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Comparison of ^{99m}Tc-methyl diphosphonate bone scintigraphy and ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography to predict histologic response to neoadjuvant chemotherapy in patients with osteosarcoma

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Abstract

We compared the usefulness of ^{99m}Tc-methyl diphosphonate (^{99m}Tc-MDP) bone scintigraphy and ^{18}F-fluorodeoxyglucose (FDG) for positron emission tomography/computed tomography (PET/CT) in predicting histologic response in patients with osteosarcoma receiving neoadjuvant chemotherapy (NAC).

We retrospectively reviewed 62 patients with high-grade osteosarcoma who had received 2 cycles of NAC and surgery. All patients underwent ^{99m}Tc-MDP bone scintigraphy and ^{18}F-FDG PET/CT before and after NAC. ^{99m}Tc-MDP uptake in the primary tumor was measured quantitatively as the maximum tumor-to-nontumor ratio (T/NT$_{max}$) and ^{18}F-FDG uptake was measured as the maximum standardized uptake value (SUV$_{max}$), before and after NAC. The percent changes of T/NT$_{max}$ (percent changes of the maximum tumor-to-nontumor ratio [Δ%T/NT$_{max}$]) and SUV$_{max}$ (percent changes of the maximum standardized uptake value [Δ%SUV$_{max}$]) after NAC were calculated and the correlations between these parameters were evaluated. After surgery, the effects of NAC were graded histopathologically (good vs poor) and the optimum cut-off values of Δ%T/NT$_{max}$ and Δ%SUV$_{max}$ for predicting histologic response were assessed using the receiver operating characteristic (ROC) curve analysis.

Δ%T/NT$_{max}$ and Δ%SUV$_{max}$ were positively correlated with each other ($r = 0.494$, $P < .01$). Based on the ROC curve analysis, both Δ%T/NT$_{max}$ (area under the curve [AUC] = .772, $P < .01$) and Δ%SUV$_{max}$ (AUC = .829, $P < .01$) predicted good histologic response. However, there was no significant difference between the AUCs of Δ%T/NT$_{max}$ and Δ%SUV$_{max}$ ($P = .44$). The sensitivity and specificity for predicting good histologic response were 83.3% and 75.0%, for the criterion Δ%T/NT$_{max} < -12.5$%, and 80.0% and 81.3% for the criterion Δ%SUV$_{max} < -49.0$%, respectively.

The ^{99m}Tc-MDP bone scan and ^{18}F-FDG PET scan are non-inferior to each other in predicting the histologic response of osteosarcoma treatments. The ^{99m}Tc-MDP bone scan and ^{18}F-FDG PET scan showed respective advantages with differing features. Therefore, physicians should consider which scan is appropriate for their own institute based on the advantages of each scan and the circumstances of the institute.

Abbreviations: Δ%SUV$_{max}$ = percent changes of the maximum standardized uptake value, Δ%T/NT$_{max}$ = percent changes of the maximum tumor-to-nontumor ratio, ^{18}F-FDG = ^{18}F-fluorodeoxyglucose, ^{99m}Tc-MDP = ^{99m}Tc-methyl diphosphonate, NAC = neoadjuvant chemotherapy, PET/CT = positron emission tomography/computed tomography.

Keywords: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography, ^{99m}Tc-methyl diphosphonate bone scintigraphy, histologic response, neoadjuvant chemotherapy, osteosarcoma

1. Introduction

Osteosarcoma is not a common malignancy.[1] In the United States, <1% of patients who are newly diagnosed with cancer each year are diagnosed with osteosarcoma.[1] However, it is the most common malignant osseous tumor in children.[1] Before the 1980s, the survival rate of patients with osteosarcoma was about 20% in the United States.[1,2] Even when the primary tumor was controlled, about 80% of patients did not survive due to metastasis. Since then, the survival rate has dramatically improved through the use of chemotherapy.[3] Chemotherapy is therefore currently established as a standard part of osteosarcoma treatment.[4]

For the treatment of osteosarcoma, neoadjuvant chemotherapy (NAC), surgical resection of the primary tumor and adjuvant chemotherapy are included in the current strategy.[5] Furthermore, it has been reported that the histologic response to preoperative chemotherapy is one of the most important prognostic factors for predicting survival.[5,6] However, tumor necrosis, as an indicator of histologic response, is typically checked with the resected specimen after surgery. It is difficult to differentiate the histologic responder or non-responder with NAC prior to surgery. If information about histologic response could be obtained before resection, it would be helpful in making treatment decisions for patients in advance. Therefore, non-invasive imaging methods have been extensively studied for checking histologic response.[7–11] Among them, ^{99m}Tc-methyl diphosphonate (^{99m}Tc-MDP) bone scan and ^{18}F-fluorodeoxy-glucose (FDG) for positron emission tomography/computed tomography (PET/CT) have been used to evaluate the histologic response after treatment. However, to date, there has been no study that directly compared ^{99m}Tc-MDP bone scan and ^{18}F-FDG PET for predicting histologic response.

In this study, we compared directly the parameters of ^{99m}Tc-MDP bone scan and ^{18}F-FDG PET for predicting histologic response of NAC in the same cohort of the patients with osteosarcoma.

2. Methods

2.1. Patients

A total 62 patients with osteosarcoma were retrospectively reviewed between September 2006 and December 2012. All the patients were treated with NAC and complete resection of the primary tumor. Surgical resection was performed between 6 and 10 weeks after completion of the NAC. ^{99m}Tc-MDP bone scan and ^{18}F-FDG PET were performed before and after NAC. The initial scans were obtained within 2 weeks of NAC. The follow up scans after chemotherapy were obtained within 2 weeks prior to surgery. Magnetic resonance imaging (MRI) for evaluating the size of the primary tumor was performed within 2 weeks before NAC.

Our current study analyzed a total of 62 cases, including 21 of 26 cases that had been analyzed in our previous report[10] along with 41 new cases.

All patients underwent 2 cycles of NAC with high-dose methotrexate, adriamycin, and cisplatin according to the modified T10 protocol.[10,12] The protocol was described in detail in a previous report.[10] Surgical resection of the primary tumor was performed after completion of NAC. A surgical specimen was used for assessing histologic response according to the previous report.[10,13] A tumor with ≥90% necrosis was considered a good response.[13]

The study design was approved by the Review Board of our institution (IRB No.: K-1712-002-031), and written informed consents were exempted by the IRB. All procedures were performed in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

2.2. Image acquisition

2.2.1. ^{99m}Tc-MDP bone scan. A whole body bone scan (anterior and posterior images) was performed 3 hours after intravenous injection of 740 to 925 MBq of ^{99m}Tc-MDP using SymbiaT (Siemens Medical Solutions, Malvern, PA). A low energy, high resolution parallel collimator was used. The photopeak was centered at 140 keV and the matrix size was 256×1024.

2.2.2. ^{18}F-FDG PET/CT. The ^{18}F-FDG PET/CT scan was performed as described in the previous report.[10] Patients were intravenously injected with ^{18}F-FDG (8.14 MBq/kg) after fasting for a minimum of 6 hours and blood glucose level did not exceed 7.2 mmol/L. The PET images were acquired 1 hour after injection using a PET/CT scanner (Biograph6; Siemens Medical Solutions, Malvern, PA). The CT images were obtained for attenuation correction immediately before the acquisition of PET images (130 kVp, 30 mA, 0.6 s/CT rotation, and a pitch of 6). The images were reconstructed with the ordered subsets expectation maximization algorithm (iteration 2, subset 8).

2.2.3. MRI. MR images were obtained with a 3.0-T MRI scanner (MAGNETOM Trio A Tim; Siemens Medical Solutions, Erlangen, Germany). T1-weighted sequence images with or without gadolinium enhancement and T2-weighted sequence without fat suppression images were obtained from all patients. Gadodiamide (Omniscan; GE Healthcare) was injected intravenously. On coronal sections of nonenhanced T1-weighted images, tumor lengths were evaluated, and on axial sections of enhanced T1-weighted sequence without fat suppression, the widths and depths of the tumors were measured.[10]

2.3. Image analysis

For the bone scan, the maximum pixel counts of the primary tumor (anterior image, TA_{max}; posterior image, TP_{max}) were obtained by manually drawing the region of interest (ROI), including the lesion with increased uptake compared with adjacent normal bone. To obtain the reference values, the same sized ROI was manually drawn in the contra-lateral area. With this contra-lateral ROI, the maximum pixel counts of the nontumor area (anterior images, NTA_{max}; posterior images, NTP_{max}) were acquired. The geometric mean count (GMC) was calculated for tumor or nontumor regions using the following equation[14]:

$$GMC\_tumor = \sqrt{TA_{max} \times TP_{max}}, GMC\_non\,tumor = \sqrt{NTA_{max} \times NTP_{max}}$$

The tumor to nontumor ratio (T/NT_{max}) was calculated as GMC_tumor divided by GMC_non-tumor. T/NT_{max} before the chemotherapy was defined as $T/NT_{max}1$. T/NT_{max} after the chemotherapy was defined as $T/NT_{max}2$. The percentage change in T/NT_{max} ($\Delta\%T/NT_{max}$) between $T/NT_{max}1$ and $T/NT_{max}2$ was calculated using the following formula: $\Delta\%T/NT_{max} = (T/NT_{max}2 - T/NT_{max}1)/T/NT_{max}1 \times 100$.

For the ^{18}F-FDG PET scan, the maximum SUV value (SUV_{max}) of the primary tumor was acquired by manually drawing the

volume of interest (VOI). The pre-chemotherapy SUV_{max} was defined as $SUV_{max}1$ and the post-chemotherapy SUV_{max} was defined as $SUV_{max}2$. The percentage change in SUV_{max} ($\Delta\%SUV_{max}$) between $SUV_{max}1$ and $SUV_{max}2$ was calculated using the following formula: $\Delta\%SUV_{max} = (SUV_{max}2 - SUV_{max}1)/SUV_{max}1 \times 100$.

Tumor volume was defined at the initial MRI prior to the NAC as following the ellipsoid formula: $0.53 \times$ tumor length $\times$ tumor width $\times$ tumor depth.[10]

2.4. Statistics

To predict histologic response, the receiver operating characteristic (ROC) curve analyses were performed using the parameters from the ^{99m}Tc-MDP bone scan and ^{18}F-FDG PET scan. The areas under the curve (AUCs) for each parameter were calculated and the optimal cut-off values of each parameter for prediction of the histologic response were obtained based on the Youden index. Spearman rank correlation analysis was performed to compare the parameters between the ^{99m}Tc-MDP bone scan and ^{18}F-FDG PET scan. To evaluate the influence of the clinical features on the histologic response, logistic regression analyses were performed. P values $<.05$ were regarded as statistically significant. Statistical analyses were performed using commercial software (Medcalc version 16.4.3, Medcalc software, Ostend, Belgium).

3. Results

3.1. Patient characteristics

Detailed clinical features are described in Table 1. After completion of NAC and surgical resection, good histologic response occurred in 30 patients. The other 32 patients showed poor histologic response.

3.2. ROC curve analysis

In the ROC curve analysis of histologic response using ^{18}F-FDG PET parameters, the AUC for $\Delta\%SUV_{max}$ had the largest value (0.829) compared with other parameters (Fig. 1A). The ROC curve of $\Delta\%SUV_{max}$ was significantly different from that of $SUV_{max}1$ ($P<.01$), whereas the ROC curve of $\Delta\%SUV_{max}$ was not dissimilar from that of $SUV_{max}2$ ($P=.80$). In the ROC curve analysis using ^{99m}Tc-MDP bone scan, $\Delta\%T/NT_{max}$ showed the largest value of the AUC (0.772) (Fig. 1B). The ROC curve of $\Delta\%T/NT_{max}$ was not significantly different from the curves of $T/NT_{max}1$ and $T/NT_{max}2$ ($P=.12$ and $P=.97$, respectively). Based on the ROC curve analysis, $\Delta\%SUV_{max}$ and $\Delta\%T/NT_{max}$ were selected as representative parameters of ^{18}F-FDG PET and ^{99m}Tc-MDP bone scan for further analysis.

The optimal cut-off values of $\Delta\%SUV_{max}$ and $\Delta\%T/NT_{max}$ for histologic response after NAC were calculated as -49.0% and -12.5%, respectively. Table 2 shows the sensitivity and specificity for predicting histologic response using the optimal cut-off values of $\Delta\%SUV_{max}$ and $\Delta\%T/NT_{max}$. Both parameters could predict histologic response with high sensitivity and specificity. In addition, the ROC curves using these parameters did not show a statistically significant difference ($P=.44$) (Fig. 1C).

3.3. Correlation of parameters between ^{99m}Tc-MDP bone scan and ^{18}F-FDG PET

A moderate positive linear correlation between $\Delta\%SUV_{max}$ and $\Delta\%T/NT_{max}$ was observed in the scatter plot ($P<.01$, rho $=.494$)

Table 1	
Patient characteristics.	
Characteristics	**No. of patients (%), $n=62$**
Age, y	
≤ 15	40 (64.5%)
>15 to ≤ 40	21 (33.9%)
>40	1 (1.6%)
Sex	
Male	46 (74.2%)
Female	16 (25.8%)
AJCC stage	
IIA	23 (37.1%)
IIB	35 (56.5%)
III	2 (3.2%)
IV	2 (3.2%)
Tumor volume, cm^3	
≤ 150	44 (71.0%)
>150	18 (29.0%)
Location	
Distal tibia	3 (4.8%)
Proximal tibia	21 (33.9%)
Distal femur	28 (45.2%)
Proximal femur	1 (1.6%)
Distal humerus	1 (1.6%)
Proximal humerus	2 (3.2%)
Proximal fibula	2 (3.2%)
Distal radius	3 (4.8%)
Proximal radius	1 (1.6%)
Pathologic subtype	
Osteoblastic	45 (72.6%)
Chondroblastic	3 (4.8%)
Fibroblastic	8 (12.9%)
Other	6 (9.7%)
Histologic response	
Good	30 (48.4%)
Bad	32 (51.6%)
Total	62 (100.0%)

AJCC = American Joint Committee on Cancer.

(Fig. 2). The mean values of $\Delta\%SUV_{max}$ and $\Delta\%T/NT_{max}$ were -36.8 and 13.4, respectively ($P<.01$).
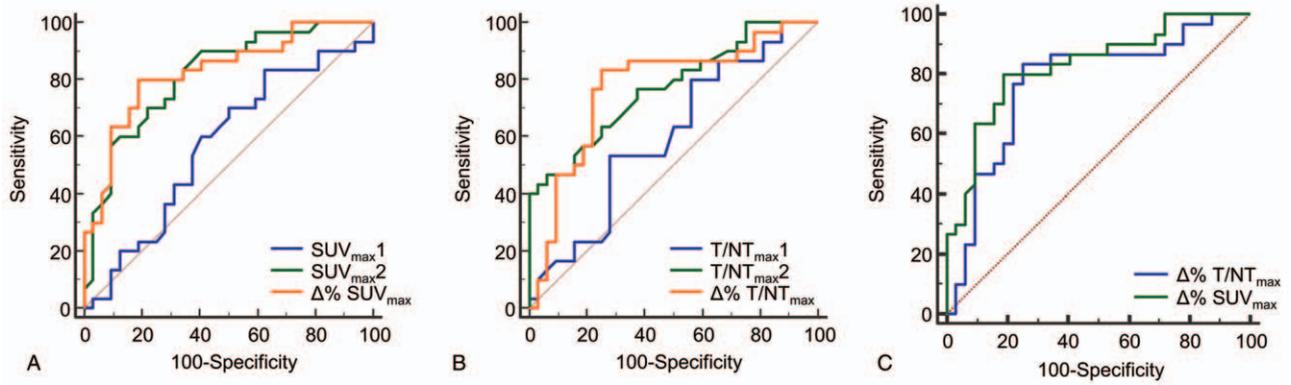
3.4. Prognostic values for histologic response

The various clinical features including age, sex, American Joint Committee on Cancer (AJCC) stage, tumor volume based on MRI images, location of the primary tumor, and pathologic type were not statistically significant factors for histologic response based on the univariate logistic regression analyses. However, $\Delta\%SUV_{max}$ and $\Delta\%T/NT_{max}$ were significant prognostic factors for histologic response based on univariate (both $P<.01$) and multivariate logistic regression analyses (both $P<.01$) (Table 3).

Representative images of good and poor histologic response are shown in Figs. 3 and 4.

4. Discussion

In this study, we evaluated the histologic response in patients with osteosarcoma after completion of NAC using ^{99m}Tc-MDP bone scintigraphy and ^{18}F-FDG PET/CT. The percentage change in SUV_{max} of the ^{18}F-FDG PET scan and the percentage change in tumor to nontumor ratio in the ^{99m}Tc-MDP bone scan significantly predicted the histologic response of preoperative

Figure 1. ROC curve analysis between the histologic response and each parameter of the ^{18}F-FDG PET and ^{99m}Tc-MDP bone scans. In ROC curves using the ^{18}F-FDG PET parameters (A), Δ%SUV$_{max}$ shows the largest AUC value (0.829). The AUC values for SUV$_{max}$1 and SUV$_{max}$2 are 0.571 and 0.817, respectively. In ROC curves using ^{99m}Tc-MDP bone scan parameters (B), the AUC for Δ%T/NT$_{max}$ has the largest value (0.772). The AUC values for T/NT$_{max}$1 and T/NT$_{max}$2 are 0.601 and 0.770, respectively. The ROC curves regarding Δ%SUV$_{max}$ and Δ%T/NT$_{max}$ are compared (C). Two curves did not show significant difference ($P=0.44$). ^{18}F-FDG PET = ^{18}F-Fluorodeoxyglucose positron emission tomography, ^{99m}Tc-MDP = ^{99m}Tc-methyl diphosphonate, Δ%SUV$_{max}$ = percent changes of the maximum standardized uptake value, Δ%T/NT$_{max}$ = percent changes of the maximum tumor-to-nontumor ratio, AUC = area under the curve, ROC = receiver operating characteristic.

Table 2

Predictive values of pretreatment ^{99m}Tc-MDP bone scan and ^{18}F-FDG PET for the histologic response.

Parameter (modality)	Optimal cut-off value	Sensitivity	Specificity	AUC of ROC curve	P-value for AUC
Δ%SUV$_{max}$ (PET)	≤−49.0%	80.0%	81.3%	0.829	<.01[*]
Δ%T/NT$_{max}$ (bone scan)	≤−12.5%	83.3%	75.0%	0.772	<.01[*]

Δ%SUV$_{max}$ = percent changes of the maximum standardized uptake value, Δ%T/NT$_{max}$ = percent changes of the maximum tumor-to-nontumor ratio, ^{18}F-FDG = ^{18}F-fluorodeoxyglucose ^{99m}Tc-MDP = ^{99m}Tc-methyl diphosphonate, AUC = area under the curve, PET = positron emission tomography, ROC = receiver operating characteristic.
[*] Statistically significant.
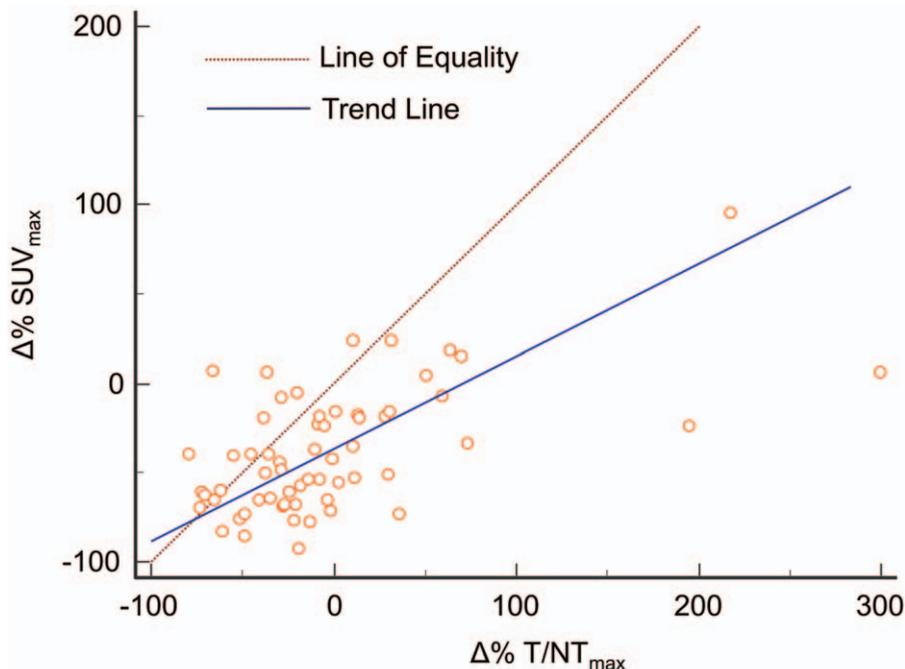
Figure 2. The correlation between Δ%SUV$_{max}$ and Δ%T/NT$_{max}$. A moderate positive correlation exists between the 2 parameters ($P<.01$, rho=.494). Δ%SUV$_{max}$ = percent changes of the maximum standardized uptake value, Δ%T/NT$_{max}$ = percent changes of the maximum tumor-to-nontumor ratio.

Table 3

Parameters related with histologic response after neoadjuvant chemotherapy in the univariate and multivariate analyses.

Parameter	Cut-off value	Univariate P value	Multivariate		
			Relative risk	95% confidence interval	P value
Age	15≤, 15–40, 40>	NS			NS
Sex		NS			NS
AJCC stage		NS			NS
Tumor volume	150 cm^3	NS			NS
Location		NS			NS
Pathologic subtype		NS			NS
Δ%SUV$_{max}$	−49.0%	<0.01[*]	32.192	2.624–394.992	<0.01[*]
Δ%T/NT$_{max}$	−12.5%	<0.01[*]	32.623	3.026–351.658	<0.01[*]

Δ%SUV$_{max}$ = percent changes of the maximum standardized uptake value, Δ%T/NT$_{max}$ = percent changes of the maximum tumor-to-nontumor ratio, AJCC = American Joint Committee on Cancer, NS = non-significant.
[*] = significant.

chemotherapy in patients with osteosarcoma. To the best of our knowledge, this is the first attempt to directly compare ^{99m}Tc-MDP bone scintigraphy and ^{18}F-FDG PET/CT for predicting treatment response.

It was reported that many parameters of ^{18}F-FDG PET/CT are correlated with the histologic response after NAC in the patients with osteosarcoma. For instance, in our previous studies, Δ%SUV$_{max}$, metabolic tumor volume (MTV) before NAC, and SUV$_{max}$ after NAC are associated with histologic response.[10,15] Im et al[16] reported that SUV$_{max}$, peak SUV (SUV$_{peak}$), MTV, and total lesion glycolysis (TLG) during and after NAC are correlated with histologic response. It was reconfirmed through the current study that, Δ%SUV$_{max}$, the representative parameter, is correlated with the histologic response after NAC.

Bone scan using ^{99m}Tc-MDP is a sensitive tool for detecting primary bone tumor and bone metastasis,[8] but it has limitations in reflecting the treatment response in a relatively short time.[17] While ^{18}F-FDG PET directly reflects the metabolism of viable cells, the ^{99m}Tc-MDP uptake on bone scan is based on blood flow and ion exchange, meaning that the bone scan reflects indirect osteoblastic activity rather than direct detection of viable tumors.[8] Despite such weakness of the bone scan, it was reported that the changes in tumor-to-background ratio (TBR) on bone scan before and after NAC in patients with osteosarcoma is associated with histologic response.[8] Such is consistent with our results. In the current study, Δ%T/NT$_{max}$ on the ^{99m}Tc-MDP bone scan predicted the histologic response after NAC.

Δ%T/NT$_{max}$ on ^{99m}Tc-MDP bone scan and Δ%SUV$_{max}$ on ^{18}F-FDG PET showed positive correlation with statistical significance. Similarly, Franzius et al[18] reported that tumor to nontumor ratios on ^{18}F-FDG PET scans before NAC show a significant positive correlation with tumor to nontumor ratios on ^{99m}Tc-MDP bone scintigraphy before NAC. When comparing the AUC curves for Δ%SUV$_{max}$ on the ^{18}F-FDG PET scan and Δ%T/NT$_{max}$ on the ^{99m}Tc-MDP bone scan for prediction of histologic response, the AUC values of the 2 parameters were not statistically different. This suggests that both modalities are non-inferior to each other in predicting histologic response. Furthermore, multivariate analyses showed that both parameters are independent prognostic factors for histologic response. Clinical data other than the parameters of ^{99m}Tc-MDP bone scan and ^{18}F-FDG PET showed no significant correlation with histologic response. Notably, the tumor volume at initial diagnosis, known as an important independent prognostic factor for metastasis-free survival,[12] did not show any significant

correlation with histologic response. This result is consistent with that of a previous report.[19]

However, in our results, the differences between the values before and after treatment were much greater in Δ%SUV$_{max}$ than in Δ%T/NT$_{max}$. Furthermore, although there is no significant difference, the AUC value of Δ%SUV$_{max}$ was slightly greater than that of Δ%T/NT$_{max}$. This suggests that the change from before and after NAC can be more easily detected on the ^{18}F-FDG PET scan than on the ^{99m}Tc-MDP bone scan. This may be the result of differences in imaging modalities. The PET/CT image is tomographic while the bone scan is planar. Therefore, PET/CT provides higher resolution images with higher sensitivity and specificity in lesion detection compared with conventional planar bone scans.[20] It is not easy to directly compare PET, a tomographic image, with the bone scan, a planar image. The sensitivity of bone scan for lesion detection is reported to be 70% to 90%.[21] However, SPECT, a tomographic image, can increase the sensitivity for lesion detection to 95%.[21] In this study, SPECT images were not included because it is not a routinely performed test and this study is a retrospective study. When bone SPECT can be performed to evaluate the treatment response of the primary tumor, lesions can be evaluated with higher sensitivity and higher resolution when compared with the bone scan. Superior resolution of SPECT over the bone scan can provide better ability to differentiate the lesion in the bone versus soft tissue area.

Another weakness of the bone scan compared with PET is the method used to quantify the uptakes. In the current study, semi-quantitative methods were adapted. However, the tools for direct measurement of SUVs have been developed in SPECT, which can solve the quantification problem.[22] It will be essential to compare quantitative results from SPECT and PET for further clarification of this study. Furthermore, it will also be necessary to compare ^{18}F-FDG PET with ^{18}F-NaF PET, a novel PET tracer, which exhibits higher sensitivity than bone scans and bone SPECT.

To date, there have been several studies that compared FDG PET/CT and bone scans in osteosarcoma patients, mainly focusing on metastasis. It was reported that ^{18}F-FDG PET/CT not only displays more sensitivity in detecting bone metastasis than the ^{99m}Tc-MDP bone scan in the diagnosis of osteosarcoma,[15,23] but also predicts overall and event-free survival of osteosarcoma patients.[18] In addition to the different level of information that may be acquired by PET/CT and a bone scan, another feature of PET/CT is patient convenience. Because the
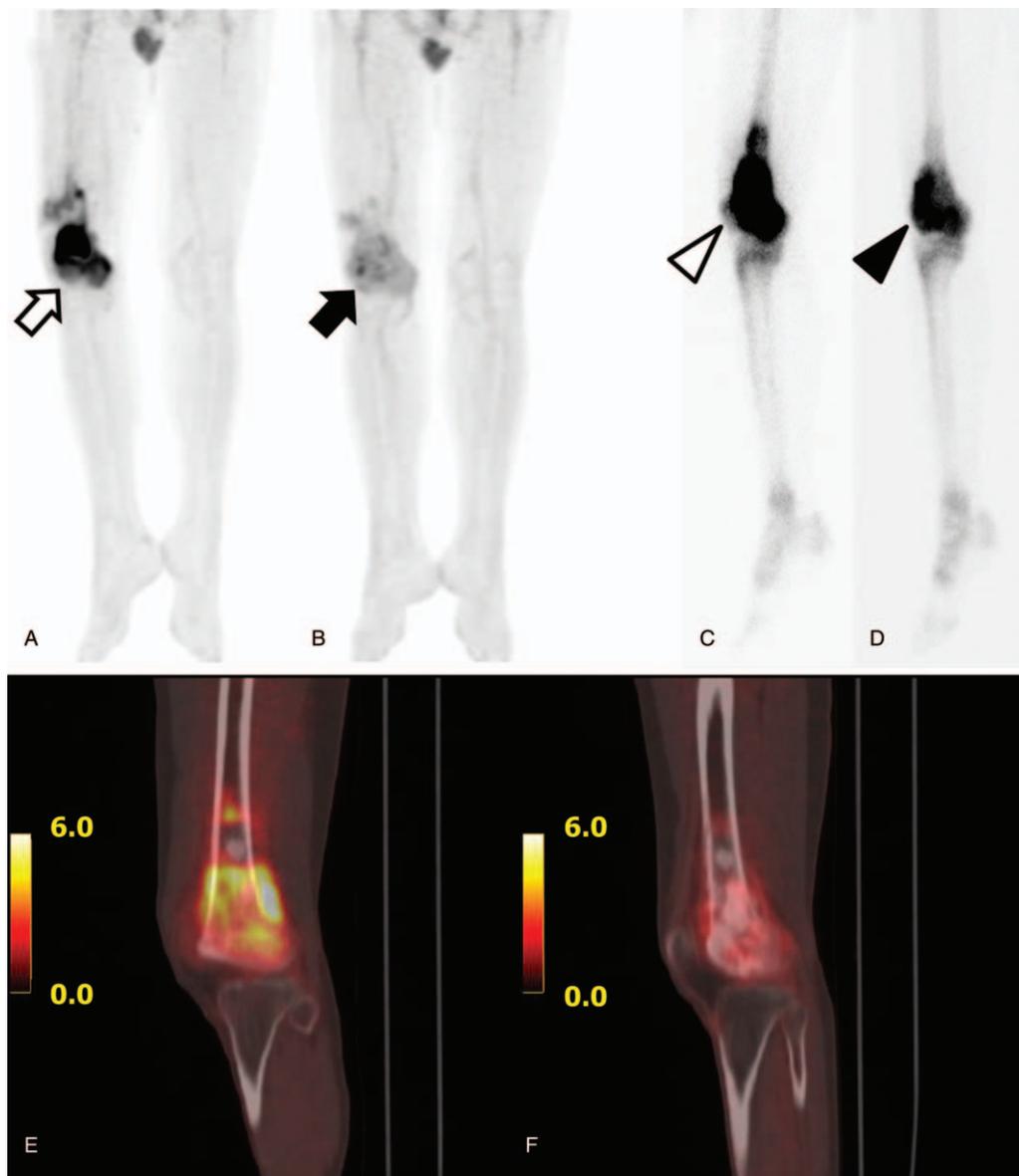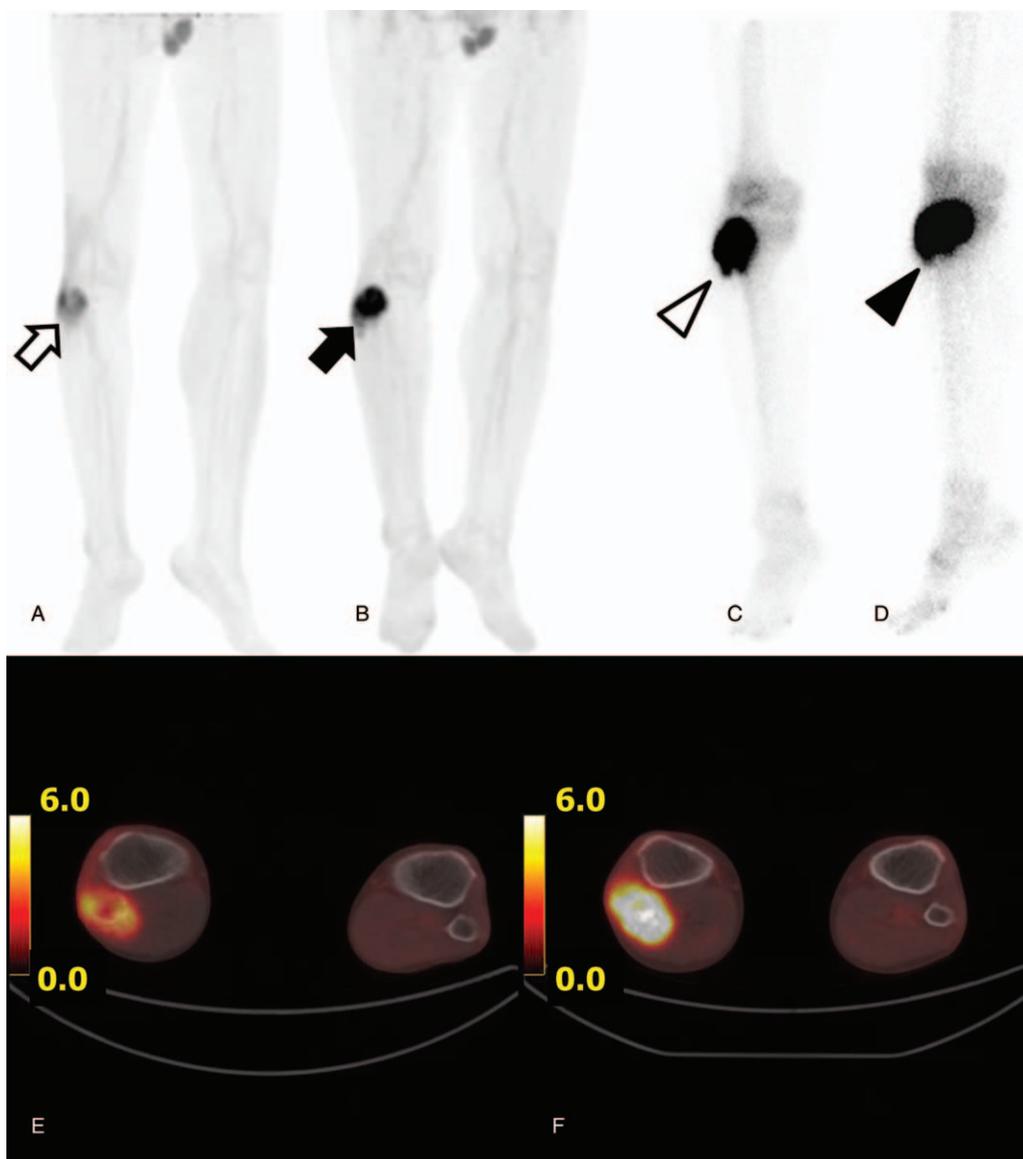
Figure 3. A 17-year-old male patient underwent neoadjuvant chemotherapy due to osteosarcoma at the right distal femur. The ^{18}F-FDG PET images before chemotherapy (A) and after chemotherapy (B) are shown as maximum intensity projections. The sagittal fused ^{18}F-FDG PET images before chemotherapy (E) and after chemotherapy (F) are shown. $SUV_{max}1$ of the tumor (white arrow) is 9.4 and $SUV_{max}2$ of the tumor after chemotherapy (black arrow) is 3.7. The value of $\Delta\%$ SUV_{max} is −60.9%. The bone scan images before chemotherapy (C) and after chemotherapy (D) are shown. $T/NT_{max}1$ of initial primary tumor is 15.2 (white arrowhead) and $T/NT_{max}2$ of tumor after chemotherapy is 4.2 (black arrowhead). $\Delta\%T/NT_{max}$ is −72.1%. After surgical resection of the tumor, 95.0% necrosis was observed, which indicated good histologic response with neoadjuvant chemotherapy. $SUV_{max}1 = $ prechemotherapy maximum standardized uptake value, $SUV_{max}2 = $ postchemotherapy SUV_{max}, $T/NT_{max}1 = $ maximum tumor-to-nontumor ratio before the chemotherapy, $T/NT_{max}2 = T/NT_{max}$ after the chemotherapy, $\Delta\%SUV_{max} = $ percent changes of the SUV_{max}, $\Delta\%T/NT_{max} = $ percent changes of T/NT_{max}.

^{18}F-FDG PET scan is performed <2 hours after the injection of ^{18}F-FDG, the total time required is much less than that for a ^{99m}Tc-MDP bone scan. On the other hand, some advantages of the ^{99m}Tc-MDP bone scan are its cost-effectiveness[24] and low radiation exposure. The effective dose of a bone scan for an adult is approximately 3 to 4 mSv,[25] whereas the effective dose of a ^{18}F-FDG PET/CT whole body scan using 10 mCi of ^{18}F-FDG is about 7 mSv with additional radiation exposure by CT.[26] Bone scans may reduce cost and total radiation exposure when compared with PET/CT.

There are some limitations to our study. First, the scanners for PET and bone scan can affect the uptake count of FDG and MDP.

The estimated cut-off values for $\Delta\%SUV_{max}$ on the PET scan and for $\Delta\%T/NT_{max}$ on the bone scan may differ. Second, the flare phenomenon may be observed in the bone scan after treatment. It has been mostly observed in patients with breast and prostate cancer.[27] Although there is no report of specific incidence of flare after treatment of osteosarcoma, sufficient time interval after treatment to exclude the flare phenomenon would be needed. In this study, the time interval from the end of the treatment to the bone scan may have been relatively short. Sufficient consideration should be given to the possibility of a flare phenomenon when predicting therapeutic response using bone scans.

Figure 4. A 34-year-old male patient with osteosarcoma at right proximal tibia who underwent neoadjuvant chemotherapy. The ^{18}F-FDG PET images before chemotherapy (A) and after chemotherapy (B) are shown as a maximum intensity projection. The axial fused ^{18}F-FDG PET images before chemotherapy (E) and after chemotherapy (F) are shown. $SUV_{max}1$ of the tumor (white arrow) is 4.7 and $SUV_{max}2$ of the tumor after chemotherapy (black arrow) is 8.2. The value of $\Delta\%$ SUV_{max} is 73.8%. The bone scan images before chemotherapy (C) and after chemotherapy (D) are shown. $T/NT_{max}1$ of initial primary tumor is 2.5 (white arrowhead) and $T/NT_{max}2$ of tumor after chemotherapy is 27.1 (black arrowhead). $\Delta\%T/NT_{max}$ is 983.6%. After surgical resection of the tumor, 5.0% necrosis was observed, which indicated poor histologic response with neoadjuvant chemotherapy. $SUV_{max}1 =$ prechemotherapy maximum standardized uptake value, $SUV_{max}2 =$ postchemotherapy SUV_{max}, $T/NT_{max}1 =$ maximum tumor-to-nontumor ratio before the chemotherapy, $T/NT_{max}2 = T/NT_{max}$ after the chemotherapy, $\Delta\%SUV_{max} =$ percent changes of the SUV_{max}, $\Delta\%T/NT_{max} =$ percent changes of T/NT_{max}.

In conclusion, ^{18}F-FDG PET/CT and ^{99m}Tc-MDP bone scintigraphy have been found to be non-inferior to each other in predicting the histologic response of treatments. Both scans had their own advantages although with differing features. Therefore, it is advised that physicians should consider which scan is appropriate for their institute based on the advantages and features of each scan and the circumstance of the institute. If PET/CT is not available, the ^{99m}Tc-MDP bone scan may be a non-invasive tool for predicting the histologic response to NAC in patients with osteosarcoma.

Author contributions

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