Nuclear Medicine in Healthcare

6

Clinical PET/CT, Nuclear Cardiology and Radionuclide Therapy: Current Status & New Developments

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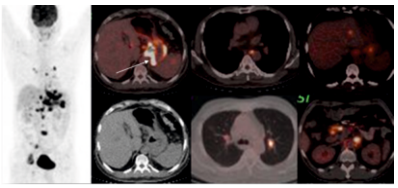

PET-CT MIP and fused axial images

ABSTRACT

This review discusses the current practices and newer developments in 3 important domains of Nuclear Medicine: (a) Clinical PET/CT, (b) Nuclear Cardiology & (c) Radionuclide Therapy. Their applications in cancer and non-oncological diseases through each of these modalities have been enumerated and discussed, citing specific clinical illustrations in each given scenario, with enlistment of various radiotracers and their specific uses.

KEYWORDS: *Nuclear medicine, PET/CT, Radionuclide Therapy, Oncology, Cardiology, Radiopharmaceuticals*

Introduction

Molecular imaging involves in vivo characterization of biologic processes and their measurement at the cellular and molecular level. This enables early discovery of changes in tissues since functional alteration in tissues often precedes changes in anatomy. In Nuclear Medicine, radiolabelled molecules called radiopharmaceuticals are used for diagnosis and treatment of disease. Rapid developments in diagnostic methods and analysis have led to a paradigm change in disease management, with the process of diagnosis and treatment shifting from standard to personalized treatment[1].

Developments

One major development in the molecular imaging is the Positron Emission Tomography/Computed Tomography (PET/CT). Positron emission tomography (PET) is increasingly being used for the diagnosis, staging, restaging and follow-up of various cancers and also for various benign applications. It has an important role in the evaluation of various tumors including solitary pulmonary nodules, non–small cell lung carcinoma, lymphoma, melanoma, breast cancer, and colorectal cancer [2]. PET is based on the detection of annihilation photons (γ) released when positron emitting radionuclides, such as F-18, Ga-68, C-11, and O-15, emit positrons (β^+) that undergo annihilation with electrons. The photons thus released have energies of 511 keV (0.511 MeV) and are detected by the detector in the PET scanner. FDG is currently the most widely used PET radiopharmaceutical in clinical oncology in addition to its clinical applications in cardiology and neurology [3].

PET with FDG allows direct evaluation of the cellular glucose metabolism. Glucose has been shown to be a major source of energy for the cancer cells. Tumor cells are usually fast growing in comparison to normal cells, and thus require additional energy to sustain their rapid growth rate. Whole-body FDG-PET/CT imaging is used to detect the spread of disease before they are noted by other imaging modalities, thus, improving staging and patient treatment, monitoring drug therapy and differentiating between active tumor and necrotic scar tissue which may be indistinguishable by other imaging modalities. When treating patients with chemotherapeutic agents or radiation therapy, standard anatomic imaging using CT or MR imaging may not be able to show the efficacy of therapy through structural changes early in the course. By using ^{18}F-FDG-PET to monitor the bio-chemical changes in the tumor site, the effectiveness of therapy can be determined early [4].

Various PET radiotracers have been used clinically, and can be classified based on their mechanism of localization:

Metabolism

- Glucose metabolism: ^{18}F-fluorodeoxyglucose (FDG), cyclotron produced, half-life 110 minutes (most commonly used)
- Bone metabolism: ^{18}F-fluoride
- Membrane lipid synthesis: ^{11}C-acetate, ^{18}F-choline.
- Amino acid transport & metabolism: ^{11}C-methionine, ^{18}F-tyrosine.

Perfusion

- ^{15}O-water (cyclotron produced, $T_{1/2}$ = 2 min)
- ^{13}N-ammonia (cyclotron produced, $T_{1/2}$ = 10 min)
- ^{82}Rubidium chloride (generator produced, $T_{1/2}$ = 78 sec)

DNA Synthesis

- ^{18}F-fluorothymidine (FLT), ^{11}C-Thymidine

Receptor Expression

- Somatostatin receptors: ^{68}Ga-DOTA-TATE/TOC/NOC (Neuroendocrine tumors)

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- Estrogen receptors: ^{18}F-fluoroestradiol(Breast cancer)
- Dopamine receptors: ^{18}F-fluoroDOPA (Neuroendocrine tumors)
- Benzodiazepine receptors: ^{18}F-flumazenil (Epilepsy)

Hypoxia

- ^{18}F-MISO, ^{64}Cu-ATSM

Angiogenesis

- ^{68}Ga-RGD (arginine-glycine-aspartic acid)

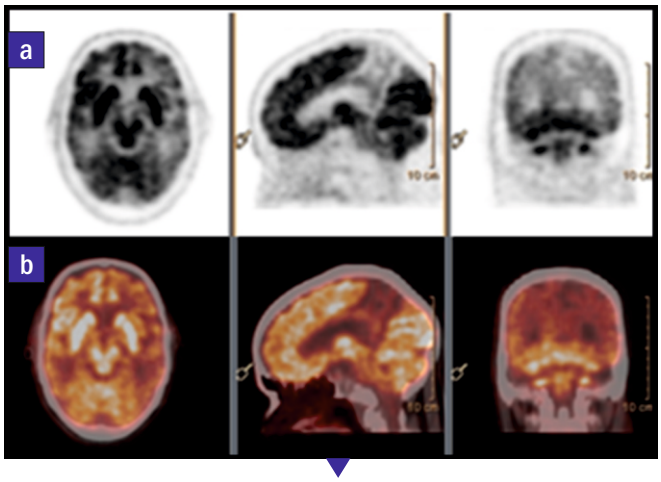
Applications

Neurology

PET is extensively used in neurology. In patients with different subtypes of dementia, FDG-PET shows distinct spatial patterns of metabolism in the brain and can help clinicians to make a reasonably accurate early diagnosis, for appropriate management or prognosis. Specific patterns help differentiate Alzheimer's dementia, frontotemporal dementia, dementia in patients with mild cognitive impairment and HIV-dementia complex [5]. PET has an important role in initial staging and restaging of brain tumors. In gliomas, PET is done for the assessment of response to a certain anticancer therapy including its (predictive) effect on the patients' outcome and the differentiation of treatment-related changes (eg, pseudo-progression and radiation necrosis) from tumor progression at follow-up [6]. PET helps to identify the focus of seizures in drug refractory epilepsy thus guiding the surgical management. The utility of PET in different neuropsychiatric disorders is also being actively explored.

Nuclear Cardiology: SPECT and PET

RMC has been carrying out radionuclide myocardial perfusion scintigraphy studies since more than three decades and over the years the technique itself has evolved, making it more reliable and robust, with additional ventricular functional



Images of a 62 years old male with memory loss. FDG-PET (a) and PET/CT fused (b) axial, sagittal and coronal images show left posterior parietotemporal hypometabolism suggestive of early Alzhiemer's disease.

Non-FDG PET Radiotracers used at the Radiation Medicine Centre for patients

PET Radiotracers	Biochemical Process	Mechanism of Uptake or Localization	Clinical Indications
[18F] Fluoride	Bone metabolism	Incorporation in the hydroxyapatite crystals in bone	Evaluation of bone metastases/ benign bone lesions.
[18F] Fluorothymidine (FLT)	DNA synthesis	Substrates for thymidine kinase (TK-1) for DNA synthesis and reflects tumor cell proliferation rate	Disease Proliferation: carcinoma of brain, breast, lung, cervix, marrow disorders
[^{18}F]FMISO	Hypoxia	Intracellular reduction and binding	Brain tumors, breast carcinoma, myocardial ischemia
[18F] Fluoro-ethyl-tyrosine (FET)	Amino Acid	Amino acid metabolism & reflects tumor cell proliferation rate	Differential Diagnosis and grading of Brain tumors, Treatment response
^{68}Ga-DOTATATE	Receptor Binding	Specific binding to somatostatin receptor (SSTR-II, III, V)	Neuroendocrine tumors
^{68}Ga-PSMA-11	Receptor Binding	Binding to Prostate-specific membrane antigen (PSMA), cell surface protein expressed abundantly in prostate carcinoma.	Castrate resistant prostate cancer
^{68}Ga- RGD (arginine-glycine-aspartic acid)	Angiogenesis	High affinity towards the integrin αvβ3 over-expressed on the tumor vasculature.	Carcinoma of thyroid, breast, lung, glioma, ischemic heart disease.

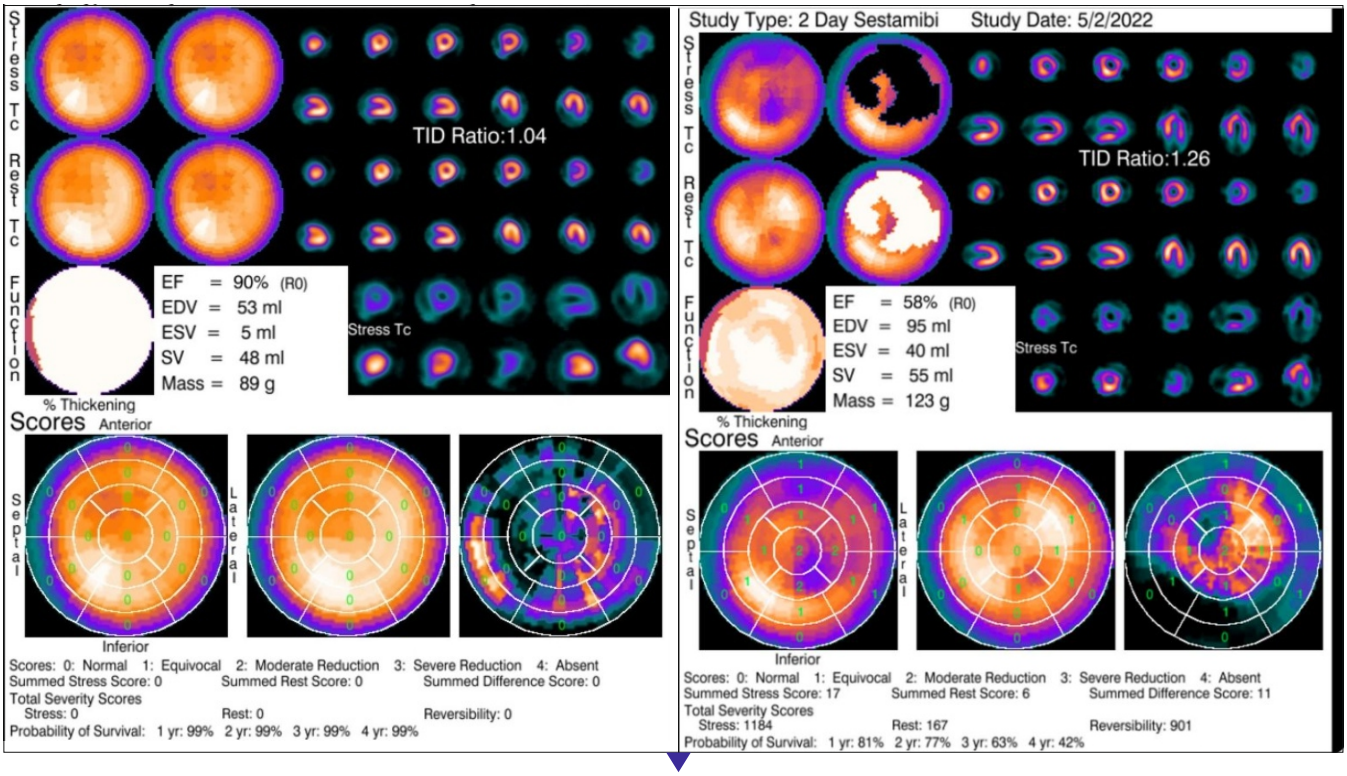
information that further defines the prognosis in these patients. Thallium-201 chloride was used clinically for imaging myocardial perfusion scintigraphy studies at RMC before two decades. Because of its relatively long half-life and low-energy X-ray emission, it is not the ideal agent for imaging, giving a relatively large radiation dose with lower image quality than technetium agents. Since early part of the 2000s, 99mTc-MIBI radionuclide myocardial perfusion scintigraphy (MPS) has been established using as the main functional cardiac imaging technique at RMC for the assessment of ischaemic heart disease (IHD). Despite a growing number of alternative functional imaging techniques, MPS still remains the most widely used technique in assessing IHD and predicting prognosis.

Myocardial perfusion scintigraphy (MPS) using single photon emission computed tomography (SPECT) or positron emission tomography (PET) is a well-established mode of investigation in the diagnosis of acute-onset chest pain as well as evaluation of patients with known coronary artery disease. MPS is used to look at the changes in blood flow with stress. Traditionally, we use treadmill for physical stressing to increase oxygen demand in healthy arteries, leading to coronary vasodilatation and increased blood flow. In stenosed arteries, there is no increased flow despite the increased demand for oxygen. This results in ischaemia with associated symptoms (pain). In Fig.1 both normal and reversible perfusion defects have been shown.

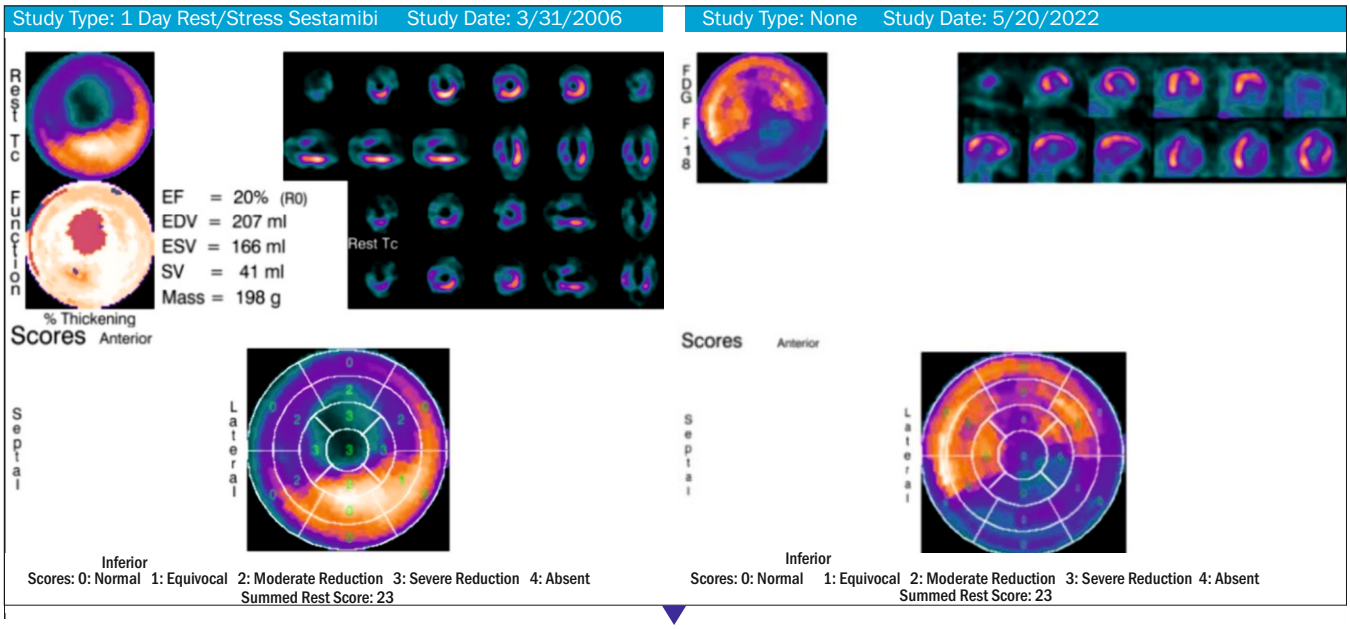
In patients who are unable to do physical exercise, dobutamine can be used to the same effect. Direct infusion of adenosine for coronary vasodilatation was soon introduced at RMC since early 2000. This has a short half-life of about 10 s, with the effects being reversible within minutes of stopping the infusion. This made adenosine a fast, safe and reliable drug to use for assessing the myocardial perfusion reserve in normal coronary arteries and the loss of perfusion reserve in significantly stenosed coronary arteries (commonly termed "ischaemia"). These pharmacological agents are now widely used in RMC to assess myocardial perfusion with no loss of diagnostic accuracy for identifying significant stenosis. Other than referrals from major hospitals of Mumbai, we get more than 300 referrals for MIBI MPS studies from BARC hospital mainly for diagnosis of ischemic heart disease and also to look for significance of borderline coronary artery disease.

PET exhibits unparalleled advantages regarding the absolute quantitation of myocardial blood flow and myocardial flow reserve. Typical perfusion agents used in PET include O-15 H_2O, N-13 NH_3, and Rb-82, which have defined first-pass extraction fractions. Another promising agent for myocardial perfusion PET is F-18 flurpiridaz.

^{18}F-FDG PET cardiac imaging has a high sensitivity in detecting viable myocardium. FDG uptake is considered as the biomarker of viable myocardium and a perfusion/metabolism mismatch (i.e., impaired perfusion with increased/preserved metabolism) is characteristic of ischemic viable myocardium that should be rescued through a revascularization procedure. For the detection of viable myocardium, glucose loading with/without intravenous insulin injection is required to enhance F-18 FDG uptake in the normal and the ischemic viable myocardium. (7) We have used ^{18}F-FDG PET scan to assess myocardial viability since the year 2002. This has a role in clinical practice in influencing patient management and improving clinical outcome. Unnecessary cardiac intervention thus can be avoided if FDG-PET study indicates no significant viable myocardium. In the next figure extensive viable myocardium is seen which after revascularization can improve left ventricular ejection fraction.



Images on the left-hand side show normal myocardial perfusion and right sided images show reversible myocardial perfusion defects in antero-septal and antero-lateral segments.



The left sided images show large myocardial perfusion defects in antero-septal and antero-lateral segments and the right sided images show significant FDG uptake in corresponding antero-septal and antero-lateral segments, suggesting as viable myocardium.

Oncology

PET is extensively used in the management of various malignancies like lymphomas, lung cancer, head and neck cancers, breast carcinoma, gastro-intestinal malignancies (esophageal, gastric, GIST, colorectal and anal malignancies), genitourinary malignancies (bladder, penile, cervix, endometrial), melanoma, mesothelioma, multiple myeloma, neuroblastoma, paraneoplastic syndromes, sarcomas, thymic carcinoma and carcinoma of unknown primary [8].

Detection and Initial Staging of Tumor

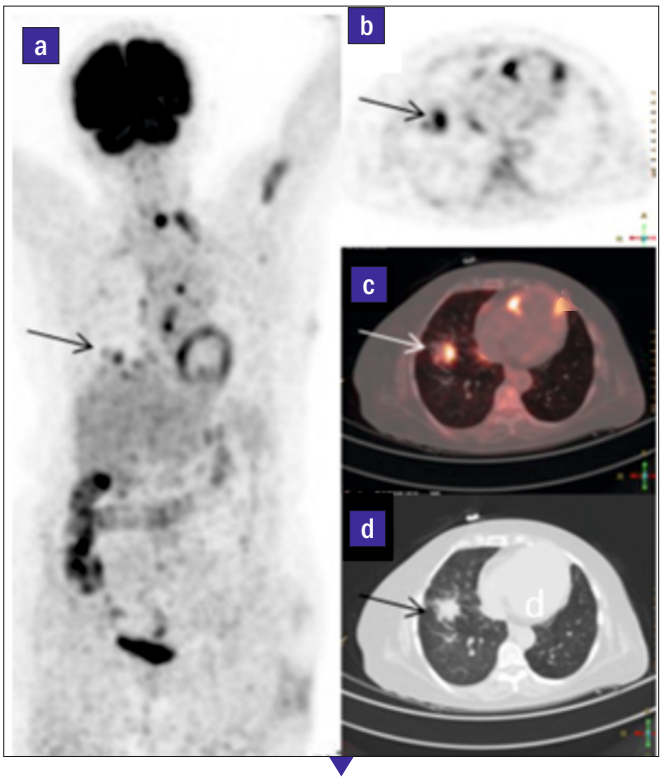
FDG-PET/CT has a vital role in the detection and staging of various malignancies, including lung carcinoma, breast carcinoma, lymphoma, carcinoma cervix and so on. It has been used in initial staging of patients with locally advanced or metastatic breast cancer or when conventional staging studies (e.g., CT or bone scan) are equivocal or suspicious and initial staging in patients with non-small cell lung cancer and selected patients with small cell lung cancer. PET helps in characterization of an indeterminate pulmonary nodule which is around 8-10 mm in diameter. In esophageal cancer, it helps in guiding the initial staging, primarily to assess resectability. In melanoma, PET helps in detection and localization of potential extranodal metastatic disease. PET forms a part of standard protocol in routine pre-treatment staging of patients with Hodgkin's lymphoma and different Non-Hodgkin Lymphoma subtypes. In colorectal cancer, it helps in pre-operative evaluation of patients with potentially resectable metastatic disease [2, 8, 9].

Monitoring Response to Treatment in Cancer

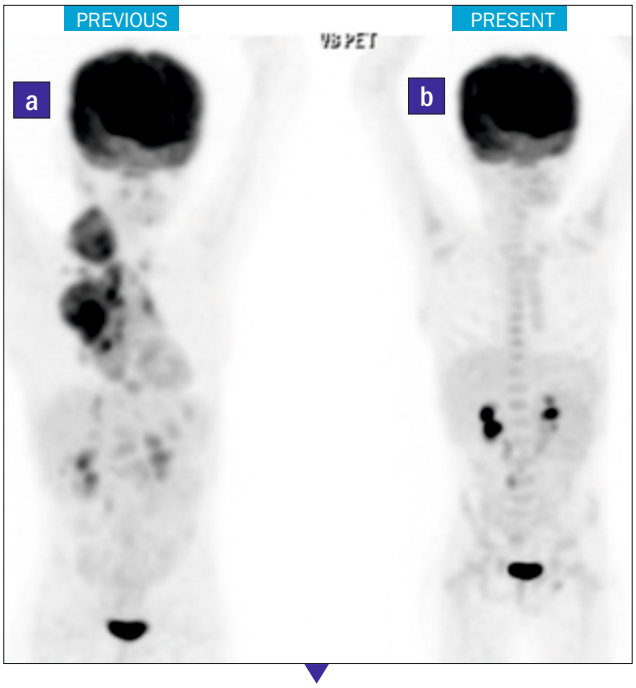
PET/CT is often done as a baseline imaging prior to treatment and then during or post-treatment for early response assessment. It is performed in esophageal cancer following definitive chemoradiation and in lymphoma after chemotherapy and/or radiation therapy. Interim PET or early treatment response after two cycles of chemotherapy helps in prognostication and may modify treatment in lymphomas, if there is no response or there is progression of the disease seen on PET/CT [9]. In gastrointestinal stromal tumors (GIST), FDG-PET/CT has a definite role in staging and evaluation of the response to imatinib mesylate [9].

Restaging of Cancer and Follow-up Evaluation for Recurrence

Early detection of recurrence is clinically important and can improve the prognosis and survival of patients with cancer. CT may underestimate the actual tumor burden by overlooking small tumor clusters in areas of distorted anatomy after treatment. FDG-PET is an effective whole-body imaging



The maximum intensity projection (MIP) (a) and axial PET (b), fused (c) and CT (d) images of a patient with carcinoma right lung show FDG avid 2 cm sized soft tissue mass involving the lower lobe of right lung, SUV max 4.62. The biopsy revealed adenocarcinoma. There was no evidence of metastatic disease and the tumor was deemed surgically resectable.



FDG-PET MIP images (a) of a 27 years old male with diffuse large B cell lymphoma at initial staging (left image) PET/CT shows right cervical and mediastinal lymph nodal involvement. MIP (b) of the same patient after six cycles of chemotherapy showing no abnormal FDG uptake anywhere in the body suggesting complete metabolic response.

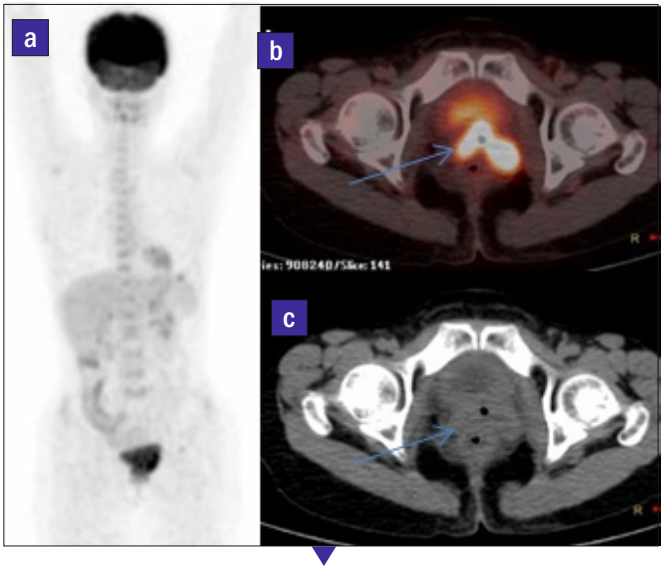
technique that detects metabolic changes preceding structural findings [10]. PET/CT plays an important role in the evaluation of recurrent colorectal cancer with elevated CEA level (carcinoembryonic antigen). The recent studies show a very large role of FDG-PET/CT for detection of recurrence [8, 9, 10, 11, 12]. Many of these patients go on to receive treatment with curative intent, thus indicating the importance of early detection of recurrent disease [10, 11, 12] PET–CT is also a very helpful modality in the assessment of ovarian cancer recurrence; it can detect and localize the recurrence with high accuracy in this situation, thus can influence and modify the treatment plan, and reduces the need for second look surgery. A recent study showed the accuracy, sensitivity, specificity, of PET/CT scan were 95.77%, 85.7%, 97.89% respectively [13].

PET is also helpful in the follow-up or surveillance of various carcinomas like breast cancer (8). PET/CT has a high sensitivity in the early detection of relapse or second primary cancer in patients with head and neck squamous cell carcinomas, with significant management implications [13].

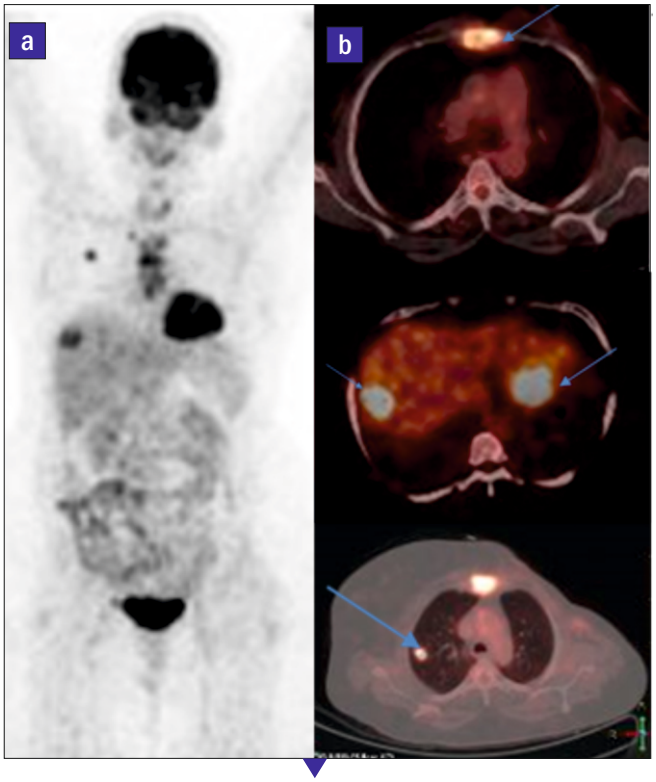
PET/ CT based Radiotherapy Planning

PET/CT has been used in the radiotherapy (RT) planning of cervical cancer, lung cancer, head and neck cancers, brain tumors and more. It correctly delineates the diseased area so that the radiation can be targeted to the tumor cells and spare the normal cells. This improves the efficacy of the treatment and reduces toxicity to normal tissues [14].

FDG-PET/CT imaging has been used for contouring the target for RT, and has been shown to change the irradiated volume significantly compared with CT imaging alone. Modern advanced imaging techniques with image fusion and motion management in combination with current generation highly conformal RT techniques have increased the precision of RT, and have made it possible to reduce dramatically the risks of long-term side effects of treatment while maintaining the high cure rates for these diseases [15].



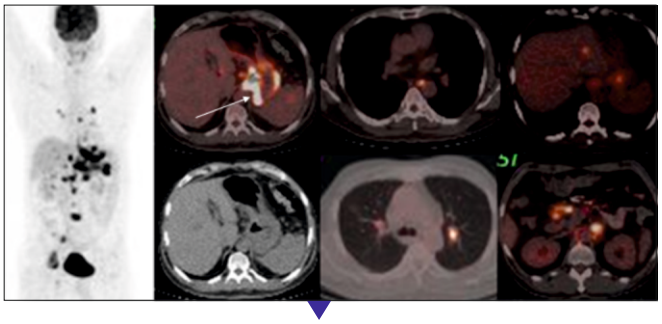
Images of 42 years old female with carcinoma cervix, post-radiation therapy. ^{18}F-FDG PET/CT (MIP, fused axial and CT) images reveal FDG avid soft tissue thickening in the cervix suggestive of residual active disease.



Images of 48 years old female with carcinoma left breast, post-surgery, chemotherapy and radiation therapy 2 years previously, now presented with backache. FDG-PET/CT MIP (a) and fused axial (b) images showed recurrent metastatic disease in sternum (SUVmax 7.90), liver (SUVmax 7.97) and right lung (SUVmax 8.69).

PET-CT guided Biopsy

PET-directed biopsy has an increasing role in the diagnosis and staging of various diseases. Molecular image–guided biopsy approaches have great potential to increase the detection rate and improve diagnostic accuracy and therefore can have an impact on treatment decisions and patient care. If the biopsy is directed from the hypermetabolic area shown on the PET images, it is likely to result is revealing viable tumor cells and thus, give more definitive results. PET-CT guided biopsy are done for a variety of tumors including lung, breast, prostate and head and neck tumors [16].



50 years old male presented with unexplained weight loss. ^{18}F-FDG PET/CT (MIP and fused axial images) done to look for unknown primary tumor, showed FDG avid wall thickening involving the proximal stomach, predominantly gastroesophageal junction (likely primary tumor), SUVmax 25.84, FDG avid paraesopaheal, gastrohepatic, perigastric, peripancreatic and retroperitoneal nodes. FDG avid hypodense liver lesion, multiple skeletal lesions, FDG avid nodule in upper lobe of left lung, 6mm, SUV max 12.29 (likely metastatic lesions). Gastroesophageal growth biopsy was reported as adenocarcinoma, poorly diferentiated.

Unknown primary tumor in patients presenting with metastases

Many times, patient presents with a swelling in the neck due to lymph node metastases or back pain due to bone metastases, or some other symptom due to metastatic disease. However, the primary remains unknown. Whole body ^{18}F-FDG PET/CT is an effective method for detecting the primary tumors in patients with carcinoma of unknown primary. Additionally, it can also determine disease extent and contribute significantly to clinical patient management. The primary can be found in as either head and neck tumor or lung or breast tumor or other organs based upon the site of metastasis [17].

Other Non-oncological Indications for PET-CT

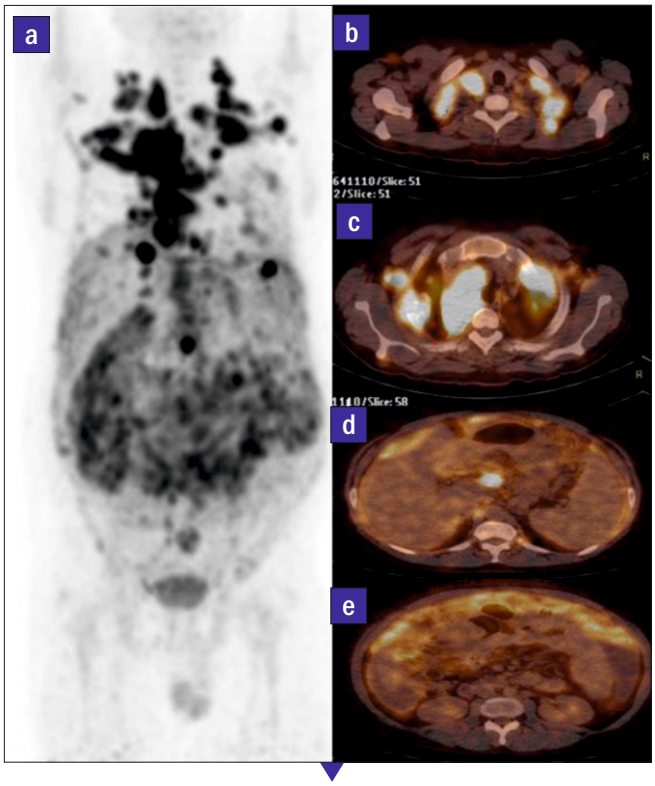
Whole body FDG-PET/CT is a sensitive diagnostic technique for the evaluation of fever of unknown origin (FUO) by facilitating anatomical localization of focally increased FDG uptake, thereby guiding further diagnostic tests to achieve a final diagnosis. FDG-PET/CT has become a common procedure in the workup of FUO when other diagnostic clues are absent [18].

^{18}F-FDG-PET/CT has also been used in baseline evaluation and treatment response assessment in infectious diseases like tuberculosis (TB). It is particularly useful in detecting the disease in previously unknown sites, and allows the most appropriate site of biopsy to be selected. ^{18}F-FDG-PET/CT is also very valuable in assessing early disease response to therapy, and plays an important role in cases where conventional microbiological methods are unavailable and for monitoring response to therapy in cases of multidrug-resistant TB or extrapulmonary TB [19].

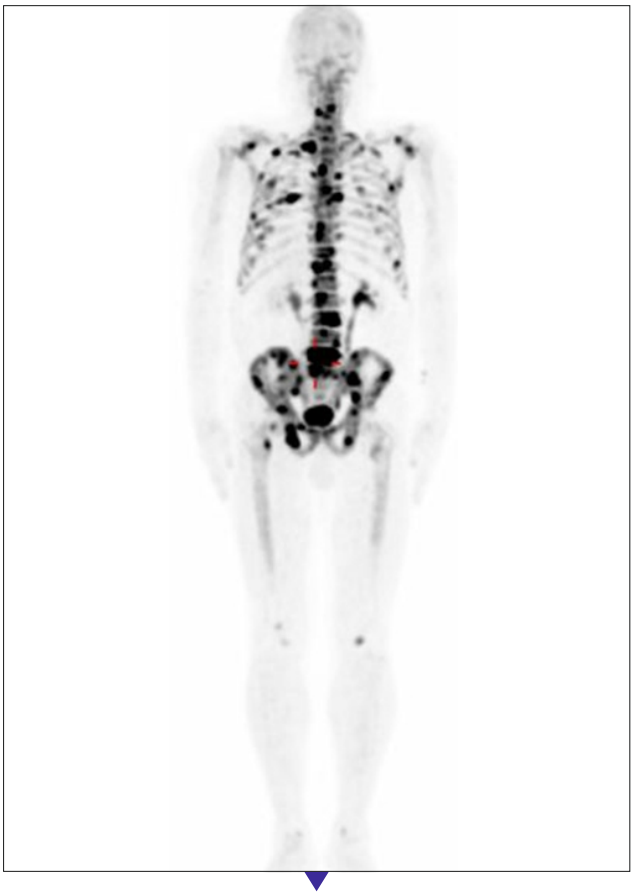
However, there are few limitations of PET scan like limited resolution, physiological variations of FDG distribution, inability to detect mucinous tumors and radiation to the patient (about 6-10 mSv). Hence, judicious medical justification has to be made with every PET/CT referral.

Non-FDG Radiopharmaceuticals used for PET/CT Imaging

F-18 Sodium Fluoride (NaF) PET/CT: It is used for imaging skeletal system evaluation, in oncology as whole body bone scan for evaluation of skeletal metastases, primary bone tumors and various benign skeletal conditions like



FDG-PET/CT images of a 31 years old male with fever of unknown origin MIP (a) and axial fused images (b, c, d, e) showed FDG avid bilateral cervical, axillary, mediastinal and abdominal lymph nodes and omental deposits. Biopsy from the left cervical lymph node showed caseating granulomatous lymphadenitis and patient was diagnosed to have tuberculosis.



^{18}F-fluoride PET/CT image (MIP) of 57 yrs old male with carcinoma prostate, serum PSA=335 ng/ml showing multiple foci of increased tracer uptake in the bones suggestive of extensive skeletal metastases.

osteomyelitis, for bone graft viability and metabolic bone disease.

^{68}Ga-PSMA-11 PET/CT

Prostate-specific membrane antigen (PSMA) is a type II transmembrane glycoprotein that is overexpressed in prostate carcinomas. PSMA expression is considered, at present, one of the most successful targets for therapy in nuclear medicine. It is used as an effective diagnostic and prognostic biomarker of prostate cancer. PSMA-based PET/CT imaging evolved as the procedure of choice in case of biochemical recurrence even with lower serum PSA levels, namely when PSMA-PET/CT scanning allows the optimization of the treatment strategy. 68Ga-PSMA-PET/CT was associated with sensitivity and specificity values of 33-93%, and >99% respectively in detecting recurrent disease [20]. To reduce the incidence of residual disease after surgery, PSMA-PET/CT should be considered also in patients with intermediate- and high-risk prostate carcinoma prior to radical prostatectomy. PSMA-PET is effective for imaging disease in the prostate, lymph nodes, soft tissue, and bone in a "one-stop–shop" examination. Finally, PSMA is an excellent theragnostic agent offering the possibility to highlight lesions by PET/CT imaging, and subsequently to irradiate metastatic sites with beta (^{177}Lu-PSMA-617) or alpha particle emitters (^{225}Ac-PSMA-617) [21].

^{68}Ga-DOTATATE PET/CT

SSTR-based ^{68}Ga-tetraazacyclododecanetetraacetic acid (DOTA)–peptide PET/CT is an exciting imaging modality that has shown significant advantages over conventional imaging in diagnosis and management of neuroendocrine tumors (NETs). It studies the somatostatin receptor (sstr) expression. In the recently updated National Comprehensive Cancer Network (NCCN) guidelines, ^{68}Ga-DOTATATE PET/CT has been added as an appropriate evaluation tool along with site-specific anatomical imaging using multi-phase CT, multiphase MRI, or endoscopic ultrasound [22]. According to the SNMMI appropriate use criteria guidelines, SSTR based PET should be the preferred imaging modality for initial diagnosis, selection of patients for peptide receptor radionuclide therapy (PRRT), and localization of unknown primaries [22].

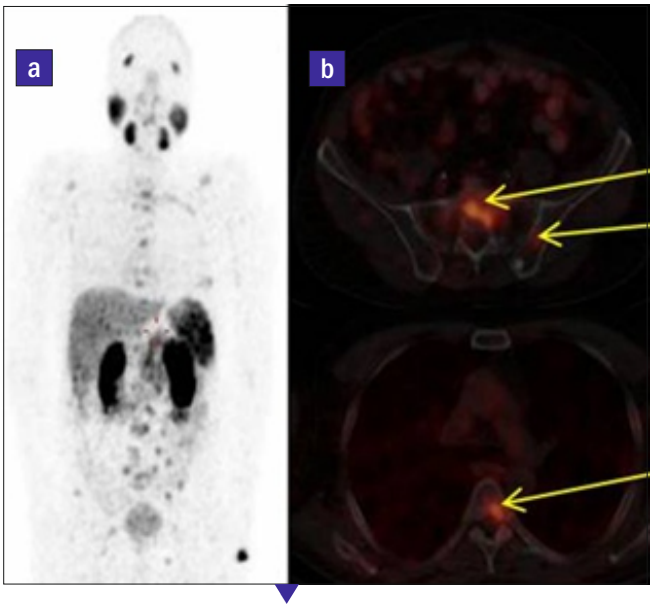
PET/MRI

PET/MRI is the most recent development in the field of hybrid imaging. It may enable the potent for 'one stop shop' combination of anatomical, metabolic and molecular imaging. The PET/MR has applications in the field of neuroscience, oncology, musculoskeletal disease, etc., thus, turning out to be a frontier in the era of complementary hybrid imaging. Yet, it also requires further investigations on the various other applications of PET/MRI for pre-clinical and clinical trials [23].

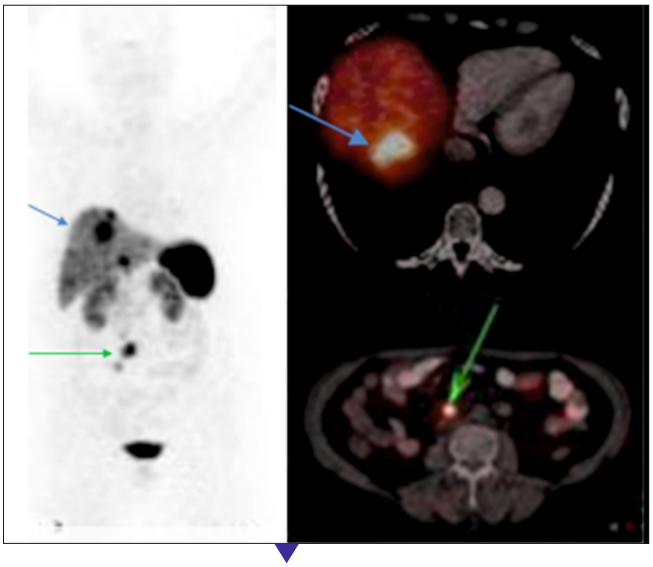
Thus, in today's times, multimodality molecular imaging plays vital role in the diagnosis and management of various oncologic and non-oncological diseases. Artificial intelligence is also being explored in Nuclear Medicine in planning, image acquisition, interpretation, and reporting PET/CT with immense future potentials.

Radionuclide Therapy

A number of new radionuclides & radiopharmaceuticals have been developed for different therapeutic applications in nuclear medicine. The choice of a particular radiopharmaceutical is dependent upon to a large extent by the diagnosis and character of the disease, the appropriate emissions, linear energy transfer, and physical half-life and by the carrier used to selectively transport the radionuclide to the desired site [24].



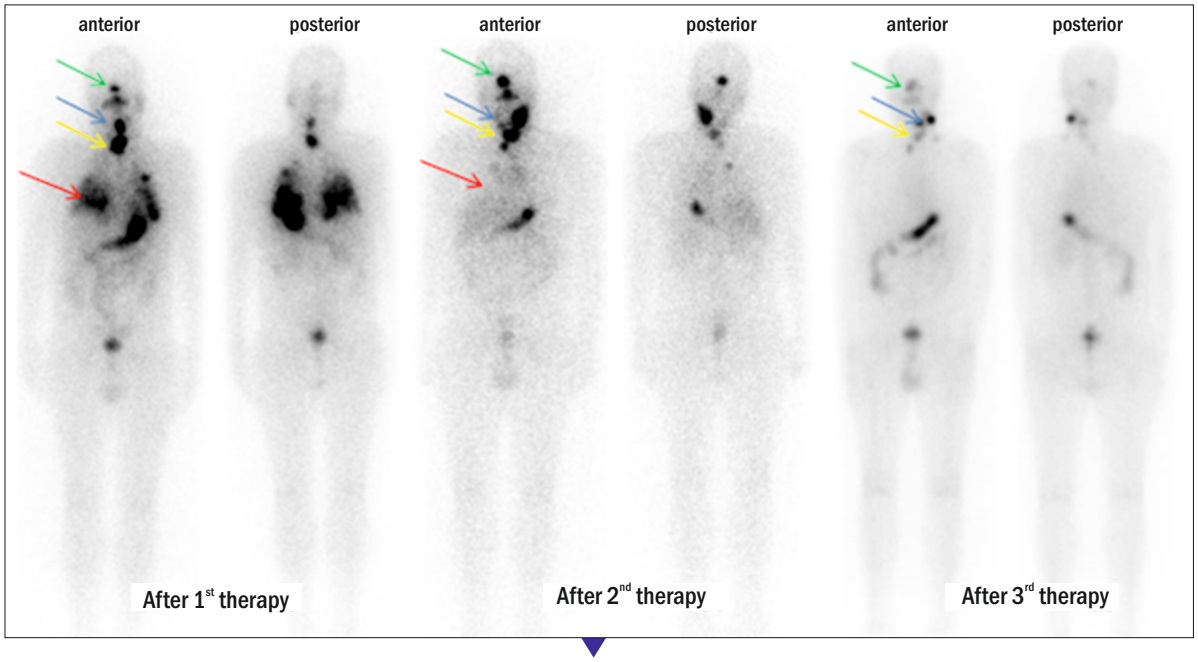
^{68}Ga-PSMA-11 PET/CT images of 72 year old man with castration resistant prostate adenocarcinoma, post radical prostatectomy, hormonal therapy and chemotherapy. Presented with raised serum PSA of 52 ng/ml. Images show multiple foci of increased tracer uptake in the bones as shown in MIP (a) and axial fused images of representative skeletal metastatic sites. The patient was subsequently referred for ^{177}Lu-PSMA-617 therapy.



^{68}Ga-DOTATATE PET/CT MIP and fused axial images of a 67 years old male with pancreatic neuroendocrine tumor (MIB1-20%), post-surgery, showing liver (blue arrow) and paraaortic lymph nodal metastasis (arrow). The patient was subsequently referred for PRRT.

Thyroid

Thyroid disorders have been successfully treated by means of administration of radioiodine (^{131}I-NaI) since the 1940s. The efficacy and safety of this treatment and the advantages over thyroid surgery made its success worldwide, and recommendations have been released by several scientific societies including the European Association of Nuclear Medicine and Molecular Imaging and the American Society of Nuclear Medicine. Radioactive I-131, given its abundant beta and gamma emissions and its mode of uptake similar to the normal physiological uptake of elemental iodine in the thyroid gland, has been a logical choice for treating a number of benign and malignant thyroid disorders. The



Iodine-131post-therapy scan images of 31 years old male with papillary carcinoma thyroid with thyroid bed residual (yellow arrow) and metastatic disease in cervical nodes (blue arrow), both lungs (red arrow) and base of skull (green arrow) showing radiotracer uptake after 1st therapy. Images after 2nd therapy and 3rd therapy show decrease in the cervical nodes and base of skull metastases and resolution of lung metastases (cumulative I-131 dose 721 mCi).

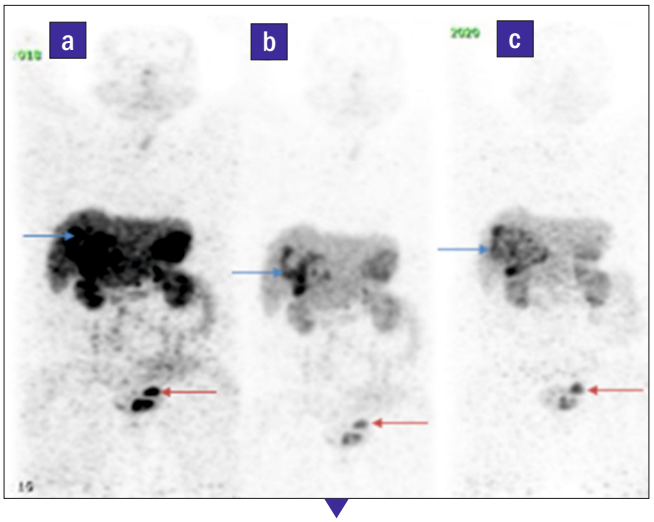
indications for ^{131}I treatment of thyroid benign diseases include hyperthyroidism and subclinical hyperthyroidism (about 8–10 mCi), toxic nodular goiter and autonomously functioning toxic nodule (higher activities may be needed in the latter conditions). Differentiated thyroid cancers are typically iodine-avid and can be effectively treated with radioiodine. In most patients, radioactive iodine therapy (RAI) is done for ablation of residual tissue or with adjuvant intent in case of suspected persistent disease after surgery [25]. Post surgical I-131 ablation of normal thyroid remnants permits using the serum thyroglobulin as a tumor marker. I-131 ablation may also help treat microscopic disease. I-131 therapy has been used for locoregional neck, mediastinal, and distant thyroid cancer metastases, while it is not useful for treating patients with anaplastic, or medullary thyroid cancer. Patients with low risk and no known metastases are commonly treated with 30 to 50 mCi to ablate normal remaining thyroid tissue. Those with regional metastases typically receive 100 to 150 mCi and with distant metastases receive 200 to 250 mCi [26]. Over the years, radioiodine therapy of differentiated thyroid cancer has proven to be an effective and low-risk treatment for eradication of thyroid remnant after total thyroidectomy, to theoretically destroy suspected but unproven residual disease after surgery (adjuvant therapy) or in patients with metastatic disease with curative or palliative intent [25].

Peptide receptor radionuclide therapy (PRRT)

The somatostatin receptor targeted PRRT is now considered as an important treatment modality for advanced, metastatic or inoperable, progressive Neuroendocrine neoplasms. ^{177}Lu-DOTA-TATE and ^{90}Y-DOTA-TOC/TATE (beta emitters) have received regulatory approvals in multiple countries, and more recently ^{225}Ac-DOTA-TATE (alpha emitter) is used as an investigational agent. The efficacy of PRRT is assessed in 3 scales: symptomatic response and improvement in health related quality of life (HRQoL), biochemical response in terms of reduction/increase in tumor markers (serum CgA, 24 hours urinary 5-HIAA levels) and imaging response (by RECIST and PERCIST scales). The patients have shown remarkable symptomatic improvement and better quality of life (including those with functioning disease uncontrolled with SSAs such as long acting octreotide/lanreotide) [27]. A recent study reported symptomatic improvement in 90% of patients. The biochemical response in terms of reduction of serum CgA/urinary 5-HIAA is in around 60%-70% of patients. On imaging, partial objective response was seen in around 30% of patients (complete response in 2%-6%). Additionally, stable disease is documented on imaging (either RECIST or PERCIST scale assessment) in around 60% who had otherwise demonstrated progressive disease on octreotide or lanreotide [28].

PSMA based radioligand therapy (PRLT)

Patients with metastatic castration resistant prostate carcinoma (mCRPC) are treated with androgen receptor signaling targeted inhibitors, such as abiraterone and



^{68}Ga -DOTATATE PET MIP Images of 60 years old female with colorectal neuroendocrine tumour (MIB1 index: 20%) with liver metastases. ^{68}Ga-DOTATATE MIP images at baseline (a) shows SSTR expressing rectal lesion and liver metastases. Images after 2 cycles of PRRT (177Lu-DOTA-TATE) (b) and 6 cycles of PRRT (c) show necrosis and disease stabilization.

enzalutamide, and chemotherapy such as docetaxel and cabazitaxel. More recently, PSMA targeted therapy has been used. Patients with end-stage mCRPC responded better to treatment with ^{177}Lu-PRLT than patients with mCRPC resistant to two lines of established drugs to third-line treatment [29]. A prospective study by Hofman et al showed that PRLT had an impressive response rate and tolerability. A preliminary presentation of a prospective randomized trial, TheraP, NCT03392428, ClinicalTrials.gov, supports that PRLT gives a better outcome than third-line treatment with cabazitaxel [30]. Oncologists can use the findings to optimize patient selection, predict treatment outcomes, and improve the effect of PRLT [31].

Radionuclide therapy for bone pain palliation

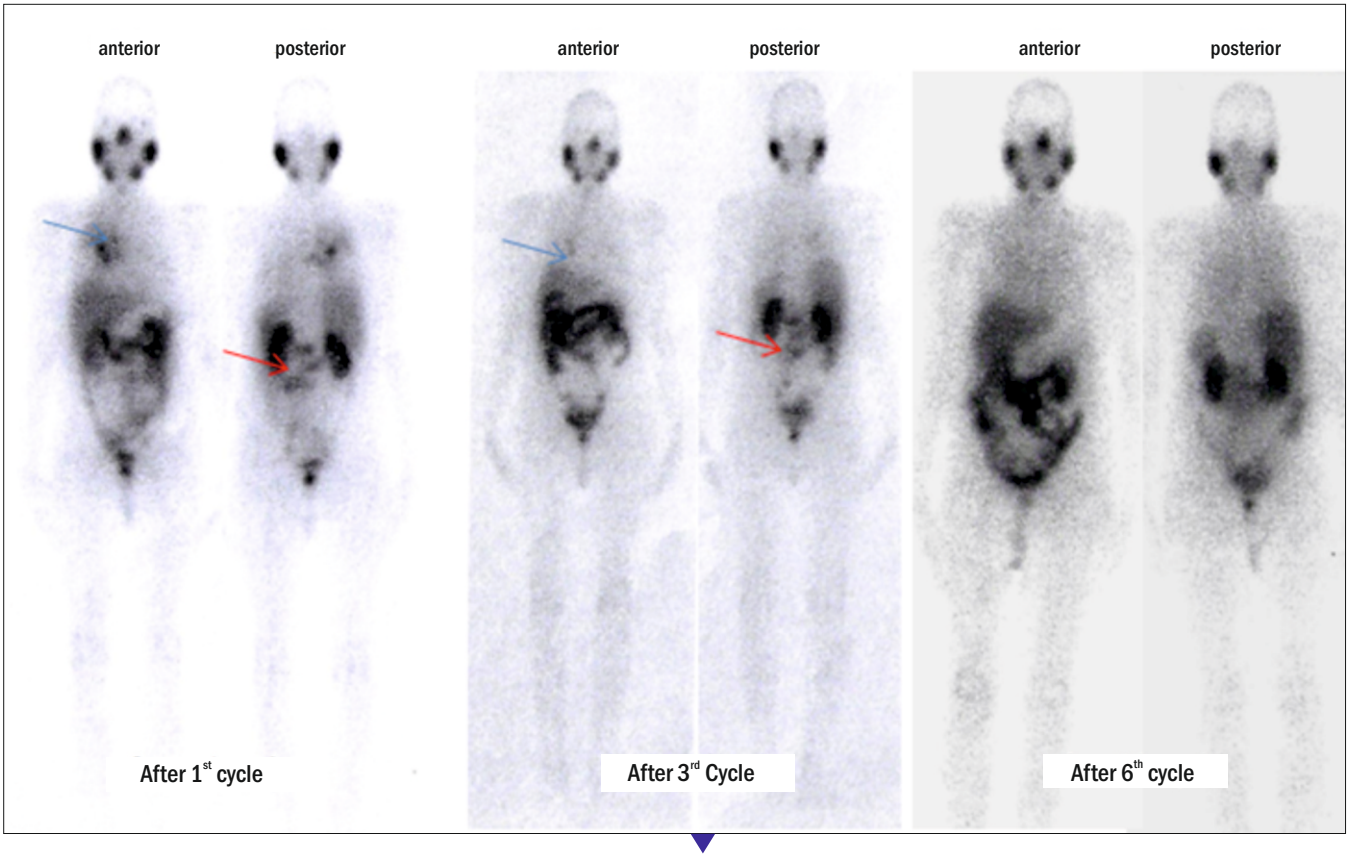
The skeleton is a potential metastatic target of many malignant tumors. Up to 85% of prostate and breast cancer patients may develop bone metastases causing severe pain in many of them. In patients suffering from multilocular, mainly osteoblastic lesions and pain syndrome, systemic radionuclide therapy is recommended for pain palliation. Low-energy beta-emitting radionuclides (^{153}Samarium-ethylenediaminetetrameth-ylenephosphonate (EDTMP) and ^{89}Strontium chloride) deliver high radiation doses to bone metastases and micrometastases in the bone marrow, but only negligible doses to the hematopoietic marrow. The response rate regarding pain syndrome is about 75%; about 25% of the patients may even become pain free. The therapy is repeatable, depending on cell counts. Concomitant treatment with modern bisphosphonates does not interfere with the treatment effects. Clinical trials using new radionuclides like ^{223}Radium and/or combinations of chemotherapy and radionuclides are aiming at a more curative approach [32].

Radioimmunotherapy (RIT)

RIT has been in use and has progressed significantly with the discovery of new molecular targets, the development of new stable chelates, the humanization of monoclonal antibodies (mAbs), and the use of pre-targeting techniques. Two products targeting the CD20 antigen are approved in the treatment of B cell lymphoma: ^{131}I-tositumomab (Bexxar) and ^{90}Y-ibritumomab tiuxetan (Zevalin). RIT can be integrated in clinical practice for treatment of patients with relapsed or refractory follicular lymphoma or as consolidation after induction chemotherapy in frontline treatment in FL patients. High-dose treatment, RIT as consolidation, RIT in the first-line treatment, fractionated RIT, and use of new humanized mAbs, in particular targeting CD22, showed promising results in B cell lymphoma. In solid tumors, that are more resistant to radiations and less accessible to large molecules such as mAbs, clinical efficacy remains limited. Pre-targeting approaches have been of potential in increasing the therapeutic index of radiolabeled antibodies. Finally, new beta emitters such as lutetium-177 (like ^{177}Lu-Trastuzumab for breast carcinoma or ^{177}Lu-Rituximab) with better physical properties will further enhance the safety and applicability of RIT. Moreover, alpha emitters such as Bismuth-213 or Astatine-211 offer the theoretical possibility to eradicate the last microscopic clusters of tumor cells, in the setting of consolidation. Personalized dosimetry protocols, particularly based on quantitative positron emission tomography (PET) imaging, is considered to be developed to optimize injected activity [33].

^{131}I- Metaiodobenzylguanidine (MIBG) therapy

MIBG is structurally similar to the neurotransmitter norepinephrine and specifically targets neuroendocrine cells



Post ^{177}Lu-PSMA-617 therapy scan images of 71 years old male with metastatic castration resistant prostate cancer with mediastinal nodes (blue arrow) and lower lumbar vertebral metastases (red arrow) showing radiotracer uptake in scan after 1st therapy. Images after 3rd cycle and 6th cycle show reduction and subsequent resolution of these lesions.

including some neuroendocrine tumors. The indications of I-131 MIBG therapy include treatment-resistant neuroblastoma, unresectable or metastatic pheochromocytoma and paraganglioma, unresectable or metastatic carcinoid tumors, and unresectable or metastatic medullary thyroid cancer (MTC). I-131 MIBG therapy is one of the considerable effective treatments in patients with advanced neuroblastoma, pheochromocytoma, and paraganglioma. On the other hand, I-131 MIBG therapy is an alternative method after more effective novel therapies are used such as radiolabeled somatostatin analogs and tyrosine kinase inhibitors in patients with advanced carcinoid tumors and MTC [34].

Targeted alpha therapy

Targeted alpha therapy attempts to deliver systemic radiation selectively to cancer cells while minimizing systemic toxic effects and may lead to additional treatment options for many cancer types. Alpha-emitting radionuclides have been approved for cancer treatment since 2013, with increasing degrees of success, as new targets, synthetic chemistry approaches, and alpha particle emitters are identified. From a radiobiological perspective, alpha particles are more effective at killing cells compared to low linear energy transfer radiation. The short range of alpha particles makes them a potent tool to irradiate small lesions or treat solid tumors by minimizing unwanted irradiation of normal tissue surrounding the cancer cells, assuming a high specificity of the radiopharmaceutical and good stability of its chemical bonds. Clinical approval of $^{223}RaCl_2$ in 2013 was a major milestone. In addition, ^{225}Ac-PSMA-617 treatment benefit in metastatic castrate-resistant prostate cancer patients, refractory to standard therapies, is another remarkable achievement [35].

Thus, the therapeutic applications of systemic radiopharmaceuticals have been in use since many decades and are rapidly progressing to achieve more efficacy and treatment response in various tumors like thyroid cancer, prostate cancer, neuroendocrine tumors, and more. Newer approaches like targeted alpha therapy are opening new avenues of treating a variety of cancers while sparing the surrounding normal tissue most effectively.

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