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. ^{18}F-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; ^{11}C-methionine; ^{11}C-choline; ^{18}F-FMISO

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-[^{18}F]fluoro-2-D-deoxyglucose {[^{18}F]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 [^{18}F]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-fluorotethyltyrosine 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 (7) 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-^{11}C] tyrosine (10) as well as unnatural aliphatic {e.g., [^{11}C]AIB} and alicyclic {e.g., [^{11}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-[^{18}F]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 tumor 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 [11C] acetate (^{11}C-ACE) or with ^{18}F resulting in the analogue tracer [^{18}F]fluoroacetate (^{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 lipid synthesis 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 $\alpha v\beta 3$, 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 heterogenity 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 menigiomas ^{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 menigiomas 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

1. Rohren EM, Turkington TG, Coleman RE. Clinical applications of PET in oncology. Radiology 2004;231:305-32.
2. Grégoire V, Haustermans K, Geets X, et al. PET-based treatment planning in radiotherapy: a new standard? J Nucl Med 2007;48 Suppl 1:68S-77S.
3. Geets X, Daisne JF, Gregoire V, et al. Role of 11-C-methionine positron emission tomography for the delineation of the tumor volume in pharyngo-laryngeal squamous cell carcinoma: comparison with FDG-PET and CT. Radiother Oncol 2004;71:267-73.
4. Weber WA, Wester HJ, Grosu AL, et al. O-(2- [18F] Fluoroethyl)-L-tyrosine and L-[methyl-11C]methionine uptake in brain tumours: initial results of a comparative study. Eur J Nucl Med 2000;27:542-9.
5. Picchio M, Crivellaro C, Giovacchini G, et al. PET-CT for treatment planning in prostate cancer. Q J Nucl Med Mol Imaging 2009;53:245-68.
6. Padhani A. PET imaging of tumour hypoxia. Cancer Imaging 2006;6:s117-s121. Retraction in: Cancer Imaging

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2007;7:1.

7. Bading JR, Shields AF. Imaging of cell proliferation: status and prospects. J Nucl Med 2008;49 Suppl 2:64S-80S.

8. Hawkins RA, Huang SC, Barrio JR, et al. Estimation of local cerebral protein synthesis rates with L-[1-11C] leucine and PET: methods, model, and results in animals and humans. J Cereb Blood Flow Metab 1989;9:446-60.

9. Kubota K, Yamada K, Fukada H, et al. Tumor detection with carbon-11-labelled amino acids. Eur J Nucl Med 1984;9:136-40.

10. Pruim J, Willemsen AT, Molenaar WM, et al. Brain tumors: L-[1-C-11]tyrosine PET for visualization and quantification of protein synthesis rate. Radiology 1995;197:221-6.

11. McConathy J, Goodman MM. Non-natural amino acids for tumor imaging using positron emission tomography and single photon emission computed tomography. Cancer Metastasis Rev 2008;27:555-73.

12. Rau FC, Weber WA, Wester HJ, et al. O-(2-[(18)F] Fluoroethyl)-L-tyrosine (FET): a tracer for differentiation of tumour from inflammation in murine lymph nodes. Eur J Nucl Med Mol Imaging 2002;29:1039-46.

13. Barrio JR, Huang SC, Phelps ME. Biological imaging and the molecular basis of dopaminergic diseases. Biochem Pharmacol 1997;54:341-8.

14. Stout DB, Huang SC, Melega WP, et al. Effects of large neutral amino acid concentrations on 6-[F-18]Fluoro-L-DOPA kinetics. J Cereb Blood Flow Metab 1998;18:43-51.

15. Sundin A, Garske U, Orlefors H. Nuclear imaging of neuroendocrine tumours. Best Pract Res Clin Endocrinol Metab 2007;21:69-85.

16. Nuutinen J, Sonninen P, Lehikoinen P, et al. Radiotherapy treatment planning and long-term follow-up with [(11)C] methionine PET in patients with low-grade astrocytoma. Int J Radiat Oncol Biol Phys 2000;48:43-52.

17. Schinkelshoek M, Lopci E, Clerici E, et al. Impact of 11C-methionine positron emission tomography/ computed tomography on radiation therapy planning and prognosis in patients with primary brain tumors. Tumori 2014;100:636-44.

18. Weber DC, Zilli T, Buchegger F, et al. [(18)F] Fluoroethyltyrosine- positron emission tomography-guided radiotherapy for high-grade glioma. Radiat Oncol 2008;3:44.

19. Niyazi M, Geisler J, Siefert A, et al. FET-PET for malignant glioma treatment planning. Radiother Oncol 2011;99:44-8.

20. de Certaines JD, Larsen VA, Podo F, et al. In vivo 31P MRS of experimental tumours. NMR Biomed 1993;6:345-65.

21. Shindou H, Shimizu T. Acyl-CoA:lysophospholipid acyltransferases. J Biol Chem 2009;284:1-5.

22. Schwarzenböck SM, Kurth J, Gocke Ch, et al. Role of choline PET/CT in guiding target volume delineation for irradiation of prostate cancer. Eur J Nucl Med Mol Imaging 2013;40 Suppl 1:S28-35.

23. Würschmidt F, Petersen C, Wahl A, et al. [18F] fluoroethylcholine-PET/CT imaging for radiation treatment planning of recurrent and primary prostate cancer with dose escalation to PET/CT-positive lymph nodes. Radiat Oncol 2011;6:44.

24. Chang JH, Lim Joon D, Lee ST, et al. Intensity modulated radiation therapy dose painting for localized prostate cancer using ^{11}C-choline positron emission tomography scans. Int J Radiat Oncol Biol Phys 2012;83:e691-6.

25. Picchio M, Berardi G, Fodor A, et al. (11)C-Choline PET/ CT as a guide to radiation treatment planning of lymph-node relapses in prostate cancer patients. Eur J Nucl Med Mol Imaging 2014;41:1270-9.

26. Souvatzoglou M, Krause BJ, Pürschel A, et al. Influence of (11)C-choline PET/CT on the treatment planning for salvage radiation therapy in patients with biochemical recurrence of prostate cancer. Radiother Oncol 2011;99:193-200.

27. Padhani AR, Krohn KA, Lewis JS, et al. Imaging oxygenation of human tumours. Eur Radiol 2007;17:861-72.

28. Piert M, Machulla HJ, Picchio M, et al. Hypoxia specific tumor imaging with 18F-fluoroazomycin arabinoside. J Nucl Med 2005;46:106-13.

29. Vāvere AL, Lewis JS. Cu-ATSM: a radiopharmaceutical for the PET imaging of hypoxia. Dalton Trans 2007:4893-902.

30. Holland JP, Barnard PJ, Collison D, et al. Spectroelectrochemical and computational studies on the mechanism of hypoxia selectivity of copper radiopharmaceuticals. Chemistry 2008;14:5890-907.

31. Hendrickson K, Phillips M, Smith W, et al. Hypoxia imaging with [F-18] FMISO-PET in head and neck cancer: Potential for guiding intensity-modulated radiation therapy in overcoming hypoxia-induced treatment resistance. Radiother Oncol 2011;101:369-75.

32. Toma-Dasu I, Uhrdin J, Antonovic L, et al. Dose prescription and treatment planning based on FMISO-PET hypoxia. Acta Oncol 2012;51:222-30.

33. Choi W, Lee SW, Park SH, et al. Planning study for

available dose of hypoxic tumor volume using fluorine-18-labeled fluoromisonidazole positron emission tomography for treatment of the head and neck cancer. Radiother Oncol 2010;97:176-82.

34. Dirix P, Vandecaveye V, De Keyzer F, et al. Dose painting in radiotherapy for head and neck squamous cell carcinoma: Value of repeated functional imaging with (18) F-FDG PET, (18)F-fluoromisonidazole PET, diffusion-weighted MRI, and dynamic contrast-enhanced MRI. J Nucl Med 2009;50:1020-7.

35. Lin Z, Mechalakos J, Nehmeh S, et al. The influence of changes in tumor hypoxia on dose-painting treatment plans based on 18F-FMISO positron emission tomography. Int J Radiat Oncol Biol Phys 2008;70:1219-28.

36. Lee NY, Mechalakos JG, Nehmeh S, et al. Fluorine-18-labeled fluoromisonidazole positron emission and computed tomography-guided intensity-modulated radiotherapy for head and neck cancer: A feasibility study. Int J Radiat Oncol Biol Phys 2008;70:2-13.

37. Grosu AL, Souvatzoglou M, Röper B, et al. Hypoxia imaging with FAZA-PET and theoretical considerations with regard to dose painting for individualization of radiotherapy in patients with head and neck cancer. Int J Radiat Oncol Biol Phys 2007;69:541-51.

38. Dalah E, Bradley D, Nisbet A. Simulation of tissue activity curves of (64)Cu-ATSM for sub-target volume delineation in radiotherapy. Phys Med Biol 2010;55:681-94.

39. Chao KS, Bosch WR, Mutic S, et al. A novel approach to overcome hypoxic tumor resistance: Cu-ATSM-guided intensity-modulated radiation therapy. Int J Radiat Oncol Biol Phys 2001;49:1171-82.

40. Buck AK, Herrmann K, Shen C, et al. Molecular imaging of proliferation in vivo: positron emission tomography with [18F]fluorothymidine. Methods 2009;48:205-15.

41. Barwick T, Bencherif B, Mountz JM, et al. Molecular PET and PET/CT imaging of tumour cell proliferation using F-18 fluoro-L-thymidine: a comprehensive evaluation. Nucl Med Commun 2009;30:908-17.

42. Troost EG, Bussink J, Hoffmann AL, et al. 18F-FLT PET/CT for early response monitoring and dose escalation in oropharyngeal tumors. J Nucl Med 2010;51:866-74.

43. Han D, Yu J, Yu Y, et al. Comparison of (18) F-fluorothymidine and (18)F-fluorodeoxyglucose PET/CT in delineating gross tumor volume by optimal threshold in patients with squamous cell carcinoma of thoracic esophagus. Int J Radiat Oncol Biol Phys 2010;76:1235-41.

44. Liu J, Li C, Hu M, et al. Exploring spatial overlap of high-uptake regions derived from dual tracer positron emission tomography-computer tomography imaging using 18F-fluorodeoxyglucose and 18F-fluorodeoxythymidine in nonsmall cell lung cancer patients: a prospective pilot study. Medicine (Baltimore) 2015;94:e678.

45. Haubner R, Decristoforo C. Radiolabelled RGD peptides and peptidomimetics for tumour targeting. Front Biosci (Landmark Ed) 2009;14:872-86.

46. Haubner R, Weber WA, Beer AJ, et al. Noninvasive visualization of the activated alphavbeta3 integrin in cancer patients by positron emission tomography and [18F] Galacto-RGD. PLoS Med 2005;2:e70.

47. Beer AJ, Haubner R, Sarbia M, et al. Positron emission tomography using [18F]Galacto-RGD identifies the level of integrin alpha(v)beta3 expression in man. Clin Cancer Res 2006;12:3942-9.

48. Norden AD, Drappatz J, Wen PY. Advances in meningioma therapy. Curr Neurol Neurosci Rep 2009;9:231-40.

49. Campbell BA, Jhamb A, Maguire JA, et al. Meningiomas in 2009: controversies and future challenges. Am J Clin Oncol 2009;32:73-85.

50. Gehler B, Paulsen F, Oksuz MO, et al. [68Ga]-DOTATOC-PET/CT for meningioma IMRT treatment planning. Radiat Oncol 2009;4:56.

51. Henze M, Schuhmacher J, Hipp P, et al. PET imaging of somatostatin receptors using [68GA]DOTA-D-Phe1-Tyr3- octreotide: first results in patients with meningiomas. J Nucl Med 2001;42:1053-6.

52. Khan MU, Khan S, El-Refaie S, et al. Clinical indications for Gallium-68 positron emission tomography imaging. Eur J Surg Oncol 2009;35:561-7.

53. Graf R, Nyuyki F, Steffen IG, et al. Contribution of 68Ga-DOTATOC PET/CT to target volume delineation of skull base meningiomas treated with stereotactic radiation therapy. Int J Radiat Oncol Biol Phys 2013;85:68-73.

54. Thorwarth D, Henke G, Müller AC, et al. Simultaneous 68Ga-DOTATOC-PET/MRI for IMRT treatment planning for meningioma: first experience. Int J Radiat Oncol Biol Phys 2011;81:277-83.