FDG PET Uptake as a Predictor of Pain Response in Palliative Radiation Therapy in Patients with Bone Metastasis[1]

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Purpose: To evaluate the relationship between fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET) maximum standardized uptake value (SUV_{max}) and pain response to radiation therapy (RT) in patients with bone metastasis.

Materials and Methods: Institutional ethical board approval for the study was obtained, with informed consent, for this prospective study. Thirty-one patients with metastatic bone pain who underwent FDG PET/computed tomography before RT were included. Patients were diagnosed with lung (n = 16), breast (n = 7), stomach (n = 2), and head and neck cancers (n = 3), as well as unknown primary tumor (n = 3). Eighty-five painful metastatic locations with FDG PET scans geographically corresponding to 40 treatment fields were evaluated. Pain scores using visual analog scale or faces pain rating scale and SUV_{max} at each location were recorded. All patients were treated with a single fraction 8 Gy RT. Pain scores after RT were assessed at weeks 2, 4, 8, 12, 16, 20, and 24. The pretreatment pain scores and pain response to RT were compared with FDG PET SUV_{max} of each location. Pearson correlation, independent t test, one-way analysis of variance, and χ^2 tests were used for statistical analysis.

Results: Median SUV_{max} and initial pain scores for all locations were 7.2 (range, 1.5–22.5) and 6 (range, 2–8), respectively. Median follow-up time was 24 (range, 3–112) weeks. Median SUV_{max} was 4.5 (range, 3.1–7.3), 4.75 (range, 1.5–10.3), 8.8 (range, 5.2–11.9), and 12.1 (range, 7–22.5) for pretreatment pain scores of 2, 4, 6, and 8, respectively. SUV_{max} was correlated with pretreatment pain scores ($P < .0001$). SUV_{max} and pretreatment pain scores were also significantly associated with pain response to RT. Median SUV_{max} for locations with complete response, partial response, pain progression, and indeterminate response was 5.2, 9.75, 10.8, and 6.4, respectively ($P \leq .001$).

Conclusion: FDG PET SUV_{max} correlated with initial pain severity and pain response to RT and can be used as a predictive factor for treatment response in patients with painful bone metastasis treated with palliative RT.

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Bone metastases are a common manifestation of cancer that can cause severe pain. Radiation therapy (RT) can variably palliate pain caused by bone metastases (1–3). However, response of pain to palliative RT in patients with bone metastasis varies among patients receiving the same treatment. While 50%–80% of the patients with painful bone metastasis treated with RT experience some relief, only 20%–50% have a complete response (1–3). Local tumor-related factors may be associated with different treatment response rates (4,5).

Fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET) is increasingly being used for response evaluation in RT (6,7). Patients with high tumor FDG uptake are shown to have a less favorable outcome in various diagnoses (8–12). Metabolic tumor volume and tumor activity are blamed for recurrence and posttreatment residual disease (13,14). This association may also exist in patients with bone metastasis. Metabolic activity of the painful metastatic location in patients with bone metastasis may potentially be responsible for different treatment response rates to RT and may be predictive of the response rate.

The purpose of this study was to analyze the relationship between FDG PET maximum standardized uptake value (SUV_{max}) and response of pain to RT in patients with bone metastasis.

Materials and Methods

Institutional ethical board approval for the study and informed consent from each patient were obtained.

Advances in Knowledge

- Median maximum standardized uptake value (SUV_{max}) was 5.2, 9.75, 10.8, and 6.4 for painful locations with complete response, partial response, pain progression, and indeterminate response, respectively ($P \leq .001$).
- FDG PET SUV_{max} correlated with initial pain severity, as well as pain response to palliative radiation therapy, in patients with bone metastasis.

Patients and Study Design

Thirty-one patients with bone metastases were prospectively included between December 2009 and June 2012. Eighty-five painful metastatic locations in 40 (median, 1; range, 1–6) treatment fields were evaluated. Patient and treatment details are given in Table 1.

Criteria for patient eligibility into the study included biopsy-proved cancer diagnosis, Eastern Cooperative Oncology Group performance status with a score of 2 or lower, PET/computed tomography (CT) scan in the past 4 weeks showing bone metastasis, metastatic bone pain location which can be pointed to by the patient and can be correlated with the metastatic location on PET/CT images. Patients with a history of chemotherapy in the past 4 weeks, history of previous RT to the same location, indication for surgery, and spinal cord compression were not eligible. Nonspinal treatment fields including more than three painful locations (eight patients, 35 painful locations) were excluded from the study to find painful locations easily. Two patients with painful bone metastasis, but no FDG uptake on PET/CT images were also excluded from the study.

All patients had undergone pre-RT FDG PET/CT scanning for staging purposes and were referred for palliative RT for metastatic bone pain. According to the Society of Nuclear Medicine recommendations (15), 10–15 mCi (370–555 MBq) of FDG (Mon.FDG [18F] I.V. Injectable Solution; Eczacibasi-Monrol Nukleer Urunler San. ve Tic. A. S., Kocaeli, Turkey) was administered intravenously. Whole-body FDG PET/CT images were acquired 60 minutes after FDG injection by using a PET/CT system (Biograph Duo LSO; Siemens Medical Solutions, Hoffman Estates, Ill).

Implications for Patient Care

- FDG PET SUV_{max} can be used as a predictive factor for treatment response in patients with painful bone metastasis treated with radiation therapy.
- Additional studies are needed to evaluate whether different radiation therapy dose and fractionation schedules can be used for painful metastatic bone lesions with different FDG PET SUV_{max}.

Pretreatment pain scores at each painful location obtained by using the visual analog scale or the faces pain rating scale (16) (A.K., with 6 years of experience) and SUV_{max} (M.Y., with 16 years of experience) of the same location on PET/CT scans were recorded.

All patients were treated with single-fraction 8-Gy external-beam RT. Post-RT pain scores and the need for analgesics were assessed and recorded by one author (A.K.) at weeks 2, 4, 8, 12, 16, 20, and 24.

Response evaluation criteria suggested by the International Bone Metastases Consensus Working Party were used for pain response evaluation (Table 2) (17).

Pretreatment pain scores and response of pain to RT were compared with FDG PET SUV_{max} of the painful locations. A patient-specific analysis was also performed by using average SUV_{max} and pain scores for patients with more than one painful location.

Statistical Analysis

Statistical analysis was conducted by using a statistical package software (PASW Statistics, version 18; SPSS,

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Abbreviations:
ANOVA = analysis of variance
FDG = fluorine 18 fluorodeoxyglucose
RT = radiation therapy
SUV = standardized uptake value
SUV_{max} = maximum SUV

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Guarantors of integrity of entire study, M.A., A.K., H.E.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, M.A., A.K., F.A.; clinical studies, M.A., A.K., H.E., M.Y.; statistical analysis, A.K.; and manuscript editing, M.A., A.K.

Conflicts of interest are listed at the end of this article.

Table 1

Patients and Treatment Details

Details	Datum*
Diagnosis (n = 31)	
Lung cancer	16
Breast cancer	7
Head and neck cancer	3
Unknown primary neoplasm	3
Stomach cancer	2
Treatment field locations (n = 40)	
Vertebrae	26
Pelvis	7
Humerus	5
Femur	2
No. of treatment fields per patient (n = 31)	
One field	24
Two fields	5
Three fields	2
No. of painful locations per treatment field (n = 40)	
1	21
2	5
3	7
4	3
5	3
6	1

* Data are the numbers of patients for diagnosis, numbers of locations for treatment field locations, numbers of fields for treatment field per patient, and numbers of locations for painful locations per treatment field.

Table 2

Treatment Response Categories Used for Pain Response Evaluation

Response	Definition
Complete response	A pain score of 0 at treated site with no concomitant increase in analgesic intake (stable or reducing analgesics in OMED)
Partial response	Pain reduction of 2 or more at the treated site on a scale of 0–10 without analgesic increase, or analgesic reduction of 25% or more from baseline without an increase in pain
Pain progression	Increase in pain score of 2 or more above baseline at the treated site with stable OMED, or an increase of 25% or more in OMED compared with baseline with the pain score stable or 1 point above baseline
Indeterminate response	Any response that is not captured by the complete response, partial response, or pain progression definitions

Note.—Adapted, with permission, from reference 17. OMED = daily oral morphine equivalent.

Figure 1

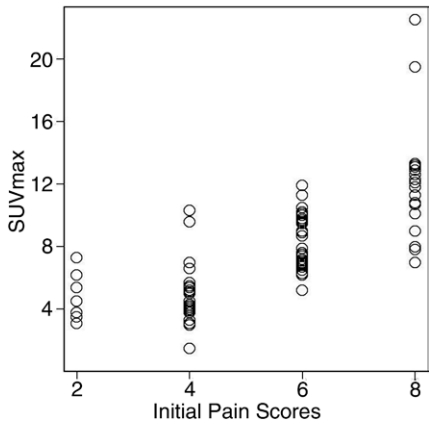

Figure 1: SUV_{max} and initial pain score relationship ($P < .0001$). ○ = one location.

Chicago, Ill). The relationship between pre-RT pain scores and SUV_{max} of the painful locations and patients were analyzed by using the Pearson correlation. To analyze the relationship between post-RT treatment response and the SUV_{max} and pre-RT pain scores, the independent t test was used for two variables (complete response and partial response), and the one-way analysis of variance (ANOVA) test was used for more than two variables (complete response, partial response, indeterminate response, and pain progression). The χ^2 test was used to analyze the relationship between treatment response and pre-RT performance status, primary diagnosis, and treatment locations. P values of less than .05 were considered to indicate a significant difference. An interactive program for power and sample size calculations (PS: Power and Sample Size Calculation version 3.0, 2009; William D. Dupont and Walton D. Plummer, Jr, Department of Biostatistics, Vanderbilt University, Nashville, Tenn) was used to perform a posteriori power analysis.

Results

Mean patient age was 54 years (range, 35–68 years) and 49 years (range, 24–68 years) for men (n = 19) and women (n = 12), respectively. Median follow-up time was 24 weeks (range, 3–112 weeks).

In addition to the location-specific analysis, a patient-specific statistical analysis was also performed by using mean SUV_{max} and pain scores for patients with more than one painful metastatic location.

Median SUV_{max} and initial pain scores of 85 painful locations were 7.2 (range, 1.5–22.5) and 6 (range, 2–8). SUV_{max} was strongly correlated with pretreatment pain scores (r = 0.737, $P < .0001$). Median SUV_{max} of painful locations was 4.5 (range, 3.1–7.3), 4.75 (range, 1.5–10.3), 8.8 (range, 5.2–11.9), and 12.1 (range, 7–22.5) for initial pain scores of 2 (n = 8), 4 (n = 26), 6 (n = 32), and 8 (n = 19), respectively ($P < .0001$) (Fig 1).

At weeks 2, 4, 8, 12, and 16, one, three, four, two, and three patients were deceased, respectively (Tables 3, 4).

SUV_{max} was associated with pain response to RT ($P \leq .001$). Complete response was observed at 34 locations, partial response was observed at 46 locations, and indeterminate response was observed at five locations at posttreatment week 2. Treatment responses at all evaluation weeks are shown in Table 3. Median SUV_{max} (calculated from the medians in all locations together from weeks 2 to 24) for locations with complete response, partial response, pain progression, and indeterminate response was 5.2 (range, 1.5–13.2), 9.75 (range, 3.1–22.5), 10.8 (range, 9.6–13.3), and 6.4 (range, 5.4–6.9), respectively ($P \leq .001$) (Table 3).

Treatment response of locations with lower SUV_{max} was better than

Table 3

Median SUV_{max} for Each Response Group at Post-RT Weeks 2, 4, 8, 12, 16, 20, and 24: Location-specific Analysis

Post-RT Time	CR	PR	IR	PP	*P* Value*	No. of Patients
Week 2	5.1 (*n* = 34)	9.0 (*n* = 46)	10.8 (*n* = 5)	. . .	<.0001	31 (*n* = 85)
Week 4	5.0 (*n* = 37)	9.6 (*n* = 46)	. . .	. . .	<.0001	30 (*n* = 83)
Week 8	5.1 (*n* = 40)	10 (*n* = 26)	. . .	. . .	<.0001	26 (*n* = 66)
Week 12	5.4 (*n* = 37)	10.1 (*n* = 17)	. . .	6.4 (*n* = 4)	<.0001	21 (*n* = 58)
Week 16	5.4 (*n* = 30)	10.2 (*n* = 16)	. . .	6.4 (*n* = 4)	<.0001	19 (*n* = 50)
Week 20	5.3 (*n* = 28)	9.7 (*n* = 17)	. . .	. . .	.001	15 (*n* = 45)
Week 24	5.3 (*n* = 28)	9.7 (*n* = 17)	. . .	. . .	.001	15 (*n* = 45)

Note.—CR = complete response, IR = indeterminate response, PP = pain progression, PR = partial response. *n* = Number of painful locations evaluated.

* Treatment responses at weeks 2, 12, and 16 were analyzed by using the one-way ANOVA test. Treatment responses at weeks 4, 8, 20, and 24 were analyzed by using the independent-samples *t* test.

Table 4

Median SUV_{max} for Each Response Group at Post-RT Weeks 2, 4, 8, 12, 16, 20, and 24: Patient-specific Analysis

Post-RT Time	CR	PR	IR	PP	*P* Value*	No. of Patients
Week 2	5.1 (*n* = 13)	9.5 (*n* = 17)	10.8 (*n* = 1)	. . .	<.008	31
Week 4	4.8 (*n* = 12)	10.05 (*n* = 18)	. . .	. . .	<.001	30
Week 8	5.55 (*n* = 16)	10.55 (*n* = 10)	. . .	. . .	<.001	26
Week 12	6.15 (*n* = 12)	10.55 (*n* = 8)	. . .	6.3 (*n* = 1)	<.001	21
Week 16	6.7 (*n* = 11)	10.8 (*n* = 7)	. . .	6.3 (*n* = 1)	<.006	19
Week 20	6.7 (*n* = 9)	10.55 (*n* = 6)	. . .	. . .	.04	15
Week 24	6.7 (*n* = 9)	10.55 (*n* = 6)	. . .	. . .	.04	15

Note.—CR = complete response, IR = indeterminate response, PP = pain progression, PR = partial response. *n* = Number of patients evaluated.

* Treatment responses at weeks 2, 12, and 16 were analyzed by using the one-way ANOVA test. Treatment responses at weeks 4, 8, 20, and 24 were analyzed by using the independent-samples *t* test.

treatment response of locations with higher SUV_{max} ($P < .001$). The median SUV_{max} of all painful locations was 7.2. Median pain scores according to the median SUV_{max} of 7.2 for the whole group are shown in Figure 2.

Median SUV_{max} and initial pain scores (calculated from the means in all patients together) of 31 patients were 8.2 (range, 3.5–14.3) and 6 (range, 2–8), respectively. SUV_{max} was well correlated with pretreatment pain scores ($r = 0.744$, $P < .001$) (Fig 3). Median SUV_{max} was 4.6 (range, 3.5–6.7), 4.8 (range, 3.8–10.3), 8.2 (only one patient included), 9 (range, 6.3–11.9), 12.3 (range, 9.6–14.3), and 11.6 (range, 11.4–13) for initial pain scores of 2 ($n = 3$), 4 ($n = 9$), 5 ($n = 1$), 6 ($n = 12$), 7 ($n = 3$), and 8 ($n = 3$), respectively ($P < .001$).

SUV_{max} was associated with pain response to RT ($P \leq .04$). Complete response was observed in 13 patients, partial response was observed in 17 patients, and indeterminate response was observed in one patient at post-treatment week 2. Treatment responses of patients at all evaluation weeks are shown in Table 4. Median SUV_{max} (calculated from the medians in all patients together from weeks 2 to 24) for patients with complete response, partial response, pain progression, and indeterminate response was 6 (range, 3.5–11.9), 10.3 (range, 4.8–14.3), 6.3 (only one patient was included), and 10.8 (only one patient was included), respectively ($P \leq .04$) (Table 4).

Treatment response of patients with lower SUV_{max} was better than in patients with higher SUV_{max} ($P \leq .04$).

The initial pain score was also correlated with treatment response (Tables 5, 6).

Two patients underwent repeat treatment off protocol at weeks 20 and 60, after partial response to the initial RT. The first patient received a diagnosis of a small-cell lung carcinoma, and the second received a diagnosis of an unknown primary neoplasm. The pain locations were iliac bone for the first patient and lumbar vertebra for the second. Initial pain scores and SUV_{max} were 4 and 10.3, respectively, for the first patient and 6 and 9.7, respectively, for the second.

There was no significant association between patients' pre-RT performance status or location of bone metastasis and treatment response. Post hoc power analysis indicated that the difference in the mean response of matched pairs between baseline pain score and treatment response was 4.82 ± 1.30. We were able to reject the null hypothesis that the response difference is zero, with probability (power) of greater than .99. The type I error probability of this test associated with the null hypothesis was .05.

Discussion

FDG PET is commonly used for staging of cancer patients and is increasingly being used for response evaluation in RT (6,7).

In this study, we observed that initial pain scores were correlated with SUV_{max} of the metastatic location, and the response of the pain to palliative RT was better in the lesions with lower SUV_{max}. SUV_{max} assessed with FDG PET was a predictive biomarker of initial pain severity and a significant predictor of treatment response in patients treated for palliation of metastatic bone pain.

Investigators in some prior studies have shown a relationship between high FDG uptake and tumor proliferative

Figure 2

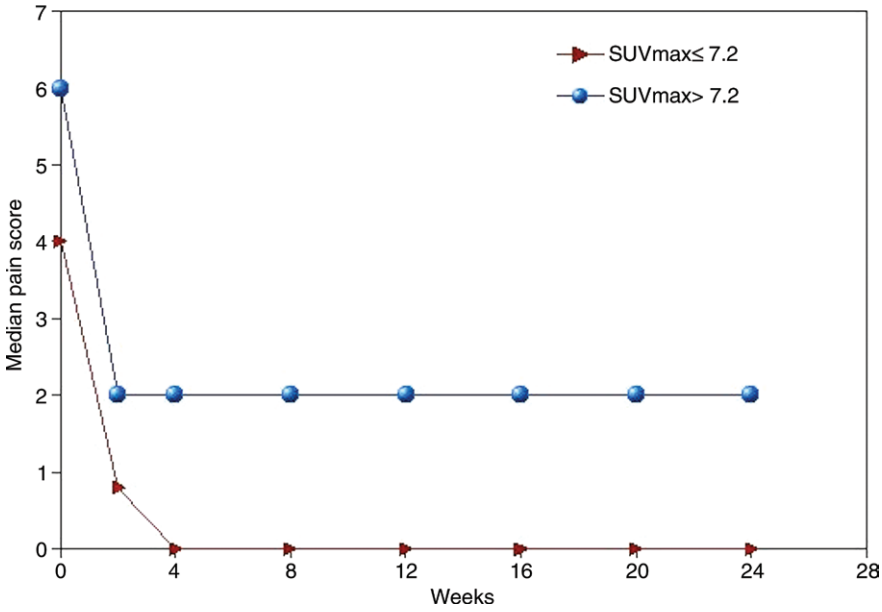

Figure 2: Median pain scores at each evaluation week according to the median SUV_{max} of 7.2 for the whole group.

Figure 3

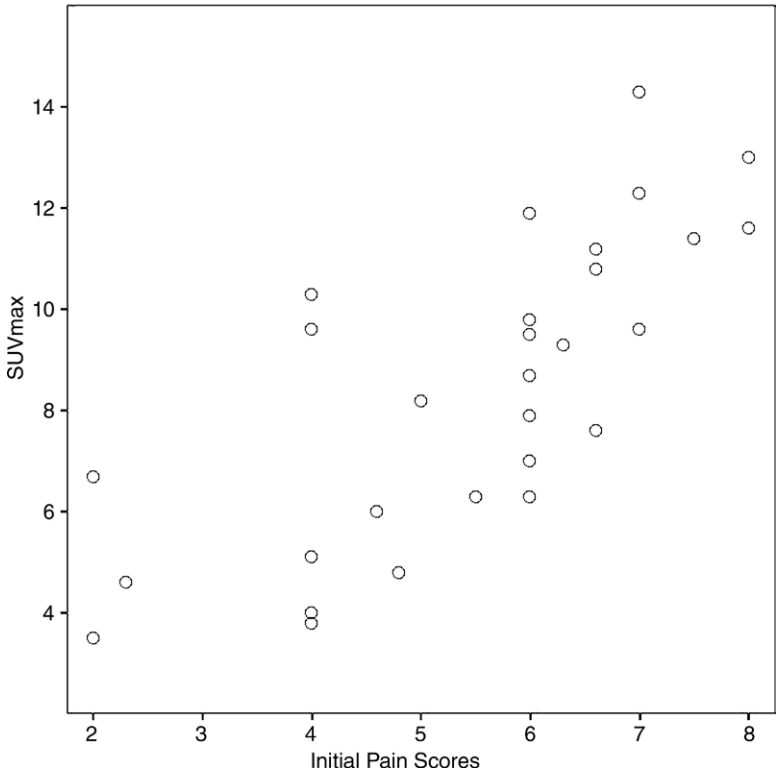

Figure 3: Mean SUV_{max} and mean initial pain score relationship in each patient for 31 patients.

activity (18), cell viability (19), low apoptosis rate (20), hypoxia (21), and p53 overexpression (22).

Researchers in prior studies have suggested that higher standardized uptake value (SUV) is correlated with a poorer clinical outcome in patients with several malignancies (8–12). Brun et al (23) showed a correlation between SUV and metabolic rate by using FDG PET in a series of patients with head and neck cancer who were treated with radical RT. Vesselle et al (24) reported a strong correlation between high SUV and poorly differentiated tumors in patients with non–small-cell lung cancer.

Allal et al (25) suggest that patients with head and neck cancer and a high FDG uptake should be considered at increased risk of treatment failure and may benefit from more aggressive multimodality treatment combinations. We studied the association of FDG PET SUV with bone metastases.

In our study, treatment outcome was better in painful locations with lower SUV_{max}. This result is comparable with the results of the above-mentioned studies outside of bone. We also observed an association between the initial pain scores and SUV_{max}. Thus, increased SUV_{max} may be a predictor of pain severity at the metastatic location. Although each painful metastatic location is evaluated separately in clinical practice, pain response of multiple painful locations in a common patient may not be independent. Thus, a separate patient-specific analysis was performed.

Different fractionations are being used for palliation of bone metastases. The researchers in many studies reported similar response rates with single-fraction RT compared with multiple fractionation in patients with metastatic bone pain (3,26–28). For bone metastases, clinical practice guidelines (29) have recommended single-fraction RT. Single-fraction treatment is very convenient for the patients; however, the repeat treatment rate is increased up to 2.5 fold with this technique (3,28). The higher repeat treatment rate may be explained with the choice of initial fractionation (30). In their

Table 5

Initial Pain Score for Each Response Group at Post-RT Weeks 2, 4, 8, 12, 16, 20, and 24: Location-specific Analysis

Post-RT Time	CR	PR	IR	PP	*P* Value*	No. of Patients
Week 2	3.9 (*n* = 34)	6.3 (*n* = 46)	7.2 (*n* = 5)	. . .	<.001	31 (*n* = 85)
Week 4	4 (*n* = 37)	6.6 (*n* = 46)	. . .	. . .	<.001	30 (*n* = 83)
Week 8	4.2 (*n* = 40)	6.3 (*n* = 26)	. . .	. . .	<.001	26 (*n* = 66)
Week 12	4.3 (*n* = 37)	6.6 (*n* = 17)	. . .	5.5 (*n* = 4)	<.001	21 (*n* = 58)
Week 16	4.3 (*n* = 30)	6.6 (*n* = 16)	. . .	5.5 (*n* = 4)	<.001	19 (*n* = 50)
Week 20	4.2 (*n* = 28)	6.2 (*n* = 17)	. . .	. . .	<.001	15 (*n* = 45)
Week 24	4.2 (*n* = 28)	6.2 (*n* = 17)	. . .	. . .	<.001	15 (*n* = 45)

Note.—CR = complete response, IR = indeterminate response, PP = pain progression, PR = partial response. *n* = Number of painful locations evaluated.

* Treatment responses at weeks 2, 12, and 16 were analyzed by using the one-way ANOVA test. Treatment responses at weeks 4, 8, 20, and 24 were analyzed by using the independent-samples *t* test.

Table 6

Initial Pain Score for Each Response Group at Post-RT Weeks 2, 4, 8, 12, 16, 20, and 24: Patient-specific Analysis

Post-RT Time	CR	PR	IR	PP	*P* Value*	No. of Patients
Week 2	4 (*n* = 13)	6.2 (*n* = 17)	6 (*n* = 1)	. . .	<.001	31
Week 4	3.6 (*n* = 12)	6.4 (*n* = 18)	. . .	. . .	<.001	30
Week 8	4.2 (*n* = 16)	6.3 (*n* = 10)	. . .	. . .	.001	26
Week 12	4.2 (*n* = 12)	6.4 (*n* = 8)	. . .	6 (*n* = 1)	.013	21
Week 16	4.3 (*n* = 11)	6.4 (*n* = 7)	. . .	6 (*n* = 1)	.05	19
Week 20	4 (*n* = 9)	6.2 (*n* = 6)	. . .	. . .	.023	15
Week 24	4 (*n* = 9)	6.2 (*n* = 6)	. . .	. . .	.023	15

Note.—CR = complete response, IR = indeterminate response, PP = pain progression, PR = partial response. *n* = Number of patients evaluated.

* Treatment responses at weeks 2, 12, and 16 were analyzed by using the one-way ANOVA test. Treatment responses at weeks 4, 8, 20, and 24 were analyzed by using the independent-samples *t* test.

retrospective study comparing morphologic and metabolic changes in bone metastases in response to systemic therapy in patients with metastatic breast cancer with PET/CT, Tateishi et al (31) showed that a decrease in SUV of the lesion after systemic therapy was an independent predictor of response duration in patients with breast cancer who have bone metastasis. This finding suggests that SUV_{max}, as a predictor of pain response may have a role in the prediction of the patients with metastatic bone pain who need repeat RT. This possible association was not observed in our study. In this study, only two painful locations needed repeat treatment. Larger studies are needed to evaluate the possible association between the SUV_{max} and repeat treatment rates in patients with painful bone metastases who are treated with palliative RT.

In this study, treatment response of locations with a higher initial pain score was more robust as compared with the treatment response of locations with lower pain scores. One of the possible reasons for this finding may be that the pain scale of 0–10 is not sensitive enough to evaluate the change in locations with low initial pain scores, if the response is not complete. Initial pain score also can be used to predict treatment response and it would be more efficient compared with the PET scan. However, it is a subjective evaluation and depends on each patient's sense of pain and, thus, is less reliable compared with SUV_{max}. Authors of this study do not suggest that a PET scan routinely be used only for the purpose of treatment response evaluation in patients with bone metastasis until researchers in further larger studies evaluate its additional benefits.

The diagnostic accuracy of FDG PET and bone scintigraphy for detection of bone metastases is comparable (32). However, because FDG PET is much more expensive and is not easily accessible, compared with bone scintigraphy, in clinical practice it is not used primarily to detect bone metastases but is used predominantly for clinical staging. Thus, the number of patients included in this study is limited and may lead to a potential of population bias. Also, because accumulation of FDG is dependent on metabolic activity, FDG PET was not used in tumors with a slower metabolic rate, such as prostate adenocarcinomas.

The results of the current study showed that FDG PET SUV_{max} of the painful metastatic locations is correlated with initial pain score and response of pain to RT in patients with bone metastasis and can be used as a predictor of outcome in this patient group. Further clinical studies are needed to show whether there is a relationship between increased repeat treatment rate and SUV_{max} of the painful location.

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