



Assessment of tumour depth in early tongue cancer: Accuracy of MRI and intraoral ultrasound

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ABSTRACT

Objectives: Complete resection of tongue cancer is necessary to achieve local control. Unfortunately, deep resection margins are frequently inadequate. To improve deep margin control, accurate knowledge of tumour thickness is pivotal. Magnetic resonance imaging (MRI) and intraoral ultrasound (ioUS) are frequently applied for tumour staging. This study explores the accuracy of these techniques to estimate depth of invasion.

Materials and Methods: The data of patients with a T1-2 tongue cancer that had been treated surgically between 2014 and 2018 were retrospectively analysed. Measurements that had been taken by either MRI or ioUS were compared with those taken during histopathology.

Results: A total of 83 patients with tongue cancer had undergone a pre-operative MRI and 107 had been studied through an ioUS. Tumour thickness measured by MRI ($r = 0.72$) and ioUS ($r = 0.78$) correlated significantly ($p < 0.001$) with histopathological depth of invasion (DOI). In tumours with a DOI of 0–10 mm, MRI has a mean absolute difference with histopathology of 3.1 mm (SD 3.2 mm) and ioUS of 1.6 mm (SD 1.3 mm). In tumours with a DOI greater than 10 mm, MRI has a mean absolute difference of 3.5 mm (SD 3.0 mm) and ioUS of 4.7 mm (SD 3.5 mm).

Conclusion: Estimation of histopathological DOI in tongue cancers with DOI till 10 mm is very accurate through use of ioUS. ioUS tends to underestimate DOI in tumors exceeding 10 mm DOI. MRI tends to overestimate DOI in both thin and thick tumours. Since ultrasound measurements can be performed during surgery, ioUS could potentially guide the surgeon in the achievement of adequate resection margins.

Introduction

Most tongue cancers are detected as early stage (cT1 or cT2, cN0) tumours, for which complete surgical resection is the preferred treatment [1,2]. To achieve local control, a margin of at least five millimetres (5 mm) at the tumour front is widely accepted as adequate. A retrospective analysis of 105 patients with early-stage tongue cancers who were treated in our centre revealed 11% ‘positive’ margins (i.e. tumour within resection margin) and 63% ‘close’ margins (i.e. tumour within 0–5 mm of resection margin) [3]. These results are in line with those found at other head and neck centres, which have reported up to 36% positive and 48% close resection margins in early oral cancers [4]. Submucosal and deep resection margins in particular are often

inadequate. In cases of positive resection margins or close margins with unfavourable growth characteristics (i.e. non-coherent, vascular invasive and perineural growth), patients are exposed to adjuvant treatment, which consists of either re-resection or (chemo)radiotherapy. Both adjuvant treatments have major drawbacks. Although re-resection can be performed during the same operation after intraoperative margin assessment, in daily practice it is executed mainly as a second stage procedure. However, a ‘clear margin’ after revisional surgery does not equate to an initially negative margin; some study authors even assume that re-resections do not significantly improve local control at all [5]. Adjuvant (chemo)radiotherapy is associated with extended morbidity effects, both locally and systemically, such as neurotoxicity, xerostomia, mucositis, fibrosis and osteoradionecrosis [6–8].

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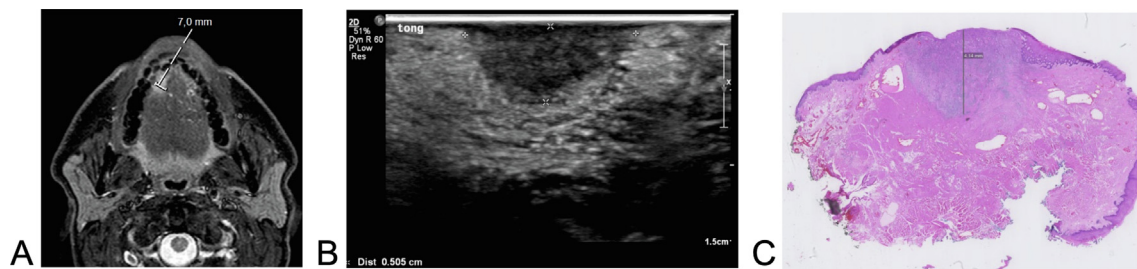


Figure 1. Example measurements of tongue cancer on: A: MRI (axial STIR image), TT 7 mm; B: ioUS (note that the tumour is hypoechoic in comparison with the normal echogenic tongue musculature), TT 5.05 mm, and C: haematoxylin and eosin stained histopathology, DOI 4.4 mm.

To reduce morbidity that is associated with adjuvant treatment, refinement of surgical management is necessary. Surgical resection of the tumour is usually guided visually and by touch. Improvements should focus on deep resection margins because these are often insufficient [3]. To obtain adequate deep resection margins, accurate knowledge of the tumour thickness (TT) or depth of invasion (DOI) is crucial. The interchangeable use of the terms TT and DOI is incorrect. TT is defined as the distance from the tumour surface to the deepest level of invasion and is commonly used in preoperative imaging, whereas DOI is defined as the distance from the reconstructed mucosal surface or basement membrane to the deepest level of invasion and is basically a histopathological characteristic [9]. Magnetic resonance imaging (MRI) and intraoral ultrasound (ioUS) are frequently used to measure TT. Multiple systematic reviews with meta-analyses have confirmed that measurement of TT by ioUS and/or MRI correlates with histopathological DOI. These reviews included the use of both high- and low-frequency transducers, while today high-frequency ioUS transducers are considered to be standard equipment in centres where head and neck cancers are treated [10,11]. To improve control of resection margins, the use of ioUS or intraoperative ex-vivo MRI has been studied recently [12,13]. Although these techniques are promising, more detailed information is needed regarding the accuracy and amount of under- or overestimation of DOI through use of imaging by either MRI or ioUS before these techniques can be used as guidance for the surgeon during the resection of tongue cancer.

The aim of this study is to analyse the accuracy of pre-operatively measured TTs by MRI and/or ioUS compared with the histopathological DOIs of the resection specimens of small (cT1-T2) tongue cancers. If these techniques are accurate enough, i.e. they visualise the invasive tumour front adequately, they can potentially be used to aid in the control of intraoperative submucosal and deep resection planes.

Material and methods

Institutional review board approval statement

The study protocol was approved by the medical research ethics committee of our institute and the study was conducted in accordance with the 1964 Declaration of Helsinki and guidelines for Good Clinical Practice.

Retrospective cohort

The data of all patients who had been treated surgically in our centre between January 2014 and December 2018 for clinical T1 or T2 squamous cell carcinomas (SCC) of the tongue were analysed retrospectively. Patients who had undergone preoperative measurement of TT by MRI and/or ioUS were included in the analysis. The following clinical characteristics were retrieved from the medical files: gender, age at diagnosis, clinical tumour-node-metastasis (TNM) classification (according to TNM 7th ed. guidelines from the American Joint Committee on Cancer (AJCC)), clinical appearance of the tumour

(endophytic or exophytic) and timespan between MRI or ioUS and surgery. Measurements of TT were retrieved from the radiology reports and those of DOI from the histopathology reports. Dedicated head and neck radiologists and pathologists executed all measurements.

MRI, ioUS and histopathology

During diagnostic workup, many patients had received a MRI (1.5 Tesla or 3.0 Tesla MR unit, Achieva, Philips Medical Systems, Best, The Netherlands) and/or an ioUS (EpiQ 5, with CL15-7 transducer, Philips Medical Systems, Best, The Netherlands) by which TT was routinely measured. MRI examinations were performed using a dedicated head and neck coil. The scan protocol included: axial T1-weighted, non-enhanced, axial and coronal short tau inversion recovery (STIR), and axial and coronal T1-weighted images (T1W1) with fat-suppressed, contrast-enhanced sequences. Slice thickness was 4 mm for axial and 3 mm for coronal sequences (no interslice gap). The measurements of TT were performed on the axial sequence on which the tongue tumour was most conspicuous. Either the STIR or the T1-weighted fat-suppressed contrast-enhanced sequence was selected for this purpose. Subsequently, the axial slice with the maximal TT was selected for measurement (example shown in Figure 1A).

In ioUS, the 15 MHz ‘hockey-stick shaped’ transducer was placed perpendicularly without pressure on the tumour, with the tongue in a non-protruded position, to create an axial image in which maximal TT was measured from the transducer to the end of the echolucent border (example shown in Figure 1B). The resection specimen was fixed in formalin overnight and perpendicular slices were cut from anterior to posterior after marking the mediocranial and laterocaudal margins with permanent ink. All slices were paraffin-embedded and processed and tissue sections of 4 µm thickness were cut and stained with haematoxylin and eosin. DOI was defined as described above; an example is shown in Figure 1C [14].

Statistical analysis

The correlation between TT as measured on images and the histopathology was drawn using scatter plots and calculated using Pearson’s product correlation. The absolute differences between histopathology and MRI or ioUS were calculated for each individual patient. Differences in correlation between thin tumours (DOI 0–10 mm) and thicker tumours (DOI greater than 10 mm) were evaluated with the independent samples Mann-Whitney U Test. Statistical tests were carried out using IBM SPSS Statistics for Windows software, Version 25.0. Armonk, NY: IBM Corp., 2018. P-values < 0.05 (two tailed) were considered to be statistically significant.

Results

Descriptive analysis

Between 2014 and 2018, 209 patients who had a clinically grade T1

Table 1
Cohort of 146 cT1-2 tongue SCC patients 2014 – 2018.

Variable	Patients (%)
Sex	
Male	74 (51%)
Female	72 (49%)
Age	
Mean	64 years
Range	34 – 87 years
Clinical T classification	
cT1	84 (58%)
cT2	62 (42%)
Morphology	
Exophytic	26 (18%)
Endophytic	120 (82%)
MRI TT	
No	63 (27%)
Yes	83 (73%)
Timespan between MRI and surgery	
Mean	18 days
Range	1 – 45 days
ioUS TT	
No	39 (49%)
Yes	107 (51%)
Timespan between ioUS and surgery	
Mean	17 days
Range	0 – 49 days
Histopathological DOI	
Mean (SD)	7.3 mm (5.1 mm)
0 – 10 mm (thin tumour)	113 (77%)
over 10 mm (thick tumour)	33 (23%)

or T2 SCC of the oral tongue (according to TNM 7th ed. guidelines from the American Joint Committee on Cancer (AJCC)) were treated in our institute. One-hundred and fourtysix of these patients received ioUS and / or MRI measurement(s) of the tongue tumour thickness preoperatively. Demographic variables of these patients are listed in Table 1. TT was measured in 83 patients on MRI and in 107 patients on ioUS. Of these, 44 patients underwent both imaging modalities. The average timespan between MRI or ioUS and surgery was 17 or 18 days (range 0 – 40 days or 1 – 38 days) respectively. One-hundred and thirteen patients (77%) had a thin tumour (DOI 0–10 mm), and 33 patients (23%) a thick tumour (DOI greater than 10 mm). The mean DOI was 7.3 mm (SD 5.1 mm).

Correlation of MRI and ioUS measurements with histopathology

Figure 1 illustrates an example of MRI, ioUS and histopathological imaging. Measurements of TT on MRI and ioUS both correlated significantly with histopathological DOIs with a Pearson correlation (r) of 0.72 ($p < 0.0001$) and 0.78 ($p < 0.001$) respectively (Figure 2). In the 44 patients that had both imaging modalities preoperatively these correlations were similar. The Pearson correlation was stronger in exophytic tumours (MRI $r = 0.85$ and ioUS $r = 0.87$) than in endophytic tumours (MRI $r = 0.71$ and ioUS $r = 0.77$).

For MRI, there was no significant difference ($p = 0.247$) in correlation between thin and thick tumours. The mean absolute difference between TT on MRI and histopathological DOI was 3.2 mm (SD 3.1 mm, range 0 – 14 mm). In thin tumors DOI was underestimated by more than 3 mm in 2/53 patients (3.8%) and by more than 5 mm in 0/53 patients (0%) and overestimated by more than 3 mm in 15/53 patients (28.3%) and by more than 5 mm in 10/53 patients (18.9%). In thick tumors DOI was underestimated by more than 3 mm in 3/30 patients (10%) and by more than 5 mm in 2/30 patients (6.7%) and overestimated by more than 3 mm in 7/30 patients (23.3%) and by more than 5 mm in 5/30 patients (16.7%).

For ioUS, there was a significant difference ($p < 0.001$) in correlation between thin and thick tumours. The mean absolute difference between TT on ioUS and histopathological DOI in thin tumours was

1.6 mm (SD 1.3 mm, range 0 – 8 mm) and in thick tumours 4.7 mm (SD 3.5 mm, range 1 – 14 mm). In thin tumours, DOI was underestimated by more than 3 mm in 2/86 patients (2.3%) and by more than 5 mm in 0/86 patients (0%) and overestimated by more than 3 mm in 1/86 patients (7.0%) and by more than 5 mm in 1/86 patients (1.2%). In thick tumours, DOI was underestimated by more than 3 mm in 11/21 patients (53.5%) and by more than 5 mm in 5/21 patients (23.8%) and overestimated by more than 3 mm in 1/21 patients (4.8%) and by more than 5 mm in 0/21 patients (0%).

Discussion

The accuracy of the measurement of TT through use of either MRI or ioUS to estimate histopathological DOI is established in a consecutive cohort of 146 patients with clinically early-stage tongue cancers. Both imaging modalities correlate significantly with the histopathological DOI. The present results are in line with our meta-analysis on patient-specific data ($r = 0.82$ for T1-2 tongue cancers based on 9 studies) [10], but do not exactly match two recent meta-analyses that reported correlation coefficients of 0.96 for ioUS and 0.87 for MRI, or another meta-analysis with a correlation coefficient of 0.95 for ioUS in oral cancer [11,15]. Some of the studies included in the meta-analyses used ioUS during the operation in the unconscious patient instead of preoperatively in a conscious patients, which may influence an exact measurement of the tumor thickness. Furthermore, two studies with a very high correlation made a different comparison: Taylor et al. ($r = 0.99$) compared ioUS with macroscopic TT of the resection specimen instead of microscopic DOI and Yamane et al. ($r = 0.99$) compared the ex vivo ultrasound TT of the resection specimen with histopathology [16,17].

Although correlations per se are interesting, we believe that detailed information about the amount of over- or underestimation of these different imaging modalities is clinically more relevant: in clinical practice, surgeons generally attempt to take a 10 mm clinical margin to achieve a histopathological margin of at least 5 mm [3,10]. Taking this into account, ioUS- and MRI-guided resections are expected to be able similarly to obtain clear margins: underestimation of more than 3 mm and especially 5 mm could thread surgical margin control. Oncologic safety is crucial when implementing a new technique. Excessive overestimation could lead to over resection of healthy tongue tissue and decrease of oral function. Taken this into account, in tumours with a DOI up to 10 mm (pT1-2 tumours in the 8th TNM classification), ioUS seems superior over MRI in accuracy, with a mean absolute difference 1.6 mm (SD 1.3 mm) and 3.2 mm (SD 3.1 mm) respectively. This is in line with two previous studies on the same topic that concordantly reported a better correlation with histopathology when ioUS was used compared with MRI, especially in small (< 5mm thick) tumours [18,19]. Although the amount of underestimation of 3 mm on MRI is comparable with ioUS in tumours with a DOI up to 10 mm, the rate of overestimation on MRI is higher. Furthermore, ioUS can be used to guide resections intra-operatively, while MRI can only be used ex vivo. In tumours with a DOI greater than 10 mm (pT3 tumours in the 8th TNM classification), accuracy of ioUS drops and seems to underestimate DOI while the accuracy of MRI is independent of DOI.

There are several explanations for the underestimation of DOI of tongue cancers in both MRI and ioUS. The first is the timespan between performance of imaging and surgery: in both patients for whom the resection margins were underestimated on ioUS by more than 10 mm, this interval was more than four weeks. In one patient, a TT of 7 mm was measured on both ioUS and MRI, and 20 mm on histopathology 30 days later. In the other patient, a TT of 12 mm was measured on ioUS and 26 mm on histopathology 37 days later. A second reason for the underestimation of the DOI could be the pressure applied on the tumour by the intraoral probe. To prevent this phenomenon, a “non-contact technique” can be used [20,21]. A third reason could be that protrusion with traction of the tongue during ultrasound measurement

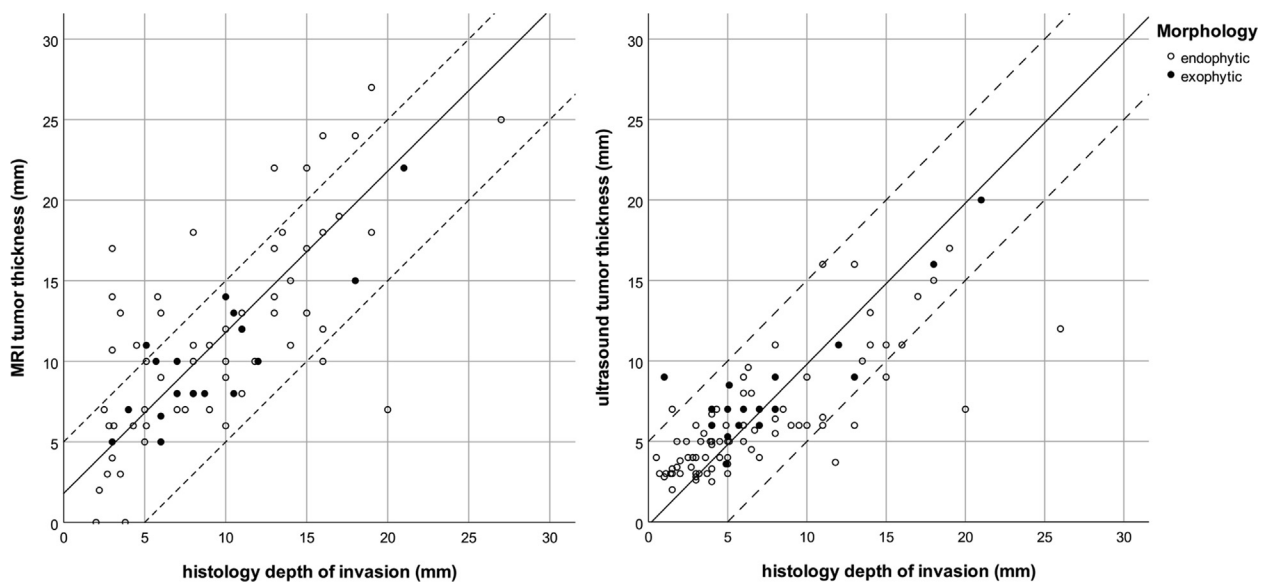


Figure 2. Correlation of measurements of TT on MRI and ioUS with measurements of DOI on histopathology. Left: MRI, Pearson correlation 0.738 ($p < 0.001$). Right: ioUS, Pearson correlation 0.792 ($p < 0.001$). Lines are mean over- or underestimations of imaging modalities. Dotted lines mark 5 mm under- or over-estimations.

could lead to flattening of the tumour, which would result in an underestimation when compared with measurement during histopathological examination of the surgical specimen. In addition, in larger and thicker tumors it is harder to protrude the tongue and visualize the complete tumour with the ultrasound probe. Especially in more posteriorly located tumours, the DOI could thereby be underestimated [20].

Overestimation of the DOI could be explained by shrinkage of the resection specimen during formalin fixation or a slicing error from the cutting plane during histological processing. The amount of shrinkage of TT is unclear. Several studies investigated the amount of shrinkage of (sub)mucosal tissues in tongue cancer resections. Most of them focussed on shrinkage of the healthy tissue in the resection margin. Johnson et al found an average shrinkage of 30% of mucosal resection margins in 8 patients [22]. A more recent study of Mistry et al in 16 tongue cancer patients had comparable results with a shrinkage of 23% for mucosal resection margins [23]. Umstad et al. analysed in vivo, post-resection, and post-formalin fixation shrinkage of both the surgical margin and the tumor width, in 19 oral cancers (of which 13 tongue cancers). Most shrinkage was seen between in vivo and post-resection (6.4% for tumor shrinkage and 14.9% for margin shrinkage). Total shrinkage after fixation was 10.7% on tumor level and 11.3% on margin level [24]. Furthermore, inflammation surrounding the tumour could mimic or blur the boundaries that are observed in images, especially on T2-weighted sequences, although less in STIR and contrast-enhanced T1 window level with fat suppression sequences [25].

We believe that this study outlines in detail the accuracy of both MRI and ioUS when used to determine TT in tongue cancers, however several limitations should be addressed. First, as shown in Table 1, not all patients with early tongue cancer underwent a measurement of the TT by both modalities. Since this was a retrospective clinical analysis it must be realised that, in some cases, excisional biopsies had been performed already on referral and that imaging of small T1 tumours with both ioUS and MRI was not routinely performed in our daily practice. MRI of small primary tumours was frequently skipped because they were often hardly visible on the images, and only ultrasound of the neck was employed for lymph-node assessment [26]. Furthermore, a tongue tumour must be accessible to the ioUS probe. This could be hampered in cases in which tumours extend to the posterior tongue, in patients with restricted mouth opening or in patients with a high gag-reflex. Secondly, because of the retrospective nature of this study, measurements

of TT on MRI and ioUS have been compared with the histopathological DOI. Although these are by definition two different entities, this difference seems clinically insignificant: a recent study that compared TT and DOI in 203 oral SCCs reported a median difference of 0.0 mm and a mean difference of 0.7 mm between TT and DOI measurements [9]. Large discrepancies such as TT that exceeded DOI, e.g. in verrucous carcinomas due to exophytic tumour growth, were rare [27].

In conclusion, the TT that is measured on both MRI and ioUS for tongue cancers correlates well with histopathological DOI measurements. In tumours with a DOI up to 10 mm (pT1-2 tumours in the 8th TNM classification), ioUS is more accurate than MRI and should be the preferred imaging technique since MRI tends to overestimate DOI. In thicker tumors (pT3 tumours in the 8th TNM classification), the accuracy of preoperative ioUS measurement drops which lead to underestimation of DOI, while the accuracy of MRI is independent of TT. We recommend future studies to investigate this by intraoperative ioUS measurement followed by ex vivo resection specimen imaging, in order to find out which factor could explain this drop in ultrasound accuracy. Since ioUS is highly accurate in tumours with a DOI till 10 mm, it has the potential to guide the surgeon in obtaining adequate resection margins both by in-vivo imaging during the resection and by ex-vivo control of the resection specimen in the operating room. By doing so, an immediate and precise re-resection may be performed in case of insufficient free margins [12,28]. This may reduce the production of inadequate resection margins, reduce the amount of unnecessarily removed healthy tissue and, most importantly, reduce the number of second procedure re-resections that are performed or the amount of adjuvant (chemo)radiotherapy that is undergone, which in the end improves the quality of life of patients.

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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