Utility of ^{18}F-FDG PET/CT in risk assessment of Medication-related osteonecrosis of jaw

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Abstract

Objective: The clinical utility of quantitative fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) for classification of medication-related osteonecrosis of the jaw (MRONJ) was determined. **Subjects and Methods:** Seventy-one lesions in 59 patients clinically diagnosed as MRONJ, based on American Association of Oral and Maxillofacial Surgeons (AAOMS) diagnostic criteria by Japanese Society of Oral Surgery specialists and who received ^{18}F-FDG PET/CT examinations, were enrolled. For analysis, standard uptake values (SUV), including maximum (SUVmax), peak (SUVpeak), and mean (SUVmean) were evaluated, and also metabolic lesion volume (MLV) for total volume above the threshold, and total lesion glycolysis (TLG), calculated as MLV×SUVmean. To compare quantitative values between clinical stages, one-way repeated measures analysis of variance and subsequent post-hoc analysis were used. **Results:** The mean SUVmax values for AAOMS stage 1 (n=13), 2 (n=43), and 3 (n=15) patients were 3.68±0.83, 6.15±1.32, and 9.92±1.63, respectively, while MLV values were 6.51±5.53, 8.76±9.74, and 13.92±13.89, respectively, and TLG values were 16.84±17.23, 31.36±35.25, and 66.27±58.51, respectively. Maximum SUV and TLG showed significant differences between clinical stages ($P<0.0001$ and $P=0.0029$, respectively). With stage increase, MLV showed a mild increasing tendency, though the difference between stages was not significant ($P=0.13$), while SUVmax value differences between individual stages were significant in subsequent post-hoc analysis ($P<0.0001$). Furthermore, post-hoc analysis indicated that the stage 3 TLG value was significantly greater than that of stage 1 and 2 ($P<0.01$ and $P<0.05$, respectively). **Conclusion:** For MRONJ patients, SUVmax and TLG derived from quantitative ^{18}F-FDG PET/CT results are reliable objective indicators useful for disease activity evaluation and staging.

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Introduction

Medication-related osteonecrosis of the jaw (MRONJ) develops in patients with current or previous antiresorptive or antiangiogenic agent treatment, who then show exposed bone or that can be probed through an intraoral or extraoral fistula in the maxillofacial region persisting for at least eight weeks, without history of jaw radiation therapy or obvious jaw metastatic disease [1]. It is known as a severe adverse effect of antiresorptive therapy that significantly affects quality of life, with the prevalence of MRONJ significantly rising in recent years from use of antiresorptive drugs in a variety of clinical applications. A three-stage classification system proposed by the American Association of Oral and Maxillofacial Surgeons (AAOMS) is based on the presence of infection or inflammation and not only infection [1], along with various treatment strategies. Patients classified as stage 3, the most serious, are often recommended to undergo surgical treatment, while those with stage 1 or 2 usually receive conservative treatment, such as antimicrobial medication and local irrigation, though reported cure rates are lower as compared to extensive surgery results [1-3]. Medication-related osteonecrosis of the jaw stage is a prognostic factor related to treatment success, with patients diagnosed in an advanced stage showing a lower likelihood of cure. An increasingly critical factor is early detection before stage progression.

Use of nonspecific clinical and radiological imaging methods, such as X-rays, computed tomography (CT), and magnetic resonance imaging (MRI), makes MRONJ diagnosis challenging, especially when no evidence of exposed bone is noted [4]. Distinctive related imaging findings are unusual, while correlation with clinical signs may not always be noted [5]. On the other hand, molecular imaging, such as with bone scintigraphy or fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT), can be utilized for detection of minimal and subclinical changes in bones that occur earlier than those shown by conventional methods [6, 7].

Osteomyelitis is the most common histological finding in MRONJ cases. Notably, because of activation of macrophages and neutrophils by inflammatory reactions leading to increased glucose uptake, ^{18}F-FDG PET/CT has been reported useful for diagnosis [7-11]. Nevertheless, to the best of our knowledge, no studies have examined the correlation of ^{18}F-FDG uptake with MRONJ stage. Thus, the usefulness of quantitative values determined based on ^{18}F-FDG PET/CT findings for MRONJ classification was examined in the present study.

Subjects and Methods

Patients

Following approval from the Ethics Committee of our institution (No. 3144), the present study was conducted in a retrospective manner. Fifty-nine patients (25 males, 34 females; mean age 68.9±11.3 years) affected by malignant tumors and diagnosed with MRONJ based on ^{18}F-FDG PET/CT results by Japanese Society of Oral Surgery specialists at our hospital between June 2012 and May 2024 were enrolled. A total of 71 MRONJ lesions located in mandible (n=56) or maxilla (n=15) were noted in the 59 patients of the study (breast cancer, n=33; prostate cancer, n=10; lung cancer, n=9; blood tumor, n=3; uterine cancer, esophageal cancer, renal cell carcinoma, rectal cancer, n=1 each). For treatment with a bone-modifying agent, 41 patients received denosumab injection and 18 zoledronate injection for bone metastasis. Patient characteristics are presented in Table 1.

Staging criteria for AAOMS have been presented [1], as briefly noted following. stage 1 is for asymptomatic patients with no evidence of infection, though found to have exposed and necrotic bone, or fistulae probing to bone. Patients with exposed and necrotic bone, or fistulae probing to bone, associated with infection, shown by pain and erythema in an exposed bone region with/without purulent drainage are classified as stage 2. The most serious is stage 3, used for findings of exposed and necrotic bone, or fistulae that probe to bone along with pain, infection, and at least one of the below: exposed and necrotic bone beyond the alveolar bone region (i.e., mandible inferior border and ramus, maxillary sinus and zygoma in maxilla) causing a pathologic fracture, extra-oral fistula, oral antral/oral nasal communication, or osteolysis extending to the mandible inferior border or floor of the sinus.

^{8}F-FDG PET/CT

Our institution has four PET/CT scanning devices available (Gemini GXL16, Gemini TF64, Ingenuity TF: Philips Medical Systems, Eindhoven, The Netherlands; Discovery IQ: GE Healthcare, Waukesha, WI, USA), which were used for ^{18}F-FDG PET/CT examinations of the present patients. Prior to scanning, each was asked to fast for five hours, then blood glucose measurement was performed immediately before ^{18}F-FDG injection (4.0MBq/kg body weight for GXL16, 3.0MBq/kg for TF64, 3.7MBq/kg body weight for Ingenuity TF and Discovery IQ), with <160mg/dL noted in all. Static emission images were then obtained approximately 60 minutes following the injection. Helical CT scan imaging was performed from the top of the head to mid-thigh with the following parameters used for attenuation correction and anatomic localization: tube voltage 120kV (all four scanners), effective tube current auto-mA up to 120mA (GXL16), 100mA (TF64), 155mA (Ingenuity TF) or 15-390mA (Smart mA: noise index

Table 1. *Patient characteristics and demographics.*

	Number	%
Sex		
Male	25	42.4
Female	34	57.6
Age		
Mean	68.9±11.3	
Range	33-87	
Primary cancer		
Breast cancer	33	55.9
Prostate cancer	10	16.9
Lung Cancer	9	15.3
Multiple myeloma	3	5.1
Uterine Cancer	1	1.7
Esophageal Cancer	1	1.7
Renal cell carcinoma	1	1.7
Rectal Cancer	1	1.7
Type of antiresorptive therapy		
Injection		
Denosumab	41	69.5
Zoledronate	18	30.5
Location		
Mandible	56	78.8
Maxilla	15	21.2
MRONJ stage		
I	13	18.3
II	43	60.6
III	15	21.1

25) (Discovery IQ), gantry speed 0.5 rotations/second, detector configuration 16×1.5mm (GXL16), 64×0.625mm (TF 64, Ingenuity TF), or 16×1.25mm (Discovery IQ), slice thickness 2mm, and transverse field of view 600mm (GXL16, TF 64, Ingenuity TF) or 700mm (Discovery IQ). Following the CT examination, PET imaging was immediately performed from head to mid-thigh for 90 seconds (GXL16, TF64, Ingenuity TF) or 180 seconds (Discovery IQ) for each bed position in three-dimensional mode. Normal breathing was allowed during PET scanning. For GXL16 examinations, attenuation-corrected PET images were reconstructed using a line-of-response row-action maximum likelihood algorithm, while for those performed with the TF64 and Ingenuity, an ordered-subset expectation maximization (OSEM) iterative reconstruction algorithm (33 subsets, three iterations), and with the Discovery IQ Q.Clear, a block sequential regularized expectation maximization (BSREM) iterative reconstruction algorithim (β=400) were utilized.

Data analysis

The ^{18}F-FDG PET/CT images were retrospectively reviewed by a nuclear medicine expert with board certification and 14 years of oncologic ^{18}F-FDG PET/CT experience. During analysis of the present patient findings, performed using the GI-PET software package (AZE Co., Ltd., Tokyo, Japan), which can harmonize SUV obtained with different PET/CT systems using phantom data [12], knowledge of other imaging results, or clinical or histopathologic data were not provided. The maximum concentration in the target lesion (injected dose/body weight) was used to define SUVmax, while calculation of SUVpeak was done with use of a volume region of interest (ROI) sized 1.2cm in diameter placed on the hottest site, with the result then normalized using the following equation: SUVpeak×(lean body mass)/(total body mass). Fluorine-18-FDG-avid tumor volume was employed to define metabolic lesion volume (MLV), with 40% of SUVmax used as the margin threshold. Calculation of total lesion glycolysis (TLG) was then performed, as follows: SUVmean× MTV, with SUVmean representing mean SUV value.

Statistical analysis

Values are presented as the mean±standard deviation (SD). Clinical stage quantitative values were compared using one-way repeated measures analysis of variance, which was followed by multiple comparisons using McNemar's test with Tukey-Kramer adjustment. A Mann-Whitney test was used to analyze quantitative value differences between two groups. SAS, version 9.3 (SAS Institute Inc., Cary, NC, USA), was employed for statistical analysis with significance indicated by a P value <0.05.

Results

The present cohort of 59 patients was found to have 71 MRONJ lesions, with 13 (18.3%) determined to be stage 1, 43 (60.6%) to be stage 2, and 15 (21.1%) to be stage 3. Findings for a representative stage 2 case are shown in Figure 1. Figure 2 presents quantitative analysis results (SUVmax, SUVpeak, SUVmean, MLV, TLG) as boxplots.

The mean SUVmax value for the 13 stage 1 lesions was 3.68± 0.83 (range 2.25-4.99), for the 43 stage 2 lesions was 6.15±1.32 (3.77-9.46), and for the 15 stage 3 lesions was 9.92±1.63 (7.73-12.38), thus those values were significantly different between each of the clinical stages (P<0.0001). Additionally, the SUVmax value for stage 3 was found in post hoc analysis to be significantly greater as compared to stage 1 and 2 (both, P<0.01), with the SUVmax value for stage 2 significantly greater than that for stage 1 (P<0.01).

The mean SUVpeak value for stage 1 was 2.92±0.79 (range 1.51-4.22), for stage 2 was 4.62±1.09 (2.78-7.01), and for stage 3 was 7.27±1.30 (5.02-9.89), with significant differences between the clinical stages (P<0.0001) again noted. Subsequent post hoc analysis also indicated a significantly higher SUVpeak value for stage 3 as compared to the stage 1 and 2 values (both, P<0.01), and the SUVpeak value was significantly higher for stage 2 as compared to stage 1 (P<0.01).

Mean SUV values also showed significant differences (P< 0.0001), as those for stage 1, 2, and 3 were 2.35±0.52 (range 1.34-3.13), 3.53±0.78 (1.90-5.40), and 5.51±1.23 (2.36-7.09), respectively. Thereafter, post hoc analysis showed that the stage 3 SUVmean value was significantly higher as compared to the values for stage 1 and 2 (both, P<0.01), with the SUVmean value for stage 2 significantly higher as compared to that for stage 1 (P<0.01).

Mean MLV (cm^3) values for stage 1, 2, and 3 were 6.51±5.53 (range 1.41-20.35), 8.76±9.74 (2.16-46.59), and 13.92±13.89 (2.43-48.0), respectively. A mild tendency to increase as stage increased was noted, though the difference between stages was not significant (P=0.13).

Finally, mean TLG values for stage 1, 2, and 3 were 16.84± 17.23 (range 3.17-59.76), 31.36±35.25 (7.26-153.32), and 66.27±58.51 (16.67-221.14), respectively, with a significant difference noted between clinical stages (P=0.0029). Post hoc analysis performed thereafter indicated that the TLG value for stage 3 was significantly higher as compared to stage 1 and 2 (P<0.01 and P<0.05, respectively), though no significant difference was found between stage 1 and 2.

Discussion

The present is the first known study conducted to examine differences between clinical stages noted in examinations of patients with MRONJ based on various quantitative values determined from ^{18}F-FDG PET/CT imaging results. Notably, all examined ^{18}F-FDG PET/CT quantitative parameters, especially the three related to SUV, i.e., SUVmax, SUVpeak, and SUVmean, as well as MLV and TLG were enhanced along with increased clinical stage determined for the patients. Two previous studies noted SUVmax values for MRONJ lesions similar to those in the present series of cases. In the study by Fleisher et al. (2014) [7], mean SUVmax was 6.6 for 25 MRONJ lesions in 23 patients, while Raje et al. (2008) [13] noted that 10 of 11 patients with MRONJ showed abnormal ^{18}F-FDG uptake in the jaw, with an average SUVmax of 7.5±2.9 (range 3.3-11.8). In similar to these two studies, the mean SUVmax for 71 MRONJ lesions in 59 patients was 6.5±2.4 (range 2.3-12.4) in our series.

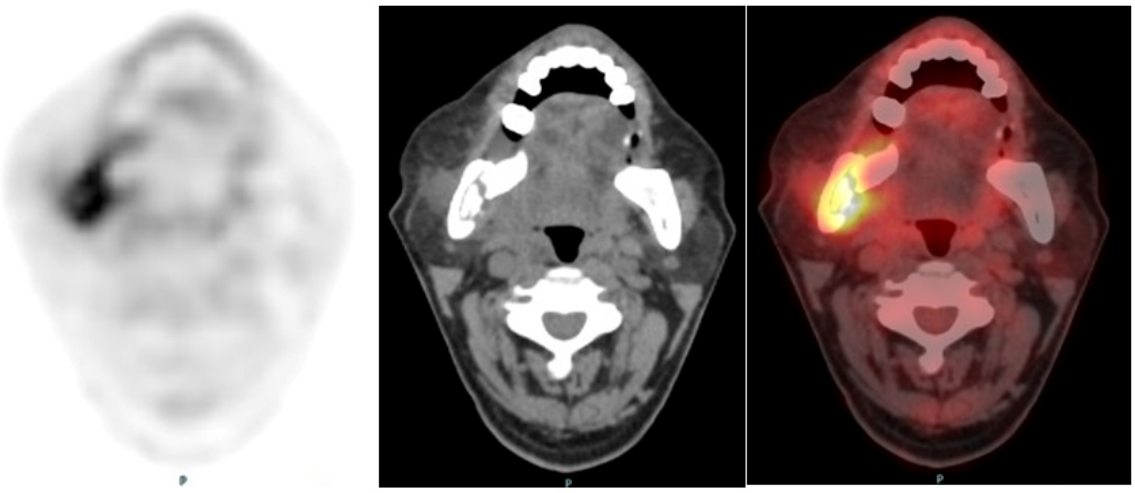

Figure 1. Medication-related osteonecrosis of the jaw (MRONJ) stage 2 in right side of mandible in 63-year-old man who had previously received chemotherapy and denosumab injection for lung cancer for nodular, bony, and hepatic metastases. a) ^{18}F-FDG PET, b) CT, and c) fused-PET/CT images showing osteolytic change and bone sequestrum with significant 18F-FDG uptake on right side of mandible. Calculated quantitative SUVmax, SUVpeak, SUVmean, MLV, and TLG values were 7.73, 6.52, 4.58, 35.90 (cm^3), and 164.44, respectively.

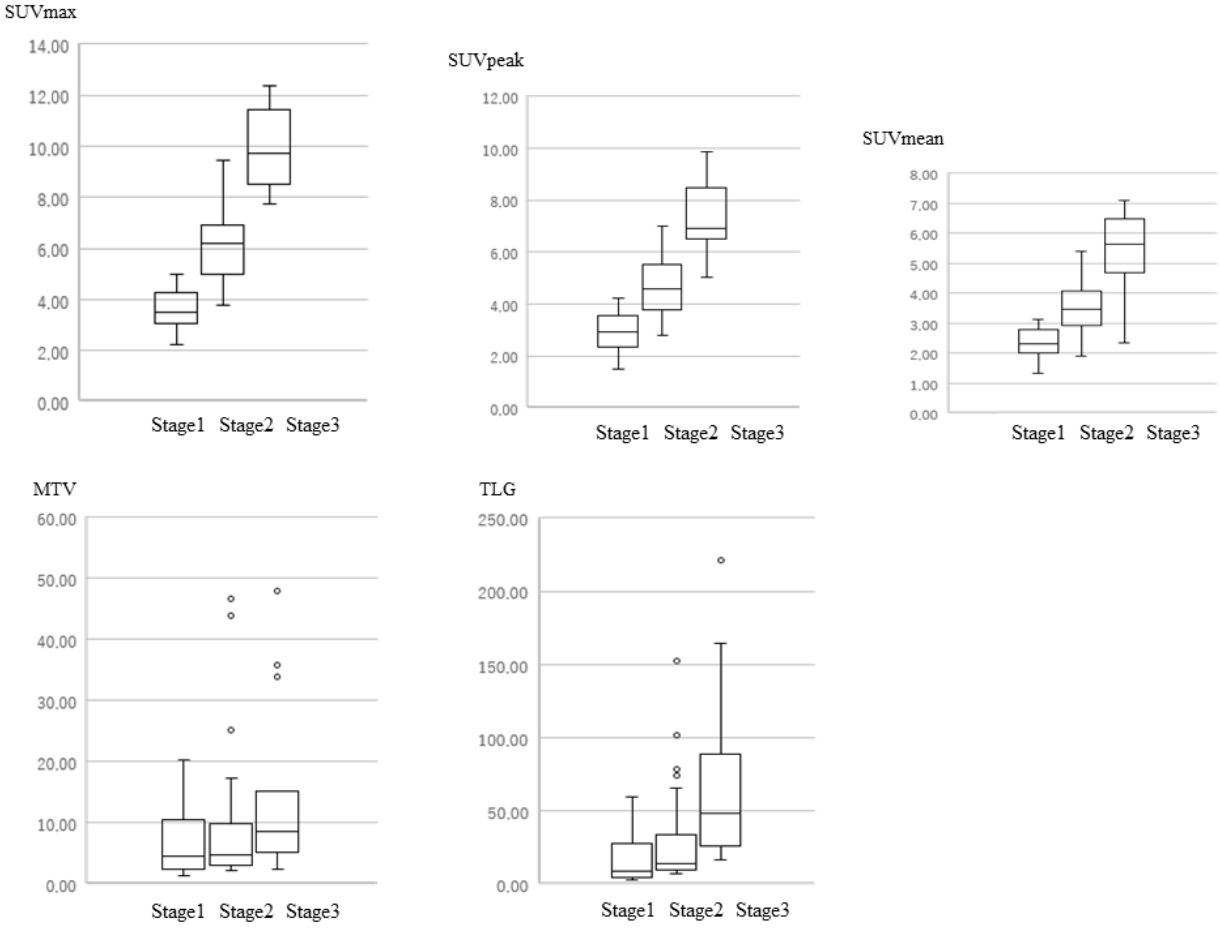

Figure 2. Quantitative values related to clinical stage. a) Maximum SUV related to clinical stage. There were significant differences noted between clinical stages ($P<0.0001$). Subsequent post hoc analysis indicated that SUVmax values were significantly different between any two stages ($P<0.0001$). b) Peak SUV related to clinical stage. There were significant differences noted between clinical stages ($P<0.0001$). Subsequent post hoc analysis indicated that SUVpeak values were significantly different between any two stages ($P<0.0001$). c) Mean SUV related to clinical stage. There were significant differences noted between clinical stages ($P<0.0001$). Subsequent post hoc analysis indicated that SUVpeak values were significantly different between any two stages ($P<0.0001$). d) Metabolic lesion volume (cm^3) related to clinical stage. A mild tendency to increase as stage increased was noted, though the difference between stages was not significant ($P=0.13$). e) Total lesion glycolysis related to clinical stage. There were significant differences noted between clinical stages ($P=0.0029$). Subsequent post hoc analysis indicated that the TLG value for stage 3 was significantly higher as compared to the values for stage 1 and stage 2 ($P<0.01$ and $P<0.05$, respectively).

The primary factors used for diagnosis of MRONJ are clinical manifestations and history of bone-modifying agent administration [1, 2], with plain radiography, CT, and MRI examination findings employed for both diagnosis and assessment of progression [4, 5]. The most commonly used radiology modality is panoramic radiography, which can show persistent tooth sockets following extraction. Characteristic CT findings indicating MRONJ, though not specific, include bony sclerosis, periosteal reaction, and bone sequestration in an advanced stage, while findings useful for differential diagnosis are chronic sclerosing osteomyelitis of the jaw, osteoradionecrosis, metastasis, and Paget's disease. Low signals in T1- and T2-weighted, and inversion recovery (IR) MRI findings suggest a low water content correlated with an insufficient quantity in cells and vessels. In contrast, unexposed diseased bone found in a subjacent location often indicates T1 hypointensity, and T2 and IR hyperintensity, thus suggesting high water content and inflammation that are associated with hypercellularity, osteogenesis, and hypervascularity. While these imaging modalities can also be used after structural alterations to visualize lesions, inflammation activities or early changes in MRONJ are not revealed. In contrast, molecular imaging performed with bone scintigraphy or ^{18}F-FDG PET/CT provides the ability to detect minimal subclinical changes in bone at an earlier stage as compared to conventional radiography methodologies, including X-rays, CT, and MRI [6, 7]. A comparison of the sensitivity of bone scintigraphy with that of ^{18}F-FDG PET was conducted in 2007 using only four patients with BRONJ, and the authors speculated that bone scintigraphy was an inferior diagnostic tool, mainly because of the poor resolution [14]. More recently, we presented findings showing that quantitative values obtained with technetium-99m bone scintigraphy are useful for evaluations of MRONJ patients for disease activity, staging [15], and therapeutic response [16].

Regarding ^{18}F-FDG PET/CT for cancer patients, findings showing a sensitivity of 65.7% and specificity of 55.6% have been presented [8], thus indicating moderate levels for diagnosis of MRONJ in clinical practice settings. A lack of ^{18}F-FDG uptake does not exclude the possibility of MRONJ disease. Unfortunately, ^{18}F-FDG PET/CT findings are not highly specific because of some amount of ^{18}F-FDG uptake in cases with advanced periodontal and periapical inflammation. Shimamoto et al. (2008) reviewed ^{18}F-FDG PET-positive dental infection findings, and noted an average SUVmax value of 3.5±1.0 for mild and 4.2±0.9 for severe cases [17]. In another study, Kito et al. (2012) noted average and maximum SUVmax values of 2.7±1.0 and 5.3, respectively, for 44 teeth in patients with advanced periodontal inflammation, and also average and maximum SUVmax values of 2.8±1.0 and 4.9, respectively, for 31 teeth under the condition of advanced periapical inflammation [18]. Physiological ^{18}F-FDG uptake around the jaw is often observed in PET findings of such cases, though SUVmax is lower than that seen in MRONJ cases, as noted in those previous reports [7, 13] and also the present series of cases. Our series did not include patients with periodontal or periapical inflammation.

This study is limited by the relatively low number of patients analyzed, which limits the ability to determine significant associations. It will be necessary to conduct a larger prospective study to verify the usefulness of ^{18}F-FDG PET/CT quantitative values to detect early status disease, and also provide more detailed assessments related to the severity and progression of MRONJ.

In conclusion, the evaluation of activity related to MRONJ is difficult when only conventional imaging is used for analysis. Based on the present findings, it is considered that ^{18}F-FDG PET/CT findings are useful to some extent for evaluating disease activity and staging aimed at guiding treatment planning.

The authors declare that they have no conflicts of interest

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