Am J Nucl Med Mol Imaging 2024;14(4):230-238
www.ajnmmi.us /ISSN:2160-8407/ajnmmi0156847

Original Article

Analysis of bone single-photon emission CT/CT and diffusion-weighted MR imaging in medication-related osteonecrosis of the jaw: focusing on the correlation between standardized uptake values and apparent diffusion coefficient values

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Received March 27, 2024; Accepted August 8, 2024; Epub August 25, 2024; Published August 30, 2024

Abstract: The purpose of this study is to investigate bone SPECT/CT and diffusion-weighted MR imaging (DWI) in medication-related osteonecrosis of the jaw (MRONJ), focusing on the correlation between standardized uptake values (SUVs) and apparent diffusion coefficient (ADC) values. Twenty-nine patients with MRONJ who underwent SPECT/CT and DWI were included in this study. SUVs (maximum and mean) with SPECT/CT, and ADC values (maximum, mean and minimum) with DWI were analyzed on characteristics in MRONJ, such as stage, location, medication and underlying disease, by Mann-Whitney U test. Furthermore, the correlation between SUVs and ADC values for characteristics in MRONJ were assessed by Spearman's rank correlation test for nonparametric data. A *p*-value lower than 0.05 was considered as statistically significant. SUVs and ADC values have no significant differences for all characteristics in MRONJ. Negative correlations were found in all cases and in stage 2 cases, and no correlations were found in stage 3 cases. In addition, negative correlations were found in maxillary cases, mandibular cases, non-bisphosphonate cases, osteoporosis cases, and malignant tumor cases. In conclusion, this study found multiple correlations between SUVs and ADC values in MRONJ, especially in stage 2. Suggesting that ADC values and SUVs may change with disease progression and the possibility of predicting MRONJ progression by SUVs and ADC values.

Keywords: Radionuclide imaging, single-photon emission-computed tomography, apparent diffusion coefficient, medication-related osteonecrosis of the jaw

Introduction

Antiresorptive agents, including bisphosphonates and denosumab, are commonly used for osteoporosis and tumors with bone metastases [1]. Medication-related osteonecrosis of the jaw (MRONJ) is a serious adverse effect reported in patients treated with antiresorptive agents and angiogenesis inhibitors [2]. Symptoms of MRONJ have been reported to include pain, swelling, bone exposure, fistulae, erythematous, ulcerated soft tissue or pathologic fractures [3]. These symptoms can significantly impair the health and quality of life of MRONJ patients [4]. However, MRONJ stage evaluation is done by clinical symptoms, and the relationship with the stage of quantitative evaluation by imaging has not been well reported.

Diffusion-weighted MR imaging (DWI) with apparent diffusion coefficient (ADC) maps is a useful tool in MR images that can provide a quantitative measure of the diffusivity of water in each voxel of biological tissue [5]. In the head and neck region, ADC has been shown to be useful in predicting and diagnosing lesions [6]. ADC in the bone marrow of MRONJ has also been reported and its usefulness has been investigated [7].

Bone single-photon emission CT/CT (SPECT/CT) is diagnostic imaging modality that can show physiological changes in bone, and standardized uptake values (SUVs) obtained from bone SPECT/CT enable quantitative evaluation of lesions [8, 9]. Currently, there are several reports on the use of bone SPECT/CT SUV for the evaluation of MRONJ [10-12]. However, SPECT/CT has several drawbacks such as taking a long time, exposing the patient to radiation, and being invasive, because radioisotopes are administered intravenously and their accumulation is visualized.

MRONJ shows more severe clinical manifestations as the stage advances, but the details of its progression are not clear. Although there are reports of SUV and ADC values at each stage of MRONJ, however, to our knowledge, no correlation between SUV and ADC values has been reported in the literature. The purpose of this study is to

https://doi.org/10.62347/FFPG9819

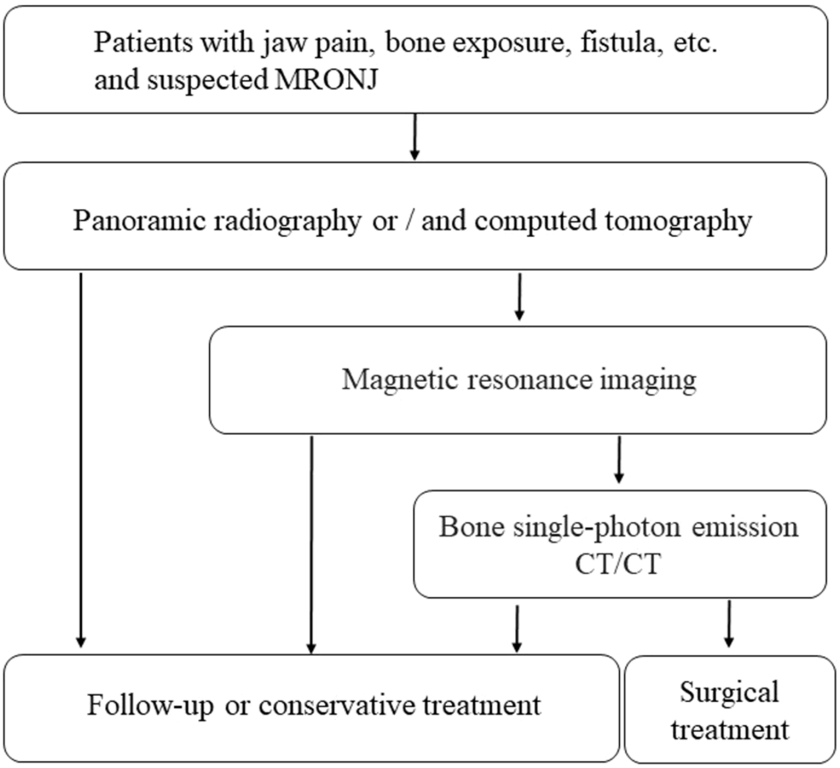

Figure 1. Flowchart of MRONJ imaging examinations at our hospital. Patients with suspected MRONJ will first undergo panoramic radiographs and CT. Next, an MRI is performed to confirm the status of the bone marrow. Subsequently, SPECT/CT is performed when considering surgical treatment.

examine the differences between stage 2, stage 3 and other characteristics and stage progression in MRONJ, focusing on the correlation between SUV and ADC.

Material and methods

Patients

This study was approved by the ethics committee of our university (ECNG-R-318). After providing written informed consent, 29 patients (10 men and 19 women; mean age 74.7 years [range, 48-91 years]) with clinically considered MRONJ who underwent SPECT/CT and MRI at our university hospital from March 2022 to December 2023 were included. **Figure 1** shows the process of imaging examination in MRONJ at our hospital. Diagnosis and staging of MRONJ were based on clinical symptoms in accordance with the 2022 American Association of Oral and Maxillofacial Surgeons (AAOMS) position paper [13].

Patients' medications were classified into 2 groups: bisphosphonate (BP) cases (5 minodronate, 3 alendronate, 3 ibandronate, 2 zoledronate and 1 risedronate) and non-bisphosphonate (non-BP) cases (14 denosumab and 1 bevacizumab). Patients' underlying diseases were classified into 2 groups: osteoporosis cases (15 cases) and malignant tumor cases (5 prostate cancer, 3 breast cancer, 2 lung cancer, 1 kidney cancer, 1 thyroid cancer, 1 rectal cancer and 1 multiple myeloma). All patients with MRONJ were diagnosed and treated for osteoporosis or malignant tumor at other hospital.

Imaging acquisition

SPECT/CT scans were obtained by a SPECT/CT scanner (Optima NM/CT 640, GE Healthcare, Tokyo, Japan), equipped with 4-slices CT scanner for attenuation correction, following our institution's protocol [8-12]. Patients were administered an intravenous injection of 740 MBq of ^{99m}Tc-hydroxymethylene diphosphonate (^{99m}Tc-HMDP, Clear Bone Injectable, Nihon Medi-Physics, Tokyo, Japan) 4 hours before SPECT acquisition.

The SPECT scan was acquired using low-energy high-resolution collimator, the 140 keV photoenergy peak for ^{99m}Tc, a 128 × 128 matrix of 4.2 mm pixel size, and a total of 60 projections (30 steps) over 360° with a dwell time of 10 s/step. Subsequent to the SPECT acquisition, a low-dose CT transmission scan was performed with 120 kV and 20 mA using a 512 × 512 matrix size. The CT data were generated with a 2.5 mm slice thickness.

The MR images were obtained using a 1.5 T MR imaging unit (EXCELART Vantage MRT 2003, Canon Medical Systems, Otawara, Japan) with a head coil. The images acquired were T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), short tau inversion recovery imaging (STIR), DWI and ADC maps and were acquired according to the following our institution's protocol [14]. The DWI sequence was obtained with b values of 0 and 800 s/mm^2 using an EPI technique (TR 8476 ms, TE 80 ms). The ADC maps were automatically generated from the DWI images.

Image analysis

For SPECT/CT, after imaging, all imaging data were transferred to a workstation for image reconstruction. Reconstruction was performed using MI software (GEniE-Xeleris 4DR, GE Healthcare, Tokyo, Japan) to produce SPECT/CT images according to our institution's protocol [12].

The quantitative SPECT/CT parameters were calculated using a commercially available software (Q. Volumetrix MI, GE Healthcare, Tokyo, Japan), following our institutions protocol [12]. The volume of interest (VOI) for SUV was drawn over the lesions automatically using the transaxial, coronal and sagittal SPECT/CT images.

The maximum SUV (SUVmax) and mean SUV (SUVmean) were calculated for quantitative analysis of HMDP uptake,

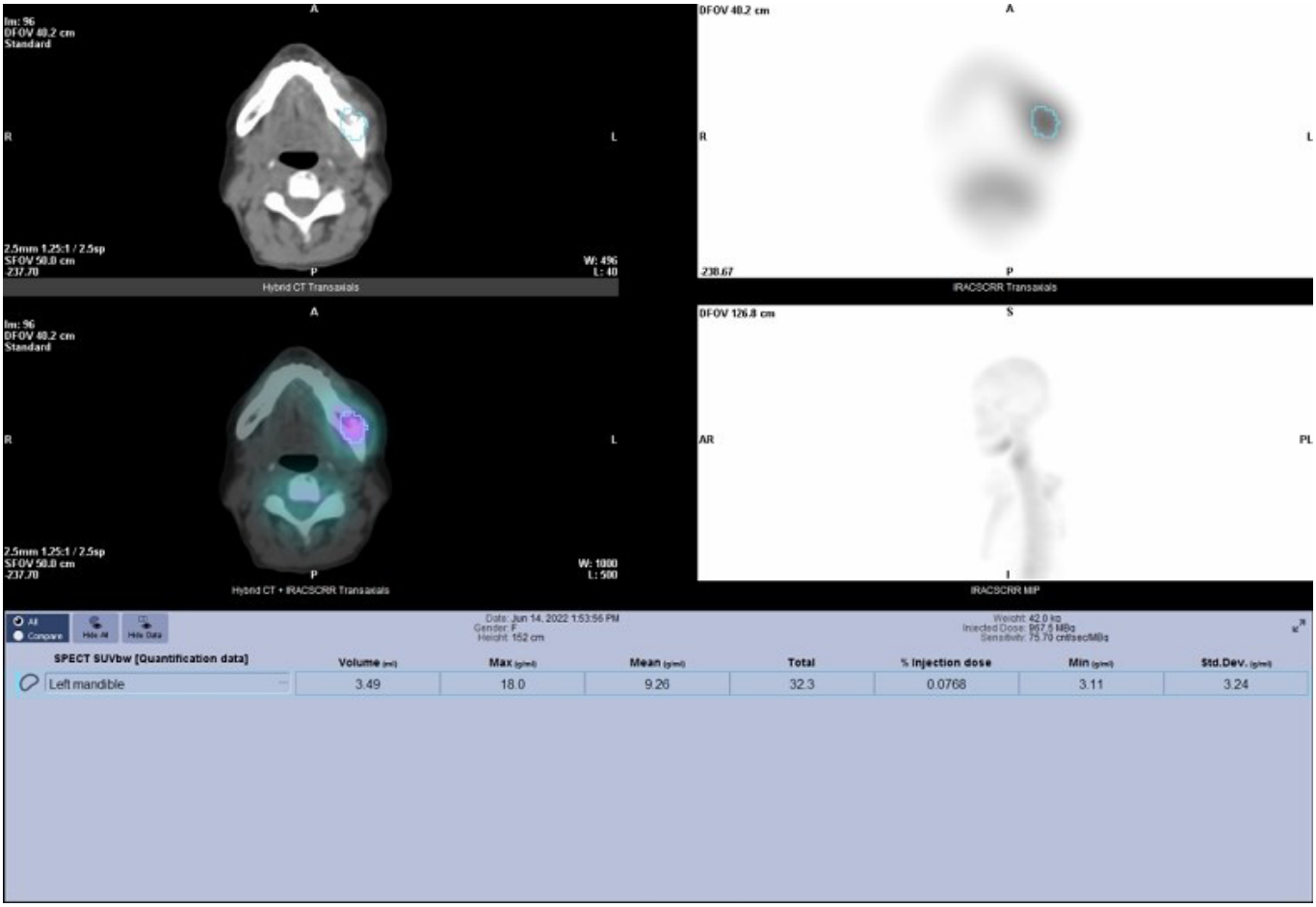

Figure 2. Medication-related osteonecrosis of the jaw of the left side of the mandible in a 61-year-old female. ^{99m}Tc-hydroxymethylene diphosphonate accumulation was shown in the left mandible. The volume of interest (sky blue) was set on lesion. Maximum SUV and mean SUV were 18.0 and 9.26, respectively.

as follows: SUVmax = (maximum radioactivity/voxel volume)/(injected radioactivity/body weight); SUVmean = (total radioactivity/VOI volume)/(injected radioactivity/body weight). **Figure 2** shows a SPECT/CT image of MRONJ. The accumulation of ^{99m}Tc-HMDP in the left mandible reflects osteosclerosis and osteolytic reaction due to the inflammatory response of MRONJ. A VOI is also set in the same area.

For MR images, a region of interest (ROI) was set on the ADC map to obtain ADC values. The ROI was placed such that it was the largest within the lesion with reference to T1WI, T2WI, and STIR, and the ADC values were automatically measured. Maximum ADC value (ADCmax), mean ADC value (ADCmean) and minimum ADC value (ADCmin) were recorded. **Figure 3** shows MR images (T1WI, T2WI, STIR, DWI, and ADC map) of the same MRONJ case. Low signal intensity on T1WI and decreased bone marrow signal in the left mandible, and high signal intensity on T2WI and STIR, which we consider an inflammatory response. High signal intensity was observed on DWI, indicating the presence of diffusion limitation, and a ROI was set on the ADC map. Two oral and maxillofacial radiologists independently reviewed and evaluated SPECT/CT and MR images, reaching a consensus.

Statistical analysis

For statistical analysis, Mann-Whitney U test was performed in SUV and ADC values for characteristics. The relationship between SUV and ADC values was assessed by Spearman's rank correlation test for nonparametric data. Those statistical analyses were performed using the statistical package, IBM SPSS Statistics, version 26 (IBM Japan, Tokyo, Japan). A *p*-value lower than 0.05 was considered as statistically significant.

Results

Table 1 shows the SUVmax and SUVmean for characteristics in MRONJ. Stage 2 showed lower values for both SUVmax and SUVmean than stage 3, but the differences were not significant (SUVmax: P = 0.195, SUVmean: P = 0.403). BP cases showed higher values for both SUVmax and SUVmean than non-BP cases, but the differences were not significant (SUVmax: P = 0.477, SUVmean: P =

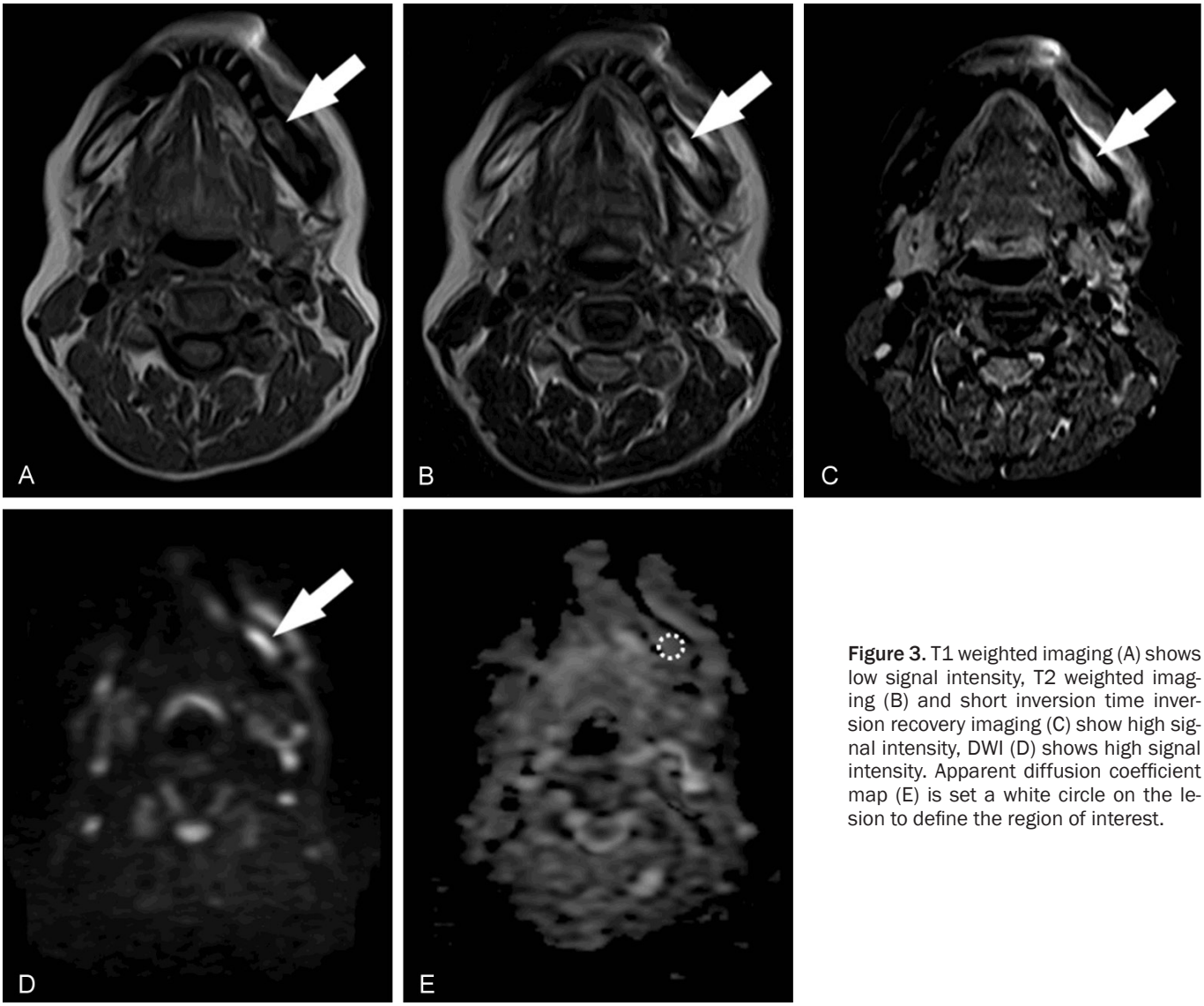

Figure 3. T1 weighted imaging (A) shows low signal intensity, T2 weighted imaging (B) and short inversion time inversion recovery imaging (C) show high signal intensity, DWI (D) shows high signal intensity. Apparent diffusion coefficient map (E) is set a white circle on the lesion to define the region of interest.

Table 1. Maximum and mean SUVs for characteristics in medication-related osteonecrosis of the jaw

Characteristics	Maximum SUV		*p*-value	Mean SUV		*p*-value
	Mean ± SD	Range		Mean ± SD	Range	
Total (n = 29)	17.1 ± 8.11	5.49-38.4		8.19 ± 4.23	3.23-19.7	
Stage			0.195			0.403
Stage 2 (n = 19)	15.5 ± 7.14	5.49-38.4		7.76 ± 3.92	3.23-19.6	
Stage 3 (n = 10)	20.0 ± 9.35	10.4-38.2		9.02 ± 4.86	3.47-19.7	
Location			0.581			0.477
Maxilla (n = 6)	18.5 ± 10.88	5.49-38.2		7.84 ± 6.13	3.23-19.7	
Mandible (n = 23)	16.7 ± 7.48	7.72-38.4		8.28 ± 3.76	3.24-19.6	
Medication			0.477			0.186
Bisphosphonates (n = 14)	18.4 ± 8.71	7.72-38.4		9.11 ± 4.17	3.24-19.6	
Non-bisphosphonates (n = 15)	15.7 ± 7.56	5.49-38.2		7.33 ± 4.24	3.23-19.7	
Underlying disease			0.561			0.914
Osteoporosis (n = 15)	16.9 ± 9.11	5.49-38.4		8.30 ± 4.26	3.23-19.6	
Malignant tumor (n = 14)	17.2 ± 7.21	10.4-38.2		8.08 ± 4.35	4.94-19.7	

SUV, standardized uptake value; SD, standard deviations.

Table 2. Maximum, mean and minimum ADC values for characteristics in medication-related osteonecrosis of the jaw

Characteristics	Maximum ADC (× 10^{-3} mm^2 s^{-1})		*p*-value	Mean ADC (× 10^{-3} mm^2 s^{-1})		*p*-value	Minimum ADC (× 10^{-3} mm^2 s^{-1})		*p*-value
	Mean ± SD	Range		Mean ± SD	Range		Mean ± SD	Range	
Total (n = 29)	1.59 ± 0.26	0.93-2.23		1.35 ± 0.27	0.76-2.12		1.07 ± 0.35	0.49-1.98	
Stage			0.735			0.636			0.668
Stage 2 (n = 19)	1.58 ± 0.25	0.93-2.23		1.35 ± 0.29	0.76-2.12		1.07 ± 0.37	0.55-1.98	
Stage 3 (n = 10)	1.61 ± 0.30	1.32-2.22		1.36 ± 0.26	1.14-1.89		1.08 ± 0.33	0.49-1.63	
Location			0.937			0.102			0.232
Maxilla (n = 6)	1.49 ± 0.20	1.37-1.74		1.25 ± 0.16	1.14-1.58		1.04 ± 0.15	0.96-1.33	
Mandible (n = 23)	1.61 ± 0.28	0.93-2.23		1.38 ± 0.29	0.76-2.12		1.08 ± 0.38	0.55-1.98	
Medication			0.715			0.425			0.201
Bisphosphonates (n = 14)	1.61 ± 0.34	0.93-2.23		1.33 ± 0.34	0.76-2.12		1.01 ± 0.39	0.55-1.98	
Non-bisphosphonates (n = 15)	1.57 ± 0.19	1.32-1.91		1.38 ± 0.20	1.14-1.79		1.14 ± 0.31	0.96-1.63	
Underlying disease			0.561			0.451			0.201
Osteoporosis (n = 15)	1.67 ± 0.28	1.36-2.23		1.40 ± 0.29	1.02-2.12		1.11 ± 0.36	0.65-1.98	
Malignant tumor (n = 14)	1.51 ± 0.24	0.93-1.91		1.31 ± 0.25	0.76-1.79		1.04 ± 0.35	0.49-1.63	

ADC, apparent diffusion coefficient; SD, standard deviations.

0.186). There were no clear trends or significant differences in other characteristics in SUVs. **Table 2** shows the ADCmax, ADCmean and ADCmin for characteristics in MRONJ. Maxillary cases showed lower values for ADCmax, ADCmean, and ADCmin than the mandible cases, but the differences were not significant (ADCmax: P = 0.937, ADCmean: P = 0.102, ADCmin: P = 0.232). Osteoporosis cases showed higher values for ADCmax, ADCmean, and ADCmin than the malignant tumor cases, but the differences were not significant (ADCmax: P = 0.561, ADCmean: P = 0.451, ADCmin: P = 0.201). There were no clear trends or significant differences in other characteristics in ADC values.

Table 3 shows the correlation between SUVs and ADC values for characteristics in MRONJ. In all cases, significant correlation was shown between SUVmax vs. ADCmax (r = -0.492, P = 0.007) and SUVmax vs. ADCmean (r = -0.501, P = 0.006). Significant correlations were also observed in stage 2 cases (SUVmax vs. ADCmax, SUVmax vs. ADCmean, SUVmean vs. ADCmean, SUVmean vs. ADCmin), maxillary cases (SUVmean vs. ADCmean, SUVmean vs. ADCmin), mandibular cases (SUVmax vs. ADCmax), non-BP cases (SUVmax vs. ADCmax, SUVmax vs. ADCmean), osteoporosis cases (SUVmax vs. ADCmean, SUVmax vs. ADCmin), and malignant tumor cases (SUVmax vs. ADCmax, SUVmax vs. ADCmean). No significant correlation was found in stage 3 cases and BP cases.

Figure 4 shows the correlation between SUVmax (X) and ADCmax (Y) in all cases, and a correlation was observed (Y = -0.011X + 1.781 (R^2 = 0.242, P = 0.007, n = 29)). It shows that ADCmax decreases as SUVmax increases in MRONJ. **Figure 5** shows the correlation between SUVmax (X) and ADCmax (Y) in stage 2 cases. There was a correlation at P = 0.020 (Y = -0.015X + 1.823 (R^2 = 0.281, P = 0.020, n = 19)). Although a few outliers are observed, a good correlation is observed, and a trend toward more cases with higher ADC values is observed compared to **Figure 4**. **Figure 6** shows the correlation between SUVmean (X) and ADCmin (Y) in maxillary cases. There was a correlation at P = 0.005 (Y = -0.103X + 1.141, R^2 = 0.889, n = 6). The maxillary cases tended to be biased due to the small number of cases, which may have resulted in a strong correlation. **Figure 7** shows the correlation between SUVmax (X) and ADCmax (Y) in malignant tumor cases. There was a correlation at P = 0.002 (Y = -0.018X + 1.817, R^2 = 0.549, n = 14). As in **Figure 5**, several outliers and ADC values exceeding 1.5 are observed in many cases.

Discussion

In this study, we found multiple correlations between SUVs and ADC values in MRONJ, especially in stage 2, whereas in stage 3 there was no correlation. In addition, we found several correlations in patient characteristics, and there were no significant differences in SUVs and ADC values for characteristics.

Ogawa et al. [12] reported SUVmax in each characteristic of MRONJ: 15.59 ± 8.06 for stage 2 cases, 21.51 ± 7.15 for stage 3 cases, 13.62 ± 5.70 for patients on denosumab, 22.98 ± 11.73 for patients on minodronate, 18.69 ± 8.57 for patients with osteoporosis cases, 12.28 ± 4.32 for patients with bone metastases from malignant tumors. The authors show that SUVmax is higher in stage 3 compared to stage 2, suggesting that SUV may increase with the progression of MRONJ stages. In this study also, a higher SUV is observed for stage 3 compared to stage 2. Muraoka et al. [7] reported ADCmean in Stage 2 and Stage 3 of MRONJ as 1.56 ± 0.15 × 10^{-3} mm^2 s^{-1} and 1.20 ± 0.13 × 10^{-3} mm^2 s^{-1}, respectively. The authors showed

Table 3. Correlation between SUVs and ADC values for characteristics in medication-related osteonecrosis of the jaw

Characteristics	Correlation coefficient (*p*-value)	
	Maximum SUV	Mean SUV
All cases (n = 29)		
Maximum ADC	-0.492 (0.007)	-0.189 (0.327)
Mean ADC	-0.501 (0.006)	-0.358 (0.057)
Minimum ADC	-0.306 (0.106)	-0.315 (0.097)
Stage		
Stage 2 (n = 19)		
Maximum ADC	-0.530 (0.020)	-0.416 (0.077)
Mean ADC	-0.504 (0.028)	-0.499 (0.030)
Minimum ADC	-0.439 (0.060)	-0.467 (0.044)
Stage 3 (n = 10)		
Maximum ADC	-0.442 (0.200)	-0.006 (0.987)
Mean ADC	-0.406 (0.244)	-0.188 (0.603)
Minimum ADC	-0.212 (0.556)	-0.261 (0.467)
Location		
Maxilla (n = 6)		
Maximum ADC	-0.657 (0.156)	-0.086 (0.872)
Mean ADC	-0.600 (0.208)	-0.829 (0.042)
Minimum ADC	-0.429 (0.397)	-0.943 (0.005)
Mandible (n = 23)		
Maximum ADC	-0.430 (0.040)	-0.251 (0.248)
Mean ADC	-0.391 (0.065)	-0.323 (0.133)
Minimum ADC	-0.263 (0.226)	-0.233 (0.285)
Medication		
Bisphosphonates (n = 14)		
Maximum ADC	-0.349 (0.221)	-0.147 (0.615)
Mean ADC	-0.398 (0.159)	-0.187 (0.523)
Minimum ADC	-0.473 (0.088)	-0.169 (0.563)
Non-bisphosphonates (n = 15)		
Maximum ADC	-0.718 (0.003)	-0.352 (0.198)
Mean ADC	-0.647 (0.009)	-0.489 (0.064)
Minimum ADC	-0.161 (0.567)	-0.356 (0.193)
Underlying disease		
Osteoporosis (n = 15)		
Maximum ADC	-0.318 (0.248)	-0.114 (0.685)
Mean ADC	-0.539 (0.038)	-0.332 (0.226)
Minimum ADC	-0.636 (0.011)	-0.396 (0.143)
Malignant tumors (n = 14)		
Maximum ADC	-0.741 (0.002)	-0.273 (0.345)
Mean ADC	-0.557 (0.039)	-0.477 (0.085)
Minimum ADC	0.095 (0.748)	-0.253 (0.383)

SUV, standardized uptake value; ADC, apparent diffusion coefficient; SD, standard deviations.

that ADC values are lower stage 3 than stage 2, suggesting that ADC values may be lower with progression of MRONJ stage.

In this study, correlations were observed for SUVmax and ADCmax, SUVmax and ADCmean, SUVmean and ADCmean, and SUVmean and ADCmin in stage 2, and no correlations in stage 3. Ogura et al. [15] noted that DWI and ADC maps reflect histopathological features of inflammatory diseases of the mandible. Ciobanu et al. [16] showed the presence of osteonecrosis and inflammatory infiltrate in histopathologic changes in MRONJ. Tetradis et al. [17] noticed the appearance of unremovable necrotic bone and increased inflammatory infiltrate around it in the progression of MRONJ. DWI and ADC are influenced by the local water diffusion, and ADCmax is considered to be influenced by the single pixel with the highest diffusion and ADCmin is considered to be influenced by the single pixel with the lowest diffusion. Stage 2 is considered to be the stage previous to stage 3, during which inflammatory infiltration and generation of osteonecrosis are considered to be occurring simultaneously. Therefore, both ADCmax and ADCmin showed correlations. In addition, stage 2 is considered to be correlated with a mixture of cases with high ADC and low SUVs, and cases with low ADC and high SUVs, suggesting that stage 2 is currently undergoing lesion expansion compared to stage 3. Tetradis et al. [17] noted prolonged inflammatory response as a characteristic feature in MRONJ. It is important to quantitatively assess the process of long-term inflammatory changes in MRONJ and the current state of the patient.

Minami et al. [18] noted that SUVmax is one voxel within a lesion, but SUVmean is dependent on the VOI. Suh et al. [19] stated that SUVmax is suitable for lesion evaluation and SUVmean depends on the size of the VOI, and it is difficult to set the exact same size VOI. In this study, SUVmax has many significant correlations compared to SUVmean.

MRONJ has changed to recommend lower stage surgery in AAOMS Position Paper 2022 compared to AAOMS Position Paper 2014 [13, 20]. This indicates that it is becoming possible to perform surgeries with higher success rates. Feng et al. [21] indicate age ≤ 65 years, chemotherapy, preoperative MRONJ duration ≥ 12 months, lesion location in the maxilla, lesion location in the molar area, and serum albumin < 40 g/L may be risk factors in MRONJ. The authors also report on usual stage 2 and refractory stage 2. Miles et al. [22] reported

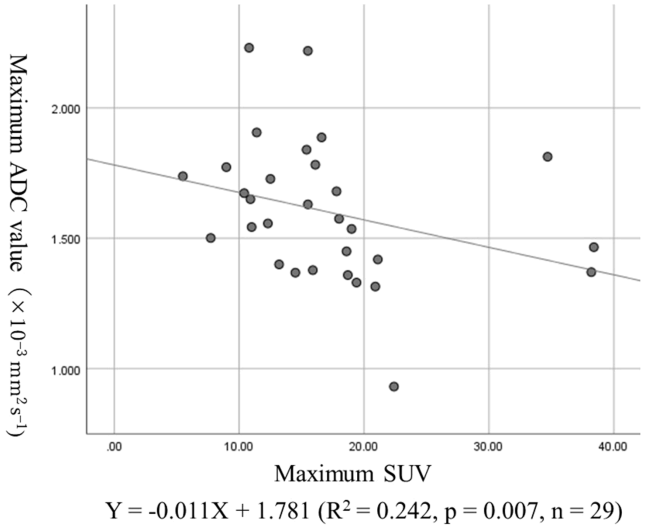

Figure 4. Correlation diagram showing the relationship between maximum SUV and maximum ADC in all cases.

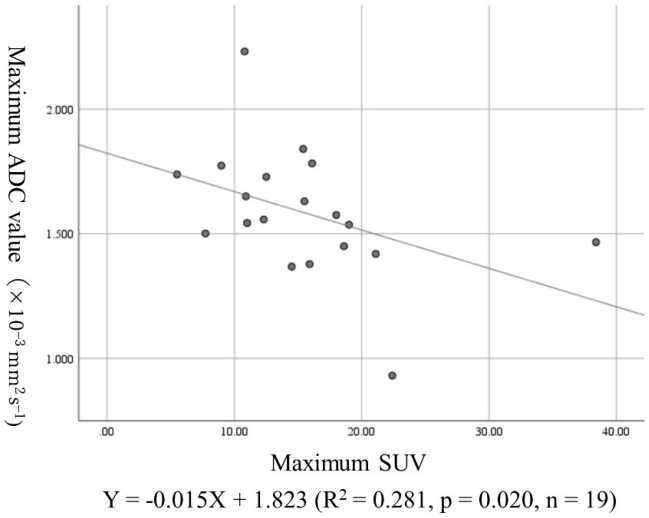

Figure 5. Correlation diagram showing the relationship between maximum SUV and maximum ADC in stage 2 cases.

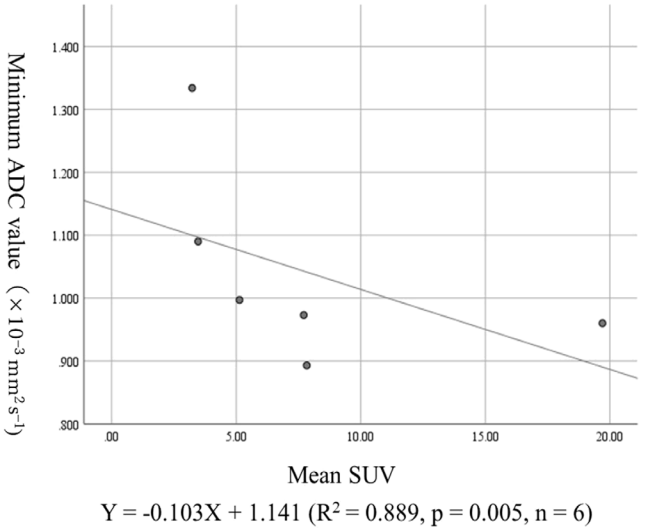

Figure 6. Correlation diagram showing the relationship between mean SUV and minimum ADC in maxillary cases.

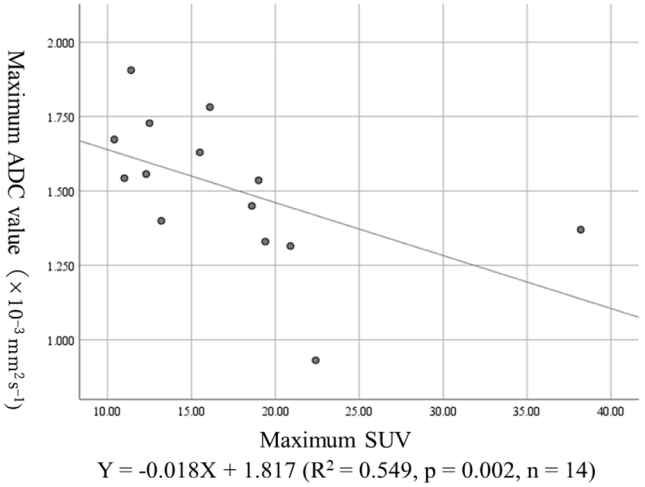

Figure 7. Correlation diagram showing the relationship between maximum SUV and maximum ADC in malignant tumor cases.

a 10.3% rate of worsened status in MRONJ with continued use of bone resorption inhibitors. Therefore, the selection of appropriate surgical and conservative treatment options and surgical procedures is important. Several reports have shown the usefulness of SUV, as it is a quantitative measure and can assess the physiological status of the maxilla and mandible regardless of stage, and may be useful in the selection of appropriate treatment [9-12, 23-25]. However, few studies have quantitatively compared SPECT/CT with other modalities. In this study, quantitative pathophysiological changes in imaging examinations in MRONJ were demonstrated by investigating the correlation between SUV and ADC values. In addition, multiple correlations were observed in stage 2 cases, suggesting that ADC values can provide active or reduced bone metabolism as well as SUV. Because MRI is more widespread and easier than SPECT/CT to examine the physiological status of bone, it may allow appropriate pathological evaluation in a larger number of patients.

This study has several limitations. The number of cases was relatively small, a definitive diagnosis could not be obtained by biopsy, and stage 1 cases were not included in this study. Therefore, further study is necessary.

In conclusion, this study found multiple correlations between SUVs and ADC values in MRONJ, especially in stage 2, whereas in stage 3 there was no correlation. There were cases with high ADC values and low SUVs, and cases with low ADC values and high SUVs in stage 2 of MRONJ, suggesting that ADC values and SUVs may change with disease progression and the possibility of predicting MRONJ progression by ADC values and SUVs.

Disclosure of conflict of interest

None.

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