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A meta-analysis of margin size and local recurrence in oral squamous cell carcinoma

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SUMMARY

Objectives: Excision margins for oral squamous cell carcinoma (OSCC) are poorly understood. Close (<5 mm) and involved (<1 mm) pathological margins are key indicators of the need for adjuvant treatment. This review aimed to assess the impact of pathological margin size on local recurrence rates.
Methods: MEDLINE and EMBASE were searched for studies that looked at local recurrence following excision of primary OSCC without adjuvant therapy. Five studies met the inclusion criteria.
Results: Recurrence rates were pooled to give a 21% absolute risk reduction (95% confidence interval 12–30%, $p =< 0.00001$) in local recurrence with margins clear by more than 5 mm. Unweighted pooled recurrence rates were 20% in patients with margins clear by more than 5 mm.
Conclusion: These findings suggest that a 5 mm pathological margin is the minimum acceptable margin size in OSCC.

Introduction

Oral cavity squamous cell carcinoma (OSCC) is increasingly common worldwide [1–3] and represents an increasing burden on health services. The mainstay of treatment is primary surgery, with adjuvant radiotherapy or chemotherapy used when indicated [4,5]. Adjuvant therapies are well researched with their use based on high quality evidence [6–8].

Surgery involves removal of the tumour with a margin of clinically uninvolved tissue, arbitrarily taken approximately 1 cm from the visible tumour edge [9,10], with the aim of ensuring removal of microscopic tumour extension. This is not evidence based, in contrast to cutaneous SCC, where guidelines for surgical excision are based on good quality evidence about microscopic tumour spread [11,12].

The adequacy of excision is assessed pathologically, and the pathological margin size is a major consideration in determining the need for further treatment [5]. The pathological margin is almost invariably smaller than the surgical margin due to both microscopic tumour extension and tissue shrinkage. The amount of shrinkage is yet to be accurately quantified, with figures of 9.2–75% quoted in the literature [13–15].

Guidance on pathological margins for OSCC is issued by the UK Royal College of Pathologists [16]. It categorises a margin <1 mm as involved, 1–5 mm as close and >5 mm as clear [16]. These categories do not appear to be related to risk of recurrence [9], and studies that have looked at the relationship between margin size and recurrence have shown conflicting results. Margins of <1 mm are generally acknowledged to be a poor prognosticator [17–19], but margins of other sizes have shown broad variability in their relationship with recurrence. Close margins particularly cause on-going confusion within the literature [9,20,21]. They are generally defined as having a prognostic significance as compared to clear margins, but suggested values vary, including <1.6 mm [9], 2 mm [19], 5 mm [22,23], 7 mm [24], and 10 mm [25]. Furthermore, some studies have shown no prognostic significance associated with margin size [9,22,26].

The inconsistency in findings can be attributed at least partly to varying study designs adjusting differently for various patient, tumour and treatment related factors that may or may not influence recurrence rates [17,26,27]. Common confounders include the grouping of patients with cancers of the larynx and pharynx with those of the oral cavity [9,20,21], under the umbrella term of head and neck cancer, despite the later presentation of these more posterior tumours, and their better response to radiotherapy [18]. A second issue is the combination of patients who received adjuvant radiotherapy with those who did not in analysis of margins [17,27,28]. As radiotherapy is given to reduce the risk of

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recurrence it will confound the relationship between margin and outcome. A third issue is lack of adjustment for tumour related factors, in particular markers of disease aggression such as tumour size and depth, differentiation, invasive pattern, and perineural and lymphovascular invasion, when analysing margins [22,27,28]. This is of importance as more aggressive disease may require larger margins, or adjuvant treatment, to prevent recurrence.

Furthermore, many studies use survival or locoregional recurrence as primary outcome measures [19,28–30]. Primary surgery is best assessed by its ability to prevent local recurrence, as regional or distant recurrences temporally isolated from a local recurrence are likely due to metastasis in transit at the time of, or prior to, surgery. Survival is influenced by many factors and is difficult to interpret as a marker of margin adequacy. Local recurrence rates should therefore be used as the standard measure of the effectiveness of surgery to the primary tumour.

Despite a paucity of consistent evidence about the relationship between margin size and local recurrence, close or involved margins are a key determinant of the need for adjuvant therapy [5]. Clarifying the relationship between margins and local recurrence is a priority due to the morbidity associated with both excessive surgery and unnecessary adjuvant treatment.

A systematic review has the potential to advance understanding in this area by allowing evaluation of a larger sample of patients than would be possible with primary research, whilst avoiding common confounders. As no randomised control trials in this area exist [18], a review of cohort studies, which form the majority of literature in this area, is the most appropriate method.

This review aims to determine whether a wider pathological margin reduces local recurrence rates in patients with OSCC treated by primary surgery without adjuvant therapy.

Methods

This review was undertaken in line with the 2009 PRISMA guidelines [31], using Cochrane methodology adapted for a review of cohort studies [32].

Medline and Embase were searched using the terms ‘head and neck cancer’, ‘squamous cell carcinoma’, ‘surgical procedures’ and ‘margins’. It was deliberately broad in covering all head and neck neoplasms to ensure retrieval of all relevant papers in all languages [18]. Reference lists of articles and reviews relevant to the research question were checked for further studies [32].

To be eligible for inclusion, studies must have reported outcomes from patients treated with primary surgery alone for a primary SCC of the oral cavity. Surgical specimens must have been assessed pathologically, and margins must have been reported as clear or close/involved, with definitions of the categories included in the paper. Local recurrence rates must have been reported separately for each margin category. The addition of radiotherapy and/or chemotherapy as adjuvant treatment must have been recorded, and it must have been clear which patients were given adjuvant treatment, to allow exclusion of these patients. Studies looking at salvage surgery or palliative surgery were excluded, as were studies that included data for head and neck sites other than the oral cavity, unless oral cavity data was reported separately. Papers including data from revised margins were excluded [33].

Searching identified 1165 original records. Title screening excluded 914 records and abstract screening further 183.

The manuscripts of the 68 remaining studies were obtained and were screened to determine inclusion or exclusion. Full text screening included bias assessment, based on the Cochrane group bias assessment for cohort studies [34]. Papers that were deemed to be at uncertain, medium or high risk of bias in more than four sections were excluded. Screening excluded a further 63 papers, with the most common reasons being due to a lack of separate reporting of patients given radiotherapy, and insufficient outcome data. Fig. 1 shows the exclusion of studies at each stage of the research.

Accordingly, five studies met the inclusion criteria. Data extracted comprised author, publication year, country of origin, age, sex ratio, follow up period, sample size, oral subsites, T stage, adjuvant treatment, margin category definitions, number of patients in each margin category, number of patients with local recurrence in each margin group, *p*-values (if used), and hazard ratio (if used). Data on other prognostic factors was not extracted due to a lack of inclusion of such factors within the included studies. Local recurrence was assumed to be at the site of the original tumour, differentiated from second primaries and independent to regional recurrence [35]; however, this was not explicitly stated in the included papers.

Studies including patients treated with adjuvant therapy had data from the surgery alone group extracted and the total number of patients was adjusted to represent the surgery alone group.

Summary measures used were percentage overall local recurrence rates in each margin group, with 95% confidence intervals and *p*-values calculated to indicated the size of the difference between margin categories in each study.

Meta-analysis was undertaken using Review Manager 5.0. Heterogeneity was assessed using Cochrans Q, Tau^2, and I^2 statistics [32]. An inverse variance approach was taken due to the small size of most included studies, with a random-effects model used to take into account within study and between study variation [32], which was judged likely due to differences in surgical practice and follow up, and observer differences in pathological analysis.

Subgroup analysis was undertaken comparing T1/2 tumours with T3/4 [23,36] tumours. Summary statistics were used, as this data was obtainable only from two studies. Data on other prognostic factors was not available to complete further subgroup analyses.

Results

A summary of the five included studies is given in Table 1. Patient demographics were similar across studies. Follow up was greater than two years for all studies. Two studies included multiple oral cavity subsites [23,36], one included only the buccal mucosa [38], one only the tongue [25], and one only the floor of mouth [45]. Four of the studies contained additional patients who had undergone adjuvant radiotherapy.

Table 2 gives simple summary data for each individual study. All included studies combined ‘close’ and ‘involved’ margins, giving a single cut off value for margin adequacy. Close and involved margins will be referred to as ‘positive’ in this paper to ensure clarity. All but one study defined a less than 5 mm margin as positive, with only Hicks et al. using a 10 mm cut off [25]. The inclusion of dysplasia at the margin in positive margins varied between studies. The method of margin sampling i.e. from the resected specimen or tumour bed was not described in any of the studies.

Number and percentages of clear and close margins according to the individual study are given, along with the number and percentage of local recurrences for each margin group. Confidence intervals and *p*-values were calculated using a chi-squared test to assess the difference in local recurrence rates between patients with clear and positive margins in each study. These results are shown graphically in Fig. 2. Rates of local recurrence differ between studies, but there is a clear trend towards increased recurrence in groups with smaller margin size. The local recurrence rate with a 10 mm margin cut off was lower in both groups than all other studies.