Fluorine-18 labeled amino acids for tumor PET/CT imaging

Yiqiang Qi¹,²,*, Xiaohui Liu¹,²,*, Jun Li⁴, Huiqian Yao⁵ and Shuanghu Yuan²,³

¹School of Medicine and Life Sciences, University of Jinan-Shandong Academy of Medical Sciences, Jinan, Shandong, China
²Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong Cancer Hospital affiliated to Shandong University, Jinan, Shandong, China
³Shandong Academy of Medical Sciences, Jinan, Shandong, China
⁴Department of Thoracic Surgery, Shandong Provincial Hospital, Jinan, Shandong, China
⁵Department of Surgery, Juye Coalfield Central Hospital, Heze, Shandong, China

*Authors contributed equally to this work

Correspondence to: Shuanghu Yuan, email: yuanshuanghu@sina.com

Keywords: Fluorine-18 labeled amino acids, positron emission tomography/computed tomography (PET/CT), tumor metabolism, molecular imaging

Received: May 25, 2017 Accepted: July 25, 2017 Published: August 04, 2017

Abstract

Tumor glucose metabolism and amino acid metabolism are usually enhanced, ¹⁸F-FDG for tumor glucose metabolism PET imaging has been clinically well known, but tumor amino acid metabolism PET imaging is not clinically familiar. Radiolabeled amino acids (AAs) are an important class of PET/CT tracers that target the upregulated amino acid transporters to show elevated amino acid metabolism in tumor cells. Radiolabeled amino acids were observed to have high uptake in tumor cells but low in normal tissues and inflammatory tissues. The radionuclides used in labeling amino acids include ¹⁵O, ¹³N, ¹¹C, ¹²³I, ¹⁸F and ⁶⁸Ga, among which the most commonly used is ¹⁸F [1]. Available data support the use of certain ¹⁸F-labeled AAs for PET/CT imaging of gliomas, neuroendocrine tumors, prostate cancer and breast cancer [2, 3]. With the progress of the method of ¹⁸F labeling AAs [4–6], ¹⁸F-labeled AAs are well established for tumor PET/CT imaging. This review focuses on the current status of key clinical applications of ¹⁸F-labeled AAs in tumor PET/CT imaging.

Introduction

The clinical applications of tumor PET imaging are very extensive, including diagnosis, confirming status of lymph node and distant metastasis, and evaluating of curative effect. ¹⁸F-labeled AAs have been used for tumor PET imaging for decades, these are an important class of PET imaging agents that target the increased levels of AA transport by many types of tumor cells. System L AA transporter has been a major focus of imaging agents development, and work in this field has led to several ¹⁸F-labeled AAs as PET tracers, such as ¹⁸F-FET, ¹⁸F-FDOPA, ¹⁸F-D-FMT, ¹⁸F-FAMT, ¹⁸F-OMFD, and ¹⁸F-FACBC. Recently, emerging ¹⁸F-labeled AAs have been developed that target system A, xCT, glutamine, and cationic amino acid transporters [7]. So far, the main clinical applications of ¹⁸F-labeled AAs are gliomas, neuroendocrine tumors, prostate cancer and breast cancer PET/CT imaging.

Mechanism of amino acid metabolism for tumor PET imaging

Certain AA transporters, particularly LAT1 and ASCT2 [8–10], are upregulated in a wide range of different types of tumors, there is growing evidence that some AA transporters and their substrates interact with the mammalian target of rapamycin (mTOR) pathway, which regulates cell proliferation and protein synthesis [11, 12]. These upregulated AA transporters increase much more amino acid uptake of tumors. ¹⁸F-labeled amino acids are an important class of tumor imaging agents suitable for PET/CT. PET is a kind of radiotracer-based imaging method, which can provide unique, noninvasive molecular and functional information about tumor biology that complements more anatomically based modalities, such as magnetic resonance imaging (MRI) and computed tomography (CT). ¹⁸F-labeled AAs detect increased tumor...
amino acid metabolism levels by targeting upregulated AA transporters in PET imaging, the key of that is the amino acid transport system [1, 2, 13, 14]. Amino acids enter cells through membrane-associated transporter, and more than 20 amino acid transporters have been discovered in mammalian cells [15–18]. According to the need for sodium ions, amino acid transport system can be divided into the following two categories [10, 19–21]: (1) Na’-dependent amino acid transport systems, including system ASC (alanine-serine-cysteine preferred), system A (alanine preferred), system N (glutamine, aspartic acid and histidine preferred), X- AG(transport L-glutamic acid, D-/L-aspartic acid) and B0(transport neutral and basic amino acids); (2) Na’-undependent amino acid transport systems, including system L (leucine preferred), γ’ (CAT) (selectively transport basic amino acids), γ’L (transport neutral and basic amino acids), b0(transport neutral and basic amino acids) and X- C (transport cystine and glutamic acid). The system A, system L and system ASC are the most common amino acid transport systems [16, 22–26].

PET tracers based on 18F-labeled amino acids

18F-labeled amino acids are an class of the most commonly used tracers for tumor PET imaging, the ideal PET tracers based on 18F-labeled AAs should conform to the following conditions: (1) can be quickly transported to the tumor cells, and have a high uptake rate and a certain retention time; (2) do not combine with non-protein and inflammatory tissue; (3) have a high plasma clearance rate; (4) have a better blood-brain barrier permeability for the brain tumors; (5) have a relatively simple and practical labeling method [18, 27]. At present, clinical commonly used 18F-labeled amino acids are basically in line with the above conditions, these are listed in Table 1.

Clinical applications of 18F-labeled amino acids in tumor PET/CT imaging

Gliomas

Gliomas are occurring in the neuroectodermal, are also known as neuroectodermal tumors or neuroepithelial tumors. Contrast-enhanced MRI plays a critical role in glioma imaging, including diagnosis, monitoring response to therapy, staging, and assessing for recurrence, but has limited accuracy for distinguishing between recurrence and radiation necrosis, and evaluating the nonenhancing portions of gliomas. The value of 18F-labeled AAs PET in delineating metabolic tumor volume, evaluating the tumor metabolic load and as a reference for treatment response is better than MRI. The metabolic information of 18F-FDG PET/CT has improved the diagnostic evaluation of a number of human malignancies [28–31]. However, 18F-FDG is limited by high uptake in normal brain, that interfere with the identification of glioma and normal brain. Two major advantages of 18F-labeled AAs for glioma imaging are their relatively low uptake and retention in normal brain and ability to visualize the entire glioma volume, compared with 18F-FDG PET/CT [7, 27, 32]. 18F-labeled AAs that useful for glioma PET/CT imaging include 18F-FDOPA, 18F-OMFD, 18F-FET, 18F-FAMT, 2-FTyr, 18F-BPA, 18F-FSPG and 18F-FGln, the most commonly used are 18F-FDOPA and 18F-FET. Both visual and semiquantitative indices of 18F-FDOPA PET detected glioblastoma recurrence with high accuracy and were predictive for PFS (progression-free survival) [33]. There was a study suggests that 18F-FET PET/CT adds valuable diagnostic information in brainstem and spinal cord glioma, particularly when the diagnostic information derived from MRI is equivocal [34]. A systematic review and meta-analysis indicates that 18F-FET PET/CT demonstrated excellent performance for diagnosing primary brain tumors [35]. 18F-FET may also be used for distinguishing recurrent brain metastasis from radiation necrosis after radiation therapy [36], but additional data are needed in this field. 18F-FDOPA uptake on PET was associated with IDH (isocitrate dehydrogenase) mutation in newly diagnosed gliomas [37]. 18F-FDOPA PET/CT and fused 18F-FDOPA PET/MRI are also used for detecting striatal involvement in children with gliomas [38]. 18F-BPA (boron phenylalanine) is used for the tumor/normal tissue ratio in boron neutron capture therapy of gliomas and other head and neck cancers [39–41]. 18F-FSPG was a novel PET radiopharmaceutical which demonstrated high uptake in intracranial malignancies studies of both small animal and human [42]. 18F-FGln showed high uptake in gliomas but low background brain uptake, facilitating clear tumor delineation [43–46].

Neuroendocrine tumors

Neuroendocrine tumors (NETs) are a class of heterogeneous tumors that originate from peptidergic neurons and neuroendocrine cells, arise in different anatomic locations and are associated with symptoms resulting from the hormones or vasoactive peptides. Neuroendocrine tumors include carcinoid tumors, pheochromocytomas and parangangiomas, pancreatic islet cell tumors, medullary thyroid cancer, neuroblastoma, and small cell lung cancer [7, 47]. These tumors have been known as tumors with amine precursor uptake and decarboxylation (APUD) [48, 49]. APUD tumor cells can uptake and decarboxylate amine precursor such as 5-hydroxy-L-tryptophan (5-HTP) and L-dihydroxyphenylalanine (L-DOPA) and pass through aromatic L-aminio acid decarboxylase (AADC) to decarboxylate them to the corresponding 5-hydroxy-L-tryptamine and dopamine. 18F-FDOPA has proved a valuable tool for the assessment of neuroendocrine tumors. 18F-FDOPA PET/CT is highly
sensitive in posttreatment evaluation of patients with pheochromocytomas and paragangliomas, and better than MRI and CT [50–52]. 18F-FDOPA is also suited for imaging gastroenteropancreatic neuroendocrine tumors and neuroblastoma [53–56]. 18F-FDOPA PET/CT detected more positive body regions and lesions of carcinoid tumors than the combination of CT and SRS [55, 57–61]. 18F-FDOPA may play a potentially useful role in medullary thyroid cancer PET imaging as a better or at least complementary model [55, 57–61]. However, for pancreatic islet cell tumors, the 18F-FDOPA PET is not significant [55, 62–66].

Prostate cancer

According to the WHO global tumor epidemiology statistics (GLOBOCAN 2008), prostate cancer in 2008 ranked second in global male malignancy incidence (second only to lung cancer), accounting for 14% of all men with cancer [67]. CT and MR imaging has limited accuracy to detect the primary tumor and regional lymph node metastases. Typically, prostate cancer has a lower 18F-FDG uptake rate. Recent studies with 18F-FACBC and 18F-FACPC have shown that these 18F-labeled AA tracers can accurately detect tumor and regional lymph node metastases with better specificity and sensitivity [7, 68, 69]. Because 18F-FACBC is slowly excrete into the bladder, the background radioactivity in the pelvic cavity is low, and the tumor and lymph node metastasis of primary and recurrent prostate cancer can be clearly visualized [70]. In addition, there were studies show that 18F-FACBC was superior in detecting prostate cancer recurrence in patients with recurrent prostate cancer compared with 11In-capromab or 11C-choline [71–74]. Since the half-life of 11C is only 20.3 minutes, the use of 11C-choline PET is limited in institute with on-site cyclotron. Furthermore, in the case of natural amino acids such as L-[11C]-methionine (MET), rapid metabolism usually produces radiolabeled metabolites, which can confuse kinetic analysis and reduce image quality [75, 76]. 18F-FACBC could be considered an alternative tracer superior to 11C-choline in the setting of patients with biochemical recurrence after radical prostatectomy [71, 77–80]. 18F-fluciclovine PET/CT is also used for distinguishing between prostate tumours and benign tissue and for assessment of tumour aggressiveness [81]. A study of 18F-FACBC PET/CT used in the planning of radiation therapy for prostate cancer patients has also been reported [82].

Breast cancer

Recent studies [83–85] have shown that 18F-fluciclovine that is a leucine analog radioactive tracer can also be used for breast cancer PET/CT imaging. 18F-fluciclovine PET/CT visualizes malignant tumors including invasive lobular breast cancer (ILC) and invasive ductal breast cancer (IDC). In primary and metastatic breast cancers, 18F-fluciclovine uptake was significantly higher than benign breast lesions and normal breast tissue. Changes in 18F-fluciclovine avidity were strongly

| Table 1: Clinical applications of 18F-labeled amino acids |
|---------------------|---------------------|---------------------|---------------------|
| Abbreviation       | Full name of tracers | Transport system | Clinical applications |
| 18F-FDOPA          | L-3,4-dihydroxy-6-[18F]-fluoro-phenylalanine | System L and Amino acid decarboxylase | Brain tumors and Neuroendocrine tumors |
| 18F-OMFD           | 3-O-methyl-6-[18F]-fluoro-L-3,4-dihydroxyphenylalanine | System L | Brain tumors |
| 18F-FET            | O-(2-[18F]-fluoroethyl)-L-tyrosine | System L | Brain tumors |
| 18F-FAMT           | L-3-[18F]-fluoro-alpha-methyl tyrosine | System L | Brain tumors, Oral cavity cancer and Non-small cell lung cancer |
| 2-FTyr             | 2-[18F]-fluoro-L-tyrosine | System L | Brain tumors |
| 18F-FGln           | 4-[18F]-fluoro-glutamine | System L and ASCT2 | Brain tumors and Breast cancer |
| 18F-F-D-FMT        | O-[18F]-fluoromethyl-D-tyrosine | System L | Non-small cell lung cancer |
| 18F-FSPG (BAY 94-932) | (4S)-4-[18F]-fluoro-propionyl-L-glutamate | System X\textsubscript{C}\textsuperscript{-} | Brain tumors, Lung cancer and Liver cancer |
| 18F-FASu           | 18F-5-fluoroaminosuberic acid | System X\textsubscript{C}\textsuperscript{-} | Breast cancer |
| 18F-FACBC          | anti-1-amino-3-[18F]-fluorocyclobutane-1-carboxylic acid | System L and ASCT2 | Breast cancer and Breast cancer |
| 18F-FACPC          | anti-1-amino-2-[18F]-fluorocyclopentane-1-carboxylic acid | System L and ASCT2 | Prostate cancer |
| 18F-Cis-FPro       | cis-4-[18F]-fluoro-L-proline | System A and B\textsuperscript{8+} | Urinary system tumors |
associated with a reduction in the percentage of tumor on pathology caused by treatment [3]. In addition to detecting and locating breast cancer, 18F-fluciclovine may provide a new tool for the exploration of amino acid transport and metabolism in breast cancer. 18F-fluciclovine also detected lymph nodes and bone metastases, but liver metastases were less effective due to the high physiological uptake of the tracer in liver parenchyma. The highest uptake of 18F-fluciclovine appears in Nottingham grade 3 cancers and triple-negative breast cancers, suggesting that 18F-fluciclovine may play a role in identifying more aggressive malignancies [83–85]. 18F-FASu may serve as a valuable target for the diagnosis and treatment monitoring of certain breast cancers and may provide more sensitive detection than 18F-FDG in certain tumors [86, 87]. 18F-FGln PET could be used to track cellular glutamine pool size of triple-negative breast cancers [88].

CONCLUSIONS

18F-labeled amino acids have been developed for preclinical and clinical tumor PET/CT imaging. 18F-FDOPA and 18F-FET are well established for diagnosis, monitoring response to therapy, staging, and assessing for recurrence of gliomas. 18F-FDOPA has proved a valuable tool for the assessment of neuroendocrine tumors. It is highly sensitive in posttreatment evaluation of patients with pheochromocytomas and paragangliomas, and suited for imaging gastroenteropancreatic neuroendocrine tumors and neuroblastoma. Studies with 18F-FACBC and 18F-FACPC have shown that these 18F-labeled AA tracers can accurately detect tumor and regional lymph node metastases of prostate cancer with better specificity and sensitivity. 18F-fluciclovine used in breast cancer PET/CT imaging have been reported. 18F-fluciclovine PET/CT visualizes malignant tumors including invasive lobular breast cancer (ILC) and invasive ductal breast cancer (IDC). In primary and metastatic breast cancers, 18F-fluciclovine uptake was significantly higher than benign breast lesions and normal breast tissue. In the future, we have some innovative and interesting 18F-labeled amino acid analogues available, such as 18F-BAAs (boramino acids), which demonstrated distinctly high AA transporter-mediated tumor uptake and rapid clearance from normal organs and tissues [7]. However, the role of 18F-labeled amino acids PET will be limited to diagnostic imaging only. In the era of theranostic medicine, the peptide-receptor imaging and further peptide-receptor radionuclide therapy (PRRT) are emerging for somatostatin-related neuroendocrine tumors and prostate cancers, for example, DOTA-TOC and DOTATATE PET/CT [89–93].

CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

FUNDING

This study was funded by the Natural Science Foundation of China (NSFC81172133, NSFC81372413), the Special Fund for Scientific Research in the Public Interest (201402011), the Projects of Medical and Health Technology Development Program in Shandong Province (2014WS0058) and the Outstanding Youth Natural Science Foundation of Shandong Province (JQ201423).

REFERENCES

1. 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.
2. McConathy J, Yu W, Jarkas N, Seo W, Schuster DM, Goodman MM. Radiohalogenated nonnatural amino acids as PET and SPECT tumor imaging agents. Med Res Rev. 2012; 32:868–905.
3. Ulaner GA, Goldman D, Corben A, Lysashchenko SK, Gönen M, Lewis JS, Dickler M. A prospective clinical trial of 18F-Fluciclovine PET/CT neoadjuvant therapy response in invasive ductal and invasive lobular breast cancers. J Nucl Med. 2016; 58:1037–1042.
4. Stenhagen IS, Kirjavainen AK, Forsback SJ, Jørgensen CG, Robins EG, Luthra SK, Solin O, Gouverneur V. [18F] fluorination of an arylboronic ester using [18F]selectfluor bis(triflate): application to 6-[18F]fluoro-L-DOPA. Chem Commun (Camb). 2013; 49:1386–8.
5. Wagner FM, Ermert J, Coenen HH. Three-step, "one-pot" radiosynthesis of 6-fluoro-3,4-dihydroxy-L-phenylalanine by isotopic exchange. J Nucl Med. 2009; 50:1724–9.
6. Liu Z, Chen H, Chen K, Shao Y, Kiesewetter DO, Niu G, Chen X. Boramino acid as a marker for amino acid transporters. Sci Adv. 2015; 1:e1500694.
7. Huang C, McConathy J. Radiolabeled amino acids for oncologic imaging. J Nucl Med. 2013; 54:1007–10.
8. Witte D, Ali N, Carlson N, Younes M. Overexpression of the neutral amino acid transporter ASCT2 in human colorectal adenocarcinoma. Anticancer Res. 2002; 22:2555–7.
9. Shennan DB, Thomson J. Inhibition of system L (LAT1/CD98hc) reduces the growth of cultured human breast cancer cells. Oncol Rep. 2008; 20:885–9.
10. Fuchs BC, Bode BP. Amino acid transporters ASCT2 and LAT1 in cancer: partners in crime. Semin Cancer Biol. 2005; 15:254–66.
11. Ganapathy V, Thangaraju M, Prasad PD. Nutrient transporters in cancer: relevance to Warburg hypothesis and beyond. Pharmacol Ther. 2009; 121:29–40.
12. Nakanishi T, Tamai I. Solute carrier transporters as targets for drug delivery and pharmacological intervention for chemotherapy. J Pharm Sci. 2011; 100:3731–50.
13. Wagner CA, Lang F, Bröer S. Function and structure of heterodimeric amino acid transporters. Am J Physiol Cell Physiol. 2001; 281:C1077–93.
14. Langen KJ, Bröer S. Molecular transport mechanisms of radiolabeled amino acids for PET and SPECT. J Nucl Med. 2004; 45:1435–6.
15. Mackenzie B, Erickson JD. Sodium-coupled neutral amino acid (System N/A) transporters of the SLC38 gene family. Pflugers Arch. 2004; 447:784–95.
16. Verrey F. System L: heteromeric exchangers of large, neutral amino acids involved in directional transport. Pflugers Arch. 2003; 445:529–33.
17. Ishiwata K, Kubota K, Murakami M, Kubota R, Senda M. A comparative study on protein incorporation of L-[methyl-3H] methionine, L-[1-14C]leucine and L-2-[18F]fluorotyrosine in tumor bearing mice. Nucl Med Biol. 1993; 20:985–9.
18. Jager PL, Vaalburg W, Pruim J, de Vries EG, Langen KJ. Fluorinated amino acids for tumour imaging with positron emission tomography. Eur J Nucl Med Mol Imaging. 2002; 29:681–90.
19. Verrey F, Closs EI, Wagner CA, Endou H, Morimoto E, Anders MW, Endou H. Transport of amino acid-related compounds mediated by L-type amino acid transporter 1 (LAT1): insights into the mechanisms of substrate recognition. Mol Pharmacol. 2002; 61:729–37.
20. Uchino H, Kanai Y, Kim DK, Wempe MF, Chairoungdua A, Bruford EA. The ABCs of solute carriers: physiological, pathological and therapeutic implications of human membrane transport proteins. Pflugers Arch. 2004; 447:465–8.
21. Closs EI, Boissel JP, Habermeier A, Rotmann A. Structure and function of cationic amino acid transporters (CATs). J Membr Biol. 2006; 213:67–77.
22. Verrey F, Closs EI, Wagner CA, Palacin M, Endou H, Kanai Y. CATs and HATs: the SLC7 family of amino acid transporters. Pflugers Arch. 2004; 447:532–42.
23. Kanai Y, Hediger MA. The glutamate and neutral amino acid transporter family: physiological and pharmacological implications. Eur J Pharmacol. 2003; 479(1-3): 237-47.
24. Kanai Y, Hediger MA. The glutamate/neutral amino acid transporter family SLC1: molecular, physiological and pharmacological aspects. Pflugers Arch. 2004; 447:469–79.
25. Verrey F, Closs EI, Wagner CA, Endou H, Kanai Y, Hediger MA. The glutamate and neutral amino acid transporter family SLC1: molecular, physiological and pharmacological aspects. Pflugers Arch. 2004; 447:469–79.
26. Laverman P, Boerner OC, Corstens FH, Oyen WJ. Fluorinated amino acids for tumour imaging with positron emission tomography. Eur J Nucl Med Mol Imaging. 2002; 29:681–90.
27. Schirrmeister H, Kühn T, Gühlmann A, Santjohansen C, Hörster T, Nüssle K, Koretz K, Glatting G, Rieber A, Kreienberg R, Buck AC, Reske SN. Fluorine-18 2-deoxy-2-fluoro-D-glucose PET in the preoperative staging of breast cancer: comparison with the standard staging procedures. Eur J Nucl Med. 2001; 28:351–8.
28. van der Hiel B, Pauwels EK, Stokkel MP. Positron emission tomography with 2-[18F]-fluoro-2-deoxy-D-glucose in oncology. Part III: Therapy response monitoring in breast cancer, lymphoma and gliomas. J Cancer Res Clin Oncol. 2001; 127:269–77.
29. Czernin J, Allen-Auerbach M, Schelbert HR. Improvements in cancer staging with PET/CT: literature-based evidence as of September 2006. J Nucl Med. 2007; 48:78S–88S.
30. Juweid ME, Cheson BD. Positron-emission tomography and assessment of cancer therapy. N Engl J Med. 2006; 354:496–507.
31. Galldiks N, Langen KJ. Amino Acid PET - An Imaging Option to Identify Treatment Response, Posttherapeutic Effects, and Tumor Recurrence. Front Neurol. 2016; 7:120.
32. Herrmann K, Czernin J, Cloughesy T, Lai A, Pomykala KL, Benz MR, Buck AK, Phelps ME, Chen W. Comparison of visual and semiquantitative analysis of 18F-FDOPA-PET/CT for recurrence detection in glioblastoma patients. Neuro Oncol. 2014; 16:603–9.
33. Tscherpel C, Dunkl V, Ceccgon G, Stoffels G, Judov N, Rapp M, Meyer PT, Kops ER, Ermelt J, Fink GR, Shah NJ, Langen KJ, Galldiks N. The use of O-(2-18F-fluoroethyl)-L-tyrosine PET in the diagnosis of gliomas located in the brainstem and spinal cord. Neuro Oncol. 2016; 19:710–718.
34. Dunet V, Rossier C, Buck A, Stupp R, Prior JO. Performance of 18F-fluoro-ethyl-tyrosine (18F-FET) PET for the differential diagnosis of primary brain tumor: a systematic review and Metaanalysis. J Nucl Med. 2012; 53:207–14.
35. Galldiks N, Stoffels G, Filis CP, Piroth MD, Sabel M, Ruge MI, Herzog H, Shah NJ, Fink GR, Coenen HH. Gallium PET for the differential diagnosis of local recurrent brain metastasis from radiation necrosis. J Nucl Med. 2012; 53:1367–74.
36. Verger A, Mettellus P, Sala Q, Colin C, Bialecki E, Taieb D, Chintot O, Figarella-Branger D, Guedj E. IDH mutation effects, and tumor recurrence. Front Neurol. 2016; 7:120.
37. Rapp M, Meyer PT, Kops ER, Ermelt J, Fink GR, Shah NJ, Langen KJ. Role of O-(2-(18F)-fluoroethyl)-L-tyrosine PET for differentiation of local recurrent brain metastasis from radiation necrosis. J Nucl Med. 2012; 53:1367–74.
38. Laverman P, Boerner OC, Corstens FH, Oyen WJ. Fluorinated amino acids for tumour imaging with positron emission tomography. Eur J Nucl Med Mol Imaging. 2007; 44:1306–1311.
39. Morana G, Puntoni M, Garrà ML, Massollo M, Lopoi E, Naseri M, Severino M, Tortora D, Rossi A, Piccardo A. Ability of F-DOPA PET/CT and fused (18f)F-DOPA PET/MRI to assess striatal involvement in paediatic glioma. Eur J Nucl Med Mol Imaging. 2016; 43:1664–72.
40. Miyatake S, Tamura Y, Kawabata S, Iida K, Kuroiwa T, Maruhashi A, Ono K. Boron neutron capture therapy for malignant tumors related to meningiomas. Neurosurgery. 2007; 61:82–90; discussion 90–1.
41. Aihara T, Hiratsuka J, Morita N, Uno M, Sakurai Y, Ono K, Harada T. First clinical case of boron neutron capture therapy for head and neck malignancies using 18F-BPA PET. Head Neck. 2006; 28:850–5.
41. Miyatake S, Kawabata S, Kajimoto Y, Aoki A, Yokoyama K, Yamada M, Kuroiwa T, Tsuji M, Imahori Y, Kirihata M, Sakurai Y, Masunaga S, Nagata K, et al. Modified boron neutron capture therapy for malignant gliomas performed using epithermal neutron and two boron compounds with different accumulation mechanisms: an efficacy study based on findings on neuroimages. J Neurosurg. 2005; 103:1000–9.

42. Mittra ES, Kohlin N, Mosci C, Kumar M, Hoehne A, Keu KV, Jagaru AH, Mueller A, Berndt M, Bullich S, Friebe M, Schmitt-Willich H, Gekeler V, et al. Pilot Preclinical and Clinical Evaluation of (4S)-4-[18F]Fluorodihydroxyphenylalanine (18F-FDOPA) L-Glutamate (18F-FSPG) for PET/CT Imaging of Intracranial Malignancies. PLoS One. 2016; 11:e0148628.

43. Venneti S, Dunphy MP, Zhang H, Pitter KL, Zanzonico P, Campos C, Carlin SD, La Roca G, Lyashchenko S, Ploessl K, Rohle D, Omuro AM, Cross JR, et al. Glutamine-based PET imaging facilitates enhanced metabolic evaluation of gliomas in vivo. Sci Transl Med. 2015; 7:274ra17.

44. Zhu L, Ploessl K, Zhou R, Mankoff D, Kung HF. Metabolic Imaging of Glutaminolysis in Tumors by 18F-(2S,4R)4-fluoroglutamine. J Nucl Med. 2017; 58:533–537.

45. Lieberman BP, Ploessl K, Wang L, Qu W, Zha Z, Wise DR, Chodosh LA, Belka G, Thompson CB, Kung HF. PET imaging of glutaminolysis in tumors by 18F-(2S,4R)4-fluoroglutamine. J Nucl Med. 2011; 52:1947–55.

46. Hassanein M, Hight MR, Buck JR, Tantawy MN, Nickels ML, Hoeksma MD, Harris BK, Boyd K, Massion PP, Manning HC. Preclinical Evaluation of 4-[18F] Fluoroglutamine PET to Assess ASCT2 Expression in Lung Cancer. Mol Imaging Biol. 2016; 18:18–23.

47. Kulke MH, Siu LL, Tepper JE, Fisher G, Jaffe D, Haller DG, Ellis LM, Benedetti JK, Bergsland EK, Hobday TJ, Van Cutsem E, Pingpank J, Oberg K, et al. Future directions in the treatment of neuroendocrine tumors: consensus report of the National Cancer Institute Neuroendocrine Tumor clinical trials planning meeting. J Clin Oncol. 2011; 29:934–43.

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

49. van Eeden S, Offerhaus GJ. Historical, current and future perspectives on gastrointestinal and pancreatic endocrine tumors. Virchows Arch. 2006; 448:1–6.

50. Heimburger C, Veillon F, Taieb D, Goichot B, Riehm S, Petit-Thomas J, Averous G, Cavalcanti M, Hubelé F, Chabrier G, Namer IJ, Charpiot A, Imperiale A. Head-to-head comparison between (18)F-FDOPA PET/CT and MR/CT angiography in clinically recurrent head and neck paragangliomas. Eur J Nucl Med Mol Imaging. 2017; 44:979–987.

51. Feral CC, Tissot FS, Tosello L, Fakhry N, Sebag F, Pacak K, Taieb D. (18)F-fluorodihydroxyphenylalanine PET/CT in pheochromocytoma and paraganglioma: relation to genotype and amino acid transport system L. Eur J Nucl Med Mol Imaging. 2017; 44:812–821.
65. Anderson MA, Carpenter S, Thompson NW, Nostrant TT, Elta GH, Scheiman JM. Endoscopic ultrasound is highly accurate and directs management in patients with neuroendocrine tumors of the pancreas. Am J Gastroenterol. 2000; 95:2271–7.

66. Hellman P, Hennings J, Akerström G, Skogseid B. Endoscopic ultrasonography for evaluation of pancreatic tumours in multiple endocrine neoplasia type 1. Br J Surg. 2005; 92:1508–12.

67. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010; 127:2893–917.

68. Shoup TM, Olson J, Hoffman JM, Votaw J, Eshima D, Eshima L, Camp VM, Stabin M, Votaw D, Goodman MM. Synthesis and evaluation of [18F]-amino-3-fluorocyclobutan-1-carboxylic acid to image brain tumors. J Nucl Med. 1999; 40:331–8.

69. Suzuki H, Inoue Y, Fujimoto H, Yonese J, Tanabe K, Fukasawa S, Inoue T, Saito T, Suito U, Ueno M, Otaka A. Diagnostic performance and safety of NMK36 (trans-1-amino-3-[18F]fluorocyclobutanecarboxylic acid)-PET/CT in primary prostate cancer: multicenter Phase IIb clinical trial. Jpn J Clin Oncol. 2016; 46:152–62.

70. Schuster DM, Votaw JR, Nieh PT, Yu W, Nye JA, Master V, Bowman FD, Issa MM, Goodman MM. Initial experience with the radiotracer anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid with PET/CT in prostate carcinoma. J Nucl Med. 2007; 48:56–63.

71. Nanni C, Schiavina R, Boschi S, Ambrosini V, Pettinato C, Brunocilla E, Martorana G, Fanti S. Comparison of 18F-FACBC and 11C-choline PET/CT in patients with radically treated prostate cancer and biochemical relapse: preliminary results. Eur J Nucl Med Mol Imaging. 2013; 40:S11–7.

72. Schuster DM, Nieh PT, Jani AB, Amzat R, Bowman FD, Hallak RK, Master VA, Nye JA, Odewole OA, Osunkoya AO, Savir-Baruch B, Alaei-Taleghani P, Goodman MM. Anti-3-[(18)F]FACBC positron emission tomography-computed tomography and (111)In-capromab pendetide single photon emission computerized tomography-computed tomography for recurrent prostate carcinoma: results of a prospective clinical trial. J Urol. 2014; 191:1446–53.

73. Nanni C, Schiavina R, Brunocilla E, Boschi S, Borghesi M, Zanoni L, Pettinato C, Martorana G, Fanti S. 18F-Fluciclovine PET/CT for the Detection of Prostate Cancer Relapse: A Comparison to 11C-Choline PET/CT. Clin Nucl Med. 2015; 40:e386–91.

74. Schuster DM, Nanni C, Fanti S. Evaluation of Prostate Cancer with Radiolabeled Amino Acid Analogs. J Nucl Med. 2016; 57:61S–66S.

75. Derlon JM, Bourdet C, Bustany P, Chatel M, Theron J, Darcel F, Syrota A. [11C]-methionine uptake in gliomas. Neurosurgery. 1989; 25:720–8.

76. Kameyama M, Shirane R, Itoh J, Sato K, Katakura R, Yoshimoto T, Hatazawa J, Itoh M, Ido T. The accumulation of 11C-methionine in cerebral glioma patients studied with PET. Acta Neurochir (Wien). 1990; 104:8–12.

77. Nanni C, Zanoni L, Pultrone C, Schiavina R, Brunocilla E, Lodi F, Malizia C, Ferrari M, Rigatti P, Fonti C, Martorana G, Fanti S. (18)F-FACBC (anti l-amino-3-(18)F-fluorocyclobutan-1-carboxylic acid) versus (11)C-choline PET/CT in prostate cancer relapse: results of a prospective trial. Eur J Nucl Med Mol Imaging. 2016; 43:1601–10.

78. Brunocilla E, Schiavina R, Nanni C, Borghesi M, Cevenini M, Molinaroli E, Vagnoni V, Castellucci P, Ceci F, Fanti S, Gaudiano C, Golferri R, Martorana G. First case of 18F-FACBC PET/CT-guided salvage radiotherapy for local relapse after radical prostatectomy with negative 11C-Choline PET/CT and multiparametric MRI: New imaging techniques may improve patient selection. Arch Ital Urol Androl. 2014; 86:239–40.

79. Schiavina R, Concetti S, Brunocilla E, Nanni C, Borghesi M, Gentile G, Cevenini M, Bianchi L, Molinaroli E, Fanti S, Martorana G. First case of 18F-FACBC PET/CT-guided salvage retroperitoneal lymph node dissection for disease relapse after radical prostatectomy for prostate cancer and negative 11C-choline PET/CT: new imaging techniques may expand pioneering approaches. Urol Int. 2014; 92:242–5.

80. Nanni C, Schiavina R, Brunocilla E, Borghesi M, Ambrosini V, Zanoni L, Gentile G, Vagnoni V, Romagnoli D, Martorana G, Fanti S. 18F-Fluciclovine compared with 11C-choline PET/CT in patients with biochemical relapse after radical prostatectomy: a prospective study in 28 patients. Clin Genitourin Cancer. 2014; 12:106–10.

81. Elschot M, Selnes KM, Sandmark E, Krüger-Stokke B, Størkersen Ø, Tessem MB, Moestue SA, Bertilsson H, Bathen TF. A PET/MRI study towards finding the optimal [(18)F]Fluciclovine PET protocol for detection and characterisation of primary prostate cancer. Eur J Nucl Med Mol Imaging. 2017; 44:695–703.

82. Schreibmann E, Schuster DM, Rossi PJ, Shelton J, Cooper S, Jani AB. Image Guided Planning for Prostate Carcinomas With Incorporation of Anti-3-[18F]FACBC (Fluciclovine) Positron Emission Tomography: Workflow and Initial Findings From a Randomized Trial. Int J Radiat Oncol Biol Phys. 2016; 96:206–13.

83. McConathy J, 18F-Fluciclovine (FACBC) and Its Potential Use for Breast Cancer Imaging. J Nucl Med. 2016; 57:1329–30.

84. Tade FI, Cohen MA, Styblo TM, Odewole OA, Holbrook AL, Newell MS, Savir-Baruch B, Li X, Goodman MM, Nye JA, Schuster DM. Anti-3-18F-FACBC (18F-Fluciclovine) PET/CT of Breast Cancer: An Exploratory Study. J Nucl Med. 2016; 57:1343–7.

85. Ulaner GA, Goldman DA, Gönen M, Pham H, Castillo R, Lyashchenko SK, Lewis JS, Dang C. Initial Results of a Prospective Clinical Trial of 18F-Fluciclovine PET/CT in Newly Diagnosed Invasive Ductal and Invasive Lobular Breast Cancers. J Nucl Med. 2016; 57:1350–6.
86. Webster JM, Morton CA, Johnson BF, Yang H, Rishel MJ, Lee BD, Miao Q, Pabba C, Yapp DT, Schaffer P. Functional imaging of oxidative stress with a novel PET imaging agent, 18F-5-fluoro-L-aminosuberic acid. J Nucl Med. 2014; 55:657–64.

87. Yang H, Jenni S, Colovic M, Merkens H, Poleschuk C, Rodrigo I, Miao Q, Johnson BF, Rishel MJ, Sossi V, Webster JM, Bénard F, Schaffer P. (18)F-5-Fluoroaminosuberic Acid as a Potential Tracer to Gauge Oxidative Stress in Breast Cancer Models. J Nucl Med. 2017; 58:367–373.

88. Zhou R, Pantel AR, Li S, Lieberman BP, Ploessl K, Choi H, Blankemeyer E, Lee H, Kung HF, Mach RH, Mankoff DA. [(18)F](2S,4R)4-Fluoroglutamine PET Detects Glutamine Pool Size Changes in Triple-Negative Breast Cancer in Response to Glutaminase Inhibition. Cancer Res. 2017; 77:1476–1484.

89. Holmboe S, Hansen PL, Thisgaard H, Block I, Müller C, Langkjær N, Høilund-Carlsen PF, Olsen BB, Mollenhauer J. Evaluation of somatostatin and nucleolin receptors for therapeutic delivery in non-small cell lung cancer stem cells applying the somatostatin-analog DOTATATE and the nucleolin-targeting aptamer AS1411. PLoS One. 2017; 12:e0178286.

90. Naik C, Basu S. Peptide Receptor Radionuclide Therapy with (177)Lu-DOTATATE for Metastatic Neuroendocrine Tumor Occurring in Association with Multiple Endocrine Neoplasia Type 1 and Cushing’s Syndrome. World J Nucl Med. 2017; 16:126–132.

91. Hänscheid H, Lapa C, Buck AK, Lassmann M, Werner RA. Dose Mapping after Endoradiotherapy with (177)Lu-DOTATATE/-TOC by One Single Measurement after Four Days. J Nucl Med. 2017. http://doi.org/jnumed.117.193706 [Epub ahead of print].

92. Gauthé M, Sarfati J, Bourcigaux N, Christin-Maitre S, Talbot JN, Montravers F. Pituitary Adenoma Recurrence Suspected on Central Hyperthyroidism Despite Empty Sella and Confirmed by 68Ga-DOTA-TOC PET/CT. Clin Nucl Med. 2017; 42:454–455.

93. Papamichail DG, Exadaktylou PE, Chatzipavlidou VD. [Neuroendocrine tumors: Peptide receptors radionuclide therapy (PRRT)]. Hell J Nucl Med. 2016; 19:75–82.