The assessment of bone marrow infiltration with 18FDG-PET in non-haematopoietic solid tumors

Hematopoetik olmayan solid tümörlerde 18FDG-PET ile kemik iliği infiltrasyonunun değerlendirilmesi

Ayşe Ocak Duran, Mevlude Inanc, Oktay Bozkurt, Ersin Ozaslan, Mahmut Uçar, Metin Ozkan

Department of Medical Oncology, Erciyes University, Faculty of Medicine, Kayseri, Turkey

Dergiye Ulaşma Tarihi: 25.12.2016 Dergiye Kabul Tarihi: 31.07.2017 Doi: 10.5505/aot.2017.92486

ÖZET

GİRİŞ ve AMAÇ: Çalışmamızın amacı, solid tümörlere bağlı kemik iliği metastazı (KİM) düşünülen ve kemik iliği biyopsisi (KİB) yapılmış hastalarda 18F-Fluorodeoxyglucose kullanılarak yapılan positron emission bilgisayarlı tomografisinin (18FDG-PET/CT) tanısal değerini araştırmaktır.

YÖNTEM ve GEREÇLER: Solid tümör nedeniyle KİM olduğu düşünülen ve hem 18FDG-PET/CT hem de KİB yapılmış 53 hasta geriye dönük olarak incelendi.

BULGULAR: 53 hasta içinde, 18FDG-PET/CT ile 36 hastada, KİB ile 33 hastada KİM metastazı tespit edildi. 9/53 hastada (16,9%) her iki yöntem de KİM olmadığını gösterdi. 25/53 hastada (47.2%) her iki yöntem de KİM olduğunu gösterdi. 18FDG-PET/CT (+) olan 36 hastadan, KİB'ne göre 25 hastada KİM mevcut idi (yanlış pozitif, 11/36, %30,5). 18FDG-PET/CT (-) olan 17/53 hastadan, KİB'ne göre 8 hastada KİM mevcut değildi (yanlış negatif, 8/17, %47,5). KİB'ne göre KİM olan hastalarda, olmayanlara göre SUVmax değeri önemli derecede yüksek idi [7.1 (2.5-22.2) vs 3.3 (2.2 – 16.0, p = 0.79), p=0.024].

TARTIŞMA ve SONUÇ: Bu ön sonuçlar, kemik iliğinin değerlendirilmesinde 18FDG-PET/CT'nin KİB'den daha üstün olmadığını önermektedir. Bununla birlikte KİM değerlendirilmesi için SUVmax değeri dikkate alınmalıdır.

Anahtar Kelimeler: Kemik iliği metastazı, solid tümör, 18FDG-PET/CT

ABSTRACT

INTRODUCTION: We aimed to investigate the diagnostic value of positron emission computed tomography using 18F-Fluorodeoxyglucose (18FDG-PET/CT) in bone marrow metastasis (BMM) due to solid tumors in patients who undervent bone marrow biopsy (BMB).

METHODS: 53 patients who suspected BMM from solid tumors and underwent both 18FDG-PET/CT scans and BMB were evaluated retrospectively. We also looked at the predictive value of the maximum standardized uptake value (SUVmax) to detection of metastases from solid tumors.

RESULTS: Among 53 patients, BMM was detected in 36 patients via 18FDG-PET/CT and 33 patients via BMB. In 9/53 cases (16,9%) both techniques showed no BMM. In 25/53 cases (47.2%) both techniques unclosed BMM. Among these 36 18FDG-PET/CT (+) patients, 25 patients had BMM accoding to the BMB (false positive, 11/36 patients, 30,5%). Among 17/53 18FDG-PET/CT (-) patients, 8 patients had BMM according to the BMB (false negative, 8/17 patients, 47.5%). SUVmax in patients with BMM was significantly higher than in patients without BMM according to the BMB [7.1 (2.5-22.2) vs 3.3 (2.2 – 16.0, p = 0.79), p=0.024].

DISCUSSION AND CONCLUSION: These preliminary results suggest that 18FDG-PET/CT could not be superior to BMB for bone marrow assessment. However, SUVmax value should be considered for the assessment of BMM.

Keywords: bone marrow infiltration, solid tumour, 18FDG-PET/CT

Inroduction

Bone marrow (BM) is a frequent site of metastatic cancers, in particular from the lypmphoma and solid tumors such as lung and breast cancers (1). The early detection of bone marrow metastases (BMM) is very important for staging patients according to the poor prognostic factors and choosing therapy. (2,3). BM infiltration is found much more frequently (approximately 50–85%) at autopsy and this means that we are unable to recognize with the routine staging procedures (4).

Detection of BMM is difficult and many imaging modalities have been developed

Adress for correspondence: Department of Medical Oncology, Erciyes University, Faculty of Medicine, Kayseri - Turkey
e-mail: **neda986@gmail.com**
Available at www.actaoncologicaturcica.com

for the assessment of BM. Bone marrow biopsy (BMB) is considered as the "gold standard" method for the assessment of BMM in different cancers (5). Positron emission tomography/computed tomography using ^{18}F-Fluorodeoxyglucose (^{18}FDG-PET/CT), which is allowing a complete evaluation of the entire skeleton at relatively low cost has been shown to be a useful modality for staging malignant tumors, evaluating metastasis and efficacy of treatment (6,7). ^{18}FDG-PET/CT is increasingly used for the detection of metastases and diagnosis of primary bone tumours (8-10). Magnetic resonance imaging (MRI) of bone marrow also one of the current approach for the assesment of BMM (10).

There has been no previous study by now comparing ^{18}FDG-PET/CT to BMB with respect to bone marrow infiltration caused by solid tumours. In the present study we aimed to evaluate the ability of ^{18}FDG-PET/CT in detecting BMM in patients with solid tumors. We also looked at the predictive value of the maximum standardized uptake value (SUVmax) to detection of metastases from solid tumors.

Methods

Patient population

From March 2011 to December 2012, 53 consecutive patients (26 women, mean age: 55) with various solid tumours underwent BMB for evaluate BMM were included in the study. ^{18}FDG-PET/CT was avaible in all these patients. Inclusion criterion was a timeframe of less than 1 month between ^{18}FDG-PET/CT and BMB (mean 8.3 days, range 0–31 days, median 10.1 days). The solid tumours consisted of the following: breast carcinoma n = 17, lung carcinoma n = 14 (small cell 7, non-small cell 7), testis carcinoma n = 1, blader carcinoma n = 1, prostate carcinoma n = 3, nasopharynx carcinoma n = 1, gastric carcinoma n = 3, renal cell carcinoma n = 2, malignant melanoma n = 1, leiomyosarcoma n = 2. colon cancer n = 1, hepatocellular carcinoma n = 1, unknown (NET, AMPULLA) 6. Patients were devided four groups according to the BMB and ^{18}FDG-PET/CT results: Group 1 was consisted of BM positive and ^{18}FDG-PET/CT positive patients (n:25), Group 2 was consisted of BM positive and ^{18}FDG-PET/CT negative patients (false negative group, n=8), Group 3 was consisted of BM negative and ^{18}FDG-PET/CT positive patients (false positive group, n=11) and Group 4 was consisted of BM negative and ^{18}FDG-PET/CT negative patients (n=9).

PET scan:

^{18}FDG-PET/CT was carried out using a hybrid PET-CT imager (Biograph LSO, Siemens Medical Solutions, Erlangen, Germany) after injection of ^{18}FDG. The delay between FDG injection and PET images acquisition (3D mode) ranged from 46 to 184min (median 78min). CT images were recorded for attenuation correction and image fusion using a low-dose CT protocol. PET Images reconstruction was performed using a FORE rebinning and attenuation weighted OSEM algorithm. Fused images were visually interpreted together with standardized uptake value (SUV) recording for each abnormal uptake focus. At visual analysis, an increased, non physiological FDG-uptake, was recorded as positive. The absence of uptake was defined as a negative finding. The maximum standardized uptake value (SUVmax) was determined in regions of interest (ROI) drawn on the attenuation- corrected PET/CT images around suspected lesion sites. SUV calculation for the 3D PET data was performed automatically through the following formula:

SUV (g/cc)= K(Bq/cc) x [b.w(kg)/A_{inj}(Bq)] x 1000g/kg where K is the calibrated pixel-value (in Bq/cc), b.w. is the body weight of the patient and Ainj is the injected activity in Bq corrected for the decay at the time of acquisition.

Statistical analysis

Statistical analysis was performed using SPSS v.16.0 for Windows (SPSS Inc., Chicago, IL). The distribution of the variables was analyzed with The Kolmogorov-Smirnov test for comparing the categorical variables, Chi-square test was used. Student t-test and Mann-Whitney U tests were used to compare parametric and non-parametric variables. Data are expressed as mean ± SD for parametric variables and median (minimum-maximum) for non-parametric variables. $p<0.05$ was accepted as statistically significant.

Receiver operating characteristic (ROC) curve analysis was performed in order to determine the best cut-off value of SUVmax and the sensitivity and specificity at that point were obtained for predicting BMM.

Adress for correspondence: Department of Medical Oncology, Erciyes University, Faculty of Medicine, Kayseri - Turkey
e-mail: **neda986@gmail.com**
Available at www.actaoncologicaturcica.com

Results

From March 20011 to December 2012, 53 consecutive patients with various solid tumours underwent BMB for evaluate BMM were included in the study. ^{18}FDG-PET/CT was avaible in all these patients. Main characteristics of patents were presented in Table 1. Median age was 55 years (range: 27–86 years). ^{18}FDG-PET/CT detected BM lesions in the 36/53 patients and BMB detected BM lesions in the 33/53 patients. In 9/53 cases (16,9%) both imaging techniques showed concordantly no bone marrow infiltration. In 25/53 cases (47.2%) both BMB and ^{18}FDG-PET/CT unclosed BMM. Among 36 ^{18}FDG-PET/CT (+) patients, 25 patients had BMM accoding to the BMB (false positive, 11/36 patients, 30,5%). Among 17/53 ^{18}FDG-PET/CT (-) patients, 8 patients had BMM according to the BMB (false negative, 8/17 patients, 47.5%). Sensitivity and specificity of ^{18}FDG-PET/CT was 75% and 45% respectively.

In our study, SUVmax values were available in 36 patients in the study and the SUVmax in patients with BMM was significantly higher than in patients without BMM according to the BMB [7.1 (2.5-22.2) vs 3.3 (2.2 – 16.0, p = 0.79), p=0.024].

ROC curve analysis showed that SUVmax at a cut-off point of 3.95 mg/L was highly sensitive (83%) and specific (67%) for predicting BMM from solid tumors (AUC = 0.731, p =0.026). Patients were devided two groups according to the best cut-off value of SUVmax for predicting BMM and high BMM rate was seen according to the BMB in high SUVmax group (SUVmax > 3,95, Table 2).

Discussion

The early detection of BMM can significantly change the staging and treatment strategy of the malignant disease. (11,12). As compared to standard morphological methods, molecular imaging techniques applied to BM lesion investigation had high diagnostic accuracy especially in haemato lymphoid disorders (7,13) ^{18}FDG-PET/CT images are able to show diffuse BM involvement as intense activity throughout the skeletal system (14). However, up to now, only a few studies exist which directly evaluate the sensitivity and specificity of ^{18}FDG-PET/CT with respect to BMM due to lymphoma and infiltration from solid tumours. Also a few studies compared the effectiveness of BMB, ^{18}FDG-PET/CT and MRI with respect to BM infiltration (2, 15,16). A few studies investigating the sensitivity and specificity of the ^{18}FDG-PET/CT for detection of BM involvement in patients with lymphoma and solid tumors are available. Recently, investigators reported that ^{18}FDG-PET/CT is highly specific for detection of BM involvement in patients with lymphoma (true negative rate 91 to 100% and a positive predictive value of 100%) (17,18). Daldrup-Link et al. observed the 90% sensitivity in detecting BMM in cancer patients (15).

A few studies compare the effectiviness of MR, ^{18}FDG-PET/CT and skeletal scintigraphy with respect to BMM in patients with lyphoma and solid tumors. Ghanem et al. reported that MRIs greater sensitivity (78%), specificity (88%), and diagnostic accuracy (82%) than ^{18}FDG-PET/CT in detecting BMM and infiltration in cancer patients (19). When comparing ^{18}FDG-PET/CT with bone scintigraphy, initial data suggest that ^{18}FDG-PET/CT is more sensitive than conventional bone imaging [15,20]. Daldrup-Link et al. observed the following degrees of sensitivity: 90% ^{18}FDG-PET/CT, 82% MRI and in 71% skeletal scintigraphy in detecting bone marrow infiltration in cancer patients (15).

The significance and the best diagnostic method of bone marrow infiltration in solid tumors remains controversial. In the present study, we observed 33/53 bone marrow involvement by BMB with solid tumors. All patients were assesed with ^{18}FDG-PET/CT and the sensivity and specifity of ^{18}FDG-PET/CT was 75% and 45% respectively. Thus, PET scan seems to have a low sensitivity and specifity for the detection of bone marrow infiltration in patients with solid tumors.

According to our results, SUVmax values which obtained from ^{18}FDG-PET/CT can also be used for predicting BMM from solid tumors. We reported that SUVmax value in patients with BMM was significantly higher than in patients without BMM according to the BMB [7.1 (2.5-22.2) vs 3.3 (2.2 – 16.0, p = 0.79), p=0.024]. Thus, SUV max value may be used for detection of BM involvement in patients with lymphoma and solid tumors.

Our study did not confirm the results of previous studies that investigate the effectiveness of PET scan in lymphomas and solid tumors. In these studies, sensitivity and

Adress for correspondence: Department of Medical Oncology, Erciyes University, Faculty of Medicine, Kayseri - Turkey
e-mail: **neda986@gmail.com**
Available at www.actaoncologicaturcica.com

specificity of PET scan are higher then our study. Our study population were very heterogeneous in terms of types of cancer and this might create a certain bias in our direct comparison. Further prospective studies with a selected patient group are necessary. According to our results, SUVmax values were predicted BMM with a very high sensitivity and specificity and so, we can use SUVmax values for prediction of BMM from solid tumors.

Conclusion

These preliminary results suggest that ^{18}FDG-PET/CT could not be superior to BMB for bone marrow assessment. However, SUVmax value should be considered for the assessment of BMM.

Disclosure of interest

The authors declare that they have no conflict of interest concerning this article.

Table 1: Characteristics and labarotory parameters of patient population

	BMM (+)	BMM (-)	p	PET/CT(-)	PET/CT(+)	p
Age (years)	58 ± 13	50 ± 8	0.03	60 ± 11	53 ± 12	0.1
Gender (Male)	19 (57%)	8 (42%)	0.3	9 (56%)	18 (50%)	0.7
Smoking (n, %)	8 (24%)	3 (15%)	0.4	3 (18.8)	8 (22%)	0.7
HT (n, %)	5 (15%)	3 (15%)	0.9	2 (12%)	6 (16%)	0.7
SUVmax	7.1(2.5-22.2)	3.3 (2.2-16)	0.02	-	6.6(2.2-22.2)	
WBC	5.1(1.3-16.4)	5.3(1.4-16.6)	0.8	6.3(1.3-9.9)	5.2(1.4-16.6)	0.4
Hemoglobin	10.2 ± 2.4	10.7 ± 2.0	0.3	10.2 ± 2.1	10.5 ± 2.3	0.8
Neutrophil	3.6(0.5-13.2)	3.4 (0.5-9.2)	0.5	3.8(0.5-7.9)	3.5(0.7-13.2)	0.3
Lymphocit	0.6(0.04-2.94)	0.7(0.05-2.9)	0.8	0.6(0.05-2.9)	0.6 (0.04-2.9)	0.8
LDH	557(143-3065)	290 (122-2239)	0.05	434 (139-2239)	557 (122-3065)	0.4
Total protein	6.5 ± 0.8	6.5 ± 0.8	0.2	6.2 ± 0.9	6.2 ± 0.9	0.8
Albumin	3.0 ± 0.8	3.1 ± 0.8	0.8	2.8 ± 0.8	3.1 ± 0.8	0.5

BMM: bone marrow metastasis, PET/CT: positron emission tomography/computed tomography, HT: mhypertension, SUVmax: the maximum standardized uptake value, LDH: lactate dehydrogenase

Adress for correspondence: Department of Medical Oncology, Erciyes University, Faculty of Medicine, Kayseri - Turkey
e-mail: **neda986@gmail.com**
Available at www.actaoncologicaturcica.com

Table 2: Association between high/low groups of SUVmax and BMM

	Low SUVmax Group (n, %)	High SUVmax Group (n, %)	p
BMM (-)	8 (66.7%)	4 (33.3%)	0.005
BMM (+)	4 (16.7%)	20 (83.3%)	

SUVmax: The maximum standardized uptake value, BMM: bone marrow

References

1. Shpall EJ, Gee AP, Hogan C, et al. Bone marrow metastases. Hematol Oncol Clin North Am 1996;10:321–343.
2. Altehoefer C, Ghanem N, Ho¨gerle S, Moser E, Langer M. Comparative detectability of bone metastases and impact on therapy of magnetic resonance imaging and bone marrow scintigraphy in patients with breast cancer. Eur J Radiol 2001;40:16–23
3. Baur A, Stäbler A, Nagel D, et al. Magnetic resonance imaging as a supplement for clinical staging system of Durie and Salmon? Cancer 2002;95:1334–1345
4. Abrams HL, Spiro R, Goldstein N. Metastases in carcinoma: analysis of 1000 autopsied cases. Cancer 1950;3:336–340
5. Cheng G, Chen W, Chamroonrat W, Torigian DA, Zhwang H, Alavi A. Biopsy versus FDG-PET/CT in initial evaluation of bone marrow involvement in pediatric lymphoma patients. Eur J Nucl Med Mol Imaging 2011;38:1469–76
6. Brink I, Schumacher T, Mix M, et al. FDG-PET on the primary staging of small-cell lung cancer. Eur J Nucl Med Mol Imaging 2004;31:1614–1620
7. Wahl RL, Zasadny K, Helvie M, Hutchins GD, Weber B, Cody R. Metabolic monitoring of breast cancer chemohormonotherapy using positron emission tomography: initial evaluation. J Clin Oncol 1993;11:2101–2111
8. Franzius C, Daldrup-Link HE, Wagner-Bohn A, et al. FDG-PET for detection of recurrences from malignant primary bone tumors and comparison with conventional imaging. Ann Oncol 2002;13:157–160
9. Franzius C, Sciuk J, Daldrup-Link HE, Jurgens H, Schober O. FDG-PET for detection of osseous metastases from malignant primary bone tumours: comparison with bone scintigraphy. Eur J Nucl Med 2000;27:1305–1311
10. Ribrag V, Vanel D, Leboulleux S, et al. Prospective study of bone marrow infiltration in aggressive lymphoma by three independent methods: whole-body MRI, PET/CT and bone marrow biopsy. Eur J Radiol. 2008 May;66(2):325-31. Epub 2007 Jul 24.
11. Evangelista L, Baretta Z, Vinante L, et al. Tumour markers and FDG PET/CT for prediction of disease relapse in patients with breast cancer. Eur J Nucl Med Mol Imaging. 2011 Feb;38(2):293-301. doi: 10.1007/s00259-010-1626-7. Epub 2010 Sep 30.
12. Bredella MA, Steinbach L, Caputo G, Segall G, Hawkins R. Value of FDG-PET in the assessment of patient with multiple myeloma. Am J Radiol 2005;184: 1199–204.
13. Wahl RL, Quint LE, Greenough RL, Meyer CR, White RI, Orringer MB. Staging of mediastinal non-small cell lung cancer with FDG PET, CT, and fusion images: preliminary prospective evaluation. Radiology. 1994;191:371–377.
14. Chiang SB, Rebenstock A, Guan L, Alavi A, Zhuang H. Diffuse bone marrow involvement of Hodgkin lymphoma mimics hematopoietic cytokine-mediated FDG-uptake on FDG-PET imaging. Clin Nucl Med 2003;28:674–6.
15. Daldrup-Link HE, Franzius C, Link TM, et al. Whole-body MR imaging for detection of bone metastases in children and young adults: comparison with skeletal scintigraphy and FDG-PET. AJR Am J Roentgenol 2001;177:229–236
16. Franzius C, Daldrup-Link HE, Wagner-Bohn A, et al. FDG-PET for detection of recurrences from malignant primary bone tumors and comparison with conventional imaging. Ann Oncol 2002;13:157–160
17. Muslimani AA, Farag HL, Francis S, et al. The utility of 18-F-fluorodeoxyglucose positron emission tomography in evaluation of bone marrow involvement by non-Hodgkin lymphoma. Am J Clin Oncol 2008;31:409–412.
18. Pelosi E, Penna D, Deandreis D, et al. FDG-PET in the detection of bone marrow disease in Hodgkin's disease and aggressive non-Hodgkin's lymphoma and its impact on clinical management. Q J Nucl Med Mol Imaging 2008;52:9–16.
19. Ghanem NA, Pache G, Lohrmann C, et al. MRI and (18)FDG-PET in the assessment of bone marrow infiltration of the spine in cancer patients. Eur Spine J. 2007 Nov;16(11):1907-12. Epub 2007 Apr 3.
20. Ghanem N, Altehoefer C, Ho¨gerle S, et al. Comparative diagnostic value and therapeutic relevance of magnetic resonance imaging and bone marrow scintigraphy in patients with metastastic solid tumors of the axial skeleton. Eur J Radiol 2002;43:256–261

Adress for correspondence: Department of Medical Oncology, Erciyes University, Faculty of Medicine, Kayseri - Turkey
e-mail: **neda986@gmail.com**
Available at www.actaoncologicaturcica.com