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What is the real prognostic value of close margins in oral oncology?

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A B S T R A C T

Aim: The surgical margin is usually considered an important prognostic factor in oral oncology. However, the real value of a close surgical margin and its relationship with survival is still unclear. Thus, the present report sought to identify the relationship between close surgical margins and overall 3-year survival, whilst also analyzing the association between such margins and recurrence.

Materials and Methods: The medical records of 200 patients affected by oral squamous cell carcinoma were retrospectively reviewed. The patients were divided into three groups: positive margin (0–2 mm), close margin (2–5 mm), and negative margin (>5 mm). The relationship between surgical margins and overall survival and recurrence rate was analyzed.

Results: Surgical margins and reoperation were found to have no significant association with overall survival ($P > 0.05$). Overall survival was 63% in our sample. Specifically, this was 50%, 64.7% and 66.2% in patients with positive, close and free margins, respectively. Perineural invasion, pN, and locoregional or cervical recurrences were the factors most directly related to overall survival.

Discussion: The results of this study indicate that surgical margins are not directly related to overall survival and other factors might significantly influence patient outcomes. Advanced T stage, node involvement, perineural invasion, and ECS are strongly linked with patient survival ($P < 0.05$). These findings should be carefully evaluated in patients with close surgical margins. Our results indicate that an aggressive adjuvant treatment of patients with close surgical margins could help in obtaining a similar pattern of overall survival with patients with negative margins.

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Introduction

The analysis of surgical margins is generally considered to be a main prognostic factor in patients affected by oral squamous cell carcinoma (OSCC), and represents the only factor potentially controllable by the surgeon.¹⁻³ Moreover, it indicates if the tumor has been completely removed and helps to guide postoperative adjuvant treatments. According to the current literature, surgical margins are usually classified into 3 subtypes: free (>5 mm), close (between 2 and 5 mm) and positive (0-2 mm).² However, even if this classification is widely accepted and used there is no consensus on the real prognostic value of surgical margins. This is particularly true in the case of close margins.^{4,5} A positive margin is an indicator for postoperative adjuvant therapy or reoperation whilst a clean margin is an indicator for clinical follow-up or adjuvant therapy (radiotherapy and/or chemotherapy) in the presence of poor prognostic factors.^{2,6}

Unfortunately, the real value of close surgical margins is still not completely clear. Some authors suggest that close margins are related to poor outcomes in terms of overall survival and disease-free survival.^{3,7} Thus, reoperation or adjuvant treatment (radiotherapy ± chemotherapy) are required to complete the oncological treatment and increase the odds of survival. On the other hand, recent reports have demonstrated that patients with close margins may show similar patterns of overall survival and DFS to patients with free margins.⁴ In particular, Dik et al recently reported that a surgical margin ≥ 3 mm with ≤ 2 unfavorable histopathological factors might only be treated with clinical follow-up, due to the low risk of local recurrence shown by this group of patients.⁵ Thus, the real interpretation of the surgical margin and its relationship with OS represents a highly controversial issue. Even if the surgeon attempts to resect a 10 mm margin, tissue shrinkage will modify the size of the sample analyzed by the pathologist. Consequently, the margin observed under the microscope is always smaller than the margin obtained during the primary surgery.⁷ In addition, the real benefit of reoperation in the case of close or infiltrated margins has not been clearly demonstrated.⁵ All of these factors could determine the postoperative management of patients with OSCC, particularly in the case of close surgical margins. Therefore, the main aim of the present report was to identify the relationship between surgical margins and 3-year overall survival. The association between surgical margins and recurrence (local, locoregional, and cervical) was also analyzed, whilst a number of other pathological features were studied to evaluate the impact of each one on patient survival.

Materials and methods

Between 2007 and 2015, a retrospective study was conducted analyzing the medical records of 200 previously untreated patients with OSCC. The study was approved by the Hospital Universitario Virgen de las Nieves Institutional Review Board. All patients were treated with tumorectomy. Neck dissection was performed at the primary surgery when clinical and radiological exploration suggested simultaneous cervical involvement or tumor thickness >4 mm. The neck dissections included Levels I-III or IV (tongue and floor of the mouth cancers) in patients with clinically negative neck. However, neck dissection was extended to Level I-V if clinical or radiological examination evidenced signs of nodal involvement. The treatment strategy of all patients was approved by a multidisciplinary oncological committee composed of maxillofacial surgeons, oncologists, pathologists, radiotherapists, and radiologists. The clinical stage of the primary tumor was established following the recommendations of the International Union Against Cancer (UICC).⁸ It is interesting to note that our protocol does not discriminate between positive

and close margins. All margins <5 mm are considered positive and patients are treated with reoperation or adjuvant treatment with radiotherapy and chemotherapy if the margin could not be extended. Adjuvant treatment with radiotherapy and/or chemotherapy was also administered in all patients with positive neck dissection and/or poor prognostic factors (T3, T4, ECS, nerve and vascular invasion) regardless of the surgical margin. The fact that our classification does not include close margins – unlike others that do consider this group – was the main reason for conducting this retrospective analysis.

The pathologist reports were used to analyze the exact value of the surgical margins (resection margin closest to the tumor) and to reclassify each patient. In particular, patients with resection margins >5 mm were classified as free margins, whilst patients with surgical margins between 2–5 mm and 0–2 mm were reclassified as close and positive, respectively. In addition, several pathological features such as T-stage, N stage, tumor thickness, ECS, vascular invasion, and perineural invasion were analyzed. 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 3 years of follow-up. Statistical analyses were conducted using SPSS version 19 software. Frequency and percentages were used to evaluate the incidence of each factor. A bivariate analysis was conducted to reveal which variables were related to mortality as a dichotomous variable. The Pearson or Fisher chi-square test was used for the qualitative variables, whilst numerical variables were analyzed using the Student *t* test. A Kaplan-Meier test was carried out to obtain an overall 3-year survival analysis. Log-rank tests were used to determine the univariate significance of each factor. Variables found to be significant with univariate analysis were included in a multivariate Cox proportional hazards regression model to calculate the hazard ratio and its 95% confidence interval (CI). The *P* value was set at 0.05.

Results

The series comprised 200 patients with oral squamous cell carcinoma, of which 136 were males (68%) and 64 were females (32%). Patient ages ranged between 19 and 91 years, with a mean of 64.17 years. The sites affected by the primary tumor are described in the [Table 1](#). Seventy-five tumors were staged as T1 (37.5%), 65 as T2 (32.5%), 27 as T3 (13.5%), and 33 as T4 (16.5%). Neck dissection was performed in a total of 171 patients (85.5%). In particular, this was performed at the same time as the tumorectomy in 143 patients (71.5%) and after observing a histological tumor with a thickness >4 mm in 28 patients (14%). Node involvement was observed in 73 patients (36.5%) at histopathological examination and signs of ECS were evidenced in 40 of these cases (40/73, 54.7%). 29 patients were classified as Nx (14.5%), 98 as N0 (49%), 21 as N1 (10.5%), 49 as N2 (24.5%), and 3 as N3 (1.5%). A total of 45 patients (22.5%) presented a tumor thickness ≤ 4 mm. However, 155 (77.5%) showed a tumor thickness >4 mm. Perineural invasion was documented in 60 patients (30%). However, only 35 patients showed signs of vascular invasion (17.5%). Free surgical margins were reported in 130 patients (65%) (including reoperation). Positive and close margins were observed in 36 (18%) and 34 (17%) patients, respectively. A total of 25 patients (12.5%) underwent second surgery to extend the primary surgical margins. Of 110 patients (55%) received postoperative radiotherapy to complete the oncological treatment strategy and 56 of these also received chemotherapy (28%). Recurrence was observed in 75 patients (37.5%). The average rate of local, locoregional, and cervical recurrences was 7%, 18.5%, and 12%. Several factors such as pT ($P=0.001$), pN ($P=0.001$), tumor thickness ($P=0.009$), vascular invasion ($P=0.001$), ECS ($P=0.001$), perineural invasion ($P=0.001$), and recurrence ($P=0.001$) showed a significant impact on overall survival ([Table 1](#)) ([Figs 1, 2, and 3](#)). In spite of all of these factors showing a significant association with overall survival in the univariate analysis, only pN (N2 and N3), perineural invasion and recurrence (locoregional and cervical) showed a significant negative impact on survival when analyzed in a multivariate Cox proportional hazards regression model. Thus, patients with perineural infiltration are 2.58 (95% CI, 1.52–4.39) times more likely to die when compared with patients without signs of perineural invasion. Similarly, N2 and N3 patients have 3.93 (95% CI, 2.26–6.84) times more risk of death than patients with N0/Nx. The

Table 1

Relationship between the variables analyzed in the study and overall survival.

	n		Survival	P
Site	Tongue	87 (43.5%)		
	FOM	44 (22%)		
	Buccal mucosa	26 (13%)		
	Retromola zone	18 (9%)		
	Other	25 (12.5%)		
pT	T1	75 (37.5%)	74.7%	0.001
	T2	65 (32.5%)	58.5%	
	T3	27 (13.5%)	70.4%	
	T4	33 (16.5%)	39.4%	
pN	Nx	98 (49%)	75.9%	0.001
	N0	29 (14.5%)	75.5%	
	N1	21 (10.5%)	52.4%	
	N2	49 (24.5%)	36.7%	
ES	N3	3 (1.5%)	33.3%	
	+	40 (54.7%)	37.5%	0.001
	-	33 (45.2%)	67.4%	
Tumor thickness	<0.4	45 (22.5%)	80%	0.009
	>0.4	155 (77.5%)	58.1%	
Margin	Positive	36 (18%)	50%	0.212
	Close	34 (17%)	64.7%	
	Negative	130 (65%)	66.2%	
Vascular invasion	+	35 (17.5%)	37.1%	0.001
	-	165 (82.5%)	68.3%	
Perineural invasion	+	60 (30%)	46.7%	0.001
	-	140 (70%)	70%	
Reoperation	+	25 (12.5%)	28%	0.319
	-	175 (87.5%)	38.3%	
Recurrence	No	125 (62.5%)	93.5%	0.001
	Local	14 (7%)	81.3%	
	Loco-regional	37 (18.5%)	13.3%	
	Cervical	24 (12%)	19.4%	

analysis of N1 patients did not reveal a significant association with a poorer outcome in terms of overall survival. Importantly, the risk of death is 9.86 (95% CI, 5.83-16.68) times higher in patients showing cervical or locoregional recurrence.

Surgical margins ($P=0.212$) and reoperation showed no significant association with overall survival ($P=0.319$). Overall survival was 63% in our sample. Specifically, survival was 50%, 64.7%, and 66.2% in patients with positive, close, and free margins, respectively (Fig 4). However, surgical margins were associated with a higher risk of developing locoregional or cervical recurrences ($P=0.001$). The average rate of locoregional or cervical recurrence was 48.3% in patients with positive margins. This might be explained due to the high number of patients with advanced stages included in this group. Thus, the recurrence rate could be related to the stage of disease at diagnosis and not only to the value of the mucosal margins. In contrast, cervical or locoregional relapse was observed in 38.2% and 35.3% of patients with close and negative surgical margins, respectively. In addition, 8.3% of patients with positive margins and 11.7% of patients with close margins experienced a local recurrence during follow-up. Otherwise, the local recurrence rate was 6.9% in patients with negative margins. Re-operation showed no significant association with the frequency of suffering a local, locoregional, or cervical recurrence during follow-up ($P=0.338$).

Discussion

In the last 30 years, several studies have aimed to establish the real value of surgical margins in oral squamous cell carcinoma. However, this still represents a very controversial issue.^{2,4,5,7,9}

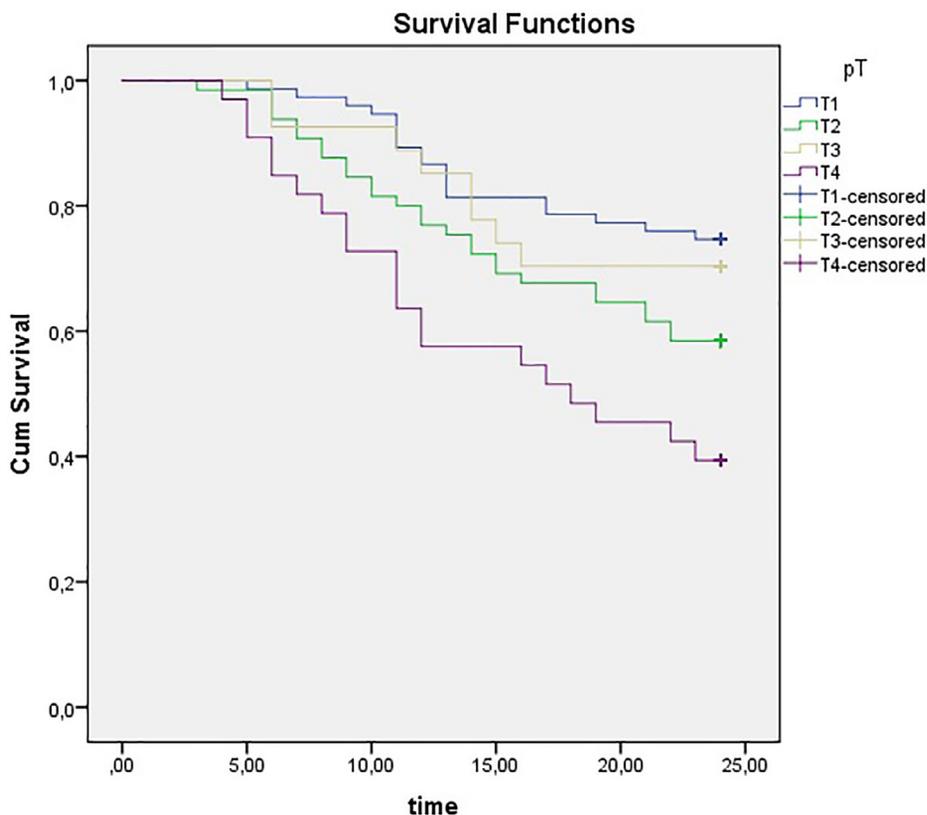


Fig. 1. Relationship between T-stage and overall survival. (Color version of figure is available online.)

The meaning of free and positive margins is clear; patients with free margins may require only a clinical follow up (early stages, T1N0/1 and T2N0) or adjuvant treatment with radiotherapy \pm chemotherapy in the presence of poor prognostic factors (T3, T4, N+, ECS, surgical margins, nerve and vascular invasion) and positive margins are usually treated with reoperation or adjuvant treatment with radiotherapy \pm chemotherapy.^{2,5} On the other hand, clinical management of patients with close resection margins is more complicated and several factors must be considered before deciding a treatment strategy. Reoperation, adjuvant treatment, or both, represent the three main treatment strategies in this group. In this regard, reoperation might play a key role and could help to avoid the necessity of adjuvant treatment. However, it is not widely accepted that re-operation may be useful in improving overall survival rates. According to Ch'ng et al reoperation or adjuvant therapy are not required in the case of close surgical margins (<5 mm) and a maximum of 1 poor histological prognostic factor.¹⁰ Similarly, Dik et al also suggested that a watch and wait strategy might be safe enough to manage patients with close margins >3 mm and ≤ 2 unfavorable histopathological features.⁵ Zanoni et al found similar patterns of overall survival between patients with close surgical margins (2.3-5 mm) and those with free margins (>5 mm). According to these authors, 2.2 mm would represent the optimal cutoff to consider a margin as clean and requiring no other treatments in the absence of any other poor prognostic factor.⁴ On the other hand, a number of authors have reported poorer outcomes in patients with close margins and advise treating these patients with reoperation or adjuvant treatment.^{1,7,11-13} In our series, reoperation and surgical margins did not show a statistically significant association with overall survival. Patients with infiltrated margins showed

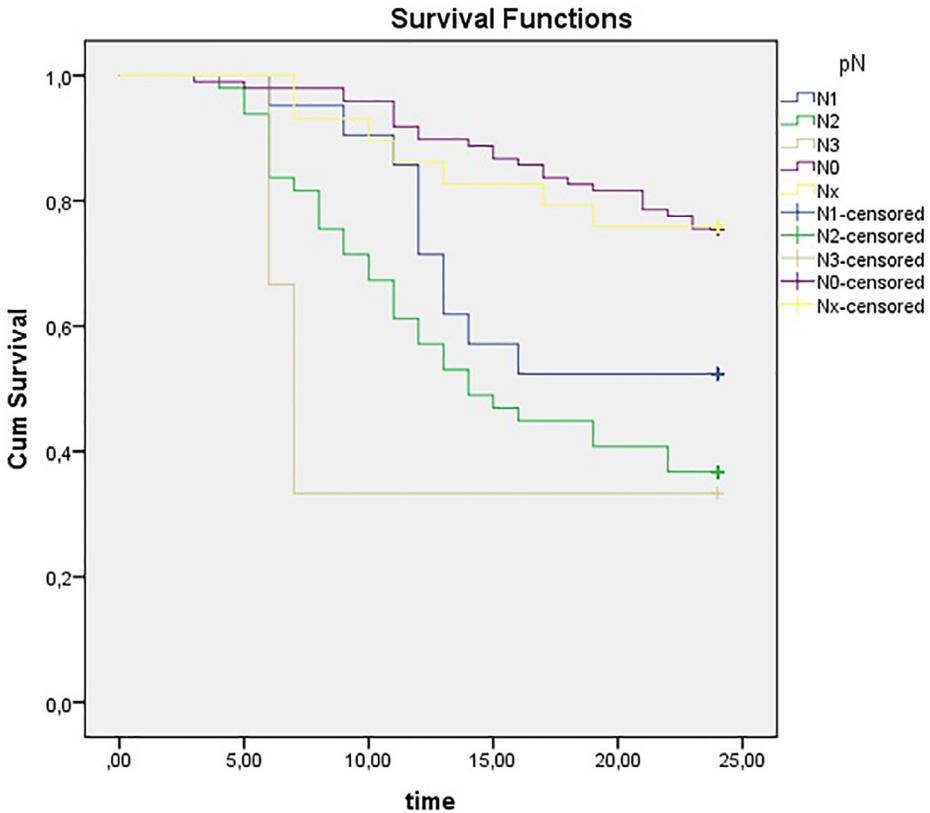


Fig. 2. Relationship between N-stage and overall survival. (Color version of figure is available online.)

poorer outcomes in terms of overall survival. Specifically, 3-year overall survival was 50% in patients with positive margins. In contrast, overall survival was 64.7% and 66.2% in patients with close and negative margins ($P=0.212$). In the present study, 25 patients (12.5%) underwent second surgery to extend the margin, of which 11 presented a positive margin, whilst the other 14 belonged to the close margin group. Postoperative radiotherapy was administered in 20 of 34 patients (58.8%) with close margins and 16 of these patients (47%) also received chemotherapy. Hence, in the present study the treatment strategy was relatively aggressive in patients with close resection margins. According to our data, other prognostic factors and not only surgical margins should be considered to choose the proper treatment of patients with close margins. However, analysis of the survival curve revealed anomalous trend in patients with T2 cancers. In particular, T2 cancers showed poorer outcomes than T3 in terms of overall survival. The main explanation for this data could be related to the difference in sample size ($n65$ vs $n27$). No other differences in terms of reoperation or adjuvant treatment were found between the groups. Fourteen of 65 patients staged as T2 (21.5%) presented close margins at postoperative pathological examination. Eight of these (57.1%) underwent a second surgery to extend the margin and no adjuvant treatment was added to the protocol strategy. Moreover, 3 of these 8 patients (37.5%) died during the first 3 years of follow-up. Interestingly, all these 3 tumors would be staged as T3 with the last UICC TNM classification. Thus, these tumors could have been undertreated using the previous TNM system. In our opinion, reoperation should be considered only in small T1 in the absence of poor histological factors. In these cases, a sufficiently wide extension could be carried out without causing an excessive functional alteration. In contrast, the oncological

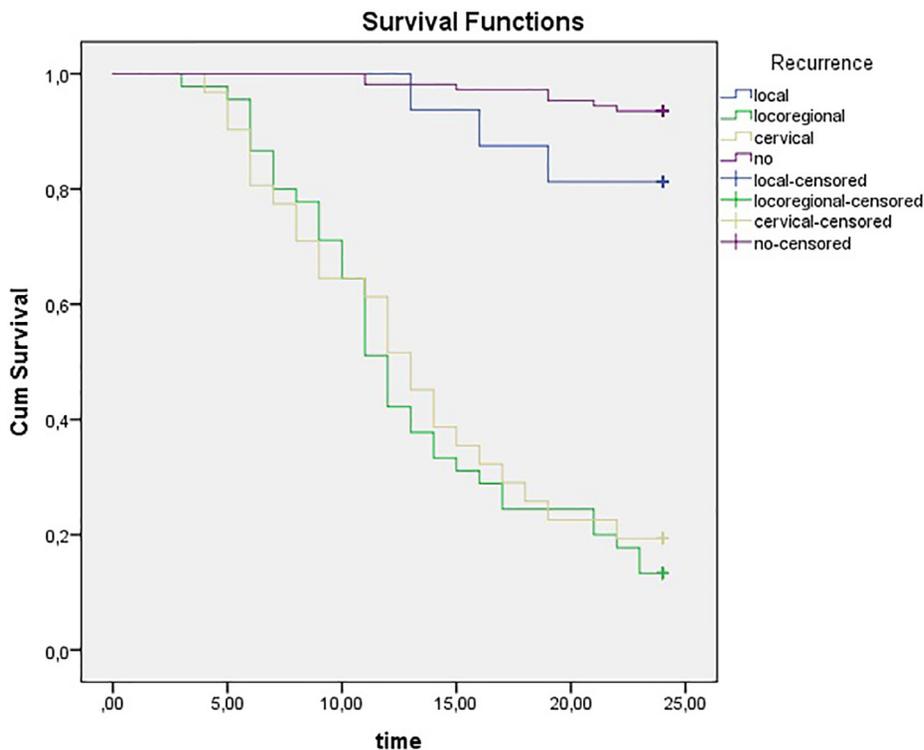


Fig. 3. Relationship between recurrence and overall survival. (Color version of figure is available online.)

benefit offered by reoperation does not justify the loss of function in the case of T2 tumors. In these cases, a reoperation would probably indicate a wider extirpation and, consequently, a reconstruction with free or locoregional flaps. Unfortunately, it is impossible to know exactly whether the extension has been effectively carried out in the correct area.⁷ Moreover, specific patterns of tumor invasion may also influence the validity of reoperation.¹⁴ Hence, we suggest that it is appropriate to always consider adjuvant treatment in the case of close margins (radiotherapy \pm chemotherapy). This is particularly true in the presence of poor histological prognostic factors. Nowadays, it is not reasonable to disregard the group with close margins and to therefore administer chemotherapy to all patients with surgical margins between 2 and 5 mm in the absence of other poor prognostic factors. In this regard, it is always more difficult to achieve 5 mm of free margins due to the considerable technological advances in the field of pathology.

In light of the latest scientific evidence and on the basis of the results of the present study, we have decided to change our protocol to incorporate the group with close surgical margins. Now, only T1 tumors with close or infiltrated margins and without poor prognostic factors underwent second surgery to extend the surgical margin. In contrast, radiotherapy is always proposed in patients with close margins and ≤ 2 poor prognostic factors according to patient comorbidities. Postoperative chemotherapy is usually added to the protocol strategy if pathological analysis reveals > 2 poor prognostic factors (T3, T4, N+, ECS, vascular invasion and perineural invasion). Consequently, a watch and wait strategy alone is never implemented in patients with close surgical margins. Several papers demonstrate the negative impact of close surgical margins in oral oncology and hence we do not consider it appropriate to leave a close margin without further treatment.^{1,3,11,15,16} The results of this study suggest that surgical margins might not be directly related to overall survival and other factors may have a bigger impact on patient outcomes. Advanced T stage ($P=0.001$), node involvement ($P=0.001$), perineural invasion

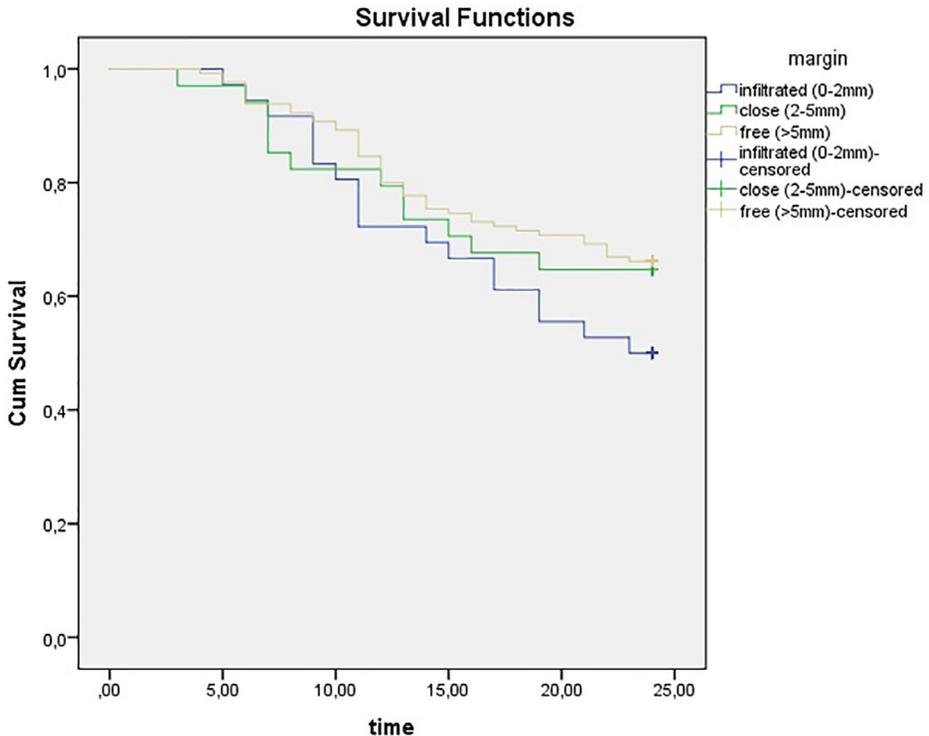


Fig. 4. Relationship between surgical margins and overall survival. (Color version of figure is available online.)

($P=0.001$), and ECS ($P=0.001$) are all significantly linked to overall survival and these findings should be carefully evaluated in patients with close surgical margins. In particular, the risk of death in patients with N2 and N3 disease is 3.93 times higher than in N0 patients ($P=0.001$). N1 patients also showed a higher risk of death than N0 patients (HR 1.493) ($P=0.08$). Although this latter difference did not reach statistical significance, we firmly believe that it requires more in-depth analysis. N1 disease at early stages may indicate a tumor with a highly aggressive behavior. It seems that some tumors may present metastatic capacity from the first cell. In these cases, the pathology could be considered systemic from the beginning, as occurs with cancer affecting other locations of the body. Radiotherapy might be particularly useful in managing patients staged as T1N1 even in the absence of other poor prognostic factors. Perineural invasion also revealed to be an important prognostic factor for oral squamous cell carcinoma. Specifically, patients showing perineural invasion presented 2.58 (95% CI, 1.52-4.39) times more risk of dying during the first 3 years of follow-up. In addition, patients that experienced cervical or locoregional recurrences showed 9.86 (95% CI, 5.83-16.68) times more risk of death due to the tumor. Interestingly, locoregional and cervical recurrence were significantly more frequent in N+ patients. This might suggest that tumors with metastatic capacity could also present greater local aggressiveness. Hence, all these factors must be carefully analyzed in order to adequately evaluate patients with close surgical margins. Our results indicate that an aggressive adjuvant treatment of patients with close surgical margins could help in obtaining a pattern of overall survival similar to that of patients with free surgical margins (64.7% vs 66.2%).

Unfortunately, there are no reliable markers for predicting the behavior of oral squamous cell carcinoma, and this presents a considerable challenge for the preoperative and postoperative management of these patients. Further studies are needed to better understand the real value of surgical margins and their impact on patient overall survival. However, we must not disregard

the fact that surgery represents only the first step of treatment in many cases, and the necessity of adjuvant treatment cannot only depend on the status of surgical margins. Close surgical margins should be considered as another poor prognostic factor in oral oncology, and adjuvant treatment might be useful in this group of patients.⁷

Declaration of Competing Interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.cupr.2019.100500](https://doi.org/10.1016/j.cupr.2019.100500).

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