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Review Article

☆Symposium: Imaging modalities for drug-related osteonecrosis of the jaw (5), utility of bone scintigraphy and ^{18}F-FDG PET/CT in early detection and risk assessment of medication-related osteonecrosis of the jaw (secondary publication)

Satoru Watanabe*, Kenichi Nakajima, Seigo Kinuya

Department of Nuclear Medicine, Kanazawa University Hospital, Kanazawa, Japan

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SUMMARY

Medication-related osteonecrosis of the jaw (MRONJ) is a significant side effect of antiresorptive and antiangiogenic drugs. Since MRONJ is intractable, early detection is the best way to limit progression. Bone scintigraphy and ^{18}F- fluorodeoxyglucose positron-emission tomography can detect minimal and subclinical changes in bones earlier than conventional radiological modalities. A differential diagnosis including MRONJ is recommended when abnormally high uptakes are incidentally detected in the jaws of patients who have bone metastases. Quantitative analysis of uptakes, such as bone scan index of the jaw using neural network analysis and maximum standardized uptake value, could differentiate MRONJ from common dental diseases and be useful for the early detection and risk assessment of MRONJ.

1. Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is a significant side effect of antiresorptive and antiangiogenic drugs. Details of MRONJ are explained in other reviews of this special issue. Although advanced MRONJ is intractable, early detection and treatment of MRONJ lead to improved prognosis. The present review aimed to introduce the utility of bone scintigraphy and ^{18}F-fluorodeoxyglucose (FDG) positron-emission tomography (PET)/computed tomography (CT) in early detection and risk assessment of MRONJ.

2. Importance of early MRONJ detection

Early detection of MRONJ has increased in importance, and the staging system has changed [1]. MRONJ was initially classified from stage 1 to stage 3, and stage 1 was defined as having exposed and necrotic bone in patients who are asymptomatic and have no evidence of infection. In 2009, stage 0 was added to the conventional stages, and defined as having jaws with no clinical evidence of necrotic bone but presenting with nonspecific clinical findings, radiographic changes, and symptoms. Furthermore, an at-risk category was proposed. An at-risk category means that even if there is no apparent necrotic bone and symptom, patients who have been treated with antiresorptive and/or antiangiogenic therapy should be careful about MRONJ.

In addition, there is a big difference between stage 1 and stage 2 MRONJ, and early detection before proceeding to stage 2 is important. Stage 1 MRONJ, which is asymptomatic, could go undetected. Because most patients without symptoms seldom see a dentist, discovered stage 1 cases could be only a part of the whole stage 1 population. In contrast, most patients with stage 2 MRONJ consult dentists by themselves because they have clinical symptoms, such as pain and erythema. However, the healing probability of MRONJ at advanced stages 2 and 3 is significantly lower than that at less advanced stages [2,3]. If lesions can be detected and the risk can be assessed before the development of stage 2 MRONJ, it will help prevent severe diseases and lead to improved prognosis.

Nuclear imaging with bone scintigraphy and FDG PET can detect minimal and subclinical changes in bones earlier than conventional radiography, X-ray CT scan, and magnetic resonance imaging. In addition, we can find unexpected abnormalities of the jaw during

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* Corresponding author at: Department of Nuclear Medicine, Kanazawa University Hospital, Kanazawa, 13-1 Takara-machi, Kanazawa 920-8641, Japan.
E-mail address: watanabe@nmd.m.kanazawa-u.ac.jp (S. Watanabe).

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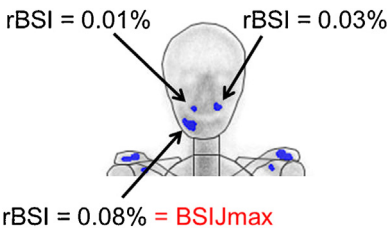

Fig. 1. Example of a bone scintigraphy image analyzed by the artificial intelligence software. The software could automatically detect abnormal uptakes, which were filled in blue, and calculate each regional BSI (rBSI), which was defined as the fraction of abnormality to the entire skeleton. Among the rBSIs, the largest one in the jaw was manually selected and defined as the maximum BSI of the jaw (BSIJmax).

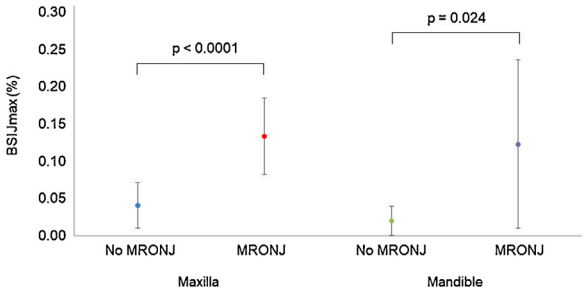

Fig. 2. Comparison of BSIJmax between patient groups. In MRONJ group, all patients underwent bone scintigraphy for bone metastasis assessment 3 months before the diagnosis of stage 2 MRONJ.

bone scintigraphy and FDG PET for oncologic assessment because they can evaluate the whole body.

3. Early detection by bone scintigraphy

Several studies have reported that bone scintigraphy can detect early MRONJ [4,5]. However, conventional evaluation of bone scintigraphy is visual and qualitative, and the diagnosis might be varied according to readers' experiences. In contrast, a computer-aided diagnosis of bone scintigraphy using a bone scan index (BSI) has been shown to enhance diagnostic accuracy and reproducibility of bone metastases and provide prognostic information [6,7]. BSI is a quantitative marker of the spread for bone metastases using neural network analysis. There are more than 50 related papers and several guidelines refer to BSI. As a new application, we investigated a diagnostic ability of BSI for early detection of MRONJ [8].

A total of 44 cancer patients who were treated with antiresorptive drugs and who underwent bone scintigraphy for bone metastasis assessment at our hospital were retrospectively evaluated. The cohort consisted of two groups. In the MRONJ group, all 17 patients were diagnosed with stage 2 MRONJ by experienced dentists and incidentally underwent bone scintigraphy 3 months (the average 2.8 ± 1.9 months, range 0.5–6.0) before the first diagnosis of stage 2 MRONJ. In the control group, all 27 patients were treated with anti-resorptive drugs without a development of MRONJ. We evaluated uptakes in the jaw by BSI (Fig. 1). The artificial intelligence software BONENAVI could automatically detect abnormal uptakes and calculate each regional BSI (rBSI), which was defined as the fraction of abnormality to the entire skeleton (%). Among the rBSIs, the largest one in the jaw was manually selected and defined as the maximum BSI of the jaw (BSIJmax).

As a result of the analysis, the BSIJmax was significantly higher in patients who developed MRONJ than in those who did not, 3 months before the diagnosis of stage 2 MRONJ (Fig. 2). Using the cutoff values of 0.09% in the maxilla and 0.06% in the mandible, BSIJmax for predicting stage 2 MRONJ showed a sensitivity and specificity of 88 and 96%, respectively, in the maxilla, and 64 and 89%, respectively, in the mandible 3 months before the diagnosis. BSIJmax could be useful for early detection of MRONJ.

A differential diagnosis including MRONJ is recommended when areas of high BSIJmax are detected in patients treated with antiresorptive drugs. Because the pathogenic mechanism of MRONJ is not yet completely understood, the detection of early MRONJ is essential. Dentists can examine the area of high BSIJmax carefully and contribute to preventing advanced MRONJ and understanding the early pathogenic mechanism.

Early MRONJ found by bone scintigraphy could increase in the future. The most frequent type of cancer was prostate cancer in our MRONJ cohort. The prevalence of prostate cancer ranks itself first amongst other types of male cancer in the US, and prostate cancer is also rapidly increasing in Japan. For monitoring men with metastatic castration-resistant prostate cancer, regular bone scintigraphy every 3–6 months was supported by the majority of international prostate cancer experts [9]. If we frequently monitor many patients with prostate cancer by bone scintigraphy, the possibility of early detection of MRONJ by bone scintigraphy also increases.

MRONJ is a rare disease, and MRONJ studies of multicenter data are essential. It would be ideal if we analyze Japanese multicenter data with BSIJmax and could contribute to the understanding of the mechanism of MRONJ. In Germany, where Watanabe studied abroad, studies on osteonecrosis of the jaw using bone scintigraphy are relatively active, and Japan should not delay this research [5,10,11].

4. BSIJmax of common dental diseases and MRONJ

Except for MRONJ, common dental diseases also cause positive tracer uptakes in the jaw. We retrospectively evaluated 130 patients who underwent both bone scintigraphy for bone metastasis assessment and dental examination at our hospital [12]. All patients underwent dental examination within 3 months of bone scintigraphy and did not develop MRONJ.

As a result of the analysis, BSIJmax was significantly higher in areas where severe periodontitis was observed than in areas where mild periodontitis was observed. In addition, BSIJmax in areas where periodontitis and/or apical periodontitis were observed was significantly lower than the BSIJmax of the above-mentioned MRONJ cohort where patients underwent bone scintigraphy 3 months before the diagnosis of stage 2 MRONJ. BSIJmax could be useful for differentiating MRONJ from common dental diseases.

5. Early detection by FDG PET

Except for prostate cancer, FDG PET/CT is often used to replace bone scintigraphy to assess metastases. Although high FDG uptakes in the jaw are often observed in routine PET, they do not attract much attention because they are recognized as a benign disease incidentally found during the examination of a malignant disease. However, they could include lesions that progress to refractory advanced MRONJ.

We retrospectively evaluated a total of 53 patients who underwent oncologic assessment by FDG PET/CT [13]. The cohort consisted of two groups. In the MRONJ group, all 12 patients were diagnosed with stage 2 MRONJ at an average of 3 months after PET. The control group was comprised of 41 consecutive patients with breast cancer who had never been treated with agents that are associated with risk of MRONJ. FDG uptake in the jaw was analyzed based on maximum standardized uptake value (SUVmax) and the error of SUVmax due to dental metallic artifact was corrected using a standard correction method integrated into the PET/CT equipment.

As a result of the analysis, SUVmax in the jaw was significantly higher in patients who developed MRONJ than in those who did not, 3 months before the diagnosis of stage 2 MRONJ. SUVmax in the jaw tended to be higher as the timing of PET was closer to the diagnosis of stage 2 MRONJ. FDG PET could detect lesions before they progress to refractory advanced MRONJ.

Various studies support the present results, and the SUVmax of MRONJ has been reported to be relatively high. Fleisher et al. reported a mean SUVmax of 6.6 for 25 MRONJ lesions [14]. Raje et al. also reported that 10 of 11 patients with MRONJ had abnormal FDG uptakes in the jaw and an average SUVmax of 7.5 ± 2.9 (range 3.3–11.8) [15].

In contrast, less FDG is generally uptaken by common dental and periodontal diseases than by MRONJ. Shimamoto et al. reported that 88% of dental infections were FDG-PET negative [16]. They also found, in FDG-PET positive dental infections, an average SUVmax of 3.5 ± 1.0 and 4.2 ± 0.9 in mild and severe dental infections, respectively. In addition, Kito et al. reported average and maximal SUVmax of 2.7 ± 1.0 and 5.3, respectively, in 44 teeth in the setting of advanced periodontal inflammation [17]. They also reported average and maximal SUVmax of 2.8 ± 1.0 and 4.9 in 31 teeth in the setting of advanced periapical inflammation. Although physiological FDG uptakes around the jaw are often observed during daily PET, their SUVmax is lower than the above-mentioned SUVmax of MRONJ [18,19].

6. Cautions

Although most high tracer uptakes in the jaw are caused by common diseases other than MRONJ, they are also important to detect for prevention of MRONJ. Common dental and periodontal diseases are crucial risk factors for MRONJ and several studies reported that 71%–84% of patients with MRONJ presented with periodontitis [20,21]. In addition, tooth extraction is associated with a 16- to 33-fold increased risk for MRONJ [22,23]. Considering the condition 3 or 6 months prior to the diagnosis of stage 2 MRONJ, some could have had stage 0 or 1 MRONJ, and others could have had only a common disease such as periodontitis. Bone scintigraphy and FDG PET alone cannot always distinguish early MRONJ from common dental diseases. However, distinguishing them is not essential for the prevention of advanced refractory MRONJ. The importance of discovering and investigating early MRONJ and/or high-risk lesions potentially resulting in MRONJ should be emphasized.

Bone scintigraphy and FDG PET have several limitations. The main purpose of these high-cost examinations is to evaluate malignancies, and they indirectly detect MRONJ via osteoblasts' activity and inflammation. In addition, BSIJmax and SUVmax might be affected by various technical and physiological factors.

7. Conclusion

A differential diagnosis including MRONJ is recommended when abnormally high uptakes are incidentally detected in the jaws of patients who have bone metastases during routine bone scintigraphy and FDG PET. Quantitative analysis of uptakes in the jaw using BSIJmax and SUVmax could be useful for predicting the development of MRONJ.

Conflict of interest

K. Nakajima has a collaborative research work with FUJIFILM Toyama Chemical, Co. Ltd., Tokyo, Japan for the development of software.

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