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Original Article

Risk factors for dental findings of the development of medication-related osteonecrosis of the jaw: Investigation of 3734 teeth in cancer patients receiving high dose antiresorptive agents

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Abstract *Background/purpose:* Local infection is a risk factor for medication-related osteonecrosis of the jaw (MRONJ), along with invasive dental treatment of the bone; the tooth that is the source of infection should be extracted prior to the administration of bone resorption inhibitors. However, which teeth should be extracted remains unclear. This study aimed to determine the relationship between dental findings prior to high-dose antiresorptive agent (ARA) administration and the subsequent development of MRONJ.
Materials and methods: Patients with cancer who were scheduled to receive high-dose ARAs and referred to our hospital between 2011 and 2020 were included in this retrospective study. Apical lesions, enlargement of the periodontal space, thickening of the lamina dura, alveolar bone resorption of >1/3, periapical osteosclerosis, and local infection symptoms in each tooth were investigated using medical records and panoramic radiographs.

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Results: A total of 172 patients, 329 jaws, and 3734 teeth were registered. MRONJ developed in 68 teeth in 33 jaws of 32 patients. In tooth-by-tooth analysis, fewer teeth ($P < 0.001$), apical lesions ($P < 0.001$), periapical osteosclerosis ($P < 0.001$), local infection symptoms ($P = 0.002$), and one or more dental findings ($P < 0.001$) were significant factors for MRONJ development. In jaw-by-jaw analysis, old age, local infection symptoms, and number of radiographic abnormalities per tooth were significant. In patient-by-patient analysis, patients with diabetes and those with fewer teeth developed MRONJ.
Conclusion: Patients with fewer teeth, apical lesions, periapical osteosclerosis, and local infection were more likely to develop MRONJ. Therefore, these teeth should be treated as much as possible before ARA administration.

Introduction

Patients scheduled to receive antiresorptive agents (ARAs) should have dental work performed beforehand to prevent medication-related osteonecrosis of the jaw (MRONJ).[1–3] However, dental work is time-consuming, and it is sometimes difficult to complete all treatments before ARA administration. In cases of bone metastases from cancer or hypercalcemia, in particular, ARA administration often cannot be delayed until dental treatment has been completed.

Dental treatment includes a wide range of procedures, including periodontal, endodontic, and surgical procedures. Which of these should be prioritized when the time required to administer ARAs is limited? We conducted a study aimed at determining which dental findings put patients at higher risk of developing MRONJ. We examined the findings on panoramic radiographs taken during ARA administration that showed a high risk of patients developing MRONJ, tooth-by-tooth. We also examined the risk of developing MRONJ due to oral factors using the jaw-by-jaw method.

Materials and methods

A total of 172 patients (329 jaws and 3734 teeth) who received high-dose ARA (bisphosphonate and/or denosumab) treatment and were referred to the Oral and Maxillofacial Surgery or Oral Management Center of Nagasaki University Hospital between 2011 and 2020 were included in the study. Panoramic radiography was performed at the first visit. The following information was extracted from the medical records: Age, sex, MRONJ site (upper or lower jaw), smoking habit, diabetes, use of corticosteroids, white blood cell count, serum albumin and creatinine levels, type of ARA administered, local infection symptoms of the gingiva (pus discharge, pain, redness, and swelling), and number of remaining teeth. Patients in whom MRONJ had already developed were excluded. Panoramic radiography, apical lesions of $\geq$3 mm, enlargement of the periodontal space, thickening of the lamina dura, alveolar bone resorption of $>$1/3, and periapical osteosclerosis of each tooth were investigated (Fig. 1). Follow-ups were performed for as long as possible, and when MRONJ developed, the time of onset was recorded. The extracted data were analyzed on a tooth-by-tooth, jaw-by-jaw, and patient-by-patient basis.

All statistical analyses were performed using SPSS software (version 26.0; Japan IBM Co., Ltd., Tokyo, Japan). Uni- and multivariate analyses were performed using Cox regression analysis. Covariates for the multivariate analysis were selected using a stepwise method. Cumulative incidence was calculated using the Kaplan—Meier method and analyzed using the log-rank test. Two-tailed $P < 0.05$ was considered significant. Receiver Operating Characteristic (ROC) curve analysis was also performed on the number of imaging events per tooth (total number of imaging events/number of remaining teeth) and the development of MRONJ on a jaw-by-jaw basis.

The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects by the Ministry of Health, Labor, and Welfare of Japan. Ethical approval was obtained from the Institutional Review Board (IRB) of Nagasaki University Hospital (2208080). As this was a retrospective study, informed consent was waived. The research plan, highlighting the guaranteed opt-out opportunity, was published on the homepage of the hospital, according to the instructions of the IRB.

Results

Patient characteristics and factors related to the development of MRONJ

The background characteristics of the 172 patients are listed in Table 1. This study included 102 men and 70 women with a mean age of 62.3 years.

The primary tumors were breast cancer in 54 cases, lung cancer in 41 cases, multiple myeloma in 20 cases, prostate cancer in 17 cases, and other cancers in 40 cases; the ARA types were bisphosphonate in 77 cases, denosumab in 88 cases, and denosumab followed by bisphosphonate in 7 cases. MRONJ occurred in 32 of the 172 patients. The cumulative incidence rates from the start of treatment were 4.8% at 1 year, 13.8% at 2 years, 18.1% at 3 years, 25.6% at 4 years, and 31.2% at 5 years, with the incidence rate increasing as the duration of treatment increased (Fig. 2).

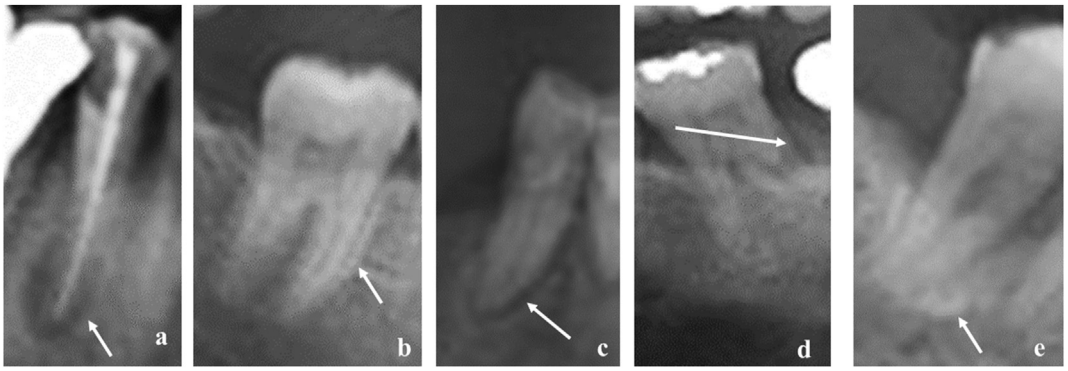

Figure 1 Panoramic radiograph. a. Apical disease (white arrow) b. Thickening of the lamina dura (white arrow) c. Enlargement of the periodontal space (white arrow) d. Alveolar bone resorption of >1/3 (white arrow) e. Periapical osteosclerosis (white arrow)

Table 1 Patient characteristics (n = 172).

Variable		Number of patients/value			*P*-value*
		Total	MRONJ (−)	MRONJ (+)	
Sex	Male	102	82	20	0.842
	Female	70	58	12	
Age	Mean ± SD	62.3 ± 11.7	61.3 ± 11.8	66.8 ± 10.6	0.016
Smoking habit	(−)	141	114	27	1.000
	(+)	30	25	5	
Diabetes	(−)	152	127	25	0.119
	(+)	19	13	6	
Corticosteroid	(−)	151	123	28	1.000
	(+)	20	17	3	
Sort of ARAs	BP	77	64	13	0.804
	DMB	88	70	18	
	Both	7	6	1	
Leukocyte (/μL)	Mean ± SD	5284 ± 4174	5340 ± 4441	5042 ± 2749	0.721
Albumin (g/L)	Mean ± SD	3.33 ± 0.686	3.28 ± 0.730	3.54 ± 0.686	0.078
Creatinine (mg/dL)	Mean ± SD	0.763 ± 0.268	0.752 ± 0.279	0.810 ± 0.214	0.287
Number of teeth	Median [25–75% tile]	24.0 [17.0–27.8]	25.0 [17.0–28.0]	22.5 [16.0–25.0]	0.051

* Fisher's exact test for categorized data, T test for parametric continuous data, and Mann-Whitney *U* test for non-parametric continuous data.Abbreviation: MRONJ: medication-related osteonecrosis of the jaw; ARAs: antiresorptive agents; BP: bisphosphonate; DMB: denosumab.

Patient-by-patient analysis

Variables excluding individual tooth findings were examined in relation to MRONJ development. Older age and fewer remaining teeth were significant risk factors associated with the development of MRONJ in univariate analysis. In multivariate analysis, diabetes ($P = 0.009$) and a low number of remaining teeth ($P < 0.001$) were significant risk factors for development (Table 2).

Tooth-by-tooth analysis

A total of 3734 teeth were registered. Apical lesions, enlargement of the periodontal space, thickening of the lamina dura, alveolar bone resorption of >1/3, periapical osteosclerosis, and local infection were observed in 244 (6.5%), 440 (11.8%), 329 (8.8%), 907 (24.3%), 231 (6.2%), and 205 (5.5%) teeth, respectively (Table 3). A total of 2402

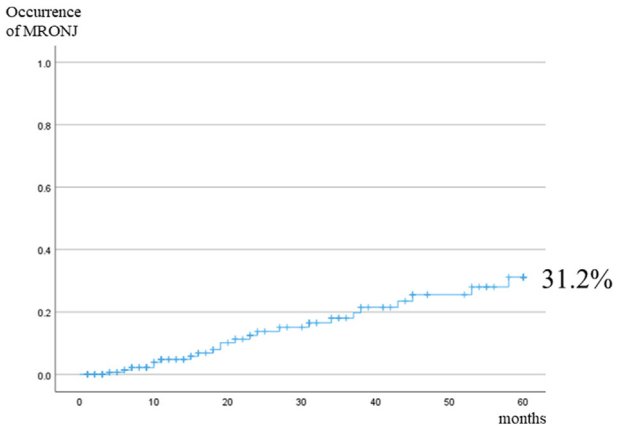

Figure 2 Five-year cumulative incidence of medication-related osteonecrosis of the jaw (MRONJ) from the start of treatment (Kaplan-Meier method).

teeth (64.3%) had at least one of the aforementioned dental symptoms.

MRONJ developed in 68 teeth. In univariate analysis, being male ($P = 0.021$), old age ($P = 0.002$), a smoking habit ($P < 0.001$), diabetes ($P = 0.003$), higher serum creatinine levels ($P = 0.043$), fewer teeth ($P < 0.001$), apical lesions ($P < 0.001$), enlargement of the periodontal space ($P < 0.001$), thickening of the lamina dura ($P = 0.005$), alveolar bone resorption of >1/3 ($P < 0.001$), periapical osteosclerosis ($P < 0.001$), and local infection symptoms ($P < 0.001$) were significant factors for developing MRONJ. Patients with one or more of the aforementioned dental findings showed a significantly higher risk of developing MRONJ ($P < 0.001$). Multivariate analysis showed that fewer teeth ($P < 0.001$), apical lesions ($P < 0.001$), periapical osteosclerosis ($P < 0.001$), local infection symptoms ($P = 0.002$), and one or more dental findings ($P < 0.001$) were significantly correlated with the development of MRONJ (Table 4) (Fig. 3).

Jaw-by-jaw analysis

A total of 329 jaws were included. Apical lesions, enlargement of the periodontal space, thickening of the lamina dura, alveolar bone resorption of >1/3, periapical osteosclerosis, and local infection were observed in 127 (38.6%), 166 (50.5%), 119 (36.2%), 196 (59.6%), 113 (34.3%), and 26 (7.9%) jaws, respectively (Table 5). In total, 262 (79.6%) teeth exhibited one or more of the aforementioned symptoms.

MRONJ developed in 33 jaws. In the univariate analysis, old age ($P = 0.019$), fewer teeth ($P = 0.009$), apical lesions ($P = 0.004$), periapical osteosclerosis ($P = 0.017$), and local infection symptoms ($P < 0.001$) were significant risk factors for the development of MRONJ. The number of radiographic abnormalities ($P = 0.003$) and total number of radiographic abnormalities/number of remaining teeth ($P < 0.001$) were also significantly correlated with the development of MRONJ. Furthermore, those who had one or more of the above-mentioned radiographic abnormalities showed a significantly higher risk of developing MRONJ ($P = 0.012$). Multivariate analysis showed that old age ($P = 0.028$), local infection symptoms ($P = 0.001$), and the number of radiographic abnormalities per tooth ($P = 0.003$) were significantly correlated with the development of MRONJ (Table 6).

In the jaw-by-jaw ROC analysis, the incidence of MRONJ was significantly higher when the number of radiographic abnormalities per tooth was greater than 1.1 (AUC = 0.632) (Fig. 4). The 5-year cumulative MRONJ incidence rate was 13.3% in jaws with less than 1.1 radiographic abnormalities per tooth, and 35.7% in those with 1.1 or more radiographic abnormalities per tooth (Fig. 5).

Discussion

In the present study, cancer patients receiving high-dose ARAs had a significantly higher risk of developing

Table 3 Dental findings of 3734 teeth in panoramic X-ray.

Findings		Number of teeth
Apical lesion	(−)	3490 (93.5%)
	(+)	244 (6.5%)
Enlargement of periodontal space	(−)	3294 (88.2%)
	(+)	440 (11.8%)
Thickening of lamina dura	(−)	3405 (91.2%)
	(+)	329 (8.8%)
Alveolar bone resorption of more than 1/3	(−)	2827 (75.7%)
	(+)	907 (24.3%)
Periapical osteosclerosis	(−)	3503 (93.8%)
	(+)	231 (6.2%)
Local infection symptom	(−)	3529 (94.5%)
	(+)	205 (5.5%)
One or more of the above dental findings	(−)	2402 (64.3%)
	(+)	1332 (35.7%)

Table 2 Univariate and multivariate analysis of risk factors for developing MRONJ per patient (N = 172).

Variable		*P*-value	HR	95% CI
i) Univariate analysis				
Sex	Male vs. female	0.632	1.192	0.581—2.445
Age		0.030	1.035	1.003—1.068
Smoking habit	(−) vs. (+)	0.798	0.882	0.338—2.304
Diabetes	(−) vs. (+)	0.341	1.548	0.630—3.803
Corticosteroid	(−) vs. (+)	0.447	0.628	0.190—2.082
Sort of ARAs	BP vs. DMB vs. both	0.251	1.432	0.778—2.642
Leukocyte (/μL)		0.321	1.003	0.997—1.010
Albumin (g/L)		0.877	0.958	0.558—1.645
Creatinine (mg/dL)		0.124	3.044	0.736—12.588
Number of teeth		0.005	0.932	0.887—0.979
ii) Multivariate analysis (stepwise selection)				
Diabetes		0.009	2.248	1.228—4.115
Number of teeth		<0.001	0.794	0.740—0.853

Abbreviation: MRONJ: medication-related osteonecrosis of the jaw; ARAs: antiresorptive agents; BP: bisphosphonate; DMB: denosumab; HR: hazard ratio; 95% CI: 95% confidence interval.

Table 4 Univariate and multivariate analysis of risk factors for developing MRONJ per teeth (N = 3734).

Findings		*P*-value	HR	95% CI
i) Univariate analysis				
Sex	Female vs. male	0.021	1.760	1.089–2.844
Age		0.002	1.034	1.012–1.056
Site	Upper vs. lower jaw	0.088	1.523	0.940–2.469
Smoking habit	(−) vs. (+)	<0.001	1.711	1.480–1.977
Diabetes	(−) vs. (+)	0.003	2.392	1.339–4.270
Corticosteroid	(−) vs. (+)	0.282	0.630	0.272–1.461
Leukocyte (/10^2 μL)		0.158	1.003	0.999–1.007
Albumin (g/L)		0.315	1.222	0.826–1.809
Creatinine (mg/dL)		0.043	2.639	1.003–6.741
Sort of ARAs	BP vs. DMB vs. both	0.246	1.279	0.844–1.937
Number of teeth		<0.001	11.046	6.793–17.963
Apical lesion	(−) vs. (+)	<0.001	11.046	6.793–17.963
Enlargement of periodontal space	(−) vs. (+)	<0.001	6.076	3.721–9.922
Thickening of lamina dura	(−) vs. (+)	0.005	2.433	1.303–4.544
Alveolar bone resorption of more than 1/3	(−) vs. (+)	<0.001	4.429	2.736–7.168
Periapical osteosclerosis	(−) vs. (+)	<0.001	10.478	6.360–17.263
Local infection symptom	(−) vs. (+)	<0.001	7.734	4.440–13.472
One or more of the above dental findings	(−) vs. (+)	<0.001	24.489	10.501–57.107
ii) Multivariate analysis (stepwise selection)				
Number of teeth		<0.001	0.809	0.751–0.872
Apical lesion	(−) vs. (+)	<0.001	4.132	2.435–7.011
Periapical osteosclerosis	(−) vs. (+)	<0.001	2.585	1.524–4.387
Local infection symptom	(−) vs. (+)	0.002	2.439	1.371–4.338
One or more of the above dental findings	(−) vs. (+)	<0.001	10.202	3.460–30.083

Abbreviation: MRONJ: medication-related osteonecrosis of the jaw; ARAs: antiresorptive agents; BP: bisphosphonate; DMB: denosumab; HR: hazard ratio; 95% CI: 95% confidence interval.

subsequent MRONJ if they had teeth with apical lesions, periapical osteosclerosis, or local infection symptoms.

Patients receiving ARAs are at increased risk of developing MRONJ. Various risk factors of MRONJ have been reported.[4–12] Local factors related to the occurrence of MRONJ include dentoalveolar surgery, anatomical factors (mandible), denture use, and concomitant inflammatory oral diseases, such as periodontal disease or periapical

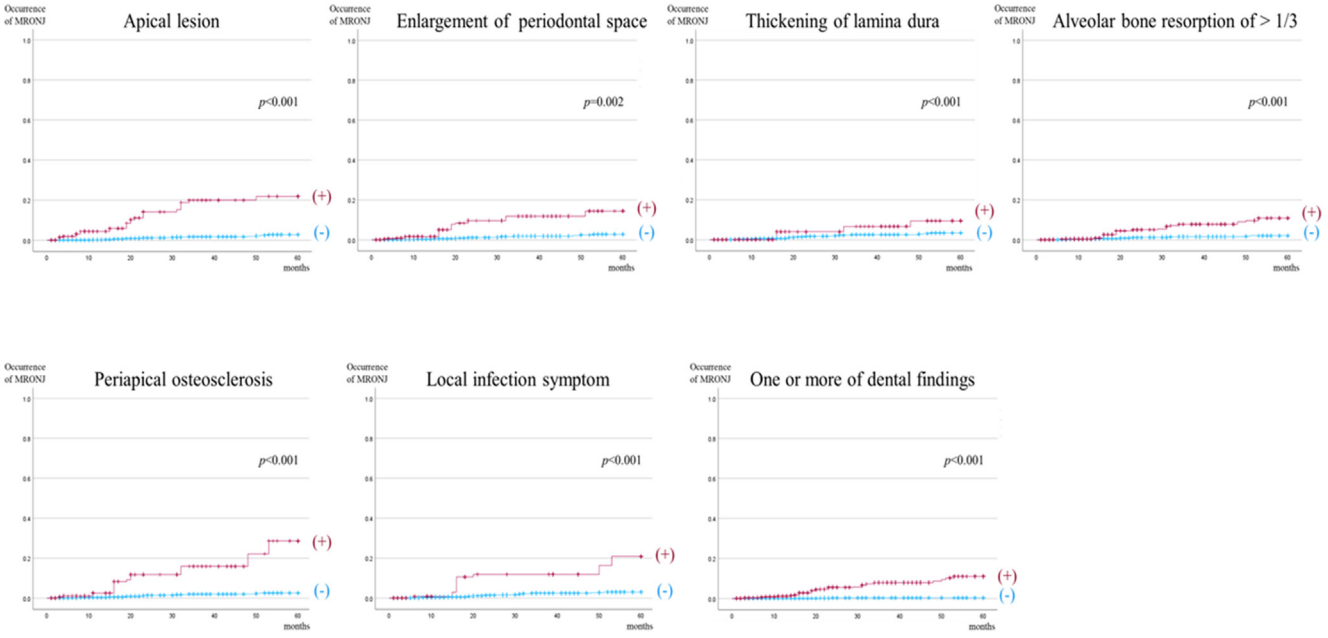

Figure 3 Cumulative incidence for each image finding in tooth-by-tooth analysis (Kaplan–Meier method and the log-rank test).

Table 5 Dental findings of 329 jaws in panoramic X-ray.

Findings		Number of jaws
Apical lesion	(−)	202 (61.4%)
	(+)	127 (38.6%)
Enlargement of periodontal space	(−)	163 (49.5%)
	(+)	166 (50.5%)
Thickening of lamina dura	(−)	210 (63.8%)
	(+)	119 36.2%)
Alveolar bone resorption of more than 1/3	(−)	133 (40.4%)
	(+)	196 (59.6%)
Periapical osteosclerosis	(−)	216 (65.7%)
	(+)	113 (34.3%)
Local infection symptom	(−)	303 (92.1%)
	(+)	26 (7.9%)
One or more of the above dental findings	(−)	67 (20.4%)
	(+)	262 (79.6%)

pathology (AAOMS2022).[13] Among these, dentoalveolar surgery, including tooth extraction, is considered the most important local risk factor, and it is recommended that ARAs be withdrawn for several months prior to tooth extraction in these patients, or that tooth extraction be avoided as much as possible at the outset. Conversely, there are reports of persistent local infection in teeth that require extraction, and that it is the local infection in the tooth to be extracted that is at risk for MRONJ, not the surgical invasion of the bone itself.[14–16] We previously reported that patients with cancer who received high-dose ARAs and whose teeth were the source of infection had a significantly higher incidence of MRONJ if they avoided tooth extraction after adjusting for background factors using propensity score matching,[16] and stated that teeth with apical lesions >3 mm, periodontal pockets deeper than 4 mm, and local infection symptoms should be extracted. However, this study included 92 patients with teeth that showed abnormal radiographic findings, while in the present study, factors associated with the development of MRONJ in a larger number of patients, including those without abnormal radiographic findings, were examined.

First, the factors associated with each tooth were examined. Apical lesions, periapical osteosclerosis, thickening of the lamina dura, alveolar bone resorption of >1/3, and enlargement of the periodontal space are reactive changes in the bone around the teeth, and ARAs may affect these bone responses, making it difficult to distinguish them from changes due to local infection.[17,18] Therefore, it is important to diagnose these changes using bone imaging before administering ARAs. In our current study, the risk of developing MRONJ was significantly higher in the presence of apical lesions, periapical osteosclerosis, one or more of the above dental findings, and local infection symptoms before ARA administration. Therefore, treatment of endodontic disease and occlusal trauma should be performed

Table 6 Univariate and multivariate analysis of risk factors for developing MRONJ per jaws (N = 329).

Findings		*P*-value	HR	95% CI
i) Univariate analysis				
Sex	Female vs. male	0.539	1.246	0.618–2.511
Age		0.019	1.038	1.006–1.071
Site	Upper vs. lower jaw	0.818	1.084	0.547–2.145
Smoking habit	(−) vs. (+)	0.535	1.305	0.563–3.023
Diabetes	(−) vs. (+)	0.199	1.794	0.735–4.374
Corticosteroid	(−) vs. (+)	0.505	0.667	0.202–2.196
Leukocyte (/10^2 μL)		0.478	1.002	0.996–1.009
Albumin (g/L)		0.831	0.943	0.548–1.621
Creatinine (mg/dL)		0.206	2.549	0.598–10.859
Sort of ARAs	BP vs. DMB vs. both	0.454	1.258	0.690–2.295
Number of teeth		0.009	0.885	0.808–0.970
Apical lesion	(−) vs. (+)	0.004	2.806	1.390–5.664
Enlargement of periodontal space	(−) vs. (+)	0.108	1.767	0.882–3.538
Thickening of lamina dura	(−) vs. (+)	0.572	1.229	0.601–2.513
Alveolar bone resorption of more than 1/3	(−) vs. (+)	0.070	1.982	0.946–4.155
Periapical osteosclerosis	(−) vs. (+)	0.017	2.307	1.162–4.579
Local infection symptom	(−) vs. (+)	<0.001	5.365	2.513–11.453
Number of radiographic abnormalities		0.003	1.059	1.020–1.100
Number of radiographic abnormalities per tooth		<0.001	2.046	1.401–2.986
One or more of the above dental findings	(−) vs. (+)	0.012	6.384	1.512–26.959
ii) Multivariate analysis (stepwise selection)				
Age		0.028	1.042	1.005–1.081
Local infection symptom	(−) vs. (+)	0.001	3.762	1.674–8.454
Number of abnormal dental findings per tooth		0.003	1.922	1.250–2.956

Abbreviation: MRONJ: medication-related osteonecrosis of the jaw; ARAs: antiresorptive agents; BP: bisphosphonate; DMB: denosumab; HR: hazard ratio; 95% CI: 95% confidence interval.

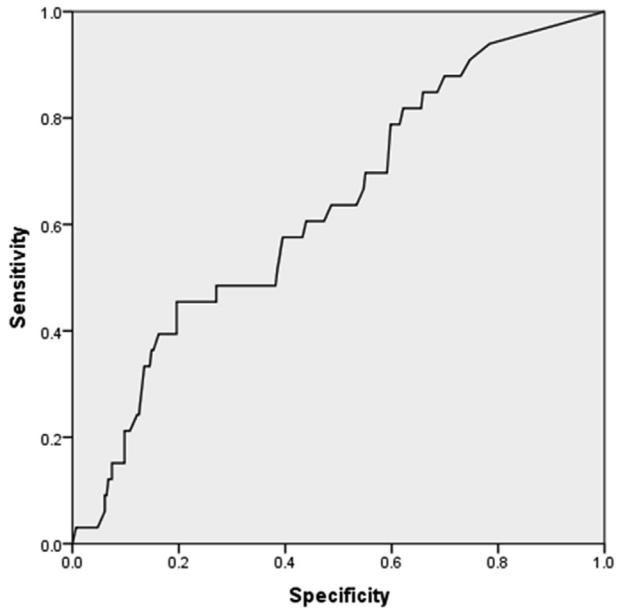

Figure 4 Receiver operating characteristic curve analysis.

as much as possible prior to the administration, without priority. Ueda et al. also reviewed 679 patients scheduled to receive ARAs. They reported that root apex lesions were a risk factor for developing MRONJ and that teeth should be extracted before ARA administration.[19] However, it is difficult to treat some dental diseases before administration. If everything is to be treated within a short period, tooth extraction may be an option; however, there is no evidence that tooth extraction prevents the development of MRONJ, and some reports suggest that tooth extraction at sites of chronic inflammation may actually predispose patients to MRONJ.[20] In addition, if multiple tooth extractions are necessary, the invasiveness of the procedure may be significant and reduce the quality of life. While dental treatment should be performed on a small number of teeth if there is time to do so, treatment methods for patients who need treatment for multiple teeth should be considered in the future.

Next, we examined the risk of developing MRONJ on a jaw-by-jaw basis. Old age, local inflammatory symptoms, and number of abnormal dental findings per tooth were significant factors in the development of MRONJ. Old age was the only significant systemic factor. Local infection symptoms are also important factors in any analysis, and anti-inflammatory treatment prior to ARA administration is essential.

ROC analysis showed a tendency for MRONJ to develop with a higher number of imaging events per tooth, although the AUC was not sufficient, and 1.1 events per tooth was the cutoff value. In other words, if there are more imaging events per tooth, the jaw is at a higher risk of developing MRONJ and patients with more imaging events per tooth should be considered high-risk. In addition, a high number of imaging events is likely to indicate that the patient is not receiving adequate dental care. Therefore, it may be difficult to obtain cooperation for dental treatment before ARA administration. In a prospective study of 253 patients with bone metastases from prostate cancer, Mücke et al. reported a 2.59-fold higher risk of developing bisphosphonate-related osteonecrosis of the jaw (BRONJ) in the group that did not receive dental intervention every 3 months during treatment with zoledronic acid than in the group that did.[21] Therefore, it is important to increase the motivation for oral management in patients with a high number of imaging events per tooth.

In the patient-by-patient analysis, diabetes and the number of remaining teeth were significant factors in the

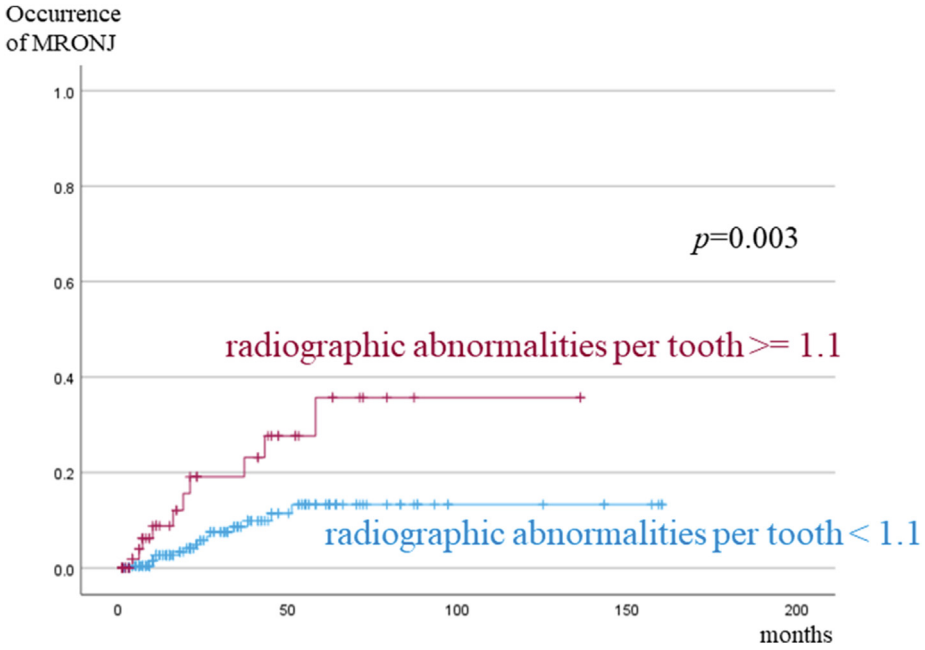

Figure 5 Five-year cumulative medication-related osteonecrosis of the jaw (MRONJ) incidence rate with a cutoff value of 1.1 radiological abnormalities per tooth.

development of MRONJ. Considering the jaw-by-jaw analysis, it is important to note that advanced age and diabetes are systemic factors in. In addition, it is important to provide guidance on oral hygiene, because a small number of remaining teeth may indicate poor oral hygiene.

This study had some limitations. First, because of the retrospective, single-center nature of the study, there may have been some bias in the registered patients, and it is unclear whether the results obtained can be generalized. Second, most patients with dental diseases did not undergo any subsequent dental intervention; therefore, it was not possible to determine whether dental treatment reduced the risk of developing MRONJ. However, this study clarified the relationship between dental disease and the onset of MRONJ using a large number of teeth and provided valuable data for the establishment of future MRONJ prevention methods.

Patients with diabetes, fewer teeth, dental diseases, such as apical disease, thickening of the lamina dura, alveolar bone resorption of more than 1/3, periapical osteosclerosis, and local infection symptoms are more likely to develop MRONJ. Therefore, it is important to improve the oral environment prior to ARA administration.

Declaration of competing interest

The authors declare no conflict of interest. This research received no external funding.

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None.

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