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Incidence, predictors and impact of positive bony margins in surgically treated T4 stage cancers of the oral cavity

Arjun Singh, Manish Mair, Hitesh Singhvi, Ankit Mahuvakar, Deepa Nair, Sudhir Nair, Pankaj Chaturvedi*

Head and Neck Oncology Department, Tata Memorial Hospital, Mumbai, India

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ABSTRACT

Objectives: A sea of literature addressing the adequacy of mucosal/soft tissue surgical margins in oral cavity cancers is available, but no mention exists regarding bony margins. We aim to study the predictors and impact on survival of positive bony margins and propose a safe margin distance.

Methods: This is a retrospective study of 400 consecutive surgically treated pT4 oral cavity squamous cell carcinoma patients between January 2012 and December 2015. The factors predicting positive bony margins were determined using chi-square test. Kaplan Meier and Cox regression hazard models were used for survival analysis. The median follow up was 36 months.

Results: The only factor that significantly predicted positive bony margins was lymphovascular emboli. The 3-year OS with bony margin positivity was 36.9%, compared to 67.5% for patients with adequate margins. When the tumor infiltrated the bone beyond mucosa (20.25%) the survival outcomes were significantly worse than the other patterns. Microscopic spread was seen in 10% cases, at a distance of 8 mm, the presence of which significantly impacted survival outcomes. Analysis of the receiver operating curve identified a cutoff of more than 15 mm as appropriate for classifying adequate bony margins. When the margins were taken above this, a significant positive impact on survival outcomes was present.

Conclusion: The presence of lymphovascular emboli may impact the status of bony margins. Based on our results, to achieve an "adequate margin in bone" we propose taking the bony cut at least 15 mm away from the clinically discernible tumor when treating advanced oral cancers.

Introduction

The paramount objective of any oncologic treatment is complete eradication of disease rendering the least undesirable iatrogenic effects. To judge the adequacy of surgery, margin status is taken as the most common criterion, and it is well established that positive margins are considered a poor prognostic factor for survival outcomes in oral squamous cell carcinoma. For more than three decades the literature has presented varied schools of thought concerning adequate soft tissue and mucosal margin distances, but the evidence on adequate bony margin is sparse. Many contemporary concepts have now resulted in an intriguing number of margin distances, challenging the universally followed 5 mm cut-off [1]. For bone, an adequate margin of 0.5–1 cm from involved or suspicious bone, or removing two teeth on either side of involved bone is practiced [2]. Novel methods of intraoperative bony margin assessment have also been described, but they all have their own limitations.

With almost half of all oral cavity cancers initially presenting with bone involvement, it is important to have a greater understanding of the interaction between disease and tissue in terms of osseous invasion and microscopic spread [2]. While initially it was believed that involvement was via the lymphatic channels through the mandible en route to the cervical basin, invasion has now been established by direct extension [3,4]. The more contemporary literature suggests that rather than bone involvement per say, the pattern of invasion is more important, with a significantly higher rate of local recurrence in the infiltrative versus the erosive pattern [5]. However, the evidence is quite limited when it comes to the occult spread of the disease along the bone. This microscopic spread is one of the main reasons for having positive resection margins, and furthermore, the spread is not detected via frozen section, leading to a perplexing dilemma when the final histopathology reports bony margin involvement by disease. This not only complicates the possibility of a revision surgery and need for additional reconstruction, but also the need for intensification of adjuvant

* Corresponding author.
E-mail address: chautrvedi.pankaj@gmail.com (P. Chaturvedi).

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management.

To avoid such situations and improve the survival outcomes of advanced oral cancers, a precisely defined cut-off margin for bone is required at which the risk of local recurrence reduces substantially, improving the overall survival outcomes. To address these issues, we systematically analyzed the incidence and predictors of positive bony margins as well as its impact on survival outcomes. The secondary aim of the study was to look at the presence of microscopic tumor spread along the bone, and subsequently propose an adequate bony resection margin required during advanced oral cancer surgeries.

Material and methods

We retrospectively reviewed the charts of 400 consecutive treatment naïve surgically treated pT4 oral squamous cell carcinoma patients (alveolo-buccal complex), operated at our centre from January 2012 to December 2015. All patients underwent appropriate imaging to identify the presence of any skin and/or bone involvement. At our institute we follow a standardized systematic histopathology reporting system where the mucosal and soft tissue (including bone as well) margin distance from the gross tumor is measured in all dimensions using a bread loafing method, followed by microscopic sampling of the same margin distances. All other clinical and pathologic parameters were obtained from the electronic medical records of the hospital. All patients included in the study received adjuvant therapy as per our institute protocol. When depth of invasion was more than 10 mm, or more than 5 mm with other adverse factors like perineural invasion (PNI), lymphovascular emboli (LVE) or poor grade of differentiation, or in the presence of metastatic neck nodes without extranodal extension (ENE), radiotherapy (RT) was prescribed. Concomitant chemotherapy (CCRT) was added in cases of positive margins or presence of ENE.

Statistical analysis

We analyzed the data using SPSS 25.0 (IBM, Armonk, NY). To identify the prognostic factors associated with positive bony margins, we ran a univariate analysis using chi-square test. Disease free survival (DFS) and Overall survival (OS) was calculated by Kaplan-Meier analysis. To assess the impact of a particular variable on survival outcomes, we ran a univariate analysis (Log-rank test) of selected variables based on their clinical relevance. All significant variables were subsequently analyzed with a Cox-regression analysis using forward stepwise selection (Multivariate analysis). We also calculated the DFS and OS for 4 differing margin status groups, i.e. uninvolved, bone margin involved, mucosal margin involved and both margins involved. Microscopic spread in bone was determined by the difference between the distance from gross tumor to cut margin, and, the distance from microscopic tumor to cut margin. To understand the biology of the disease, we divided the entire cohort into three categories as depicted in Fig. 1. Survival outcomes were assessed for each of the three categories using Kaplan-Meier analysis. The receiver operating characteristic (ROC) curves were utilized to identify the ideal cut off of adequate bony margins having the best sensitivity and specificity for survival outcomes.

Results

The demographic, clinical and histopathological details of the study group are summarized in Table 1. The mean age of the patients was 52.67 years with male to female ratio of 3.7:1. They were classified as pT4 due to the presence of bony invasion in 85.5% (n = 342), skin involvement in 29.3% (n = 117) and both in15.75% (n = 63). Almost half the patients had metastasis to the neck nodes (51.75%, n = 207). Overall margin positivity was seen in 14.3% (n = 57) out of which bone margin positivity comprised 10.5% (n = 42).

Factors influencing positive bone margin

For this analysis, we considered only those patients with bone erosion (n = 342). The only factor that notably impacted positive bony margins was LVE (p-0.006), while other factors like PNI (p-0.076), nodal metastasis (p-0.376), ENE (p-0.656), grade (p-0.719) and skin margin positive (p-0.708) had no statistical significance. Even though not statistically significant, patients with PNI had a higher probability of bony margin involvement (28.6% in positive bony margins vs 22.1% in free margins). Out of the 264 segmental mandibulectomies performed 27 had positive bone margins, while in bite composite resections (n = 103) and maxillectomies (n = 19) only 9 and 6 patients had positive bone margins, respectively.

Follow up and impact of positive margins on survival

The median follow up period was 36 months. At the latest follow up, 60% were alive without disease, 8.3% had presence of disease, and 31.8% were dead (120 due to disease and 7 due to other causes). We found that the DFS was significantly affected by nodal metastasis (p-0.000), grade (p-0.005), and presence of bone erosion (p-0.038). The presence of positive margin also had an impact on DFS, however marginally not significant (p-0.091). The OS was significantly affected by nodal metastasis (p-0.000) and presence of any margin being positive (p-0.032) (Tables 2 and 3).

Bone margin positive versus mucosal/soft tissue margin positive

We further analyzed which of the two, i.e. bone or mucosa/soft tissue margin positivity, had a greater detrimental impact on survival outcomes. Bone margin positivity had a negative impact on both DFS and OS (p-0.016 and p-0.016, respectively) while soft tissue margin positivity impacted only OS (p-0.034) and not DFS. The 3-year survival with bony margin positivity was 36.9%; with mucosal margin positive being 52.1% and 67.5% for patients with adequate margins. This shows that bone margin positive patients had a worse survival outcome compared to mucosal/soft tissue margin positivity.

Microscopic spread of tumor in the bone

The mean and median distance of microscopic spread along the bone in the entire cohort was 0.71 and 0.5 cm, respectively and was seen in 10% of the study population. The presence of this microscopic spread significantly impacted the DFS (p-0.039) and OS (p-0.023) of these patients (Fig. 2). Based on the form of spread, we divided the cohort in three groups as shown in Fig. 1. We found that the tumor spread was more in the bone as compared to the mucosa (Group 1) in 24.4%. In this group, the mean and median spread of tumor in the bone beyond the mucosa was 0.86 and 0.7 cm (0.6–4.5 cm). The mucosal spread of the disease beyond the involved bone was seen in 70.4% (Group 2), and disease stopped at the same level for both mucosa and bone in 5.2% (Group 3). Interestingly, Group 1 had a worse survival outcome as compared to the other two groups. Moreover, microscopic spread of tumor in the bone, beyond the grossly visualized tumor, was detected in 10% of the cases.

Adequate margin cut off survival outcomes

Using the ROC curve, the ideal cut-off for adequate bony margin having the best sensitivity and specificity for survival outcomes was found to be 15 mm (Fig. 3). The mean distance of the tumor from bony cut margin was also 15 mm (Range 0–45 mm). Based on this, we divided patients into two groups, one who had bony margins of 15 mm or more and other with less than 15 mm. A significantly better OS (p-0.014) and DFS(p-0.023) was seen when bony margins were taken 15 mm or more during tumor resection (Fig. 4).

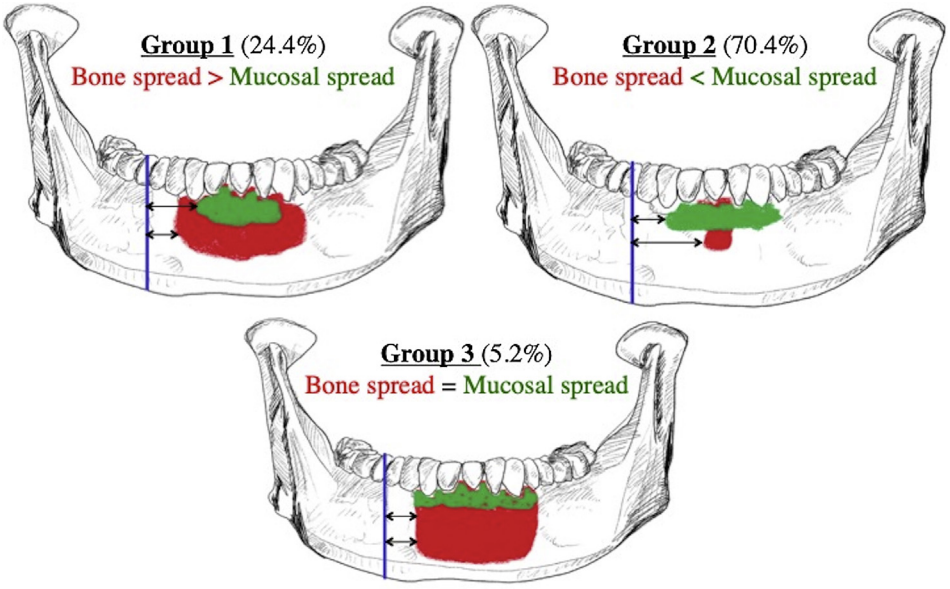

Fig. 1. Patterns of spread in bone and mucosa.

Table 1
Tumour and histopathological characteristic of the patients in the study group.

Tumor and patient characteristics	Total n = 400 patients (%)
Age	
Mean	52.67
Median	53.00
Gender	
Male	315 (78.8)
Female	85 (21.3)
Median Follow up	36 months
Lymphovascular Emboli (LVE)	
Yes	13 (3.3)
No	387 (96.8)
Perineural Invasion (PNI)	
Yes	93 (23.3)
No	307 (76.8)
Grade	
Well differentiated	81 (20.3)
Moderately differentiated	229 (57.3)
Poorly differentiated	90 (22.5)
Nodal status (pN)	
N0	193 (48.3)
N1	78 (19.5)
N2a	15 (3.8)
N2b	94 (23.5)
N2c	20 (5.0)
Extranodal extension (ENE)	
Yes	169 (42.3)
No	231 (57.8)
Bone erosion	
Present	342 (85.5)
Absent	58 (14.5)
Skin involvement	
Yes	117 (29.3)
No	283 (70.8)
Margin status	
Overall margin	
Adequate	343 (85.8)
Involved (< 1mm)	57 (14.3)
Bone	
Involved (< 1mm)	42 (10.5)
Mucosa/Soft tissue	
Involved (< 1mm)	15 (3.8)

Table 2
Factors affecting Disease Free Survival (DFS).

Factors	Univariate Analysis* P-value	Multivariate Analysis** P-value (Hazard Ratio)	95% Confidence Interval
Nodal Metastasis (Node negative Vs. Node positive)	0.000	0.000 (2.292)	1.609–3.264
ENE	0.000	–	–
Grade	0.000	0.005 (1.650)	1.159–2.349
Skin positivity	0.671	–	–
Sex	0.106	–	–
PNI	0.012	0.256 (1.237)	0.857–1.787
LVI	0.288	–	–
Bone erosion	0.014	0.038 (1.842)	1.034–3.281
Any margin overall positive	0.004	0.091 (1.412)	0.946–2.108

* Kaplan Meier analysis.
** Cox regression analysis.

Table 3
Factors affecting Overall Survival (OS) in the study group.

Factors	Univariate Analysis* P value	Multivariate Analysis** P-value (Hazard Ratio)	95% Confidence Interval
Nodal Metastasis (Node negative Vs. Node positive)	0.000	0.000 (2.360)	1.611–3.459
ENE	0.000	–	–
Grade	0.006	0.101 (1.394)	0.938–2.074
Skin positivity	0.972	–	–
Sex	0.046	0.073 (1.443)	0.967–2.152
PNI	0.063	–	–
LVI	0.698	–	–
Bone erosion	0.039	0.116 (1.655)	0.883–3.103
Any margin overall positive	0.002	0.032 (1.582)	1.041–2.403

* Kaplan Meier analysis.
** Cox regression analysis.

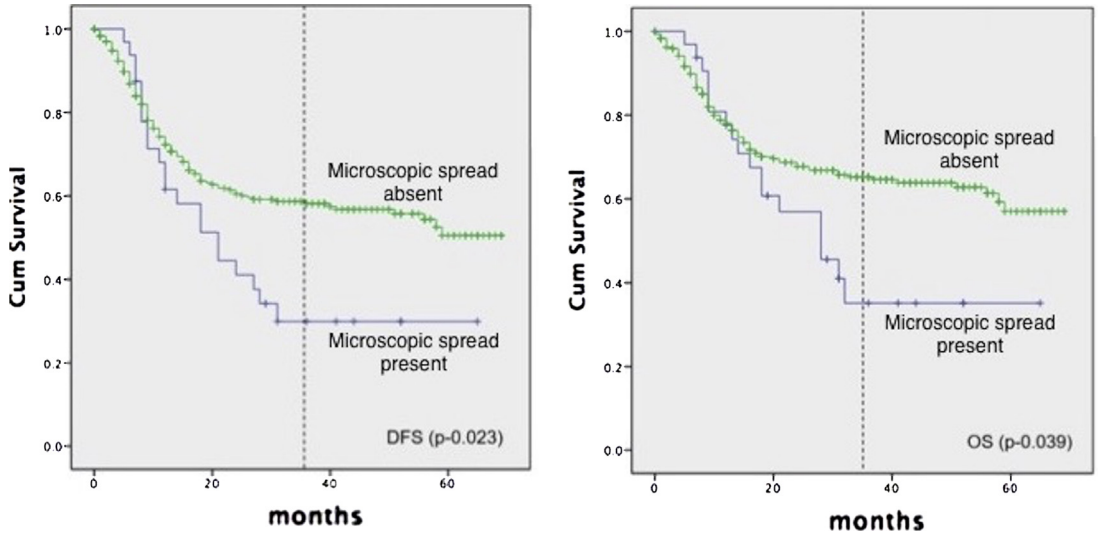

Fig. 2. Survival outcomes when microscopic spread in bone is present.

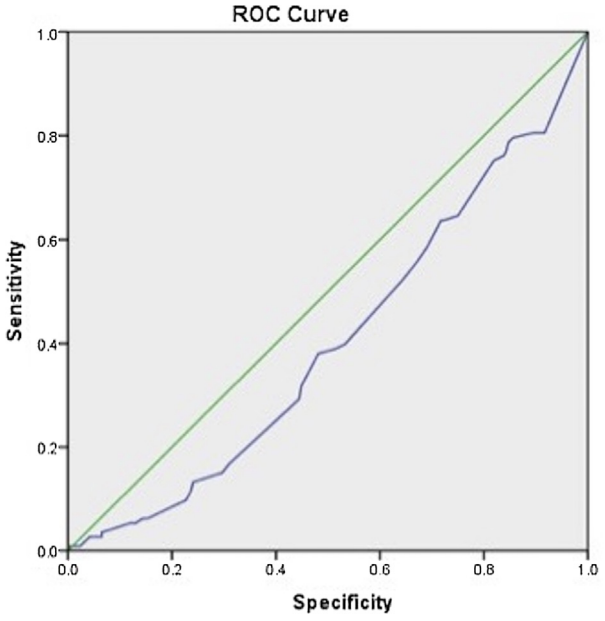

Fig. 3. ROC curve (highest sensitivity and specificity was at 15 mm).

Discussion

Surgical margin status is one of the most significant factors impacting survival outcomes in oral cancers. With the recent transformational advances in cancer management, one would expect a decline in the rate of positive surgical margins (PSM), however, Orosco et al found no significant change over the past 15 years [6]. One of the early studies on margins by Loore et al have shown the incidence of PSM increases proportional to the T stage, ranging from 21 to 55% in T1 to T4 tumors respectively. Subsequently, this higher stage as well as the presence of positive margins have doubled the local recurrence rate as compared to those with negative margins (36% vs 18%) [7]. While all these studies deal with overall positive margin (bony and mucosal) status, we have specifically studied the impact of bony margins on these advanced oral cavity tumors. While only few other series mention an occult spread in bone beyond the tumor, most of them have dealt with a heterogeneous group of early and advanced tumors, skewing the results in either direction. To eliminate this bias, we included only T4 stage disease in our study and found a 10.5% incidence of positive bony margins and overall margin positivity rate of 14.3%. Earlier studies from our institute have shown a similar 13–14% incidence of overall margin positivity in advanced oral cancers [8,9].

We found that the incidence of positive bony margins was higher in patients with LVE. There is abundant literature, which shows that LVE and PNI have a significant impact on mucosal PSM, but ours is the only study showing their impact specifically on bony margins [10]. In concordance with the available literature, our study showed that presence of positive surgical margins had a negative impact on survival outcomes. Nonetheless, it was interesting to find that positive bony margins had a negative impact on both, overall and disease-free survival, while involved mucosal margins impacted overall survival alone. This might be because adjuvant treatment is more effective for residual mucosal disease, which is more vascular and oxygenated (less hypoxic) than on residual bony disease (more hypoxic). Much of the early research work on the effectiveness of radiation on hypoxic tissues suggests that oxygen deficiency is a major source of radiation resistance and the hypoxia can exist in human tumors as a result of a limitation in diffusion [11]. Contrary to our results, Petrovik et al reported that positive bony margin status did not have any impact on local and regional recurrence free survival when post-operative radiotherapy was administered. However, only those patients who underwent marginal mandibulectomies were included in this study and around 80% of the study population had T1/T2 disease. Moreover, they considered close and positive bony margins together, which were seen only in 8 patients translating into biased outcomes [12].

Intraoperative frozen section analysis is not capable of accurately detecting disease at bony margins. Alternative methods include cytopathologic and/or histologic assessment of select portions of the bony margin or medullary scrapings using conventional frozen section. These methods are yet to be validated in large studies and currently may not add any significant survival benefit. Thus in the event of a PSM, re-resection in bone is difficult, as it can be considered only in the post-operative setting, unlike mucosal margin which can be revised if found involved on intra-operative frozen section. The dilemma increases further when reconstruction is done using a free flap. Surgery will then entail part of the reconstructed bone as well as the native bone margin which would significantly increase the risk of flap failure, eventually delaying the adjuvant therapy prescribed and negatively impacting survival [13].

Thus it is absolutely vital to decide what constitutes an adequate bony margin while resecting a T4 oral cancer and since the literature on this is sparse, we derived a cut-off for an adequate bony margin. The mean and median spread of tumor in the bone beyond the mucosa was

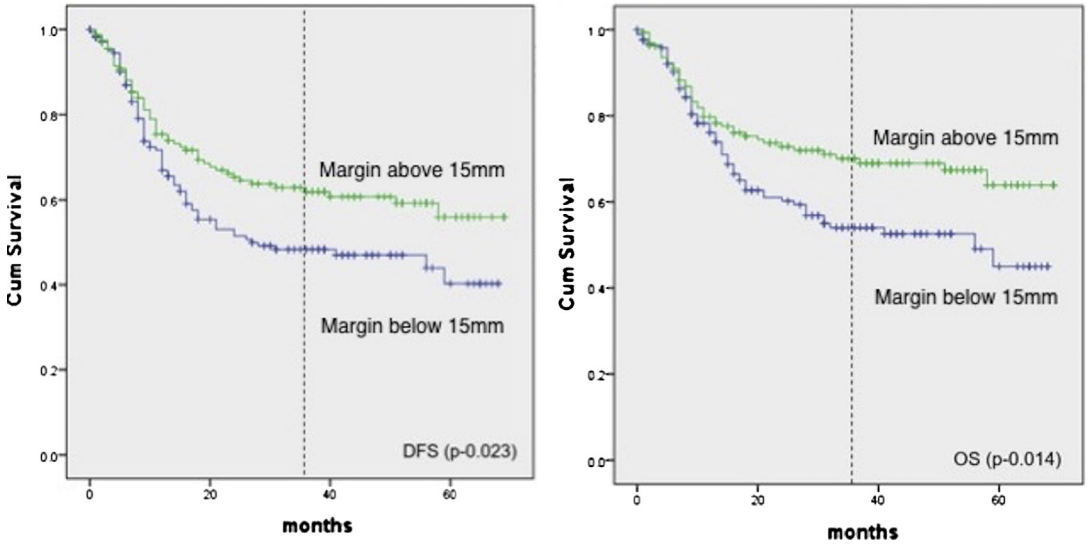

Fig. 4. Survival outcomes above and below 15 mm bony margins.

0.86 and 0.7 cm (0.6–4.5 cm) and the ROC derived cut-off was found to be 15 mm. Both these factors had a negative impact on survival outcomes. From the above measures we can conclude that, if we take our bony cut at 15 mm away from the visualized disease in the bone or the mucosa, we should be able to achieve adequate margins in a significant majority of cases. Furthermore, the literature reports an incidence of microscopic mucosal spread of 8.9% which has a significant impact on survival outcomes [14]. In our study, 10% of the cases had microscopic spread in bone of 8 mm, further reinforcing our recommendation of 15 mm to achieve adequate bony margins.

Conflict of interest

We do not have any financial and personal relationships with other people or organization that could inappropriately influence their work. There are no conflicts of interest to declare.

Author contribution

All authors have contributed equally.

Role of funding source

There is no role of funding source in this article. We confirm that we had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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