"A COMPARATIVE STUDY ON DIAGNOSTIC ACCURACY OF MRI AND INTRA ORAL ULTRASOUND IN ASSESSING DEPTH OF INVASION (DOI) OF TONGUE CARCINOMA WITH HISTOPATHOLOGICAL EXAMINATION AS GOLD STANDARD"

Dissertation submitted to

THE TAMILNADU Dr. M.G.R.

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Of

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GOVT KILPAUK MEDICAL COLLEGE

CHENNAI- 600010

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CHENNAI- TAMILNADU, INDIA

MAY 2022

CERTIFICATE

This is to certify that the dissertation **"A COMPARATIVE STUDY ON DIAGNOSTIC ACCURACY OF MRI AND INTRA ORAL ULTRASOUND IN ASSESSING DEPTH OF INVASION (DOI) OF TONGUE CARCINOMA WITH HISTOPATHOLOGICAL EXAMINATION AS GOLD STANDARD"** titled submitted by **Dr. S. RAJKUMAR** appearing for **M.D (RADIODIAGNOSIS)** degree examination in May 2022 is a bonafide record of work done by him under my guidance and supervision in partial fulfillment of requirement of the Tamil Nadu Dr. M.G.R. Medical University, Chennai. I forward this to the Tamil Nadu Dr. M.G.R Medical University, Chennai.

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DECLARATION

I**, Dr. S. RAJKUMAR** solemnly declare that this dissertation **"A COMPARATIVE STUDY ON DIAGNOSTIC ACCURACY OF MRI AND INTRA ORAL ULTRASOUND IN ASSESSING DEPTH OF INVASION (DOI) OF TONGUE CARCINOMA WITH HISTOPATHOLOGICAL EXAMINATION AS GOLD STANDARD"** is a bonafide work done by me at Government Kilpauk Medical College, under the supervision of **Dr. K. GOPINATHAN, M.D.(RD), DNB.,** Professor, Government Kilpauk Medical College. This dissertation is submitted to the Tamil Nadu Dr. M.G.R Medical University, towards partial fulfillment of requirement for the award of M.D. Degree Radio diagnosis.

Place: Chennai Signature of the candidate

Date:

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CERTIFICATE - II

This is to certify that this dissertation work titled dissertation **"A COMPARATIVE STUDY ON DIAGNOSTIC ACCURACY OF MRI AND INTRA ORAL ULTRASOUND IN ASSESSING DEPTH OF INVASION (DOI) OF TONGUE CARCINOMA WITH HISTOPATHOLOGICAL EXAMINATION AS GOLD STANDARD"** of the candidate **Dr. S. RAJKUMAR** with Registration Number 201918253 for the award of **M.D** degree in the branch of **(RADIODIAGNOSIS).** I personally verified the urkund.com website for the purpose of Plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion page and result shows 8% of plagiarism in this dissertation.

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CERTIFICATE OF APPROVAL

The Institutional Ethics Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for "A COMPARATIVE STUDY ON DIAGNOSTIC ACCURACY OF MRI AND INTRA ORAL ULTRASOUND IN ASSESSING DEPTH OF INVASION (DOI) OF TONGUE CARCINOMA WITH HISTOPATHOLOGICAL EXAMINATION AS GOLD STANDARD" Submitted by Dr. Raj Kumar. S, Post Graduate M.D. Radiodiagnosis, Govt. Kilpauk Medical College, Chennai-10.

Proposal is APPROVED.

The Institutional Ethics Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

18/11/2021

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BACKGROUND:

With the advent of AJCC 8th edition, Depth of Invasion (DOI) is given significance for T staging of oral tongue cancers.

AIM and OBJECTIVE:

To compare the accuracy of depth of invasion in tongue carcinoma measured by MRI and intraoral USG and correlating it with histopathological examination as gold standard.

MATERIALS AND METHODS:

A comparative cross sectional study designed to compare the value of depth of invasion measured on T2 weighted MR images in Siemens 1.5T Avanto and intraoral USG using high frequency transducer (3 – 16 Mhz) in Samsung HS 40. The parameters assessed were depth of invasion, tumour thickness and pre operative T staging was given based on DOI value in accordance with the AJCC 8th edition. Study population was 76 and study period was from December 2020 to November 2021. All cases with stage T4 were excluded from our study.

RESULTS:

The statistical analyses were performed using SPSS and a 'p' value of <0.05 was considered significant. Bland Altman plots were utilised and for USG, P value in regression is 0.001 which is less than significant p value of 0.05 which means that there is no significant difference. For MRI, P value in regression is 0.158 which is more than significant p value of 0.05 at 95% confident interval which means that there is significant difference.

CONCLUSION:

Hence DOI measured by intraoral USG is correlating well with the post surgical HPE DOI and can be used as an effective imaging tool for staging.

INTRODUCTION

Oral cavity cancers are one of the most common cancers in this era, ranking eighth worldwide. Oral cavity squamous cell carcinoma (OCSCC) is seen in both males and females with risk factors being tobacco intake, betel nut chewing, alcohol, etc. Human Papilloma Virus infection is also considered a risk factor for developing oral cavity cancers. The incidence of oral cavity cancers is on a global rising trend and it has been accounted as the cause for 8.8 million deaths in an epidemiological survey in 2015.

Oral tongue is the most common subsite among all oral cavity cancers. Tongue carcinoma is one of the most common cancers in Indian male population primarily owing to tobacco, betel nut chewing. Tobacco consumption is the cause of approximately 22 percent of cancer related deaths. Owing to the absence of anatomical barrier, it is more prone for occult nodal metastases, perineural invasion, vascular invasion.

With the advancements in early diagnosis and accurate pre operative radiological assessment, there has been increase in survival rates of oral tongue cancer patients. Significant progress has been made in the management of tongue carcinoma in the past few years. Developments in surgical techniques and adjuvant treatment like

neoadjuvant chemoradiation have led to significant improvements in prognosis for some patients.

With the oral tongue being accessible site for diagnosis and biopsy, oral tongue squamous cell carcinoma can be detected easily on clinical examination and tissue diagnosis is made by taking a biopsy specimen.

Once the histopathological diagnosis is made, pre operative radiological assessment stands tall in setting up the adequate treatment protocol for the patient.

The tumor is examined morphologically by Intra oral Ultrasonogram and Magnetic Resonance Imaging (MRI) for evaluation of extent of tumor. Cervical nodal metastases can be assessed in pre operative radiological examination. With the advent of Diffusion weighted imaging (DWI), assessment of cellularity of the lesion is made possible. They also play a major role in assessing the viability of tumor post radiotherapy.

In cases which have distant metastases, computed tomography (CT) is the main modality used to evaluate the disease. Positron emission tomography (PET)-CT is useful in detecting occult nodal metastasis.

The 8th edition of American Joint Committee on Cancer (AJCC) & Union for International Cancer Control (UICC) TNM – Tumor, Node, Metastases staging manual which was published in 2017 brought upon landmark changes in the staging of oral cavity cancers. Depth of Invasion

(DOI) was given significant role in the T staging of oral cavity tumors. Involvement of extrinsic muscles which was given as T4a in AJCC 7th edition has been removed now.

Oral tongue cancers can be ulcerative or ulceroproliferative. Depth of invasion depends primarily on the deepest extent of the tumor from the normal mucosa – tumor interface. Hence increase in depth of invasion has been proved to be directly proportional to the presence of nodal metastasis, perineural spread.

Proper assessment of depth of invasion and the need for finding the optimal radiological modality for quantifying it is necessary in the staging and follow-up of tongue cancer. Tumor thickness (TT) which has been frequently interchangeably used with the term Depth of Invasion (DOI) is not given significance in the recent AJCC guidelines.

With Depth of Invasion being the gamechanger in staging and the subsequent treatment regimen for oral cavity cancers, this study aims to compare the diagnostic accuracy of Magnetic Resonance Imaging and Intra oral Ultrasound examination for detecting Depth of Invasion with Histopathological Examination as the gold standard.

REVIEW OF LITERATURE

ANATOMY OF ORAL CAVITY

EMBRYOLOGICAL DEVELOPMENT OF TONGUE

Development of tongue begins from the 4th week of the intrauterine life. Tongue is derived from the first four pharyngeal arches in fetal life. Tuberculum impar is the medial swelling which develops from the first pharyngeal arch. Later on, lateral lingual swellings (two in number) begin to grow from fifth week of fetal life from the first pharyngeal arch. Lateral swellings increase in size and when they merge with medial swelling (tuberculum impar), anterior two thirds of tongue is formed.(1)

Hence anterior two thirds of tongue is basically derived from first pharyngeal arch resulting in it getting its nerve supply from 5th cranial nerve – Trigeminal nerve via its mandibular branch.

Hypobranchial eminence is a median swelling which is derived from the mesoderm of 2nd to 4th pharyngeal arches. The hypobranchial eminence forms the posterior one third of tongue. The ninth cranial nerve, glossopharyngeal nerve innervates the mucosa overlying the posterior third of tongue.

Posterior most part of the tongue arises from 4th pharyngeal arch by formation of third median swelling. So it derives its nerve supply from the superior laryngeal nerve.

The myoblasts from occipital somites give rise to the muscles of the tongue. With the exception of palatoglossus, all other muscles of tongue are innervated by the 12th cranial nerve, hypoglossal nerve. There are four extrinsic tongue muscles namely the genioglossus, hyoglossus, palatoglossus, styloglossus. They originate from structures adjacent to tongue. Function of extrinsic muscles is mobility of the tongue.

The intrinsic muscles of tongue are four paired muscles namely superior and inferior longitudinal, transverses and verticalis muscles. Contrary to the extrinsic muscles, origin and insertion of intrinsic muscles lie within the tongue. Function of intrinsic muscles is changing shape of tongue.(2)

Development of taste buds over the lingual epithelium start at 8th week of gestation. Many taste bud primordia originate from 9th to 11th week. The primordia cells metamorphose into various cell types around the 11th through 13th week of gestation. Taste pores develop during this period.

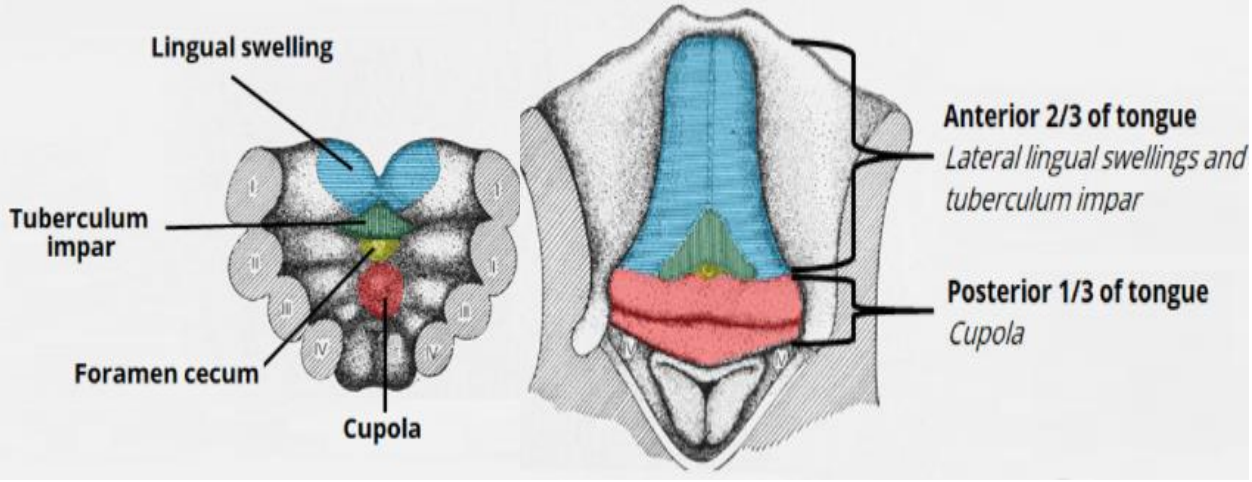


Figure 1:Embryology of tongue

Cellular level

Connective tissue compartment and vasculature of tongue are derived from the neural crest cells. Formation of interstitium and tongue bud are initiated by the neural crest cells. Occipital somite cells get migrated into the primordium of tongue to give rise to muscles of tongue.(1)

Biochemical level

Multiple genes interact with each other to form the biochemical framework for formation of tongue. These genes include

- PAX 3
- PAX 7
- DLX

At the time of tongue morphogenesis, TGF Beta plays a significant role in proliferation of the myogenic cells of tongue.

Molecular level

At the molecular level, regulatory factors which play a crucial role include:

- Myf 5 (Myogenic factor 5)
- MRF4 (Muscle specific regulatory factor 4)
- MyoD (Myoblast determination protein)

ANATOMY OF ORAL CAVITY

Anteriorly the oral cavity extends from the vermilion junction of lips to communicate with oral cavity posteriorly. Superior extent is to the junction of hard and soft palate and the inferior extent is upto the line of circumvallate papillae on dorsal tongue.(2)

Oral cavity proper contains the buccal mucosa, mandibular and the maxillary arches, the retromolar trigone, anterior two third of tongue called the oral tongue, the floor of mouth and the hard palate.(3)

Dorsal tongue contains villi and specialized taste receptors. Ventral tongue is under surfaced, does not contain villi.

Oral tongue: It is made up of skeletal muscle fibres which extend anteriorly from the line of circumvallate papilla to the under surface of tongue at the junction of floor of mouth. Oral tongue can be further divided into four areas- 1. the lateral borders which are the common site for malignancy, 2. the tongue tip, 3. dorsum of tongue, 4. undersurface of tongue which is non villous.(2)

Base of tongue: Also known as the posterior one third of tongue is bounded anteriorly by the circumvallate papilla, posteriorly by the epiglottis.

Buccal mucosa: The inner surface of lips and cheeks are lined by the buccal mucosa on both sides till the line of attachment of

ptyergomandibular raphe and mucosae of alveolar ridge which are located posteriorly.

Floor of mouth:

It is a semilunar space containing hyoglossus and mylohyoid muscles which are divided by the frenulum in midline. Sublingual salivary glands reside within the floor of mouth. The ducts of bilateral submandibular glands drain into the floor of mouth.(4)

Hard palate: Roof of oral cavity is formed by the hard palate which is a semilunar surface juxtaposed between mucosal membrane covering the palatine bones and the upper alveolar ridge.

Retromolar trigone: RMT is the mucosa which overlies ramus of mandible at the level of third molar tooth to apex located adjacent to maxillary tuberosity.

Palatine tonsils: One on either side lying in tonsillar fossa between palatopharyngeus and cricopharyngeus which are the anterior and posterior tonsillar pillars respectively.

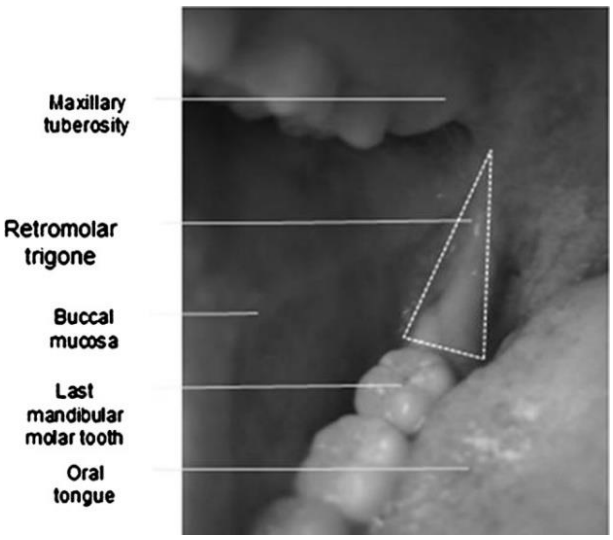


Figure 2: Oral tongue and retromolar trigone

VASCULAR SUPPLY

The oral cavity is supplied by different branches of the external carotid artery viz. branches of facial, lingual and maxillary arteries. Oral tongue is supplied by the lingual artery. Blood supply to the upper dentition and gingiva are from alveolar arteries which in turn are branches of maxillary artery. Inferior alveolar artery supplies the lower dentition and mandible.(4)

LYMPHATIC DRAINAGE OF ORAL TONGUE

The deep cervical nodes drain the lymphatics of tongue lying between the posterior belly of digastric and superior belly of omohyoid muscles. (4)

Principal lymph gland of the tongue is the main lymphatic gland which is situated at the level of bifurcation of common carotid artery on

either side. Lymphatic vessels of the tongue is broadly divided into four groups namely:

1) Apical – from tip of tongue to suprahyoid glands and principal gland of tongue
2) Lateral – from the margin of tongue – either pierce the mylohyoid muscle to end in submandibular glands or to the superior deep cervical level
3) Basal – from circumvallate papillae to superior deep cervical level
4) Median – Either penetrating mylohyoid which form the diaphragm of the mouth to reach submandibular level or into the superior deep cervical level.

CERVICAL NECK NODE ANATOMY:

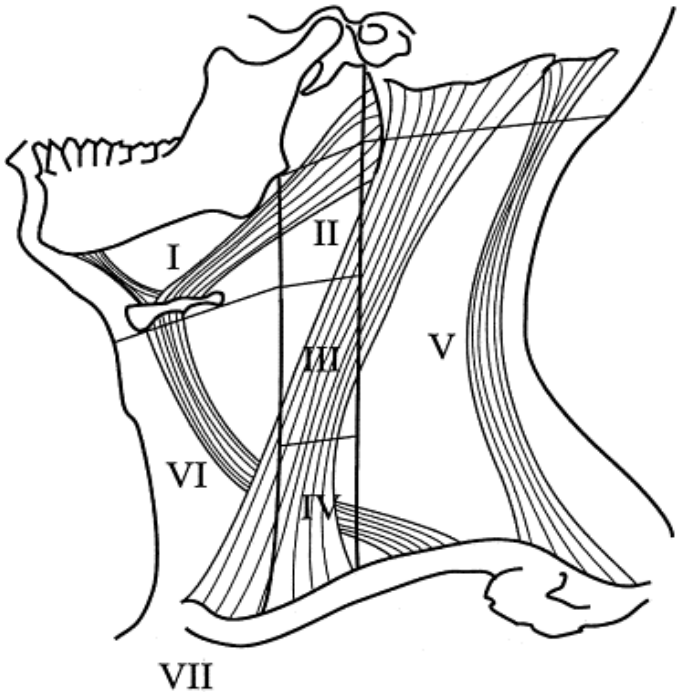


Figure 3: Cervical node stations

Level Ia – submental group:

It is bounded superiorly and laterally by the mandible whereas the hyoid bone forms the inferior margin. The platysma lies anteriorly and mylohyoid muscle lies posteriorly. These boundaries give a triangle configuration for submental group.(5)

Anterior margin (tip) of oral tongue, mental portion, and mid lower lip drain primarily into the submental node station.

Level Ib – submandibular group:

Mylohyoid muscle forms the superior boundary and hyoid forms the floor. Posterior margin of the submandibular gland forms the posterior boundary of this group of lymph nodes.

Efferents from submental group, palates, maxilla and mandibular alveolar carcinomas, floor of mouth, anterior oral tongue lesions drain into the submandibular group of lymph nodes.

Level II – Upper jugular:

Also called upper deep jugulodigastric nodes – they are bounded by posterior belly of digastric cranially and caudally by hyoid bone. Nodes lying behind the posterior margin of the submandibular gland between the base of skull and hyoid bone come under this group.(4)

Forms primary drainage for nasal cavity, larynx, pharynx, middle ear, submandibular and sublingual glands. Also collects efferents from submental and submandibular group of nodes.

Level III – Middle jugular:

They lie between the hyoid bone cranially and cricoid cartilage caudally. It is bounded by the anterior border of sternocleidomastoid muscle anteriorly and its posterior border posteriorly. Internal carotid artery and scalenus muscles form the medial border.(4)

Efferents from level II, V, retropharyngeal group of nodes drain into this level.

Level IVa – Lower jugular:

It lies between the cricoid cartilage and a virtual line 2 cms above the sternoclavicular joint level. Boundaries are same as level III in the anterior, posterior, lateral aspects. Medial boundary is formed by the common carotid vessels and scalene muscles.

It forms the drainage pathway for efferent lymphatics from levels III and V. Lower jugulodigastric nodes also get direct lymphatic drainage of lesions from larynx, thyroid and hypopharynx.(4)

Level IVb – Medial supraclavicular:

Inferior extension of level Iva till the level of manubrium sterni. Posterior boundary of this nodal station is formed by anterior border of scalene muscles, lung apex, brachiocephalic vessels.

Oesophagus drains directly into this nodal station. It also collects the efferents of levels Iva and V. Pretracheal and recurrent laryngeal nodes also drain into this level.

Level Va and Vb – Posterior triangle group:

Bounded anteriorly by sternocleidomastoid and posteriorly by trapezius muscles. Medial border is formed by scalene muscles. An imaginary line at the level of cricoid cartilage is used to delineate upper Va and lower Vb posterior triangle group cervical lymph nodes.(4)

Efferents from scalp and retro auricular nodes drain into this group and it also has direct lymphatic drainage from oropharynx, nasopharynx predominantly from posterior aspect.

Level Vc – Lateral supraclavicular group:

It is the inferior continuation of Va and Vb stations, bounded medially by scalene. Superiorly it extends from an imaginary line 2 cm above the level of manubrium sterni. Laterally it is bound by trapezius and clavicle.

Efferents from levels Va and Vb drain into this group.

Level VI – Anterior compartment:

This group is symmetric and lies along the midline in neck. It can be further sub classified into VIa (superficially located anterior jugular nodes) and VIb (deeply located prelaryngeal, pre and para tracheal nodes in neck). Delphian nodes come under this group.

Efferents from lower face, chin, anterior floor of mouth, oral tongue tip, thyroid, larynx, hypopharynx can drain into this nodal station.

INCIDENCE AND RISK FACTORS OF CARCINOMA OROPHARYNX:

Carcinoma oropharynx is the 6th most common malignancy worldwide and is on an increasing global trend.(6) The most frequent subtype is squamous cell carcinoma of oral cavity. Oral tongue is the most common subsite within the oral cavity, followed by lips, floor of mouth and buccal mucosa.

The incidence of oral cancer worldwide is 6 per 1 lakh population. (6) It is on an increasing trend in India affecting 20 people per 100000 people.(7) Oral cavity cancers are frequently diagnosed only at later stage of progression thus resulting in poor survival rate. Inadequate access to treatment and delay in diagnosis are considered important factors leading to poor outcome in rural India. With the advent of imaging modalities, adequate assessment of oral tongue lesions are made possible.

Tobacco usage, chewing of betel nut, chronic alcohol intake, Human Papilloma virus (HPV) infection are the most common risk factors of oral cavity cancer. Poor dental hygiene and diet are postulated as risk factors for oral cancer.(8)

According to International agency for research on cancer, India's caseload of oral cancer are hypothesized to increase multifold from 1 milion to 1.7 million in a decade.(7)

Histological classification of oral cavity cancers according to WHO 2017:

Epithelial tumors:

- Squamous cell carcinoma
- Oral epithelial dysplasia – low grade and high grade
- Proliferative verrucous leukoplakia

Papillomas:

- Squamous cell carcinoma
- Condyloma acuminata
- Verruca vulgaris
- Multifocal epithelial hyperplasia

Soft tissue and neural tumors:

- Granular cell tumors
- Rhabdomyoma
- Lymphangioma
- Hemangioma
- Nerve sheath tumors
- Kaposi Sarcoma
- Myofibroblastic sarcoma

Oral mucosal melanoma

Salivary type tumors

- Mucoepidermoid carcinoma
- Pleomorphic adenoma

Hematolymphoid tumors:

- CD30 +ve lymphoproliferative disorder
- Plasmablastic lymphoma
- Langerhans cell histiocytosis
- Extramedullary myeloid sarcoma

Squamous cell carcinoma is the most common histological subtype of all and constitutes more than 50 percent of all tongue malignancies. Biopsy and histopathological examination prior to imaging is done as the first step.

After confirmation of malignancy with histopathology, further imaging is done to assess the local staging and distant spread of the tumour.

High rates of local recurrence are associated with traditional tongue cancer surgery with rates of 5%-20%. But with the combination of surgery of primary tumor and nodal dissection along with the use of neoadjuvant and adjuvant therapy, there has been a significant decrease in the rates of local recurrence and improvement in survival of the patients.(9)

The aim of the surgeon is to achieve a microscopic tumor-free margins after surgical resection. But in spite of this there is a risk of local recurrence with positive margins and occult cervical nodal metastases. So proper preoperative assessment of the tumour identifies high risk patients in whom the depth of invasion is high. With increase in depth of invasion, there is high chance of occult cervical nodes in whom the nodes are clinically negative.

Hence the status of the presence of occult nodal lesion with increase in depth of invasion forms the centre stage of the recent update in AJCC 8th edition.(9)

Selective neck dissection abbreviated as SND was the surgical method of choice for eliminating cervical nodes in cases of head and neck malignancies. As it resulted in more comorbidities to the patient in the form of shoulder and neck dysfunction, a more novel approach of super selective neck dissection abbreviated as SSND was utilized. In SSND, only two nodal levels were resected.

About 20 to 44 percent of patients with oral cavity cancer have occult cervical nodal metastases.(10) So it is seen rational to do elective neck dissection in whom the risk factor is high.

CONCEPT OF DEPTH OF INVASION:

Before the advent of the AJCC manual 8th edition, tumor thickness was given utmost significance rather than depth of invasion. A tumor

thickness of more than 4 mm was considered significant and the patient was deemed to have occult nodes even in clinically negative patients.(11)

Imaging done prior to the initiation of treatment, clinician's physical examination findings and history of the patient are utilised in forming out the clinical stage classification. Post operative histopathological examination of the surgical specimen plays a pivotal role in forming the pathological stage classification.

Even though the two terms viz. Tumor thickness and tumor depth of invasion are used synonymously which is erroneous, there is a basic histological difference between the two.(12)

TUMOR THICKNESS VS DEPTH OF INVASION:

Tumor thickness (TT) is the distance measured from the surface of the tumor to the point of deepest invasion, whereas Depth of invasion (DOI) is defined as the distance from the basement membrane of the surface epithelium to the deepest point of invasion of the tumor.(13)

Increasing DOI and the microvascular proliferation caused by neoplastic growth might determine the proximity to blood vessels and lymphatics, thus facilitating the ability of the tumor to metastasize.

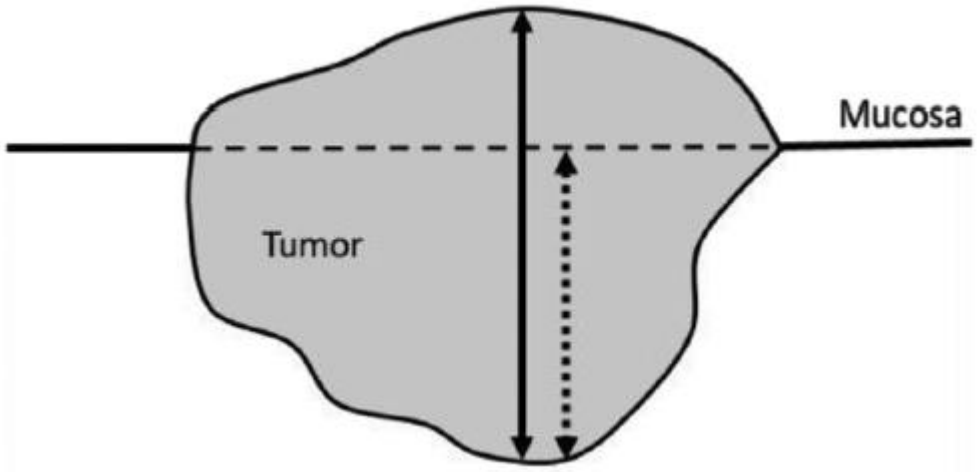


Figure 4: Construction of Tumor – mucosa interface line

From the gross diagram, it is clear that depth of invasion doesn't take into account the exophytic part of the tumor. Although tumor thickness (TT) has been shown to be related to the risk of cervical node metastases, DOI has been shown recently to be a more reliable predictor with regards to prognostication.(14)

Tongue carcinoma can be morphologically classified into three types.(15)

They are:

- Flat tumor in which Tumor thickness (TT) is the same as Depth of Invasion (DOI)
- Exophytic tumor in which Tumor thickness (TT) is greater than Depth of Invasion (DOI)
- Ulcerative tumor in which Tumor thickness (TT) is lesser than Depth of Invasion (DOI)

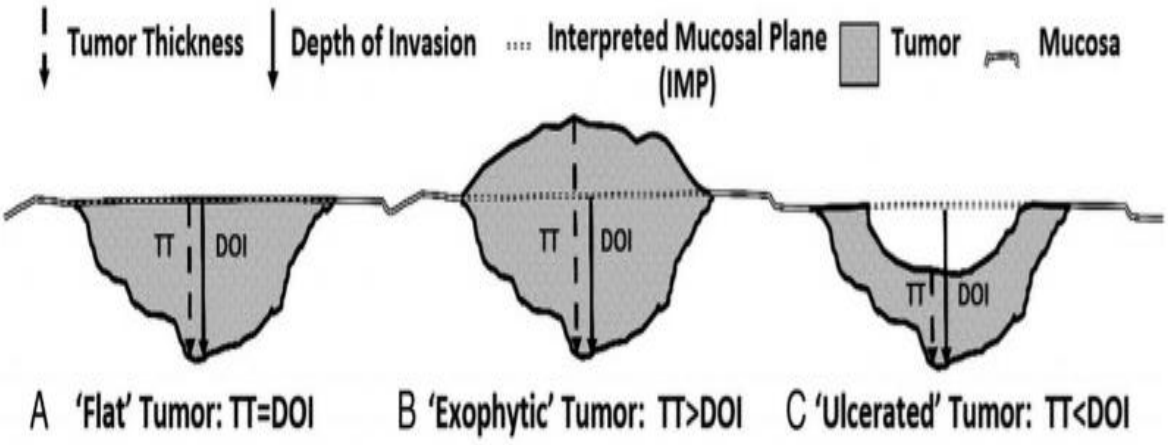


Figure 5: Different morphologies of tongue carcinoma – A: Flat tumor;

B : Exophytic tumor; C: Ulcerated tumor

Hence the ulceroproliferative lesions which are the most common tongue cancer morphology encountered comes under the B subtype - Exophytic tumor where the tumor thickness will be more than depth of invasion.

The TNM staging of the oral cavity carcinoma as per the AJCC (American Joint Committee On Cancer 8th edition)(16)

Primary tumour

* **TX:** primary tumor cannot be assessed
* **T0:** no evidence of primary tumor
* **Tis:** carcinoma in situ
* **T1:** Tumor ≤ 2 cm with depth of invasion (DOI) ≤ 5 mm

* **T2:** Tumor ≤ 2 cm with DOI > 5 mm and ≤ 10 mm or tumor > 2 cm and ≤ 4 cm with DOI ≤ 10 mm

* **T3:** Tumor > 2 cm and ≤ 4 cm with DOI > 10 mm or tumor > 4 cm with DOI ≤ 10 mm or any tumor

* **T4:**

Moderately advanced or very advanced local disease

T4a: Moderately advanced disease

Tumor > 4 cm with DOI > 10 mm or

Tumor invades adjacent structures only (Eg. Cortical bone of mandible/ maxilla or involves maxillary sinus or face)

T4b: Very advanced diseases

Tumor invades masticator space, pterygoid plates, skull bases or causes encasement of the internal carotid artery.

Note : Depth of invasion is different from tumor thickness

Superficial erosion of bone / tooth socket is not sufficient enough to label a tumor as stage T4a.

Regional lymph nodes

- **NX:** Tumors in which lymph nodes could not be assessed
- **N0:** no evidence of regional lymph node metastasis

- **N1**: Metastasis to a single ipsilateral lymph node which is less than or equal to 3 cm in greatest dimension and without extranodal extension
- **N2:** Metastasis to a single ipsilateral node which is less than or equal to 3 cm in greatest dimension but with positive extranodal extension Or > 3 cm but ≤ 6 cm in greatest dimension and without extranodal extension.

Or

- metastases in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension and without extra nodal extension.

Or

To bilateral or contralateral lymph nodes(s), none > 6 cm in greatest dimension and without extranodal extension.

- N2a: Metastasis in either
- Single ipsilateral lymph node that is ≤ 3 cm and ENE+ or
- Single ipsilateral lymph node that is > 3 cm but ≤ 6 cm in greatest dimension and ENE
- N2b: Metastasis in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension and ENE
- N2c: Metastasis in bilateral or contralateral lymph node(s), none > 6 cm in greatest dimension and ENE

- N3 : Metastasis in a lymph node > 6 cm in greatest dimension and without extranodal extension or in a single ipsilateral node > 3 cm in greatest dimension and with extranodal extension or multiple ipsilateral, contralateral or bilateral nodes, any with extranodal extension or a single contralateral node of any size and with extranodal extension.
- N3a: Metastasis in a lymph node that is > 6 cm in greatest dimension and without extranodal extension.
- N3b: Metastasis in either
- Single ipsilateral lymph node, > 3 cm and with extranodal extension or
- Multiple ipsilateral, contralateral or bilateral lymph nodes, any with extranodal extension or Single contralateral lymph node of any size and with extranodal extension.

Note : Letters ‘U’ and ‘L’ are used to denote whether the node is above or below the level of lower border of cricoid cartilage respectively.

Midline nodes are designated as ipsilateral nodes rather than contralateral nodes

Selective neck dissection includes dissection of 10 nodes and modified radical / radical neck dissection includes dissection of more than or equal to 15 cervical nodes.

Distant metastasis

- **M0:** no distant metastasis by imaging; no evidence of tumor in other sites or organs (this category is NOT assigned by pathologists and can be worked up in radiological assessment)
- **M1:** Presence of distant metastasis

AJCC Prognostic stage grouping for oral cavity(15)

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1 – T3	N1	M0
Stage IVA	T4a	N0- N1	M0
	T1 – T4a	N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

IMAGING MODALITIES FOR PREOPERATIVE STAGING(17)

Preoperative staging of tongue cancer is divided into-

- Local Staging.
- Distant Staging.

Local staging mainly involves the assessment of the depth of invasion of tumor, extension of tumor into adjacent structures like

- Masticator space, pterygoid plates
- Maxillary sinus
- Cortex of mandible / maxilla
- Other regions of face
- Floor of mouth
- Base of tongue
- Assessment of invasion of hyoglossus, mylohyoid, geniohyoid muscles
- Cervical lymph node status.
- Distant staging assesses the extent of metastatic disease.(17)

Several modalities are being used now for both local staging as well as metastatic work-up of tongue cancer of which the primarily used ones are magnetic resonance imaging (MRI), intra oral Ultrasound, Computed Tomography (CT), Single Photon Emission Computed

Tomography (SPECT), PET – CT (Positron Emission tomography) particularly for evaluation of distant metastasis. (18)

Magnetic Resonance Imaging (MRI):

MRI is the workhorse in pre operative imaging of oral cavity carcinoma. Sequences employed are diffusion weighted imaging (DWI), T2, STIR,T1, perfusion with and without contrast agent.(16)

MRI is sensitive in finding out the smaller lesions which can be easily missed on CT due to poor soft tissue resolution in CT. MRI is superior in depicting the local spread of the lesion, evaluation of complications which occur during surgery, post radiotherapy assessment of the lesion because of presence of diffusion weighted imaging in its armamentarium.

Dense cellular elements in the tumor tissue make it appear hyperintense on diffusion weighted images. The quantification of diffusion restriction is made out by the help of apparent diffusion coefficient (ADC) maps. Sensitivity and specificity is around 90 percent with the help of ADC maps.

Within one to two cycles after chemotherapy, response assessment can be done with the help of diffusion weighted imaging.

Diffusion weighted imaging can also be utilized for the evaluation of lymph nodes and for differentiating reactive versus malignant nodes. Recent studies indicate that morphology of the node (irregular margins,

round shape rather than oval) in T2 weighted imaging also increase the sensitivity in detecting nodal spread of oral cancers.

ASSESSMENT OF DEPTH OF INVASION IN MRI:

Depth of invasion (DOI) is defined as the distance from the basement membrane of the surface epithelium to the deepest point of invasion of the tumor. It can be evaluated in MRI by three different methods.(17)

1st method is the measurement of DOI using axial T2 weighted images. Two lines are drawn (a and b). 'a' is the line which is drawn from the midline lingual septum medially to the unaffected normal appearing tongue mucosa on the lateral aspect. 'b' is the line which is drawn from midline lingual septum medially and laterally it is extended till the point where the tumor has the deepest point of invasion.(17)

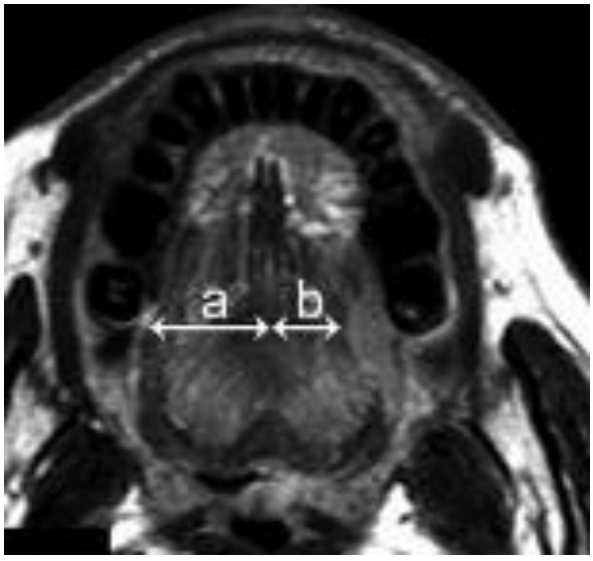


Figure 6: T2 axial image in a patient with left lateral border of tongue growth (DOI = a -b)

The tumor is on the left lateral border of tongue involving its anterior two third. From this image, the depth of invasion (DOI) is calculated by subtracting b from a. (ie. DOI equals to a-b).

The second method of detecting depth of invasion from MRI is in T2 weighted or STIR axial sequences.(17)

In this method, reference line is drawn on axial sections which is determined by the point of tumor – normal mucosa interface on both sides of the tumor(anterior and posterior).

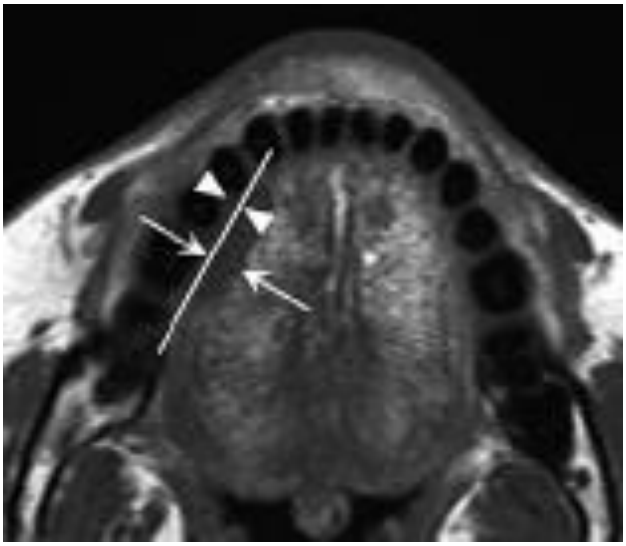


Figure 7 : Patient with right lateral border of tongue growth

After drawing this reference line, a perpendicular line is drawn from the reference line leading towards the point of deepest invasion of the tumor medially. In this above mentioned pictorial reference, tumor is occupying the right lateral border of tongue involving its anterior two third. At the normal tongue mucosa – tumor interface on both anterior and posterior aspects, a reference line is drawn connecting them.

From the reference line, a dotted line is made till the point of deepest invasion which is the DOI.

Third method is utilization of coronal T2 weighted image for assessing the depth of invasion. In this method, the protruding / proliferative component of an ulceroproliferative lesion is ignored.(17)

Only the ulcerative / invading component of the tumor is measured. Similar to the 2nd method in which reference line connecting the tumor – normal tongue surface interface on both sides is made out, this method connects the points in superior and inferior aspects.

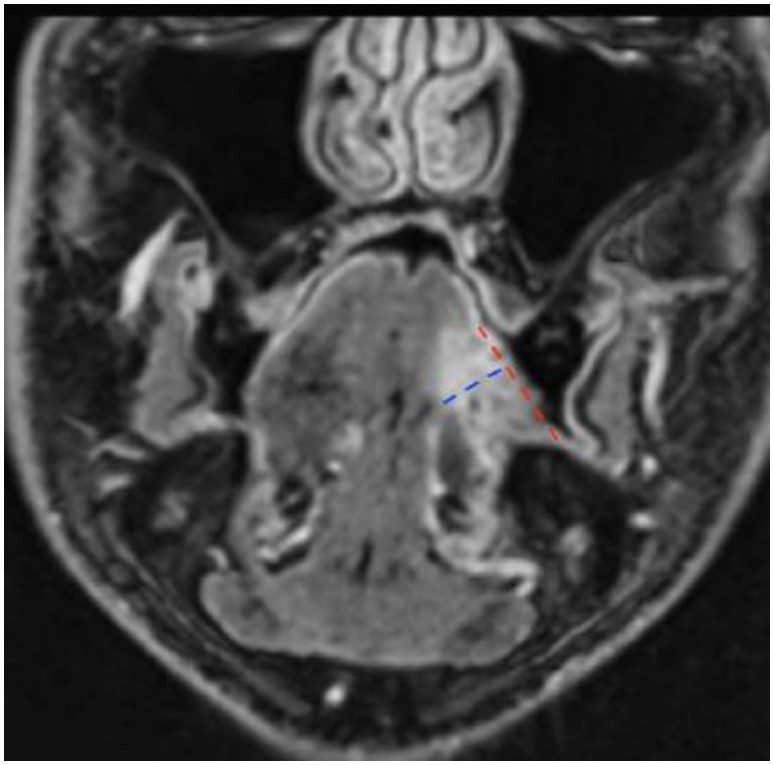


Figure 8: Coronal T2 weighted image in a patient with left lateral border of tongue malignancy

In the pictorial representation above, tumor is seen occupying the dorsal surface of tongue, line connecting the tumor – normal mucosa interface is made and from which a perpendicular line could be drawn till the deepest point of invasion.

Literature review suggests that there has been many studies evaluating the correlation of tumor thickness (TT) with the histopathological examination rather than the Depth of invasion (DOI).

Tumor thickness (TT) is calculated by summing up the maximum amount of protrusion to the deepest point of invasion.

In the 2nd and 3rd methods which were used to calculate the depth of invasion, the protruding component is not taken into account, only the invading portion is given significance. And it is evident that tumor thickness will be equal to depth of invasion in case of flat tumors as they don't have a proliferative component.(17)

ASSESSMENT OF EXTRINSIC MUSCLES OF TONGUE

Moderately advanced local disease in AJCC manual 7th edition which was practiced previously included invasion of palatoglossus, styloglossus, genioglossus and hyoglossus muscles under stage T4a. But the major update in the 8th edition in addition to the importance of depth

of invasion is the removal of invasion of extrinsic muscles from T4a status.

Invasion of extrinsic muscles have proven to be indirect indicator of nodal involvement and recurrence of the disease.(19) It has been considered as a surrogate marker for nodal recurrence.

Hence pre operative reporting of MR imaging should include tumour infiltration of hyoglossus, genioglossus, geniohyoid, mylohyoid muscles for all practical purposes. The infiltration of hyoglossus and mylohyoid could not be assessed clinically without the help of imaging and it has long been in the grey area for clinicians. The extent of resection during surgery can be determined based on the preoperative imaging whether there is infiltration or not.(18)

Mylohyoid muscle acts as oral diaphragm which separates the sublingual and submandibular spaces. Origin is from the mylohyoid line in the mandible medial surface and insertion is into the hyoid bone.

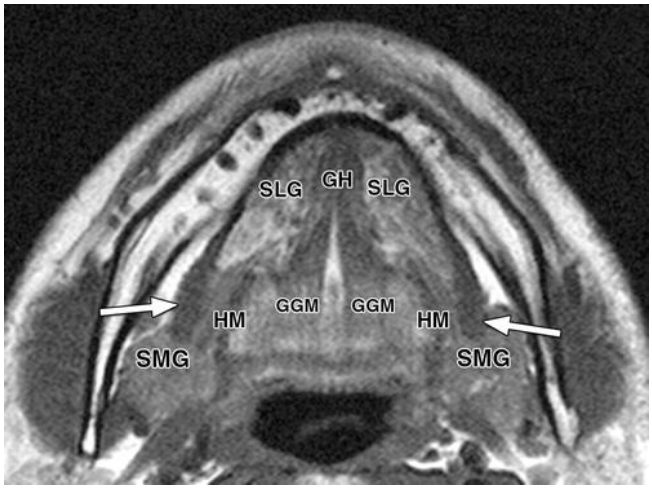


Figure 9: Axial T1 weighted image at floor of mouth level.

Arrows – mylohyoid muscle which separates submandibular gland (SMG) and sublingual gland (SLG). Hyoglossus muscle (HM) lies posterior to mylohyoid muscle.

Anatomical variant of mylohyoid gap can occur in some patients through which a ranula in sublingual space can extend into the submandibular gland which is termed as plunging ranula.(20)

ASSESSMENT OF NODAL STATUS:

RECIST criteria version 1.1 states that the lymph nodes should be measured in short axis and should be greater than or equal to 15 mm to be called pathological.(21) Nodes more than 10 mm but lesser than 15 mm are called non target pathological sites.

However it is not necessary for a malignant node to be enlarged in size in case of metastatic deposit. Even a small node can harbor metastasis within it. Hence size is not given importance in assessing nodal status and differs from station to station. Nodes lesser than 1 cm in an already biopsy proven case of tongue cancer should be carefully assessed if it is in the drainage pathway for that particular site.

Crossed lymphatic pathways are common in tongue carcinoma and it is not uncommon to come across contralateral cervical nodes even in T1 and T2 lesions.(22) Morphological changes provide high sensitivity

and specificity in detecting nodal spread. Most valuable indicator is the presence of necrosis with in the enlarged lymph node.(23)

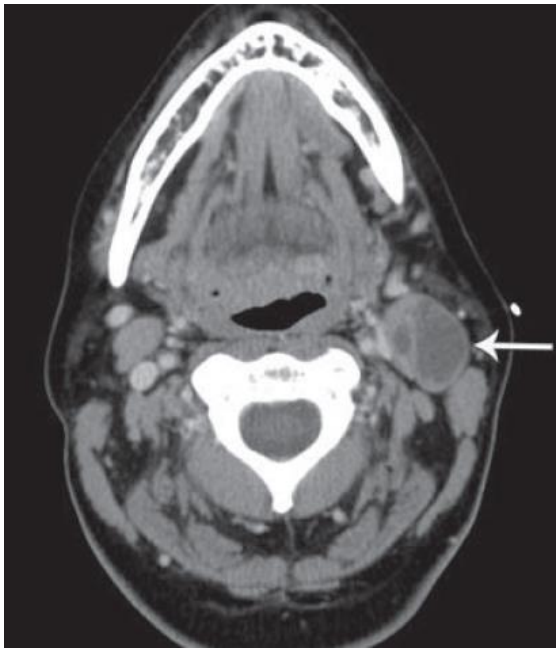


Figure 10: Necrotic left upper jugulodigastric (level II) node in A CASE OF TONGUE CARCINOMA

Necrosis is indicated by areas of low density / non enhancing portion with in the enlarged lymph node or T2 hyperintensity within the node which shows peripheral irregular enhancement post contrast administration.(22) Central areas represent necrosis because of lymphatic obstruction however they may also consist of fibrous tissue, tumor cells and edmeatous fluid.

Shape and margins:

Normal benign node will have smooth margins and reniform appearance. But invasion of tumor cells will lead to loss of its oval/reniform nature and become round in shape. Margins become

irregular. As tumor cells grow, there will be breach of tumor capsule which results in extra capsular spread of tumor. Extracapsular extension suggests upstaging of N category according to TNM classification. Signs of extracapsular extension on imaging are breach of nodal capsule, irregular margins, heterogeneous enhancement, adjacent perinodal inflammatory fat stranding.

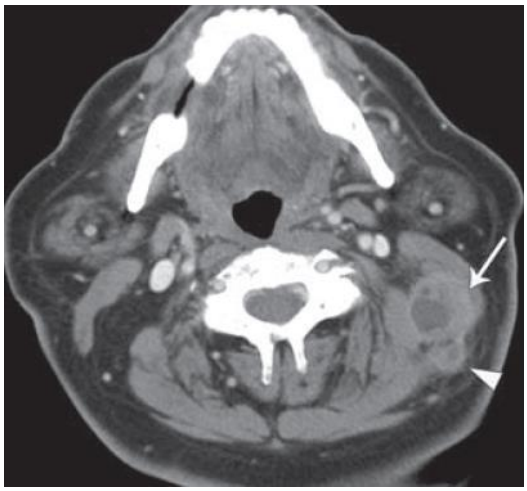


Figure 11: Left level V node with extracapsular extension because of irregular margins, perinodal inflammatory fat stranding.

ULTRASONOGRAM:

Assessment of Cervical nodes:

The following features are assessed while doing ultrasound examination in detection of cervical nodal spread.

- Size criteria which differs for different groups
- Shape of node
- Echogenicity
- Presence of fatty hilum which appears hyperechoic

- Margins – for detecting extranodal extension

Ratio of short axis / long axis diameter of the node is calculated and if it is lesser than or equal to 0.5 it is considered as oval or flat lymph node.(24) Oval lymph nodes are considered benign as they maintain the reniform nature.

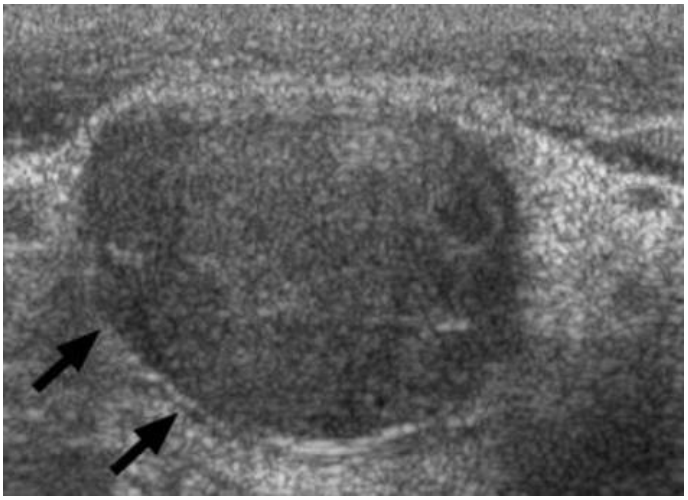


Figure 12: Enlarged cervical node with loss of echogenic fatty hilum

Hypoechoic nature of the lymph node with respect to the adjacent muscle and loss of fatty hilum should arise the suspicion of tumour spread. Calcification is not commonly seen in cervical nodes except in cases of papillary carcinoma arising from thyroid gland.(23)

Although matted nature of cervical lymph nodes with adjacent oedema is a typical feature of granulomatous (tuberculous) aetiology, it can also be seen in metastatic nodes with extra nodal spread as there is

breach in node capsule and there is matted appearance when nodes with extra capsular spread are adjacent to each other.

On Doppler USG, presence of fatty hilum in normal or reactive lymph node will show central vascularity. But when metastasis occurs, the pattern of vascularity turns out to be peripheral or mixed.(25) Hence the presence of peripheral vascularity on colour Doppler ultrasound is considered a significant indicator of nodal involvement.(26)

TAF (Tumour Angiogenic Factor) stimulates angiogenesis and recruits peripheral vessels when nodes are involved by tumour spread.

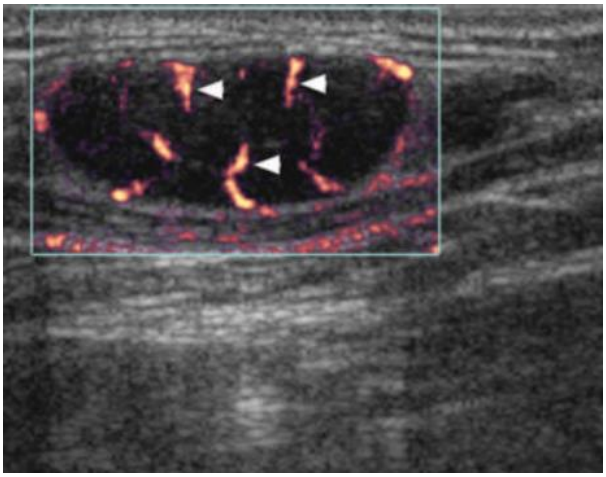


Figure 13: Cervical node with peripheral vascularity in a case of tongue carcinoma with metastasis.

PERINEURAL INVASION

Perineural invasion is one of the most important independent factors affecting the prognosis of oral squamous cell carcinoma.(27) There has been controversy regarding addition of perineural invasion in

TNM staging for many years, but multiple studies have showed significant correlation between presence of perineural invasion and aggressive status of the primary lesion.(28) Perineural invasion is defined as that form of spread of primary tumor by neurotropism, i.e spread along nerves. Histopathologically it is defined as the presence of tumor cells around atleast one third of the nerve circumference

Post operative histopathological examination shows perineural invasion in four forms namely complete encirclement, incomplete crescent like encirclement, sandwiching onion skinning, partial invasion and neural permeation.

Detection of perineural invasion in pre operative imaging is crucial because its presence warrants aggressive treatment in addition with surgery.

Pterygopalatine fossa is considered the crossroads for perineural spread in head and neck malignancies. Presence of normal fat within the pterygopalatine fossa rules out perineural spread in most cases.(29)

From pterygopalatine fossa, the tumor can enter

Infratemporal fossa – Through pterygomaxillary fissure – Most commonly seen in oral cavity squamous cell carcinoma

Middle cranial fossa – Through foramen rotundum and Vidian canal

Orbit – Through inferior orbital fissure

Nasal cavity – Through sphenopalatine foramen

Palate – Through greater and lesser palatine foramen

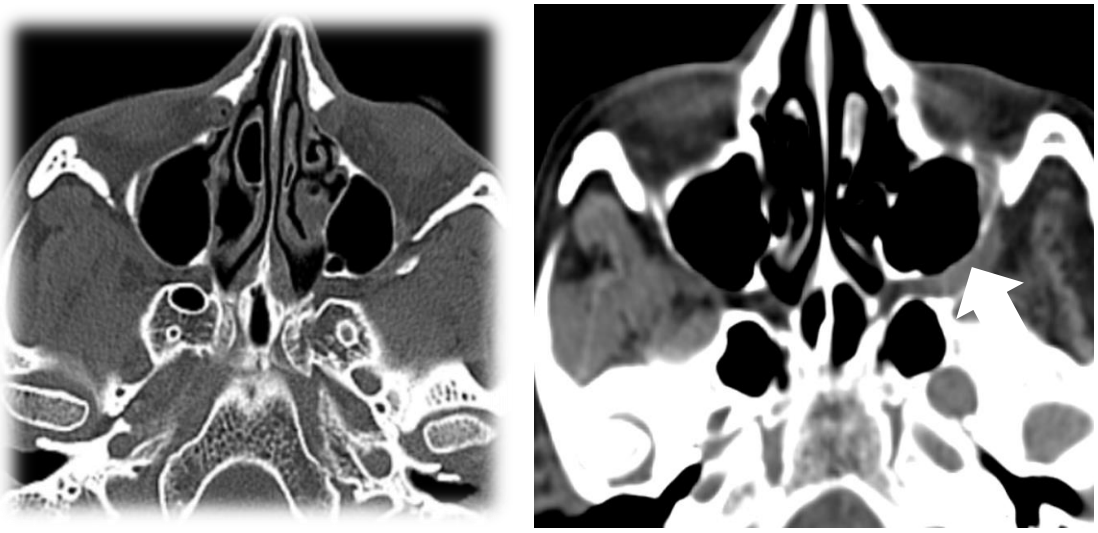


Figure 14: A: Presence of normal fat filled pterygopalatine fossa. B: Left pterygopalatine fossa fat is obliterated by soft tissue because of perineural spread (arrow).

Another important anatomical landmark to look for perineural spread in tongue carcinoma is mandibular foramen. Inferior alveolar nerve which is a branch of third division (mandibular) of trigeminal nerve courses through this foramen to enter the mandible.

In the axial section, it is located at the internal surface of ramus of mandible on either side. Obliteration of mandibular foramen fat is an indirect sign of perineural spread via the inferior alveolar nerve.

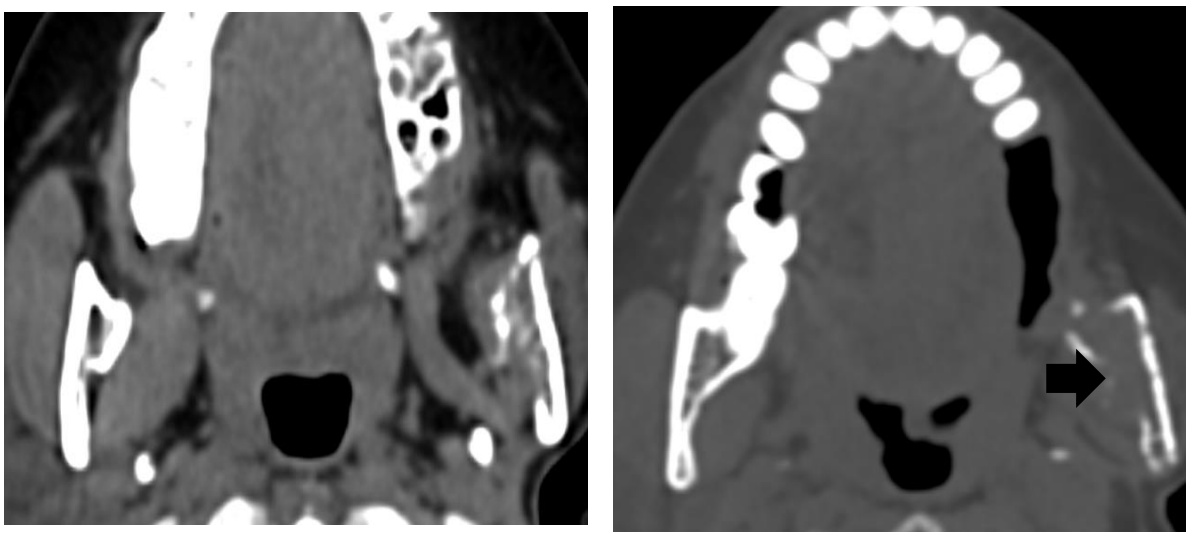


Figure 15: A: Axial CT image showing normal fat filled mandibular foramen on the right. B: Loss of fat and mandibular involvement denoting perineural spread on the left resulting in erosion (black arrow).

Spread of oral tongue carcinoma through the mandibular nerve leads to mandibular invasion resulting in upgrading of tumor status. Thus perineural spread is an independent prognostic factor affecting the survival rate.(30)

Hence perineural spread warrants post surgical adjuvant radiotherapy to prevent recurrence of the disease and to add survival benefit of these patients.

OTHER MODALITIES:

SPECT – SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY

Gamma radiation is used in the mapping the metabolic activity of the malignant lesions in SPECT. Various Isotopes namely 3-D Technetium 99 DPD (dicarboxy propan SPECT) and Technetium 99 MIBI can be utilized as sources of radiation.(31)

Sentinel lymph nodes in oral cancers are detected by using

1. Pre operative lymphoscintigraphy
2. SPECT / CT
3. Injection of the patent blue dye.

Intra operative free hand SPECT is a novel technique for sentinel lymph node biopsy. It is an intra operative technique in which three gamma cameras are used. Above the patient, two cameras are kept and the surgeon uses the 3rd camera and mobilizes it over the patient. This technique can find out the exact site of sentinel node which is draining the tumor and its relationship and boundaries with adjacent to the surrounding normal soft tissue.

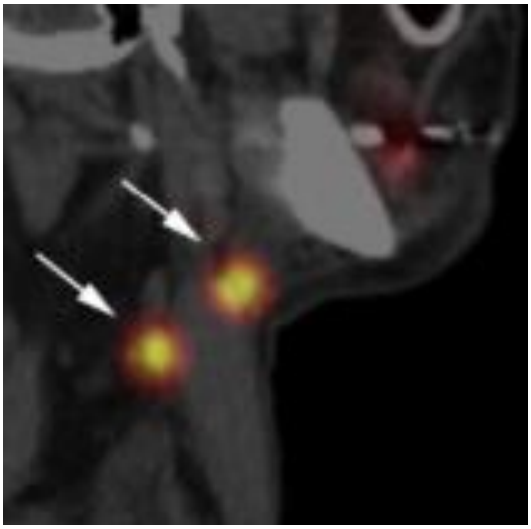


Figure 16: Sagittal SPECT image showing uptake in cervical node.

Thus it helps in delineating the correct extent of lymph node involvement. It is also useful in assessing the lymph flow into the above mentioned sentinel node thus giving the operating surgeon a cushion of changing the scope of resection with the selective removal of cervical nodes which are metastatic.

There is also a reported sensitivity close to 100 % in detecting mandible involvement with the help of SPECT.(32)

POSITRON EMISSION TOMOGRAPHY (PET):

18 FDG (fluorodeoxyglucose) is the agent of choice in Positron Emission Tomography. The metabolic activity in tumors is detected with the help of FDG PET. It can be employed before planning adjuvant modalities and to predict the patient survival devoid of recurrence.(33)

Most common utility of PET is the detection of lymph nodes and distant metastasis. Reported sensitivity and specificity is close to 90 percent.(34)

Apart from 18 FDG PET, 18F-FAMT (fluoroalfa-methylothyrosine) can also be used. FAMT is primarily used to assess the initial proliferative capability of the tumor cells. Hence FAMT is not useful to evaluate the bone involvement and to define the tumor boundary.

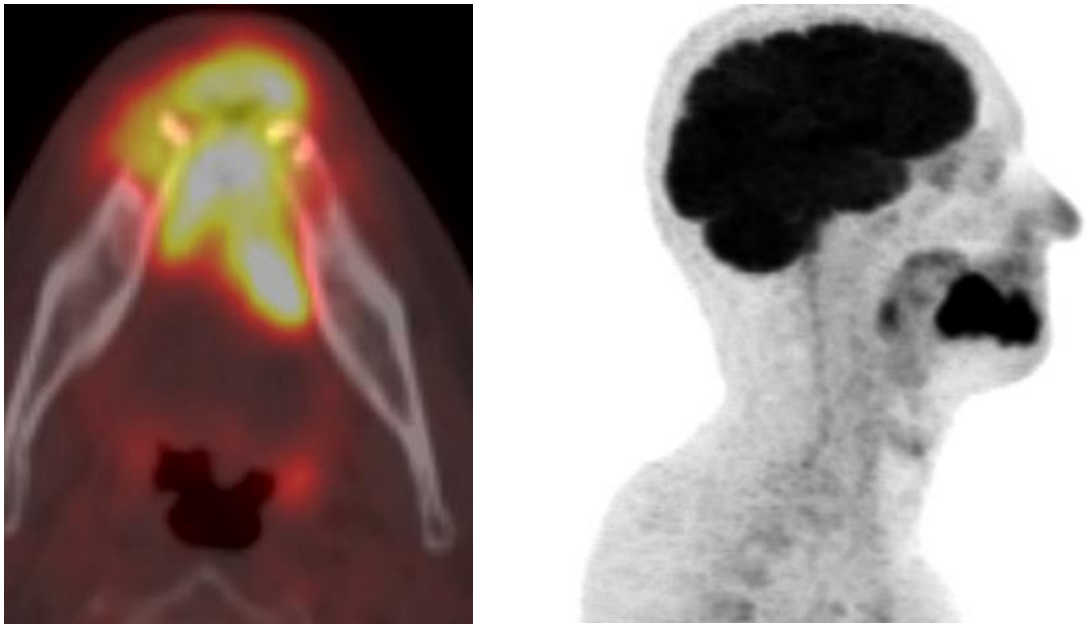


Figure17: PET uptake in tongue lesion and mandible

An efficient tool in detection of recurrent disease and distant metastasis is FDG PET/CT. It is also sensitive in detecting out the tumor recurrence from surgical scar / fibrosis when compared to MRI.(34)

Hence PET is recommended for stage IV oral cavity cancers and not useful when the patient presents in an early stage.

TREATMENT PROTOCOL

Treatment protocol for tongue malignancies vary from centre to centre and it depends primarily on the T status and N status of the patient. Patients with positive distant metastases (N1) invariably are put under palliative therapy.

Single modality treatment (either radiotherapy or surgery) is preferred for T1 and T2 stage tumors. Wide local excision and hemiglossectomy are done depending on the extent of the tumor. Along with the excision of primary tumor, supra-omohyoid neck dissection (SOHND) is done in all cases for nodal clearance to look for pathological presence of tumor in cervical nodes.

In SOHND, the nodal stations removed are level Ia, bilateral level Ib, II and III. In extended supra omohyoid neck dissection (ESOHND), along with SOHND, level IV nodes are also removed.

From the pathological evaluation, they are given T staging based on size, presence or absence of extra nodal extension.

In case of pathologically proven lymph nodal metastasis prior to surgery, comprehensive modified radical neck dissection is done for nodal clearance. MRND is in turn divided into three types based on the anatomical structure preserved viz. internal jugular vein / spinal accessory nerve / sternocleidomastoid.

Hence, the protocol followed in our centre is to do wide local excision / hemiglossectomy combined with modified radical neck dissection (for all node positive tumors prior to surgery). Resection of floor of mouth muscles is based on the presence or invasion of mylohyoid, hyoglossus, geniohyoid in preoperative MRI.

The presence of muscular invasion carries a high risk of orocutaenous fistula and should be treated promptly. The presence of perineural invasion in itself implies the involvement of inferior alveolar nerve along with invasion of mandible. Hence hemimandibulectomy is done invariably in all perineural invasion positive cases irrespective of nodal status as it carries high risk of recurrence and poor survival rates.

PROGNOSIS OF ORAL CAVITY TUMORS

Survival, epidemiology and end results programme (SEER) database tracks the follow up and prognosis of patients who are diagnosed as cases of oral cavity cancer for 5 subsequent years and lists the expected 5 year survival rate. The database is maintained by the National Cancer Institute (NCI).(35)

The following are the expected 5 year survival rate of oral cavity cancers with respect to their localized, regional or distant spread at the time of diagnosis.

Lip:(35)

SEER STAGE	**5 YEAR SURVIVAL RATE (expressed in percentage)**
Local	94
Regional	66
Distant	32
Combined	92

TONGUE: (35)

SEER STAGE	**5 YEAR SURVIVAL RATE (expressed in percentage)**
Local	82
Regional	68
Distant	40
Combined	67

FLOOR OF MOUTH:(35)

SEER STAGE	**5 YEAR SURVIVAL RATE (expressed in percentage)**
Local	76
Regional	38
Distant	20
Combined	51

OROPHARYNX:(35)

SEER STAGE	**5 YEAR SURVIVAL RATE (expressed in percentage)**
Local	62
Regional	57
Distant	29
Combined	49

AIMS AND OBJECTIVES

AIM:

To compare the diagnostic accuracy of magnetic resonance imaging and intra oral ultrasound in detecting the depth of invasion in tongue carcinoma patients and correlating it with histopathological examination as gold standard.

OBJECTIVES:

- To radiologically assess the pre operative depth of invasion of carcinoma tongue.
- To evaluate the imaging features of tongue carcinoma using intra oral ultrasound and MRI.
- To assess the nodal status with preoperative imaging based on established sonographic features of malignancy.

MATERIALS AND METHODS

STUDY METHODOLOGY:

STUDY DESIGN:

Comparative cross sectional study

STUDY PERIOD:

From December 2020– November 2021, for a period of 12 months

STUDY POPULATION:

Patients of both sexes attending the outpatient department and those admitted in the wards in Government Royapettah Hospital affiliated to Government Kilpauk Medical College and Hospital, Chennai.

INCLUSION CRITERIA:

- Patients with tongue carcinoma irrespective of nodal status.
- Patients having lesion in anterior two third of tongue.

EXCLUSION CRITERIA:

- Posterior one third of tongue involvement
- Patients with ankyloglossia
- Patients with recurrent / residual lesions
- Patients with trismus
- Patients who underwent chemo/radiotherapy

- Cases who are non compliant for MRI (claustrophobia, patients with metallic implants such as cochlear implants, pacemakers, defibrillators or with metallic catheters)
- Distant metastases
- Those not willing to participate in the study

DATA COLLECTION:

Data collection was performed in the included study group using a standard questionnaire/ proforma that includes the basic patient details such as name, age, sex, address, education status, occupation, dietary habits and history of smoking/ alcohol, duration of the illness and history of previous chemoradiation.

General examination and local examination of the patient was done and recorded in the proforma.

METHODOLOGY

The study was started after obtaining institutional ethical committee clearance. All the included cases were subjected to imaging after obtaining written consent.

After the initial history taking and clinical examination including local examination, the patients were subjected to Intra oral Ultrasound examination and Magnetic resonance imaging using dedicated neck coil.

MRI was done using Siemens Magnetom Avanto 1.5 Tesla Machine. The radiofrequency coil used was phased array coil.

Imaging protocol used for the study was as follows:

- T1 W axial and coronal planes with neck coil
- T2 W sequence in axial, sagittal and coronal plane
- STIR sequence in axial and coronal planes
- Diffusion weighted imaging in axial plane
- A cotton ball is stuck into each ear of patients to decrease the influence of noise
- Image acquisition is completed within 20mins

Parameters set for **T1** were:

TR (repetition time): 400 – 620 ms

TE (echo time): 10 – 30 ms

Flip angle: 90 degrees

Parameters set for **T2** were:

TR: 2000 – 4000 ms

TE: 80 – 120 ms

Flip angle: 90 degrees

Slice thickness: less than 3 mm

Interval gap: 0.5

FOV: 320 x 320 mm

Matrix: 256 x 192

Patients are well explained about the procedure and are advised to leave metallic pins, jewellery, hearing aids and other metallic objects outside the MRI gantry.

The patients are then positioned in the MRI machine in supine position and the MRI in taken with the neck coil.

Figure 18:1.5T Siemens Magnetom Avanto MRI Machine

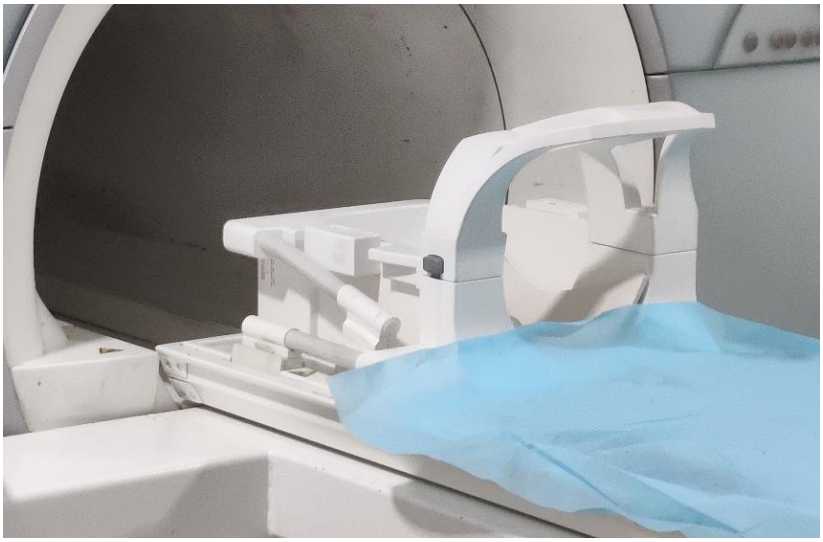


Figure 19:Neck coil used for MRI examination

INTRA ORAL USG EXAMINATION:

Intra oral Ultrasound was done in Samsung HS 40 machine with a broad bandwidth linear array high frequency transducer (LA 3-16A).

The transducer was wrapped up with a probe cover and coupling gel was applied within and external to it. After getting informed consent from the patient, the probe was placed gently over the lesion in anterior two third of tongue for assessing the depth of invasion.

Figure 20: Intra oral USG with linear high frequency transducer

Simultaneously the presence of internal vascularity, presence or absence of cervical lymph nodes pattern of invasion (tentacular vs pushing borders), and their morphological features were documented.

Among the cases, those with ankyloglossia were eliminated from the study as they could not be subjected to Intra oral Ultrasound examination.

The lesions were classified into anterior two third of tongue and posterior one third based on their relationship with circumvallate papilla.

Only those patients with anterior two third tongue involvement were included in our study and those with previous history of treatment of

tongue carcinoma like radiotherapy were eliminated. The sample size of the study is 76.

MRI and intra oral ultrasound were done on the same day and depth of invasion, tumor thickness, maximum size of tumor, presence or absence of cervical nodal metastases were documented.

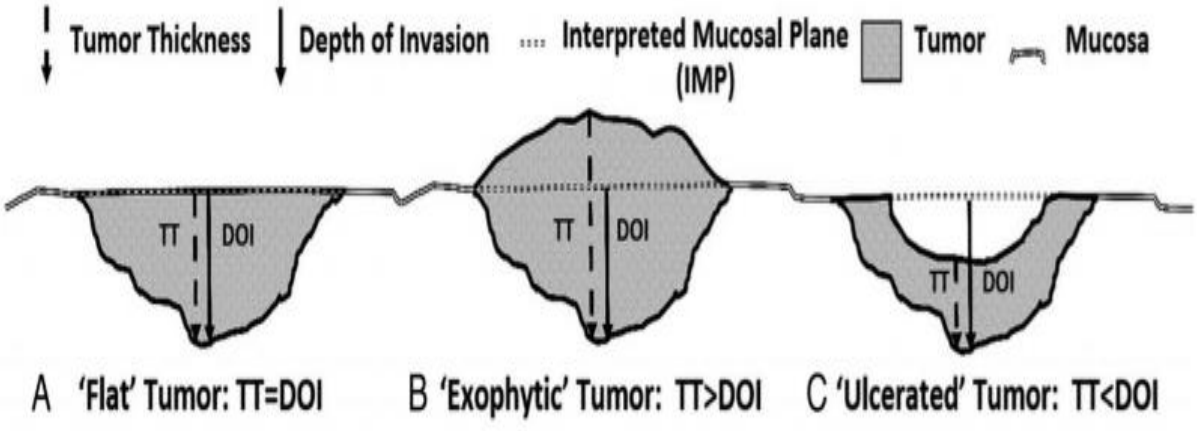
Node with extracapsular extension, perineural spread were assessed on MR imaging. Pattern of invasion was documented and categorized as tentacular or pushing margins depending on the deeper margin.

The cases are followed up after surgery and the histopathological depth of invasion was compared with the USG and MRI depth of invasion values.

HISTOPATHOLOGICAL EXAMINATION:

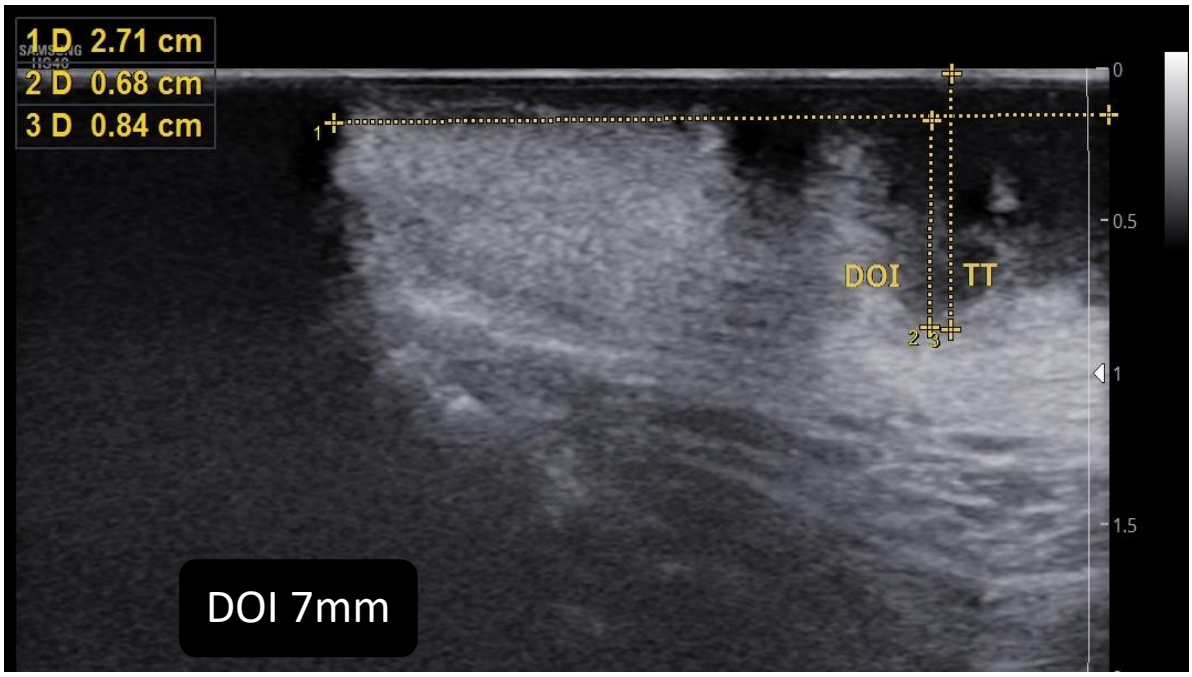
The resected surgical specimen should be kept in formalin solution of overnight fixation. Thin slices measuring approximately 2-3 mm were cut along the long axis of the tumor. In the histopathological examination, the depth of invasion was calculated by measuring the distance from the tumor – mucosa interface to the deepest point of invasion as given in the image below. For ulcerative lesions, it was calculated from the ulcer base till the maximum point of invasion.

For patients who underwent nodal dissection, the presence of tumor involvement was assessed with microscopic examination.

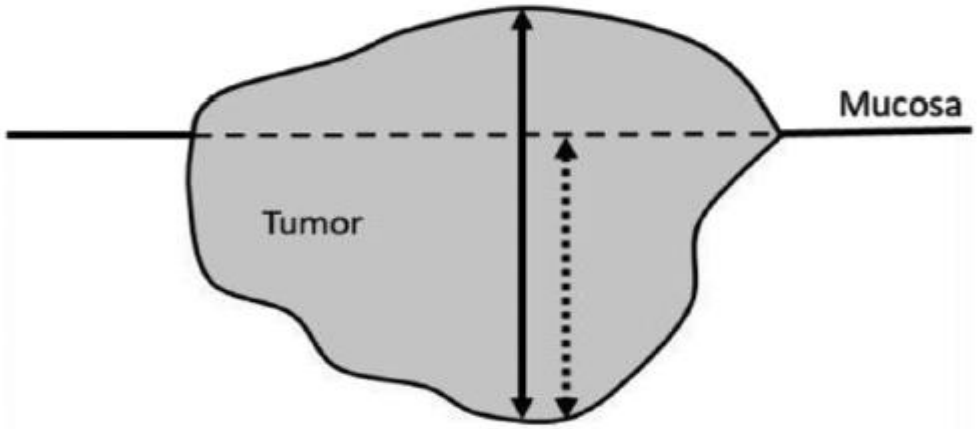


CASE 1

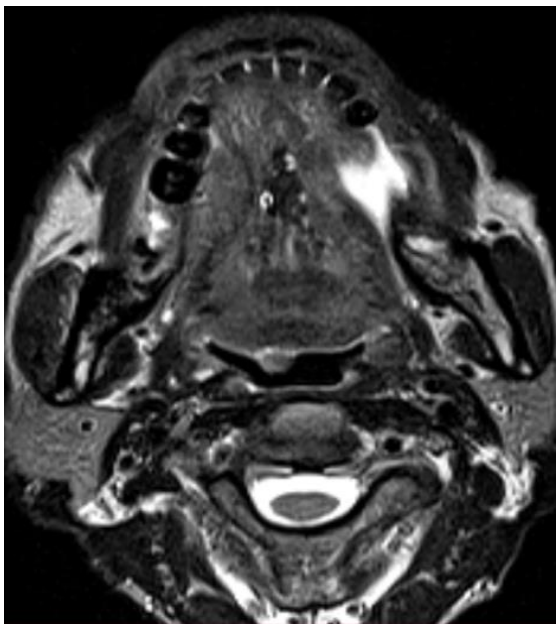
A 42 year old female patient came with complaints of ulceroproliferative lesion in right lateral border of tongue involving its anterior two third.

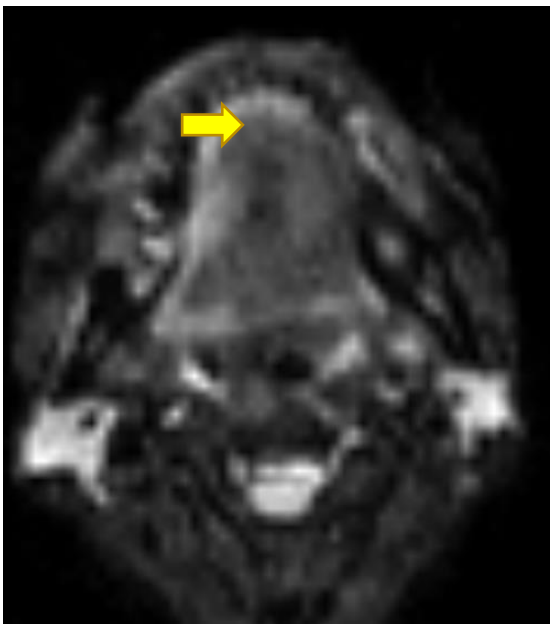


Intra oral ultrasound shows ulceroproliferative growth in the right lateral border with depth of invasion of 7 mm. Tumor thickness of 8.4 mm.



A line connecting the tumor – normal mucosa interface on both sides was constructed for assessing the depth of invasion.

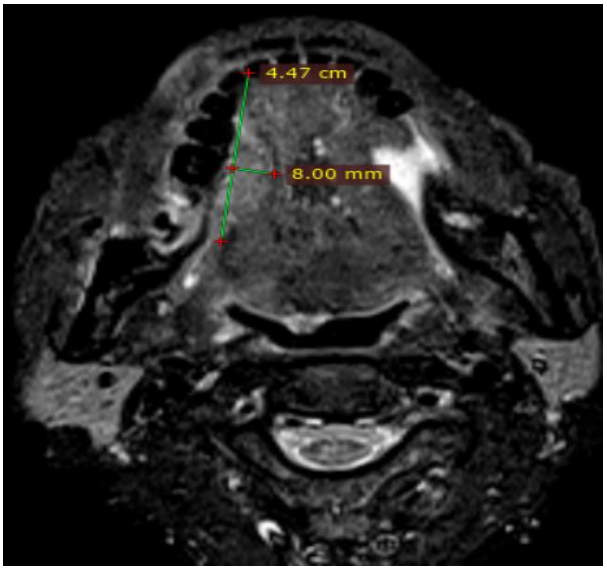




.

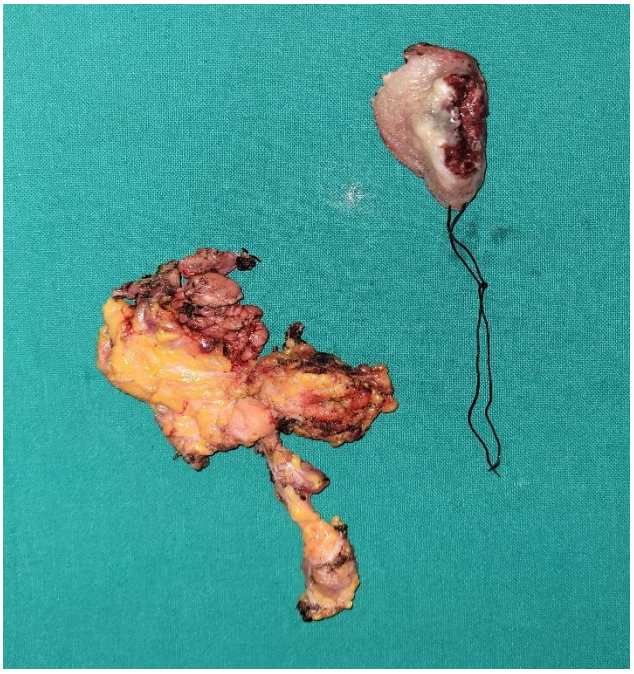
MRI with neck coil shows an ulceroproliferative diffusion restricting T2 hyperintense lesion in the anterior two third of right lateral border of tongue without crossing midline / involvement of tip.

Depth of invasion was calculated on T2 weighted axial image by constructing an imaginary line between the tumor – normal tongue mucosa interface on both sides (anterior and posterior). From this imaginary line, a perpendicular line is drawn medially into the deepest point of invasion.

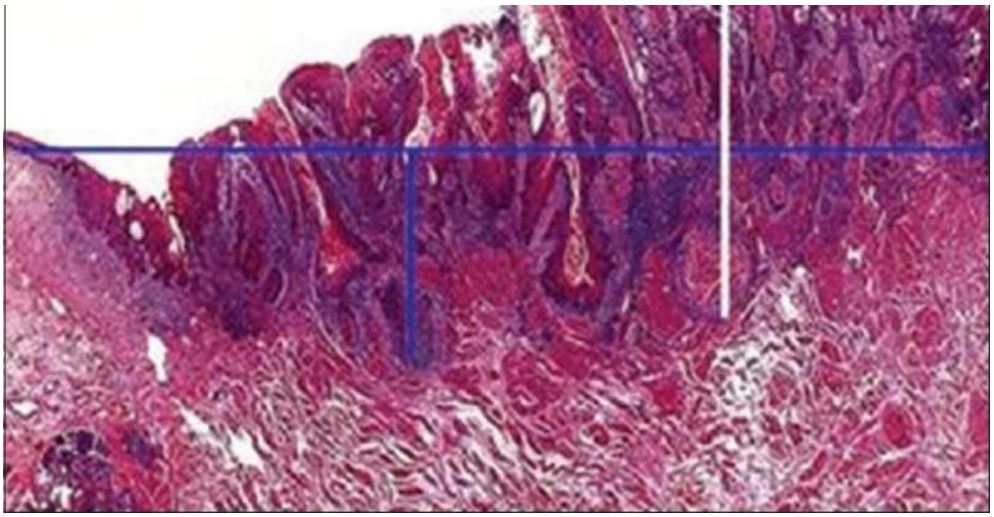


DOI calculated from MRI is 8 mm which is 1 mm higher than the value derived by intra oral USG.

Patient underwent wide local excision and extended supra omohyoid neck dissection and the specimen was subjected to histopathological analysis.



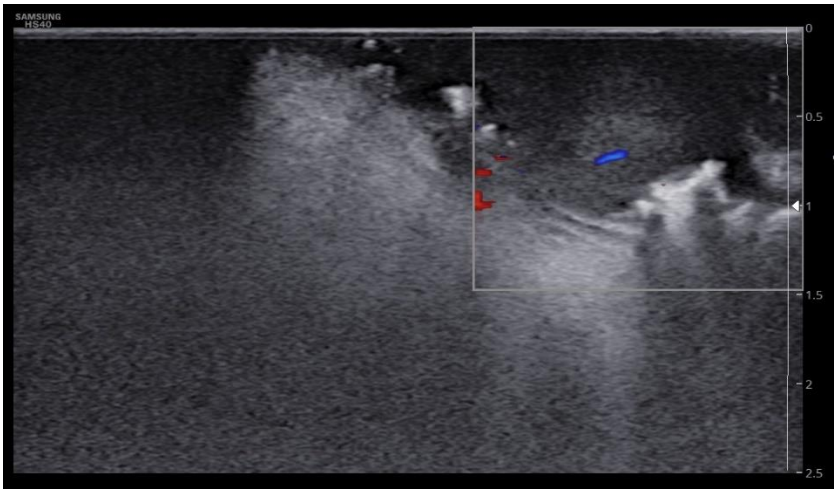
DOI calculated from HPE is taken as the gold standard. It showed a value of 7 mm. Depth of invasion was calculated in histology as the distance from the point of breach of normal basement membrane till the deepest point of invasion.



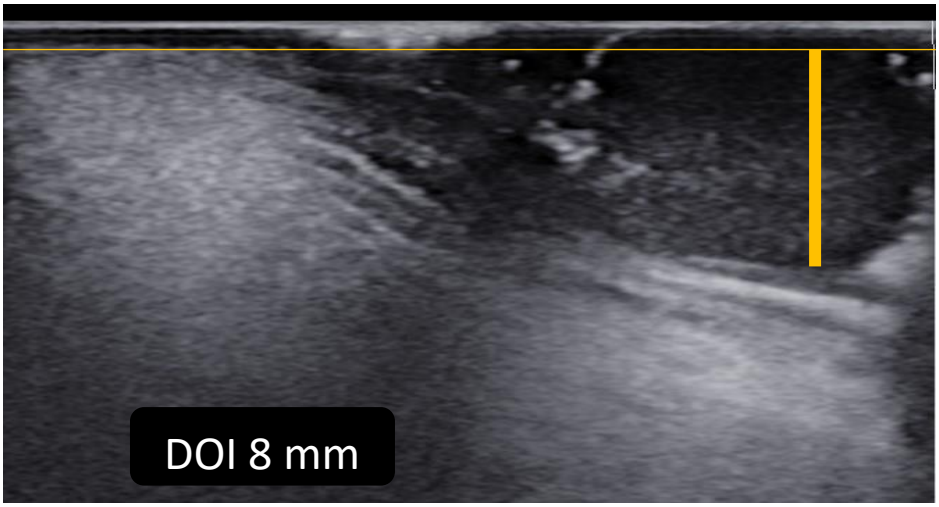
CASE 2

50 year old male, chronic tobacco chewer came with complaints of ulceroproliferative growth over the right lateral border of tongue, biopsy was done prior to imaging which revealed to be moderately differentiated squamous cell carcinoma. Pre operative imaging was done to assess the depth of invasion.

Intra oral ultrasound was done which showed ulceroproliferative lesion with internal vascularity.

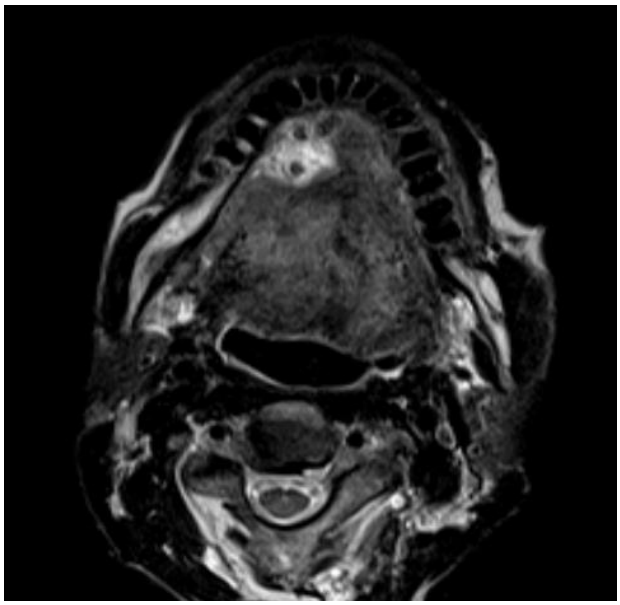


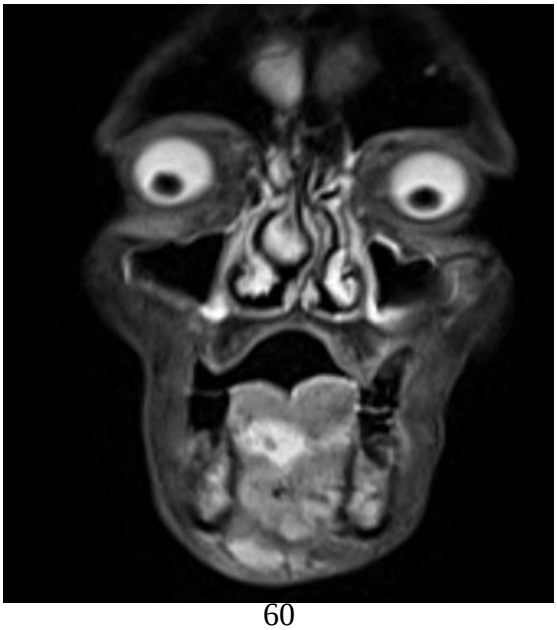
Depth of invasion was assessed by using the same method and the value was 8 mm by USG.

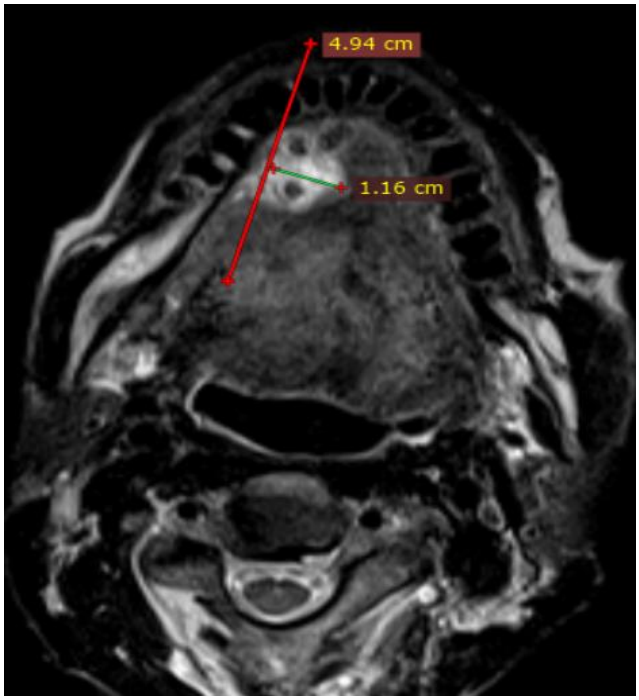


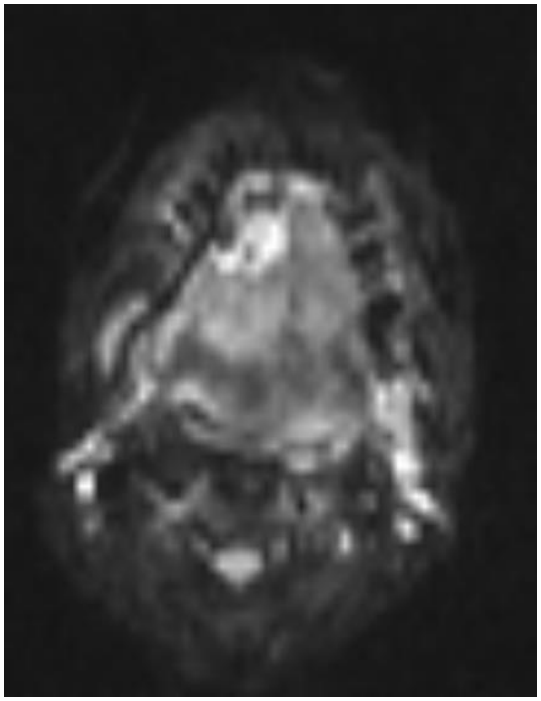
MRI revealed diffusion restricting T2 heterointense lesion with intra lesional hypointense foci and surrounding edema (likely caused by biopsy prior to MRI).

DOI was measured by using the same method since it was also an ulceroproliferative lesion.



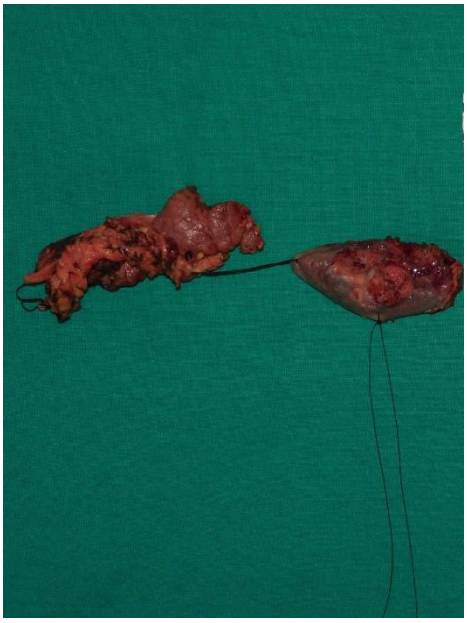






DOI in MRI was found to be 11.6 mm which is 3.6 mm higher than the one evaluated by USG. DOI on post operative histopathological specimen was found to be 9 mm.

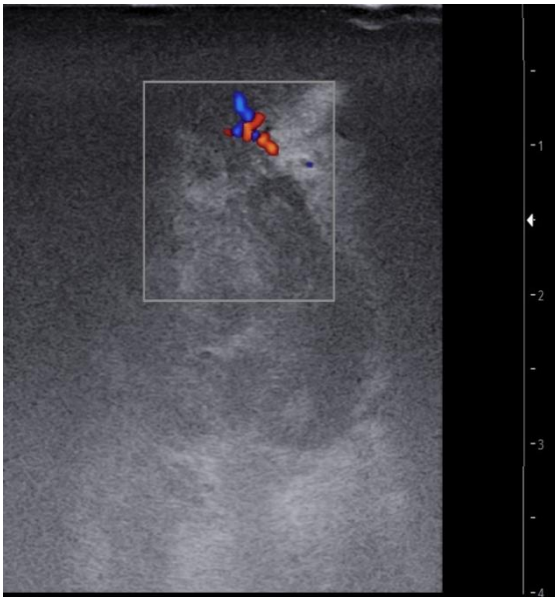
Hemiglossectomy with extended supra-omohyoid neck dissection (ESOHND) was done for this patient.

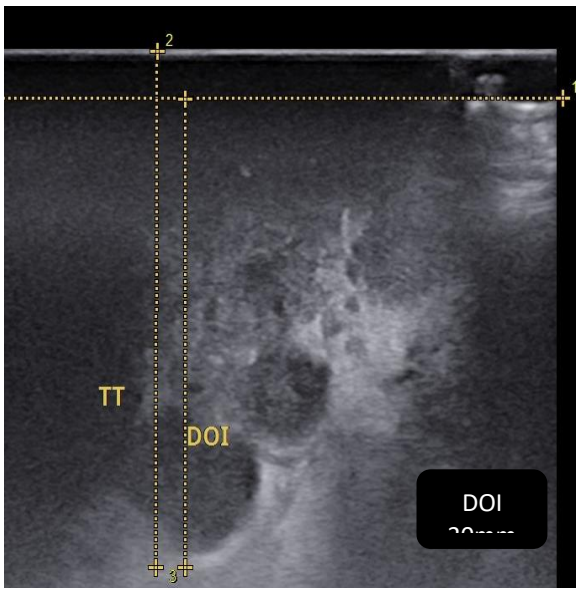


CASE 3

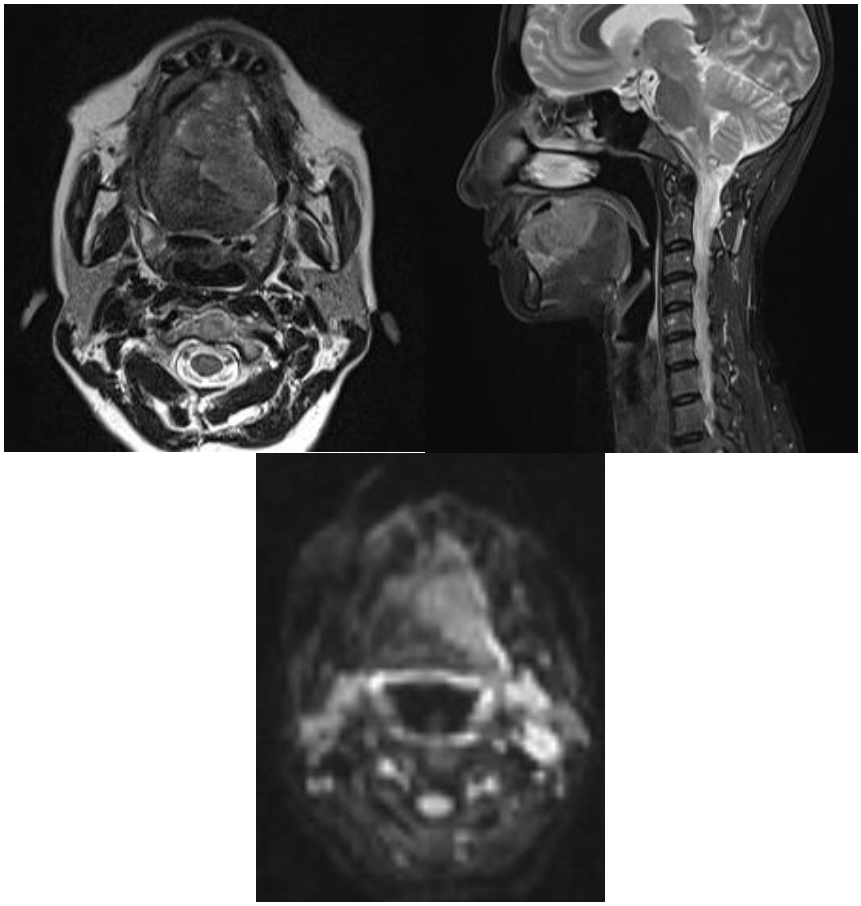
A 46 year old male, chronic smoker, tobacco chewer came with complaints of large ulceroproliferative lesion on the left lateral border of tongue.

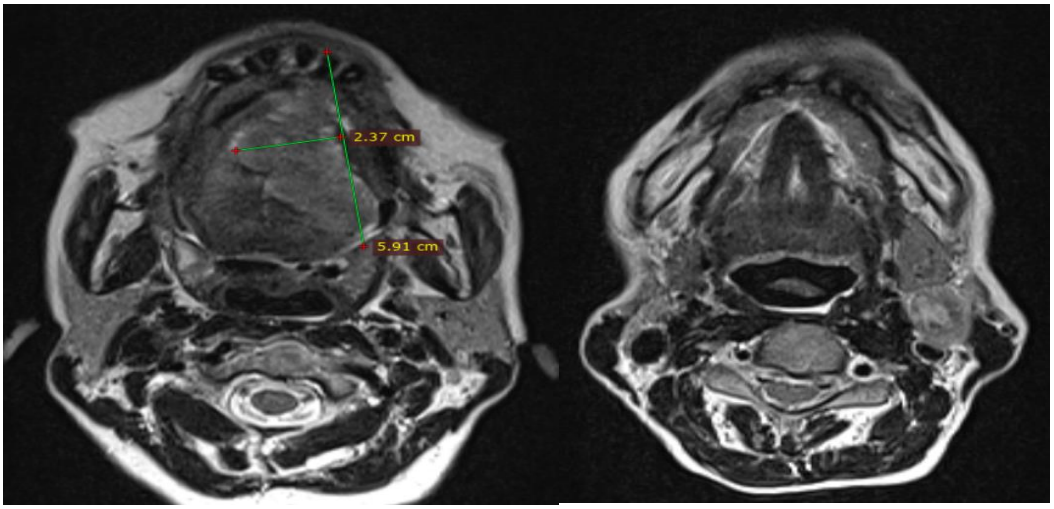
Intra oral USG was done which showed an irregular lesion with intralesional vascularity and irregular lobulated margins. Tumor thickness was measured from the external surface of tumor till deepest point.





The patient subsequently underwent MRI which showed an irregular ulceroproliferative lesion crossing the midline arising from the left lateral border.





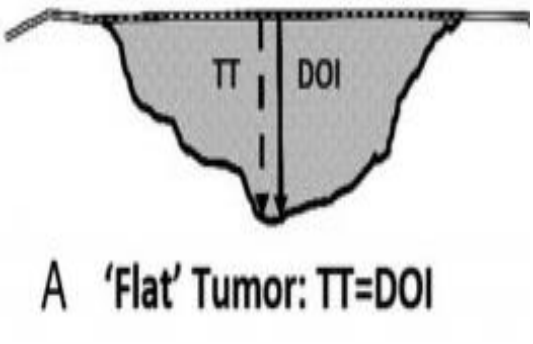
Diffusion restricting T2 hyperintense lesion arising from left lateral border crossing midline with involvement of tip was found. DOI from MRI was 23.7 mm. Left upper deep cervical node with perinodal inflammation and possibility of extracapsular extension (ENE+) was raised.

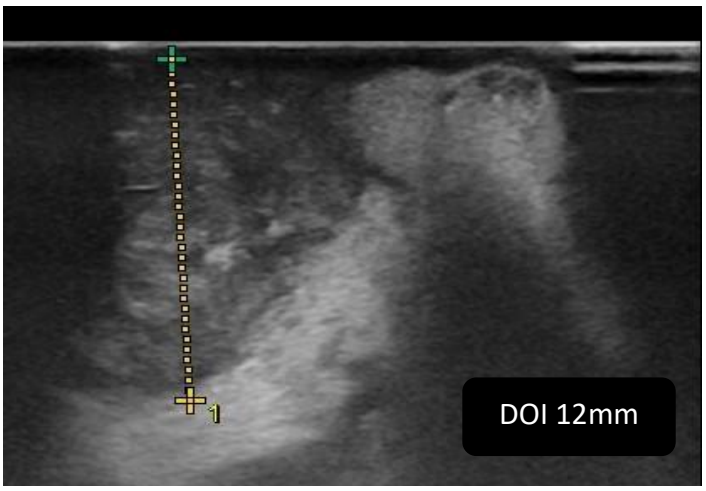
Glossectomy specimen showed depth of invasion of 20 mm.

CASE 4

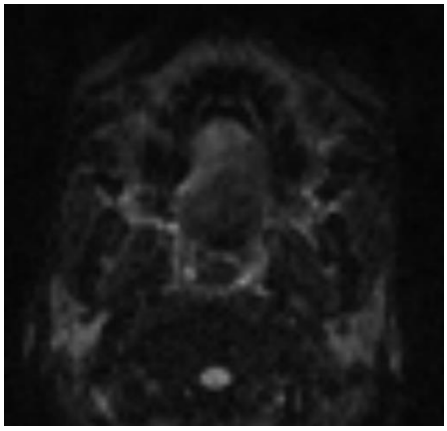
A 49 year old female with history of tobacco chewing came with ulcerative lesion in right lateral border of tongue with prior biopsy with HPE of squamous cell carcinoma.

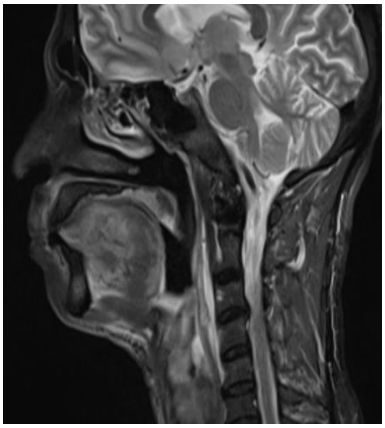
Since it is was a flat type of ulcerative lesion, depth of invasion and tumor thickness were same. Intra oral USG was done which showed heteroechoic lesion with depth of invasion/tumor thickness of 12 mm.

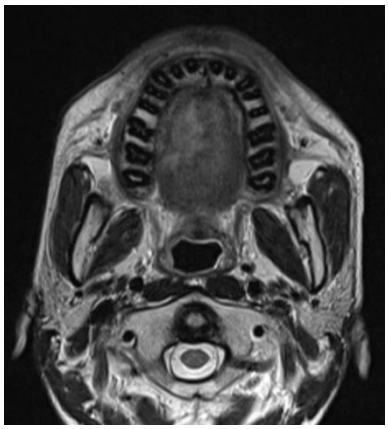




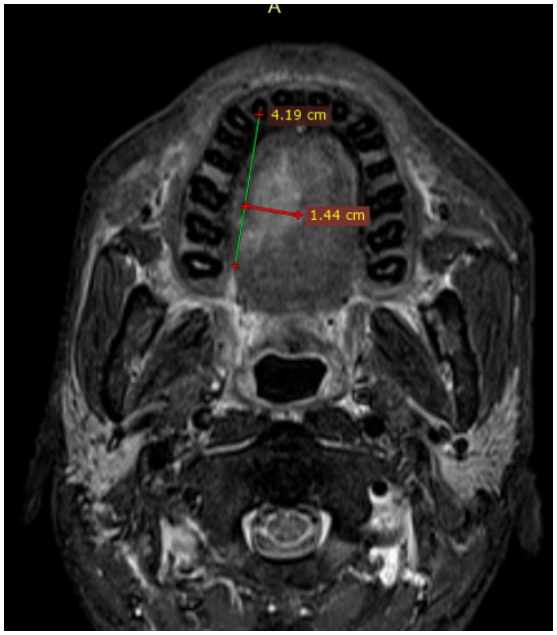
Subsequently MRI was done, which showed diffusion restricting T2 hyperintense lesion arising from right lateral border.



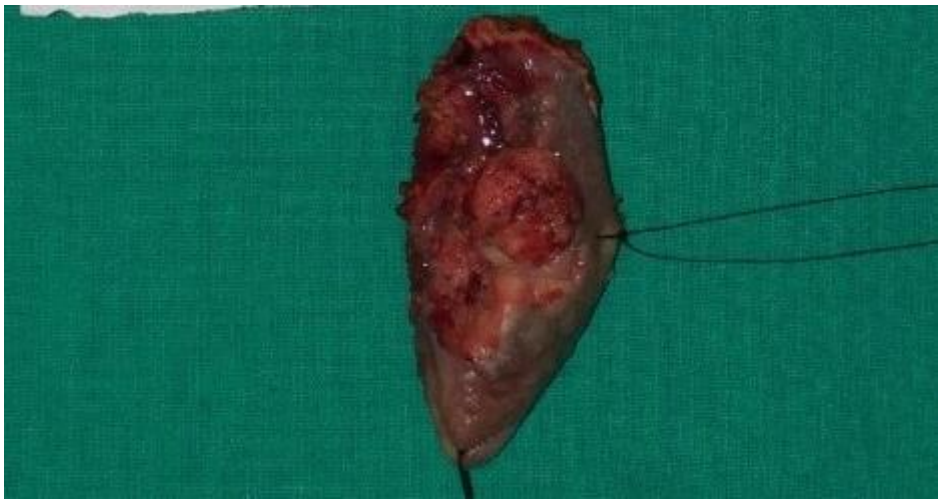




Depth of invasion was measured and found to be 14.5 mm on the T2 W axial image by constructing the mucosa – tumor interface line.



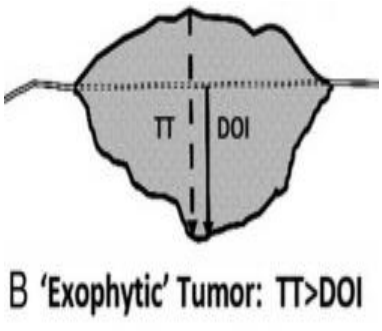
Since there was no involvement of contralateral side, the patient underwent right hemiglossectomy with margin clearance and post operative DOI was found to be 12.5 mm.

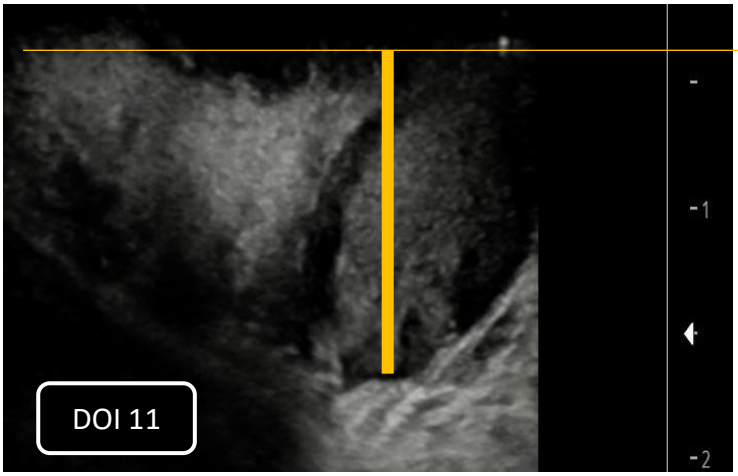


CASE 5

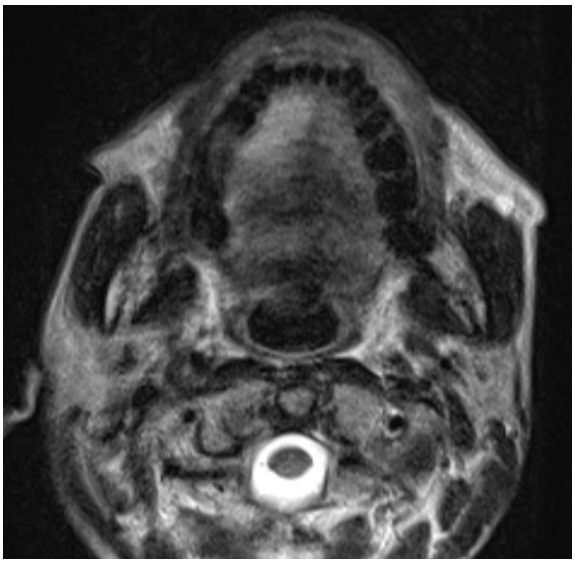
A 34 year old smoker with chronic history of tobacco chewing came with an ulceroproliferative lesion in the right lateral border of tongue with biopsy proven malignancy.

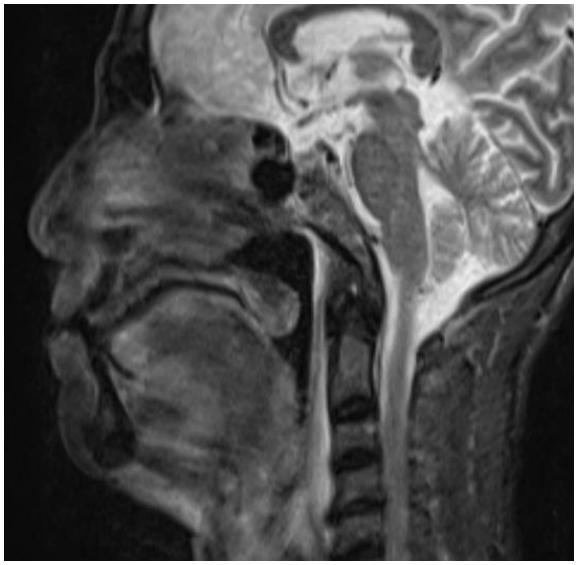
Intra oral USG was done to evaluate the DOI which was found to be 11mm.

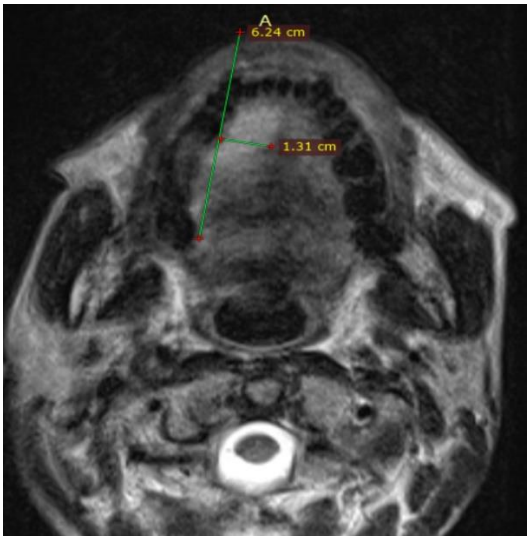


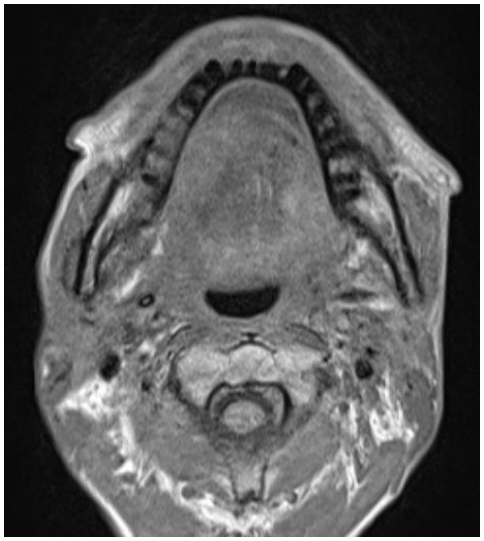


MRI revealed diffusion restricting T2 hyperintense lesion arising from right lateral border involving the tip, extending medially just upto the midline.









Depth of invasion measured on the axial T2w image was found to be 13.1mm.

Patient subsequently underwent right hemiglossectomy and the postoperative HPE showed the depth of invasion to be 10 mm.

STATISTICAL ANALYSIS

The Data was entered in a excel worksheet and double checked. IBM SPSS version 22 software is used for statistical analysis.

A total of 76 patients were examined for whom the radiological results including the depth of invasion (DOI), tumor thickness (TT) measured on both MRI and USG were entered on the master-chart.

Clinical data like tobacco history, history of biopsy prior to imaging, the nature of lesion viz. ulceroproliferative vs ulcerative, involvement of tongue tip, involvement of contralateral side, the presence

of nodal spread, with or without extra nodal extension (ENE+/-), the presence of perineural spread were documented. The pattern of invasion (tentacular/ pushing) was also documented.

Statistical analysis was primarily made for detecting the correlation coefficient between USG, MRI & post surgical histopathological examination. Agreement between the two imaging measurements was evaluated using Bland Altman plots. Subgroup analysis was also done to demystify the various confounders causing the difference in depth of invasion in pre and post operative examination.

The association between the pre operative depth of invasion and the presence of cervical lymph node metastasis was found by using the ROC – receiver operating characteristic curve and area under the curve. The cut off value was found to be 4mm.

92 patients were examined clinically and out of them, 14 patients did not undergo surgery. Since they were subjected to pre operative radiotherapy for downstaging of tumor, they were not included in the study.

Two patients were excluded from the study as the lesion was present in ventral surface of the tongue and it was very small and could not be assessed with intra oral USG.

The sample population is 76 and all of them underwent surgery. Pre operative MRI and intra oral USG was done for all 76 of them and post operative histopathological depth of invasion was documented.

No patient from our study group had evidence of distant metastases at the time of examination.

CHARACTERISTICS OF STUDY POPULATION

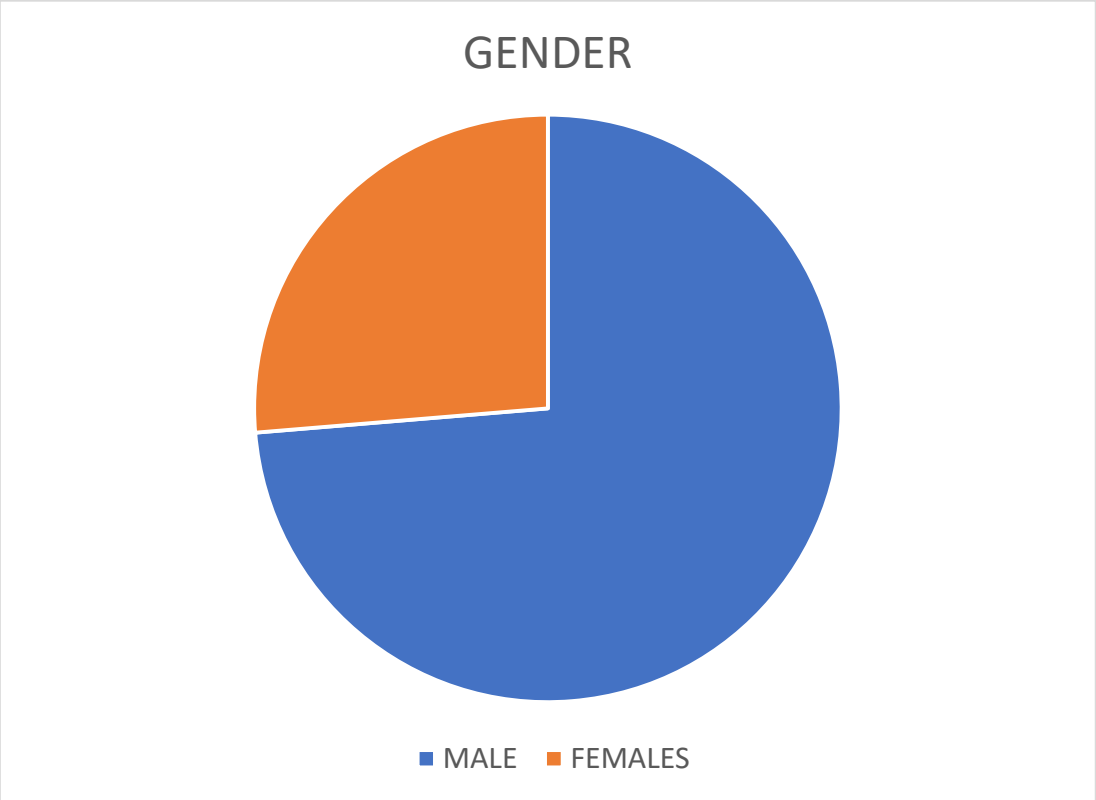
Table 1:

Characteristics	N= 76		Std. Deviation	P value
Gender	Male	56		0.001
	Female	20		
Age	Mean	49.59	9.408	0.001
	Median	49.50		
	Std. Error of Mean	1.079		
Biopsy prior to imaging	Yes	41	0.495	0.001
	No	35		
Staging of the tumor	1	16	0.691	**0.05**
	2	40		
	3	20		
Morphology of lesion	Ulcero-proliferative	43	0.499	**0.001**
	Ulcerative	33		

GENDER:

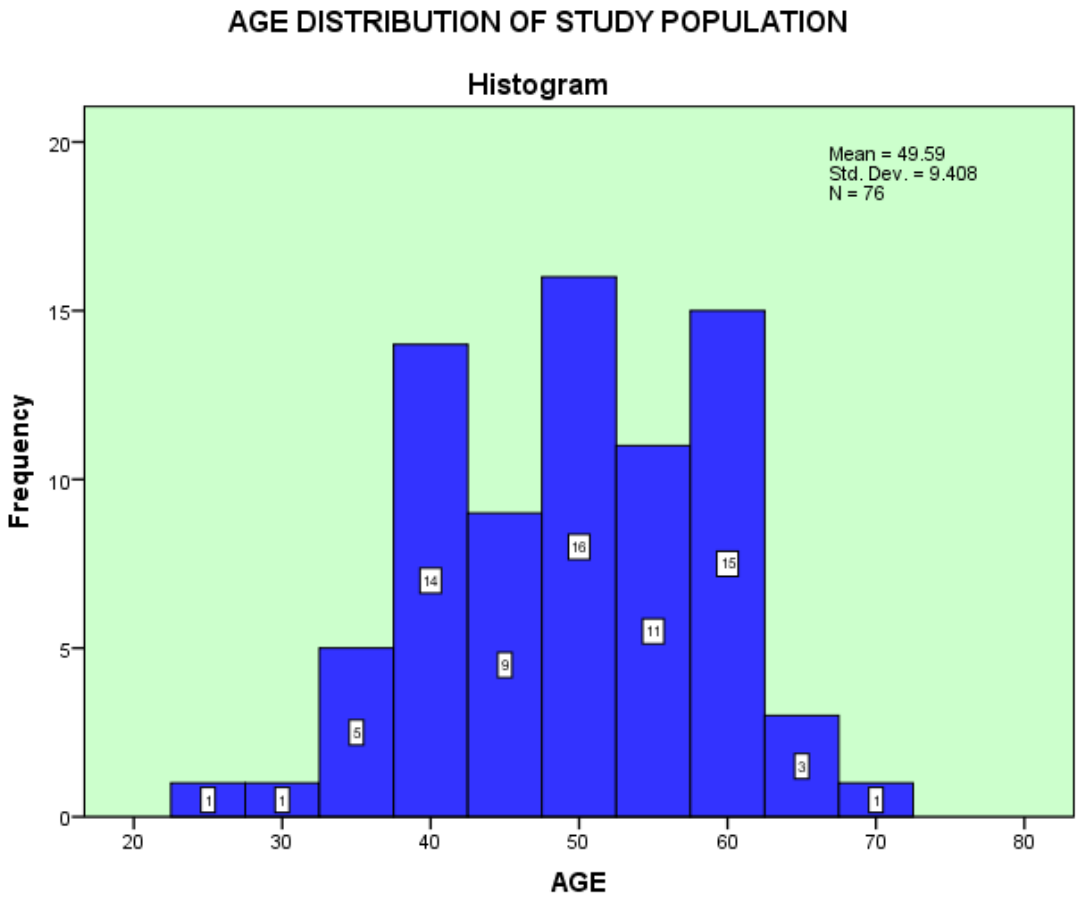
Table 2 :

Gender	Frequency	Percent	Valid percent
FEMALE	20	26.3	26.3
MALE	56	73.7	73.7
Total	76	100.0	100.0



Out of the 76 patients, 56 were males, 20 were females

AGE DISTRIBUTION:



The mean age group of the population is 49.59 with standard deviation of 9.408.

Table 3:

n	Valid	76
	Missing	0
Mean		49.59
Std. Error of Mean		1.079

Median		49.50
Mode		38[a]
Std. Deviation		9.408
Variance		88.511
Range		45
Percentiles	25	41.25
	50	49.50
	75	57.75

MORPHOLOGY OF LESION:

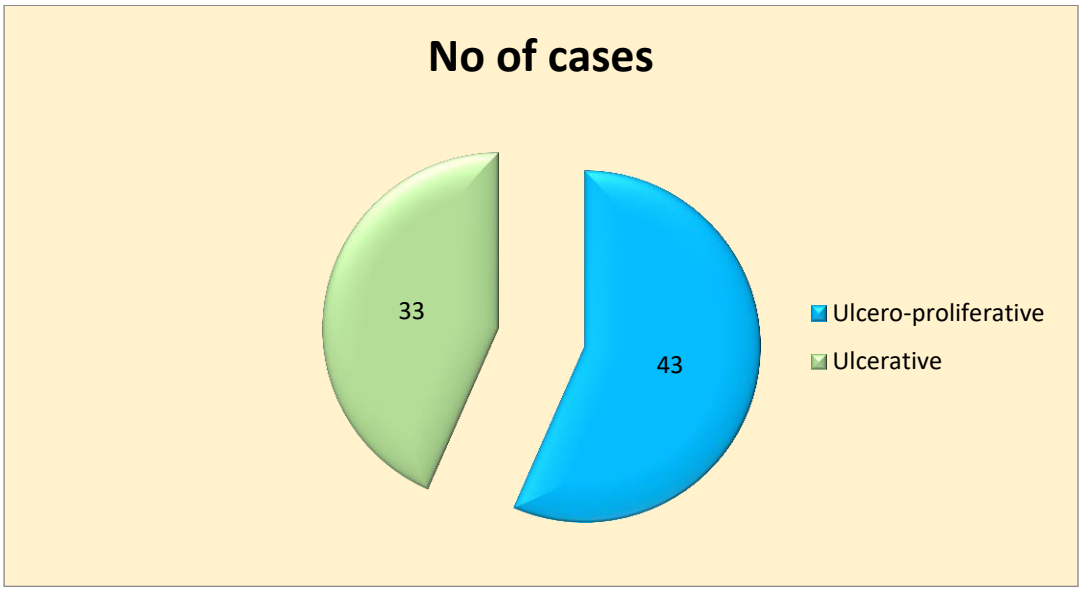


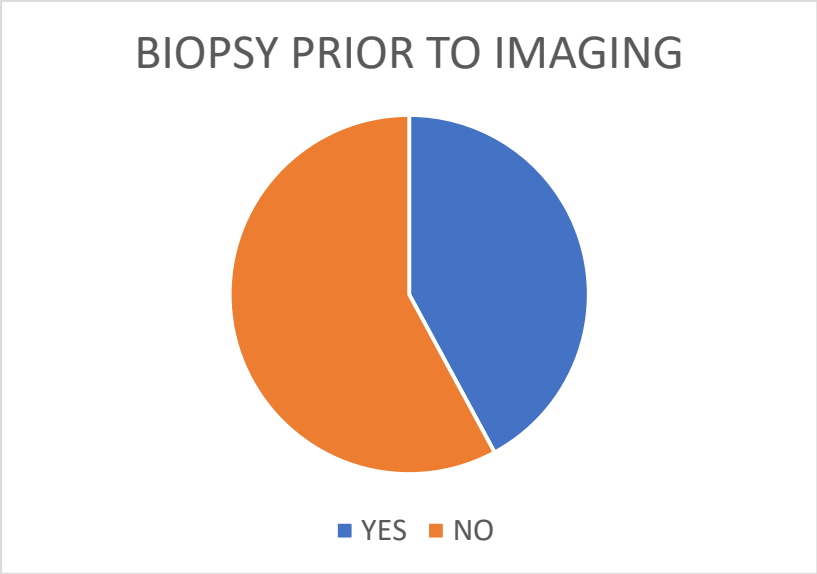
Table 4: ULCEROPROLIFERATIVE -0 / ULCERATIVE -1

N Valid	**76**
Mean	**0.43**
Standard Deviation	**0.499**

		Frequency	Percent	Valid Percent
Valid	0	43	56.6	56.6
	1	33	43.4	43.4
	Total	76	100.0	100.0

BIOPSY PRIOR TO IMAGING:

One of the most significant confounding factor analysed was whether the history of biopsy prior to imaging had any impact in the depth of invasion as edema and haemorrhage are prone to occur within the tumor after biopsy.



Among the 76 patients, 32 had already underwent biopsy prior to imaging and revealed to be squamous cell carcinoma.

Table 5:

BIOPSY PRIOR TO IMAGING YES -1 NO- 0

N	**Valid**	76
	Missing	0
Mean		0.41
Standard Deviation		0.495

Table 6:

Correlations

		BIOPSY PRIOR TO IMAGING YES -1 NO- 0	HISTOLOGICAL DOI (mm)
BIOPSY PRIOR TO IMAGING YES -1 NO- 0	Pearson Correlation	1	.523**
	Sig. (2-tailed)		.000
	N	76	76
HISTOLOGICAL DOI (mm)	Pearson Correlation	.523**	1
	Sig. (2-tailed)	.000	
	N	76	76

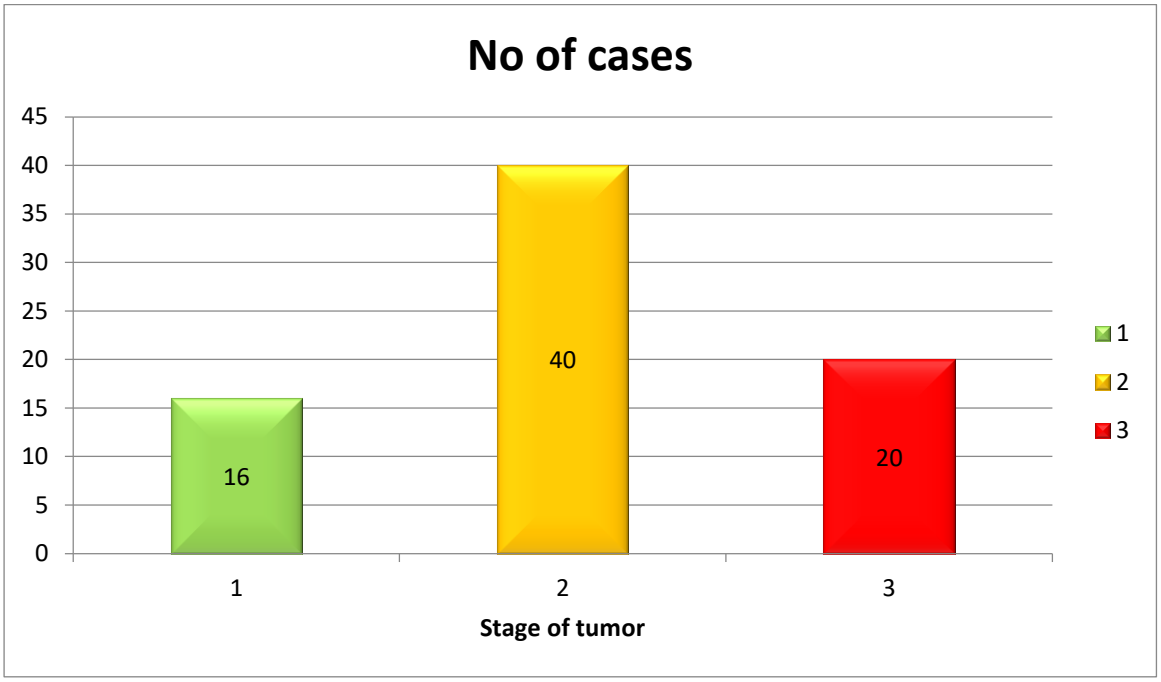
**. Correlation is significant at the 0.01 level (2-tailed).

From the table 6, Pearson correlation value is 0.523 which is significantly higher than the P value of 0.01. So the statistical significance is achieved.

Hence for all cases for whom biopsy was done prior to imaging, there was significant increase in depth of invasion in pre operative assessment by imaging. It is attributed to the presence of haemorrhage and edema which occur post biopsy.

STAGING:

T staging was done clinically in accordance with the AJCC 8th edition depending on both the depth of invasion and the maximum size of tumor.



Highest number of cases were found in stage T2 – 40 cases with mean of 2.05 and standard deviation of 0.691.

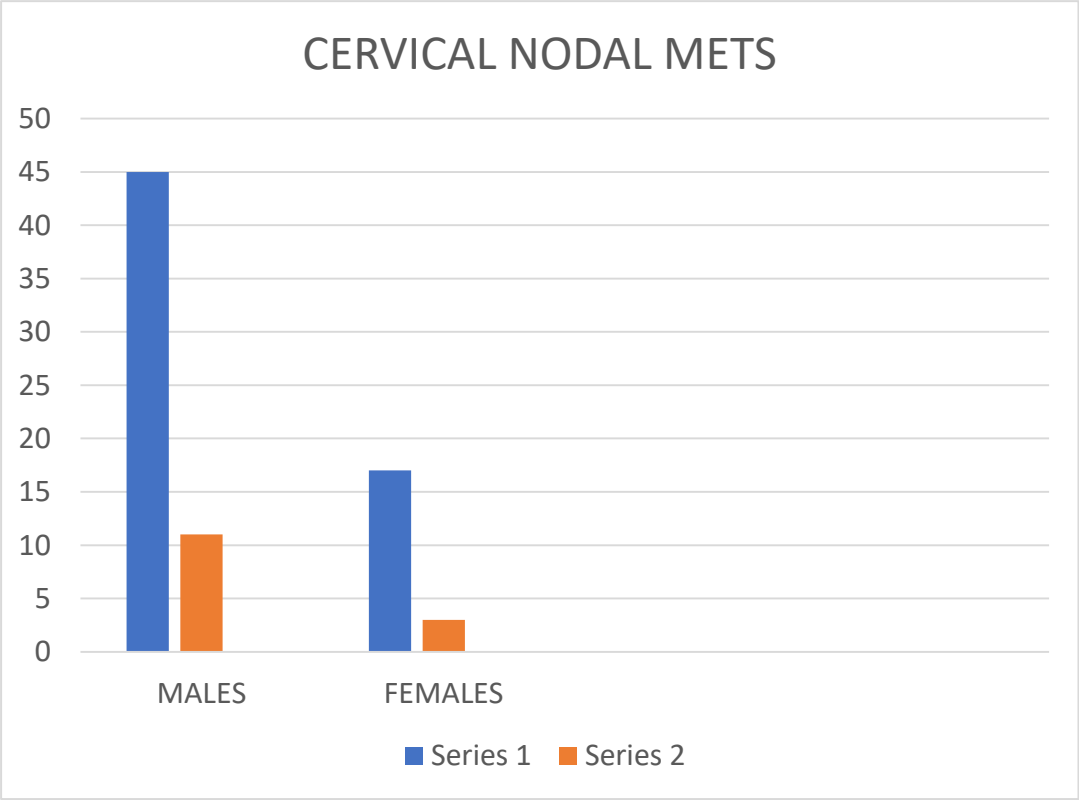
Table 7:

N	Valid	76
	Missing	0
Mean		2.05
Std. Deviation		0.691

		Frequency	Percent	Valid Percent
Valid	1	16	21.1	21.1
	2	40	52.6	52.6
	3	20	26.3	26.3
	Total	76	100.0	100.0

The mean stage from the study population was found to be 2.05 with standard deviation of 0.691.

CERVIAL NODAL METASTASIS:



Among the 56 male patients, 45 had node positive tumor from the extended supraomohyoid neck dissection / modified radical neck dissection depending on the clinical staging of the tumor. The rest 11 patients had reactive nodes.

Among the 20 female patients, 17 cases had node positive tumor and the rest of the patients had reactive nodes.

CORRELATION BETWEEN INCREASING DEPTH OF INVASION AND PRESENCE OF CERVICAL NODAL METASTASIS:

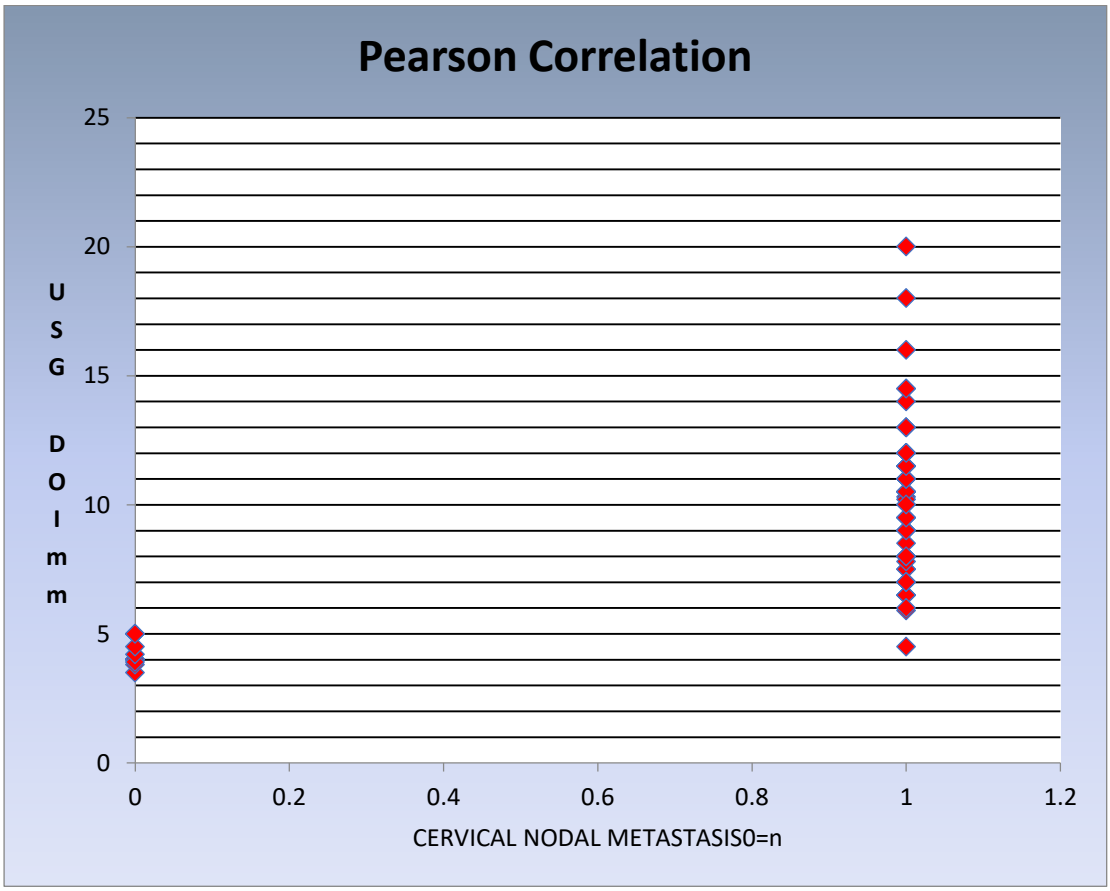


Table 8:

Correlations

		CERVICAL NODAL METASTASIS	USG DOI (mm)
CERVICAL NODAL METASTASIS	Pearson Correlation	1	.653**
	Sig. (2-tailed)		.000
	N	76	76
USG DOI (mm)	Pearson Correlation	.653**	1
	Sig. (2-tailed)	.000	
	N	76	76

**. Correlation is significant at the 0.01 level (2-tailed).

From the graph and table 7, for all node positive tumors, the pre operative depth of invasion was found to be more than 4 mm.

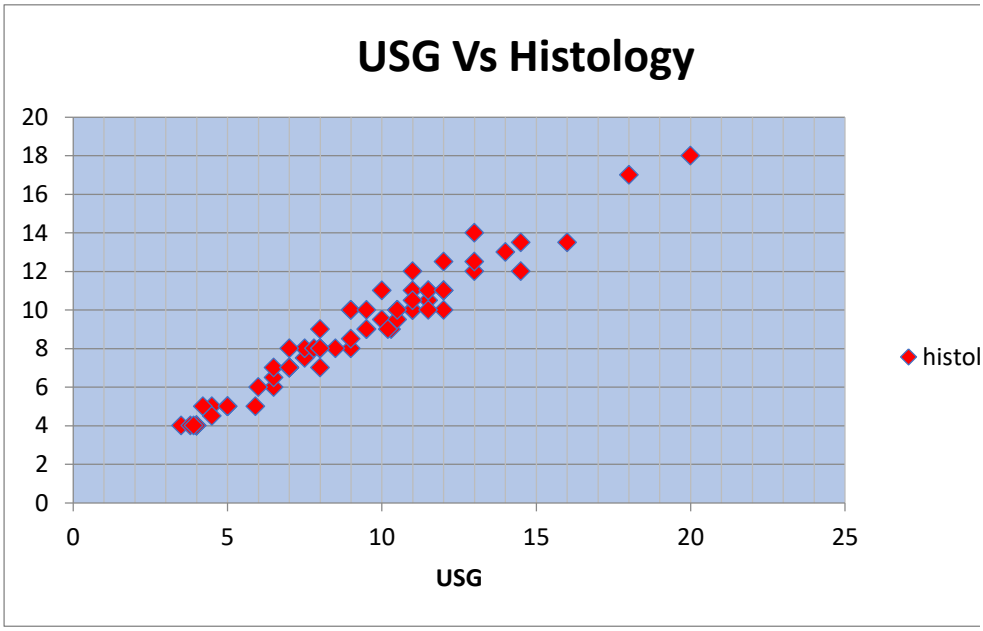
For node negative patients, the highest depth of invasion in preoperative imaging is 5 mm (one patient).

From the Table 7, Pearson correlation value is 0.653 which is higher than the cut off value of 0.01, so it is statistically significant.

Table 9:
CORRELATIONS:- USG vs HISTOLOGICAL

		USG DOI (mm)	HISTOLOGICAL DOI (mm)
USG DOI (mm)	Pearson Correlation	1	.979**
	Sig. (2-tailed)		.000
	N	76	76
HISTOLOGICAL DOI (mm)	Pearson Correlation	.979**	1
	Sig. (2-tailed)	.000	
	N	76	76

*. Correlation is significant at the 0.01 level (2-tailed).R value =0.979



Thus the correlation coefficient for USG (r value) is 0.979.

BLAND ALTMAN PLOTS:

ULTRASOUND VERSUS HISTOLOGY:

Table 10:

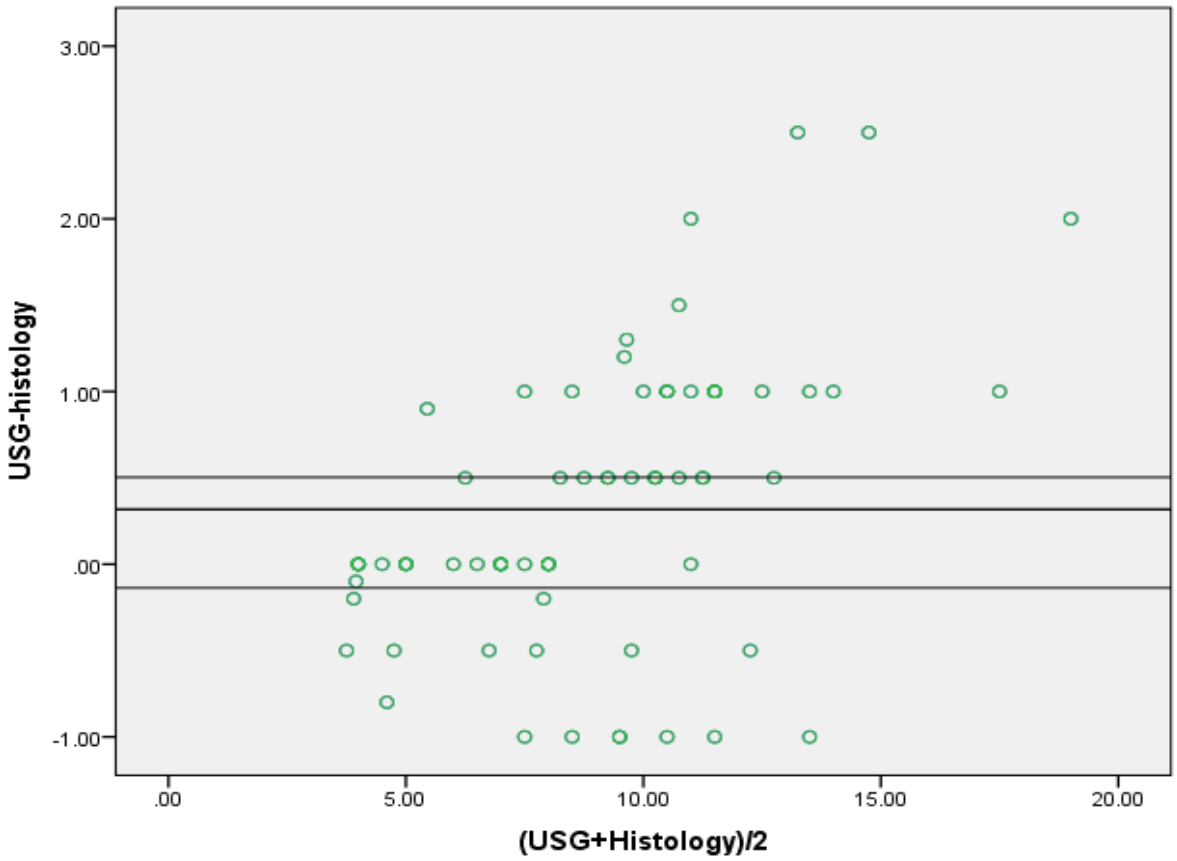
One sample statistics

	N	Mean	Std. Deviation	Std. Error Mean
Difference	76	-.3171	.78764	.09035

Table11: One sample test

	Test value = 0					
					95% Confidence Interval of the Difference	
	t	df	Sig. (2-tailed)	Mean Difference	Lower	Upper
Difference	-3.510	75	.001	-.31711	-.4971	-.1371

BLAND ALTMAN PLOT GRAPH USG VS HISOLOGY



Y axis: Difference { Ultrasound –Histology}
X axis : Mean {Ultrasound +Histology}/2

The central dark line is the bias, upper and lower lines form the upper and lower limit of agreement respectively.

From the table 9, for the sample size of 76, the mean difference between the depth of invasion estimated by histopathological examination (gold standard) and intra oral USG is -0.31711.

That is, intra oral USG preoperatively had estimated an additional 0.31711 when compared to post operative HPE.

The standard deviation is 0.78764 and the standard error of mean is .09035.

Table 12:

T TEST:

One-Sample Statistics

	N	Mean	Std. Deviation	Std. Error Mean
USG-histology	76	.3171	.78764	.09035
(USG+Histology)/2	76	8.8296	3.28661	.37700

Table 13:

One-Sample Test

	Test Value = 0					
					95% Confidence Interval of the Difference	
	t	df	Sig. (2-tailed)	Mean Difference	Lower	Upper
USG-histology	3.510	75	.001	.31711	.1371	.4971
(USG+Histology)/2	23.421	75	.000	8.82961	8.0786	9.5806

Table 14:

Regression:

Variables Entered/Removed[a]

Model	Variables Entered	Variables Removed	Method
1	(USG+Histology)/2[b]	.	Enter

a. Dependent Variable: USG-histology
b. All requested variables entered.

Table 15:

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.510[a]	.260	.250	.68213

a. Predictors: (Constant), (USG+Histology)/2

Table 16:

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	12.096	1	12.096	25.996	.000[b]
	Residual	34.432	74	.465		
	Total	46.528	75			

a. Dependent Variable: USG-histology
b. Predictors: (Constant), (USG+Histology)/2

Table 17:

Coefficients[a]						
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-.762	.226		-3.377	.001
	(USG+Histology)/2	.122	.024	.510	5.099	.000
a. Dependent Variable: USG-histology						

To arrive at the mean difference between mean values, we used T test and standard deviation and standard error of mean were calculated.

Regression analysis was done to detect the exact difference between the two modalities.

At 95 percent confidence interval, there was lower limit of -0.4971 and upper limit of -0.1371. Mean difference in values between USG and histological depth of invasion is -0.31711.

P value in regression is 0.001 which is less than the significant p value of 0.05 which means that there is no significant difference is values between the two modalities viz. Intra oral USG and histopathological examination.

Hence there is good agreement between depth of invasion measured by pre operative intra oral USG and that of the histopathology.

Statistical analysis was made then for correlation of MRI and histopathological depth of invasion.

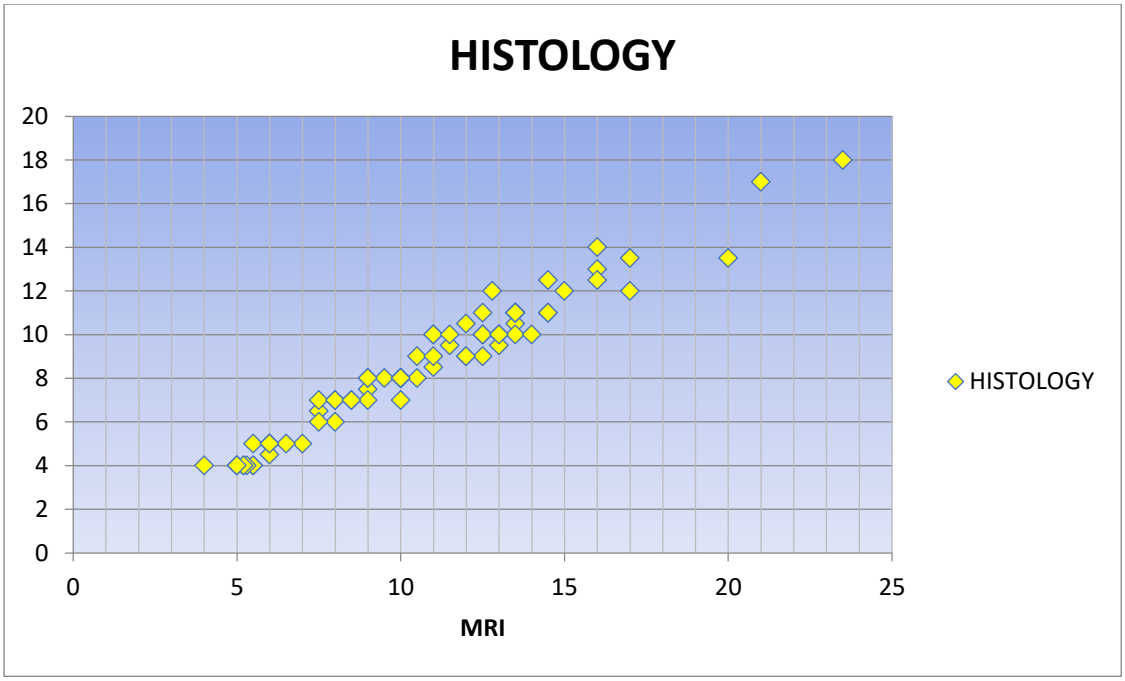
Table 18:

MRI VS HISTOLOGY

Pearson **Correlations**

		HISTOLOGICAL DOI (mm)	MRI DOI (mm)
HISTOLOGICAL DOI (mm)	Pearson Correlation	1	.897**
	Sig. (2-tailed)		.000
	N	76	76
MRI DOI (mm)	Pearson Correlation	.897**	1
	Sig. (2-tailed)	.000	
	N	76	76

. Correlation is significant at the 0.01 level (2-tailed).R value=0.897



Hence the correlation coefficient for MRI (r value) is 0.897.

Table 19:

BLAND ALTMAN PLOTS:

MRI VERSUS HISTOLOGY:

One-Sample Statistics

	N	Mean	Std. Deviation	Std. Error Mean
MRI-Histology	76	2.1513	1.17172	.13441

Table 20:

One-Sample Test

	Test Value = 0					
					95% Confidence Interval of the Difference	
	t	df	Sig. (2-tailed)	Mean Difference	Lower	Upper
MRI-Histology	16.006	75	.000	2.15132	1.8836	2.4191

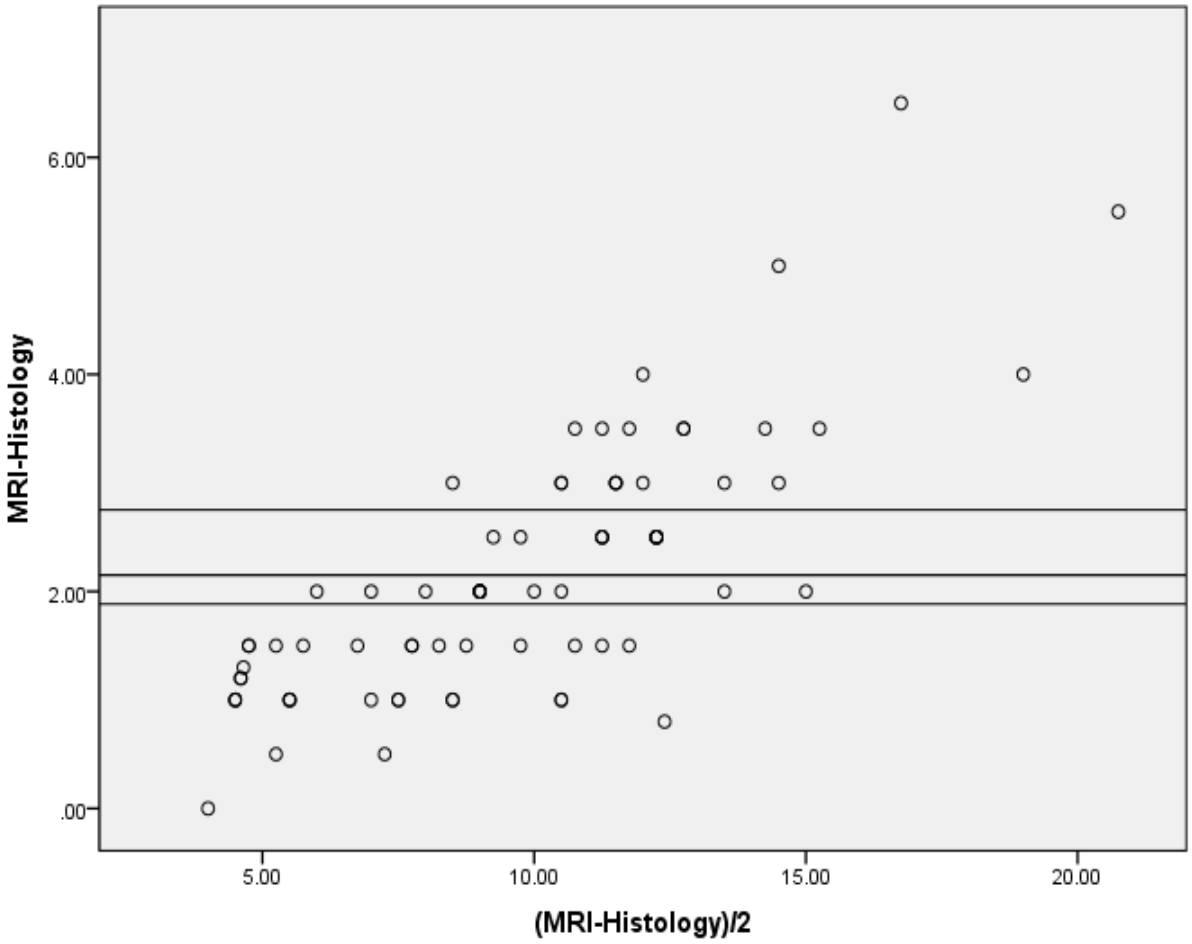
To arrive the mean difference between mean values, we used T test and standard deviation and standard error of mean were calculated.

Mean difference between the pre operative MRI and post surgical histopathological depth of invasion was found to be 2.15132.

The correlation coefficient for USG is found to be 0.979 and MRI is found to be 0.897. Hence both modalities can be used effectively to detect the depth of invasion.

But in order to find the agreement between these variables which can establish even more stronger correlation between the two, regression analysis has been made using Bland Altman plots.

Bland–Altman plots: MRI DOI versus Histology



Y axis: Difference { MRI DOI –Histology}

X axis :Mean {MRI DOI +Histology}/2

Regression analysis was done to detect the exact difference between the two modalities.

Table 21:

Variables Entered/Removed[a]

Model	Variables Entered	Variables Removed	Method
1	mean[b]	.	Enter

a. Dependent Variable: difference
b. All requested variables entered.

Table 22:

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.777[a]	.604	.599	.74210

a. Predictors: (Constant), mean

Table 23:

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	62.217	1	62.217	112.976	.000[b]
	Residual	40.753	74	.551		
	Total	102.970	75			

a. Dependent Variable: difference
b. Predictors: (Constant), mean

Table 24:

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	.358	.251		1.426	.158
	mean	-.257	.024	-.777	-10.629	.000

a. Dependent Variable: difference

P value in regression is 0.158 which is more than significant p value of 0.05 at 95 percent confidence interval which means that there is significant difference between the values measured in pre operative MR imaging and the post operative histopathological depth of invasion.

DISCUSSION

In our study both intra oral USG and MRI have proven to be effective tools in evaluating depth of invasion with correlation coefficient of 0.979 and 0.897 respectively.

Thus in order to establish a stronger scale of agreement between these variables, regression analysis have been employed.

The agreement between ultrasound, MRI and histopathological depth of invasion were estimated by means of doing Bland Altman plots.

The mean difference between depth of invasion on histology and ultrasound was 0.31 mm with standard deviation of 0.787.

The mean difference between depth of invasion on histology and MRI was 2.1 mm with standard deviation of 1.171.

For USG, P value in regression is 0.001 which is less than the significant p value of 0.05 which means that there is no significant difference in values between the two modalities viz. Intra oral USG and histopathological examination.

For MRI, P value in regression is 0.158 which is more than significant p value of 0.05 at 95 percent confidence interval which means that there is significant difference between the values measured in pre operative MR imaging and the post operative histopathological depth of invasion.

With the help of regression analysis, many outliers were found in MRI external to the line of agreement and clinically & radiologically significant differences between the values were found.

Hence there is good agreement between depth of invasion measured by pre operative intra oral USG and that of the histopathology.

In order to seek for the potential factor causing this variation in pre and post operative depth of invasion, we assessed the statistical significance of whether biopsy prior to imaging can lead to increase in depth of invasion in pre operative imaging.

From the table 6, Pearson correlation value is 0.523 which is significantly higher than the P value of 0.01. So the statistical significance is achieved.

Hence for all cases for whom biopsy was done prior to imaging, there was significant increase in depth of invasion in pre operative assessment by imaging. It is attributed to haemorrhage and edema during biopsy. On the contrary, for those cases in which biopsy was not performed prior to imaging, there was no significant difference in values.

In our study, statistical significance has been achieved for node positive tumors when the cut off value of more than 4 mm has been used.

This is in accordance with Yesuratnam et al in which applying a cutoff of > 4 mm yielded significant results in predicting the node positive status of the disease.(36)

In the past, research articles have been published comparing the role of ultrasound and MRI in the accurate evaluation of tumor thickness keeping the histopathological examination as gold standard.(15)

Ever since the introduction of depth of invasion as the primary factor for T staging of oral tongue malignancies, there hasn't been any significant large centre study for predicting the diagnostic accuracy.

As soon as the AJCC 8th edition landed, a pilot study by Yoon et al was published in AJNR, in which there was very high correlation of depth of invasion and tumor thickness measured by intra oral USG compared with post surgical histological values.(37) In this study, intra operative USG was done on 26 patients and achieved correlation coefficient of 0.95. In our study, higher correlation coefficient has been achieved (0.979).

In our study, the agreement between pre operative intraoral USG and histopathology have been achieved which is in line with the meta analyses done by Marchi et al in 2020 which showed pooled Pearson correlation coefficient (r value) of 0.96 for USG and pooled r of 0.87 for MRI. They concluded that promising results could be achieved with both USG and MRI for pre operative accurate determination of depth of

invasion but USG stands just tall with a higher pooled r and r to z transformed value which was closely related to the post operative findings.(38) The conclusion is in accordance with our study.

From our study, it is evident that both USG and MRI are effective but slight over estimation of depth of invasion on MRI could be attributed to the perilesional edema on T2 weighted images.

Yesuratnam et al found high correlation between ultrasound and tumor thickness using logistic regression models and found correlation coefficient of 0.80 for ultrasound which is higher than 0.69 for MRI.(36)

Natori et al in the largest study about USG and tongue carcinoma till date, provided good correlation ($r^2 = 0.74$) in more than 100 patients and achieved good reliability for intra oral USG examination.

Pre operative MRI served as a good tool in determination of tumor thickness in pre AJCC 8th edition era where depth of invasion was not considered as a significant indicator. Lam et al in their paper in AJR 2004 gave satisfactory results for measuring tumor thickness for tongue cancer staging with correlation co efficient of 0.93.(39)

In a study by Vidiri et al, excellent inter reader reliability was achieved (ICC=0.91) between MRI derived depth of invasion and that of histology.(17)

Similarly, Park et al in a study in 2011 found high correlation between MRI and histological depth of invasion (r value of 0.95) and found cut off of 9.5 mm for node positive tumors. This is in contrast to our study where we found USG to be correlating well with histology and a cut off of more than 4 mm for node positive tumors.(40)

Contrary to our study, Filauro et al found mean difference between MRI and histological DOI to be lower than that of USG and histology. Spearman correlation of 0.83 was achieved with MRI, which was higher than their USG value of 0.76. This is in contradiction to our study, where many outliers were found in MRI versus histology.(18)

Post surgical shrinkage of the tumor specimen has been a topic of debate of late because of fixation process. The shrinkage can lead to minor underestimation of dimensions in any lesion depending on the organ of surgery. During the fixation, shrinkage of the tissues are bound to happen in around 10 percent of cases.(41) But in our study only oral tongue cancers were taken into account in which the shrinkage pattern is more consistent in all directions, hence minimizing the variability of shrinkage.

CONCLUSION

To conclude, our study found both intra oral ultrasound and MRI as effective tools for preoperative assessment of depth of invasion in oral tongue malignancies. Strong correlation was found between USG, MRI and histological values. Intra oral ultrasound had even higher strength of agreement with post operative histopathological examination. This could be attributed to the perilesional edema found on T2 weighted MRI images.

Biopsy prior to imaging was considered as a significant confounding factor and values were found to be higher in pre operative imaging than the actual depth of invasion.

Strong correlation was also achieved in predicting cervical nodal metastasis keeping the cut off value of more than or equal to 4 mm depth of invasion.

It can help the clinicians by improving the plan for prophylactic neck dissection for disease in early stage.