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How Often is Cancer Present in Oral Cavity Re-resections After Initial Positive Margins?

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Objective: To evaluate the rate at which carcinoma is present in the re-resection specimen following initial positive margins during head and neck cancer surgery and its impact on oncologic outcomes.

Study Design: Retrospective chart review.

Methods: A single institution retrospective chart review of patients that underwent curative-intent surgery for oral cavity cancer was performed. Final pathology reports were reviewed to identify patients with initial positive margins who underwent re-resection during the same operation. Initial positive margin was defined as severe dysplasia, carcinoma in situ (CIS), or carcinoma. Cox proportional hazards and Kaplan–Meier analyses were used to assess for associations with survival outcomes.

Results: Among 1873 total patients, 190 patients (10.1%) had initial positive margins and underwent re-resection during the same surgery. Additional carcinoma, CIS, or severe dysplasia was found in 29% of re-resections, and 31% of patients with initial positive margins had final positive margins. Half of the patients with a final positive margin had a positive margin at an anatomic site different than the initial positive margin that was re-resected. The median follow-up was 636 days (range 230–1537). Re-resection with cancer and final positive margin status was associated with worse overall survival (OS; $p = 0.044$ and $p = 0.05$, respectively). However, only age, T4 disease, and surgery for recurrent oral cavity cancer were independently associated with OS ($p < 0.001$, $p = 0.005$, and $p = 0.001$, respectively).

Conclusions: Fewer than a third of oral cavity re-resections contain further malignancy, which may suggest that surgeons have difficulty relocating the site of initial positive margin. Final positive margins are often at anatomic sites different than the initial positive margin.

Key Words: clinical research, head and neck, oral cavity, positive surgical margin, reresection, squamous cell carcinoma.

Level of Evidence: 4

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INTRODUCTION

The goal of oncologic surgery is complete resection of the cancer with clear surgical margins. In head and neck cancer surgery, the margin status is the most important prognostic factor.[1–5] A positive surgical margin not only increases the risk of local recurrence at 5 years by 90% but it also increases the risk of all-cause mortality by 90%.[6] As a result, final positive surgical margins are an indication for adding chemotherapy to adjuvant radiotherapy, an addition that impacts the quality of life during and following cancer treatment.[7,8]

To ensure complete resection of the tumor with clear surgical margins, head and neck surgeons rely on intraoperative frozen section analysis.[9] If a positive surgical margin is identified, the pathologist communicates this back to the surgeon in the operating room, and further resection is attempted. However, studies suggest that head and neck surgeons have difficulty relocating the positive margin site. One study demonstrated a 9 mm average relocation error of a peripheral margin and a relocation of over 10 mm in >32% of cases.[10]

Despite the importance of negative margins in head and neck cancer surgery, there has been little investigation into the accuracy and value of re-resection. A subgroup analysis of 50 re-resections from a larger cohort found that 20% of re-resection samples contained further malignancy.[11] In a subgroup analysis of 149 oral cavity with initial positive margins, re-resection to negative final margin status did not improve local recurrence rates compared to those with a final positive margin regardless of re-resection.[12] To date, no study has focused solely on patients who underwent re-resection of an initial positive margin. In the present study, we aim to evaluate the rate at which carcinoma is present in re-resection and its impact on oncologic outcomes.

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METHODS

Patients diagnosed or treated for oral cavity cancer between January 1, 2000 and December 2022 were identified by querying the Vanderbilt University Medical Center (VUMC) Research Derivative (RD), an Institutional Review Board (IRB) approved, searchable database of electronic health records, with the following *International Classification of Diseases* (ICD) codes: a manual review of each patient's final pathology report was conducted to determine (a) if the patient had an initial positive margin identified on frozen section analysis, (b) underwent subsequent re-resection during the same operation, and (c) if the re-resection sample was analyzed by pathology. Positive margins (initial and final) were defined as cut through of severe dysplasia, carcinoma in situ (CIS), or carcinoma. Tumor bed margin sampling approach was self-reported to be used in vast majority of cases during the study period.

The following clinical information were collected: surgery for primary or recurrent disease, prior treatment, oral cavity cancer subsite, pathologic T stage, histology of cut through, histology on re-resection, and final margin status. Anatomic subsites included lip, oral tongue, floor of mouth, buccal mucosa, upper and lower gum, retromolar trigone, and hard palate. The following oncologic outcome data were collected: evidence of local, regional, or distant recurrence; evidence of death; cause of death; and date of last follow-up.

Descriptive statistics were performed to describe clinical and outcome information. Primary endpoints of local recurrence-free survival (LRFS), disease-free survival (DFS), and overall survival (OS) were estimated by the Kaplan–Meier method. Cox proportional hazards model was used to evaluate the impact of covariates on LRFS and OS. An alpha of 0.05 was the threshold for significance. All statistical analyses were conducted using R statistical software (R project, Vienna, Austria).

RESULTS

Between 2000 and 2022, a total of 1873 patients underwent surgical treatment of primary or recurrent oral cavity cancer during the study period. An initial positive margin with subsequent re-resection was recorded in 190 (10%) of those patients. The majority of patients underwent surgery for primary disease (65%). Most patients were male (57%) with a median age of 65 (range 54–72). The most common primary tumor site was oral tongue (37%) followed by floor of mouth (15%). Eighty-eight patients (44%) underwent surgery for locally advanced disease (T3/T4). Clinical characteristics and oncologic outcomes are described in Table I.

Of the 190 patients who underwent re-resection, 56 (29%) had further malignancy identified on the re-resection sample. Among these 56 patients, 27 had carcinoma, 5 had CIS, and 24 had severe dysplasia.

Fifty-eight (31%) of patients had at least one final positive margin, with 29 (50%) of these patients having a positive margin at a different margin site than the one that was re-resected. Table II depicts the distribution of cases with a final positive margin, and cases with final positive margins at anatomic sites different than the initial positive margin, stratified by primary tumor subsite. Within this database of patients with initial positive margins who underwent reresection, oral tongue cancers had the highest number of cases with final positive margins at 19. Eight of the 19 cases had final positive margins at anatomic sites different than the initial positive margin. In contrast, seven of the eight mandibular alveolar ridge primary cancers had final positive margins at a site different than the initial positive margin.

TABLE I.
Descriptive Characteristics.

Characteristics	$N = 190$*
Age	65 (54, 72)
Sex	
Female	81 (43%)
Male	109 (57%)
Average time to follow-up (days)	636 (230, 1,537)
T stage	
1/1a	56 (32%)
2	43 (24%)
3	12 (6.8%)
4/4a/4b	66 (37%)
Unknown	13
Primary tumor site	
Oral tongue	70 (37%)
Floor of mouth	29 (15%)
Mandible	53 (28%)
Buccal mucosa	11 (5.8%)
Pharynx	2 (1.1%)
Palate	3 (1.6%)
Retromolar trigone	7 (3.7%)
Other	15 (7.9%)
Recurrent disease (yes)	67 (35%)
Re-resection with cancer? (yes)	56 (29%)
Final margin with cancer? (yes)	58 (31%)
Outcomes	
Local recurrence? (yes)	37 (19%)
Any recurrence? (yes)	82 (43%)
All-cause mortality	61 (32%)

*Median (IQR); *n* (%); range.

TABLE II.
Number of Final Positive Margins and Disparate Initial and Final Positive Margins Stratified by Primary Tumor Subsite.

Primary Tumor Subsite	Cases with Final Positive Margins	Cases with Final Positive Margins at Anatomic Sites Different Than Initial Positive Margin
Oral tongue	19	7
Mandibular alveolar ridge	8	7
FOM	8	4
Mandible (bone)	7	3
Buccal	7	3
Oropharynx/ tonsil	6	3
Retromolar trigone	3	2
Total	58	29

Figure 1 depicts the frequency of final positive margins at various anatomic locations. Oral tongue margins were the most positive anatomic location on final pathology, followed closely by the floor of mouth. In 10 cases, a final positive margin was initially sent for frozen section, falsely identified to be negative, and subsequently found to be positive on permanent section. In the remaining 80 cases, the final positive margin was not sent for frozen section analysis.

The median follow-up time was 636 days (range 230–1537). Local recurrence occurred in 37 patients (19%), any recurrence in 82 (43%), and death from any cause in 61 (32%). Kaplan–Meier log rank analysis found that re-resection containing cancer ($p = 0.04$; Fig. 2A) and final positive margin status ($p = 0.052$; Fig. 2B) were associated with worse OS. Neither re-resection with malignancy nor final margin status was associated with LRFS ($p = 0.51$ and $p = 0.35$, respectively; Fig. 3A,B) or DFS ($p = 0.032$ and $p = 0.96$; Fig. 4A,B).

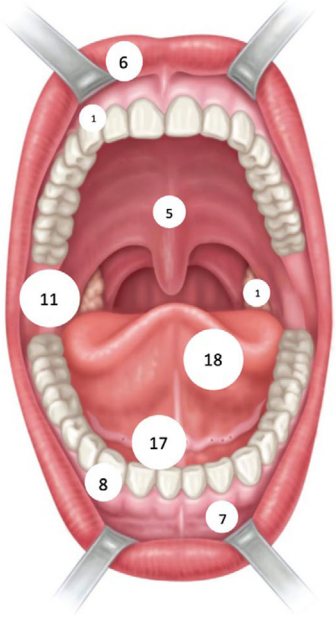
Cox proportional hazards model to explore associations between survival and clinical and oncologic characteristics is shown in Tables III and IV. Buccal ($p = 0.015$) and palate ($p < 0.001$) primary tumor sites were associated with worse local recurrence (Table III). There was no significant association between local recurrence and age ($p = 0.4$), recurrent disease ($p = 0.11$), positive re-resection ($p > 0.9$), or positive final margin status ($p = 0.5$). Age ($p < 0.001$), T4 disease ($p = 0.005$), and surgery for recurrent disease ($p = 0.001$) were independent predictors of OS (Table IV).

DISCUSSION

We sought to evaluate the rate at which carcinoma is present in the re-resection following initial positive margin during head and neck cancer surgery and its impact on oncologic outcomes. In our sample of 190 re-resections, we found that only 29% contained further malignancy. Despite subsequent re-resection, 31% of patients still had final positive margins. The oral tongue and floor of mouth were the margin sampling sites that were most often positive on final pathology. Twenty-nine (50%) cases with a final positive margin had a positive margin at an anatomic site different than the one that was re-resected. Among the 19 oral tongue primary cancers that were re-resected, seven had final positive margins at a site different than the one that was re-resected.

On survival analysis, final margin status and re-resection containing further malignancy were associated with worse OS. However, on regression analysis, neither were independent predictors of OS. Age, recurrent, and T4 disease were independent predictors for OS. It is unclear why positive margins were not independent prognosticators for survival. It could be that our study is based out of a high-volume, academic center where patients with positive margins are likely to get the appropriate adjuvant chemoradiation therapy. A larger, multi-institutional study may be able to shed light on this question.

Regression analysis identified palate and buccal mucosa primary sites as independent predictors of worse locoregional control. Previously published national cancer database studies have found that patients with a hard palate primary had greater odds of a positive final margin.[13,14] The authors suggested this may be in part due to the inability to perform frozen section analysis on bony portions of resection specimens.[14] For buccal mucosa primaries, some suggest that poor accessibility of the tumor and lack of a significant deep margin may lead to increased difficulty with surgical resection.[15,16]



Positive Margin Location	Frequency
Tongue	18
FOM	17
Buccal	11
Mandibular Alveolar Ridge (mucosa)	8
Mandible (bone)	7
Lip	6
Soft Palate	5
Tonsil	1

Fig. 1. Most common positive margin location. Frequency of final positive margins at various anatomic locations. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

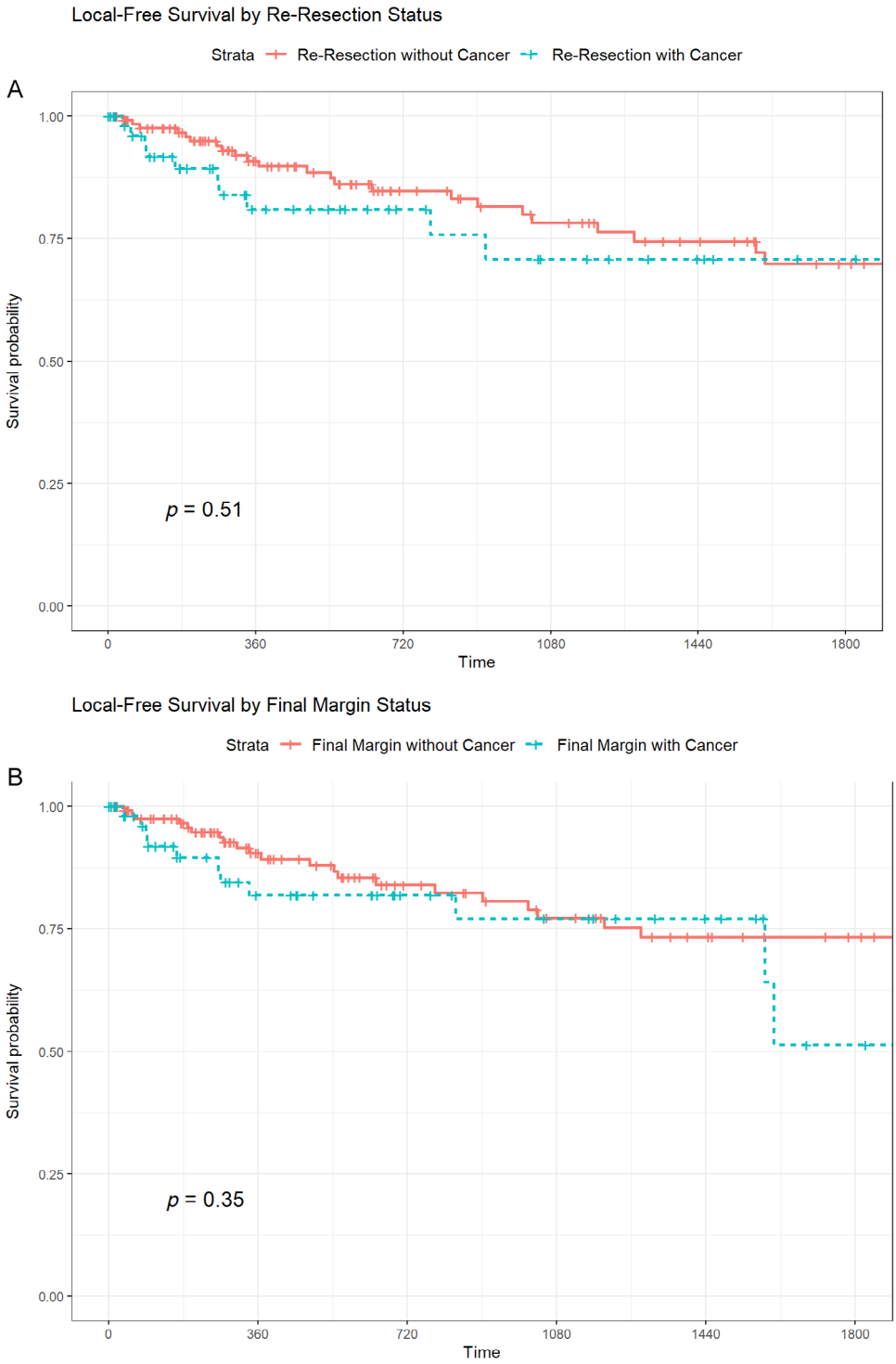


Fig. 2. Local recurrence-free survival (LRFS). Kaplan–Meier log rank analysis of the association between (A) re-resection containing further cancer and (B) final margin status on LRFS. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

Interestingly, we found that buccal and palate primary subsites were associated with worse locoregional control irrespective of final margin status.

Our study is consistent with the study by Coutu et al. who conducted a retrospective chart review of patients who underwent surgical management of oral cavity squamous cell carcinoma between 2010 and 2019 and found that, of the 50 patients who underwent additional excision of an initial positive margin, only 20% of the re-resection specimens contained further malignancy.[11] Similarly, we found that 29% of re-resection specimens contained further malignancy. Both studies highlight that surgeons may have difficulty in relocating the site of the initial positive margin.

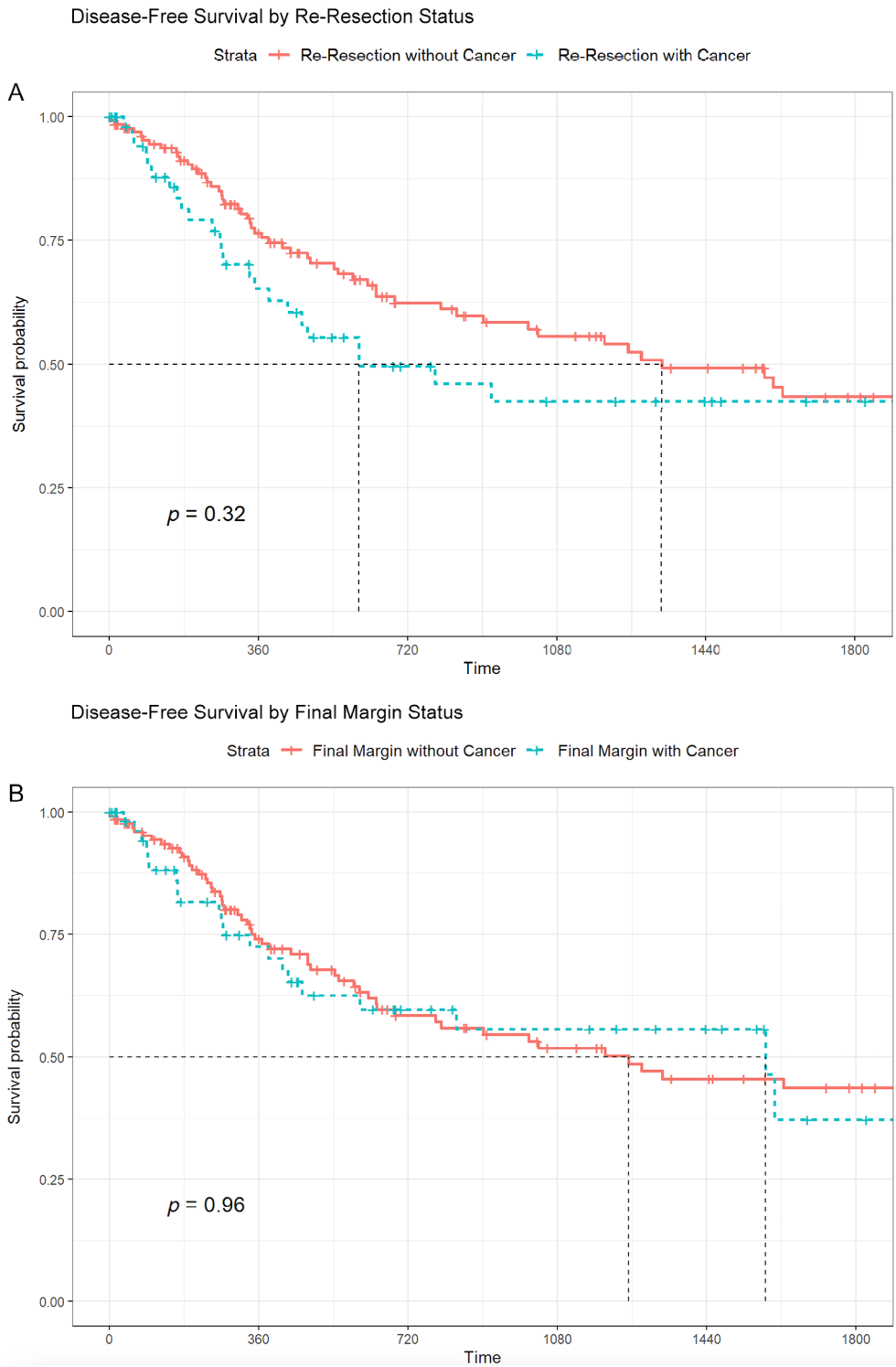


Fig. 3. Disease-free survival (DFS). Kaplan–Meier log rank analysis of the association between (A) re-resection containing further cancer and (B) final margin status on DFS. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

Coutu and colleagues also evaluated the impact of re-resection containing further malignancy on survival. They found re-resection with cancer to be associated with a trend toward worse average LRFS (18.5 vs. 66.0 months, $p = 0.054$), worse DFS (16.3 vs. 45.5 months, $p = 0.008$), and worse OS (29.4 vs. 68.4 months, $p = 0.011$). Our study also found re-resection status to be associated with worse OS ($p = 0.044$), however, this was not an independent predictor for survival on multivariate analysis.

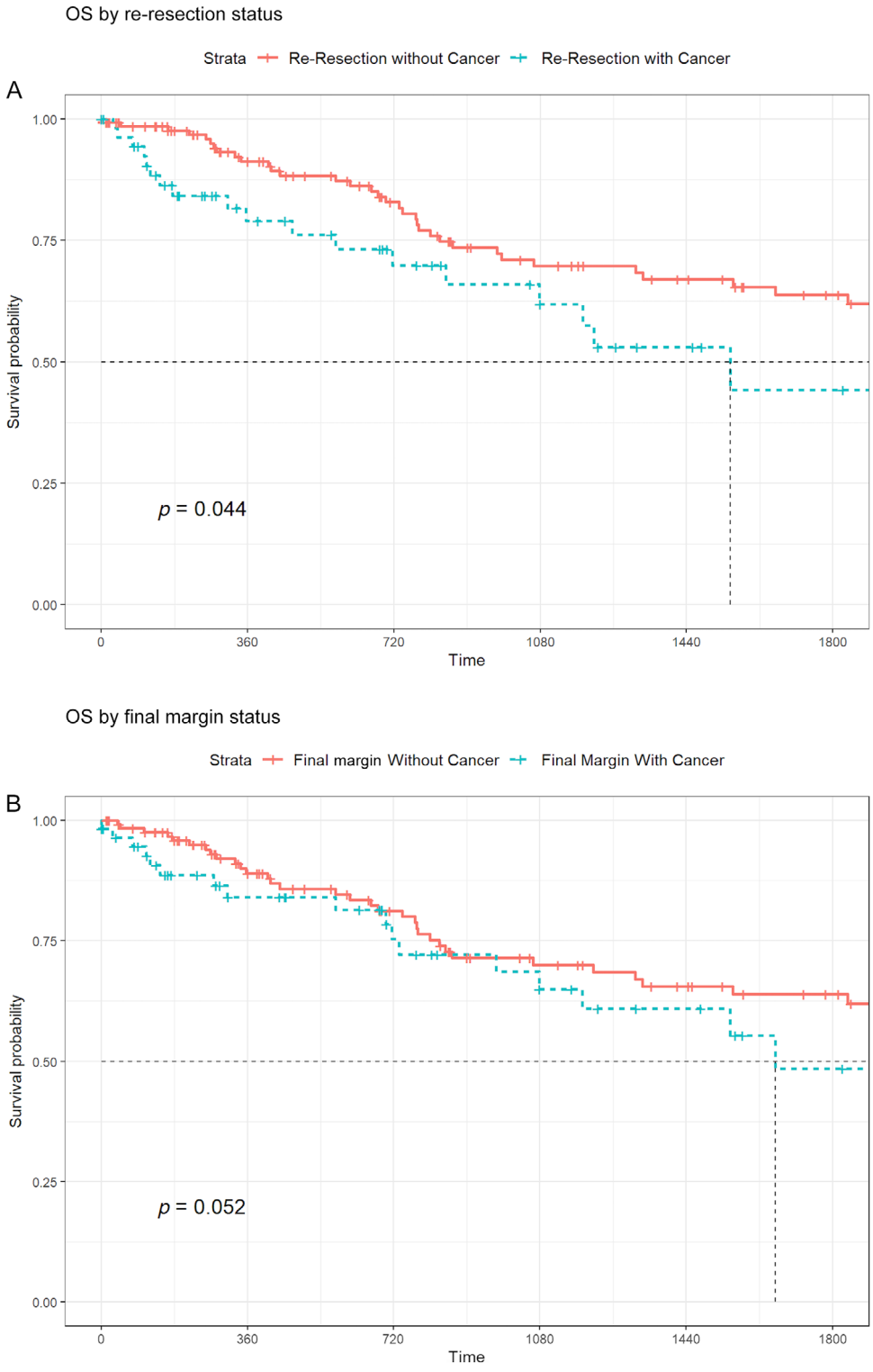


Fig. 4. Overall survival (OS). Kaplan–Meier log rank analysis of the association between (A) re-resection containing further cancer and (B) final margin status on OS. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

With regards to final margin status, Buchakjian et al. previously suggested that re-resection to R0 did not improve local recurrence rates compared to those with a final positive margin regardless of re-resection.[12] Priya and colleagues also suggested that revision to negative margins did not improve patient outcomes.[17] Contrastingly, our work, the largest evaluation of re-resections during oral cavity oncologic surgery, found

TABLE III.
Clinicopathologic Parameters and Local Recurrence.

Characteristic	HR	95% CI	*p*-value
Age	1.02	0.99, 1.04	0.2
Recurrent disease			
No	—	—	
Yes	1.54	0.78, 3.04	0.2
Re-resection with cancer?			
No	—	—	
Yes	1.01	0.42, 2.45	>0.9
Final margin with cancer?			
No	—	—	
Yes	1.19	0.50, 2.79	0.7
Primary tumor site			
Oral tongue	—	—	
Floor of mouth	1.65	0.60, 4.53	0.3
Mandible	1.04	0.41, 2.64	>0.9
Buccal mucosa	4.58	1.34, 15.7	0.015
Pharynx	—	—	>0.9
Palate	17.2	3.52, 83.9	<0.001
Retromolar trigone	—	—	>0.9
Other	1.04	0.29, 3.76	>0.9

CI = confidence interval; HR = hazard ratio.

TABLE IV.
Clinicopathologic parameters and overall survival.

	Overall Survival		
Characteristic	HR	95% CI	*p*-value
Age	1.03	1.01, 1.05	0.002
T-stage			
1	—	—	
2	1.61	0.73, 3.53	0.2
3	1.85	0.41, 8.37	0.4
4	2.68	1.34, 5.34	0.005
Primary or recurrent			
Primary	—	—	
Recurrent	2.13	1.22, 3.69	0.007
Re-resection w/cancer?			
No	—	—	
Yes	1.44	0.76, 2.75	0.3
Final margin w/cancer?			
No	—	—	
Yes	1.04	0.55, 1.97	>0.9

CI = confidence interval; HR = hazard ratio.

that resecting to R0 impacted survival outcomes. This highlights the value of intraoperative frozen section analysis and further resection following an initial positive margin.

Our study was the first to compare the anatomic location of initial positive margin compared to final positive margin. The final margin sampling locations that were most often positive were the oral tongue and floor of mouth mucosa. This may highlight that grossly appreciating residual tumor in these areas is particularly challenging. Fifty percent of the patients with a final positive margin had a positive margin at a different anatomic site than the one that was re-resected. Seven of 19 oral tongue cases with final positive margins had a final positive margin at a site different than the initial positive margin. Whereas seven of the eight mandibular alveolar ridge primary cases with final positive margins had a final positive margin at a site different than the initial positive margin. This may suggest a mismatch between the margins deemed most worrisome by the surgeon and the actual site of cut through or underlying aggressive primary tumor disease. Margin sampling technique, tumor bed sampling versus specimen-based sampling, may impact both initial and final margin status. Some suggest that there is a lack of reliability when sampling from the tumor bed, which make it difficult to know whether a main specimen margin has been replaced by a subsequent re-resection.[12] The specimen-based approach may allow for more targeted margin analysis and improve communication between surgeon and pathologist regarding margin sampling sites. Maxwell et al. determined that the specimen-driven approach was associated with improved locoregional control.[18] We were unable to definitively determine margin sampling technique of each surgery based on chart review, but future studies should evaluate the impact of sampling on accuracy of re-resection and final margin status.

Our findings demonstrate a need for further innovation and novel techniques to help guide margin relocation. Recent studies have highlighted the value of 3D scanning with annotation of margin sampling site for enhanced communication between surgeons and pathologists.[19,20] Another combined 3D scanning with augmented reality to accurately guide re-resection.[21] Finally, intraoperative adjuncts, such as fluorescence[22] and ultrasound,[23] can further improve margin analysis and excision.

Our study was limited by its relatively small sample size and retrospective nature. In addition, our median follow-up time was relatively short at 1.7 years. However, given that 90% of recurrences are within 2 years of treatment, we should have captured a majority of recurrences.[24] A larger multi-institutional study to account for differences across programs and long-term follow-up data may provide increased insight into the value of re-resection.

CONCLUSION

Only 29% of re-resections contained further malignancy, which may suggest that surgeons have difficulty relocating the site of positive margin and resecting the remaining cancer. Half of the patients with a final positive margin had a positive margin at an anatomic site different than the one that was re-resected.

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