## Review  Article

# Application of PET/CT in the Diagnosis of Oral Cancer

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### A R T I C L E  I N F O
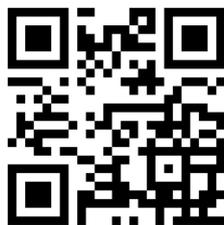
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### A B S T R A C T

Nuclear medicine is one of the latest and cutting edge innovations in the diagnosis of Head and Neck Cancer. The extensive development of fusion imaging that can acquire both anatomic and functional images in a single scan has been a true evolution in medical imaging. Nuclear medicine aids in imaging the metabolism and other physiological process of specific organism human beings and thereby unveils the various functional and biochemical processes with accuracy which makes it a very dynamic and powerful tool in diagnosis and treatment of diseases. The purpose of this review is to discuss the application of nuclear medicine studies in the diagnosis of Head and Neck cancer..

### Introduction

Nuclear medicine is a medical specialty in which radioactive materials are used for diagnosis by imaging and non-imaging techniques and for therapy in many disease processes.

In nuclear medicine procedures, radionucleidesare combined with other elements to form chemical compounds, or else combined with existing pharmaceutical compounds, to form radiopharmaceutical. These radiopharmaceuticals, once administered to the patient, can localize to specific organs. This property of radiopharmaceuticals allows nuclear medicine to image disease process in the body, based on the cellular function and physiology, rather than physical changes in the tissue anatomy.[1]

Nuclear medicine is "endo-radiology" because it records radiation emitting from within the body rather than radiation that is generated by external sources like X rays.  Nuclear medicine imaging Studies are generally more organ or tissue specific (e.g.: lungs scan, heart scan, bone scan, brain Scan, etc.) than those in conventional radiology imaging, which focus on a particular section of the body (e.g.: chest X-ray, abdomen/pelvis CT scan, head CT scan, etc.).[1]

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## Hybrid scanning techniques

Nuclear medicine scans can be superimposed, using software on CT or MRI to highlight the part of the body in which the radiopharmaceutical is concentrated. This practice is often referred to as image fusion, for example SPECT/CT and PET/CT. The fusion imaging technique in nuclear medicine provides information about the anatomy and function, which would otherwise be unavailable, or would require a more invasive procedure or surgery.[2]

## Nuclear Imaging

Radioisotope imaging is based upon making the tissues radioactive and the patient becoming the source of ionizing radiation. This is done by injecting certain radioactive compounds into the patient that have an affinity for particular tissues — so-called *target tissues.* The radioactive compounds become concentrated in the target tissue and their radiation emissions are then detected and imaged, using a gamma camera.[1]

This investigation allows imaging the function of the target tissue to be examined under both static and dynamic conditions. Areas where uptake is good-image demonstrates positive uptake or a "hot spot"and areas of non-uptake refereed as "cold spot". Both cold and hot spots are significant for the presence of disease. Innuclear medicine procedures ionizing X-rays with energies of 20-510 Kev is used to generate an image. The patient, rather than machine, is the source of radiation.The sensitivities of nuclear medicine imaging are high. The specifity of nuclear medicine procedure is low.[1]

## Positron Emission Tomography

PET is more advanced imaging modality , sensitivity 100 times than that of gamma camera, relies on positron-emitting radionuclides, was discovered by Dr. David Townsend & Dr. Ron Nutt Invented in 1970 Nuclear imaging lack accurate anatomic landmarks for precise localization and characterization of findings, despite the fact that specific radiopharmaceuticals are used for assessment and diagnosis of specific disease processes. These considerations explain why morphologic (CT) and functional imaging modalities (SPECT and PET) are complementary and not competing techniques. Diagnosis and characterization of disease by both CT and MRI imaging is based on morphologic criteria such as size, texture and tissue attenuation. CT and MRI provide information regarding changes in organ size and tissue density, as well as their precise spatial localization and topographic landmarks. PET imaging, on the other hand, is based on the bio-distribution of a radioactive agent over time and space, enabling visualization of dynamic physiological and pathophysiological processes that define the functional characteristics of disease. To overcome this limitation so these hybrid modalities allow in a single diagnostic procedure a combined evaluation of function and structure, while obtaining the most from each modality.[3]

**PET/CT PET produces a** three-dimensional picture of functioning processes in the human body, allowing for the evaluation of tissue metabolic activity. In PET a positron emission radionuclide or tracer are able to track a specific biologic process at molecular level which is injected into the patient. As these radioactive tracers decay, they emit positrons, which are then

detected using a PET scanner. The resulting images will help distinguish between normal and abnormal cellular/molecular activity. Positron emitters are radionuclides like fluorine-18, carbon-11, oxygen-15 and nitrogen-13, which in their non-radioactive state are normal constituents of all biologically active molecules.[4]

## How PET works:

A simple way to describe the tumor growth process is that tumors need to divide, multiply and invade the neighboring structures or tissues and spread to distant sites, a process called metastasis. To grow and metastasize, tumors require energy and the utilization of glucose – the fuel used by the body to produce energy - provides the necessary elements for this activity. While normal cells use glucose, there is an increased consumption of glucose within tumour cells. Fluorine-18, a glucose analogue like FDG is used as a tracer because flourine-18 is quick to decay, thus limiting patients radiation exposure and it is also a natural indicator of cellular metabolic state, particularly increased in cancer cellular deposits and therefore easily detectable In diagnosing cancer with PET/CT, the most commonly used biologically active model is F18-FDG, a glucose analogue labeled with a radioactive element, the positron emitter fluorine-18, which allows the evaluation of glucose metabolism in normal and abnormal cells.[4]

## Role of PET/CT in Oral Cancer:

Oral cancer constitutes about 3-4% of all cancers in western industrialized countries, mainly affects middle aged people, and is more common in men than in women. In India where the habit of chewing tobacco with betel nut, reverse smoking and alcohol usage are common , there is a striking incidence of oral cancer which accounts for as many as 30-40% of all cancers. Increasing incidence of oral cancer necessitates in depth probing of various investigating and treatment therapies for better prognosis and treatment of the disease.

The most common sites in head and neck cancers are larynx, tongue, floor of the mouth, tonsils, and salivary glands, although these carcinomas can arise in almost any location in the nasopharynx, oropharynx, or hypopharynx.[5]

Most head and neck cancers are relatively advanced at the time of presentation; less than one-third is Stage I or II. The staging, treatment, and prognosis are tumor dependent, but as with most other tumors, early detection and treatment offer the best chance of long-term survival. The vast majority (>75%) of these cancers occur in theventral surface of tongue or within the tonsillar fossa.

Role of PET/CT in head and neck cancer is staging primary head and neck cancer, Identifying sites of recurrence, Distinguishing postoperative change from residual disease, Finding the site of an unknown primary tumor, Assessing the response to therapy and acting as a prognostic tool.[6]

## FDG uptake by different anatomic structures in oral cavity:

Low to moderate FDG uptake occurs in the tonsils and at the base of the tongue because of the physiologic accumulation in the lymphatic tissue in Waldeyer's ring. Variable but usually low FDG uptake is visible in the salivary glands, which physiologically secrete low amounts of glucose. A moderately increased FDG uptake can be seen in the anterior part of the floor of the mouth corresponding to the genioglossus muscle,

which prevents the tongue from falling back insupine patients. Muscular uptake can be seen in the masticator muscles, the tip of the tongue, and muscles of the face, neck, and larynx in nervous patientsand in patients who speak during the FDG uptake phase. In nervous patients,muscular uptake can be avoided by using medication, such as diazepam, for musclerelaxation. If patients do not close their eyes during the study, muscles of the eyes and eyelids will also show increased uptake.[7]

**Staging of head and neck cancer:**

Head and neck cancers are staged according to the TNM classification.  Although the description of T-stage varies withthe site of the primary tumor, generally tumors <2cm are staged as T1, 2–4 cm as T2, >4 cm as T3, and tumors invading into adjacent neck structures are staged as T4. Cervical nodes are staged as N1 for a single ipsilateral node<3 cm, N2 indicates single or multiple nodes between 3 and 6 cm, and N3 refers to node(s) >6 cm in thegreatest dimension. The nodes are considered to be metastatic if>15 mm for jugulodigastric nodes and >10 mm for other neck nodes. In addition, roundshape with central necrosis, presence of more than three nodes or presence ofextracapsular invasion also indicates metastatic disease Metastatic disease, which is most commonly seen in the lungs, bone, and liver, results in an M1 designation.

The sensitivity of 18 F-FDG PET for the detection of cervical nodal metastasis on alevel-by-level basis was significantly higher than that of CT/MRI, whereas their specificities appeared to be similar. Visual correlation of 18 F-FDG PET and CT/MRI showed a trend of increased diagnostic accuracy over 18 F-FDG PET alone. [8,9]

FDG uptake in a lymph node is significantly more accurate in predicting nodal metastases. In comparative studies, sensitivity and specificity of PET in detection of nodal metastases was found between 70–100% and 82–94%, respectively, compared to 58–85% and 58–96% for CT/MRI. FDG PET may be falsely negative in small nodes <1 cm in diameter or in completely necrotic nodes. False-positive FDG uptake in cervical nodes can be due to inflammation.[5]

Theclinically negative neck (N0 neck) is particularly challenging. Only 25–30% of patients with N0 neck are found to have metastatic neck nodes at surgery. This means that the majority of patients with N0 neck undergoing a potentially morbid neck dissection are unlikely to benefit from this procedure.[5,10]

**PET in detection of distant metastasis**

PET has made a major impact on the detection of distant metastases in NasoPharyngeal Carcinoma patients with primary lesions and stage M0 disease, especially those who also have stage N2–3 disease. Because of the higher incidence of distant metastases in patients with recurrent NPC than in those with primary tumors, 18 F-FDG PET is also recommended for assessing recurrent NPC before embarking on salvage therapy.[11]

A major advantage of FDG PET over conventional imaging in pretherapy staging of

head and neck cancer is its ability to detect synchronous and/or metastatic disease in the chest and Abdomen.[12]Several studies suggest thatPET finds unexpected distant metastasis in approximately 10% of patients with locally advanced head and neck cancer.[5] The pattern of normal FDG uptake in the Head &Neck region iscomplex, and the combination ofanatomical

and functional information seen in PET/CT has enabled these patterns to be more clearly defined.[13]PET/CT has established itself as important in the detection of local recurrent disease aftertreatment of head and neck cancer. This is important because detection and treatment of this recurrent disease can improve the survival and the quality of life of the patient.[13]

**Carcinoma of Unknown Primary tumor:**

The other indication of FDG PET/CT in H&N cancer is in the detection of an unknown primary tumor .[13, 6]

Cervical nodal metastases from an unknown primary tumor constitute approximately 2% of newly diagnosed head and neck cancers. The most common sites of the primary tumor are tonsil and base of tongue.[5]This modality should be used when a patient presents with enlarged nodes in the neck and the biopsiesshows an epithelial cancer but the primary tumor cannot be found after clinical examination, panendoscopy, CT scan, and possibly MRI scan.[13]These patients are routinely treated with wide-field radiation therapy, which includes the entire pharynx, larynx, and bilateral neck. The wide-field irradiation definitely reduces the risk of tumor recurrence; however, it causes significant effect on morbidity rate of patient. Correct localizationof the primary tumor substantially reduces the complications associated with radiotherapy by decreasing the size of the radiation portal and may also improve survival. Even after an extensive workup the detection rate of the primary tumor is <50%.[5]

**Detection of Residual and Recurrent Disease after Treatment**

Early detection of recurrent head and neck cancer is important because the disease-free survival after salvage surgery is highly dependent on the stage of the recurrent tumor. Diagnosis of recurrence is difficult with CT or MRI because of the loss of symmetry and inflammation associated with healing from surgery and with radiotherapy. Routine biopsy of treated areas is also not recommended because of increased risk of bleeding and infection in irradiated tissue and potential false-negative biopsies due to sampling errors. FDG PET is more sensitive and specific than CT or MRI in detection of residual or recurrent disease.[5]

The role of PET in the follow-up of head and neck cancer was reviewed in a meta-analysis by Isles et al.[12]The mean pooled sensitivity and specificity of FDG PET for recurrent disease at primary site following radiotherapy or chemoradiation therapy was 94 and 82%, respectively.The sensitivity and specificity for FDG PET in the assessment of the treatment response in the neck was 86 and 97%, respectively.

Appropriately timed post treatment PET may be useful in predicting outcome after definitive RT and in distinguishing viable tumors from normal tissue changes after Radiotherapy in patients with head and neck carcinomas.PET studies at 4 months after completion of Radiotherapy may more accurately reflect disease status.[14]

**Radiotherapy Planning:**

FDG PET-CT is beginning to be used frequently as an adjunct to radiotherapy treatment Planning. Incorporation of FDG PET into radiotherapy planning may significantly alter the target gross tumor volume (GTV). The GTV may be increased because a metabolically active tumor can be detected in normal sized nodes. The PET-based GTV may be

smaller than CT-based GTV in some patients because the tumor may not be metabolically active in its entirety or because of benign enlarged nodes that are not hypermetabolic.[5]Combining structural and metabolic information with coregistered CT–FDG PET using a dedicated scanner might be the method of choice in the future.[15]

**Conclusion:**

The key utilization of molecular imaging is in the interrogation of biologic processes in the cells of a living subject in order to report on and reveal molecular abnormalities that form the basis of disease. Molecular imaging with radiolabeled tracers along with PET/CT and SPECT/CT currently plays a pivotal role in the management of patients with cancer. It assists in choosing the most appropriate therapy by refined staging, it evaluates the response to both chemotherapy, be it cytotoxic or cytostatic, and radiotherapy, and finally it contributes to the early detection of recurrence. The use of PET-CT for the definition of biological tumor volumes and "dose painting" in radiotherapy planning holds promise for less toxic but more efficient tumor control, although long-term confirmation is still required.

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