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# MRI DETERMINED TUMOR DEPTH IN TONGUE CARCINOMA- A PREDICTOR FOR NODAL METASTASIS

Oncology

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## ABSTRACT

**Background:** In India, tongue carcinoma is the second most common carcinoma after gingivo-buccal carcinoma among oral cancers. The incidence of tongue carcinoma is on the rise in India as the data from most of the registry sites suggest. The most important prognostic factor in the case of tongue carcinoma is considered to be the presence and extent of cervical nodal metastasis. **Objective:** The present study was conducted to find out a cut-off value for tumor depth assessed by MRI for determination of nodal metastasis in cases of oral tongue carcinoma **Material And Methods:** It was a prospective observational study in which all new patients of stage I and stage II tongue carcinoma attending OPD in Yashoda Hospital, Somajiguda during the study period were investigated with Magnetic Resonance Imaging technique before undergoing surgery. The MRI findings were then compared with Histopathological findings obtained after surgery. The relationship between tumor depth as assessed by MRI and cervical nodal metastasis as assessed by histopathology were analyzed using appropriate statistical tests of significance and the cut-off value of tumor depth for predicting nodal metastasis was found by Receiver Operator Characteristic curve analysis. **Results:** It was found that mean tumor depth was 6.160 mm ± 2.485mm as assessed by MRI while the same based on histopathological examination was 5.625mm ± 2.187mm ($p>0.05$). It was found that the cervical nodal metastasis rate in cases with MRI tumor depth <or=3mm was 11.1%, with MRI tumor depth 3-9 mm, it was 43.5% and with MRI tumor depth >9mm, it was 100%. The optimum cut off as calculated by computing Youden's index came out to be 7 mm in case of MRI determined tumor depth.

## KEYWORDS

## INTRODUCTION

Oral squamous cell carcinomas form the 15th most common type of carcinomas in the world which constitutes 2.1% of all cancers except non-melanoma skin cancer.[1] There are about 0.2 million new cases every year worldwide with 0.1 million deaths each year.[2] In India it is the third most common carcinoma after Breast Cancer and Cancer Uteri in total population and second most common among men after Lung carcinoma.[3] India has long been regarded as the epicenter for this globally spread health problem as it has a very large population and thus the number of people affected with this carcinoma is also one of the largest in the world. World Health Organization has declared it as a major public health problem in India.[4] Age standardized incidence rate in India is 7.5 per 100,000 population while in western Europe and USA it is 4.6 and 3.8 per 100,000 population respectively.[1]

Among the various sub-sites (gingivobuccal, buccal, palates, lips etc), tongue is the most common site for oral squamous cell carcinomas in the world while in India, it is the second most common carcinoma after gingivo-buccal carcinoma. However, the incidence of tongue carcinoma is on rise in India as the data from most of the registry sites suggest.[2]

The most important prognostic factor in case of tongue carcinoma is considered to be the presence and extent of cervical nodal metastasis apart from tumor thickness, proximity to mid-line, location of tumor etc. The presence of cervical node metastasis decrease survival rate by more than 50%.[5-7]

Stage I and II carcinomas are preferably managed by a single modality, i.e. Surgery. Current management strategies advocate elective neck dissection in most cases of tongue carcinoma (stage I and II) over wait and watch policy, especially in those cases with tumor > 4mm in thickness and poorly differentiated.[2] This has always remained a matter of debate as a few studies have shown that there is no significant difference in survival between hemiglossectomy alone and hemiglossectomy with radical neck dissection.[8] This excess morbidity of elective neck dissection can be prevented in certain early stage cases if nodal metastasis can be predicted accurately prior to surgery.

Every surgeon's goal thus remains to assess as precisely as he can the nodal status along with tumor thickness in cases of biopsy proven tongue carcinoma before deciding on treatment plan. There are various ways in which this can be done. Apart from clinical assessment, which is limited by one's ability to determine an exact measurement of depth of invasion based on palpation or patient intolerance to palpation due to pain, soft tissues can be imaged radiologically and assessed. Owing to superior soft tissue contrast capability, MRI is the imaging modality of choice in local assessment of head and neck malignancies, including tongue cancer.[9-11]

Some researchers have tried to predict the chances of cervical nodal metastasis using depth of tumour invasion measured at MRI as many studies have suggested a strong relationship between tumor depth and nodal metastasis[12-14], though controversies exist in relation to the cut-off point for decision making regarding elective neck dissection. Many studies have suggested the cut-off point to be 5mm. One meta-analysis report has suggested the optimal cut-off to be 4mm[14] while one study has proposed a cut-off value of >9.7 mm tumour thickness for a decision to perform elective neck dissection.[3] Moreover, assessment of depth of invasion with MRI may be limited by motion artifact due to long image acquisition times.

So, it becomes necessary that the investigative role of MRI be explored in detail for decision making in management of tongue carcinoma as this will eventually reduce morbidity on account of overtreatment, especially in early stages of carcinoma when no nodal metastasis is there. In Indian setting, where such prediction of nodal metastasis will be more useful by decreasing the burden on health system, such studies become more important.

### Aim And Objective:

The aim of the present study was to assess predictive value of MRI determined tumour depth in determining nodal metastasis in cases of oral tongue carcinoma with the objective to find out a cut-off value for tumor depth assessed by MRI for determination of nodal metastasis in cases of oral tongue carcinoma.

## MATERIALS & METHODS

### Study Design:

A Prospective, observational study

### Study Setting:

Yashoda super-speciality Hospital, Somajiguda, Hyderabad

### Study Population:

All patients of tongue carcinoma attending OPD in Yashoda Hospital, Somajiguda during the study period.

### Study Participants:

All biopsy proven squamous cell tongue carcinoma patients attending Surgical Oncology OPD of the hospital during the time period from June2017- October 2017.

**Inclusion Criteria-**

1. Early cases of tongue carcinoma (Stage I and II)
2. Those who had not received any treatment ever for the tongue carcinoma.
3. Those who gave consent for participation in the study

**Exclusion Criteria-**

1. Those having late stage of carcinoma
2. Those patients in which MRI was contraindicated (Pace-maker implants)
3. Those patients who had previous head and neck radiation or chemoradiation.
4. Those who were not willing to participate in the study.
5. Those with tongue carcinoma of posterior 1/3 of tongue as it would have change management protocol.

**Methodology:**

Institute's Research ethics committee approval was obtained prior to the commencement of study. Then all the patients attending the OPD of Surgical Oncology department of the hospital during the study period, who fulfilled the inclusion criteria, were included in the study.

The patients were examined clinically. Then AJCC TNM staging was done for all the cases based on clinical findings and only stage I and Stage II patients were included in the study.

Then each of the patients included in study was subjected to Magnetic Resonance Imaging (MRI) of oral cavity and neck. The MR imaging protocol adopted was as follows:

**MR Imaging Protocol:**

All the imaging was performed by 1.5-T superconductive scanner (Sigma HDxt Ge). Sequences of 4mm thickness with 1mm intersection gap were taken.

Routine T1Weighted Imaging (T1WI) (Axial,coronal and sagittal), T2 Weighted Imaging (T2WI) (Axial, coronal and sagittal), STIR(Short tau inversion recovery) sequences, followed by post contrast axial and coronal T1W sequences were performed.

**Image Analysis:**

**I) Depth Of Tumor Invasion:**

Coronal gadolinium-enhanced T1-weighted sequence was used to measure depth of invasion for tongue where tumours lie vertically and hence, easy to calculate. A horizontal line joining the two tumour-mucosa junctions was drawn as a reference line. Depth of invasion was measured by drawing perpendicular lines from the reference line to the point of maximal tumour projection and invasion and then calculated the greatest radiologically determined tumour thickness by adding these two parameters.

If the tumour was ulcerative, the reference line was determined in the same way to be considered as the presumed original surface level, exophytic lesions were ignored and length measurement was simplified to represent invasion ability.

**II) Neck Nodes In MRI**

T1 axial gadolinium enhanced images of the neck were taken for evaluating neck nodes. After image analysis and determination of depth of tumor, the patients were taken up for surgery. The procedure for surgery was wide local excision and ipsilateral neck dissection.

**Details Of Surgery:**

**A. Excision Of Primary**

Wide local excision of tumor with adequate margin (clear margin of 1cm at least in each dimension) was done

**B- Management Of Neck:**

Elective Neck Dissection was done in all the selected patients. Level-1 to Level-4 cervical lymph nodes were removed, preserving spinal accessory nerve, internal jugular vein and sternocleidomastoid muscle.

**Histopathology Procedure:**

Tissue samples were then sent for histopathologial examination in formalin jars.

The areas of interest within the tissues were cut into small pieces, numbered and labelled and put through a series of procedures to end up with a prepared slide. These steps include dehydrating the tissue, placing it into a wax block to harden it, slicing extremely thin layers off of the block (less than half a millimeter thick), mounting these on a glass slide, staining them so that the tissue is visible under the microscope and covering them with a cover slip so that the tissue on the slide will be preserved for many years. This process of histopathology examination took one-two days for each patient. The tumor depth was thus measured and nodal status was assessed.

Outcome measures were tumor depth assessed on MRI examination, nodal status assessed by MRI examination and tumor depth along with nodal status assessed by histo-pathological examination of tissue sample.

**ZaData Management And Statistical Analysis:**

The data so obtained was entered in statistical software SPSS 19 version. The MRI findings and Histopathological findings were then compared. The relationship between tumor depth as assessed by MRI and cervical nodal metastasis as assessed by histopathology were analyzed using appropriate statistical tests of significance and the cut-off value of tumor depth for predicting nodal metastasis was found by Receiver Operator Characteristic curve analysis. ROC curves were constructed using Epitools epidemiological calculator.

Tumor depth: An imaginary line indicating the level of the adjacent intact mucosa or of the basal membrane was drawn on the MRI film/ Histopathology section. The depth of the tumor was measured from this line to the deepest point of invasion in this study.

**RESULTS**

A total of 56 patients including 12 females were included in the study. The mean age of patients was 59.53 ± 15.42 years. The majority of patients, i.e. 17 (30.3%) were in the age group 60-70 years. The mean age for males was 62.29 ± 14.47years and that for females was 49.42 ± 15.13 years. The tumor characteristics of these patients are given in Table no 1. Majority were in the size range of 2-3 cm with most common site of occurrence being lateral border of tongue.

**Table 1: Tumor Characteristics Of Study Participants**

| | | |
|---|---|---|
| **Site of Tumor** | | |
| Tip of tongue | 1 | 1.8% |
| Dorsum of tongue | 7 | 12.5% |
| Lateral borders | 46 | 82.1% |
| Undersurface | 2 | 3.6% |
| **Size of Tumor** | | |
| <or=1cm | 4 | 7.1% |
| 1-2 cm | 14 | 25% |
| 2-3 cm | 21 | 37.5% |
| 3-4 cm | 17 | 30.3% |
| **Stage of Tumor** | | |
| Stage I | 18 | 32.1% |
| Stage II | 38 | 67.9% |

**Table 2: Comparison of MRI and Histopathology examination based depths of tumor/lesion of Oral Tongue carcinoma**

| | **Mean** | **SD** | |
|---|---|---|---|
| MRI determined depth of tumor | 6.160 mm | 2.485 | p=0.228 (NS) |
| Histopathology examination based depth of tumor | 5.625 mm | 2.187 | |

Though MRI determined tumor depth was found to be more than histopathologically determined tumor depth, on comparison by applying Student's unpaired t test, it was found that this difference was not statistically significant (p>0.05).

**Table 3: Nodal status in relation to depth of lesion/tumor as recorded by MRI**

| **Depth of tumor as recorded by MRI** | **Cervical nodal metastasis present (n=26) (histology)** | **Cervical nodal metastasis absent (n=30) (histology)** |
|---|---|---|
| < or= 3 mm (n=9) | 1 | 8 |
| 3-9 mm (n=39) | 17 | 22 |
| >9 mm (n=8) | 8 | 0 |

Table 3 shows the nodal status in patients included in the study in relation to the tumor depth as recorded by MRI. It was observed that all eight patients who had tumor depth >9 mm were having occult cervical

nodal metastasis present as confirmed by histopathology. Seventeen out of 39 (i.e. 43.5%) patients with tumor depth between 3-9 mm were having cervical nodal metastasis while only one (11.1%) out of nine patients who had tumor depth less than or equal to 3 mm was found to be having cervical nodal metastasis. When the association between nodal status and tumor depth among patients with different tumor depths was tested using chi square test, it was found to be statistically significant in cases of tumor depth < or equal to 3mm verses tumor depth >3 mm($p<0.05$).

Also, the cut off value of tumor depth as determined by MRI for discriminating the positive nodal metastasis and negative nodal metastasis was determined using Receiver Operating Characteristic (ROC) analysis. At each value of tumor depth, the sensitivity and specificity for outcome were calculated and then a plot was generated with 1-specificity on x-axis and sensitivity on y-axis. The recommended or optimum cut off value of MRI determined tumor depth was found from this plot (curve also known as ROC curve) by calculating Youden Index, i.e. the cut off value at which sensitivity-(1-specificity) was maximum.

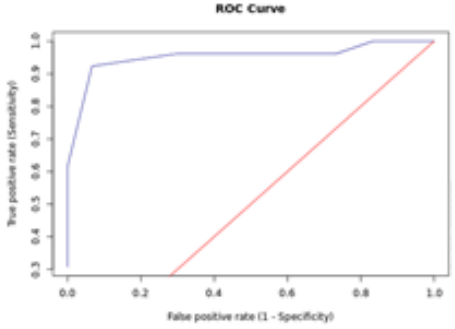


**Figure 1:** Receiver Operator Characteristics Curve plotted as sensitivity vs 1-specificity for MRI determined tumor depth as predictor of cervical nodal metastasis.

The area under the curve is 0.953 ($p<0.01$). The optimum cut off as calculated by computing Youden's index came out to be 7 mm in this case i.e. maximum [sensitivity- (1-specificity). The sensitivity at the cut off 7 mm MRI determined tumor depth was 92.3% and the specificity was also 92.3%.

Based on this optimum cut off value of MRI determined tumor depth, further analysis was done and it was found that there was a statistically significant difference between number of patients with tumor depth <7 mm and patients with tumor depth >or=7 mm who had cervical nodal metastasis. ($p<0.001$)

## DISCUSSION

It was found that mean tumor depth as calculated on observations determined by Magnetic Resonance Imaging of oral cavity was 6.160 mm ± 2.485mm while the mean tumor depth as calculated on observations based on histopathological examination was 5.625mm ± 2.187mm. This difference could be due to shrinkage of histopathology specimen. The shrinkage factor in the present study was calculated to be 0.91. This difference was not statistically significant ($p>0.05$).

The results are in agreement with other studies. Goel et al. in 2016[15] found mean MRI tumor thickness to be 8.47mm and histological tumor thickness to 6.85mm with a shrinkage factor of 0.8 in their study. This difference between the mean thicknesses in the present study and in the study conducted by Goel et al. could be due to the fact that they included all stages of Oral Squamous cell carcinoma patients (including tongue) in their study while in the present study, only stage I and stage II tongue carcinoma patients were included. The results of present study are not in agreement with the study conducted by Alsaffar et al.[16] in which a good correlation was not observed between radiological and histopathological depths ($r = -0.211$; $p = 0.56$ in case of superficial tumors, i.e depth less than 5mm) while in cases of tumor depths more than 5mm, the correlation observed was good ($r=0.731$, $p<0.01$)

When the relationship between MRI determined tumor depth and nodal metastasis was explored in the present study, it was found that the cervical nodal metastasis rate in cases with MRI tumor depth <or=3mm was 11.1%, with MRI tumor depth 3-9 mm, it was 43.5% and with MRI tumor depth >9mm, it was 100%.These results show as the depth increases, the nodal metastasis rate also increase. Also, a significant difference was found in nodal metastasis rate in the groups- < or =3mm and >3 mm.

These observations are consistent with other studies such as those conducted by Goel et al. wherein they found that in patients with tumor depth upto 3mm, the nodal metastasis rate was10%, in patients with depth 3-9 mm-50% nodal metastasis and depth >9mm-65% nodal metastasis. The 100% nodal metastasis in the present study can be explained by the fact that very few patients in our study were there who had depth >9mm. Keski Santti et al. in 2007, Zeng et al. in 2003 and Yuen et al. in 2000 [17-19] found similar results. Kane et al. in 2006 [20] also found a relationship between microscopic tumor depth and cervical nodal metastasis (p value=0.026). Sahin et al.[13] found a significant relationship between invasive depth and neck metastasis (p=0.017). Fukano et al.[21] reported that in tumors with depth less than 5mm, the cervical metastasis rate was 5.9% while in cases with depth more than or equal to 5mm, it was 64.7%.

The optimum cut off as calculated by computing Youden's index came out to be 7 mm in case of MRI determined tumor depth. The sensitivity at the cut off 7 mm MRI determined tumor depth was 92.3% and the specificity was 92.3%. MRI determined tumor depth here seems to be one of the useful techniques because of both good sensitivity and specificity for predicting cervical nodal metastasis before surgery and thus plan adequately and properly for management. It allows surgeons to decide whether elective neck dissection is required or not.

Though many authors have reported various cut offs for tumor depths predicting cervical nodal metastasis in cases of clinically N0 patients of tongue carcinoma, but the prediction is mostly based on histopathology determined depth of tumor.

In the present study, the ROC analysis revealed 7mm as optimum cut off point for MRI determined tumor depth in order to predict cervical nodal metastasis which is close to the cut-offs suggested by various authors. Iwai et al.[22] found the rate of cervical metastasis to vary statistically significantly between patients having tumor thickness <6 mm and those with > or = 6 mm and thus suggested elective neck dissection in cases with tumor thickness 6 mm or more. Okura et al.[23] found tumor thickness to be significantly associated with cervical lymph node metastasis and suggested MRI depth of 9.7 mm to be cut off for decision making regarding elective neck dissection.

## CONCLUSIONS

MRI determined tumor depth correlates very well with histopathology determined tumor depth ($r>0.9$) with a shrinkage factor of 0.9. So, MRI imaging modality definitely gives a fair idea of real infiltration depth of tumor. The depth of tumor (MRI determined) has been found to be statistically significantly associated with nodal status.

As a predictor for cervical nodal metastasis, cut off for radiological depth was calculated by ROC analysis and Youden index estimation. The cut off was 7 mm. MRI is a useful modality for predicting cervical nodal metastasis with an accuracy (overall accuracy 92.3% at the recommended cut off of 7 mm) and thus preventing the unnecessary morbidity due to elective neck dissection in patients of early stage tongue cancer (stage I and stage II).

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