Diagnostic value of $^{18}$F-FDG PET/CT in discriminating between benign and malignant lesions of the ribs

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Abstract

**Purpose:** Imaging biomarkers for rib mass are needed to optimize treatment plan. We investigated the diagnostic value of metabolic and volumetric parameters from $^{18}$F-fluorodeoxyglucose (FDG) positron-emission tomography/computed tomography (PET/CT) in discriminating between benign and malignant lesions of the ribs.

**Patients and methods:** Fifty-seven patients with pathologically proven diagnosis of rib lesions were retrospectively enrolled. The size of rib lesions, the maximum, mean, and peak standardized uptake value (SUVmax, SUVmean, SUVpeak), tumor-to-background ratio (TBR), metabolic tumor volume (MTV), and total lesions glycolysis (TLG) were measured. The FDG uptake patterns (segmental and discrete) and CT findings (soft tissue involvement and fracture) were also reviewed.

**Results:** Among the multiple parameters extracted from PET/CT, the MTV of malignant lesions was significantly higher than that of benign lesions (median: 4.7 vs 0.2, respectively, $P = .041$). In receiver operating characteristics curve analysis, MTV had the largest area under curve of 0.672 for differentiating malignant from benign lesions. For identifying malignant lesions, an MTV threshold of 0.5 had a sensitivity of 85.0%, specificity of 47.1%, positive predictive value of 79.1%, negative predictive value of 57.1%, and accuracy of 73.7%. The presence of adjacent soft tissue involvement around rib lesions showed a significant association with malignancy (odds ratio = 6.750; 95% CI, 1.837–24.802, $P = .003$).

**Conclusions:** The MTV is a useful PET/CT parameter for assisting in the differential diagnosis of suspected malignant lesions of the ribs. CT finding of adjacent soft tissue involvement around rib was significantly associated with malignant lesions of the ribs.

**Abbreviations:** AUC = area under curve, FDG = fluorodeoxyglucose, MTV = metabolic tumor volume, NPV = negative predictive value, OSEM = ordered subsets expectation maximization, PET/CT = positron emission tomography/computed tomography, PSF = point-spread-function, PPV = positive predictive value, ROC = receiver operating characteristics, SD = standard deviations, SUV = standardized uptake value, TBR = tumor-to-background ratio, TLG = total lesion glycolysis, TOF = time-of-flight, VOI = volume of interest.

**Keywords:** fluorodeoxyglucose 18, metabolic tumor volume, positron-emission tomography computed tomography, rib, sensitivity and specificity, standardized uptake value

1. Introduction

Neoplasms of the ribs account for 3%–8% of skeletal masses.[1–3] The spectrum of rib lesions ranges from benign tumors such as fibrous dysplasia to malignancies, including metastasis or direct invasion from adjacent malignancies such as breast cancer, lung cancer, and mediastinal tumor.[4] Patients with rib tumors usually have chest wall pain, a palpable mass, or both. Although some primary
uptake is typically higher in malignant bone lesions than in benign lesions.\textsuperscript{[7–10]} In particular, when bone tumors of the same histologic type, such as chondrosarcoma, were compared, the \textsuperscript{18}F-FDG uptake of high-grade tumors was greater than that of low-grade tumors. The metabolic parameters derived from \textsuperscript{18}F-FDG PET/CT, such as maximum standardized uptake value (SUV\textsubscript{max}), improved the prediction of clinical outcomes and recurrence for primary bone tumors.\textsuperscript{[11,12]} Peak SUV (SUV\textsubscript{peak}) was also reported as a prognostic factor in osteosarcoma.\textsuperscript{[13]} In addition to PET-derived parameters, the morphologic features obtained from CT images simultaneously acquired with PET data could be helpful for determining the aggressive biological potential of bone lesions.

Metabolic tumor volume (MTV) is defined as the metabolically active volume of tumor tissues above a predefined SUV threshold measured by \textsuperscript{18}F-FDG PET/CT, and total lesion glycolysis (TLG) is calculated as the measured MTV multiplied by mean SUV (SUV\textsubscript{mean}). A number of studies have evaluated the clinical value of volumetric parameters derived from \textsuperscript{18}F-FDG PET/CT, including MTV and TLG, and demonstrated their prognostic significance for osteosarcoma.\textsuperscript{[13,16,17]} However, few studies have reported the clinical significance of the volumetric parameters of \textsuperscript{18}F-FDG PET/CT for patients with rib neoplasms, which may be attributed to their rarity among malignant bone tumors. In this study, we hypothesized that volumetric parameters and morphologic features obtained from CT images may have additive value in distinguishing malignant rib lesions. In this study, we analyzed the diagnostic value of metabolic and volumetric parameters derived from preoperative \textsuperscript{18}F-FDG PET/CT images obtained from patients with suspected malignant rib lesions. In addition, we reviewed the morphologic findings on CT for the further discrimination of malignant rib lesions.

2. Materials and Methods

2.1. Study subjects

The included patients in this retrospective study were patients with rib lesions suspected to be malignant and who underwent \textsuperscript{18}F-FDG PET/CT between January 2010 and December 2020 (Fig. 1). All patients underwent excisional or needle biopsy and/or surgical resection, and their final diagnosis was confirmed histologically. Patients with any reported primary/synchronous malignancies on \textsuperscript{18}F-FDG PET/CT were excluded from this study. Patients with hematologic malignancies combined with bone marrow involvement and those with more than 5 newly appeared bone lesions showing FDG uptake were also excluded from this study.\textsuperscript{[10]} The study design and waiver of informed consent were approved by the institutional review board of our institution (no. 2021-1027).

2.2. PET/CT image acquisition

All patients fasted for at least 6 hours before PET/CT scanning. The plasma glucose level measured before \textsuperscript{18}F-FDG injection was <150 mg/dL in all patients. \textsuperscript{18}F-FDG was intravenously administered at a dose of 5.18 MBq/kg (range, 114.3–488.4 MBq); 1 hour after \textsuperscript{18}F-FDG administration, PET/CT scanning was performed with different systems (Discovery PET/CT 690, 690 Elite, 710; GE Healthcare; Biograph 40 TruePoint PET/CT; Siemens). First, low-dose CT acquisition was performed from the skull base to the upper thigh using the following parameters: 120 kVp, automatic mA, 40 mm collimation, and 3.75 mm thickness for the GE Healthcare machines; 120 kVp, CARE Dose 4D, 28.8 mm collimation, and 5.0 mm thickness for the Siemens machine. A PET scan of the same area was acquired after the CT scan in the 3-dimensional mode with 6 to 7 beds (2 and 2.5 minutes per bed position on the GE Healthcare and Siemens machines, respectively). Images were corrected for attenuation and reconstructed using the 3-dimensional ordered subset expectation maximization (OSEM) method with time-of-flight (TOF) and point-spread-function (PSF) algorithms (192 x 192 matrix, 4 iterations, 18 subsets, 4 mm postsmoothing on GE Healthcare; 168 x 168 matrix, 3 iterations, 21 subsets, 3 mm postsmoothing on Siemens).

2.3. Visual analysis of PET/CT

The pattern of FDG uptake on PET images was classified as segmental or focal and discrete or nondiscrete. Segmental FDG uptake was defined as FDG uptake along the length of the rib lesion that was at least twice that of the width.\textsuperscript{[10]} A discrete uptake pattern was defined as FDG uptake intensity at least twice that of contralateral rib uptake. The CT images were further analyzed by searching for the presence of fracture and evidence of the involvement of soft tissue in lesions demonstrating FDG uptake. Multiple lesions were defined as more than 1 rib lesion.

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**Figure 1.** Flowchart of subject enrollment.
2.4. Quantitative analysis of PET/CT images

\(^{18}\)F-FDG PET/CT images were reviewed by a nuclear medicine board-certified physician (S.J.C) who was blinded to the clinical data using a dedicated workstation and software (Mirada XD3; Mirada Medical). The size of rib lesions on transaxial CT images was measured. For the quantitative analysis of \(^{18}\)F-FDG PET/CT images, volumes of interest were delineated around rib lesions showing higher than normal FDG uptake on transaxial images, and SUVmax, SUVmean, and SUVpeak were measured. The SUVs were normalized to the lean body mass. The tumor-to-background ratio (TBR) was calculated as the SUVmax of a rib lesion divided by the SUVmean of the contralateral rib. The SUVmean of the contralateral rib was measured using a spherical volume of interest (VOI) (1 cm in diameter) placed on the rib contralateral to a suspected malignant rib lesion. The MTV was measured using an automated contouring program with a threshold of liver SUVmean plus 2 standard deviations (SDs). The liver SUVmean and SDs were measured using a spherical VOI (3 cm diameter) placed on the right lobe of the liver. The TLG was calculated by multiplying the MTV by its corresponding SUVmean.

2.5. Statistical analysis

Pearson chi-square test and Fisher exact test were used to compare the pattern of FDG uptake and CT findings between benign and malignant lesions. The \(^{18}\)F-FDG PET/CT parameters (size, SUVmax, SUVmean, SUVpeak, TBR, MTV, and TLG) of benign and malignant lesions of the ribs were compared using the Mann–Whitney U test. Receiver operating characteristic (ROC) curve analysis of the PET/CT parameters was performed, and their diagnostic performance was compared. A P value < 0.05 was considered statistically significant. Statistical analyses were performed using a dedicated software (SPSS Statistics, version 18.0; IBM).

3. Results

3.1. Profile of the included patients

Among 135 patients with a pathologically proven rib mass, 57 patients were finally enrolled in this study. The clinical characteristics of these patients are summarized in Table 1. Of these 57 patients, 40 patients (40/57, 71.2%) were diagnosed with malignant rib lesions and the ribs compared using the Mann–Whitney U test. Receiver operating characteristic (ROC) curve analysis of the PET/CT parameters was performed, and their diagnostic performance was compared. A P value < 0.05 was considered statistically significant. Statistical analyses were performed using a dedicated software (SPSS Statistics, version 18.0; IBM).

3.2. Visual analysis

Segmental FDG uptake was observed in 27 malignant lesions (27/40, 67.5%) and 8 benign lesions (8/17, 47.1%). The rates of discrete FDG uptake in benign and malignant lesions were high (88.2% and 80.0%, respectively). Adjacent soft tissue involvement around rib lesions was significantly more common with malignant lesions than with benign lesions (odds ratio = 6.750; 95% CI, 1.837–24.802, P = .003; Table 2).

3.3. Quantitative analysis

A comparison of the quantitative PET/CT parameters is presented in Table 3. The MTV values (median, interquartile) of benign and malignant lesions were 0.2 [0.1; 7.6] and 4.7 [1.2; 22.4], respectively, which were significantly different (P = .041; Fig. 2). Other PET/CT parameters (size, SUVmax, SUVmean, SUVpeak, TBR, and TLG) did not show significant differences between benign and malignant lesions. In ROC curve analysis, the largest area under the curve (AUC) among the PET/CT parameters was 0.672 with a sensitivity of 85.0%, specificity of 47.1%, positive predictive value (PPV) of 79.1%, negative predictive value (NPV) of 57.1%, and accuracy of 73.7% when 0.5 was used as the MTV cut-off value for the differential diagnosis (Fig. 3). Data on the diagnostic performance of various MTV cut-off values for distinguishing between benign and malignant lesions are presented in Supplemental Table 1, http://links.lww.com/MD/G864. The diagnostic performance of all PET/CT parameters according to a cut-off value is summarized in Table 4, and representative cases are shown in Figs. 4–6.

4. Discussion

In this retrospective study, we evaluated the diagnostic value of metabolic and volumetric parameters derived from \(^{18}\)F-FDG PET/CT for patients with suspected malignant rib lesions. The MTV calculated using a relative threshold (liver SUVmean + 2 SDs) showed a significant difference between benign and malignant rib lesions and had the highest diagnostic value. Therefore, the MTV was the best PET/CT parameter for characterizing the malignancy of rib lesions.

The volumetric parameters of \(^{18}\)F-FDG PET/CT (e.g., MTV or TLG) have been introduced to overcome the limitations of the metabolic parameters of \(^{18}\)F-FDG PET/CT (e.g., SUVmax or SUVpeak), and several studies have published diagnostic values for differentiating malignant from benign bone and soft tissue tumors. These studies evaluated the diagnostic performance of the MTV and TLG using various threshold values with a fixed SUVmax of 2.0 or 2.5 or 40%, 50%, and 75% of SUVmax. Additionally, Chen et al presented a regression model using SUVmax and a heterogeneity factor (calculated from a
metabolism volume-threshold function from 40% to 80%) and found that it showed diagnostic performance superior to that of individual volumetric parameters.\[19\] Im et al reported that the MTV and TLG obtained using a liver-based threshold (liver SUVmean + 2 SDs) were the parameters with the most statistically significant predictive value for event-free survival (hazard ratios = 11.774 and 13.121, respectively, at posttherapy).\[13\] We evaluated the MTV and TLG using a liver-based threshold, which would be less influenced by the variability in SUV measurements caused by multiple PET/CT systems. Although the MTV cut-off was as small as 0.5, the MTV yielded the largest AUC among the various parameters of 18F-FDG PET/CT investigated in our study. On the other hand, the TLG showed lower sensitivity, accuracy, and AUC values, which may be attributed to the heterogeneous SUVmean values of benign lesions with aggressive features in our cohort. In addition, there may be errors in the SUV calculation due to differences in scan acquisition or image reconstruction parameters across various PET/CT systems.\[20,21\] Despite these conditions, the MTV demonstrated a statistically significant difference between malignant and benign rib lesions in our study.

Although the metabolic and volumetric parameters derived from 18F-FDG PET/CT have been used in the diagnosis of bone tumors, morphologic assessment remains necessary to investigate their malignant biological potential. CT as part of a PET/CT examination provides additional anatomical information. On CT, the edge of more aggressive tumors may appear fuzzy or unsharp, indicating active osteolysis.\[9\] The lack of a sclerotic margin might be a high-risk feature suggesting an excessive rate of osteolysis caused by the tumor. Moreover, aggressive tumors often extend through the bone cortex directly into adjacent soft tissues.\[22\] Our study showed that a higher odds ratio was obtained for bone lesions with adjacent soft tissue involvement compared with lesions showing a segmental FDG uptake pattern in patients with malignant lesions. There are some contradictory findings related to the diagnostic value of SUVmax for differentiating malignant fractures in the acute phase. A number of studies found significantly higher FDG uptake in malignant fractures than in benign fractures in the acute to subacute phase.\[7,23\] However, Ravenel et al reported a SUV of 9.3 for acute benign fractures of the pelvic bone.\[24\] These findings highlight the diagnostic value of CT findings on PET/CT images.

SUVmax is a PET/CT parameter widely used for quantitative analysis. Several previous studies on rib tumors used

### Table 2

Comparison of PET uptake patterns and morphologic features on CT images between benign and malignant lesions.

| PET/CT finding | Benign lesions (n = 17) | Malignant lesions (n = 40) | Odds ratio (95% CI) | P value |
|----------------|----------------------------|----------------------------|---------------------|---------|
| Number of lesions | Single 17 (100.0%) 32 (80.0%) 0.653 (0.533–0.801) 0.090 | Multiple 0 8 (20.0%) | | |
| PET uptake pattern | Segmental 8 (47.1%) 27 (67.5%) 1.817 (0.541–6.101) 0.331 | Discrete 15 (88.2%) 32 (80.0%) 0.533 (0.101–2.823) 0.706 | | |
| CT finding | Soft tissue involvement 4 (23.5%) 27 (67.5%) 6.750 (1.837–24.802) 0.003* | Fracture 5 (29.4%) 11 (27.5%) 0.910 (0.260–3.187) 0.883 | | |

CI = confidence interval.

*P < 0.05.

### Table 3

Median of PET parameters in the overall population as well as comparatively between the 2 groups of benign and malignant rib lesions [interquartile range].

| PET/CT parameters | Overall | Benign lesions | Malignant lesions | P value |
|-------------------|---------|----------------|-------------------|---------|
| Size (cm)         | 4.8 [2.8; 6.8] | 5.5 [4.5; 6.7] | 4.4 [2.8; 7.5] | 0.232   |
| SUVmax            | 5.0 [3.5; 7.6] | 3.1 [2.2; 6.5] | 5.1 [3.8; 7.6] | 0.631   |
| SUVmean           | 1.6 [1.1; 2.5] | 1.1 [0.9; 2.4] | 1.6 [1.1; 2.5] | 0.780   |
| SUVpeak           | 3.5 [2.4; 5.1] | 2.2 [1.7; 4.4] | 3.5 [2.5; 5.1] | 0.588   |
| TBR               | 7.8 [5.6; 11.0] | 5.5 [3.7; 10.1] | 8.0 [6.3; 10.9] | 0.577   |
| MTV               | 4.0 [0.5; 22.4] | 0.2 [0.1; 7.6] | 4.7 [1.2; 22.4] | 0.041*  |
| TLG               | 10.9 [1.6; 53.0] | 0.5 [0.2; 34.4] | 17.2 [3.4; 53.0] | 0.054   |

MTV = metabolic tumor volume, SUVmax = maximum standardized uptake value, TBR = tumor-to-background ratio, TLG = total lesion glycolysis.

*P < 0.05.

![Figure 2](image-url)

Figure 2. Comparison of 18F-FDG PET/CT parameters for benign and malignant lesions of the ribs. (A) Size (P = .232), and (B) SUVmax (P = .631) showed no significant difference and also revealed a high range of overlap compared with MTV. However, (C) MTV (P = .041) showed significantly higher values in malignant rib lesions than in benign lesion of ribs.
SUVmax and reported sensitivity values in the range of 68.0 to 89.5% with cut-off values of 2.7–4.7. [7,11,12,25] Annovazzi et al reported that a SUVmax cut-off of 2.6 discriminated low-grade chondrosarcoma from enchondroma, [25] and another study reported a significantly higher SUVmax for high-grade chondrosarcoma compared with low-grade chondrosarcoma. [11] SUVmax showed a similar diagnostic value in recurrent chondrosarcoma, which was associated with the tumor grade. [12] Additionally, malignant fractures showed increased intramedullary FDG uptake compared with that of benign fractures. [7] However, Choi et al reported that SUVmax was significantly higher for rib metastases (58 lesions) compared with benign rib lesions (206 lesions) with a SUVmax cut-off of 2.4, which is contrary to our result. [10] One possible reason for the discrepancy might be the small sample size in our study (40 malignant and 17 benign lesions). Another possible reason might be the large proportion of low-grade primary malignant lesions included in this study (25.0%; e.g., chondrosarcoma, plasmacytoma, and low-grade sarcoma).

Benign bone lesions such as Langerhans cell histiocytosis and giant cell tumor are thought to originate from monocyte-macrophage lineage cells. [26,27] Macrophages play a key role in the inflammatory process, and high FDG uptake in inflammatory cells due to intracellular glucose metabolism is a well-known feature. A number of publications reported that Langerhans cell histiocytosis and giant cell tumor can have a high SUV and mimic malignancy. [14,15] The highest SUVmax of our false positive lesions was 17.0 (giant cell tumor). Another benign bone lesion, fibrous dysplasia (FD), is one of the most common benign lesions and has morphologic features showing intramedullary bone expansion, which is well-defined on radiographic and CT images. Several studies have stated that the appearance of FD might mimic that of malignant lesions. Su et al reported that the SUVs of 11 patients with FD ranged from 1.76 to 11.4 and found that FD lesions with a low CT density often had higher SUVs compared with those of lesions with a high CT density. Therefore, it should be noted that the use of SUVmax alone would be limited in differentiating between benign and malignant lesions considering the variability in the SUVmax range of benign bone tumors.

SUVmax, which is defined as the highest voxel within a drawn VOI, may be affected by signal noise and might indicate statistical fluctuations in the count when the acquisition time is too short. [28] Therefore, SUVpeak has been recommended.

### Table 4

| PET/CT parameters | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Accuracy (%) | AUC | Cut-off value | P value |
|-------------------|----------------|----------------|---------|---------|--------------|-----|--------------|---------|
| Size (cm)         | 22.5           | 100.0          | 100.0   | 32.4    | 45.6         | 0.601| 8.5          | 0.232   |
| SUVmax            | 87.5           | 35.3           | 76.1    | 54.5    | 71.9         | 0.540| 2.5          | 0.631   |
| SUVmean           | 67.5           | 47.1           | 75.0    | 38.1    | 61.4         | 0.524| 1.2          | 0.780   |
| SUVpeak           | 85.0           | 35.3           | 75.6    | 50.0    | 70.2         | 0.547| 2.0          | 0.589   |
| TBR               | 90.0           | 29.4           | 75.0    | 55.6    | 70.2         | 0.547| 5.0          | 0.577   |
| MTV               | 85.0           | 47.1           | 79.1    | 57.1    | 73.7         | 0.672| 0.5          | 0.041   |
| TLG               | 77.5           | 58.8           | 81.6    | 52.6    | 71.9         | 0.662| 3.3          | 0.054   |

* AUC = area under the curve, NPV = negative predictive value, PPV = positive predictive value, ROC = receiver operating characteristics.

*P < 0.05.
as an alternative to SUVmax.\textsuperscript{29,30} SUVpeak is defined as the average SUV calculated within a fixed VOI, often including the highest pixel value. As a VOI contains several pixels, SUVpeak is presumed to be less affected than SUVmax by signal noise.\textsuperscript{31,32} In the discrimination of malignant vertebral bone lesions from benign lesions in oncologic patients, SUVpeak achieved an AUC of 0.671, which was higher than that of SUVmax (0.630).\textsuperscript{33} In our study, the AUC of SUVpeak was not significantly different compared with that of SUVmax, and there was no statistically significant difference in sensitivity, specificity, PPV, NPV, and accuracy in the differentiation of malignant lesions. The diagnostic value of the TBR of 18F-FDG PET/CT for bone tumors was first described by Schulte et al,\textsuperscript{14} who reported sensitivity, specificity, and accuracy values of 93.0\%, 66.7\%, and 81.7\%, respectively, for discriminating malignant bone lesions using a cut-off value of 3.0. In our study, the TBR showed the highest sensitivity 90.0\% and the lowest specificity of 29.4\%.

Our study has some limitations. Although we analyzed a cohort of patients who met the inclusion criteria, we evaluated only a relatively small number of patients at a single institution. In addition, some studies investigating the differential diagnostic value of 18F-FDG PET imaging for patients with rib tumors were limited by their retrospective design and the low incidence of these tumors, which are also the limitations of our study.

5. Conclusion

In conclusion, the MTV showed excellent performance in discriminating between benign and malignant lesions of the ribs and better diagnostic accuracy compared with that of SUVmax. Soft tissue involvement around the rib lesions was highly correlated with malignant lesions of the ribs. 18F-FDG PET/CT could be used to determine the treatment strategy for patients with rib lesions.

Author contributions

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