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The role of FDG uptake to predict the need for re-irradiation in patients treated with 8 Gy (X-ray) single fraction palliative radiotherapy for bone metastases

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► ***Original article***

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ABSTRACT

***Background*:** The study aims to evaluate the relationship between the maximum standardized uptake value (SUVmax) of fluorodeoxyglucose positron emission tomography (FDG-PET) before radiation therapy (RT) and the further need for re-irradiation (re-RT) in patients with bone metastases (BM), and to predict the complete response using pre-treatment SUVmax. ***Materials and Methods*:** Fifty-three patients with 133 painful BMs were accepted into the study. Pain scores and SUVmax at painful BM were recorded. Eight Gray in single fraction palliative RT was administered to all of the patients. A total of 7 patients (8 osseous lesions) underwent re-RT. Factors associated with re-RT were analyzed using Cox regression analysis. ***Results*:** The ideal SUVmax cut-off to predict complete response was 7.95. Median SUVmax was 12.75 (±4.1) and 7 (±3.36) in patients who required re-RT due to pain progression and in those who did not, respectively ($p<0.001$). ***Conclusion*:** FDG uptake may be predictive of the need for re-RT in patients with painful BM. This may impact decisions with single-fraction RT which is associated with higher rates of partial response and further need for re-RT at the same location in patients with high SUVmax. Pre-treatment FDG uptake also may be useful in predicting a complete response.

INTRODUCTION

Bone metastasis (BM) is the common cause of pain together with other significant symptoms worsening the quality of life in cancer patients. Radiation therapy (RT) is an important modality in the palliation of painful BM besides curative management of cancer. Maintaining effective pain control with palliative RT is the major goal for painful BM. Several randomized trials and meta-analyses have reported significant responses to RT with different fractionation schemes [single fraction (SF) vs. multiple fractions (MF)]. However, some authors reported that patients treated with SF required higher rates of re-irradiation (re-RT) [1,2].

Positron emission tomography (PET) with the glucose analog F-18 fluorodeoxyglucose (FDG) is an efficient imaging for diagnosis and staging of most malignancies in addition to its use in evaluating the response to treatment [3-7]. The maximal standardized uptake value (SUVmax) of FDG in primary malignancies is reported to predict a worse outcome [3-7]. In patients with BM, changes in SUVmax before and after RT may be a predictor of local control [8-11]. BM with initial higher SUVmax was found to be associated with lower rates of complete pain response in patients treated with a dose of 8 Gray (Gy) SF palliative RT [12]. This may suggest that pain response and need for re-RT may be predicted with the FDG uptake of BM before RT However, the data about its use in the decision or prediction of treatment response to palliative RT is not yet enough in patients with BM. Furthermore, the response prediction of BM to palliative RT is not well-established by a method, and the relationship between the initial FDG uptake in metastatic bone lesions and the need for re-RT in the same location has not been researched yet.

We aimed to evaluate the association between FDG SUVmax and further need for re-RT in patients with BM treated with SF RT (8 Gy). Additionally, we aimed to predict a complete pain response in these patients using pre-RT SUVmax in this study.

MATERIALS AND METHODS

Patients

Fifty-three consecutive patients with 133 metastatic osseous lesions attended to Radiation Oncology Department and underwent RT for pain palliation between March 2010 and November 2015 were accepted in this study. The prospective study was conducted with approval by the Local Clinical Research and Ethical Review Board (Date: 18.12.2008, Number: 12-2008/229).

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The eligibility criteria of the study were; (a) proven diagnosis of cancer, (b) BM confirmed with PET/computed tomography (CT) which was performed within the past 4 weeks (mean, 10.3±4.3 days) before RT, (c) denotable pain location at the metastatic bone which is confirmed by the PET/CT images, (d) patients with Eastern Cooperative Oncology Group performance status ≤3. Patients who received bone-modifying agents and/or systemic therapy >4 weeks were accepted as eligible for the study. Patients with pathologic fracture or risk of fracture at the metastatic bone, spinal cord, or cauda equina compression, previous palliative RT or surgery for the same site, planned operation for fixation of the bone, or patients treated previously with radionuclides for bone pain were excluded in the study. Additionally, patients with BM from hematologic malignancies and prostate cancers, performance status 4 or life expectancy <4 weeks, and patients who received chemotherapy <4 weeks were excluded.

FDG-PET

FDG PET/CT scanning was performed in all of the patients with the purpose of pre-treatment staging. Glucose levels of the patients were measured prior to FDG administration to ensure whether the levels were within the normal range (80-120 mg/dL). Intravenous 10–15 milli-Curie (mCi) [370–555 mega Becquerel (MBq)] of FDG (Mon. FDG [18F] I.V. Injectable Solution; Eczacibasi-Monrol Nukleer Urunler San. ve Tic. A. S., Kocaeli, Turkey) was administered to the patients by the recommendations of Society of Nuclear Medicine [13]. Whole-body scanning with a PET/CT system (Biograph Duo LSO; Siemens Medical Solutions, Hoffman Estates, Ill) was done 60 minutes after the FDG injection.

Pain evaluation

Pain assessment and physical examination were done by a radiation oncologist at the pre-treatment evaluation. A 10-point pain scores numerical scale was used for pain assessment. “No pain” was scored with 0 and “worst possible pain” was scored with 10. Patients were asked to define the symptoms and localization of the pain. Pain scores and SUVmax at the location of pain on PET/CT were recorded. All opioids were converted into the oral morphine equivalent dose by assessing the dose, administration route, and drug name to standardize the analgesic use the day before the treatment.

Radiotherapy

Treatment planning was done using the three-dimensional conformal RT planning system (Precise PLAN 2.11, Elekta, Crawley, UK). According to the International Commission on Radiation Units and Measurements Report 50, 100% dose was defined as the planning target volume isocenter. While planning target volume was covered with 95% of the dose, the maximum dose did not exceed 107%. Using a linear accelerator device and a multileaf collimator, 8 Gy external RT was applied to the planning target volume with an SF using 6 and/or 18 MV X-rays from two opposed areas.

Follow-up

After completion of RT, patients were evaluated at each visit with a full history and physical examination. Response to treatment was evaluated by clinical examination once a month throughout survival, the first being four weeks after the end of RT. The radiation oncologist used the faces pain rating scale to assess the severity of pain at BM. The treatment response criteria assessment by the international consensus was used in scoring the pain response after RT (table 1) [14]. Re-RT was administered to the patients who had progressive pain with radiological findings at post-treatment follow-ups.

Table 1. 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
OMED; daily oral morphine equivalent.	

Statistical analyses

Spearman correlation was used to determine the relationship between the SUVmax of the BMs before RT and the initial pain score. Analysis of the relationship between the SUVmax and post-RT treatment response was done by Mann-Whitney U and Kruskal Wallis tests. Univariate Cox regression analyses were used to determine the prognostic factors predicting re-RT. The Multivariate Cox regression was used to determine the prognostic predictors of re-RT with the variables that were statistically significant by the univariate Cox regression model. *P-value* ≤0.05 was accepted as statistically significant. In addition, to determine the optimal cut-off value of SUVmax for estimating complete pain response, receiver-operating characteristic (ROC) analysis was performed. Statistical package software (PASW Statistics, version 23; SPSS, Chicago, Ill) was used to conduct statistical analysis.

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RESULTS

The median patient age for males (n=28) and females (n=25) was 53 (24–76) and 51 (28– 68) years, respectively. Patient characteristics and treatment summary are presented in table 2. The median follow-up time was 32 weeks (3–134). Median SUVmax and initial pain score of 133 painful metastatic lesions were 6.8 (1.5–23.1) and 6 (2–8), respectively. Before RT, the median SUVmax of BMs was 4.6 (±1.42), 4.45 (±1.66), 9 (±2.33), and 12.6 (±3.49) for pain scores of 2 (n=13), 4 (n=32), 6 (n=42), and 8 (n=30), respectively. SUVmax was significantly related to pre-treatment pain score (r = 0.826, $p < 0.0001$) (figure 1). SUVmax was also found to be related to pain response to RT ($p<0.001$). Complete pain response was observed at 62 locations, and partial pain response was observed at 63 locations at posttreatment week 4. Median SUVmax of painful BMs were 5.1 (±1.96) and 10.3 (±3.52) for complete and partial pain responses at week 4 after completion of RT, respectively ($p<0.0001$). According to SUVmax, treatment responses at 4, 8, 12, 16, 20, 24 and 32 weeks are shown in table 3.

The best cut-off SUVmax to predict complete pain response was 7.95 in the ROC analysis [AUC: 0.91 (0.86–0.96); $p<0.001$] with a sensitivity of 74% and specificity of 88% (figure 2). Complete and partial pain response rates according to SUVmax ≤7.95 (when all weeks were calculated) were 88.5% (±4.6) and 11.5% (±4.5), respectively, and according to SUV>7.95, the rates were 25.5% (±11.5) and 74.5% (±11.5), respectively. Complete and partial pain response rates at 4 to 32 weeks according to cut-off SUVmax 7.95 are shown in detail in table 4.

Table 2. Patients' characteristics and treatment details.

Sex	***(n=53)***
Male	28
Female	25
Median age	***53***
Male	53
Famele	51
Primary cancer site	***(n=53)***
Lung cancer	25
Breast cancer	15
Head and neck cancer	4
Unknown primary neoplasm	4
Stomach cancer	4
Pancreas cancer	1
Metastasis type	***(n=53)***
Solitary	11
Multiple	42
Systemic therapy	***(n)***
Chemotherapy*	44
Bone-modifying agent	47
Opioids required	48
Treatment field	***(n=65)***
Vertebra	42
Pelvis	7
Humerus	9
Femur	7
Number of treatment fields (per patient)	***(n=53)***
One	44
Two	6
Three	3
Number of painful lesions per treatment field	***(n=65)***
1	29
2	15
3	15
4	2
5	3
6	1

*Lung cancer; taxane/gemcitabine (n=4), platinum (n=4), bevacizumab/pemetrexed (n=2), platinum/etoposide (n=10), Breast cancer; trastuzumab/vinorelbine (n=2), capecitabine/trastuzumab (n=3), platinum (n=3), taxane (n=4), Head and Neck cancer; cetuximab and/or platinum (n=3), Stomach cancer; taxane/platinum (n=4), Unknown primary neoplasm; platinum and/or cetuximab (n=4), Pancreas cancer; gemcitabine (n=1)

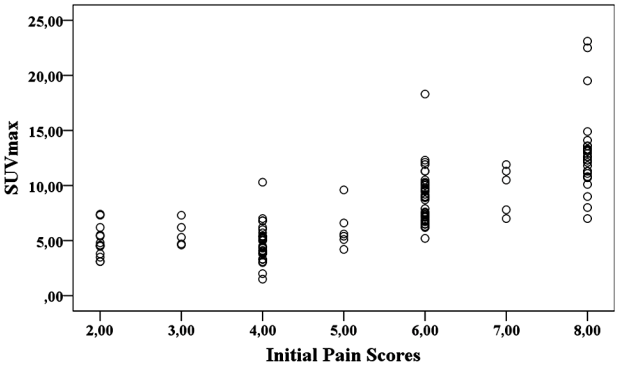

Figure 1. Relationship between the maximum standardized uptake value (SUVmax) and pain scores

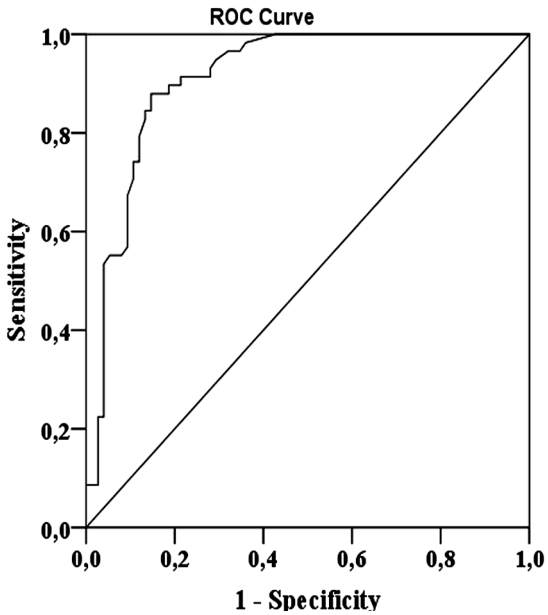

Figure 2. Ideal cut-off value ROC curve.

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The partial pain response rate was higher in the metastatic lesions with SUVs greater than cut-off SUVmax and some of these patients underwent re-RT because of pain progression. A total of 7 patients (8 osseous lesions) underwent re-RT after pain progression and the median progression time was 20 weeks (12–40). The median SUVmax in patients who received re-RT was 12.75 (±4.1) while it was 7 (±3.36) in those who not required re-RT (p<0.001). The SUVmax distributions by treatment responses are shown in figures 3A and 3B.

The results of Cox regression analyses for re-RT are shown in Table 5. In the univariate analyses, gender (p=0.05), primary cancer type (p=0.03), metastatic localization (p < 0.03), and the SUVmax (p<0.001) were found significantly related to re-RT. In the multivariate analysis, only SUVmax (p=0.02) was found significantly related to re-RT. Complications such as spinal cord compression or bone fracture were not observed in the patients during post-RT follow-ups.

Table 3. Median SUVmax for CR, PR and PP distributions by weeks after radiotherapy (RT).

Post-RT Follow-up (weeks)	*CR*	*PR*	*PP*[a]	*p-value*	*Number of Patients*[b]
4	5.1 (n=62)	10.3 (n=63)		<0.0001[c]	50 (n=125)
8	5.2 (n=67)	10.5 (n=44)		<0.0001[c]	47 (n=111)
12	5.4 (n=65)	10.7 (n=33)	17.7 (n=2)	<0.0001[d]	38 (n=100)
16	5.4 (n=59)	10.7 (n=27)	10.3 (n=1)	<0.0001[d]	35 (n=87)
20	5.4 (n=56)	10.7 (n=23)	11.7 (n=2)	<0.0001[d]	33 (n=81)
24	5.3 (n=53)	10.5 (n=19)	11.7 (n=2)	<0.0001[d]	31 (n=74)
32	5.3 (n=42)	8.95 (n=18)		<0.0001[c]	21 (n=60)

CR, complete response; PR, partial response; PP, pain progression
n = Number of painful lesions evaluated.
[a] One metastatic lesion that received re-irradiation due to PP at week 40 is not shown here.
[b] Eighteen patients died in the first 16 weeks, and fourteen patients died between 16 and 32 weeks.
[c] The Mann-Whitney U test
[d] The Kruskal Wallis H test

Table 4. CR and PR rates according to SUVmax cut-off value.

	SUVmax ≤ 7.95		SUVmax > 7.95		
Weeks	**CR % (n)**	**PR % (n)**	**CR % (n)**	**PR % (n)**	**p-value***
4	79.7 (59)	20.3 (15)	6 (3)	94 (48)	< 0.001
8	92.4 (61)	7.6 (5)	13.3 (6)	86.7 (39)	< 0.001
12	91.6 (55)	8.8 (5)	26.3 (10)	73.7 (28)	< 0.001
16	90.4 (47)	9.6 (5)	35.3 (12)	64.7 (22)	< 0.001
20	90.2 (46)	9.8 (5)	35.7 (10)	64.3 (18)	< 0.001
24	90.2 (46)	9.8 (5)	33.3 (7)	66.7 (14)	< 0.001
32	84.8 (39)	15.2 (7)	28.6 (3)	71.4 (11)	< 0.001

CR: Complete response, PR: Partial response, n = Number of painful lesions. * The Mann-Whitney U test

Table 5. Univariate and multivariate analyses for re-irradiation.

Univariate	**P value**	**HR**	**95% CI**
Age	0.18	1.056	0.975-1.144
Gender	0.05	1.965	1.022-3.780
Performance status	0.97	1.040	0.094-11.473
Primary cancer (breast vs. other)	0.03	2.335	1.087-5.013
Location (spinal vs. non–spinal)	0.03	4.790	1.140-20.116
Metastatic lesion (multiple vs. solitary)	0.11	2.421	0.436-13.507
Number of painful fields	0.24	0.592	0.244-1.437
Bone-modifying agent	0.8	0.047	0.001-6.499E+12
SUV_{max}	< 0.001	1.341	1.188-1.514
Multivariate			
Gender	0.6	0.515	0.041-6.470
Primary cancer (breast vs. other)	0.65	0.681	0.129-3.589
Location (spinal vs. non–spinal)	0.71	0.716	0.058-8.863
SUV_{max}	0.02	1.632	1.036-2.570

SUV_{max}; Maximum standardized uptake value, CI; confidence interval
HR; hazard ratio

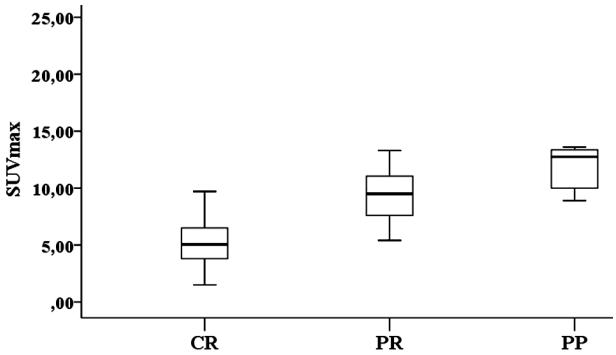

Figure 3A. SUVmax distributions according to treatment responses. SUVmax; maximum standardized uptake value, CR; complete response, PP; pain progression, PR; partial response. Center bold lines are the median values, and the bottoms and tops of the boxes are the 25th and 75th percentiles, respectively.

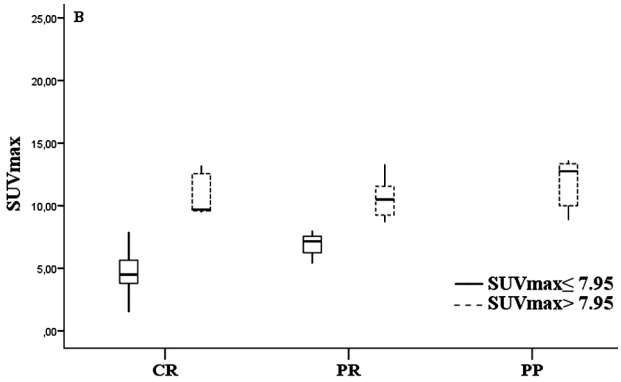

Figure 3B. SUVmax distributions of treatment responses according to cut-off value. SUVmax; maximum standardized uptake value, CR; complete response, PP; pain progression, PR; partial response. Center bold lines are the median values, and the bottoms and tops of the boxes are the 25th and 75th percentiles, respectively.

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DISCUSSION

Our results showed that painful BM with lower SUVmax had better response to treatment and pre-treatment pain severity was correlated with initial SUVmax of the BM. Also, there was a correlation between higher pre-treatment SUVmax and the further need for re-RT in patients treated with SF RT. FDG-PET is frequently used to evaluate response to RT for primary malignancies [15-18]. High SUV of the primary tumor before [15, 16] and after [15-18] RT is associated with a worse treatment response. Few studies in the literature investigate the initial FDG uptake in the BM and the response to palliative RT in these patients.

FDG-PET has been shown as effective in determining the response to RT of primary cancers in several studies. Pre-RT high SUV has significantly been associated with higher recurrence rates of the primary tumor [3, 4, 6 ,7, 19-21] which is consistent with our findings. Three retrospective studies have investigated the correlation between SUVmax of the metastatic tumor and long-term local control in patients with BM [8-10]. Zhao *et al.* [8] found that a higher pre-RT SUVmax was a predictor for the progression in the previously irradiated area. Choi *et al.* [9] showed that there was a significant correlation between higher SUV and improved local control in patients with BM of hepatocellular carcinoma which is contrary to our study's findings. This contradiction may be explained by the difference between the study populations and the less radiosensitive nature of hepatocellular carcinoma when compared to the malignancies, and the differences in the designs of the studies and the irradiation doses used. In Tateishi *et al.*'s retrospective study evaluating the morphologic and metabolic changes in PET/CT after systemic therapy in breast cancer patients with BM, reduction in the tumor's SUV was reported to be useful in predicting the length of response [10].

In our previous prospective study [12], we found that SUVmax of the BM was related to the initial pain severity of these patients, and higher SUVmax at the metastatic lesion was related to incomplete pain response to the palliation with SF RT. In the prospective study of Tahara *et al.* [11], while neither pre-RT SUVmax nor post-RT SUVmax was related to the pain response, the change in SUVmax (pre-RT SUVmax − post-RT SUVmax) was related to the treatment response to RT in patients with BM. They reported that performing FDG-PET both pre- and post-RT may be useful in predicting the outcome of pain control in the treatment area after RT for painful BM. Unlike our previous [12] and the present studies, they could not find a relationship between pre-RT SUVmax and pain response to RT. The difference in results between the studies may be related to the heterogeneity in the responder group of Tahara *et al.*'s study which was composed of complete and partial responses together, while the responders were categorized as complete and partial in our study. However, factors leading to the difference between the findings of the studies are not clear enough, and further studies are needed to validate the findings.

Individualized RT for BM has been shown applicable to optimize fractionation and improve local control by several studies [22-24]. In Yamada *et al.*'s study [24] which investigated local control for spinal metastases, high-dose RT with SF was applied, and local control of the metastases was found better. This technique may be used in patients with higher pre-RT SUVmax to obtain better tumor control and better pain response according to the findings of our study.

While planning RT for patients due to painful BM, SUVmax may be a facilitator for the prediction of re-RT. In the study, we aimed to determine whether SUVmax might have a role in predicting incomplete pain response and the need for re-RT to avoid repetitious treatments. To our knowledge, this is the first study investigating the pre-treatment SUVmax to predict complete pain response in patients treated with SF RT for painful BM. Higher rates of partial response and the need for re-RT for the same location in patients with higher SUV who underwent SF RT despite similar pain responses with MF may be explained by tumor recurrence related to uncontrolled tumor cells with high tumor burden. Additionally, according to the linear-quadratic model, SF RT with a dose of 8 Gy has lower BED compared to MF regimens which may also explain the higher rates of re-RT in patients initially treated with SF RT. Treatment with schedules with lower BED (SF, 8 Gy) may result in less tumor cell death, repopulation of the tumor, and finally re-RT due to painful recurrences. To the results of this study, doses with higher BED may be prescribed in patients with high SUV (>7.95), or SF RT may be considered in patients with non-complicated BM with low SUV (≤7.95).

The treatment response of the patients with a higher initial pain score was stronger as compared to the ones with a lower pain score. This finding may be related to the inadequacy of the pain scale of 0–10 in evaluating the change in severity of pain if the response is not complete in locations with low initial pain scores. A pain scale of 0–10 is cost-effective and easy to attain compared to the PET scan, but it is not an objective method and the patient's sensitivity to pain may be variable. However, routine use of PET scans should not be considered only for the evaluation of response to palliative RT in patients with BM until its additional benefits are proven by further studies with larger study populations.

Limitations

The major limitation of the study is the small patient population with non-homogenized primary can-

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cers. Second, BM is not categorized regarding to involvement of the osseous cortex or soft tissue. In addition, tumor sizes are not measured by image analysis. Another limitation is that multiple painful locations described by the patients may not be independent, thus accurate evaluation of pain scores in multiple metastatic sites was difficult. Finally, the cost-effectiveness of performing FDG PET/CT before and after RT in patients with BM is still unclear, when the aim is the palliation of pain and the patient can state the treatment response.

CONCLUSION

The initial status of metabolic activity in the painful metastatic bone may potentially be responsible for the further need for re-RT. FDG SUVmax may predict the need for re-RT in patients with painful BM initially treated with 8 Gy of SF RT. This may help the decision of treatment with SF RT which is associated with higher rates of incomplete pain response and further probability of re-RT at the same location in patients with high SUVmax (>7.95). However, further studies with a larger number of patients are required.

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***Ethical considerations*:** This study was approved by the Ethics Committee of the Faculty of Medicine at Gaziantep University (number: 12-2008/229 and date: 18.12.2008). All procedures including the informed consent process were carried out in compliance with the ethical standards of committees (institutional and national) responsible for human experiments, the 1975 Declaration of Helsinki, and its version revised in 2000.

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***Author contributions*:** Supervision, conceptualization, methodology, validation, writing, review, and editing: (A.K). Formal analysis, visualization, preparation, writing —original draft: (A.K) and (M.A). All authors have read and agreed to the submitted version of the manuscript. Yours sincerely.

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