Does Clearance of Positive Margins Improve Local Control in Oral Cavity Cancer? A Meta-analysis

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Abstract

Objectives. To compare local recurrence-free survival (LRFS) in early oral cavity cancer (OCC) patients with positive/close frozen section (FS) cleared with further resection (R1 to R0) or positive FS not cleared (R1) to those with negative margins on initial FS analysis (R0).

Data Sources. PubMed, EMBASE, and Cochrane.

Review Methods. We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) for reporting in our study. Only English-language articles that included patients with OCC and local recurrence (LR) comparisons between R0 and initially R1 to final R0 or final R1 groups were included. We requested the raw data from the corresponding authors of eligible studies and performed an individual participant data (IPD) meta-analysis of LRFS outcomes across groups.

Results. Pooled LRFS data from 8 studies showed that patients in the R1 to R0 group had worse LRFS compared to the R0 group (hazard ratio [HR] = 2.897, \( P < .001 \)). Patients in the R1 group were also found to have worse LRFS compared to the R0 group (HR = 3.795, \( P < .001 \)). When compared to final R1 group, the initially R1 to final R0 only showed a trend toward better LRFS.

Conclusion. Margin revision of initially positive margins to “clear” based on FS guidance does not equate to an initially negative margin and does not significantly improve local control. These findings call into question the effectiveness of the current methodology of intraoperative FS in OCC resections and call for a prospective study to determine what system of resected specimen analysis best predicts completeness of resection.

Keywords
oral cancer, tongue cancer, frozen section, microscopic cut-through, positive margin, margin revision

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O oral cavity cancer (OCC) is a common malignancy in the United States with an expected 33,950 new cases resulting in 6800 deaths by the end of 2018.1 The management of OCC is primarily surgical with the aim of completely removing the tumor and achieving negative margins. Positive margins on final pathologic examination have been regarded as an adverse prognostic feature associated with a higher risk of local recurrence (LR) and poorer survival.2-11 The National Comprehensive Cancer Network (NCCN) lists positive margins as an indication for re-resection or adjuvant radiation in its clinical practice guidelines.12

Intraoperative frozen section (FS) analysis has long been thought of as a way to predict final margin status after initial resection and manage positive margins in a single operative setting. Recent studies, however, have shown that the efficacy of FS in guiding further resection in patients with OCC is questionable.9,11,13-16 Studies show that re-resection in the same procedure based on FS guidance does not improve oncologic outcomes, particularly local recurrence-free survival (LRFS).10,13-16

Despite a lack of robust evidence of its benefit at the time, Meier et al17 found that in a survey of American Head and Neck Society (AHNS) members conducted in 2005, 97% of respondents reported using FS to guide further resection. In addition, 90% of AHNS members considered a
positive FS that they re-resected to a negative FS during the same procedure as an overall negative margin. Although FS has been reported to be highly specific for identifying clear margins, reports of its sensitivity vary significantly, with some studies documenting sensitivities as low as 15% for detecting positive margins.\textsuperscript{18-21}

It is important to note, however, that FS sampling and analysis methodologies are far from standardized, and it is therefore difficult to draw generalizable conclusions from any individual study. FS sampling techniques can be broadly categorized into 2 methods: specimen-based and patient-based sampling.\textsuperscript{9,22} In the former, samples are taken by either the pathologist or the surgeon from the specimen itself, while in the latter, the surgeon samples the tumor bed left behind after resecting the specimen. Amit et al\textsuperscript{23} reported a sensitivity of 91% when using specimen-based FS compared to 22% when the FS was patient based. Other studies have reported better oncologic outcomes when specimen-based FS was used intraoperatively.\textsuperscript{6,24,25} Consequently, the NCCN guidelines currently recommend that evaluation of margins using FS should be primarily specimen based; patient-based sampling can be used as an alternative.\textsuperscript{12} Despite this, the practice of patient-based FS sampling is still quite prevalent,\textsuperscript{17} and recommendations regarding the proper orientation of sampled areas to the resected specimen are poorly followed.\textsuperscript{22}

Further evidence that brings into question the utility of FS includes a study from Mair et al,\textsuperscript{26} which showed that a patient-based FS was associated with a lower LRFS (5-year LRFS: 44 vs 61%) and OS (5-year OS: 58 vs 77%) among patients who had FS compared to patients with no FS.

The evidence accumulated to date on this topic should motivate us to reconsider our FS practices, given that the average cost of intraoperative FS is $3123/patient.\textsuperscript{21} Important questions to ask are (1) whether it is justified to perform FS if its use does not improve local control and (2) whether there is a specific approach to FS that, when followed, can more reliably result in improved local control over other current approaches. There is an opportunity not only to improve outcomes by determining a more effective methodology of FS analysis but to make it a cost-effective modality.

In this review, we aim to take a step toward answering some of these questions by investigating how local control in patients with positive (<1 mm)/close (1 to <5 mm) FS margins cleared by further resection (R1 to R0) and patients with positive FS not cleared (R1) compare to the local control achieved in patients with negative margins on initial resection (R0). We performed an individual participant data (IPD) meta-analysis to quantify the effect of each margin group on 5-year LRFS. We used LRFS because we feel it is the most reliable indication of the effectiveness of primary site resection in early OCC. We do not report overall survival (OS) in this meta-analysis as this is beyond the scope of this study, nor is it the most relevant metric in measuring the effectiveness of primary site resection.

**Methods**

**Search Strategy and Inclusion/Exclusion Criteria**

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed for the reporting of this review.\textsuperscript{27} A systematic literature review was performed to identify studies assessing oncologic outcomes based on the margin status of OCC. In November 2017, we comprehensively searched PubMed, Embase and Cochrane to identify eligible studies for our review. Key search terms included oral cancer, tongue cancer, positive margin, microscopic cut through, and margin revision. MeSH search terms used were “((positive margin) OR margin revision) OR microscopic cut through) AND oral cancer” OR “((positive margin) OR margin revision) OR microscopic cut through) AND tongue cancer.” Titles and abstracts were screened to determine relevance to our topic. All studies in which FS was used in the management of OCC were included regardless of their quality or publication date. Only English-language studies were included. Additional studies were identified by reviewing the reference list of articles assessed and including articles the authors were aware of from other reading. Raw data were requested from the corresponding author when a study was deemed eligible. Variables assessed in the included studies, if available, were year of publication, sample size, population demographics, tumor location, pathologic T-staging, pathologic N-staging, margin status, closest margin, margin revision, LR status, time to LR, vital status, and follow-up duration.

**Level of Evidence**

We used the Oxford Center for Evidence-Based Medicine levels of evidence to classify the studies. Studies are classified into 1 of 4 levels: (1) systematic reviews of randomized trials, (2) randomized trials, (3) nonrandomized controlled prospective studies, and (4) retrospective studies.\textsuperscript{28}

**Statistical Analysis**

We performed a meta-analysis of the hazard ratio (HR) of 5-year LRFS among different margin groups using Stata 13 (StataCorp LP, College Station, Texas). Cochran’s $Q$, $\tau^2$, and $P^2$ were used to assess the heterogeneity of included studies. Inverse variance method and random-effects model were used to pool HRs of included studies.

**Results**

**Search Results**

Our comprehensive search of PubMed, EMBASE, and Cochrane yielded 80 records after duplicates were removed (Figure 1). Forty-three additional studies were identified by reviewing the reference list of full-text articles assessed or the authors were aware of them from other reading. In total, 123 records were reviewed to determine relevance to our review. Twelve authors were contacted to provide raw data for 14 studies. Eventually, only 8 studies were included in the quantitative analysis. Reasons for exclusion were (1)
full-text article not available, (2) further resection under FS guidance not reported, (3) no LR data analyzed in the study, (4) data overlap between studies, (5) short follow-up time, (6) raw data no longer available and data could not be extracted from the study, (7) no response from corresponding author, and (8) impossible to identify patients who had revision for positive/close margin from the raw data. All studies were performed retrospectively and thus regarded as level IV studies. Raw data was available for 7 studies.\textsuperscript{9,11,13,14,29,30} Raw data was cleaned to exclude patients who did not meet our criteria. Reasons for exclusion of patients were (1) patients had non-OCC, (2) patients had non-squamous cell carcinoma (SCC), (3) patients received neoadjuvant treatment prior to resection, (4) patients with close margins who had no re-resection, (5) patients with close margins re-resected to close, and (6) patients with a final margin $<5$ mm considered negative. For the eighth study included in our quantitative analysis,\textsuperscript{15} the raw data were not available as per the authors, but the HR was extracted from the study and pooled with the other
HRs. This study met our criteria without the need for cleaning raw data. However, their data could not be included in all subgroup analyses.

**Key Findings of Included Studies from Systematic Review**

Most studies included in this meta-analysis showed that margin revision does not improve local control. Three studies showed that patients with positive (<1 mm) margins cleared (≥1 mm) under FS guidance had poorer local control compared to those with initially clear (≥1 mm) margins. Buchakjian et al\(^1\) also showed that patients with positive margins cleared had comparable LR rates to those with persistently positive margins. Two studies showed that patients with positive (0 mm) margins cleared to negative (≥5 mm) had worse LRFS compared to those with initially negative (≥5 mm) margins.\(^1\) On further analysis, Patel et al\(^1\) showed that node-negative patients with positive margins revised to negative by FS guidance had equal LRFS to node-negative patients with initially negative margins. However, node-positive patients with positive margins revised to negative by FS guidance had much worse LRFS compared to node-positive patients with initially negative margins. Priya et al\(^9\) showed that revision of positive (<1 mm) margins to negative (≥5 mm) did not improve outcomes.\(^2\)

On the other hand, 2 studies showed that revised margins had equal local control to initially negative margins.\(^2\) Backes et al\(^2\) showed that patients with R0 resection (definition not provided) had equal LRFS to patients with R0 on further resection, and both groups had better LRFS compared to patients with R1 resection (definition not provided). Brandwein-Gensler et al\(^3\) showed that all margin groups had equal LRFS.

**IPD Meta-analysis Included Patient Characteristics**

After cleaning the raw data, a total of 1427 patients were analyzed; 911 patients were males, 958 patients had T1/T2 disease (as defined by the American Joint Committee on Cancer [AJCC] seventh edition), 851 patients were node negative, 951 patients had R0 resection, 327 had R1 to R0 resection, and 149 had R1 resection. In total, 385 of 944 R0, 180 of 327 R1 to R0, and 79 of 149 R1 resection patients received adjuvant treatment. Table 1 shows demographics per study in further detail.

**IPD Meta-analysis Results**

LRFS was calculated for all patients in individual studies from the time of first surgery to the time of first event (LR or locoregional recurrence). Patients with no LR reported were censored at time of the last follow-up.

In this study, we divided patients into 4 groups for sake of analysis:

- Initially R0 group: patients with negative margins on initial resection, negative defined as ≥5 mm from

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Sample Included</th>
<th>Age, Mean (SD), y</th>
<th>Sex, Male/Female, No.</th>
<th>Margin Status, No.</th>
<th>T-stage, No.</th>
<th>N-stage, No.</th>
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<tr>
<td>Backes et al(^2)</td>
<td>2017</td>
<td>45</td>
<td>55.1 (10.8)</td>
<td>38/7</td>
<td>24 R0</td>
<td>36 T1/2</td>
<td>27 N0</td>
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<td>9 T3/4</td>
<td>18 N1</td>
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<td>8 R1</td>
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<tr>
<td>Brandwein-Gensler et al(^3)</td>
<td>2005</td>
<td>99</td>
<td>63.3 (15.0)</td>
<td>44/55</td>
<td>33 R0</td>
<td>68 T1/2</td>
<td>59 N0</td>
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<td>53 R1 to R0</td>
<td>29 T3/4</td>
<td>38 N1</td>
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<td>13 R1</td>
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<tr>
<td>Buchakjian et al(^1)</td>
<td>2016</td>
<td>270</td>
<td>62.2 (13.7)</td>
<td>150/120</td>
<td>67 R0</td>
<td>184 T1/2</td>
<td>198 N0</td>
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<td>118</td>
<td>60.2 (10.9)</td>
<td>82/36</td>
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<td>83 T1/2</td>
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<td>Patel et al(^1)</td>
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<td>547</td>
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<td>Priya et al(^9)</td>
<td>2012</td>
<td>184</td>
<td>51.3 (12.1)</td>
<td>139/45</td>
<td>155 R0</td>
<td>95 T1/2</td>
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<td>88/36</td>
<td>78 R0</td>
<td>100 T1/2</td>
<td>77 N0</td>
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<td></td>
<td>46 R1 to R0</td>
<td>24 T3/4</td>
<td>47 N1</td>
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<tr>
<td>Varvares et al(^1)</td>
<td>2015</td>
<td>40</td>
<td>61 (12.3)</td>
<td>25/15</td>
<td>22 R0</td>
<td>26 T1/2</td>
<td>27 N0</td>
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<td>5 R1</td>
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Abbreviation: NA, not applicable.

\(^\ast\)Patel et al\(^1\) data reported from the study. No raw data was provided.
the normal tissue margin on pathologic specimen exam
Initially R1 to final R0 group: patients with positive margins on initial resection cleared to close or negative and patients with close margins cleared to negative. Positive margin was defined as \(<1\) mm and close as \(1\) to \(<5\) mm. This includes patients who were re-resected from positive to close.
Initially R1 to negative group: a subgroup that includes only the patients re-resected to negative (\(\geq5\) mm)
Final R1 group: includes patients with persistently positive margins regardless of re-resection

Multiple group comparisons were performed to assess the effect of different margin status groups by pooling HR across studies. Heterogeneity was variable depending on the groups compared. To control for any heterogeneity, we used the random-effects model for all comparisons.

**R1 to R0 Compared to R0 Resection**
A total of 1278 patients were analyzed from all 8 studies (Figure 2A). In total, 327 were in the R1 to R0 group compared to 951 in the R0 group; 180 of 327 R1 to R0 and 385 of 944 R0 patients received adjuvant treatment. R1 to R0 patients showed a significantly worse 5-year LRFS compared to R0 patients (HR = 2.592; 95% CI, 1.873-3.588, \(P < .001\)). Heterogeneity: Cochran’s \(Q = 7.25, \tau^2 = .0081, I^2 = 3.5\%\), \(P = .403\).

**R1 to Negative Compared to R0 Resection**
A total of 1046 patients were analyzed from 6 studies (Figure 2B). In total, 186 patients were in the R1 to negative group compared to 860 in the R0 group; 106 of 186 R1 to negative and 355 of 853 R0 patients received adjuvant treatment. R1 to negative patients showed a significantly worse 5-year LRFS compared to R0 patients (HR = 2.415; 95% CI, 1.682-3.469, \(P < .001\)). Heterogeneity: Cochran’s \(Q = 4.84, \tau = 0, I^2 = 0\%\), \(P = .436\).

**R1 Compared to R0 Resection**
A total of 423 patients were analyzed from 4 studies (Figure 2C). In total, 144 patients were in the R1 group compared to 279 patients in the R0 group; 74 of 144 R1 and 152 of 274 R0 patients received adjuvant treatment. R1 patients showed a significantly worse 5-year LRFS compared to R0 patients (HR = 3.672; 95% CI, 2.143-6.249, \(P < .001\)). Heterogeneity: Cochran’s \(Q = .47, \tau = 0, I^2 = 0\%\), \(P = .926\).

**R1 Compared to R1 to R0 Resection**
A total of 319 patients were analyzed from 4 studies (Figure 2D). In total, 144 patients were in the R1 group compared to 175 patients in the R1 to R0 group; 74 of 144 R1 and 93 of 175 R1 to R0 patients received adjuvant treatment. R1 patients showed a trend toward worse 5-year LRFS compared to R1 to R0 patients but did not reach significance (HR = 1.523; 95% CI, .992-2.338, \(P = .055\)). Heterogeneity: Cochran’s \(Q = 2.57, \tau = 0, I^2 = 0\%\), \(P = .463\).
R1 to Negative Compared to R0 Resection in Patients with T1/2N0 Disease

A total of 198 node-negative patients were analyzed from 4 studies (Figure 3). Forty-nine of them were in the R1 to negative group compared to 149 in the R0 group; 14 of 49 R1 to negative and 69 of 147 R0 patients received adjuvant treatment. R1 to negative patients showed significantly worse 5-year LRFS compared to R0 patients in this subgroup (HR = 3.251; 95% CI, 1.344-7.868, \( P = .009 \)). Heterogeneity: Cochran’s \( Q = 3.51, \tau = .1193, I^2 = 14.4\% \), \( P = .320 \).

R1 to R0 Compared to R0 Resection in Patients with Tongue Cancer

A total of 245 patients with oral tongue cancer were analyzed from 5 studies (Figure 4A). In total, 101 of them were in the R1 to R0 group compared to 144 in the R0 group. R1 to R0 patients showed significantly worse 5-year LRFS compared to R0 patients in this subgroup (HR = 2.575; 95% CI, 1.207-5.496, \( P = .014 \)). Heterogeneity: Cochran’s \( Q = 4.65, \tau = .1063, I^2 = 13.9\% \), \( P = .325 \).

R1 to R0 Compared to R0 Resection in Patients with Floor of Mouth Cancer

A total of 144 patients with floor of mouth cancer were analyzed from 4 studies (Figure 4B). Fifty-one of them were in the R1 to R0 group compared to 93 in the R0 group. R1 to R0 patients showed significantly worse 5-year LRFS compared to R0 patients in this subgroup (HR = 3.439; 95% CI, 1.610-7.346, \( P = .001 \)). Heterogeneity: Cochran’s \( Q = .84, \tau = 0, I^2 = 0\% \), \( P = .841 \).

R1 to R0 Compared to R0 Resection in Other OCC Sites

A total of 253 patients with OCC in subsites other than oral tongue or floor of mouth were analyzed from 5 studies (Figure 4C). Seventy-nine of them were in the R1 to R0 group compared to 174 in the R0 group. R1 to R0 patients showed significantly worse 5-year LRFS compared to R0 patients (HR = 2.278; 95% CI, 1.109-4.676, \( P = .025 \)). Heterogeneity: Cochran’s \( Q = 5.33, \tau = .1672, I^2 = 24.9\% \), \( P = .255 \).

Discussion

In this meta-analysis, we analyzed data from studies that used FS to clear positive/close margins in patients with oral cavity squamous cell carcinoma (OCSCC). A total of 1427 patients from 8 studies were analyzed, most of whom had early (T1/2N0) disease. In our analysis, we found that R1 to R0 patients have poorer LRFS when compared to R0 patients regardless of additional clearance. Similar results were seen when R1 to R0 and R0 groups were analyzed by oral cavity subsite. Furthermore, R1 to R0 patients showed almost equal LRFS to R1 patients, although R1 patients showed a trend toward worse LRFS. These results can be interpreted in a number of ways: (1) our current FS sampling technique and margin revision strategy is not significantly improving local control and needs modification, and/or (2) positive margin is a marker of aggressive disease, even in this group of early staged cancers, regardless of whether FS is guiding re-resection accurately. These questions could be answered in a prospective controlled study where the different methods of frozen section analysis and re-resection are rigorously standardized for each cohort, allowing for the interpretation of the data to come to a meaningful conclusion. Thus, we do not recommend elimination of FS at the moment but do recommend a standardization of approaches, more rigorous collection and storage of margin data, and better communication between surgeons and pathologists. Alternatives for intraoperative assessment of margins that have been investigated in the literature include (1) gross exam only,5,26 (2) ultrasound (US), and (3) optical imaging. US has been found to be a good adjunct for resecting deep margins31 while optical imaging has been shown to be good for mucosal margins.32

Positive margin status has long been recognized as an adverse prognostic indicator in OCSCC.2-11 Loree and Strong3 showed that patients with positive margins had a reduction in 5-year OS and a doubling of LR risk when compared to patients with negative margins. While most studies are in firm agreement that positive margins are an...
adverse prognosticator, the definition of a positive margin varies in the literature. Invasive carcinoma at the margin up to ≤7 mm from the margin has been reported as positive or inadequate. The most acceptable definition for clear margin is ≥5 mm, although values between 1 and 7 mm have been reported as clear. A meta-analysis by Anderson and colleagues in a study of patients who underwent surgery without adjuvant therapy suggested that 5 mm is the minimum acceptable margin for oral cancer resections as margins <5 mm have higher LR.

Given this demonstrated association, the goal of OCS CC surgery is to achieve complete extirpation of the tumor with negative margins during primary resection. For decades, FS has been thought of as an important tool to guide resection and decision making intraoperatively. FS has been reported to have high accuracy (meaning that the final read on the frozen section slide is identical to the read at the time of frozen section), ranging between 96% and 99%.

However, when attempting to correlate tumor bed margins to a positive specimen margin, sensitivity of FS drops to 15% to 40%, indicating that a positive margin is probably missed at least 60% of the time using patient-based FS. Furthermore, as discussed in the introduction, pursuing further resection after a positive FS result has not been shown to improve oncologic outcomes. This may in part be attributable to surgeons resecting the wrong areas when revising positive FS. Kerawala and Ong demonstrated that surgeons are likely to be off the correct revision area by more than 10 mm approximately one-third of the time.

Figure 4. Forest plots summarizing the hazard of worse local recurrence-free survival when R1 to R0 is compared to R0 stratified by oral cavity cancer (OCC) subsites. (A) Oral tongue (OT) only. (B) Floor of mouth (FOM) only. (C) OCC subsites other than OT and FOM.
Byers and colleagues\textsuperscript{38} investigated 216 patients with cancers of the oral cavity, oropharynx, and hypopharynx. Positive margins on FS were resected to negative when possible. Patients with OCC with revised positive margins were found to have a LR rate of 13%, almost equal to those with initially negative margins, 12%. Patients with persistently positive margins had a much worse LR rate of 80%. Two-year survival of patients with persistently positive margins was lower than patients with revised positive margins and negative margins on initial resection. In a longer follow-up study from the same institution, Scholl et al\textsuperscript{39} reported that patients with oral cancer with positive margins cleared to negative had worse local control and 5-year overall survival compared to patients with initially negative margins. Patients with initially positive margins cleared to negative benefited from adjuvant radiotherapy, which brought LR rates down to equal those with initially negative margins. The authors questioned the need for FS if 80% of resected margins were clear on initial resection, as their study showed, and if adjuvant radiotherapy will be used for patients with positive margins anyway.

Pathak et al\textsuperscript{4} reported an almost similar clearance rate of 67.4% even when FS was not used compared to 70.4% when FS was used to guide resection. In their study, patients with and without FS showed equal primary site failure and disease-specific survival. Mair et al\textsuperscript{26} also examined the incidence of positive/close margins in patients who had resection with gross examination compared to patients with FS. After revision with and without FS, the incidence was similar in both groups, 6.63% and 6.69%, respectively. Both groups were also found to have equal OS and disease-free survival.

Most recent studies also show that the use of FS for positive margin revision does not improve local control when compared to initially clear margins.\textsuperscript{9-11,13-16,40,41} However, when evaluating the literature, it is difficult to compare studies because of the different margin cutoffs used and subsites analyzed. In our review, we tried to harmonize the data from these studies by (1) including only patients with primary OCSCC and no previous treatment, (2) defining negative margins as \( \geq 5 \) mm on initial resection, and (3) excluding patients with close margins who did not undergo revision.

Other studies that we could not include in our quantitative analysis, due to lack of author response or short follow-up, also looked at FS for margin revision. Gokavaranur et al\textsuperscript{40} studied a group of patients with OCSCC. They found a worse locoregional recurrence-free survival and OS in patients with positive margins on FS even if revised to clear compared to those with initially negative FS. In a separate study, they also compared patients with positive margins cleared to patients with positive margins not cleared and found no difference in LR and OS between groups.\textsuperscript{41} They concluded that FS use might not be as beneficial as thought and that a surgeon should aim for negative margins from the first cut. Mair et al\textsuperscript{26} also reported that patients undergoing re-resection for positive/close margin did not have improved survival.

In our study, the compilation of these results reaffirms the conclusion that revision of margins under FS guidance does not improve LRFS even when controlling for T-stage and N-stage. Limitations of this study include the following: (1) it is based on retrospective studies with different study designs; (2) despite the increased power of the pooled sample within this study, the imbalance in patients across groups makes the results challenging to interpret; (3) some studies were not included in the analysis due to absence of data or nonresponse of authors; (4) studies in languages other than English were not included, which could result in loss of important studies; (5) we limited the analysis to 5-year LRFS; and (6) we were unable to control for a number of factors, including the effect of radiation.

**Conclusion**

Margin revision of initially positive margins to “clear” based on FS guidance does not equate to an initially negative margin and does not significantly improve local control in patients with OCSCC. Given that many surgeons feel that an R1 to R0 resection is equal to an initial R0 resection, this has implications for how adjuvant therapy is offered to this group of patients and could result in some patients not receiving adjuvant radiation therapy who could benefit from it. Due to the limitations of our study and the studies included in our analysis, we cannot recommend abandoning FS in OCSCC resection cases; rather, a structured evaluation of current FS practices should be done to determine which method best predicts local control. A prospective multicenter study with a standardized FS sampling technique (specimen vs patient based), margin revision strategy and margin cutoff definition is needed to better understand the impact of FS on oncologic outcomes in OCSCC management.

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**Author Contributions**

Mustafa G. Bulbul, conception, design, execution and analysis, drafting, revision and approval, agreed to be accountable for all aspects of work; Osama Tarabichi, conception, design, execution and analysis, drafting, revision and approval, agreed to be accountable for all aspects of work; Rosh K. Sethi, conception, design, execution and analysis, drafting, revision and approval, agreed to be accountable for all aspects of work; Anuraag S. Parikh, conception, design, execution and analysis, drafting, revision and approval, agreed to be accountable for all aspects of work; Mark A. Varvares, conception, design, execution and analysis, drafting, revision and approval, agreed to be accountable for all aspects of work.

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