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Impact of Pathological Excision Margin Status on Survival of Sri Lankan Patients with Oral Squamous Cell Carcinoma

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Abstract

Introduction: In Sri Lanka, chewing betel quid significantly contributes to the aetiology of oral squamous cell carcinoma (OSCC). Due to quid induced changes in the stroma, the behaviour of OSCC is unique. We analyzed the impact of pathological excision margins (PEM) on survival of these patients.

Material and methods: Patients treated for OSCC over a 13-year period were included. 3-year (250) and 5-year (186) survival data were available. Both mucosal and deeper surgical margins were measured histologically and grouped as three main categories and 5 sub-categories. Completely excised (A and B), Close (B and C) and Involved (E). Group A (6.5 mm and above), B(5.5-6 mm), C (3.5-5 mm), D (1.5-3 mm) and E (Less than 1 mm).

Results: M: F ratio was 3:1. Buccal mucosa (54%), tongue (19.2%) were mostly involved. The highest incidence of close or involved margins occurred in clinical stages IV(48%) and III (17%). Group E had the highest recurrence rate (59%) and the lowest 3 year (41%) and 5 year (31%) survival. Involved, close and completely excised margins significantly reduced the 3-year survival (p=0.029). Further, logistic regression revealed that age (p=0.042), stage (p=0.0001) and deep margin status (p=0.0001) had significant influence on survival.

Conclusions: Higher stages of the disease had a significant chance of close or involved margins. Achieving a clear PEM showed significant improvement in 3-year survival and local disease control. Deep marginal clearance is an independent prognosticator, significantly correlated with disease free survival.

Keywords: Excision margin; Oral cancer; Oral squamous cell carcinoma; Sri Lanka.

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Introduction

In Sri Lanka, OSCC is identified as the most common cancer among males and 8th among females [1]. Chewing betel leaf with smokeless tobacco and areca nut (BSTA) is shown to be the most common reason for OSCC in the South and South-Eastern Asia (SSEA) and the incidence in this region is much higher [2]. Therefore, these OSCCs are "betel quid induced (BQI)" and may behave uniquely due to the changes in their Extracellular Matrix (EM).

The 5-year overall survival of OSCC patients who chewed areca nut is shown to be significantly less than those who didn't [3]. These OSCC patients have a 19.1 times higher chance of having a coexisting oral potentially malignant conditions such as Oral Submucous Fibrosis (OSF) or leukoplakia with Oral Epithelial Dysplasia (OED) [4]. Hence, their Pathological Excision Margins (PEM) have a greater chance of being close or positive. Furthermore, wide surgical excision to accommodate extensive lesions bordering OED results in poor recovery and high morbidity. These patients have field-cancerization which predispose to a higher chance of local recurrences and the incidence of a second primary cancer [3]. The effects of BSTA on the extracellular matrix and submucosal fibrosis may also affect the immediate post-surgical tissue shrinkage. Mistry et al, in a study in a group of BQI OSCC patients from India had 50% less immediate postoperative shrinkage in the buccal mucosal cancers [5].

In addition, the fibrosis in the extra-cellular matrix caused by BCTA, is believed to cause lymphatic occlusions, resulting in a decreased tumour metastasis to the neck. Sigh et al, showed 81% negative necks in T4 patients with OSF, while it was 28.6% in patients without [6]. Chaturvedi et al and Siriwardena et al, both found a reduce trend in metastasis to the neck in the background of OSF [7, 8].

With the influence of the BQI EM, disease progression of OSCC can be significantly different to OSCC without BQI EM. Therefore, we aim to investigate the influence of pathological excision margins on recurrence and overall survival (3 and 5 year) of Sri Lankan OSCC patients whose aetiology is BSTA.

Materials and methods

Histologically confirmed primary OSCC cases treated with surgery at Oral and Maxillofacial units of Sri Lanka for a period of 13 years were included. All patients were reviewed and monitored closely during the first 5-years and annually thereon. The cases that have lost to follow-up and the cases that have less than 3 years follow-up at the time of analysis, were excluded from the study. All excisional biopsy specimens of selected cases were retrieved from the Department of Oral Pathology, Faculty of Dental Sciences, University of Peradeniya. Demographic, clinical and histopathological data were gathered from patient's clinic and hospital records. All margins taken for the purpose of surgical pathology report were re-assessed and distance from the main tumour to mucosal margins (lateral margins) and to the deep margin were recorded using the stage micrometer. Measurement was started to record from 0.5 mm with 0.5 mm intervals (0 mm was recorded as involved) up to 6.5 mm and beyond. Both lateral and deeper PEMs were separately measured histologically and recorded. Both margins were separately analyzed. Out of the two measurements from each case, the closest measurement was recorded. For the purpose of statistical analysis readings were grouped as group A (6.5 mm or more), B (5.5-6 mm), C (3.5-5mm), D (1.5-3 mm) and E (1 mm or less-Involved).

Statistical analysis

Statistical analysis was performed using SPSS (Windows version 16) software. Data was analyzed using descriptive statistics. Pearson's Chi-square test was used to compare proportions. The statistical significance was accepted at $p < 0.05$. Logistic regression was used to identify the relationship between margins with recurrence and survival and Kaplan Meier survival curves were generated to compare survival with different parameters.

Results

A total of 250 patients (Males: Females were 3:1) with follow-up details were included in the study. Total sample was grouped into age categories and many patients were within 51-60 (31.6%) and 61-70 (32%) age groups. There were 4 patients who were less than 30 years of age. With reference to the site, OSCC of the buccal mucosa (BM) was predominant (54%) followed by the tongue (19.2%). Fifty percent (50%) of the patients were stage IV, while, stage 1 had the lowest cases with only 7.2%. From this study group, all patients completed 3-years follow up while 186 had 5-years and above.

The most obvious factors influencing overall survival were, the site of the primary and the stage of the disease. OSCC of the tongue showed worse outcomes for both 3-year ($p=0.002$) and 5-year ($p=0.022$) overall survival compared to lower alveolar ridge (LAR) and BM (Figure 1). Furthermore, a highly significant statistical correlation was identified between overall survival and the stage of the disease for 3-yrs ($p<0.001$) and for 5-yrs ($p=0.004$) (Figure 2). With advancing stage of the disease, the overall survival rate was significantly reduced irrespective of the site.

When considered the groups from A-E, although there is no significant relationship with regards to 3-year survival and marginal clearance, there is a clear improvement of the overall survival. The same is clearly visible with 5-year overall survival. Furthermore, majority of local recurrences and regional recurrences were within 3 years after the surgery. There were few cases of local recurrences, nodal metastasis (regional recurrences) after 3 years (Table 1).

Table 2 describes the recurrences following radiotherapy. There is no proper relationship with recurrence with post operative radiotherapy. The reason is the poor compliance of patients.

When all patients were categorized as clear margins (groups A and B), close margins (groups C and D) and involved margins (group E), a statistically significant association was found only between 3-year survival rate and the PEM status ($p=0.029$) (Figure 3) and not with the 5-years the survival ($p=0.114$).

When the lateral margins and the deep margins were considered separately, the lateral margin clearance showed no significant benefit at 3 ($p=0.186$) or 5-year ($p=0.421$) survival. Deep margin clearance was statistically correlated with a better survival at 3-years ($p= 0.005$). However, the deep margin clearance was not statistically significant for 5-year survival ($p=0.067$).

Majority of the sample included the close margin category (48%) followed by <1 mm group (34%). The rest was with clear margins (18%). Most patients present with late stage of the disease and the possibility of obtaining a clear margin was reduced and most stage IV cases had PEMs <1 mm and the results were significant statistically (p=0.032) (Figure 4). The highest involved excision margins were seen in patients with LAR cancer, whereas, lower lip had the least (Figure 5). Many patients were treated with surgery and 43.2% had post-operative radiotherapy. When the treatment type and survival are considered, there was no significant association.

In order to identify the individual predictors for survival, forward and backward stepwise logistic regression was applied. Variables used were age, sex, stage, lateral margin, deep margin and treatment and when compared with survival, age, stage and deep margin were identified as individual predictors for survival (p=0.042, p<0.001, p<0.001) respectively. Logistic Regression procedure, requesting backward elimination of predictors was also carried out in order to confirm the independent prognosticators mentioned above (p=0.039, p=0.001, p=0.001).

Table 1: 3-year and 5-year survival and recurrences by margin status.

Group	Margin category	3-year survival Percentage/proportions	3-year recurrence (local) (regional)	5-years survival percentage/ proportions	5-year recurrence (local) (regional)
A	>6.5 mm	100% / (8/8)	nil	100% (5/5)	nil
B	5.5-6.5 mm	59.46% / (22/37)	(4/37) (5/37)	41.67% / (10/24)	(*1/24) (0/24)
C	3.5-5 mm	61.9% (52/84)	(16/84) (7/84)	44.07% (26/59)	(**4/59) (0/59)
D	1.5-3 mm	58.36%, (21/36)	(9/36) (2/36)	40.7% (11/27)	(**2/27) (0/27)
E	<1 mm/0-1 mm	48.24% (41/85)	(44/85) (6/85)	32.39% (23/71)	(**4/71) (0/71)

•Second primary ** recurrences in between 3-5 years

Table 2: Recurrence after radiotherapy related to margins.

Margin category	RT+	RT-	total	RT+ rec +	RT- rec +	RT+ rec +	RT- rec +
>6.5 mm	2	5	7	0/2 (0%)	0/5 (0%)	3/16 (18.75%)	5/31 (16.1%)
5.5-6.5 mm	14	26	40	3/14 (21.4%)	5/26 (19.2%)		
3.5-5 mm	41	43	84	16/41(39%)	9/43 (20.9%)	21/53 (39.6%)	16/67 (23.8%)
1.5-3 mm	12	24	36	5/12 (41.6%)	7/24 (29.1%)		
<1 mm/0-1 mm	39	44	83	18/41 (46.15%)	23/42 (52.27%)	18/41 (46.15%)	23/42 (52.27%)

RT radiotherapy, **RT+** radiotherapy given, **RT-** radiotherapy not given, **rec+** recurred, **rec-** not recurred

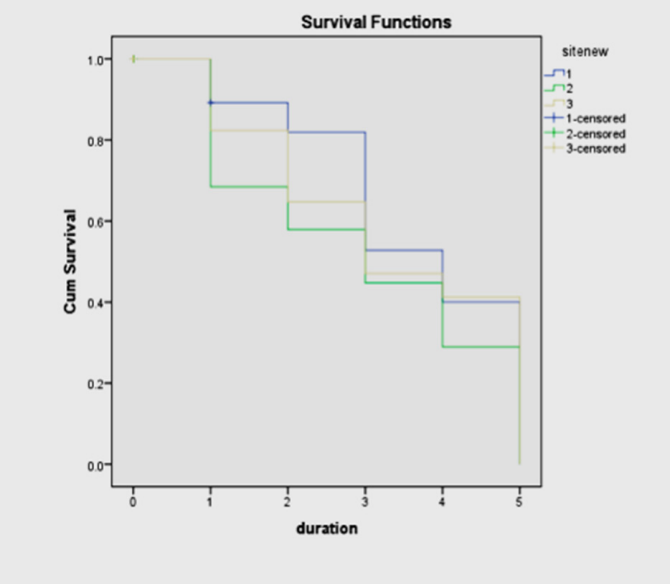


Figure 1: Survival in relation to the sites 1-BM, 2-tongue, 3 lower alveolar ridge.

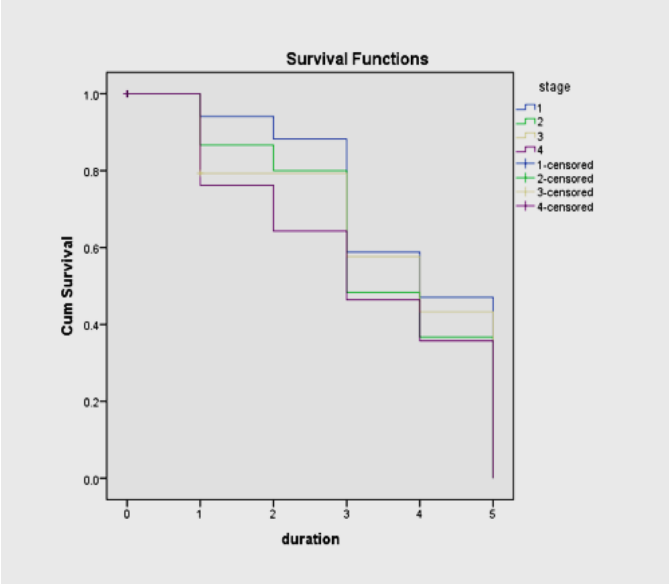


Figure 2: Survival by stage (1-stage 1, 2-stage 2, 3-stage 3, 4-stage 4).

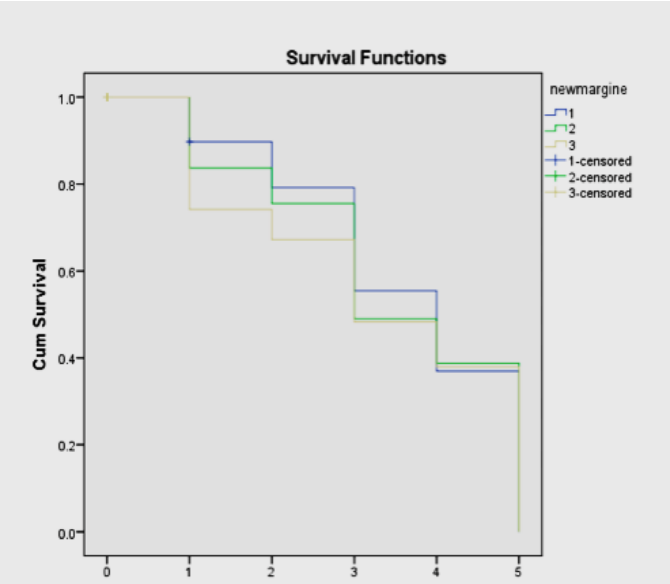


Figure 3: Survival by margin 1-group 1(clear), 2-group 2 (close), 3-group 3 (involved).

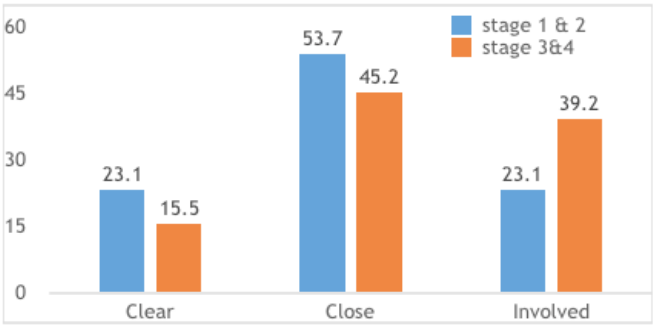
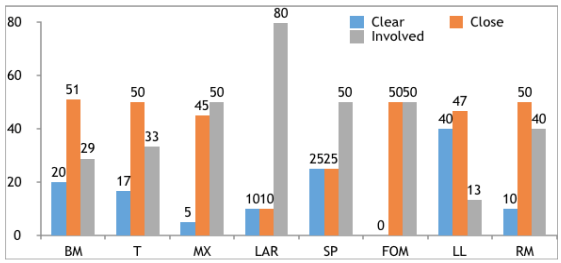


Figure 4: Association between stage of the disease and marginal clearance.



BM-Buccal mucosa,T-tongue, MX- maxilla, LAR- lower al ridge, SP-soft palate, FOM- Floor of the mouth, LL-lower lip, RM-retromolar region

Figure 5: Margin clearance by each site.

Discussion

Our study assessed the PEM of OSCC patients against 3-year (250 patients) and 5-year (186 patients) survival. The main purpose was to assess the PEM status and its influence on the overall survival of the patients with OSCC who chewed betel quid.

Habit of chewing BSTA is identified as the main aetiology for OSCC in Sri Lanka and mostly in a the poor socio-economical group 9. Our study agreed with the socio-demographic findings of previous Sri Lankan cohorts in confirming that the BM predominate as the primary site, elderly males (50-70 years) are mostly affected and most patients present to hospital at stage III and IV of the disease 10.

The age and survival

Patients with OSCC over 60-years have poor general health and they fare poorly than younger patients [11]. Even at a higher stage of the disease, the younger patients have shown better survival outcome than the older counterparts [12]. Warnakulasuriya et al, in their study in the UK, showed a better prognosis among the younger age of less than 45 years [13]. The findings were quite different in the study by Garavello et al, where tongue cancer had a higher mortality in patients younger than 40 years [14]. As BSTA is the main causative agent in Sri Lanka, the usual age group is over the age of 30 years [15]. In our cohort, the age group below 30 years were 1.6%, and the age group 41-50 were 10%, whereas the age range of 51 to 70 years included close to 63%. Logistic regression showed increasing ages as an independent risk factor for both 3-year and 5-year survival.

The stage of the disease and survival

In our study, a clear reduction in survival was seen in patients diagnosed as stages III and IV. Though, the stages III and IV of oral cancer receive post-operative radiotherapy, their local control and survival benefits remains very low, especially for stage IV. We found that involved and close margins were mostly found in the stages III and IV indicating the difficulty of complete excision of such tumours and the added negative influence on survival. This finding is supported by Roeland et al, in their study which showed that stages I and II had a higher chance of being completely excised than stages III and IV (22.6% vs 5.1%) [16].

The primary site of cancer and survival

LAR had the highest incidence of involved margins (<1 mm) (80%) followed by maxilla, soft palate and the floor of the mouth. In contrast, lower lip had the least involved margins (13.3%) and the highest percentage of clear margins (40%). Most studies report higher incidence of close margins with BM, tongue and mandibular alveolus. The site of the primary tumour influence prognosis due to the lympho-vascular supply which influence metastasis and the ability to achieve a clear excision margin. Tongue and floor of the mouth (FOM) are the most common sites to have the worse prognosis due to the anatomical location in close proximity to the lymph nodes of the neck which encourage early metastasis. In addition, most of the tongue and floor of the mouth cancers are diagnosed late in contrast to the lip lesions, which in turn affects the prognosis of these patients [17]. Our study group had the worst survival with tongue as the primary site followed by the LAR and BM respectively. In contrast to this, oral cancer of the BM is considered as a site of high loco-regional failure even in the initial stages of the disease [18]. Five year disease specific survival data from the Memorial Sloan-Kettering cancer centre ranks BM at the sixth place in a descending order for survival, indicating the significance of this site to others [19]. Shaw et al, points out that squamous cell carcinoma of the BM presents at a late stage and frequently have involved margins; thus the reason for the poor prognosis. The authors further emphasize the fact that in SSEA countries where habitual betel chewing which is the cause for cancers of BM, has a better prognosis than similar lesions in the

western countries that occur due to tobacco smoking and alcohol [20].

The PEM and survival

PEM in patients with OSCC have a significant influence on survival. Though, most studies agree on a positive PEM to have a significantly poor prognosis, McMahon et al, in their multicentre study failed to implicate PEM as an independent predictor of survival and loco-regional control [21,22]. Barry et al, showed that close PEM didn't have an influence on recurrences or in survival in patients with early stage tongue cancer [23]. Weijer et al, reported that, there was no significant increase in recurrences in patients with close deep margins [24].

Interestingly, how the close PEM affects the overall prognosis is unclear. Wong et al, found that close excision margins between 1mm to 1.6 mm did not necessarily increased the chances local recurrences, but reduced the overall survival. They postulate that the closeness of the tumour to the surgical margins correlate to the tumour size and aggressiveness and has no direct correlation [25]. They found a resection margin of less than 1.6 mm had a significantly higher reduction in 5-year survival and recommends a close margin to be recognized as 1-2 mm. This cut-off margin has been shown to vary with different studies. Chiou et al and Dik et al claim that margins over 3mm to have the same survival benefit of a margin over 5 mm and 6 mm respectively [26,27]. Similarly, Zanoni et al and Nason et al, recommend margins over 2.2 mm and 3 mm respectively. For aggressive disease where the surgery is the main treatment modality, a more liberal PEMs of over 7 mm and 1 cm are suggested [28,29]. Due to this vast variation in results, the best PEM is difficult to assess.

We studied a group of patients whose aetiology was predominantly betel chewing. Therefore, the influence of PEM on recurrences and survival of these patients are important as the changes in the extracellular matrix may influence the biological behaviour of the cancer.

We noted a clear reduction in 3-year and 5-year survival when the PEM was involved (1 mm or less). When the deep PEMs were categorized to involved (<1 mm), close (1.5-5 mm) and clear (5.5-6.5 mm), a statistical significance was found on 3-year survival but not on 5-year survival. This result agrees with a meta-analysis by Anderson et al, that showed a PEM of over 5 mm to have a better prognosis regardless of the sub site of the oral cancer [30]. This relationship was not noted with the lateral margins. The patient who had PEM over 6 mm, all survived, though the sample size was low to draw a statistically significant result.

Conclusion

A deep PEM of less than 1 mm clearly had a negative influence on the overall 3-year and 5-year survival of our patients with betel quid induced oral cancer. When deep PEMs were divided as close (1.5-5 mm) and completely excised (over 5.5 mm), the 3-year survival significantly improved. Therefore, attempting PEM over 5 mm would be recommended. In our study, the deep margin status had the most significant influence. Therefore, a 3-dimensional tumour clearance is of outmost importance.

Declarations

Data availability statement: Apart from the data within the text, raw data can be provided upon request

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Conflict of interest disclosure: The authors have declared that there is no conflict of interests

Ethics approval statement: The study used archival data,

Patient consent statement: Not applicable.

Permission to reproduce material from other sources: Not relevant.

Clinical trial registration: Not relevant.

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