Emerging clinical applications of PET based molecular imaging in oncology: the promising future potential for evolving personalized cancer care

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Abstract

This review focuses on the potential of advanced applications of functional molecular imaging in assessing tumor biology and cellular characteristics with emphasis on positron emission tomography (PET) applications with both 18-fluorodeoxyglucose (FDG) and non-FDG tracers. The inherent heterogeneity of cancer cells with their varied cellular biology and metabolic and receptor phenotypic expression in each individual patient and also intra-and inter-lesionally in the same individual mandates for transitioning from a generalized "same-size-fits-all" approach to personalized medicine in oncology. The past two decades have witnessed improvement of oncological imaging through CT, MR imaging, PET, subsequent movement through hybrid or fusion imaging with PET/CT and single-photon emission computerized tomography (SPECT-CT), and now toward the evolving PET/MR imaging. These recent developments have proven invaluable in enhancing oncology care and have the potential to help image the tumor biology at the cellular level, followed by providing a tailored treatment. Molecular imaging, integrated diagnostics or Radiomics, biology-driven interventional radiology and theranostics, all hold immense potential to serve as a guide to give "start and stop" treatment for a patient on an individual basis. This will likely have substantial impact on both treatment costs and outcomes. In this review, we bring forth the current trends in molecular imaging with established techniques (PET/CT), with particular emphasis on newer molecules (such as amino acid metabolism and hypoxia imaging, somatostatin receptor based imaging, and hormone receptor imaging) and further potential for FDG. An introductory discussion on the novel hybrid imaging techniques such as PET/MR is also made to understand the futuristic trends.

Key words: Molecular imaging; oncology; personalized medicine; positron emission tomography/computerized tomography; positron emission tomography/magnetic resonance

Introduction

The following three can be identified as the major thrust application areas in the domain of personalized cancer care where the evolving molecular imaging will have important clinical impact:

- The right therapeutic agent/modality: As assessed by the surrogate diagnostic imaging molecules

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- The right time: Interval imaging during early course of therapy and changing to salvage schedule at the earliest opportunity in case of ineffective therapy
- The right dose (e.g. tailoring of radiation plan, chemotherapy agents and their doses, extent of surgery, radiopharmaceutical therapy and their doses): Functional imaging with various tracers exploring tumor biology from multiple aspects.

All these are possible if we could have the personalized blueprint of tumors which can be made possible with biomarkers, known as Radiomics. The importance of histopathological data and *in vitro* diagnostics has been greatly promising in personalized medicine in oncology and other clinical disciplines. *In vivo* molecular imaging, whether by using radionuclide or non-radioactive imaging technologies, addresses some of the practical shortcomings of the *in vitro* biomarker tests (which assess the unique variables of individual's genetic material, proteins, and other biological molecules i.e. biomarkers). Visual mapping of intra-and inter-tumoral heterogeneity (due to differences in cellular characteristics) which may be observed during the disease course, leading to varying degrees of response among the different primary and metastatic sites or even within the same lesion in the same individual can be studied in great detail with molecular imaging.[1] These are termed as "regional proteomics" or "Radiomics," and these make *in vivo* imaging modalities more feasible and practical to reliably explore the tumor. Molecular imaging involves imaging of functional aspects where cellular level dynamics of pathological processes using various *in vivo* markers [Table 1]. In this review, we shall focus on the current trends in radionuclide molecular imaging in the mainstream clinical setting.

Table 1: Key areas of applications for molecular imaging in oncology

Clinical decision making step	Potential areas of impact
Diagnosis	(Molecular) tumor size Tumor viability Tumor distribution Tumor staging
Guided biopsy	From viable areas - better outcome
Treatment planning	Radiotherapy planning - reduction or increase in field size depending on tumor biology - right dose to the right areas due to intra- and inter-tumoral variations Surgical planning - what to remove and what to leave
Early assessment of treatment response	A major strength of functional molecular imaging which helps in tailoring therapy appropriately Eliminating/modifying ineffective therapy - increase in cost-effectiveness and reduction in patient morbidity Increase in confidence of oncologist
Targeted imaging and therapy (theranostics)	Targeted molecules can be used for prior imaging and then therapy (based on image findings) For example, management of neuroendocrine tumors with somatostatin analogs has also brought nuclear theranostics in mainstream oncology care

Radionuclide Molecular Imaging: An Introduction to Single-photon Emission Computerized Tomography and Positron Emission Tomography

Radioisotope based-molecular imaging has emerged at the forefront in the area of personalized medicine. The older methods of radionuclide imaging like planar and single-photon emission computerized tomography (SPECT) are also based on molecular level techniques. With the advent of positron emission tomography combined with computerized tomography (PET/CT) with fluorodeoxyglucose (FDG) and other novel molecules, mainstream molecular imaging appears to have unlimited potential today.

Both SPECT and PET imaging involve injection of radiopharmaceuticals labeled with "short-lived" gamma and positron emitting radioisotopes, respectively. These can provide information of biological processes *in vivo* through quantitative tomographic images using a gamma camera or PET scanner. These techniques have the sensitivity needed to visualize most interactions between physiological targets and ligands, which can enable non-invasive detection down to the picomolar level. The target molecules are labeled with suitable radioisotopes and with suitable imaging characteristics for SPECT or PET imaging. PET imaging has greater advantages with respect to sensitivity and resolution, and also the ability of positron emitters being labeled to normal elements of the cell, hence has been gaining significantly more clinical popularity over the last decade.[2]

Over the past decade, PET/CT, especially using F18-FDG, has become an indispensable tool in oncology, mainly in the staging work-up and response to therapy including recurrent tumor. Among non-FDG PET agents [e.g. 3′-18F-fluoro-3′-deoxythymidine and 18F-1-(2′-deoxy-2′-fluoro-β-d-arabinofuranosyl) thymine, 60/62/64Cu-labeled diacetyl-bis (N4-methylthiosemicarbazone) and 18F-fluoromisonidazole, L-(methyl-11C) methionine, 16β-18F-fluoro-5α-dihydrotestosterone and 16α-18F-fluoro-17β-estradiol], many are being studied for use in oncology, especially in monitoring therapy,[3] SPECT imaging is used more often worldwide and many tracers ranging from the well-established radioiodine for thyroid cancer and radiolabeled metaiodobenzyl guanidine and radiolabeled octreotide analogs for neuroendocrine tumors (NETs)[4] to the newer anti-CD20 radiolabeled antibodies 90Y-ibritumomab tiuxetan and 131I-tositumomab for lymphoma have been approved for clinical use. Other futuristic agents like radiolabeled annexin molecules used for the detection of cell apoptosis have shown great promise in clinical trials.[5]

Emerging Role of 18F-fluorodeoxyglucose in Assessing Tumor Biology

The rationale for the use of FDG in PET imaging in oncology is the fact that the vast majority of malignant cancer phenotypes exhibit an increased glycolytic rate (Warburg effect). PET imaging with 18F-FDG provides metabolic information of anatomic tumors qualitatively. FDG has also been used as a quantitative biomarker since the first reports on standardized uptake value (SUV) measurement in breast cancer. The SUV is a widely used metric for assessing tissue accumulation of tracers. SUV can be normalized to body mass, lean body mass (SUL), or body surface area. Comparison of SUV linearly with time was tried as a parameter for assessing response in tumors and quantifying it. It was proven beyond doubt that the SUV of FDG in tumors reduced with response to therapy. Data supports that 18F-FDG PET is a useful tool for response assessment in a variety of malignancies, at the end of treatment, mid treatment, and when performed soon after treatment is initiated, and has led to the advent of the PET response criteria in solid tumors PERCIST.[6] Recently, FDG-PET has taken a very important step further from anatomical-based imaging in that it allows the characterization of tumor biology; aggressive tumors tend to have higher levels of FDG uptake, while less aggressive tumors tend to have lower levels of FDG uptake and this has been shown histologically [Figures 1 and 2]. This new dimension of diagnostic information that is provided by FDG-PET can be used to improve determination of disease prognosis and treatment planning.

Degree and extent of FDG uptake of tumors was found to be an independent predictor of prognosis and tumor aggressiveness [Table 2] in most cancers.[7] *In vivo* imaging offers two added advantages: (i) aids to eliminate sampling error which may occur with histopathology (ii) allows mapping of the intra-and inter-tumoral heterogeneity.

Non-fluorodeoxyglucose Positron Emission Tomography Tracers in Oncology: An Enumeration

Currently, a number of non-FDG-PET tracers are in use or hold potential for future clinical use. With advances in radiochemistry and better understanding of tumor biology, we would be continuing to witness the advent of more tracers in the clinical routine [Table 3].

Overview of Salient Pathways, Positron Emission Tomography/Single-photon Emission Computerized Tomography Tracers and Their Potential Clinical Applications

Imaging of tumor hypoxia

One of the biggest challenges to efficacious treatment in oncology is tumor hypoxia. The presence of hypoxic/anoxic areas is a characteristic feature of about 50–60% of locally advanced solid tumors.[14]

These cells become resistant to conventional anticancer therapies like radiotherapy (RT; intrinsic dependence of RT on oxygen to cause damage to the tumor cell) and chemotherapy (by causing cells within hypoxic regions to cycle more slowly and by providing a selection mechanism for cells with reduced susceptibility for apoptosis). Various mechanisms have been postulated; the most popular is through expression of hypoxia inducible factors (HIFs) such as HIF1α and HIF2α.[15]

The current gold standard for direct *in vivo* determination of tumor oxygenation is a commercially available oxygen electrode – the Eppendorf electrode – which is practically demanding. Non-invasive methods for detection of presence and extent of tumor hypoxia can have a significant impact on clinical outcome, based upon the use of nitroimidazole derivatives [Figure 3 and Table 4].[14]

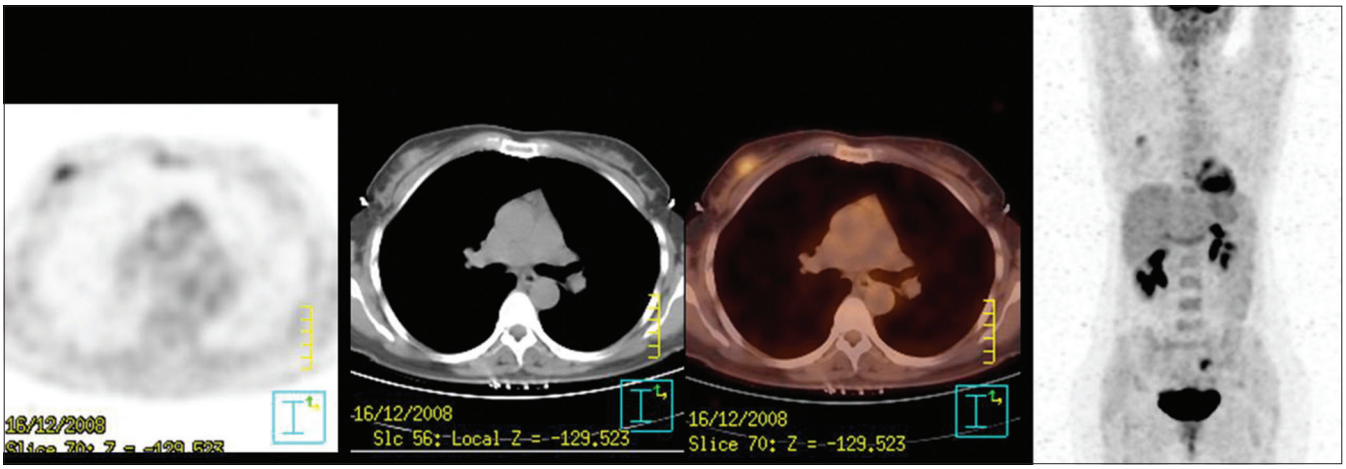

Figure 1: Right breast ER-positive, PR-positive, c-erbB 2–negative invasive ductal carcinoma, tumor size: 4 × 3 cm, SUVmax 1: 1.6, SUVmax 2: 1.6 (no change) (Reprinted with permission from Basu *et al.*[8])

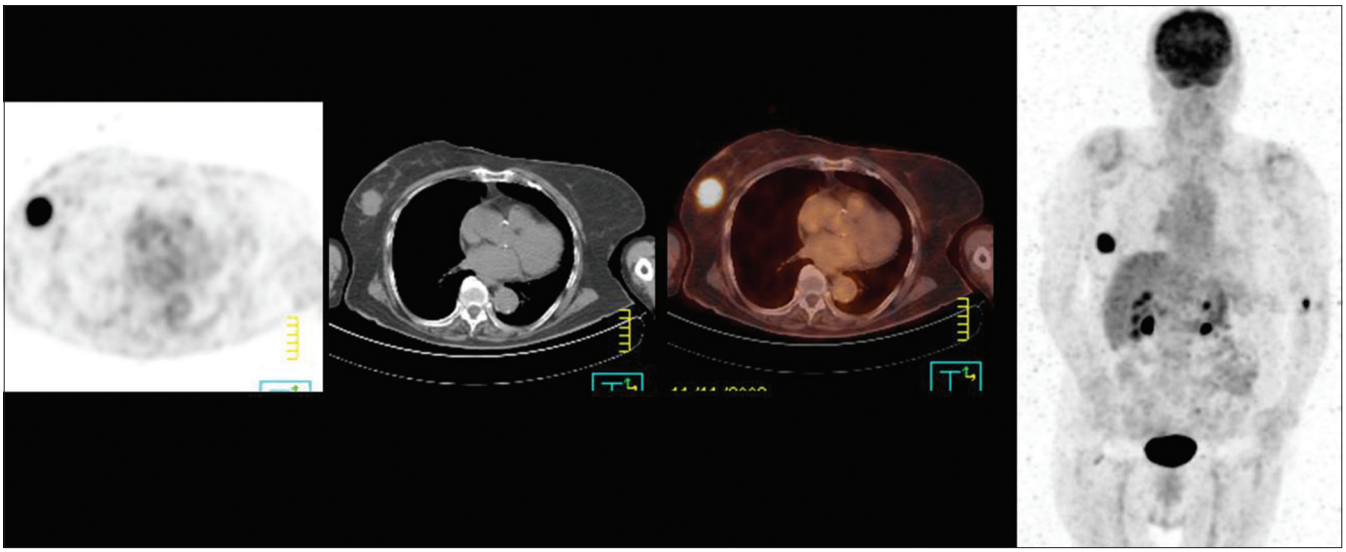

Figure 2: Right breast invasive ductal and triple-negative breast carcinoma (size 4.5 × 4 cm) and SUVmax: 14 (Reprinted with permission from Basu *et al.*[8])

Table 2: Recent data on the potential future role of FDG in assessing tumor biology

Type of cancer	Correlation of FDG uptake in relation to tumor biology	Comment
Breast cancer	Low tumor grade independently associated with (false?) negative results Triple-negative breast cancer associated with enhanced FDG uptake[8,9]	Positive correlation of FDG uptake with tumor biology (figures 2 and 3)
Thyroid cancer	Survival correlated with disease volume on FDG-PET FDG volume greater than 125 ml had significantly reduced short-term survival[10]	A negative FDG-PET scan in a patient with thyroid cancer should not be regarded as false negative, but as true negative in terms of overall prognosis
Lymphomas	Prognosis of patients with a pretreatment SUVmax ≤5 was better than that of patients with a pretreatment SUVmax >5[11] Interim PET findings emerged as a strong prognostic indicator[11]	Degree of glycolysis (FDG uptake) of lymphoma and early interim PET allows prediction of tumor grade and prognosis
Prostate cancer	Multiple factors like Gleason's score, S. PSA levels, and FDG uptake have been included for prognostication	Negative FDG-PET scan in prostate cancer indicates less-aggressive tumor behavior (as demonstrated by lower PSA levels and the tendency to lower Gleason scores) than a positive FDG-PET scan
Hepatocellular carcinoma	Comparison of FDG and C-11 acetate uptake[12]	Low FDG uptake in HCC appears to be associated with better tumor differentiation and outcome than high FDG uptake
Neuroendocrine tumors	Studies to compare uptake of FDG and SSR (dual tracer)[13]	High FDG uptake suggests an aggressive behavior and the possibility of treatment refractoriness of the cells at the site, whereas low uptake would indicate a biologically indolent lesion

FDG: Fluorodeoxyglucose, PET: Positron emission tomography, SUVmax: Maximum standardized uptake value, PSA: Prostate-specific antigen, HCC: Hepatocellular carcinoma, SSR: Somatostatin receptor

Imaging of tumor proliferation

Imaging biomarkers (IB) of proliferation, cell death, and tumor heterogeneity can be thought of as possible tools in molecular imaging. One of the IBs is ([18] F)-3′-deoxy-3′-fluorothymidine with PET (FLT-PET).[16]

Increased proliferation is a hallmark of many cancers; several tracers have been tested to track the DNA synthesis pathway. Thymidine, which is incorporated into DNA but not RNA, has been used in laboratory studies to measure tumor growth. One such tracer is 18F-labeled 39-deoxy-39-fluorothymidine (18F-FLT). Several studies on breast, lung, and brain tumors [Figure 4] have demonstrated that retention of 18-F FLT correlated with tumor proliferation.[17] Another novel potential application is measurement of simplified quantitative parameters of FLT uptake which could be of use for prognostication of therapy, for example, with tyrosine kinase inhibitors.[18,19] This has been found to be independent of perfusion parameters.

Amino acid targeting for positron emission tomography imaging

In addition to increased glucose metabolism, which principally forms the basis of F-18 FDG-PET oncology imaging, increased amino acid transport and metabolism is also a characteristic of cancer cells. Methionine is a physiological amino acid which is transported into the cells by neutral amino acid transporter and metabolized. C-11 labeled methionine (C-11 MET) was first developed

Table 3: Enumeration of newer PET tracers for molecular imaging in oncology

PET tracer (molecule)	Molecular mechanism of tumor uptake	Preliminary clinical data on future applications in oncology
[18F] fluoroethyl-l-tyrosine (FET)	Amino acid transport system	Clinical management of cerebral gliomas
11C-methionine (MET)	Amino acid transport system	Clinical management of cerebral gliomas
C11-choline	Cell membrane synthesis targeting related to upregulation of choline kinase associated with cancer	Enhanced sensitivity and accuracy for the preoperative staging of prostate cancer in pelvic lymph nodes in prostate cancer
18F-FMISO (nitroimidazoles)	Nitroimidazoles are reduced to RNO2 radicals, bind covalently to intracellular macromolecules and remain within hypoxic cells	GBM, head and neck cancers. Hypoxia-specific treatment in patients with head and neck cancer
Ga-68-DOTATATE and others	SSTR uptake	Neuroendocrine tumor imaging and targeted therapy
18F-FES	Hormone receptor A binding through protein bound to albumin or SSBP (also known as sex hormone-binding globulin) to ER	ER imaging in breast cancer for prognosis, and prediction of response to hormone therapy
C-11 acetate	Uptake dependant on FAS expression in tumors	Prostate cancer for detection of recurrence
68Ga PSMA	Binding to PSMA	Androgen independence, metastasis in prostate cancers
18F-galacto-RGD and 18FAH111	Target the integrin molecule $\alpha v\beta 3$	Assessment of angiogenesis-inhibiting drugs

FAS: Fatty acid synthase, ER: Estrogen receptor, PSMA: Prostate-specific membrane antigen, SSBP: Sex steroid–binding protein, SSTR: Somatostatin receptor, PET: Positron emission tomography

Table 4: Hypoxia imaging: Available and potential PET/SPECT tracers

Agent	Category	Clinical data	Comments
[18F] FMISO	PET Nitroimidazole compounds	Yes	Thorough clinical evaluation*
[18F] FAZA	PET Nitroimidazole compounds	Yes	Prelim results only##
[18F] FETA	PET Nitroimidazole compounds	No	-
[18F] FETNIM	PET Nitroimidazole compounds	Yes	Limited experience in head and neck tumors only
[18F] EF5, [18F] EF3, [18F] EF1	PET Nitroimidazole compounds	Yes	Clinical feasibility studies only
[124I] IAZA and [18F] FAZA	PET Nitroimidazole compounds	No	-
Cu-ATSM	PET Non-nitroimidazole compound	Yes	Holds the greatest promise for the future#
[123I] IAZA	SPECT agent Nitroimidazole compounds	Yes	Clinical feasibility studies only
Tc99m BMS 181321, BRU59-21	SPECT agent Nitroimidazole compounds	Yes	Clinical feasibility studies only

*Various preclinical and clinical data have shown significant correlation between hypoxic area within tumors (intra-tumoral) and between various tumors (inter-tumoral), correlating with immunohistochemistry findings for the same. Studies have shown [18F]FMISO uptake to be an independent prognostic marker for predicting outcome of radiotherapy in head and neck cancers. It may predict freedom from disease as well as overall survival, *In vivo* experiments (preclinical and clinical) have given conflicting results when showing a correlation between the uptake of [18F]FDG and the existence of hypoxia in tumors, #Cu-ATSM has one of the best selectivity for hypoxic tissue and shows a rapid delineation of tumor hypoxia and high tumor to background ratios, ##Radiation treatment planning and intensity-modulated radiotherapy based on [18F]FAZA uptake measurements are feasible. PET: Positron emission tomography, SPECT: Single-photon emission computerized tomography, [18F]FMISO: [18F] fluoromisonidazole, [18F]FAZA: [18F] fluoroazomycin-arabinofuranoside, [18F]FETA: [18F] fluoroetanidazole, [18F]FETNIM: [18F] fluoroerythronitroimidazole, [124I]IAZA: [124I] iodoazomycinarabinoside

by Comar *et al.* (1976).[20] It was first evaluated for tumor imaging by Syrota *et al.* (1982). It was later evaluated for various cancers; the highest clinical utility has been seen in evaluation of brain tumors due to its advantage of low brain uptake in normal brain tissue. Currently, C-11 MET PET has been one of the most useful imaging techniques for evaluation of recurrence versus radiation necrosis in gliomas. Recently, 18F-fluoroethyltyrosine (FET) and 18F-fluorodopa PET/CT have demonstrated excellent promising for assessing brain tumors, particularly the low-grade ones where FDG shows limitations [Figure 5]. Even though the most studied radiolabeled amino acid for PET imaging of brain tumors is MET, other 18F-labeled aromatic amino acid analogs have been developed recently for tumor imaging, including FET and l-3,4-dihydroxy-6-[18F] fluorophenylalanine (FDOPA). The main advantage of this is the relative long half-life of flourine-18 (at 110 min) in comparison to the short half-life of [11C] (20 min) that requires an onsite cyclotron.[21]

Cell membrane synthesis targeting

Up-regulation of choline kinase is often associated with cancer, a strong rationale behind using 11C-choline in oncology. 11C-choline has been reported to be a new agent

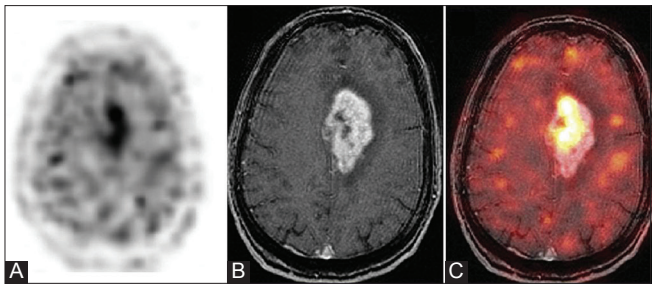

Figure 3(A-C): (A-C) [18 F] EF5-PET/MR imaging of malignant brain tumor hypoxia for radiation treatment planning. Axial [18F] EF5 PET (A), axial MR (B), and fused PET/MR images (C) show uptake of [18F] EF5 in the anterior portion of tumor, indicating intralesional hypoxia. Note discrepant findings between [18F] EF5 uptake in lesion and structural appearance of lesion. Hypoxic tumors are resistant to either radiation or chemotherapy. Hypoxia agents may play a major role in selection of appropriate patients for radiation therapy planning (Reproduced with permission from[21])

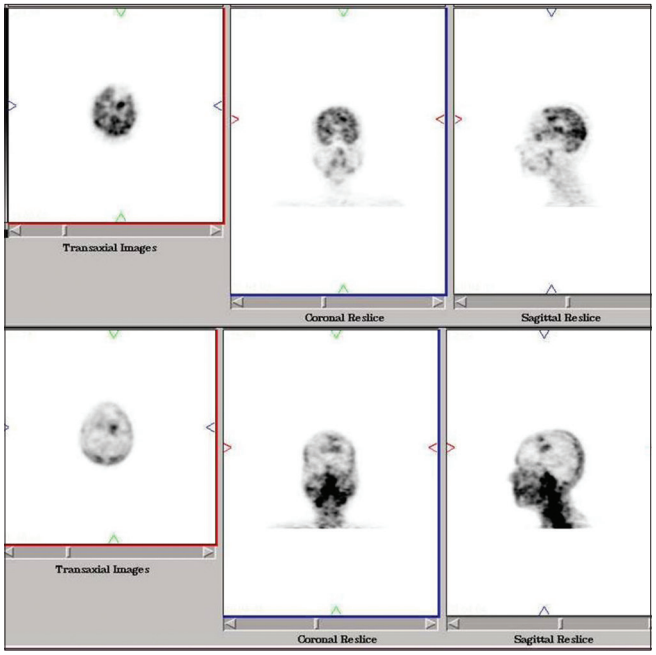

Figure 4: Comparing PET with FDG (upper panel) and FLT (lower panel) in the same patient with metastatic brain tumor. The absence of normal gray matter uptake has been a major advantage of newer PET tracers compared to FDG in brain tumor imaging

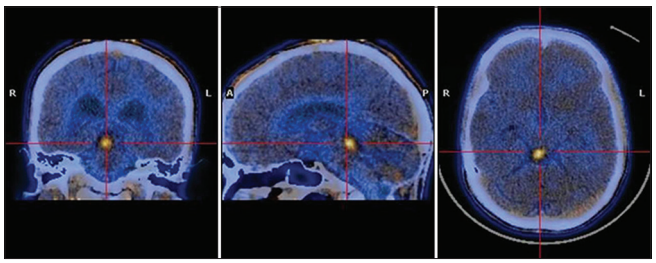

Figure 5: A 19-year-old male, a post-operative case of right-sided pilocytic astrocytoma. FET-PET/CT illustrating residual lesion noted in right midbrain tectal plate (Courtesy: Dr. A. Jaimini and Dr. A. Mondal, INMAS, New Delhi)

for PET of brain tumors and other cancers.[22] In particular, 11C-choline PET has been shown to provide clear images of the pelvic region , of prostate carcinoma and pelvic lymph node metastasis.[22] It has been also shown to have sensitivity and accuracy for the preoperative staging of prostate cancer in pelvic lymph nodes.

Imaging of protein receptors

Estrogen receptor based imaging

Hormonal therapy has a major role in cancer care, particularly for prostate and breast cancer patients. Imaging of tumor expression of estrogen receptors (ERs) by PET and of human epidermal growth factor receptor 2 (HER2) by PET and SPECT is under way in trials predominantly involving breast cancer patients and also in studies involving uterine tumors and meningioma.[23] In breast cancer, the expression of ERs by tumor cells predicts mortality and the efficacy of antiestrogen–ER treatments and (non-hormonal) chemotherapy.

Of many tracers that have been clinically tested for imaging of ERs, 16α-18F-fluoro-17β-estradiol (18F-FES) has emerged as the leading contender. It has been shown that uptake values of 18F-FES on imaging correlate with response to therapy.

Androgen receptor imaging

18-fluorine-dihydrotestosterone (18F-FDHT) is an analog of 5α-dihydrotestosterone, the main prostatic form of androgen. Imaging of androgen receptor expression in prostate cancer has two potential roles in evaluating the response to therapy:

- Imaging of focal ectopic expression of androgen receptors may be a more tumor-specific manifestation of prostate metastases than other commonly used imaging characteristics (e.g. osseous activity on bone scintigraphy, hyper-attenuation on CT, and combinations of MRI signal patterns) and may allow better disease staging and therapeutic response assessment
- *In vivo* functional imaging of androgen metabolism can help in assessing treatment response and detecting recurrence due to development of resistance.[24]

Imaging of prostate-specific membrane antigen and therapeutic potential in prostate carcinoma

Prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer death among men in the United States.[25] Molecular imaging of prostate cancer has addressed the challenges in a multifaceted manner from staging to studying the tumor biology:

- *Variations in growth rate and challenges on use of F-18 FDG*: Higher glucose utilization is characteristic of most tumors; however, prostate cancer can vary greatly in growth rate, ranging from slow growing and less

aggressive to rapidly disseminating and aggressive, thus limiting F18-FDG–based tumor evaluation[26]

- *Tumor location*: Tumor location and excretion into bowel and urinary bladder in most of the tracers has made tumor localization challenging in the vicinity, especially with current conventional imaging agents like In-111 labeled monoclonal antibody capromab pendetide (ProstaScint).

Prostate-specific membrane antigen (PSMA) is a type II transmembrane protein that is over-expressed in prostate carcinoma, including androgen-independent, advanced, and metastatic disease as well as in a few subtypes of urinary bladder carcinoma, schwannoma, and in the tumor neovasculature of many solid tumors.[27] Because PSMA levels are directly related to androgen independence, metastasis, and progression, PSMA has proven to be an important target for the development of new radiopharmaceuticals for PET [Figure 6].[28]

The shortcoming with ProstaScint is that it recognizes an internal epitope of PSMA; hence, it is believed that cells must be dead in order for them to be imaged with this agent.[29] To circumvent this shortcoming, preclinical data and the early clinical results for new PSMA-based radiotracers had shown promise, such as with newer 89Zr-and 64Cu-labeled anti-PSMA antibodies (directed toward external epitopes) and antibody fragments, 64Cu-labeled aptamers, 68Ga-, 64Cu-, and 86Y-labeled low molecular weight inhibitors of PSMA.

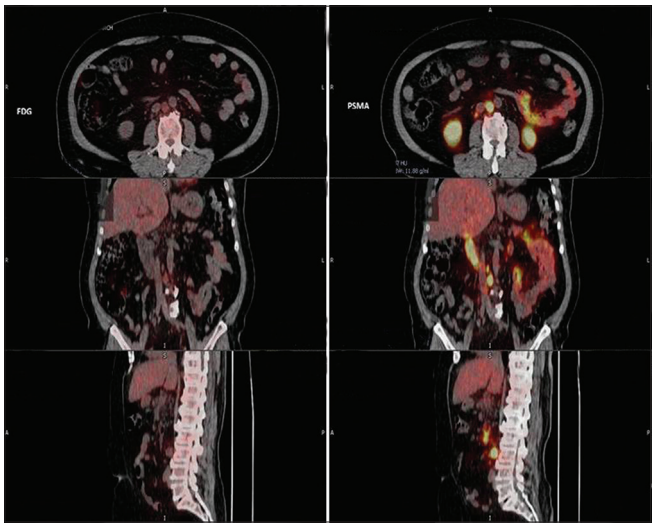

Figure 6: 68Ga-PSMA and FDG PET/CT in prostate cancer demonstrating FDG-negative PSMA +ve nodal relapse in an elderly gentleman, who was a known case of prostate cancer treated with high-intensity frequency ultrasound treatment (HIFU) in 2010; current PSA 1.98 (increased from 0.9 within 3 months). Retroperitoneal lymph node dissection was done. Histopathology was positive for nodal metastases (Courtesy: Dr. Partha S. Choudhury, Rajiv Gandhi Cancer Institute and Research Centre)

The therapeutic potential of the radiolabeled PSMA monoclonal antiobody deserves special mention here. Phase III trials with β-emitting radionuclide-labeled PSMA monoclonal antibody [(177) Lu-J591] targeted therapy for progressive metastatic castration-resistant prostate cancer have shown positive results in the form of accurate tumor targeting and PSA responses. Future for these agents as specific molecular targeted therapy appears very promising.[30]

Molecular imaging of somatostatin receptors with an introduction to radiolabeled peptide receptor therapy

NETs are unique tumors that originate almost everywhere in the body from neuroendocrine cells and the majority of NETs express somatostatin receptors (SSTR) which bind to somatostatin (SST) and can be successfully targeted for imaging and therapy. SSRI is one of the most glaring examples of the application of molecular imaging in clinical oncology.[31]

SST is a cyclic and regulatory peptide consisting of 14 amino acids, which comprises five distinct subtypes (labeled SSTR1–5). The imaging of the overexpressed SST subtype 2 (SST2) NETs has been developed and has found extensive clinical applications for almost two decades [Table 5].[31,32]

Various studies have shown the impact of SSRI in the management of NETs, with the sensitivity and specificity of PET or PET/CT reported to be 93% and 91%, respectively [Figures 7-9].[32]

In NETs, the histological tumor grading is of pivotal importance in prognostic risk stratification and has been frequently utilized for treatment decision making. In this regard, the Ki-67 labeling index or the MIB-1 labeling index is the common determinant [Figures 7-9].[13] Recently, predicting the treatment outcome more appropriately using dual tracer (SRI and FDG PET/CT) imaging approach has been proposed[13] for the tumors having MIB-1 (Ki-67) LI between 20 and 30%, where the current guidelines fall in gray areas. The human SSTR subtype 2 (hSSTr2), as a reporter gene, is under research for molecular imaging applications which have several features for potential translation to human studies.

Angiogenesis imaging

Newer techniques of cancer therapy involve clinical assays of tumor blood vessels that can be applied for individualization of vascular targeted therapies by optimizing dose selection and identifying drug resistance. So, PET imaging of angiogenesis has potential in the future with two imaging agents having entered clinical trials: 18F-galacto-RGD and 18FAH111. Both tracers target the integrin molecule αvβ3 and have various affinities for

Table 5: Imaging options available with somatostatin receptor analogs for neuroendocrine tumors

Radioisotope (radiopharmaceutical)	Indium-111 (In-111 pentetreotide), (In-111 DTPAOC), (In-111-DOTA-lanreotide), (In-111-DOTA-NOC-ATE), (In-111-DOTA-BOC-ATE)	Technetium 99m (99m) Tc-labeled hydrazinonicotinyl-Tyr3-octreotide (HYNIC-TOC)	Iodine-123 (I-123-Octreotide)	Gallium-68 (Ga-68-DOTATATE), (Ga-68-DOTATOC), (Ga-68-DOTANOC)	Copper-64 (Cu-64-DOTATATE)	Fluorine-18 (F-18 FP-gluc-TOCA)
Half-life	2.8 days	6 h	13 h	68.3 min	12.7 h	109.8 min
Imaging type	SPECT	SPECT	SPECT	PET	PET	PET

PET: Positron emission tomography, SPECT: Single-photon emission computerized tomography

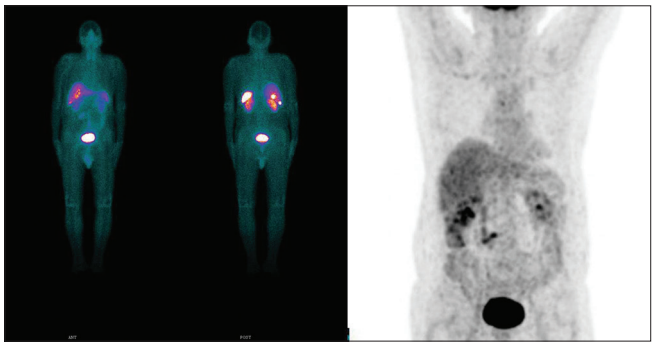

Figure 7: A 65-year-old male diagnosed to have rectal neuroendocrine tumor (MIB-8–10%, i.e. Grade 2 tumor); discordance was observed between (99m) Tc-hydrazinonicotinyl-Tyr(3)-octreotide 99mTc-HYNIC-TOC (left panel, which is avidly concentrated in the hepatic metastatic lesions) and FDG-PET/CT (right panel, MIP view; demonstrating no uptake in metastatic lesions)

other a-and b-heterodimers. The integrin αvβ3 receptor is upregulated on most tumors and several RGD-based peptide ligands, for example, 18F-galacto-RGD, have the potential for imaging a variety of tumors like breast cancer, brain tumors, lung cancers, squamous cell carcinoma of head and neck (SCCHN), differentiated thyroid carcinoma, sarcoma, and melanoma. The potential of imaging with these tracers to measure angiogenic density, which would show changes after targeted therapy even before other molecular imaging tools like F18-FDG PET or functional MRI images would reveal any changes in the tumor holds great promise.[33]

18F-fluoride positron emission tomography/computerized tomography for skeletal imaging

^{18}F-fluoride is a recently developed popular positron emitting bone imaging radiopharmaceutical. PET provides quantitatively accurate, high-resolution images with improved sensitivity compared to SPECT or planar scanners and is now frequently preferred over the planar whole-body 99mTc-methylene diphosphonate (MDP) radionuclide bone scintigraphy, in centers where it is available.

Novel agents for myeloma imaging

CXCR4 is a G-protein–coupled receptor that mediates recruitment of blood cells toward its ligand. Stromal cell-derived factor 1SDF-1 is overexpressed in disseminated disease. Radiolabeled CXCR4, i.e.[(68) Ga] Pentixafor-PET,

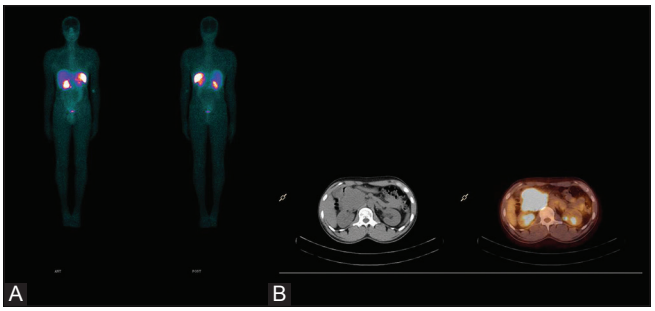

Figure 8(A and B): (A and B) A 35-year-old male having neuroendocrine tumor of pancreas with infiltration into duodenum and superior mesenteric vein on CECT. Duodenal growth biopsy was indicative of poorly differentiated neuroendocrine carcinoma. Before the scan was taken, the patient had been treated with chemotherapy with carboplatin and etoposide and referred for consideration for radiolabeled peptide receptor therapy (PRRT). The 99mTc HYNIC-TOC (A) FDG-PET/CT (B) demonstrated total concordance consistent with poorly differentiated histopathology

opens a broad field for clinical investigations on *CXCR4* expression and for CXCR4-directed therapeutic approaches in myeloma and other diseases.[34]

Future Advances in Molecular Imaging: Magnetic Resonance Imaging Combined with Positron Emission Tomography Imaging

Recent introduction of integrated whole-body PET/MR scanners (BiographmMR; Siemens Healthcare, Germany) for clinical use has lead to various technical feasibility and early clinical studies of PET/MR in oncology.

Hybrid PET/MR systems provide complementary multimodal information about perfusion, metabolism, receptor status, and function, together with excellent high-contrast soft tissue visualization without the need to expose the patient to additional radiation. Challenges remain in the field of attenuation correction in PET/MR which is important for quantitative PET imaging. MR-based methods like template, sequence, atlas and transmission-based methods are being intensively evaluated. Costs and clinical utility apart, the small bore of MRI in comparison to the PET scanner and truncation artifacts currently pose major physical limitations for this promising modality.

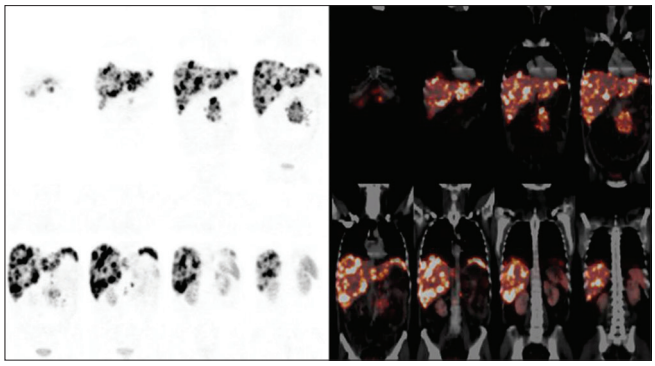

Figure 9: 68 Ga-DOTATATE PET/CT in a patient of metastatic neuroendocrine tumor being evaluated for somatostatin-targeted peptide receptor radionuclide therapy with 177Lu-DOTATATE. The left panel shows only PET and the right panel shows fused PET-CT coronal images that demonstrate multiple bilobar hepatic metastases. The superior resolution of the 68Ga-DOTA-NOC/TATE PET-CT is discrete advantage in evaluating smaller lesion, compared to the conventional planar images

Potential Areas for Application of Positron Emission Tomography/Magnetic Resonance in Clinical Oncology and Neuro-oncology

Early experiences have shown favorable results in comparison to PET/CT for evaluation of NSCLC,[35] mainly due to its multiparametric nature allowing for the additional integration of diffusion-weighted images (DWI), primary tumor (T) evaluation in head and neck cancers, evaluation of metastases (M) in brain and liver, NETs, and evaluation of pelvic tumors, especially prostate carcinoma. MRI is the first-line method of choice in neurological disorders and in many applications of neuro-oncologic imaging. So, PET/MR has become a desirable alternative for brain imaging. Promising results have been obtained in areas of intracranial mass evaluation with addition of arterial spin labeling and MR spectroscopy. FDG-PET and MRI are superior to the unimodal approach, with an accuracy rate of 94% for the differentiation of Alzheimer's disease and fronto-temporal lobar degeneration.

Conclusion

A close collaboration between the scientists, the physicists and the physicians has resulted in emergence of molecular medicine. Numerous novel molecules are showing promise for personalized care, newer drugs and assessment of their response on diseases; and potential for tailored treatment strategies for individual patients depending on the behavior of the disease. With Radiomics and theranostics gearing up for oncology of the future, this would be most applicable to the field of oncological imaging.

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Conflicts of interest
There are no conflicts of interest.

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