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ORIGINAL ARTICLE

Bone scan index of the jaw: a new approach for evaluating early-stage anti-resorptive agents-related osteonecrosis

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Abstract
Objective A computer-aided diagnosis of bone scintigraphy using a bone scan index (BSI) has not been applied to a diagnosis of anti-resorptive agents-related osteonecrosis of the jaw (ARONJ). The aim of this study was to validate a diagnostic ability of BSI for early-stage ARONJ.
Methods A total of 44 cancer patients treated with anti-resorptive drugs were evaluated retrospectively. All patients underwent bone scintigraphy and the tracer uptakes were analyzed by BSI. The software BONENAVI (FUJIFILM RI Pharma; EXINIbone, EXINI Diagnostics) could automatically detect abnormal intensities and calculate each regional BSI (rBSI). Among the rBSIs, the largest one in the jaw was manually selected and defined as maximum BSI of the jaw (BSIJmax). Uptake ratio (UR) between the maximum jaw count-to-average forehead count was also calculated. Screening accuracy of ARONJ based on 2 parameters was compared. Receiver operating characteristic analysis and Fisher's exact test were performed.
Results The BSIJmax was significantly higher in patients who developed ARONJ than in those who did not, 3 months before the diagnosis of stage 2 ARONJ ($p < 0.0001$ and $p = 0.02$ in the maxilla and mandible, respectively). Using the cutoff values of 0.09% in the maxilla and 0.06% in the mandible, BSIJmax for predicting stage 2 ARONJ showed sensitivity and specificity of 88 and 96%, respectively, in the maxilla and 64 and 89%, respectively, in the mandible at 3 months before the diagnosis. The BSIJmax >0.09% and BSIJmax >0.06% in the maxilla and mandible, respectively, were much more frequently observed in patients who subsequently developed stage 2 ARONJ 3 months after the bone scintigraphy than in those who did not ($p < 0.0001$ and odds ratio = 182 in the maxilla and $p < 0.005$ and odds ratio = 14 in the mandible). The UR showed comparable diagnostic ability.
Conclusion The BSIJ provided a new index for evaluating ARONJ. For predicting occurrence of ARONJ, the thresholds of BSIJmax = 0.09 and 0.06% in the maxilla and mandible, respectively, may be used in patients treated with anti-resorptive drugs, and a differential diagnosis including ARONJ is recommended.

Keywords Bone scintigraphy · Bone scan index (BSI) · Osteonecrosis · Jaw · Computer-aided diagnosis

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Introduction

A growing number of osteonecrosis cases involving the jaw associated with anti-resorptive agents have been reported since the first report of bisphosphonate-related osteonecrosis of the jaw (BRONJ) [1]. Therefore a new nomenclature of anti-resorptive agents-related osteonecrosis of the jaw (ARONJ) was proposed [2]. The ARONJ is intractable once it occurs, and early detection is the best way to limit progression. The most widely adopted staging

system of ARONJ has been based on position papers by the American Association of Oral and Maxillofacial Surgeons (AAOMS). They added a stage 0 category to the conventional stages 1–3 in 2009 and an at-risk category in 2014 [3, 4]. As demonstrated by these trends, early detection of ARONJ has increased in importance. However, the current case definition and staging system, which are mainly based on clinical findings, might underestimate ARONJ and lead to a delayed diagnosis [4–6]. This delayed diagnosis can influence therapeutic strategies and also explain, at least in part, why the disease is often refractory to the treatments [7]. In addition, because the pathogenic mechanism of ARONJ is not yet completely understood, the detection of early-stage ARONJ is essential.

Bone scintigraphy, which is used extensively in the diagnosis and management of oncologic diseases, can detect minimal, metabolic, vascular, and pathophysiologic changes in bone earlier than conventional radiography, X-ray computed tomography (CT) scan, and magnetic resonance imaging (MRI) [8–14]. In addition, various studies have demonstrated the usefulness of bone scintigraphy in the diagnosis of osteonecrosis of the jaw (ONJ) [15–24].

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 [25–27]. The BSI was initially proposed at Memorial Sloan-Kettering Cancer Center as a quantitative marker of the spread for bone metastases, which was a fraction of bones involved by a tumor [28]. However, no study has applied BSI to the diagnosis of ONJ. The aim of this study was to validate a diagnostic ability of BSI for early-stage ARONJ.

Materials and methods

Patients

A total of 44 cancer patients treated with anti-resorptive drugs at our hospital were evaluated retrospectively. Characteristics of the patients are summarized in Table 1. In the ARONJ group, all patients were diagnosed as stage 2 ARONJ by experienced dentists between June 2007 and November 2015 and underwent bone scintigraphy 3 months (the average 2.8 ± 1.9 months, range 0.5–6.0) before the first diagnosis of stage 2 ARONJ. In the control group, all patients were treated with anti-resorptive drugs without a development of ARONJ and underwent bone scintigraphy between January 2014 and June 2014. There was no significant difference in age between the groups. The most frequent types of cancer and anti-resorptive drugs were prostate cancer and zoledronic acid. ARONJ often developed in the mandibular bone of patients who were treated with anti-resorptive drugs for more than 3 years. This study was approved by the institutional ethics committee of our university. Informed consent from each patient was waived due to the retrospective nature of the study.

Diagnostic criteria of ARONJ

ARONJ legions were staged according to the AAOMS staging system as indicated below [4]. Stage 0 is defined as no clinical evidence of necrotic bone but nonspecific clinical findings, radiographic changes, and symptoms. Stage 1 is defined as exposed and necrotic bone or a fistula that probes to bone in patients who are asymptomatic and have no evidence of infection. Stage 2 is defined as exposed and necrotic bone or a fistula that probes to bone associated with infection as evidenced by pain and erythema with or without purulent drainage.

Whole-body bone scintigraphy

Whole-body anterior and posterior images were used for the analysis. A standard dose of 740 MBq (20 mCi) of ^{99m}Tc-methylene diphosphonate (MDP; FUJIFILM RI Pharma, Co. Ltd., Tokyo, Japan) was injected and imaged 3 h later. The matrix size was 256 × 1024 with an energy peak of 140 keV with a 15% window.

Quantitative analysis of bone scintigraphy

Tracer uptakes in the jaw were analyzed semiquantitatively by the following 2 parameters (Fig. 1). The first was the maximum BSI of the jaw (BSIJmax). The software BONENAVI (FUJIFILM RI Pharma, Co. Ltd., Tokyo, Japan; EXINIbone, EXINI Diagnostics AB, Lund, Sweden) automatically detected abnormal intensities based on the learning from a Japanese multi-center database with an artificial neural network (ANN) system, and calculated each regional BSI (rBSI), which was defined as the fraction of abnormality to the entire skeleton (%) [26]. Even when the probability of abnormality was <0.5 by the ANN system, abnormal intensities in the jaw were included. Among the rBSI automatically calculated by the software, the largest one in the jaw was manually selected and defined as BSIJmax. The other parameter was, as conventionally used, uptake ratio (UR), which was calculated as a ratio of the maximum jaw count-to-average count of the forehead. Tracer uptakes in the mandible and maxilla were analyzed separately by 2 parameters. BSIJmax and UR could be derived from ARONJ or could be due to other reasons, such as common dental or periodontal diseases and metastases.

Table 1 Characteristics of patients

	No ARONJ	ARONJ
N	27 (61%)	17 (39%)
Age (years)	66.9 ± 9.0 (42.9–83.7)	69.1 ± 9.7 (52.9–81.1)
Male	23 (85%)	15 (88%)
Types of cancer		
Prostate	17 (63%)	12 (71%)
Kidney	2 (7%)	3 (18%)
Breast	4 (15%)	1 (6%)
Lung	4 (15%)	1 (6%)
Duration of anti-resorptive drugs (years)	1.3 ± 1.4 (0.01–6.5)	3.1 ± 1.7 (0.6–6.8)
Types of anti-resorptive drugs		
Zoledronic acid	19 (70%)	14 (82%)
Denosumab	5 (19%)	1 (6%)
Both (zoledronic acid and denosumab non-simultaneously)	3 (11%)	2 (12%)
Location of stage 2 ARONJ		
Maxilla	–	8 (42%)[a]
Mandible	–	11 (58%)[a]
Cause of ARONJ		
Dental extraction	–	5 (29%)

Values are presented as *N* (%) or mean ± standard deviation (range)

ARONJ anti-resorptive agents-related osteonecrosis of the jaw

[a] Two patients had stage 2 ARONJ in both the maxilla and mandible

Statistical analysis

All the data were expressed as mean ± standard deviation. The receiver operating characteristic (ROC) analysis for predicting ARONJ was performed and the area under the curve (AUC) was calculated. The significance of high BSIJmax for the prediction of early-stage ARONJ was calculated by Fisher's exact test and the odds ratio determined. p values <5% were considered significant.

Results

Maxilla and mandible

BSIJmax and UR were compared between the maxilla and mandible (Fig. 2). The average BSIJmax in the maxilla and mandible of patients treated with anti-resorptive drugs without developing ARONJ was 0.04 ± 0.03 and 0.02 ± 0.02% ($p = 0.03$), respectively. The average BSIJmax in the maxilla and mandible of patients who developed stage 2 ARONJ was 0.13 ± 0.05 and 0.12 ± 0.11% ($p = 0.81$), respectively, 3 months before the diagnosis. The BSIJmax was significantly higher in the maxilla than in the mandible in patients who did not develop ARONJ ($p = 0.03$).

The average UR in the maxilla and mandible of patients treated with anti-resorptive drugs without developing ARONJ was 5.7 ± 1.9 and 4.7 ± 1.8 ($p = 0.049$), respectively. The average UR in the maxilla and mandible of patients who developed stage 2 ARONJ was 12.0 ± 2.8 and 7.5 ± 3.3 ($p = 0.007$), respectively, 3 months before the diagnosis. The UR was significantly higher in the maxilla than in the mandible in patients who did not develop ARONJ ($p = 0.049$) and in those who developed stage 2 ARONJ at 3 months before the diagnosis ($p = 0.007$).

Comparison between patient groups

BSIJmax and UR were compared between patient groups (Fig. 3). The BSIJmax in the maxilla and mandible was significantly higher in patients who developed ARONJ than in those who did not, 3 months before the first diagnosis of stage 2 ARONJ ($p < 0.0001$ and $p = 0.02$, respectively). Similarly, the UR in the maxilla and mandible was significantly higher in patients who developed ARONJ than in those who did not, 3 months before the first diagnosis of stage 2 ARONJ ($p < 0.0001$ and $p = 0.02$, respectively).

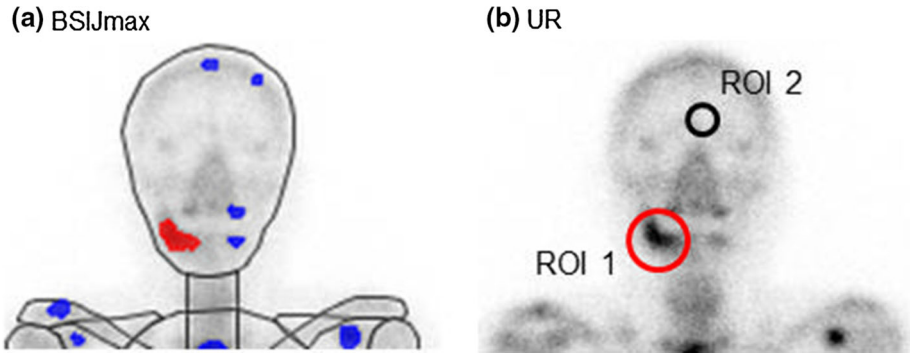

Fig. 1 Methods of semiquantitative analysis. **a** The software BONE-NAVI automatically detected abnormal intensities in bone scintigraphy and indicated them in *blue*. Among them, the largest one in the jaw was manually selected and indicated in *red*. **b** We manually placed a circular region of interest (ROI) over a high count jaw region (ROI 1), and a reference ROI over the forehead (ROI 2) to calculate a ratio of the maximum jaw count-to-average forehead count

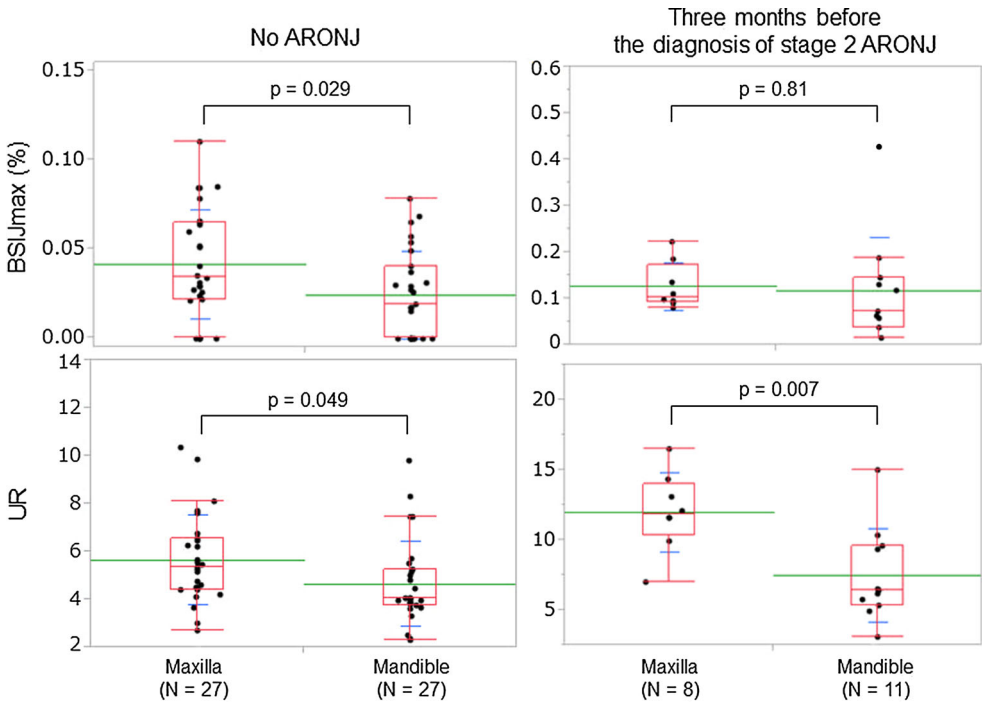

Fig. 2 Comparison of BSIJmax and UR between the maxilla and mandible. *Green* and *blue lines* are mean and standard deviation, respectively. *Outlier box plot* indicates median, 25, and 75% quartile with *whiskers* for both ends. Two patients had stage 2 ARONJ in both the maxilla and mandible

ROC analysis, optimal sensitivity, and specificity

Screening accuracy of BSIJmax and UR for predicting stage 2 ARONJ at 3 months before the first diagnosis were examined using ROC analysis (Fig. 4; Table 2). Using the cutoff value of BSIJmax = 0.09% in the maxilla, sensitivity and specificity were 88 and 96%, respectively. Using the cutoff value of BSIJmax = 0.06% in the mandible, sensitivity and specificity were 64 and 89%, respectively. Using the cutoff value of UR = 9.8 in maxilla, sensitivity and specificity were 88 and 93%, respectively. Using the cutoff value of UR = 6.0 in the mandible, sensitivity and specificity were 64 and 85%, respectively.

Significance of high BSIJmax

The significance of high BSIJmax for the prediction of early-stage ARONJ was examined by Fisher's exact test (Table 3). In patients without developing ARONJ, only 4% had BSIJmax >0.09% in the maxilla. The BSIJmax >0.09% was much more frequently observed in patients who subsequently developed stage 2 ARONJ in the maxilla 3 months after the bone scintigraphy than in those who did not ($p < 0.0001$, odds ratio = 182). Similarly, in patients without developing ARONJ, only 11% had BSIJmax >0.06% in the mandible. The BSIJmax >0.06% was much more frequently observed in patients who subsequently developed stage 2 ARONJ in the mandible 3 months after the bone scintigraphy than in those who did not ($p < 0.005$, odds ratio = 14).

Locations of ARONJ and tracer uptakes

Locations of ARONJ, BSIJmax and UR were in agreement in most of the cases as follows. In 19 stage 2 ARONJ legions, 17 (89%) legions developed in the same location with BSIJmax 3 months after the bone scintigraphy. The location of BSIJmax and UR were the same in all patients who developed stage 2 ARONJ at 3 months before the diagnosis.

Dental extraction

The relationship between BSIJmax and dental extraction was examined. In 17 patients who developed stage 2 ARONJ, 5 (29%) patients underwent dental extractions less than 1 year (average 3.4 ± 2.5 months) before the diagnosis (Table 1). Two of the five patients underwent the dental extractions at dentists without consulting their physicians who prescribed anti-resorptive drugs. In the 5 patients, 3 patients underwent bone scintigraphy before the dental extraction (average BSIJmax, 0.13 ± 0.06%) and 2 patients did so after the dental extraction (average BSIJmax, 0.05 ± 0.01%).

BSIJmax and UR

The relationship between BSIJmax and UR was examined (Fig. 5). R^2 values were 0.44 ($p < 0.0001$) and 0.57 ($p < 0.0001$) in the maxilla and mandible, respectively. Significant correlation was found between BSIJmax and

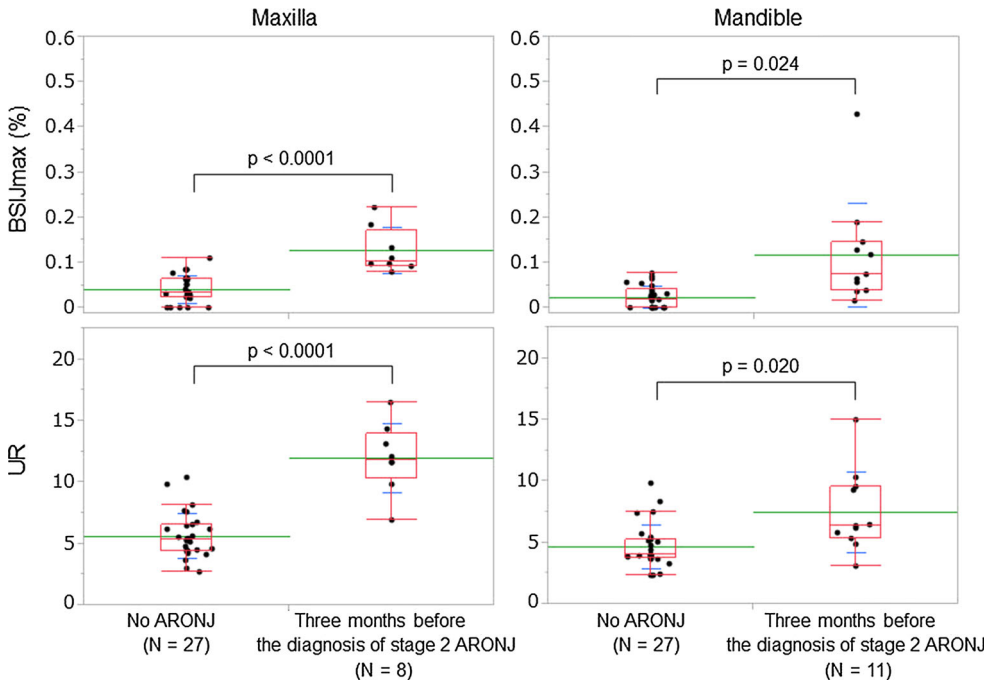

Fig. 3 Comparison of BSIJmax and UR between patient groups

UR in both the maxilla and mandible. Using the cutoff values of BSIJmax and UR separately in the maxilla, 88% (7 of 8) and 78% (7 of 9), respectively, of patients who had higher tracer uptakes than the cutoff values were correctly evaluated to develop stage 2 ARONJ 3 months after the bone scintigraphy. If both cutoff values of BSIJmax and UR were jointly used, 100% (6 of 6) of such patients were correctly evaluated. Using the cutoff values of BSIJmax and UR separately in the mandible, 70% (7 of 10) and 64% (7 of 11), respectively, of patients who had higher uptakes than the cutoff values were correctly evaluated to develop stage 2 ARONJ 3 months after the bone scintigraphy. If both cutoff values of BSIJmax and UR were jointly used, 67% (4 of 6) of such patients were correctly predicted.

Discussion

ARONJ is intractable once it occurs, and early detection is crucial. This is the first study to quantitatively evaluate the screening potential of bone scintigraphy for early-stage ARONJ. The semiquantitative parameter of BSIJmax was proposed for this purpose, and we found that the application of BSI is feasible in addition to common applications of BSI in bone metastases.

Early detection and risk assessment of BRONJ have been attempted by various methods [10–14, 29–34]. Bone scintigraphy, which is used extensively in the diagnosis and management of oncologic diseases, is a highly sensitive method for detecting bone involvement that often provides earlier diagnosis of lesions than conventional radiography, X-ray CT scan, and MRI [8–14]. In contrast, CT scans, which can provide a three-dimensional bone structure and a relationship with adjacent structures, provide little information about local metabolic or vascular changes. In addition, in CT scans and MRI images, elderly patients who have dentures would be the usual candidates for anti-resorptive drugs, and dental casting alloys sometimes produce artifacts that are inappropriate for correct diagnosis. Use of dentures, especially if they are ill-fitting, is also a risk factor for BRONJ [35, 36]. Although serum-bone metabolic markers have been proposed as a risk assessment of BRONJ, the results are controversial and lack specific anatomic information [32, 33].

The present study showed that the thresholds of BSIJmax = 0.09 and 0.06% in the maxilla and mandible, respectively, may be used for predicting occurrence of ARONJ in patients treated with anti-resorptive drugs. The merit of using BSIJmax would be objective calculation in daily clinical practice without dental records and skilled readers. This study focused on the timing before the development of stage 2 ARONJ. The healing probability of BRONJ in advanced stages 2 and 3 is known to be significantly lower than that in lower stages [37, 38]. Because patients with stage 1 ARONJ are asymptomatic, they rarely consult dentists and the diagnosis tends to be delayed.

If we detected abnormally high BSIJmax, we should take additional images and/or refer the patient to dentists for differential diagnosis. The lateral view and single-photon emission computed tomography (SPECT) images of bone scintigraphy, which are not used for routine

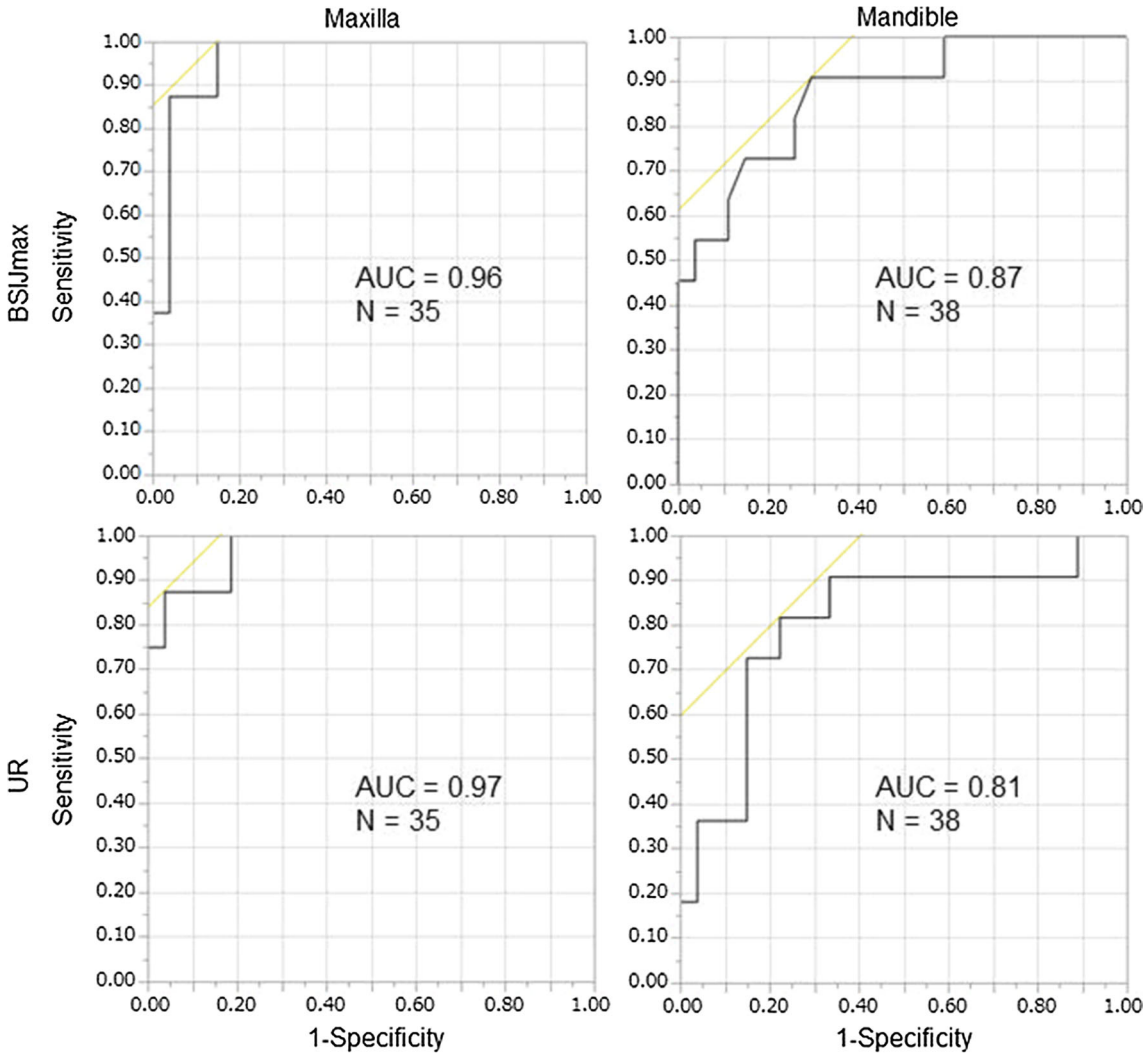

Fig. 4 Screening accuracy of ARONJ based on BSIJmax and UR evaluated by the ROC analysis. *Tangential lines* indicate the point of the highest sensitivity-(1-specificity)

Table 2 Screening accuracy of BSIJmax and UR for predicting stage 2 ARONJ 3 months before the diagnosis

	AUC	Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Maxilla ($N = 35$)						
BSIJmax	0.96	0.09%	88	96	88	96
UR	0.97	9.8	88	93	78	96
Mandible ($N = 38$)						
BSIJmax	0.87	0.06%	64	89	70	86
UR	0.81	6.0	64	85	64	85

BSIJ bone scan index of the jaw, *UR* uptake ratio, *ARONJ* anti-resorptive agents-related osteonecrosis of the jaw, *AUC* area under the curve, *PPV* positive predictive value, *NPV* negative predictive value

oncologic surveillance and BONENAVI version 2, could also be important for the evaluation of ARONJ [14–17]. Van den Wyngaert et al. reported that 50% (4 of 8) of stage 1 and 22% (2 of 9) of stage 2 lesions located on the posterior maxilla or mandible could not be reliably identified on anterior and posterior images of bone scintigraphy, while all lesions were clearly noticeable on SPECT images [15]. In addition, dentists can examine the area of high BSIJmax carefully with a dental panoramic radiograph, which is common and performed with a low cost and radiation exposure. Such careful examinations are also useful in preventing ARONJ and

Table 3 Fisher's exact test for high BSIJmax for predicting stage 2 ARONJ 3 months before the diagnosis

	ARONJ	No ARONJ
Maxilla ($N = 35$)		
BSIJmax >0.09	7 (88%)	1 (4%)
BSIJmax ≤0.09	1 (13%)	26 (96%)
		$p < 0.0001$, odds ratio = 182
Mandible ($N = 38$)		
BSIJmax >0.06	7 (64%)	3 (11%)
BSIJmax ≤0.06	4 (36%)	24 (89%)
		$p < 0.005$, odds ratio = 14

Values are presented as *N* (%)

BSIJ bone scan index of the jaw, *ARONJ* anti-resorptive agents-related osteonecrosis of the jaw

understanding the early pathogenic mechanism of ARONJ.

The maxilla and mandible should be analyzed separately to evaluate the diagnostic ability of bone scintigraphy for early-stage ARONJ for two reasons. First, the cortical bone density and thickness are less in the maxilla than in the mandible [39, 40]. Second, the pathologically increased bone uptake in stage 1 ARONJ is weaker and more susceptible to attenuation than that in stage 2 ARONJ [15]. These points may explain why the diagnostic ability of BSIJmax for early-stage ARONJ in the maxilla was superior to that in the mandible in the present study.

Other differences between the maxilla and mandible are also reported by many studies. Jiang et al. reported that the incidence of increased tracer uptakes caused by common dental diseases was significantly higher in the maxilla than in the mandible ($p < 0.001$) [41]. Arias et al. reported similar results [42]. Similarly, our study showed that BSIJmax was significantly higher in the maxilla than in the mandible in patients who did not develop ARONJ as shown in Fig. 2 ($p = 0.03$). In addition, it was reported that tracer uptakes in the jaw of patients without dental diseases were also significantly higher in the maxilla than in the mandible ($p < 0.01$) [21–23]. The reason for these differences might be partly due to the relatively higher blood supply of the maxilla compared with that of the mandible [21]. In contrast, approximately two-thirds of published BRONJ cases had occurred in the mandible and our cohort also showed similar distribution [43–45].

BSIJmax should be carefully used because it can be caused by reasons other than ARONJ, such as dental or periodontal diseases, dental extractions, and metastases. However, as dental and periodontal diseases and dental extractions are important risk factors for ARONJ, high-risk patients could be screened based on the abnormal scan results. In other words, patients who have high BSIJmax associated with dental or periodontal diseases tend to have overall bad dental health and to develop ARONJ somewhere. In our cohort, some patients underwent dental extractions at dentists without consulting their physicians who prescribed anti-resorptive drugs. Since ARONJ is intractable once it occurs, prevention is also crucial from the viewpoint of dental care. As AAOMS added an at-risk category and a stage 0 category to the conventional stages 1–3, the importance of screening high-risk patients potentially resulting in ARONJ could be emphasized. In addition, the incidence of metastases to the jaw, which also could cause BSIJmax, is very low (less than 1%) and the detection of metastasis is also an important indication in addition to ARONJ [46–48].

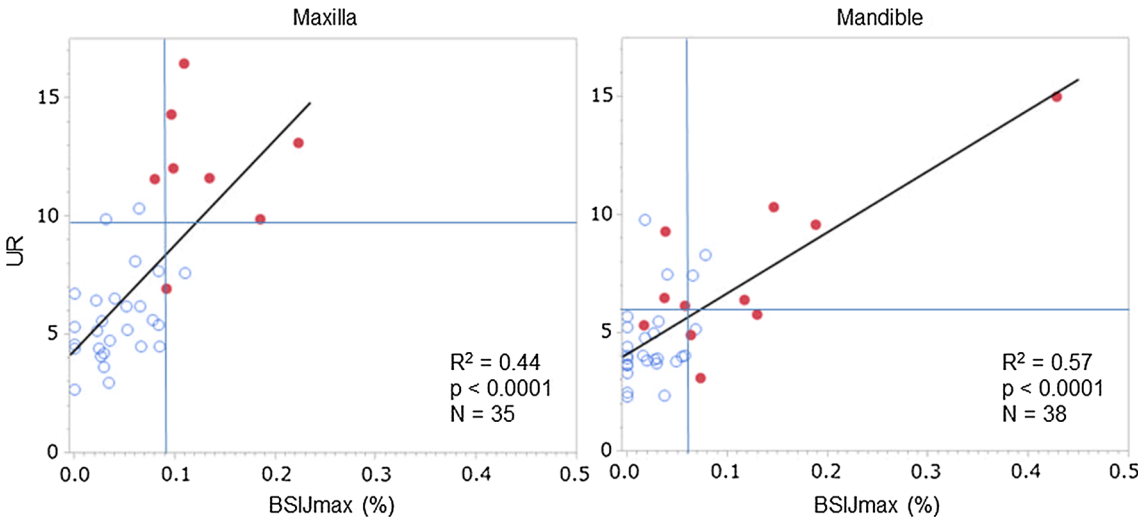

Fig. 5 *Scatter plots* for BSIJmax and UR in the maxilla and mandible. *Filled circles* indicate patients who developed stage 2 ARONJ 3 months after the bone scintigraphy. *Open circles* indicate patients who did not develop ARONJ. *Vertical* and *horizontal lines* indicate cutoff values of BSIJmax and UR, respectively

BSIJmax and a conventional parameter of UR showed the comparable screening accuracy for predicting ARONJ in the present study. In addition, the combined use of BSIJmax and UR improved the positive predictive values for ARONJ in the maxilla compared with the solitary use of either of them. Because BSIJmax and UR reflects the extent and the maximum intensity, respectively, of an abnormal tracer uptake, they may have complementary values in evaluating ONJ. Although the combined use of BSIJmax and UR did not clearly improve the positive predictive values in the mandible, the result depended on the combination of cutoff values of BSIJmax and UR. More appropriate combination of the cutoff values of BSIJmax and UR could improve the positive predictive values even in the mandible as shown in Fig. 5. Further studies in a larger cohort may be needed.

BSIJmax, which is an observer-independent parameter and objectively calculated, has some merits compared to an observer-dependent parameter of UR in feasibility and reproducibility. BSI has been adopted as a daily clinical practice of bone metastases diagnosis particularly in prostate cancer patients in Japan. Owing to the simple method, ARONJ screening by BSIJmax can be incorporated easily into the BSI analysis with minor change in the software algorithm. In contrast, the methods of UR, which had been utilized in several ONJ studies, were various regarding the delineation of regions of interest, location of the reference area, and so on [13, 15, 18]. In addition, the value of UR is influenced by the condition of the reference area, and several studies, which adopted the contralateral part as the reference area, excluded patients with bilateral abnormalities or a midline abnormality [15, 18]. BSIJmax can be objectively evaluated even in such patients who are often found in daily clinical practice.

BONENAVI has some merits compared to other software that can quantitatively analyze bone SPECT images using a standardized uptake value. Because various studies have demonstrated the usefulness of BSI for diagnosing bone metastases, BONENAVI is widely used in routine oncologic surveillance [25–27]. In contrast, it is not practical to acquire SPECT images of the jaw for all patients in daily practice. The software of SPECT image analysis may be useful for a detailed examination of high-risk patients who are screened by BSIJmax.

There are two important studies on the early detection of BRONJ using bone scintigraphy. Thomas et al. recently visually evaluated bone scintigraphy in 30 prostate cancer patients who had been treated with bisphosphonate [14]. They found that the sensitivity and specificity of bone scintigraphy for predicting BRONJ were 67 and 79%, respectively. However, visual interpretation of bone scintigraphy was subjective and the quality might have varied according to readers' experiences [49]. Furthermore, although they used lateral and anterior views of bone scintigraphy, the lateral view is not used for routine oncologic surveillance. In addition, the maxilla and mandible should be analyzed separately for minimal tracer uptakes.

Another study by O'Ryan et al. reported that among 35 patients who underwent bone scintigraphy before the clinical evidence of clear BRONJ, 66% had positive tracer uptakes in areas that later developed BRONJ [13]. However, as they admitted, increased uptakes in the jaws were often encountered in routine bone scintigraphy, even with the incidence of 56–72% [41, 42, 50], and common dental diseases were the main reasons for this. Similarly, in our study, some patients without a development of ARONJ exhibited high tracer uptakes in the jaw (Fig. 3). In addition, while our study used only the bone scintigraphy data at 3 months before the first diagnosis of stage 2 ARONJ, some scintigraphy data included in the study of O'Ryan et al. were inappropriately old, even predating ARONJ by several years.

This study has several limitations. First, BONENAVI version 2, which utilizes only anterior and posterior views of bone scintigraphy, could underestimate ARONJ. However, a new approach to analyze SPECT images with an ANN system could enhance the diagnostic ability. Second, bone scintigraphy is a relatively expensive examination and the main purpose is to evaluate bone metastases. Except for prostate and breast cancer, bone scintigraphy is often replaced by fluorodeoxyglucose positron-emission tomography for the assessment of metastases [51]. Third, bone scintigraphy represents a surrogate parameter reflecting osteoblasts' activity and detects osteonecrosis and/or inflammation indirectly [52]. Fourth, because this study was retrospective and included a relatively small number of patients in a single hospital, multicenter validation will be required.

Conclusion

The BSIJ using a quantitative bone scan provided a new approach for evaluating and screening early-stage ARONJ. For predicting occurrence of ARONJ, the thresholds of BSIJmax = 0.09 and 0.06% in the maxilla and mandible, respectively, may be used in patients treated with antiresorptive drugs. A differential diagnosis including ARONJ is recommended when we detect high BSIJmax in routine oncologic surveillance.

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Compliance with ethical standards

Conflict of interest Nothing to disclose.

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