Research Article

Bone Metastases on $_{18}$F-FDG PET/CT Imaging in Patients with Colorectal Cancer. Does Bone Scintigraphy Still Have a Role?

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Abstract

Objectives: To analyze the rates, patterns, and features of bone metastases(BM) detected using $_{18}$F-FDG PET/CT in patients with colorectal cancer(CRC) and compare them with bone scans (BS) in terms of BM detection.

Methods: A total of 920 patients with CRC who underwent $_{18}$F-FDG PET/CT scans during the period from Jan 2016 to May 2019 were retrospectively reviewed. Among these, imaging results were compared for 29 patients who underwent BS within 1 month of $_{18}$F-FDG PET/CT.

Results: In 38(4.1%) patients, 211 BM were detected on $_{18}$F-FDG PET/CT imaging. Of 211 BM detected by PET/CT, 42 were osteolytic, 30 were osteoblastic, 55 were mixed, and 84 were CT-negative. Mean SUVmax values of osteoblastic, CT-negative, osteolytic, and mixed lesions were 6.05±2.80, 5.42±2.56, 11.62±6.34 and 8.74±4.48, respectively. A total of 126 BM were detected in 16 of 29 patients who underwent both BS and PET/CT imaging. In patient-based evaluation, the sensitivity, specificity and accuracy of PET/CT and BS were 100%,76.92%,89.66% and 93.75%,46.15%,72.41% and in lesion-based evaluation these values were 99.21%,72.73%,97.08% and 52.38%,0%,48.18%, respectively.

Conclusion: $_{18}$F-FDG PET/CT is a valuable imaging method for detecting BM in colorectal cancer patients, especially since it can truly detect CT-negative or isolated BM. BS is not required for patients who have undergone PET/CT imaging.

Keywords: Bone metastases, bone scan, colorectal cancer, $_{18}$F-FDG PET/CT

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In colorectal cancer (CRC), the most common distant metastasis sites are the liver and lungs, while bone metastasis (BM) is rare. The incidence of BM from CRC is up to 23.7% in autopsy cases, but 0.96 %-10.9% in clinical cases.[1–9]

It is well known that fluorine-18 fluorodeoxyglucose ($_{18}$F-FDG) positron emission tomography (PET)/computed tomography(CT) is a useful imaging modality for CRC, particularly concerning initial staging, recurrence, and metastasis determination in those with equivocal findings on routinely used radiological imaging (such as CT, MRI) or curative resection planned for a primary tumor or metastatic lesion, to monitor the response to therapy, and for long-term cancer surveillance.[10–14] Bone scan (BS) with $_{99m}$Tc-MDP has been used extensively for the detection of BM in many oncological diseases for years. BS is more effective for the detection of osteoblastic BM from breast cancer

and prostate cancer. However, the diagnostic power of BS for detecting lytic metastases or early metastases in which morphological changes have not yet occurred is low. Many studies are comparing $_{18}$F-FDG PET/CT with BS, and especially in malignancies with osteolytic and mixed BM and metastatic lesions limited to bone marrow, $_{18}$F-FDG PET/CT has higher sensitivity and diagnostic power than BS.[15–18]

To the best of our knowledge, there is no large patient series study in the literature focusing on BM in $_{18}$F-FDG PET/CT imaging of CRC patients. The purpose of this study is to analyze the rates, patterns, and features of BM detected using $_{18}$F-FDG PET/CT in patients with CRC and also to compare its effectiveness with BS in terms of BM detection.

Methods

Patients

Medical records of 920 patients with CRC who underwent $_{18}$F-FDG PET/CT scan during the period from January 2016 to May 2019 were reviewed. $_{18}$F-FDG PET/CT images of all 920 patients and those who underwent BS and $_{18}$F-FDG PET/CT within 1 month were retrospectively analyzed. The patients with known BM before $_{18}$F-FDG PET/CT or BS and patients with other malignancies were not included in this study. For comparative evaluation, inclusion criteria were: (a) maximum one month between $_{18}$F-FDG PET/CT and BS imaging, and (b) had not undergone any systemic treatment between the two modalities.

Ethics committee approval was obtained on 12.17.2019 with decision number 1515 for this clinical study which was designed retrospectively.

^{18}F-FDG PET/CT imaging protocol

Whole-body PET scans were performed using an LSO-based full-ring PET scanner (Siemens Biograph 6, Chicago, IL, USA). After fasting for at least 6 h, 370-555 MBq ^{18}F-FDG was injected intravenously. An uptake time of 1 h was allowed for the $_{18}$F-FDG distribution within the body. Whole-body CT scans were initially obtained from vertex to the upper thigh with slice collimation of 5 mm and a slice interval of 3.4 mm. The emission data were acquired for 2.5 min per bed (6-7 beds), which were later attenuation corrected with the digital CT data. Image reconstruction used ordered subsets expectation-maximization algorithm of 2 iterations and 8 subsets. Image analysis was carried out on the Esoft multimodality computer platform (Siemens Medical Solutions, Erlangen, Germany).

$_{99m}$Tc-MDP Bone Scintigraphy protocol

Whole-body BS was performed 3-4 h after intravenous injection of 740 MBq of $_{99m}$Tc-MDP. Anterior and posterior whole-body images were acquired with high-resolution parallel hole collimator on an E.CAM dual-head gamma camera (Siemens Medical Solutions; Knoxville, TN, USA), with the energy centered at 140 KeVwith 20% energy window and scanning speed 10 cm/min. Data acquired were stored in a 256×1024 matrix. Additional static images were obtained with individual examinations if needed, but no single-photon emission computerized tomography (SPECT) imaging was performed.

Image Analysis

Two experienced nuclear medicine physicians independently examined the BS and ^{18}F-FDG PET/CT for each patient. Both readers were blind to all pathology reports and other clinical information regarding the patient, except for the diagnosis of CRC. The skeletal system was divided into 5 regions: the spine (including the whole vertebral column), the pelvis (including the iliac, ischial, and pubic bones), the thorax (including ribs and sternum), the head (including all facial and skull bones), and the appendicular skeleton (including extremities, scapulae, and clavicles). In the comparative evaluation, a total of 25 lesions, up to 5 lesions from each region, were included.

BS results were interpreted by two experienced nuclear medicine physicians based on intensity configuration and the location and number of foci showing increased tracer activity. Uptake was interpreted as positive for bone metastasis if the radiotracer activity in the lesion was greater than that in normal bone. BS was considered negative if there was no significantly increased radiotracer uptake in the bones or if radiotracer uptake was characteristic of the benign disease (such as osteodegenerative disease or fracture).

On $_{18}$F-FDG PET/CT, focally increased FDG uptake in bone exceeding normal background bone uptake was interpreted as positive for BM. However, even if bone lesion with focally increased FDG uptake was shown, the lesion was read as negative when CT images of the $_{18}$F-FDG PET/CT scan showed traumatic or degenerative changes. The BM were visually classified into four types based on their computed tomography (CT) appearance on $_{18}$F-FDG PET/CT: osteoblastic, osteolytic, mixed, and negative. The FDG maximum standardized uptake value (SUVmax) was analyzed and compared between these groups. The detection rates using BS and $_{18}$F-FDG PET/CT for BM were calculated on a per-patient basis and a per-lesion basis.

BM was verified by histological findings or radiologic evaluation such as magnetic resonance imaging(MRI) and contrast-enhanced CT or clinical follow-up including $_{18}$F-FDG PET/CT, BS, MRI, CT for at least 6 months. Positive lesions were accepted as benign if they showed regression or no significant

changes or disappeared for at least 6 months without treatment. Positive lesions were accepted as metastases if they showed regression or progression under treatment.

Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used when evaluating the study data. The suitability of quantitative data to normal distribution was tested with the Shapiro-Wilk test and graphical examinations. Kruskal Wallis test was used for comparisons of three or more groups that did not show normal distribution, and Bonferroni-Dunn test was used for binary comparisons. For comparison of qualitative data, Pearson Chi-Square test, Fisher's Exact test, McNemar's test, and diagnostic screening tests (specificity, sensitivity, etc.) were used. Statistical significance was accepted as p<0.05.

Results

Bone Metastases on $_{18}$F-FDG PET/CT imaging

Patient characteristics and clinical features are given in Table 1. FDG positive BM were detected on $_{18}$F-FDG PET/CT imaging in 38 (4.1%) (14 female, 24 male) of 920 CRC patients (394 rectum, 526 colon). BM were present in 19 (3.6%) colon cancer patients and 19 (4.8%) rectal cancer patients in the cohort group. The mean age of the patients with BM was 61.7 years (range, 32-83). Most patients with BM were at stage 3 (31.58%) or 4 (42.1%) at the time of CRC diagnosis. With $_{18}$F-FDG PET/CT imaging, only BM were detected in 4 patients. BM with only abdominal lymph node metastases was detected in 1 patient and with distant metastases in 33 patients. While 1 of the 4 patients with only BM detected on $_{18}$F-FDG PET/CT imaging had isolated BM, the other 3 patients had anamnesis of pre-detected and treated visceral metastases. Lung (55.26%) and liver (55.26%) were the most common distant metastases in patients with BM.

The total number of FDG-positive BM detected in 38 patients with $_{18}$F-FDG PET/CT imaging was 211. The number of metastatic lesions was 1 in 9 patients (lumbar 5th vertebra, sternum, thoracic 2nd vertebra-in two patients-, right hemithorax 6th rib, lumbar 3rd vertebra, occipital bone, left iliac bone), 1-5 in 18 patients, and >5 in 11 patients. While 75 (35.4%) of the BM were in the vertebral column (6 in cervical vertebra, 24 in thoracic vertebra, 45 in lumbar vertebra-sacrum), 57 (27%) were in the pelvic bones, 37 (17.5%) were in the extremities, 37 (17.5%) were in the thoracic region, and 5 (2.6%) were in the cranium.

Table 1. Demographic and clinical features of the patients with BM

Demographic and clinical features	n	(%)
Gender		
Female	14	(36.8)
Male	24	(63.2)
Tumor Site		
Colon	19	(50)
Rectum	19	(50)
Stage at Diagnosis		
Stage 1	4	(10.53)
Stage 2	6	(15.79)
Stage 3	12	(31.58)
Stage 4	16	(42.1)
BM Diagnosing Time		
At initialStage	11	(28.95)
On Followup	27	(71.05)
BM only	1	(2.63)
BM only with abdominal lymh nodes	1	(2.63)
BM with distant metastases	37	(97.37)
Lung	21	(55.26)
Liver	21	(55.26)
Brain	2	(5.26)
Peritonitis Carcinomatosa	5	(13.16)
Adrenal Gland	1	(2.63)
Pleura	1	(2.63)
Extraabdominal Lymph Nodes	10	(26.32)

BM: Bone metastases; n: number of patients.

When the CT findings of 211 BM detected by $_{18}$F-FDG PET/CT were evaluated, 42 were osteolytic, 30 were osteoblastic, 55 were mixed, and 84 were CT negative. SUVmax values of BM according to the different CT features are given in Table 2. SUVmax values of mixed and osteolytic lesions were significantly higher compared to osteoblastic and CT-negative lesions(p=0.000). There was no statistically significant difference between CT-negative and osteoblastic lesion groups (p=0.270). SUVmax values of osteolytic lesions were significantly higher than that of mixed lesions (p=0.012).

Comparison of $_{18}$F-FDG PET/CT with Bone Scan

A total of 126 BM were detected in 16 (55%) of 29 patients who had undergone both BS and 18F-FDG PET/CT imaging (Table 3). In 1 patient, while BS was negative, BM was detected with 18F-FDG PET/CT (Fig. 1). Four patients had only BM, whereas 12 patients had visceral and/or lymph node metastases with BM.

While 125 of the BM were $_{18}$F-FDG positive, 66 were MDP positive. In terms of BM detection, the sensitivity, specificity and accuracy of $_{18}$F-FDG PET/CT and BS for patient-based evaluation were 100%, 76.92%, 89.66% and 93.75%,

Table 2. Comparison of SUVmax values of BM according to CT features

CT features of BM	n	(%)	SUVmax		p
			Min-Max (Median)	Mean±Sd	
Mixed lesion	55	(26.1)	1.73-20.86 (8.63)	8.74±4.48	0.001
Lyticlesion	42	(19.9)	1.80-33.76 (11.09)	11.62±6.34	
Scleroticlesion	30	(14.2)	1.80-12.69 (5.78)	6.05±2.80	
CT negativelesion	84	(39.8)	1.41-14.64 (5.02)	5.42±2.56	
Totally	211	(100)	1.41-33.76 (6.60)	7.61±4.74	

BM: Bone Metastases; CT; Computed Tomography; SUVmax: Standardized uptake value.

Table 3. Comparison between $_{18}$F-FDG PET/CT and BS results for BM diagnosis

Results	Lesion-based analysis		Patient-based analysis	
	$_{18}$F-FDG PET/CT	BS	$_{18}$F-FDG PET/CT	BS
TP	125	66	16	15
TN	8	0	10	6
FP	3	11	3	7
FN	1	60	0	1

$_{18}$F-FDG: Fluorine-18 fluorodeoxyglucose; PET/CT: Positron emission tomograhy/Computed tomography; BS; Bone scan; BM: Bone metastases; TP: True-positive; TN: True-negative; FP: False-positive; FN: False-negative.

46.15%, 72.41% and for lesion-based evaluation these values were 99.21%, 72.73%, 97.08% and 52.38%, 0%, 48.18%, respectively. Of the 60 BM detected by $_{18}$F-FDG PET/CT but negative on BS imaging; 5 were osteoblastic, 22 were osteolytic, 2 were mixed, and 31 were CT-negative. Only 1 osteoblastic BM was MDP-positive but FDG-negative.

There were 8 false-positive lesions in 4 patients on BS and $_{18}$F-FDG PET/CT was true negative for these lesions. Four of these lesions were in the pelvic bones, 3 in the vertebral column, and 1 in the ribs. Final diagnoses in false-positive lesions were osteodegenerative change in 5 lesions, insufficiency fracture in 2 lesions, and a compression fracture in 1 lesion. There were 3 lesions (in 3 patients) in which both BS and $_{18}$F-FDG PET/CT were false-positive (Fig. 2). Histopathologic investigation made the diagnosis of giant cell bone tumor of the lesion in the right femur, while inflammatory process diagnosis was made for the lesions in the coccyx and sacrum of the other two patients.

Discussion

In the present study, 211 BM were detected with $_{18}$F-FDG PET/CT in 38 (4.1%) of 920 CRC patients (4.8% with rectal cancer; 3.6% with colon cancer). The rate of FDG-positive BM was 3.21% on initial staging, while it was 4.68% on follow-up. In a SEER database study, in which Qui et al.[19] evaluated the data of 46607 CRC patients at first diagnosis, the BM rate was 1.2% in patients with rectum cancer and 0.8%

in patients with colon cancer. Guo et al.[20] reported that 1.2% of the patients had BM in a SEER database study that included 212787 de-novo CRC patients. These rates, which are lower than our series consisting of $_{18}$F-FDG PET/CT imaging data, are due to routine imaging of CRC patients in the staging phase with CT and MRI.
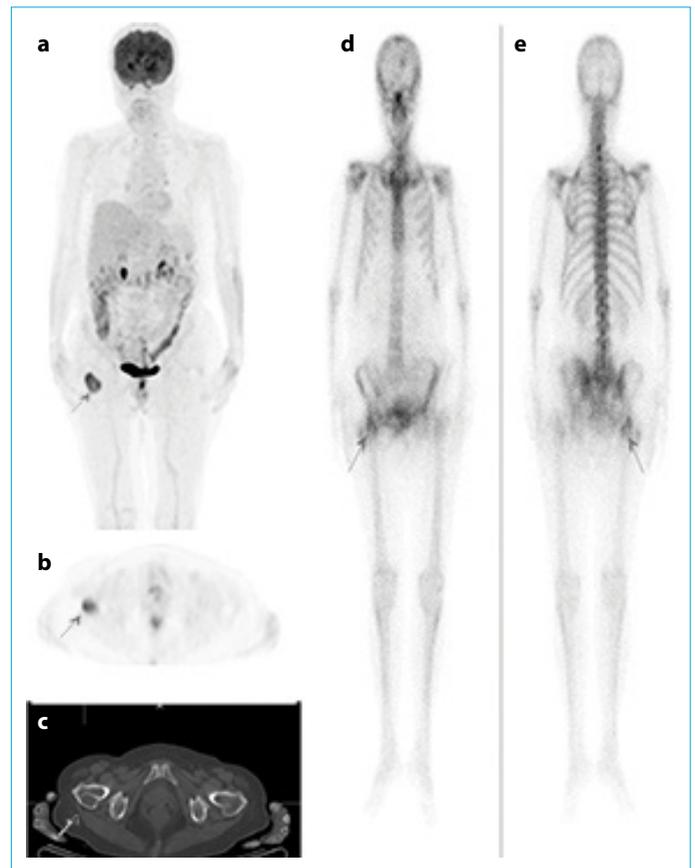
In the study by Sun et al.,[21] they detected BM in 31 (6%) of 594 CRC patients followed by curative resection. In their series, BM development was more frequent in patients with rectal cancer compared to colon cancer patients (8.56% vs. 3.47%). While only 1 of these patients had isolated BM, 15 of the remaining 30 patients had liver metastases and 19 had lung metastases. Vertebral colon (67.7%) and hippelvis (41.9%) were the most common areas of metastasis, and 18 (58%) out of 31 patients had multiple BM. Li et al.[22] in a study including 2790 CRC patients, identified BM in 74 (2.7%) patients. In this series, they reported 1 (single) BM patient rate was 67.57%. In our series, multiple BM were present in 29 (74.4%) of 38 patients.While in our study, vertebral column and pelvic bones were the most common metastasis regions, the rate of patients with multiple BM were higher. Compared to this study, the reason for the high rate in our series is that they detected BM with BS, CT, and MRI, not with $_{18}$F-FDG PET/CT. Of the patients with BM detected by $_{18}$F-FDG PET/CT in our study, 21 had lung metastases, 21 had liver metastases and 24 had lymph node metastases (14 abdominal, 10 extra-abdominal). While 1 of the 4 patients with only BM detected on $_{18}$F-FDG PET/CT imag-
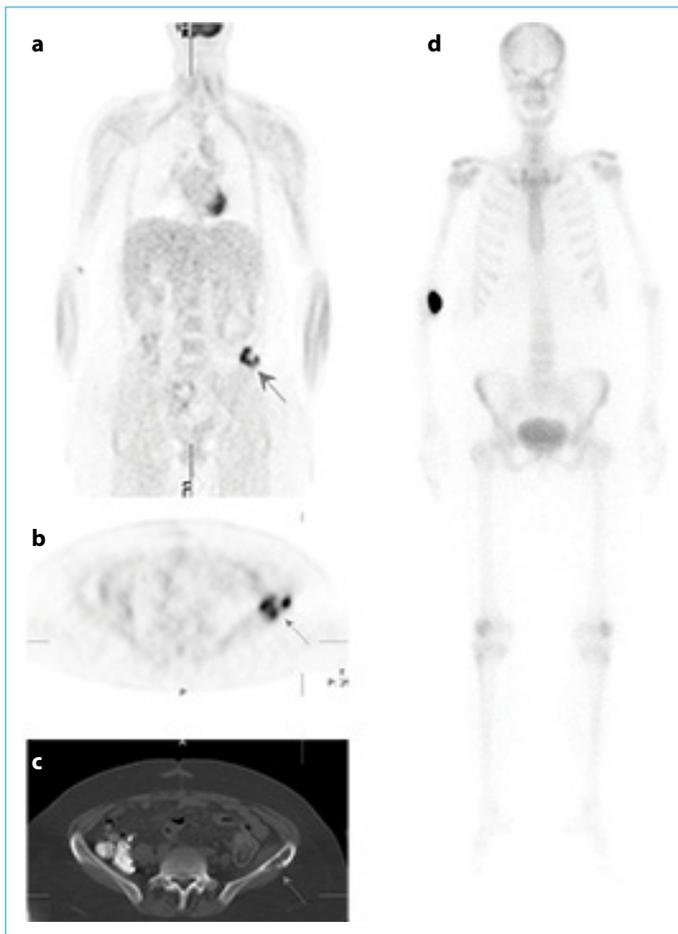
Figure 1. Whole-body PET **(a)**, axial PET **(b)**, CT **(c)** images and anterior whole-body BS **(d)**. A 65-year old male patient diagnosed with colon cancer underwent $_{18}$F-FDG PET/CT and BS imaging for restaging. FDG positive lytic lesion in left iliac bone detected on PET/CT imaging (arrow in a, b, c).Whole-body BS was negative for metastasis. Histopathological evaluation revealed metastases.

Figure 2. Whole-body PET **(a)**, axial PET **(b)**, CT **(c)** images and anterior-posterior whole-body BS **(d, e)**. A 52-year old female patient diagnosed with rectal cancer underwent $_{18}$F-FDG PET/CT and BS imaging for restaging. FDG positive lytic lesion with sclerotic rim in right femur subtrochanteric region was detected on PET/CT imaging (arrow in a, b, c).Whole-body BS showed moderate MDP uptake in same location. Both $_{18}$F-FDG PET/CT and BS were suggestive for metastases but histopathological evaluation revealed giant cell bone tumor.

ing had isolated BM, the other 3 patients had anamnesis of pre-detected and treated visceral metastases. Baek et al.[9] reported that in their study involving 5479 patients, they detected BM in 63 patients (1.1%), 73% of these patients had multiple BM and 87.3% of them had other metastases at the same time. In this study, it was reported that 74.1% of BM were determined with $_{18}$F-FDG PET/CT and 47.7% with BS, but lesion characteristics and comparative evaluation data were not reported. In the study by Roth et al.,[23] 252 CRC patients who were initially staged or restaged using $_{18}$F-FDG PET or $_{18}$F-FDG PET/CT imaging were retrospectively evaluated, and BM was detected in 14 (5.5%) patients. None of these patients had isolated BM and 8 had liver and 10 had lung metastases. However, in this study, data about the characteristics of BM were not reported.

BM in CRC patients are usually osteolytic and less frequently osteoblastic.[2,4,24] In the autopsy series, bone mar-

row metastases in CRC patients were found in 93 (27%) of 1541 cases.[25] In our study,42 out of 211 BM were osteolytic, 30 were osteoblastic, 55 were mixed, and 84 were CT negative according to the CT findings. We found that SUVmax values of mixed and osteolytic BM were significantly higher compared to those of osteoblastic and CT-negative lesions and there were no statistically significant differences between CT-negative and osteoblastic lesion groups. There are different and controversial results in the studies comparing CT features and SUVmax values of lesions in the literature. In their study of breast cancer patients, Gurkan et al.[26] did not find a significant difference between the SUVmax values of osteoblastic, osteolytic, and mixed BM. In the study by Hur et al.,[27] SUVmax values were significantly higher in osteolytic BM than in osteoblastic lesions.

$_{18}$F-FDG PET/CT and BS have different mechanisms for

BM detection. Increased activity uptake on BS imaging is due to increased osteoblastic reaction in metastatic lesions.[18]F-FDG, on the other hand, has a high rate of uptake in malignant cells with increased glucose metabolism. Therefore, BS has low sensitivity compared to $_{18}$F-FDG PET/CT for lytic metastases and bone marrow metastases where morphological changes have not yet occurred.[16,28] In the study by Liu et al.,[15] which included 117 cancer patients with a total of 459 BM, the sensitivity of $_{18}$F-FDG PET/CT was 96.6% and BS was 84.6% in terms of BM detection. In this study, 224 lesions showed characteristic osteoblastic metastases and 99 lesions were osteolytic or mixed lesions. In osteolytic or mixed lesions, the sensitivity of $_{18}$F-FDG PET was higher than BS, while in osteoblastic lesions, the sensitivity of BS was similar to $_{18}$F-FDG PET/CT. In the present study, we found that $_{18}$F-FDG PET/CT has high sensitivity, specificity, and accuracy rates for both patient-based and lesion-based evaluation compared to BS. In comparative evaluation, 125 of 126 lesions were detected by $_{18}$F-FDG PET/CT in all 16 patients with BM, while 66 MDP-positive lesions were detected in 15 of 16 patients by BS.

In BS imaging, false-positive MDP uptake is frequently seen in benign processes (such as osteoarthritis, fractures, degenerative changes). Since increased FDG uptake is associated with increased glycolysis in tissues, inflammatory processes such as osteomyelitis, bone lesions due to benign systemic diseases, benign primary bone lesions, trauma, or osteoarthritis may also cause false-positivity on $_{18}$F-FDG PET/CT imaging.[29] In our patient group with comparative evaluation, there was false-positivity in both $_{18}$F-FDG PET/CT and BS, but the number of false-positive lesions on BS (11 lesions on 7 patients) was higher than on $_{18}$F-FDG PET/CT (3 lesions in 3 patients).

Our study has some limitations. The retrospective study design may have introduced selection bias in our data. The fact that BS imaging was done conventionally and SPECT/CT was not used may have created a bias in favor of $_{18}$F-FDG PET/CT on comparative assessment. Another limitation is that histopathological verification was not used as the gold standard for the diagnostic confirmation of all bone lesions detected in patients in our cohort group.

In conclusion, $_{18}$F-FDG PET/CT is a valuable imaging method for detecting BM in CRC patients. It can truly detect CT-negative or isolated bone metastases with whole-body imaging. Also, other distant metastases can be detected simultaneously with BMs by $_{18}$F-FDG PET/CT. BS is not required for patients who have undergone PET/CT imaging. However, the possibility of false-positive benign bone lesions on $_{18}$F-FDG PET/CT imaging should be kept in mind.

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