European Journal of Surgical Oncology 45 (2019) 1033–1038

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

# Defining optimum surgical margins in buccoalveolar squamous cell carcinoma

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ARTICLE INFO

*Article history:*
Accepted 30 January 2019
Available online 5 February 2019

*Keywords:*
Buccal mucosa
Squamous carcinoma
Margin
Local recurrence free survival

ABSTRACT

*Introduction:* Surgical margin is one of the most important prognostic factors in oral cavity squamous cell carcinoma. There have been studies which refute the standard practice of considering 5 mm (mm) margin as free. Therefore we aimed to evaluate the impact of each mm of margin on the local recurrence free survival (LRFS) and to obtain a cut-off value which would impact the survival the most.
*Material and methods:* This was a retrospective study of 602 treatment naïve patients of buccoalveolar complex cancer. ROC curve was plotted for each millimetre of margin to derive the cut-off margin for maximum LRFS. Multivariate analysis was done for the margin groups to calculate the margin beyond which no significant improvement on LRFS was achieved. Early and advanced tumors were also evaluated separately.
*Results:* A cut off margin of 5.5 mm was achieved on ROC for early (T1-T2) tumors and 6.5 mm cut off was achieved for advanced (T3-T4) tumors. Based on these cut off different margin groups were made. The cohort was grouped into positive margin, 1–5.5 mm, 5.6–7 mm and > 7 mm. Hazard ratio for patients with 1–5.5 mm and positive margin was 1.886 (95%CI, 1.15 to 3.09) and 5.58 (95%CI, 1.75 to 17.78) respectively. HR for margin 5.5 mm to 7 mm was 1.15 (95% CI, 1.15 to 2.06). There was no statistically significant difference in survival between margin groups of 5.6–7 mm and > 7 mm ($p < 0.589$) for both early and advanced tumors.
*Conclusion:* Minimum surgical margins of 5.5 mm in the final histopathology should be aimed for in the bucco-alveolar carcinomas. There was significant improvement in LRFS with increasing margins upto 7 mm. Taking margins beyond 7 mm does not improve LRFS.


## Introduction

One of the most important goals of surgical excision in head and neck cancer is achievement of clear surgical margins. An inadequate margin is associated with higher risk of loco-regional failure and poorer survival [1]. Various studies have evaluated surgical tumor margin and its impact on prognosis in oral cavity cancers. However, the definition of this clear margin in terms of a mathematical value has remained contentious. A margin of 5 mm from the gross edge of the tumor had traditionally been considered as free margin. Recently there has been a study which has defined free margins as more than 2.2 mm for tongue cancers. Another study has concluded that 1 mm would be adequate cut-off for close margin [2,3].

It has been observed that tongue and buccal mucosa cancers are clinico-pathologically distinct entities indicating that their biological behaviour is different [4–6]. Thus any study on margins in oral cavity cancers should assess them separately. Therefore we studied the buccal mucosa and lower alveolus carcinoma, as they are

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https://doi.org/10.1016/j.ejso.2019.01.224
0748-7983/

amongst the common subsites of oral cancer in South East Asia [7]. With this study we aimed to evaluate the impact of surgical margins on local recurrence and survival at each millimetre of margin in patients with bucco-alveolar complex cancer and to determine what margin should be described as free surgical margin for best prognosis [8].

## Methodology

This was a retrospective cohort study with a longitudinal follow up. Institutional review board clearance was obtained for analysis. Consent waiver was obtained as this was an analysis of retrospectively collected data and the study was in compliance with Helsinki declaration. Electronic medical records were used for recording the demographic and clinical variables. The data was de-identified after the abstraction was performed.

A cohort of 602 patients of buccal mucosa and lower alveolus squamous cell carcinoma, from January 2012 to October 2013 was analysed. We labelled them together as Buccoalveolar complex cancer for this study. Patients with incomplete medical records, histology other than squamous carcinoma or having less than 6 months follow up details were excluded. We also excluded patients with carcinoma in situ and/or dysplasia at the margins and those who had taken incomplete adjuvant treatment.

All patients received appropriate adjuvant treatment after discussion in the multi-disciplinary joint clinic meeting attended by specialists from Head and Neck Surgery, Radiation Oncology, Medical Oncology, Nuclear Medicine, Pathology and Radiology.

Pathology reports were reviewed for the status of surgical margin. Closest cut margin was documented in millimetres. Tumors were staged as per the AJCC 7th edition, 2009.

Recurrences were documented after clinical examination and histopathological or radiological confirmation. The patients were followed up till May 2017. Follow up details were enlisted from the electronic medical records. When the patient's investigation reports or details were missing, patients were contacted telephonically and the required details were updated. Date of presentation of patient with recurrences in the outpatient department was considered the date of recurrence. Date of the last follow up in the out-patient department was considered for the overall survival in patients who were disease free. Site of recurrence was noted as local, regional or distant metastasis. Date of surgery was considered as baseline for calculation of the disease free survival and the overall survival.

## Statistical analysis

Primary outcome assessed was local recurrence free survival based upon each millimetre of margin. Categorical data was analysed using Pearson-chi square test or Fischer's exact test. Mann Whitney *U* test was applied on continuous variables. Survival analysis was done using Kaplan meier analysis. Comparison of the factors was done using the log-rank mantel cox test. Multivariate cox proportional hazards model was used to determine the independent effect of margin on survival. Adjusted hazards ratio was also predicted for all the factors.

ROC curve was plotted for each millimetre of margin against the local recurrence free survival status and a cut-off margin was determined for the best loco regional recurrence free survival status. Based on the cut-off derived from the ROC curve we stratified the patients into four groups: involved margin (<1 mm); from 1 mm to the cut-off value; from cut off value to 1 mm more than it; and all values above it. Survival and recurrence calculations were compared between each group using Kaplan meier curve. The fourth group was considered to confirm that no further survival advantage would be gained by taking more margin than the cut off value. Hazard ratios were also calculated for different groups.

In order to nullify the effect of adjuvant therapy upon the survival, we stratified patients based upon the adjuvant therapy received (no adjuvant therapy, adjuvant radiotherapy, adjuvant chemo-radiotherapy). In these groups individually we looked at local recurrence free survival based upon the margin cut-off we obtained through the ROC curve.

To analyse the effect of margin status on early (T1-T2) and advanced stage (T3-T4) tumors, ROC curves for them were plotted separately. All statistical tests were 2 sided and p value of 0.05 was considered significant.

## Results

### *Demography*

Records of 602 patients with buccoalveolar complex cancer were reviewed. 21 patients were lost to follow up, 11 patients defaulted the adjuvant treatment advised and 7 patients did not have squamous cell carcinoma histology. All these patients were excluded from the analysis. A total of 563 patients were included in the analysis. The study population characteristics are summarized in Table 1.

### *Margins and survival*

40% (226) patients had recurrences. There were local recurrences in 17.8% (100) patients. The overall survival of the whole cohort was 48.5 months. The overall disease free survival was 43.1 months. The local recurrence free survival was 53.6 months. The local recurrence rate at each mm of margin is shown in Table 2. The table shows that there is an overall trend of improved local recurrence free survival with increasing margin, the survival plateaus beyond 6 mm margin.

A ROC curve was plotted between the margin and the local failure to obtain a cut-off margin for maximum local control. We derived a cut off value of 5.5 mm with sensitivity of 69.8% and specificity of 50% for maximum survival. The area under the ROC curve was 0.63 (Fig. 1).

### *Impact of tumor stage*

We developed a ROC curve (local recurrence and margins) for early (T1-T2) and advanced (T3-T4) tumors separately. We obtained a cut-off 5.5 mm for T1-T2 (AUC 0.61) and 6.5 mm for T3-T4 (AUC 0.64) (Fig. 2).

Based on the cut off values we divided the cohort into 4 groups- Involved margin, 1 mm–5.5 mm, 5.6 mm to 7 mm and > 7 mm. The five years local recurrence free survival for margin >7 mm, 5.6–7 mm, 1–5.5 mm was 82.3%, 81.8% and 67.5% respectively. The local recurrence free survival for positive margin was 42.9%. The survival significantly improved when the margin increased from 5.5 mm to 5.6–7 mm group (log rank test, $p < 0.024$). However, there was no further improvement in survival if any added margin was taken beyond 7 mm (between the 5.6–7 mm and > 7 mm group; log rank test $p < 0.589$). (Fig. 3).

### *Stratification according to adjuvant therapy*

To negate the effect of adjuvant treatment upon survival we stratified the cohort based upon the type of adjuvant therapy administered. We found that the local recurrence free survival was significantly lower in close and positive margin groups as compared to the free margin one in all the three strata. Thus in the

**Table 1**
Basic demographic details and LRFS.

| Variable | No. of patients (%) | LRFS (months) | Univariate | Multivariate |
|---|---|---|---|---|
| Gender | | | | |
| Male | 442 (78.5) | 53.6 | 0.438 | 0.47 |
| Female | 121 (21.5) | 55.4 | | |
| pT stage | | | | |
| T1 | 86 (15.3) | 53.7 | 0.926 | 0.73 |
| T2 | 176 (31.3) | 54.6 | | |
| T3 | 33 (5.8) | 51.8 | | |
| T4 | 268 (47.6) | 53.8 | | |
| Pathological Nodal stage | | | | |
| N+ | 224 (39.8) | 52.4 | 0.157 | 0.14 |
| N Zero | 339 (60.2) | 54.8 | | |
| Extracapsular spread | | | | |
| Present | 185 (32.9) | 53.3 | 0.566 | 0.302 |
| Absent | 378 (67.1) | 54.4 | | |
| Peri Neural Invasion | | | | |
| Present | 73 (12.9) | 49.3 | 0.070 | 0.501 |
| Absent | 490 (87.1) | 54.5 | | |
| Lymphovascular emboli | | | | |
| Present | 4 (0.7) | 27.2 | 0.011 | 0.04 |
| Absent | 559 (99.3) | 54.1 | | |
| Depth of invasion | | | | |
| <5 mm | 85 (15.1) | 54.8 | 0.240 | 0.236 |
| 5–10 mm | 200 (35.5) | 55.6 | | |
| >10 mm | 278 (49.4) | 52.3 | | |
| Grade | | | | |
| Well Differentiated | 79 (14.0) | 54.1 | 0.136 | 0.106 |
| Mod Differentiated | 390 (69.3) | 54.9 | | |
| Poor Differentiated | 94 (16.7) | 49.8 | | |
| Microscopic Spread (Worst Pattern of invasion) | | | | |
| Present | 42 | 36.9 | 0.000 | 0.000 |
| Absent | 521 | 54.9 | | |

**Table 2**
Local recurrences for each millimetre margin and its Local recurrence free survival.

| Margin (in mm) | No. of patients (n = 563) | local recurrence | LRFS months (95% CI) |
|---|---|---|---|
| 0 | 9 | 4 | 29.5 (13.3–45.7) |
| 1 | 8 | 2 | 38.8 (30.5–47.1) |
| 2 | 13 | 6 | 30.5 (17.9–43.1) |
| 3 | 11 | 5 | 39.4 (24.3–54.6) |
| 4 | 11 | 2 | 47.3 (39.1–55.5) |
| 5 | 138 | 31 | 51.1 (47.4–54.8) |
| 6 | 78 | 11 | 55.3 (51.3–59.3) |
| 7 | 57 | 9 | 54.5 (49.4–59.6) |
| 8 or more | 238 | 30 | 56.5 (54.3–58.6) |

adjuvant therapy strata too the cut off margin remained significant. The mean LRFS for margin of > 7 mm, 5.6–7 mm, 1 mm–5 mm and < 1 mm in patients receiving Radiotherapy was 55.1, 53.5, 49.4 and 28.7 months respectively ($p < 0.04$). The corresponding survival for patients receiving CTRT was 58.9, 54.8, 47.2 and 17.8 months respectively ($p < 0.000$).

*Microscopic spread*

7.6% (42) patients had microscopic spread beyond the gross margins. Its presence led to changes in the margin status in 40.5% (17) of cases thereby significantly impacted survival ($p < 0.01$). The LRFS for patients with microscopic spread was 39.6 months vs 54.9 months in patients without (Log rank test, $p < 0.000$). The HR for microscopic spread was 2.19, (95% CI 1.20–4.01).

## Discussion

There are a few studies which have analysed the impact of margins on the local recurrence. Most of the studies have defined the close margin as 1–5 mm [1,9,10] and more than 5 mm as adequate. There are few others who have found that higher margins may be required [11]. Majority of these studies are of the era when adjuvant chemoradiotherapy was not advised for positive margins and adjuvant radiotherapy was not considered for close margins [12,13]. So, we wanted to assess that whether in the present era of adjuvant therapy, inadequate margins still affected prognosis and if it did so, then what was the optimum margin beyond which there would be no further impact on survival.

Most of the studies on margins in oral cancer have included all subsites of oral cavity taken together. It has been shown that different subsites in oral cavity have a different biologic behaviour and are pathologically distinct. Therefore clubbing them together for such an analysis is probably not correct [4,12]. In our study we have analysed only bucco-alveolar complex cancer. We chose this sub-site as the incidence of buccal mucosa and lower alveolus cancer is high in South East Asia due to the rampant tobacco usage [7].

The margin status has been shown to affect the local recurrence and survival. Several studies investigating the margin cut-off, report an improved outcome with increasing margin [14,15]. In the present analysis, we observed an improvement in local control

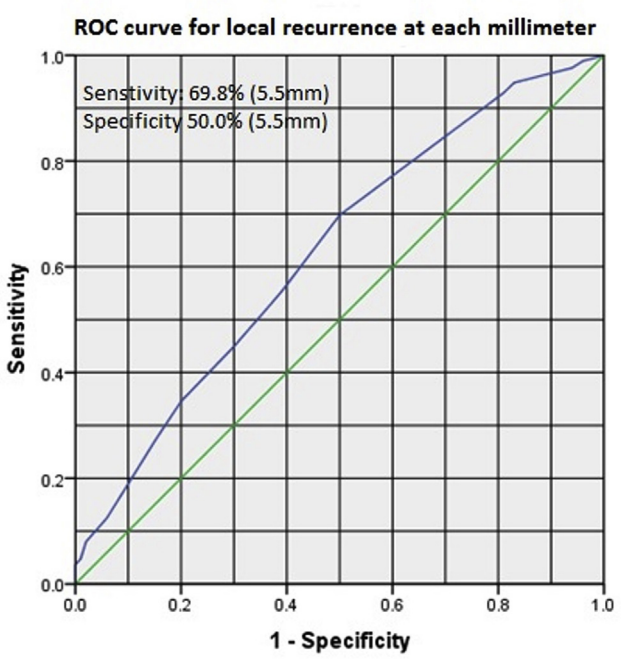


**Fig. 1.** ROC curve for margin cut-off of all patients.

from 5.6 to 7 mm, beyond 7 mm no further improvement was noted. In our study we had also stratified the cohorts based on type of adjuvant therapy received in order to see if adding adjuvant therapy could negate the adverse impact of inadequate margins. We found that in the adjuvant therapy sub-groups (none, adjuvant radiotherapy, adjuvant chemo-radiotherapy) margin of 5.6–7 mm is associated with improved LRFS as compared to margins less than 5.5 mm.

However a recent study has showed that a margin of 2.2 mm was adequate for tongue cancers. This difference might be due to different subsite assessed and more number of patients with early stage tumors. Their study had 85% patients with T1-T2 tumors, whereas only 46% patients in our cohort were early stage tumors. In another study the authors concluded that margin beyond 1 mm does not show any improvement in local control. However, their data showed a relative risk for local recurrence of 1.34 and 14% local recurrence rate at 4 mm margin [3]. According to the ROC curve obtained in our study, a margin more than 5.5 mm would confer the best local control. The meta-analysis by Anderson et al. had also concluded that there is risk reduction in recurrence at more than 5 mm margin. However they had not evaluated the outcome beyond 5 mm margin and the exact impact on local recurrence could not be definitely based upon this meta-analysis as they had not analysed the impact of adjuvant therapy. Moreover they had not included the studies with uniform criteria. One study described margins with dysplasia and carcinoma in-situ as free margins. The stage of the patients was also not considered for evaluation in the analysis. Therefore the analysis though suggested a margin of 5 mm as free it did not include several important prognostic factors into consideration, which we have included in our study [7].

In any oncological surgery a major concern is of the presence of microscopic disease beyond the gross margin. To cater to this the surgeon removes an additional cuff of normal tissue around the tumor. Frozen section is often utilized intra-operatively for knowing the margin status and for guiding the revision of margins if necessary [10]. In our study we found that microscopic spread beyond gross disease was seen in 7.4% patients. Another study from our institute also showed its incidence to be only 8.7% [8,10]. But when present, the microscopic spread significantly increases the chances of having an inadequate margin. In our study 40.5% patients with microscopic spread had inadequate margins. Similar results have been reported in other studies on pattern of invasion [16,17]. We found that the microscopic spread significantly impacted the local recurrence free survival. As the incidence of microscopic spread is more in advanced T stages [16], we hypothesized that the margin requirements for early and advanced tumors may be different. So we divided our patients into two groups-, early (T1-T2) and advanced (T3-T4). Most of the early stage tumors are not associated with other adverse clinico-pathological factors and the compromised margins may be the only poor prognostic factor leading to requirement of adjuvant therapy. The ROC plots were obtained for both early (T1-T2) as well as advanced (T3-T4) stage tumors. As expected by us, the cut off for early and advanced stages

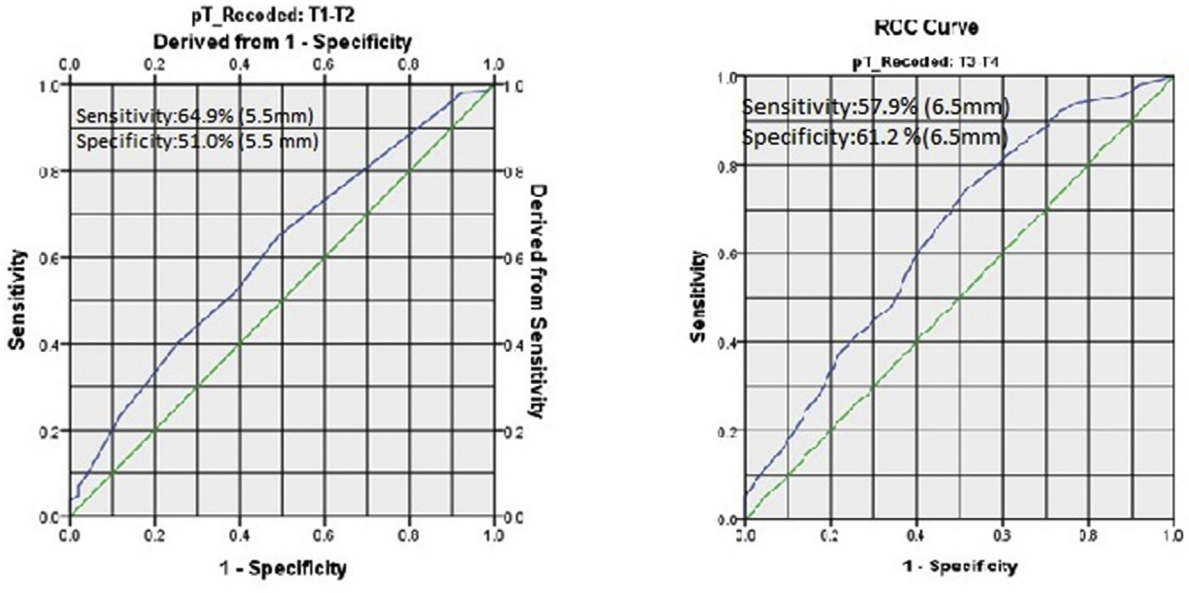


**Fig. 2.** ROC curve for Early T1-T2 (cut off 5.5 mm) and AdvancedT3-T4 tumors (cut off 6.5 mm).

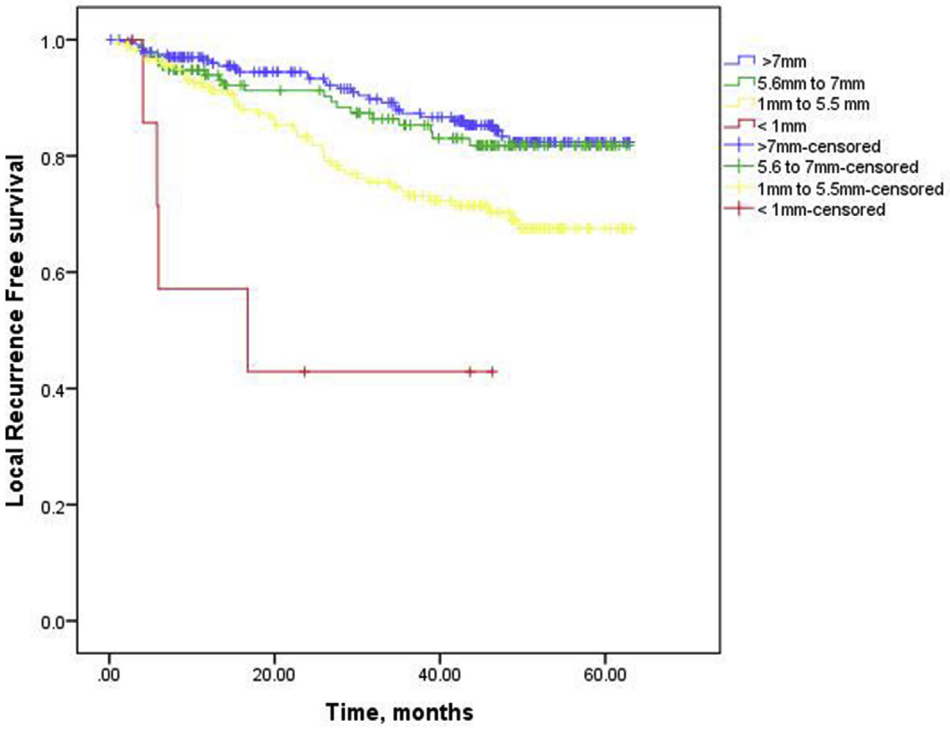


**Fig. 3.** Local Recurrence free survival based on the margin groups.

were different - 5.5 and 6.5 mm respectively. We wanted to find out the margin beyond which there would be no further improvement in survival. Since there were two different cut-offs for early and advanced stage, therefore we grouped the upper limits of early and advanced stage as one group. We grouped the cohort into groups with margins as <1 mm, 1–5.5 mm, 5.6–7 mm and more than 7 mm. We found that LRFS significantly improved with margin of more than 5.5 mm and a margin of more than 7 mm did not translate into survival benefit.

The local recurrence free survival for margin > 7 mm and 5.6 mm–7 mm was 56.3 months and 55.4 months respectively ($p < 0.589$). The local control was maximum with margin of more than 5.5 mm–7 mm and beyond 7 mm margin there was no significant improvement in local control. A retrospective analysis by Liao et al. had also demonstrated that margin less than 7 mm is associated with unfavourable outcome [18].

Our study examined the relationship between local recurrences and incremental change in margins in patients of bucco-alveolar complex carcinoma who were treated surgically. Standard management approach and synoptic pathological reporting had been followed in the study thus removing any role of bias due to incomplete treatment or any deviation from standard treatment guidelines.

However despite being meticulously performed this study had the regular drawbacks of a retrospective study design. But actually conducting a prospective trial in this regard may not be ethically possible as a margin of 5 mm is considered free as per the standards of care. So conducting a prospective evaluation with a study arm achieving a margin less than 5 mm would not be ethical. Therefore robust retrospective data like ours may only provide the evidence on this subject.

## Conclusion

In this study we have found that a margin of 5.5 mm for early tumors and 6.5 mm for advanced tumors is required. Minimum surgical margins of 5.5 mm in the final histopathology should be aimed for in the bucco-alveolar carcinomas. There was significant improvement in LRFS with increasing margins upto 7 mm. Taking margins beyond 7 mm does not improve LRFS.

## Conflict of interest

None (for all Authors).

## Funding source

None.

## Disclosure

There is no conflict of interest.

## Financial disclosure

None (for all Authors).

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