**Nuclear imaging: A trendy imaging modality in dentistry.**

**I. Introduction:**

World Health Organization (WHO) considers NM as an autonomous imaging modality and is defined as combining the applications of different radioactive materials in the diagnosis or treatment of the disease, and the research in the field of medicine [1].

Nuclear medicine is the specialty of medical science and imaging which uses radionuclides/ radioisotopes that depend on the radioactive decay process in the diagnosis and treatment of disease [2]. Nuclear imaging assesses both the physiologic/biochemical changes and helps in differentiating between metabolically dying or deceased cells and those, that are actively metabolizing, which in turn helps in detecting lesions before morphologic change is evident [3].

NM uses very small amounts of radioactive materials (radiopharmaceuticals) to diagnose and treat diseases. Radiopharmaceuticals are introduced into the patient usually by intravenous injection, swallowing & inhalation. Radio pharmaceuticals also known as Radio nuclides/ Radioisotopes are unstable atoms of a chemical element, which have a different number of neutrons in the nucleus (same number of protons and the same chemical properties). The existence measured in “half-lives [3].”

The applications of nuclear medicine in dentistry are not understood completely. This chapter emphasizes the basic principles of various nuclear imaging modalities and their applications in the oral and maxilla-facial region. The diagnostic features of NM in the field of the oral and maxilla-facial region should be taken into consideration and dentists should be provided with an insight into the various aspects of this specialized field of imaging for the perfection of diagnosis, treatment, and proper follow-up[4].

**II. History:**

Chemistry Nobel Prize winner Georg Charles de Hevesy was the first to use radioactive isotopes to study the metabolic processes of plants and animals [7]. Hermann Blumgart was the first to perform human use of radioactive tracers in 1925. He measured the "velocity of the circulation" by measuring the time it took the injected solutions of radon to flow from one arm to another. He carried out his experiments in animals with Bismuth-210, injecting it intramuscularly in rabbits to follow the dynamic behavior of the tracer. De Hevesy is the father of nuclear medicine[Wagner HN][16].

The discovery of artificial radioactivity in 1934 and the production of radionuclides by Oak Ridge National Laboratory for medicine-related use in 1946 [2].

Nuclear medicine's golden era of recognition by the medical community began in 1946 when a successful treatment of thyroid cancer using radioiodine (I-131) was done by Henkin RE et al [17].

Many radionuclides are discovered for medical use, Technetium-99 discovery by C. Perrier and E. Segre in 1937 is the most widely utilized element in different nuclear medicine imaging studies. Pioneering works by Benedict Cassen in developing the first rectilinear scanner and Hal O. Anger’s scintillation camera (Anger camera) broadened the young discipline of nuclear medicine into a full-fledged medical imaging specialty. More recent developments in nuclear medicine include the invention of the PET. PET/CT imaging is now an integral part of oncology for diagnosis, staging, and treatment monitoring [2].

**III. Different types of Radio-nuclide imaging:**

A. Scintigraphy

B. PET

C. SPECT

D. Fusion imaging

 a. PET-CT

 b. PET-MRI

 c. SPECT-CT

E. Lympho-scintigraphy

**A. Scintigraphy:**

The word “Scint” in Latin refers to “spark”. Bone scintigraphy is a functional imaging technique that can detect osteoblastic changes with only a 10% change above the normal value [3].

Bone scintigraphy is done by injecting Technetium-99m- methylene diphosphonate [Tc-99m-MDP] with 140 KeV gamma energy. It has a short physical half-life of 6 h and has a high ratio of up to 40% affinity to the hydroxyapatite [2]. Tc-99m-MDP undergoes chemisorption and binds to the bone matrix. The underlying principle is that Tc-99m-MDP tends to accumulate in areas of active or high bone turnover, depending on the degree of osteoblastic activity and the presence of vascularisation [3, 7].

Diseases that occur due to increased metabolic activity /high new bone formation/ or increased turnover, appear as areas of increased tracer uptake, known as “hot spots.”Inactive metabolic conditions decreased or lack of new bone formation, or reduced blood supply appear as "Cold spots" on bone scans [5]. Image acquisition involves a computed scintillation camera that records the gamma rays emitted by the patient. The camera has a scintillation crystal that fluoresces at the time of interaction with the gamma rays. This fluorescence is detected by photomultiplier tubes, which transform the flashes of light into electronic signals to produce an image that is displayed on a computer monitor[4].

Bone scans include Standard Bone Scan, 3-Phase Bone Scan, and SPECT. Standard bone scan employs capturing of static images 3 hours after injection of a radiopharmaceutical. The 3-phase study comprises a flow assessment, a blood pool image, and delayed static views acquisition. The dynamic flow study requires rapid sequential images for sixty seconds during the intravenous administration of the radiotracer. This is followed by a blood pool image reflecting tissue hyperemia and is acquired immediately after the flow study. Three hours after radiotracer administration, the bony uptake of technetium-99m labeled diphosphonates is maximal, and a significant proportion of the unbound tracer will have been excreted by the kidneys [11].

SPECT studies entail acquiring rotating delayed static images, generally, sixty-four projections over 360º, followed by computer reconstruction to provide three-dimensional multiplanar slices in the axial, coronal, and sagittal planes, relative to the patient's body [4]. Any pathology involving an osteoblastic response such as infection, inflammation, primary or secondary tumors, metabolic bone disease, or trauma will manifest as increased uptake on a bone scan [5].

**Indications of scintigraphy:**

1. Pre-operative evaluation of the malignant lesions.
2. Initial changes in the TMJ joint lead to joint disc abnormalities.
3. Salivary scintigraphy helps in measuring the fluid movement in acinar glands.
4. To assess the extent of bone activity in fibro-osseous lesions,
5. Inflammatory lesions of the jaws.
6. Cysts of the jaws.
7. Fractures.

**B. PET:**

Detects altered metabolism in biological tissues. PET uses tracers that target physiological mechanism such as glucose metabolism and enables imaging and quantification of cellular function [1].

The emergence of PET as a choice for diagnosis, tumor and nodal staging, monitoring the prognosis of therapy, and assessment of recurrence in cancer has led to an increasing demand for advanced imaging technology [3].



 **Fig: 1 Basic mechanism of PET**

A PET scanner contains several rings of detectors around the patient. The detector's crystals are often made of bismuth germanate. Electronically coupled opposing detectors simultaneously identify the pair of photons by using coincidence detection circuits that measure annihilation events within 10-20 ns. The annihilation reaction occurs along the line where two detectors join. Raw PET scan data contains coincidence lines, which are recognized as projections. The data is processed using back projection and iterative reconstruction algorithms to form several contiguous axial slices. PET computer then reconstructs the transverse images from the projection data [6].

**Fig. 2. Annihilation coincidence detection (ACD).**

 When a positron is emitted by nuclear transformation, it scatters through matter losing its energy, and annihilates with an electron, resulting in two photons that are emitted in opposite directions (left). When two interactions are detected simultaneously, assumed that annihilation occurred on the line connecting the interactions (line of response, LOR). ACD acts as a collimator for the positron emission tomography (PET) scanner by determining the path of the detected photons.

Commonly utilized PET radioisotopes include 11C, 13N, 15O, 18F, 64Cu, 124I, and 89Zr. These radioisotopes may be used to label more organic compounds (such as glucose, amino acids, neurotransmitters, DNA nucleosides, antibodies, etc.), which permit non-invasive, whole-body molecular imaging of tumor biology [5].

Most clinical applications of PET scans have employed 18F-labeled fluoro-2-deoxyglucose (18F-FDG), which is a glucose analog radio-pharmaceutical with a half-life of 110 min and is mostly used for studying brain and heart glucose metabolism and detecting cancer metastases [6].

The uptake of 18F-FDG is based on the 'the Warburg effect' - neoplastic cells do not obey normal homeostatic control mechanisms that regulate growth and metabolism, thus they consume large amounts of glucose to fuel their growth and hypermetabolism. 18F-FDG PET/CT is now a key diagnostic tool in oncology, including in (H&N) head and neck cancer [5].

Standardized uptake value (SUV) is used in PET imaging for a semi-quantitative analysis, calculated as a ratio of (1) the mean region of interest (ROI) activity in mega-becquerels per milliliter and (2) the injected activity in mega-becquerels, divided by the body weight in grams [6].

**Clinical applications of PET;**

1. Oral squamous cell carcionoma.
2. Detect pathology earlier than a CT scan or MRI, a stage when no palpable nodes in the neck.
3. Response to tumor treatment, diagnosing recurrence, residual pathology, and distant metastases are effectively done by PET scan.

**C.** **Single-Photon Emission Computed Tomography [SPECT]:**

Uses gamma rays and is very similar to a gamma camera with its ability to provide true 3-dimensional information. Most radiopharmaceuticals used in nuclear medicine and SPECT are labeled with radionuclides that emit photons [1]. SPECT uses single photon gamma-ray emission as the source of information, rather than X-ray transmissions as used in conventional Computed Tomography. SPECT is similar to PET and uses radioactive tracer material and detection of gamma rays. The tracers used in SPECT emit gamma radiation, which is measured directly, whereas in PET tracers emit positrons that annihilate with electrons up to a few millimeters away, causing two gamma photons to be emitted in opposite directions at 1800 to each other[3].

Nagamachi et al investigated the usefulness of Thallium 201 (201TI) SPECT in 18 head and neck cancer patients and noted that all the primary tumors and cervical metastatic lymph nodes had shown increased uptake in both early and late images but did not show any correlation with the tumor size and its histological type (Nagamachi et al.1996) [13].

**D. Fusion imaging:**

Fusion imaging is the amalgamation of various advanced imaging modalities used in oral and maxillofacial imaging today, which takes a lion's share in improvising diagnostic and formulation of effective treatment outcomes [14].

**Fusion imaging commonly includes**:

a. Positron emission computed tomography (PET CT)

b. Positron emission tomography-magnetic resonance imaging (PET-MRI)

c. SPECT-CT

d. SPECT- CT with scintigraphy

**a.Positron emission computed tomography(PET-CT)**

Dr. David Townsend, an imaging physicist in 2000 working at the University of Pittsburgh, actually put the two units together in one gantry. This allows for the immediately sequential collection of both the PET and the CT data sets, with minimal potential for mis-registration [14].

Hybrid PET/CT imaging allows fusing the anatomic data of CT with the functional information of PET, offering improved localization of metabolic abnormalities and thus, more accurate detection of malignant lesions in the head and neck. In the post-therapy setting, the PET/CT helps in differentiating a recurrent or residual tumor from post-therapy inflammatory changes [6].

PET/CT is highly sensitive (>95%), for identifying malignancy in the head and neck region. The diagnostic performance for the detection of the primary tumors in the oral cavity was 96.3% for PET/CT, 77.8% for CT, and 85.2% for MRI. The fused PET/MRI images offered higher sensitivity and specificity to the presence of malignancy, when compared with MRI and PET separately [1].

There has been growing relevance in the use of PET/ CT-guided intensity-modulated radiotherapy (PET/CT-guided IMRT) for tumor contouring, for accurate delineation of the target volume, and for sparing normal tissues from effective radiation therapy, because of its ability to provide both anatomic and functional information [6].

**Indications of PET/CT scan [7]:**

a. To differentiate between benign from malignant lesions.

 b. Identify the unknown primary tumor if metastasis is the first tumor manifestation or if the para-neoplastic syndrome is present.

c. Staging of a known tumor condition.

 d. Determine response to therapy in the case of known tumors.

e. Assessing the presence of residual tumor disease.

f. Determining recurrence, for example, with increasing tumor marker concentration.

 g. Selecting the exact site for biopsy.

h. Help with radiotherapy planning and non-oncological issues.

**Contraindications of PET –CT [7]:**

a. Children below 2 years of age.

b. Pregnant women.

c. Persons over 60 years of age.

d. Persons with complications after the previous administration of a contrast medium.

e. Persons with acute and chronic circulatory and respiratory failure.

f. Persons with hepatic and renal failure (also dialyzed patients).

g. Persons with asthma and pulmonary edema.

h. Persons with allergies.

**Advantages of PET –CT scan**

1. Provides anatomic and functional details, accurately.
2. Less expensive.
3. Less time-consuming.
4. Provides minimum inconvenience to the patient.

**Disadvantages of PET –CT scan**

1. Pregnant women are unsuitable for a PET CT scan
2. More radiation exposure.

**b. Positron Emission Tomography-Magnetic Resonance Imaging (PET-MRI);**

PET/MRI is a fusion imaging technology that incorporates both MRI soft-tissue morphological imaging and PET functional imaging. About Nodal-staging, PET/MRI does not seem to be beneficial when compared with PET/CT but provides similar N-staging accuracy when applied as a whole-body staging approach (Buchbender et al. 2012) [3].

The idea of combining PET and MRI imaging devices in a single system was first suggested in the early-mid 1990s (Hammer 1990, Hammer et al 1994). PET detectors capable of measuring strong magnetic fields (Shao et al 1996) and prototype MRI-compatible PET scanners capable of imaging small animals simultaneously with MRI started to appear soon (Christensen et al 1995, Shao 1997). Only after about 15 years of development, human systems capable of sequential (Zaidi et al 2011) or simultaneous PET and MRI acquisitions of the whole body become available commercially (Delsoet al 2011) [14].

**Indications of PET –MRI [14]:**

1. Soft tissue tumors

2. In pediatric patients in turn reduction of radiation exposure

3. TNM staging

**Absolute contraindications of PET-MRI [14]:**

a.Implanted electric and electronic devices are a strict contraindication to magnetic resonance imaging, and in particular: Heart pacemakers (especially older types)

Insulin pumps

Implanted hearing aids

Neuro-stimulators

Intracranial metal clips

Metallic bodies in the eye.

**Advantages of PET-MRI**

1. Better soft tissue contrast.
2. Non-ionizing radiation.
3. Exposing patients to high doses of ionizing radiation forms the main drawback of PET-CT. Researchers have reported a single exposure of PET-CT to be almost equivalent to 1-year dosage of

Extra-terrestrial radiation.PET–MRI in this aspect proves to be a better imaging modality by providing detailed, efficient, accurate, morphological, and functional details in a 30 to 60-minute examination.

**Disadvantages**

1. Expensive.
2. Diagnostic inaccuracy.

**c.Single positron emission computed tomography (SPECT-CT):**

SPECT combination with CT enables a direct correlation of anatomic information and functional information, resulting in better localization and definition of scintigraphy findings [1].

Vermeeren et al determined the additional value of single photon emission computed tomography with CT (SPECT/CT) for detection and localization of sentinel nodes in 38 patients with melanoma of the head and neck and reported that SPECT/CT had depicted an additional sentinel node in 16% of the patients and clearly showed the anatomic location of the nodes in all patients (Vermeeren et al. 2011) [3].

The first SPECT/CT system combined a dual head g-camera and an integrated x-ray transmission system mounted on the same gantry. The CT image is used for attenuation correction in addition to anatomic imaging, and the CT and SPECT images are fused with computer assistance, for display [14].

**Advantages;**

1. Good image quality with high spatial resolution, contrast, and improved signal-to-noise image characteristics of SPECT.
2. Determination of anatomy and extension of lesion.
3. Accurate anatomic location of the lesion from CT.

**Disadvantages:**

1. Artifacts are more.
2. Additional knowledge is required for accurate interpretation.

**d.SPECT- CT with scintigraphy:**

Software fusion to co-register SPECT with CT and MRI has been explored with good results, although it is time-consuming and not practical for routine clinical use. The awareness is growing in the literature that, SPECT/CT applied to bone scintigraphy improves diagnostic performance, primarily by increasing specificity for better distinguishing between benign and malignant processes. SPECT/CT combines the high spatial resolution of CT and high sensitivity of SPECT, which is useful for postoperative complications and for assessment of low back pain, bone infections, and chronic benign diseases of the joints [14].

**E. Lymphoscintigraphy:**

Lymphoscintigraphy involves the acquisition of plane and tomographic images after injecting a suitable radio-pharmaceutical usually technetium 99m through lymphatics. The goal of lymphoscintigraphy is to identify and localize all sentinel lymph nodes(SLNs) for surgical biopsy. The SLN is the first lymph node receiving drainage from the primary tumor. In case the SNL has no signs of any malignancy, the remaining lymph nodes are highly likely to be negative as well. The removal of only the SLNs eradicates the need for the removal of other lymph nodes and thus reduces the accompanying side effects and thus improves prognosis [11].

Lymphoscintigraphy is showing excellent promise in oral malignancies and is an interesting scan modality. The radioactive contrast is taken up through lymphatic channels to the first level of draining lymphatic area, Which is generally called the sentinel node and lymphatic spread pattern [9].

Lymphatic mapping can be performed well by either using radio-labeled tracers or vital blue dye (VBD). In conventional lymphoscintigraphy, the main tracer used is technetium 99m-labeled radio colloids and the most widely used radiotracer in the United States is technetium 99m-sulfur colloid, and in Europe, technetium 99m-albumin-based nano colloid is used. They both lack optimal rapid clearance of the injection site, high accumulation within the first node, and minimal tracer uptake in the distant nodes [7].

**Advantages of nuclear medicine [3]:**

a. Diagnosis before any morphologic changes occur.

b. Primarily gives images of function, including physiology, biochemistry, or metabolism, by analyzing the dynamic behavior of molecules in organs and tissues at different levels.

c. With the help of interactive display it allows easy demonstration of whole body images, which helps in detecting the metastatic activity.

d. After the injection of the tracer isotope, detailed examinations can be performed on different sites and at different times to elucidate findings without repeated radiation exposure.

**Disadvantages of nuclear medicine [3]:**

1. As compared to other imaging modalities (CT/MRI) the spatial resolution is in general poor.
2. The cost of the machine used is relatively high.
3. The cost of examination is also high and depends on the cost of radiopharmaceuticals used.
4. Patients are exposed to ionizing radiation administered to their bodies.
5. Radionuclides administered to the patient cause internal whole-body exposure in a non-uniform manner determined by the biodistribution and clearance kinetics of that tracer.
6. There is a risk of unavoidable high irradiation from PET tracers to the personnel when interacting with

**Conclusion**

Nuclear diagnostic Techniques are being used commonly in routine practice, and dentists need to be familiar with commonly used scans in nuclear medicine concerning oral lesions.

Nuclear medicine imaging techniques have evolved as a routine diagnostic method to evaluate the osteoblastic activity around implants and in periodontal disease, also to identify the fractures, benign and metastatic tumors, bone grafts, and TMJ disorders at a very early stage, and thus aids to bring about an intervention therapy. Bone scan,

SPECT imaging and PET scans are techniques that help in diagnosing Oral/dental pathologies and tumors in the surrounding periodontal/oro-maxillary regions, which may have to be dealt with by dentists at initial stages, though may later require an oncologist.

 Nuclear medicine is an ideal specialty to adapt to the new discipline of molecular medicine, because of its emphasis on function and its utilization of imaging agents that are specific to a particular disease process.

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