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Imaging Recommendations for Diagnosis, Staging, and Management of Oral Cancer

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Abstract

Oral cavity cancers contribute to a majority of cancers in India. Clinical examination alone cannot determine the deeper extent of the disease; therefore, need for cross-sectional imaging including computed tomography and magnetic resonance imaging becomes indispensable for pre-treatment evaluation to decide optimal plan of management. Oral cavity squamous cell cancers (OSCC) can be treated with surgery alone, whereas deep muscle, neurovascular, osseous, or nodal involvement on imaging suggests advanced disease that requires a combination of surgery, radiation, and/or chemotherapy. Because of the complex anatomy of the oral cavity and its surrounding structures, imaging is crucial for locoregional staging and early detection of distant metastases. Imaging plays indispensable role not only in diagnosis but also in planning the management. An optimal guideline paper for developing countries like India is lacking that not only helps standardize the management but will also assist oncologists make reasonable decisions and reduce the unnecessary imaging. This imaging guideline paper will discuss the optimal imaging in diagnosis and management OSCC for Indian subcontinent.

Keywords
- computed tomography
- guidelines
- magnetic resonance imaging
- oral cancer
- imaging

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Introduction

Head and neck cancers are the sixth most common cancer worldwide, with oral cavity squamous cell carcinoma (OSCC) being the most common and having the high morbidity and fatality rates.[1] For proper management, timely diagnosis and correct tumor staging are vital. Radiologic imaging is routinely used to assess the disease extension in supplementation with clinical examination. The most common histology is SCC, which accounts for the vast majority of oral cancers.[2] The symptoms of malignancy, the methods by which it spreads, and the prognosis are all highly variable, and are largely determined by the anatomic region where the initial tumor develops. For diagnostic assessment and appropriate treatment planning, it is of utmost importance to understand the oral anatomy and most typical pathways of dissemination of OSCC.[3]

Risk Factors and Etiopathogenesis

Risk factors for OSCC include quid chewing, poor oral hygiene, tobacco, alcohol consumption, and sharp tooth/denture.[4,5] The World Health Organization describes the oral potentially malignant disorders that may transform into carcinoma later in life. These include leukoplakia, erythroplakia, erythroleukoplakia, oral submucous fibrosis, smokeless tobacco keratosis, lichen planus, and discoid lupus erythematosus.[6] The morphological spectrum of oral potentially malignant disorders varies from acanthosis, hyperkeratosis, to dysplasia and carcinoma in situ.[7]

Epidemiology and Clinical Presentation in India and Global

Oral cancer constitutes sixth most frequent malignancies in Asia with approximately 274,300 new cases occurring each year.[8] Age standardized incidence rate (ASIR) in Sri Lanka, Taiwan, Bangladesh, India, and Pakistan, is far more than the world ASIR (10.5 for men and 4.02 for women). In India, ASIR of 12.7/100,000 in men (Bombay) and 10.0/100,000 in women (Bangalore) has been reported.[9] The plausible reason is the rampant use of chewed tobacco and common custom of chewing beetle quid containing areca nut along with slaked lime. Patients usually present with nonhealing ulcer, pain, bleeding, poorly fitting dentures, speech alteration, and neck lymph nodes.[10] Examination includes inspection of the oral cavity along with palpation of the lesion under anesthesia to assess the submucosal extent of disease. The neck is thoroughly palpated to detect lymph node metastasis that is large in size, hard in consistency, and may be fixed to surrounding structures.[11] The upper aerodigestive tract should be examined for any synchronous second primary. Biopsy of tumor and/or lymph nodes is done to establish the diagnosis and further workup is planned after histological confirmation.

Imaging Referral Guidelines

The American Joint Committee on Cancer/International Union Against Cancer staging method is a tool that allows physicians all over the globe to stage cancer before any therapy, after surgical resection, and at the time of recurrence.[12] Staging divides patients into prognostic groups, making it easy to choose the best treatment strategy, schedule treatment, and predict prognosis based on the stage of the disease. Updates in the 8th edition are as shown in ►**Table 1**.[13]

Clinical/Diagnostic Workup Excluding Imaging

Oral cavity lesions tend to present with classical history of long-standing nonhealing ulcers associated with pain and are easily accessible to visual and bimanual examinations; hence majority of the oral cavity malignancies are diagnosed clinically.[14] Examination also permits evaluation of the local extent of the tumor. Apart from physical examination, endoscopic examination also plays an important in deep-seated lesions or lesion involving the larynx or pharynx. Punch biopsies of the oral cavity lesions or ulcers can be performed per orally in most of the cases.[15] Majority of these tumors are SCCs. There is no defined role of tumor markers in head and neck malignancy apart from the human papilloma virus and Epstein–Barr virus statuses.[16]

Imaging Guidelines

While local examination provides an idea of the local extent, evaluation of detailed extension of the tumor and presence of bony erosion, perineural spread, nodal and distant metastases require cross-sectional examination.[17] All the above findings have implications on the treatment and outcome of the patient. The various subsites of oral cavity include lips, buccal mucosa, oral or anterior two thirds of tongue, upper and lower alveolus with gingiva, retromolar trigone (RMT), floor of mouth (FOM), and hard palate. The various diagnostic modalities employed are ultrasonography (USG), contrast-enhanced computed tomography (CECT), contrast-enhanced magnetic resonance imaging (CE-MRI), and fluorodeoxyglucose positron emission tomography (FDG-PET). Imaging-guided interventions like biopsy and fine-needle aspiration cytology (FNAC) are also essential for tissue diagnosis in deep-seated or recurrent lesions. We will further discuss these modalities and their relevance below. The preferred imaging modality in various settings, CT and MRI protocols, are summarized in ►**Tables 2** to **4**.[18,19]

Screening

There are no studies supporting the benefit of imaging-based screening tests in the diagnosis of oral cavity cancers. Since oral cavity is easily accessed by visual examination, the need for imaging screening is not defined till date. However, as there are high rates of malignant transformation with the premalignant lesion like leukoplakia, erythroplakia, oral submucous fibrosis, and lichen planus, these lesions are kept on clinical follow-up and biopsy can be performed to detect malignant transformation at an earlier stage.[20]

Table 1 Difference in 7th and 8th edition of American Joint Committee on Cancer clinical staging for oral cancers[13]

	Seventh edition	Eighth edition
T1	Tumor < 2 cm	Tumor ≤ 2 cm, ≤ 5 mm depth of invasion
T2	Tumor 2–4 cm	Tumor ≤ 2 cm, >5 mm and ≥ 10 mm depth of invasion or tumor > 2 cm but ≤ 4 cm and depth of invasion ≤ 10 mm
T3	Tumor > 4 cm	Tumor > 4 cm and depth of invasion < 10 mm or tumor <4cm and depth of invasion >10 mm
T4a	Moderately advanced local disease Lip: tumor invades through the cortical bone or involves inferior alveolar nerve, floor of mouth, or skin of face Oral cavity: tumor involves adjacent structures such as cortical bone of maxilla or mandible, maxillary sinus or skin of face, or extrinsic muscles of tongue	Extrinsic muscles of tongue removed, included extensive tumors with bilateral tongue involvement or tumor > 4cm and depth of invasion > 10mm
T4b	Very advanced local disease; tumor invades masticator space, pterygoid plates, skull base and/or encases the internal carotid artery	No change
N1	Metastases to single lymph node, 3 cm or less in greatest dimension	Same, except node must be extranodal extension negative
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension	Same, except node must be extranodal extension negative
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension	Same, except nodes must be extranodal extension negative
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension	Same, except nodes must be extranodal extension negative
N3	Metastases to node > 6 cm	Subdivided into 3a: Same as N3 before, but extranodal extension negative 3b: any node with extranodal extension

Table 2 Preferred imaging modality in various setting

Imaging setting	Preferred imaging modality
Screening	CECT or CE-MRI[a] (no proven role)
Diagnosis:	
a) Diagnostic	For gingivobuccal cancer—CECT PNS and thorax For tongue carcinoma—CE-MRI[a] plus NCCT thorax FDG-PET-CT
b) Intervention	CT-guided biopsy/FNAC for deep-seated lesions USG-guided biopsy/ FNAC for nodes and superficially seated lesions
Management	
a) Post-surgery	CECT/ CE-MRI[a] (OR) FDG-PET-CT
b) Neoadjuvant, adjuvant or palliative chemotherapy	CECT/CE-MRI[a] (OR) FDG-PET-CT
Follow-up	FDG-PET-CT (OR) CECT/CE-MRI[a]

Abbreviations: CECT, contrast-enhanced computed tomography; CE-MRI, contrast-enhanced magnetic resonance imaging; FDG-PET-CT, fluorodeoxyglucose positron emission tomography-computed tomography; FNAC, fine-needle aspiration cytology; NCCT, noncontrast CT, PNS, para nasal sinus; USG, ultrasonography.
[a]CECT—for majority of oral cavity subsites, CE-MRI—oral tongue and floor of mouth.

Table 3 CT oral cavity imaging protocol

Parameter	Characteristics
Scanner type	Helical scanner
Slice thickness	0.75 mm
Intravenous contrast	Iodine-based contrast agent at 3 to 5mL/sec flow rate (total volume—80 mL)
Maneuvers	Puffed-cheek technique
Acquisition time	40–50 seconds
Reconstruction	Bone algorithm reconstruction Multiplanar reconstruction in coronal plane or parasagittal plane
Anatomical coverage	Pituitary fossa to arch of aorta. Include thorax and upper abdomen in venous phase—staging

Abbreviation: CT, computed tomography.

Diagnosis

Imaging plays a key role in the disease assessment of oral cavity cancer. The current modality of choice for primary diagnosis of oral cavity lesions (excluding oral tongue and hard palate) is CECT head and neck with puffed cheek technique and bone algorithm reconstruction. For oral tongue and FOM lesions, MRI head and neck is the preferred modality. FDG-PET-CT can also be employed for diagnosis in appropriate settings.[18] The role, advantage, and drawback of each modality have been briefly explained below.[21,22]

Table 4 MRI oral cavity imaging protocol

Sequence	Plane of acquisition	Slice thickness
T1W FS-FSE	Coronal	4 mm
STIR	Coronal	4 mm
T2W FS-FSE	Sagittal	4 mm
T2W FS-FSE	Axial	4 mm
T1W FS-FSE	Axial	4 mm
DWI	Axial	4 mm
Postgadolinium contrast T1W FS-FSE	Axial, coronal, and sagittal planes	4 mm

Abbreviation: DWI, diffusion-weighted imaging; FS-FSE, fat-saturated fast spin echo; MRI, magnetic resonance imaging; STIR, short tau inversion recovery; T1W, T1-weighted.

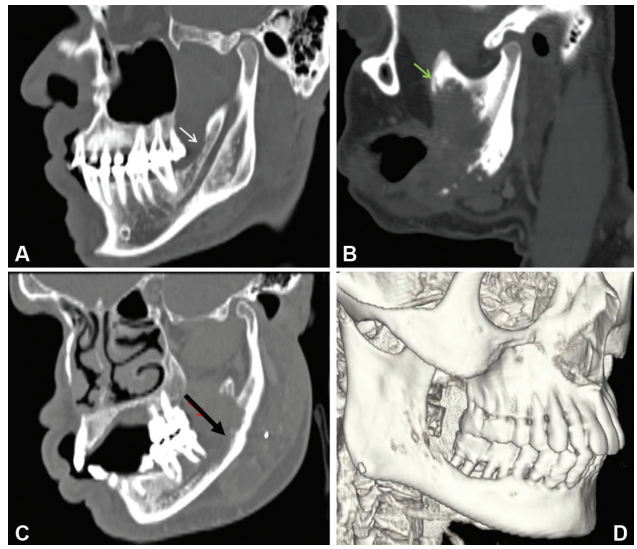

Fig. 2 (**A**) Oblique sagittal reformatted images showing superficial cortical erosion (white arrow) of the mandible, (**B**) erosion of the coronoid process of the mandible (Green arrow), (**C**) cortical and medullary erosion with involvement of inferior alveolar canal (black arrow) of mandible. (**D**) Shaded surface display image shows erosion of mandible and important in planning surgical reconstruction.

Oral cavity: CECT head and neck with puffed cheek technique enables detailed evaluation of the oral cavity. Puffed cheek technique improves the contour and margin delineation as compared to the conventional CECT.[23] Also, this technique separates the mucosal surface from alveolus enabling better assessment of subtle lesions that may otherwise be missed in routine imaging. With puffed cheek technique structures like buccal mucosa, gingival, buccal vestibule and RMT are better delineated (►**Fig. 1**).[24] Bone algorithm reconstruction is routinely performed in all oral cavity malignancies to assess for bony erosion. Patterns of bony erosion affect the surgical technique; hence, it is mandatory to perform and report the bony erosion (►**Fig. 2** and ►**Supplementary Table S1**).[25] CECT enables identification of the depth of invasion (DOI), local and regional extent of the tumor, presence of bony erosion, and perineural spread. Surgical resection is possible in disease with involvement of low infratemporal fossa (ITF) or retroantral ITF and superficial or deep cortical bony erosion.[18,26] Detailed explanation of the all the above entities is beyond the scope of this article. CECT has its own disadvantages like less soft tissue resolution compared to CE-MRI, which can be used as a problem-solving tool in detecting subtle lesions, or for demonstrating perineural or intracranial spread. MRI is not an ideal initial modality for oral cavity imaging as it is time consuming and can have motion artefacts.

Tongue: CE-MRI has better soft tissue resolution and hence it is the modality of choice for evaluation of tongue. MRI better defines the DOI, muscles of tongue involvement, midline extension, FOM, neurovascular structure, and posterior third tongue involvement.[27] However, for the evaluation of mandibular cortical bone involvement CECT is preferred to MRI.

Artefacts: Both CT and MRI images are susceptible to artefacts in the presence of dental implants or amalgams. However, CT has its advantage in this aspect, as it permits

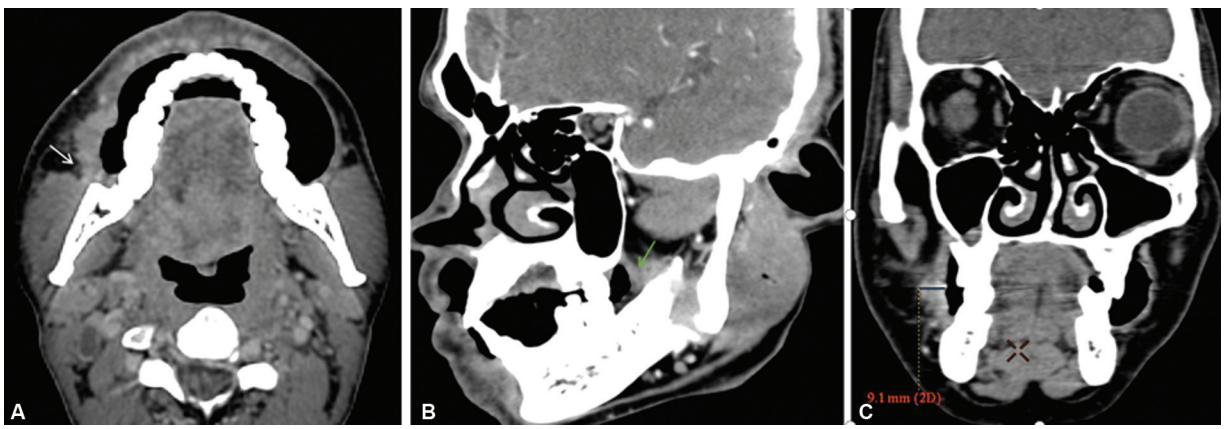

Fig. 1 (**A**) Axial section shows an ill-defined thickening involving right buccal mucosa buccinator complex with loss of fat planes with masseter muscle (white arrow). (**B**) Sagittal oblique shows an ill-defined thickening involving retromolar trigone region (green arrow) highlighting importance of oblique reformation. (**C**) Coronal reformatted images show technique to measure depth of invasion.

Table 5 Imaging findings of perineural spread

Direct signs	Indirect signs
1.Nerve enhancement 2.Nerve enlargement 3.Foramina fat plane obliteration 4.Foramina enlargement and destruction 5.Intracranial spread	1. Denervation atrophy. 2. Denervation enhancement In acute or subacute phase, T2 hyperintense edema in the corresponding muscle develops postcontrast enhancement. In chronic phase, muscle atrophy shows hyperintense signal on T1 and T2-weighted sequences due to fatty replacement

artefact reduction via employment of tube angulation and algorithms like metal artefact reduction.[18]

Interventions: Oral cavity lesions are usually sampled per orally in clinical setting; however, image guidance is required if the lesion is deep seated as in masticator space, ITF, parapharyngeal or retropharyngeal space. Generally, CT-guided sampling is preferred in these deep-seated subsites.[28] FDG-PET-CT has major advantage in guiding the sampling to the site of FDG avidity. USG can be employed for sampling of superficial seated lesions, lymph nodes, etc.

Staging

The role of imaging in staging relies on identifying locoregional extent and nodal and distant metastases. CECT whenever performed for initial workup should include thorax and upper abdomen as part of staging evaluation. Involvement of the ITF, masticator space, and presence of perineural spread are important predictors of locoregional staging. Perineural spread (►**Supplementary Table S2**) of disease can be identified as thickening, enhancement of nerve, and widening of neural foramina as shown in ►**Tables 5** and **6**.[18,29,30] Even though CECT can detect the presence of perineural spread, MRI is more sensitive as it can depict even subtle perineural spread. The most commonly involved nerve being mandibular in gingivobuccal cancer and maxillary division of trigeminal nerve in carcinoma hard palate is shown in ►**Figs. 3** and **4**. ITF involvement (►**Supplementary Table S3**) can be subdivided as high and low ITF, based on the presence of disease involvement above or below the level of the sigmoid notch of mandible.[18,31–34] Regional metastasis is common to the cervical lymph nodes. The frequent sites of distant metastases in oral cavity cancers are lungs, liver, bones, and mediastinal nodes. Cervical lymph node metastases can be detected by USG as it better depicts the morphology, shape, presence of cystic change, and nature of fatty hilum. Also, USG guidance can be used for sampling of these nodes for FNAC or biopsy. CECT and CE-MRI both equally depict the extranodal extension (ENE), an important prognostic marker

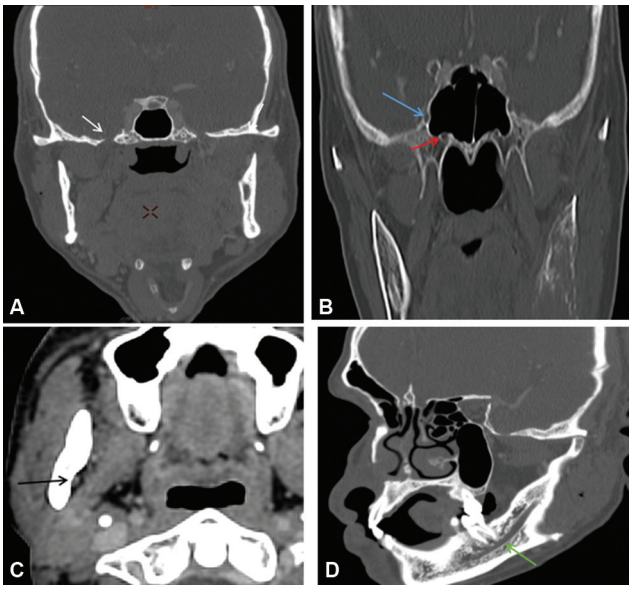

Fig. 3 Multiplanar reformatted images showing normal structures acting as conduit for perineural spread (**A**–**D**) foramen ovale (white arrow), foramen rotundum (blue arrow), vidian canal (red arrow), mandibular foramen (black arrow), and inferior alveolar canal (green arrow).

Table 6 Key points in evaluation of each nerve

Nerves	Key findings
1. Ophthalmic branch of trigeminal nerve(V1)	Obliteration of the orbital fat pad and enhancement of V1 in the orbit and the cavernous sinus
2. Maxillary branch of the trigeminal nerve(V2)	Obliteration of the fat pads in the pterygopalatine fossa; enlargement of the infraorbital fissure and thickening and enhancement of V2 in the round foramen and cavernous sinus
3. Mandibular branch of the trigeminal nerve(V3)	Obliteration of the fat pads of the mental or mandibular foramen and of the parapharyngeal fat below the foramen ovale; enlargement or erosion of foramina; thickening and enhancement of V3 in the parapharyngeal space and foramen ovale; abnormal bone marrow in the jaw; signs of denervation of the masticatory muscles
4. Trigeminal nerve	Obliteration of Meckel's cave
5. Facial nerve	Obliteration of the fat pad of the stylomastoid foramen and abnormal enhancement
6. Geniculate ganglion	Enlargement, obliteration and sclerosis of the geniculate fossa
7. Greater superficial petrosal nerve	Obliteration of the fat pad and enlargement or erosion of the vidian canal
8. Auriculotemporal nerve	Tumor growth in the posterior mandible

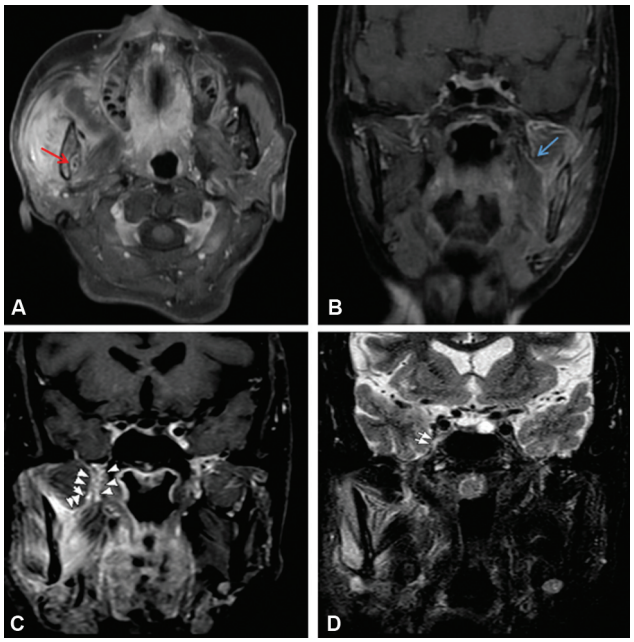

Fig. 4 (**A**) Axial postcontrast magnetic resonance imaging showing right upper Guillain-Barre syndrome mass with associated enhancement along right mandibular nerve in mandibular foramen suggesting perineural spread (red arrow). (**B**) Coronal postcontrast image showing enhancement along the infratemporal fossa component of the left mandibular (blue arrow). (**C** and **D**) Coronal postcontrast image showing enhancement and thickening of the right mandibular nerve involving foramen and suspicious intracranial extension superiorly (white arrowheads and arrow).

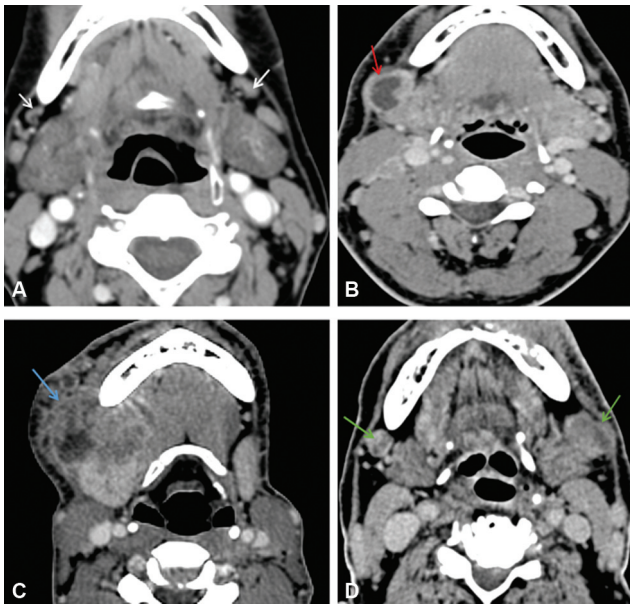

Fig. 5 (**A**) Bilateral reactive nodes are seen with maintained fatty hilum (white arrow). (**B**) Necrosis is seen in the right level IB node (red arrow). (**C**) Right level IB node with extranodal extension is seen (blue arrow). (**D**) Metastatic bilateral necrotic IB nodes are seen with capsular irregularity in the left IB node suspicious extranodal extension (green arrow).

in predicting advanced nodal disease and local recurrence and are considered the best imaging modality for nodal metastases (►**Fig. 5**).[35,36] Usually, the imaging modality that is used to assess the primary lesion can also evaluate the regional metastases. Most frequent site of distant metastases is lung and many times they tend to cavitate. Routine chest radiograph can detect overt lung metastases, while for detection of smaller or subpleural lesions, CECT is mandatory.[37] Furthermore, one can miss lesions in the hidden areas of radiograph. FDG-PET-CT has incremental value in detection of subtle metastases and detecting extrathoracic metastases. In addition, it also provides the standardized uptake value.[38]

Management

The various treatment modalities available for oral cavity cancers are surgery, chemotherapy, and radiation therapy either as single modality or in combination. Response assessment in neoadjuvant, adjuvant, and palliative settings aims at the detection of the residual disease and documents increase or decrease in disease burden and presence of new metastases.[17] Response assessment in most of the oral cavity cancers is best done with CECT as it can better detect the presence of residual disease (►**Fig. 6**). CE-MRI is the ideal modality for assessing response for oral tongue lesions. Surgical resection or radiation therapy is known to cause various post-treatment changes in the tissue distortion and these changes should be kept in mind while reporting.[39,40] There are some key findings in gingivobuccal sulcus and tongue cancers on imaging that have vital implications for the management plan. Gingivobuccal sulcus cancers with low ITF involvement on imaging are resectable. High ITF involvement is a relative contraindication for surgery with posterior high ITF (pterygopalatine fossa and pterygomaxillary fissure) involvement requiring palliative care, while anterior high ITF (retroantral fat) involvement is still amenable for surgery. Superficial/cortical bone erosion does not alter the T stage of the disease. Mandible preserving surgery can be done if anteroposterior extent of paramandibular soft tissue is less than 1 cm and directs marginal mandibulectomy if it is more than 1 cm. Deep cortical erosion or marrow involvement upstages the disease to T4a and requires segmental mandibulectomy. Perineural spread of disease is resectable if limited to infra-notch compartment but warrants palliative management if supra-notch extension is present. In tongue cancers, when tumor thickness is more than 4 mm elective neck dissection is done in view of the greater risk of nodal metastases. DOI of more than 10 mm is a marker of poor prognosis for which adjuvant treatment is recommended. When disease crosses the midline contralateral neck, dissection and radiation are warranted. Total glossectomy with flap reconstruction has to be done when bilateral neurovascular bundles get involved. Bone erosion in tongue cancers requires mandibulectomy with reconstruction and invasion of FOM reconstruction with flaps. Involvement of vallecula, pre-epiglottic space, and hyoid are relative contraindications for surgery. Extension to masticator space deems the disease nonresectable. Imaging in a clinically node-negative disease helps to pick up occult/skip nodal metastases that warrants elective neck dissection. High

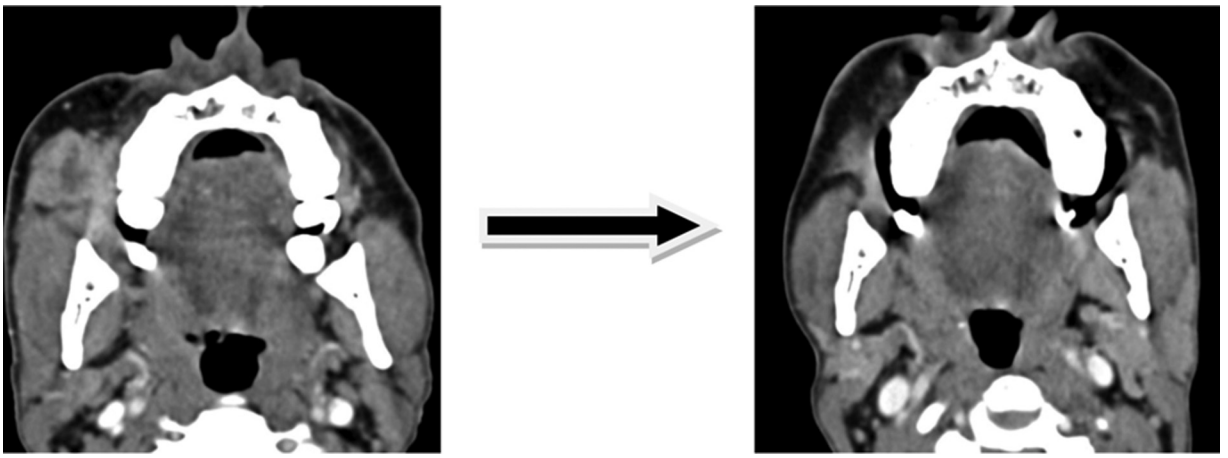

Fig. 6 Axial multidetector computed tomography images showing downstaging of T4b disease post induction chemotherapy.

nodal burden on CT warrants PET-CT/CT thorax in view of increased risk of distant metastases. Adjuvant treatment is required if ENE is present.

Follow-Up

Follow-up or surveillance in post-treatment setting aims at the detection of recurrence at the earliest. The timeline for first post-treatment surveillance imaging is usually 3 months post-treatment. However, the National Comprehensive Cancer Network criteria suggest that first surveillance imaging should be performed between 3 and 6 months of completion of therapy.[41] While CECT is preferred for majority of the oral cavity subsites, CE-MRI is preferred for tongue imaging. Radiologists needs to be aware of the possible post-treatment appearance following surgeries or radiation therapy in head and neck as they cause distortion of normal anatomy and fibrosis that make detection of residual or recurrent disease challenging. FDG-PET-CT can be used as a problem-solving tool in distinguishing recurrent tumor from post-treatment changes.[42,43]

Principles of Management

The mainstay of treatment for oral cancers is surgery with or without adjuvant therapy. For early-stage disease (stages I and II), the treatment is single modality, whereas for advanced stage disease (stages III and IVA), the treatment is multimodality.[17] The primary disease is excised with adequate margin of more than 5 mm all around the tumor. Neck dissection is performed in all cases. Elective neck dissection clearing level I to III is performed for node negative neck. Modified radical neck dissection clearing level I to IV or V is performed preserving all the nonlymphatic structures namely internal jugular vein, spinal accessory nerve, and sternocleidomastoid muscle that are sacrificed only if involved by the disease. For advanced disease (stages III and IV), it is surgical resection followed by radiation therapy with or without concurrent chemotherapy. Inoperable cases are directly treated with radiation therapy with or without concurrent chemotherapy.[44] Best supportive care is recommended if the general condition of the patient is poor precluding any treatment. The stage-wise prognosis (5-year survival rate) in oral cavity cancers is 85.2, 82.9, 56.3, and 42.6% for stages I, II, III, and IV respectively.[45]

Follow-Up Imaging and Management of Recurrent Disease Including Specific Interventional and Palliative Measures

The main aim of follow-up imaging is diagnosing and treating the recurrent disease at the earliest. Most cases of oral cavity malignancy recur either in the postoperative bed or in the cervical lymph nodes. Image-guided tissue sampling plays an important role in documenting these recurrences. Surgery should be offered to the patients if the recurrence is excisable. However, when the recurrence cannot be excised with clear margins or in the presence of distant metastasis, nonsurgical treatment should be offered that includes chemotherapy or chemoradiation. These recurrent tumors tend to be resistant to many conventional chemotherapeutic drugs and immunotherapy and targeted therapies could be the options for such patients. There is some emerging data that oligometastatic cases with solitary lung recurrence can be treated with radio frequency or microwave ablation, metastasectomy, or stereotactic body radiotherapy; however, the practice varies across the globe.[46,47]

Summary of Recommendations

1. Oral cavity cancers have better outcomes if detected early and treated with timely surgery.
2. Imaging plays a crucial role in diagnosing, staging the disease, treatment planning on case-to-case basis, and surveillance of disease.
3. Modality of choice for majority of oral cavity cancers is CECT, while for oral tongue and FOM, CE-MRI is performed.
4. FDG-PET-CT is used as a problem-solving tool and in the setting of recurrent or residual disease.

Conflict of Interest
None declared.

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