Review Article

Imaging Advances in Oral Cavity Cancer and Perspectives from a Population in Need: Consensus from the UK-India Oral Cancer Imaging Group

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ABSTRACT

Oral squamous cell carcinoma (OSCC) accounts for a third of the cancer burden in India, with a correspondingly high cancer-specific mortality. Although treatment of OSCC in India mirrors that of high-income nations, extreme burden of disease, late presentation, and the associated advanced stage of disease pose unique challenges in a resource-constrained environment. Despite a multimodal treatment paradigm, survival rates are low. Often the cause for late presentation is the delayed diagnosis, inappropriate investigation and referral, and compromised or incorrect treatment, leading to poor patient outcomes and costs to the health-care provider. To address these issues, the first UK-India Symposium on Advances in Oral Cancer Imaging Symposium was organized in Bangalore, India, in April 2019; participants included radiologists, imaging scientists, clinicians, and data scientists from the United Kingdom, India, Singapore, and the United States. Following the discussions held during this meeting, in this manuscript, we present evidence-based guidance for the role of imaging in OSCC, recommendations for service development, and details of future potential for evolution in head and neck imaging.

Key words: Computerized tomography, magnetic resonance imaging, molecular imaging, mouth neoplasms, ultrasonography

INTRODUCTION

Oral squamous cell carcinoma (OSCC) accounts for a third of the cancer burden in India, with a correspondingly high cancer-specific mortality.[1] The widespread use of tobacco and areca nut underpins this high incidence.[2] While alcohol and tobacco are strong etiological agents irrespective of geographical region, developed nations, in particular, have witnessed a rapid rise in human papillomavirus-related

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oropharyngeal cancers in recent times.[3] Although treatment of OSCC in India mirrors that of high-income nations, extreme burden of disease, late presentation, and the associated advanced stage of disease pose unique challenges in a resource-constrained environment. Advanced OSCC even when treated maximally and adequately portends a poor prognosis with a 5-year overall survival in the range of 20%–40%.[4] Despite a multimodal treatment paradigm, survival rates are low. Often, the cause for late presentation is the delayed diagnosis, inappropriate investigation and referral, and compromised or incorrect treatment, leading to poor patient outcomes and costs to the health-care provider. The key to overcoming this crucial determinant is appropriate diagnosis and imaging coupled with proper investigations and referral. This can improve patient outcomes and reduce the costs to the health-care provider.

To address these issues, the first UK-India Symposium on Advances in Oral Cancer Imaging Symposium was organized in Bangalore, India, in April 2019; participants included radiologists, imaging scientists, clinicians, and data scientists from the United Kingdom, India, Singapore, and the United States. Following the discussions held during this meeting and an extensive review of the literature, in this manuscript, we present evidence-based guidance for the role of imaging in OSCC, recommendations for service development, and details of future potential for evolution in head and neck imaging.

ROLE OF IMAGING IN ORAL CANCER

Importance of pretreatment imaging

The anatomy of the oral cavity is complex and comprises several subsites: oral tongue, floor of the mouth, buccal mucosa, alveolus, hard palate, and retromolar trigone. Routine pretreatment cross-sectional imaging is necessary for accurate staging of the primary tumor, determination of cervical nodal metastases, and identification of distant metastases or synchronous malignancy.[5] Even in patients with early (clinically) staged (stage I/II) disease, the advantages of pretreatment cross-sectional imaging are the ability to identify subclinical local spread and occult nodal metastases, and as baseline for adjuvant radiotherapy planning.[6] As surgery is the preferred modality of treatment in resectable oral cancer, preoperative imaging is often important to determine the extent of disease to support a complete circumferential excision.

Preoperative imaging also facilitates peri-operative planning and has become increasingly useful for planned reconstruction. In advanced cases, imaging guides decision-making around tumor operability, which often cannot be determined clinically. In the uncommon situation whereby neoadjuvant chemotherapy has been employed, imaging is used as a response assessment tool.[7]

Imaging as a tool to aid preoperative clinical decision-making

In certain contexts, imaging plays an integral role in patient triaging. The expertise required to successfully treat OSCC varies considerably on the basis of disease extent. For early-stage disease (Stage I–II), surgery is often adequate and can be delivered with relative ease, while for advanced stage nonmetastatic disease (III–IV), multimodal therapy (surgery with adjuvant radiotherapy/chemoradiotherapy) is required, necessitating clinicians and teams with critical skill sets. The nonmetastatic advanced-stage disease is best managed with multidisciplinary care, which can ideally be introduced preoperatively.[8]

Determination of resectability is a crucial step in treatment planning, as subclinical tumor spread is common. Once deemed unresectable, patients are offered nonsurgical therapy with palliative intent. Even when deemed resectable, extensive disease requires more advanced facilities, clinical expertise, and levels of care to avoid perioperative morbidity and mortality. Many centers may not have these facilities, and as such appropriate pretreatment imaging assessment represents a critical step facilitating the appropriate referral of this patient group.

Imaging in perioperative planning

In addition to the requirement for essential facilities and infrastructure, advanced OSCC cases may benefit from multidisciplinary expertise in the pursuit of optimal outcomes; elements frequently available only at referral centers. Anatomical variations and previously operated surgical fields present significant challenges. Areas suspicious for subclinical spread may require frozen section diagnosis to confirm the extent of resection. Extensive resection frequently necessitates technically demanding microvascular reconstruction, the access to which may be confined to specific centers. Preoperative planning based on imaging may help better refine decisions regarding reconstruction, resulting in appropriate referrals or arranging for a microvascular surgeon, ensuring better outcomes. Table 1 shows the imaging findings in OSCC relevant to management.

Imaging for monitoring/prediction of treatment response

Standard computerized tomography (CT), magnetic resonance imaging (MRI), and fluorodeoxyglucose positron emission tomography (FDG-PET) are frequently

Table 1: Imaging findings in oral squamous cell carcinoma relevant to management

Subsite	Imaging finding	Implication in management
Oral tongue	Tumor thickness/depth of invasion	Stratification of tumors by thickness might guide selection for elective management of the neck[14]
	Midline extension	Elective management of bilateral neck nodal basins[21]
	Tumor invading the sublingual space	Potential tumor spread to submandibular and parapharyngeal spaces[22]
	Floor of mouth involvement	Guide toward compartmental resection of the oral tongue and floor of the mouth for adequate surgical clearance[23]
	Bilateral neurovascular bundle involvement	May require total glossectomy and appropriate reconstruction[24]
	Vallecula or preepiglottic space involvement	Resectability needs to be carefully determined. A total glossectomy with resection of the supraglottic larynx is likely to cause severe postoperative aspiration and long-term tube dependence; in certain, selected cases total glossolaryngectomy a more suitable surgical option[25]
	Hyoid bone involvement	Requires en-bloc resection of adjoining hyoid bone for adequate surgical clearance
	Tonsillar pillar and oropharynx involvement	Extent of resection and resectability need to be carefully determined due to potential submucosal spread that may not be reliably identified through examination
Floor of the mouth	Bone erosion	Superficial cortical erosion of the mandible may be managed with marginal mandibulectomy, while significant erosion or medullary involvement requires segmental mandibulectomy[26]
	Paramandibular spread	Significant paramandibular soft-tissue spread even in the absence of cortical erosion of the mandible necessitates segmental mandibulectomy for adequate soft-tissue margins[27]
	Ventral tongue involvement	Extent of ventral tongue involvement determines the extent of en-bloc glossectomy required, and the ability to preserve the neurovascular bundles
	Skin involvement	Planning the extent of resection and mode of reconstruction
Lip	Submucosal spread	Planning the extent of resection and mode of reconstruction
	Bone erosion	Superficial cortical erosion of the mandible may be managed with marginal mandibulectomy, while significant erosion or medullary involvement requires segmental mandibulectomy[26]
Buccal	Masticator space involvement (cT4b)	Extent of resection required and resectability are key issues here; medial pterygoid and masseter involvement have better outcomes and are comparable to pT4a, while lateral pterygoid and temporalis involvement have worse outcomes and may need more extensive resections[4,28,29]
	Bone involvement	Extent of cortical erosion and paramandibular spread determine extent of resection required
	Maxillary involvement	Extent of maxillary resection determined
	Pterygopalatine fossa and intracranial involvement	Considered unresectable[4,28,29]
Alveolus	Extent of bone involvement	Extent needs to be carefully determined to prevent positive bony margins
Hard palate	Extent of bony involvement	Required to plan resection and reconstruction; extensive resections require microvascular reconstruction[30]
	Greater palatine nerve involvement	Required to plan extent of resection
Nodal disease	Preoperative determination of nodal disease	Required for neck dissection in contralateral neck node metastases and planning of adjuvant radiotherapy delivery
	Advanced nodal disease	Prevertebral fascia involvement and common carotid artery encasement (>270°) are considered unresectable[31,32]

used in the prediction of treatment response in head and neck squamous cell carcinomas (HNSCC) patients treated with nonsurgical modalities. These techniques lack sensitivity and specificity in evaluating treatment response, constraining their utility.[9-11] Due to the increased incidence of false positives immediately after chemoradiation therapy, follow-up FDG-PET scanning is only recommended after 12–16 weeks of the completion of radiation therapy, which may lead to "lost opportunity" for detecting treatment nonresponders.[12]

Imaging as a prognostic tool

Preoperative imaging has been shown to predict known prognostic determinants in oral cancer, such as bone involvement, nodal involvement, extranodal extension, and perineural invasion.[6] Although the sensitivity and specificity vary with the imaging modality and with several patient-related factors, reliable prognostic detail can be achieved for a proportion of patients. Capability to detect occult nodal disease remains suboptimal as a consequence of reduced specificity,[13] evidenced by a requirement to surgically stage the neck in apparently node-negative disease.[14]

There has been an increasing interest in newer imaging-based biomarkers, which show promise and have undergone various levels of clinical validation; for example, imaging-derived tumor thickness,[15-17] heterogeneity of the tumor,[18] and tumor volume.[19,20] Lack of standard data acquisition protocols as well as the need for sophisticated data analyses software for the derivation of quantitative parameters has hampered the translation of these techniques toward standard clinical practice.

CURRENT STATUS OF ORAL CANCER IMAGING IN INDIA AND CHALLENGES IN IMAGE ACQUISITION, ANALYSIS, AND INTERPRETATION

Cross-sectional imaging, including CT and MRI, is the standard of care for pretreatment workup, yet often lacks standardization. This is particularly problematic in countries, such as India, with heterogeneous service provision. Lack of streamlined referral processes frequently results in patients being imaged in any number of standalone imaging centers or institutions. Suboptimal image quality and lack of appropriate, standardized MRI sequences persist in many centers and can result in delayed and/or inappropriate treatment with consequent impact on patient outcome. Substandard imaging often also leads to cost escalation for patients/providers through a necessity for repeat imaging scans at designated treatment centers. Standardization of imaging-based diagnostic algorithms and imaging acquisition protocols is vital for a resource-constrained country like India.[33-35] Exemplars of imaging heterogeneity are:

Infrastructure variability

There is a wide variation in the scanning infrastructure across the country, ranging from single-slice CT scanners to state-of-the-art multislice CT scanners. The imaging acquisition protocols also vary, partly due to the absence of national guidelines or imaging protocols; most large head and neck cancer centers follow international guidelines with or without institutional modifications. Furthermore, there is no central Picture Archiving and Communication System for clinician access, meaning that these patients are referred with physical films or plates, assessment of images in multiplanar formats. This leads to a waste of resources and time for repeat imaging or inadequate clinical evaluation where repeat imaging is not feasible/not performed.

Lack of national head and neck imaging standardization

An acute shortage of subspecialty radiologists with adequate experience in the field of head and neck cancer imaging is apparent, due in part to the lack of dedicated head and neck imaging fellowships in India. Similarly, India lacks a national head and neck imaging body responsible for introducing and maintaining standards and quality assurance in reporting. Given the burden of disease in the subcontinent, general radiologists need to be well-versed with head and neck cancer anatomy despite lacking targeted head and neck training in their radiology residency programs, formalized curricula, or competencies for residency or fellowship training.

RECOMMENDATIONS FOR ROUTINE IMAGING IN ORAL CANCER

The role of plain radiography in OSCC assessment is limited to initial global impression in relation to clinically detected cancer and possible cortical bone erosion. Plain radiography has a place in the assessment of the dentition, overall configuration, status of pneumatization, and structures of maxilla and mandible, but has limited role in the routine evaluation of oral cancer.

More definitive imaging methods such as multidetector computed tomography (MDCT) and MRI are essential for improving structural details of the oral lesion and for further definitive staging of malignant lesions. MDCT is currently the single most important imaging modality of imaging oral cancer.[36] It has the ability to adequately evaluate the soft tissues, bony details, nodal anatomy, structures, and evaluation of distant disease spread. Wide availability, reasonable cost, and short duration imaging time make it a practical choice in comparison to MRI or FDG-PET.[37,38] By comparison to MDCT, MRI offers better contrast, greater soft-tissue details, and ability to gather wider tissue parameters and avoidance of ionizing radiation.

The necessity for contrast dye injection is common to both modalities; although uncommon, adverse reactions to contrast agents are seen for both CT and MRI contrast (CT utilizing nonionic iodinated nonionic low or iso-osmolar contrast agents like iohexol, iopamidol, iotralon, and MRI utilizing gadolinium-based agents typically). Similarly, optimal renal function is needed in both contexts.

Computerized tomography protocol

CT examination of the buccal mucosa should be performed using the puffed-cheek technique, where the patient is instructed to "blow out their cheeks" and keep them distended during the image acquisition.[39,40] This allows excellent visualization of the gingivobuccal sulcus, a common site due to tobacco chewing-related OSCC. The puffed-cheek method delineates lesions better that are otherwise not well seen with the cheeks at rest. CT examination of the oral cavity is typically performed in the axial plane with and without intravenous contrast from the level of the skull base to the diaphragm. Contrast-enhanced images should be acquired 20–25 s after contrast injection, from skull base extending caudally to the level of the diaphragm. One hundred to one hundred and twenty milliliters contrast agent is administered at a rate of injection of 2–3 ml/s. Volumetric data of 5 mm thickness are obtained. The initial demonstration of puffing the cheek followed by a trial of "puffing of the cheek" is rehearsed before the definitive examination. Images are reconstructed with soft tissue and bone algorithm with <1 mm reconstruction intervals. Thoracic dataset, which is used to screen for lung metastases, is processed separately with a field of view according to patient size. Images are reformatted in coronal, axial, and sagittal orientations. 3-D rendering of the surface of the lesion is performed with the preset options (3-D bone, neck 3-D, and other modified protocols). Volumes of 3-D images are viewed in the axial and coronal planes, with curved reconstructions performed for lesions in the anterior part of the oral cavity and around the retromolar trigone.[41,42]

There is an increased need to optimize and standardize CT technique and basic parameters of image acquisition since some of the prior examinations are performed at different medical facilities. Two essential imaging elements in CT imaging are to perform the examination with the puffed-cheek technique and acquire the volumetric 5 mm acquisition dataset from skull-base to the level of the diaphragm. Contrast amount and injection rates need to be standardized. Reporting template should be created with essential elements to be included in the proforma.

Magnetic resonance imaging protocol

Typical MR examinations for OSCC are performed on a 1.5T/3T scanner with 8 channel dedicated head–neck coil. Standard T1-, T2-weighted images and contrast-enhanced fat-saturated images are also acquired. A section thickness of 3–5 mm is optimal in most situations. For gross nodal assessment, section thickness of 5 mm is utilized. The puffed cheek technique can also be utilized in MRI. Additional techniques for improving the quality of images of the oral cavity involve utilizing spacers within the vestibule of the mouth to separate it from the teeth and the alveolar ridges. MRI is the preferred technique for lesions of the oral tongue, floor of the mouth, and lesions involving the bone marrow or having suspicion of perineural spread. Unless contraindicated, MRI examination should include contrast-enhanced images obtained in all three planes with fat-suppressed T1-weighted images. Gadolinium-based contrast agents are generally injected as an intravenous bolus injection, at a flow rate of approximately 2 mL/s.[43,44] MRI is also helpful in the early detection of perineural extension, detection of intracranial disease, and bone marrow involvement.[45,46]

Noncontrast magnetic resonance angiography, perfusion MRI, and spectroscopy offer additional options and information. MRI is particularly useful in evaluating the encasement of the carotid arteries. Perfusion-weighted MR imaging is finding increasing utility in the evaluating tumor response to therapy.[47,48] Evidence in support of the use of these modalities in the routine staging of OSCC is currently being sought.

Positron emission tomography computerized tomography imaging

PETCT imaging is most commonly performed using 18-fluoro-deoxy-glucose (^{18}FDG) with a dual-head contrast injector. The standard dose of ^{18}FDG is 5 MBq/kg body weight. In addition, full-dose intravenous contrast is used for the CT imaging unless contraindicated. PETCT is not often used as a first-line investigation in OSCC unless as part of the workup for an unknown primary malignancy, however it is useful in suspected metastatic disease.[49,50]

Additional imaging techniques

Ultrasonography is well established in the evaluation of the neck and is especially used for the assessment of thyroid and lymph nodes. Ease of use, universal availability, and noninvasive nature of the technique supports its use. However, as a technique, it remains constrained by interobserver variability and lack of clear imaging format, making it difficult for the referring surgeon to interpret the images. The importance of high-resolution ultrasound imaging in demonstration of the superficial tumor invasion, salivary gland/duct involvement is highlighted by some studies[51,52] but currently does not influence therapeutic decision-making.

Selection of appropriate/optimal imaging methods for oral squamous cell carcinoma

With the ideal protocols described above, any decision to utilize a particular imaging modality depends on the availability of imaging resources, local expertise, and on the clinical need for advanced, often specific information. Geographically, most of the disease burden of OSCC is in southeast-Asian countries, which are often resource limited. With this in mind, the following imaging selection protocol is proposed:

1. MDCT with intravenous contrast along with puffed cheek technique as the sole imaging modality in resource-limited regions
2. Optimized imaging choices depending on the clinical need in centers with state-of-the-art facilities:
    a. MDCT for lesions of the oral cavity, including retromolar trigone region
    b. MRI for the oral tongue, hard and soft palate, for advanced disease with bone marrow or skull base

involvement, or when there is an indication to exclude perineural spread

3. Nodal assessment is optimally performed with CT or MRI. In addition, ultrasound-guided fine-needle biopsy can be useful in defining involved cervical nodes
4. Chest evaluation is best undertaken with MDCT performed in concert with primary site CT. In an Indian context, it is important to consider other causes for pulmonary abnormalities such as tuberculosis
5. PETCT is the method of choice for evaluating distant metastases but is generally performed subsequent to initial staging cross-sectional imaging (MDCT and/or MRI).

RECOMMENDATIONS FOR A RESOURCE-CONSTRAINED SETTING

As India is a developing nation with a high proportion of patients resorting to out-of-pocket expenditure for their health-care costs, we also propose the following recommendations shown in Table 2 for a resource-scarce setting:

FUTURE PERSPECTIVES IN ORAL CANCER IMAGING

There is renewed interest in ultrasound with microbubble contrast technique for the examination of target lymph nodes.[53] High-resolution ultrasonography with dynamic contrast-enhanced examination of lymph nodes may emerge as an effective technique in the assessment of early nodal involvement by malignancy and response to chemotherapy. It has also been used to assess the depth of invasion of early oral and oropharyngeal cancer and assess margin status intraoperatively, however it has not been assessed on a large enough scale to determine reliability in routine clinical practice,[54]

Diffusion-weighted imaging (DWI) is a quantitative MRI technique that is sensitive to water-molecular diffusion within the tissue and has been extensively used in the brain. The apparent diffusion coefficient (ADC) parameter, which is derived from DWI, has been shown to correlate with cell density and brain tumor grade, making the technique potentially useful for the detection of OSCC as well as monitoring treatment response. Dynamic contrast-enhanced (DCE)-MRI, another quantitative MRI method, on the other hand, provides a window into the tumor hemodynamics and is sensitive to tumor blood flow and vascular permeability. Both DWI and DCE-MRI methods have been extensively used for predicting short- and long-term treatment response as well as overall survival in HNSCC patients.[55-64] DWI derived low baseline ADC[55-57,61,62] and DCE-MRI derived high baseline volume transfer constant (K^{trans})[55,57,58,60,63,64] as well as high mean intracellular water life time (τ_i)[19] from metastatic neck lymph nodes indicate improved prognosis in patients with HNSCC, and thus hold promise in the evaluation of OSCC as well.

PET imaging, although well established, has been rapidly evolving to improve diagnostic yield in OSCC patients. ^{18}FDG-PET has been used extensively to prognosticate OSCC and HNSCC of other subsites as well. In addition to SUV_{max},[65-68] other parameters such as metabolic tumor volume[69-72] and total lesion glycolysis[73-75] can accurately predict treatment response outcomes and survival. Higher pretreatment FDG uptake from the metastatic neck nodes using PET has been associated with the occurrence of distant metastases in HNSCC patients.[75] However, nonspecific and overlapping findings have also been reported with FDG-PET, thus raising doubts about its use as a reliable marker for predicting distant metastases.[76]

Newer techniques, such as magnetic resonance spectroscopy (MRS), have been incorporated into imaging[77,78] for improved sensitivity and specificity, however progress has been limited, due to the relatively lower sensitivity of MRS in comparison to MRI. Large multicentric collaborations are required to standardize these techniques for routine clinical work. Their cost and

Table 2: Recommendations for oral squamous cell carcinoma imaging in a resource-constrained setting

Imaging	Clinical scenario	Recommendation
Imaging of primary	Early tongue or buccal tumors (cT1/T2) with no clinical suspicion of bone involvement	Consider only clinical evaluation
	Advanced tumors (cT3/4) or other subsites	MDCT
Imaging of the neck	cN0 patients in whom cross-sectional imaging for primary is not being performed	Ultrasound of the neck
	cN+patients or those in whom cross-sectional imaging is being performed for the primary	Same modality is used for the assessment of the neck
Imaging of metastasis	Clinical evidence of metastases	Limited imaging to establish diagnosis (e.g., chest X-ray for lung metastases, ultrasound, and fine-needle aspiration for liver metastases)

MDCT: Multidetector computed tomography

technical expertise required for image acquisition and interpretation may also prohibit widespread implementation for routine use.

Machine learning approaches and their application to a population in need

Given the mismatch between the demand for and the supply of radiologists with expertise in head and neck cancer, the appeal of machine learning approaches to the Indian scenario is apparent. Automated interpretation of imaging allows for reduced burden for reporting specialists and more efficiency, with potentially speedy and appropriate referral based on the treatment facilities required; this is often an issue in the developing world with significant loss of time and money in the referral pathway.[79] Machine learning approaches also have the potential to reduce cost of imaging,[80] another important consideration in resource-constrained environment.

The development of these machine learning-based approaches requires the acquisition of large standardized high-quality imaging datasets, for both training and validation.[81] But given the incidence of OSCC in the Indian subcontinent, concerted efforts between comprehensive cancer centers would allow for standardization of image acquisition through well-established protocols, which would yield large high-quality datasets that can address critical prognostication questions, form the basis of imaging-based clinical trials and use machine-learning-based approaches to address automated reporting.

CONCLUSION

Oral cancer imaging remains a vital part of the management of this highly prevalent cancer. Standardization of image acquisition and interpretation has the potential to reduce pretreatment delays and streamline management, resulting in improved outcomes and reduced health-care-related expenditure. The establishment of a standardized imaging network can also pave the way for machine learning algorithms and multicentric clinical trials in the subcontinent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Disclosure

This material has never been published and is not currently under evaluation in any other peer-reviewed publication.

Ethical approval

The permission was taken from the Institutional Ethics Committee before starting the project. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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