



An update on PET-based molecular imaging in neuro-oncology: challenges and implementation for a precision medicine approach in cancer care

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Abstract: PET imaging using novel radiotracers show promises for tumor grading and molecular characterization through visualizing molecular and functional properties of the tumors. Application of PET tracers in brain neoplasm depends on both type of the neoplasm and the research or clinical significance required to be addressed. In clinical neuro-oncology, ¹⁸F-FDG is used mainly to differentiate tumor recurrence from radiation-induced necrosis, and novel PET agents show attractive imaging properties. Novel PET tracers can offer biologic information not visible via contrast-enhanced MRI or ¹⁸F-FDG PET. This review aims to provide an update on the complementary role of PET imaging in neuro-oncology both in research and clinical settings along with presenting interesting cases in this context.

Keywords: Positron emission tomography (PET); brain tumors; magnetic resonance imaging (MRI); precision medicine; molecular imaging; ⁶⁸Ga-DOTA-peptide; ⁶⁸Ga-labeled PSMA

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Introduction

Brain neoplasms include primary brain neoplasms which stem from the brain parenchyma, and metastatic lesions originating from other primary malignancies outside of the brain. The former is less frequent than the latter. According to the American Cancer Society report, approximately 24,000 of new cases are diagnosed with primary brain

neoplasms every year while about 17,000 death occurs due to primary brain tumors every year in USA (1,2). Brain metastases comprise more than half of intracranial tumors in adults (3), with incidence of 9% to 17% in patients with cancer (4). Tumors of the brain and the other parts of the nervous system are the most leading cause of death from cancer among males before 40 years of age and females aged

less than 20 years (2). The most common sites of origination include lung, breast, and skin (melanoma). Moreover, in about 15% of metastatic brain lesions, the primary site of the tumor remains undiscovered (3).

The most common types of primary brain tumors include glioma which is the most lethal brain tumor, accounting for about 45% to 50% of total primary brain tumors, followed by meningiomas, the second commonest, and comprising nearly 15% of all the primary brain neoplasms. The other types of primary brain tumors occur with less incidence (5,6). Gliomas are divided into several groups including astrocytoma, oligodendroglioma, choroid plexus tumors, ependymal tumors, and embryonal tumors (1). According to the WHO Classification of Tumors of the Central Nervous System (CNS) 2016 (1), tumors are graded into four grades based on the histopathologic characteristics in which grade 1 represents benign features and grade 4 indicates the most malignant tumors (1). Current practice in tumor grading relies on histologic studies that require tissue biopsy of brain neoplasms. The potential complications during and after the procedure and the invasive nature of tissue biopsy remain the main challenges of tumor grading. Recently, the emergence of novel technologies, such as molecular genomics, novel tracers and imaging techniques, offer the potential to identify the molecular properties and grading of the neoplastic tissues noninvasively. Positron emission tomography (PET) modality with a wide range of radiotracers may have the capacity as a complementary imaging modality to routine clinical practice.

Chemotherapy, radiotherapy, surgical resection, and stereotactic radiosurgery (SRS) are the available standard treatments (5). The estimation for prognosis of nervous system neoplasms is a challenging issue and remains rather poor, particularly for the patients with metastatic lesions. The median survival rate in patients with and without treatment is as low as only 3–21 and 1–2 months, respectively (3,7). Among primary brain tumors, glioblastomas are the most fatal; These patients often do not survive beyond few months despite optimal multimodal treatments (8). Recent high throughput molecular and genomic technologies have revealed high molecular heterogeneity among phenotype of glioblastoma. This heterogeneity is responsible for treatment failure and poor prognosis (9,10). Regarding the noninvasive nature of neuroimaging modalities, identifying of a prognostic imaging indicator correlated with histopathologic grades of the tumor, molecular characteristics, or clinical outcome of the disease is of vital value in disease prognostication

and improve the patient care as well (11). PET imaging using novel radiotracers show promise in tumor grading and molecular characterization through visualizing various molecular and functional properties in tumor lesions (5,11,12). This application of PET imaging is discussed in the current review.

Role of neuroimaging in brain tumors

Neuroimaging plays a pivotal role in various aspects of brain neoplasms evaluation during the clinical course of the disease. These include precise anatomic localization, tumor grading, delineation of tumor extent and margins for pre-surgical or radiotherapeutic planning, determination of ideal site for biopsy, identifying the involvement of vital structures, early response assessment, discrimination of tumor recurrence from reactive changes after therapy and prognostication. However, the definitive diagnosis is still made upon tissue biopsies (5,11). Presently, magnetic resonance imaging (MRI) with gadolinium contrast agent is used as the standard method of choice in the practice of brain tumors. MRI enables visualizing anatomic details in the routine clinical setting (5). Perfusion-weighted MR measures the blood flow parameters; magnetic resonance spectroscopy (MRS) measures the concentration of metabolites within tissues; and diffusion tensor imaging (DTI) assess brain tumor by mapping the white matter (11,13). Functional MR imaging (fMRI) using the Blood Oxygen Level Dependent (BOLD) technique provides functional map for each patient facilitates the surgical planning and averts the unsolicited collateral damage to vital brain regions during surgery and radiotherapy (5).

PET and brain tumors

Many PET tracers have been produced for imaging in oncology, with different physiochemical identities, biologic targets, and labeled radionuclides. Among these, merely a few tracers have been employed for the imaging of brain tumor in humans. Since more than three decades ago, PET modality has been utilized for brain tumor imaging in both clinical practice and research setting. The glucose analog 2-deoxy-2-[fluorine-18] fluoro-D-glucose (^{18}F -FDG) is the standard molecular imaging agent applied for brain lesions in the routine practice. In clinical neuro-oncology, ^{18}F -FDG has been utilized mainly to differentiate the tumor recurrence from radiation-induced changes. Novel PET offers biologic information not visible via ^{18}F -FDG PET

modality or contrast-enhanced MRI alone.

Role of PET imaging in the delineation of tumor volume

Although the delineation of entire tumor volume is crucial in the diagnostic evaluations and pre-surgical resection or pre-radiotherapy planning, proper tumor delineation in the routine clinical practice remains a challenge. The reason is that the function of Blood-Brain-Barrier (BBB) that keeps contrast agents (CT or MR) outside of the brain parenchyma. Brain tumors, those which have intact BBB, such as low-grade gliomas do not enhance following the injection of intravenous CT or MR contrast agent, while high-grade glioma tumors usually have impaired BBBs and are enhanced with contrast agent. However, several high-grade tumors may not enhance with contrast agent, and even there are often non-enhancing regions within enhanced tumors in cases of glioblastomas (5). On the other hand, imaging of extra-axial lesions, which located outside of the brain, and metastases that interrupt BBB integrity do not suffer these issues.

Many of PET tracers can pass through the BBB owing to be the substrate of BBB transporters. Only those molecules or compounds can cross the BBB which are substrate for biological transporters located on the luminal surface of the BBB (5). Although the ^{18}F -FDG PET is a standard modality in oncologic imaging, this tracer suffer from its relative lack of specificity and high background uptake in healthy brain tissue that could lead to false negative or false positive results in lesions less than 5 mm (11). Two strategies have been developed to improve ^{18}F -FDG PET modality: (I) co-registration of ^{18}F -FDG PET with MR imaging in which MR imaging enables us to outline region of interest (ROI) accurately and any enhanced ^{18}F -FDG uptake represents an active process, and (II) delayed image acquisition, that is based on the lower rate constant of FDG-6-phosphate degradation at prolonged period of time in the tumor lesion compared with the healthy brain tissue, in which ^{18}F -FDG PET imaging is performed at an extended time interval between injection and PET imaging (6).

Recently, novel PET-tracers have been developed which have demonstrated better results than ^{18}F -FDG PET imaging (5,6). Among them, radiolabeled amino acids have shown promising potential in accurate tumor volume delineation, active metabolic volume, and better results in pre-surgical or pre-radiotherapy planning (5,6,14). An investigation revealed that the utility of hybrid imaging

through fusing amino acid PET (or SPECT) with MR (or CT) imaging in the reirradiation planning of recurrent high-grade gliomas significantly improved survival time compared with CT or MR imaging alone (14). Investigators recruited 44 participants with recurrent high-grade gliomas after previous surgical resection and adjuvant conventional radiotherapy \pm chemotherapy (temozolomide). For treatment planning of fractionated stereotactic radiotherapy (FSRT), the gross tumor extent was delineated using hybrid imaging modality through fusing ^{123}I -methyl-tyrosine (IMT) single-photon computed emission tomography (SPECT) or ^{11}C -methionine positron emission tomography (MET-PET) with computed tomography (CT) or MRI in 82% of the subjects and by CT/T1gadolinium-MRI image fusion in 18% of them (Figures 1,2). Results showed that treatment designing using fused PET (SPECT)/MR (CT) imaging was correlated with the improvement of survival compared to treatment designation based on CT/MRI alone.

Brain tumor grading and molecular characterization using PET imaging

Accurate tumor grading is an immediate step in the evaluation and management of brain tumors. Investigators have been focusing on the concept of “non-invasive tumor grading”, to identify a grading imaging marker which is capable to correlate with the histological grading of tumor tissues (11). ^{18}F -FDG uptake is usually higher in high grade glioma (WHO grade III and IV) than low grade tumors (WHO grade II) (15). The usefulness of ^{18}F -FDG PET for grading of glioma tumors is hindered by the low tumor-to-background ratio due to physiologically enhanced glucose metabolism of cortical and subcortical component in the brain (15). In the other studies, ^{18}F -FDG-PET failed to be correlated with ki-67 index, which is a histological indicator of cell proliferation (16,17).

An increased uptake in the fluorothymidine (FLT) PET imaging are shown in high grade tumors as well (18-25). Collet and colleagues (18) demonstrated that the FLT-PET imaging is superior to several advanced MR imaging modalities including both diffusion and perfusion weighted MR imaging and even MRS in noninvasive tumor grading. A total of thirty-nine patients with spread gliomas whose tumors were pathologically proven to be grade II, III, or IV were included. They were investigated using conventional MRI and perfusion, diffusion, and proton MR spectroscopy (1H-MRS) and ^{18}F -FLT-PET imaging prior to surgery. Apparent diffusion coefficient (ADC), relative cerebral

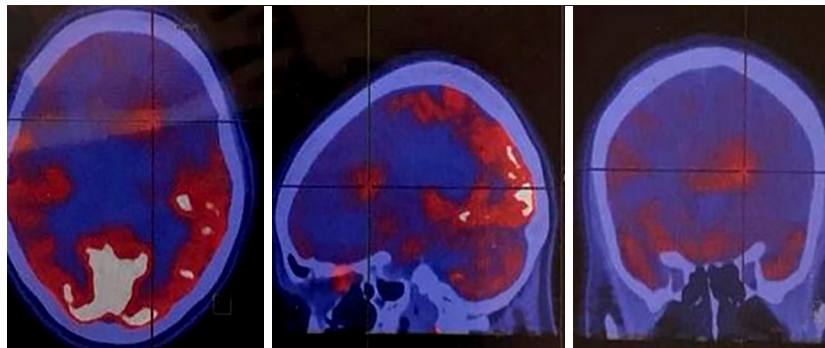


Figure 1 ^{18}F -FDG PET/CT scan of high-grade astrocytoma. There is asymmetry increased uptake in the left frontoparietal parasagittal region. ^{68}Ga -DOTATATE PET/CT scan showed no abnormal activity (not shown).

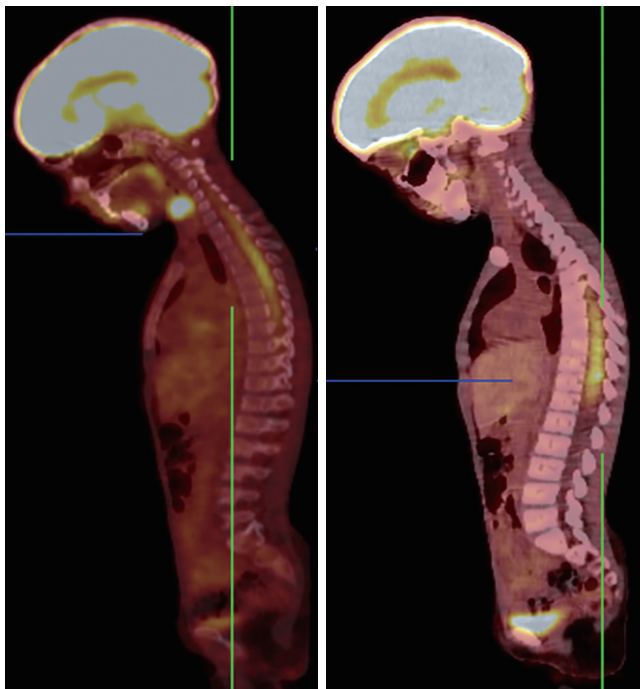


Figure 2 ^{18}F -FDG PET/CT scan of a patient with spinal cord medulloblastoma. PET/CT images demonstrated diffuse enhanced FDG uptake in spinal cord at level of T5-T11.

blood volume (rCBV), Cho/Cr, NAA/Cr, Cho/NAA and FLT SUV were compared among grades. Results revealed that the mean value of ^{18}F -FLT uptake FLT_{mean} ($R^2 = 0.36$) and FLT_{max} ($R^2 = 0.5$) were the best indicators that correlate with tumor grades, even superior to MRS especially regarding differentiation between doubtful grade III and IV tumors.

Of the remarkable progress in advanced molecular

profiling and genomic characterization in brain tumors, particularly in gliomas, was the revision of the classification and management of gliomas toward molecular profiling and genomic characterization by WHO in 2016 (1). Vomacka and colleagues (26) have intended to ascertain a reader-independent glioma detection and characterization of aggressive sub-component through a voxel-wise analysis of diagnostically-related static and kinetic ^{18}F -FET PET values. 162 subjects with newly diagnosed gliomas were enrolled and were separated into groups upon histologic, genetic, and molecular characteristics. They measured the biological tumor volume (BTV), and also for every enclosed voxel, the late slope ($\text{Slope}_{15-40 \text{ min}}$), the time-to-peak (TTP), and the tumor-to-background ratios ($\text{TBR}_{5-15 \text{ min}}$, $\text{TBR}_{20-40 \text{ min}}$) were calculated. The percentage portion of these parameter inside the BTV was assessed with the percentage volume fractions (PVFs) and cumulated percentage volume histograms (PVHs). The potential of these voxel-based parameters to differentiate among molecular genetics properties and histologic grades was appraised and compared with volume-of-interest (VOI)-based values. In the voxel-wise analysis, high grade glioma tumors, WHO grade III and IV, and IDH-wild type gliomas predominantly contained high proportion of voxels with negative slope, high early peak, and high TBR. It also has been shown that PVHs with $\text{TTP} < 20 \text{ min p.i.}$, $\text{Slope}_{15-40 \text{ min}} < 0 \text{ SUV/h}$, and $\text{TBR}_{5-15 \text{ min}}$ and $\text{TBR}_{20-40 \text{ min}} > 2$ yielded the most significant difference between tumor grades. Moreover, voxel-based parameters compared with VOI-indices showed better accuracy in both tumor grading and IDH mutation status. The researchers provided an automated and reader-independent method for voxel-wise ^{18}F -FET PET glioma analysis that has potential to

differentiate among WHO grades of glioma tumors and between IDH mutations subtypes. Finally, they concluded that the designated method potentially offers a rapid determination of aggressive subdivision of tumor within the BTV, and parametric 3D ^{18}F -FET PET information may contribute to guiding biopsy acquisition in heterogeneous-nature glioma tumors.

Promises of new artificial amino acids in non-invasive tumor grading

So far, many amino acid transporters have been detected at molecular level and have been described in the human body. Natural amino acids are absorbed via amino acid transport systems that important systems include the A, L, and alanine-serine-cysteine (ASC) amino acid transport systems (27). L amino acid transport systems are Na^+ -independent, and the principal transport pathway for phenylalanine, tyrosine, methionine, and their analogs, but, System A and ASC systems are Na^+ -dependent (27). However, the literature is scarce regarding the application of radiolabeled amino acids transported through an amino acid transporter system in the cancer management investigations.

[N-methyl- ^{11}C]-methylaminoisobutyric acid (MeAIB) is a synthetic amino acid transported through system A neutral amino acid transports and is recently used for brain tumors (28). In 2018, Nishii and colleagues (28) studied the ability of MeAIB for noninvasively differentiating high-grade from low-grade gliomas in clinical setting and compared it with the ability of [S-methyl- ^{11}C]-L-methionine (MET)-PET. Thirty-one individuals (male: 16, female: 15) participated in the study. They were separated into two groups: Group A comprised of individuals who were diagnosed with benign lesion such as low-grade astrocytoma tumors, grade II or less, or other low-grade astrocytomas ($n=12$). Group B including patient with malignant brain tumors such as glioblastoma multiforme (GBM), recurrent GBM, or anaplastic astrocytoma ($n=19$). All of the participants underwent MeAIB-PET and MET-PET imaging. The results showed that the SUV_{max} values were 1.20 ± 1.29 for the group A patients and 2.94 ± 1.22 for group B patients on MeAIB-PET imaging. The tumor-to-contralateral normal brain tissue (T/N ratio) was 3.77 ± 2.39 in group A patients and 16.83 ± 2.39 in group B patients. In MET-PET, the SUV_{max} was 3.01 ± 0.94 in group A patients and 4.72 ± 1.61 in group B patients, and the T/N ratio was 2.64 ± 1.40 for group A and 3.21 ± 1.14 for group B. The investigators concluded that the MeAIB-PET imaging

yielded higher accuracy than the MET-PET imaging in distinguishing low-grade from high-grade brain tumors.

Assessment of response to treatment using hybrid imaging

Regarding the highly aggressive and heterogeneous nature of brain tumors, especially GBM as the most common and fatal of those, earlier response assessment is vital in the management of brain tumors. At present, current clinical practice relies upon conventional imaging to appraise the response. It remains a challenge to determine the treatment efficacy due to the lack of accuracy of conventional modalities in differentiating between pseudoprogression (PsP) including treatment-induced changes, and true tumor progression (tumor growth or recurrence) (6,11). In recent years, investigators have made great efforts to overcome the challenges through utilizing molecular imaging like PET imaging, which uses a vast range of tracers with different properties, and with combined anatomical and functional modalities e.g., PET/MR (11,29-32). FDG-PET, the current standard PET agent, utilization in differentiating between pseudo- and true progression has shown variable results (6). In addition, high background uptake may limit its ability regarding small lesion detection (11). Recently, new PET tracers have demonstrated better results than the traditional FDG-PET in differentiating PsP and true progression of tumors (33,34). Gao *et al.* evaluated the diagnostic precision of ^{11}C -choline PET in differentiating PsP from true tumor progression through a meta-analysis. With a total of 118 patients (134 scans), the pooled sensitivity and specificity were 0.87 (95% CI: 0.78, 0.93) and 0.820 (95% CI: 0.69, 0.91), respectively. They conclude that ^{11}C -choline has the potential to differentiate PsP and true progression of tumors (35). Some studies have further suggested that O-[2-(^{18}F)fluoroethyl]-L-tyrosine (^{18}F FET)-PET can potentially solve this problem (31,36). Galldiks and colleague studied the detection of pseudoprogression in glioblastoma patients using ^{18}F -FET-PET. They investigated a total of 22 patients with new contrast-enhanced (CE) areas or lesions that enhanced with contrast (>25%) on MR imaging during the first 12 weeks after finishing the course of therapy. Patients underwent ^{18}F -FET-PET as well to differentiate PsP from true progression. They showed that the best ^{18}F -FET TBR_{max} cut-off value for diagnosis of PsP was 2.3 (sensitivity 100%, specificity 91%, accuracy 96%) (31). Lohmann *et al.* explored the potential of combined FET-PET/MRI

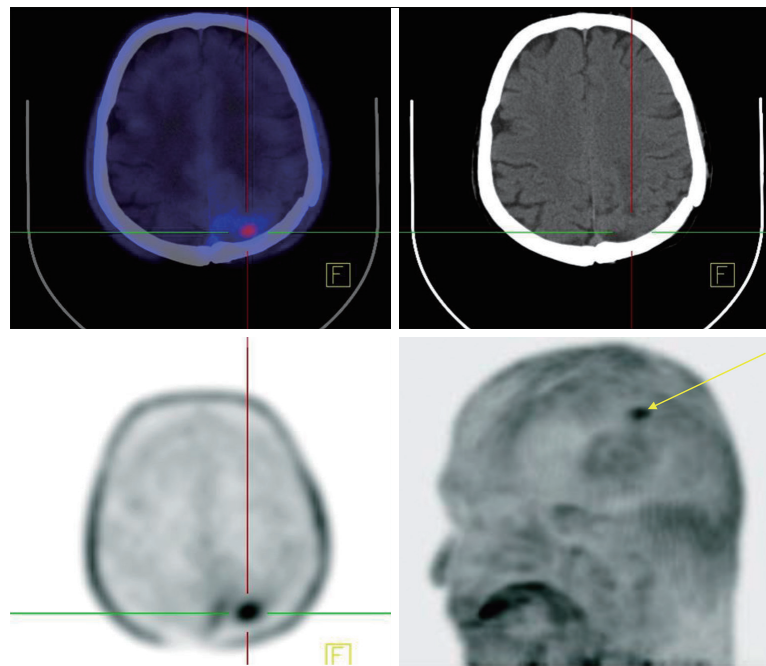


Figure 3 ^{18}F -FET PET/CT scan representing tumor recurrence in the posterior left occipital lobe (arrow).

in distinguishing of PsP from true progression in the brain metastasis. A total of 52 patients who showed new or progressive contrast-enhancement lesions on MR imaging after ending the radiotherapy underwent the FET-PET as well. The results showed that the CE-MRI had an accuracy of 81% (sensitivity, 67%; specificity, 90%) in PsP diagnosis. The diagnosis accuracy for FET-PET was 83% (sensitivity, 88%; specificity, 75%). They combined the two modalities and achieved a diagnostic accuracy of 89% (sensitivity, 85%; specificity, 96%). Thus, it may be the right time to shift from conventional imaging to the fused anatomical/molecular imaging approach which uses new agents to improve diagnostic accuracy and provides further insight into the tumor characteristics (*Figure 3*).

Application of novel PET tracers in brain tumors

Somatostatin receptor (SSTR) imaging in brain neoplasms other than neuroendocrine tumors (NETs)

Somatostatin is a neuropeptide released by endocrine cells, neurons, and immune cells which its functions include neuroregulation (sensory, motor, and cognition) and cell growth inhibition by paracrine and autocrine pathways (37,38). Somatostatin works through a group of

transmembrane G protein-coupled receptors that enter the cell following binding to specific ligands (39). So far, six subtypes of somatostatin receptors (SSTRs) are discovered including SSTR 1, 2A, 2B, 3, 4, and 5. A broad spectrum of brain tumors express different subtypes of SSTR on their surface including frequent primary brain tumors e.g., gliomas and meningiomas, pediatric brain tumors (medulloblastomas), pituitary adenomas, and supratentorial primitive neuroendocrine tumors (PNETs) (40-43). Dutour and colleague (44) have shown that gliomas and meningiomas, as the first and second most common primary brain tumors, are positive for different subtypes of SSTR. It was demonstrated that although all of them have at least one SSTR subtype, many of these harboring multiple SSTR subtypes. They provided proofs on detecting SSTRs in both tumors and their surrounding tissues, particularly blood vessels. Concerning gliomas, low-grade gliomas (WHO grade I, II) depicted higher expression levels compared to high-grade gliomas (WHO grade III, IV) (45). To date, three ^{68}Ga -DOTA peptides are developed for clinical imaging comprised of ^{68}Ga -DOTA-TOC, ^{68}Ga -DOTA-NOC, and ^{68}Ga -DOTA-TATE. The shared property of these ^{68}Ga -DOTA peptides is the ability in binding to SSTR2, and they differ with regard to their SSTR subtype affinity and profile (*Figures 4,5*).

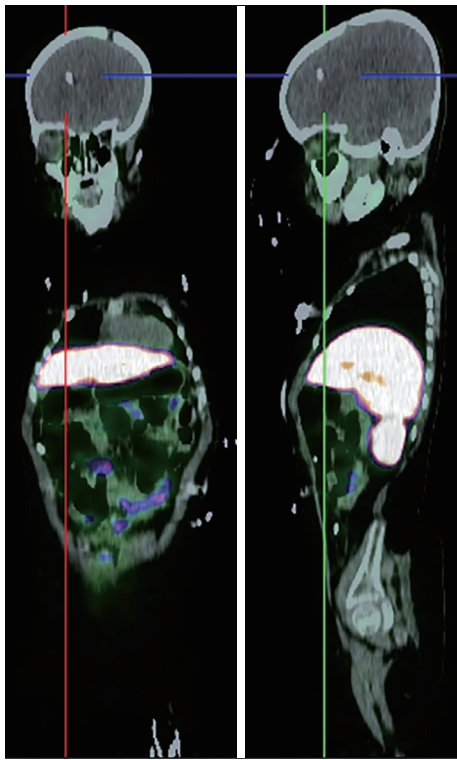


Figure 4 ^{68}Ga -DOTATATE PET/CT scan of glioma. There is radiotracer uptake in a large mass in an ill-defined mass with increased uptake with SUVmax =10.48.

^{68}Ga -DOTA-peptide in meningiomas

Meningioma is the second most frequent primary brain tumor and is benign in 90% of cases. The current standard imaging modality in diagnosis is conventional MR imaging (43). Although the SSTR receptors are positive in the healthy leptomeningeal cell, the meningioma cells express higher levels of them (46,47). Afshar-Oromieh *et al.* (48) aimed to compare the ability in detecting meningioma lesions between ^{68}Ga -DOTA-peptide PET/CT and contrast-enhanced MRI (CE-MRI) within a total of 134 patient. They revealed that ^{68}Ga -DOTA-peptide PET/CT has higher accuracy compared to CE-MRI in meningioma detection (190 *vs.* 171). The investigators concluded that ^{68}Ga -DOTA-peptide PET/CT could play a complementary role with MRI in cases where MRI finding has failed in definitive diagnosis or lack of feasibility for biopsy. Another promising potential of ^{68}Ga -DOTA-peptide PET/CT was reported by Milker-Zabel and colleagues (49) through a study that showed target volume delineation using ^{68}Ga -DOTA-PET/CT and MRI in comparison to

CT or MRI alone has changed the radiotherapy planning in 73% of 26 patients. Gehler *et al.* (50) reported similar results as well. One example of this modality in meningioma is illustrated in *Figure 6*.

^{68}Ga -DOTA peptide in medulloblastomas

Medulloblastoma is the most prevalent type of the brain tumor among pediatrics, with the highest incidence between the ages of 3 to 9 years (43,51). The primary treatment is craniospinal radiotherapy with significant rates of cure but together with severe neurocognitive decline (43). It has been revealed that medulloblastomas express high levels of SSTR receptors, with highest expressed subtype being SSTRs 2 and 3 (45,52). Up to our knowledge, no study has been published yet on medulloblastoma evaluation using ^{68}Ga -DOTA-peptide PET/CT. It is possible that ^{68}Ga -DOTA-peptide PET/CT can have a valuable role in the management of medulloblastomas.

Role of prostate-specific membrane antigen (PSMA) in brain tumors imaging

PSMA is a type II transmembrane glycoprotein which is overexpressed in prostate cancer and its expression levels are positively associated with tumor grade and stage (53). Also, PSMA expression is increased with conditions like hormone resistance, metastatic lesions, and anaplastic properties in tumor (54). Although PSMA was found in prostate glands for the first time but further histologic studies revealed it could be found in other healthy tissue as well, including salivary glands, lacrimal glands, duodenal epithelium, proximal tube cell of the kidney (55,56). Of note, it has been detected in healthy tissues (as mentioned earlier), benign conditions (e.g., meningiomas in the brain), and malignant tumors both prostatic-originated and non-prostatic-originated tumors, therefore questioning the sensitivity and specificity of PSMA as a specific prostatic tracer (53,57,58). Since the development of ^{68}Ga -labeled PSMA, a PSMA-targeted small molecule labeled with ^{68}Ga , investigators are equipped not only to visualize the prostate cancer throughout the human body, but also to use it as a therapeutic target (59-61). Although PSMA has been developed to assess the management of prostate cancer, the expression of PSMA has been seen in different nonprostatic malignant and nonmalignant conditions causing to probable difficulties in the analysis of PSMA-targeted studies. On the other hand, this limitation may indicate favorable in imaging and therapeutic agent for other nonprostatic

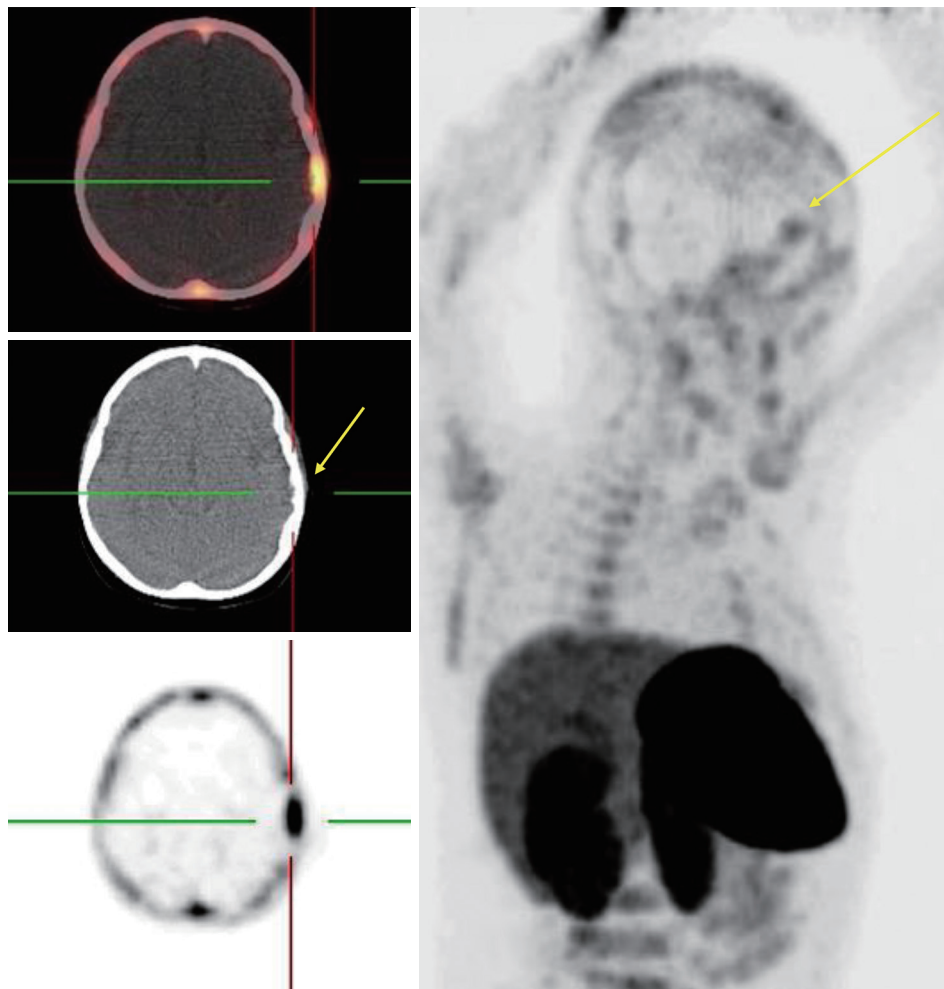


Figure 5 ^{68}Ga -DOTATATE PET/CT scan of neuroblastoma. There is focal uptake in the skull representing bony invasion (arrow).

conditions (53,56). ^{68}Ga labeled PSMA is increasingly incorporated in the routine clinical assessment of patients affected by prostate cancer. Whole-body ^{68}Ga -PSMA scan can be useful in the initial staging of intermediate or high risk prostate cancers and in restaging after biochemical clue of tumor recurrence (62,63) (Figure 7).

Healthy brain tissue does not show any PSMA uptake which makes it a promising tracer in detecting metastasis of prostatic cancer to the brain, but studies reported new connections between PSMA uptake and nervous system tumors other than prostatic metastasis (57,59). Up to present, several studies have reported PSMA expression in few nervous system tumors (53) including meningiomas, schwannomas, peripheral nerve sheath tumors as well as

other benign conditions such as sympathetic chain ganglia (58,64-71). So far, two prostatic cancer patients are reported who showed incidental increased uptake of ^{68}Ga -PSMA-11 (PET/CT) with corresponding MRI imaging consistent with meningiomas (58,64). PSMA-radiotracer uptake in other neurogenic conditions occurs in scenarios similar to meningiomas. Regarding the low incidence of prostatic cancer metastasis to the brain and lack of tracer uptake by the healthy brain, it seems reasonable to consider further imaging or even examining tissue biopsies to confirm the diagnosis. These recent studies gave us better insights into the PSMA expressions status throughout the body and, with this in mind, increased uptake of PSMA-targeted tracers in the brain of prostatic cancer subjects may require further

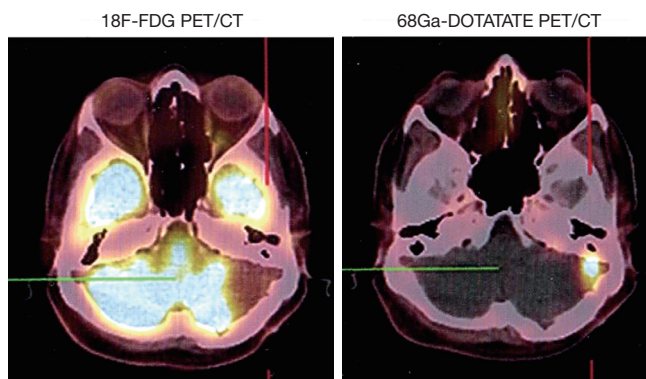


Figure 6 ^{68}Ga -DOTATATE PET/CT scan of meningioma. An intense focus of uptake is detected in the left vermis of the left cerebellum representing remnant/recurrence tumor. Absent uptake in the same region on ^{18}F -FDG PET/CT.

imaging to establish the diagnosis.

Imaging-based precision medicine using PET in the patients with the brain tumors

National Institutes of Health (NIH) have described the precision medicine as “an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person” (72). This requires clinicians and investigators to tailor specified treatments for each of the affected individuals through targeting cancer cells with less damage to the normal tissues (72,73). Medicine is facing a significant paradigm shift from reactive to a proactive manner in all aspects of clinical practice and healthcare through the development of precision medicine and high throughput molecular technologies (12,74). Molecular imaging has the capacity to play a substantial role in the development and future application of precision medicine at the front line of cancer investigations, especially neuro-oncology (72). Immuno-PET, a PET imaging technique that takes advantage of antibodies as targeting probes, has shown promising results in noninvasively assessing the expression levels of tumor-related antigens *in vivo* (75,76). In some reported cases, investigators have suggested that Immuno-PET is superior to magnetic resonance imaging (MRI) and ^{18}F -FDG PET regarding the sensitivity and specificity of cancer assessment (77,78). In one preclinical study, CD146 expression was explored using both tissue studies and longitudinal Immuno-PET for glioblastoma in determining sensitivity

and specificity of diagnosis and therapeutic potentials (75). The investigators generated an innovative ^{89}Zr -labeled monoclonal antibody (mAb), ^{89}Zr -Df-YY146, for targeting and measurement of CD146 expression in a mouse model of glioblastoma. They performed immunofluorescence microscopy, flow cytometry, and Western blot with two cell lines of glioblastoma, U87MG and U251, as *in vitro* assays to define their expression level of CD146. Also, YY146's CD146-binding affinities in comparison to that of Df-YY146 were assessed using flow cytometry. ^{89}Zr -Df-YY146 ability in targeting CD146 was explored through sequential PET imaging *in vivo*. In addition, ex-vivo biodistribution, CD146 blocking and histological assessment were performed to verify ^{89}Zr -Df-YY146 specificity and PET data validation as well. *In vitro* assays demonstrated increased expression level of CD146 in U87MG cells, but negligible level CD146 in U251 cells. Flow cytometry showed no difference in affinity between Df-YY146 and YY146. ^{89}Zr -labelled-Df-YY146 proceeded with outstanding yield (~80%), radiochemical purity (>95%), and specific activity (~44 GBq/ μmol). Longitudinal PET showed considerable and permanent ^{89}Zr -Df-YY146 uptake in mice harboring U87MG tumor cells, with significantly lesser in CD146-negative U251 lesions at 48 hours after tracer administration. Tracer uptake in U87MG tumor cells was effectively hindered in a competitive inhibition assays that supported the ^{89}Zr -Df-YY146 specificity. Eventually, ex-vivo biodistribution confirmed the accuracy of PET values and histological studies strongly correlated tracer uptake with *in situ* expression level of CD146. Given the significant, specific and persistent uptake of ^{89}Zr -Df-YY146 by brain tumors, it may be interesting to perform non-invasive PET scan to evaluate CD146 expression which may serve as a novel tool for intervention guidance and response assessment to the treatment. Therefore, PET imaging, especially Immuno-PET modality in combination with quantitative analytical software tools, may play a key role in diagnosis, molecular profiling, treatment, and response assessment through accurately visualizing different molecular characteristics and pathophysiologic processes (5,6,72,75,77,78).

Conclusion and prospective

PET imaging with a vast range of radiotracers has the ability to visualize versatile molecular properties and pathophysiological processes within the human body. Given the present paradigm shift in the medicine from reactive to proactive approaches, molecular characterization and

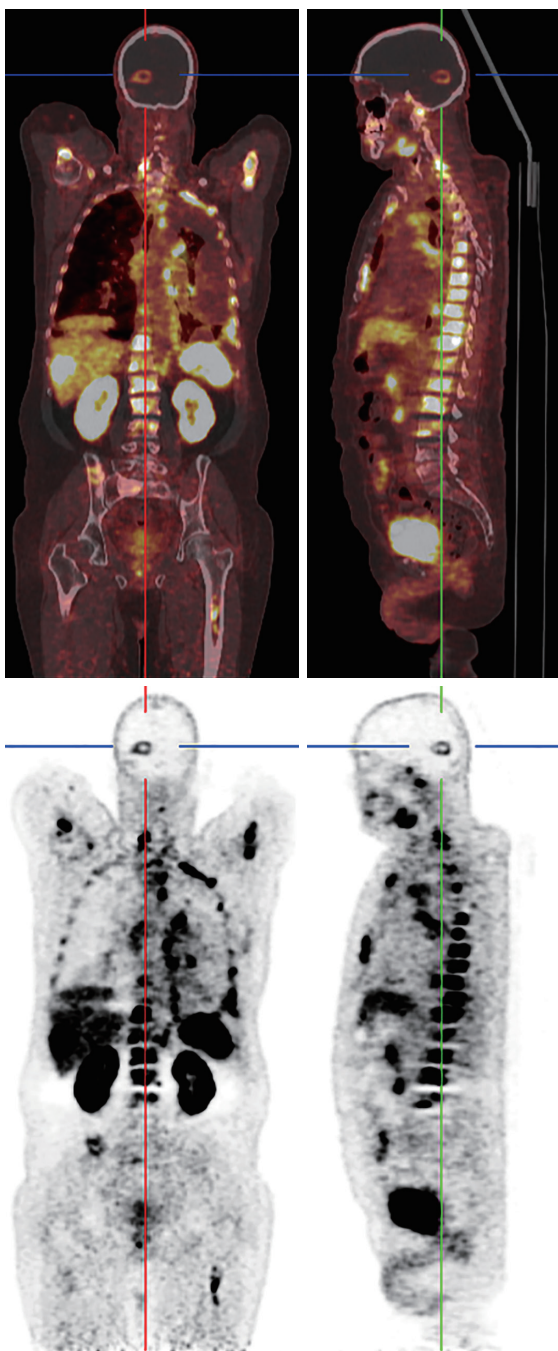


Figure 7 ^{68}Ga -PSMA PET/CT scan of prostate cancer. In addition to widespread metastases, there is focal uptake in the brain.

localization are considered as a mainstay of it. PET tracers can play an eminent role in providing tailored treatment through carrying radiolabeled payloads to a target-specified site. PET imaging has the potential to be considered as an

important complementary modality in addition to MRI for improving the accuracy in various aspects of brain tumor management.

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Footnote

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