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Stratification of Surgical Margin Distances by the Millimeter on Local Recurrence in Oral Cavity Cancer: A Systematic Review and Meta-Analysis

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Abstract

Background: There are limited data supporting the commonly suggested 5 mm margin cutoff as the optimum value in defining clear margins in oral cancer.

Methods: A database search of Pubmed/Medline, Web of Science, and EBSCOhost was performed from inception to June 2022. A random-effects model was chosen for this meta-analysis. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed throughout this study.

Results: Seven studies met study criteria (2,215 patients). The risk ratio was significantly higher for margins <5 mm when compared to those ≥5 mm (2.09 (95%CI: 1.53 to 2.86, I^2=0.47)). Subgroup analysis (I^2 =0.15) of margin distances of 0.0–0.9, 1.0–1.9, 2.0–2.9, 3.0–3.9, and 4.0–4.9 mm calculated risk ratios for local recurrence of 2.96, 2.01, 2.17, 1.8, and 0.98, respectively.

Conclusions: Margins between 4.0–4.9 mm had similar risk ratios for local recurrence compared to ≥5 mm, while margins <4.0 were significantly higher.

Keywords

oral cancer; surgical margin; head and neck surgery; local recurrence; oral squamous cell carcinoma

Introduction

Surgical margin status has long been regarded as the most significant prognosticator for postoperative outcomes in head and neck surgery.[1] Conventionally, intraoperative decision making for margin adequacy is guided by surgeon decision-making and augmented by frozen histopathological analysis to determine appropriateness of the resection, or the need for further re-excision of the tumor bed.[2, 3] The utility of using surgical margins from final histopathologic analysis to guide adjuvant therapy has also been well established,[4, 5]

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The authors report no conflicts of interest as positive or close margins have been demonstrated to be closely associated with both decreased overall survival and increased rates of local and locoregional recurrence in head and neck cancers.[6] Indeed, a positive surgical margin may increase both the chances for local recurrence and the risk for all-cause mortality by up to 90% for oral cavity malignancies.[7, 8]

Despite the great importance placed on obtaining adequate margins in head and neck surgery, the definitions regarding clear, close, and positive margins are poorly defined. As per NCCN guidelines, a positive margin has been defined as malignant infiltration directly on the margin.[5] However, positive margins are defined differently across guidelines, with the Royal College of Pathologists defining positive margins as including invasive cancer within 1 mm of the margin.[9] This discordance is further exemplified by a survey of American Head and Neck Society members, where only 46% of otolaryngologists defined clear margins as being ≥ 5 mm.[10] Although 5-mm has been most widely recognized as the threshold for clear margins, there have been limited empiric data to support this cutoff. Furthermore, several studieshave suggested that margins less than 5 mm may have no difference in survival as compared to 5 mm.[11]

The present authors feel that the conventional 5 mm recommendation for clear margins is should be reinvestigated and redefined. In an attempt to address this, they opted for exploring the satisfying PICOS 18 criteria (Population, Intervention, Comparison, Outcomes, Study Design) question: "in patients with oral squamous cell carcinoma (OSCC) who underwent surgical extirpation, do the rates of local recurrence differ across 1 mm increments (0.0–0.9 mm, 1.0–1.9 mm, 2.0–2.9 mm, 3.0–3.9 mm, 4.0–4.9 mm) when compared to the traditional 5 mm standard for clear margins?" via a systematic review of the current literature. Other outcome measures including distant recurrence rates, overall survival, and disease free survival were excluded from this investigation due to insufficient available data. The results are reported herein.

Materials and Methods

Literature Search and Study Selection

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and adhered to the applicable sections of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) proposal.[12, 13] Author K.Y performed a systematic database search across Pubmed/Medline, Web of Science, and EBSCOhost with no restrictions on years published up to June 2022. Several search terms including, "local recurrence," "margin" or "oral cancer," and several Boolean operators including "AND" or "OR" were used in various permutations. The full search methodology is better characterized by Appendix S1. Inclusion criteria required that patients must have been diagnosed with oral squamous cell carcinoma with higher-granularity information pertaining to surgical margin distances by 1 mm increments (0.0–0.9 mm, 1.0–1.9 mm, 2.0–2.9 mm, 3.0–3.9 mm, 4.0–4.9 mm). Furthermore, all studies must have provided data on the number or rate of local recurrences per each 1 mm increment. Exclusion criteria included non-English studies, case reports, animal studies, cadaveric studies, review articles, letters to the editor, opinion pieces, abstracts, and non-published studies. All studies with

<50 subjects or where patients underwent prior surgery for the primary oral malignancy or neck dissection were excluded. Patients with malignancies arising from extra-oral cavity sites or diagnoses of non-squamous cell cancers were excluded as well.

Data Extraction

Authors H.B and C.K independently screened studies by titles and abstracts, and one additional study was found through handsearching.[14] Author K.Y subsequently resolved all conflicts and performed a full-text assessment for all included articles. Authors K.Y and H.B independently extracted data from the included studies using a previously created abstraction form and negotiated any conflicts. Here, data on study characteristics (author names, publication date), clinical information (staging, follow-up time), 1–5 mm incremental surgical margin status, and metrics measuring local recurrences were extracted. The primary outcome measure was the risk ratio of local recurrence with <5 mm margins compared to the traditional ≥5 mm metric.

Quality Assessment

All included studies were evaluated using the Newcastle-Ottawa Scale (NOS) for Cohort Studies.[15] According to this scale, the score (maximum = 9) is based on the quality of selection (4), comparability (2), and participant outcomes (3). Studies were classified into three groups: poor (0–3 points), moderate (4–6 points), or good scores (7–9 points). Quality assessment was conducted by authors K.Y and H.B, and all disagreements were then negotiated with senior author A.C.B. The 2011 Oxford Centre for Evidence-Based Medicine guidelines was used to determine the level of evidence of all included studies.[16]

Data Analysis

SPSS software version 28 (IBM Corp., Armonk, New York, USA) was used for all statistical analyses. Means and standard deviations were calculated for continuous variables. A random effects model with restricted maximum likelihood (REML) estimation was used in the current meta-analysis to measure the risk ratios for local recurrences regarding margins <5 mm against those ≥5. This same model was applied with subgroup stratification based on surgical margin distances of 0.0–0.9 mm, 1.0–1.9 mm, 2.0–2.9 mm, 3.0–3.9 mm, and 4.0–4.9 mm against ≥5 mm margins. Forest plots comparing logarithmic risk ratios were constructed for the both the main and subgroup analyses. Heterogeneity was assessed through the I2 index, defined as low (0–50%), moderate (50–75%), and high (75–100%).[17] Funnel plots were constructed and Egger's test was conducted to assess the studies for potential publication bias.[18] All calculations were conducted with an α of 0.05.

Results

Study and Patient Characteristics

Of the initial 1,203 identified titles, 7 studies were included after the screening process outlined by Figure 1.[14, 19–24] Of all studies that were excluded after full-text analysis, the majority (70) did not provide finer-granularity data on 1 mm increments for all surgical margins that were <5 mm. Other studies investigating data on 1 mm increments only provided data on hazard ratios or locoregional spread.[25–28] Publication dates for studies ranged from 2009–2020, with a total of 2,215 included patients. Median ages ranged from 60–66 years for all included studies, and the gender was predominately male (65.2%). The three most frequent oral cavity subsites were the tongue (45.4%), gingivo-buccal mucosa (40.6%), and the floor of the mouth (10.5%). Further information regarding primary site, staging, histopathologic grade, adjuvant therapies, quality assessment, and levels of evidence are best characterized by Table 1.

Surgical Margin Status on Local Recurrence

All 7 included studies were pooled together, with patients being stratified by surgical margin distances < 5 and ≥ 5 mm, as depicted in Table 2. The corresponding findings are represented by the forest plot displayed in Figure 2. Here, all margins < 5 mm were found to have significantly higher risk ratios for local recurrence when compared to their ≥ 5 mm counterparts (2.09 (95%CI: 1.53 to 2.86). Egger's test yielded a p-value of 0.87 signifying no publication bias. All corresponding funnel plots are displayed in Appendix S2. Heterogeneity was found to be low but bordering on moderate ($I^2 = 0.47$). Of the 7 included studies, Barry et al, Yamada et al, and Singh et al, would not have reached statistical significance alone when comparing margin distances < 5 mm and ≥ 5 mm.[19, 22, 24] Of these 3 investigations, Singh et al. provided the largest recommendation of 7.6 mm when defining clear margins.

Surgical Margin Distance on Local Recurrence

Subgroup analysis was performed on the aforementioned sample, with stratification into 5 categories by mm increments: 0.0–0.9 mm, 1.0–1.9 mm, 2.0–2.9 mm, 3.0–3.9 mm, 4.0–4.9 mm, as shown in Table 3. Compared to > 5 mm, margin distances between 0.0–0.9 mm had a risk ratio of 2.96 (95%CI: 2.15 to 4.07). The risk ratios for 1.0–1.9 mm, 2.0–2.9 mm, and 3.0–3.9 mm were also higher when compared to that of > 5 mm, at 2.01 (95%CI: 1.29 to 3.13), 2.17 (95%CI: 1.73 to 2.73), and 1.81 (95%CI: 1.21 to 2.73), respectively. The risk ratio for 4.0–4.9 mm margins compared to > 5 mm was found to be 0.98 (95%CI: 0.52 to 1.85). Heterogeneity (I^2=0.15) was found to be low for this subgroup analysis. The findings from this subgroup analysis are best represented by Figure 3. While risk ratios were found to be significantly higher for distances of 0.0–0.9 mm, 1.0–1.9 mm, 2.0–2.9 mm, 3.0–3.9 mm ($p < 0.001$), there were no statistically significant differences between surgical margin distances of 4.0–4.9 mm and those that were >5 mm ($p = 0.96$). Funnel plots (Appendix S2) and Egger's test confirmed that no publication bias was present across the subgroups. The findings from this subgroup analysis are more completely summarized in Table 4.

Discussion

The current meta-analysis has confirmed that positive/close (<5 mm) margins are associated with a greater risk for local recurrence when compared to traditionally clear (≥5 mm) margins. Indeed, these findings have been more extensively corroborated in a recent meta-analysis performed by Hamman et al., who also reported positive/close margins being significantly associated with poorer survival.[6] However, Hamman et al.'s investigation does not provide any higher granularity data on the optimal distance threshold for differentiating clear and close margins. An earlier systematic review conducted by Bungum et al. identified

6 studies that investigated surgical margin distances <5 mm, but the authors concluded that the variability in findings and recommendations of the included investigations rendered drawing any coherent conclusions infeasible. The current review incorporates an updated list of studies with the objective of quantitatively assessing the impact of surgical margin distance on local recurrence rates. All included studies were noted to be of moderate-to-good quality based on the NOS.

The present study indicates that surgical margins from 4.0–4.9 mm may yield a comparable risk ratio for local recurrence as margin distances following the standard > 5 mm. These findings were supported by Yanamoto et al.'s retrospective review of 187 patients, where the authors ultimately recommended obtaining surgical margin distances > 4 mm.[29] Liao et al. provided similar recommendations after finding that margins less than 4 mm were an independent predictor for poor local control in their retrospective study of 331 patients.[30] Furthermore, the current investigation confirmed that margin distances within the 0.0–0.9 mm, 1.0–1.9 mm, 2.0–2.9 mm, and 3.0–3.9 mm ranges were associated with statistically significant increased risks for local recurrence. Interestingly, this finding conflicts with several other investigations that have reported margins >3 mm as being the optimum cutoff threshold.[14, 26] In a large retrospective study of 381 patients by Zanoni et al, the optimal threshold was determined to be 2.2 mm based on local recurrence free survival (LRFS).[28] Tasche et al's investigation of 422 patients went as far as to report that 1 mm margins were sufficient to be defined as negative.[23] In contrast, several studies have suggested that 5 mm margins are insufficient when defining clear margins. For instance, Singh et al. found that only margin distances ≥ 7.6 mm were adequate for classification as clear margins.[22] Daniell et al. focused their analysis on comparing 10 mm and 15 mm margin distances, concluding that the latter was associated with significantly lower rates of local recurrence.[31]

There were also several studies excluded from the current systematic review due to reporting different outcome measures, including locoregional recurrence and survival outcomes. Similar to the included investigations, these studies provided data on 1 mm increments for surgical margin distances <5 mm. Chiou et al.'s retrospective study investigated a total of 110 patients with buccal squamous cell carcinoma, and the authors determined that surgical margin distances ≥3 mm were associated with significantly lower risks for locoregional failure.[26] However, the same authors reported that survival outcomes were improved with margins ≥ 2mm regarding overall survival (OS), disease free survival (DFS), disease-specific survival (DSS), and distant metastasis-free survival (DMFS). Thus, the authors recommended that margins <3 mm may be used to guide post-operative adjuvant therapy planning, while margins <2 mm should be the cutoff for more aggressive postoperative treatment. Jain et al.'s investigation found that margin distances of ≥ 2mm were associated with improved DFS, but no differences within surgical margin distances (between 1–5 mm) were reported in regards to LRFS.[27] The authors surmised that no formal recommendations could be drawn until their analyses could be further validated.

There are several possible explanations as to why these differences have been observed across the literature. The majority of the aforementioned studies have been conducted in single-institution settings with relatively limited cohorts of surgeons, and thus these results may not be generalizable to other populations. Different methods of margin sampling were performed, including those sampling from the specimen versus tumor bed, which has been associated with worse local control.[32] Several studies focused on specific primary sites, which may prevent the findings in the current study from being generalizable across all oral cavity sites. Furthermore, postoperative therapy was not standardized across the included studies, with some patients receiving radiotherapy, chemoradiotherapy, or no adjunctive treatment at all. Unfortunately, many of these differences cannot be changed due to the retrospective nature of the included studies. While prospective trials would allow researchers to better investigate this question of optimal surgical margin thresholds, there are significant challenges in running surgical trials that may render this option infeasible.[33] For these reasons, we cannot recommend that surgeons adhere to the findings reported in this study, as it is impossible to make treatment plans based off of data from non-randomized retrospective data. However, the current study has confirmed a need to reexamine the validity of the widely-recommended surgical margin distance of 5 mm, calling for the redefinition of what optimal clear margins should be. Furthermore, continued caution should be exercised when considering the recommendations from papers suggesting margins < 5 mm until more robust research is reported.

This study has limitations that should be discussed. First, none of the included studies in this meta-analysis were prospectively conducted, and there were no control arms to reduce the impact of extraneous variables. Additionally, there were no patient-level data available from the included studies, preventing further stratification and subgroup analysis by covariates including subsite, depth of invasion, T-staging, nodal status, perineural invasion, other pathological features, or demographic information. Similarly, subgroup analysis regarding difference in outcomes between deep versus lateral margins were precluded by the lack of patient-level data from contributing studies. Without the ability to perform additional subgroup analysis, our findings may be subject to biasing from confounders. Additionally, there were small to near-moderate amounts of heterogeneity associated with the current analyses, which may be explained by certain studies only investigating cancers of specific primary sites or stages. Furthermore, many studies grouped cases with malignant infiltration at the margin and <1 mm from the margin in the same category, precluding further subgroup analysis between these two distinct categories. It is important to mention that several studies did not feature patients under certain 1 mm increments, and there were very limited data pertaining to 1mm increments >5 mm. Nevertheless, this study marks the first meta-analysis to investigate the validity of the conventional 5 mm clear margin cutoff in comparison to incremental margins less than 5 mm in their effect on local cancer recurrence.

Conclusion

Surgical margin distances <4 mm were significantly associated with higher risk ratios for local recurrence when compared to those ≥5 mm ($p < 0.001$). When performing subgroup analysis, the risk ratio for margin increments of 0.0–0.9 mm, 1.0–1.9 mm, 2.0–2.9 mm, and 3.0–3.9 mm were found to be significantly higher for local recurrence ($p < 0.001$). There were no statistically significant differences in the risk ratio for local recurrence for margins of 4.0–4.9 and ≥5 mm, however ($p = 0.96$). This study calls for the further evaluation of surgical margin distance constituting a clear margin. Caution should be maintained when considering recommendations from studies suggesting optimal margin distances <5 mm until more robust data are available.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Data Availability Statement:

The data supporting the findings of the current study will be provided by the corresponding author upon reasonable request.

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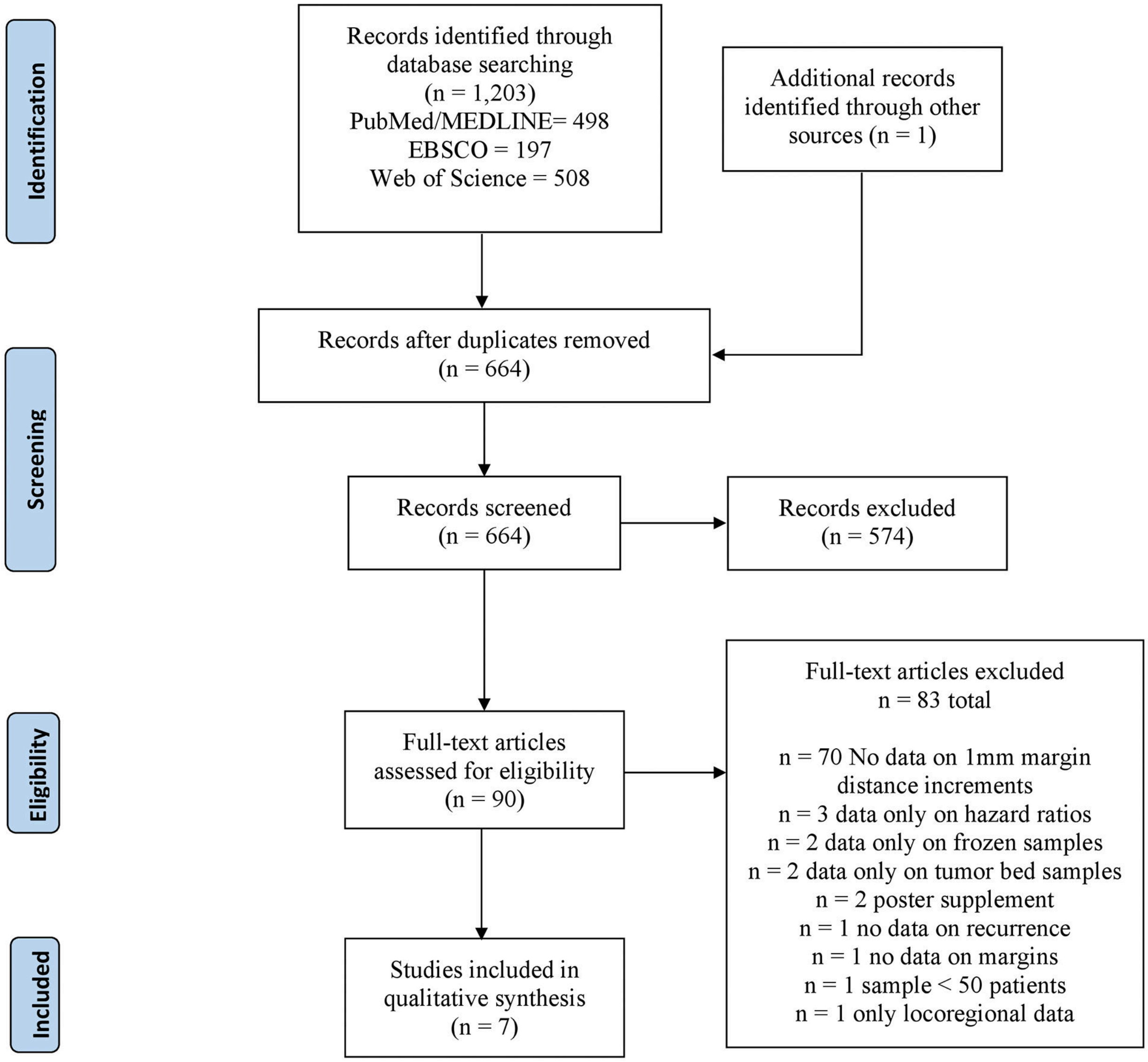

Figure 1.

PRISMA Flow Diagram for Search and Review Strategy.

Adapted flowchart from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines

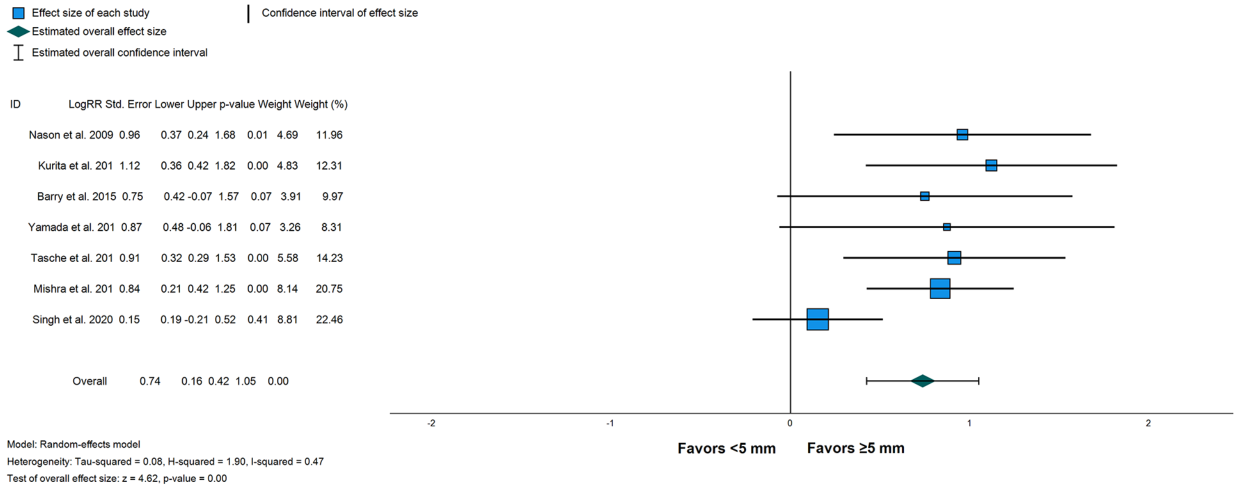

Figure 2.

Forrest plot of the risk ratios for local recurrence between margins < 5 mm and ≥ 5 mm.

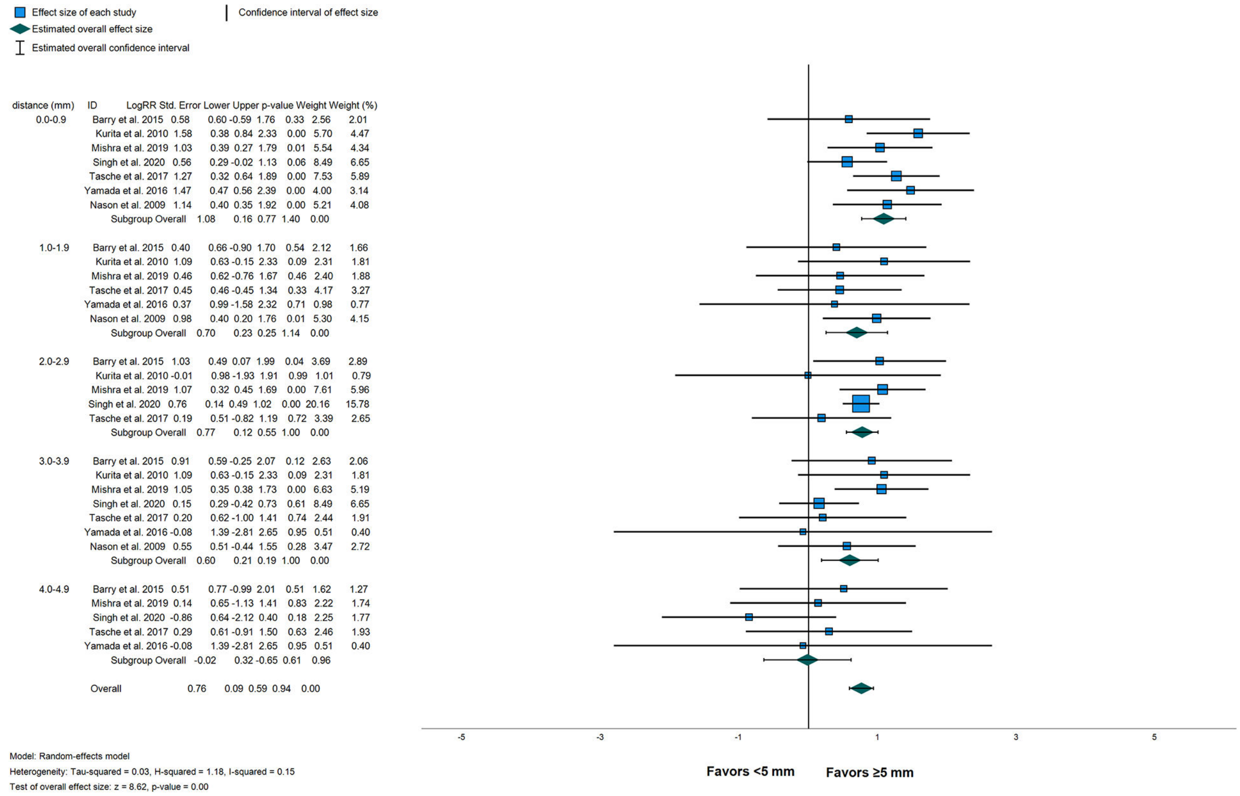

Figure 3.

Forrest plot of the risk ratios for local recurrence between margins < 5 mm and ≥ 5 mm with subgroup analysis of 1 mm increments < 5 mm

Table 1.

Study and Participant Characteristics

Study	Barry et al. 2015[19]	Kurita et al. 2010[20]	Mishra et al. 2019[21]	Nason et al. 2009[14]	Singh et al. 2020[22]	Tasche et al. 2017[23]	Yamada et al. 2016[24]
Average age (range)	60 (52–68) median	66 (no range) median	-	63.3 +/− 12 years mean	-	61 (53–71) median	66 (27–84) median
female	184	60	121	-	95	174	57
Primary Site							
Tongue	143	67	-	-	451	190	59
Floor of Mouth	103	15	-	-	-	78	14
Gingivo-Buccal	45	65	563	-	-	89	53
Other	4	1	-	-	-	65	1
Staging							
T-1,2	295	68	262	-	-	277	59
T-3/4	0	80	301	-	-	145	68
N0	177	-	339	-	-	296	72
N+	118	-	224	-	-	125	55
ECS	61	-	185	-	185	74	-
Histopathologic Features							
PNI yes	63	-	73	-	131	151	-
VI yes	55	-	4	-	7	117	-
Grade (well)	-	95	79	-	-	73	83
Grade (moderate)	-	45	390	-	-	267	38
Grade (poor)	-	8	94	-	-	70	6
Treatment and Follow-up							
RT (radiation)	114	44	-	-	193	120	35
CT (chemo)	-	-	-	-	-	-	-
RT + CT	-	-	-	-	143	53	-
f/u time (months)	24	42	6	36	6	6	2
f/u measure	minimum	median	minimum	median	minimum	minimum	2- year local control rate
Quality Assessment and Level of Evidence							
Newcastle-Ottawa Scale (NOS)	7	6	6	7	6	6	6
Levels of Evidence (I-V)	IV	IV	IV	IV	IV	IV	IV

Abbreviations: perineural invasion (PNI), vascular invasion (VI), radiotherapy (RT), chemotherapy (CT), follow up (f/u)

Table 2.

Studies Stratified by <5 mm and ≥5 margin distances

Authors	# <5 mm margins	# LR <5 mm	# no LR <5 mm	% LR <5 mm	# ≥5 mm margins	# LR ≥5 mm	# no LR ≥5 mm	% LR ≥5 mm
Barry et al. 2015[19]	173	21	152	**0.12**	122	7	115	**0.06**
Kurita et al. 2010[20]	32	11	21	**0.34**	116	13	103	**0.11**
Mishra et al. 2019[21]	52	19	33	**0.37**	511	81	430	**0.16**
Nason et al. 2009[14]	182	40	142	**0.22**	95	8	87	**0.08**
Singh et al. 2020[22]	32	16	16	**0.50**	419	180	239	**0.43**
Tasche et al. 2017[23]	260	69	191	**0.27**	94	10	84	**0.11**
Yamada et al. 2016[24]	34	7	27	**0.21**	93	8	85	**0.09**
Total Sample	765	183	582	**0.24**	1450	307	1143	**0.21**

Abbreviations: Local Recurrence (LR)

Table 3.

Studies Stratified by 1 mm Surgical Margin Increments

Authors	Barry et al. 2015[19]	Kurita et al. 2010[20]	Mishra et al. 2019[21]	Nason et al. 2009[14]	Singh et al. 2020[22]	Tasche et al. 2017[23]	Yamada et al. 2016[24]
# 0.0–0.9 mm	39	11	9	61	4	135	16
# LR	4	6	4	16	3	51	6
# no LR	35	5	5	45	1	84	10
% LR	0.10	0.55	0.44	0.26	0.75	0.38	0.38
# 1–1.9 mm	35	6	8	80	-	42	8
# LR	3	2	2	18	-	7	1
# no LR	32	4	6	62	-	35	7
% LR	0.09	0.33	0.25	0.23	-	0.17	0.13
# 2–2.9 mm	50	9	13	-	5	39	-
# LR	8	1	6	-	5	5	-
# no LR	42	8	7	-	0	34	-
% LR	0.16	0.11	0.46	-	1.00	0.13	-
# 3–3.9 mm	28	6	11	41	12	23	5
# LR	4	2	5	6	6	3	0
# no LR	24	4	6	35	6	20	5
% LR	0.14	0.33	0.45	0.15	0.50	0.13	0.00
# 4–4.9 mm	21	-	11	-	11	21	5
# LR	2	-	2	-	2	3	0
# no LR	19	-	9	-	9	18	5
% LR	0.10	-	0.18	-	0.18	0.14	0.00
# ≥ 5 mm	122	116	511	95	419	94	93
# LR	7	13	81	8	180	10	8
# no LR	115	103	430	87	239	84	85
% LR	0.06	0.11	0.16	0.08	0.43	0.11	0.09

Abbreviations: Local Recurrence (LR)

Table 4.

The Effect of 1 mm Surgical Margin Incremental Distances on LR

Parameter	Sample Size	Risk for LR (Risk Ratio)	Confidence Interval (95%)	P-value*
Margin Status				
Negative Margins (≥5mm)	1450	1	`	`
Positive/Close (>5mm)	765	2.09	1.53–2.86	**<0.001**
Margin Threshold				
0.0–0.9	275	2.96	2.15–4.07	**<0.001**
1.0–1.9	179	2.01	1.29–3.13	**<0.001**
2.0–2.9	116	2.17	1.73–2.73	**<0.001**
3.0–3.9	126	1.81	1.81–1.21	**<0.001**
4.0–4.9	69	0.98	0.52–1.85	0.96

*P-value for association as determined from meta-analysis