study with a large sample size is required to assess the correlation of margin status as an independent factor.

Table 5 Number of patients with positive risk factors stagewise

		Tumor, node, metastasis (TNM) stage				Total
		StageI	Stage II	Stage III	Stage IV	
Risk factors	Positive	3	4	0	8	15
	Negative	3	1	2	12	18
Total		6	5	2	20	33

Table 7 Impact of margin status on local recurrence, second primary tumor, and neck and distant metastases

Tumor margin	Local recurrence: n	Second primary tumor: n	Neck metastasis: n	Distant metastasis: n	n (%)
Clean margin – $\geq$ 5 mm	2		1	1	4/7 (57.1%)
Close margin – 2–4 mm	5*		2	1*	7/13 (53.8%)
Involved margin –$\leq$ 1 mm	3	1	2		6/13 (46.1%)
Total	10	1	5	2	

Note: *One patient presented local recurrence and distant metastasis, but we have disregarded the distant metastasis in the table and counted him in the local recurrence group.

Discussion

The purpose of the present study was to evaluate the long-term survival outcomes and the failure patterns in SCCs of the maxillary alveolus. The sample was composed of 33 patients who were treated surgically with a curative intent. We wanted to assess the effect of primary tumor stage, nodal metastasis, histological grade, habits and margin status on patient survival and their complex interactions.

The rate of disease recurrence, which included local failure, cervical recurrence and distant metastasis, was of 45.4% (15 out of 33 patients), which is high as compared with other studies such as those by Moratin et al.[12] and Brown et al.[13] The most likely explanation for this is the small sample size and the fact that in the early days we were selective in the performance of neck dissections in patients with early-stage tumors. In the present study the rate of recurrence increased with the primary tumor stage: it was of 33% for T1, and increased to 56% to 57% for stages T2 and T4.

The decision to address the neck in SCCs of the maxillary alveolus is still under debate, with no clear indications to date. This is probably due to the relatively small number of cases of SCC of the maxillary alveolus as compared with more common sites such as the tongue and buccal mucosa. In the early days, neck dissection was not presented as an option to patients with early-stage tumors, but this has changed over the years, as more patients with early-stage disease are undergoing neck dissections. Recent papers[3,9,10] demonstrate a risk higher than previously thought of occult metastasis from SCC of the maxillary alveolus. Elective neck dissection is now recommended even for N0 patients in early T stages.[14] The results of the present study contradicts those of the aforementioned studies. We have found no significant difference regarding the risk of developing nodal metastasis in any T stage, possibly due to the small sample size. We observed a very similar rate of nodal metastasis in all T stages, perhaps due to several early-stage tumors which were clinically T1/T2, but were subsequently upstaged to pT4. However, we cannot recommend any changes in the treatment algorithm of SCC of the maxillary alveolus based on our observations.

We studied the effect of margin status as an independent factor in the development of local recurrence, neck node metastasis, distant metastasis, and the second primary tumor. Our results were in contradiction to those of other studies, such as the one by Siriwardena et al.[15] Well- and moderately-differentiated types had a better prognosis as compared with the poorly-differentiated type in terms of local and nodal disease recurrence. Another study[12] found similar results for tumor differentiation and nodal recurrence. We found a positive association between the risk factors of the patient (alcohol consumption, smoking, use of smokeless tobacco etc.) and advanced T stages, which had already been proven by a recent meta-analysis.[16] More than 50% of our patients who had a history of a known risk factor were in stage IV upon initial presentation. This reinforces the strong and proven correlation regarding the use of tobacco, alcohol, and their byproducts alone or in combination and the development of oral cancer.

The risk of developing occult metastasis in the present study was of 15.15% for all stages combined. For individual T stages, the risk of occult metastasis ranged from 14% to 19% approximately, which is below the 20% cut-off value reserved for elective neck dissection. Different authors[17–21] have reported rates of risk of developing occult metastasis ranging from 12% to 29%.

Neck dissection in T1 patients is still controversial. Throughout the years, we have modified our practice to perform neck dissection for every T stage except very small T1 tumors. We now perform neck dissections at level I-III for ipsilateral neck in well-lateralized tumors and bilateral if the tumor is approaching or crossing the midline. In the present study, a large number of T4 patients did not undergo neck dissection due to bone involvement in some cases early-stage (T1/2 tumors, which were subsequently upstaged to pT4 . They were submitted to adjuvant treatment to the primary tumor and the neck. It is well established that neck dissection should be performed if the risk of occult metastasis is higher than 15% to 20%.[22,23]

We cannot definitely explain the variation in the results of certain parameters as compared with those of other studies; this could be due to the fact that most papers that have analyzed the tumor parameters, rates of recurrence, and other clinicopathological data regarding SCC of the maxillary alveolus are limited due to the changing treatment regimens, and observation also made by Eskander et al.[8] We agree with this observation because, unlike a decade ago, now there is a low threshold at our center: we perform neck dissections even in early-stage tumors, and the change in practice has most definitely impacted our results.

Conclusion

Squamous cell carcinoma in the maxillary alveolus is relatively rare as compared with other oral subsites. There is

insufficient data to correctly predict the outcomes of treatment and patterns of failure. There is a need for multicenter trials to correctly identify the prognostic factors and define the correct immediate treatment in early-stage SCCs.

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Conflict of Interests
The authors have no conflict if interests to declare.

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