Eur J Nucl Med Mol Imaging (2013) 40:1141–1145
DOI 10.1007/s00259-013-2459-y

EDITORIAL

Critical considerations on the combined use of ^{18}F-FDG and ^{18}F-fluoride for PET assessment of metastatic bone disease

Gang Cheng · Thomas C. Kwee · Sandip Basu · Abass Alavi

Received: 8 March 2013 / Accepted: 6 May 2013 / Published online: 22 May 2013

^{18}F-Fluoride positron emission tomography (PET) imaging is a highly sensitive imaging modality in detecting bone lesions and is superior to traditional ^{99m}Tc-diphosphonate scintigraphy [1, 2]. Apparently, it seems an attractive approach to combine ^{18}F-fluoride PET (which has high sensitivity for the detection of osseous metastasis) with ^{18}F-fluorodeoxyglucose (FDG) PET (which has been established as the single most important tumor imaging modality). Combined ^{18}F-fluoride and ^{18}F-FDG imaging in a single PET/CT scan has been proposed as a method to improve cancer diagnosis, staging, and therapy monitoring, with additional advantages of reducing the number of patient visits, shortening scanning time, and avoiding radiation exposure from additional CT imaging (if PET/CT were to be performed with each of these PET tracers separately).

In a 1998 pioneer study, Hoegerle et al. introduced the combined use of ^{18}F-fluoride PET and ^{18}F-FDG PET as an advanced metabolic imaging approach for the evaluation of cancer [3]. In 2009, a pilot study was published [4, 5] by another research group, with data obtained for ^{18}F-FDG PET/CT alone, ^{18}F-fluoride PET/CT alone, and combined ^{18}F-FDG and ^{18}F-fluoride PET/CT in the same group of patients. This had attracted immediate attention and discussion [6, 7]. More recently, a full report from the same research group has been published, with data from 115 cancer cases. In their protocol, 555 MBq (15 mCi) of ^{18}F-FDG+185 MBq (5 mCi) of ^{18}F-fluoride were combined to make a cocktail tracer, while a single PET/CT image was obtained starting at 60 min after intravenous administration of the combined radiotracers [4, 5]. The authors of that study concluded that combined use of ^{18}F-fluoride and ^{18}F-FDG in a single PET/CT scan improved the diagnostic accuracy as compared with ^{18}F-FDG PET/CT imaging alone [4, 5]. While very appealing at first sight, there are several critical issues associated with combined ^{18}F-FDG and ^{18}F-fluoride imaging, and these will be highlighted in the following sections.

First, one of the prerequisites for (cost-effectively) performing combined ^{18}F-fluoride and ^{18}F-FDG PET/CT imaging is that there must be solid evidence that ^{18}F-fluoride PET/CT provides additional information (detection of more metastatic osseous lesions) to ^{18}F-FDG PET alone. However, available data do not support this argument. Most of our knowledge in this regard is derived experience from bone scans. Numerous publications are available comparing the diagnostic accuracy of ^{18}F-FDG PET/CT versus bone scintigraphy. For most tumor types, ^{18}F-FDG PET is superior to single photon bone scintigraphy. Liu et al. [8] and Chang et al. [9] independently reported comprehensive meta-analyses of the diagnostic properties of ^{18}F-FDG PET or PET/CT versus bone scintigraphy in the detection of osseous metastases in patients with lung cancer (between January 1995 and August 2010), and both found that ^{18}F-FDG PET or PET/CT has higher sensitivity and specificity than bone scintigraphy. Similar findings have been reported

Gang Cheng, Thomas C. Kwee, and Sandip Basu contributed equally to this work.

G. Cheng
Department of Radiology, Philadelphia VA Medical Center,
3900 Woodland Avenue,
Philadelphia, PA 19104, USA

T. C. Kwee
Department of Radiology, University Medical Center Utrecht,
Utrecht, The Netherlands

S. Basu
Radiation Medicine Centre (Bhabha Atomic Research Centre),
Tata Memorial Hospital Annexe, Parel, Bombay 400012, India

G. Cheng · A. Alavi (✉)
Division of Nuclear Medicine, Department of Radiology,
Hospital of the University of Pennsylvania, 3400 Spruce Street,
Philadelphia, PA 19104, USA
e-mail: abass.alavi@uphs.upenn.edu

in a meta-analysis comparing the diagnostic value of ^{18}F-FDG PET or PET/CT versus bone scintigraphy in detecting bone metastases in patients with breast cancer [10]. The value of further dedicated bone scanning in addition to ^{18}F-FDG PET/CT imaging has also been questioned in patients with Hodgkin's lymphoma [11] and pediatric sarcoma [12]. In fact, a meta-analysis to compare ^{18}F-FDG PET, MRI, and bone scintigraphy for the diagnosis of bone metastases in all cancer types investigated (including 145 studies published from January 1995 to January 2010) revealed that ^{18}F-FDG PET and MRI had comparable accuracy and both were significantly more accurate than bone scintigraphy for the diagnosis of bone metastases. On either per-patient basis or per-lesion basis, the pooled sensitivity and specificity of FDG PET was significantly superior to bone scintigraphy [13].

It is generally believed that ^{18}F-fluoride PET imaging, especially PET/CT, is superior to traditional bone scan. Information from CT images also improves the diagnostic specificity of a fluoride PET study. However, there are limited data in the literature evaluating its diagnostic performance. There are a few studies that examined the performance of ^{18}F-fluoride PET or PET/CT in identifying osseous metastases and reported excellent results [2, 14, 15]. However, we noticed that these studies had very small sample size and most studies lacked histological confirmation and direct comparison with whole-body MRI. These studies heavily depended on clinical follow-up as a critical reference standard, but this is technically difficult because increased ^{18}F-fluoride activity tends to be long lasting. Especially, very limited (and controversial) information is available in the literature comparing the diagnostic accuracy of ^{18}F-FDG PET versus ^{18}F-fluoride PET. Iagaru et al. reported in a pilot study that ^{18}F-fluoride PET/CT outperformed ^{18}F-FDG PET/CT in detecting osseous metastasis [16]. At the same time, findings from other investigators favor ^{18}F-FDG over ^{18}F-fluoride [17, 18]. Even with prostate cancer, the advantage of ^{18}F-fluoride PET over ^{18}F-FDG PET is questionable [19, 20].

The underlying reason for the advantages of ^{18}F-FDG PET imaging has been explored. It has to be realized that osseous metastases occur (originate) in the red bone marrow rather than in the cortical bone and that ^{18}F-FDG PET detects bone marrow lesions [21, 22]. This partially explains the high sensitivity and also good specificity in detecting bone marrow metastases in most malignancies [8, 23–29]. The accuracy of ^{18}F-FDG PET in detecting and evaluating marrow metastases is as good as MRI in most cases [13, 30]. In contrast, the uptake of ^{99m}Tc-methylene diphosphonate (MDP) or ^{18}F-fluoride reflects activity of bone remodeling, which serves as indirect evidence for osseous metastasis, and is often a relatively late event of reactive bone formation after bone marrow involvement. Of note, both ^{18}F-FDG PET and MRI (which can provide both anatomical and functional information) are able to detect and characterize bone marrow lesions; given the complementary nature of both techniques and the rise of PET/MRI systems, this combination may eventually prove to provide the highest diagnostic and prognostic accuracy in patients (suspected of) metastatic bone marrow disease.

Second, although the sensitivity of ^{18}F-fluoride PET is high for osteoblastic lesions, its low specificity is an important concern. As pointed out in the Society of Nuclear Medicine practice guidelines, the degree of ^{18}F-fluoride uptake itself cannot differentiate benign from malignant lesions [31]. It has to be noted that neither ^{18}F-FDG nor ^{18}F-fluoride is specific, but when bone lesions are considered, the lack of specificity is a more problematic issue for the latter. It is well known that numerous benign bone lesions cause increased activity on ^{18}F-fluoride PET imaging, and the ^{18}F-fluoride uptake is often intense and long lasting. For example, degenerative change is the most common finding on ^{18}F-fluoride imaging with intense uptake, but often has only mild to moderate ^{18}F-FDG uptake [32]. In addition, healed fractures are often non-^{18}F-FDG-avid [33] but can have intense ^{18}F-fluoride uptake for months or years.

Because increased ^{18}F-fluoride activity is highly nonspecific, and because this activity is often intense, adding ^{18}F-fluoride to ^{18}F-FDG PET imaging immediately compromises the specificity of ^{18}F-FDG PET: (1) For any bone-related uptake, it is not known if one is dealing with ^{18}F-FDG uptake or ^{18}F-fluoride uptake, and this interpretation may be different in several situations. Particularly ^{18}F-fluoride uptake can be nonproportional to CT findings (for example, intense ^{18}F-fluoride uptake is commonly observed in regions with mild to moderate degenerative changes), which could obscure or conceal ^{18}F-FDG-avid metastatic lesions in the same location or nearby locations with low/moderate ^{18}F-FDG activity. (2) Both ^{18}F-FDG and ^{18}F-fluoride PET imaging have diffuse background activity in trabecular bone. The combined use of both tracers will lead to higher background activity in the trabecular bone (where metastatic lesions often occur), thereby reducing lesion conspicuity. Thus, small lesions with mild ^{18}F-FDG uptake are likely to be missed, compromising both sensitivity and specificity of ^{18}F-FDG PET. (3) As Hoegerle et al. pointed out in their pioneering work of the cocktail procedure, one limitation of the combined use of ^{18}F-fluoride and ^{18}F-FDG is a decreased lesion to background ratio on FDG PET, due to the distribution of free ^{18}F-fluoride throughout the extracelluar fluid space [3]. This increased background activity, due to additional use of ^{18}F-fluoride, is likely to compromise the diagnostic performance of ^{18}F-FDG PET/CT including soft tissue lesions. (4) Not only the quality of ^{18}F-FDG PET is compromised, ^{18}F-FDG uptake

in the bone/bone marrow may also compromise the ^{18}F-fluoride signal on the combined ^{18}F-fluoride/^{18}F-FDG scan. This is particularly a concern in patients with diffuse (nonmalignant) bone marrow ^{18}F-FDG uptake, as commonly observed in patients who are anemic, (oncological) patients with bone marrow inflammatory changes, and patients who have received chemotherapy or bone marrow-stimulating agents in the recent past [34, 35].

Third, the combined approach will limit appropriate early therapeutic response monitoring which is a major advantage of PET imaging for many tumor types. It should be emphasized that ^{18}F-FDG is the tracer of choice in this domain and metabolic response invariably precedes that detected by other modalities including osteoblastic response. In addition to the compromise in the diagnostic accuracy, it would be difficult to make a correct comparative estimate of the disease burden in the follow-up study or to evaluate treatment response on the combined ^{18}F-fluoride/^{18}F-FDG scan. While ^{18}F-FDG-avid metastatic bone marrow lesions may be normalized within days after successful treatment [36, 37], foci of tracer activity on dedicated bone scanning (i.e., ^{99m}Tc-diphosphonate scintigraphy or ^{18}F-fluoride PET) are often long lasting even after successful treatment [22]. It would be impossible to determine whether an abnormal osseous uptake is due to ^{18}F-FDG or due to ^{18}F-fluoride on the combined study.

In addition, a post-therapy metabolic flare phenomenon of bone marrow ^{18}F-FDG uptake may compromise the interpretation of ^{18}F-fluoride PET interpretation. Similarly, the osteoblastic flare phenomenon on bone scintigraphy and ^{18}F-fluoride PET, often observed in breast, prostate, and lung cancer, may confound the assessment of therapeutic response in ^{18}F-FDG-avid skeletal lesions. The latter is more worrisome because ^{18}F-fluoride uptake tends to be more intense and lasts longer compared to therapy-induced ^{18}F-FDG activity [38].

Fourth, the value of standardized uptake values (SUVs), as is routinely used in current practice, is lost if combined cocktail ^{18}F-fluoride/^{18}F-FDG PET/CT imaging is used. While SUV measurement is still possible with the cocktail procedure (if the procedure is strictly standardized), SUV values obtained under this circumstance would be totally different from those obtained from FDG-alone PET or ^{18}F-fluoride-alone PET. In fact, extraosseous uptake of ^{18}F-fluoride in the primary malignancy has been reported [39]. At the same time, it is unknown how often increased ^{18}F-fluoride should be expected in soft tissue malignancies and to what extent; therefore, it is impossible to tell which portion of the SUV is contributed from FDG and which is from ^{18}F-fluoride. For lesions with overt abnormality, visual analysis may be sufficient [4, 5]. However, not all lesions are clear-cut. Although it should not be used as a sole criterion in determining if a lesion is benign or malignant, the SUV can be a very helpful adjunct, both for diagnostic and therapeutic response monitoring purposes. The nonavailability of the SUV negatively affects evaluation of not only osseous lesions, but all other lesions. This is especially important when comparing a lesion with blood pool or liver activity, and when comparing a lesion with a prior study.

In addition, the nonavailability of SUV would also compromise one of the strengths of ^{18}F-FDG imaging, i.e., defining tumor biology and thus providing prognostic information [40]. This may also apply to prostate cancer for which an ^{18}F-FDG PET/CT may identify significant additional lesions not detected by a bone scan [20]. Morris et al. reported that increased FDG uptake in progressive metastatic prostate cancer represented active disease sites on subsequent studies, indicating that FDG PET may help to discriminate between active versus quiescent osseous lesions in these patients [41]. In a prospective study that used a long-term follow-up, it was shown that the level of ^{18}F-FDG uptake in prostate cancer is an independent prognostic factor: Most (80 %) ^{18}F-FDG-only lesions at baseline become positive on follow-up bone scan, and SUVs are inversely correlated with prognosis [42]. Thus, it could be clinically important to know if an osseous metastasis (as well as other tumor lesions) is ^{18}F-FDG-avid or just ^{18}F-fluoride-avid, but this information cannot be provided by the combined approach.

Fifth, the methodological limitations of the published studies on this topic should be noted. Iagaru et al. [5] reported that combined ^{18}F-FDG and ^{18}F-fluoride PET whole-body imaging detected more osseous metastases in 29 patients among a total of 115 patients evaluated. However, it is unclear if tumor stage was changed or not because of these additional findings. Furthermore, the majority (62.1 %) of cases showing more osseous lesions on the combined imaging than on ^{18}F-FDG PET/CT were prostate cancer patients, which often are non-^{18}F-FDG-avid, thus limiting the patient spectrum to which these findings are applicable. Finally, since bone scintigraphy and ^{18}F-fluoride PET are highly nonspecific, indeterminate lesions are common. The authors of this study [5] did not have a reference standard to determine the nature of the additional lesions seen on ^{18}F-fluoride PET or to classify “uncertain” lesions on ^{18}F-FDG PET, which can be regarded as an important methodological shortcoming [43].

Lastly, increased radiation exposure and cost of additional tracer usage have to be considered. Again, in most cases, additional bone scintigraphy/^{18}F-fluoride PET is not indicated if ^{18}F-FDG PET/CT is performed, while for prostate cancer, ^{18}F-FDG PET/CT is not indicated according to current guidelines. Besides, a recent meta-analysis comparing the cost-effectiveness between ^{18}F-fluoride PET or PET/CT versus planar or single photon emission computed

tomography (SPECT) bone scan failed to demonstrate any cost-effective advantage for ^{18}F-fluoride PET or PET/CT in the assessment of metastatic bone lesions [2].

In summary, ^{18}F-FDG PET/CT is a reliable imaging tool in the detection of osseous metastasis in most cases. A dedicated bone scan (including ^{18}F-fluoride PET/CT) may not be indicated in many cancers for the evaluation of osseous metastasis, especially at early stages. Combined use of dual tracers may compromise the imaging quality of both studies, especially for ^{18}F-FDG PET with respect to its ability to detect lesions in the bone marrow. We have no doubt that ^{18}F-fluoride PET may be valuable and provide some additional value in some selected cases and selected cancers, where ^{18}F-FDG is of limited value. However, the value of using the combined approach is limited in most situations. The logical notion, thus, is that for ^{18}F-FDG-avid tumors, there is no evidence in the literature that ^{18}F-fluoride PET/CT detects more osseous lesions than ^{18}F-FDG PET/CT, while for non-^{18}F-FDG-avid tumors, ^{18}F-FDG PET/CT is not indicated. Both the rare occasions (when both ^{18}F-FDG PET and ^{18}F-fluoride PET are indicated) and the advantages of performing a dual tracer PET remain to be defined.

Conflicts of interest None.

References

1. Grant FD, Fahey FH, Packard AB, Davis RT, Alavi A, Treves ST. Skeletal PET with 18F-fluoride: applying new technology to an old tracer. J Nucl Med 2008;49:68–78.
2. Tateishi U, Morita S, Taguri M, Shizukuishi K, Minamimoto R, Kawaguchi M, et al. A meta-analysis of (18)F-fluoride positron emission tomography for assessment of metastatic bone tumor. Ann Nucl Med 2010;24:523–31.
3. Hoegerle S, Juengling F, Otte A, Altehoefer C, Moser EA, Nitzsche EU. Combined FDG and [F-18]fluoride whole-body PET: a feasible two-in-one approach to cancer imaging? Radiology 1998;209:253–8.
4. Iagaru A, Mittra E, Yaghoubi SS, Dick DW, Quon A, Goris ML, et al. Novel strategy for a cocktail 18F-fluoride and 18F-FDG PET/CT scan for evaluation of malignancy: results of the pilot-phase study. J Nucl Med 2009;50:501–5.
5. Iagaru A, Mittra E, Mosci C, Dick DW, Sathekge M, Prakash V, et al. Combined 18F-fluoride and 18F-FDG PET/CT scanning for evaluation of malignancy: results of an international multicenter trial. J Nucl Med 2013;54:176–83.
6. Bailey DL. Combined (18)F-FDG and fluoride approach in PET/CT imaging: is there a clinical future? J Nucl Med 2010;51:165–6. author reply 166–7.
7. Basu S, Rao R. Combined (18)F-FDG and fluoride approach in PET/CT imaging: is there a clinical future? J Nucl Med 2010;51:165. author reply 166–7.
8. Liu T, Xu J-Y, Xu W, Bai Y-R, Yan W-L, Yang H-L. Fluorine-18 deoxyglucose positron emission tomography, magnetic resonance imaging and bone scintigraphy for the diagnosis of bone metastases in patients with lung cancer: which one is the best?—a meta-analysis. Clin Oncol (R Coll Radiol) 2011;23:350–8.
9. Chang M-C, Chen J-H, Liang J-A, Lin C-C, Yang K-T, Cheng K-Y, et al. Meta-analysis: comparison of F-18 fluorodeoxyglucose-positron emission tomography and bone scintigraphy in the detection of bone metastasis in patients with lung cancer. Acad Radiol 2012;19:349–57.
10. Liu T, Cheng T, Xu W, Yan W-L, Liu J, Yang H-L. A meta-analysis of 18FDG-PET, MRI and bone scintigraphy for diagnosis of bone metastases in patients with breast cancer. Skeletal Radiol 2011;40:523–31.
11. Shulkin BL, Goodin GS, McCarville MB, Kaste SC, Krasin MJ, Hudson MM, et al. Bone and [18F]fluorodeoxyglucose positron-emission tomography/computed tomography scanning for the assessment of osseous involvement in Hodgkin lymphoma in children and young adults. Leuk Lymphoma 2009;50:1794–802.
12. Walter F, Czernin J, Hall T, Allen-Auerbach M, Walter MA, Dunkelmann S, et al. Is there a need for dedicated bone imaging in addition to 18F-FDG PET/CT imaging in pediatric sarcoma patients? J Pediatr Hematol Oncol 2012;34:131–6.
13. Yang HL, Liu T, Wang XM, Xu Y, Deng SM. Diagnosis of bone metastases: a meta-analysis comparing (18)FDG PET, CT, MRI and bone scintigraphy. Eur Radiol 2011;21:2604–17.
14. Yen R-F, Chen C-Y, Cheng M-F, Wu Y-W, Shiau Y-C, Wu K, et al. The diagnostic and prognostic effectiveness of F-18 sodium fluoride PET-CT in detecting bone metastases for hepatocellular carcinoma patients. Nucl Med Commun 2010;31:637–45.
15. Piccardo A, Altrinetti V, Bacigalupo L, Puntoni M, Biscaldi E, Gozza A, et al. Detection of metastatic bone lesions in breast cancer patients: fused (18)F-fluoride-PET/MDCT has higher accuracy than MDCT. Preliminary experience. Eur J Radiol 2012;81:2632–8.
16. Iagaru A, Mittra E, Dick DW, Gambhir SS. Prospective evaluation of (99m)Tc MDP scintigraphy, (18)F NaF PET/CT, and (18)F FDG PET/CT for detection of skeletal metastases. Mol Imaging Biol 2012;14:252–9.
17. Krüger S, Buck AK, Mottaghy FM, Hasenkamp E, Pauls S, Schumann C, et al. Detection of bone metastases in patients with lung cancer: 99mTc-MDP planar bone scintigraphy, 18F-fluoride PET or 18F-FDG PET/CT. Eur J Nucl Med Mol Imaging 2009;36:1807–12.
18. Chan SC, Wang HM, Ng SH, Hsu CL, Lin YJ, Lin CY, et al. Utility of 18F-fluoride PET/CT and 18F-FDG PET/CT in the detection of bony metastases in heightened-risk head and neck cancer patients. J Nucl Med 2012;53:1730–5.
19. Hsu WK, Virk MS, Feeley BT, Stout DB, Chatziioannou AF, Lieberman JR. Characterization of osteolytic, osteoblastic, and mixed lesions in a prostate cancer mouse model using 18F-FDG and 18F-fluoride PET/CT. J Nucl Med 2008;49:414–21.
20. Tiwari BP, Jangra S, Nair N, Tongaonkar HB, Basu S. Complimentary role of FDG-PET imaging and skeletal scintigraphy in the evaluation of patients of prostate carcinoma. Indian J Cancer 2010;47:385–90.
21. Basu S, Alavi A. Bone marrow and not bone is the primary site for skeletal metastasis: critical role of [18F]fluorodeoxyglucose positron emission tomography in this setting. J Clin Oncol 2007;25:1297. author reply 1297–9.
22. Basu S, Tiwari BP. Complimentary role of FDG-PET imaging and skeletal scintigraphy in the evaluation of patients of prostate carcinoma. Indian J Cancer 2011;48:513–4.
23. Cheran SK, Herndon 2nd JE, Patz Jr EF. Comparison of whole-body FDG-PET to bone scan for detection of bone metastases in patients with a new diagnosis of lung cancer. Lung Cancer 2004;44:317–25.
24. Liu F-Y, Chang JT, Wang H-M, Liao C-T, Kang C-J, Ng S-H, et al. [18F]fluorodeoxyglucose positron emission tomography is more

sensitive than skeletal scintigraphy for detecting bone metastasis in endemic nasopharyngeal carcinoma at initial staging. J Clin Oncol 2006;24:599–604.
25. Ozülker T, Küçüköz Uzun A, Ozülker F, Ozpaçac T. Comparison of (18)F-FDG-PET/CT with (99m)Tc-MDP bone scintigraphy for the detection of bone metastases in cancer patients. Nucl Med Commun 2010;31:597–603.
26. Withofs N, Grayet B, Tancredi T, Rorive A, Mella C, Giacomelli F, et al. 18F-fluoride PET/CT for assessing bone involvement in prostate and breast cancers. Nucl Med Commun 2011;32:168–76.
27. Cheng G, Chen W, Chamroonrat W, Torigian DA, Zhuang H, Alavi A. Biopsy versus FDG PET/CT in the initial evaluation of bone marrow involvement in pediatric lymphoma patients. Eur J Nucl Med Mol Imaging 2011;38:1469–76.
28. Cheng G. The diagnostic value of FDG-PET cannot be judged by iliac bone marrow biopsy. Br J Radiol 2012;85:1204–5.
29. Wu LM, Chen FY, Jiang XX, Gu HY, Yin Y, Xu JR. 18F-FDG PET, combined FDG-PET/CT and MRI for evaluation of bone marrow infiltration in staging of lymphoma: a systematic review and meta-analysis. Eur J Radiol 2012;81:303–11.
30. Basu S, Torigian D, Alavi A. Evolving concept of imaging bone marrow metastasis in the twenty-first century: critical role of FDG-PET. Eur J Nucl Med Mol Imaging 2008;35:465–71.
31. Segall G, Delbeke D, Stabin MG, Even-Sapir E, Fair J, Sajdak R, et al. SNM practice guideline for sodium 18F-fluoride PET/CT bone scans 1.0. J Nucl Med 2010;51:1813–20.
32. Rosen RS, Fayad L, Wahl RL. Increased 18F-FDG uptake in degenerative disease of the spine: characterization with 18F-FDG PET/CT. J Nucl Med 2006;47:1274–80.
33. Zhuang H, Sam JW, Chacko TK, Duarte PS, Hickeson M, Feng Q, et al. Rapid normalization of osseous FDG uptake following traumatic or surgical fractures. Eur J Nucl Med Mol Imaging 2003;30:1096–103.
34. Cheng G, Servaes S, Alavi A, Zhuang H. FDG PET and PET/CT in the management of pediatric lymphoma patients. PET Clin 2008;3:621–34.
35. Salaun PY, Gastinne T, Bodet-Milin C, Campion L, Cambefort P, Moreau A, et al. Analysis of 18F-FDG PET diffuse bone marrow uptake and splenic uptake in staging of Hodgkin's lymphoma: a reflection of disease infiltration or just inflammation? Eur J Nucl Med Mol Imaging 2009;36:1813–21.
36. Brepoels L, De Saint-Hubert M, Stroobants S, Verhoef G, Balzarini J, Mortelmans L, et al. Dose–response relationship in cyclophosphamide-treated B-cell lymphoma xenografts monitored with [18F]FDG PET. Eur J Nucl Med Mol Imaging 2010;37:1688–95.
37. Shinto A, Nair N, Dutt A, Baghel NS. Early response assessment in gastrointestinal stromal tumors with FDG PET scan 24 hours after a single dose of imatinib. Clin Nucl Med 2008;33:486–7.
38. Basu S, Alavi A. Defining co-related parameters between 'metabolic' flare and 'clinical', 'biochemical', and 'osteoblastic' flare and establishing guidelines for assessing response to treatment in cancer. Eur J Nucl Med Mol Imaging 2007;34:441–3.
39. Li Y, Tafti BA, Shaba W, Berenji GR. Extraosseous uptake of F-18 fluoride in the primary malignancy and cerebral metastasis in a case of non-small-cell lung cancer. Clin Nucl Med 2011;36:609–11.
40. Kwee TC, Basu S, Saboury B, Ambrosini V, Torigian DA, Alavi A. A new dimension of FDG-PET interpretation: assessment of tumor biology. Eur J Nucl Med Mol Imaging 2011;38:1158–70.
41. Morris MJ, Akhurst T, Osman I, Nunez R, Macapinlac H, Siedlecki K, et al. Fluorinated deoxyglucose positron emission tomography imaging in progressive metastatic prostate cancer. Urology 2002;59:913–8.
42. Meirelles GS, Schöder H, Ravizzini GC, Gönen M, Fox JJ, Humm J, et al. Prognostic value of baseline [18F] fluorodeoxyglucose positron emission tomography and 99mTc-MDP bone scan in progressing metastatic prostate cancer. Clin Cancer Res 2010;16:6093–9.
43. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD Initiative. Radiology 2003;226:24–8.