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Review

Beneath the surface: A systematic review on intraoperative imaging techniques for deep margin assessment in oral squamous cell carcinoma

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ABSTRACT

Resection margins of oral squamous cell carcinoma (SCC) are often inadequate. A systematic review on clinical intraoperative whole-specimen imaging techniques to obtain adequate deep resection margins in oral SCC is lacking. Such a review may render better alternatives for the current insufficient intraoperative techniques: palpation and frozen section analyses (FSA). This review resulted in ten publications investigating ultrasound (US), four investigating fluorescence, and three investigating MRI. Both US and fluorescence were able to image the tumor intraorally and perform ex-vivo imaging of the resection specimen. Fluorescence was also able to image residual tumor tissue in the wound bed. MRI could only be used on the ex-vivo specimen. The 95 % confidence intervals for sensitivity and specificity were large, due to the small sample sizes for all three techniques. The sensitivity and specificity of US for identifying < 5 mm margins ranged from 0 % to 100 % and 60 % to 100 %, respectively. For fluorescence, this ranged from 0 % to 100 % and 76 % to 100 %, respectively. For MRI, this ranged from 7 % to 100 % and 81 % to 100 %, respectively. US, MRI and fluorescence are the currently available imaging techniques that can potentially be used intraoperatively and which can image the entire tumor-free margin, although they have insufficient sensitivity for identifying < 5 mm margins. Further research on larger cohorts is needed to improve the sensitivity by determining cut-off points on imaging for inadequate margins. This improves the number of adequate resections of oral SCC's and pave the way for routine clinical implementation of these techniques.

Introduction

The management of oral cavity cancer is complex due to the potential functional and aesthetic consequences of treatment in this area. Surgery is the preferred treatment of choice in most cases. Its goal is complete removal of the tumor with adequate tumor-free margins [1,2]. Inadequate resection margins are associated with poorer clinical outcomes [3,4]. In cases of inadequate deep resection margins, re-resection or local adjuvant (chemo)radiotherapy might be indicated [2,5]. Unfortunately, a re-resection in a second tempo comes with relocation problems, especially since the wound bed has usually healed [6]. Furthermore, it requires a second scheduled surgery under general anesthesia. Local adjuvant radiotherapy could result in morbidities such as mucositis, fibrosis, osteoradionecrosis, and xerostomia [7,8].

The definition of an adequate margin remains a topic of discussion and ranges from > 0 mm to > 7 mm in literature [9]. Most commonly, histological margins are divided into positive (< 1 mm), close (1–5 mm), and free (≥ 5 mm) [10,11]. Especially, obtaining free deep resection margins is challenging. Literature reports that resection margins are < 5 mm in 30 % – 85 % of the procedures, possibly because detailed intraoperative feedback is lacking [12]. In a conventional setting, the deep margin can be estimated intraoperatively by usage of preoperative imaging, visual inspection, and palpation. Frozen section analysis (FSA), utilized by many surgeons, allows intraoperative analysis of resection margins for residual tumor tissue. FSA can be performed on the tumor bed or on the specimen. With FSA however, one samples only a small fraction of the entire margin. Therefore, this technique is prone to false-negative results [12,13]. Furthermore, in the case of a positive FSA, relocating the original spot for a re-resection is difficult [14]. Therefore, initial positive margins, regardless of re-resections based on FSA, lead to worse outcomes than initially free margins [15–17]. The ideal intraoperative imaging technique for oral squamous cell carcinoma (SCC) is

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able to guide the resection real time and is applicable for both mucosal, submucosal, deep as well as bony margins.

There are multiple (systematic) reviews that give an overview of available intraoperative techniques for deep-margin assessment in patients with oral SCC. However, some reviews discuss techniques that are based on random sampling, which still may lead to sampling errors and location problems, as witnessed in FSA. Other reviews focus on techniques able to differentiate SCC from healthy tissue but do not measure the extent of the tumor-free margin. Furthermore, some reviews investigate either other sites than the oral cavity, only compare two techniques, or focus on the superficial (sub)mucosal margins. [13,18–20].

This systematic review aims to outline and compare the clinical intraoperative imaging techniques that are currently being investigated to obtain free deep surgical resection margins in patients with oral SCC. It focusses on the ability of the technique to identify, localize, and estimate the extent of the tumor-free margin by imaging the margins of the whole specimen.

Materials and methods

This systematic review was carried out according to the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines [21].

Eligibility criteria

A publication was considered eligible in case 1) the study population consisted of patients with a SCC of the head and neck area containing a sub-group of oral cavity SCC; and 2) it analyzed a technique that aimed to assess the extent of the entire resection margin; and 3) it was used or will be used intraoperatively (i.e. in theatre directly before the incision, during the resection or immediately after the resection) on the fresh specimen; and 4) the margins were compared to the histological margins; and 4) the number of true positives (TP), false positives (FP), false negatives (FN), true negatives (TN), the number of free margins, or the number of positive margins were mentioned or could be extracted from the publication; and 5) the publication focused on deep margin assessment.

Exclusion criteria were: 1) publications before 2010; 2) non-clinical studies; 3) publications that described techniques that only used white light for tumor/margin visualization e.g. *trans*-oral robotic surgery (TORS) without visual enhancement; 4) publications describing head and neck cancers with < 50 % oral cancers or without subgroup analysis of oral cancer in the intervention group; 5) techniques that only investigate bony margins; 6) publications in languages other than English, Dutch, or German; 7) techniques that require the specimen to be cleaved; 8) dose-finding or dose-escalating studies.

Search strategy

A systematic search for publications was conducted in PubMed and Embase on August 31st, 2023 (KK). In PubMed, the search term focused on Title, Abstract, and MeSH-terms and included carcinoma, all subsites of the oral cavity and margins of excision. Moreover, the terms “thickness” or “depth of invasion” were also included. The same search terms were used in Embase, but instead of the aforementioned MeSH-terms, the “explode function” was used. The search syntax is shown in supplement 1.

EndNote (Version 19.3.3, Clarivate Analytics, Philadelphia, PA, USA) was used to de-duplicate using the method described by Bramer et al. [22]. Subsequently, data was exported to Rayyan QCRI (Hamad Bin Khalifa University, Ar Rayyan University, Qatar). At least two of the three screening authors (CA, KK, and RN) independently screened all titles and abstracts for relevance using predetermined inclusion and exclusion criteria and achieved consensus by discussion. The remaining publications were included or excluded by reading full texts by two screening authors (CA, KK). A reference and citation check was performed on the selected publications to ensure the whole field of interest was covered.

Critical appraisal

The two screening authors (CA, KK) critically appraised the included publications separately using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool (Whiting, 2011). The following signaling questions were utilized:

Risk of bias: 1) Patient selection: did the study consist of a consecutively or randomly selected patient cohort? Was a relevant control group utilized? Were inappropriate exclusions avoided? 2) Index test: was the index test interpreted without knowledge of the reference standard? 3) Reference test: was the reference standard interpreted without knowledge of the index test? 4) Flow and timing: were the reference standard and index test conducted equally for all patients? Were all patients included in the statistical analysis?

Applicability was evaluated based on the first three items and their criteria: 1) Patient selection: did the study include both small (T1-T2) and large (T3-T4) oral SCCs? 2) Index test: did the publication give a clear definition of a positive index test? Could a positive index test be evaluated objectively? If applicable, was a clear description of the used dosage or devices given? 3) Reference test: was the definition of a free margin ≥ 5 mm? If frozen sections were applied, were they guided by the imaging technique?

All items were scored with 2 points when they complied, 1 point when there was unclarity, and 0 points when they did not comply. Each category was scored by summing the points and dividing them by the number of items. The scores were considered low if 0 – 0.5, intermediate if 0.6 – 1.4, and good if 1.5 – 2.0 (Fig. 2).

Data extraction

The following information was extracted from the included publications: year of publication, imaging technique, subsite of the oral cavity, study methodology (prospective or retrospective), assessed margin, in- or ex-vivo measured, number of included tumors, number of measured margins, surgical margin aim, immediate revision, definition histological positive margin, definition histological free margin, TP, FP, FN, TN, and number of tumors with positive or free margins (whole specimen or margin-based). The definition of a TP was an inadequate margin based on the imaging technique and confirmed by histology. The definition of a TN was an adequate margin based on the imaging technique and confirmed by histology. An adequate margin was defined as ≥ 5 mm, unless otherwise stated. If possible, the number of TP, TN, FP, FN, and positive and free margins were re-calculated for ≥ 5 mm. Some authors were contacted and requested to elaborate on their results. The sensitivity, specificity, and forest plots were calculated by using MetaDTA: Diagnostic Test Accuracy v2.0.5 [23,24].

Results and technique discussion

Search strategy

The search yielded 19.656 records (Fig. 1). After removing duplicates, records in a language other than English, Dutch, or German, and non-original publications, 9.284 records remained. These were screened on title and abstract according to the predetermined inclusion and exclusion criteria. The full texts of the remaining 164 publications were screened, and 17 publications were included in this review. No additional publications were found after checking the references of the included studies.

Critical appraisal

The 17 included studies were scored on risk of bias and applicability

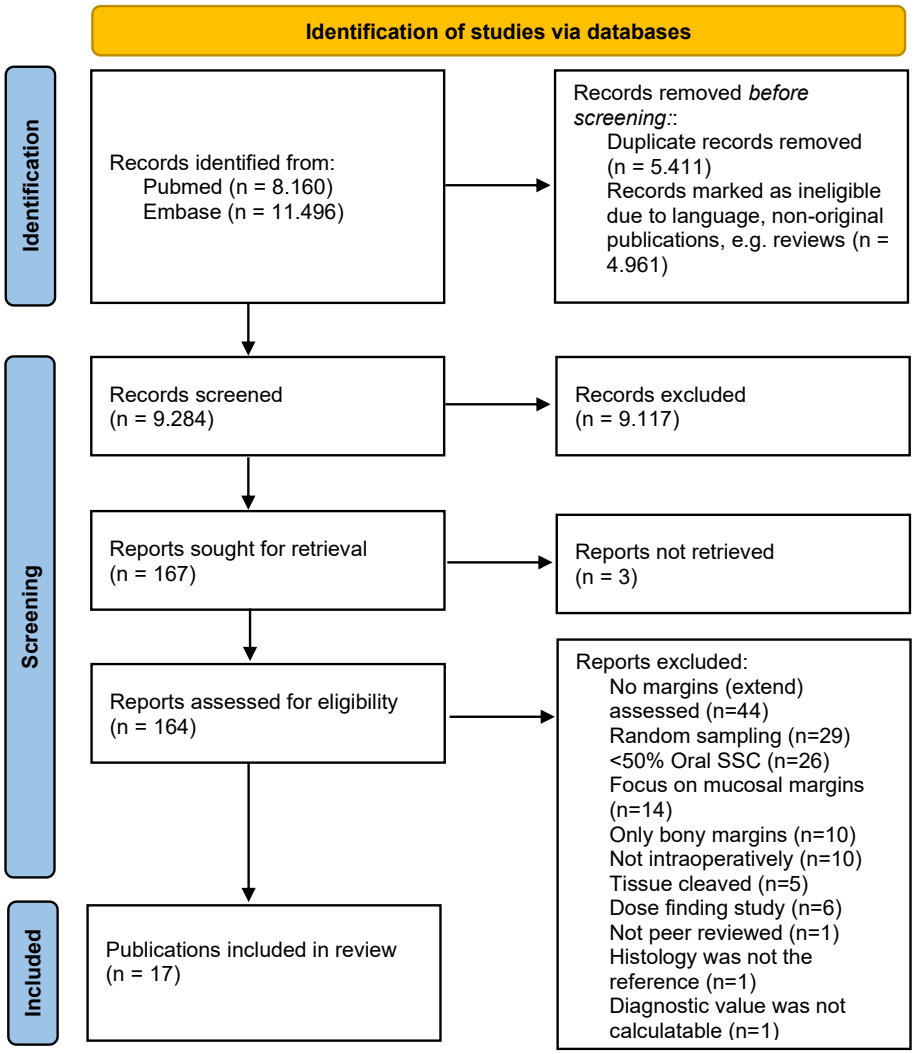

Figure 1. Search strategy according to the PRISMA [21].

to our review question according to QUADAS-2 (Fig. 2). There were no studies with a high risk of bias in the categories "patient selection", and "flow and timing". In the study of Steens et al., risk of bias was suspected because the index test results were interpreted in a non-blinded fashion [25]. In four studies, the reference standard was not blinded for the index test results, potentially resulting in bias for the category "reference standard" [26–29]. Only three studies mentioned that the reference standard was blinded for the index test results [30–32].

The applicability of the category "patient selection" was intermediate or good for all the studies. The applicability of the category "index test" was intermediate in all the studies because most index tests were subjective and therefore operator-dependent. Only the index tests of

Figure 2. Critical appraisal according to QUADAS-2. The green checkmark indicates low risk of bias or good applicability, the yellow exclamation mark indicates intermediate risk of bias or intermediate applicability, and the red cross indicates high risk of bias or low applicability.

studies investigating fluorescence could potentially be objective; however, none of the studies predefined the cut-off value for a positive test beforehand [31,33]. The applicability of the category "reference standard" was low for Wu et al. because their definition of a free margin was not described and because FSA was not guided by the imaging technique, which made it unclear whether these free margins were achieved due to the index test or the FSA [34].

Imaging techniques

Three different imaging techniques emerged from our search and are described separately in this systematic review: ultrasound (US), fluorescence, and magnetic resonance imaging (MRI).

Ultrasound

US is an imaging technique that can determine the tumor thickness and the deep border of the tumor accurately [35]. There are two methods for intraoperative US imaging: visualization of the surgical resection margin in-vivo to adjust the resection plane if needed, and ex-vivo imaging of the specimen to determine the margins and the possible need for an immediate re-resection.

Ten studies that investigated the use of intraoperative US were included in this review (Table 1). Nine out of 10 investigated 2D US and one study investigated 3D US [36]. Eight out of 10 studies used in-vivo and ex-vivo imaging and two studies only used ex-vivo imaging on the specimen [36,37]. All studies used 5 mm as a cut-off value for free margins, which made it possible to compare these studies. Nevertheless, some studies strived for a certain minimal US measured margin and considered a re-resection in case of a smaller measured margin [26–30,38]. Therefore, we assumed this minimal margin was achieved by doing an immediate re-resection in case of a smaller measured margin, unless otherwise stated. Five studies focused on the ability of US to image the deep margin [29,37–40]. Bulbul et al. and Nilsson et al. used US to image the deep resection plane and also described the overall margin outcome. The other five studies imaged both deep and superficial margins [26–28,30,36]. Five studies aimed for a $\geq$ 5 mm margin from the tumor during the surgery [26–28,30,38] and 3 studies aimed for $>$ 10 mm [29,39,40]. The acquisition time varied between 5 and 10 min for the studies that used US in the operating theatre [27,28,37–39]. For one study, this was 33 min, because the imaging technique consisted of manual segmentation of a volumetric dataset to create a US-based 3D margin model [36]. The 10 patients from the pilot study of de Koning et al., 2021, had a 100 % overlap with the patients in the study of de Koning et al., 2022. There was also a 23 patient overlap between Au et al. and Bulbul et al [30,39]. These 10 and 23 patients were only included once when calculating the total number of tumors and margins, as well as when determining the medians. In total, 169 tumors and 371 margins were analyzed by US and compared to histology. For the included US studies, the median percentage tumors with a $\geq$ 5 mm overall margin was 59 % (range: 8 % – 63 %) for the US group, while it was 41 % (range: 16 % – 48 %) in the control group [26,28,30,36,38,39]. The median percentage of tumors with a $\geq$ 5 mm deep margin was 76 % (range: 38 % – 100 %) for the US group, while this was 59 % (range: 56 % - 67 %) in the control group [26,28–30,37–40]. All studies investigated SCC of the tongue, except for Adriaansens et al., who focused on SCC of the buccal mucosa, a probably more difficult to visualize tumor location [26]. They found that one of the 13 patients with buccal mucosal cancer had a tumor with free margins and that 60 % of the margins (five margins per specimen) were free. Without this study, the median for overall free margins in tongue tumors in the US group was 60 % (range: 55 % – 63 %) and this was 82 % (range: 66 % – 100 %) for deep free margins.

For all the studies it was possible to calculate the sensitivity and specificity for inadequate margins ($<$ 5 mm), except for the study of Kodama et al. (Table 2, Fig. 3). Kodama et al. placed a needle 10 mm from the deepest portion of the invasive front of the tumor under US guidance, in four patients. All margins were clear in those 4 patients; therefore, the sensitivity was not calculable, and the specificity was 100 %.

Four studies compared an intervention group to a control group. De Koning, 2022 et al. found the largest reduction in positive margins, from 15 % in the control group to 5 % in the intervention group, and the most increase in free margins from 16 % to 55 %, respectively [28]. However, the frequency of free margins in the control groups of the studies of de Koning et al. (16 % and 17 % free margins) were relatively low compared to the control groups of Nilsson et al. and Bulbul et al. (41 % and 48 % free margins respectively), meaning there was more room for improvement in the study of de Koning et al.

Bekedam et al. had a sensitivity of 100 % when taking the smallest distance of different US measurements into account; this was the highest sensitivity of the studies investigating US. However, they only investigated 8 tumor margins. The position of the transducer was tracked, making a 3D reconstruction of the US images possible. However, multiple US acquisitions were performed, introducing variability in the 3D volumes of the same specimen, and the successive manual segmentation also introduced variability [36]. Furthermore, the range of the average resection margin was large.

Fluorescence

Four studies investigating the use of fluorescence were included in this systematic review (Table 3) [31,33,34,41]. Two studies used indocyanine green (ICG) fluorescence intravenously [33,34]. They used ICG as a contrast agent, which accumulates in abnormal tissues with enhanced permeability and retention, such as tumor tissue [33,34]. When excited by light of a specific wavelength, ICG re-emits light in the near-infrared spectrum, which can be detected by near-infrared fluorescence (NIF) imaging equipment [34]. There are also contrast agents that use antibodies that bind to tumor tissue. These antibodies are coupled with a fluorescent dye. Cetuximab-800CW is an epidermal growth factor receptor targeting tracer, consisting of cetuximab, an antibody, and IRDye800CW, the fluorescent dye that can be detected with NIF imaging equipment [31,42]. De Wit et al. pre-administered unlabeled cetuximab intravenously to prevent rapid plasma clearance and occupy off-target receptors, after which cetuximab-800CW was administered [31]. Filip et al. used 5-aminolevulinic acid (5-ALA), which was administered orally. It concentrates in mitochondria as the fluorescent metabolite protoporphyrin IX, which emits light in visible red-pink light when exposed to blue light [41]. Malignancies with high metabolic activity might be more fluorescent compared to the surrounding structures. All four studies used a variety of oral SCC subsites.

Wu et al. used fluorescence to image the specimen in-vivo for three purposes: 1) before the start of the resection to determine the margins, 2) during the resection to check the cutting plane 3) after the resection to image the wound bed and the specimen ex-vivo [34]. Pan et al., de Wit et al. and Filip et al. imaged the tumor in-vivo but did not use fluorescence to guide the surgical margin. Moreover, they imaged the wound bed and imaged the specimen ex-vivo [31,33,41]. De Wit et al. used two closed-field devices to image the specimen ex-vivo. These closed-field devices eliminate ambient light and enable standardization of imaging between specimens. They also pre-dosed the patient with unlabeled cetuximab to prevent rapid plasma clearance of the tracer and occupy off-target receptors in normal tissue, to improve contrast between the tumor and healthy tissue. De Wit et al. also imaged bony margins with their technique [31]. Pan et al. only imaged mucosal and deep soft tissue margins [33]. Wu et al. probably used their technique for both bony and soft tissue margins [34]. It was unclear if bony margins were imaged in the study of Filip et al.[41].

The percentage of tumors or patients that had positive margins varied between 8 % and 25 % (median: 15 %). The percentage of tumors or patients that had free margins varied between 28 % and 90 %

Table 1
Included studies investigating ultrasound. Pros = prospective, retro = retrospective. N.G = not given. *= values in study adjusted to review.

	Methodology	Deep or superficial margin assessed	Tumor location	In- or Ex-vivo	Number of tumors and/or margins	Acquisition time (minutes)	Surgical margin aim (mm)	Immediate revision	Definition histological positive margin (mm)	Definition histological free margin (mm)	Histological positive deep margin (%)	Histological positive overall tumors and/or margin (%)	Histological free deep margin (%)	Histological free overall tumors and/or margin (%)	Probes
(Au et al., 2023)	Retro	Both	Tongue	Both	29	N.G.	≥ 5	Yes	< 5	≥ 5	8/29 (28)	Tumors: 11/29 (38)	21/29 (72)	Tumors: 18/29 (62)	N.G.
(Adriaansens et al., 2023)	Pros	Both	Buccal mucosa	Both	13 (65 margins on histology, 62 imaged)	N.G.	5 – 10	Yes, based on US or surgeon	< 1	≥ 5	2/13 (15)	Tumors: 3/13 (23), margins: 3/65 (5)	5/13 (38)	Tumors: 1/13 (8), margins: 39/65 (60)	in-vivo: L16-4Hs, ex-vivo: L20-5 s (Mindray)
(Nilsson et al., 2022)	Pros vs. Retro	Both	Tongue	Both	110 (intervention: 34 control: 76)	5–10	5 – 10	Yes, based on US or FSA	< 0.01	≥ 5	Intervention: 1/34 (3), control: 5/76 (7).	Tumors intervention: 1/34 (3) control: 9/76 (12)	Intervention: 26/34 (76) control: 45/76 (59)	Tumors intervention: 20/34 (59) control: 31/76 (41)	18 MHz high frequency linear 8870 probe (BK medical)
(de Koning et al., 2022)	Pros vs. Retro	Both	Tongue	Both	136 (intervention:40 tumors,193 margins), control: 96 tumors)	5–10	5 – 10	Yes, based on US or surgeon	< 1	≥ 5	Intervention: 1/38 (3), control: 5/96 (5)	Tumor intervention: 2/40 (5) control: 14/96 (15)	Intervention: 33/38, two missing value (87) control: 54/96 (56)	Tumor intervention: 22/40 (55) control: 15/96 (16)	in-vivo: L16-4Hs, ex-vivo: L20-5 s (Mindray)
(Bekedam et al., 2021)	Pros	Both	Tongue	Ex-vivo	8	33	N.G.	No	< 1 *	≥ 5 *	N.G.	Tumors: 0/8 (0)	N.G.	Tumors: 5/8 (63)	10 MHz intraoperative convex transducer (T-shape, BK Medical)
(Bulbul, et al., 2021)	Retro vs. Retro	Both	Tongue	Both	44 (intervention: 23 control: 21)	5–10	10 – 15	N.G.	0	≥ 5	Intervention: 0/23 (0) control: 1/21 (5)	N.G.	Intervention: 18/23 (78) control: 14/21 (67)	Tumors intervention: 16/23 (70) control: 10/21 (48)	L15–7io; (Philips)
(de Koning et al., 2021)	Pros vs. Retro	Both	Tongue	Both	101 (intervention: 10 control: 91)	no longer than frozen sections	5 – 10	Yes, based on US or surgeon	< 1	≥ 5	Intervention: 0/10 (0), control: 3/91 (3)	Tumors intervention: 1/10 (10) control: 9/91 (10)	Intervention: 8/10 (80) control: 54/91 (59)	Tumors intervention: 7/10 (70) control: 15/91 (16)	in-vivo: L16-4Hs, ex-vivo: L20-5 s (Mindray)
(Brouwer de Koning et al., 2020)	Pros	Deep	Tongue	Ex-vivo	29 (2/31 excluded because base of tongue)	< 5	N.G.	No	< 1 *	≥ 5 *	0/29 (0)	N.G.	19/29 (66)	N.G.	5–10 MHz ProSound SSD-Alpha 5 (Aloka)
(Tarabichi et al., 2018)	Retro	Deep	Tongue	Both	12	N.G.	> 10	N.G., FSA was an option	< 1 *	≥ 5	0/12 (0)	N.G.	11/12 (92)	N.G.	L15-7io; (Phillips)
(Kodama et al., 2010)	Pros	Deep	Tongue	Both	4	N.G.	10	No	< 1	≥ 5	0/4 (0)	N.G.	4/4 (100)	N.G.	7.5-MHz sector probe (Aloka)

Table 2
The true positives (TP), false negatives (FN), false positives (FP), and true negatives (TN) per study. N.A. = not applicable. R1 = Reader 1, R2 = Reader 2. O = Overall: deep and superficial margins of the specimen were assessed. D = Deep: deep margin of the specimen was analyzed. W = Wound bed: wound bed was assessed. S = Single: the narrowest margin (one) per specimen was analyzed. M = Multiple: multiple margins per specimen analyzed (deep and superficial in multiple directions).

Imaging technique	Author, Year	Assessed margin	Single or multiple margins measured per specimen	TP	FN	FP	TN
Ultrasound	Au et al., 2023	O	S	0	11	0	18
		D	S	0	8	0	21
	Adriaansens et al., 2023	O	M	14	15	6	27
	Nilsson et al., 2022	O	S	0	14	0	20
		D	S	0	8	0	26
	de Koning et al., 2022	O	M	9	29	15	140
	Bekedam et al., 2021	O	S	3	0	2	3
	Bulbul, et al., 2021	O	S	0	7	0	16
		D	S	0	5	0	18
	de Koning et al., 2021	O	S	2	2	0	6
	Brouwer de Koning et al., 2020	D	S	7	3	1	18
	Tarabichi et al., 2018	D	S	0	1	0	11
	Kodama et al., 2010	D	S	0	0	0	4
Fluorescence	Wu et al., 2022	O *	S	0	1	1	11
		W*	N.A.	0	1	1	11
		O *	M	0	1	1	127
	Pan et al., 2020	O*	S	2	0	2	16
		W *	N.A.	2	0	2	16
	de Wit et al., 2023	D	M[#]	40	11	17	54
	Filip et al., 2023	W *	N.A.	1	0	0	3
MRI	Giannitto et al., 2021	O	S	1	0	0	9
	Heidkamp et al., 2020	R1: O	M	5	9	8	95
		R2: O	M	1	13	20	87
	Steens et al., 2017	O	S	6	2	0	2

*TP, FN, FP, TN are not based on the definition of inadequate margin of < 5 mm or based on an unclear definition, see Table 3 for the used definition.
[#]Based on an SBR ≥ 1.5, the optimal cut-off for the detection of close margins.

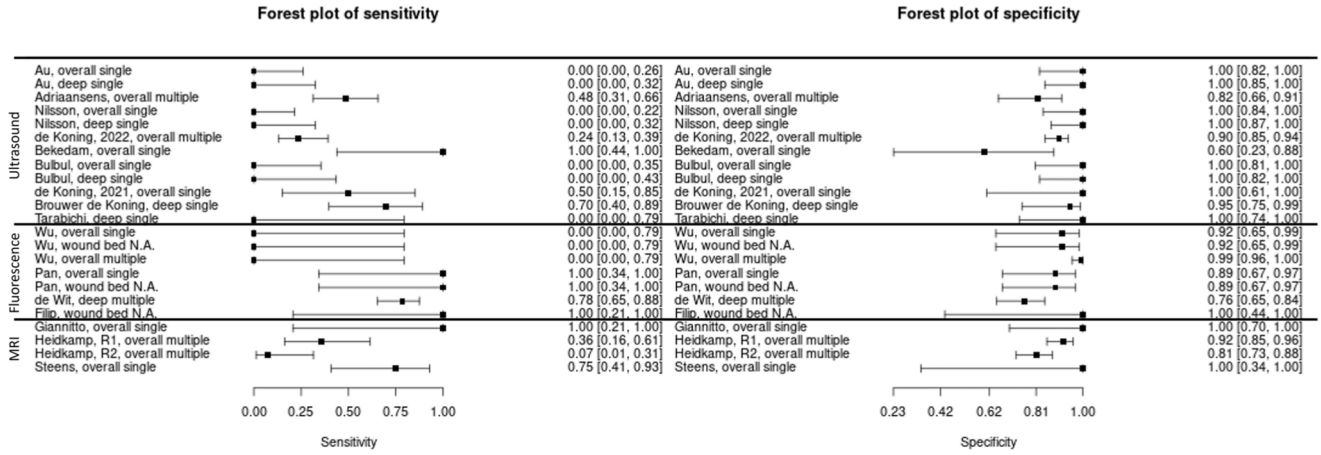

Figure 3. Forest plots of sensitivity and specificity for the included studies. It was not possible to calculate the sensitivity for Kodama et al., the specificity was 100 %.

(median: 75 %). However, the studies used different definitions for positive and free margins, which makes it difficult to compare them (Table 3).

The sensitivity and specificity were calculated for all four studies (Table 2, Fig. 3). In only a few cases in the studies of Wu et al., Pan et al., and Filip et al., the wound bed was fluorescence positive, resulting in a sensitivity ranging from 0 % to 100 % and a specificity of 89 % to 100 %. When fluorescence was used to assess the wound bed for residual cancer in the study of de Wit et al., only one fluorescent spot was found. However, no residual cancer was found at this spot, resulting in a positive predictive value (PPV) of 0 %. This false-positive fluorescent spot turned out to be an artery. De Wit et al. did not mention if they expected a positive spot in the wound bed in the remaining 64 patients, for example in the case of a 0 mm margin (cut-through), resulting in an incalculable sensitivity and specificity. The PPV of a fluorescent spot in the wound bed was also 0 % in the study of Wu et al. [34]. They explained that this could be due to the ability of ICG to accumulate also in dense tissue, normal glands, gingiva, or inflammatory tissue, besides tumor tissue [34].

The sensitivity and specificity of the ex-vivo assessment of the specimen ranged from 0 % to 100 % and 76 % to 99 %, respectively. However, the definition of a free margin was not mentioned by Filip et al. and Wu et al. and was 0 mm in the study of Pan et al. [33,34,41]. Therefore, the sensitivity of 78 % and specificity of 76 % reported by de Wit et al. are most applicable for this review and these results can be compared to other techniques. To calculate the sensitivity and specificity, we used the by the authors recommended signal-to-background ratio (SBR) of > 1.5 to identify positive and close margins.

The applicability of fluorescence, scored according to the QUADAS-2 tool, was intermediate because of potential interobserver variability. At the moment, an experienced clinician is required to execute the procedures for margin assessment with a SBR [31]. However, with the application of a standardized imaging interpretation, fluorescence could be less interobserver-dependent than the other imaging techniques. De

Table 3
Included studies investigating fluorescence. Pros = prospective, retro = retrospective. N.G. = not given. For de Wit et al. the number of patients with free margins were noted because one patient had two tumors.

	Methodology	Deep or superficial margin assessed	In- or ex-vivo	Number of tumors and/or, margins	Fluorescence & dose	Acquisition time (minutes)	Surgical margin aim (mm)	Immediate revision	Definition histological positive margin (mm)	Definition histological free margin (mm)	Number of positive tumors and/or, margins (%)	Number of free tumors and/or margins (%)	Device
(Wu et al., 2022)	Retro vs. Retro	Both	Both	Tumors: intervention:13 control: 16, margins: intervention: 129 control: 112	ICG: 0.75 mg/kg 10 h before surgery	N.G.	15 – 20 from fluorescence	Yes, based on fluorescence after FSA confirmation	N.G.	N.G.	Tumors: intervention: 1/13 (8) Control: N.G., margins: intervention: 1/129 (1) control: 7/112 (6)	N.G.	NIF imaging equipment (Nanjing Nuoyuan Medical Devices, Co., Ltd.)
(Pan et al., 2020)	Pros	Both	Both	Tumors: 20	ICG: 0.75 mg/kg 6–8 h before surgery	N.G.	N.G.	Yes, based on fluorescence	0	> 0	Tumors: 2/20 (10)	Tumors: 18/20 (90)	REAL-IGS, NuoYuan Medical Devices Co., Ltd, Nanjing, China integrated with a hand-held NIF spectrometer (Maya 2000 Pro, Ocean Optics, Dunedin, FL, USA).
(de Wit et al., 2023)	Pros	Both	Both	Tumors: 66 (patients: 65) margins: 122	75 mg unlabeled cetuximab and 15 mg cetuximab-800CW 2 days before surgery	5	10	Biopsy of fluorescent positive wound bed	< 1	≥ 5	Patients: 13/65 (20), margins: 14/122 (11),	Patients: 18/65 (28), margins: 71/122 (58),	In-vivo: SurgVision Explorer Air® (SurgVision GmbH) Ex-vivo: SurgVision Explorer Air® coupled to a dedicated closed-field imaging box (Vault, SurgVision GmbH) and the Pearl-Trilogy® (LI-COR Biosciences, Lincoln)
(Filip et al., 2023)	Pros	Deep	Both	Tumors: 4 (3/7 excluded because no oral cavity)	20 mg/kg 5-ALA 3–5 h before surgery	N.G.	N.G.	No	N.G.	N.G.	Tumors: 1/4 (25)	Tumors: 3/4 (75)	405 nm blue light fluorescence-guided headlight system, the operating microscope with blue light capabilities and a handheld camera with an external filter

Wit et al. used the SBR to identify close or positive margins, although the SBR was not predefined. None of the other studies defined an SBR to identify positive or close margins. The study of de Wit et al. was the only non-dose-escalating study investigating fluorescence molecular imaging (FMI) [31]. The extent of the margin can be estimated ex-vivo, which, in combination with a closed-field device, also enables standardization of imaging [43].

Compared to the other studies, the use of 5-ALA had practical disadvantages. There was a need to cover the skin for up to 72 h after administration and the operating room lights also needed to be covered with a filter to prevent the transmission of light below 470 nm, to prevent the consequences of photosensitivity. Within a small sample size (n = 4), they found a sensitivity and specificity of 100 % [41].

Magnetic resonance imaging

Magnetic resonance imaging (MRI) has been used to visualize the tumor-free margins intraoperatively in three studies with a small sample size (n = 10) per study (Table 4). The whole specimen is scanned in an ex-vivo setting, and the goal is to visualize the mucosal and deep margins, which can provide feed-back for the surgeon during the same session. Giannitto et al. [44] used a 1.5 Tesla (T) MRI-system, Heidkamp et al.[32] a 3 T MRI-system, and Steens et al. [25] a 7 T MRI-system. None of the studies used the margins measured by the MRI-system for intraoperative feedback. The percentages tumors with a $\geq$ 5 mm margin varied between 20 % and 90 % (median: 70 %). The acquisition time ranged from 16 to 90 min. All three studies immersed the specimen in perfluoropolyether to eliminate magnetic susceptibility artifacts arising from the air-to-tissue transition. Furthermore, the three studies investigated this technique only for SCC of the tongue, therefore information about bony margins is lacking.

The sensitivity and specificity for the three studies were calculated for a 5 mm margin determined by the MRI-system and histology (Table 2, Fig. 3). Heidkamp et al. analyzed the sensitivity and specificity for identifying < 5 mm margins on MRI by analyzing only 3 margins (cranial, caudal, and deep). Two readers analyzed the MRI-scans, and those measurements were compared to histology [32]. Giannitto et al. and Steens et al. looked at only one margin per specimen [25,44]. The sensitivity of Giannitto et al. and Steens et al. was much higher than the sensitivity found by Heidkamp et al. This could be because Steens et al. and Giannitto et al. looked at the whole specimen, while Heidkamp et al. looked at multiple margins within multiple slices per tumor. Moreover, it is unclear if the narrowest margin measured on histology was located at the same site on MRI in the studies of Giannitto et al. and Steens et al. Also, variation in the MRI systems, sequences used, and bore size could play a role in the observed sensitivity differences. Presumably, the lower the field strength of the MRI system and the wider the bore, the lower the signal-to-noise ratio, which can hamper the visualization of fine details [25,32]. Also, the different radiofrequency coils used in the studies, which are important in MR image quality, could play a role in the found differences in sensitivity [45].

Distinguishing oral mucosa from the resection plane was difficult and thereby mentioned as a limitation in two out of three studies [25,32]. Also, the acquisition times varied between 16 and 90 min, which is relatively long for intraoperative implementation, especially when compared to the other imaging techniques.

General discussion

In oral SCC, the tumor-free margin is an important prognostic factor that can be influenced by the surgeon [46]. Unfortunately, obtaining free resection margins is challenging, and a technique that can determine the extent of the tumor-free margin intraoperatively is needed. Three different imaging modalities emerged after a literature search and were analyzed in this systematic review, which can potentially determine the extent of the tumor-free margin in the deep resection plane

Table 4
Included studies investigating MRI. Pros = prospective, retro = retrospective, R1 = reader 1, R2 = reader 2.*= values in study adjusted to review.

	Methodology	Deep or superficial margin assessed	In- or ex-vivo	Number of tumors and/or margins	Acquisition time (minutes)	Surgical margin aim	Immediate revision	Definition histological positive margin (mm)	Definition histological free margin (mm)	Number of positive tumors (%)	Number of free tumors and/or margins (%)	Coil and MRI-system
(Giannitto et al., 2021)	Pros	Both	Ex-vivo	Tumors: 10	23 (range: 16 – 40)	N.G.	Yes, based on FSA	< 1	≥ 5	1/10 (10)	9/10 (90)	A four channel phased array surface carotid coil (Magnetom Aera, Siemens) and a 1,5 T MRI system (Magnetom Aera, Siemens)
(Heidkamp et al., 2020)	Pros	Both	Ex-vivo	Tumors: 10 margins: 160 (R1:117, R2:121)	30	N.G.	No	< 1	≥ 5	N.G.	Tumors: 7/10 (70), margins:143/160 (89)	A bilateral four-channel phased array surface carotid coil (Machnet BV, Roden) and a 3 T MRI system (Magnetom Skyra, Siemens Healthineers)
(Steens et al., 2017)	Pros	Both	Ex-vivo	Tumors: 10	< 90	N.G.	No	< 1 *	≥ 5 *	1/10 (10)	2/10 (20)	An integrated circular polarized transmit/receive 1H volume coil and a Bruker ClinScan horizontal-bore MR system, interfaced to a Siemens Syngo VB15 console (Bruker BioSpin)

during cancer resection. US is the most investigated technique, with ten publications. Four publications investigated fluorescence, and three publications focused on MRI. Most studies focused on the narrowest margin of the entire specimen instead of multiple margins at different locations of the specimen. We believe that it is more accurate to look at the agreement per location of the predicted margin by the imaging technique and the corresponding histological margin. Focusing on the narrowest margin per specimen could be less accurate because if there is a margin of < 5 mm on histology, it could be at an entirely different location than the < 5 mm margin indicated by the imaging technique. However, the narrowest margin is probably more interesting for the individual patient and clinical practice.

Seven studies did not perform a re-resection to improve margin status based on the findings on ex-vivo images [25,30,32,36,37,40,41]. Four studies used FS or a biopsy to analyze margins, whether or not guided by the imaging technique, to identify or confirm positive or close margins [29,31,34,44]. All studies had the intention of improving the deep margin status, whether for immediate implementation or for eventual application. However, the definition of 'deep margin' was not always clear. Some studies defined the deep margin as the central part beneath the tumor [26–28]. But most studies did not mention their definition of the deep margin. The definition of a deep margin is important to be able to compare the performance of different studies and techniques.

Intraoperative intraoral US and MRI tend to have higher specificity than sensitivity. Fluorescence molecular imaging (FMI) with cetuximab tends to have a higher sensitivity than US or MRI. The sensitivity of these techniques could be enlarged by increasing the cut-off margin for re-resection. US and ICG fluorescence were the only techniques that enabled real-time in-vivo guidance, which is preferable over a re-resection, probably due to relocation problems [15–17]. However, until now the application of US for bony resections in oral SCC was not investigated. In the future, US could guide the soft tissue resection in-vivo, while FMI, ex-vivo US, and MRI could identify the positive or close margins and FSA (relatively high specificity) could confirm these margins. FMI is the only technique which was investigated to aid in obtaining information about the bony margins. Furthermore, to improve the comparability of the imaging techniques and studies, we would advise to define a generally accepted clear definition of a deep margin or for each author to at least mention what definition was used. Also, more subsites in the oral cavity could be investigated. Most of the included studies focused on the oral tongue and larger cohorts are needed to prove the superiority of the imaging technique over visual inspection and palpation.

We deliberately did not discuss the intraoperative assessment of resection margins method [46], diffuse reflectance or "Raman" spectroscopy [47–49], Spider Mass spectroscopy [50], hyperspectral imaging [51,52], touch imprint cytology [53,54], and 3D positron emission tomography and X-ray computed tomography (3D-PET-CT) [55] in this review, as these techniques only image a small proportion of the resection margin, margins were not correlated to histology, or the technique was able to only identify tumor cells at the cut surface of the specimen.

Conclusion

For oral SCC currently three imaging techniques are used intraoperatively which can image the entire tumor-free soft tissue margin: US, fluorescence, and MRI. Overall, the sensitivity of these techniques is currently insufficient for identifying < 5 mm margins, and further research on larger cohorts is needed to improve the sensitivity by determining cut-off points for a re-resection. This would improve the diagnostic value needed for the clinical implementation of these much desired additional techniques to obtain adequate resection margins.

CRediT authorship contribution statement

C.M.E.M. Adriaansens: Writing- original draft, Validation, Data curation, Writing – review & editing, Visualization, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **K.J. de Koning:** Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **R.J.J. van Es:** Writing – review & editing, Visualization, Supervision. **R. de Bree:** Writing- review & editing, Visualization, Supervision, Methodology. **Rob Noorlag:** Writing – review & editing, Visualization, Supervision, Methodology, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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