Newer positron emission tomography radiopharmaceuticals for radiotherapy planning: an overview

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Abstract: Positron emission tomography-computed tomography (PET-CT) has changed cancer imaging in the last decade, for better. It can be employed for radiation treatment planning of different cancers with improved accuracy and outcomes as compared to conventional imaging methods. ¹⁸F-fluorodeoxyglucose remains the most widely used though relatively non-specific cancer imaging PET tracer. A wide array of newer PET radiopharmaceuticals has been developed for targeted imaging of different cancers. PET-CT with such new PET radiopharmaceuticals has also been used for radiotherapy planning with encouraging results. In the present review we have briefly outlined the role of PET-CT with newer radiopharmaceuticals for radiotherapy planning and briefly reviewed the available literature in this regard.

Keywords: Positron emission tomography (PET); PET-computed tomography (PET-CT); radiotherapy planning; ¹¹C-methionine; ¹¹C-choline; ¹⁸F-FMISO

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Introduction

Positron emission tomography (PET) has added a new dimension in cancer imaging. It can lead to significant changes in the management of cancer patients with improvement of treatment outcome. Advent of hybrid imaging modality, i.e., combination of PET with structural imaging, such as computed tomography (CT), provides the most accurate imaging information in many common cancers. The most commonly used PET radiopharmaceutical is 2-[¹⁸F]fluoro-2-D-deoxyglucose ([¹⁸F]FDG), a radiolabelled analogue of glucose. FDG PET-CT has now become one stop shop imaging modality in diagnosis, staging, restaging and prognostication of many cancers. However, FDG is a nonspecific tracer and uptake of FDG is also noted in various benign conditions, such as different infective/inflammatory processes. So in quest for searching specific markers over the last decade a variety of new PET radiopharmaceuticals are entering the picture. These include radiolabelled amino acids, nucleoside derivatives, choline derivatives, nitroimidazole derivatives, and peptides targeting a variety of different receptors. Through these different tracers, molecular imaging using PET enables the visualization of various molecular pathways in tumour biology including metabolism, proliferation, oxygen delivery and protein synthesis as well as receptor and gene expression. PET with these radiopharmaceuticals can be used for tumour staging, for prediction of response to therapy, detection of early recurrence, and evaluation of modifications in organ function after treatment (1). The role of PET-CT imaging in radiation oncology treatment planning has simultaneously evolved (2). Here, it can provide additional information for target volume selection and delineation. Though [¹⁸F]FDG is most commonly used...
for this purpose, other newer radiopharmaceuticals can also provide helpful information which may improve radiation treatment planning. $^{11}$C-methionine is currently one of the best available PET tracers for delineating brain tumour contours (3). $^{18}$F-fluorotyrosine also has potential for radiation treatment planning in patients with brain tumours (4). For imaging prostate cancer $^{11}$C- and $^{18}$F-labelled choline derivatives are promising tracers (5). Also tracers allowing non-invasive determination of the oxygen supply of the tumour are of interest for radiation treatment planning, these tracers include $^{18}$F-FMISO, $^{18}$F-FAZA, and $^{64}$Cu-ATSM (6). $^{18}$F-fluorothymidine is a nucleoside derivative which allows monitoring of thymidine kinase activity, a surrogate marker for tumor cell proliferation, which may also add information for radiation treatment planning. In this review article role of the newer radiopharmaceuticals used for the radiation treatment planning are discussed.

Amino acid radiopharmaceuticals

Radiolabelled amino acids are well-established agents for PET based tumour imaging. Amino acids are usually labelled with $^{11}$C and $^{18}$F. $^{11}$C labelled amino acids include naturally occurring amino acids like L-$^{[11]}$C leucine (8), L-[methyl-$^{[11]}$C] methionine ($^{[11]}$C-MET) (9), and L-$^{[1]}$C tyrosine (10) as well as unnatural aliphatic (e.g., $^{[1]}$C-AIB) and alicyclic (e.g., $^{[1]}$C-ACPC) amino acids (11). However, the most well-established and widely evaluated $^{11}$C-labelled amino acid is $^{11}$C-MET. In contrast to $^{11}$C-labelled amino acids, labelling with $^{18}$F-fluorine always results in unnatural amino acids. Most commonly aromatic amino acids are used for labelling with $^{18}$F. The most well-established tracer for clinical studies are O-$^{[2]}$-[F]$^{18}$fluoroethyl]-L-tyrosine ($^{[18]}$F FET) and 3,4-dihydroxy-6-$^{[18]}$F fluoro-L-phenylalanine ($^{[18]}$F-FDOPA).

Amino acid tracers were initially developed to measure protein synthesis rates. However, it was noted that the rate of amino acid transport seems to be the major determinant of tracer uptake in tumour imaging studies rather than the protein synthesis rate. Usage of unnatural instead of natural amino acids can lead to improved metabolic stability resulting in avoidance of problems with metabolites which may decrease tumour specificity and complicate kinetic analysis. Moreover, from animal studies it was noted that $^{18}$F-FET, in contrast to $^{11}$C-MET, is not accumulated in inflammatory tissue making it potentially superior for distinguishing neoplasm from inflammation (12). $^{18}$F-FDOPA is an $^{18}$F-labelled analogue of the naturally occurring L-DOPA and has been used extensively for evaluating the dopaminergic system in the brain. There is a physiological high uptake and retention of $^{18}$F-FDOPA in substantia nigra and striatum (13). But it also shows high uptake in primary brain tumours due to augmented amino acid transport. Current data suggest that transport of $^{18}$F-FDOPA is mainly mediated by the L amino acid transporter system (14). In addition to brain tumour imaging, $^{18}$F-FDOPA has also been used for imaging extracranial tumours (15). It was found that the enzyme aromatic amino acid decarboxylase (AADC), for which $^{18}$F-FDOPA is a substrate, is expressed in many tumours of neuroendocrine origin. Role of $^{11}$C-MET PET and $^{18}$F-FET PET in radiation treatment planning of both high and low grade gliomas has been extensively investigated in the literature. Nuutinen et al. (16) in a study of 31 patients with low grade glioma found that patients may benefit from radiotherapy volume definition with $^{11}$C-MET PET, which seems to disclose residual tumour better than magnetic resonance imaging (MRI) in selected cases. A similar study by Schinkelshoek et al. (17) found that use of $^{11}$C-MET PET-CT can have significant impact in radiation treatment planning in patients with primary brain tumour. Weber et al. (18) and Niyazi et al. (19) evaluated role of $^{18}$F-FET PET in high grade glioma and both of them concluded that $^{18}$F-FET PET can lead to significant change in evaluation of gross tumour volume and biological tumour volume during radiation treatment planning. Apart from glioma, Geets et al. (3) evaluated role of $^{11}$C-MET PET-CT in radiation treatment planning of 23 patients with pharyngo-laryngeal squamous cell carcinoma. They however concluded that $^{11}$C-MET PET-CT did not cause a significant change in the gross tumour volume as compared with CT probably because of high uptake of $^{11}$C-MET in normal pharyngeal mucosa and salivary glands surrounding the tumour.

Lipid imaging radiopharmaceuticals

Radiolabelled choline and acetate are two important PET radiopharmaceuticals employed for imaging lipid synthesis and uptake. Choline was initially labelled with $^{11}$C-carbon, which results in the isotopic tracer. However, to benefit from the longer half-life $^{18}$F-labelled derivatives were developed. Labelling with $^{18}$F results in the analogue tracers $^{[18]}$F fluoromethylcholine ($^{[18]}$F-FCH) and $^{[18]}$F fluoroethylcholine ($^{[18]}$FFECH). Radiolabelled acetate is another tracer especially used for prostate cancer imaging.
Similarly to choline, the compound was labelled either with $^{11}$C resulting in the isotopic $[^{11}]$C-ACE or $^{18}$F resulting in the analogue tracer $[^{18}]$F-FAC. In many cancers high levels of phosphorylcholine have been found, whereas in the corresponding normal tissue only low levels are found (20). Phosphorylcholine is the first intermediate in the incorporation of choline into phospholipids by the Kennedy pathway (21). However, whether the corresponding choline kinase reaction or an upstream transporter mainly determines tracer accumulation is currently not entirely clear. In contrast to the myocardium where $^{11}$C-ACE is quickly metabolized to $^{11}$C-CO$_2$ via the tricarboxylic acid cycle, which is then rapidly released from the cells, in cancer cells $^{11}$C-ACE enters the lipidsynthesis and therefore, becomes trapped intracellularly.

Due to limited sensitivity and specificity in differentiating between benign and malignant prostatic tissues in primary prostate cancer, initially there was little enthusiasm for target volume delineation based on choline PET/CT. Irradiation planning for the treatment of single lymph node metastases on the basis of choline PET/CT is controversial due to its limited lesion-based sensitivity in primary nodal staging. In high-risk prostate cancer, choline PET/CT might diagnose lymph node metastases, which potentially can be included in the conventional irradiation field. Prior to radiation treatment of recurrent prostate cancer, choline PET/CT may prove useful for patient stratification by excluding distant disease which would require systemic therapy. In patients with local recurrence, choline PET/CT can be used to delineate local sites of recurrence within the prostatic resection bed allowing a boost to PET-positive sites. In patients with lymph node metastases outside the prostatic fossa and regional metastatic lymph nodes, choline PET/CT might influence radiation treatment planning by enabling extension of the target volume to lymphatic drainage sites with or without a boost to PET-positive lymph nodes (22). The role of $^{18}$F-fluorocholine PET/CT in radiation treatment planning has been studied by many investigators. Würschmidt et al. (23) in 26 patients with prostate cancer (7 primary, 19 recurrent) found that FEC-PET/CT planning could be helpful in dose escalation to lymph nodal sites of prostate cancer. Many investigators have studied the role of $^{11}$C-choline PET/CT in radiation treatment planning of prostate cancer (24-26) and found that $^{11}$C-choline PET/CT is a valuable tool for planning and monitoring radiation treatment planning and dose painting for localized prostate cancer using $^{11}$C-choline PET is technically feasible.

**Hypoxia imaging tracers**

Hypoxia, technically defined as a state of low oxygen tension, presents a unique therapeutic challenge in the treatment of solid malignancies. It can be either chronic or acute. Chronic hypoxia is due to the limited distance of oxygen diffusion through tissue, whereas acute hypoxia is secondary to transient perfusion changes from abnormal tumour vasculature. Tumour hypoxia is considered as an important factor for resistance to radiotherapy and appears to be an independent risk factor for tumour progression. Thus, imaging oxygenation of tumours is of great interest especially for radiation treatment planning. At the moment, the most common PET tracers for imaging hypoxia are 1-[(2-nitro-1-imidazolyl)-3-$[^{18}]$F]fluoro-2-propanol ($[^{18}]$F-FMISO), 1-[(5-$[^{18}]$F]fluoro-5-deoxy-a-D-arabinofuranosyl]-2-nitroimidazole ($[^{18}]$F-FAZA) and $[^{64}$Cu] copper(II)-diacetyl-bis(N4)-methylthiosemicarbazone ($[^{64}$Cu-ATSM). $[^{18}]$F-FMISO has a partition coefficient near 1 indicating that it can unspecifically penetrate almost all cell membranes. Intracellular nitroreductases transfer an electron to the nitro group of the nitroimidazole. In normoxic cells this electron is rapidly transferred back to oxygen and $[^{18}]$F-FMISO changes back to its original structure allowing diffusion of the tracer out of the cell. When oxygen is lacking a second electron transfer occurs which reduces the nitroimidazole to a very reactive intermediate, which binds to proteins and RNA within the cell and therefore, becomes trapped intracellularly. Thus, $[^{18}]$F-FMISO uptake is inversely related to the intracellular partial pressure of oxygen (27). The same mechanism mediates the accumulation of $[^{18}]$F-FAZA by hypoxic cells. Due to the included sugar moiety $[^{18}$F-FAZA is more hydrophilic than $[^{18}]$F-FMISO. This leads to a more rapid renal elimination of $[^{18}]$F-FAZA and results in a higher contrast between hypoxic and normoxic tissues (28). There are several proposed trapping mechanisms for $[^{64}$Cu-ATSM (29). Most recent studies including chemical, electrochemical, spectroscopic and computational methods suggest a slightly revised trapping mechanism (30). Although the mechanism of cellular-uptake is uncertain it is assumed that, based on the properties of $[^{64}$Cu-ATSM, cellular uptake is due to passive diffusion independent from the oxygenation status of the cell. In the cell, via an enzyme-mediated reduction, [Cu (I) ATSM] is generated in normoxic as well as hypoxic cells. In normoxic cells, rapid and facile re-oxidation occurs resulting in the neutral Cu (II) starting complex $[^{64}$Cu-ATSM which can penetrate the cell.
membrane and thus, not only diffuse into but also out of the cell. In hypoxic cells, strongly depending on the pH, [Cu (I) ATSM] is protonated, which results in the instable [Cu (I)-ATSMH]. [Cu (I)-ATSMH] dissociates allowing interaction of Cu (I) with proteins within the cell leading to the final trapping products.

The presence of hypoxia in tumour is of clinical significance, as the oxygen tension for hypoxic cells is high enough to allow for clonogenic survival, but low enough to be protected from the effects of ionizing radiation. These treatment-resistant hypoxic cells, by serving as a nidus for subsequent tumour regrowth and repopulation, as well as for regional and distant dissemination, presented a therapeutic dilemma for which various methods of therapy would be developed to address. Given that hypoxia is associated with treatment resistance and worse outcomes, current investigations are now focusing on how to optimally integrate hypoxia imaging into the radiation treatment planning process. This would identify patients with hypoxic tumours at baseline and allow for monitoring of changes in hypoxia in response to therapy. Such an approach could serve as a platform to integrate treatment modifications such as radiation dose escalation to regions of persistent hypoxia, or to incorporate novel hypoxia cytotoxins or radiosensitizers. Using hypoxia imaging for guiding intensity-modulated radiation as a means to overcome hypoxia-induced treatment resistance has been investigated using $^{18}$F-MISO specially in case of head and neck carcinoma (31-36). Similar studies have also been reported with $^{18}$F-FAZA (37) and $^{64}$Cu-ATSM (38,39). Identifying a specific subgroup of patients with hypoxic tumours before initiation of radiation therapy will be of paramount importance. The question of which hypoxia PET agent should be used for specific tumour subtypes or subpopulations will require additional investigation.

**Proliferation radiopharmaceuticals**

Radiopharmaceuticals which are commonly used as tumour cell proliferation markers include $^{11}$C-thymidine and 3'-[$^{18}$F]fluoro-3'-deoxythymidine ($^{18}$FFLT), a thymidine analogue where the hydroxyl function in position 3 is replaced by $^{18}$F-fluorine (40). Although imaging of tumour cell proliferation with $^{11}$C-thymidine has been shown to be feasible in patients, it has several disadvantages. It is labelled with $^{11}$C which has a half-life of only 20 min which necessitates the presence of onsite cyclotron. Furthermore, its fast and complex metabolism was an obstacle to wider acceptance as a PET radiopharmaceutical (41). As a practical alternative, $^{18}$F-FLT has been developed. $^{18}$F-FLT enters the cell via nucleoside transporters and to a lesser extent via passive diffusion (42). However, the rate-limiting step for $^{18}$F-FLT uptake is the initial phosphorylation by thymidine kinase-1 (41). Though further phosphorylation is possible but, based on the missing 3'-hydroxyl function, only negligible amounts are incorporated into the DNA. However, due to the negative charge of the phosphate group, it is unable to penetrate biological membranes and thus, is trapped inside the cell. There is some dephosphorylation via 5'-deoxynucleotidases, but the rate is relatively slow compared to the thymidine kinase activity. Thus, the accumulation of $^{18}$F-FLT-phosphates forms the basis of $^{18}$F-FLT-PET imaging.

In contrast to $^{18}$F-FDG PET, which provides a measure of the total viable tumor cell density, $^{18}$F-FLT PET identifies the proliferating cell compartment within the GTV. Although the number of tumor cells is greatly reduced during cytotoxic treatment, cells that survive are triggered to repopulate more effectively during the intervals between treatments, and this process of repopulation is an important cause of treatment failure. $^{18}$F-FLT PET can define tumor subvolumes with high proliferative activity, and escalation of radiation dose within these regions can counteract accelerated repopulation and improve the tumor control probability (42). Several investigators evaluated the effectiveness of $^{18}$F-FLT PET for radiotherapy planning in oropharyngeal tumours (42), esophageal carcinoma (43), and lung carcinoma (44).

**Angiogenesis imaging radiopharmaceuticals**

Angiogenesis is a complex multistep process involved in a variety of pathological processes including rheumatoid arthritis, diabetic retinopathy, psoriasis, restenosis and tumour growth (45). One target structure involved in the angiogenic process is the integrin $\alpha_\text{v}$$\beta_3$, which mediates the migration of activated endothelial cells during vessel formation. It was found that peptides containing the amino acid sequence Arg-Gly-Asp (single letter code: RGD) bind with high affinity to this receptor. For imaging with PET, peptides have been labelled with, $^{18}$F-flourine, $^{68}$Ga-gallium or $^{64}$Cu-copper. Most intensively studied in preclinical as well as clinical settings is the $^{18}$F-labelled glycosylated-cyclic pentapeptide ($^{18}$F-Galacto-RGD) (46). Its role was evaluated in patients with malignant melanoma, glioblastoma, head
and neck cancer, breast cancer, sarcoma, non-small cell lung cancer and prostate cancer (47). Tracer uptake in these lesions showed marked heterogeneity with SUV’s ranging from 1.2 to 10.0. This great inter- as well as intra-individual heterogeneity in tracer uptake was found indicating great differences in receptor expression and thus, the importance of such imaging modalities for radiation therapy planning and controlling.

**Somatostatin receptor radiopharmaceuticals**

Meningiomas are the most common intracranial primary tumours, accounting for approximately a total of 14–20% of all brain tumours in adults (48). Surgical resection is the preferred treatment (49). Postoperative-radiation therapy improves long-term local control and prevents tumour re-growth, especially after incomplete surgical removal. For target volume definition CT and MRI are the standard techniques. However, there are some limitations of these techniques for target delineation in infiltrative lesions (50). Meningiomas show over-expression of a variety of receptors including the somatostatin-receptor subtype 2 (SSTR2) (51). In contrast to $^{18}$FFDG, SSTR PET showed very high meningioma-to-background ratio and may supply additional information allowing more detailed target volume definition (52). At the moment all routinely used radiolabelled somatostatin analogues for PET are labelled with $^{68}$Ga-gallium (52). The most prominent labelling precursors are 1,4,7,10-tetraazacyclododecane-N,N’,N’’,N’’’-tetraacetic-acid-DPhe1-Tyr3-octreotide (DOTATOC) and 1,4,7,10-tetraazacyclododecane-N,N’,N’’,N’’’-tetraacetic-acid-D-Phe1-Tyr3-octreotate (DOTATATE). Gehler et al. (50) evaluated the role of $^{68}$Ga-DOTATOC PET-CT in radiation treatment planning of 26 patients with skull base meningioma. They concluded that $^{68}$Ga-DOTATOC PET-CT information may strongly complement patho-anatomical data from MRI and CT in cases with complex meningioma and is thus helpful for improved target volume delineation especially for skull base meningiomas and recurrent disease after surgery. In a similar study by Graf et al. (53) in 48 patients with 54 skull base meningiomas $^{68}$Ga DOTATOC PET-CT seemed to improve the target volume delineation often leading to a reduction of GTV compared with results from conventional imaging. Along the similar lines, Thowarth et al. (54) evaluated role of $^{68}$Ga DOTATOC PET-MRI in radiation treatment planning of meningiomas with encouraging results.

**Future directions**

A multimodal adaptive clinical trial approach is needed for the routine incorporation of novel imaging PET radiopharmaceuticals in radiation treatment planning. Pre-treatment imaging should be performed to properly identified candidates. Serial imaging examinations can be performed during radiation therapy to evaluate treatment response and to select highest-risk areas warranting treatment modifications, such as radiation dose escalation. It is hoped that further investigations of new PET radiopharmaceuticals in radiation treatment planning, with careful attention to assessments of clinical efficacy, patient tolerance and safety, will lead to improved outcomes for those currently at greatest risk for treatment failure and disease dissemination.

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**Footnote**

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**References**


