

Surgical margins in head and neck squamous cell carcinoma: what is ‘close’?

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Abstract The aim of this systematic review is to evaluate the definition of close margin in head and neck squamous cell carcinoma (HNSCC), and its possible prognostic significance. An appropriate string was run on PubMed to retrieve articles discussing the ‘close’ surgical margin issue in HNSCC. A double cross-check was performed on citations and full-text articles retrieved. In total, 348 articles were identified. Further references were included by using the option “Titles in your search terms” option in PubMed. 15 papers were finally included for qualitative synthesis. In vocal cord surgery of HNSCC, a close margin could be considered to be ≤ 1 mm, in the larynx ≤ 5 mm, in the oral cavity ≤ 4 mm, and in the oropharynx ≤ 5 mm. In each patient, the choice of extent of close margin should be balanced against general condition, tumor stage, and functional issues to indicate appropriate adjuvant therapy.

Keywords Squamous cell carcinoma · Head and neck surgery · Oral cavity · Larynx · Oropharynx · Surgical margins · Close margins

Introduction

Radicality in neoplasm surgical treatment is the most important principle in oncologic surgery. The completeness of removal clearly requires a cuff of healthy tissue around the neoplastic tissue, whose dimensions generally vary depending on several factors such as the district or type of tumor. These basic principles also apply to head and neck squamous cell carcinoma (HNSCC), which certainly represents the most important pathology in terms of epidemiology and surgical oncology in the head and neck district. In post-operative follow-up, it is common practice among surgeons, radiotherapists and oncologists to discuss the appropriate adjuvant treatment for each patient, based on the definitive histology and pTNM. Other than the stage, the risk factors and comorbidities of the patient, and the district of head and neck, in most cases, the margin status is an issue that can influence the decision-making process, particularly for chemo-radiotherapy, since guidelines and data in the literature document worsening of prognosis in patients with positive resection margins (R1-microscopic or R2-macroscopic) [1–3]. Although what is a clear margin and what is an involved one are intuitive, what lies between involved and clear, commonly defined as ‘close’, is a concept that is much less clear. In the literature and clinical practice, the measure of close is expressed in millimeters of distance from the tumor, but how many millimeters has not been definitively established with regard to HNSCC. Consequently, it seems that the prognostic significance of close is also unclear.

Even the guidelines do not thoroughly tackle this subject. In general, the National Comprehensive Cancer Network (NCCN) defines R close as ≤ 5 mm without distinction for any subsite in HNSCC. In fact, the NCCN does not report any algorithm considering close margins as

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an indication for adjuvant treatment; only for salivary glands is a close margin considered as just R1. American Society of Clinical Oncology (ASCO) and European Oncology Institute (IEO) guidelines give indications for adjuvant treatment both for R1 and R close; even in those cases, R close is defined as ≤ 5 mm without any subsite distinction. Moreover, although American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) guidelines mention involved margins (R1 and R2) in their classifications regarding tumor excision surgery, actually there is not a shared definition of “close margins” in Head and Neck district, and even in many other anatomical regions in oncologic surgery.

In any case, using a unique definition of close for every subsite of head and neck is probably inappropriate, since every district has different characteristics in terms of lymphatic drainage, vascularization, and presence of biologic barriers (e.g. cartilage, bones, fascia). Moreover, the term ‘close’ should be associated, not with a purely spatial concept, but with its prognostic significance, so as to give correct indications for further treatments that are, in most cases, associated with high morbidity.

Using a systematic literature review and critical literature analysis, the present study aims to evaluate the definition of ‘close’ in HNSCC, and the evidence supporting its possible prognostic significance. Gathering and summarizing this evidence could help in guiding the decision-making process for adjuvant therapy for patients who have undergone surgery for HNSCC.

Materials and methods

PRISMA 2009 guidelines were considered and applied whenever possible in this systematic review.

The following search string was run on PubMed:

(margin OR margins OR ((resection OR surgical OR close) AND (margins OR margin))) AND (“carcinoma, squamous cell”[MeSH]) AND (“Neck”[Mesh] OR “Head”[Mesh] OR “Pharynx”[Mesh] OR “Larynx”[Mesh] OR “Tongue”[Mesh] OR “Palatine Tonsil”[Mesh] OR “Vocal Cords”[Mesh] OR “Lip”[Mesh] OR “Palate”[Mesh] OR “Mouth”[Mesh] OR “Nose”[Mesh]).

After running the above search string in July 2011, abstracts and titles obtained were screened independently by two of the authors (MAC and MB), who subsequently met and discussed disagreements on citation inclusion. Further searches were included using the option “Titles in your search terms”.

Inclusion criteria for citations were:

- Abstract in which the margin issue in head and neck surgery was mentioned
- English, Spanish, Italian and French language

Exclusion criteria were:

- Simple mention of ‘positivity’ or ‘negativity’ of the margins, or margins cited *a propos* of surgical technique in outcome studies, with no further information related to the margin issue
- Unrelated topics (e.g. intraoperative frozen-section assessment of margins; molecular studies on margins; preoperative instrumental assessment of margins; etc.)
- Districts other than head and neck
- Tumors other than SCC
- Case reports
- Veterinary articles

Then the full texts of the articles identified were obtained for a second screening, again by MAC and MB, who met and discussed disagreements on article inclusion. Inclusion criteria for full-text articles identified were:

- Article dealing with the prognostic value of ‘close’ margins, at least in part of the article

Exclusion criteria were:

- Irrelevant or insufficient information
- Positive and close margins considered together
- SCC considered together with other kinds of neoplasms
- Literature reviews

A further manual check of the references included in the articles was performed. The final number of articles included in the present review was identified and the main information was extracted and summarized.

Results

In total, 348 articles were identified after running the above search string in PubMed. Additional references were included using the option “Titles in your search terms” (Fig. 1). After an initial check, full-text retrieval, and manual cross-checking of references included in the articles, 15 studies were finally included for qualitative synthesis in this study (Fig. 1). Four studies dealt with the larynx, while seven dealt with the oral cavity, and three with both the oral cavity and oropharynx. In one article, the oral cavity (lip excluded), oropharynx and laryngo-hypopharynx were analyzed together.

A summary of the 15 studies is included in Table 1 (1–15).

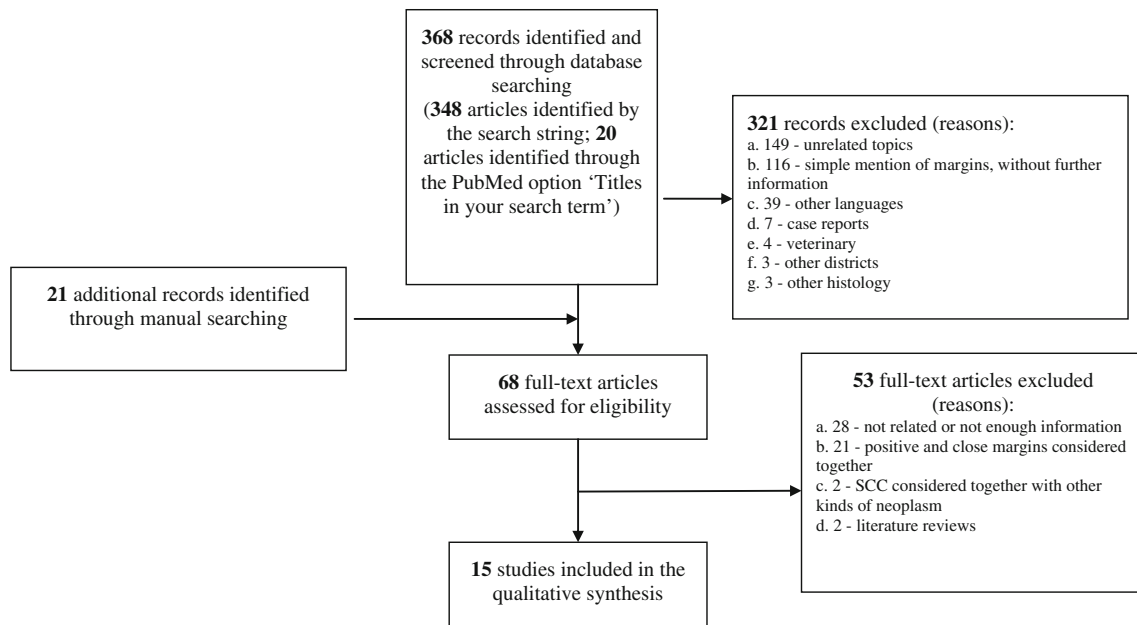


Fig. 1 Flow diagram for the study

Discussion

Local recurrence in head and neck malignant neoplasms can be influenced by the involvement of resection margins [3, 16–18]. Radical surgery requires an adequate margin of healthy tissue around the lesion. AJCC and UICC guidelines focus their attention on involved margins, while NCCN, ASCO, and IEO guidelines define R close as ≤ 5 mm without any distinction for anatomical subsite. However, in the scientific literature, there is currently no consensus with regard to how wide this margin should be.

During the process of paper selection, some interesting common exclusion features were found. In fact, many of the full-text articles evaluated contained only a simple mention of margins, without any reference to their prognostic value and their influence in the decision-making process. Furthermore, we had to rule out many of them because of their lack of any reference to the specific influence of *close* margins.

Another important exclusion principle was that several authors considered positive and close margins jointly as a prognostic factor in the follow-up. In the authors' opinion, this attitude is totally arbitrary and cannot be considered to be scientifically valid, because no scientific evidence allows us to combine these into a single prognostic category. Furthermore, some articles, particularly those about paranasal sinuses, reported different histotypes (including HNSCC) in a single large category of 'malignant neoplasm', although in reality, we cannot exclude the possibility that different histological varieties differ from one another in terms of aggressiveness and risk of recurrence.

As regards the tumor site, among the full-text articles included, and also in the majority of the excluded articles, the oropharynx was often treated in conjunction with the oral cavity, although these two anatomical areas may obviously present some differences. In fact, oropharyngeal cancers are less sensitive to radiotherapy and have a poorer prognosis [19].

The level of evidence of the 15 articles included in the final selection was 2b, because all of the papers selected were obtained from cohort studies, although in some cases, they were about historical cohorts, and the general approach of the authors was retrospective. Various prognostic end points were found in the final full-text selection, although many authors stressed the relationship between close margins and DFS (disease-free survival) or local recurrence.

Larynx

Analyzing and commenting on the results by district, with regard to the larynx, a difference was found in the definition of close margins depending on the type of intervention. In fact, in two different studies, the authors treated patients with a total or partial laryngectomy and both considered close margins as ≤ 5 mm [1, 4]. In the other two studies, the authors [2, 5] performed laser cordectomy, defining close margins as 1–2 mm. This difference based on the type of surgery practiced is even more important when placed in the context of modern functional surgery, which seeks a conservative-but-radical approach. Sessions et al. [1] tried to determine the best therapeutic approach

Table 1 Studies summary

Study	District	Operation	Close margin definition	Prognostic evaluation of close margins on	Adjuvant RT (y/n)	Prognostic influence	Level of evidence/grade of recommendation
Sessions et al. [1]	Larynx	Total or partial laryngectomy	≤5 mm	5-year disease-specific survival rate; 5-year cumulative disease-specific survival	y	W	2b/B
Spector et al. [4]	Larynx	Total laryngectomy	≤5 mm	5-year disease-specific survival; mean survival	y	W	2b/B
Hartl et al. [5]	Larynx	Laser cordectomy	≤2 mm	Local recurrence	n	NSSW	2b/B
Ansarin et al. [2]	Larynx	Laser cordectomy	≤1 mm	8-year disease-free survival; 5-year overall survival	y	5-year with and without RT: W; 8-year with RT: NSSW and without RT: W	2b/B
Loree et al. [3]	Oral cavity	Radical surgery	≤5 mm	Local recurrence	y	W	2b/B
Zeleftsky et al. [6]	Oral cavity	Radical surgery	≤5 mm	Local recurrence	y (all)	NSSW	2b/B
Dixit et al. [7]	Oral cavity	Radical surgery	≤2 mm	Locoregional failure	y	With RT: NSSW; without RT: W	2b/B
Weijers et al. [8]	Oral cavity	Radical surgery	≤ 5 mm	Local recurrence	n	NSSW	2b/B
Liao et al. [9]	Oral cavity	Radical surgery	≤ 4 mm	5-year local control rate	y	W	2b/B
Liao et al. [9]	Oral cavity	Radical surgery	≤7 mm	Local control; disease-specific survival; overall survival	y	W	2b/B
Nason et al. [11]	Oral cavity	Radical surgery	≤2 mm	Recurrence; 5-year survival	y	W	2b/B
Zeleftsky et al. [12]	Oral cavity and oropharynx	Radical surgery	≤5 mm	7-year actuarial control rate	y (all)	With RT < or > 60 Gy: NSSW	2b/B
Sutton et al. [13]	Oral cavity and oropharynx	Radical surgery	≤5 mm	Recurrence; median disease-free interval (days); overall survival	y	W	2b/B
McMahon et al. [14]	Oral cavity and oropharynx	Radical surgery	≤5 mm	Disease-specific survival	y	NSSW	2b/B
Ravasz et al. [15]	Oral cavity (lip excluded), oropharynx and laryngo-hypopharynx	Radical surgery	≤5 mm	Local failure	y (all)	NSSW	2b/B

W worsening, NSSW not-statistically significant worsening

for the treatment of T₃N₀M₀ (stage III) glottic carcinoma. They performed seven different types of treatment, including radiation therapy alone or combined with conservative or radical surgery, and they noticed that

recurrence, complication and survival rates were not related to treatment modality, but to the degree of involvement of the surgical margins. In fact, patients with clear surgical margins had a significant survival advantage compared to

patients with close (less than 5 mm) or with involved margins (analyzed separately). Spector et al. [4] made a retrospective evaluation of stage IV glottic carcinoma, considering five different surgical and adjuvant treatment modalities. Even in this case, they found statistically similar survival, recurrence and complication rates in relation to treatment modalities and a statistically significantly worse survival rate in patients with close margins (less than 5 mm), when compared to patients with clear margins.

As mentioned above, in the case of less advanced glottic cancers, resection margins are considered suspicious (or 'close') in a range from 1 to 2 mm [2, 5], and in our review, early-stage squamous cell glottic carcinomas (pTis, pT1a, pT1b and T2) were treated with the five cordectomy types on the basis of involvement of the anatomical subsite. Hartl et al. [5] concluded that the recurrence rate was significantly higher for pT1b tumors (involvement of both vocal cords) compared to pTis and pT1a tumors (carcinoma in situ or limited to one vocal cord). They also stated that local recurrence rate did not differ significantly among the three types of pathological resection margins (clear, involved and close—less than 2 mm) and that in their experience, suspicious margins could be managed with a 'watch-and-wait' attitude. Conversely, analyzing the study by Ansarin et al. [2] on early glottic cancers using Fisher's exact test, close margins were found to have a poorer prognostic influence when compared with those considered negative on 5-year overall survival, independent of the use of adjuvant RT. However, a difference was found between the use of surgery and adjuvant RT versus surgery alone in the 8-year disease-free survival, in that the patients with close versus negative margins who underwent RT did not show a significant worsening of prognosis. This means that, for long-term survival, radiotherapy should be taken into account as an adjuvant treatment for close margins, considering close to be less than 1 mm.

Oral cavity

Another important district evaluated was the oral cavity (in some of the studies, combined with the oropharynx, in terms of both prognostic and therapeutic outcomes). In this anatomic area, a range from 2 to 7 mm was considered for the definition of 'close' in the studies [3, 6–11]. From this, it can be seen that the range used by various authors is very large and might have affected survival, despite the application of the same type of surgery. This strengthens our impression of a lack of standardization of suspicious/close margin size. Moreover, some controversial data emerge when comparing different studies. In a retrospective review of 398 patients surgically treated (\pm adjuvant RT) for squamous carcinoma of the oral cavity (excluding the lip), Loree et al. [3] found that the local recurrence rate for the

close margin category (≤ 5 mm) was significantly different from the negative margin rate. On the other hand, using the same margin size (< 5 mm) for two anatomical oral cavity subsites, namely, the floor of the mouth and the oral tongue, Zelefsky et al. [6] concluded that this prognostic factor did not have a significant impact on local control. In their multivariate analysis, the only independent variable that predicted for local failure was the anatomic subsite (5-year local failure was significantly worse for oral tongue than for floor of the mouth). In addition, in a retrospective study on only surgically treated squamous cell neoplasms of the tongue and floor of the mouth by Weijers et al. [8], the comparison between local recurrences in patients with free surgical margins > 0.5 mm and patients with free surgical margins < 0.5 mm did not show a statistically significant difference. The lowest value for close margin in the oral cavity was described as ≤ 2 mm by two authors: Nason et al. [11] demonstrated that recurrence-free survival for SCC was similar for patients with involved and with close margins and significantly worse than that observed in patients with negative margins. Dixit et al. [7] evaluated the efficacy of postoperative RT for squamous cell carcinomas of the buccal mucosa and concluded that radiotherapy was effective in decreasing locoregional failure in patients with close (less than 2 mm) margins. In fact, close margins not treated with RT showed a poorer prognosis, when compared with negative margins.

Moreover, the effect of interval between surgery and postoperative radiotherapy on local failure was margin-dependent. In fact, when the interval was greater than 30 days, there was a significant detrimental effect on locoregional control only in patients with close margins. In two different studies, Liao et al. [9, 10] analyzed the survival in oral cavity squamous cell carcinomas, in relation to pathological margins. They found that, in SCC of the buccal mucosa, adequate pathological margins are deemed to play a crucial role in ensuring satisfactory local control and they stated that the presence of pathological margins ≤ 4 mm (close) is an independent predictor of poor local control and should be treated with adjuvant RT. In their experience, a close margin ≤ 4 mm was an independent risk factor for local control both for patients treated with surgery alone and for those treated with surgery plus adjuvant therapy [9]. However, in another article published by the same authors, they concluded that the optimal pathological margin for oral cavity squamous cell carcinomas should be > 7 mm. Thus, despite a cut-off of 7 mm being the most reliable in their experience, they concluded that in the case of margins of 4–5 mm, patients must receive adjuvant therapy, and that for patients who did not receive postoperative adjuvant therapy, even in the presence of pathological margins of 5–7 mm, close follow-up examination is recommended [10].

Oropharynx

Although questionable, three studies in our review reported SCC of both the oral cavity and oropharynx in a single category [12–14]. In all three studies, close margins were considered ≤ 5 mm. Two studies [12, 14] did not find a statistically significant impact of close margins on prognosis, while the third study reported a poorer prognosis with close margins compared to negative margins [13].

Other districts

Finally, in our selection of articles, we also included a study where close margins were considered ≤ 5 mm, according to the international guidelines, and the authors considered a single value for all of the anatomical sites in the head and neck district [15]. They included only patients with multiple indications for postoperative irradiation (always performed) and they concluded that close resection margins did not significantly affect the risk of local failure. This kind of approach with a universal value for all of the anatomical subsites in head and neck oncologic surgery contrasts with our intention to define a shared evaluation system for the status of resection margins, but always keeping in mind the diversity that exists in therapeutic, functional and prognostic terms between the different ENT districts.

Two of the articles examined in this review considered various categories of positive margins together. Loree et al. [3] concluded that all positive margin sub-categories, that is close, premalignant, ca. in situ, and microscopic invasion, carry a comparable increased risk of local recurrence when compared with the negative margin group. Ravasz et al. [15] observed a non-significant difference in local failure between the groups with negative and positive resection margins (ca. in situ, close, infiltrative tumor at the margin). Regarding this above-mentioned issue, present authors strongly believe that also a *histologic* standardization of close margin in head and neck surgery should be made, since it could help to overcome some redundancies used to classify positive margins, and could lead to a simpler and targeted classification for determining prognostic and therapeutic indications. For sure, it may be very different to consider a distance of a carcinoma in situ, premalignant lesions, severe dysplasia, or other kinds of mucosal alterations from resection margins.

Another important aspect to be considered in association with the definition of the term ‘close’ is that of margin discrepancy after resection and pathologic processing. Some authors considered margin shrinkage in oral cancer and its impact on ensuring an adequate resection of the neoplasm [20, 21]. Cheng et al. [21] concluded that margin

discrepancies in oral SCC after resection and specimen processing are highly significant. In their study, there was a significant difference in margin discrepancy based on oral cavity subsite and tumor stage (late stages showed greater discrepancies). This emphasizes the importance of collaboration between surgeons, who see the macroscopic margins, and pathologists, who add definitive information about the microscopic margin status, even with the shrinkage variability.

It should be stressed that the ‘close’ margin issue is also debated and controversial in other branches of surgery. In particular, in breast surgery, the association between a resection margin that is defined as close and the subsequent risk of recurrence after conservative surgery and radiation is controversial [22–27]. Moreover, HNSCC close margins must be interpreted not only in relation to the different anatomical districts, but also balancing a conservative surgery that preserves the basilar physiologic mechanisms of the ENT organs with the adequacy of resection of all of the edges of the tumor, since the crucial functional aspects of the ENT district, such as swallowing, phonation and breathing, and the consequent quality of life of patients should always be kept in mind. Almost all of the studies that met the criteria for our review were about the larynx and oral cavity, so further experience, in particular, for the nose and paranasal sinuses, skin and lower lip, has to be added.

According to all these considerations, in our opinion, the term ‘close’ must be used with caution not only by surgeons, but also by pathologists, because this simple word conceals several treating and prognostic implications, which could lead to inappropriate medical choices. From this, in the authors’ opinion, there is a need for international consensus conferences and further studies with more evidence, to reach a standardization of the definition of close margins, weighted on single patient’s risk factors, in the various anatomical subsites of the head and neck district.

Conclusions

Based on the best literature evidence currently available with regard to HNSCC, and summarizing the data analyzed, the authors conclude that, in vocal cord surgery, a close margin could be considered as ≤ 1 mm, in the larynx as ≤ 5 mm, in the oral cavity as ≤ 4 mm and in the oropharynx as ≤ 5 mm. The choice of extent of close margin should be balanced against general condition, tumor stage, and functional issues to indicate appropriate adjuvant therapies for each patient. Further experience for nose and paranasal sinuses, skin and lower lip, has still to be reported.

Conflict of interest None.

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