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ORIGINAL ARTICLE

Fluorine-18-fluorodeoxyglucose-positron emission tomography evaluation in metastatic bone lesions in lung cancer: Possible prediction of pain and skeletal-related events

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Bone metastasis; FDG; glucose activity; small cell lung cancer; SUVmax.

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Abstract

Background: Fluorine-18-fluorodeoxyglucose-positron emission tomography (FDG-PET) uptake in primary lesions has been well studied, but little information is available about metastatic bone lesions in patients with lung cancer. The present study was performed to evaluate the relationships between metastatic bone FDG uptake and clinical parameters in patients with lung cancer.

Methods: FDG uptake was evaluated as the maximum standardized uptake (SUVmax) value of each targeted bone lesion, and the bone to primary lesion ratio of SUVmax (B/P ratio) was calculated. Forty-nine patients (27 men and 22 women) with a diagnosis of lung cancer (small cell lung cancer [SCLC], $n = 7$; non-small cell lung cancer [NSCLC], $n = 42$) with bone metastasis, and a total of 185 bone metastatic lesions were evaluated.

Results: The SUVmax in bone and the B/P ratio were significantly higher in patients with pain and subsequent development of skeletal-related events than in those without pain or skeletal-related events, respectively. In addition, the SUVmax in metastatic bone lesions and the B/P ratio in SCLC were significantly lower than those in NSCLC, despite similar FDG uptake in the primary tumor.

Conclusion: Our findings suggest that FDG-PET evaluation in metastatic bone lesions could be useful to predict initial pain and subsequent clinical outcomes of local bone status in initially diagnosed lung cancer patients with bone metastasis. In addition, our results suggest that there could be histological differences in the biological activity of bone metastatic lesions in lung cancer, especially between SCLC and NSCLC.

Introduction

Positron emission tomography (PET) with fluorine-18-fluorodeoxyglucose (FDG) is routinely used for the diagnosis and staging of lung cancer.[1,2] As increased tumor uptake of FDG-PET reflects glucose metabolism and the proliferative activity of tumor cells,[3–7] the biological activity of FDG-PET has facilitated the prediction of treatment outcome in patients with lung cancer.[8–14] One meta-analysis suggested that the primary tumor standardized uptake value (SUV) on FDG-PET is of prognostic value in surgically resected and advanced non-small cell lung cancer (NSCLC).[7] In addition, decreased FDG uptake after chemotherapy or chemoradiotherapy is a better predictor of tumor reduction, progression-free survival, and overall survival (OS) than computed tomography (CT) findings.[10–13] Many studies regarding FDG uptake in the primary lesion and clinical outcomes in patients with lung cancer have been conducted. However, few studies regarding the role of

FDG-PET for assessing metastatic lesions in patients with lung cancer have been published. Bone is one of the most common sites of metastases in lung cancer,[15,16] and pain is the most common symptom related to bone metastasis.[16] Bone metastasis could cause significant complications, referred to as skeletal-related events (SREs), including spinal cord compression, intractable pain, pathological fractures, and humoral hypercalcemia. SREs ultimately have severe adverse effects on quality of life. Several groups have studied the relationships between bone metastasis and SUVmax uptake in patients with malignancies.[17–20] SUVmax assessed with FDG-PET/CT is a predictive biomarker of initial pain severity,[17,18] and decreased SUVmax after palliative radiotherapy for metastatic bone sites is a significant predictor of the response in patients with bone pain.[18–20] However, these studies did not focus on patients with lung cancer alone, and limited information is available regarding FDG-PET/CT assessment in metastatic bone lesions in patients with lung cancer. To our knowledge, there have been no previous studies of FDG-PET/CT assessment of bone metastasis in patients with lung cancer, particularly according to histological differences, the presence of bone metastatic pain, and the subsequent development of SREs.

We evaluated the relationships between FGP-PET uptake in bone metastasis and clinical characteristics in patients with lung cancer. This study was performed to examine whether parameters of FDG-PET/CT in metastatic bone lesions differ between histological types and/or are related to clinical manifestations, such as initial pain and SREs, in patients with lung cancer.

Methods

This retrospective study was approved by the institutional review board of Shinshu University School of Medicine (approval number: 3962) and was conducted in accordance with the principles of the Declaration of Helsinki.

Study population and methods

We retrospectively investigated consecutive patients with lung cancer who received treatment at Shinshu University Hospital and underwent FDG-PET/CT examination at the Positron Imaging Center, Aizawa Hospital, between April 2010 and June 2015. FDG-PET/CT was performed for all patients as part of an initial staging examination. Patients eligible for this study were required: (i) to have pathologically proven lung cancer or recurrence after surgery, and (ii) bone metastasis diagnosed by radiographic and FDG-PET examinations. Histological or cytological specimens containing tumor cells were examined for *EGFR* mutations by peptide nucleic acid-locked nucleic acid PCR clamp assay, for *ALK* by immunohistochemical analysis, and for *EML4-ALK* fusion by dual fluorescence in situ hybridization. All subjects were chemotherapy- and/or palliative radiotherapy-naïve for metastatic bone lesions. After diagnosis of metastatic lung cancer, subjects were treated with an appropriate chemotherapy regimen and/or radiotherapy according to the guidelines for diagnosis and treatment of lung cancer edited by the Japanese Society of Lung Cancer (https://www.haigan.gr.jp/modules/guideline/index).

Intravenous zoledronic acid or subcutaneous denosumab was used to manage bone metastasis. We analyzed the electronic medical records of eligible patients and checked for the presence of pain associated with bone metastases and SREs. The presence of bone cancer pain was evaluated at the time of FDG-PET examination and SREs had been checked during the clinical course after therapy in each patient. SREs were defined as pathological fractures, newly developed bone pain, or requiring palliative radiotherapy or spinal cord compression. Hypercalcemia was not included in the definition of SREs. OS was defined as the interval from initial diagnosis to the date of death or the last follow-up.

Instruments and fluorine-18-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) examination

Original FDG using a cyclotron facility and PET-CT images were obtained at Aizawa Hospital. All patients fasted for at least five hours prior to the PET-CT study and showed a blood glucose level < 150 mg/dL at the time of FDG injection. Patients received an intravenous injection of FDG at a dose of 4 MBq/kg and then rested for approximately one hour before undergoing imaging. Image acquisition was performed using a dedicated PET-CT scanner (Discovery PET/CT 600; GE Healthcare, Waukesha, WI, USA). A low-dose CT scan for attenuation correction and anatomical localization was performed, followed by acquisition of emission images from the head to the thigh in three-dimensional acquisition mode at two to three minutes per bed position. PET images were reconstructed iteratively with attenuation correction.

Evaluation of FDG-PET uptake and the maximum standardized uptake value (SUVmax)

For semiquantitative analysis, spherical regions of interest (ROIs) were placed at the primary lung tumor and bone lesions in each subject on the PET-CT images and SUVmax was obtained. SUVmax was defined at the peak value on one pixel with the highest counts within the ROI.

FDG uptake was evaluated as the SUVmax of each target lesion and the bone to primary lesion ratio of the SUVmax (B/P ratio) was calculated. As the SUVmax in small tumors could underestimate the metabolic activity as a result of partial volume averaging,[21] the target lesion size criteria were defined as > 10 mm in bone and > 20 mm in the primary tumor on FDG-PET/CT.

Two radiologists, independent of the present study, checked the radiologic features of bone metastases, and divided the sample into osteoblastic, osteolytic, and undeterminable metastasis. The SUVmax was evaluated according to the radiologic findings and histological types of lung cancer.

Data and statistical analysis

Data are presented as means ± standard deviation. The SUVmax of bone metastases and the B/P ratio were compared between histological types and radiologic features, with and without painful lesions, and with and without the development of SREs. The data were compared using the two-tailed Student's *t* test, and $P < 0.05$ was taken to indicate statistical significance. Receiver operating characteristic (ROC) curves were constructed to determine the diagnostic power of SUVmax in bone lesions to predict initial pain and the subsequent development of SREs. The sensitivity against false positivity (1 – specificity) was plotted. OS was analyzed using the Kaplan–Meier method and differences in the resulting distributions were compared between groups using the log-rank test. Pearson's correlation was used to evaluate OS and the number of bone metastases.

Results

Clinical characteristics

A total of 139 patients with lung cancer underwent FDG-PET/CT examination at Aizawa Hospital between April 2010 and June 2015. Among them, 49 patients (27 men, 22 women) had a diagnosis of lung cancer with bone metastasis and were eligible for inclusion in the study. The patient demographics are listed in Table 1. The patients ranged in age from 35 to 84 years, with a median age of 67 years. Pathological examination revealed the histological types of NSCLC: adenocarcinoma ($n = 31$), squamous cell carcinoma ($n = 6$), large cell carcinoma ($n = 3$), and large cell neuroendocrine carcinoma ($n = 2$). The remaining seven cases had SCLC. Fifteen and seven patients with adenocarcinoma had *EGFR* mutations and *ALK* fusion genes, respectively. The numbers of bone metastases in each patient are shown in Table 1. Nine patients had one, two, three, and four bone metastases, respectively, and 13 patients had > 5 bone metastases.

Table 1 Patient characteristics (n = 49)

Characteristic	N (%)
Age - year	
Median	67
Range	35–84
Gender	
Male	27 (55)
Female	22 (45)
Current status of disease	
Stage IV	41 (84)
Recurrence	8 (16)
Histologic type	
Adenocarcinoma	31 (64)
EGFR mutations	15 (31)
ALK fusions	7 (14)
Squamous cell carcinoma	6 (12)
Large cell carcinoma	3 (6)
Large cell neuroendocrine carcinoma	2 (4)
Small cell carcinoma	7 (14)
Numbers of bone metastases	
1	9 (18)
2	9 (18)
3	9 (18)
4	9 (18)
5–11	13 (27)

There were 185 bone metastatic lesions in the 49 patients included in the study. The locations of metastatic bone lesions are summarized in Table 2. Vertebrae and ilia were the predominant metastatic bone sites. The B/P ratio was not calculated in eight patients because of the small size of the primary tumor and recurrence in extrathoracic organs after thoracic surgery; thus, the B/P ratio in SUVmax was evaluated in 41 patients.

The initial chemotherapy regimens are listed in Table 3. Most patients were treated with platinum doublet chemotherapy, but in six patients, only palliative radiotherapy for

Table 2 Regions of bone metastases (n = 185)

Regions	Total number of bone metastases	Number of painful bone metastases
Cervical vertebrae	13	4
Thoracic vertebrae	29	10
Lumbar vertebrae	27	7
Sternum	8	0
Rib bone	28	1
Humerus	3	1
Sacral bone	17	3
Ischial bone	4	2
Ilium bone	27	4
Pubis	5	0
Femur	14	4
Others	10	2

Table 3 Initial therapies administered

Therapy	*n*
Platinum doublet chemotherapy	26
Platinum doublet + bevacizumab	4
Non-platinum chemotherapy	3
EGFR-TKIs	9
ALK-TKIs	1
Only palliative radiation therapy for bone metastases	3
Best supportive care	3

TKI, tyrosine kinase inhibitor.

bone metastasis or best supportive care were administered. No patients presented with hypercalcemia at the initial diagnosis or during the subsequent clinical course.

FDG-PET evaluation

The mean SUVmax value of FDG in the primary lesions and bone metastases were 9.5 ± 4.6 (range: 2.3–23.4) and 7.7 ± 4.0 (range: 1.8–36.5), respectively. There was no significant difference in the SUVmax of the primary tumor between SCLC (8.2 ± 3.8) and NSCLC (9.7 ± 4.8). However, the mean SUVmax of bone metastases in SCLC was 3.9 ± 1.5 (n = 29), which was significantly lower than that in NSCLC (7.0 ± 4.1, n = 156; P < 0.001) (Fig 1). The mean B/P ratio of SUVmax for bone metastases in SCLC (0.57 ± 0.3, n = 29) was also significantly lower than that in NSCLC (0.94 ± 0.73, n = 136; P < 0.01) (Fig 1). The mean SUVmax and the B/P ratio of painful bone metastases were 8.5 ± 5.6 (n = 38) and 1.2 ± 1.1 (n = 37), respectively, and were significantly higher than in patients without pain bone metastases (6.0 ± 3.3 in SUVmax, n = 147, P < 0.001; 0.78 ± 0.5 in B/P ratio, n = 128, P < 0.01) (Fig 2). The mean SUVmax in bone metastases with SREs was 9.1 ± 6.0 (n = 26) compared to 6.1 ± 3.4 (n = 159) in cases without SREs (Fig 3). This difference was also statistically significant (P < 0.001). Similarly, the mean B/P ratio with the development of SREs (1.3 ± 1.2, n = 23) was significantly higher than in patients without SREs (0.8 ± 0.54, n = 142; P < 0.01) (Fig 3). Based on the ROC curve, the SUVmax at a cutoff value of 6.0 showed good predictive performance for pain (sensitivity 71%, specificity 63%) (Fig 4a) and SREs (sensitivity 79%, specificity 62%) (Fig 4b) in lung cancer patients with bone metastatic lesions.

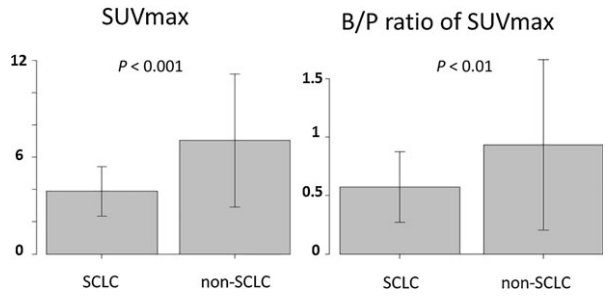

Figure 1 Comparisons of maximum standardized uptake value (SUVmax) in metastatic bone lesions and bone to primary lung tumor SUVmax ratio (B/P ratio) between small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).

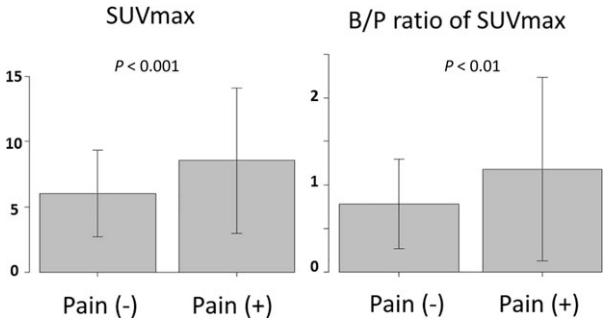

Figure 2 Comparisons of maximum standardized uptake value (SUVmax) in metastatic bone lesions and bone to primary lung tumor SUVmax ratio (B/P ratio) in patients with lung cancer with and without painful bone lesions.

The numbers of bone metastases and painful bone metastases according to histological and radiographic types are summarized in Table 4. None of the SCLC patients exhibited the osteolytic type, but there were no specific patterns in the histological types and radiologic features in the bone lesions. SREs were observed in one SCLC patient (1/25 bone metastases), which was significantly lower than the number of SREs experienced in squamous cell carcinoma patients (7 SREs/21 bone metastases) (< 0.05), but not in adenocarcinoma patients (18 SREs/111 bone metastases) (P = 0.15). The SUVmax values according to the radiologic features, pain, and SREs are shown in Table 5. The SUVmax in osteolytic bone metastases was significantly higher than in undeterminable and osteoblastic types. Regarding painful and SRE bone metastases, significant differences were observed in the undeterminable bone

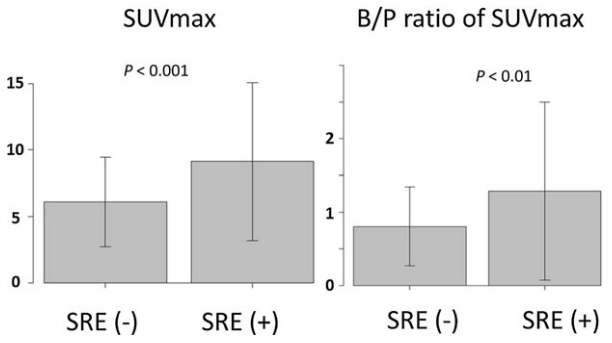

Figure 3 Comparisons of maximum standardized uptake value (SUVmax) in metastatic bone lesions and bone to primary lung tumor SUVmax ratio (B/P ratio) in patients with lung cancer with and without subsequent development of skeletal-related events (SREs).

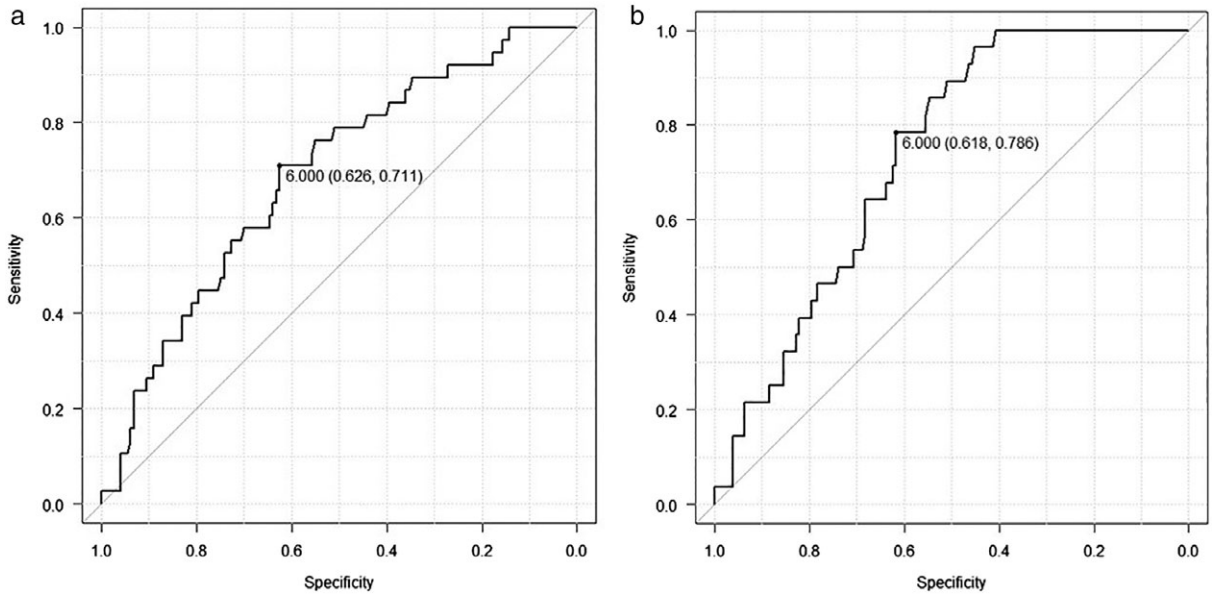

Figure 4 Receiver operating characteristic (ROC) curve of maximum standardized uptake value (SUVmax) values in metastatic bone lesions in patients with lung cancer for predicting (**a**) pain and (**b**) subsequent skeletal-related events.

Table 4 Number of bone metastases and painful bone metastases according to histological and radiographic types

	Undeterminable				Osteolytic				Osteoblastic			
Event	Ad	SCC	SCLC	Others	Ad	SCC	SCLC	Others	Ad	SCC	SCLC	Others
Total number of bone metastases	57	5	25	18	29	16	0	0	25	0	4	6
Number of painful bone metastases	12 (21%)	0	1 (4%)	1 (6%)	12 (41%)	8 (50%)	0	0	4 (16%)	0	0	0
Number of SREs	7 (12%)	0	1 (4%)	0	10 (34%)	7 (44%)	0	0	1 (4%)	0	0	0

Ad, adenocarcinoma; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; SREs, skeletal-related events.

metastatic type but not in the osteolytic and osteoblastic types.

Survival

OS was analyzed in 41 patients with primary lung cancer. The median survival time was 24 months (95% confidence interval [CI] 9.9–46.5) and the one-year survival rate was 60% (95% CI 42–75%). There was no significant difference in survival between patients with and without painful bone metastasis at initial diagnosis (median survival time 24 months [95% CI 8.0–30.6] with vs. 31.5 months [95% CI 9.7–58.1] without; data not shown). The OS of the 24 patients with a B/P ratio of SUVmax < 1 was 18.2 months (95% CI 9.2–30.6), while that of the 17 patients with a B/P ratio of SUVmax ≥ 1 was

Table 5 SUVmax values according to radiographic features, pain, and SREs

Undeterminable		Osteolytic		Osteoblastic	
6.3 ± 4.4		8.4 ± 3.4†		5.1 ± 2.1	
Pain (+)	Pain (–)	Pain (+)	Pain (–)	Pain (+)	Pain (–)
10.0 ± 8.5	5.7 ± 3.1‡	8.0 ± 2.8	8.6 ± 3.8	6.0 ± 1.3	5.0 ± 2.1
SREs (+)	SREs (–)	SREs (+)	SREs (–)	SREs (+)	SREs (–)
12.3 ± 10.1	5.8 ± 3.3‡	8.1 ± 2.7	8.5 ± 3.8	6.1 ± 2.8	5.1 ± 2.1

†Significant difference between other undeterminable and osteoblastic groups. ‡Significant difference between with and without pain or skeletal-related events (SREs). [a] SUVmax, maximum standardized uptake value.

46.5 months (95% CI 4.9–58.1). There was no significant difference in the B/P ratios of SUVmax < 1 and SUVmax ≥ 1 ($P = 0.39$). However, we found a significant and negative correlation between the number of bone metastases and OS (Fig 5).

Discussion

This study evaluated the FDG-PET uptake in metastatic bone lesions at initial diagnosis in patients with lung cancer. We found that the SUVmax in painful metastatic bone lesions was significantly higher than in patients with painless bone metastases. The initial SUVmax of metastatic bone lesions can be useful to predict subsequent SREs in patients with lung cancer with bone metastasis.

Several studies have indicated that SUVmax assessed with FDG-PET is a predictive biomarker of initial pain severity in patients with malignancy.[17–20] Our findings confirm that the FDG-PET SUVmax in metastatic bone lesions is associated with painful bone metastasis in patients with lung cancer, suggesting that biological and/or metabolic parameters determined using FDG-PET could be useful to evaluate the status of metastatic bone lesions in lung cancer patients. In addition, we showed that increased SUVmax was associated with subsequent SREs during the clinical course in patients with lung cancer, which has not been evaluated by previous studies.[17–20] This finding provides novel biological insight into the use of FDG-PET for the assessment of metastatic bone lesions in lung cancer patients. Although the sensitivity and specificity were not always sufficient, the SUVmax value of 6.0 was useful to evaluate initial pain and subsequent SREs. As our sample was too small to determine the optimal SUVmax value for anticipating metastatic bone status, further clinical studies could confirm the relationship between initial SUVmax in metastatic bone at diagnosis and subsequent SREs in patients with lung cancer and/or other malignancies.

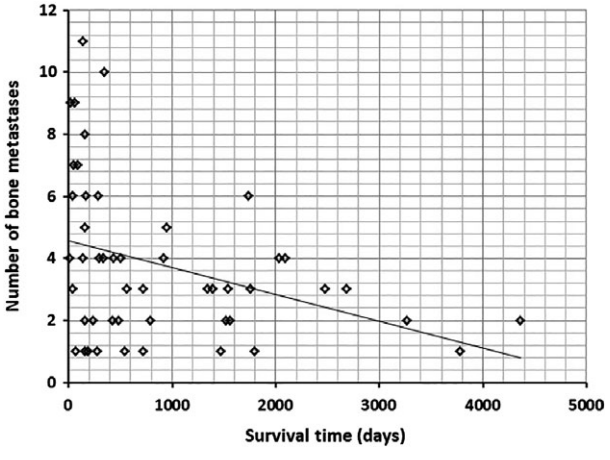

Figure 5 There was a significant negative correlation between overall survival and the number of bone metastases (r = −0.353).

In general, the SUVmax of metastatic lesions in lung cancer patients is reported to be lower than that of the primary tumor.[12] We calculated the B/P ratio in each metastatic bone lesion and found that the B/P ratio in SUVmax in patients with painful bone metastasis was significantly higher than in those without pain, and an increased B/P ratio could be a predictive factor of SREs. Increased uptake of FDG in metastatic lesions could reflect glucose metabolism and the proliferative activity of tumor cells in metastatic bone.[3–7] Thus, the B/P ratio could also be a predictive factor of clinical manifestations in metastatic bone sites in patients with lung cancer. Kaira *et al.* reported that a higher ratio of metastatic to primary lesions in lung cancer patients (> 0.75) showed a poorer prognosis than in patients with a lower ratio (< 0.75).[12] We evaluated survival according to B/P ratio cutoff values of 0.75 and 1.0, but found no differences between survival and the B/P ratio (< 0.75 vs. > 0.75 and < 1.0 vs. > 1.0, respectively).

In the present study, there were no significant differences in SUVmax in primary lesions among the histological types; no consistent results have been reported in other studies regarding differences between histological types.[22,23] However, we found that the original value of metastatic bone lesions and the B/P ratio in SUVmax were significantly lower in SCLC than in NSCLC. In addition, the SCLC patients in our sample developed fewer SREs. We are unable to explain the mechanism and relationship between the lower uptake in metastatic bone and the subsequent lower frequency of SREs; however, our results are noteworthy. FDG-PET/CT has been shown have high sensitivity and specificity for the detection of bone metastasis in patients with lung cancer compared to bone scintigraphy.[1,2,24–26] The diagnostic accuracies of FDG-PET/CT are independent of the histological differences in lung cancer.[24–26] Although in general most lung cancer metastasis to bone results in osteolytic lesions,[15,16] FDG-PET has a lower sensitivity for detecting sclerotic than lytic bone lesions in patients with breast cancer.[27] Conflicting results have been reported regarding an association between glucose transporters (GLUT1 and GLUT3) and an increased FDG uptake in NSCLC.[4,6,7] To our knowledge, no previous reports have investigated the differences in morphological characteristics (osteolytic, osteosclerotic, or mixed components) and GLUT1 and GLUT3 expression in metastatic bone lesions between SCLC and NSCLC. In addition, the incidence of SREs is reported to be significantly lower in patients with SCLC than in patients with NSCLC.[28] Further studies of the clinical significance of FDG uptake in metastatic bone lesions according to histological types are required.

There were several limitations to the present study. First, the study had a retrospective design and the patient sample was derived from a single institute. Second, the sample was too small to observe differences in histological types and/or therapy, including positivity for driver mutations. Finally, most metastatic bone lesions in our study were not histopathologically confirmed as metastases. Further case-control studies according to histological and/or biological types in patients with lung cancer are required.

The findings of the present study indicate that FDG-PET uptake in metastatic bone and the ratio to primary tumor were useful to detect painful bone metastasis and subsequent clinical outcomes of local bone control in patients with lung cancer. Although the mechanism remains to be determined, we demonstrated differences in biological metabolites in metastatic bone lesions between SCLC and NSCLC. FDG-PET examination and study could provide further clinical information in patients with malignancies, including lung cancer.

Disclosure

No authors report any conflict of interest.

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