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Magnetic resonance imaging accuracy in assessing depth of invasion in tongue squamous cell carcinomas and predicting cervical nodal metastasis

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Abstract. – OBJECTIVE: The aim of this study was to evaluate magnetic resonance imaging (MRI) accuracy in assessing the depth of invasion (DOI) compared to pathological DOI in oral tongue squamous cell carcinoma (SCC) and to determine whether MRI-measured DOI can predict lymph node metastasis in the cervical region.

PATIENTS AND METHODS: This retrospective study comprised 36 patients diagnosed with oral tongue SCC who underwent head and neck MRI 1-30 days before surgery and were surgically treated at King Fahad Medical City between January 2017 and November 2022. Relevant information was collected from the patients' records, and the data were analyzed to determine the radiological-histopathological correlations for the DOI and ascertain the cutoff point for nodal metastasis.

RESULTS: A value for Pearson's correlation coefficient between MRI-measured and pathological DOI was 0.86, indicating that these measures were highly associated and consistent with each other. The MRI-measured DOI coronal view (CV) was slightly overestimated than the pathological DOI by 1.72 mm. The cutoff values for the MRI-measured DOI CV and pathological DOI that indicated nodal metastasis were 7.08 mm and 9.04 mm, respectively.

CONCLUSIONS: Preoperative MRI is a valuable tool to accurately stage oral tongue SCC by measuring the depth of tumor invasion.

Key Words:
Head and neck, Lymph node metastasis, Magnetic resonance imaging, Squamous cell carcinoma, Tongue neoplasm.

Introduction

Malignancy is the leading cause of mortality, responsible for over 10 million deaths in 2020[1]. Reducing cancer-related mortality depends on a better understanding of cancer prevention, early detection, and care. The oral cavity contains eight sub-sites, including the tongue. The International Agency for Cancer Research reports that oral cavity cancers contribute to 180,000 deaths per year and are among the top 20 most common cancers worldwide[2].

Accurate diagnosis and staging of tongue cancer help to select an appropriate therapeutic approach, including tumor excision and removal of cervical lymph nodes if necessary. Depth of invasion (DOI) is a histological parameter that measures between the basement membrane and the deepest point of tumor tissue in the underlying structure.

Since the DOI is a postoperative histopathological parameter measured in excised tumors, treatment selection is more challenging. Based on the DOI, the

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patient's stage may be upgraded because of recent modifications in the American Joint Committee on Cancer (AJCC) staging system[3]. A second surgery or chemo-radiotherapy may be planned after assessing DOI. Furthermore, literature[3-6] shows the usefulness of DOI in oral cancer as an independent predictor of lymph node metastasis, tumor staging, tumor recurrence, and survival prognosis. As DOI alone can change the tumor staging, preoperative staging must be more accurate than postoperative pathological staging, which is crucial for surgical planning[7]. Various methods have been used to determine DOI preoperatively using ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI); of these, MRI is the investigation of choice for evaluating tongue cancers. It provides essential information on tumor location, dimensions, infiltration, and DOI; however, the accuracy and predictive value of MRI-measured DOI are variable and have not been validated. Therefore, this study aimed to assess the MRI-measured DOI and whether it can be used to predict metastatic neck lymph nodes in cases of oral tongue squamous cell carcinoma (SCC).

Patients and Methods

This retrospective study was conducted at King Fahad Medical City (KFMC), Saudi Arabia. The Institutional Review Board approval (22-399) was obtained from KFMC before data collection. Because of the retrospective nature of this study, informed consent was waived. We included patients diagnosed with oral tongue SCCs who had head and neck MRI 1-30 days before surgery and were surgically treated at our hospital between January 2017 and November 2022. Patients receiving neoadjuvant chemotherapy or radiotherapy were excluded, as well as those with significant dental artifacts, no preoperative MRI, missing records or pathological data, and other head and neck malignancies. Seventy patients with missing MRI data were excluded.

MRI-Measured DOI

All MRI scans were completed using a Signa Premier, GE Healthcare (Florence, South Carolina, USA) with a 3 mm section thickness. The MRI protocol included T1WI gadolinium contrast-enhanced and fast spin echo (FSE) T2WI images TR/TE 3000/80 (axial and coronal view) sequences. The MRI-measured DOI was calculated by measuring the distance between the deepest point of tumor invasion and the simulated vertical normal mucosal border. The reference line (blue line) along the tongue contour was determined as a vertical line joining the junctions of the malignant tissue and normal mucosa on both sides. A perpendicular (yellow) line was drawn from the deepest point of tumor invasion to the reference line to calculate the invasive portion (Figure 1).

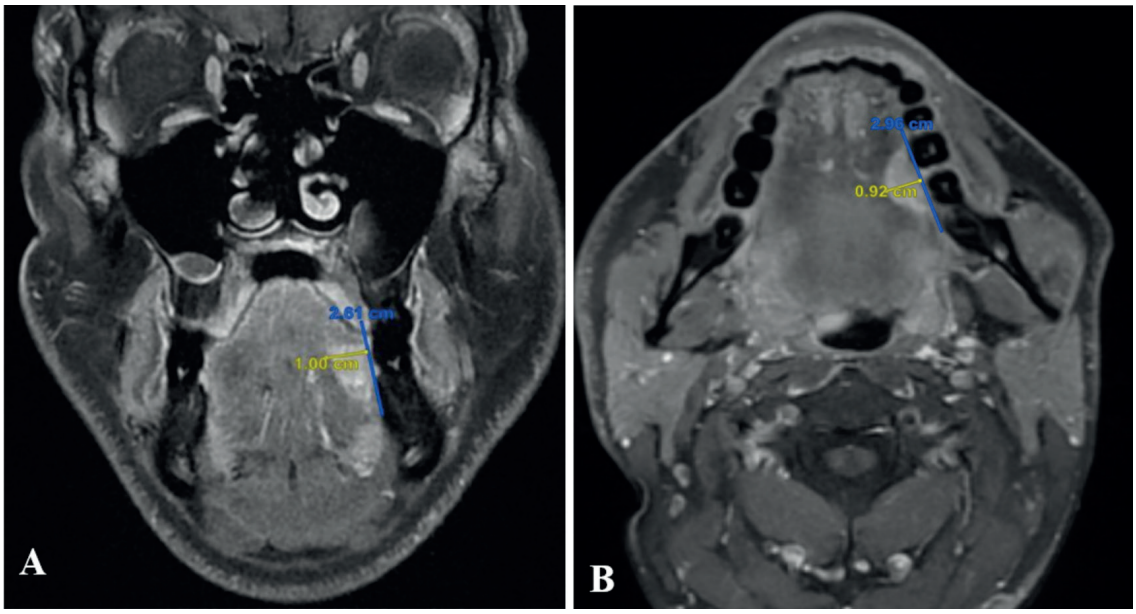

Figure 1. MRI-measured DOI on contrast-enhanced T1 coronal (**A**) and axial (**B**)-weighted MRI. DOI, depth of invasion; MRI, magnetic resonance imaging.

For ulcerative tumors, the reference line was drawn similarly to the assumed baseline plane. Exophytic lesions were disregarded, and the length measurement focused on depicting the invasion ability. Two radiologists specialized in head and neck measured the MRI-measured DOI independently from contrast-enhanced T1WI with coronal and axial views. Both raters were blinded to each other's assessment and the pathological data. The average of the MRI-measured DOI from both raters was calculated in each case and used for further analysis. The final MRI-measured DOI was calculated by taking a mean of the DOI in the coronal view (MRI-measured DOI CV) and axial view (MRI-measured DOI AV). The three methods (MRI-measured DOI CV, MRI-measured DOI AV, and final MRI-measured DOI) were then compared based on the histopathological DOI to determine the most accurate method for DOI estimation.

TNM staging was performed by histopathological examination of the post-operative tissue sample and compared with MRI TNM (Tumor size, Nodal metastasis, Distant metastasis) staging[8]. T1 Tumor measured ≤2 cm in the greatest dimension with DOI ≤5 mm, while T2 tumor measured ≤2 cm with DOI >5 mm, and the T3 tumor measured >2 cm and ≤4 cm along with DOI >10 mm. T4a was selected in the presence of locally advanced disease measuring >4 cm with DOI >10 mm, T4b was assigned to cases of an advanced disease characterized by skull base invasion, or cancer invading pterygoid plates or masticator space or if the tumor encased the internal carotid artery.

Measurement of Inter-Rater Reliability

Interobserver reliability was measured using paired *t*-test and intraclass correlation coefficients (ICCs). The following ICC values were used to assess the agreement: <0.4 - poor agreement, 0.4-0.75 - fair to good agreement, and >0.75 - excellent agreement. The mean of two DOI readings was used as the final MRI-measured DOI.

Histological Analysis

Following partial glossectomy or subtotal glossectomy surgeries, the specimens were preserved in formalin solution, and DOI was subsequently determined. The pathological DOI was obtained from the histopathological and lymph node pathology reports. The association between MRI-measured DOI CV and pathological DOI was determined.

Statistical Analysis

Pearson's correlation coefficients were calculated to assess the association between the radiological and histopathological DOI measurements. We investigated the association of the differences between MRI-measured DOI CV measures and pathological DOI using several demographic and clinical measurements and determined the association between variables using multiple regression analysis. We fitted a linear model with the difference in these two measures as the dependent variable and age, sex, smoking, morphology, comorbidities, tumor location, duration between MRI and surgery, and pathological DOI as the independent variables. We performed binary logistic regression analysis to decide the optimal cutoff value of the MRI-measured DOI CV or pathological DOI to predict the presence of positive neck lymph nodes. Statistical significance was set at $p<0.05$. We used the SPSS® software version 25.0.0.1 (IBM Corp., Armonk, NY, USA) for statistical analyses.

Results

We reviewed 36 patients (16 men and 20 women) in this study, with a mean age of 53.78 years. Approximately 69.44% of the patients had a pathological DOI >10 mm. Descriptive data of the patients are shown in Table I.

On comparing the reliability of the MRI-measured DOI CV, DOI AV, and final DOI with that of pathological DOI using a paired *t*-test, MRI-measured DOI CV measurements showed a mean difference of 1.72 [standard error (SE) = 0.63] with pathological DOI. The average of MRI-measured DOI AV and final MRI-measured DOI measurements had a mean difference with pathological DOI of 2.03 (SE = 0.65) and 1.88 (SE = 0.65), respectively (Table II). The MRI-measured DOI CV was chosen for further analysis owing to its accuracy and proximity to the histopathological DOI. The mean MRI-measured DOI CV was 17.33 mm compared to the mean pathological DOI, which was 15.61 mm.

All ICC values were >0.9, indicating a high degree of agreement between raters. A high degree of consistency was observed in the measurements by the two raters, and a comparison between their evaluations showed no significant difference ($p=0.36$).

A Pearson's correlation coefficient (PCC) of 0.86 revealed a strong association and con-

Table I. Demographic data of the patients.

	N = 36	%
Gender		
Male	16	44.4
Female	20	55.6
Age (Mean, SD)	53.8	15.9
Pathological T stage		
T2	11	30.6
T3	18	50.0
T4	7	19.4
Positive LN	18	50.0
Morphology		
Infiltrative	26	72.2
Ulcerative	4	11.1
Localized	6	16.7
Pathological DOI		
5-10 mm	11	30.6
> 10 mm	25	69.4
Duration between MRI and surgery		
1 week or less	11	30.6
1-2 weeks	9	25.0
2-3 weeks	9	25.0
3-4 weeks	7	19.5
> 10 mm	25	69.4

SD, standard deviation; T, tumor; LN, lymph node; DOI, depth of invasion; MRI, magnetic resonance imaging.

sistency between MRI-measured DOI CV and pathological DOI. We found that the average difference between the pathological DOI and the MRI-measured DOI CV increased with an increasing tumor size stage. For the T2, T3, and T4 tumor size stages, the MRI-measured DOI CV and pathological DOI differences were 1.52 mm (MRI: 8.53 mm; pathological: 7.02 mm), 1.16 mm (MRI: 17.45 mm; pathological: 16.29 mm), and 3.16 mm (MRI: 22.94 mm; pathological: 19.78 mm), respectively. This showed high accuracy between the MRI-measured DOI CV compared to pathological DOI for almost all tumor size stages ($p<0.001$).

There was good agreement between the tumor stages determined by pathological DOI and MRI-measured DOI with a kappa value of 0.68. The tumor stage estimated from the MRI-measured DOI CV matched that estimated from the pathological DOI, with a sensitivity of 85.94%. Similarly, the specificity of the MRI-measured DOI CV and the pathological DOI was 84.76% (Table III).

Multiple regression analysis determined the association between MRI-measured DOI CV measures and pathological DOI using several demographic and clinical measurements. The results revealed that none of the variables (except

Table II. Paired *t*-test comparing MRI measurements with pathological DOI.

Total	Mean	Mean pathological DOI	Mean difference	Std. Error	95% CI		*t*-statistic	*df*	*p*-value
					Lower	Upper			
MRI-coronal view	17.33	15.61	1.72	0.630	0.442	3.00	2.732	35	**0.010**
MRI-axial view	17.64	15.61	2.03	0.653	0.70	3.35	3.106	35	**0.004**
Final MRI	17.49	15.61	1.88	0.61	0.65	3.10	3.098	35	**0.004**

DOI, depth of invasion; MRI, magnetic resonance imaging; CI, confidence interval.

Table III. Association between T staging based on radiological depth compared to pathological depth.

Coronal view MRI-measured DOI	Pathological DOI			
	T2	T3	T4	Total
T2	6	0	0	6
T3	5	16	0	21
T4	0	2	7	9
Total	11	18	7	36
Sensitivity	85.94%			
Specificity	84.76%			
PPV	83.7%			
Kappa coefficient	0.681, 95% CI (0.469, 0.893)			

DOI, depth of invasion; MRI, magnetic resonance imaging; CI, confidence interval; PPV, positive predictive value; T, tumor.

for ulcerative morphology) had a significantly higher difference between MRI-measured DOI and pathological DOI than localized morphology (p=0.043). The association between perineural invasion, lymphovascular invasion, extracapsular extension, and the presence of positive lymph nodes (LNs) on MRI-derived DOI CV was significantly higher for perineural invasion (p=0.013). The MRI-derived DOI CV cutoff was 7.08 mm, indicating a probability of positive LN presence of 45%. The cutoff for the pathological DOI was 9.04 mm.

Discussion

Histopathological examination is the gold standard for measuring DOI and is expressed in millimeters. Neck dissection is indicated when DOI exceeds 3 or 4 mm. Therefore, accurate preoperative DOI measurements are essential[9]. MRI and CT are valuable options for evaluating oral tongue SCCs, and MRI is preferred. Recent AJCC guidelines[3,10] for the staging of oral cancer mentioned DOI as an important parameter to determine tumor grading. Whether examined clinically or histopathologically, DOI >5 and >10 mm were categorized as stage T2 and T3, respectively[10]. This affects the management plan and patient prognosis.

A Pearson's correlation coefficient of 0.86 was found between MRI-measured DOI CV and pathological DOI, asserting an association and consistency with each other. This also indicates that MRI can predict the actual DOI with high accuracy. The ICC values were >0.9, indicating that the two radiologists agreed with each other almost perfectly. Lam et al[11] found that MRI DOI (T1W) and histopathological DOI were strongly correlated (PCC = 0.851), suggesting the feasibility of MRI for the preoperative evaluation of DOI in tongue cancer patients. Waech et al[12] also showed that CT- and MRI-derived DOI correlated significantly with histological DOI. Park et al[13] also noted a significant correlation between the MRI and histological DOI (PCC = 0.941) among patients with tongue cancer.

Murakami et al[14] reported a good reproducibility of MRI-DOI on coronal FSE sequences between the two radiologists and between MRI and histopathological DOI with ICC values of 0.65 and 0.58, respectively. A recent study found PCCs of 0.80 and 0.85 for radiologists 1 and 2, respectively (p<0.001)[15]. Similarly, another study found low interobserver variation (PCC = 0.96, p<0.001)[16]. For T1W1 and T2W1, a meta-analysis found a higher ICC with T1WI (0.92) than with T2WI (0.79)[17]. Similar findings were reported by Preda et al[18] regarding DOI evaluation in patients with tongue cancer. This is because the DOI in T2W1 can be confused with inflammation or edema and shows a similar T2 repetition time with the tumor[19].

We found a kappa value of 0.68, showing a high degree of agreement between the tumor stages determined by pathological and radiological DOI. The agreement in determining the sensitivity and specificity of pathological and radiological depth was moderate (kappa = 0.48). Most previous studies in the literature have reported similar findings. Mair et al[15] found a moderate association between MRI and histological DOI, with a 0.68 kappa value (p=0.03). Vidiri et al[20] also found a strong correlation between two independent radiologists that determined DOI on reconstructed coronal MRI images (kappa = 0.70) and good agreement between pathological and radiological T staging with 0.74 and 0.60 kappa values for radiologists A and B, respectively.

In June 2009, a study conducted in Korea by Shim et al[4] demonstrated the usefulness of MRI in determining DOI in tongue cancer. A correlation coefficient of 0.85 between T2-weighted MRI DOI and histopathological depth was reported with 84% accuracy. In our study, the MRI-measured DOI CV was slightly overestimated compared to the pathological DOI by 1.72 mm. The potential confounders contributing to this overestimation are the shrinkage of the surgical specimens by 7-20% or approximately two-thirds of their size after resection and immersion in formalin, limited MRI resolution[21-23], the presence of inflammation or edema around the tumor[17,24-27], and artifacts derived from tongue movement and swallowing[28]. Dental hardware artifacts (including implants, fixed prostheses, and dental amalgams) can obscure MRI readings due to the extended duration of MRI examinations[29].

Li et al[17] found a 0.869 ICC between DOIs derived from MRI and histopathological examinations; however, the values were slightly overestimated than the histopathological DOI by 1.64 mm (p<0.001). Yesuratnam et al[24] compared the preoperative MRI-derived DOI with postoperative histopathological DOI among 81 patients

and found a mean difference of 3.19±4.87 mm and 2.99±4.41 mm for T2-weighted MRI and T1 post-contrast MRI measurements, respectively. Another study[25] revealed a difference of 1.64±1.32 mm in assessing DOI between MRI and pathological specimens with a false positive mean DOI of 2.3 mm. Recently, Mair et al[15] found mean MRI-derived and histological DOI of 13.7 mm and 12.45 mm, respectively, considering a shrinkage factor of 0.6 mm and low interobserver variation between two radiologists (correlation coefficient: 0.96; $p<0.001$).

We found that the cutoff point for the MRI-measured DOI CV was 7.08 mm, indicating a probability of positive LN presence of 45%, whereas a similar cutoff point for pathological DOI was 9.04 mm. According to Xu et al[30], the optimal cutoff values to predict cervical lymph node metastasis with MRI-measured DOI and pathological DOI were 7.5 mm and 5.0 mm, respectively, with 82.0% specificity and 86.9% sensitivity. Jung et al[22] found a good association of MRI-derived DOI with nodal metastasis with cutoff values of 10.5 mm and 11.5 mm for T1- and T2-weighted images, respectively; however, the cutoff value to determine the nodal metastasis on histopathological examination was 8.5 mm. According to Tam et al[31], the optimum DOI to detect an occult metastasis was 7.25 mm. The cutoff values for MRI-derived DOI for oral tongue cancer and tongue base were 9.5 and 14.5 mm, respectively[23]. Mair et al[15] and Mao et al[25] found cutoff values of 4.6 mm and 8 mm, respectively, for the MRI-measured DOI to detect lymph node metastasis.

Limitations

This study had some limitations owing to its retrospective nature, single-center, and small sample size. Furthermore, due to a high proportion of late-presenting cases, assessing MRI-measured DOI for T1 tumors was not possible. Therefore, further multi-centric prospective studies, including larger sample sizes, are needed to confirm the reliability of our MRI-measured DOI at all T stages and its use in predicting subclinical nodal metastasis.

Conclusions

MRI is a valuable tool for preoperative estimation of DOI, increasing the staging accuracy in patients with tongue SCC compared to postoperative pathological staging. We found good agreement among observers in evaluation the DOI in tongue cancer. Estimating DOI using an MRI within 30 days before surgery helps in surgical planning, including the extent of elective neck dissection. MRI-measured DOI CV can predict cervical nodal metastasis, improving preoperative staging of tongue cancer.

Ethics Approval

This study was designed and approved by the Ethical Review Board (Reg. 22-399, Dated 31st August, 2022) of King Saud University, Riyadh, Saudi Arabia.

Informed Consent

Due to the retrospective nature of this study, informed consent was waived by the institution's ethical board.

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Conflict of Interest

The authors declare no potential conflicts of interest for the research, authorship, and publication of this article.

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Data Availability

The authors assert that the information supporting the conclusions of their research is accessible in the paper and its additional resources. Upon request, the corresponding author can provide the raw data that supports the result of this study.

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Bushra Alharbi, Mohammed Alessa, Hoda Alsayid, Latefa Alareek, Khalid Alqahtani, Saleh Aldhahri: Concepts, Design, Data analysis, Statistical analysis, Manuscript preparation, Manuscript review; Bushra Alharbi, Saleh Alqaryan, Rayyan Alqurayyan, Razan Alamoudi, Doaa Alghamdi, Khalid Alqahtani, Saleh Aldhahri: Definition of intellectual content, Literature search, Experimental studies, Data acquisition, Manuscript editing.

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