Role of ^{18}F FDG PET in Differentiating Benign and Malignant Primary Bone Tumors

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ABSTRACT

^{18}F FDG PET is useful in differentiating benign from many kinds of malignant tumors including bone tumors. Many reporters found significant difference of SUV (standardized uptake value) between benign and malignant primary bone tumors. However, some benign bone tumors specially histolytic and Giant cell containing lesions show high accumulation of FDG, which increases false positive rates in FDG-PET. So, consideration of histologic subtypes should be included in analysis of SUV at FDG PET of primary bone tumors. Furthermore, high accumulation of FDG in inflammatory lesions like chronic osteomyelitis and rheumatoid arthritis should also be considered. Dual time-point imaging and determination of retention index provide more help in the differentiation of malignant from benign tumors and is recommended for unclear bone lesions. To differentiate benign from malignant vertebral compression fractures PET showed slightly higher sensitivity over MRI and provide better specificity when both modalities are combined. PET provides opportunity of whole body screening to pick up new lesions and also guide FNAC in case of indeterminate results.

Key words: FDG PET, Primary bone tumors

INTRODUCTION

The differentiation of benign and malignant intraosseous lesions can open be accomplished by means of radiographs, computed tomography (CT) and magnetic resonance imaging (MRI). Radiographs including CT and X-ray provide important information about the appearance, intraosseous extent and internal characteristics of bone tumors. MRI is highly sensitive for the detection of bone marrow abnormalities, cortical destruction or soft tissue tumors adjacent to or infiltrating adjacent bones. (1) However, these modalities cannot assess tumor activity and

metabolism, which are crucial to differentiate malignancy from benignancy and to plan the first operative procedures. (2)

Positron emission tomography (PET) with 2-[fluorine-2-deoxy-d-glucose (FDG) has been used extensively to differentiate malignant tumors from benign lesions in many organ systems (3-5) Its usefulness has also been reported in distinction of benign from malignant bone tumors and in the assessment of grade of musculoskeletal sarcomas. (6-9)

Intravenously injected FDG is first transported into cells by glucose transporters and then phosphorylated into FDG-6-phosphate by hexokinase in same way as glucose is phosphorylated into glucose-6-phosphate. While glucose-6-phosphate is further catalyzed in a normal glucose metabolism pathway, FDG-6-phosphate is not transformed by phosphoglucose isomerase and therefore remains trapped in cells.(10) The accumulated ^{18}F-FDG-6 phosphate reflects glucose uptake & metabolism in cells. Detecting photons generated via beta decay of ^{18}F,PET can show the distribution of glucose metabolism in human body. (11)

Accumulation of FDG is generally quantified by the standardized uptake value (SUV). Quantification of glucose metabolism by FDG PET has enabled physicians to differentiate malignancy from benignancy, identify the primary site of carcinoma of unknown origin, decide stages of malignant tumors and evaluate chemotherapy responses in various cancers.(2)

This review reveals role of FDG PET in differentiating benign and malignant primary bone tumors, cut off point of SUV in this differentiation, role of histologic types of tumors cells, importance of considering benign bone lesions showing relatively high FDG uptake as well as the role of dual-time point imaging.

DIFFERENTIATION OF MALIGNANT FROM BENIGN BONE TUMORS

Since Warburg reported in 1956 that a cell line that had produced sarcoma in CH3/He mice showed higher glucose metabolism than acell line had not (12), malignant tumors, such as hepatoma (13,14), leukemia (15), colon cancer, melanoma, carcinoma of urinary bladder (14), and so on, have been known to show high glucose metabolism.

Some authors have reported higher glucose uptake in malignant musculoskeletal tumors than in benign tumors and tried to differentiate malignant from benign tumors using an SUV cut off of

1.9-3.9. (2) Earlier reports indicate the excellent ability of 18F-FDG PET to differentiate malignant from benign musculoskeletal tumors (6,9,16) and compression fractures. (17)

However several authors have revealed some benign tumors with high SUV causing high false positive rate in trials to differentiate malignancy from benignancy with FDG-PET.(18,19)

In a study by Akoi et al. (19), there was statistically significant difference between benign (2.18+1.52) and malignant (4.34+3.19) lesions though a considerable overlap was observed in SUV between some benign and malignant tumors. Malignant lymphomas and Ewing sarcomas showed extremely high SUVs. Osteosarcomas and chondrosarcomas demonstrated relatively high SUVs. The types of benign lesions that showed a high accumulation of FDG were Giant cell tumor, chondroblastoma, Langerhans cell histocytes, fibrous dysplasia and sarcoidosis. Giant cell tumors (n=5; SUV 4.64 1.05) showed significantly higher accumulation of FDG than chondrosarcomas (n=7; SUV 2.23 0.74). There was no statistically significant difference in SUV between fibrous dysplasias and osteosarcomas (P=0.127) or between fibrous dysplasias and chondrosarcomas (P==0.667). Furthermore, high accumulation of FDG has been reported in many kinds of inflammatory calls, including chronic osteomyelitis and rheumatoid arthritis.(20-22) Histocytes and Giant cells in a tissue are in monocyte-macrophase lineage (23, 24). Macro phases play a central role in the host response to injury and infection and their energy is predominantly supplied by means of intracellular glucose metabolism, which may be attributed to high FDG uptake. (25,26)

ROLE OF DUAL-TIME POINT IMAGING

^{18}F FDG PET usually is performed one hour after ^{18}FFDG administration. Some studies have shown that delayed PET (2-3 hours post injection) might help in differentiating malignant lesions from benign ones (27-32). Sahlmann et al (33) investigated glucose metabolism in 17 patients with chronic osteomyelitis and four patients with malignant bone lesions by using a dual time point ^{18}F FDG PET (30 and 90 min after injection). They concluded that dual time point ^{18}F FDG PET may be of value in differentiation between chronic osteomyelitis and malignant bone lesions.

Tian R et al (34) studied 67 patients with bone lesions detected by computed tomography (CT) and magnetic resonance imaging. Whole body PET-CT imaging was performed at 1 hour (early

after the ^{18}F FDG injection and delayed imaging at 2 hours post injection was performed only in the abnormal region. The final diagnosis revealed 53 malignant bone lesions in 37 patients and 45 benign bone lesions in 30 patients. There were statistically significant differences in the SUV maxE between the malignant and benign lesions (p=0.03). The mean SUVmaxE was 6.8+ 4.7 for malignant lesions and 4.5 + 3.3 for benign lesions. With a cut off value of 2.5 for the SUVmaxE, the sensitivity, specificity and accuracy were 96.0%, 44.0% and 72.4% respectively. The retention index (RI) was calculated according to the equation: RI= (SUVmaxD-SUVmaxE) x 100/SUVmaxE. There were significant differences in the RI between the malignant and benign lesions (p=0.004). But there was overlap between the two groups. This study indicated that dual-time point^{18} F FDG PET may provide more help in differentiating malignant tumors from benign ones.

Bredella et al. (17) reported the usefulness of ^{18}F FDG PET for the differentiation of benign and malignant fractures and indicated that dual-time point imaging may provide more help in this differentiation.

Xiu et al. (32) analyzed the retention index (RI) of 46 patients with pulmonary nodules with borderline levels of increased^{18} F FDG activity on the initial PET scan. They found that the dual-time point imaging yielded most accurate result when the RI threshold of 10% was used. Mavi et al. (31) investigated 152 patients with newly diagnosed breast cancer who underwent dual-time point imaging for preoperative staging. They found that the sensitivity and accuracy was improved in dual-time point imaging.

Whereas Hamada et al. (35) found no significant difference in the RI between malignant and benign soft tissue lesions. However, there was bias in their case selection.

COMPARISON OF PET-CT WITH MRIIN DISTINGUISING BENIGN VS MALIGNANT VERTIBRAL BONE DISEASE

A recent prospective study by Aggarwal A et al. (36) comparing MRI and ^{18}F FDG PET-CT in 24 patients with nontraumatic spontaneous vertebral compression fractures concluded that FDG PET-CT can be considered as adjunctive method for diagnosing and differentiating malignant from benign vertebral compression fractures. In comparison with MRI, FDGPET-CT showed

slightly higher sensitivity and lower specificity. (17,37) PET-CT missed one patient in each of the groups. When both the modalities were combined, the specificity for diagnosing a benign lesion was 100%.

A major problem in selecting mean SUV max as the sole criteria for differentiating benign and malignant lesions is that no single cut off can be suggested. According to Laufer et al, the mean SUV values of lesions active with cancer were 7.1 and 2.1 in benign lesions.(38) However, Harkiratet al, reported SUV max values of 21 in tuberculosis.(39) Despite these limitations, PET-CT has multiple advantages. First, whole body screening picks up sites other than the involved spine, thereby giving a broader picture of disease. Second, in cases of indeterminate FNAC results, the site of FNAC can be guided by involvement of more accessible sites such as subcutaneous lymph nodes, other bones, thyroid gland etc. Finally in cases where empirical therapy is started, repeating PET-CT can monitor the disease progress and response to therapy.

CONCLUSION

Positron emission tomography (PET) using ^{18}F FDG is being used along with computed tomography (CT) and magnetic resonance imaging (MRI) in differentiation of benign and malignant intraosseous lesions. Nuclear medicine physicians should be aware of a high accumulation of FDG in some benign bone tumors and tumor like lesions, specially histocytic and Giant cell containing lesions. Dual-time point ^{18}F FDG PET may provide more help in this differentiation and is specially recommended for the unclear bone lesions.

REFERENCES

1. Erlemann R.MRI is highly sensitive for the detection of bone marrow abnormalities, cortical destruction or soft tissue tumors adjacent or infiltrating neighboring bones. Eur J Radiol**2006**; 58(1): 48-67.
2. Yanagawa T, Watanabe H, Shinozaki T, Takagishi K. Usefulness of FDG PET in primary bone tumors. The Open Bone Journal, **2010**;2:19-23.
3. Strauss LG, Conti PS. The applications of PET in oncology, J Nuc Med 1991;32:623-648.

4. Hoh CK, Schiepers C, Seltzer MA, et al. PET in oncology: Will it replace the other modalities? SeminNucl Med 1997;27:94-106.
5. Brock CS, Meikle SR, Price P. Dose fluorine-18 fluorodeoxy glucose metabolic imaging of tumors benefit oncology?.Eur J Nucl Med 1997>/DATE; 24:691-705.
6. Kern KA, Brunetti A, Norton JA, et al. Metabolic imaging of human extremity musculoskeletal tumors by PET.J Nucl Med 1988;29:181-186.
7. Adler LP, Blair HF, Makley JT, et al. Noninvasive grading of musculoskeletal tumors using PET.J Nucl Med 1991;32:1508-1512.
8. Griffeth LK, Dehdashti FD, McGire AH, et al. PET evaluation of soft-tissue masses with fluorine-18 fluoro-2-deoxy-d-glucose. Radiology 1992;182:185-194.
9. Dehdashti FD, Siegel GA, Griffeth LK, et al. Benign versus malignant intraosseous lesions: discrimination by means of PET with 2-[F-18] fluoro-2-deoxy-d-glucose. Radiology 1996;200:243-247.
10. Gallagher BM, Fowler JS, Gutterson NI, MacGregor RR, Wan CN, Wolf AP. Metabolic trapping as a principle of oradiopharma-ceutical design: some factors responsible for the biodistribution of [18F] 2-deoxy-2- fluoro-D- glucose. J Nucl Med 1978; 19: 1154-61.
11. Van Ginkel RJ. Hoekstra HJ, Pruim J, et al FDG-PET to evaluate response to hyperthermic isolated limb perfusion for locally advanced soft-tissue sarcoma. J Nucl Med 1996;37: 984-90.
12. Warburg O. On the origin of cancer cells. Science 1956; 123: 309-14.
13. . Weinhouse S. Glycolysis, respiration and anomalous gene expression in experimental hepatomas: G.H.A Clowes memorial lecture. Cancer Res 1972; 32:2007-16
14. . Rousset M, Paris H, Chevalier G, Terrain B, Murat JC, Zweibaum A.Growth related enzymatic control of glycogen metabolism in cultured human tumor cells. Cancer Res 1984; 44:154-60
15. Gottschalk S, Anderson N, Hainz C, Echhardt SG, Serkova NJ. Imatinib (ST1571)-mediated changes in glucose metabolism in human leukemia BCR-ABL-positive cells.Clin cancer Res 2004; 10:6661-8
16. Feldman F, Van Heertum R, Monas C. 18FDG PET scanning of benign and malignant musculoskeletal lesions. Skeletal Radiol 2003; 32:201-8

17. Bredella MA, Essary B, Torriani M, Ouellette HA, Palmer WE. Use of FDG PET in differentiating benign from malignant compression fractures, Skeletal Radiol**2008**; 37:405-13
18. Shin DS, Shon OJ, Han DS, Choi JH, Chun KA, Cho IH. The clinical efficacy of (18) F – FDG-PET/CT in benign and malignant musculoskeletal tumors. Ann Nucl Med **2008**; 22: 603-9.
19. Aoki J, Watanabe H, Shinozaki T, et al. FDG PET of primary benign and malignant bone tumors: standardized uptake value in 52 lesions. Radiology 2001;219:774-7.
20. Guhlmann A, Brechy-Krauss D, Suger G, et al. Chronic osteomyelitis: detection with FDG PET and correlation with histopathologic findings. Radiology 1998;206:749-754.
21. Palmer WE, Rosenthal Dl, Schoenberg Ol, et al. Quantification of inflammation in the wrist with gadolinium-enhanced MR imaging and PET with 2-[F-18]- fluoro-2-deoxy-d-glucose. Radiology 1995;196:647-655.
22. Brudin LH, Valid SO, Rhodes CG, et al. Fluorine-18 deoxglucose uptake in sarcoidosis measured with positron emission tomography. Eur J Nucl Med 1994; 21: 297-305.
23. Jhnston J Giant cell tumor of bone: the role of the giant cell in orthopedic pathology. OrthopClin North Am 1977; 8: 751-770.
24. Ling L, Klein MJ, Sissons HA, Steiner GC, Winchester RJ. Expression of la and monocyte-macrophage lineage antigens in giant cell tumor of bone and related lesions. Arch pathol Lab Med 1988;112: 65-69.
25. Meszaros K, Lang CH, Bagby GJ, Spitzer JJ. Contribution of different organs to increased glucose consumption after endotoxin administration. J Biol Chem 1987;262:10965-10970.
26. Gamelli RL, Liu H, He L, Hofmann CA. Augmentation of glucose transporter-1 in macrophages following thermal injury and sepsis in mice. J LeukocBiol 1996;59:639-647.
27. Zhuang H, Proudehnad M, LambrightES et at. Dual time point 18 F-FDG PET imaging for differentiating malignant from inflammatory processes. J Nucl Med 2001; 42(9):1412-1417

28. Lan XL, Zhang YX, Wu ZJ, Jia Q, Wei H, Gao ZR. The value of dual time point 18 F-FDG PET imaging for the differentiation between malignant benign lesions. Clinical Radiology **2008**; 63(7):756-764.
29. Matthies A, Hickeson M, Cuchiara A, Alavi A. Dual time point 18F-FDG PET for the evaluation of pulmonary nodules.J Nucl Med 2002; 43(7):871-875.
30. Ma S-Y, See L-C, Lai C-H, et al. Delayed 18F-FDG PET for detection of para-aortic lymph node metastases in cervical cancer patients. J Nucl Med 2003; 44(11):1775-1783.
31. Mavi A, Urhan M, Yu JQ et al. Dual time point 18F-FDG PET imaging detects breast cancer with sensitivity and correlates well with histologic subtypes. J Nucl Med **2006**; 47(9):1440-1446.
32. Xiu Y, Bhutani C, Dhurairaj T, et at. Dual time point FDG PET imaging in the evaluation of pulmonary nodules with minimally increased metabolic activity. ClinNucl Med **2007**; 32(2):101-105.
33. Sahlmann CO, Siefker U, Lehmann K, Meller J. Dual time point 2-[18F]fluoro-2`-deoxyglucose positron emission tomography in chronic bacterial osteomyelitis. Nucl Med Commun 2004; 25(8):819-823.
34. Tian R, Su M, Tian Y, Li F, Li L, Kuang A, Zeng J. Dual-time point PET/CT with F-18 FDG for the differentiation of malignant and benign bone lesions. SkeletolRadiol**2009**; 38: 451-458.
35. Hamada K, Tomita Y, Ueda T, et al. Evaluation of delayed$_{18}$F-FDGPET in differential diagnosis for malignant soft-tissue tumors. Ann Nucl Med **2006**;20(10): 671-675.
36. Aggarwal A, Salunke P, ShekharBR,Chhabra R, Singh P Bhattacharya A, Garg R. The role of magnetic resonance imaging and positron emission tomography combined in differentiating benign and malignant lesions contributing to vertebral compression fractures. SurgNeurolInt**2013**; 4: 323.
37. Cho WI, Chang UK. Comparison MR imaging and FDG PET/CT in the differential diagnosis of benign and malignant vertebral compression fractures. J Neurosurg Spine **2011**; 14:177-83.
38. Laufer I, Lis E, Pisinski L, Akhurst T, Bilsky MH. The accuracy of [(18)F] fluorodeoxy glucose positron emission tomography as confirmed by biopsy in the diagnosis of spine metastases in a cancer population. Neurosurgery **2009**; 64:107-13.

39. Harkirat S, Anand SS, Indrajit IK, Dash AK. Pictorial essay: PET/CT in tuberculosis. Indian J Radiol Imaging **2008**; 18:141-7.