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Influence of primary tumor surgical margins on overall survival and local recurrence in patients with squamous cell carcinoma: meta-analysis

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SUMMARY

Aim. The aim of this meta-analysis was to determine the influence of surgical margins on the prognostic parameters of patients with oral squamous cell carcinoma.

Materials and methods. The literature review was carried out according to PRISMA principles and the database search was performed using following keywords: "Carcinoma, Squamous Cell (Mesh)", "Squamous Cell Carcinoma of Head and Neck (Mesh)", "Margins of Excision (Mesh)". The review included studies with humans, published in English, no longer than 10 years ago, in which patients underwent resection of the primary tumour and the resections were examined histologically and the margins between healthy tissues and tumour were speicified.

Results. 5 of the included studies examined the impact of surgical margins on overall survival and 10 on local recurrence. In all 5 studies, surgical margins were considered an effective prognostic indicator for the overall survival. Examining the impact of surgical margins on the local recurrence, 7 studies indicated that it is an effective prognostic parameter. Quantitative analysis of the data revealed that a 3 mm surgical margin was safe.

Conclusions. Primary tumor surgical margins are an effective prognostic parameter for the overall survival and the local recurrence in patients with oral squamous cell carcinoma. 3 mm surgical margins can be concidered as a safe distance and minimum acceptable separation point between close and involved margins.

Keywords: Oral squamous cell carcinoma, primary tumor surgical margins, overall survival, local recurrence.

INTRODUCTION

Oral squamous cell carcinoma is a rapidly spreading aggressive disease which affects approximately 300,000 people worldwide every year (1). It is the most common cancer found in the oral cavity, accounting for 90 percent of all malignancies of oral cavity (2). According to Karnov *et al.*, even though overall 5-year survival rate has increased by 12 percent during the past 30 years, the number of cases per 100,000 people has increased slightly less than 80% (3).

The main course of oral squamous cell carcinoma treatment is surgical resection of the tumour, optionally with the addition of adjuvant treatment (radiotherapy or chemotherapy). The aim of the surgical resection is to completely remove the tumour, including healthy adjacent tissues, leaving no viable cancer cells. In 1998, the Royal College of Pathologists published guidelines for safe resection limits, which stated that <1 mm resection margins of the tumour were considered very close, a distance of 1–5 mm was considered close, and >5mm was considered a clear margins (4). 5mm distance is considered optimal when performing surgical tumour resection, therefore optimal distance within the resection limits ensures the best prognosis for overall survival and local recurrence (5, 6). In addition, usually with >5mm margins, adjuvant treatment is not indicated.

In some cases, >5mm margins are surgically difficult to obtain due to important anatomical structures, tumour size, location, macroscopically unnoticeable and intangible cancerous tissues (7). In the literature, the concept of safe margins has recently become controver-

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sial, with questions raised about whether a 5 mm margin can truly be considered safe (6, 8). Several studies indicated alternative demarcation points such as 2.2 mm (9), 3 mm (10) without finding any statistically significant difference in prognostic parameters compared with 5 mm. For some patients, smaller surgical margins could potentially dismiss adjuvant treatment. Therefore, the aim of this meta-analysis was to determine the influence of surgical margins on the prognostic parameters of patients with oral squamous cell carcinoma.

MATERIAL AND METHODS

Methods

A systematic review was based on the PRISMA guidelines. The protocol for the systematic review was registered in PROSPERO (International prospective register of systematic reviews) database. Registration number: CRD42022325612.

The focused question for this study was developed according to PICOS model, based on the patient, intervention, control and result:

- Population (P) – Patients who underwent primary tumour resection in oral squamous cell carcinoma
- Intervention/Exposure to risk factor (I) – Primary tumour resection margins are close or involved
- Control (C) – Primary tumour resection margins are clear.
- Outcome (O) – Local recurrence

What effect do the margins of primary tumour resection have on the local recurrence?

Search strategy

The search for scientific articles was conducted using PubMed, ScienceDirect, Wiley Online Library, and LILACS databases. Electronic database search was performed using following keywords: "Carcinoma, Squamous Cell (Mesh)," "Squamous Cell Carcinoma of Head and Neck (Mesh)," "Margins of Excision (Mesh)". A unique keyword combination and search strategy was used for each database. Reference lists of selected scientific articles were also analysed.

Eligibility criteria

Inclusion criteria:

1. Studies in which patients have oral squamous cell carcinoma and the resection of the primary tumour was performed;
2. Studies indicating whether additional radiotherapy, chemotherapy or radiotherapy and chemotherapy treatment after initial surgical treatment was applied;
3. Studies in which tumours are examined histologically and the boundaries of healthy tissue-tumour are specified;
4. Studies investigating the effect of resection margins on local recurrence and overall patient survival;
5. Studies in which the follow-up time was at least 2 years.

Exclusion criteria:

1. Studies of patients with non-squamous cell carcinoma, or non-oral squamous cell carcinoma, or not primary tumour;
2. Studies involving patients who had undergone prior surgical treatment for squamous cell carcinoma, radiotherapy, or chemotherapy;
3. Studies that do not accurately describe and compare primary tumour resection limits;
4. Literature reviews, meta-analyzes, clinical case studies, conference reports, abstracts and master's theses, dissertations;
5. Patients with distant metastases.

Study selection and data collection process

An independent author (A.V.) conducted an electronic search and selected studies with titles and abstracts that appeared to meet the eligibility criteria for the review. Subsequently, studies with appropriate titles and abstracts were further evaluated for potential inclusion based on the criteria. During the final selection process, full-text articles were assessed, and only those meeting the inclusion criteria were included.

Methodological quality

The risk of bias was assessed using ROBINS-I tool (11) for retrospective cohort studies. This tool was used to assess possible research errors in terms of patient selection, classification of interventions, deviation from the intended intervention, missing outcome data, measurement of results, selection of published results.

Synthesis of results

The systematic literature review was performed according to PRISMA (Preferred Reporting Item for Systematic Review and Meta-Analyses) criteria (12). The entire chronology of the selection of scientific articles was documented using a PRISMA flow chart. After completing the search for scientific articles, the following data were collected for each study: main author, year of publication, study type, sample size, mean age distribution, distance from primary tumour resection, local tumour recurrence, overall patient survival, patient follow-up time. The primary variables in this systematic review of the literature were primary

tumour resection margins (mm), local tumour recurrence (%) and overall patient survival (%).

A meta-analysis was performed using the Review Manager 5.4.1 computer program. Heterogeneity of the studies was determined by Cochran's Q and I2 tests. I2 test values were interpreted according to Higgins *et al.*: 0% to 40% heterogeneity not relevant, 30% to 60% moderate heterogeneity, 50% to 90% strong heterogeneity, 75% to 100% significant heterogeneity (13). In interpreting the I2 test value, attention was also paid to the value of P, which indicates the statistical significance of heterogeneity. Separate meta-analyses were performed to compare the effect of clear, close, and involved margins on primary tumour resection on local tumour recurrence. A meta-analysis was also performed to compare smaller tumour resection baselines (2 and 3 mm) with the optimal tumour resection baseline (5 mm). In the meta-analysis, the magnitude of the effect was assessed by calculating the odds ratio and confidence intervals (95% p.i.). The effect measure was calculated using a random effects model, in which the results of the studies are summarized according to the inverse variance method.

RESULTS AND DISCUSSION

Study selection

3401 scientific articles were identified after searching with keywords and activating filters in the databases. After removing duplicates, 2948 studies remained. After reviewing the titles and abstracts of scientific publications, 16 articles were selected for full-text analysis. When the selection criteria were applied, 10 (9, 10, 14-21) scientific articles were included in the analysis of qualitative data, 6 (16-21) of them were included in the quantitative data analysis. 3 publications were rejected because patients underwent radiotherapy prior to surgery (22-24), 1 study was rejected because it was not limited to squamous cell carcinoma (25), 2 publications were rejected because no data were available on the margins of the tumour resection (26, 27). The detailed process of searching for scientific articles is depicted in the methodological diagram of PRISMA Flow (Figure 1).

Characteristics of included studies

10 scientific articles were included in the systematic review. All included studies were retrospective studies. A total of 2,780 patients were studied, ranging from 53 to 669 subjects. The mean age of the patients ranged from 50 to 63.6 years. In all studies, the minimum period of clinical follow-up was greater than 24 months, while the longest mean follow-up was 120 months. In 1 scientific article, the localization of the primary tumour was in the lining of the tongue, 1 in the buccal mucosa, 1 in the mucosa of the alveolar ridge, and the remaining 7 in all areas of the mouth. The dependence of local recurrence on the distance of the primary tumour resection was evaluated in all included publications, and the dependence of the overall survival on the distance of the primary tumour resection was evaluated in 8 out of 10 publications. The most relevant research characteristics are selected and placed in the tables, which can be found in Tables 1 and 2. They analysed: main author, year of publication, year of retrospective inclusion, number of patients, mean age, time of clinical follow-up, tumour localization, stage T (T1-2 and T3-4), stage N (N0 and N1-3), treatment (surgical and surgical and adjuvant), evaluation criteria (local recurrence and overall survival), margins of primary tumour resection.

Risk of bias of the included studies

The assessment of risk of bias in the included studies was performed using ROBINS-I tool for retrospective cohort studies. 9 (9, 10, 14-17, 19-21) of the included studies had a low risk of bias, while 1 study (18) had a moderate risk of bias. A detailed assessment of the risk of bias is presented in Figure 2.

Qualitative synthesis of results

Factors affecting the margins of primary tumour resection

Three studies included in the systematic review investigated the influence of various factors on the margins of primary tumour resection (10, 16, 21). Three studies investigated the dependence of resection margins on the T stage (10, 16, 21), two on the degree of tumour differentiation (16, 21), and one on the depth of tumour invasion and tumour diameter (16).

In two articles no statistically significant correlation was found between T stage and the margins of primary tumour resection, while one study found the relationship statistically significant. Priya *et al.* (21) concluded that resection margins decrease with advanced T stage, however the correlation is not statistically significant (p=0.193). Bajwa *et al.* (16) also found no statistically significant relationship between tumour resection margins and T stage (p=0.13). On the other hand, in the study conducted by Brinkman *et al.* (10), the results showed that tumour resection margins were statistically significantly smaller for patients with advanced T stage compared to those with less advanced T stage.

A study by Priya *et al.* (21) indicated that the risk of involved tumour margins increased with a lower degree of tumour differentiation, but no statistically significant difference was found (p=0.5). A study by

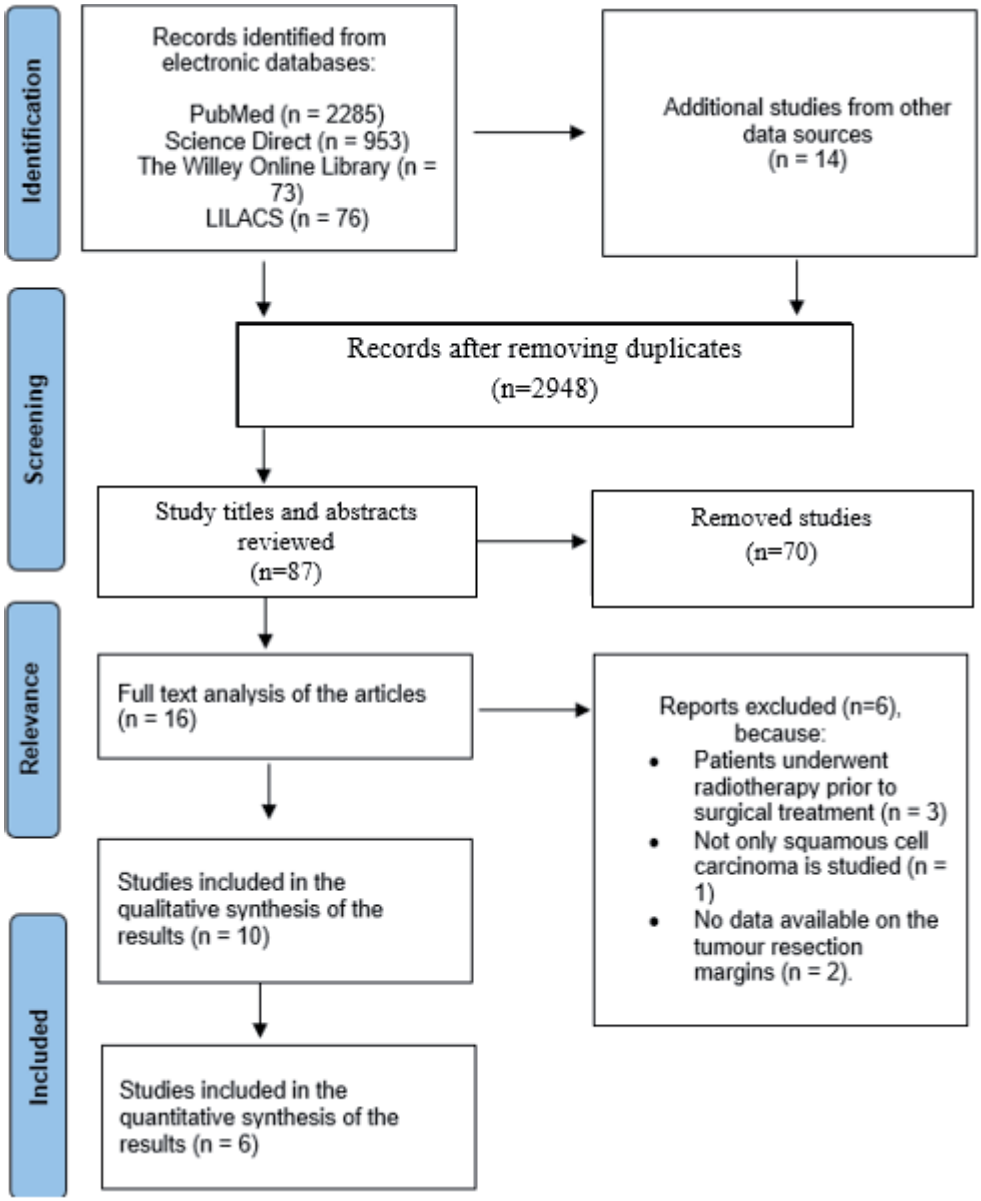

Fig. 1. PRISMA flow diagram

Bajwa *et al.* (16) also suggested that there is no significant difference between well-differentiated and less differentiated tumours, therefore the degree of tumour differentiation cannot be considered as a prognostic tool to predict tumour resection limits.

A study by Bajwa *et al.* (16) investigated the relationship between the distance of the primary tumour resection margins, the tumour diameter and invasion depth. The results indicated that there is a statistically significant inverse correlation between the two variables – the larger the tumour diameter and the depth of invasion, the smaller resection margins at $p < 0.01$.

The effect of primary tumour resection margins on overall survival rates

Five studies (10, 14, 16, 17, 20) included in the systematic review of the literature investigated the effect of tumour resection margins on overall patient survival. Brinkman *et al.* (16) investigated the dependence of overall survival on the intervals of resection margins, which were divided into intervals increasing by one millimetre. The results were displayed using the risk ratio (RS) and the Kaplan-Meier survival curve. Using 3 mm as a reference, a statistically significant difference was found between adjacent categories (1-2.9 mm and >3 mm) in overall survival, but no statistical significance was found when using 2 mm as a reference.

In two articles primary tumour resection margins were divided into clear (≥5 mm), close (1-4.9 mm) and involved (0 mm) margins (14, 20). In the first study (14), clear and close margins had similar overall survival results over 5 years, 74% and 77%, respectively.

Table 1. General characteristics of the selected studies

Author, year of publication	Year of retrospective inclusion	Number of patients	Mean age (years)	Follow up time (months)	Tumour localisation
Chiou 2010	2000 - 2008	110	53.7	25 (mean)	Buccal mucose
Hoffmannova 2010	1994 - 2004	147	59.4	120 (mean)	All areas
Priya 2012	2003 - 2003	306	50	26.5 (mean)	All areas
Dillon 2015	1995 - 2012	54	60.5	47 (mean)	All areas
Stathopoulos 2017	1995 - 2006	53	56.3	>60	All areas
Tasche 2017	2005 - 2014	432	62.14	>24	All areas

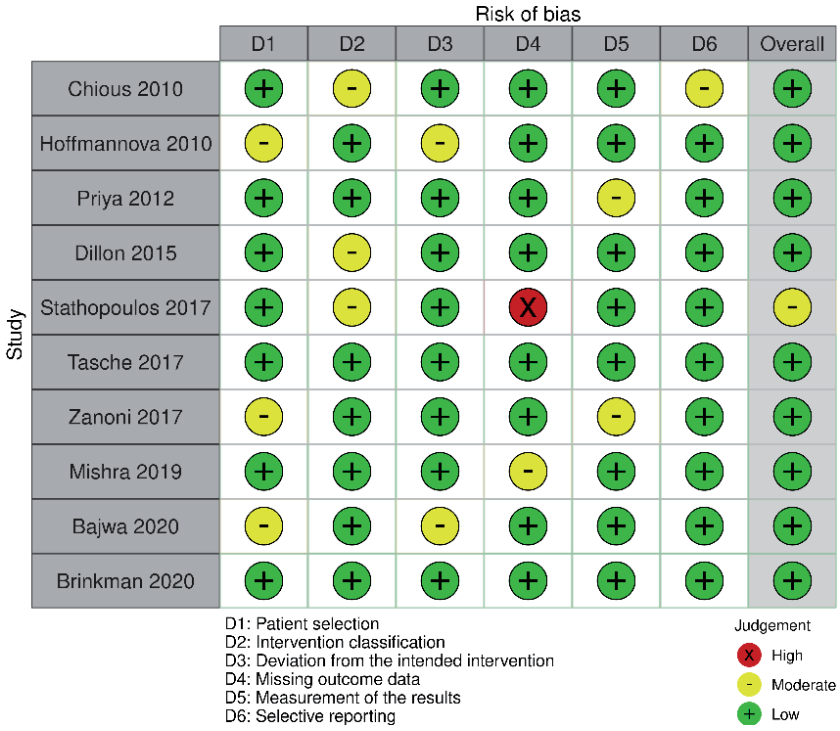

Fig. 2. Quality assessment

On the other hand, the involved margins had a much lower overall survival rate of 63%, and this difference was statistically significant (p<0.05). In the second study (20), the overall 5-year survival in the group of patients who underwent primary tumour resection with clear margins was 48%, compared with 24% and 18% in the close and involved margin groups, respectively. The difference between clear and close resection margins was statistically significant (p=0.024), as was the difference between close and involved margins (p = 0.006). In the study by Dillon *et al.* (14), the margins of tumour resection were divided into clear (≥5 mm), close (1–4.9 mm), and very close (0.1–1 mm). Overall 2-year survival rate was highest in patients with clear resection margins compared with close or very close resection margins. The results were 78%, 62% and 50% respectively and the difference between the groups was not statistically significant (p=0.093). Meanwhile, Mishra *et al.* (17) determined that there is no statistically significant difference on overall patient survival rates between 5.6-7 mm and >7 mm resection margins (p<0.589).

The influence of primary tumour resection margins on local recurrence

Ten of the included studies investigated the relationship between primary tumour resection margins and local recurrence (9,10,14-21). In all ten studies, the inverse relationship between local recurrence and resection margin distance was demonstrated: the greater the resection margin distance, the lower the chance of local recurrence.

In two studies included in the systematic review of the literature, the Kaplan-Meier survival curve was used, with the first study (10) using 3 mm and the second (9) using 2.2 mm as a reference point. In the first study, a statistically significant difference was found between adjacent categories (1-2.9 mm and >3 mm) for local recurrence, RS=2.00 (95% CI 1.04, 4.03). In a second study using ROC curve analysis, the optimal tumour resection margins were estimated to be 2.2 mm. In the Kaplan-Meier analysis, this distance was compared to the traditionally optimal distance of 5 mm. At 2 years, the absolute difference between the 2.2-5 mm and >5 mm groups for local recurrence was 1.7%, which was not statistically significant (p>0.05).

Multivariate Cox regression model was used in two studies included in the systematic review of literature (14, 16). In the first article (14), patients with clear resection margins were found to have a

Table 2. General characteristics of the selected studies

Author, year of publication	T stage		N stage		Treatment		Evaluation criteria		Resection margins of primary tumour resection
	T1-2	T3-4	N0	N1-3	S*	S+A**	LR***	OS****	
Chiou 2010	63.6%	36.4%	76.4%	23.6%	29.1%	70.9%	+	+	1, 2, 3, 4, 5 mm
Hoffmannova 2010	48.9%	51.1%	51.7%	48.3%	0%	100%	+	+	0 mm, 0.1-5 mm, >5 mm
Priya 2012	54.6%	45.4%	53.3%	40.5%	34.7%	65.3%	+	+	<1 mm, 1-5 mm, >5 mm
Dillon 2015	46%	54%	50%	50%	28%	72%	+	+	<1 mm, 1-5 mm, >5 mm
Stathopoulos 2017	-	-	-	-	100%	0%	+	-	1-5 mm, >5 mm
Tasche 2017	66%	34%	70%	30%	59%	41%	+	-	0, 1, 2, 3, 4, 5 mm, >5 mm
Zanoni 2017	86.1%	13.9%	72.2%	27.8%	75.1%	24.9%	+	+	0 mm, 0.1-2.2 mm, 2.3-5 mm
Mishra 2019	46.6%	53.4%	60.2%	39.8%	0%	100%	+	+	0, 1, 2, 3, 4, 5, 6, 7 mm, ≥8 mm
Bajwa 2020	95.9%	4.1%	73.3%	26.7%	71.5%	28.5%	+	+	0 mm, 0.1-0.9 mm, 1-5 mm, >5 mm
Brinkman 2020	61.5%	38.5%	42.2%	57.8%	53.3%	46.7%	+	+	<1 mm, 1-5 mm, >5 mm

*S – surgical; ** S+A – surgical+adjuvant, *** LR – local remission, ****OS – overall survival.

statistically significantly (p=0,01) lower risk of local recurrence compared to patients with very close margins – RS=0.22 (95% CI, 0.07-0.71), whereas the difference between close and very close margin groups was not statistically significant (p=0.27) although patients with close resection margins had a lower risk of local recurrence – RS=0.68 (95% CI, 0.34-1.36). The second study (16) showed that the risk of local recurrence with close resection margins was similar to clear resection margins RS=0.99 (95% CI 0.50-1.95). However, involved margins had significantly worse results, when RS=5.01 (95%CI 2.02-12.39).

Four studies compared clear, close and involved resection margins and their influence on local recurrence (14, 16, 20, 21). Two studies found that the incidence of local recurrence was statistically significantly lower in patients with clear resection margins than close, similarly the close resection margins had lower recurrence rate than involved margins (20, 21). In a study by Hoffmannova *et al.* (20), the incidence of local recurrence was 35.9% and 31.3% in patients with clear and close margins of primary tumour resection, compared with 85.7% at involved margins. In the study of Priya *et al.* (21), the incidence of local recurrence was 13.7% at clear margins, compared to 16.7% at close margins (p=0.001). With involved margins, the incidence of local recurrence was 21.3%, and the difference between the close margins was statistically significant (p=0.037). Contrary to the previous studies, Stathopolous *et al.* (18) did not find a statistically significant difference between clear and close tumour resection margins (p>0.05). Local recurrence occurred in 9.375% of patients with clear resection of the primary tumour, meanwhile with close resection margins the recurrence occurred in 14.3% of patients. In a study by Dillon *et al.* (14), 48% of patients experienced local recurrence at 2 years and 58% at 5 years. The researchers estimated that the probability to have a local recurrence within 2 years at clear, close, and involved limits was 0.22, 0.48, and 0.58, respectively and over 5 years – 0.22, 0.57, 0.71 respectively.

Quantitative synthesis of results

Meta-analysis data showed that the resection of the primary tumour within clear margins reduces the risk of local recurrence, compared to close margins, but the difference is not statistically significant (OR (odds ratio) =0.85, 95% CI=0.55, 1, 31; p=0.47), no heterogeneity was found between studies (I2=0%, p=0.75). Meanwhile, close resection margins showed a statistically significant reduction in the risk of local recurrence compared to involved margins (SD=0.23, 95% CI=0.09, 0.56; p=0.001), with moderate heterogeneity between studies (I2=50%, p=0.13).

Resection of the primary tumour at margins ≥2 mm but <5 mm showed a statistically significant increase in the risk of local recurrence compared to ≥5 mm (SD=2.22, 95% CI=1.26, 3.92; p=0.006), with moderate heterogeneity between studies (I2=56%, p=0.13).

Resection at margins ≥3 mm but <5 mm increases the risk of local recurrence compared to ≥5 mm margins but it is not statistically significant (HR=1.90, 95% CI=0.94, 3.85; p=0.07), no heterogeneity was found between studies (I2=0%, p=0.39).

Forest plot diagrams of the meta-analysis are show in Figure 3.

DISCUSSION

During the review of this systematic literature, 10 included studies were analysed (5, 6, 14-21). All studies included were retrospective and conducted only with humans. Qualitative analysis of the publications reviewed the factors influencing the primary tumour resection margins and the influence of the primary tumour resection margins on overall survival and the incidence of local recurrence. A quantitative analysis of 6 publications that were clinically and methodologically homogeneous was also performed.

3 studies have been reviewed to ascertain what factors influence the margins between resection boundaries (10, 16, 21). In all three studies, it was found that the more advanced the T classification, the lower the margins for tumour resection. However, only one study justified this difference as statistically significant (10). Two publications indicated that the degree of tumour differentiation is not a reliable prognostic indicator for determining the distance of resection margins, as no statistically significant difference was found between resection margins of high and low degree of differentiation tumours (16, 21). One of the studies studied found that tumour diameter and invasion depth could serve as an effective prognostic indicator for predicting the margins primary tumour resection (16). This confirmed fact previously reported by the Royal College of Pathologists that tumour size and invasiveness parameters can serve as reliable prognostic indicators (4).

Five studies have been used to review the dependence of overall survival on resection margins (10, 14, 16, 17, 20). Two studies examined the dependence of overall 5-year survival on clear, close, and involved margins (14, 20). The difference between close and involved margins on overall survival was reported as statistically significant in both studies, but only one study (20) found a statistically significant difference between clear and close margins. In another study, no significant difference was found between close and clear margins and their effect on overall 2-year survival (14). Brinkman *et al.* (16)

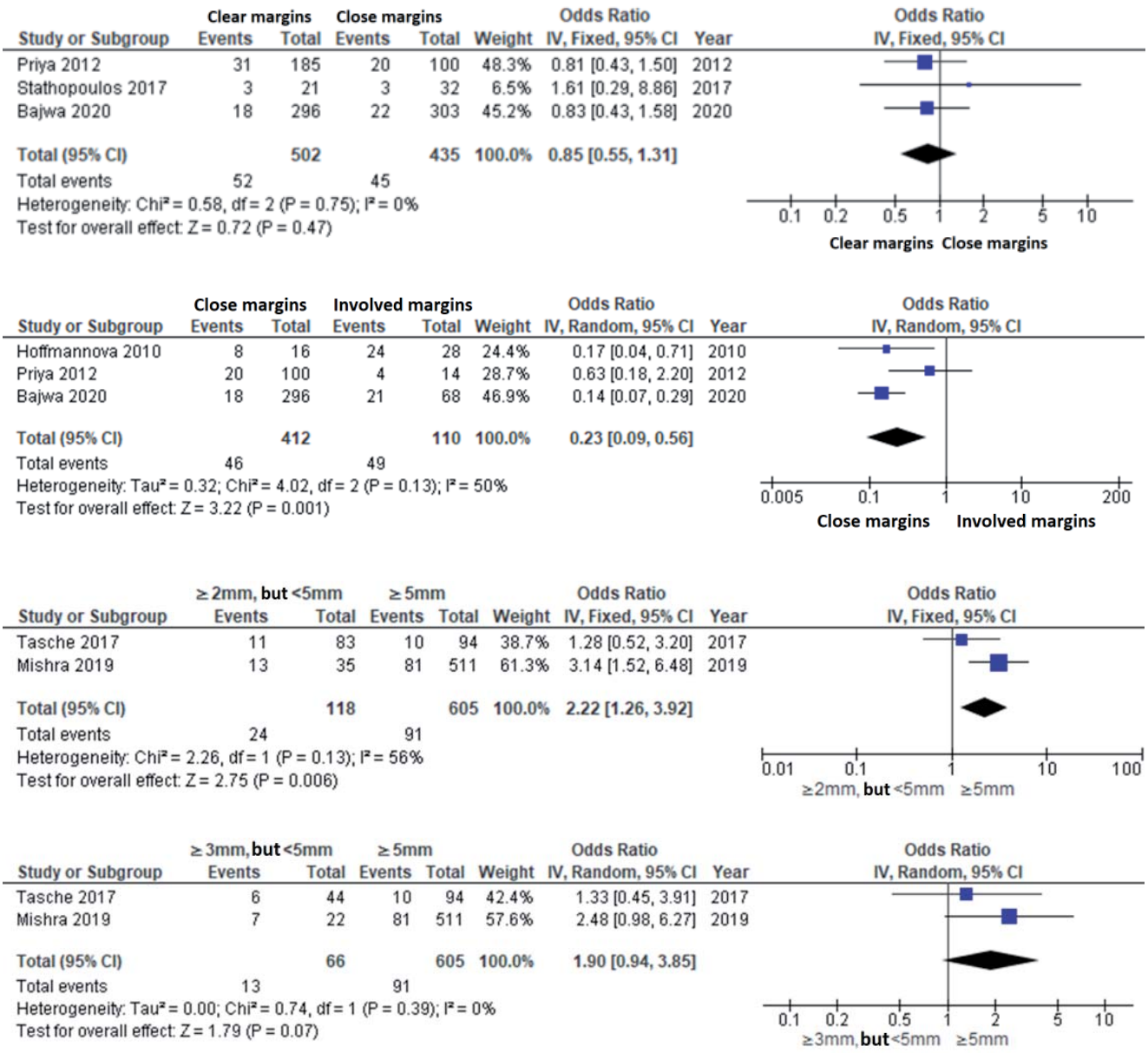

Fig. 3. Quantitative subgroup analysis

reported that if clear resection margin is considered at least 3mm, statistically significant difference on overall 2-year survival rate is observed between close and clear resection margins. When using 2 mm as reference point for determining clear resection margins, no statistically significant difference was found.

All the studies included in the systematic analysis investigated the dependence of local recurrence on the margins of the primary tumour resection (9, 10, 14-21). In two studies, results were calculated based on whether the patient received adjuvant therapy (9, 15). In one study, the reference point for clear margins was set at 3 mm (10) and in another at 2.2 mm (9). Nevertheless, both studies indicated that these limits could be considered safe given the occurrence of local recurrence within 2 years. The results of a study by Dillon *et al.* (14) showed that patients are slightly more likely to develop local recurrence if primary tumour resection is performed at close rather than clear margins. However, in contrast to the previous studies, three publications indicated that the difference between clear and close margins of tumour resection for the occurrence of local recurrence was statistically insignificant (14, 16, 18). In all studies comparing the risk of local recurrence at clear margins and involved or very close margins, the risk was found to be statistically significantly lower at clear margins (14, 16, 20, 21).

Quantitative analysis of the data with 3 studies revealed that although the risk of local recurrence after tumour resection is lower with clear rather than close margins, the difference was not statistically significant (16, 18, 21). However, at involved resection margins, the risk of local recurrence becomes significantly higher than at close margins (16, 20, 21). Quantitative

data analysis also included 2 studies investigating the effect of resection margin distance separated by 1 mm intervals on the occurrence of local recurrence (17, 19). Initially, with 2 mm as a reference point for safe margins, the margins were compared with the generally accepted optimal margins of 5 mm. In comparison, the risk of local recurrence was statistically significantly higher with 2 mm as the optimal distance. However, with using 3 mm as a reference point and compared to 5 mm, the risk of local recurrence was not statistically significantly higher, leading to the conclusion that 3 mm can be used as a safe reference point for resection.

The studies included in the systematic review of the literature did not mention the use of tobacco and alcohol by patients after treatment of oral squamous cell carcinoma. The literature suggests that these risk factors play an important role in the overall survival of patients and the onset of local relapse (3). Also, only three included publications examined the tumour localization - the mucosa of the cheek (15), the mucosa of the tongue (9), and the mucosa of the alveolar ridge of the cheek (17). It is well known that the risk of local recurrence also depends on the anatomical location of the cancer, for instance carcinoma closer to the lower jaw (6), the cheek mucosa, or the bottom of the mouth (24), showing much worse results. Another possible limitation in this study is the fact that resections sent for biopsy tend to shrink (28-30). If the tissue is fixated in a formalin solution, it may shrink up to 40-50%, which means that the 5 mm margin visible in the tissue during pathological examination should be at least 8 mm clinically. The degree of shrinkage of a tissue depends directly on the solution or substance in which it is fixated, as well as on a particular anatomical location (6, 23).

The last similar systematic review of the literature was conducted in 2015 (31). At that time, the authors found no evidence that a primary tumour resection margin of less than 5 mm could be considered safe. In this systematic review of the literature, evidence was provided that at resection margins less than 5 mm, the rates of local recurrence and overall survival may be significantly lower than at margins greater than 5 mm. As a result, it can be assumed that resection margins less than 5 mm apart can be considered safe. Clear, close, very close and involved margins can also serve as excellent prognostic indicators.

CONCLUSIONS

1. The diameter of the primary tumour and the depth of invasion were found to be significant indicators for predicting the resection margins.
2. Primary tumour resection margins were found to be an effective indicator for predicting the overall survival of the patient with oral squamous cell carcinoma.
3. Primary tumour resection margins were found to be an effective indicator for predicting the risk of local recurrence of the patient with oral squamous cell carcinoma. Additionally, 3 mm can be considered safe distance and reference point between close and clear resection margins.

CONFLICT OF INTEREST

None

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