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Feasibility study of ultrasound-guided resection of tongue cancer with immediate specimen examination to improve margin control – Comparison with conventional treatment

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ABSTRACT

Objectives: Squamous cell carcinoma of the tongue (SCCT) is preferably treated by surgery. Free resection margins (≥5 mm) provide local control and disease-free survival. However, close (1–5 mm) and positive margins (<1 mm) are frequently encountered. We present our first experience of in-vivo ultrasound (US) guided SCCT re-sections followed by ex-vivo US control on the resection specimen to obtain free margins. We compare the results with those from a hisorical cohort of 91 conventionally treated SCCT patients.
Materials and methods: Ten patients with SCCT were included in a consecutive US-cohort. We aimed for a 5–10 mm margin during surgery, while we visualized the resection plane on US. Ex-vivo US measurements on the resection specimen determined whether there was any need for an immediate re-resection. US measurements were then compared with histopathology. Histopathological margins were compared with a consecutive cohort of 91 patients who had undergone conventional surgery for a SCCT.
Results: In the US cohort, 70% of the margins were free. In the conventional cohort, this figure was 17% (P = 0.005). US predicted minimal histopathological margin distance with a mean ± SD error of 1.9 ± 1.8 mm. The mean ± SD of the histopathological overall submucosal/deep margin distance was 7.9 ± 2.1 mm in the US cohort and 7.0 ± 2.2 mm in the conventional cohort (P = 0.188). Ex-vivo examination through use of US indicated an immediate re-resection, which prevented local adjuvant treatment.
Conclusion: Use of US-guided SCCT resection is feasible and improves margin control.

Introduction

Squamous cell carcinoma of the tongue (SCCT) is preferably treated by surgery. Free margin status, i.e. a minimal histopathological margin distance of ≥5 mm, is essential for local control and disease-free survival [1,2]. A close (1–5 mm) or positive (<1 mm) margin status is frequently encountered; analysis of SCCTs that have been surgically treated between 2004 and 2010 in our centre revealed that 64% of the patients had a close and 26% had a positive margin status. Submucosal and deep margins in particular are often inadequate [2]. These results are in line with those that have been published in the literature, which report that oral cancer patients have up to 45% close-margin status and up to 43% positive-margin status after surgery [3].

Close or positive margin status frequently leads to a requirement for adjuvant therapy such as re-resection or (chemo)radiation [1,2]. A previous study that was conducted in our centre revealed that adjuvant treatment at the primary tumour site was given to 35% of the patients with oral cancer. This could have been diminished by better surgical margin control [2]. One major disadvantage of re-resection is that relocation of close or positive margins poses a challenge that could result in uncertainty about definitive margin status [4,5]. (Chemo)radiation affects the patients' quality of life due to significant morbidity and (oral)

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discomfort due to, e.g., mucositis, fibrosis and possible osteoradionecrosis.

Conventional SCCT resections are guided by digital palpation and preoperative imaging. However, digital palpation does not provide accurate information about intra-operative margin distances. The only method that can provide supplementary intra-operative feedback on margin distances is analysis of frozen sections, but this method is not routinely available in every centre. Moreover, it offers low sensitivity in predictions of close/positive margin status due to its low sample rate [6,7]. There is no reliable, standard method that reduces either the risk of close/positive margins or the risk of overtreatment, i.e. excessively large margin distances.

Intraoral ultrasound (US) is an accurate method that is used to predict histopathological tumour thickness (TT) in early SCCT [8,9]. US-guided tumour resections are conducted in several surgical disciplines [10,11]. In a large trial that involved 134 palpable breast-cancer patients, Krekel et al. [10] showed that US-guided breast-sparing surgery was superior to conventional, palpation-guided surgery when clinicians aimed for a free margin status. Several small projects have studied US-guided resections of SCCT [12–14]. In the most recent study, Tarabichi et al. [14] used a US-guided surgery technique on 12 patients who had early SCCT. The researchers completed all procedures successfully without any complications that were related to the use of US. They aimed for a 10 mm margin distance; they achieved a deep histopathological margin distance of 9.7 ± 1.2 mm (mean ± SD). Their study confirmed the safety of this approach and suggested that US-guided resection of SCCT could be used to acquire free margin status without excessive margin distances [14]. Brouwer de Koning et al. [15] evaluated how ex-vivo US measurements on resection specimens could be used to predict the minimal margin distance on definitive histopathological results. They found a mean ± SD error of only 1.1 ± 0.9 mm, which suggests that ex-vivo US measurements are reliable as well.

In line with these promising studies, we present our first experiences with US-guided SCCT resections. The presented method combines both intraoral in-vivo US measurements and immediate intra-operative ex-vivo US measurements of the resection specimen. With this method we aimed for a free margin status that did not incorporate overtreatment. In this study, the feasibility of this method was evaluated in a consecutive cohort of ten patients. US-measured TT and margin distances were compared with histopathological results. Histopathological margin distances were compared with those that were obtained in a retrospectively evaluated consecutive cohort of 91 patients who had been conventionally treated for SCCTs, to gain insight into undertreatment and overtreatment in conventionally resected SCCT.

Materials and methods

This study was performed in accordance with the 1964 Declaration of Helsinki and guidelines for good clinical practice. The local independent Medical Ethics Review Board of our institute approved the study protocol (trial ID: NL8336).

US cohort

Patient inclusion

A consecutive cohort of ten patients who underwent treatment for SCCT between November 2019 and January 2020 was investigated (Tables 1 and 2). Patients were enrolled for the study during visits to our outpatient clinic. A patient was eligible for inclusion if: 1) a SCCT was diagnosed; 2) the tumour's mucosal surface was within reach of the US probe; 3) the tumour was detectable as a hypoechoical region on US; and 4) the surgical treatment was scheduled to be performed under general anesthesia. A 16 MHz hockey-stick-shaped US probe (L16-4Hs, Mindray Bio-Medical Electronics, Shenzhen, China) was used for intraoral examination. This probe provides better accessibility in the oral cavity than a symmetrically-shaped US probe (Fig. 1). A technical physician (KJK) measured the TTs during these examinations.

Table 1
Demographical data and tumour characteristics US and conventional cohorts.

	US cohort (n = 10)	*Conventional cohort (n = 91)*	*P-value*
Gender (n)			
Male (%)	7 (70)	53 (58)	0.736
Female (%)	3 (30)	38 (42)	
History (n)			
Oral cancer (%)	1 (10)	7 (8)	0.579
Age (years)			
Mean ± SD	59.9 ± 12.2	66.6 ± 12.7	0.117
Depth of invasion (mm) Median (IQR)	6.2 (3.6–7.4)	6.1 (3.7–9.5)	0.446
Pathological tumour stage (n)[b]			
pT1 (%)	3 (30)	33 (36)	0.527
pT2 (%)	9 (60)	37 (41)	
pT3 (%)	1 (10)	21 (23)	
Growth pattern (n)			
Non-cohesive (%)	7 (70)	44 (48)	0.318
Perineural (%)	4 (40)	25 (28)	0.467
Vaso-invasive (%)	2 (20)	5 (5)	0.142

Intra-operative technique

Under general anaesthesia, the TT was measured through use of the hockey-stick-shaped US probe (Fig. 1**A-B**). A mucosal margin distance of 10 mm was marked around the lesion. The surgeon then resected the tumour from the anterior by use of a monopolar diathermic surgical knife. When the resection plane reached under the anterior mucosal tumour border, US measurements were performed again. It was ensured that a thin layer of air was created between the specimen and the wound bed, by placing the specimen back in its original location (Fig. 1**C**). This was visible as a hyperechoical border on US (Fig. 1**D**). The closest distance from the tumour border to the resection plane was measured. The surgeon used this distance as feedback to aim at an echographical margin distance of between 5 mm and 10 mm. The same procedure was repeated when the resection plane reached the middle portion and posterior mucosal border of the tumour. The resected specimen was then marked with sutures for orientation. During the same session, a high-resolution, symmetrically-shaped 20 MHz US probe (L20-5s, Mindray) was used to measure ex-vivo the margins at five locations: anterior, posterior, cranio/medial, caudo/lateral and central (Figs. 1E-F and 2). If one or more of these margin distances was measured as less than 5 mm on US, an immediate re-resection was executed on the corresponding location of the tumour bed. A note was made of occasions when the tumour border was hard to distinguish ("unclear") and this problem provoked a discussion about its location during surgery. A technical physician (KJK) or a head and neck oncological surgeon (RJJE) performed the US measurements. An experienced radiologist (JWD) was consulted for image acquisition and understanding.

Conventional cohort

To analyse the conventional treatment of SCCT, we selected a consecutive cohort of 91 patients who had histological T1-3 SCCTs (*Tumour, nodes and metastases (TNM) Classification of Malignant Tumours,* 8th edition) [16] and who were conventionally treated between July 2014 and September 2018 in our centre. The exclusion criterion was the performance of excisional biopsies or surgery without curative intention. The results of frozen-section analysis were not analysed as a variable, since this analysis method was used in only 2% of the cases. Demographic and clinical data were extracted from the medical electronic database (Table 1).

Table 2
Patient-specific clinical data, TT and margin distances found by US and histopathology.

	Clinical data				Tumour thickness					Margin distance			Other				
					Measured			Error		Minimal		Error	Re-resection based on US		Growth pattern			US border
#	Head and neck cancer history	Pathological tumour stage	Location	SNP (protocol)	In-vivo US	Ex-vivo US	Histopathology	In-vivo US	Ex-vivo US	Ex-vivo US	Histopathology	Ex-vivo US	Performed	At close location	Non-cohesive	Perineural	Angio-invasive	Distinguishable
1	Yes	pT1	B	2-day	5.5	5.9	3.7	1.8	2.2	6.5	6.4	0.1	No	-	Yes	No	No	U
2	No	pT2	B	2-day	6.5	10.5	10.4	-3.9	0.1	7.2	1.1	6.1	No	-	Yes	No	Yes	C
3	No	pT3	B	No	10.0	10.2	10.2	-0.2	0.0	3.9	2.2[a]	1.7	Yes	Yes	No	No	No	C
4	No	pT2	B	2-day	6.5	6.6	5.7	0.8	0.9	6.8	5.2	1.6	No	-	Yes	Yes	Yes	C
5	No	pT1	D	1-day	4.8	5.0	3.5	1.3	1.5	5.8	5.0	0.8	No	-	Yes	No	No	U
6	No	pT2	B	2-day	6.3	6.8	6.7	-0.4	0.1	7.1	9.0	-1.9	No	-	No	No	No	C
7	No	pT2	B	2-day	5.1	5.1	7.0	-1.9	-1.9	5.2	6.2	-1.0	No	-	Yes	No	Yes	C
8	No	pT2	B	2-day	3.4	3.2	6.7	-3.3	-3.5	3.8	0.2	3.6	Yes	Yes	Yes	Yes	Yes	C
9	No	pT2	B	No	9.5	6.7	5.7	3.8	1.0	5.2	5.5	-0.3	No	-	Yes	No	No	C
10	No	pT1	B	2-day	4.5	6.4	3.2	1.3	3.2	7.3	4.9	2.4	No	-	No	No	No	C

Abbreviations: B: border of the tongue, D: dorsal surface of the tongue, C: clear, U: unclear.
[a]This patient received an intra-operative resection margin based on US, changing minimal margin distance from 2.2 to 5.3 mm. This distance is taken into account in all other analyses.

Histopathological examination

The resection specimens from both the US and conventional cohorts were paraffin-embedded and dyed for orientation. Specimens were cut into slices of ~3–5 mm. The mean thickness of the slices was determined retrospectively by dividing the reported length of the specimens by the reported number of slices. A 4 μm thin section of each slice was obtained, and each was stained with haematoxylin and eosin and digitalised. The TTs and tumour growth patterns (non-cohesive, perineural and vaso-invasive) were recorded. Margin distances at submucosal/deep level at the five specific locations (anterior, posterior, cranio/medial, caudo/lateral and central, Fig. 2) were determined by a dedicated senior pathologist in training (SAK) and a dedicated head and neck pathologist (SMW). Margin distances were determined by use of a digital ruler or were calculated by multiplying the number of tumour-free slices as determined through use of a microscope with the mean slice thickness.

Analysis

In the US cohort, we calculated the mean prediction errors in the histopathological results for TT (both for in-vivo and ex-vivo US) and for minimal margin distance (only for ex-vivo US). In both cohorts, the measured margin distances at submucosal/deep level were categorised as: "overtreatment" (defined as a margin of >10 mm), free (≥5 mm), close (1–5 mm) and positive (<1 mm) margins. The frequency of occurrence of these categories was determined for each of the five submucosal/deep locations: anterior, posterior, cranio/medial, caudo/lateral and central (Fig. 2). In cases in which patients underwent re-resections that changed the margin distances at that location, the margins were re-defined for these analyses.

The minimal margin was taken to determine the definitive margin status in both cohorts. The mean minimal margin distances were determined in both cohorts and compared with each other. All location-specific margin distances (Fig. 2) were averaged to determine the "overall margin distance" of the resection specimen. For both cohorts, the mean location-specific margin distances and mean overall margin distances were compared with each other.

Fisher's exact tests were performed to identify statistically significant differences in frequency of demographical data, clinical data and margin status between both cohorts. Independent sample t-tests were performed to identify statistically significant differences in mean values of demographical data, clinical data and histopathological margin distances. In cases in which data were not normally distributed (according to histograms, Q-Q plots and Shapiro-Wilk tests), Mann-Whitney U tests were performed instead, to identify differences between medians.

Calculations and tests were performed through use of IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp., 2012).

Results

Demographical and clinical data

Table 1 shows the demographical and clinical data of both the US and conventional cohorts. No significant differences were found between groups regarding gender, age, history of oral cancer, T classification, depth of invasion or histopathological growth pattern.

US cohort

Table 2 shows patient-specific clinical data and compares the TTs that were measured echographically and margin distances with the histopathology of the US cohort. One patient (no. 1) had experienced two previous primary SCCTs. Eight patients had received a sentinel node procedure (SNP), i.e. a peritumoural injection of a radioactive nanocolloid tracer. In one patient (no. 5), the nanocolloid had been injected on the same day as the surgery was performed (one-day protocol), while the seven other patients had received it one day prior to surgery (two-day protocol). All procedures were completed without any complications that were related to the use of US. The use of US in-vivo led to a predicted TT with a mean ± SD error of 1.9 ± 1.4 mm, while its use ex-vivo led to a predicted TT with a mean ± SD error of 1.4 ± 1.3 mm. The mean ± SD error of the minimal margin distance between ex-vivo US and histopathology was 1.9 ± 1.8 mm.

Three patients (nos. 2, 3 and 8) initially were classified with close or positive margin status (Table 2). Patient no. 3 had an immediate intra-operative re-resection, because a 2.2 mm margin distance was found by use of US in the resection specimen. Since this re-resection induced a free margin of 5.3 mm according to histopathological examination (Table 2), local adjuvant treatment was prevented. Patient no. 8 received an immediate intra-operative re-resection at a location that showed a histopathological close distance, yet this appeared not to be found at the location of the minimal margin distance. It was determined that extensive microscopic non-cohesive growth had occurred. Small

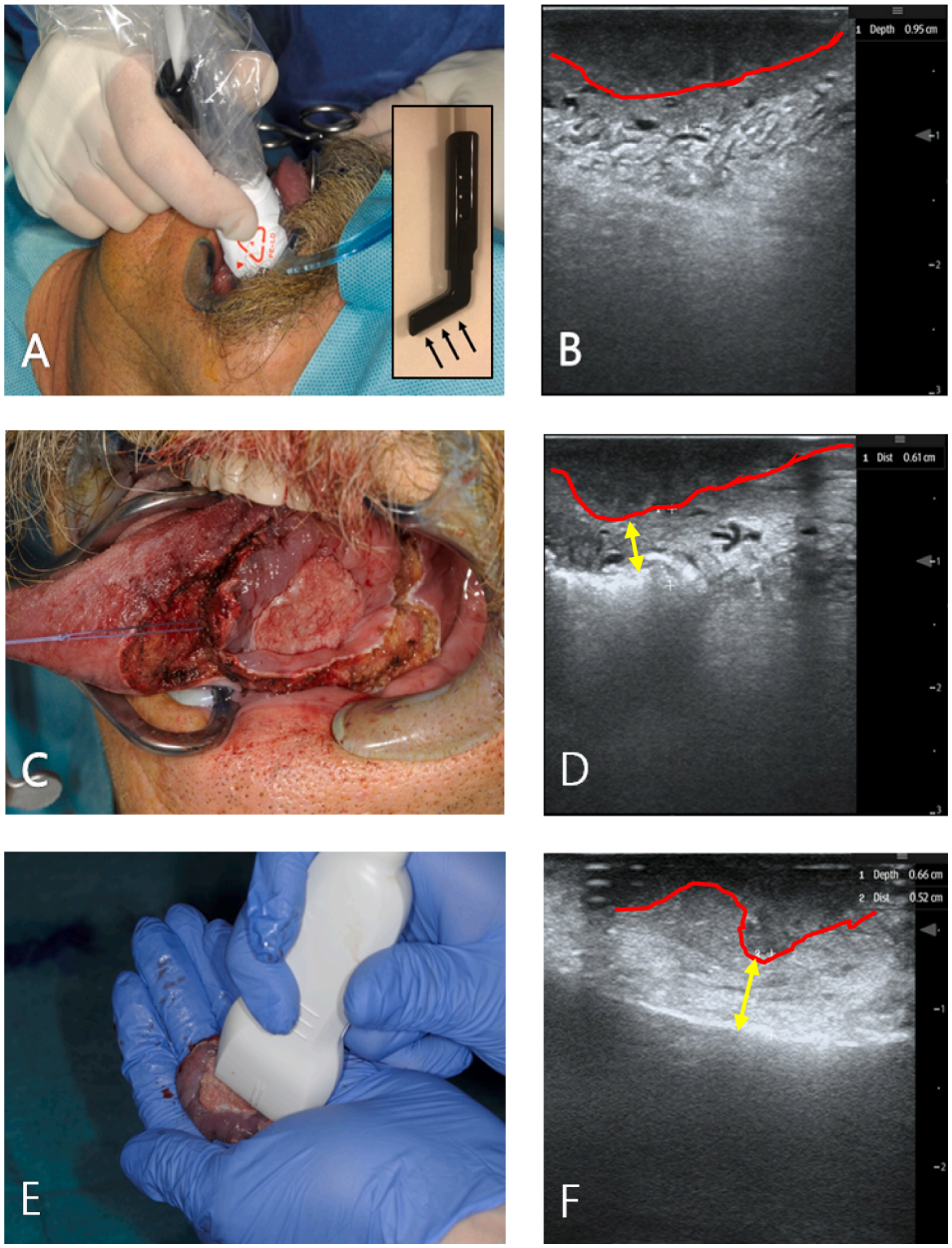

Fig. 1. Photographs of the surgical workflow used in this study (patient 9). The tumour border is marked with a red line and the margin distance at the central location is depicted with yellow arrows. A-B: intraoral US for in-vivo determination of TT with the 16 MHz hockey-stick-shaped probe (indent, black arrows point to transducer). C: resection of the lesion with a 10 mm mucosal margin. The resection plane has reached the middle of the tumour. D: the resection plane is visible as a white border during in-vivo examination. E-F: ex-vivo determination of TT and margin distances with the 20 MHz probe.

tumour nests (of diameter 0.5 mm) were found close to the resection plane (minimal margin distance 0.2 mm), and these nests caused this margin to be undetectable during ex-vivo US (Fig. 3**A**).

Two patients, nos. 1 and 5, had tumour borders that were hard to distinguish on US during surgery (Table 2). These difficulties gave rise to discussion about the exact location of the borders. In patient no. 1, who had undergone two previous ipsilateral resections of SCCT, deeply included salivary tissue was mistaken for tumour on US because of a similar echodensity in both tissue types (Fig. 3**B**). Patient no. 5 was the only one who underwent a one-day SNP protocol.

US vs. conventional cohort

In some cases that were part of the conventional cohort, location-specific margin distances were not measurable (in 9%, 5% and 2% of the anterior, posterior and caudal locations, respectively), due to lack of information in the histopathological reports and the absence of digital sections. The location-specific margin distances are depicted in Fig. 2 for both cohorts. Considering the US cohort, overtreatment was found most often at the central location (50%). Considering the conventional cohort, overtreatment was found most often at the posterior location (33%), while the most close and positive margins were found at the caudo/lateral location (41%).

Table 3 compares the histopathological margin results of both cohorts. Free margin status was significantly more frequent in the US cohort (70%) than in the conventional cohort (17%); these figures are also depicted in Fig. 2. There is a significant difference ($P = 0.007$) between the mean margins for the two cohorts at the central location: 9.2 mm in the US cohort (SD: 4.1 mm) and 6.2 mm (SD 3.3 mm) in the conventional cohort. The mean minimal margin distance was significantly different ($P = 0.046$) between the cohorts: 4.9 mm (SD: 2.5 mm) in the US cohort and 3.5 mm (SD 2.0 mm) in the conventional cohort. The mean overall margin distances were not significantly different.

Discussion

This feasibility study has evaluated the applicability of US-guided resection of SCCT combined with direct ex-vivo control of the

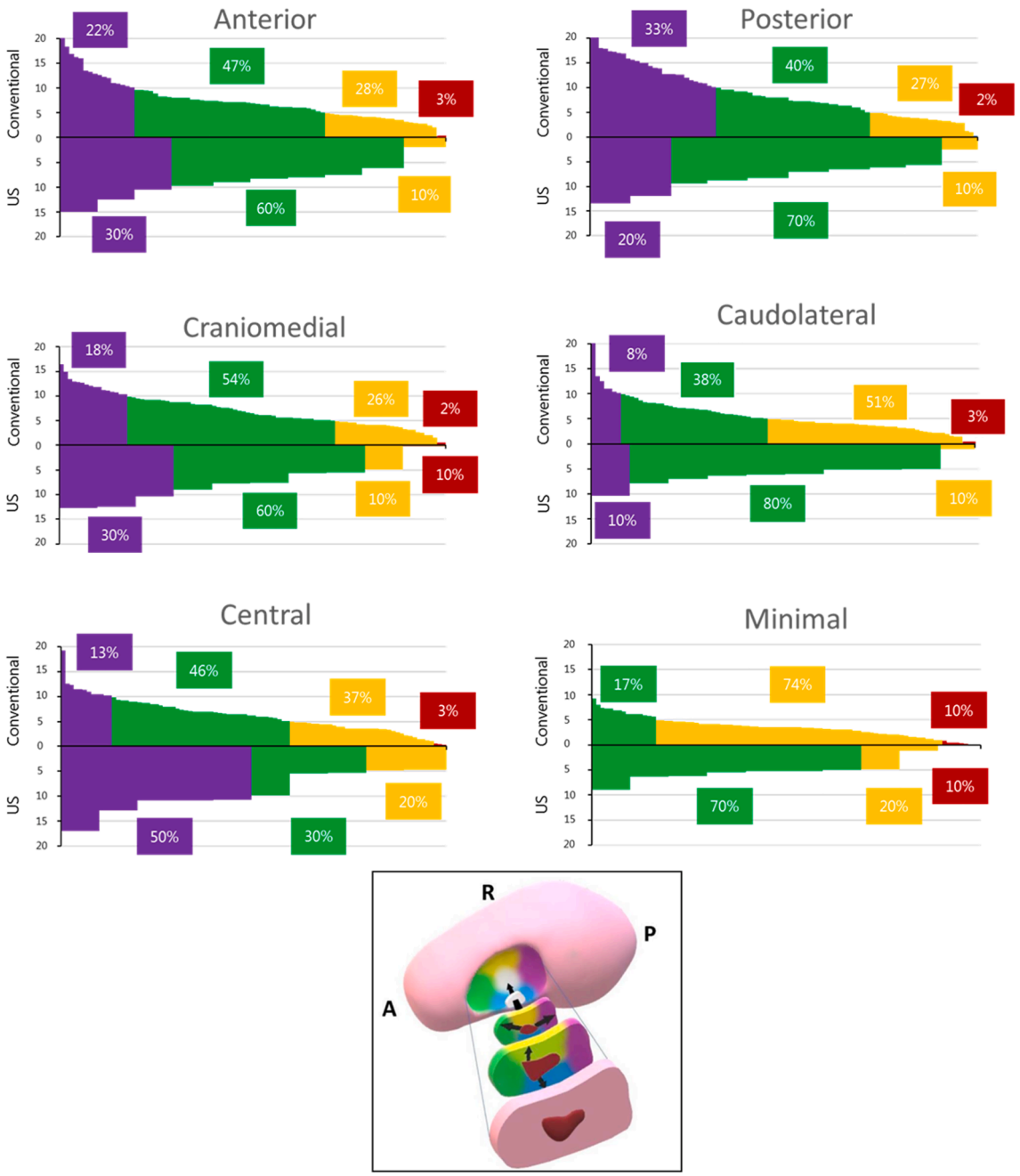

Fig. 2. Depiction of margin distances in specific directions at submucosal/deep level, together with the minimal distances of both cohorts. Purple: overtreatment; green: free margins; orange: close margins; red: positive margins. Numbers in coloured boxes represent frequency. In the black box, the specific locations for margin assessment at submucosal/deep levels are visualised in a virtually sliced resection specimen. Note that mucosal levels are not evaluated. Green: anterior; purple: posterior; yellow: cranio/medial; blue: caudo/lateral; white: central. The black arrows indicate examples of the measured margin distance in all directions. A: anterior; P: posterior; R: right side of tongue.

resection specimen. Histopathological results were compared with those that were obtained through conventional treatment of SCCT. To our knowledge, this is the first study that has evaluated margins at five different submucosal/deep locations. As such, it has demonstrated both the locations at which it is difficult to achieve adequate resection margins and the locations where improvement can be made in terms of preventing overtreatment, i.e. margins of >10 mm.

This study has exposed several advantages of the used methodology. First, because of its shape, the 16 MHz hockey-stick-shaped probe proved to be useful to visualise intraoral in-vivo tumour borders (Fig. 1**A-B**). It did not cause disproportionate discomfort to the patient during inclusion tests that were performed in our outpatient clinic. Second, the 20 MHz probe provided images that showed a higher resolution during ex-vivo US measurements. This improved resolution contributed to the achievement of a precise re-resection in the same session for one patient (Table 2). Third, the application of US did not extend surgical time more than the use of frozen sections would have done. Moreover, sample rate was higher and costs were lower than if frozen sections had been used [6,7]. Lastly, the resection plane was clearly visible in all cases because an air layer was created between the resection specimen and the wound bed. Other methods have been applied that aim for an echographic free margin; these involve the placement of sutures [17], needles [12,13] or retractors [18] under the echographic tumour border. However, we prefer this more

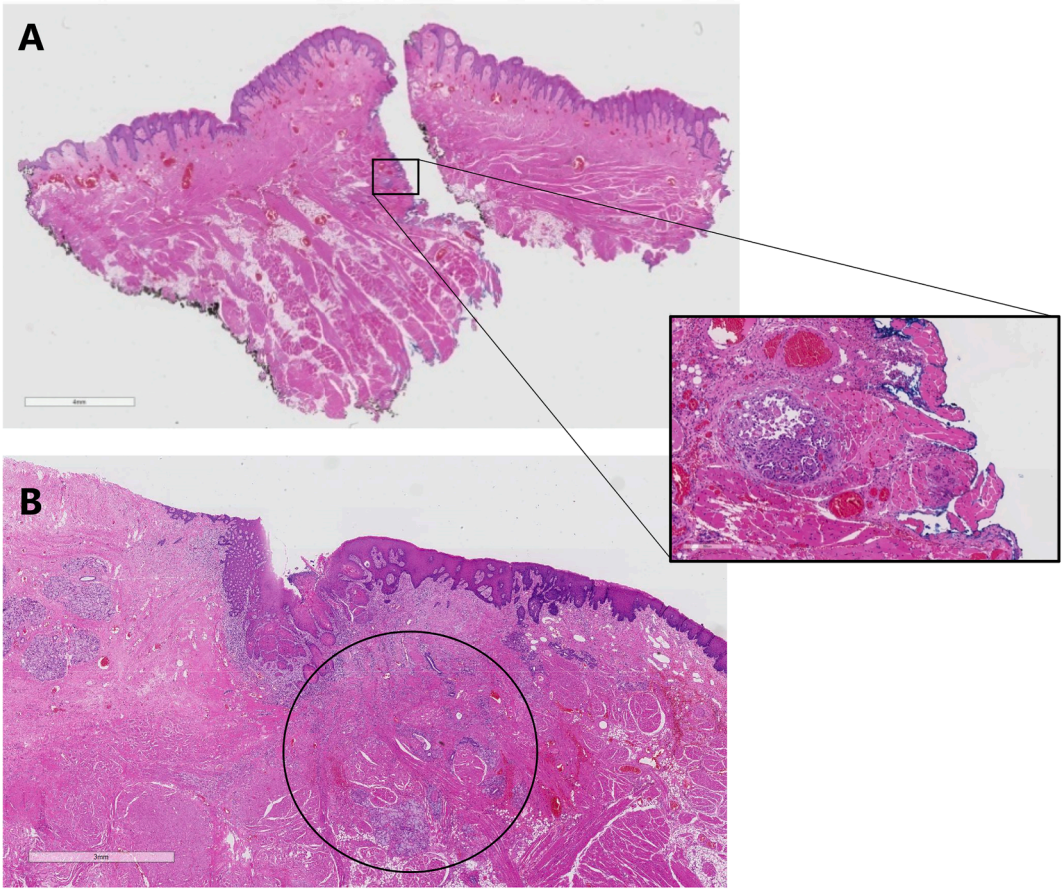

Fig. 3. Microscopic views of HE-stained histopathological sections of tumours taken from two patients. A: patient 8. In the black box, an infiltrative, microscopic tumour nest is detectable due to microscopic perineural growth. It caused a close margin from the resection plane (blue ink). The nest was not detectable on US. B: patient 1. Deep salivary gland tissue can be seen in the black circle. This caused a false-positive measurement during US examination. Its location is probably due to previous SCCT surgery.

Table 3
Histopathological margins found in US and conventional cohorts.

	US cohort (n = 10)	*Conventional cohort (n = 91)*	*P-value*
Margin status (n)			
Free (%)	7 (70)	15 (17)	**0.005**[a]
Close (%)	2 (20)	67 (74)	
Positive (%)	1 (10)	9 (10)	
Margin distances (mm) –mean ± SD			
Submucosal/deep			
- Anterior	9.3 ± 3.7	7.4 ± 4.4	0.200
- Posterior	7.6 ± 3.4	8.9 ± 5.6	0.462
- Cranio/medial	7.6 ± 3.8	7.1 ± 3.3	0.616
- Caudo/lateral	6.1 ± 2.4	5.5 ± 3.2	0.613
- Central	9.2 ± 4.1	6.2 ± 3.3	**0.007**[b]
Minimal	4.9 ± 2.5	3.5 ± 2.0	**0.046**[b]
Overall	7.9 ± 2.1	7.0 ± 2.2	0.188

[a] Statistical significance was determined with Fisher's exact test.
[b] Statistical significance was determined with independent *t*-test.

straightforward method, which shows less chance of tumour seeding as it images the resection plane itself, similar to the technique of Tarabichi et al. [14].

US-guided resection seems to increase the minimal resection margin and thereby improve free margin status (70%) when compared with conventional surgery (17%). This is in line with a comparable study by Beak et al [12]. These researchers increased the deep, free margin status from 55% in a conventional cohort to 95% of patients in the US cohort. In our study, at all specific locations the frequency of free resection margin status was improved (see Fig. 2). Most improvement was seen at the caudo/lateral location. This might be because the tongue must be torqued to display this location. The torque stretches the margin, which may generate a risk of overestimation when no US is applied. Thus, US guidance seems to provide better margin control than conventional treatment.

US guidance seems not to lead to resection of excessive amounts of healthy tissue, given the mean overall margin distance of 7.9 mm (Table 3). Aiming for a 10 mm echographic margin, however, will lead to overtreatment at some specific locations. This can be seen in the mean margin distances at the central location, as shown in Fig. 2 and Table 3. These findings are in line with those published in the literature; Tarabichi et al. [14] also had deep resection margins of more than 10 mm in 42% (5/12) of the patients studied. However, US guidance can also prevent excessively large resections of healthy tissue, as can be seen at the posterior location shown in Fig. 2; the posterior course of the resection can be determined more precisely than without US guidance, since the anterior and deep resection planes are already visualised. US-guided resection has the potential to lead to resections of just the right amount of tissue, instead of insufficient or excessive resection margins. In breast cancer, Krekel et al. showed that US-guided resections generated significantly more free margins, but with a smaller volume of the resection specimen when compared with conventional surgery [10].

Several notable results were found when US measurements were compared with the histopathology results. The smaller mean error that was found in the prediction of histopathological TT with use of ex-vivo

US (1.4 mm) suggested that the ex-vivo US method was more reliable than in-vivo US (1.9 mm). This might be in line with the results of Umstattd et al., [19] who found that an overall mucosal tumour shrinkage of 19.6% occurred immediately after the resection (from in to vivo to ex-vivo), but that there was no shrinkage after formalin fixation (from ex-vivo to histopathology). The fact that we found a higher mean error in the prediction of minimal margin distance (1.9 mm) than Brouwer de Koning et al. (1.1 mm) [20] might be due to pressure on the resection specimen. Although Brouwer de Koning et al. used a non-contact technique with US gel, we prefer a contact technique that offers more control over the resection specimen. A future study to assess reproducibility and reliability of different US-measurement techniques, e.g. hand-held, gel-based or water-based, may clarify the optimal method.

Although these results are promising, several limitations of US-guided resection of SCCT should be addressed. First, we encountered several false-positive measurements (i.e. overestimation of TT during use of US) in patient nos. 1, 5 and 10 (Table 2). In patient no. 1, this was due to previously relocated deep salivary gland tissue that was mistaken for tumour. Despite this patient having undergone two previous ipsilateral SCCT resections, we decided to include the results for this patient, since our conventional cohort also contained patients with a history of oral cancer. In patient no. 5, a peritumoural tracer injection that was performed during the one-day SNP may have made the tumour less distinct on US (Fig. 3**B**). Patient no. 10 had a dense muscular layer directly under the tumour front that changed abruptly into fatty tissue, which was perhaps mistaken for tumour front. However, similar cases should be investigated to confirm this.

Second, we encountered several false-negative measurements (i.e. underestimation of TT during use of US) in patient nos. 7 and 8 (Table 2). This might be explained by the presence of microscopic, non-cohesive and perineural growth towards the central location, the small size of which lay outside the limits of the echographic spatial resolution (Fig. 3**A**). Therefore, aiming for a 10 mm echographic margin rather than 5–10 mm might be more appropriate in such cases to control non-cohesive infiltrative growth in the resection margin.

Third, harmonisation of the in-vivo orientation with the ex-vivo orientation of the resection specimen should be improved. Although immediate ex-vivo US examination seems more efficient than frozen section analysis, [6] it does not solve the problem of relocating close or positive margins on the tumour bed. This is difficult and not always accurate [4,6]. Therefore, it is preferable to aim for a resection with a direct free margin status rather than even immediate re-resections [4].

Fourth, when US is used, experience and skills are required to differentiate between TT and the depth of invasion (an important determinant in tumour-staging [16]), in case the tumour has an exophytic component. This is because the exophytic part of the tumour can only be visualised if there is a minimal amount of pressure from the probe. However, Klein Nulent et al. found that TT measured by US was a good predictor of depth of invasion [8].

Regarding these limitations, we advise that US should be used for guidance in the resection of SCCTs and that clinicians should be aware of its restrictions and pitfalls. Moreover, we advise that an experienced radiologist should be consulted for image acquisition and image interpretation during the first sessions.

In conclusion, this study has demonstrated that performance of resections of SCCT under US guidance, combined with immediate intraoperative ex-vivo measurements as a final check, is feasible. It was found that, when compared with a cohort of conventionally treated SCCT, it improved resection margin status without resection of excessive amounts of healthy tissue. Future studies should validate these findings in larger cohorts and investigate whether the use of US guidance during resections of SCCT indeed improves resection margin status, reduces the requirement for adjuvant treatments and ultimately improves local tumour control, thereby improving the quality of life of patients.

Role of the funding source

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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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