Surgical margins of the oral cavity: is 5 mm really necessary?

James Fowler, Yael Campanile, Andrew Warner, Francisco Laxague, Naif Fnais, Kevin Fung, Adrian Mendez, Danielle MacNeil, John Yoo, David Palma and Anthony Nichols*

Abstract

Background: Squamous cell carcinoma is the most common malignancy of the oral cavity. Primary treatment involves surgical resection of the tumour with a surrounding margin. Historically, the most commonly accepted margin clearance is 5 mm. This distance is controversial, with recent publications suggesting closer margins do not impact local recurrence and survival. The objective of this study is to determine the closest surgical margin that does not impact local recurrence and overall survival.

Methods: A retrospective review of the London Health Sciences Centre Head and Neck Multidisciplinary Clinic between 2010 and 2018 was performed. Demographic data, subsite, tumour staging, treatment modality, margins, and survival outcomes were analyzed. The primary endpoint was local recurrence free survival. Secondary endpoints included recurrence-free survival and overall survival. Descriptive statistics, as well as univariable and multivariable Cox proportional hazards regression modelling were performed for all patients.

Results: Four-hundred and twelve patients were included in the study, with a median follow-up of 3.3 years. On univariable analysis, positive margins and margins < 1 mm were associated with significantly worse local recurrence-free survival, recurrence-free survival, and overall survival ($p < 0.05$), compared to margins > 5 mm. Patients with surgical margins > 1 mm experienced similar outcomes to those with margins > 5 mm. Multivariable analysis identified age of diagnosis, alcohol consumption, pathological tumour and nodal category as predictors of local recurrence free survival.

Conclusions: Although historical margins for head and neck surgery are 5 mm, similar outcomes were observed for margins greater than 1 mm in our cohort. These findings require validation through multi-institutional collaborative efforts.

Keywords: Margin, Squamous cell, Carcinoma, Oral cavity
Background
In recent years, the incidence of oral cavity cancer (OCC) has slowly been increasing. Globally, cancers of the oral cavity represent the 16th most common cancer [1], and is the most common non-cutaneous malignancy of the head and neck [2]. In 2020, there were approximately 377,000 new diagnoses of OCC worldwide, and 178,000 associated deaths [3]. Squamous cell carcinoma accounts for greater than 90% of these cases [4, 5], with the oral tongue and floor of mouth being the most common sites. [2]

Treatment of oral cavity squamous cell carcinoma (OCSCC) involves complete surgical resection of the tumour with adequate surrounding margins. Commonly this is followed by radiation with or without chemotherapy, when indicated. Overall survival, rate of recurrence, and need for adjuvant therapy is greatly dependant on resection of the tumour with margins clear of invasive carcinoma [6–8]. Historically, 5 mm of surrounding tissue not involved with cancer is considered a “clear” margin [9]. However, 5 mm margins are not always easily achievable due anatomical constraints and tissue contracture with formalin fixation. Depending on the surgical site and tumour stage, tissue contracture can result in a 20–50% reduction in margin distance [10, 11]. Attainment of these historical margins requires a larger specimen to be taken intra-operatively to compensate for the associated contracture, thus resulting in larger defects and increased patient morbidity.

Margin status is controversial within the literature, with recent studies suggesting lesser margins do not significantly impact local recurrence and overall survival [12–17]. At the London Health Sciences Centre (London,
Ontario, Canada) we have historically defined clear margins as 3 mm or greater. The purpose of the present study is to determine the closest surgical margin that does not significantly impact local recurrence and overall survival for patients with oral cavity cancer.

Methods
Ethics approval was obtained for the study (HSREB 7182). Retrospective review of patients seen in the London Health Sciences Centre (LHSC) Head and Neck Multidisciplinary Clinic between 2010 and 2018 was carried out. All patients diagnosed with OCSCC and underwent surgical resection (± adjuvant therapy) were included in the study. Patients with multiple primaries, or previous head and neck cancers were excluded. Patient data including demographics, tumour subsite, staging, treatment modality, surgical margins, recurrence, and overall survival were all collected and analysed. The primary endpoint for the study was local recurrence free survival (LRFS), while overall survival (OS) and recurrence free survival (RFS) were both secondary endpoints.

All statistical analysis was performed using SAS version 9.4 software (SAS Institute, Cary, NC, USA). Descriptive statistics were generated for all patient variables. Univariable and multivariable Cox proportional hazards regression were performed for all survival end points. All models were evaluated using Harrell’s concordance and integrated time-dependent area under the curve values. All eligible variables were incorporated into a multivariable regression model and sequentially removed using backward elimination techniques until all remaining covariates had \( p \)-values < 0.05. Kaplan–Meier estimates were generated for all survival end points, stratified by margin depth (mm), and compared using the log-rank test.

Results
A total of 412 patients were included in the analysis. The median follow-up duration was 3.3 years.

Patient demographics
Detailed patient demographics are shown in Table 1. The average age of diagnosis was 63 years old, with the majority of the patients being male (68%). Most patients had good overall performance scores with 90% of patients having an Eastern Cooperative Oncology Group (ECOG) scores of 0 or 1. With regards to smoking, 77% of patients were current or previous smokers, and the average number of pack years was 35. Alcohol abuse was common, with 37% of patients consuming more than 20 drinks per week.

Tumour characteristics and treatment modality
The most common subunits of the oral cavity involved were the oral tongue (47%), floor of mouth (17%), and mandibular alveolus (13%). The majority of patients presented with early T1/T2 disease (58%), while T3 and T4 disease accounted for 12% and 29%, respectively. Clinically, no nodes were appreciated on imaging or physical exam preoperatively in 69% of patients. At the time of primary tumour resection, 75% of patient underwent neck dissection. Sixty-five percent of neck dissections were unilateral. Post-resection, forty-five percent of patients underwent adjuvant radiation therapy, and an additional 19% received chemotherapy as well (Table 2).

Surgical margins
On final pathology, the average margin distance was 2.70 ± 2.44 mm. Nineteen percent of specimen margins were positive, and 24% were within 1 mm of invasive carcinoma (Table 3).

Univariable analysis
Compared to margins > 5 mm, positive margins \((p = 0.03)\) and margins < 1 mm \((p = 0.03)\) had significantly poorer LRFS. This correlates with a hazard ratio of 2.15 for positive margins (95% CI, 1.10–4.18), and 2.01 for margins < 1 mm (95%CI, 1.05–3.83). Patients

Table 1 Patient demographics

| Variable                                      | N    | Relative frequency |
|-----------------------------------------------|------|--------------------|
| Age at diagnosis – mean±SD                   | 412  | 63.7 ± 12.3        |
| Male – n(%)                                   | 412  | 280 (68.0)         |
| ECOG performance status – n (%)              |      |                    |
| 0                                             | 273  | 99 (36.3)          |
| 1                                             | 148  | 54.2               |
| 2                                             | 17   | 6.2                |
| 3                                             | 8    | 2.9                |
| 4                                             | 1    | 0.4                |
| ECOG performance status – n (%)              |      |                    |
| 0–1                                           | 273  | 247 (90.5)         |
| 2–4                                           | 26   | 9.5                |
| Smoking status – n (%)                       |      |                    |
| Current                                       | 410  | 213 (52.0)         |
| Previous                                      | 101  | 24.6               |
| Never                                         | 96   | 23.4               |
| Smoking pack-years – mean±SD                  | 295  | 35.6 ± 21.6        |
| Alcohol misuse – n (%)                       |      |                    |
| Current                                       | 396  | 110 (27.8)         |
| Previous                                      | 37   | 9.3                |
| Never                                         | 249  | 62.9               |
| Alcohol per week – mean±SD                    | 339  | 12.6 ± 19.6        |
| Immunosuppression – n (%)                     | 412  | 8 (1.9)            |
| Previous non-head-and-neck cancer – n (%)    | 412  | 47 (11.4)          |
with surgical margins > 1 mm experienced similar outcomes to those with margins > 5 mm. Like LRFS, a positive margin or a margin < 1 mm resulted in poorer RFS (p = 0.04 and 0.04, respectively) and OS (p = 0.03 and 0.05, respectively). Figure 1 illustrates Kaplan–Meier curves for each survival end-point.

Multivariable analysis

Strongest predictors of LRFS were age of diagnosis (p = < 0.001), pathologic tumour stage (p = 0.003), pathologic nodal stage (p = < 0.001), and alcohol consumption per week (p = < 0.001). Surgical margins were not retained on multivariable analysis. Summary of results are available in Table 4. Time-dependent area under the curve plot for LRFS comparing multivariable analysis and margin status is depicted in Fig. 2.

Discussion

Although 5 mm has been considered the historic standard within the oral cavity, this is not based on level 1 evidence. Herein we present the largest Canadian study analysing surgical margins of the oral cavity. Our findings are consistent with other recent studies [12–17], which suggest 5 mm margins may not be necessary.

In a recent survey of the American Head and Neck Society, 56% of respondents classified a clear margin as > 5 mm on microscopic evaluation [18]. Although this consensus is held true for most head and neck surgeons, there has been a strong push within the literature to redefine the definition for clear margin. In a study by Zanoni et al., [14] surgical margins of 381 patients with OCSCC were analyzed. Their findings indicate that patients with surgical margins ≤ 2.2 mm had significantly poorer LRFS, while those between 2.3 and 5.0 mm showed no significant difference. A similar investigation was conducted by Tasche et al. [15] In their retrospective review of 432 patients, they determined that there was a significant increased risk of recurrence with margins < 1 mm in close agreement with our study. Additional resection beyond 1 mm did not correspond to a significant difference in recurrence rates. Lastly, Bajwa et al [13] performed a retrospective, multicentre analysis (n = 669) assessing impact of surgical margins on LRFS, disease free survival (DFS), and OS. The results of their study revealed margins < 1 mm were associated with significantly poorer LRFS and DFS. These studies compliment the findings of the current paper well. Despite these findings, larger, multicentre analyses are still required for widespread adoption of new definition for clear margins. We are initiating such a multicentre study in collaboration with multiple other Canadian centres.

In the present study, multivariable analysis revealed age of diagnosis, tumour stage, pathologic nodal stage, and alcohol consumption per week were the strongest predictors of LRFS. Age of diagnosis, tumour staging, pathologic staging are all predictive factors that have been reported in previous studies [5, 6, 19]. Surprisingly, surgical margins were not retained on final analysis in our study. This finding contradicts the multivariable analysis of Bajwa et al. [13] and Zanoni et al. [14] We hypothesize

| Variable | N | Relative frequency |
|----------|---|-------------------|
| Oral cavity subsite – n (%) | | |
| Oral tongue | 412 | 193 (46.8) |
| Floor of mouth | 68 | 16 (16.5) |
| Mandible alveolus | 52 | 12 (6.3) |
| Mandible alveolus | 26 | 6 (3.3) |
| Retromolar trigone | 26 | 6 (3.3) |
| Buccal | 24 | 5 (2.4) |
| Other | 23 | 5 (2.4) |
| Clinical T stage – n (%) | | |
| T1 | 412 | 110 (26.7) |
| T2 | 130 | 31 (31.6) |
| T3 | 51 | 12 (2.4) |
| T4 | 121 | 29 (4.6) |
| Clinical N stage – n (%) | | |
| N0 | 412 | 284 (68.9) |
| N1 | 48 | 11 (2.7) |
| N2 | 79 | 19 (4.6) |
| N3 | 1 | 0 (0) |
| Neck dissection – n (%) | 412 | 310 (75.2) |
| Regional neck surgery laterality – n (%) | | |
| Bilateral | 310 | 109 (35.2) |
| Unilateral | 201 | 64 (4.8) |
| Adjuvant Therapy | | |
| None – n (%) | 412 | 146 (35.4) |
| Radiotherapy – n (%) | 187 | 45 (10.2) |
| Chemoradiotherapy – n (%) | 79 | 19 (4.7) |

Table 2 Tumour characteristics and treatment modality

Table 3 Surgical margin characteristics

| Variable | N | Relative frequency |
|----------|---|-------------------|
| Closest margin (mm) – mean ± SD, median | 401 | 2.70 ± 2.44 |
| Closest margin (mm) – n (%) | | |
| 0 (positive) | 401 | 74 (18.5) |
| >0, ≤ 1 | 95 | 23 (7.3) |
| >1, ≤ 2 | 43 | 11 (3.5) |
| >2, ≤ 3 | 65 | 19 (6.3) |
| >3, ≤ 5 | 73 | 18 (2.5) |
| >5 | 51 | 13 (4.4) |
| Positive patient margins – n (%) | 408 | 79 (19.4) |
| Re-excision of suspected close margin– n (%) | 412 | 73 (17.7) |
| Re-excision positive margin status – n (%) | 73 | 14 (19.2) |
that this may be due to lack of power. We will re-examine this as part of our future multicentre analysis.

Our study is not without limitations. Adjuvant therapy is a major confounding factor within our study, with 45% of patients undergoing radiation therapy post-operatively. Due to the retrospective design, it is not possible to determine the cause and effect relationship that this had on margin status, LRFS, RFS, and OS. Our study is also single centred and of modest sample size. Further multicentre analysis is required to validate our findings.

Conclusions
Our study has shown that surgical margins < 1 mm were associated with poorer LRFS, OS, and RFS. Moreover, comparing surgical margins > 1 mm versus > 5 mm showed no significant difference for disease control. Lastly, our study identified predictive factors for LRFS, which included age of diagnosis, tumour stage, pathological nodal stage, and alcohol consumption per week. The future direction of this study will be in partnership with Collaborative Research Initiative of the Canadian Society.
Table 4  Multivariable analysis – predictive factors associated with local recurrence free survival

| Variable                          | Hazard Ratio (95% CI) | P-value |
|----------------------------------|-----------------------|---------|
| Age of diagnosis (per 5 years)   | 1.20 (1.09, 1.32)     | <0.001  |
| Alcohol per week (per 10 drinks) | 1.26 (1.16, 1.38)     | <0.001  |
| Pathologic T stage (vs. T1)      | 2.17 (1.20, 3.92)     | 0.010   |
| T3-4                             | 2.78 (1.55, 5.01)     | <0.001  |
| Pathologic N stage (vs. N0)      | 1.05 (0.51, 2.18)     | 0.887   |
| N1                               | 2.95 (1.90, 4.58)     | <0.001  |

Multivariable analysis—local recurrence free survival

Fig. 2  Time-dependent area under the curve plot for local recurrence-free survival comparing margins (0 mm, 0.01–1 mm, 1.01–2 mm, 2.01–5 mm, vs. > 5 mm) and multivariable model (adjusting for age, alcohol use and pathological T and N stage)

of Otolaryngology. The existing database has collected surgical outcomes data from approximately five thousand of patients. We plan to utilize this dataset to examine margin status with markedly greater statistical power to strengthen our conclusions.

Abbreviations
OCC: Oral cavity cancer; OCSCC: Oral cavity squamous cell carcinoma; LHSC: London health sciences centre; LRFS: Local recurrence free survival; OS: Overall survival; RFS: Recurrence free survival; ECOG: Eastern cooperative oncology group; DFS: Disease free survival.

Acknowledgements
Not applicable.

Author contributions
JF preformed the literature review and constructed database for study. YC input patient data into database. AW performed statistical analysis. FL and NF formatted database. AN and DF proposed the concept for this report. AN, KF, AM, DM, and JY all contributed patient data for the database used in this study. All authors wrote, reviewed, and edited the manuscript. All authors read and approved the final manuscript before submission.

Funding
Dr. Nichols was supported by the Wolfe Surgical Research Professorship in the Biology of Head and Neck Cancers Fund.

Availability of data and materials
All data generated or analysed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
Ethics approval/REB Number (HSREB 7182). Consent was waived for retrospective data analysis. No personal or identifiable information was collected.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details

1 Department of Otolaryngology – Head and Neck Surgery, Victoria Hospital, 1200 Kilmuir Street South, London, ON, Canada. 2 Department of Radiation Oncology, Western University, 3 Western University, London Health Science Centre, Western University, Room B3-431A, 800 Commissioners Road East, London, ON N6A 5W9, Canada. 3 Western University, London, ON, Canada. 4 Department of Radiation Oncology, Western University, London, ON, Canada.

Received: 7 January 2022   Accepted: 23 May 2022

Published online: 04 October 2022

References
1. Miranda-Filho A, Bray F. Global patterns and trends in cancers of the lip, tongue and mouth. Oral Oncol. 2020;102: 104551.
2. Chi AC, Day TA, Neville BW. Oral cavity and oropharyngeal squamous cell carcinoma—an update. CA: A Cancer J Clin. 2015; 65(5):401–421. https://doi.org/10.3322/caac.21293.
3. Global cancer observatory. lip and oral cavity. 2020. https://gco.iarc.fr/today/data/factsheets/cancers/1-Lip-oral-cavity-fact-sheet.pdf
4. Kain JJ, Birkeland AC, Udayakumar N, Morlandt AB, Stevens TM, Carroll WR, Rosenthal EL, Warram JM. Surgical margins in oral cavity squamous cell carcinoma: current practices and future directions. Laryngoscope. 2020;130(1):128–38.
5. Gokavarapu S, Chander R, Parvatani N, Puthamakula S. Close margins in oral cancers: implication of close margin status in recurrence and survival of pT1N0 and pT2N0 oral cancers. Int J Surg Oncol. 2014;1:6.
6. Varvares MA, Poti S, Kenyon B, Christopher K, Walker RJ. Surgical margins and primary site resection in achieving local control in oral cancer resections. Laryngoscope. 2015;125(10):2298–307.
7. Kurita H, Nakashiyri Y, Nishizawa R, Xiao T, Kamata T, Koike T, Kobayashi H. Impact of different surgical margin conditions on local recurrence of oral squamous cell carcinoma. Oral Oncol. 2010;46(11):814–7.
8. Sutton DN, Brown JS, Rogers SN, Vaughan ED, Woolgar JA. The prognostic implications of the surgical margin in oral squamous cell carcinoma. Int J Oral Maxillofac Surg. 2003;32(1):30–4.
9. Seethala RR, Altemani A, Fennis RL, Fonseca I, Grepp D, Ha P, Nagao T, Skalova A, Stenman G, Thompson LDR. Data Set for the Reporting of Carcinomas of the Major Salivary Glands: Explanations and Recommendations of the Guidelines From the International Collaboration on Cancer Reporting. Arch Pathol Lab Med. 2019;143(5):578–86. https://doi.org/10.5858/arpa.2018-0422-SA.
10. Mistry RC, Qureshi SS, Kumar S. Post-resection mucosal margin shrinkage in oral cancer: quantification and significance. J Surg Oncol. 2005;91(2):131–3.
11. Johnson RE, Sigman JD, Funk GF, Robinson RA, Hoffman HT. Quantification of surgical margin shrinkage in the oral cavity. J Sci Special Head Neck. 1997;19(4):281–6.
12. Solomon J, Hinther A, Matthews TW, Nakoneshny SC, Hart R, Dort JC, Chandarana SP. The impact of close surgical margins on recurrence in oral squamous cell carcinoma. J Otalaryngol-Head Neck Surg. 2021;50(1):1–7.
13. Bajwa MS, Houghton D, Java K, Trianafyllou A, Khattak O, Bekiroglu F, Schache AG, Brown JS, McCaul JA, Rogers SN, Lowe D. The relevance of surgical margins in clinically early oral squamous cell carcinoma. Oral Oncol. 2020;10:104913.
14. Zanoni DK, Migliacci JC, Yu B, Katabi N, Montero PH, Ganly I, Shah JP, Wong RJ, Ghosein RA, Patel SG. A proposal to redefine close surgical margins in squamous cell carcinoma of the oral tongue. JAMA Otolaryngol-Head Neck Surg. 2017;143(6):555–60.
15. Tasche KK, Buchakjian MR, Pagedar NA, Sperry SM. Definition of "close margin" in oral cancer surgery and association of margin distance with local recurrence rate. JAMA Otolaryngol-Head Neck Surg. 2017;143(12):1166–72.
16. Barry C, Shaw R, Woolgar J, Rogers S, Lowe D, Brown J. OP081: evidence to support: a 3 mm margin as oncologically safe in early oral SCC. Oral Oncol. 2013;49:S37.
17. Nason RW, Binahmed A, Pathak KA, Abdoh AA, Sándor GK. What is the adequate margin of surgical resection in oral cancer? Oral Surg Oral Med Oral Pathol Oral Radiol Endodontol. 2009;107(5):625–9.
18. Bulbul MG, Zenga J, Tarabichi O, Parikh AS, Sethi RK, Robbins KT, Puram SV, Varvares MA. Margin practices in oral cavity cancer resections: survey of American head and neck society members. Laryngoscope. 2021;131(4):782–7.
19. Jang JY, Choi N, Ko YH, Chung MK, Son YI, Baek CH, Baek KH, Jeong HS. Differential impact of close surgical margin on local recurrence according to primary tumor size in oral squamous cell carcinoma. Ann Surg Oncol. 2017;24(6):1698–706.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.