IONIZING RADIATION BASED DIAGNOSTIC AND THERAPEUTIC TECHNIQUES

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Abstract:

The commonly utilized ionizing radiations in Medicine can be classified into (a) electromagnetic waves such as gamma rays and X-rays or (b) charged particles such as alpha particles and beta particles. A radiation is termed ionizing when it has enough energy to eject one or more electrons from atoms or molecules in the irradiated medium. Both diagnostic imaging and therapy using ionizing radiation have been substantially employed to improve health care services and patient outcomes over the years.

HISTORY OF IONIZING RADIATION AND ITS MEDICAL APPLICATIONS :

In 1895, Radiography was discovered. While utilizing a cathode ray tube at his laboratory at Wuerzberg University in Germany, Wilhelm Conrad Roentgen made the discovery of X-rays. When high voltage is applied to the cathode ray tube which is shielded with a heavy black paper, it glowed with a fluorescent green light. From this, he concluded that a new "ray" was being released from the tube and gave it the name "X-ray" because it could travel through even thick black paper and ignite phosphorescent elements in the space. He found that while most solid items could be penetrated by this radiation, bone and metal were not among them. Radiographs were being taken in both the US and Europe within a month of its discovery; six months later, they were being used on the front lines of war to help soldiers who had been wounded find the bullets that had struck them. They noticed skin erythema, which gave them the notion to use X-rays to treat various lesions. The first patient who received radiation was in June 1896 by J.J. Thomson, when he found that X-rays could ionize gas. Researchers used this phenomenon to discover electrons in 1897.

In 1896, French physicist Henri Becquerel discovered natural radioactivity. He discovered that, when exposed to sunlight, some minerals will glow or fluoresce. Using photographic plates, he was able to capture this luminescence on film. Uranium was one of the first mineral Becquerel dealt with. On photographic film, he recorded radiation emanating from uranium. Together with Marie and Pierre Curie, received the 1903 Nobel Prize in Physics for this discovery.

Marie Curie, a French physicist of Polish descent, and her husband Pierre Curie also discovered polonium and radium, two other radioactive elements. With the help of her daughter Irene, Curie supported the use of radium to lessen suffering during World War I. She never lost her passion for science and contributed significantly to the creation of a radiation laboratory in Warsaw, where she was born. She and Pierre shared half of the 1903 Nobel medal in Physics for Physics for their investigation into the spontaneous radiation found by Becquerel. Becquerel received the other half of the medal. She was awarded a second Nobel Prize in 1911, this time in Chemistry, for her contributions to the study of radioactivity[1].

Most of the time, it was a serendipitous observation that led to a medical imaging device to be developed, while working in physics labs and experimenting with simple x-ray images. Subsequently, the cyclotron and nuclear reactors opened the door for nuclear medicine; and one of the co-inventors of MRI was initially working on an alternative option for x-ray diffraction for the analysis of crystal structures[2].

In this overview, we shall look at various therapeutic and diagnostic Nuclear Medicine Techniques commonly used in the clinical scenario.

[A]. RADIOMOLECULAR THERANOSTICS AND THERAPEUTIC NUCLEAR MEDICINE THROUGH NUCLEAR MEDICINE:

INTRODUCTION:

The principle of radionuclide therapy is based on tracer localization with selective delivery of radiation dose to disease site or metastatic sites. Thus, the surrounding normal tissue suffers little or no effect. The term 'Theranostics' means combined diagnostics and therapy to assess patients' disease status and individualize treatment for optimal results.

Characteristics of ideal therapeutic radionuclides include the following:

-Radionuclides emitting particulate high or moderate energy radiation (α or β)

-Low energy gamma emission for dosimetry and scintigraphy studies

-Long half-life, usually ranges from six hours to eight days.

-Easily available and inexpensive

In 1941, Dr Hertz used ^{131}I for treatment of hyperthyroidism while in 1946, Seidlin et al. used Radioactive Iodine (RAI) for effective metastatic thyroid cancer treatment[3]. The FDA approved the use of ^{131}I for the treatment of thyroid cancer in 1951[4].

1. Radioiodine (^{131}I) therapy:

a. ^{131}I therapy for benign thyroid disorders:

^{131}I is a radionuclide that emits high energy beta and gamma radiation ($E\beta^{max}$ 0.606 MeV, gamma energy: 364 keV with a half-life of 8.02 days). The range of beta particle in tissue is 0.8mm, which allows good penetration and dose delivery to tissues. RAI with ^{131}I utilizes the production of beta particles with high energy to damage the thyroid gland tissue.

Indications of ^{131}I therapy:

- Patients with hyperthyroidism/Graves' disease
- Toxic multinodular goitre
- Toxic Adenoma
- Solitary autonomous functioning thyroid nodule (AFTN)

Radioiodine is one of cornerstone treatment options for autonomous functioning thyroid nodule and toxic multinodular goiter[5].

Patient Selection criteria:

- Relapse of thyrotoxicosis after withdrawal of anti-thyroid medications or following 12 to 24 months of anti-thyroid medication, there is persistence of thyrotoxicosis.
- Pre-therapy thyroid scintigraphy and RAI uptake and scan showing increased trapping by thyroid gland.

The dose of RAI is based of empirical or dosimetric approach:

Empirical approach: treatment with 8-15 mCi RAI

Dosimetry approach: 80 to 200 μCi/g of thyroid tissue delivers 50-100 Gy to thyroid tissue[3].

The treatment's goal is to accomplish a euthyroid/hypothyroid status that is replaceable by levothyroxine supplements.

Patients are followed up post-RAI after 6-8 weeks with clinical evaluation and thyroid function tests.

Euthyroidism or hypothyroidism occurs starting post-4 weeks after treatment with RAI; >80% patients become hypothyroid by 16 weeks[5].

b. Treatment of thyroid carcinoma with high doses of ^{131}I:

The most prevalent endocrine malignancy is thyroid carcinoma. The most prevalent type is differentiated thyroid cancer (DTC), which is further divided into papillary thyroid carcinoma and follicular thyroid carcinoma. Papillary thyroid carcinoma spreads via regional lymphatic vessels while follicular variant is a more aggressive variant with poor prognosis and disseminates via hematogenous route, resulting in distant metastasis. Other histological

variants viz. Hurtle cell, Papillary thyroid carcinomas with tall cells and columnar cells behave more aggressively and have poor prognosis.

Patients are categorized into three risk categories based on the American Thyroid Association (ATA) risk stratification system, viz. low, middle, and high. Definite treatment of DTC consists of total thyroidectomy. It is followed by low-dose RAI scan after 3-4 weeks of surgery. The aims of radioiodine (^{131}I) therapy in DTC:

-Radio-ablation of residual thyroid tissue following thyroidectomy

-Treatment of microcarcinoma either at locoregional or distant sites

-Treatment of metastases in lymph nodes

-Therapy of distant metastases

The patient preparations for diagnostic and therapeutic dose of ^{131}I radioiodine includes the following steps:

TSH level > 30 uIU/L

2-3 weeks of low-iodine diet

Radioiodine scan- 4 weeks after surgery.

Therapeutic dose of radioiodine in carcinoma thyroid [6]

Indication	Fixed Dose regimen
Thyroid Remnant Ablation	30-50 mCi
Adjuvant therapy	100-150 mCi
Metastatic disease	200-250 mCi

Patients are followed up after 6 months with low-dose RAI scan to assess treatment response and disease status. Patients are started on thyroid hormones with TSH levels <0.1 mIU/L. Usually multiple cycles (2-4) are required in metastatic cases at an interval of 1 year. (Fig 1)

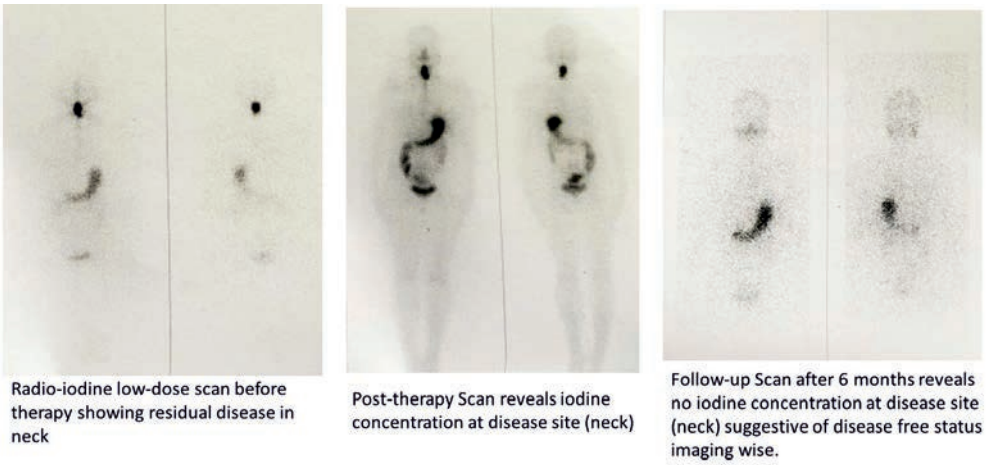

Fig 1. A 37-year-old male, known case of papillary thyroid carcinoma with lymph node metastases, post-total thyroidectomy, referred for Radio-iodine scan. RAI scan reveals residual disease in neck. Patient was treated with 145mCi RAI and 6 months later on follow-up, low dose RAI scan was repeated which showed no abnormal iodine uptake in neck and wholebody. Tg levels were <1ng/nL. Suggestive of disease free status.

Recurrence rates and mortality rates associated with DTC were lower in individuals treated with RAI following surgery than in those who did not get ^{131}I therapy, according to a 1994 study by Mazzaferri on a population of 1500 patients followed-up for four decades[7]. Anaplastic, medullary and poorly differentiated thyroid carcinoma are aggressive variants which do not concentrate radioiodine. They can be treated with surgery, radiotherapy, chemotherapy or PRRT (peptide receptor radionuclide therapy)

2. ^{131}I-*meta*-*I*odobenzylguanidine (mIBG) therapy:

meta-*I*odobenzyl-guanidine (mIBG) is a nor-adrenaline (norepinephrine) analogue which is concentrated especially in tumors originating from neuroectodermal tissue, which has dense adrenergic innervation. mIBG when labelled with ^{131}I, is used as therapeutic agent in the treatment of neuroectodermal tumors delivering targeted radiotherapy to tumoral sites. In 1984, mIBG was first used in the treatment of a patient suffering from neuroblastoma in Europe[8].

Indications for mIBG therapy are:

-Stage III or IV Neuroblastoma

-metastatic/inoperable Pheochromocytoma, Paragangliomas

-metastatic carcinoid tumors

-metastatic or recurrent medullary thyroid carcinomas

Patients are initially subjected to $^{123}I/^{131}I$-mIBG diagnostic scans prior to therapy. Scans showing adequate tracer uptake and retentions in lesions are considered eligible for therapy (Fig 2).

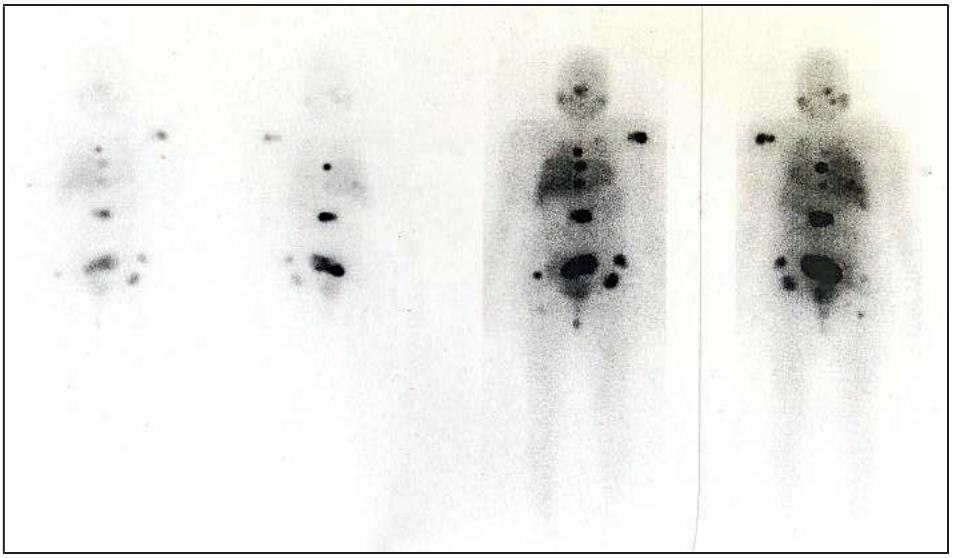

Fig 2. A 56-year-old female, known case of pheochromocytoma with multiple skeletal metastases, post right adrenalectomy, ^{131}I-MIBG scan was suggestive of multiple ^{131}I-mIBG avid skeletal metastases. The patient complained of severe pain with high Plasma free metanephrines – 790pg/mL. Patient received 2-3 cycles of ^{131}I-MIBG therapy, pain reduced substantially and plasma free metanephrines level dropped to 276 pg/mL.

Patient preparation: Oral stable iodine prevents thyroidal uptake of ^{131}I-mIBG, given in the form of KI (potassium iodide) 130 mg/day which equates to 16 drops/day diluted in glass of water (for adults) started 48-24 hrs prior to therapy and continued for 10-14 days later.

Dose: ^{131}I-mIBG activity per cycle ranges from 100-200mCi (3.7 GBq to 7.4 GBq). Further dose is modified in patients with myelosuppression and impaired renal function. Total of 4-5 cycles are given at an interval of 3-6 months depending on response of patient to previous therapy.

Further dose is modified when myelosuppression and decreased renal function are present in individuals. Total of 4-5 cycles are given at an interval of 3-6 months depending on response of patient to previous therapy.

^{131}I-mIBG is used as palliative first-line therapy to reduce pain caused by metastases, help treat symptoms, lower hormonal activity, and manage hypertension. It is used in cases of disease progression post-chemotherapy or relapse. Huihui et al. analysed 883 participants in 26 clinical studies of neuroblastoma treated with ^{131}I-mIBG and objective response rate was 39%, stable disease was seen in 31% and minor response in 15% of patients. The median event-free survival time was between 10 and 16 months. Side-effects like thrombocytopenia and neutropenia occurred in 53% and 58% patients respectively[9].

Most common side-effects include hepatotoxicity due to bone marrow irradiation. A frequent long-term side effect is hypothyroidism.

3. Peptide Receptor Radionuclide Therapy:

Neuroendocrine tumors (NETs) are heterogeneous group of neoplasms arising from the secretory cells of diffuse neuroendocrine system. They account for 0.5% of all malignancies[10]. The gastrointestinal tract (62–67%) and lung (22-27%) are the two chief locations[11]. Somatostatin is an endogenous peptide secreted by neuroendocrine cells. NETs express SSTR in 80 -100% of cases the most prevalent subtype being SSTR2, followed by SSTR1 and 5.

In PRRT, radiolabelled peptides are administered to specifically target the somatostatin receptors that are overexpressed on tumors. The commonly used ligands are DOTATATE and DOTATOC. Radionuclides such as ^{111}Indium, ^{177}Lutetium, ^{90}Yttrium are β emitters and ^{225}Actinium is an α emitter that are chelated to peptide to deliver radiation to tumor. Peptides are somatostatin receptor agonists which target SSTR2 receptors and are highly specific. PRRT is therapeutic option in metastatic, SSTR positive (Krenning's score 3 and 4), progressive on somatostatin analogues therapy. (Fig 3)

Dual molecular imaging with ^{68}Ga-DOTATATE and ^{18}F-FDG is important for better patient selection for PRRT. Krenning score correlates with good prognosis post PRRT while high FDG uptake is a poor prognostic indicator.

Radionuclide	β^{max}	Range (mm)	Half-life
^{177}Lutetium	0.497MeV	Upto 2.5mm	6.7 days
^{90}Yttrium	2.28 MeV	12mm	2.7 days
^{225}Actinium	5.9 MeV	50-100μm	10 days

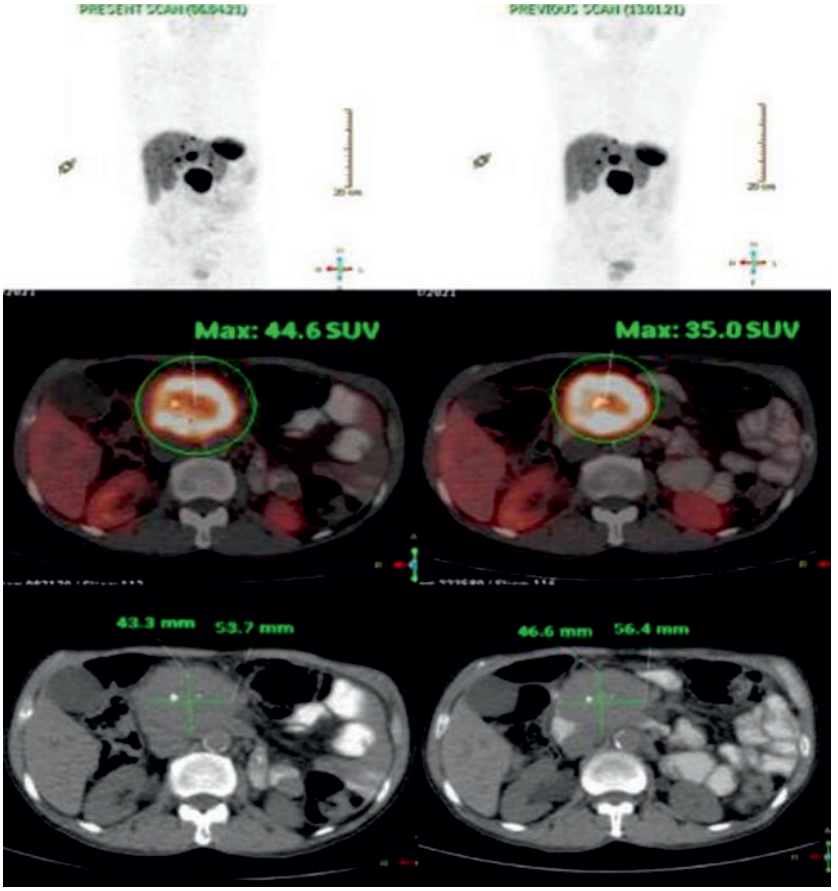

Fig 3. A 48-year-old male with known case of pancreatic head with liver metastases, received 2 cycles of 177Lu-DOTATATE PRRT, 68Ga-DOTATATE PET/CT before and after 2 cycles of therapy shows reduction in SSTR expression, increase in necrosis with stable size.

In metastatic well-differentiated NET grade 1/2, the Phase III NETTER-1 trial evaluated ^{177}Lu-DOTATATE PRRT with 30 mg octreotide LAR vs 60 mg octreotide alone. In terms of progression-free survival, greater objective response rate, and overall survival benefit, ^{177}Lu-DOTATATE PRRT was superior to high dose octreotide. [12]. Sitani et al. assessed total of 468 patients with advanced/metastatic NET post-^{177}Lu-PRRT and showed that ^{177}Lu-DOTATATE PRRT significantly improved symptoms and biochemical indicators in the majority of NET patients, resulting in disease stability in most cases. It was tolerated well with minimal toxicity. [11]. ^{177}Lu-DOTATATE PRRT is less nephrotoxic than ^{90}Y, and ^{177}Lu has gamma emission which helps in post-therapy imaging.

^{90}Y has higher β energy with longer tissue penetration range leading to better cross-fire effect useful in large and heterogeneous tumors. Major disadvantage is higher renal toxicity. Duo-PRRT is sequential administration of ^{90}Y-DOTATATE and ^{177}Lu-DOTATATE in 2 different sittings (Fig 4).

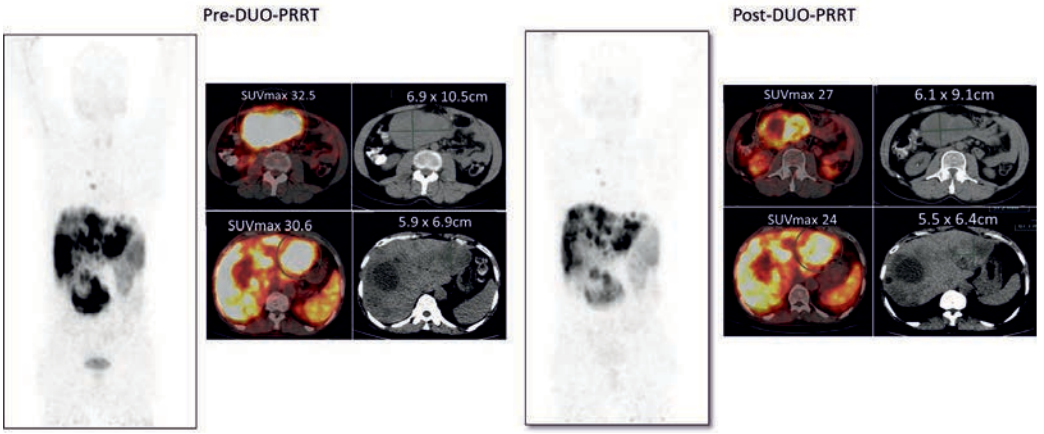

Fig 4. A 50-year-old male, diagnosed case of duodenal NET with liver metastases (MiB-I-2%) with SSTR expressing bulky duodenal and liver lesions, received DUO-PRRT: 2cycles of 177Lu-DOTATATE followed by 1 cycle of 90Y followed by 2 cycles of 177Lu-DOTATATE showing stable disease as per PERCIST and minor response as per RECIST 1.1 post-duo-PRRT. There is increase in necrosis of lesions post duo-PRRT

Tandem PRRT is combined 1:1 ^{90}Y-DOTATATE and ^{177}Lu-DOTATATE administration simultaneously. It can balance advantages and disadvantages of both radionuclides. A total of 1048 patients with metastatic and/or progressive NETs in Germany were retrospectively analyzed, 331 patients received only ^{177}Lu, 170 received ^{90}Y and 499 received ^{177}Lu + ^{90}Y. Median overall survival was higher for duo-PRRT group followed by ^{177}Lu-DOTATATE followed by ^{90}Y-monotherapy[14].

In tumors refractory to β therapy, alpha therapy is useful. ^{225}Ac has greater energy, a shorter range, and a more potent ability to kill tumor cells. It has the advantage of targeting small, scattered tumors and micrometastasis. Dose administered is 1.2 μCi/Kg. High linear energy transmission and a limited range in tissue are two benefits that alpha particles have over beta particles. Ballal et al[15]. conducted a study involving 91 patients of well-differentiated GEP NETs who received ^{225}Ac-DOTATATE, most patients had a partial response and stable disease. Progressive disease and Poor overall survival were seen in patients with bone metastases.

In the 2016 ENETS recommendations, PRRT is suggested as a second-line therapy for intestinal NET[16]. PRRT is used as palliative treatment for extensive metastatic disease, as neoadjuvant treatment in unresectable bulky tumors making them operable post few cycles of PRRT. PRRT is also used in unresectable pheochromocytomas and paragangliomas, medullary thyroid carcinomas and non-iodine concentrating poorly differentiated thyroid carcinomas which are SSTR avid on SSTR imaging.

Administration of PRRT- 4 to 5 cycles with an interval of 3 months with cumulative dose not more than 1 curie. PRRT is administered intravenously with amino acid infusions before PRRT for renoprotection. Patients are followed up with scans after 2 cycles of PRRT for response assessment.

4. PSMA (Prostate specific Membrane Antigen) directed radioligand therapy (PRLT):

Prostate cancer is the second most frequent cancer and the fifth leading cause of death in men. In India, there are 9 cases of prostate cancer for every 100,000 men[17]. Prostate cancers show initial good response to androgen deprivation therapy followed by chemotherapy but later become unresponsive to it, termed as Metastatic castration resistant prostate cancer (mCRPC). PSMA is a transmembrane glycoprotein and present on the surface of prostate and metastatic sites. It is over expressed in mCRPC. PSMA targeted radioligands are used to deliver selective targeted radiation to metastatic disease sites. PSMA ligands used in therapy are PSMA-617 and PSMA-I&T. The FDA authorized ^{177}Lu-PSMA-617 (Pluvicto) on March 23, 2022, for the treatment of patients with metastatic prostate cancer.

They are labelled with variety of β and α isotopes – β agents used are ^{177}Lu and ^{90}Y but ^{177}Lu-PSMA-617 is one of the promising ligands for therapy. The α agents that have been employed for clincal practice are ^{225}Ac and ^{223}Ra.

Indications for PSMA therapy:

-Metastatic, progressive disease following first and/or second-line chemotherapy and at least one line of abiraterone and/or enzalutamide.

- PSMA PET/CT scans with strong PSMA expression

(a). ^{177}Lu-PSMA therapy: ^{177}Lu is chosen as ideal agent because of its physical characteristics mentioned in PRRT section. Dose administered is 150-200mCi per cycle and the therapy cycles are repeated every 6-8 weeks. Usually, 4-5 cycles are administered if therapy response is documented. (Fig 5)

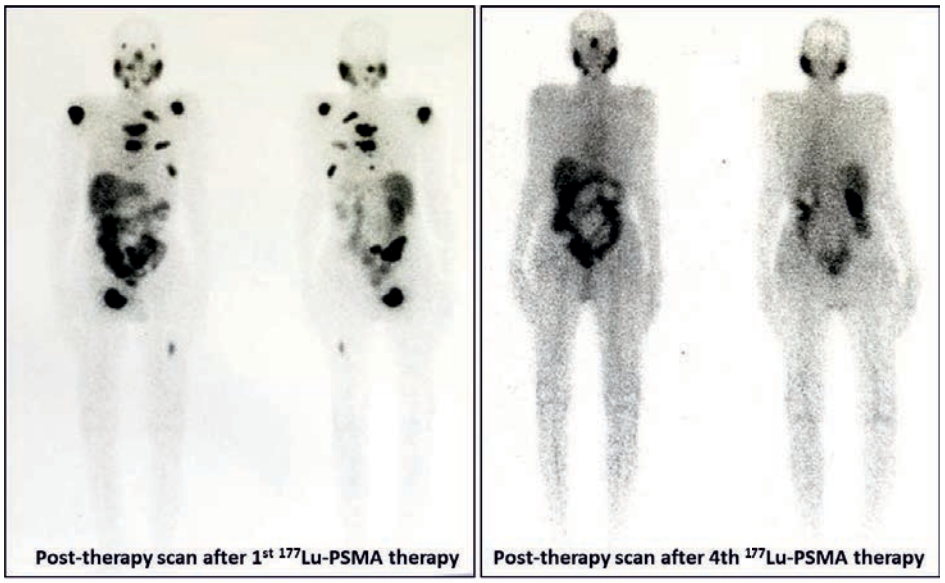

Fig 5. A 78-year-old male with metastatic castration resistant prostate cancer, Sr PSA levels >1300ng/mL (pre-therapy) received 4 cycles of 177Lu-PSMA therapy at interval of 8 weeks. Sr. PSA levels reduced to 5ng/mL and on there was complete resolution of skeletal lesions after 4 cycles of 177Lu-PSMA therapy.

Phase III VISION trial enrolled 831 mCRPC patients who received around 6 cycles of PRLT were followed-up. PRLT increased overall survival and progression-free survival based on imaging, with a relatively low frequency of side effects[18].

(b). ^{223}Radium-Therapy:

It is the first approved alpha emitting particle (2013) for the treatment of CRPC patients with painful bone metastases but no soft tissue metastases[19]. ^{223}Ra is an alpha emitter with a high linear energy transfer of 80 keV/um, Eβmax of 5.7 MeV and half-life of 11.4 days. It also emits gamma rays of 269, 271keV which can be used for imaging. ^{223}Ra behaves similar to calcium after its intravenous injection into human body and osteogenic cells get eight-fold higher irradiation than non-targeted cells resulting in a decrease in bone pain and an improvement in the patients' quality of life.

The Phase III ALSYMPCA study demonstrated higher overall survival by 3.6 months when treated with ^{223}Ra-PRLT[17]. The dose administered was 50-55kBq/Kg repeated at 4 week intervals for 5-6 cycles.

(c) ^{225}Ac-PSMA therapy:

Patients who show disease progression after ^{177}Lu-PRLT and patients with diffuse red bone marrow infiltration are ideal candidates for ^{225}Ac-PRLT. The dose regimen is 100-150kBq/Kg repeated at 8-12 week intervals. A meta-analysis by Ma et.al evaluated the efficacy and safety of ^{225}Ac-PSMA-617 in mCRPC patients. Results showed that ^{225}Ac targeted therapy had significant therapeutic effect and low toxicity. More than 60% of patients had >50% PSA decline with symptomatic relief and better quality of life. Study concluded ^{225}Ac-PSMA is an effective and safe treatment option with low toxicity[20].

5. Bone Pain Palliation with radiopharmaceuticals:

Bone metastases frequently result in unbearable pain that greatly lowers the quality of life for cancer patients. Breast, prostate, and lung carcinomas are the most common causes of bone metastases. Several bone-seeking radiopharmaceuticals have been utilised for treatment of painful bone metastases.

Radiopharmaceuticals used for Bone Pain Palliation:

Radionuclide	E_β^{max}	Gamma energy	Range	Half-life
^{32}P	1.71 MeV	-	3 mm	14.3 days
^{89}Sr	1.46 MeV	-	2.40 mm	50.5 days
^{153}Sm	0.81 MeV	103 KeV	0.6 mm	1.9 days
^{186}Re	1.07 MeV	137 KeV	1.1 mm	3.8 days
^{188}Re	2.12 MeV	155 KeV	2.7 mm	0.7 days

Advantages:

-Ability to simultaneously treat multiple sites of disease involvement

-Daycare basis

-Can be integrated with other treatment modalities

Indications:

-Metastatic malignancy

-Multiple skeletal sites involvement

-Osteoblastic lesions on bone scan.

Radionuclides like ^{89}Sr and ^{32}P with high beta radiation are chelated with HEDP. They have a higher tissue range with long half-life leading to higher antitumor effect and increased bone marrow suppression. ^{153}Sm, ^{177}Lu, ^{186}Re are preferred due to low beta energy and shorter half-life with gamma imaging properties. The standard dose is 37MBq/kg (1 mCi/kg) administered intravenously at 8 weeks intervals.

(a) ^{153}Samarium-ethylenediaminetetramethylenephosphonate (^{153}Sm-EDTMP) :

Mean β energy - 233keV with half-life of 1.9 days, gamma energy - 103keV.

Bone lesions concentrate ^{153}Sm-EDTMP, radiation dose to metastatic areas is increased five times over that of normal bone tissue. It emits gamma particles (103keV) which can be used for imaging the bio-distribution and response. It results in mild toxicity in form of reversible bone marrow suppression. Study by Tripathi et al[21] evaluated the rate of palliation response in 86 patients with metastatic bone pain following ^{153}Sm-therapy. Overall palliation response rate was 73%.

(b) ^{177}Lu-EDTMP:

Is a good alternative to ^{153}Sm due to longer half-life and higher beta energy. Also, a study by Thapa et.al revealed that pain relief with ^{177}Lu-EDTMP was 80% while with ^{153}Sm-EDTMP was 75%, pain response efficacy of ^{177}Lu-EDTMP is similar to ^{153}Sm-EDTMP and improved quality of life. Minor grade toxicity was seen in both[22].

(c) ^{188}Rhenium-hydroxyethylidenediphosphonate (^{186}Re-HEDP):

It is mainly a beta emitter with gamma component useful in imaging the bio-distribution, dosimetry and response. It is produced in ^{188}Tungsten/^{188}Re generator and easily available. The efficacy of pain relief is seen after 2-3 weeks of therapy and lasts for 2-6 months. Patients are followed-up after 6-8 weeks with bone scintigraphy, pain score, pain medications.

indications of radiation synovectomy are the following:

-Rheumatoid Arthritis, Osteoarthritis

-Reactive Arthritis, Psoriatic Arthritis

-Haemarthrosis in hemophiliacs.

Radiopharmaceuticals used for Radiosynovectomy:

Radionuclide	E_β^{max}	Half-life	Range in tissue	Uses	Dose
^{90}Yttruium	2.28 MeV	2.7 days	12mm	RSO of knee joints	185-222MBq
^{186}Rhenium	1.07 MeV	3.8 days	1.1mm	RSO of middle sized joints	55-185MBq
^{169}Erbium	100 KeV	9.5 days	0.3mm	RSO of small joints	10-40MBq

Mechanism of Action:

Radioactive particles are administered intra-articularly in joints in colloidal form. Size of the particles is 5-10 nm. Inflamed synovial tissue exposed to beta radiation undergoes coagulation necrosis and fibrosis, which reduces effusion, swelling, and discomfort. Follow-up is after 6 months with scintigram. RSO demonstrated high response rates and a improvement in life quality.

Other therapies using Ionizing radiation:

Radioimmunotherapy:

It is a combination of therapeutic radionuclide (^{90}Y or ^{131}I) with a monoclonal antibody used to treat malignancies such as non-Hodgkin's lymphoma (NHL) and Her2+ breast cancer.

Anti-CD20 antibodies radiolabelled with ^{90}Y-ibritumomab Tiuxetan or ^{131}I-tositomumab are available commercially for treatment of relapsed NHL. They showed good response rates. ^{177}Lu-Trastuzumab used in Her2-neu overexpressing breast cancers.

Intra-arterial Hepatic PRRT using ^{90}Y-microspheres:

Radiolabelled therapeutic microspheres are delivered via hepatic artery to deliver selective internal radiation directly to the region of tumor. Hepatic artery primarily supplies blood to tumours while portal vein supplies normal liver parenchyma, therefore, tumors selective receive high dose energy can be delivered through this approach. ^{90}Y-SIR-spheres has been

FDA approved for treatment of hepatic metastasis from colon cancer and ^{90}Y-Theraspheres has been approved for treatment of unresectable hepatocellular carcinoma.

External beam Radiotherapy:

Radiation beams used in external radiation therapy come from photons, protons or electrons; however, photon beams are used in most radiation therapy machines, which can reach tumors located deep within the body. Photon beams disperse little amounts of radiation along their route as they move through the body. After they pass into the tumor, these beams continue into surrounding normal tissue.

Proton beams are also able to penetrate deep-seated malignancies in the body. Proton beams, on the other hand, cease as soon as they reach the tumor and do not disperse radiation while passing through the body. Radiation exposure to normal tissue may be minimized using proton beams, however high expenses and size of the machines limit their use.

Photon beams are delivered by linear accelerator, proton beams by particle accelerator and electron beams by linear or particle accelerator.

Delivering the maximum amount of radiation prescribed to the tumor while protecting the adjacent normal tissue is the aim of radiotherapy. For each type, a computer is used to evaluate tumor images and determine the most accurate treatment course and dosage. The term *teletherapy* refers to treatment from a distance, while *brachytherapy* refers to treatment delivered from within, through a sealed source inside the body. Of these, teletherapy is the commonest form, wherein the patient sits or lies down and an external ionizing radiation is directed towards the particular tumor site.

In 3-D conformal radiation therapy (3-D CRT), radiation beams are delivered from different directions which matches the shape of tumor. In intensity-modulated radiation therapy (IMRT), strength of beam is pointed to a certain area and this allows less damage to nearby normal tissues. In image guided radiation therapy (IGRT), radiation oncologist uses imaging scans like CT or MRI before each treatment and adjusts the position of patient to avoid the unwanted radiation exposure to normal tissues. In stereotactic radiosurgery (SRS), large dose of radiation is given to a small tumor area in one session. It is usually used for brain tumor.

Proton beam radiotherapy is mainly used for tumors that are close to critical structures such as melanoma of eye, tumors of spine, sarcoma near base of the skull and certain head and neck tumors etc.

EBRT technology	Uses	Advantages
3-D CRT	Brain tumors, gynecologic malignancies, lung cancer, gastrointestinal (GI) cancer, and breast cancer	Wide-spread availability, uniform dose and results
IMRT	Head & neck, brain, breast, lung, prostate, gynecologic, and gastrointestinal cancers	Offers a high degree of precision and compliance

	prostate, gynecologic, and gastrointestinal cancers	and compliance
IGRT	Head and neck, lung and prostate cancers	Decreased toxicities to normal nearby tissue due to a significant reduction in set-up margins
SBRT	Pancreatic, head and neck, spinal, renal, and oligometastases	Delivers substantial radiation doses to the tumor with minimal chance of death or postoperative complications
Proton Particle therapy	Prostate cancer, chordoma, stage II–III NSCLC, and hepatocellular carcinoma, sarcomas, renal cell carcinomas, melanomas, and glioblastoma	Reduction in normal tissue doses and higher biological effectiveness

[B]. IMAGING WITH IONIZING RADIATION: A BRIEF ENUMERATION

I. PLANAR IMAGING WITH GAMMA RAYS, SPECT and PET:

Gamma rays are electromagnetic radiation, which have no mass and electric charge, and they travel at the speed of sound. These gamma photons are able to penetrate through most materials except lead due to their very high energy. Imaging with gamma rays uses this penetrative property, which are emitted by various nuclei of radioactive elements.

Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography(SPECT) are two nuclear medicine imaging technique, in which PET uses positron emitting radioisotopes like ^{18}F-FDG and SPECT uses gamma emitting radioisotopes like ^{99m}TC. The detectors used in PET and SPECT typically consist of a scintillation crystal that transforms incident gamma radiation into visible scintillation light and a photodetector that collects the scintillation light and turns it into an electrical pulse. Based on the buildup of radioactive tracer molecules, these imaging techniques provide functional information. However, because SPECT and PET lack anatomical information, their integration with anatomical imaging technologies like CT or MRI is called Hybrid SPECT-CT or PET-CT imaging[23]. Imaging with gamma rays has wide range of functions including thyroid imaging, brain imaging, cardiac imaging, infection imaging and wide variety of tumor imaging.

1. Thyroid scintigraphy:

Scintigraphic evaluation of the thyroid gland, which enables the determination of ^{123} Iodine or ^{99m}Tc-pertechnetate uptake and distribution, is the most accurate method for the diagnosis and quantification of thyroid function, such as autonomy, as well as the detection of ectopic thyroid tissue. Additionally, thyroid scintigraphy and radioiodine uptake assays are helpful for separating hyperthyroidism from thyroiditis and, respectively, iodine-induced hyperthyroidism[24]. (Fig 6).

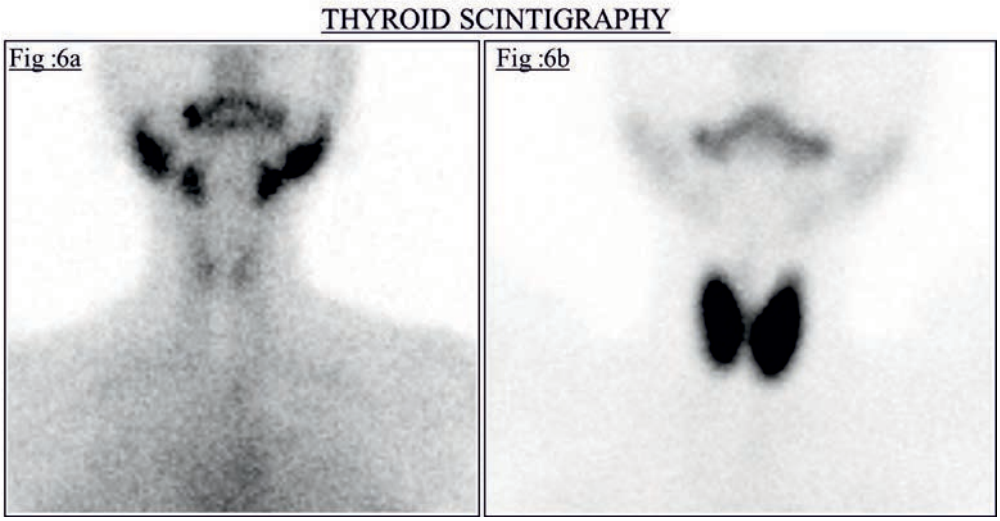

Fig 6. ^{99m}Tc Pertechnetate scan showing thyroiditis (Fig 6a) and Graves' disease (Fig 6b)

2. Parathyroid imaging:

In primary hyperparathyroidism (pHPT), nuclear medicine parathyroid imaging is a well-established approach to detect overactive parathyroid glands, but it may also be helpful in secondary hyperparathyroidism (sHPT) prior to surgical intervention. The presence and number of hyperactive parathyroid glands can be determined via parathyroid radionuclide imaging using scintigraphy or positron emission tomography (PET). It is also helpful to identify ectopic parathyroid glands[25,26]. The following imaging modalities can be utilized to localize parathyroid adenomas: 99mTc-sestamibi dual phase planar with or without SPECT/CT, dual isotope imaging in combination with ^{123}I-iodide, ^{11}C-Methionine PET/CT and ^{18}F-Fluorocholine PET/ CT(6).

3. Skeletal scintigraphy:

Patients with primary osteoblastic skeletal or metastatic illness can benefit from skeletal scintigraphy's valuable information for diagnosis, staging, restaging, and treatment monitoring[27]. It is also having high sensitivity for detecting a wide variety of metabolic bone disorders like Paget's disease, fibrous dysplasia, hyperparathyroidism etc, even though it is non-specific. (Fig 7)

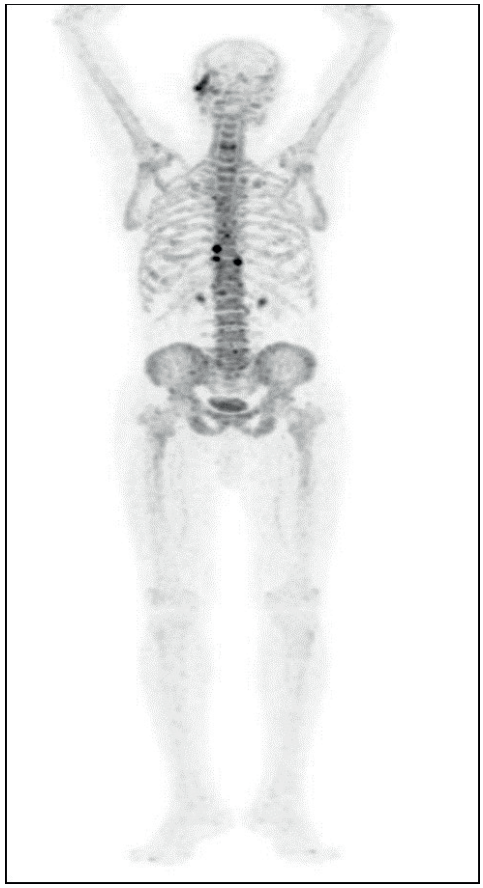

Fig 7. ^{18}F-NaF skeletal PET imaging showing skull based osteomyelitis

Technetium-99m (^{99m}Tc) complexed to a diphosphonate, either methylene diphosphonate (MDP) forming ^{99m}Tc-MDP or hydroxydiphosphonate (HDP) forming ^{99m}Tc-HDP.

The most used radiopharmaceutical for skeletal scintigraphy is ^{99m}Tc-MDP (methylene diphosphonate), a SPECT agent. Osteoblastic activity and, to a lesser extent, skeletal vascularity are the two main factors that influence the uptake of ^{99m}Tc-labelled diphosphonate in the skeleton[28]. In the mineral phase of bone, crystalline hydroxyapatite is complexed with MDP and HDP by a process known as chemisorption. Specifically, ^{99m}Tc phosphonates localize to bone in proportion to osteoblastic activity as shown at areas of bony remodeling and, to a lesser extent, in proportion to blood flow and the radiotracer delivered by it. PET agent used for skeletal imaging is ^{18}F-NaF PET. The uptake mechanism for ^{18}F-NaF PET is comparable to that of ^{99m}Tc-MDP. To create fluoroapatite, ^{18}F ions interact with hydroxyl ions (OH) on the surface of bone's hydroxyapatite. With more binding sites (such as in osteoblastic/lytic processes) or more blood flow, processes that increase bone exposure result in greater absorption. Blood flow is the rate-limiting process.

4. Hepatic scintigraphy: (Fig 8)

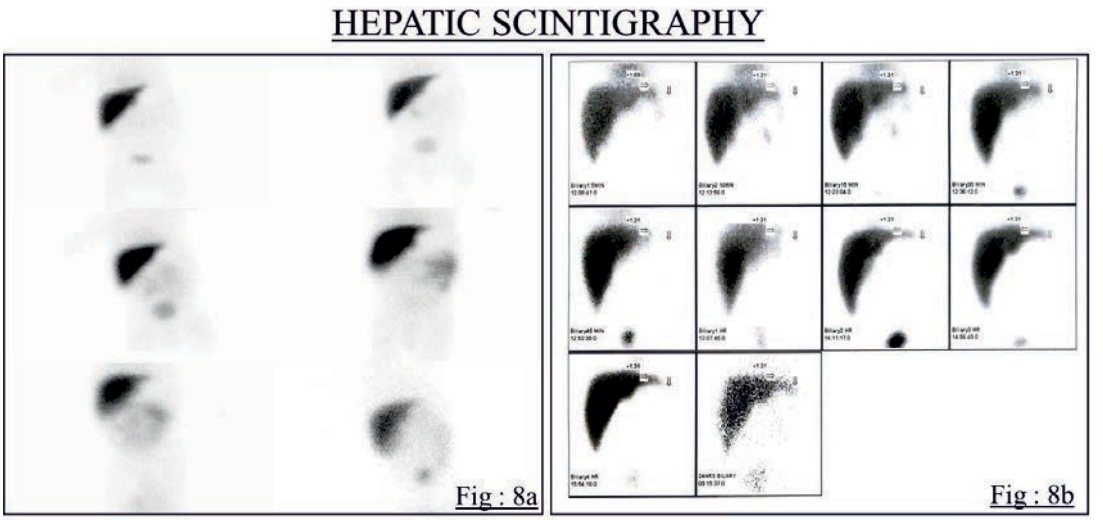

Fig 8. ^{99m}Tc-HIDA hepatobiliary study: Fig 8a shows normal hepatobiliary function. Fig 8b shows Mild hepatomegaly with preserved hepatocellular function. In view of non visualization of radiotracer in the gut even by 24 hours, thus diagnosis of biliary atresia can not be ruled out.

Liver imaging with radiolabelled sulphur colloid is used for hepatic imaging (taken up by Kupffer cells in the liver), while biliary scintigraphy or 'Cholescintigraphy' is a commonly used Nuclear Medicine imaging for evaluation of liver function of bile metabolism from uptake of bilirubin in the liver to drainage into bowel.

The classification of liver imaging agents, based upon the function they perform, is enlisted in the below-mentioned table:

	Morphology	^{99m}Tc -Sulphur colloid, ^{198}Au, ^{67}Ga-Citrate
	Physiology	
a)	Hepatobiliary agents	^{99m}Tc-HIDA, ^{99m}Tc-PG, ^{131}I-rose Bengal
b)	Receptor specific agents	^{99m}Tc-GSA, ^{111}In-Octreotide, ^{99m}Tc-monoclonal antibody, ^{99m}Tc-monoclonal antibodies
c)	Blood pool agents	^{99m}Tc-RBC, ^{99m}Tc-albumin

5. Renal scintigraphy: Renal scintigraphy is most commonly used to assess renal perfusion and function, obstruction (diuretic renography), renovascular hypertension (captopril renogram), infection (renal morphology scan), presurgical quantitation (nephrectomy), renal transplant, congenital anomalies, and masses. (Fig 9a and 9b)

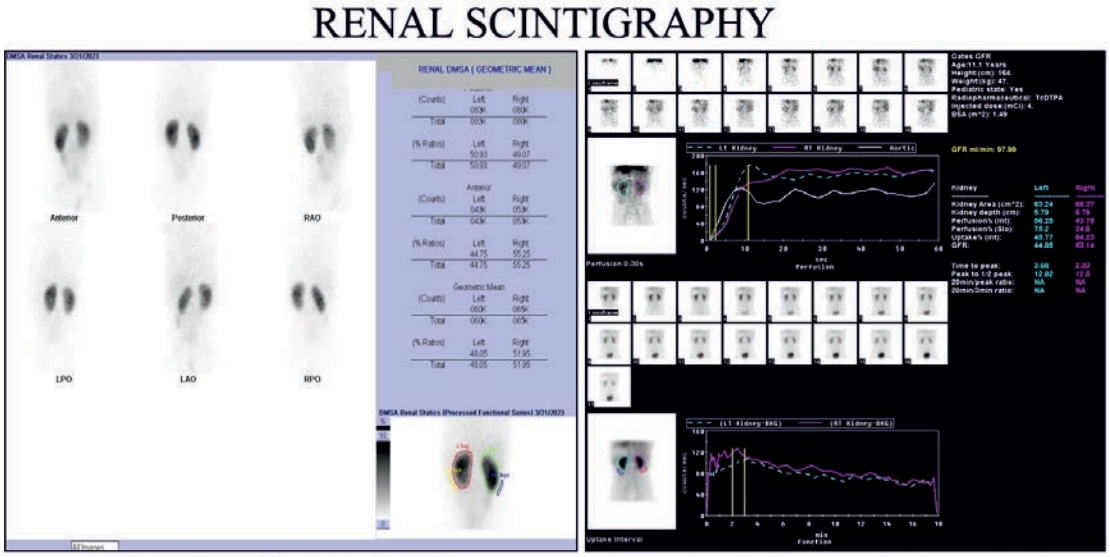

Fig 9a : Normal ^{99m}Tc-DMSA scan

Fig 9b: Normal ^{99m}Tc-DTPA renogram study

Fig 9. Renal Scintigraphy

RENAL RADIOTRACERS: a classification based upon specific renal function evaluation

Clinical question	Agent
Perfusion	^{99m}Tc-MAG3, ^{99m}Tc-DTPA, ^{99m}Tc-GHA
Morphology	^{99m}Tc-DMSA, ^{99m}Tc-GHA
Obstruction	^{99m}Tc-MAG3, ^{99m}Tc-DTPA, ^{99m}Tc-OIH
Relative function	All
GFR quantification	^{125}I-Iothalmate, ^{51}Cr-EDTA, ^{99m}Tc-DTPA
ERPF quantification	^{99m}Tc-MAG3, ^{99m}Tc-OIH

The mechanism of localization of renal radiotracers employed for assessing kidney function and drainage are numerated below:

Radiotracers	Mechanism of uptake
^{99m}Tc -DTPA	Glomerular filtration(100%)
^{99m}Tc-MAG3	Tubular secretion (100%)
^{131}I and ^{123}I hippuran	Tubular secretion (80%) and glomerular

	filtration (20%)
^{99m}Tc-DMSA	Cortical binding (40%)
^{99m}Tc-Glucoheptonate	Glomerular filtration (80%) and cortical binding (20%)

6. Cardiac scintigraphy and PET:

Radionuclide molecular imaging of the heart provides non-invasive functional information that is complimentary to the more invasive imaging like coronary angiography and ventriculography. Myocardial perfusion imaging or scintigraphy (MPS) using single photon emission computed tomography (SPECT) or positron emission tomography (PET) is a well-established mode of investigation in the diagnosis and evaluation of patients with known coronary artery disease. For stressing, traditionally, treadmill test for physical stressing (TMT) and adenosine or dobutamine are employed for pharmacological stress testing.

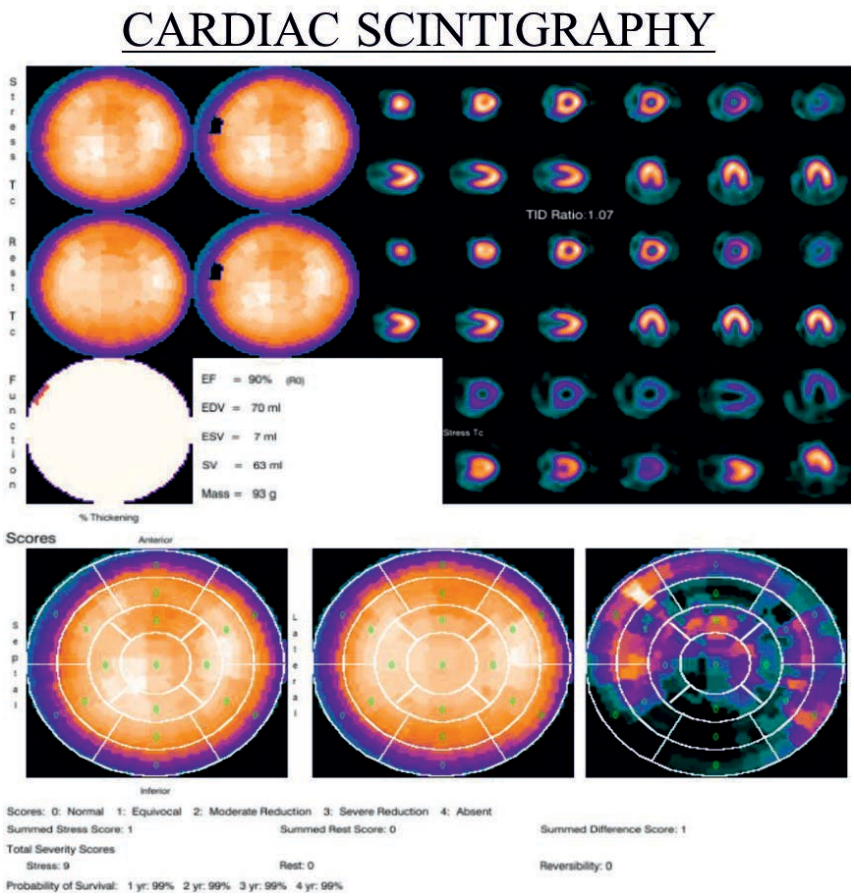

Fig 10. ^{99m}Tc-Sestamibi myocardial perfusion scintigraphy showing all myocardial segments show normal perfusion showing normal perfusion on cardiac stress and rest MPI.

The commonly used radiotracers for Cardiac Perfusion and Viability Assessment are enlisted in the below-mentioned table (Fig 10):

CLINICAL QUESTION	Radiotracer Employed
Myocardial perfusion	SPECT agents: ^{201}Tl-Chloride, ^{99m}Tc-Sestamibi, ^{99m}Tc-Tetrophosmin PET agents: ^{13}N-Ammonia, ^{82}Rubidium, ^{15}O-Water
Viability	^{201}Tl-Chloride, ^{18}F-FDG usually in combination with ^{99m}Tc-Isonitriles or PET perfusion tracers
Fatty acid metabolism	^{123}I-BMIPP, ^{11}C-Palmitate
Presynaptic cardiac neurotransmission	SPECT agent : ^{123}I – *meta*-Iodobenzyl-guanidine(mIBG) PET agent : ^{11}C-Meta-hydroxyephedrine, ^{18}F-Fluoronorepinephrine

7. Brain scintigraphy and PET:

Radionuclide imaging of brain is useful along with the anatomical imaging methods. Even though Regional cerebral blood flow (rCBF) measurement is a key component of SPECT imaging, which is used to evaluate a variety of features of brain physiology. The radiopharmaceuticals most frequently utilized for rCBF SPECT imaging include ^{99m}Tc-HMPAO and ^{99m}Tc-ECD. A normal study shows symmetrical radiotracer distribution within the brain, whereas abnormalities are indicated by areas of relatively reduced activity. Brain perfusion SPECT plays an important role in diagnosis of Alzheimer's disease, frontotemporal dementia, multiple infarct dementia, pick disease, Creutzfeldt-Jakob disease, etc. that are only a few neurological disorders which influence rCBF, and SPECT is crucial in the identification of these conditions. These tracers are also useful for investigation of seizures. Epilepsy may be sometimes associated with a focal space occupying lesion and this can be detected my CT or MRI. In other cases, where CT and MRI are normal, a cerebral perfusion scan helps pinpoint the seizure focus, which is useful for guiding surgical planning. Also ^{111}In-DTPA is helpful for evaluation of shunt patency and to diagnose CSF leak. ^{201}Tl is used to diagnose tumor recurrence versus fibrosis/necrosis, which is now vastly replaced by the PET agents like FDG-PET and FET-PET. Iodine-123-beta-carbomethoxy-3 beta-(4-iodophenyltropane) (CIT) and ^{123}I-FP-CIT(DaTSCANS) are helpful in the confirmation or rejection of the loss of dopamine-producing nerve cells in parkinsonian disorders.

8. Infection imaging:

Infection imaging is another area where SPECT and PET tracers have been utilized. The below-mentioned table enlists some important tracers and their mechanism of uptake for infection and inflammation (Fig 11).

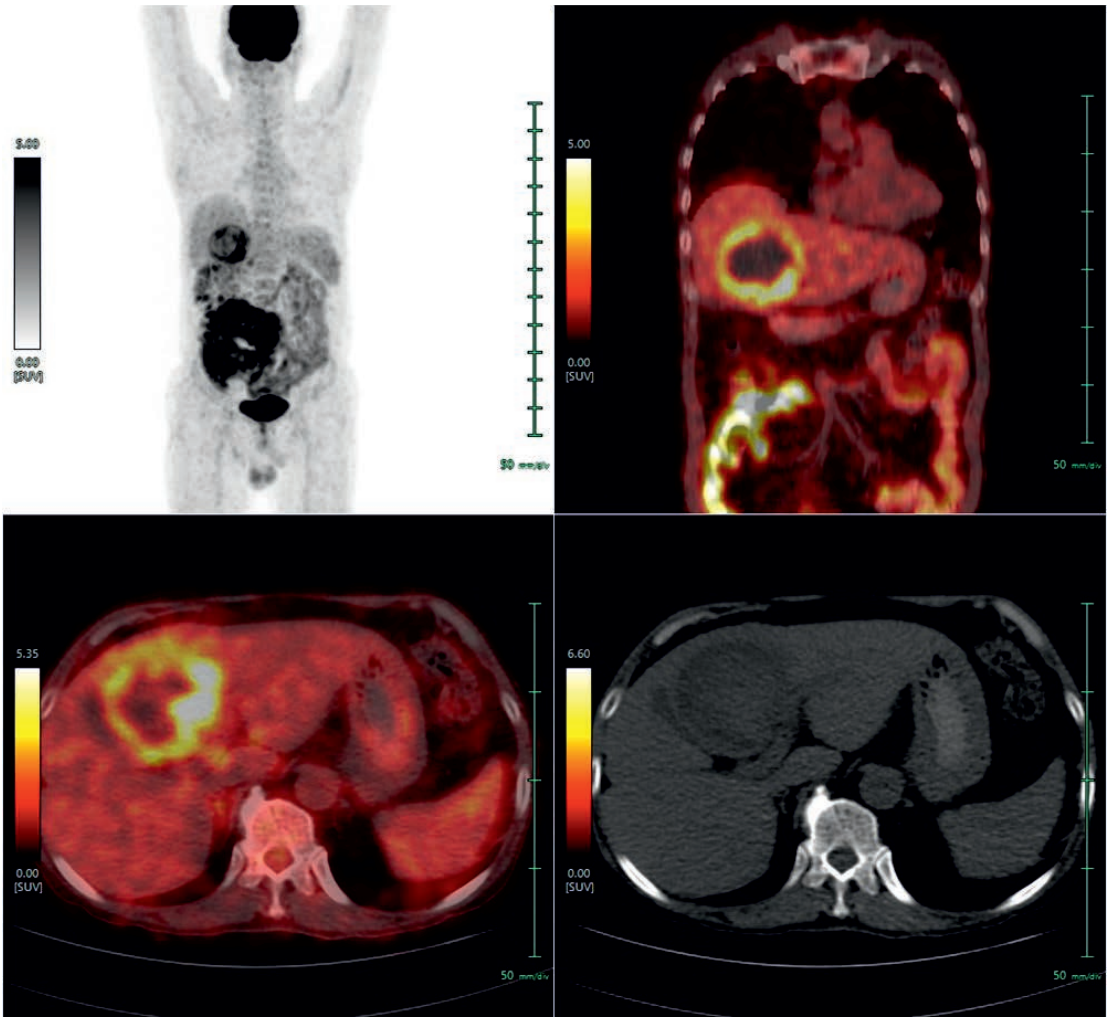

Fig 11. ^{18}F-FDG-PET/CT FOR INFECTION IMAGING. A 60-year-old male patient, presented with Pyrexia of Unknown Origin (PUO); CRP: 122.7mg/dl; normal d dimer; sputum AFB & C/S negative; malaria negative; Patient was on antibiotics. The ^{18}F-FDG-PET/ CT scan demonstrated well defined, peripherally hypointense and centrally iso-intense liver lesion in segment IVA with peripheral FDG avidity, associated with central photopenia, the clinical and scan findings were favorable for liver abscess.

SPECT and PET tracers	Mechanism of uptake
^{67}Ga-Citrate	Transferrin and lactoferrin binding
^{99m}Tc-HMPAO	Migration of leukocytes
Leukoscan (Tc-anti-NCA-90 FAB anti-granulocyte antibody)	Increased vascular permeability and binding & migration of antibody-labelled granulocytes.
^{99m}Tc-Ciproflaxacin	Binds to DNA gyrase enzyme in living bacteria
Radiolabelled human non-specific immunoglobulin G	Inflammation-related macromolecular entrapment and increased capillary permeability
FDG-PET	GLUT receptor (1 & 3)overexpression on the activated inflammatory cells (neutrophils and the monocyte/macrophage family) & Hexokinase activity

9. Tumor imaging:

SPECT and PET tracers play a major role in tumor imaging. Over the past 3 decades FDG-PET/CT has found very important applications for oncological imaging.

a) Examples of SPECT tracers for Tumor Imaging: ^{201}Tl-Thallium, ^{111}In-Octreotide, ^{123}I-mIBG, 99mTc-Sestamibi, ^{131}I-Iodine, ^{123}I-Iodine etc.

b) Examples of PET tracers for Tumor Imaging: ^{18}F-FDG, ^{11}C-Thymidine, ^{18}F-Flurothymidine, ^{11}C-Methionine, ^{11}C-Choline, ^{18}F-Fluorocholine, ^{11}C-Tyrosine, ^{18}F-Fluorotyrosine.

[^{18}F] Fluorodeoxyglucose, abbreviated as [^{18}F] FDG, or FDG, is a radiopharmaceutical, used widely in the positron emission tomography (PET) imaging for cancer and non-oncological disorders, including cardiac, neuropsychiatry and infection-inflammation imaging. FDG-PET/CT has grown over the last three decades impacting diagnosis, initial staging, and restaging, treatment response monitoring and disease prognosis in a wide variety of malignancies. (Fig 12)

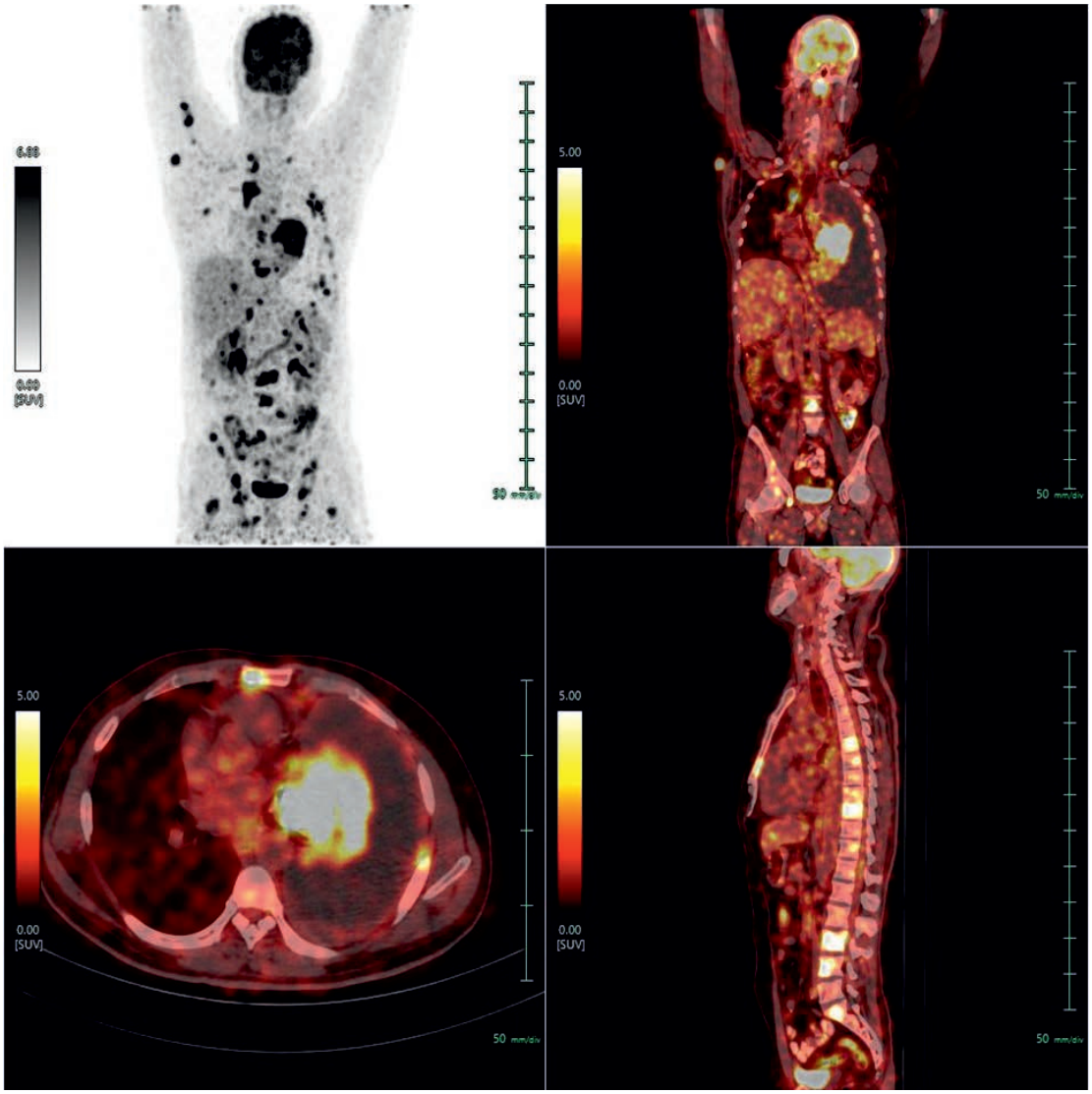

Fig 12. ^{18}F-FDG PET/ CT FOR CARCINOMA STAGING. ^{18}F-FDG-PET/ CT was done in a patient with carcinoma lung shows

- **FDG avid left lung mass with left sided pleural effusion. – Metabolically active biopsy proven primary lung carcinoma.**
- **FDG avid mediastinal, cervical lymph nodal and multiple lytic skeletal lesions – Metabolically active mediastinal and cervical lymph nodal & skeletal metastases.**

***PET/ CT staging as per 8th edition of AJCC is T3N3M1c – Stage IV**

II. IMAGING USING X-RAYS:

A number of clinical modalities have been used for diagnostic purposes. These include:

1. **Conventional radiography (X-rays) and dental X-rays:**
   In conventional radiography, an image is created by creating an X-ray beam and passing it through the patient to a radiation detector or a piece of film. Depending on tissue density, different soft tissues attenuate x-ray photons in different ways; the denser the tissue, the whiter (more radiopaque) the image.
2. **Mammography:**
   This is an x-ray imaging technique employed to inspect the breast in order to examine and detect early signs of breast pathologies such as breast carcinoma, wherein it functions as a screening and diagnostic tool.
3. **DEXA Scans (bone density):**
   Dual-energy X-ray absorptiometry (DEXA) is an imaging method that used to measure bone mineral density
4. **CT Scans:**
   A computed tomography (CT) scan is a type of medical imaging procedure that uses x-rays to produce images of different body cross-sections, and constitutes a very important modality for both benign and malignant disorders of several body organs.
5. **Fluoroscopy:** Images of moving objects or structures are generated continuously using an X-ray beam.

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Abbreviations :

- AFTN – Autonomously Functioning Thryoid Nodule
- CT – Computed Tomography
- DEXA - Dual-energy X-ray absorptiometry
- DTC – Differentiated thyroid cancer
- FDA – Food and Drug Administration
- FDG- Flurodeoxyglucose
- GLUT – Glucose transporter
- KI - Potassium iodide
- mCRPC-Metastatic Castration-Resistant Prostate Cancer
- NHL- Non-Hodgkin’s Lymphoma
- pHPT- Primary hyperparathyroidism

- PET – Positron Emission Tomography
- PRRT - Peptide Receptor Radionuclide Therapy
- PSA- Prostate specific antigen
- PSMA- Prostate specific Membrane Antigen
- PRLT- PSMA (Prostate specific Membrane Antigen) directed radioligand therapy
- RAI – Radioactive Iodine
- rCBF- Regional cerebral blood flow
- RSO- Radiation Synovectomy
- sHPT - Secondary hyperparathyroidism
- SPECT – Single Photon Emission Tomography
- SSTR-Somatostatin receptor
- TMT-Treadmill test
- TSH – Thyroid stimulating hormone
- mIBG- *meta*-Iodobenzyl-guanidine
- NET- Neuroendocrine tumors
- 3D-CRT- 3D- conformal radiation therapy
- IMRT – Intensity Modulated radiation therapy
- IGRT -Image guided Radiation therapy
- SRS- Stereotactic radiosurgery