

Original

Relationship between Fluorine-18 Fluorodeoxyglucose PET/CT Uptake and the Plasma Cell Infiltration Rate in the Bone Marrow of Multiple Myeloma Patients

Tsengel Ganbold¹⁾, Yoshihiro Nakagami^{1,2)}, Kensuke Inamura¹⁾, Yosuke Misu¹⁾, Mariko Kumazawa¹⁾, Hiroaki Arakawa¹⁾, Motoshi Ichikawa³⁾, Kinuko Mitani³⁾, Kazuyuki Ishida⁴⁾, Daisuke Kano⁵⁾, Shota Hosokawa⁶⁾, Yasushi Kaji¹⁾

1) Department of Radiology, School of Medicine, Dokkyo Medical University

2) PET Center, Dokkyo Medical University Hospital

3) Department of Hematology and Oncology, School of Medicine, Dokkyo Medical University

4) Department of Diagnostic Pathology, School of Medicine, Dokkyo Medical University

5) Department of Pharmacy, National Cancer Center Hospital East

6) Department of Radiation Science, Graduate School of Health Sciences, Hirosaki University

Summary

Background: The current study investigated the relationship between maximum standardized uptake values (SUV_{max}) on Fluorine-18 Fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) and the plasma cell proliferation percentage in the bone marrow as well as hematological and biochemical test results of patients with multiple myeloma (MM). Moreover, we identified if differences exist in parameters across different types of paraproteins and stages.

Material and methods: Patients clinically and pathologically diagnosed with MM between 2012 and 2019 were selected from the database of the Dokkyo Medical University Hospital, Japan. Unsuitable patients were excluded from the current study to avoid false uptake. We examined 60 patients and hematological and biochemical tests were recorded and evaluated. The percentage of plasma cells in bone marrow aspiration samples was calculated. In PET/CT images, the SUV_{max} of the region of interest of the right posterior ilium (aspiration area) was measured. Relationships were examined using Spearman's correlation coefficient, and differences were identified using the Kruskal-Wallis test with SPSS.

Results: A positive correlation was observed between FDG uptake and the percentage of plasma cells ($r = 0.672$, $P < 0.0001$).

Conclusion: Increased FDG uptake by bone marrow correlated with the percentage of plasma cells. Some biochemical and hematological parameters were statistically different according to the stage and types of paraproteins. PET/CT is suitable for evaluating the condition of a patient and the activity of the MM lesion.

Key Words: FDG uptake, Multiple Myeloma, PET/CT, Plasma Cell

Introduction

Multiple myeloma (MM) is the second most common blood cancer worldwide, accounting for 1% of all cancers. It is characterized as a malignant hematological disorder with the uncontrollable monoclonal proliferation of malignant plasma cells^{1,2)}. According to Global

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Reprint requests to: Yoshihiro Nakagami

ynakagam@dokkyomed.ac.jp

PET Center, Dokkyo Medical University Hospital, 880 Kitakobayashi, Mibu, Shimotsuga, Tochigi 321-0293, Japan

cancer statistics 2018, MM represented 0.9% of new malignancies and 1.1% of the causes of cancer-related deaths³.

Positron emission tomography/computed tomography (PET/CT) with the radiopharmaceutical Fluorine-18 Fluorodeoxyglucose (FDG) accumulates in more metabolically active tissues and provides morphological and functional information regarding the human body^{4,9}. It is very useful for detecting bone damage; more than 80-90% of MM patients have bone lesions^{10,11}, which is a myeloma-defining event. PET/CT also has the capacity to identify skeletal and extramedullary lesions with a sensitivity of approximately 80-90% and specificity of 70-100%¹²⁻¹⁶.

The International Myeloma Working Group (IMWG) consensus recommends the mandatory use of FDG PET/CT to confirm a suspected diagnosis of MM, smoldering MM, and solitary plasmacytoma and to provide useful prognostic information^{17,18}. The European Society of Medical Oncology and European Myeloma Network guidelines also recommends low-dose, whole-body CT and FDG PET/CT based on their availability^{5,8}.

The diagnosis and classification of MM previously required the presence of end-organ damage, known as the CRAB criteria, which pertains to an elevated calcium level, renal dysfunction, anemia, and destructive bone lesions¹⁹.

The Durie-Salmon Staging System (DSSS) shows the relationship between the extent of myeloma and associated damage, and the revised system in 2006 integrated new imaging techniques, such as FDG PET/CT and magnetic resonance imaging²⁰. The International Staging System (ISS) is based on serum beta2-microglobulin (b2m) and serum albumin (Alb) levels. The 2015 revised system includes the chromosomal abnormality t(14;16), t(4, 14), del17p and serum lactate dehydrogenase (LDH) levels²¹.

The 5-year survival rate of MM in the US was 54%; approximately 75% among those diagnosed in the early stages and 51% among those diagnosed at the late advanced stage of the disease. The survival rate of MM has been steadily increasing in the last few decades due to advances in treatment and management²².

Moreover, in MM patients, the amount of paraprotein levels usually provides many prognostic informa-

tion²³⁻²⁵. Paraprotein is a monoclonal immunoglobulin or a light chain present in the blood or urine. It is produced by a clonal population of mature B cells, most commonly called plasma cells.

The percentage of plasma cells in the bone marrow is an important index of the disease activity. According to some reports, increased plasma-cell infiltration causes a higher FDG uptake in bone marrow. However, the FDG accumulation to MM lesion clinically is often uncertain.

In this study, we investigated the relationship between FDG uptake with plasma-cell percentage and other hematological and biochemical test results based on our data.

Materials and methods

This retrospective study was approved by the Ethics Committee of Dokkyo Medical University. This study examined the data obtained between January 2012 and October 2019. First, we selected 245 patients who had the keyword MM on their report data. We then selected 101 pathologically confirmed cases. Some patients underwent PET/CT scan several times; hence, we excluded repeated cases and chose the cases where PET/CT and aspiration dates were within 1 month. We excluded patients with other malignancies and those who had received chemotherapy and hematopoietic treatments in the past 4 weeks or radiation therapy 2-3 months prior to PET/CT scans. Finally, all patients with MM proven by bone marrow aspiration biopsy were retrospectively evaluated. The patient group included either first diagnosed or recurrent cases; thus, it was a mixed group. We examined 60 patients (females: males, 27:33) aged 67.3 ± 10.2 (mean \pm standard deviation) years between 37 and 91. Since this was a retrospective study, hematological and biochemical test results such as hemoglobin (Hb), hematocrit (Ht), C-reactive protein (CRP), b2m, creatinine (Cre), Alb, LDH, calcium (Ca), white blood cells (WBC), red blood cells (RBC), paraprotein levels of M-protein, and free light chain were obtained at the nearest timing within 2 weeks before or after the PET/CT scan date. However, some results had longer time gaps (42 patients' data were within 2 weeks, 16 were within 4 weeks, and the remaining 2 were within 6 weeks). Table 1 shows the demographic and clinical properties of

patients.

18F-FDG PET/CT imaging

Prior to PET/CT, all patients fasted overnight (for at least 6 hours) and were intravenously administered FDG based on their body mass (4 MBq/kg). Blood glucose levels, which should be equal to or less than 200 mg/dL, were measured before the FDG injection.

Patients rested in a warm room during the FDG uptake time of 1 hour. Whole-body imaging was performed using PET/CT scanners (Biograph mCT Flow and Biograph mCT Horizon, Siemens Healthcare, Tokyo, Japan). The PET acquisition time was 2.2 min per field of view. CT scan data were obtained with a peak

voltage of 120 kV and tube current of 70 mAs.

To evaluate the maximum standardized uptake values (SUV_{max}) of bone marrow, the region of interest (ROI) was placed in the right posterior ilium at the level of the sacroiliac joint and the first anterior sacral foramen, which is an aspiration area. The right posterior ilium was selected to standardize the calculation of FDG uptake by bone marrow^{12,26,27}. The ROI was manually drawn around the aspiration area and was calculated using the semiautomatic image registration software package (Syngo.Via, Siemens Healthcare, Tokyo, Japan).

Bone marrow aspiration and plasma cell counting

The bone marrow was aspirated from the right iliac crest. All hematoxylin and eosin (H&E)-stained bone marrow specimens were examined under a light microscope (BX53 Olympus, Japan) and digital photos were taken using the imaging software (cellSens Standard, Olympus Corporation, Japan). Plasma cells were counted using the application, QuPath 0.2.2, (Centre for Cancer Research and Cell Biology, Queen's University Belfast, UK), which is the most widely used image analyses software program in the world²⁸. The infiltration rate of plasma cells represents the number relative to all nucleated hematopoietic cells in bone marrow. Fig. 1 and 2 show the plasma cell aspiration samples.

Table 1 Demographic and clinical properties of patients

N	60
Age (mean)* (years)	67.3 ± 10.2
Sex (females:males)	27:33
Types of paraprotein	
• IgGκ	• 31 patients (51.6%)
• IgGλ	• 19 patients (31.6%)
• IgAλ	• 5 patients (8.3%)
• IgAκ	• 2 patients (3.3%)
• IgDλ	• 2 patients (3.3%)
• IgDκ	• 1 patient (1.6%)
Durie-Salmon staging system	
• stage I	• 4 (6.6%)
• stage II	• 7 (11.7%)
• stage III	• 34 (56.7%)
• NA	• 15 (25.0%)

*Data are ± standard deviation

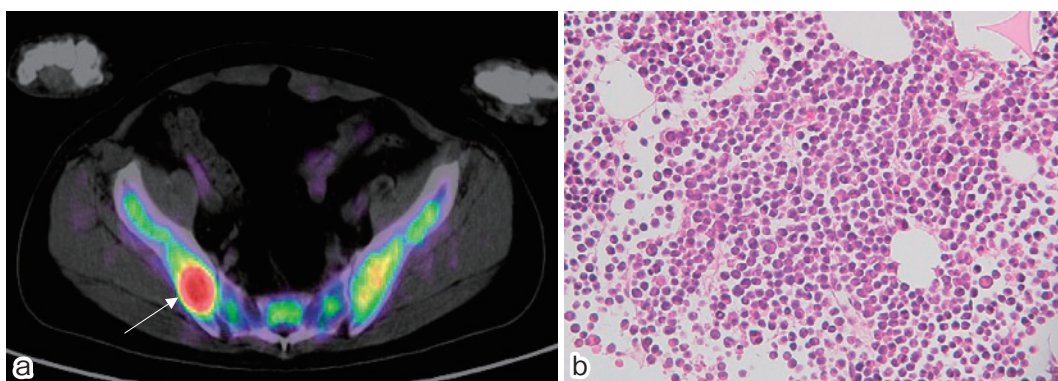


Figure 1 60 y/o male, Durie-Salmon Staging System (DSSS) III

a) Transaxial FDG PET/CT scan image demonstrates active myeloma lesion in the right posterior ilium level with SUV_{max} of 7.76 (white arrow)

b) Plasma cell aspiration sample. (H&E-stained, × 400)

Plasma-cell infiltration rate was 41.5%.

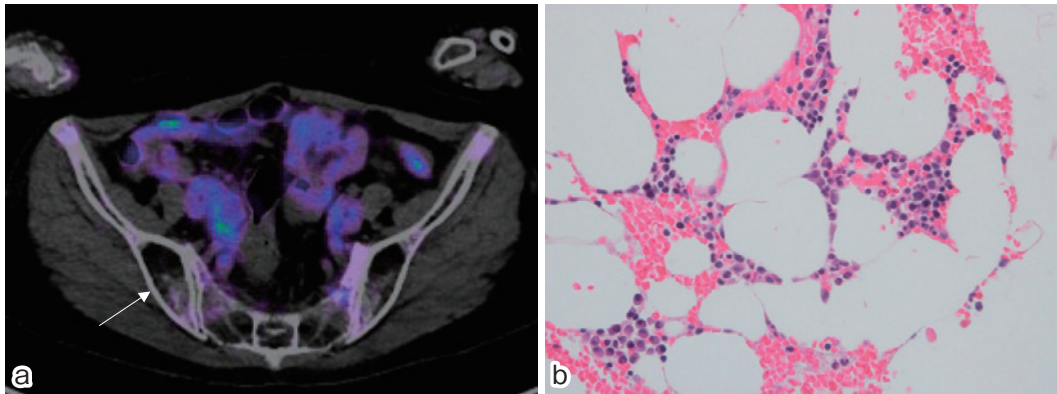


Figure 2 71 y/o female, Durie-Salmon Staging System (DSSS) N/A

- a)** Transaxial FDG PET/CT scan image shows right posterior ilium level with low FDG uptake, SUV_{max} of 1.34 (white arrow).
b) Plasma cell aspiration sample. (H&E-stained, $\times 400$)
 Plasma-cell infiltration rate was 11.5%.

Statistical analysis

Statistical analyses were performed using SPSS 27 (SPSS Inc, Chicago, Ill., USA)²⁹. The relationship between FDG uptake and the plasma-cell infiltration rate as well as other hematological and biochemical parameters was analyzed using Spearman's correlation coefficient. The differences in parameters according to the stage and types of paraprotein were calculated using the Kruskal-Wallis test. The results obtained were considered to be significant at a p-value less than 0.05 ($P < 0.05$).

Results

The average SUV_{max} of ROI of the right posterior ilium was between 1.34 and 7.76 (mean 2.74 ± 1.32), and the percentage of plasma cells in the bone marrow of the right posterior ilium was between 11.2 to 66.8 (mean 29.8 ± 11.1). The relationship between FDG uptake and plasma cell infiltration ($r = 0.672$, $P < 0.0001$) in bone marrow was positive (Table 2, Fig. 3). We calculated the relationship between PET/CT scans and the parameter results. A correlation was not observed between FDG uptake and b2m ($r = 0.198$, $P = 0.148$) (Table 2, Fig. 4).

Moreover, we evaluated the differences between hematological and biochemical parameters according to the types of paraprotein stages using Kruskal-Wallis test; the results showed statistically significant differences in the parameters of Cre ($P = 0.028$) and WBC ($P = 0.032$) with types of paraprotein; and Hb ($P = 0.011$),

Table 2 Relationship between Plasma-cell infiltration rate, hematological, biochemical parameters and FDG uptake ratio in MM patients

	mean**	r	p-value
PC infiltration rate (%)	29.8 ± 11.0	0.672	$< 0.0001^*$
Hb (g/dL)	9.7 ± 2.8	-0.165	0.208
Ht (%)	30.4 ± 7.1	-0.217	0.950
CRP (mg/dL)	0.5 ± 1.0	0.339	0.008*
Cre (mg/dL)	1.2 ± 0.88	0.103	0.436
Alb (g/dL)	3.4 ± 0.7	-0.029	0.828
Ca (mg/dL)	8.9 ± 0.9	0.187	0.157
WBC ($10^9/L$)	5.3 ± 2.2	-0.065	0.621
RBC ($10^{12}/L$)	3.1 ± 0.8	-0.213	0.102
LDH (U/L)	204.8 ± 76.9	0.009	0.946
b2 m (mg/L)	6.4 ± 6.8	0.198	0.148

*statistically significant

**Data are \pm standard deviation

PC plasma cell, Hb hemoglobin, Ht hematocrit, CRP C-reactive protein, Cre creatinine, Alb albumin, Ca calcium, WBC white blood cell, RBC red blood cell, LDH lactate dehydrogenase, b2 m beta2-microglobulin

Ht ($P = 0.023$), RBC ($P = 0.009$), and b2m ($P = 0.009$) with stage (Table 3). As the stages of 15 cases were not recorded in the data, we excluded them in the evaluation of differences according to stage; therefore, the results are based on 45 cases.

Discussion

The results of the current study revealed a correlation between FDG uptake by bone marrow on PET/CT and the plasma-cell infiltration rate in patients with

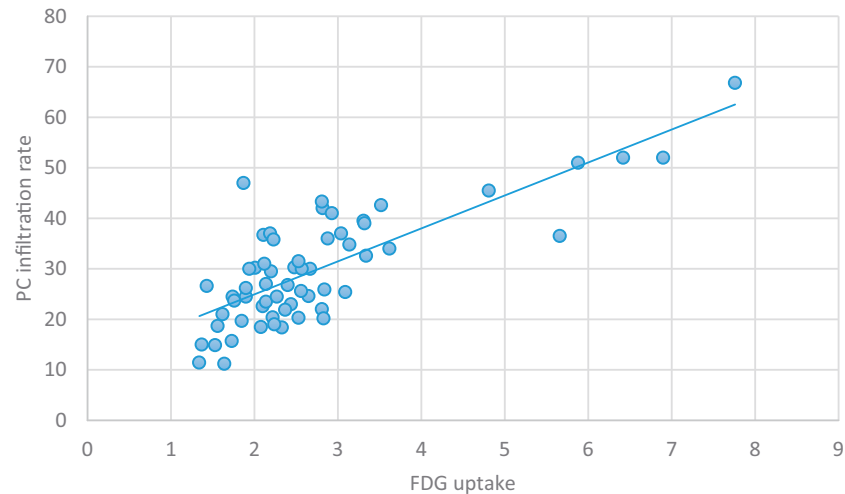


Figure 3 Relationship between FDG uptake and the Plasma-cell infiltration rate

Scatter plot of the relationship between FDG uptake and the Plasma-cell infiltration rate, derived from PET/CT scan and bone marrow aspiration sample ($r = 0.672$, $P < 0.0001$).

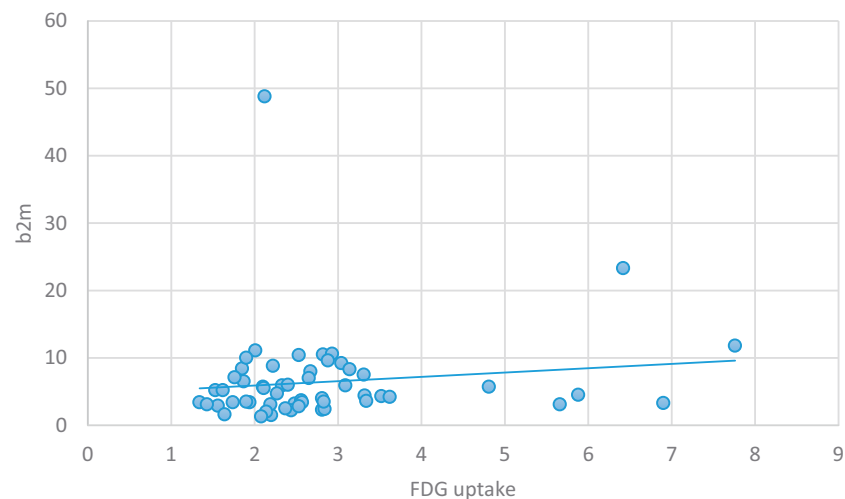


Figure 4 Relationship between FDG uptake and the b2 m

Scatter plot of the relationship between FDG uptake and the b2 m, derived from PET/CT scan and hematological test sample ($r = 0.198$, $P = 0.148$).

MM. The retrospective study by Ben et al. found that PET/CT scan results affected the planned management of two-thirds of patients with plasma cell disorders including MM⁷. In a study by Dimitrakopoulou-Strauss, PET/CT prior to and after the first course of chemotherapy appeared to be useful for identifying patients who will respond to treatment³⁰. Furthermore, studies have also shown that PET/CT scans are helpful in assessing responses to treatment³¹ and allow for better management of patients with MM³².

B2m is a low molecular weight protein found on the surface of all nucleated cells, and it acts as a serum

marker for tumor burden in lymphoid malignancies including MM. B2m is one the most useful prognostic factors in patients with MM, as well in pretreatment and asymptomatic patients^{33,34}.

Previous studies reported a correlation between FDG uptake by bone marrow and plasma cell infiltration^{12,15,26,27,35-38}, while others showed that FDG uptake correlated with b2m^{26,27} and CRP²⁷ and negatively correlated with Hb and Ht²⁷ as well as Alb²⁶. Significant prognostic laboratory parameters, such as b2m, CRP, and LDH, correlated with the number of focal FDG-avid lesions on PET/CT³⁹. In newly diagnosed MM pa-

Table 3 P values for the difference of FDG uptake, PC infiltration rate, hematological and biochemical parameters according to types of paraprotein and Durie-Salmon staging system by Kruskal-Wallis test

	Types of paraprotein	Stage**
FDG (SUV _{max})	0.141	0.353
PC infiltration rate (%)	0.796	0.170
Hb (g/dL)	0.256	0.011*
Ht (%)	0.259	0.023*
CRP (mg/dL)	0.123	0.610
Cre (mg/dL)	0.028*	0.297
Alb (g/dL)	0.102	0.372
Ca (mg/dL)	0.585	0.289
WBC (10 ⁹ /L)	0.032*	0.653
RBC (10 ¹² /L)	0.181	0.009*
LDH (U/L)	0.801	0.650
b2 m (mg/L)	0.131	0.009*

*statistically significant

** patients whose stage were NA are excluded.

FDG fluorodeoxyglucose uptake (SUV_{max}), PC plasma cell, Hb hemoglobin, Ht hematocrit, CRP C-reactive protein, Cre creatinine, Alb albumin, Ca calcium, WBC white blood cell, RBC red blood cell, LDH lactate dehydrogenase, b2 m beta2-microglobulin

tients, the presence of at least 3 focal lesions and SUV_{max} > 4.2 or extramedullary disease predicted poor progression-free survival⁴⁰. PET/CT may be used to predict the outcomes of patients with new, relapsed, or refractory MM^{37,39-44}.

Some limitations of the current study should be noted. First, current study is a retrospective study; hence, we lacked data and therefore were not able to assess some of the information, for example ISS/R-ISS. Moreover, the date gaps between PET/CT scan and aspiration, and the blood test results were different.

In the current study, a positive correlation was observed between PET/CT FDG uptake and the plasma-cell infiltration rate ($r = 0.672$, $P < 0.0001$), CRP ($r = 0.339$, $P = 0.008$). However, no correlation was observed between FDG uptake and b2m ($r = 0.198$, $P = 0.148$). At this point, the results of current study are different from past reports. B2m is one of the most useful prognostic and staging factors in patients with MM. It reflects the whole aspect of the patients with MM. However, it cannot necessarily reflect the state of the local lesion, which also applies to other laboratory param-

eters. And the correlation coefficient between FDG uptake and the plasma-cell infiltration rate is significant compared to some papers, because our population size was larger^{15,26,27}. Based on the results of our study, we can see that the plasma-cell infiltration rate correlates with FDG, CRP and b2m. Therefore, we can assume that the plasma-cell infiltration rate has the potential to reflect the bone/bone marrow involvement by FDG, body immunity condition by CRP, and prognostic value of MM by b2m, but this fact should be carefully considered.

On the contrary, FDG-PET/CT reflects the condition of a local lesion in an MM patient. The plasma-cell infiltration rate also comprises local data for pathological data. Therefore, both are similar.

Based on these findings, an increased FDG uptake on PET/CT scan indicates a higher percentage of plasma cells in bone marrow, therefore, in addition to the bone marrow aspiration, PET/CT is a potentially good predictive indicator in the follow-up period because SUV_{max} values in the bone marrow of MM patients with recurrence will be elevated. In brief, FDG-PET/CT is useful in accurately checking the local existence of MM lesions. Furthermore, FDG-PET/CT is useful in judging the curative effect of MM. On the contrary, b2m levels provide general prognostic information and are useful for staging.

The purposes are often different between FDG-PET/CT and laboratory parameters as stated above. Therefore, we may obtain clinically useful information by utilizing both methods.

Conclusion

An increased uptake of FDG on PET/CT correlated with the percentage of plasma cells in MM. Some biochemical and hematological parameters were statistically different according to the stage and types of paraproteins. Therefore, FDG PET/CT is suitable for evaluating the condition of a patient and the activity of the MM lesion.

Acknowledgments

Not applicable.

Disclosure Statement:**Ethics approval and consent to participate**

This retrospective study was approved by the Ethics Committee of Dokkyo Medical University, Tochigi, Japan.

Consent of publication

Not applicable.

Competing interest

The authors declare that they have no competing interests.

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Authors' contribution

TG, YN, YK develop the conception and design the study. TG drafted the manuscript. YN supervised the study. TG, KI, YM acquired data. TG, YN, YK, HA, MI, KM analyzed and interpreted the data. KI advised on the plasma cell counting. DK, SH advised on statistical analysis. All authors read and approved the final manuscript.

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