

Impact of surgical margins status on survival outcomes in oral cavity squamous cell carcinoma: a systematic review and meta-analysis

Elisa Bellini^{1,2*}, Gian Marco Pace^{3,4*}, Filippo Marchi^{1,2}, Alberto Paderno^{3,4}, Camilla Zimello^{3,4}, Alessia Pennacchi^{1,2}, Giuseppe Mercante^{3,4}, Giorgio Peretti^{1,2}, Giuseppe Spriano^{3,4}, Andrea Iandelli¹

¹ Unit of Otorhinolaryngology-Head and Neck Surgery, IRCCS Ospedale Policlinico San Martino, Genoa, Italy;

² Department of Surgical Sciences and Integrated Diagnostics (DISC), University of Genoa, Genoa, Italy;

³ Department of Biomedical Sciences, Humanitas University, Pieve Emanuele (MI), Italy; ⁴ Otorhinolaryngology Unit, IRCCS Humanitas Research Hospital, Rozzano (MI), Italy

* EB and GMP contributed equally to this work and share the first authorship.

Received: February 10, 2025

Accepted: March 13, 2025

Correspondence

Gian Marco Pace

E-mail: gianmarco.pace1996@gmail.com

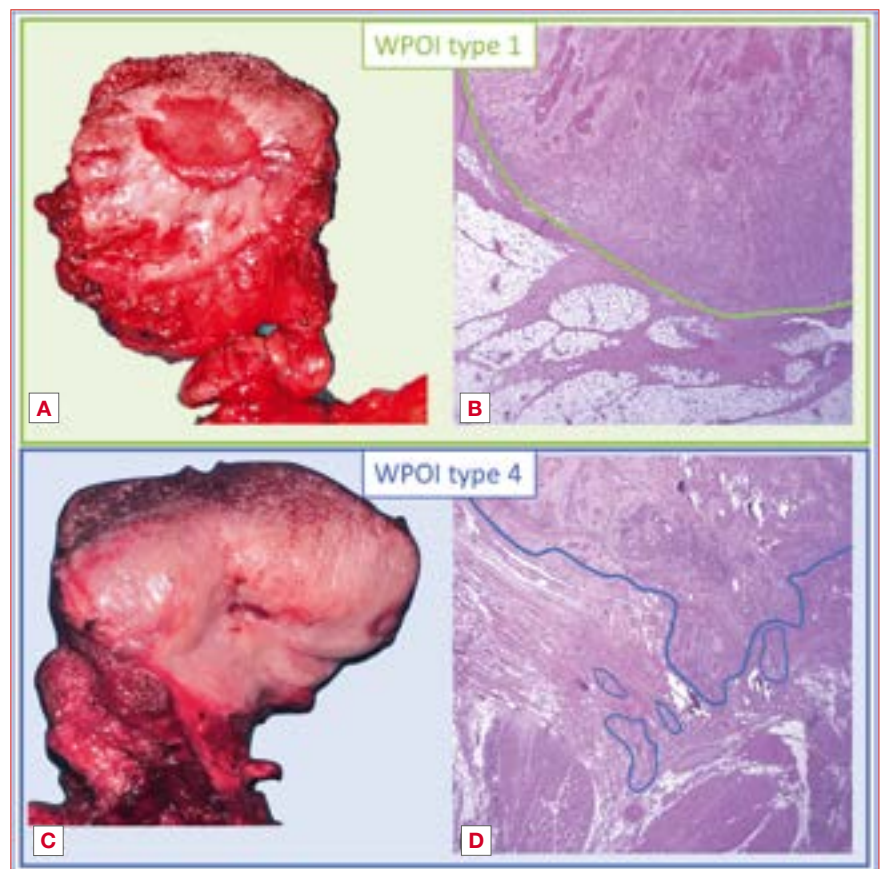
How to cite this article: Bellini E, Pace GM, Marchi F, et al. Impact of surgical margins status on survival outcomes in oral cavity squamous cell carcinoma: a systematic review and meta-analysis. Acta Otorhinolaryngol Ital 2025;45(Suppl. 1):S2-S14. <https://doi.org/10.14639/0392-100X-suppl.1-45-2025-N1044>

© Società Italiana di Otorinolaringoiatria e Chirurgia Cervico-Facciale



OPEN ACCESS

This is an open access article distributed in accordance with the CC-BY-NC-ND (Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International) license. The article can be used by giving appropriate credit and mentioning the license, but only for non-commercial purposes and only in the original version. For further information: <https://creativecommons.org/licenses/by-nc-nd/4.0/deed.en>



Cover figure. Examples of invasion patterns of oral squamous cell carcinoma: case 1 (A, B) shows an expansive front (worst pattern of invasion [WPOI] 1), while case 2 (C, D) features finger-like projections and isolated nests (WPOI 4).

Summary

Objective. The aim of this study is to analyse the impact of surgical margins on survival outcomes for patients with oral cavity squamous cell carcinoma (OCSCC).

Methods. Pooled hazard ratios (HRs) and 95% confidence interval (CI) were calculated to define the impact of positive and close margins on overall survival (OS), disease-free survival (DFS), and disease-specific survival (DSS).

Results. A total of 14 studies enrolling 4839 patients (of whom 3837 males, or 79.3%), with a median age of 59 years, were included. The incidence of positive margins was 9.1%, while that of close margins was 27.3%. The estimated pooled HRs for patients with positive surgical margins were 2.265 (95% CI: 1.431-3.584; $p = 0.003$) for OS, 2.076 (95% CI: 1.652-2.608; $p < 0.001$) for

DFS, and 2.163 (95% CI: 1.349-3.468; $p = 0.014$) for DSS. For patients with close margins, the HRs were 1.409 (95% CI: 1.064-1.866; $p = 0.024$) for OS, 1.775 (95% CI: 0.910-3.462; $p = 0.078$) for DFS, and 1.123 (95% CI: 0.425-2.974; $p = 0.658$) for DSS.

Conclusions. Positive surgical margins are a significant prognostic factor in OCSCC. Further studies are required to better define the impact of close margins.

Key words: surgical margins, oral cavity carcinoma, head and neck cancer, squamous cell carcinoma, survival

Introduction

With over 350,000 new cases and 170,000 deaths reported annually, oral cavity squamous cell carcinoma (OCSCC) is the most prevalent malignancy of the head and neck ¹. Despite advances in diagnosis and treatment ², OCSCC remains a serious public health concern, with a 5-year survival rate ranging between 50 and 85% ^{3,4}. Surgical resection is the primary treatment for OCSCC, and the achievement of negative surgical margins is a key determinant of prognosis. However, OCSCC exhibits the highest rates of positive surgical margins among cancers affecting both sexes ⁵.

In the last decades, the literature has presented varying perspectives on what defines adequate soft tissue and mucosal margin distances. Despite extensive investigation, the optimal margin threshold and its implications for survival remain topics of ongoing debate. In 1998, the Royal College of Pathologists (RCPATH) established guidelines for histological assessment of surgical margins ⁶. According to this system, margins less than 1 mm are classified as positive, 1-5 mm as close, and greater than 5 mm as clean. The prognostic impact of close margins remains poorly defined and varies across different studies and oral cavity subsites ^{7,8}.

Although tumour behaviour is influenced by various biological factors and histopathological parameters beyond the control of surgical resection, such as nodal disease, perineural invasion (PNI), lymphovascular invasion (LVI), worst pattern of invasion (WPOI), and inflammatory response, assessing the impact of margin status on OCSCC patient survival remains crucial ⁹⁻¹³.

This systematic review and meta-analysis aims to summarise current data on the role of surgical margin status on survival outcomes in OCSCC. By systematically reviewing the available literature, we aim to provide a more definitive understanding of the relationship between surgical margins and key survival metrics such as overall (OS), disease-free (DFS), and disease-specific survival (DSS).

Methods

This systematic review was reported according to the Primary Reporting Items for Systematic Reviews and Meta-

Analyses (PRISMA) statement ¹⁴. Since data were obtained from published literature, institutional review board approval and informed consent were not required. No study protocol was registered.

Eligibility criteria

All studies enrolling patients undergoing surgery for OCSCC were included. Studies had to report uni-variable and/or multivariable analyses assessing the impact of positive and/or close margins on OS, DSS, or DFS. Studies had to define positive margins as ≤ 1 mm from the tumour, close margins as > 1 mm to ≤ 5 mm, and negative margins as > 5 mm. Studies must have compared outcomes between positive and negative surgical margins and/or between close and negative surgical margins. Retrospective and prospective cohort studies were included.

Studies were excluded if they: were not in English; were not available in full-text form; reported insufficient data or data were not extractable; were ongoing projects; included less than 5 patients; included patients sourced from national databases; used different definition of positive or close margins; the article type was either a review, case report, conference abstract, letter to the editor, or book chapter. If multiple studies were performed at the same centre with overlapping time periods, the most updated and with larger sample size was included. No publication date restriction was imposed, and articles had to be published in a peer-reviewed journal.

Data source and study searching

A comprehensive literature search was conducted in the Scopus, PubMed/MEDLINE, and Google Scholar databases. An example of a search strategy was the one used for Scopus: (“oral squamous cell carcinoma” OR “OSCC” OR “oral cavity cancer”) AND (“surgical margins” OR “positive margins” OR “close margins” OR “negative margins” OR “resection margins”) AND (“survival analysis” OR “disease-specific survival” OR “overall survival” OR “disease-free survival” OR “prognosis” OR “outcomes”). The searches in the remaining databases were adjusted to fit the specific requirements for each of the individual databases. The “cited by” function on Google Scholar was used in or-

der to identify additional articles. A cross-reference search of the selected articles was performed to minimise the risk of missing relevant data. The last search was performed on October 25th, 2024.

Data collection process

A literature search was conducted independently by 3 authors (AP, CZ, EB). Records identified through database searching were merged and the duplicates removed using the reference management software EndNote® X9 (version X9.3.3). All articles were initially screened for relevance by title and abstract.

Studies that met the established criteria were downloaded and the full texts were reviewed to determine eligibility. Disagreements were resolved by referring to a fourth author (GMP). The most updated and inclusive data for each study were chosen for abstraction. A standardised Excel form was compiled by 3 authors (AP, CZ, EB) in order to extract the patient characteristics in the studies included. For one of the studies included, missing information was requested and obtained by contacting the corresponding author¹⁵. Finally, another author checked the data for accuracy (GMP).

Risk of bias and study quality assessment

The National Institute for Health and Clinical Excellence (NICE) quality assessment tool was used independently by 2 authors (EB, CZ)¹⁶. A funnel plot was created using the effect size for OS, DSS, and DFS in order to examine potential publication bias.

Data synthesis and statistical analysis

Descriptive statistics were used to summarise data from the studies included. Dichotomous variables were reported as counts and percentages, while continuous variables as median and 95% confidence interval (CI) calculated through the method described by McGrath et al.¹⁶. Clinical measures were reported as provided by the individual studies.

A meta-analysis was conducted to evaluate the overall effect of treatment on survival outcomes, specifically using the hazard ratio (HR) as the summary measure. The analysis incorporated data from multiple studies that reported HR along with 95% CIs. For each study, the standard error (SE) of the log-transformed HR was computed using the lower and upper bounds of the 95% CI. The inverse variance method to combine the effect sizes from individual studies was applied¹⁸. I^2 statistic was used to assess heterogeneity (low, 0-30%; moderate, 30-60%; substantial, 60-90%; and considerable, 90-100%)¹⁹. A more conservative random-effects model was chosen over a fixed-effects model to account for potential heterogeneity across

the included studies (Q-statistic, $p < 0.05$). The restricted maximum-likelihood estimator (REML) was used to estimate between-study variance (τ^2)²⁰. Hartung-Knapp adjustment was applied to provide more accurate CI²¹. A Forest plot was generated to visually represent the individual and pooled HRs from the included studies. Analysis of publication bias was performed by visual inspection of the funnel plot and calculating the Egger's regression intercept which statistically examines the asymmetry of the funnel plot²². All analyses were performed using the software R for statistical computing (version 4.4.1). Statistical significance was defined as $p < 0.05$.

Results

Literature search and study descriptions

As shown in Figure 1, the search strategy retrieved 2447 studies after duplicate removal. After title/abstract screening, 395 articles were selected for full text assessment. Through the application of the defined inclusion and exclusion criteria, 14 studies were included in the qualitative and quantitative analysis^{15,23-35}. The reasons behind the exclusion of the remaining studies are shown in Figure 1. Patient characteristics are shown in Tables I and II. The studies enrolled a total of 4839 patients (3837 males, or 79.3%) with a median age of 59 years (95% CI: 52.1-61.5). The status of surgical margins was reported for 4771 of 4839 patients. The incidence of positive margins was 9.1% ($n = 436/4771$), while that of close margins was 27.3% ($n = 1300/4771$). The histological incidence of other adverse features, such as extranodal extension (ENE), LVI, and PNI, was reported as 24.8% ($n = 899/3631$), 13.9% ($n = 564/4059$), and 19.9% ($n = 735/4106$), respectively. Most of the patients underwent adjuvant radiation (RT) (54.1%, $n = 2380/4403$), while only 23.7% received adjuvant chemotherapy (CT) ($n = 551/2323$). The prognostic impact of positive and close margins for the individual studies is shown in Table II.

Methodological quality and risk of bias

Table III summarises the risk of bias of the studies included using the NICE quality assessment tool. The overall quality was considerate moderate with a median score of 6/8. Only 3 studies showed a prospective design (10.6%, $n = 488/4839$), while no studies specified multicentric patient enrollment.

Funnel plots were created for OS positive and close margins, and for DFS positive and close margins (Fig. 2). Egger's test did not reveal any significant asymmetry for

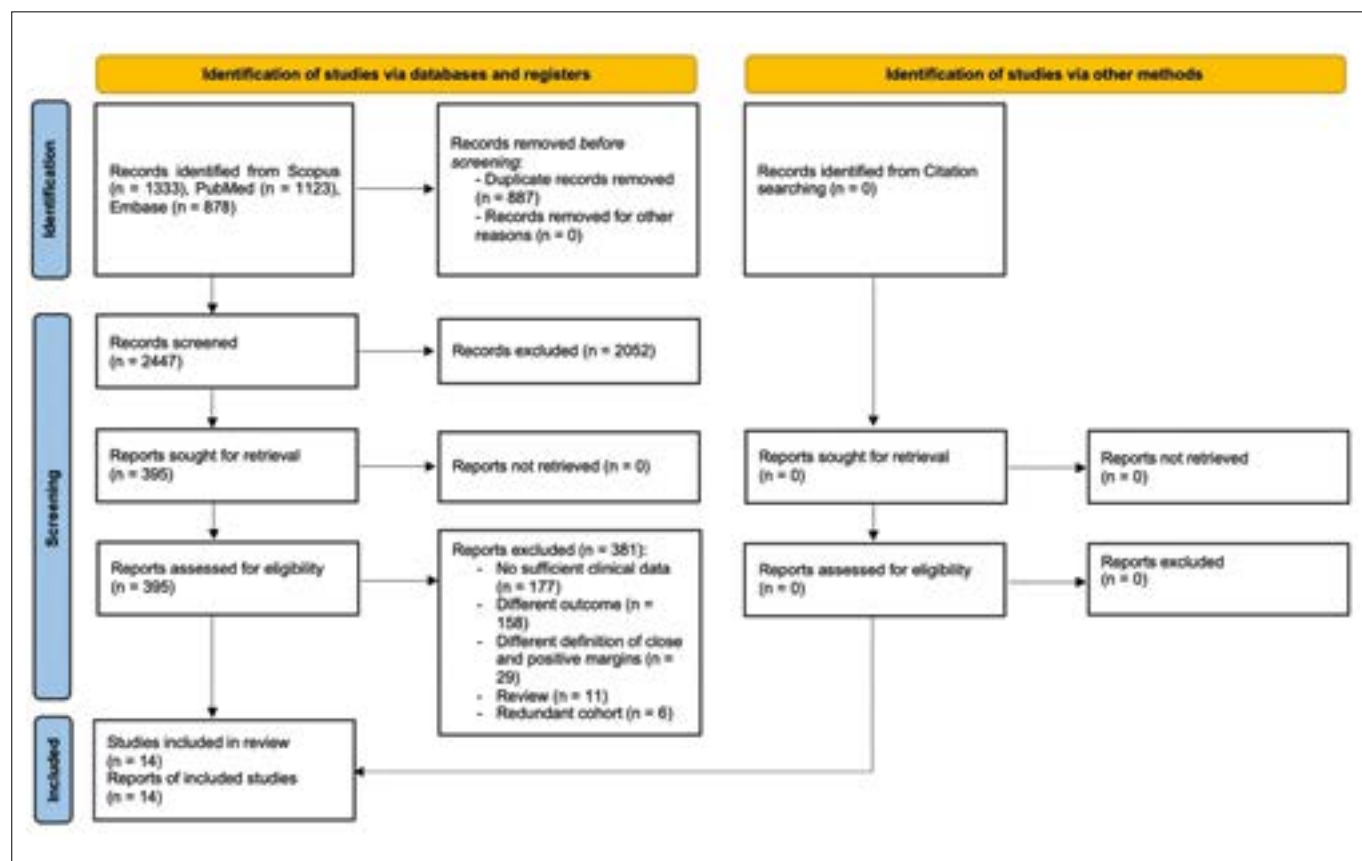


Figure 1. PRISMA flow diagram.

OS positive margins ($t = -2.1$, $df = 8$, $p = 0.0694$), close margins ($t = 1.13$, $df = 6$, $p = 0.3026$), DFS positive margins ($t = 0.40$, $df = 7$, $p = 0.6999$), or DFS close margins ($t = -0.28$, $df = 4$, $p = 0.7946$).

Overall survival

A total of 10 studies ($n = 3237$) were included to calculate the pooled OS effect size for positive surgical margins. The estimated pooled HR was 2.265 (95% CI: 1.431-3.584; $p = 0.003$), demonstrating a significant difference in OS based on margins positivity (Fig. 3A). Substantial heterogeneity was measured between studies ($Q = 22.31$, $p < 0.05$). In particular, the between-study variance was estimated at $\tau^2 = 0.17$ (95% CI: 0.02-1.72), with an I^2 value of 59.7% (95% CI: 19.1-79.9).

A total of 8 studies ($n = 2627$) were included to calculate the pooled OS effect size for close surgical margins. The estimated pooled HR was 1.409 (95% CI: 1.064-1.866; $p = 0.024$), demonstrating a significant difference in OS (Fig. 3B). Low heterogeneity was measured between stud-

ies ($Q = 10.83$, $p < 0.146$). In particular, the between-study variance was estimated at $\tau^2 = 0.0117$ (95% CI: 0.00-0.65), with an I^2 value of 35.4% (95% CI: 0.0-71.4).

Disease-free survival

A total of 9 studies ($n = 3238$) were included to calculate the pooled DFS effect size for positive surgical margins. The estimated pooled HR was 2.076 (95% CI: 1.652-2.608; $p < 0.001$), demonstrating a significant difference in DFS based on margin positivity (Fig. 4A). Low heterogeneity was measured between studies ($Q = 7.59$, $p = 0.475$). In particular, the between-study variance was estimated at $\tau^2 < 0.001$ (95% CI: 0.00-0.38), with an I^2 value of 0.0% (95% CI: 0.0-64.8).

A total of 6 studies ($n = 1883$) were included to calculate the pooled DFS effect size for close surgical margins. The estimated pooled HR was 1.775 (95% CI: 0.910-3.462; $p = 0.078$), demonstrating a non-significant difference in DFS (Fig. 4B). Considerable heterogeneity was measured between studies ($Q = 32.87$, $p < 0.05$). In particular, the

Table I. General characteristics of the studies included.

First author (year)	Country	No. of patients (males)	Age (range)	Margins	T classification	LVI	PNI	ENE	Adjuvant RT	Adjuvant CT	Follow-up (months)
Bera (2023) ²⁹	India	260 (189)	61.6 (N/A)	negative: 163/260 (62.7%); close: 46/260 (17.7%); positive: 51/260 (19.6%)	T3: 114/260 (43.8%); T4a: 105/260 (40.4%); T4b: 41/260 (15.8%)	91/260 (35%)	77/260 (29.6%)	119/260 (45.8%)	N/A	N/A	43 (N/A)
Brinkman (2020) ¹⁵	Ireland	244 (164)	63 (27-93)	negative: 60/244 (24.6%); close: 119/244 (48.8%); positive: 65/244 (26.6%)	T1: 59/244 (24.2%); T2: 91/244 (37.3%); T3: 91/244 (37.3%); T4: 56/244 (23%)	N/A	N/A	43 (17.6%)	114/244 (46.7%)	N/A	36 (N/A)
Chang (2019) ²³	Taiwan	341 (313)	52.1 (23-84)	negative: 236/341 (69.2%); close: 93/341 (27.3%); positive: 12/341 (3.5%)	T1: 72/341 (21.2%); T2: 102/341 (29.9%); T3: 89/341 (26.1%); T4a: 77/341 (22.6%); T4b: 1/341 (0.3%)	41/341 (12%)	68/341 (19.9%)	60/341 (17.6%)	201/341 (58.9%)	201/341 (58.9%)	43 (0-143)
Chen (2012) ³⁰	Taiwan	407 (347)	52 (22-90)	negative: 362/407 (88.9%); close: 31/407 (7.6%); positive: 14/407 (3.5%)	T1: 260/407 (63.9%); T2: 147/407 (36.1%)	28/407 (6.9%)	51/407 (12.5%)	N/A	35/407 (8.6%)	N/A	52 (3-126)
Jain (2020) ³¹	India	612 (428)	55 (21-85)	negative: 496/612 (81%); close: 90/612 (14.7%); positive: 26/612 (4.2%)	T1-2: 384/612 (62.7%); T3-4: 228/612 (37.3%)	213/612 (34.8%)	269/612 (44%)	148/612 (24.2%)	426/612 (69.6%)	154/612 (25.2%)	40.2 (0.5-78)
Kamalakkannan (2024) ³²	India	167 (100)	59 (50-66)	negative: 50/167 (29.9%); close: 78/167 (46.7%); positive: 39/167 (23.3%)	T1: 33/167 (20%); T2: 54/167 (33%); T3: 25/167 (16%); T4: 55/167 (33%)	34/165 (20.6%)	57/164 (34.8%)	28/167 (17%)	108/167 (64.7%)	56/167 (34%)	30 (1-120)
Kanatas (2023) ²⁴	United Kingdom	250 (141)	61.4 (N/A)	negative: 106/244 (43.4%); close: 94/244 (38.5%); positive: 44/244 (18%)	T1: 97/250 (39.1%); T2: 69/250 (27.8%); T3: 28/250 (11.3%); T4: 54/250 (21.8%)	N/A	N/A	N/A	114/250 (45.6%)	N/A	N/A
Lee (2021) ³³	Taiwan	1179 (1113)	N/A	negative: 986/1166 (84.6%); close: 159/1166 (13.6%); positive: 21/1166 (1.8%)	T3-4: 1179/1179 (100%)	94/1179 (8%)	45/1179 (3.8%)	372/1179 (32.1%)	890/1179 (75.5%)	N/A	58 (1-286)

Table I. continues.

First author (year)	Country	No. of patients (males)	Age (range)	Margins	T classification	LVI	PNI	ENE	Adjuvant RT	Adjuvant CT	Follow-up (months)
Lu (2024) ³⁴	Taiwan	485 (442)	NA	negative: 154/454 (33.9%); close: 258/454 (56.8%); positive: 42/454 (9.3%)	T1: 345/485 (71%); T2: 140/485 (29%)	8/485 (1.7%)	63/485 (13.1%)	NA	78/485 (16.2%)	15/485 (3.1%)	66.8 (NA)
Panda (2021) ²⁵	India	125 (117)	46.9 (NA)	negative: 114/125 (91.2%); positive: 11/125 (8.8%)	T1: 2/125 (1.6%); T2: 5/125 (4%); T3: 10/125 (8%); T4: 108/125 (86.4%)	12/125 (9.6%)	15/125 (12%)	36/125 (29%)	NA	NA	24 (NA)
Pandey (2009) ²⁶	India	51 (30)	54 (NA)	negative: 11/51 (22%); close: 33/51 (65%); positive: 7/51 (13%)	NA	NA	N = 7/51 (13.7%)	NA	NA	NA	NA
Solomon (2021) ²⁷	Canada	187 (115)	61.4	negative: 105/181 (58%); close: 70/181 (38.7%); positive: 6/181 (3.3%)	T1-2: 126/187 (67.4%); T3-4: 61/187 (32.6%)	16/159 (10.1%)	43/156 (27.6%)	23/187 (12.3%)	75/187 (40.1%)	19/187 (10.2%)	21.5 (NA)
Szewczyk (2024) ³⁵	Poland	326 (210)	59.1 (23-97)	negative: 75/326 (23%); close: 168/326 (51.5%); positive: 83/326 (25.5%)	cT1-2: 258/326 (79%); cT3-4: 68/326 (20.9%)	27/326 (8.2%)	40/326 (12.2%)	57/326 (17.4%)	263/326 (80.6%)	85/326 (26%)	NA
Veiga-San Roman (2024) ²⁸	Spain	205 (128)	61.5 (25-91)	negative: 117/193 (60.6%); close: 61/193 (31.6%); positive: 15/193 (7.8%)	T1-2: 186/201 (92.5%); T3-4: 15/201 (7.5%)	NA	NA	13/190 (6.8%)	76/205 (37%)	21/205 (10%)	NA

LVI: lymphovascular invasion; PNI: perineural invasion; ENE: extranodal extension; RT: radiotherapy; CT: chemotherapy.

between-study variance was estimated at $\tau^2 = 0.34$ (95% CI: 0.09-2.28), with an I^2 value of 84.8% (95% CI: 68.7-92.6).

Disease-specific survival

A total of 4 studies (n = 1848) were included to calculate the pooled DSS effect size for positive surgical margins. The estimated pooled HR was 2.163 (95% CI: 1.349-3.468; p = 0.014), demonstrating a significant difference in DSS based on margin positivity (Fig. 5A). Low heterogeneity was measured between studies ($Q = 1.42$, p = 0.701). In particular, the between-study variance was estimated at $\tau^2 = 0.00$ (95% CI: 0.00-3.562), with an I^2 value of 0.0% (95% CI: 0.0-84.7). Only 3 large studies (n = 669) were included to calculate the pooled DSS effect size for close surgical margins. The estimated pooled HR was 1.1235 (95% CI: 0.425-2.974; p = 0.658), demonstrating a non-significant difference in

DSS (Fig. 5B). Low heterogeneity was measured between studies ($Q = 2.13$, p = 0.34). In particular, the between-study variance was estimated at $\tau^2 = 0.01$ (95% CI: 0.00-6.327), with an I^2 value of 6.3% (95% CI: 0.0-90.2).

Discussion

This study reinforces the importance of surgical margins in OCSCC resection, showing significantly poorer survival for patients with positive surgical margins²⁸⁻³⁰. Achieving negative margins during primary surgical treatment is crucial as it is one of the few factors under the surgeon's control that can influence prognosis³⁶. While positive surgical margins had a significant impact on OS, DFS, and DSS, the data on the role of close margins were less conclusive, showing prognostic significance only for OS.

Table II. Survival analysis of the studies included.

First author (year)	Margins	OS positive	OS close	DFS positive	DFS close	DSS positive	DSS close
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Bera (2023) ²⁹	negative: 163/260 (62.7%); close: 46/260 (17.7%); positive: 51/260 (19.6%)	2.437 (1.379-4.308)	4.886 (3.037-7.861)	2.647 (1.604-4.366)	4.882 (3.153-7.559)	NA	NA
Brinkman (2020) ¹⁵	negative: 60/244 (24.6%); close: 119/244 (48.8%); positive: 65/244 (26.6%)	1.19 (0.72-1.96)	1.6 (0.94-2.75)	1.66 (0.9-3.04)	1.36 (0.77-2.39)	2.59 (1.19-5.63)	1.76 (0.83-3.7)
Chang (2019) ²³	negative: 236/341 (69.2%); close: 93/341 (27.3%); positive: 12/341 (3.5%)	1.186 (0.815-1.726)	3.575 (1.856-6.886)	NA	NA	NA	NA
Chen (2012) ³⁰	negative: 362/407 (88.9%); close: 31/407 (7.6%); positive: 14/407 (3.5%)	3.35 (1.41-7.94)	2.11 (0.5-8.95)	3.04 (1.1-8.4)	2.71 (1.43-5.14)	NA	NA
Jain (2020) ³¹	negative: 496/612 (81%); close: 90/612 (14.7%); positive: 26/612 (4.2%)	1.41 (0.928-2.144)	2.71 (1.496-4.909)	1.99 (1.05-3.76)	0.97 (0.64-1.47)	NA	NA
Kamalakkannan (2024) ³²	negative: 50/167 (29.9%); close: 78/167 (46.7%); positive: 39/167 (23.3%)	NA	NA	2.12 (1.3-3.45)	1.02 (0.42-2.52)	NA	NA
Kanatas (2023) ²⁴	negative: 106/244 (43.4%); close: 94/244 (38.5%); positive: 44/244 (18%)	1.15 (0.69-1.94)	2 (1.09-3.68)	NA	NA	1.77 (0.72-4.38)	0.82 (0.34-1.98)
Lee (2021) ³³	negative: 986/1166 (84.6%); close: 159/1166 (13.6%); positive: 21/1166 (1.8%)	NA	NA	2.407 (1.315-4.406)	NA	2.331 (1.235-4.4)	NA
Lu (2024) ³⁴	negative: 154/454 (33.9%); close: 258/454 (56.8%); positive: 42/454 (9.3%)	NA	1.135 (0.208-6.197)	NA	NA	NA	NA
Panda (2021) ²⁵	negative: 114/125 (91.2%); positive: 11/125 (8.8%)	NA	0.26 (0.06-1.16)	0.99 (0.44-2.26)	NA	NA	NA
Pandey (2009) ²⁶	negative: 11/51 (22%); close: 33/51 (65%); positive: 7/51 (13%)	NA	NA	1.8 (1.17-2.76)	NA	NA	NA
Solomon (2021) ²⁷	negative: 105/181 (58%); close: 70/181 (38.7%); positive: 6/181 (3.3%)	NA	NA	NA	NA	0.75 (0.09-6.12)	0.95 (0.5-1.83)
Szewczyk (2024) ³⁵	negative: 75/326 (23%); close: 168/326 (51.5%); positive: 83/326 (25.5%)	0.89 (0.42-1.88)	1.91 (0.85-4.32)	NA	NA	NA	NA
Veiga-San Roman (2024) ²⁸	negative: 117/193 (60.6%); close: 61/193 (31.6%); positive: 15/193 (7.8%)	NA	NA	2.62 (1.29-5.32)	1.55 (0.95-2.56)	NA	NA

OS: overall survival; HR: hazard ratio; CI: confidence interval; DFS: disease-free survival; DSS: disease-specific survival.

Table III. Quality assessment of case series studies checklist from National Institute for Health and Clinical Excellence.

NICE									
First author (year)	Question 1	Question 2	Question 3	Question 4	Question 5	Question 6	Question 7	Question 8	Risk of bias
Bera (2023) ²⁹	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Brinkman (2020) ¹⁵	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Chang (2019) ²³	No	Yes	Yes	Yes	No	No	Yes	Yes	5
Chen (2012) ³⁰	No	Yes	Yes	Yes	No	No	Yes	Yes	5
Jain (2020) ³¹	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Kamalakannan (2024) ³²	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Kanatas (2023) ²⁴	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Lee (2021) ³³	No	Yes	No	Yes	No	Yes	Yes	Yes	5
Lu (2024) ³⁴	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Panda (2021) ²⁵	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Pandey (2009) ²⁶	No	Yes	Yes	Yes	Yes	No	Yes	Yes	5
Solomon (2021) ²⁷	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Szewczyk (2024) ³⁵	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Veiga-San Roman (2024) ²⁸	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6

(1) Was the case series collected in more than one centre (i.e., multi-centre study)? (2) Is the hypothesis/aim/objective of the study clearly described? (3) Are the inclusion and exclusion criteria (case definition) clearly reported? (4) Is there a clear definition of the outcomes reported? (5) Were data collected prospectively? (6) Is there an explicit statement that patients were recruited consecutively? (7) Are the main findings of the study clearly described? (8) Are outcomes stratified (e.g., by abnormal results, disease stage, patient characteristics)?

Considering the intricate anatomy of the oral cavity, the challenges associated with visualisation, and the technical demands involved in resecting OCSCC, obtaining sufficient surgical margins poses substantial difficulties. A major factor is the size of the primary tumour, as the incidence of positive margins increases with advancing T categories. Moratin et al.³⁷ in a retrospective study of 567 patients, reported a positive surgical margin rate of 5.4% in T1 tumours, increasing to 27.9% in T4. Similarly, Chen et al.^{30,38} found a significantly lower incidence of positive margins (7.6%) in early-stage OCSCC.

Another factor influencing surgical margin status is the location of the tumour subsite within the oral cavity. The subsite's location can impact the ability to achieve adequate resection. Tumours situated more anteriorly generally allow for better outcomes.

There is still no consensus in the literature regarding the definition of positive and close surgical margins. According to the RCPATH, a margin is considered positive when invasive cancer is found within 1 mm of the resection edge. On

the other hand, the College of American Pathologists (CAP) defines a positive margin as the presence of tumour cells directly at the inked surface of the specimen^{38,39}. In a series of 669 patients with early OCSCC, Bajwa et al.³⁹ showed that resection margins < 1 mm independently affected survival outcomes, suggesting that margins < 1 mm should be defined as positive.

However, numerous studies in the literature continue to use different cut-off criteria, many of which are arbitrary or lack rigorous validation⁴⁰⁻⁴³. In our systematic review and meta-analysis, we included only studies that defined margins as positive if ≤ 1 mm from the tumour, close if > 1 mm to ≤ 5 mm, and negative if > 5 mm.

Compared to other head and neck sites, such as the larynx, where the distances defining close and positive margins are smaller and their impact on survival is less clearly established, OCSCC necessitates a significantly higher level of surgical aggressiveness⁴³. However, evaluating the independent effects of margin status¹⁵ on survival outcomes remains exceedingly challenging due to the overlapping

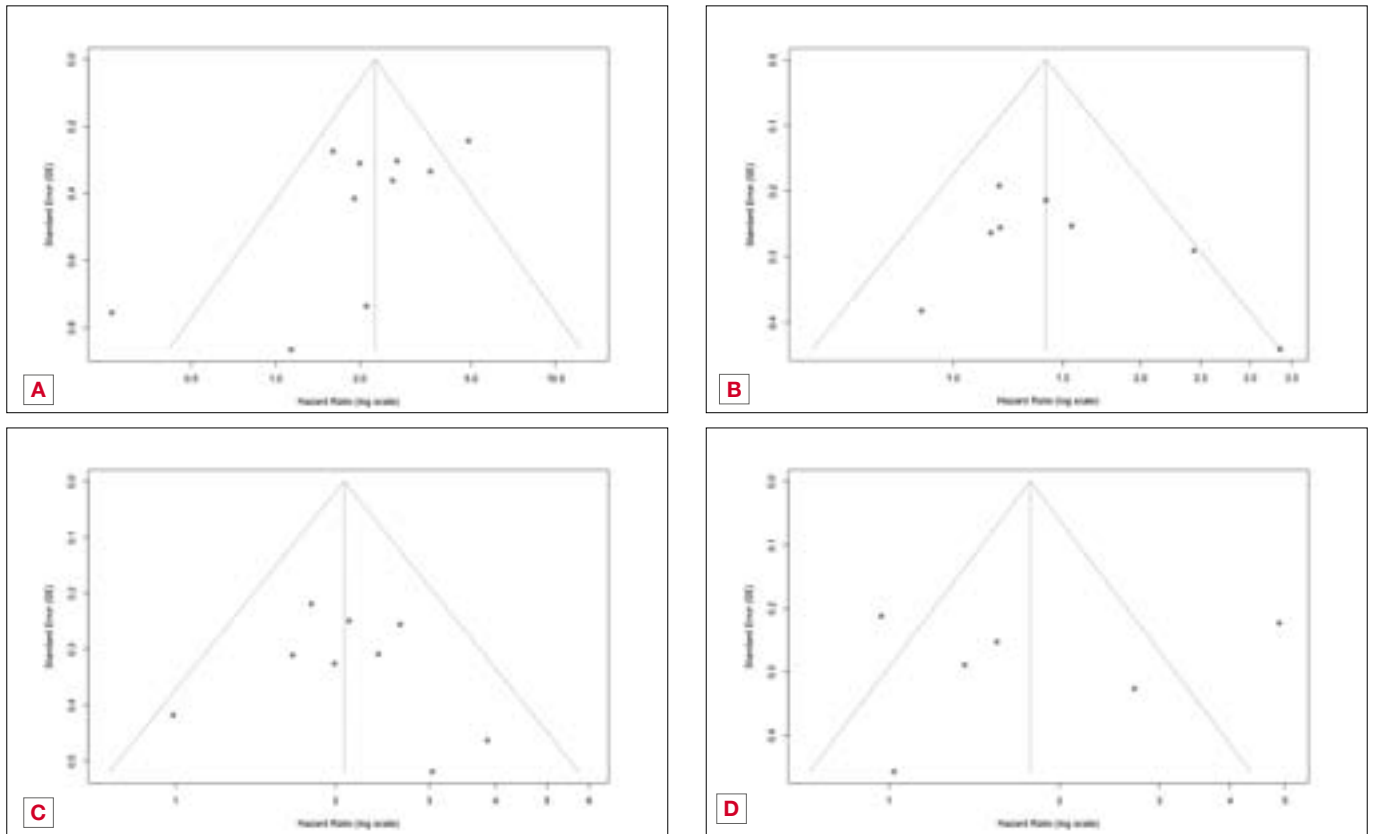


Figure 2. Funnel plots for the evaluation of publication bias using the pooled OS effect sizes for positive (A) and close margins (B), and the pooled DFS effect sizes for positive (C) and close margins (D).

presence of various biological and histological risk factors, such as LVI, PNI, nodal disease with or without ENE, and advanced stage, which vary significantly among individual patients and tumours^{31,33,34,44,45}.

According to the NCCN guidelines⁴⁶, patients with positive margins typically require additional treatment, such as re-excision, when feasible. Alternatively, systemic therapy and/or RT is recommended. While re-resection is often considered, studies report that the likelihood of detecting residual tumour is relatively low, around 30%, raising questions about the effectiveness of additional surgery in improving outcomes⁴⁷. Furthermore, revision surgery in OSCCC patients is often not feasible due to anatomical localisation or the use of flaps to reconstruct the surgical defect⁴⁸.

Kim et al.⁴⁹ conducted a retrospective study involving 441 patients with early-stage oral tongue squamous cell carcinoma. They found that 86.2% achieved clear margins after the initial surgery, while 13.8% transitioned from positive to clear margins following re-resection. The re-resection group exhibited a higher local recurrence rate, as well as challenges in accurately

identifying the positive margin site for re-excision. Instead, careful selection of patients for adjuvant therapies may prove more beneficial, especially in high-risk cases⁵⁰.

The NCCN guidelines for adjuvant therapy are based on the EORTC 22931 and RTOG 9501 trials⁵¹ in which only 25% of the patients enrolled had OSCCC. However, our results indicate that positive margins remain an unfavourable prognostic factor, regardless of the use of comprehensive treatments, including trimodal therapies. Although most studies in this review ($n = 11/14$) reported the use of adjuvant therapy, it does not appear to eliminate the prognostic significance of positive margins^{8,52}.

Moreover, tumour biology might influence the appropriate distance for defining negative margins. Kohler et al. found that the WPOI significantly affects the necessary surgical margins, especially in high-risk patients. Tumours with WPOI types 4-5 are linked to poorer survival when resected with the standard 5 mm margin, indicating that margin guidelines may need to be adjusted based on the tumour's aggressiveness and histological characteristics⁵² (Cover figure).

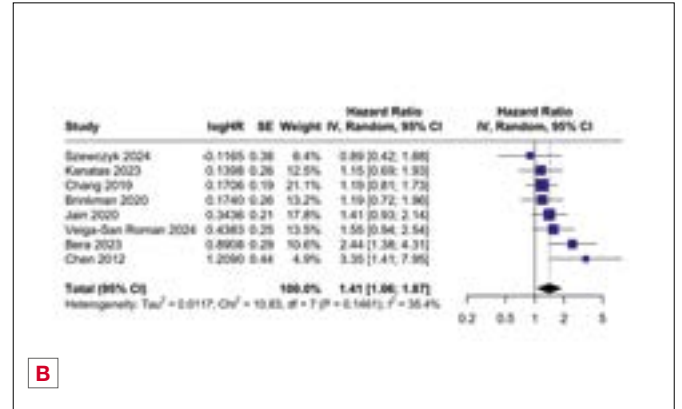
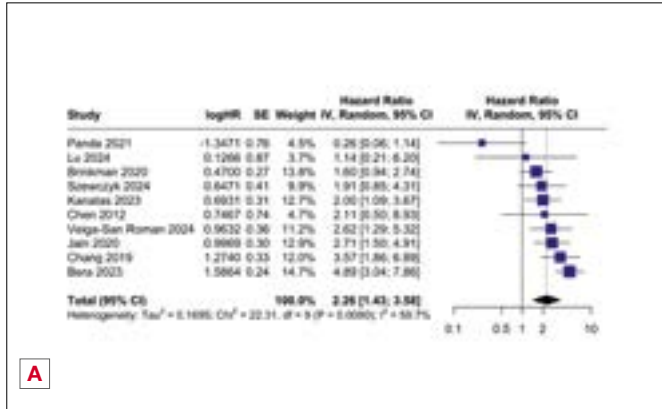


Figure 3. Forest plots showing the pooled OS for positive (A) and close (B) margin effect sizes. The dashed vertical line represents the overall measure of effect.

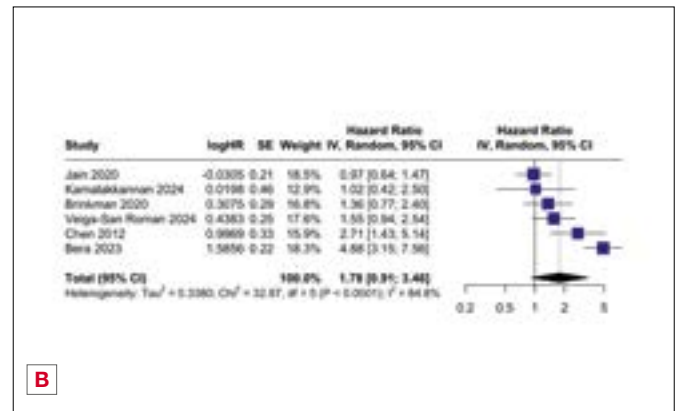
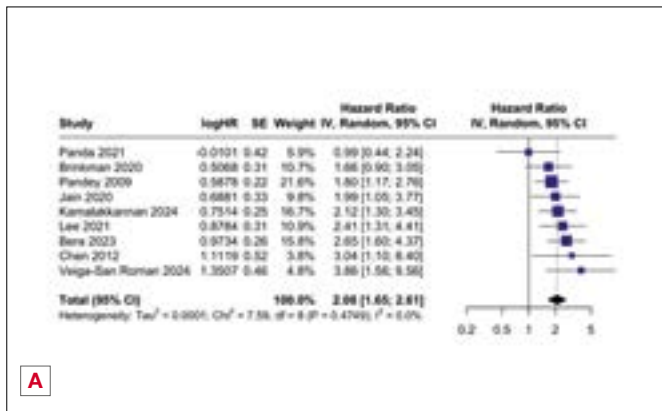


Figure 4. Forest plots showing the pooled DFS for positive (A) and close (B) margin effect sizes. The dashed vertical line represents the overall measure of effect.

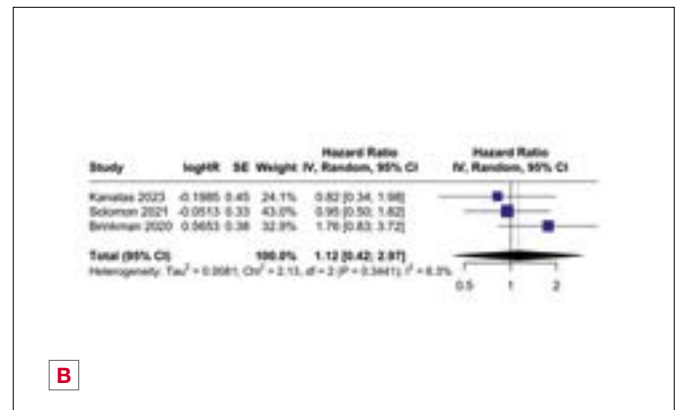
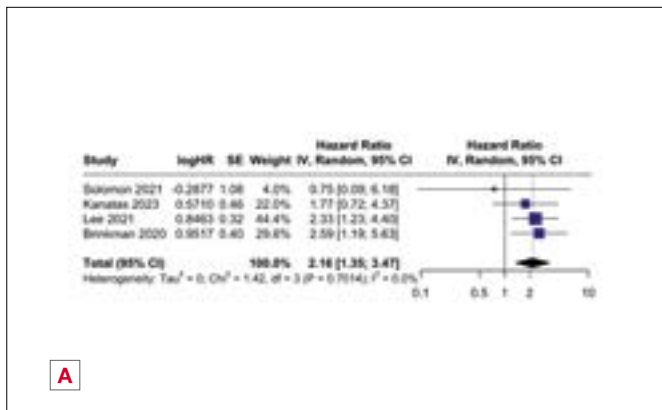


Figure 5. Forest plots showing the pooled DSS for positive (A) and close (B) margin effect sizes. The dashed vertical line represents the overall measure of effect.

As previously mentioned, the prognostic significance of close margins is less defined, with fewer studies supporting a cutoff of < 5 mm as the most effective for survival. Our systematic review and meta-analysis found a significant difference in OS between close and negative margins, but no significant difference in DFS or DSS.

The significance of close margins may vary across different anatomical subsites within the oral cavity. Sheahan et al.^{52,53} suggested that, in their analysis of 342 patients with OCSCC, close margins were associated with significantly worse DFS in tongue cancers, but not in non-tongue cancers.

Tumour biology may also play a role in defining the cutoff for close margins. Köhler et al.⁵² showed that margins of 1.7 mm are sufficient for patients with WPOI types 1-3, while those with WPOI types 4-5 require significantly wider margins.

However, the literature still lacks consensus on a 5 mm cutoff for close margins, with many studies presenting a variety of possible alternatives^{8,15,54,55}. While adjuvant therapy is routinely indicated for positive margins, the necessity of such treatment for close margin remains topic of discussion. Kim et al.⁴⁹ observed that while close margins are considered a risk factor, they do not always require adjuvant treatment. Similarly, Szewczyk et al.³⁵ pointed out that the precise risk associated with close margins has yet to be clearly defined, resulting in uncertainty about the need for adjuvant treatment(s).

These factors collectively underscore the complexity of analysing the significance of close margins in OCSCC, the need for a consensus on management, and for more detailed and biology-driven definitions to better understand their prognostic significance. Examining single factors individually does not fully capture the complexity of patient outcomes. Future research should focus on creating integrated models that combine different prognostic factors to improve survival prediction and informed treatment choices.

This meta-analysis aims to comprehensively assess survival outcomes based on surgical margin status with defined cutoffs of > 5 mm, 1-5 mm, and < 1 mm. The rigorous approach enhances the clarity of findings, offering valuable insights to guide clinical decision-making and improve patient outcomes.

This study has several limitations. First, due to the inherent nature of systematic reviews and meta-analyses, nearly all the included studies were single-centre retrospective cohorts, making them susceptible to various biases. Additionally, the inability to conduct a stratified analysis based on the primary tumour subsite further limits the findings, as subsite-specific differences could significantly affect survival outcomes. The lack of a standardised adjuvant therapy

protocol across all included studies results in an imbalance in the treatment volume received by different patients. Further multicentre prospective studies with stratification by primary tumour subsite are needed to better define survival outcomes and indications for adjuvant therapy, especially for close margins. Moreover, the limited number of studies included in the DSS sub-analysis weakens the statistical power of the findings.

Conclusions

This systematic review and meta-analysis underscore the significant impact of surgical margin status on survival outcomes in OCSCC. While positive margins were consistently associated with poorer outcomes, the prognostic implications of close margins remain less conclusive. Further research is warranted to better understand the role of close margins in this patient population and to determine the optimal adjuvant treatment(s) approach.

Conflict of interest statement

The authors declare no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

EB: data collection, contribution to manuscript drafting; GMP: data collection, statistical analysis, manuscript writing; FM: study conceptualization, manuscript writing; AP: study conceptualization, contribution to data collection, critical revision of the manuscript; CZ: data collection, contribution to manuscript writing; AP: data collection, contribution to manuscript writing; GM: supervision of study design, final critical revision of the manuscript; GP: supervision of research process, final critical revision of the manuscript; GS: senior oversight, supervision of overall study, final critical revision of the manuscript; AI: study conceptualization, manuscript writing.

Ethics approval

Ethics approval was not required for this study since all reported data were obtained from the available published literature and all patients were deidentified.

Patient consent

Informed consent was not required for this study since all reported data were obtained from the available published literature and all patients were deidentified.

Data availability

Data are available from the corresponding author upon reasonable request

Ethical consideration

Not applicable.

References

- 1 Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394-424. <https://doi.org/10.3322/caac.21492>
- 2 Bryazka D, Reitsma MB, Abate YH, et al. Forecasting the effects of smoking prevalence scenarios on years of life lost and life expectancy from 2022 to 2050: a systematic analysis for the global burden of disease study 2021. *Lancet Public Health* 2024;9:E729-E744. [https://doi.org/10.1016/S2468-2667\(24\)00166-X](https://doi.org/10.1016/S2468-2667(24)00166-X)
- 3 Ferlay J, Colombet M, Soerjomataram I, et al. Cancer statistics for the year 2020: an overview. *Int J Cancer* 2021;149:778-789. <https://doi.org/10.1002/ijc.33588>
- 4 Zaroni DK, Montero PH, Migliacci JC, et al. Survival outcomes after treatment of cancer of the oral cavity 1985-2015. *Oral Oncol* 2019;90:115-121. <https://doi.org/10.1016/j.oraloncology.2019.02.001>
- 5 Orosco RK, Tapia VJ, Califano JA, et al. Positive surgical margins in the 10 most common solid cancers. *Sci Rep* 2018;8:5686. <https://doi.org/10.1038/s41598-018-23403-5>
- 6 Helliwell T, Woolgar J. Standards and minimum datasets for reporting common cancers. Minimum dataset for head and neck histopathology reports. London: The Royal College of Pathologists; 1998.
- 7 Young K, Bulosan H, Kida CC, et al. Stratification of surgical margin distances by the millimeter on local recurrence in oral cavity cancer: a systematic review and meta-analysis. *Head Neck* 2023;45:1305-1314. <https://doi.org/10.1002/hed.27339>
- 8 Zaroni DK, Migliacci JC, Xu B, et al. A proposal to redefine close surgical margins in squamous cell carcinoma of the oral tongue. *JAMA Otolaryngol Head Neck Surg* 2017;143:555-560. <https://doi.org/10.1001/jamaoto.2016.4238>
- 9 Mishra A, Das A, Dhal I, et al. Worst pattern of invasion in oral squamous cell carcinoma is an independent prognostic factor. *J Oral Biol Craniofac Res* 2022;12:771-776. <https://doi.org/10.1016/j.jobcr.2022.08.027>
- 10 Liu C, Wang M, Zhang H, et al. Tumour microenvironment and immunotherapy of oral cancer. *Eur J Med Res* 2022;27:198. <https://doi.org/10.1186/s40001-022-00835-4>
- 11 Baba A, Hashimoto K, Kayama R, et al. Radiological approach for the newly incorporated T staging factor, depth of invasion, of the oral tongue cancer in the 8th edition of American Joint Committee on Cancer Staging Manual: assessment of the necessity for elective neck dissection. *Jpn J Radiol* 2020;38:821-832. <https://doi.org/10.1007/s11604-020-00982-w>
- 12 Kale AD, Angadi PV. Tumour budding is a potential histopathological marker in the prognosis of oral squamous cell carcinoma: current status and future prospects. *J Oral Maxillofac Pathol* 2019;23:318-323. https://doi.org/10.4103/jomfp.JOMFP_331_19
- 13 Brandwein-Gensler M, Smith RV, Wang B, et al. Validation of the histologic risk model in a new cohort of patients with head and neck squamous cell carcinoma. *Am J Surg Pathol* 2010;34:676-688. <https://doi.org/10.1097/PAS.0b013e3181d95c37>
- 14 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:N71. <https://doi.org/10.1136/bmj.n71>
- 15 Brinkman D, Callanan D, O'Shea R, et al. Impact of 3 mm margin on risk of recurrence and survival in oral cancer. *Oral Oncol* 2020;110:104883. <https://doi.org/10.1016/j.oraloncology.2020.104883>
- 16 National Institute for Health and Care Excellence. Methods for the development of NICE public health guidance. Process and Methods Guides No. 4. 2012;2012:284.
- 17 McGrath S, Zhao XF, Qin ZZ, et al. One-sample aggregate data meta-analysis of medians. *Stat Med* 2019;38:969-984. <https://doi.org/10.1002/sim.8013>
- 18 Veroniki AA, Jackson D, Viechtbauer W, et al. Methods to estimate the between-study variance and its uncertainty in meta-analysis. *Res Synth Methods* 2016;7:55-79. <https://doi.org/10.1002/jrsm.1164>
- 19 Jackson D, White IR, Riley RD. Quantifying the impact of between-study heterogeneity in multivariate meta-analyses. *Stat Med* 2012;31:3805-3820. <https://doi.org/10.1002/sim.5453>
- 20 Wood SN. Fast stable restricted maximum likelihood and marginal likelihood estimation of semiparametric generalized linear models. 2010. <https://doi.org/10.1111/j.1467-9868.2010.00749.x>
- 21 Friede T, Kieser M. A refined method for the meta-analysis of controlled clinical trials with binary outcome. *Stat Med* 2001;20:3875-3889. <https://doi.org/10.1002/sim.1009>
- 22 Egger M, Smith GD, Schneider M, et al. Papers bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-634. <https://doi.org/10.1136/bmj.315.7109.629>
- 23 Chang WC, Chang CF, Li YH, et al. A histopathological evaluation and potential prognostic implications of oral squamous cell carcinoma with adverse features. *Oral Oncol* 2019;95:65-73. <https://doi.org/10.1016/j.oraloncology.2019.06.012>
- 24 Kanatas A, Walshaw EG, Wu J, et al. Prognostic factors in oral cancer surgery: results from a UK tertiary centre. *Eur J Surg Oncol* 2023;49:755-759. <https://doi.org/10.1016/j.ejso.2022.11.595>
- 25 Panda S, Kumar R, Chandran CA, et al. Impact of skin invasion on long-term survival outcomes in gingivobuccal complex carcinoma. *Acta Otorinolaringol Esp* 2021;72:205-211. <https://doi.org/10.1016/j.otorri.2020.04.006>
- 26 Pandey M, Bindu R, Soumithran CS. Results of primary versus salvage surgery in carcinoma of the buccal mucosa. *Eur J Surg Oncol* 2009;35:362-367. <https://doi.org/10.1016/j.ejso.2008.02.008>
- 27 Solomon J, Hinthar A, Matthews TW, et al. The impact of close surgical margins on recurrence in oral squamous cell carcinoma. *J Otolaryngol Head Neck Surg* 2021;50:9. <https://doi.org/10.1186/s40463-020-00483-w>
- 28 Veiga-San Roman P, Villanueva San Vicente V, Rodriguez-Gonzalez MA, et al. Survival among treated tongue cancer patients: a single-center experience. *Discov Oncol* 2024;15:127. <https://doi.org/10.1007/s12672-024-00989-z>
- 29 Bera RN, Tripathi R. Survival outcomes and factors affecting survival in resectable locally advanced oral squamous cell carcinoma. *Indian J Otolaryngol Head Neck Surg* 2023;75:607-616. <https://doi.org/10.1007/s12070-022-03404-7>
- 30 Chen TC, Wang CP, Ko JY, et al. The impact of pathologic close margin on the survival of patients with early stage oral squamous cell carcinoma. *Oral Oncol* 2012;48:623-628. <https://doi.org/10.1016/j.oraloncology.2012.01.015>
- 31 Jain PV, Sharan R, Manikantan K, et al. Redefining adequate margins in oral squamous cell carcinoma: outcomes from close and positive margins. *Eur Arch Otorhinolaryngol* 2020;277:1155-1165. <https://doi.org/10.1007/s00405-019-05779-w>

- ³² Kamalakkannan S, Rajan F, Shanmugam J, et al. Margin status, adjuvant treatment and recurrence in buccal cancer. *Oral Oncol* 2024;156:106927. <https://doi.org/10.1016/j.oraloncology.2024.106927>
- ³³ Lee LY, Lin CY, Cheng NM, et al. Poor tumour differentiation is an independent adverse prognostic variable in patients with locally advanced oral cavity cancer: comparison with pathological risk factors according to the NCCN guidelines. *Cancer Med* 2021;10:6627-6641. <https://doi.org/10.1002/cam4.4195>
- ³⁴ Lu HJ, Chiu YW, Peng CY, et al. Parameters to assess the necessity of adjuvant therapy for early-stage oral squamous cell carcinoma. *Oral Dis* 2024 Sept 3 [Online Ahead of Print]. <https://doi.org/10.1111/odi.15123>
- ³⁵ Szewczyk M, Pazdrowski J, Pieńkowski P, et al. A matter of margins in oral cancer: how close is enough? *Cancers (Basel)* 2024;16:1488. <https://doi.org/10.3390/cancers16081488>
- ³⁶ Kowalski LP. Eugene Nicholas Myers' lecture on head and neck cancer, 2020: the surgeon as a prognostic factor in head and neck cancer patients undergoing surgery. *Int Arch Otorhinolaryngol* 2023;27:E536-E546. <https://doi.org/10.1055/s-0043-1761170>
- ³⁷ Moratin J, Horn D, Oehme M, et al. Variation of resection margins in oral cancer in dependence of tumour stage and subsite – a retrospective cohort study. *Clin Oral Investig* 2024;28:327. <https://doi.org/10.1007/s00784-024-05711-5>
- ³⁸ Brinkman D, Callanan D, Jawad H, et al. Comparison of Royal College of Pathologists and College of American Pathologists definition for positive margins in oral cavity squamous cell carcinoma. *Oral Oncol* 2022;127:105797. <https://doi.org/10.1016/j.oraloncology.2022.105797>
- ³⁹ Bajwa MS, Houghton D, Java K, et al. The relevance of surgical margins in clinically early oral squamous cell carcinoma. *Oral Oncol* 2020;110:104913. <https://doi.org/10.1016/j.oraloncology.2020.104913>
- ⁴⁰ Varvares MA, Poti S, Kenyon B, et al. Surgical margins and primary site resection in achieving local control in oral cancer resections. *Laryngoscope* 2015;125:2298-2307. <https://doi.org/10.1002/lary.25397>
- ⁴¹ Loree TR, Strong EW, York N. Significance of positive margins in oral cavity squamous carcinoma. *Am J Surg* 1990;160:410-414. [https://doi.org/10.1016/s0002-9610\(05\)80555-0](https://doi.org/10.1016/s0002-9610(05)80555-0)
- ⁴² Sutton DN, Brown JS, Rogers SN, et al. The prognostic implications of the surgical margin in oral squamous cell carcinoma. *Int J Oral Maxillofac Surg* 2003;32:30-34. <https://doi.org/10.1054/ijom.2002.0313>
- ⁴³ Iandelli A, Gabella G, Marchi F, et al. The impact of margins in laryngeal cancer patients treated with transoral laser microsurgery: a systematic review and meta-analysis. *Eur Arch Otorhinolaryngol* 2024;281:4485-4494. <https://doi.org/10.1007/s00405-024-08610-3>
- ⁴⁴ McMahon JD, Devine JC, Hetherington J, et al. Involved surgical margins in oral and oropharyngeal carcinoma: an anatomical problem? *Br J Oral Maxillofac Surg* 2011;49:172-175. <https://doi.org/10.1016/j.bjoms.2010.02.014>
- ⁴⁵ Binahmed A, Nason RW, Abdoh AA, et al. The clinical significance of the positive surgical margin in oral cancer. *Oral Oncol* 2007;43:780-784. <https://doi.org/10.1016/j.oraloncology.2006.10.001>
- ⁴⁶ National Comprehensive Cancer Network. Head and Neck Cancers (Version 2.2025). https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed January 17, 2025.
- ⁴⁷ Prasad K, Sharma R, Habib D, et al. How often is cancer present in oral cavity re-resections after initial positive margins? *Laryngoscope* 2024;134:717-724. <https://doi.org/10.1002/lary.30959>
- ⁴⁸ Scholl P, Byers RM, Batsakk JG, et al. Microscopic cut-through of cancer in the surgical treatment of squamous carcinoma of the tongue prognostic and therapeutic implications. *Am J Surg* 1986;152:354-360. [https://doi.org/10.1016/0002-9610\(86\)90304-1](https://doi.org/10.1016/0002-9610(86)90304-1)
- ⁴⁹ Kim JY, Kim Y, Kim EH, et al. Initial negative resection margin versus revised negative resection margin in patients who underwent surgery without adjuvant therapy for early-stage oral tongue squamous cell carcinoma. *Oral Oncol* 2024;159:107046. <https://doi.org/10.1016/j.oraloncology.2024.107046>
- ⁵⁰ Herman MP, Dagan R, Amdur RJ, et al. Postoperative radiotherapy for patients at high risk of recurrence of oral cavity squamous cell carcinoma. *Laryngoscope* 2015;125:630-635. <https://doi.org/10.1002/lary.24938>
- ⁵¹ Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (#9501). *Head Neck* 2005;27:843-850. <https://doi.org/10.1002/hed.20279>
- ⁵² Köhler HF, Vartanian JG, Pinto CAL, et al. The impact of worst pattern of invasion on the extension of surgical margins in oral squamous cell carcinoma. *Head Neck* 2022;44:691-697. <https://doi.org/10.1002/hed.26956>
- ⁵³ Sheahan P, Callanan D, van den Berg N, et al. Impact of close margins on oral cancer outcomes according to the oral subsite. *Head Neck* 2024; Online ahead of print. <https://doi.org/10.1002/hed.28024>
- ⁵⁴ Nason RW, Binahmed A, Pathak KA, et al. What is the adequate margin of surgical resection in oral cancer? *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009;107:625-629. <https://doi.org/10.1016/j.tripleo.2008.11.013>
- ⁵⁵ Ettl T, El-Gindi A, Hautmann M, et al. Positive frozen section margins predict local recurrence in R0-resected squamous cell carcinoma of the head and neck. *Oral Oncol* 2016;55:17-23. <https://doi.org/10.1016/j.oraloncology.2016.02.012>