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Is a "watch and wait strategy" safe to manage clinically N0 squamous cell carcinoma of the upper jaw?

Paolo Cariati*, Almudena Cabello-Serrano, Fernando Monsalve-Iglesias, Jose Fernadez-Solis, Ildefonso Martinez-Lara

Hospital Virgen de las Nieves, Granada, Spain

ABSTRACT

Purpose: The main aim of the present study is to analyze the behavior of squamous cell carcinoma (SCC) of maxillary gingiva, alveolus, and hard palate and to determine the utility of selective neck dissection in clinically N0 patients at early stages.
Material and method: Twenty-nine previously untreated patients with SCC of maxillary gingiva, alveolus, and hard palate were diagnosed and treated with at least a tumorectomy and selective neck dissection at HUVN and included in the study.
Results: A total of 34.4% of patients (10/29) showed nodal involvement at postoperative histopathologic exam. Several pathologic features such as N involvement, N stage, T stage, and locoregional failure all have a negative impact on overall survival.
Discussion: SCC of maxillary gingiva, alveolus, and hard palate shows an aggressive behavior that is comparable with other oral cavity cancers. A more aggressive treatment is thus required for improving locoregional control and overall survival. Supraomohyoid neck dissection may be useful in cT2N0M0.

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* Correspondence to: Paolo Cariati, Hospital Virgen de las Nieves, Carretera de Jaen s/n, Granada 18013 Spain.
E-mail address: paolocariati1@gmail.com (P. Cariati).

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Introduction

Management of the clinically negative neck can be difficult in patients with squamous cell carcinoma (SCC) of maxillary gingiva, alveolus, and hard palate. Specifically, to "watch and wait" represents the strategy of choice to control the neck in clinically N0 patients. This approach is based on the low risk of occult cervical metastases attributable to this malignancy.[1] In fact, elective treatment of the neck is largely indicated if the risk of presenting occult cervical metastases is greater than 15%-20%.[2,3] However, recent studies have demonstrated that SCC of the upper jaw should be considered to be as aggressive as other carcinomas of the oral cavity.[4-7] In this regard, Beltramini et al reported a node involvement rate of 21% in a series of 69 patients with SCC of the maxillary gingiva, alveolus, and hard palate. According to these authors, elective neck dissection should be indicated in patients with the following characteristics: (1) T3/T4 stage, (2) if cervicotomy is needed for microvascular reconstruction, and (3) in case of patients with poor compliance to a close follow-up.[1] In the same vein, Montes et al affirmed that SCC of maxillary gingiva, alveolus, and hard palate presents aggressive cervical metastatic behavior. These authors found a node involvement in 42.9% of 14 patients. Interestingly, 20% of these showed lymph node involvement at presentation and 21.4% developed a cervical failure during follow-up. Thus, the authors recommended an elective neck dissection even in clinically N0 patients because of the high risk of occult metastases.[4] Moreover, more clinicians are recommending a more aggressive treatment regimen to improve overall survival.[8-10] The main aim of the present study is to analyze the behavior of SCC of this specific area and to determine the utility of selective neck dissection in clinically N0 patients at early stages.

Materials and methods

Between 2000 and 2012, 29 previously untreated patients with SCC of maxillary gingiva, alveolus, and hard palate were diagnosed and treated with at least a tumorectomy and selective neck dissection at HUVN. The neck dissections included levels I-III in patients with clinically negative neck. However, the neck was recorded as clinically positive (N+) if there were any clinical or radiologic suspicion of node involvement. In these cases, an elective neck dissection of levels I-V was carried out.

The male:female ratio was 1.07:1 (15 males/14 females). Patient ages ranged between 47 and 81 years, with a mean of 70.1 (S.D: 8.401). The clinical stage of the primary tumor was determined by using the recommendations of the fifth edition of the UICC TNM classification of malignant tumors.[11] A careful clinical exploration and a CT scan of the cervicofacial area were carried out in order to ascertain the clinical stage of each patient before surgery.

A split neck dissection was performed in order to identify the lymphatic territories most affected by SCC of the upper jaw. More specifically, the surgical team identified, labeled, and separated the operation specimens in the surgical field before immersion in formalin. The specimens were examined and dissected by a single pathologist. In our study, neck levels were differentiated according to the classification proposed by the American Head and Neck Society.[12]

It is important to stress all patients with positive neck dissection and/or poor prognostic factors (T3, T4, ECS, surgical margins, nerve, and vascular invasion) received adjuvant treatment with RT ± QT.

Several pathologic features such as T stage, N stage, tumor thickness, surgical margins, and locoregional failure were also considered. Tumor thicknesses were divided into 2 groups: <0.4 cm and >0.4 cm. At the time of analysis, all surviving patients had at least 5-year follow-up.

Statistical analysis was conducted using SPSS 23v. Frequency and percentages were used to evaluate the pattern of distribution of cervical metastases. A correlation test was carried out in

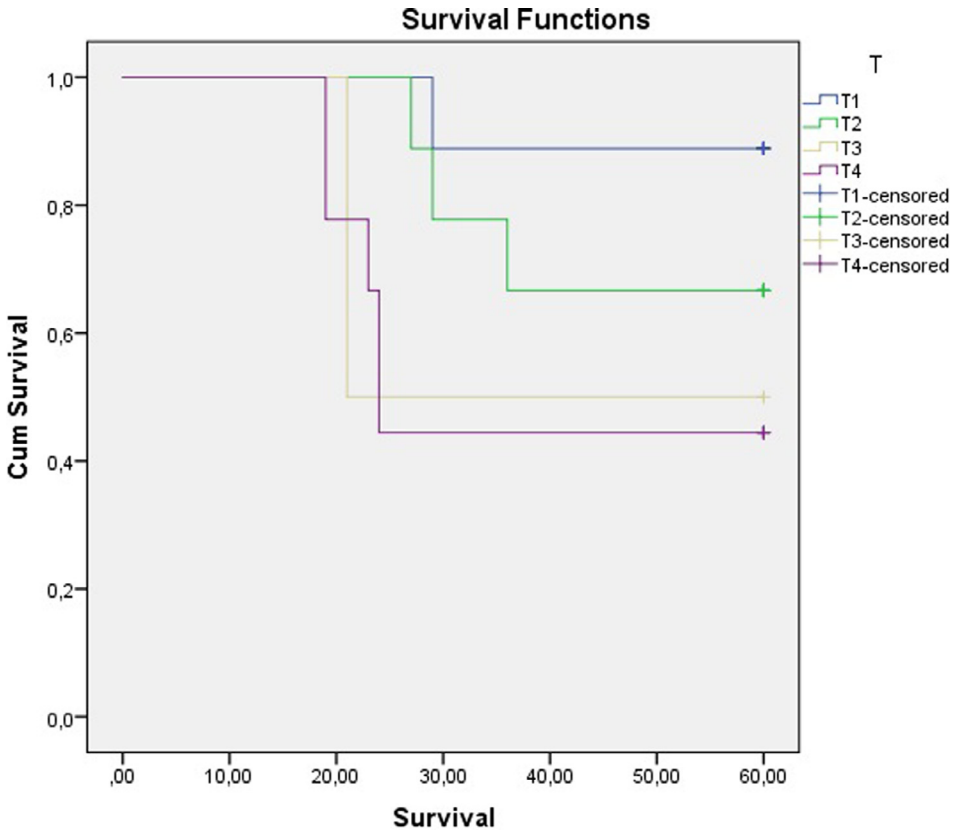

Fig. 1. Outcomes in relation to T stages.

order to analyze the relationship between variables. Chi-square was performed to compare the differences among N0 and N+ patients, and specific contingency tables allowed for the calculation of the impact of each factor on patient survival. The *P* value was set at 0.05. Finally, a Kaplan-Meier test was carried out to obtain an overall 5-year survival analysis.

Results

Hence, 29 patients were included in this study. The male:female ratio was 1.07:1 (15 males/14 females). Patient ages ranged between 47 and 81 years, with a median age of 69.7 (S.D: 7.603).

T stage

In our sample, 9 of the 29 tumors were classified as T1 (31%), 9 as T2 (31%), 2 as T3 (6.9%), and 9 as T4 (31%). T stage was found to have a strong relationship with N involvement ($P < 0.05$), N stage ($P < 0.05$), and tumor thickness ($P < 0.01$). Moreover, a nonsignificant trend toward association between T stage and 5-year overall survival was also observed ($P = 0.06$; Fig 1). Specifically, 5-year overall survival was 88.9% for T1, 66.7% for T2, 50% for T3, and 44.4% for T4. In relation to tumor thickness, 8 of the 9 T1 (88.8%) tumors presented a tumor thickness <0.4 cm. In contrast, only 1 of 9 T2 (11.1%) showed a depth of invasion<0.4 cm. In the same line, all

T3 and T4 tumors presented a tumor thickness >0.4 cm. With respect with N involvement, only 1 of the 9 T1 (11.3%) tumors were associated with positive nodes at postoperative histopathologic examination. Positive nodes were found in 22.2% of T2 patients (2/9), 100% of T3 (2/2), and 55.5% of those with T4 tumors (5/9).

Tumor thickness

Tumor thickness emerged as an extremely significant prognostic factor. This factor was significantly related to T stage ($P < 0.01$), node involvement ($P < 0.05$), and N stage ($P < 0.05$). In addition, tumor thickness was strongly associated with the risk of developing a local or regional failure during follow-up ($P < 0.01$). Specifically, no patients with a depth of invasion <0.4 cm experienced a local or regional recurrence (Table 1).

N involvement

Nineteen patients were classified as N0 (65.5%) and 10 as N+ (34.4%). N involvement proved to be the most important prognostic factor in our series. Overall survival was 65.5% at 5 years. However, overall survival was 89.5% in N0 patients and 20% in N+ patients ($P < 0.01$). T stage and tumor thickness were strongly related to the risk of presenting positive cervical nodes ($P < 0.05$). Interestingly, 10 of the 19 N0 patients (47.3%) presented a tumor thickness <0.4cm. However, no tumors with a depth of invasion <0.4 cm were found in the group of N+ patients. N involvement showed a nonsignificant trend toward association with the risk of developing a recurrence during follow-up ($P = 0.06$).

A total of 47 nodes were affected by carcinogenic cells. Level I was the most commonly affected area (55.3%; 26 of 47 affected nodes) followed by level II (34%; 16 of 47 nodes). Level III was affected in 8.5 % of cases (4 of 47 nodes). A total of 2.1% and 0% positive nodes were observed at level IV (1 of 47 nodes) and level V (0 of 47 nodes), respectively. Importantly, no isolated metastases were found at level III or IV ("skip metastasis"). All patients with involvement of these regions also presented metastatic disease at levels I or II.

Occult cervical metastases

Twenty-three patients (79.3%) were preoperatively classified as N0 and 6 (20.6%) as N (+). However, node involvement was evidenced in 17.3% of patients classified as N0 before surgery (4/23). Consequently, occult cervical metastases were evidenced in 13.7% of all patients (4/29). One of these 4 tumors was staged as T1 (25%), 1 as T2 (25%), and 2 as T4 (50%). A total of 14 positive lymph nodes were found in these 4 patients. Level I was the anatomical area most frequently affected. A total of 64.2% of occult cervical metastases affected this area (9 of 14 positive nodes). However, levels II and III tumors were affected in 21.4% (3 of 14) and 14.2% (2

Table 1
Histological features related to the presence of lymph node metastasis.

	N0	N+	*P*
T stage	8 T1 (88.8%) 7 T2 (77.7%) 0 T3 (0%) 4 T4 (44.4%)	1 T1 (11.1%) 2 T2 (22.2%) 2 T3 (100%) 5 T4 (55.5%)	<0.01
Tumor thickness <0.04 mm	47.3%	0%	<0.01
Tumor thickness >0.04 mm	52.6%	100%	<0.01
Overall survival	89.5%	20%	<0.01

Table 2
Outcome in relation to histological features.

Feature	Overall survival	*P*
T stage		0.063
T1 (n = 9)	88.9%	
T2 (n = 9)	66.7%	
T3 (n = 2)	50%	
T4 (n = 9)	44.4%	
Node involvement		0.009
N− (n = 19)	89.5%	
N+ (n = 10)	20%	
N-stage		0.01
Overall (n = 29)	65.5%	
N0 (n = 19)	89.5%	
N1 (n = 7)	28.6%	
N2 (n = 3)	0%	
ECS		0.01
− (n = 26)	73.1%	
+ (n = 3)	0%	

of 14), respectively. No positive nodes were observed at levels IV or V in patients classified as clinically N0.

N stage

Ten patients were classified as N+ in our study. Of these, 7 were staged as N1 (70%), 1 as N2a (10%), and 2 as N2b (20%). As stated previously, N stage was significantly associated with both T stage ($P < 0.05$) and tumor thickness ($P < 0.05$). No patients classified as N1 or N2 presented a depth of invasion <0.4 cm. In addition, N stage was significantly related to overall survival ($P < 0.05$). Five-year overall survival rates were 89.5%, 28.6%, and 0% for N0, N1, and N2 patients, respectively (Table 2).

Local and cervical failure

In our series, 51.7% of the patients (15/29) experienced a local or cervical recurrence. In particular, local and cervical failures were observed in 24.1% (7/29) and 27.6% (8/29) of patients, respectively. Tumor thickness >0.4 cm and close/involved surgical margins were significantly associated with a higher rate of locoregional failure (<0.01). In addition, patients that experienced a local or cervical failure showed the worst outcomes in terms of overall survival ($P = 0.06$; Fig 2). Overall survival was 57.1% in the case of local recurrence and 25% in the case of cervical relapse.

Overall survival

Overall survival was 65.5% in the present study. Nodal involvement proved to be the most significant prognostic factor ($P < 0.01$). T stage and locoregional failure showed a nonsignificant trend toward association with overall survival ($P = 0.06$).

Discussion

Management of the clinical N0 neck is controversial in oral cancer, particularly in the case of SCC of maxillary gingiva, alveolus, and hard palate. The low incidence of cervical metastases

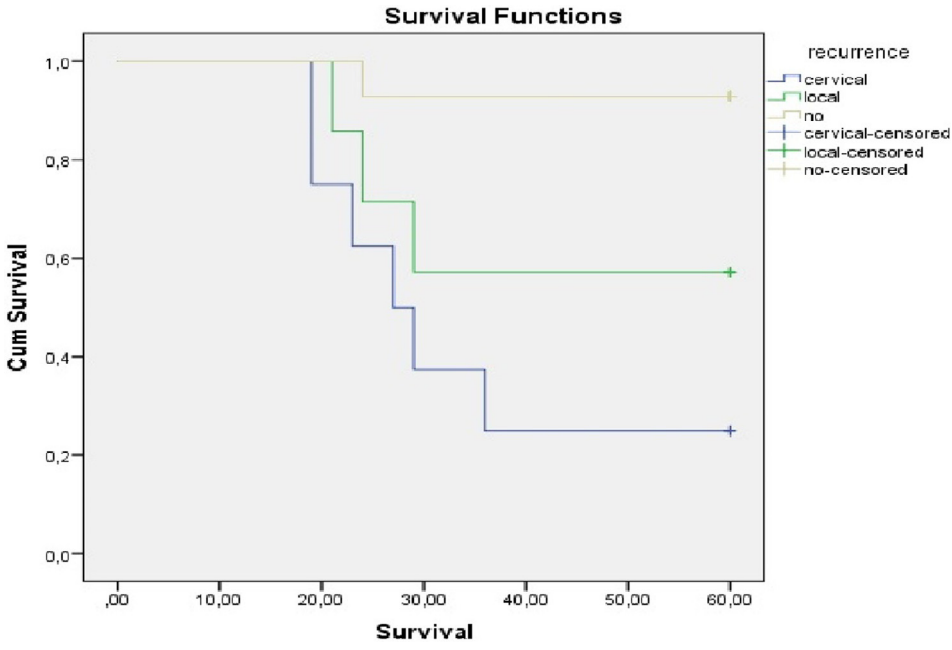

Fig. 2. Outcomes in relation to recurrence.

has historically been considered a hallmark of this disease and "watch and wait" strategy is typically used to control the neck at early stages (T1N0M0/T2N0M0).[1] However, many authors have recently suggested that maxillary SCC should be considered to be equally aggressive as other carcinomas of the oral cavity. For instance, Beltramini et al demonstrated node involvement in 21.5% of 65 patients, while 12.3% of patients (8/65) were classified as N+ at the first observation. However, 19.4% of the patients classified as N0 (6/31) experienced a cervical failure during the first year of follow-up.[1] Mourouzis et al found evidence of cervical disease in 6 of 17 patients with maxillary SCC (35.2%). Four of these patients (23.5%) were classified as N+ at presentation. However, 2 of 13 clinically N0 patients (15.3%) experienced a cervical recurrence during the first 18 months of follow-up.[13] Similarly, Ogura et al reported lymph node involvement in 6 of 21 patients at presentation (28.5%). However, 8 of 15 patients considered as clinically N0 (53.3%) developed cervical metastases during the first 2 years of follow-up.[14] In the same vein, Morris et al reported cervical involvement in 28.4% of 139 patients.[15] In our series, node involvement was evidenced in 10 of 29 patients (34.4%), with 6 of these 10 patients classified as N+, showing node involvement at presentation. However, 4 were initially classified as N0. Thus, occult metastases were observed in 13.7% of our patients (4/29). Interestingly, level I was the most affected level and 55.3% of all positive nodes were found at this level. Only 1 patient presented positive nodes at level IV (2.1%). However, this patient also showed affectation of level II and level III. Thus, no skip metastases were evidenced in the present study. Similarly, level I was the most affected area in the 6 N+ patients previously classified as clinically N0. Node involvement represents one of the most significant prognostic factors in oral oncology. In our series, N+ patients also showed drastically worse outcomes. In particular, while overall survival was 65.5% in the present study, this rate was 89.5% in N0 patients compared with only 20% in N+ patients ($P < 0.01$). These data are also comparable with other studies in the field. According to the literature, the overall survival rate for SCC of maxillary gingiva, alveolus, and hard palate ranges between 49% and 69%.[16,14] For instance, Mourouzis et al reported an overall survival rate of 58% in 17 patients with SCC of this anatomical region. Moreover, N+ patients showed the worst outcomes (50% vs 69.2%).[13] In our study, N involvement showed a significant relationship with T

stage and tumor thickness. Only 1 of 9 T1 tumors (11.3%) was associated with positive cervical nodes. In contrast, node involvement was evidenced in 22.2% of T2 (2/9), 100% of T3 (2/2), and 55.5% of T4 (5/9). With respect to tumor thickness, no tumors of the N+ group of patients presented a thickness <0.4 cm. Moreover, N involvement was also associated with a higher risk of suffering a local or cervical recurrence during follow-up.

The recurrence rate was 51.7% (15/29) in the present report. In particular, local and cervical failures were observed in 24.1% (7/29) and 27.6% (8/29) of patients, respectively. Tumor thickness and involved/affected margins were both strongly associated with a higher risk of recurrence.

Thus, considering the high rate of node involvement (34.4%) and occult metastases (13.7%) observed, we recommend a more aggressive treatment of SCC of maxillary gingiva, alveolus, and hard palate, even at early stages. Elective treatment of the cervical nodes is widely accepted in oral oncology when the risk of occult metastases exceeds 15%-20%. In our series, 22.2% (2/9) of patients with T2 tumors showed lymph node involvement after postoperative histopathologic examination. Taking this into consideration, we advise performing selective I-III neck dissection in patients with cT2N0M0 SCC of maxillary gingiva, alveolus, and hard palate. Due to the low rate of positive nodes found at levels IV and V in clinically N0 patients, we believe that supraomohyoid neck dissection could be a sufficiently safe treatment for patients with no evidence of cervical affectation before surgery. However, we recommend performing a selective I-V neck dissection in the case of N+ patients. This approach might reduce the number of undiagnosed occult metastases and improve overall survival. A "watch and wait strategy" should be considered only in the case of T1 tumors. This is supported by the fact that in our series only 1 of the 9 T1 tumors (11.1%) presented node involvement.

To summarize, this report highlights 3 central points of interest. First, SCC of maxillary gingiva, alveolus, and hard palate shows an aggressive behavior that is comparable with other oral cavity cancers. Second, a more aggressive treatment is thus required for improving locoregional control and overall survival. In particular, supraomohyoid neck dissection might be useful in treating cT2N0M0. Third, several pathologic features such as N involvement, N stage, T stage, and locoregional failure all have a negative impact on overall survival.

This study presents some limitation. First, it is a retrospective study with the consequent limitations that this may cause. Second, the sample is small. However, there are not many reports that analyze in detail the involvement of this specific anatomical area. Further researches are essential to better understand the behavior of maxillary SCC.

Conflict of interest

None.

Funding

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.currproblcancer.2018.10.004.

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