European Journal of Radiology 118 (2019) 19–24

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Research article

Magnetic resonance imaging findings of styloglossus and hyoglossus muscle invasion: Relationship to depth of invasion and clinical significance as a predictor of advisability of elective neck dissection in node negative oral tongue cancer

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ARTICLE INFO

Keywords:
Oral tongue cancer
MR imaging
Depth of invasion
Styloglossus
Hyoglossus
Extrinsic muscle
Neck dissection

ABSTRACT

Purpose: By comparing styloglossus and hyoglossus muscle invasion (SHMI) of oral tongue squamous cell cancer (OTSCC) on MR imaging to pathological depth of invasion (DOI) and prognosis, we aimed to evaluate the clinical significance of MR imaging findings of SHMI.

Method: Forty-five, early stages and clinically N0 OTSCCs were retrospectively reviewed. Data included pathological DOI, DOI on MR imagings, two-year potential cervical lymph node positive, locoregional control, disease-free survival, and overall survival. Data were statistically compared between the groups with MR evidence of SHMI (SHMI+) and without MR evidence of SHMI (SHMI-).

Results: There were 17 SHMI + and 28 SHMI-. Elective neck dissections performed on 13 cases revealed five node positive cases, all of which were SHMI + . Pathological DOI in SHMI + was significantly larger than SHMI- (average 9.0 vs 4.6 mm, $p < 0.001$). All SHMI + revealed pathological DOI larger than 4 mm. The two-year potential cervical lymph node positive rate of SHMI + was significantly higher than SHMI- ($p = 0.01$). Locoregional control rate and disease-free survival of SHMI+ were significantly lower than in SHMI- ($p = 0.02$). There was no significant difference in overall survival. Interobserver agreement in evaluation of SHMI on MR imaging was good (kappa value = 0.72, $p < 0.001$).

Conclusions: Pathological DOIs of SHMI + were all larger than 4 mm, which is the cut-off point that National Comprehensive Cancer Network recommends for neck dissection, and SHMI + had a worse prognosis than SHMI-. SHMI + can be used as a criterion for elective neck dissection.

1. Introduction

Squamous cell carcinoma is the most common malignancy of the oral cavity, and oral tongue squamous cell cancer (OTSCC) is the most common in several subsites of the oral cavity [1]. Treatment, including the necessity of elective neck dissection of patients with early-stage, clinically node-negative OTSCC, has been controversial. The American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 8th edition added a modification of the T categorization of oral cavity cancer by incorporating a depth of invasion (DOI) (< = 5 mm, > 5 mm but < = 10 mm, and > 10 mm) [2] because DOI is strongly associated with neck node metastasis, which is the most important negative prognostic factor. However, there is no description on specific details of a preoperative DOI measuring method in the AJCC Cancer Staging Manual, 8th edition. Therefore, an appropriate imaging modality to measure preoperative DOI is yet to be standardized. In previous criteria of the AJCC Cancer Staging Manual, 7th edition, extrinsic muscles invasion (EMI) by oral tongue cancer is determined as a T4a designation [3]. The extrinsic muscles of the oral tongue include the genioglossus muscle, hyoglossus muscle, styloglossus muscle, and palatoglossus muscle. In particular, styloglossus and hyoglossus muscles are located in the superficial plane beneath the mucosal surface of the oral tongue (Fig. 1).

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https://doi.org/10.1016/j.ejrad.2019.06.023
Received 7 December 2018; Received in revised form 17 May 2019; Accepted 25 June 2019

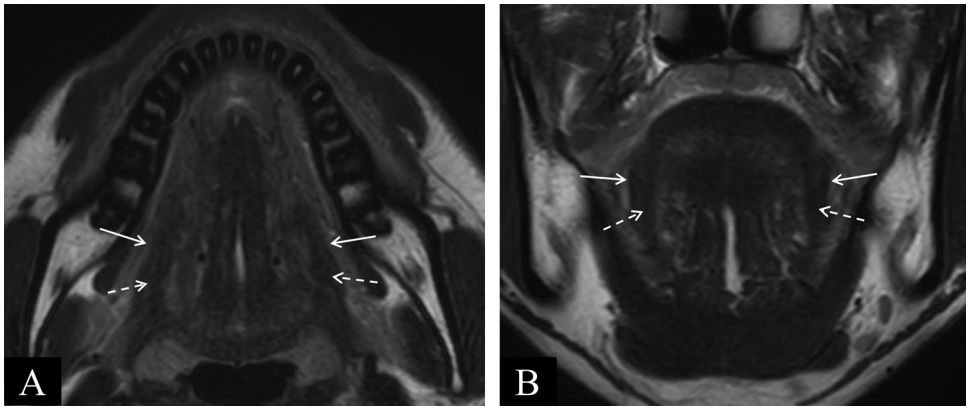

Fig. 1. Normal anatomy of styloglossus and hyoglossus muscle. A 33-year-old male. Axial and coronal T2-weighted images (A, B) show normal styloglossus muscle (arrows) and hyoglossus muscle (dotted arrows).

These anatomical features reflect the high incidence of styloglossus and hyoglossus muscle invasion (SHMI) by tongue carcinoma on MR imaging compared to other extrinsic muscles in clinical practice. EMI was excluded from T categorization in the AJCC Cancer Staging Manual, 8th edition [2] because DOI has superseded it, and EMI is difficult to assess clinically and pathologically. However, EMI including SHMI on MR imaging can be determined relatively easily by preoperative MR imaging and could have greater inter-observer reproducibility and correlation with pathological DOI. To the best of our knowledge, there are no studies that prove the relationship among MR findings of SHMI, pathological DOI and the prognosis of neck node positive in clinical N0 patients. The purpose of this study was to investigate the novel relationship between MR findings of SHMI and pathological DOI and prognosis for clarification of the clinical significance of MR findings of SHMI as a decision factor of elective neck dissection in node negative OTSCC.

2. Materials and methods

MR imaging of 45 patients obtained between May 2009 and February 2016 were retrospectively evaluated. The subjects included patients who underwent surgery for primary OTSCC. We focused on early stage OTSCC with the greatest dimension smaller than 4 cm (considered as T1–T2 lesions in the previous AJCC Cancer Staging System, 7th edition [3]) as well as those clinically and radiologically diagnosed as N0 (no neck lymph node metastasis) for pre-surgical evaluation. This study included the detectable lesions and excluded the undetectable lesions on preoperative MR imaging. The patients with non-assessable MR imaging due to technical limitations including imaging artifacts were excluded from this study. OTSCC of the lateral border was included, and dorsal, inferior, and tip lesions were excluded. Elective neck dissections were performed in 13 cases for occult lymph-node metastasis.

Two radiologists retrospectively evaluated the DOI on MR imaging for all cases, and the average value was used. The cases were divided into a group with MR evidence of SHMI (SHMI +) (Figs. 2 and 3) and a group without MR evidence of SHMI (SHMI-) (Fig. 4). SHMI + can be identified as the replacement of normal tissue by OTSCC presenting with a high signal intensity from normal styloglossus and hyoglossus muscles, which normally have a low signal intensity. Especially on T2-weighted imaging among MR sequences, SHMI was most detectable.

In evaluation of SHMI, two radiologists retrospectively evaluated and interpreted the finding on MR imaging for all cases. If the two observers reached the same result, that result was used; however, if the results differed, the final result of the cases was decided by consensus.

DOI on MR imaging was measured from the horizon line determined as the line connecting the junctions of the tumor and the normal mucosal on both sides to the deepest aspect of tumor lesion (Fig. 5A). This measurement method was used according to the pathological measurement of DOI on the AJCC Cancer Staging System, 8th edition, including descriptions that "*DOI is measured by first finding the 'horizon' of the basement membrane of the adjacent squamous mucosa. A perpendicular 'plumb line' is established from this horizon to the deepest point of tumor invasion*" [2] (Fig. 5B).

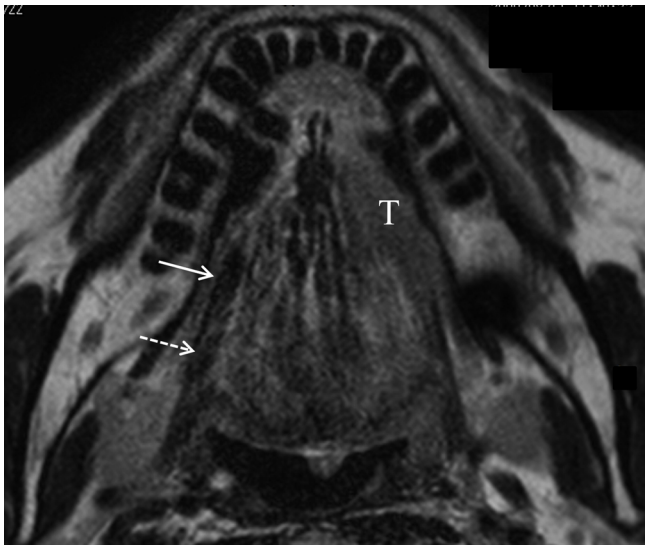

Fig. 2. Findings of SHMI + . An 80-year-old male with left oral tongue squamous cell carcinoma. Axial T2-weighted images reveal oral tongue cancer invasion (T) to left styloglossus and hyoglossus muscle. The right styloglossus muscle (arrow) and hyoglossus muscle (doted arrow) are normal.

MR imaging was performed in all patients for pretreatment evaluation. Collected data included age, sex, pathological DOI, DOI on MR imaging, two-year potential lymph node metastases (defined as cases pathologically positive for lymph node metastases at the time of operation or appearance of lymph node metastases within two years), locoregional control rate, disease-free survival rate, and overall survival. Two-year potential lymph node metastases were adopted for evaluation of neck node positivity. DOI on MR imaging was measured on axial T1-weighted images, axial and coronal T2-weighted images, and axial and coronal fat suppressed contrast-enhanced T1-weighted images without adding a slice thickness. These data were statistically compared between SHMI + and SHMI-.

MR imaging was performed on a 1.5-T system (Achieva; Philips Medical Systems, Best, The Netherlands) using a maximum gradient field strength of 33 m T/m and a 2-ch Flex S coil. All patients were

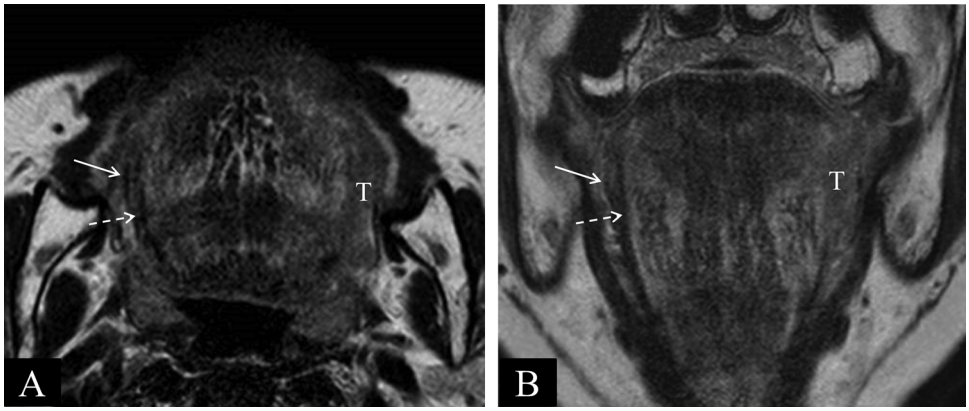

Fig. 3. Findings of SHMI+. An 81-year-old female with left OTSCC. Axial and coronal T2-weighted images (A, B) reveal oral tongue cancer invasion (T) to left styloglossus and hyoglossus muscle. The right styloglossus muscle (arrow) and hyoglossus muscle (dotted arrow) are normal.

examined in the dorsal position. All FOV were set on maxillofacial region. First, axial T2-weighted images were obtained by using the following parameters: repetition time (TR)/echo time(TE), 2800 ms/90 ms; flip angle, 90°; field of view, 15 × 15 cm; matrix size, 288 × 230; slice thickness, 3.5 mm; gap, 0.3 mm; number of excitation (NEX), 2. Axial T1-weighted images were obtained by using the following parameters: TR/TE, 680 ms/10 ms; flip angle, 90°; field of view, 15 × 15 cm; matrix size, 288 × 230; slice thickness, 3.5 mm; gap, 0.3 mm; NEX, 2. Coronal T2-weighted images were obtained by using the following parameters: TR/TE, 4300 ms/90 ms; flip angle, 90°; field of view, 15 × 15 cm; matrix size, 288 × 230; slice thickness, 3.5 mm; gap, 0.3 mm; NEX,2. Post-contrast axial fat suppression T1-weighted images were obtained by using the following parameters: TR/TE, 550/10 ms; flip angle, 90°; field of view, 15 × 15 cm; matrix size, 320 × 256; slice thickness, 3.5 mm; gap, 0.3 mm; NEX, 2. Post-contrast coronal fat suppression T1-weighted images were obtained by using the following parameters: TR/TE, 550 ms/10 ms; flip angle, 90°; field of view, 15 × 15 cm; matrix size, 320 × 256; slice thickness, 3.5 mm; gap, 0.3 mm; NEX, 2.

Welch's test (for data with unequal variances) was used to compare pathological DOI between SHMI + and SHMI-. A paired *t*-test was used to compare between pathological DOI and MR imaging on respective sequences and pathology. The cut-off value of pathological DOI between SHMI + and SHMI- was determined from the ROC curve. A Spearman's correlation test was used to evaluate the correlation between DOI and MR imaging on respective sequences and pathology. Fisher's exact test was used to compare the two-year potential neck lymph node metastasis rate between SHMI + and SHMI-. Locoregional control rate, disease-free survival, and overall survival were calculated using the Kaplan–Meier method. Censorings were determined when the patients did not visit our institution or any other hospital. Significance was evaluated using the log-rank test. Interobserver agreement in evaluation of SHMI was assessed by kappa statistics. A value of 0 to 0.20 indicated poor agreement, 0.21 to 0.40 indicated fair agreement, 0.41 to 0.60 indicated moderate agreement, 0.61 to 0.80 indicated good agreement, and 0.81 to 1.00 indicated very good agreement. All statistical analyses were performed using BellCurve for Excel (SSRI, Tokyo, Japan). A p value < 0.05 was considered to indicate statistical significance.

3. Results

Forty-five OTSCC patients (31 males [68%] and 14 females [32%]; age range, 31–86 years; average age [± SD], 63.4 ± 16.1 year) were evaluated. The mean follow-up period was 1687.1 days (range, 147–3308 days; SD, 785.3). The mean postoperative period was 1638.3 days (range, 129–3301 days; SD, 782.3). The two-year potential lymph node metastases rate was 39.5% (17/43) (The follow-up period of two cases was less than two years). The locoregional control rate and disease-free survival was 53.3% (24/45) during follow-up period. The mean period that had relapsed until locoregional recurrence or disease-free survival was 1052 days (range, 59–2868 days; SD, 803.9). The overall survival rate was 91.1% (41/45). The mean pathological DOI of all cases was 6.2 mm (range, 0.5–13 mm; SD, 3.2).

SHMI + was detected in 17 cases (37.8%), and SHMI- was detected in 28 cases (62.2%). In univariate analyses, pathological DOI of SHMI + was larger than that of SHMI- (9.0 ± 2.7 mm vs 4.6 ± 2.0 mm [average ± SD], $p < 0.001$). The cut-off value of

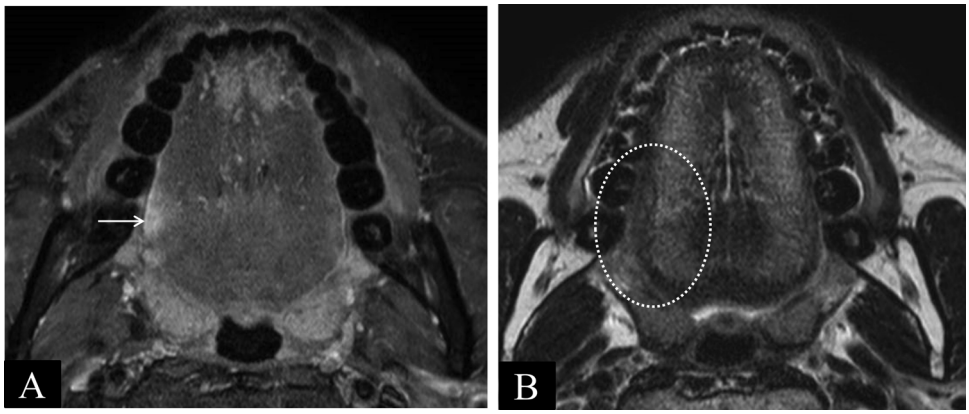

Fig. 4. Findings of SHMI-. A 50 -year-old male with right oral tongue squamous cell carcinoma. Post-contrast fat suppression T1-weighted images (A) reveal oral tongue cancer in right lateral border. However, axial T2-weighted images (B) show no finding of SHMI (within dotted circle).

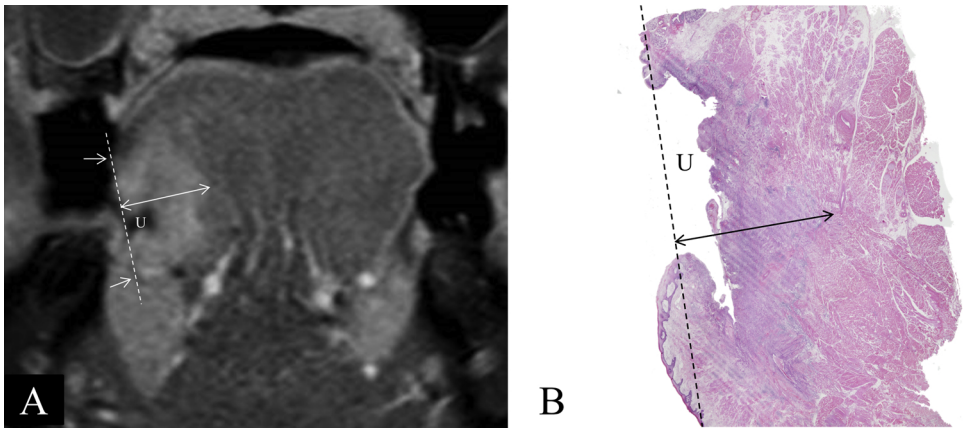

Fig. 5. Measuring radiological DOI on MR imaging and pathological DOI. A 34-year-old male with right oral tongue squamous cell carcinoma. Coronal post-contrast fat suppression T1-weighted images (A) reveal oral tongue cancer in right lateral border with ulcer formation (U). Radiological DOI on MR imaging (two direction arrow) which is defined as the longest distance of the lesion from the horizon line (dotted line) determined as the line connecting the junctions (arrows) of the tumor and the normal mucosal on both sides to the deepest aspect of the tumor is 10.1 mm. Pathological specimen on HE stained image (B) show oral tongue cancer with ulcer formation (U). Pathological DOI (two direction arrow) which is measured from the horizon line (dotted line) connecting the basement membrane of the adjacent normal squamous mucosa on both sides to the deepest point of tumor invasion is 7 mm.

pathological DOI between SHMI + and SHMI- on MR imaging was 7 mm (sensitivity [82.4%] and specificity [78.6%], area under the curve [0.89]). All SHMI + cases had pathological DOI of larger than 4 mm.

Elective neck dissections were performed in 13 cases based on clinical decisions by clinicians. Of 13 cases, 9 were SHMI +, and 4 were SHMI-. Of these 13 cases, five were pathologically positive for neck lymph node metastasis, and all five pathologically positive cases were SHMI + .

The findings of DOI on MR imaging and those of pathological DOI are presented in Table 1. In univariate analyses, the T1-weighted image, T2-weighted image, and post-contrast fat suppression T1-weighted image showed larger DOI than pathological DOI. The correlation coefficient between MR imaging and pathology was 0.80 ($p < 0.001$) in the T1-weighted image, 0.76 ($p < 0.001$) in the T2-weighted image, and 0.78 ($p < 0.001$) in the post-contrast fat suppression T1-weighted image. The detection rate of the oral tongue lesion on MR imaging was 89% (40/45) in the T1-weighted image, 87% (39/45) in the T2-weighted image, and 93% (42/45) in the post-contrast fat suppression T1-weighted image. The two-year potential lymph node metastases rate of SHMI + was significantly higher than that of SHMI- (12/17, 71% vs 5/26, 19%, $p = 0.001$). Locoregional control rate and disease-free survival of SHMI + were significantly lower than those of SHMI- (6/17, 35% vs 18/28, 64%, $p = 0.02$) (Fig. 6), and overall survival rate showed no significant difference between SHMI + and SHMI- ($p = 0.17$). Interobserver agreement in evaluation of SHMI on MR imaging (Table 2) was good (kappa value = 0.72, $p < 0.001$).

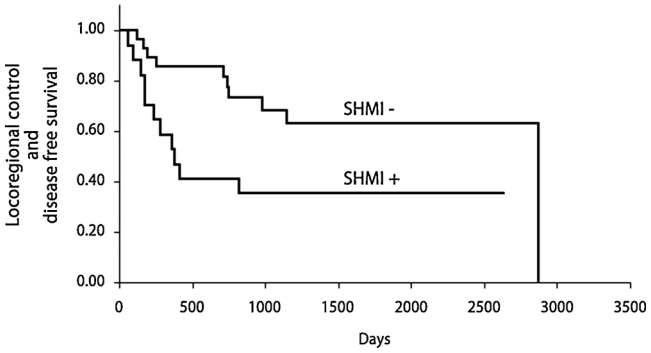

Fig. 6. Kaplan Meier curves of locoregional control rate and disease free survival.

Table 2
Interobserver agreement of MR imaging finding of Styloglossus and Hyoglossus Muscle Invasion (SHMI).

		Observer 2		
		SHMI +	SHMI-	Total
Observer 1	SHMI +	15	2	17
	SHMI-	4	24	28
	Total	19	26	45

4. Discussion

Nodal metastasis is the most important prognostic factor in oral tongue carcinoma [4,5] and results in a 50% decrease in five-year survival [6,7]. The pretreatment evaluation as well as management of the neck in clinical N0 patients is one of the most difficult problems especially in resectable oral tongue cancer cases. Occult metastasis to the cervical lymph nodes may occur in approximately 20–40% of patients with early stage (T1 and T2) oral cancer [8,9], and the most common cause of surgical treatment failure in oral tongue cancer is neck nodal recurrence [10]. Elective neck dissection has been shown to

Table 1
DOI on MR imaging and pathological DOI (mm).

	DOI on MRI	pathological DOI	Univariate *p*-value[a]	DOI difference between MR imaging and pathology	Rho between DOI on MR imaging and pathology
MR imaging sequence					
T1-weighted image	9.4 ± 3.4	6.7 ± 3.0	< .001	2.8 ± 2.3 [-1.6 - 8]	0.80
T2-weighted image	9.8 ± 3.3	6.9 ± 3.0	< .001	2.9 ± 2.4 [-2.3 - 11]	0.76
Post-contrast fat suppression T1-weighted image	9.4 ± 3.5	6.7 ± 3.2	< .001	2.7 ± 2.4 [-1.5 - 9]	0.78

Note - Data show the average ± SD, and upper and lower limit in parentheses.
[a] Paired *t*-test were used.

result in higher rates of overall and disease-free survival than therapeutic neck dissection among patients with early-stage oral squamous-cell cancer [11]. Hence, evaluation and determination of whether or not to perform elective neck dissection in the clinical N0 OTSCC patients is remarkably important.

In a previous study, one of the primary predictors of nodal metastases and determinants of prognosis was reported to be pathological tumor DOI [12]. Multiple studies have shown a strong relationship between tumor DOI and disease-free survival, overall survival, and neck metastases [13,14]. The cut-off value of DOI to determine the prognosis is most commonly set at 4 mm, because a review article by Huang et al. previously reported that a DOI greater than 4 mm (set as a cut-off point) was a strong predictor for cervical lymph node involvement [15]. Another study also used 4 mm as a cut-off value, because neck failure occurred predominantly in patients with a tumor depth greater than 4 mm in T1–T2 N0 OTSCC [16]. Tan et al. also reported that the group with DOI greater than 4 mm showed a higher local recurrence rate, and lower five-year overall survival, disease-specific survival, and local recurrence-free survival [17].

A precise DOI cut-off value is still under discussion. NCCN (National Comprehensive Cancer Network) recommends elective neck dissection in cases with DOI greater than 4 mm [18]. On the other hand, the AJCC Cancer Staging Manual, 8th edition added new DOI cut-off values of $< = 5$ mm, > 5 mm but $< = 10$ mm, and > 10 mm to T categorization [2]. According to such criteria, OTSCC with 5.5-mm DOI would be classified as T2 lesion with the necessity of neck dissection, OTSCC with 4.5 mm DOI would be classified as T1 lesion with the necessity of neck dissection, and OTSCC with 3.5 mm DOI would be classified as T1 lesion without the necessity of neck dissection. We could not find a specific paper that explains the discrepancy of recommended values for neck dissection and T categorization. However, the essential point is that pretreatment DOI estimation is an important factor for early OTSCC lesions in the determination of whether to perform neck dissection.

The AJCC manual does imply that DOI estimation is difficult. It states that *"palpation is essential to assess DOI"* but that *"DOI should be distinguished from tumor thickness, and its determination is predicted on invasion beneath the plane defined by surrounding normal mucosa,"* which would be hard to tell just by palpation [2]. When assessing a lesion with an imaging modality, the manual does recognize that the lesion is often evaluated with CT or MR imaging. There was also a study supporting that preoperative MR imaging could help us define tumor extent and DOI [19]. However, the manual somewhat denies its usefulness, saying that *"the distinction between 4 mm DOI and 6 mm DOI may not be possible (on imaging)"* [2].

In our study, we evaluated the pathological DOI for both SHMI + and SHMI- cases. Pathological DOI was larger in SHMI + than in SHMI-, with the cut-off value being 7.0 mm. These findings meant that SHMI + on MR imaging reflected the tumor size/volume, represented by pathological DOI. As we mentioned earlier, a DOI of 4 mm is associated with an increased risk of nodal metastases in early stage tongue cancers [14–16], and the NCCN recommendation for elective neck dissection is also a depth of 4 mm or larger. Our results showed that the pathological DOIs of SHMI + cases were all larger than 4 mm.

Hence, all SHMI + cases should be recommended to have elective neck dissection. A concern is that the absolute difference between radiological DOI and pathological DOI varied widely among individuals in this study (Table 1). The biggest difference was 11 mm. This case had a radiological DOI of 15.6–19 mm, whereas the pathological DOI was 8.0 mm, which was well over the cut-off value. It seems difficult to estimate a precise pathological DOI based on radiological DOI, but it is good enough to predict the pathological DOI being 4 mm or larger.

A notable finding was that all five SHMI + cases that underwent neck dissection showed neck lymph node metastases, compared to none out of four in the SHMI- neck dissection cases. In some SHMI- cases, pathological DOI was larger than 4 mm and yet turned out to be node negative with neck dissection. Overall, these results potentially imply that SHMI + cases should undergo elective neck dissection. The two-year potential lymph node metastases rate with SHMI + was significantly higher than SHMI-. This potential metastasis rate is an important factor to determine the necessity of elective neck dissection in preoperative evaluation. The actual MR imaging evaluation of EMI including SHMI was relatively easy and clear. Furthermore, interobserver agreement in evaluating SHMI on MR imaging was good in this study (Table 2). From our results, the SHMI + cases may be supportive evidence for elective neck dissection in N0 patients, and MR imaging can be a valuable tool for the pretreatment DOI evaluation.

For the modality, MR imaging has been broadly adapted for disease staging and is useful for finding prognostic parameters and differentiating between residual and post-treatment changes in head and neck cancer [20–23]. We chose MR imaging over CT imaging due to its excellent soft-tissue resolution and low influence of metal artifacts, due to the dental prosthesis. MR imaging can demonstrate a more detailed degree of tumor extension and is used widely to stage head and neck malignant disease. Preoperative MR imaging could help us to define tumor extent and DOI [24,25]. A few reports stated that radiologic tumor thickness measured on contrast-enhanced T1-weighted images had a significant correlation with histologic tumor thickness [4,19,24]. A strong correlation between tumor thickness on MR imaging and pathological thicknesses (correlation coefficient = 0.68, $p < 0.001$) was reported [26]. Alsaffar et al. reported a strong correlation between MR imaging and pathological thicknesses especially in deep tumors than superficial ones [27]. In our study, the radiological DOI on respective MR imaging sequences also correlated strongly to the pathological DOI. MR imaging might be a good tool to estimate the pretreatment DOI measurement. One thing to note is that the radiological DOIs on respective MR imaging sequences were significantly greater than the pathological DOIs. The possible cause of this discrepancy may be the shrinkage of specimens during formalin fixation [28] and an MR imaging effect by adjacent inflammation and edema [24]. Lam et al. reported that the average differences between pathological and radiological DOIs were 1 mm in T1-weighted imaging and 2 mm in T2-weighted imaging [24]. The difference between pathological and radiological DOIs in our study was about 3 mm. The pathological DOI may be estimated by subtracting 1–3 mm from the radiological DOI. However, the detailed cause of the discrepancy remains uncertain.

Despite the radiological DOI being significantly larger, the actual differences between radiological DOI and pathological DOI in each case varied widely (Table 1). With this result in mind, we should be careful when taking preoperative DOI measurements based on MR imaging before applying it to estimate pathological DOI.

Whereas the contrast-enhanced T1-weighted images are said to have a good correlation to tumor thickness, we found that T2-weighted imaging is useful for SHMI detection. On T2-weighted imaging, the EMI/SHMI can be detected as a replacement of normal muscle (low signal intensity) by invasive tumor tissue (high signal intensity).

There has been discussion about whether the invasion of styloglossus and hyoglossus muscles is truly reflected by the tumor staging. Boland et al. reported that because these muscles are located on the superficial layer from the mucosal surface of the tongue, their use as inclusion criteria in the T4a staging does not appear to be justified based upon their anatomical position [29]. The limitation was that the study was done using a computer model based on only one patient. Using this particular patient had inherent positioning problems due to the patient being edentulous. A computer model could lead to inaccurate identification of the musculature compared to the MR imaging evaluation. Murthy et al. argued for the removal of extrinsic muscle involvement in defining stage T4 of the oral cavity from the AJCC Cancer Staging Manual, 8th edition because of the proximity of the hyoglossus and styloglossus to the mucosal surface [30]. In our results, pathological DOI of STMI + was on average 9 mm, which is not considered as T3 but is defined as T2 in the AJCC Cancer Staging Manual,

8th edition.

There were several limitations to our study. It was a retrospective study and was limited to a small number of patients. It was also a single-center study. Larger studies would be needed to confirm our results.

5. Conclusion

All SHMI + cases showed pathological DOI larger than 4 mm. The two-year potential cervical lymph node positive rate was also significantly higher, and locoregional control rate and disease-free survival were also significantly lower in SHMI + . Patients who were proven to have pathologically occult lymph node metastases were all SHMI + . SHMI + can be used as a criterion for elective neck dissection in line with the NCCN recommendation.

Disclosure

The authors have no relevant financial disclosures.

IRB statement

This study was approved by the institutional review board (IRB); informed consent was waived.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgement

This study is recipient of a cum laude award at the 12th Asian Oceanian Congress of Neuroradiology (AOCNR 2018), 18-20 May 2018, Taipei, Taiwan.

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