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Original Article

A retrospective study on odontogenic and non-odontogenic medication-related osteonecrosis of the jaw: Potential differences in clinical features and treatment outcomes

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KEYWORDS
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Abstract *Background/purpose:* Local infections, such as periodontal disease or apical lesions, and invasive dental procedures, such as tooth extraction, are thought to trigger medication-related osteonecrosis of the jaw (MRONJ) development. However, some cases of MRONJ develop without any obvious odontogenic triggers. We conducted a retrospective study to clarify the characteristics of non-odontogenic MRONJ.
Materials and methods: We retrospectively reviewed data of 229 patients with mandibular MRONJ who underwent surgery. Based on imaging findings, we classified MRONJ as odontogenic MRONJ involving a dental infection and non-odontogenic MRONJ with no dental involvement. Clinical and imaging findings and treatment outcomes of both types of MRONJ were compared.
Results: Overall, 193 patients were classified as having odontogenic MRONJ and 36 as having non-odontogenic MRONJ. Non-odontogenic MRONJ was slightly more common among patients

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with malignancies who received denosumab; however, the difference was not significant. Univariate and multivariate analyses showed that patients with MRONJ with non-odontogenic triggers had significantly poorer treatment outcomes than their counterparts.
Conclusion: Non-odontogenic MRONJ exists without the involvement of odontogenic infection as a cause of MRONJ. Compared with that in odontogenic MRONJ, the treatment outcome in non-odontogenic MRONJ is poor. Further studies are required to clarify the true nature of non-odontogenic MRONJ.

Introduction

The first report of medication-related osteonecrosis of the jaw (MRONJ) was reported nearly 20 years ago, and its pathogenesis, treatment, and prevention have gradually become clearer. Risk factors for MRONJ include systemic factors such as the primary disease, type and administration duration of antiresorptive agents (ARA), diabetes, use of steroids and immunosuppressive drugs, and local factors such as invasive dental procedures and local infection.[1] Surgical dental procedures such as tooth extraction have been avoided because they have been considered an important risk factor for MRONJ. Local infection in the tooth to be extracted is a greater risk factor than tooth extraction itself; thus, extraction of the infected tooth is advised for MRONJ prevention.[2,3]

Although local infection is considered one of the primary causes of MRONJ, it can also develop from sites with no dental infection, such as apical lesions or periodontal disease, or sites where no teeth are present. The main pathogenesis of MRONJ is generally considered to be a localized dental infection that causes osteomyelitis, followed by ARA-induced bone metabolism disorders and hematogenous insufficiency. However, another possible mechanism is that ARA medication causes aseptic osteonecrosis, which spreads to the periosteum and mucosa, resulting in mucosal defects and infection by oral bacteria or that MRONJ is caused by some type of infection (such as infection from ulcers associated with ill-fitting dentures, torus, or blood-borne infections) in addition to aseptic osteonecrosis.[4,5] The mechanism of MRONJ is the same as that of osteonecrosis of the femoral head in patients receiving steroids, in which bone metabolism and blood circulation failures occur in ARA-treated patients, resulting in necrosis of the jawbone, which is then infected. The Position Paper of the Korean Association of Oral and Maxillofacial Surgeons also described that it is not clearly defined whether osteonecrosis occurs first and then the necrotic lesion becomes infected or the infected lesion induces osteonecrosis.[6] However, in the absence of infection, clinical signs do not appear, and cases of aseptic osteonecrosis of the jaw prior to the development of infection are rarely encountered.

Few studies have investigated the pathogenesis of MRONJ. MRONJ may develop at sites where there are no teeth to serve as a source of infection or in edentulous patients, but there are few studies as for the pathogenesis of non-odontogenic origin MRONJ. Otsuru et al.[7] reported a periosteal reaction—dominant type of MRONJ that started in the osseous body rather than the alveolar region, had a cutaneous fistula rather than bone exposure in the oral cavity as the initial manifestation, and was associated with an extensive periosteal reaction on computed tomography (CT). Dental infections, such as apical lesions and periodontal disease, are unlikely to explain the development of this type of MRONJ. The purpose of this study was to retrospectively investigate MRONJ cases in our department and divide them into two groups, odontogenic and non-odontogenic MRONJ, to determine whether there was any difference in clinical and imaging features and treatment outcomes between them.

Materials and methods

Patients

Between January 2011 and March 2024, 412 patients with MRONJ visited the Department of Oral and Maxillofacial Surgery at Nagasaki University Hospital. Among them, 270 had mandibular origins and 229 were treated surgically. This study included 229 patients with MRONJ of a primary mandibular origin who underwent surgery. The following information was collected from medical records and CT images.

Factors

Age, sex, primary disease (osteoporosis/malignant tumor), MRONJ stage,[1] type of ARA (bisphosphonate [BP] or denosumab [DMB]), duration of ARA administration, serum albumin level, trigger of MRONJ development, CT findings, and treatment outcomes were investigated. Triggers were classified as odontogenic and non-odontogenic using panoramic radiographs. "Odontogenic MRONJ" was defined as MRONJ lesions in contact with residuals of odontogenic infection, such as apical lesions and periodontal disease, or the extraction socket. "Non-odontogenic MRONJ" was defined as having no remaining dental infection or extraction socket in the vicinity of the MRONJ lesion, no extraction of teeth in the vicinity of the MRONJ lesion within 1 year, no traumatic ulceration from dentures, and no other triggers for MRONJ development in the mouth. CT images were evaluated for the presence of sequestrum separation, osteolysis (none, above the mandibular canal, including the

mandibular canal), periosteal reaction (none, attached-type, gap-type, and irregular-type),[8] and mixed-type osteosclerosis with many small radiolucent areas mixed within the bone sclerotic osteosclerosis.[9] Treatment outcome was defined as the resolution of all symptoms, including bone exposure and time to healing.

Statistical analysis

Factors associated with treatment outcomes were analyzed using univariate and multivariate Cox regression analyses. Differences in characteristics between odontogenic and non-odontogenic MRONJ were analyzed using Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables. All statistical analyses were performed using Statistical Package for Social Sciences version 26.0 (IBM Japan Co., Ltd, Tokyo, Japan). A two-tailed P value < 0.05 indicated statistical significance.

Ethics

This study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Biological Research Involving Human Subjects of the Ministry of Health, Labor, and Welfare of Japan. The study protocol was approved by the Institutional Review Board (IRB) of Nagasaki University Hospital (#24080807). As this was a retrospective study, the research plan was published on the homepage of the Clinical Research Center of Nagasaki University Hospital website, along with an opt-out option in accordance with IRB instructions.

Results

Patient characteristics

Patient characteristics are summarized in Table 1; 55 men and 174 women with an average age of 76.5 ± 10.7 years were included. The primary disease was osteoporosis in 146 patients and malignancy in 83; the type of ARA was BP for 138 patients and DMB for 91. Patients who were initially treated with BP but later switched to DMB were classified into the DMB group. Triggers of MRONJ onset were odontogenic in 193 patients and non-odontogenic in 36.

Table 1 Patient characteristics.

Variable		Number of patient's/median
Sex	Male	55
	Female	174
Age (years)	Median [25, 75 percentile]	79.0 [71.0, 84.0]
Stage	Stage 0	12
	Stage 1	16
	Stage 2	178
	Stage 3	23
Primary disease	Osteoporosis	146
	Malignancy	83
Type of ARA	BP	138
	DMB	91
Trigger	Odontogenic	193
	Unknown	36
Duration of administration (months)		48.5 [26.0, 77.0]
Serum albumin (g/dL)		3.70 [3.30, 4.10]
Separation of sequestrum	(−)	134
	(+)	95
Osteolysis	(−)	18
	Above mandibular canal	131
	Including mandibular canal	80
Periosteal reaction	(−)	150
	Attached-type	59
	Gap-/irregular-type	20
Mixed type osteosclerosis	(−)	207
	(+)	22
Total		229

Abbreviation: ARA: antiresorptive agent; BP: bisphosphonate; DMB: denosumab.

Differences between non-odontogenic MRONJ and odontogenic MRONJ

Odontogenic MRONJ lesions were contiguous or in close proximity to root apex lesions, and osteolysis was caused by periodontal disease (Fig. 1). In contrast, patients with non-odontogenic MRONJ had no causative dental infection, teeth near the MRONJ lesion, or traumatic ulcers caused by ill-fitting dentures or tori. Some lesions developed in the alveolar region and others in the osseous body; the latter were often associated with periosteal reactions (Fig. 2).

The characteristics of 193 patients with odontogenic MRONJ and 36 patients with non-odontogenic MRONJ were compared. There were no significant differences in age, sex, or stage between the two groups. In terms of ARA type, non-odontogenic MRONJ occurred more frequently among patients receiving DMB, but the difference was not significant ($p = 0.096$). Among the 193 patients with odontogenic MRONJ, 173 underwent a single surgery; 17 underwent two surgeries, and 3 underwent three surgeries. Of these patients, 10.4 % required multiple surgical procedures. Among the 36 patients with non-odontogenic MRONJ, 29 underwent a single surgery; 6, two; and 1, three, and multiple surgical procedures were performed more frequently (19.4 %); however, the difference was not significant ($p = 0.155$) (Table 2).

Treatment outcome

The cumulative cure rate for all 229 patients was 70.7 % at I year, 79.6 % at 2 years, and 84 % at 3 years (Fig. 3). In the univariate analysis, factors related to treatment outcomes were significantly worse when the primary disease was malignant ($P < 0.001$), the trigger was non-odontogenic

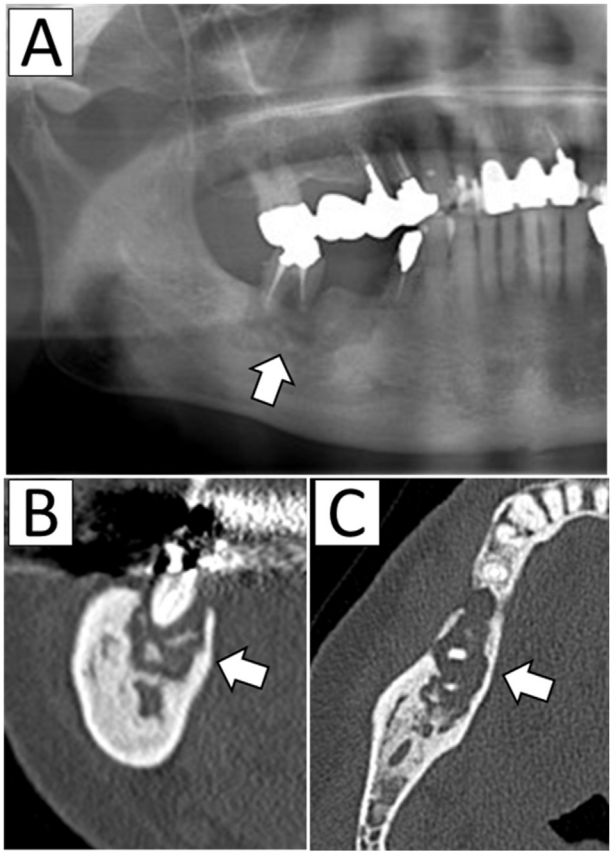

Figure 1 Odontogenic MRONJ.
Osteolysis and sequestrum separation were seen in continuity with the periapical radiolucent area. A: panoramic X-ray, B: CT of frontal sections, C: CT of axial sections.

($P = 0.011$), and mixed-type osteosclerosis was present ($P = 0.007$) (Table 3). Regarding the ARA type, there was a tendency toward a poorer prognosis among DMB-treated patients, but the difference was not significant ($P = 0.079$). In the multivariate analysis, in which factors significant in the univariate analysis were entered as covariates, all three factors —malignancy as the primary disease ($P = 0.003$), non-odontogenic triggers ($p = 0.027$), and mixed-type osteosclerosis ($P = 0.031$)— were independent poor prognostic factors (Table 4). The cure rates of these three factors using the Kaplan—Meier method were illustrated in Fig. 4.

Discussion

This study revealed the presence of non-odontogenic MRONJ with no obvious dental infection as a trigger and that non-odontogenic MRONJ was more common among high-dose DMB-treated patients, although the difference was not significant, and the prognosis tended to be significantly worse than that of odontogenic MRONJ. The AAOMS Position Paper 2022 states that both animal and human studies suggest that ARA medication, coupled with inflammation or infection, is necessary and sufficient to induce MRONJ.[1] Dentoalveolar surgeries are considered the most

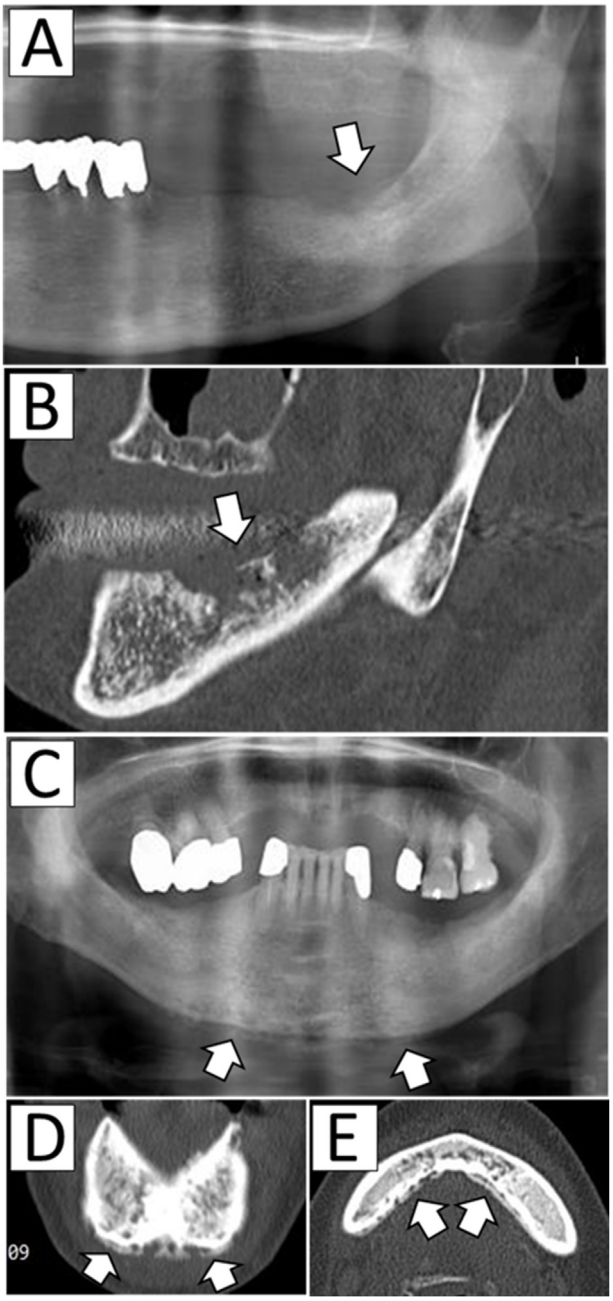

Figure 2 Non-odontogenic MRONJ.
A, B: There was an ulceration under the denture base that reached the bone, and a radiolucent area was seen from the alveolar surface to the upper mandibular canal. C, D: There was no bone exposure or fistula in the oral cavity, but a cutaneous fistula was found in the lower jaw. There was no tooth with a source of infection and no osteolysis in the alveolar region, but there was extensive periosteal reaction at the inferior margin of the mandible.

important risk factors for MRONJ. MRONJ develops in 0.15%—1.7 % of patients with osteoporosis who undergo tooth extraction and are treated with ARA,[10—13] while MRONJ develops in 1.6%—28.7 % of cancer patients receiving ARA after tooth extraction.[14—18] McGowan et al. reported in a systematic review of 102 studies including

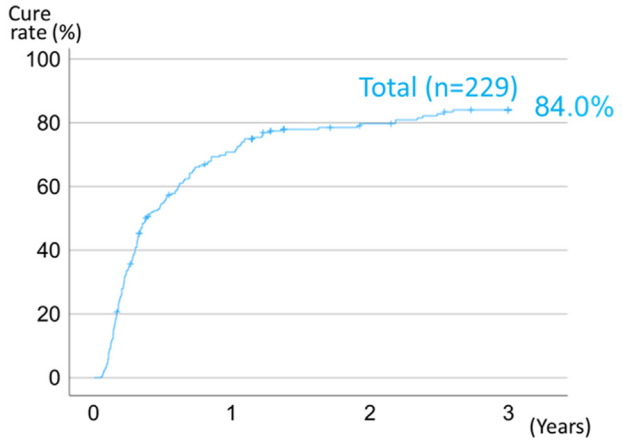

Figure 3 The cumulative cure rate of the all patients. Three-year cure rate was 84.0 %.

4106 patients that the most reported dental risk factor was tooth extraction (45 %), followed by periodontal disease (10 %).[19] Most reports indicate that tooth extraction is a stronger risk factor than local infection, such as periodontal disease. However, teeth undergoing extraction can have severe local infections that cannot be controlled using conservative treatment. Therefore, a simple comparison between extraction and local infection does not provide the correct conclusion as to whether extraction or local infection is the more important trigger for the development of MRONJ.

Soutome et al. retrospectively examined 361 patients receiving high-dose ARA and found that a significantly higher rate of MRONJ subsequently developed in patients who underwent tooth extraction, but when dental factors such as apical lesion, alveolar bone resorption, clinical signs of local infection, and number of remaining teeth were adjusted for by propensity score matching, the incidence of MRONJ was significantly lower among patients who underwent tooth extraction.[3] Nakamura et al. observed 3725 teeth of high-dose ARA patients and 5038 teeth of healthy jaws of MRONJ patients and examined the subsequent incidence of MRONJ. The results showed that MRONJ occurred significantly more frequently around teeth with local infection, and a simple comparison of extracted and non-extracted teeth showed a significantly higher incidence of MRONJ in extracted teeth, but when dental background factors were matched using propensity score matching, the incidence of MRONJ was significantly reduced in extraction cases.[20] Based on these recent studies, local infections such as periodontal disease and apical lesions seem to be more important than tooth extraction as a risk factor for MRONJ.

McGowan et al. reported in a systematic review that after tooth extraction and periodontal disease, the next most common risk factor is "spontaneous" MRONJ with no identifiable dental risk factor.[19] However, details of

Table 2 Differences between odontogenic and non-odontogenic MRONJ.

Variable		Odontogenic	Non-odontogenic	P-value
Sex	Male	148	26	0.532
	Female	45	10	
Age (years)	Median [25, 75 percentile]	79.0 [71.0, 84.5]	76.0 [70.3, 84.0]	0.371
Stage	0	11	1	0.312
	1	11	5	
	2	151	27	
	3	20	3	
Primary disease	Osteoporosis	126	20	0.265
	Malignancy	67	16	
Type of ARA	BP	121	17	0.096
	DMB	72	19	
Duration of administration (months)	Median [25, 75 percentile]	50.0 [26.0, 78.8]	46.0 [25.3, 71.3]	0.550
Serum albumin (g/dL)	Median [25, 75 percentile]	3.70 [3.30, 4.10]	3.90 [3.40, 4.20]	0.264
Separation of sequester	(−)	109	25	0.197
	(+)	84	11	
Osteolysis	(−)	6	12	<0.001
	Above mandibular canal	114	17	
	Including mandibular canal	73	7	
Periosteal reaction	(−)	122	28	0.189
	Attached-type	54	5	
	Gap-/irregular-type	17	3	
Mixed type osteosclerosis	(−)	175	32	0.758
	(+)	18	4	
Number of surgeries	1	173	29	0.155
	≥2	20	7	
Total		193	36	229

Abbreviation: ARA: antiresorptive agent; BP: bisphosphonate; DMB: denosumab.

Table 3 Factor related to treatment outcome (univariate analysis).

Variable		P-value	HR	95 % CI
Sex	Male/female	0.124	0.758	0.532–1.079
Age		0.515	1.005	0.991–1.019
MRONJ stage	Stage 3/2/1/0	0.223	0.867	0.689–1.091
Primary disease	Malignancy/osteoporosis	<0.001	0.545	0.398–0.747
Type of ARA	DMB/BP	0.079	0.763	0.564–1.032
Trigger	Non-odontogenic/odontogenic	0.011	0.564	0.364–0.875
Duration of administration		0.725	1.001	0.997–1.004
Serum albumin		0.786	1.039	0.790–1.366
Separation of sequestrum	(+)/(−)	0.372	1.846	1.207–2.823
Osteolysis	Including mandibular canal/above mandibular canal/none	0.333	1.117	0.893–1.396
Periosteal reaction	Gap−or irregular-type/attached-type/(−)	0.179	0.858	0.687–1.073
Mixed type osteosclerosis	(+)/(−)	0.007	0.443	0.246–0.796

Abbreviation: ARA: antiresorptive agent; BP: bisphosphonate; DMB: denosumab; HR: hazard ratio; CI: confidence interval.

spontaneous MRONJ have not been clarified so far. Otsuru et al.[7] reported six cases of a rare type of MRONJ (periosteal reaction−dominant type) with little osteolysis but extensive periosteal reaction; however, these cases occurred independently of teeth, and the initial manifestation was often a skin fistula rather than bone exposure into the oral cavity. These tumors were not considered odontogenic in origin. Recently, Sakamoto et al.[5] reviewed triggers of MRONJ in 145 patients and reported that 54 developed MRONJ from dental infection, 48 after tooth extraction, 15 from the denture wear area, 2 from the bone ridge, 1 from an oral mucosal ulcer, and 25 had no known cause. Dental infection is the most important risk factor for MRONJ. Surgical invasion such as tooth extraction may manifest as subclinical MRONJ (stage 0 MRONJ), although it does not represent a major risk. Additionally, there may be a significant number of MRONJ cases with unknown onset triggers that cannot be explained by dental infections or surgical invasion.

There are few reports on the pathogenesis and etiology of non-odontogenic MRONJ, MRONJ of unknown origin, or spontaneously developing MRONJ. In 2009, Lesclous et al.[4] presented the hypothesis that the pathogenesis of MRONJ is aseptic osteonecrosis caused by the action of ARA, which expands and perforates the cortical bone and oral mucosa, thus exposing the oral cavity. Although Lesclous's hypothesis does not involve dental infections, many MRONJ cases appear to develop from dental infections. Recently, Sakamoto et al.[5] proposed two other pathogenic mechanisms in addition to Lesclous's theory: preceding osteonecrosis, odontogenic type, and preceding infection type. Odontogenic osteonecrosis is based on the theory that aseptic osteomyelitis caused by ARA precedes aseptic osteonecrosis, which spreads to the surrounding infected areas caused by dental infections, mucosal ulcers caused by torus, or ill-fitting dentures, resulting in MRONJ. In the preceding infection type, bacterial osteomyelitis caused by a dental infection progresses to osteonecrosis because of the effect of ARA. According to Lesclous's theory, dental infection is not involved in the development of MRONJ, and MRONJ development cannot be prevented through dental management. MRONJ due to preceding odontogenic osteonecrosis cannot be prevented through dental management; however, the clinical onset of MRONJ can be delayed. MRONJ caused by the preceding infection type can be prevented through dental management since dental infection is the start of the disease. These onset patterns are important for preventing MRONJ.

Sakamoto et al. stated that non-odontogenic MRONJ is more common among high-dose DMB-treated patients.[5] In the present study, non-odontogenic MRONJ tended to be more common among high-dose DMB-treated patients, but the number of cases was small and the difference was not significant. Miyoshi et al.[21] reported that DMB suppressed local osteoclasts more strongly than BP as tested using histological analysis and real-time reverse transcription polymerase chain reaction (RT-PCR) of bone metabolism−related genes, and that MRONJ due to DMB use tended to have less osteolysis, difficulty in determining the extent of bone resection, and a poor postoperative course. Owing to the potent local osteoclast inhibitory effect of DMB, aseptic osteonecrosis may occur in patients treated with DMB. In our study, non-odontogenic MRONJ was associated with significantly poorer outcomes in both univariate and multivariate analyses. This may be because non-odontogenic MRONJ is more common among DMB-treated patients, making it difficult to determine the extent of resection during surgery. Non-odontogenic MRONJ may not only have a different pathogenesis but also a different nature, appropriate treatment, and prognosis compared with odontogenic MRONJ. Therefore, it is necessary to study additional cases of MRONJ.

This study had some limitations. First, because this was a retrospective study with a small number of cases, the results may not be generalizable. Second, the study was primarily based on panoramic radiographs and CT scans. Magnetic resonance imaging (MRI) or single-photon emission computed tomography-CT was not performed, and there was no evidence of prior aseptic osteomyelitis. In the future, through a prospective study, we aim to employ MRI

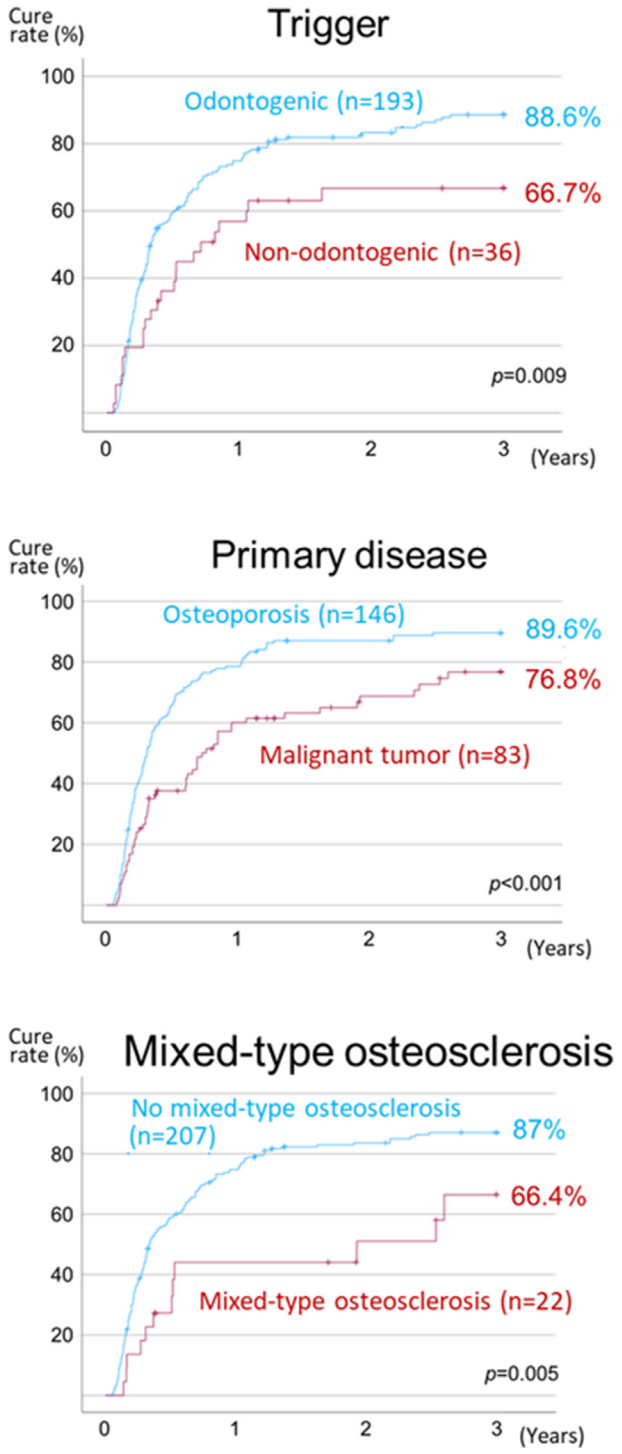

Figure 4 Factors related to the treatment outcome. Along with malignancy and mixed-type osteosclerosis, non-odontogenic trigger was associated with poor treatment outcome.

and SPECT-CT, as well as panoramic radiography and CT, histopathological examination of the operation materials, quantitative analysis of local bone metabolism–related genes using real-time RT-PCR, and bone marrow aspiration testing using real-time PCR to clarify the pathogenesis of MRONJ and its clinical significance.

Table 4 Factor related to treatment outcome (multivariate analysis).

Variable		P-value	HR	95 % CI
Primary disease	Malignancy/ osteoporosis	0.003	0.611	0.443–0.843
Trigger	Unknown/ odontogenic	0.027	0.608	0.391–0.944
Mixed type osteosclerosis	(+)/(−)	0.031	0.519	0.286–0.942

Abbreviation: HR: hazard ratio; CI: confidence interval.

Declaration of competing interest

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

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