

## Nuclear medicine in Maxillofacial Imaging -a review

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### Abstract

Nuclear medicine studies often play a significant role in the diagnosis and treatment of oral and maxillofacial diseases. While not commonly used in everyday dental practice, the dental provider should have a conversational knowledge of these imaging modalities and understand the indications and limitations of these studies. The purpose of this review is to discuss the nuclear medicine studies that have applications in the head and neck region as well as their indications, limitations, and diagnostic conclusions that can be drawn from these studies.

**Key words:** Radionuclides, Anger camera, Scintigraphy, Fluorodeoxyglucose(FDG).

### Introduction

Nuclear medicine and radioactive tracers have considerable application in dental research, because they provide one of the few practical methods for studying the limited metabolic activities of bones and teeth. The ease with which minute amounts of these radioactive materials may be accurately measured and distinguished from the mass of inert element in the tooth is particularly valuable. They are useful in studying many problems of calcification and mineral exchange. There are also opportunities of their use in investigating fluorosis, caries protection, periodontal disease, micro leakage studies of dental materials, root resorption, nutritional, and endocrine effects, as well as numerous other dental problems. Other usages of nuclear medicine in dentistry are listed Age written in teeth by nuclear tests, scintigraphic evaluation of osteoblastic activity, and evaluation of osteoblastic activity around dental implants using bone scintigraphy. Nuclear medicine can be an indicator of "active" alveolar bone loss. Nuclear medicine techniques are used as an adjunct for the diagnosis of benign tumors, carcinomas, osteomyelitis, hair line fractures, microinfarcts in the bone marrow spaces and temporomandibular joint disorders.

Nuclear medicine is a branch or specialty of medicine and medical imaging that uses radionuclides and relies on the process of radioactive decay in the diagnosis and treatment of disease.<sup>1</sup>

The multidisciplinary nature of nuclear medicine makes it difficult for medical historians to determine the birth date of nuclear medicine. This can probably be best placed between the discovery of artificial radioactivity in 1934 and the production of radionuclides by Oak Ridge National Laboratory for medicine related use in 1946<sup>1</sup>.

Many historians consider the discovery of artificially produced radionuclides by Frédéric Joliot-

Curie and Irène Joliot-Curie in 1934 as the most significant milestone in nuclear medicine.

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.<sup>1</sup>

### Principle

A radiopharmaceutical agent, which is radioactively tagged compound is administered to a patient. Many radiopharmaceutical agents act like analogs of natural biological compounds and localize to specific organs.

When a radionuclide is injected intravenously in the body of the patient it decays by the emission of  $\beta$  (Positron) particle which scatter in the tissue and annihilates with the electron and produce two back-to-back 511 keV annihilation photons which are detected by a Gamma camera.

### Gamma Camera



Nuclear medicine is referred to as emission imaging because photons are emitted from inside the patient and subsequently detected by gamma camera imaging system.

The basic design of the most common type of gamma camera used today was developed by an

American physicist, Hal Anger and is therefore sometimes called the Anger Camera. It consists of a large diameter NaI(Tl) scintillation crystal which is viewed by a large number of photomultiplier tubes.

The crystal and Photo Multiplier Tubes are housed in a cylindrical shaped housing commonly called the camera head. The crystal can be between about 25 cm and 40 cm in diameter and about 1 cm thick. The diameter is dependent on the application of the device. For example, a 25 cm diameter crystal might be used for a camera designed for cardiac applications while a larger 40 cm crystal would be used for producing images of the lungs. The thickness of the crystal is chosen so that it provides good detection for the 140 keV gamma-rays emitted by disintegration of <sup>99m</sup>Tc.

**NaI Crystal attached to photomultiplier tube**

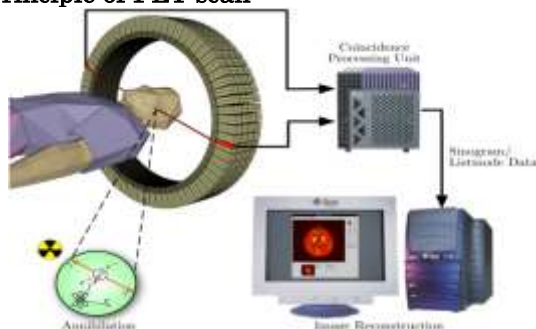


Photons collected along the tube is referred to as Line of Response (LOR). In the scanner, coincidence events are observed and identified along their lines of response (LORs) between pairs of detector elements.

To organize these raw data as they are acquired, the LORs are stored in a in such a way that all the LORs passing through a single point in the patient trace a sinusoid curve in the raw data histogram, hence the term Sinogram for the raw data format. The formation of sinograms is an important middle step in the PET data acquisition process, since necessary corrections are often applied at this level.

Tc<sup>m</sup> - which is the most common radioisotope used today.

**Principle of PET scan**



**PET scan**

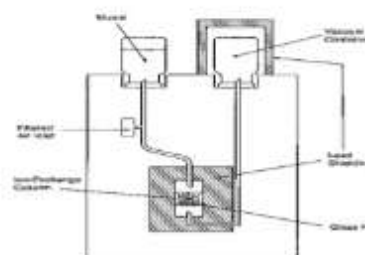


**Production of Radionuclides**

**Radioisotope Generator:** This method is widely used to produce certain short-lived radioisotopes in a hospital or clinic. It involves obtaining a relatively long-lived radioisotope which decays into the short-lived isotope of interest. A good example is <sup>99m</sup>Tc which as we have noted before is the most widely used radioisotope in nuclear medicine today. This isotope has a half-life of six hours which is rather short if we wish to have it delivered directly from a nuclear facility. Instead the nuclear facility supplies the isotope <sup>99</sup>Mo which decays into <sup>99m</sup>Tc with a half-life of about 2.75 days. The <sup>99</sup>Mo is called the parent isotope and <sup>99m</sup>Tc is called the daughter isotope.

So the nuclear facility produces the parent isotope which decays relatively slowly into the daughter isotope and the daughter is separated chemically from the parent at the hospital/clinic. The chemical separation device is called, in this example, a <sup>99m</sup>Tc Generator.

**Technetium generator**



It consists of a ceramic column with <sup>99</sup>Mo adsorbed onto its top surface. A solution called an eluent is passed through the column, reacts chemically with any <sup>99m</sup>Tc and emerges in a chemical form which is suitable for combining with a pharmaceutical to produce a radiopharmaceutical. The arrangement shown in the figure above is called a Positive Pressure system where the eluent is forced through the ceramic column

by a pressure, slightly above atmospheric pressure, in the eluent vial.

The ceramic column and collection vials need to be surrounded by lead shielding for radiation protection purposes. In addition all components are produced and need to be maintained in a sterile condition since the collected solution will be administered to patients. Finally an Isotope Calibrator is needed when a  $^{99m}\text{Tc}$  Generator is used to determine the radioactivity for preparation of patient doses and to check whether any  $^{99}\text{Mo}$  is present in the collected solution.

### Main Radionuclides used in Nuclear Medicine

$^{99m}\text{Tc}$  (Most common), Iodine-123, Gallium-67, Thallium-201, In-111

Fluorodeoxyglucose (FDG) (For PET Imaging)

Nuclear medicine provides physiological and functional information of particular organ.

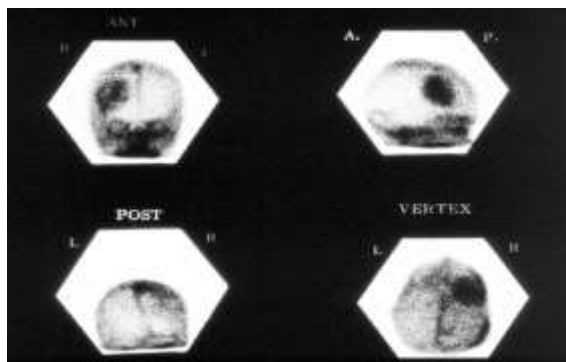
Nuclear medicine involves the following scans  
Brain scans, Lung-Ventilation - perfusion scan, Liver, Gall bladder scan (HIDA scan), Gastrointestinal scan- Bleeding scan, Renal scan, -Kidneys, Bone scan- Bone, Lymphoscintigraphy- Lymph nodes.

### Brain scan

Tracers most commonly used for assessment of cerebral tumors include  $^{18}\text{F}$ -FDG,  $^{11}\text{C}$ -Methionine and  $^{201}\text{Tl}$  and  $^{99m}\text{Tc}$ -MIBI.

C labeled derivative of thioflavin-T, 6-OH BTA-1 or PIB tracers readily bind to amyloid senile plaques and neurofibrillary tangles. Hence these tracers are helpful in the diagnosis of Alzheimer's disease.

The temporal lobe is the most common focus of Partial epilepsy and is also the region that can be accurately evaluated with FDG PET imaging. PET is of high value in identifying presurgical, interictal identification of Refractory Brain seizure foci. PET has high value of sensitivity and specificity in differentiating tumor recurrence from radiation necrosis in patients with Brain cancer. Radiation necrosis have virtually no metabolism whereas recurrent tumor has increased metabolism.



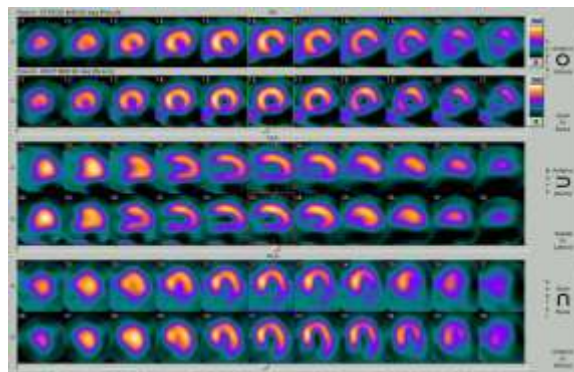
### Cardiac scan

Thallium-201 ( $^{201}\text{Tl}$ ) is the most widely used

radionuclide for assessment of myocardial viability.

Myocardial metabolism can be assessed with radioiodinated fatty acid analogs. 15-(P-[ $^{123}\text{I}$ ]-iodophenyl)-pentadecanoic acid (IPPA), an aromatic fatty acid analog and 15-(p[ $^{123}\text{I}$ ]-iodophenyl)-3-methylpentadecanoic acid (BMIPP), a branched chain fatty acid analog. These two agents can be employed in SPECT imaging for the assessment of myocardial viability.<sup>9,10</sup>

Evaluation of myocardial blood flow can be assessed with PET using  $^{13}\text{N}$ -Ammonia,  $^{82}\text{Rb}$  and  $^{15}\text{O}$ -water.<sup>12</sup>



### Renal Imaging

Renal Imaging have a variety of clinical applications including evaluating renal transplants, differentiating between obstructed and dilated collecting systems and diagnosing reflux and Renovascular Hypertension.

Two types of radioactive tracers used for renal studies. Those that cleared from plasma by glomerular filtration and those that cleared by tubular secretion. The first class comprises of  $^{99m}\text{Tc}$ -DTPA,  $^{125}\text{I}$ -Iothalamate and  $^{51}\text{Cr}$ -DTPA.  $^{99m}\text{Tc}$ -DTPA is commonly used for both imaging studies and clearance measurements.  $^{99m}\text{Tc}$ -DMSA is retained in renal cortex and minimally excreted in urine hence provide an ideal way to perform parenchymal scanning. Upto 40% of injected dose is retained in tubular cells (Proximal tubule and Loop of Henle) which enables imaging of renal cortex with fine resolution.

$^{99m}\text{Tc}$ -DMSA uptake also reflects effective renal plasma flow (ERPF) can be used as a marker of tubular dysfunction in rare disorders such as congenital tubular acidosis and in more common applications such as chemotherapy induced renal toxicity.<sup>7</sup>

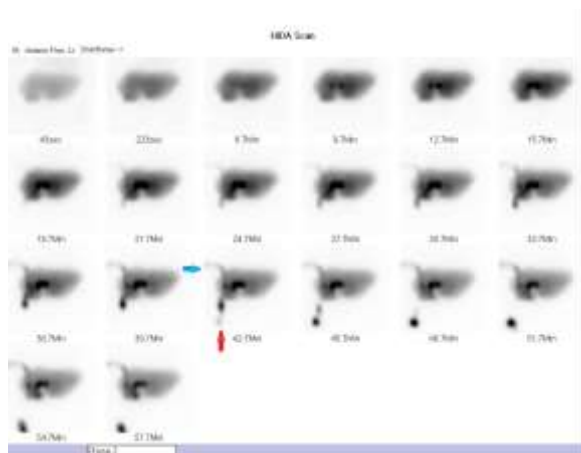
Radioiodinated orthoiodohippurate ( $^{123}\text{I}$ - or  $^{131}\text{I}$ -hippuran, OIH) which is cleared from plasma by tubular secretion<sup>18</sup>. Its clearance is 81-96% of the clearance of the reference agent para-aminohippuric acid (PAH) and makes it suitable for estimation of ERPF. Labelled with either  $^{123}\text{I}$  or  $^{131}\text{I}$ , OIH can be used for renographic studies.

$^{99m}\text{Tc}$ -mercaptoacetyl triglycine (MAG3) provides high quality renal imaging and has become the most widely used agent for renography.<sup>13</sup>

### Hida Scan ( Hepato-Imino Diacetic Acid Scan)

Tc-99m-labelled Iminodiacetic acid (IDA) compounds are used as radionuclide tracers as they share biological activity with bilirubin and are therefore also taken up, transported and excreted by Hepatocytes.<sup>17</sup>

The Patient is required to fast for atleast 4 hours but not longer than 24 hours for HIDA Scan. Because the tracer behaves like bilirubin, it should be taken up by hepatocytes and excreted into the Bile ducts. Thus the liver should be visualized first, followed by visualization of the bowel and gall bladder. The appearance of tracer in the bowel and gall bladder by 60 minutes after administration is defined as normal. Non-visualization of the gall bladder by 60 minutes is diagnostic of acute cholecystitis because this implies a functional obstruction of the cystic duct. False positive results can be caused by chronic cholecystitis, hepatic insufficiency and by fasting for less than 4 hours or more than 24 hours, the gallbladder may be filled with concentrated bile and this may lead to false positive test results by preventing tracer accumulation in the Gall bladder.<sup>17</sup>



### Bone scan

Nuclear medicine techniques for the study of bone metabolism, colloquially termed “bone scanning,” utilize a radio-labeled bone-seeking radiopharmaceutical. The label 99 m-technetium is a short-lived element with a 6-h physical half-life. Technetium is characterized by its ability to complex with carrier agents and create tissue-specific radiopharmaceuticals. In the case of bone, the technetium label is complexed with tin and a diphosphonate moiety, which gives the resultant radiopharmaceutical its bone-seeking quality. In general, the bone-seeking radiopharmaceutical is taken up in the calcifying front of forming bone. Uptake may involve complex formation with the mineralized components of bone such as calcium. Since bone resorption is usually coupled with formation behind the resorbing front, nuclear medicine is used to detect

alterations in bone metabolism in diseases of bone resorption as well as formation. In medicine, bone seeking radiopharmaceutical uptake (BSRU) is routinely used to detect osseous abnormalities prior to the time of radiographic evidence of disease.<sup>16</sup>

Nuclear medicine is an early indicator of bony metastases, primary bone tumors, infections, metabolic bone disease, and stress fractures. In dentistry, nuclear medicine has been demonstrated to be of value in the early detection of periapical pathology and growth disorders.

Tc-99m-labelled diphosphonates are injected intravenously to perform a bone scan. The Radiographic tracer distribution is indicative of osteoblastic activity as well as regional blood flow to the bone.

Whole body imaging consists of static images obtained 2-4 hours after injection. It is used for detection of Metastatic and Metabolic diseases and Bone dysplasia.

A combination of focal hyper perfusion, focal hyperemia, and focally increased bone uptake is virtually diagnostic for osteomyelitis in patients with non-violated bone. Bone scintigraphy is also useful for evaluating disease extent in Paget disease and for localizing avascular necrosis in patients with negative radiographs.

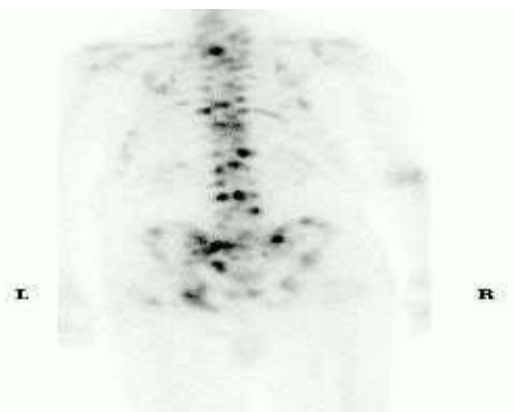
In metastatic disease all of the bones have diffusely increased uptake called as “Superscan”

In pagets disease, the spine shows foci of increased uptake in both the vertebral body and spinous process, suggestive of “Mickey mouse sign”.

Classical appearance of "Lincoln's sign" on 99mTc-MDP bone scintigraphy is seen in case of monostotic Paget disease of mandible showing increased radiotracer uptake in the body of mandible. This pattern has also been described as "black beard" sign.<sup>16</sup>

Patients with Multiple myeloma with lytic bone lesions in weight bearing bones might be susceptible to pathologic fracture may benefit since the fracture would show up as a focus of increased uptake.<sup>16</sup>

### Bone scan showing multiple metastases



### **Lymphoscintigraphy**

Accurate lymph node staging is essential for the treatment and prognosis in patients with Head and Neck cancer, Melanoma, Lymphoma. Only SPECT/CT imaging can precisely locate the sentinel lymph node.

### **For the detection of active alveolar bone loss**

Bone is a dynamic tissue in which the net balance between formation and resorption determines the final osseous architecture. Tests for periodontal disease activity need to take the dynamic nature of bone into account if activity is to be determined in a single examination. Most tests used to assess the progression of periodontal disease, such as radiography, are capable of detecting changes in the osseous architecture only after it has occurred, because a single examination represents the sum total of all past disease exacerbations and remissions. Thus, in order to detect "active" progression of alveolar bone loss by radiographs, two or more examinations must be taken, separated in time.<sup>2</sup>

Comparison of the two radiographic images will indicate if alveolar bone loss has progressed during the study period.<sup>2</sup>

A test that can detect periodontal disease activity at the time of its occurrence would be capable of indicating active periodontal disease prior to the time the bone loss is evident on radiographs.<sup>2</sup>

Since periodontal disease is a disease that affects the gums and alveolar bone supporting the teeth. Jeff coat *et al.*, in 1987 developed the hypothesis that a single measurement of bone-seeking radiopharmaceutical uptake is indicative of the rate of bone loss that is equivalent to measurements by sequential radiographic examinations.<sup>2</sup>

### **For detection of osseointegration around dental implants**

Nuclear medicine technique was comparable to the FEM to evaluate the osteoblastic activity at the implant-bone interface.

### **For detection of viability of bone grafts**

The study conducted by Berding *et al* concluded that [18F-] PET (fluoride ion and positron emission tomography) depicted increased blood flow activity in on lay grafts and regions of osteosyntheses, indicating bone repair in the graft and adjacent host bone early after surgery. For the regions of osteosynthesis, the decrease in both parameters corresponded to uncomplicated healing.<sup>3</sup>

The lack of increased influx, although flow was increased in pedicle grafts, most likely indicates that some necrosis occurred in these grafts despite patency of anastomoses. It may be concluded that [18F-] PET provides further insight into the biology of graft incorporation. There are other studies that show that bone scintigraphy performed within the first week after

the mandibular reconstruction is a useful tool to monitor the viability and early complications of micro vascularized fibular grafts and plays an important role in the decision-making process during repeated surgical exploration.<sup>4</sup> SPECT is more sensitive than planar imaging for assessing graft viability.<sup>3</sup>

### **For detection of Early osteomyelitis**

Early osteomyelitic changes that are not readily apparently seen in conventional radiographic techniques are readily appreciable on PET Scan.<sup>8</sup>

### **To differentiate between cellulitis and osteomyelitis**

A type of bone scan named focal -three phase imaging is used to differentiate cellulitis from osteomyelitis. The three phases are flow phase (1 minute after injection), the blood pool (5 minutes after injection) and the skeletal phase (2-4 hours after injection). Both cellulitis and osteomyelitis will have increased uptake in the first two phases of the bone scan however only osteomyelitis demonstrates increased activity in the third phase.<sup>8</sup>

### **For detection of salivary gland disorders**

The diagnosis and treatment of salivary gland neoplasms remain complex and challenging problems for the head and neck surgeon.

F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) scanning can be used to plan treatment of salivary gland malignancies by detecting lymph node metastases that require a neck dissection or by finding distant metastases that may not have caused abnormalities in routine blood work. This is most useful when combined with CT scanning.<sup>6</sup>

Technetium-99m (Tc-99m) pertechnetate scintigraphy with lemon juice stimulation can be used to diagnose Warthin tumors with correlation between tumor size and Tc-99m uptake.

Pleomorphic adenomas, the most common benign tumors of the Parotid gland takes up increased radionuclide uptake in Salivary scintiscan. Warthin tumors do not take up the radionuclide due to the presence of cold nodule (nodules do not take up the radionuclide-hence called as cold).<sup>6</sup>

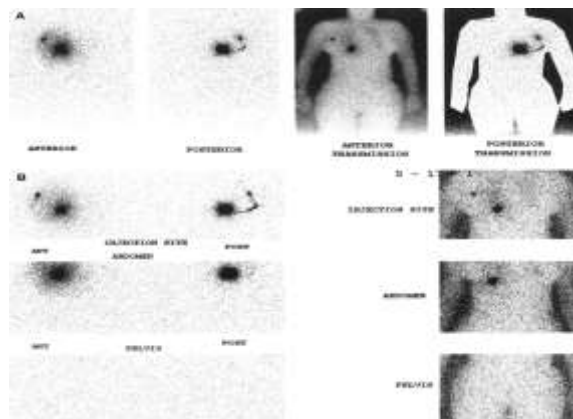
A bilaterally symmetrical increased uptake is usually physiological. An asymmetrical uptake, especially when focal, would warrant further radiological and histopathological correlation to rule out disease involvement.<sup>6</sup>

### **For detection of function of sentinel lymph nodes**

The sentinel lymph node is the first node to which lymphatic drainage and metastasis from the primary tumour occur. Precise anatomic localization of the sentinel lymph node is critical for minimally invasive surgery and to avoid incomplete removal of the sentinel

node, especially in the regions of the head and neck, the chest and the pelvis.

### Lymphoscintigraphy



### For staging and grading of orofacial malignancies, colorectal cancer, non-small cell Lung cancer, Melanoma, Lymphomas, Head and Neck cancers

PET Scans are used to detect malignant tumors, determine cancer stage and judge the effectiveness of cancer treatment. They are most often used in patients with head and neck tumors, colorectal cancers, Lymphoma, melanoma and Lung cancer.

Fluorine 18 Fluorodeoxyglucose (FDG). This is a radionuclide combined with glucose, which is the metabolism for both Malignant and Benign cells. However because malignant cells tend to grow and metabolize glucose faster than healthy tissue, malignant cells will use more of the tracer. PET Scans use the difference in metabolism to differentiate normal from abnormal tissue.<sup>14</sup>

### For determining the prognosis after treatment

PET is helpful for evaluating any relapse after surgical removal of cancer or to evaluate the effectiveness after chemotherapy or adjuvant chemoradiotherapy in treatment of head and neck cancers.

### For detection of thyroid disorders like graves disease, thyroiditis and thyroid carcinoma

Graves disease is manifested by an enlarged gland that demonstrates diffusely increased uptake. Thyroiditis appears as diffusely decreased uptake. Thyroid cancer tends to appear as a focal area of decreased activity (a solid cold nodule) on a Nuclear Medicine study.

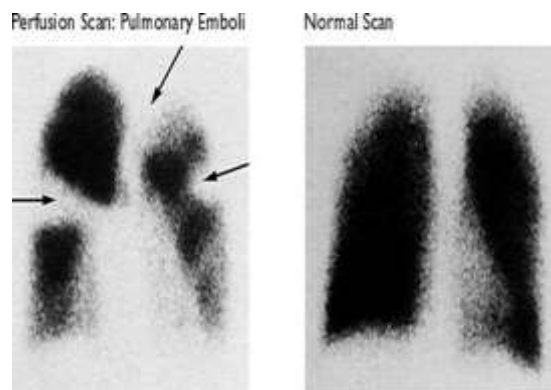
### For detection of Pulmonary Embolism

The ventilation portion is performed using either radioactive gas (xenon) or radioactive aerosol (Tc-99m-DTPA). When Radioactive gas is used, the study is accomplished in three phases: single breath/wash-in

phase, equilibrium phase, and washout phase. For studies that use radioaerosols, the radiopharmacological agent is placed in a specialized nebulizer system and the patient breathes through the mouthpiece until sufficient radioaerosol is delivered to the lungs. The Tc-99m remains in the lung long enough to obtain multiple views with a gamma camera. Tc-99m is injected into a peripheral vein to assess perfusion. The particles travel to the right side of the Heart and then to the lungs where they are filtered or trapped in the Pulmonary vascular bed. The emissions from the trapped particles are then imaged with a Gamma camera.

If an acute pulmonary embolism is present, the thrombus in the blood vessel will prevent radiotracer from reaching the portion of lung supplied by the vessel, thus a perfusion defect will result. An acute thrombus will not prevent air from being distributed to the lung through bronchi, thus the results of the ventilation scan will be normal. This combination of a perfusion defect without a corresponding ventilation defect is called a mismatch. The results of a ventilation-perfusion scan are classified as low, intermediate or high probability for a pulmonary embolism based on the number and size of defects, with higher numbers and sizes resulting in greater probability that an embolus is present.

### Ventilation-Perfusion Scan



6 mCi of <sup>111</sup>In-octreotide (<sup>111</sup>In-DTPA-pentetreotide) is used for assessing neuroendocrine tumors of Gastrointestinal tract namely Carcinoid and Islet cell tumors.

Nuclear medicine is used for detecting any mass in adrenal gland to rule out whether the adrenal gland is enlarged due to primary tumor or from a secondary tumor from a primary bronchial carcinoma which can metastasize to adrenal gland. The adrenal cortex is imaged with PET scan using iodocholesterol and the inner adrenal medullary layer can be imaged with MIBG.

### To detect occult infection

Indium (In)-111-Labelled white blood cells and

Gallium<sup>67</sup> citrate can be used to detect occult infection. To label white cells with In-111, the cells must be removed from plasma. Blood is taken from the Patient, labelled and then reinjected. Imaging is performed 24 hours after the injection. The normal distribution of white blood cells is spleen, liver and bone marrow. Activity seen outside the normal expected distribution is evidence of focal of infection. Gallium, the other agent useful in locating sources of infection ,binds to iron binding molecules. Its normal distribution is liver and Bone marrow. It is excreted by the Kidneys for the first 24 hours and through the large bowel after 24 hours.<sup>14</sup>

### For evaluating the effect of Hyperbaric oxygen therapy in treatment of Bisphosphonate Induced osteoradionecrosis of the Jaws

FDG-PET may be a useful tool for monitoring the effect of HBO therapy in BRONJ. Of particular, monitoring HBO therapy with FDG-PET may hold a promise for prognostic assessment with BRONJ.<sup>15</sup>

### Disadvantages of PET

1. Costlier
2. Poor spatial Resolution
3. Cyclotron unit is needed in the vicinity of PET Scan due to the short half-life of Radionuclides
4. Normal Functioning Salivary glands show increased uptake of Radioactive tracer
5. Uncontrolled Diabetics with Blood glucose levels > 200 mg/dl show poor uptake of radionuclides giving false positive results. Hence Patient should not eat or inject insulin before the PET scan
6. The scan takes approximately 30 minutes after the injection of FDG and performance of a whole body scan takes an additional 30-60 minutes depending upon the type of scanner
7. Normal radionuclide uptake in head and neck can be observed in facial muscles, tongue (especially when patients are talking at the time of injection of radionuclide) neck muscles, brown fat, thyroid tissue and vocal cords. The uptake of FDG can be very intense and can mimic or obscure cancer in these regions. Minimizing talking and patient movement as well as keeping the environment quiet and dimly lit both during injection and for approximately 15-20 minutes after injection may help to diminish uptake in these areas

### Conclusion

Nuclear medicine is an ideal imaging speciality to adapt to the new discipline of molecular medicine, because of its emphasis on function and its utilization of imaging agents that are specific for a particular disease process. Radionuclide bone imaging will likely remain a popular and important imaging modality.

Interpretation of the scan results, as well as shortcomings of the scan are important to understand,

as they may be required at times to be done by the dental surgeons. Nuclear Medicine helps in diagnosing oral/dental pathologies and tumors in the oral maxillofacial regions, which may have to be dealt by dentists at initial stages, though may later require an oncologist

Recently the combination of PET images with CT (Computed Tomography) images is referred to as Fusion imaging which has significant advantages over PET or CT alone by helping in discriminating Metastases from Physiological foci of activity, improving lesion detection, precisely localizing the metastatic foci, differentiating bone from soft tissue.

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