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Tumor thickness and depth of invasion in squamous cell carcinoma of tongue as indicators of the loco-regional spread of the disease: A preliminary study

Rupsa Das [a], Satya Ranjan Misra [a,*], Satya Sundar Gajendra Mohapatra [b], Pravakar Bahinipati [b], Smita Rani Priyadarshini [a], Alkananda Sahoo [a], Debahuti Mishra [c], Anamika Rai [a]

[a] Department of Oral Medicine & Radiology, Institute of Dental Sciences, Siksha 'O' Anusandhan deemed to be University, Bhubaneswar, Odish, India
[b] Department of Radiodiagnosis, Institute of Medical Sciences, Siksha 'O' Anusandhan deemed to be University, Bhubaneswar, Odisha, India
[c] Department of Pathology, Institute of Medical Sciences, Siksha 'O' Anusandhan deemed to be University, Bhubaneswar, Odisha, India

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ABSTRACT

Background: Magnetic resonance imaging (MRI) is a routinely used imaging modality for pre-treatment radiologic evaluation of tongue carcinoma, providing accurate information regarding the extent of the disease.
Aims and objectives: To investigate the role of MRI-derived depth of invasion and tumor thickness evaluation in squamous cell carcinoma of the tongue, and to assess if any correlation exists between depth of invasion, tumor thickness, nodal metastasis, muscles, and space involved.
Materials and methods: Thirty-three patients with oral squamous cell carcinoma of the tongue who had undergone pre-treatment MRI and excisional biopsy were included. The tumor thickness (TT) and depth of invasion (DOI) were evaluated on MRI and histopathologic images.
Result: The relation between different methodologies for assessing showed a very high correlation for the tumor tissue thickness ($r = 0.99$, $p < 0.05$) and depth of invasion ($r = 0.82$, $p < 0.05$). The tumor thickness and the depth of invasion increased with the loss of differentiation in the carcinoma histopathologically. As the depth of invasion increases, the extent of the spread of the carcinoma to tongue musculature, lingual septum, and spaces also increases.
Conclusion: The present study has depicted a high correlation between the tumor thickness and the depth of invasion between MRI and histopathological findings and is the first of its kind to correlate DOI to the invasiveness of the disease.

1. Introduction

Oral squamous cell carcinoma (OSCC) is the sixth most commonly occurring cancer in the world, affecting different oral subsites, amongst which the anterior two-thirds of the tongue is the most common.[1,2] Tongue carcinoma carries a poor prognosis as there is easier spread of the tumor due to the lack of any strong mechanical barrier and a rich lympho-vascular supply to the region promoting invasion, infiltration, and metastasis.[3] Surgery, which is the mainstay of treatment in OSCC, requires accurate assessment of tumor margins and wide resection to prevent recurrence.[4]

The five-year survival rate is 68 % in the initial stages to a dismal 27 % in advanced cases of OSCC due to diagnostic delays or recurrence.[2] Evidence has shown the most important prognostic marker in OSCC tongue is regional lymph node metastasis. Detection of the metastatic lymph nodes is difficult when they are subclinical or occult clinically and later lead to recurrences if the neck dissection is not performed. Hence elective neck dissection is followed as a part of the surgical protocol instead of watchful waiting to prevent neck node metastasis.[3] We performed a study to investigate the role of magnetic resonance imaging

* Corresponding author. Department of Oral Medicine & Radiology, Institute of Dental Sciences, Siksha 'O' Anusandhan deemed to be University, K-8 Kalinga Nagar, Ghatikia, Bhubaneswar 751003, Odisha, India.
E-mail addresses: rupsadas@soa.ac.in (R. Das), satyamisra@soa.ac.in (S.R. Misra), satyamohapatra@soa.ac.in (S.S.G. Mohapatra), pravakarbahinipati@soa.ac.in (P. Bahinipati), smitapriyadarshini@soa.ac.in (S. Rani Priyadarshini), alkanandasahoo@soa.ac.in (A. Sahoo), debahutimishra@soa.ac.in (D. Mishra), rai27anamika@gmail.com (A. Rai).

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(MRI)-derived depth of invasion (DOI) and tumor thickness (TT) evaluation in OSCC tongue, correlating it with histopathologic counterparts and to evaluate the relation between TT/DOI and the locoregional spread of the tumor into lymph-nodes, muscles and tissue spaces.

2. Aims and Objectives

To evaluate the relationships between DOI and TT of OSCC of tongue, as measured with preoperative T2-weighted MRI and post-operative histopathologic specimens, with cervical lymph node metastasis and tumor stage. Further to determine of any correlation exists between DOI and locoregional spread of the tumor.

3. Methods and materials

The study was approved by the institutional review board and the informed consent was taken for using MRI images and pathological data of the patients. A retrospective analysis was performed on patients who underwent curative surgery for OSCC of tongue from March 2022 to March 2023. The inclusion criteria were (1) patients with OSCC of tongue who underwent MRI examinations prior surgery and (2) the lesions were histopathologically confirmed as OSCC of tongue. The exclusion criteria were: (1) patients with other head and neck tumors; (2) patients on chemotherapy or radiotherapy and (3) poor quality of MR images.

The MRI scans were performed on a 1.5-Telsa MR unit (GE Medical System Sigma Explorer), and the section thickness was 3 mm with 0.3-mm intersection spacing was 1 mm. The scanning protocol included T1W (repetition time [TR] 912 ms, echo time [TE] 17 ms) and T2W (TR 5000 ms, TE 99 ms) axial, coronal, and sagittal sequences along with T2 axial and coronal sequences with fat suppression (FS) (TR 5830 ms, TE 99 ms) DW. Two radiologists evaluated The MRI data individually at two different time frames.

The formalin-fixed paraffin-embedded tissues of patients were sectioned into a 4-μm thickness and stained with haematoxylin and eosin. Ocular micrometre (Lawrence and Mayo Company, accuracy nearest 0.1 mm) was used to measure TT and DOI. The distance of 15 ocular divisions corresponded to 0.006 μm (μm). TT was measured from the level of adjacent normal mucosa to the deepest point of tumour invasion as described elsewhere, without considering superficial keratin or inflammatory debris. Multiple sections of the tumour were first studied to identify the area with maximum thickness. Distance from the bottom of most adjacent dysplastic abnormal rete ridge to the deepest point of invasion was measured and expressed as DOI. As with MRI, the histopathological evaluation excision biopsy sections of the patients were evaluated by two experienced pathologists who assessed the DOI independently blinded to the TT and DOI values measured on MRI.

Both histologic and radiologic TT [Fig. 2] and DOI were measured [Fig. 3] and the results were statistically correlated.

4. Statistical analysis

The measurement of the Magnetic resonance imaging inter relatability was estimated by the paired *t*-test. By using Pearson's correlation coefficient, the measurements of the MRI and histopathology were correlated and the linear fit curve was drawn to predict the pathological parameters using MRI parameters. Non-parametric tests were performed to compare different categories of independent variables. The MRI and HP techniques were compared using Mann-Whitney U (2 samples) test. ANOVA was constructed to compare the effect of different variables on the estimation of tumor tissue thickness and depth of invasion. Variables with two categories were compared using Mann-Whitney U (2 samples) test while variables with more than two categories were compared using the Kruskal-Wallis one-way ANOVA (k samples) test. All the pairwise comparisons were made after applying the Bonferroni corrections. To calculate the cut-off value of the depth of invasion by MRI technique the receiver operation characteristic (ROC) curve was used. The p-values that were smaller than 0.05 were considered statistically significant. Chi-square tests were applied to compare the relationship between the nominal variables. All the analyses were performed by SPSS 19.0 for

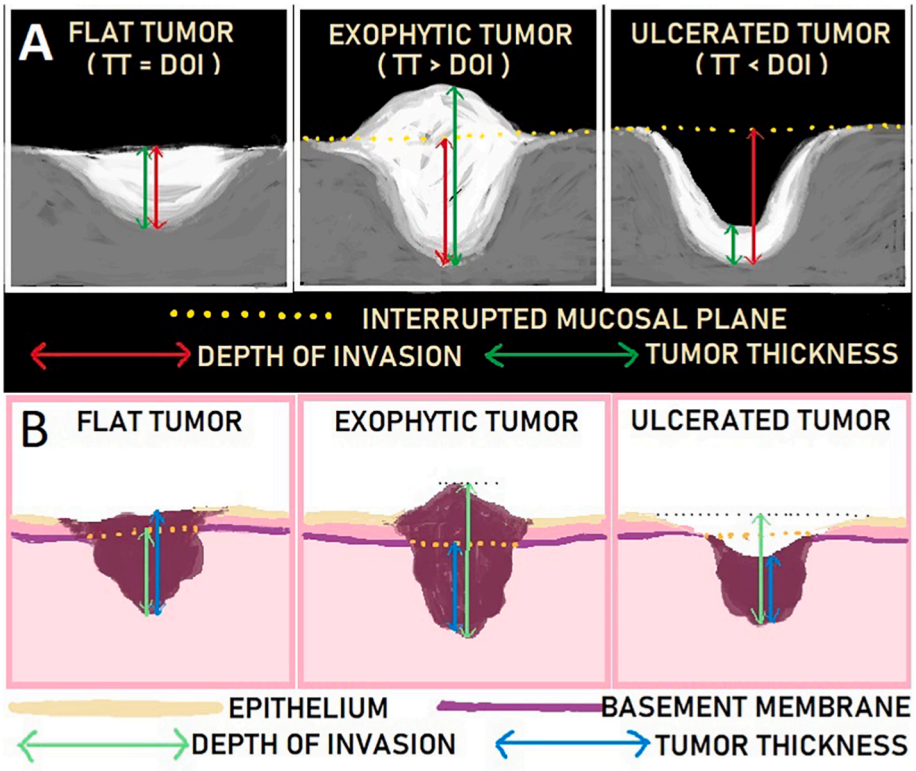

Fig. 1. Diagrammatic representation of the radiologic (A) and histopathologic (B) tumor thickness and depth of invasion in oral squamous cell carcinoma.

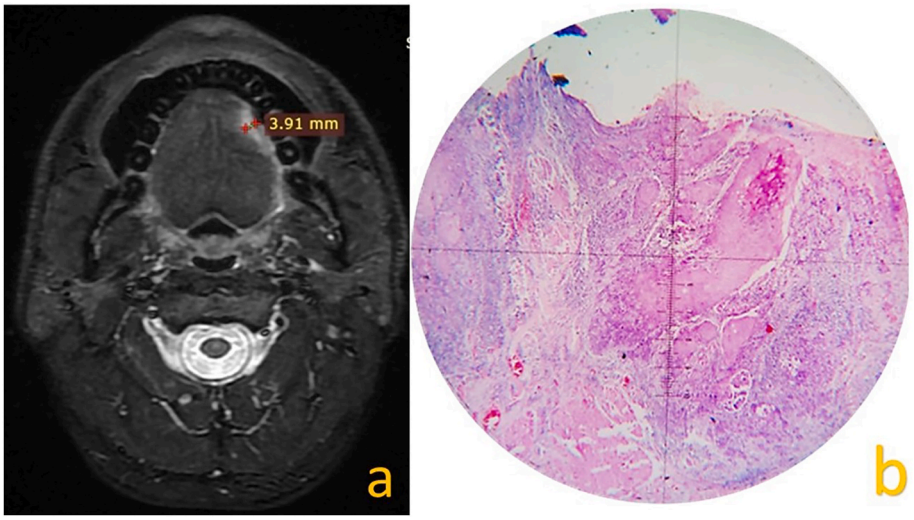

Fig. 2. Histologic and radiologic tumour thickness in tongue carcinoma.

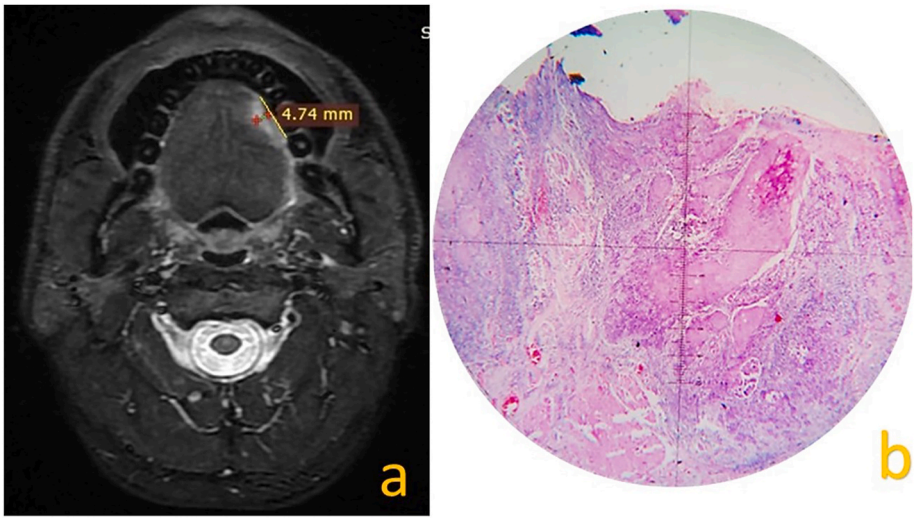

Fig. 3. Histologic and radiologic depth of invasion in tongue carcinoma.

Windows (SPSS Inc., Chicago, IL).

5. Results

Histologically proven cases of OSCC tongue with MR imaging were identified from the repository. Only 33 patients (30 males and 3 females) were included in the study. The patients were in the range of 30–72 years with a mean age of 48 years.

6. Inter-observer correlation

There was an excellent agreement between the two radiologists and the two histopathologists. The agreement between the two observers was very close for MRI DOI compared to other parameters **[Fig. 4]**.

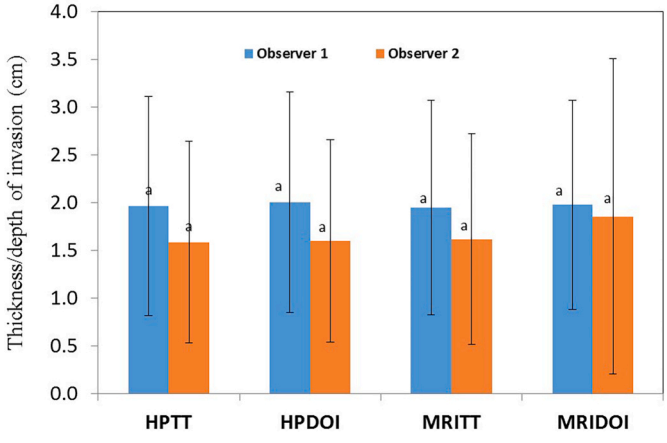

Fig. 4. Graph depicting excellent inter-observer correlation between radiologists and histopathologists.

7. Relation between histologic and radiologic parameters

The relation between different methodologies for assessing TT and DOI demonstrated very high correlation for the tumor tissue thickness ($r = 0.99$, $p < 0.05$) [Fig. 5] and depth of invasion ($r = 0.82$, $p < 0.05$) [Fig. 6]. The regression equation developed for both the parameters can be utilized in the prediction of the histopathological tissue thickness

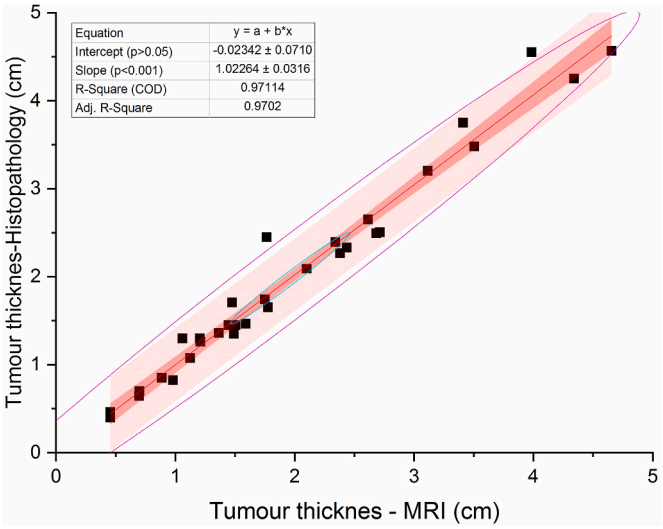

Fig. 5. The relation between MRI and HPE for assessing TT demonstrated very high correlation for the tumor tissue thickness (r = 0.99, p < 0.05).

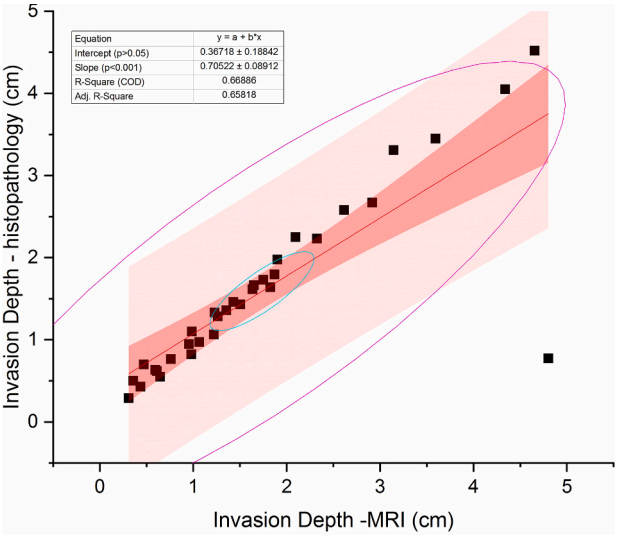

Fig. 6. The relation between MRI and HPE for assessing DOI demonstrated very high correlation for the depth of invasion (r = 0.82, p < 0.05).

(adj. R2 = 0.97) and depth of invasion (adj. R2 = 0.66).

8. Association with lymph node

Tumor parameters varied with regional lymph node metastasis. TT and DOI in tumors with lymph node metastases were significantly greater compared to the ones without. The radiologic DOI values were relatively greater compared to HP- DOI. But, values of the TT and DOI estimated by HP and MRI were statistically the same for the tumors of both categories. TT and DOI also affect the lymph node side and level of lymph node involvement. Significantly higher measurements of TT & DOI were observed in cases where bilateral lymph nodes were involved compared to no lymph node present. Although only one observation was available in the data set, tumors involving bilateral right and right and left lymph nodes were having extremely higher values for TT and DOI. Level (I, II, or multiple) of lymph node involvement also showed significantly greater values of the TT and DOI compare to no lymph involvement. The values for the tumor involving multiple levels were relatively higher compared to tumors involving levels I, II, or I and II.

Table 1
Comparison of the HP and MRI techniques for estimation of tumor associated with lymph node levels.

LYMPH NODE LEVELS	Tumor thickness (cm)		Depth of invasion (*Cm*)	
	HP	MRI	HP	MRI
I	2.16[a]±0.85	2.08[a]±076	1.68[a]±0.91	2.16[a]±1.35
II	1.93[a]±0.85	1.92[a]±0.89	1.65[a]±0.69	1.71[a]±0.78
I and II	2.32[a]±1.34	2.27[a]±1.25	1.87[a]±1.25	1.93[a]±1.36
Multiple[a]	3.16[a]±1	3.20[a]±1.02	2.44[a]±1.44	2.45[a]±1.51
None	0.76[b] ± 0.35	0.80[b] ± 0.34	0.64[b] ± 0.26	1.29[b] ± 0.25

[a] involvement of more than two lymph nodes; ± Standard deviation; values with the different superscripted letter (a-b) are significantly different (p < 0.05); values in each site for estimation technique (HP and MRI) are statistically not different (p > 0.05).

The TT and DOI values estimated by HP and MRI were the same across the categories of the tumors concerning regional lymph node metastases **[Table 1]**.

9. Involving different tissue spaces and muscles

The TT and DOI estimated by HP and MRI were significantly higher for the tumors infiltrating tissue spaces compared to the tumors not involving the tissue spaces. Values of TT and DOI involving multiples spaces were significantly higher followed by sublingual space and no space involved. Values of the TT and DOI estimated by HP and MRI were the same for the tumors across the different categories of the space involved (see Table 2).

Tumors involving multiple muscles showed significantly higher TT and DOI compared to the tumors involving hyoglossus and/or intrinsic muscle and of the tongue. The TT and DOI estimated by the HP and MRI for the categories of tumors involving different muscles were the same [Table 3].

10. Discussion

The tumor, node, metastasis (TNM) system is routinely used for clinical staging in OSCC and helps in the treatment planning as well as estimation of prognosis. But superficial or small tumors were underestimated as the classification was based on tumor size only and not the tumor volume.[5] Even sentinel lymph node biopsy (SLNB) for clinically negative neck nodes especially in tongue OSCC was advocated to detect nodal metastasis.[6] However, owing to the technique sensitivity of the procedure it was not routinely followed.[7] Later to counter these drawbacks in staging of OSCC there was the inclusion of depth of invasion (DOI) for the primary tumor in the T category of the TNM classification.[8] The American Joint Committee on Cancer (AJCC) staging manual has defined two important pathologic parameters namely the tumour thickness (TT) and the depth of invasion (DOI) for OSCC.[9] While TT is measured from the surface of an endophytic or an exophytic tumor, and from the ulcer base for an ulcer to the deepest point of invasion, DOI represents the distance from the basement membrane or the reconstructed oral mucosal surface from the deepest level of invasion of the tumor.[10] [Fig. 1] The DOI expresses the closeness of the lympho-vasculature and hence may be used to predict the regional lymph node metastasis.[11] Both TT and DOI have been measured in various studies as prognostic markers in OSCC conducted prior to the inclusion of DOI alone in the TNM staging, and the terms have been used interchangeably.[12–14]

Recent studies have shown that the DOI may be considered as an independent prognostic factor for regional lymph node metastasis and disease-free survival in patients with OSCC.[15] As per the eighth edition of the AJCC staging manual 2017, the gold standard for primary tumor staging is a histologic DOI of 5 mm–10 mm.[16] Hence surgical protocols are now dependent on DOI estimation in millimetres and it needs to be

Table 2
Comparison of the HP and DOI techniques for assessing the tumor involving different spaces.

SPACE	Tumor thickness (cm)		Depth of invasion (*Cm*)		Shrinkage
	HP	MRI	HP	MRI	
Space not involved	1.15^{c}±0.60	1.11^{c}±0.047	0.94^{b} ± 0.44	0.97^{c}±0.45	-0.036^{a} ±0.224
Sublingual space involved	2.10^{b} ± 0.96	2.07^{b} ± 0.85	1.65^{a}±0.90	1.90^{b} ± 1.19	-0.035^{a} ±0.187
Multiple space involved[a]	3.60^{a}±083	3.66^{a}±0.83	2.96^{a}±1.31	3.05^{a}±1.46	-0.1742^{a} ±0.199

[a] involvement of sub lingual along with sub-mandibular, pterygoid space and retropharyngeal space; ± Standard deviation; values with different superscripted letter (a-c) are significantly different ($p < 0.05$); values in each site for estimation technique (HP and MRI) are statistically not different ($p > 0.05$).

Table 3
Comparison of the HP and DOI techniques for assessing the tumor involving different muscles.

Muscles involved	Tumor thickness (cm)		Depth of invasion (*Cm*)	
	HP	MRI	HP	MRI
1	1.41^{b} ± 0.56	1.37^{b} ± 0.52	1.08^{b} ± 0.50	1.32^{b} ± 1.08
1,2,3	3.75	3.41	3.31	3.15
1,4	2.72^{a}±1.07	2.68^{a}±0.83	2.72^{a}±0.88	2.68^{a}±0.94
1,5	1.68^{b} ± 0.59	1.66^{b} ± 0.63	1.37^{b} ± 0.86	1.33^{b} ± 0.81
1,4,5	2.00^{a}±0.37	2.07^{a}±0.45	1.76^{a}±0.05	1.81^{b} ± 0.08
1,6	2.65	2.62	2.58	2.62
Multiple	4.10^{a}±0.56	4.17^{a}±0.59	3.75^{a}±0.96	3.97^{a}±0.93
None	0.64^{b} ± 0.18	0.71^{b} ± 0.26	0.58^{b} ± 0.27	0.63^{b} ± 0.34

[a]only one observation not included in group comparison; ± Standard deviation; values with the different superscripted letter (a-b) are significantly different ($p < 0.05$); values in each site for estimation technique (HP and MRI) are statistically not different ($p > 0.05$); 1-intrinsic muscle of the tongue; 2- mylohyoid; 3 – anterior belly of digastric; 4- genioglossus; 5- hyoglossus; 6- geniohyoid.

accurately determined. Since the DOI is estimated mainly in surgical specimens, there have been attempts to estimate it in pre-treatment imaging, and radiologic measurements of DOI have correlated with the pathologic DOI values.[17]

Pre-treatment assessment of DOI in tongue carcinoma is routinely performed using magnetic resonance imaging (MRI), which has been the diagnostic modality of choice due to its excellent soft tissue resolution. Few studies have reported the DOI estimation using MRI has higher values than those estimated by histopathologic evaluation.[18,19] This higher value has been attributed to inflammation/peri-tumor oedema, tongue movement artefacts or shrinkage in tissue specimen post--surgery.[20] However, many studies also have shown good correlation between the radiologic and histologic DOI and the former as a predictor of the invasiveness of the tumor dictating the surgical protocol.[21,22]

Tongue carcinoma has a high potential for local invasion of tissue spaces and muscle involvement in addition to early cervical lymph node metastasis. [3]The presence of regional lymph node metastasis at the time of diagnosis is one of the most important prognostic factors as it bears a strong influence on the surgical treatment plan.[23] Pre-operative assessment using MRI provides accurate visualization of the soft tissues with adequate contrast between the tumor mass and the adjacent normal tissue depicting the tumor outline in high resolution images. [11]It is therefore considered the gold standard for imaging in tongue OSCC and with the incorporation of DOI in TNM staging, a pre-operative evaluation of the DOI from MR images can also aid in prediction of invasiveness of the tumor.

A few studies have reported that incorporation of DOI in the TNM classification has led to upstaging of the T without any clinically meaningful prognostic information in early OSCC tongue patients.[24,25] Measuring TT is much easier than DOI especially in a curved organ like the tongue and since it also correlates with the nodal metastasis accurately like the DOI, it can be used as a prognostic marker.[26] Recently Salama et al. even proposed to replace DOI by TT in the TNM staging system since DOI is a complicated measurement with many challenges.[10]

With the addition of DOI in the AJCC staging system, when the DOI is more than 5 mm the T stage changes from I to II while beyond 10 mm is stage III.[8,15] Measurement of DOI can be done pre-operatively by MRI and evaluation of the resected specimen and by histopathologic analysis on haematoxylin-eosin-stained sections. All the three measurements do not accurately correspond casting a doubt on the validity of DOI. Over estimation clinically/radiologically can lead to false positive and the shrinkage of the pathologic specimens can lead to false negatives, leading to decline and excessive tumor staging respectively.[27] The core concept in DOI measurements has been to accept the less advanced measurement in case of doubt. While MRI is the best soft tissue imaging modality and is frequently used for pre-operative evaluation of OSCC tongue, false positive results have still been reported of values from 4.6 mm to 3.19 mm warranting caution as 5–10 mm is the clinical staging threshold. Though measurement of DOI can be performed on MR images accurately but there are no radiologic criteria for determining it.[15,18]

The present study on the retrospective data of thirty-three patients with OSCC tongue evaluated the radiologic and histologic TT and DOI. The present study is in line with previously published studies exploring the accuracy of MRI as a predictor of the depth of invasion in tongue carcinoma. It was seen that MRI and histopathologic evaluation used for the assessment of tumor thickness and depth of invasion exhibited a very high correlation for the tumor tissue thickness (correlation coefficient = 0.99, $p < 0.05$) and depth of invasion (correlation coefficient = 0.82, $p < 0.05$). Despite the limitations of a small sample size, according to the ROC curve, a cut-off value of 7.35 mm for TT and 7.02 mm for DOI was observed by histopathologic and radiologic evaluation respectively.

For the accurate DOI measurements optimal parameters of the MR sequence need to be developed. Some studies have used scan slices of 1 mm but then meant longer scan time and more motion artefacts without significant soft tissue resolution, hence we performed 3-mm slice scans balancing the image quality and the spatial resolution.[28,28,29] While we used T1 FS and T2 FS MR imaging sequences, the tumor and peritumoral inflammation cannot be distinguished. Tang et al. used multi-parametric MRI sequences and found that diffusion weighted imaging (DWI) and enhanced-T1 high-resolution isotropic volume examination (e-THRIVE) can differentiate between malignant tumor mass and reactive inflammation surrounding it.[30] Although the cost and scan time is increased, DOI measured on e-THRIVE MR sequences had the highest correlation with histologic DOI.

In a systematic review (SR) conducted by Li et al., in 2019 to determine the accuracy of MRI in the measurement of DOI in OSCC tongue, qualitatively and quantitatively analysed five prospective and four retrospective studies and concluded that MRI is an accurate diagnostic modality for evaluating the DOI in OSCC tongue.[31] Amongst the MR sequences it was found that T1WI was a superior imaging modality as compared to T2W2 in the assessment of DOI of the oral tongue. In another SR and meta-analysis (MA) by Voizard et al. comparing the reliability of preoperative evaluation of DOI in OSCC tongue using CT, MRI and intra-oral USG, it was found that MRI had a good reliability between rDOI and pDOI with a pooled correlation coefficient of 0.86.[32] The studies on USG concentrated more on measuring the rTT and had a high heterogeneity. CT had a poor reliability and was used in only a few studies.

Recent studies by Nilsson et al.,[33] Takamura et al.,[34] Caprioli et al.[35] and Noorlag et al.[36] concluded that intra-oral USG was the most accurate

in assessment of DOI in T1 and T2 tongue OSCC and MRI tends to overestimate DOI and even failed to evaluate many tumors. However, it must be mentioned that in routine imaging procedures using an intra-oral USG probe is difficult with a restricted mouth opening in OSCC patients and has a poor patient acceptance with the procedure causing pain while pressing an USG probe on tongue.[37] Moreover, while imaging USG probe compresses tissues and the reliability of those measurements are questionable. While USG tends to underestimate lesions more than 10 mm in size, yet it be used intra-operatively to guide the onco-surgeon to achieve adequate margins where access to pathologic assessment using frozen sections is unavailable.

The studies evaluating TT on MRI of OSCC tongue are less compared to those evaluating the DOI, as the latter is incorporated into the TNM staging. MRI derived TT correlates accurately with the pTT as demonstrated by few studies.[38,38–41] Preoperative MRI is recommended to assist in treatment planning for patients with this disease. A recent study has advocated the potential utility of RI-TT in the preoperative risk-stratification of OSCC tongue, in which excellent intra- and inter-rater reliabilities of MRI-TT correlating with pDOI was observed.[42] The present study is though limited by a small sample size and heterogenicity of the population with respect to tumor size and extension, it has shown that the radiologic TT and DOI both significantly correlate to their corresponding pathologic values. Further limitations include difficulties in determining the rDOI of tumors that are smaller than 5 mm due to high MRI slice thickness, and artefacts caused by patient movement due to the long duration of the MRI scans.

11. Conclusion

MR imaging in OSCC tongue is a routine pre-operative imaging assessment due to its high soft tissue contrast and aids in treatment planning. DOI has now been incorporated in TNM staging and dictates the surgical protocol. Both TT and DOI could be considered as independent prognostic factors, as their values have been correlated to locoregional tumor spread to cervical lymph nodes, tongue musculature, lingual septum, and tissue spaces. Due to variations in geographic area, ethnicity of the population, etiology of tumor, site and type of tongue lesion, the exact significance of the prognostic value of TT and DOI needs to be explored further. We recommend a prospective study based on defined imaging protocols and histopathologic criteria on a larger population could go a long way in serving as a determinant of prognosis, ensuring surgery with tumor-free margins, thereby improving the prognosis leading to a reduction in the oral cancer burden.

Conflict of interest statement

All authors, Author Rupsa Das, Author Satya Ranjan Misra, Author Satya Sundar G Mohapatra, Author Pravakar Bahinipati, Author Smita Rani Priyadarshini, Author Alkananda Sahoo, Author Debahuti Mishra and Author Anamika Rai declare that they have **no** conflict of interest.

Human rights statements and informed consent

'All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent was obtained from the patient for being included in the case report.

No funding has been received by any author.

Animal rights statementsstatements

'This article does not contain any studies with human or animal subjects performed by any of the authors.'

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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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