Original Article

Surgical Margins and Nodal Metastasis are Prognostic Factors in Oral Squamous Cell Carcinoma: A Meta-Analysis

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Abstract

Background: To find out whether surgical margins and nodal metastasis are prognostic factors in oral squamous cell carcinoma (OSCC). **Materials and Methods:** PubMed search was done to look for studies done on surgical margins and nodal metastasis of OSCC from 2008 to 2018. **Results:** Fixed effects meta-analysis showed a pooled estimate absolute risk reduction of −3% (95% confidence interval [CI] [−8, 2.5%]). *P* =0.2819 from the fixed margin model shows no statistically significant difference between close margins with cases of deaths due to recurrence or metastasis. The pooled odds ratio was 0.87 (95% CI 0.63–1.99, *P* = 0.3928) for the comparison between clear and closed margins for estimating the odds. It should be noted that the mean unweighted local recurrence rate for margins 5 mm or greater was 4.9% with 95% CI as −10.7%, 0.8%. **Conclusion:** The study shows that close surgical margins with nodal metastasis have a poor prognosis in OSCC; however, no statistical significance was seen in this meta-analysis.

Keywords: *Nodal metastasis, prognosis, squamous cell carcinoma, surgical margins*

Introduction

According to the World Health Organization (WHO), oral squamous cell carcinomas (OSCCs) are the most frequent head-and-neck malignancies with 390,000 new cases are reported every year.[1-3] In India, OSCCs are the sixth-most frequent malignancies among males (9.2% of cases) and the seventh-most frequent in females (3.6% of cases) not including skin cancers.[2] In total, these malignancies are 6.7% of all cancer cases. Estimates for 2007 had suggested that there would be 10.91 new cases of OSCCs for each 100,000 males and 3.58 new cases for each 100,000 females.[3-6] The incidence rate is increasing and the WHO foresees further increase in the next decades. Around 95% of oral cancers are OSCCs; the remaining 5% are sarcomas, lymphomas, and salivary gland tumors.[7,8]

The prognosis of oral cancer remains unfavorable with high mortality rates, notwithstanding advances in diagnosis and therapy, including radical surgery, novel chemotherapy, and hyper fractionated/conformational radiotherapy. Mortality rates have ranged from 2.16 to 2.96 for each 100,000 males and 0.48 to 0.70 for each 100,000 females between 1979 and 1998 in Brazil; the mortality rate has increased at an annual 0.72% rate. According to Sessions *et al*.,[9] the 5-year survival rate remains low at about 48% (overall survival) and 57% (disease-specific survival). The biological behavior of OSCC is uncertain; many of these tumors have an aggressive biological behavior at initial stages with early regional metastases and death.[10-12] On the other hand, advanced tumors may metastasize slowly, and these patients may remain disease free for long periods after surgery. This uncertainty in tumor progression has led researchers to seek factors that might alter the prognosis.[13-15] Such factors may be related to patients (age, sex, race, social and economic status, and habits such as smoking and alcohol intake), to the tumor (site, stage, tumor thickness, histopathology, and expression of certain molecular markers), and to the treatment (type of treatment and adjuvant therapy). Investigation of these factors aims to learn more about the biological behavior of the tumor and hence that specific strategies may be applied individually; thus, aggressive therapy may be given to patients with the worst prognosis.

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The presence of the neck nodal metastases is the most important prognostic factor for OSCCs. Survival rates reduce by 50%, if there is any nodal metastasis. Tumor node-metastasis (TNM) staging, the histological grade, and safety margins are other factors with unknown roles which reduces the survival rates.[15-17] Many studies have suggested that TNM staging cannot predict individual tumor biological behavior. The prognostic value of the histological grade is controversial in this tumor; studies have suggested that poorly differentiated carcinomas tend to metastasize and to have involved margins more often.[18,19] These tumors are associated with decreased survival rates. There is still controversy in the literature about surgical margin status.

Materials and Methods

The meta-analysis was undertaken in accordance with 2009 PRIMSA guidelines in PubMed search from 2008 to 2018. Terms searched were "OSCCs," "nodal metastasis," "surgical margins," and "prognosis." A total of 14 studies were reviewed and only nine studies were included in meta-analysis considering the following inclusion criteria: studies with primary surgery and postadjuvant radiation, studies with recurrences/death postsurgery, studies where the follow-up was >2 years, and studies in which surgical margins had viewed pathologically and classified with clear/close margins. Exclusion criteria were studies which had patients with salvage surgery or palliative surgery and studies which had other subsites of head and neck.

Statistical analysis

Data extracted from the nine studies were as follows: total number of patients in the study, cutoff margins classified as clear/close margins in each study, follow-up of the patients, nodal metastasis, and death of the patients. Data used for statistical analysis were based on the percentage of overall local recurrence rate in clear/close margins with 95% confidence intervals (CIs) and *P* values calculated to indicate the size of the difference between close and clear margins.

Meta-analysis was done with review manager 5.0. Heterogeneity was assessed using Cochrans Q, τ^2, and I^2 statistics, and the results are tabulated as below.

Results

The summarized data for individual studies are tabulated in Table 1. The studies tabulated in this meta-analysis were the proposed cutoff, number of patients in the study, followup months, death due to nodal metastasis/recurrence, nodal metastasis, and percentage with death due to recurrence/ metastasis; however, in one of the study conducted by Hicks *et al*.[20] margin cutoff was 10 mm. Number and percentages of clear and close margins according to the individual study are given, along with the number and percentage of cases by death or local recurrences for each margin group. CIs and *P* values were calculated using a Chi-squared test whether surgical margins and cases by deaths or recurrence and nodal metastasis are prognostic factors for survival in OSCC in each study.

These results are shown graphically in Figure 1. Rates of local recurrence and death differ between studies; however, in major proportion, there is a trend toward increased recurrence and deaths in groups with smaller margin size. In the majority of the studies, the local recurrence rate with a 10-mm margin cutoff was lower in both groups. Table 2 shows tests to measure data heterogeneity were performed for eight studies except one study with a clear margin ≥10 mm. Cochran's Q was 14.91, $P = 0.0372$, $\tau^2 = 0.00844$; $I^2 = 53.04\%$. Fixed effect modeling was performed to obtain the pooled estimates for meta-analysis. Fixed effects meta-analysis showed a pooled estimate absolute risk reduction of −3% (95% CI [−8, 2.5%]). $P = 0.2819$ from the fixed margin model shows no statistically significant difference between close margins with cases of deaths due to recurrence or metastasis. The pooled odds ratio was 0.87 (95% CI 0.63–1.99, $P = 0.3928$) for the comparison between clear and closed margins for estimating the odds. It should be noted that the mean unweighted local recurrence rate for margins 5 mm or greater was 4.9% with 95% CI as −10.7%, 0.8%.

Discussion

The efficiency of the surgery is assessed by its adequate pathological margins which are a major consideration in determining the need of further adjuvant treatment. Pathological margins are microscopically assessed margins after tissue shrinkage and tumor extension. The amount of shrinkage noted is 9.2%–75% according to the literature.[21] The classification of surgical margins according to the Royal College of Pathologists UK: <1 mm as involved margins, 1–5 mm margin are close

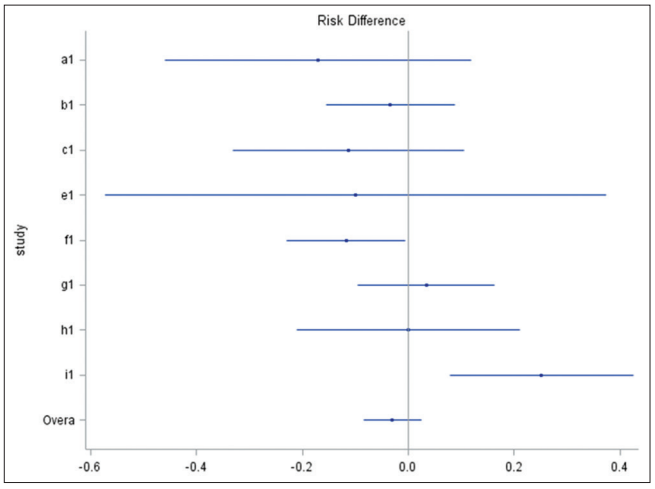

Figure 1: Risk difference for random effects between margin and recurrence

Table 1: Summarized data for individual studies are tabulated

Study	Proposed cutoff pathological-free margins (no dysplasia/CIS) (mm)	Number of patients in study	Margins		Follow-up (months)	Death due to recurrence/ metastasis (close margins)	Nodal metastases	Percentage with death due to recurrence/metastasis	95% CI	*P*
			Clear	Close						
Sadeghi *et al.*	>5	59	46	13	24	24 (9)	32	Clear: 52.2	37.7-66.6	0.274
								Close: 69.2	44.1-94.3	
Loree and Strong	>5	292	212	80	24	67 (28)	176	Clear: 31.6	25.3-37.9	0.581
								Close: 35.0	24.5-45.5	
Hicks *et al.*	>5	85	59	26	24	16 (10)	61	Clear: 27.1	15.8-38.5	0.296
								Close: 38.5	19.8-57.2	
Hicks *et al.*	>10	79	66	13	71	8 (2)	54	Clear: 12.1	4.2-20.0	0.746
								Close: 15.4	0-35.0	
Sieczka *et al.*	>5	24	20	4	108	13 (3)	13	Clear: 65.0	44.1-85.9	0.699
								Close: 75.0	32.6-100	
Clara *et al.*	>5	534	473	61	96	61 (15)	419	Clear: 12.9	9.9-15.9	0.014
								Close: 24.6	13.8-35.4	
Waseem *et al.*	>5	115	68	47	60	11 (6)	34	Clear: 16.2	7.4-24.9	0.613
								Close: 12.8	3.2-22.3	
Jose *et al.*	>5	45	30	15	60	4 (2)	26	Clear: 13.3	1.2-25.5	>0.999
								Close: 13.3	0-30.5	
Payee *et al.*	>5	100	49	51	36	21 (9)	51	Clear: 42.9	29.0-56.7	0.006
								Close: 17.6	7.2-28.1	
Total		1333	1023	310		225 (84)	806 (60.4%)	Clear: 22.0	19.5-24.5	0.062
								Close: 27.1	22.1-32.0	

CI: Confidence interval, CIS: Carcinoma *in situ*

Table 2: Tests measuring data heterogeneity

Study or subgroup	Weight (%)	Risk difference, IV 95% CI
Sadeghi *et al*.	4.0	−0.17 (−0.46-0.12)
Loree and Strong	22.5	−0.03 (−0.16-0.09)
Hicks *et al*.	7.0	−0.11 (−0.33-0.11)
Sieczka *et al*.	1.5	−0.10 (−0.57-0.37)
Clara *et al*.	26.6	−0.12 (−0.23-−0.005)
Waseem *et al*.	19.9	0.03 (−0.10-0.16)
Jose *et al*.	7.5	0.0 (−0.21-0.21)
Payee *et al*.	11.1	0.25 (0.08-0.43)
Total (8 studies)	100	−0.03 (−0.08-0.25)

Q=14.91; df=7 (P=0.0372); τ^2 =0.00844; I^2 =53.04%. Risk difference and 95% CI (reduction)=−3% (−8%-2.5%). OR and 95% CI=0.87 (0.63-1.99). OR: Odds ratio, CI: Confidence interval, IV: Inverse variance

margins, and >5 mm margin are free margins.[13] These parameters are important in the prognosis of the patient; however, studies have not shown statistically significance in terms of recurrence.

This is a first meta-analysis done with total of 1333 patients which was a reasonable number to find a conclusion regarding the two prognostic parameters. Although this study could not prove statistical significance to find margins and nodal metastasis as a prognosticator in OSCC, it highlights the areas of lacunae which needed high-quality research with multicentric trials. This analysis clearly indicates that margins of 5 mm are required to have a good prognosis of the patients and prevent local recurrences/death. Clinicians must concentrate on the surgical margins of at least 1–1.5 cm macroscopically to gain 5 mm clear microscopic pathological-free margins considering the shrinkage and tumor extent. The finding of 22% local recurrence for 5 mm or greater margins is in accordance to 25% reported by Brandwein-Gensler *et al*.[22] which showed histological factors, in general, were responsible for local recurrence. A detailed pathological study needs to be done at the margins close to the tumor: dysplasia, carcinoma *in situ*, or invasive carcinoma and needed to study the prognosis of these patients. In this meta-analysis, any of these were considered as involved margins. This meta-analysis reviewed most of the subsites in the oral cavity, while Sadeghi *et al*.[23] and Loree and Strong[24] included all subsites, with the majority of tumors on the tongue or floor of the mouth. The other articles focused on just one or two subsites which can be the reason for the bias in the respective study.[25-27] Sieczka *et al*.[28] studied on buccal mucosa alone which showed the highest recurrence rates for both involved and clear margins. All the subsites behave differently than each other due to the tumor biology and are not very understood; however, a 5-mm cutoff is required in all subsites for good prognosis along with no neck nodes.[29,30] This meta-analysis shows the other histopathological parameters such as depth, differentiation, perineural, and lymphovascular invasion, and pattern of invasion also affects the prognosis of the patient which is in accordance with other pathological studies of the literature.[31,32] There are few articles considering all parameters in terms for adjuvant therapy although they are not proven statistically significant.[33-35] In spite of these studies, it is still a question that surgical margins and nodal metastasis in isolation can affect the prognosis of the patients of OSCC. This meta-analysis of 1333 patients was unable to prove statistically significance; however, there is a slight risk of increased recurrence in close margins with a decrease in survival rate with neck node metastasis. There has to be multicentric study and comparison for two groups: clear margins and close margins to find the prognosis of the patients.

Conclusion

The study shows that surgical margins <5 mm with nodal metastasis have poor prognosis in OSCC; however, no statistical significance was seen in this meta-analysis when compared to clear margins. Further research is needed in a large scale to understand the relationship between isolated surgical margins with prognosis and isolated neck nodal metastasis with local recurrence to increase the effectiveness of the surgery as a primary treatment and need for adjuvant therapy.

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Conflicts of interest

There are no conflicts of interest.

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