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Original Article

Bone resection methods in medication-related osteonecrosis of the jaw in the mandible: An investigation of 206 patients undergoing surgical treatment

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Osteosclerosis;
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Periosteal reaction;
Surgery

Abstract *Background /purpose:* The standard treatment for medication-related osteonecrosis of the jaw (MRONJ) is surgery. However, reports on the appropriate extent of bone resection are few. We aimed to examine the relationship between the extent of bone resection and postoperative outcomes in patients with mandibular MRONJ.
Materials and methods: The clinical and imaging findings and treatment outcomes of 206 patients (258 surgeries) with mandibular MRONJ undergoing surgery were reviewed. Imaging findings were evaluated using computed tomography (CT) to sequestrum, osteolysis, periosteal reaction, and mixed-type osteosclerosis, and determine the extent of resection. In some cases, samples were taken from within the bone, and real-time polymerase chain reaction was used to confirm the presence of bacteria and fungi.
Results: The three-year cumulative cure rate was 81.7%. Patients with malignant tumors showing no osteolysis and undergoing sequestrum removal or marginal mandibulectomy had

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significantly worse prognosis than those with osteoporosis showing osteolysis and undergoing segmental mandibulectomy. Furthermore, patients with residual osteolysis, periosteal reactions, and mixed-type osteosclerosis on CT were more likely to develop recurrence. Eleven patients showed no osteolysis on CT images. Patients with cancer administered with high-dose denosumab had significantly poorer prognosis. Bacteria and fungi were also detected in samples obtained from gap-type periosteal reaction and mixed-type osteosclerosis.
Conclusion: Surgery for MRONJ requires resection of the infected bone. Aside from the osteolysis area, the gap-/irregular-type periosteal reaction and mixed-type osteosclerosis must also be included in the resection area. Methods for determining the extent of bone resection in MRONJ without osteolysis are a future challenge.

Introduction

Antiresorptive agents (ARAs), such as bisphosphonates (BPs) and denosumab (DMB), are widely used to prevent fractures in osteoporosis and treat skeletal-related events associated with cancer bone metastases and multiple myeloma.[1,2] A serious adverse event of ARAs is medication-related osteonecrosis of the jaw (MRONJ). The first report of MRONJ[3] was published 20 years ago, with subsequent reports on its diagnosis, treatment, and prevention, including position papers[4–8] and guidelines.[9] Conservative treatment, such as antimicrobial mouthwash and the administration of antimicrobial agents, has been recommended.[10] However, the effectiveness of surgical treatment has been widely reported recently.[11–15]

For the surgical treatment of patients with MRONJ, the American Association of Oral and Maxillofacial Surgeons (AAOMS) recommended in 2009 that only necrotic bone should be removed without exposing uninvolved bone, and that patients with MRONJ should avoid elective dentoalveolar surgical procedures because these surgical sites could result in additional areas of exposed necrotic bone.[4] However, better outcomes were obtained by extensive surgery, in which the surrounding healthy bone was also resected, in comparison with conservative surgery, in which only the necrotic bone was removed.[12,16–19] A multicenter study also reported that the treatment rate of MRONJ was higher with surgical treatment than with conservative treatment and patients treated with extensive surgery had better outcomes than those treated with conservative surgery.[11] The AAOMS Position Paper 2022[6] stated that both nonoperative and operative management is acceptable for all stages of disease and recommended that if surgery is the treatment of choice, stage 1 patients with disease located above the neurovascular canal should undergo marginal resection, stage 2 patients with disease located at or below the neurovascular canal in an atrophic or edentulous mandible should undergo segmental resection, and stage 3 patients should undergo segmental resection. However, to our knowledge, there have been no reports detailing the methods for determining the extent of bone resection. Thus, we aimed to investigate the preoperative and postoperative imaging findings of mandibular MRONJ surgeries in our department and propose an appropriate bone resection area.

Materials and methods

Patients

Patients with MRONJ who underwent surgical treatment at the Nagasaki University Hospital, between 2011 and 2022 were included in the study. Those who were observed for less than one month were excluded.

Variables

The following factors were retrospectively investigated from the medical records and images: age, sex, MRONJ stage, primary disease (osteoporosis/malignant tumor), type of ARAs (BP/DMB/switch from BP to DMB), duration of ARA administration, duration of drug holiday prior to surgery, bone exposure (−/+), fistula reaching bone (−/+), neutrophil-lymphocyte ratio (NLR), serum albumin, computed tomography (CT) findings, bone resection method (removal of necrotic bone, marginal mandibulectomy, edge and nerve preservation with the removal of infection (EGRI) method, segmental mandibulectomy), and treatment outcome (cure/non-cure). The MRONJ stage was classified according to the AAOMS Position Paper 2022.[6] Cure was defined as the disappearance of all clinical symptoms, including bone exposure. CT findings were examined preoperatively for separation of the sequestrum (−/+), osteolysis (-/above the mandibular canal/including mandibular canal/including inferior edge), periosteal reaction (-/attached type/gap type/irregular type), and mixed-type osteosclerosis (−/+) (Fig. 1). The type of periosteal reaction was classified according to our previously reported criteria.[20,21] A new definition of mixed-type osteosclerosis was defined as the presence of numerous small radiolucent areas indicating marked osteosclerosis. The CT findings were judged by two dentists with the clinical course concealed; if the two results differed, the decision was made by consensus. EGRI method is a surgical procedure in which the

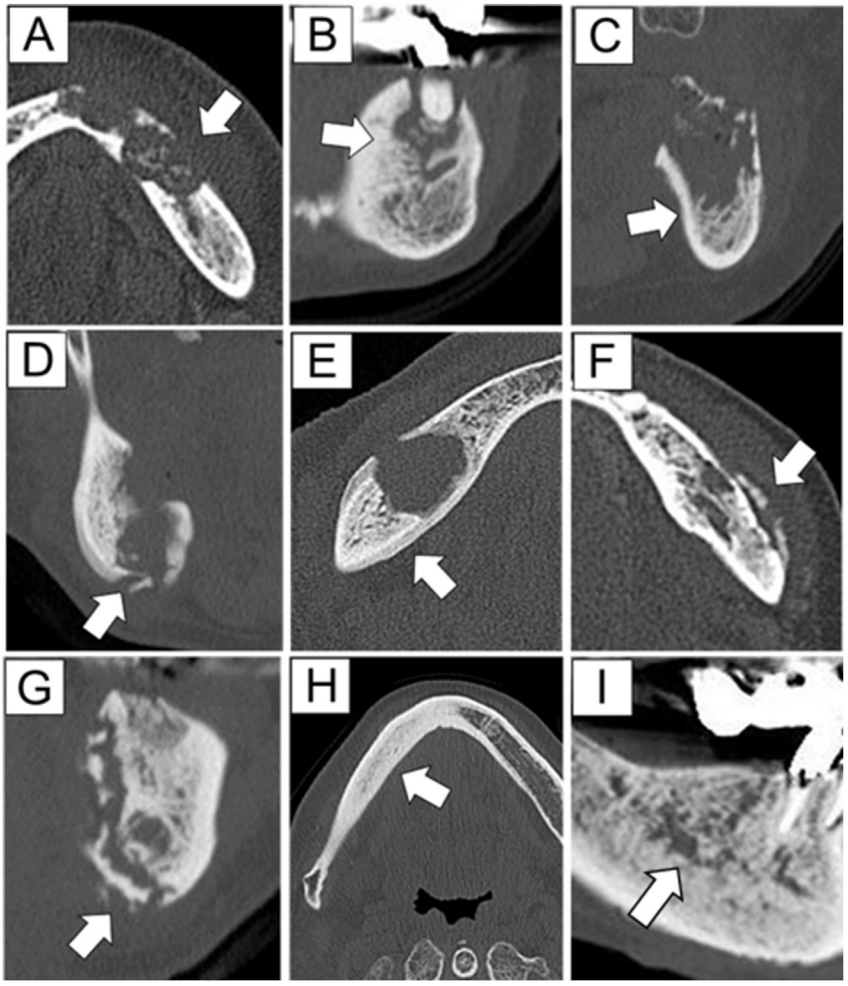

Figure 1 Computed tomography findings of medication-related osteonecrosis of the jaw. A: separation of sequestrum, B: osteolysis above the mandibular canal, C: osteolysis including the mandibular canal, D: osteolysis including the inferior edge of the mandible, E: attached-type periosteal reaction, F: gap-type periosteal reaction, G: irregular-type periosteal reaction, H: uniform-type osteosclerosis, I: mixed-type osteosclerosis.

inferior alveolar neurovascular bundle is preserved, while the cancerous bone and marrow below the mandibular canal are curetted and removed. Postoperative CT was examined for residual osteolysis (−/+), periosteal reaction (−/+), and mixed osteosclerosis (−/+) (Fig. 2).

Bacterial examination by real-time polymerase chain reaction

In several patients who underwent segmental mandibulectomy, bone samples were aseptically collected from a submandibular skin incision before extending the operative field into the oral cavity. Samples were mechanically crushed under aseptic conditions, and genomic DNA from the bone tissue was isolated using a DNA extraction kit (InstaGene Matrix; Bio-Rad Laboratories, Hercules, CA, USA) according to the manufacturer's instructions. The concentrations of total bacteria, streptococci, Methicillin-

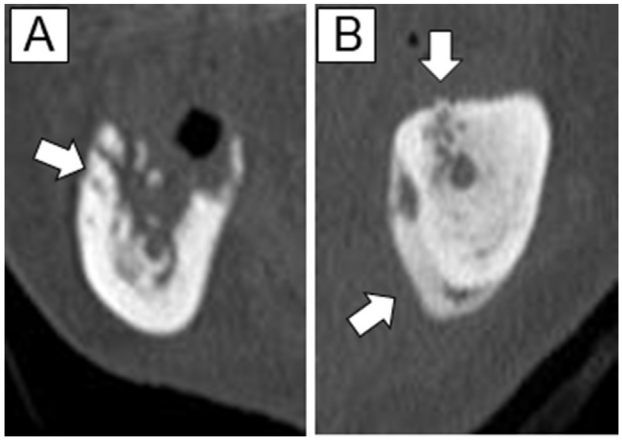

Figure 2 Postoperative computed tomography examinations. A: Osteolytic area remains unresected. B: Periosteal reaction and mixed-type osteosclerosis remain unresected.

resistant *Staphylococcus aureus*, *Candida albicans*, and *Porphyromonas gingivalis* were estimated using real-time PCR. Artificial DNA, primers, and reaction conditions used for real-time PCR were in accordance with previously reported methods.[20,22]

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA). Patient characteristics were analyzed using descriptive statistics. Univariate and multivariate Cox regression analyses were used to examine factors associated with treatment outcomes, and some factors were illustrated using the Kaplan–Meier method and tested with a log-rank test. Statistical significance was set at $P < 0.05$.

Ethics

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 Boards (IRB) of Nagasaki University Hospital (#20081722). Informed consent to participate was obtained in writing from patients who underwent bacteriological search by real-time PCR. Because part of this study is a retrospective one, patient identifiable information was removed, and the research plan was published on the homepages of Nagasaki University Hospital websites, along with an opt-out option in accordance with IRB instructions.

Results

Patient characteristics

Two-hundred-and-six patients were enrolled (women: 158; men: 48; mean age: 76.8 ± 11.1 years). The primary disease was osteoporosis in 137 patients and malignancy in 69 patients. The ARA type was BP in 127 patients, DMB in 57 patients, and 22 patients who were initially BP but switched to DMB. Osteolytic lesions on CT images were localized above the mandibular canal in 124 patients, including the mandibular canal, but did not reach the mandibular lower edge in 61 patients, including the mandibular lower edge in 10 patients. Eleven patients showed no evidence of osteolysis on CT imaging (Table 1).

Table 1 Patient characteristics.

Variable		Number of patients /mean ± SD
Sex	Female	158
	Male	48
Age	(years)	76.8 ± 11.1
MRONJ stage	Stage 0	13
	Stage 1	14
	Stage 2	163
	Stage 3	16
Primary disease	Osteoporosis	137
	Malignant tumor	69
Sort of ARA	BP	127
	DMB	57
	BP → DMB	22
Duration of ARA administration	(Months)	55.8 ± 40.5
Drug holiday for more than 3 months	(−)	178
	(+)	28
Bone exposure	(−)	121
	(+)	85
Fistula formation	(−)	77
	(+)	129
BMI		21.4 ± 3.97
NLR		3.67 ± 0.566
Serum albumin	(g/mL)	3.67 ± 0.566
Separation of seqestrum	(−)	117
	(+)	89
Osteolysis	(−)	11
	Localized above the mandibular canal	124
	Including the mandibular canal	61
	Including the mandibular lower edge	10
Periosteal reaction	(−)	131
	Attached type	53
	Gap/irregular type	22
Mixed type osteosclerosis	(−)	184
	(+)	22
Total		206

SD: standard deviation, MRONJ: medication-related osteonecrosis of the jaw, ARA: antiresorptive agent, BP: bisphosphonate, DMB: denosumab, BMI: body mass index, NLR: neutrophil-to-lymphocyte ratio.

Operation methods

We performed 258 surgeries, including multiple surgeries, in 206 patients. Removal of the separated sequestrum was performed in 62 patients, marginal mandibulectomy in 160, the EGRI method in 9, and segmental mandibulectomy in 27. In patients who underwent segmental mandibulectomy, reconstructive surgery using a vascularized fibula was performed in two patients, only metal plate transplantation was performed in 22 cases and no reconstruction was performed in two patients, considering their advanced age and general condition (Fig. 3).

Factors related to the treatment outcome

The three-year cumulative cure rate was 80.0% in the per-patient analysis of 206 patients, and 81.7% in the per-operative analysis of 258 operations (Fig. 4). Univariate analysis revealed that the following 12 factors were

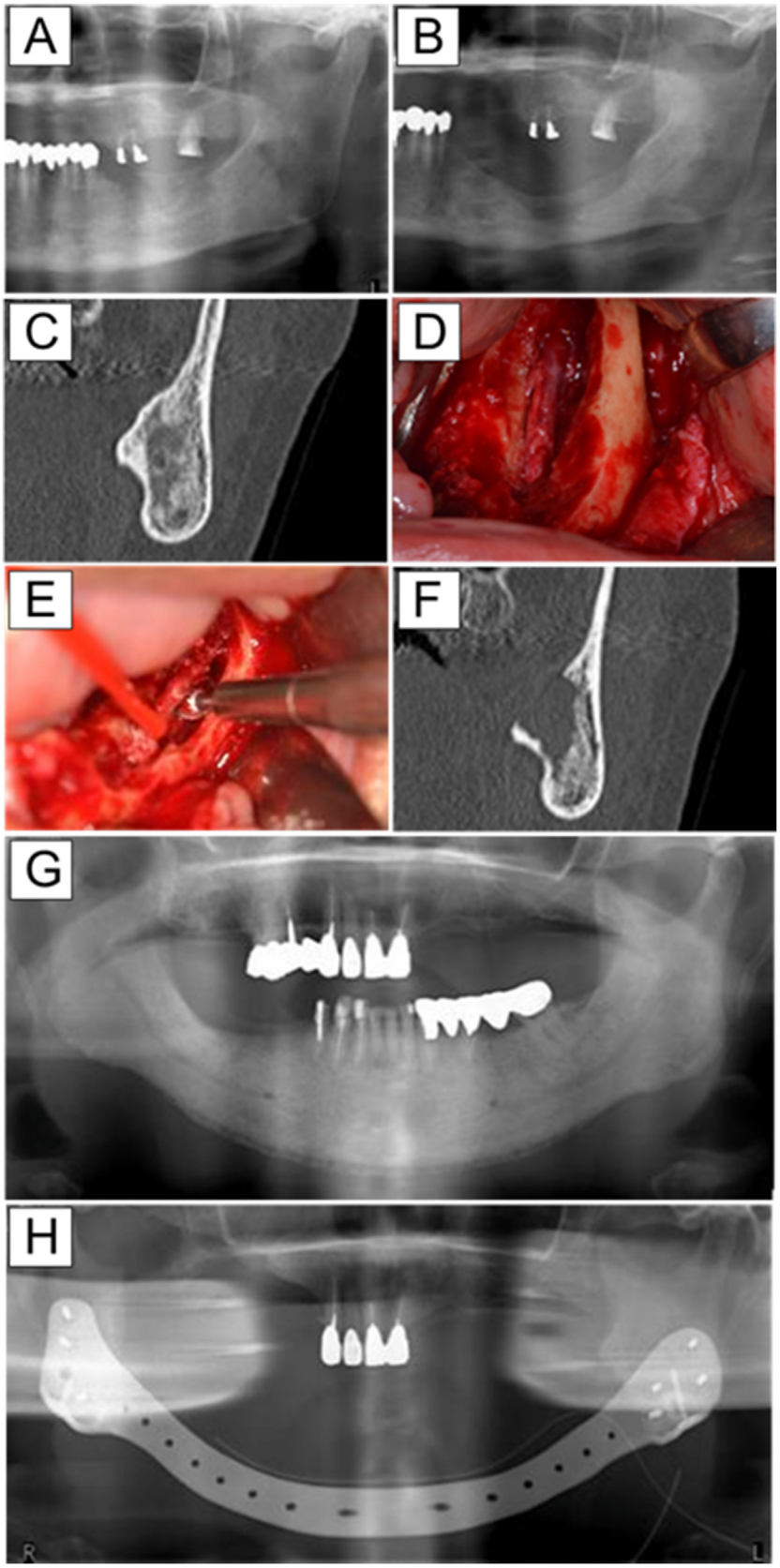

Figure 3 Surgical method of medication-related osteonecrosis of the jaw. A, B: marginal mandibulectomy, C—F: edge and nerve preservation with the removal of infection (EGRI) method, G, H: segmental mandibulectomy with metal plate reconstruction.

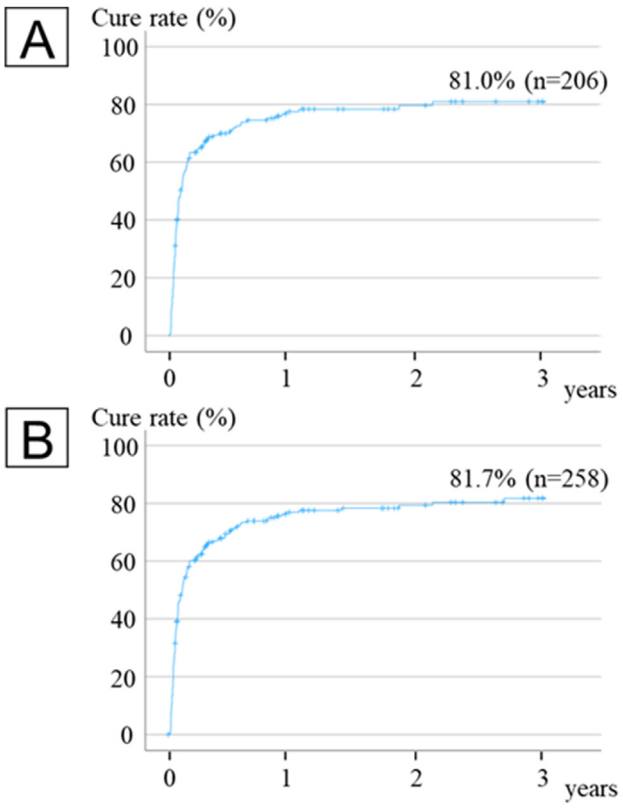

Figure 4 Cumulative cure rate. A: Per-patient analysis, B: Per-operation analysis.

significantly associated with poor prognosis: male sex, malignant tumor, presence of bone exposure, absence of fistula, non-separation of the sequestrum, no osteolytic lesion, gap-type or irregular periosteal reaction, mixed-type osteosclerosis, removal of sequestrum or marginal mandibulectomy, residual osteolytic lesion, residual gap- or irregular-type periosteal reaction, and residual mixed-type osteosclerosis (Table 2). Multivariate analysis showed that malignant tumors, no osteolysis, surgical method, residual osteolysis, residual gap- or irregular-type periosteal reaction, and residual mixed-type osteosclerosis were independent significant risk factors for a decreased cure rate (Table 3). The relationship between these six factors and cure rates was analyzed using the Kaplan—Meier method (Fig. 5).

Characteristics of non-osteolytic medication-related osteonecrosis of the jaw

Owing to the poor outcomes of non-osteolytic MRONJ, we investigated its characteristics. Univariate analysis of the differences in background factors between osteolytic and non-osteolytic MRONJ revealed that non-osteolytic MRONJ was more common in males, younger patients, patients with malignancy, and patients receiving DMB (Table 4). Multivariate analysis using these four factors as covariates revealed that non-osteolytic MRONJ was more common in patients treated with DMB (Table 5).

Here, we present a case of non-osteolytic MRONJ. A 75-year-old woman was referred to our department with bone exposure in the lingual gingiva of the right mandibular second molar region (Fig. 6A). She had received DMB for three months prior to her first visit for bone metastasis from breast cancer. Four months prior, her right mandibular second molar had been extracted due to a residual root, and DMB was initiated after the healing of the extraction socket. Panoramic radiography and CT at the initial visit showed no abnormal findings, such as osteolysis, sequestrum, or periosteal reaction, except in the residual extraction socket (Fig. 6B and C). Two months after the initial visit, a marginal mandibulectomy, including the exposed bone, was performed above the mandibular canal (Fig. 6D and E). However, one year post-surgery, bone exposure and a cutaneous fistula appeared in the right submandibular region (Fig. 6F and G). She preferred conservative treatment over surgery; therefore, oral antibiotic administration and irrigation of the exposed bone and fistulae were repeated. However, a periosteal reaction appeared and extended to the contralateral molar region (Fig. 6H). Three years after the initial surgery, segmental mandibulectomy and reconstruction using a metal plate were performed (Fig. 6I), and there was no recurrence of MRONJ since then.

Bacterial examination by real-time polymerase chain reaction

Samples obtained from six sites showing osteolysis, five sites showing a gap-type periosteal reaction, one site showing mixed-type osteosclerosis, and two sites near the resection margins with no abnormalities on CT were examined. Bacteria were not detected at the two sites near the resection margins; however, DNA of bacterial or fungal origin was detected at all 12 sites, showing gap- or irregular-type periosteal reactions and mixed-type osteosclerosis (Table 6, Fig. 7).

Discussion

This study revealed that mandibular MRONJ surgery has poor outcomes in patients with malignancies receiving high-dose ARAs or in those without osteolysis on CT images. Moreover, residual osteolysis, residual gap- or irregular-type periosteal reaction, or residual mixed-type osteosclerosis significantly reduced healing rates.

According to the AAOMS Position Paper 2022,[6] the frequency of MRONJ is less than 5% in cancer patients receiving high-dose BP or DMB. In osteoporosis patients, it is approximately 0.02—0.05% in patients receiving low-dose BP, which is comparable to the incidence of ONJ in the placebo group (0—0.02%). By contrast, the incidence of MRONJ in Japanese patients is 1.6—12.4% in high-dose patients and 0.104% or 22.9/100,000 person-years in low-dose patients, suggesting that the incidence among Japanese people is relatively higher than that in Western countries.[23]

There is a recent consensus that the standard therapy for MRONJ is surgical treatment.[11—15] The first systematic

Table 2 Factors related to treatment outcome in 258 MRONJ surgeries (univariate analysis).

Variable		*P*-value	HR	95% CI
Sex	Female vs. male	0.003	0.575	0.401—0.823
Age	(years)	0.392	1.006	0.992—1.020
MRONJ stage	Stage 1 vs. 2 vs. 3	0.748	1.038	0.826—1.305
Primary disease	Osteoporosis vs. malignant tumor	<0.001	0.426	0.312—0.583
Sort of ARA	BP vs. DMB/both	0.075	0.764	0.567—1.028
Duration of ARA administration	(months)	0.170	1.003	0.999—1.006
Drug holiday for more than 3 months	(−) vs. (+)	0.960	0.989	0.640—1.529
Bone exposure	(−) vs. (+)	0.004	0.648	0.484—0.868
Fistula formation	(−) vs. (+)	0.024	1.405	1.046—1.888
BMI		0.455	0.986	0.952—1.022
NLR		0.097	1.044	0.992—1.099
Serum albumin	(g/mL)	0.898	0.982	0.741—1.301
Separation of seqestrum	(−) vs. (+)	0.006	1.496	1.126—1.989
Osteolysis	(−) vs. (+)	0.003	4.470	1.658—12.050
Periosteal reaction	(−) vs. attached type vs. gap/irregular type	0.045	0.805	0.652—0.995
Mixed type osteosclerosis	(−) vs. (+)	<0.001	0.390	0.236—0.643
Anesthesia	Local anesthesia vs. general anesthesia	0.051	1.517	0.998—2.305
Surgical method	Removal of sequestrum vs. marginal mandibulectomy vs. segmental mandibulectomy	0.005	1.466	1.120—1.919
Residual osteolysis	(−) vs. (+)	<0.001	0.282	0.184—0.431
Residual gap/irregular type periosteal reaction	(−) vs. (+)	0.004	0.350	0.173—0.712
Residual mixed type osteosclerosis	(−) vs. (+)	<0.001	0.179	0.084—0.382

HR: hazard ratio, 95% CI: 95% confidence interval, MRONJ: medication-related osteonecrosis of the jaw, ARA: antiresorptive agent, BP: bisphosphonate, DMB: denosumab, BMI: body mass index, NLR: neutrophil-to-lymphocyte ratio.

Table 3 Factors related to treatment outcome in 258 surgeries (multivariate analysis)HR: hazard ratio, 95% CI: 95% confidence interval.

Variable		*P*-value	HR	95% CI
Primary disease	Osteoporosis vs. malignant tumor	0.004	0.618	0.444—0.859
Osteolysis	(−) vs. (+)	0.001	5.492	1.991—15.151
Surgical method	Removal of sequestrum vs. marginal mandibulectomy vs. segmental mandibulectomy	0.040	1.299	1.012—1.667
Residual osteolysis	(−) vs. (+)	<0.001	0.303	0.195—0.470
Residual gap/irregular type periosteal reaction	(−) vs. (+)	0.041	0.446	0.206—0.967
Residual mixed type osteosclerosis	(−) vs. (+)	0.003	0.302	0.136—0.674

HR: Hazard Ratio, CI: Confidence Interval.
*Multivariate Cox regression analysis performed stepwise using 12 factors that were significant in univariate analysis as covariates.

review of MRONJ treatments by Rupel et al.[16] divided the surgical procedures into conservative, extensive, and laser surgery. When only sequestrectomy and/or superficial surgical debridement of the necrotic bone associated with antibiotic therapy was performed, it was defined as a conservative surgical approach. When resection of the jawbone was performed, it was defined as an extensive surgical approach, often performed under general anesthesia. When used in surgery, lasers can ablate the bone effectively without producing major thermal side effects in adjacent tissues. It also has bactericidal, detoxifying, and biostimulatory effects that may enhance bone regeneration and facilitate wound healing after surgery. They defined this procedure as laser surgery. In a systematic review, healing rates for conservative, extensive, and laser surgeries were 50%, 84%, and 85%, respectively. Fliefel et al.[17] divided the surgical procedure for MRONJ into minimally invasive surgery, major surgery, guided debridement, and laser therapy, and stated that the complete healing rates were 39.2%, 82.1%, 48%, and 45.3%, respectively. Since their report, several systematic reviews of surgical techniques for MRONJ have been published.[24,25] Most of these evaluated autologous platelet concentrates, hyperbaric oxygen therapy, laser surgery, administration of teriparatide, ozone applications, or fluorescence-guided surgery, and concluded that the evidence was insufficient to prove

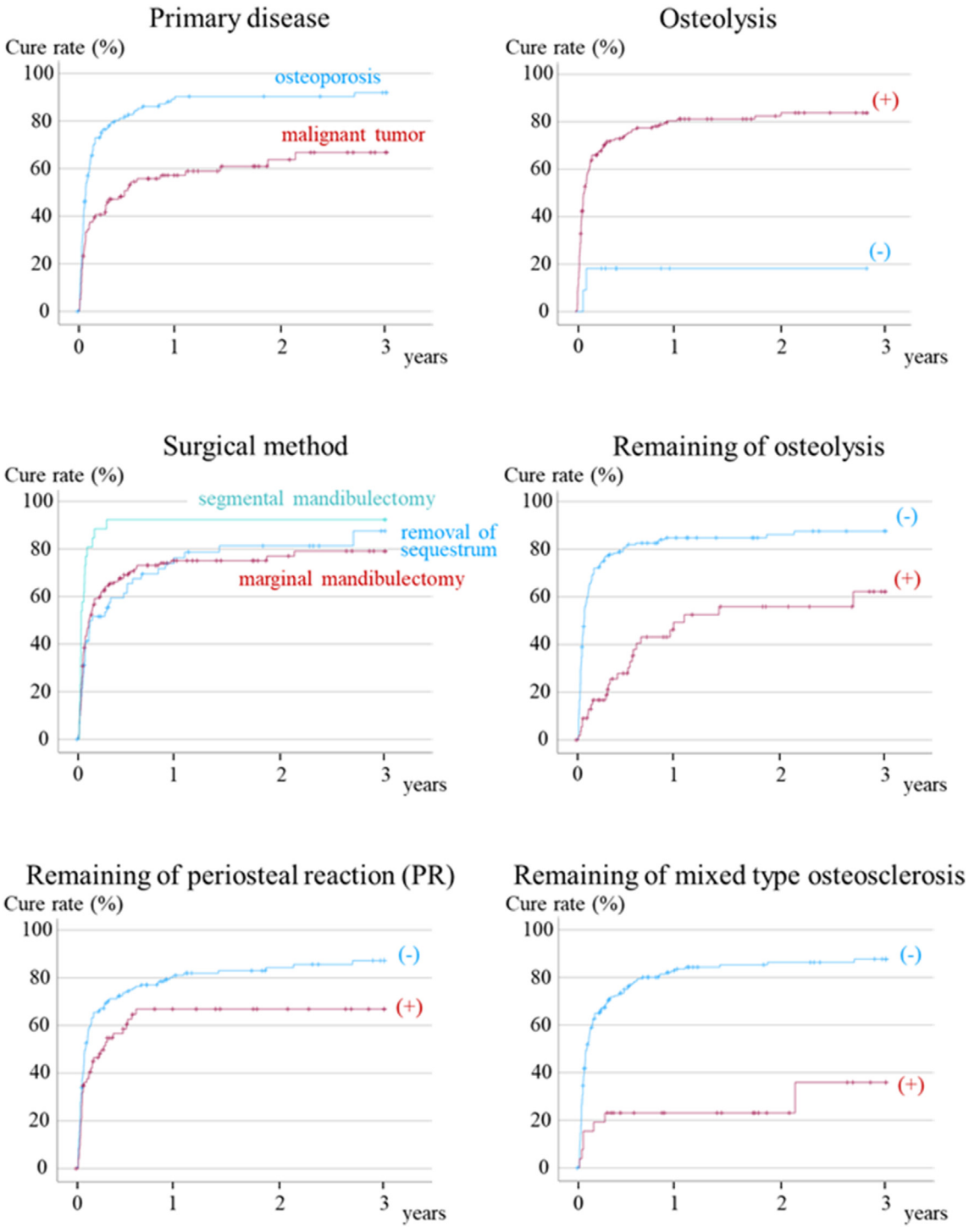

Figure 5 Factors related to the treatment outcome.

the efficacy of these adjunctive therapies. However, no previous studies have examined the extent of bone resection during surgery for MRONJ.

The goal of MRONJ surgery is to remove the necrotic bone. Therefore, we initially performed bone removal to the extent that hemorrhage was observed. However, patients with periosteal reactions on CT often do not achieve surgical cure.[26] Further, detailed images of the periosteal reaction can be classified into the "attached-type," wherein the new bone is attached parallel to the existing bone; "gap-type," wherein the new bone is parallel to the existing bone but there is a gap between the two; and "irregular-type," wherein the new bone shows irregular morphology. Moreover, the gap- and irregular-type periosteal reaction are infectious lesions rather than reactive one, by histological investigations.[20,21] ARA administration and presence of bacteria and fungi play a role in the pathogenesis of MRONJ.[7] Bone tissue of MRONJ patients is

Table 4 Differences of characteristics between osteolytic and non-osteolytic MRONJ (univariate analysis).

Variable		Osteolysis (+)	Osteolysis (−)	*P*-value
Sex	Female	153	5	0.021
	Male	42	6	
Age	(years)	77.2 ± 11.2	69.6 ± 7.22	0.027
MRONJ stage	Stage 0	12	1	0.766
	Stage 1	13	1	
	Stage 2	154	9	
	Stage 3	16	0	
Primary disease	Osteoporosis	136	1	<0.001
	Malignant tumor	59	10	
Sort of ARA	BP	127	0	<0.001
	DMB	51	6	
	BP→DMB	17	5	
Duration of ARA administration	(Months)	35.6 ± 21.2	57.2 ± 41.1	0.087
Drug holiday for more than 3 months	(−)	11	167	0.176
	(+)	0	28	
Bone exposure	(−)	117	4	0.206
	(+)	78	7	
Fistula formation	(−)	71	6	0.336
	(+)	124	5	
BMI		21.4 ± 3.94	21.7 ± 4.64	0.804
NLR		3.53 ± 2.64	3.05 ± 2.10	0.551
Serum albumin	(g/mL)	3.68 ± 0.568	3.50 ± 0.520	0.314

MRONJ: medication-related osteonecrosis of the jaw, ARA: antiresorptive agent, BP: bisphosphonate, DMB: denosumab, BMI: body mass index, NLR: neutrophil-to-lymphocyte ratio.

Table 5 Differences of characteristics between osteolytic and non-osteolytic MRONJ (multivariate analysis).

Variable		*P*-value	OR	95% CI
Sex	Female vs. male	0.146	0.327	0.072−1.475
Age		0.399	1.028	0.964−1.097
Primary Disease	Osteoporosis vs. malignant tumor	0.152	0.185	0.018−1.860
Type of ARA	BP vs. DMB vs. both	0.003	0.195	0.065−0.584

OR: odds ratio, 95% CI: 95% confidence interval, ARA: antiresorptive agent, BP: bisphosphonate, DMB: denosumab.

thought to contain healthy and necrotic bone as well as infected osteomyelitis areas that have not yet developed into necrosis. Osteomyelitis is usually reversible, but we think it may not recover under administration of ARAs and may progress to MRONJ. These led us to think that MRONJ surgery should include not only necrotic bone but also infected bone in the resection area.

Herein, although the sample size was small, several bone marrow samples were examined for bacteria using real-time PCR. The bone marrow was inherently sterile, and no bacteria were detected in the bone marrow at the resection margin of the segmental mandibulectomy. Conversely, bacteria were detected in areas showing gap-type periosteal reactions or mixed-type osteosclerosis on CT, suggesting that these areas were infectious lesions. In bacterial osteomyelitis other than MRONJ, microorganisms in the bone marrow can be expected to be controlled by antibiotics. However, in MRONJ, blood flow is poor, and we believe that surgical removal of the infected site is necessary. Bones showing gap- or irregular-type periosteal reactions or mixed-type osteosclerosis are sites of hemorrhage at the time of osteotomy, and determining the extent of osteotomy based on the presence or absence of intraoperative bleeding was considered to be not appropriate. Based on these considerations, we conclude that gap- and irregular-type periosteal reactions and mixed-type osteosclerosis sites should be included in the resection area for MRONJ surgery.

One of the first findings of this study is the existence and characteristics of non-osteolytic MRONJ. Radiographic findings of MRONJ include alveolar bone loss or resorption not attributable to chronic periodontal disease, changes to the trabecular pattern of sclerotic bone, absence of new bone in extraction sockets, regions of osteosclerosis involving the alveolar bone and/or surrounding basilar bone, and thickening or obscuring of the periodontal ligament (thickening of the lamina dura, sclerosis, and decreased size of the periodontal ligament space).[6] In contrast, we have recently been experiencing more MRONJ without evidence of osteolysis. Among the 206 patients with MRONJ, non-osteolytic MRONJ was observed in 11 (5.3%). This study included patients treated between 2011 and 2022. However, this type of MRONJ was first observed in

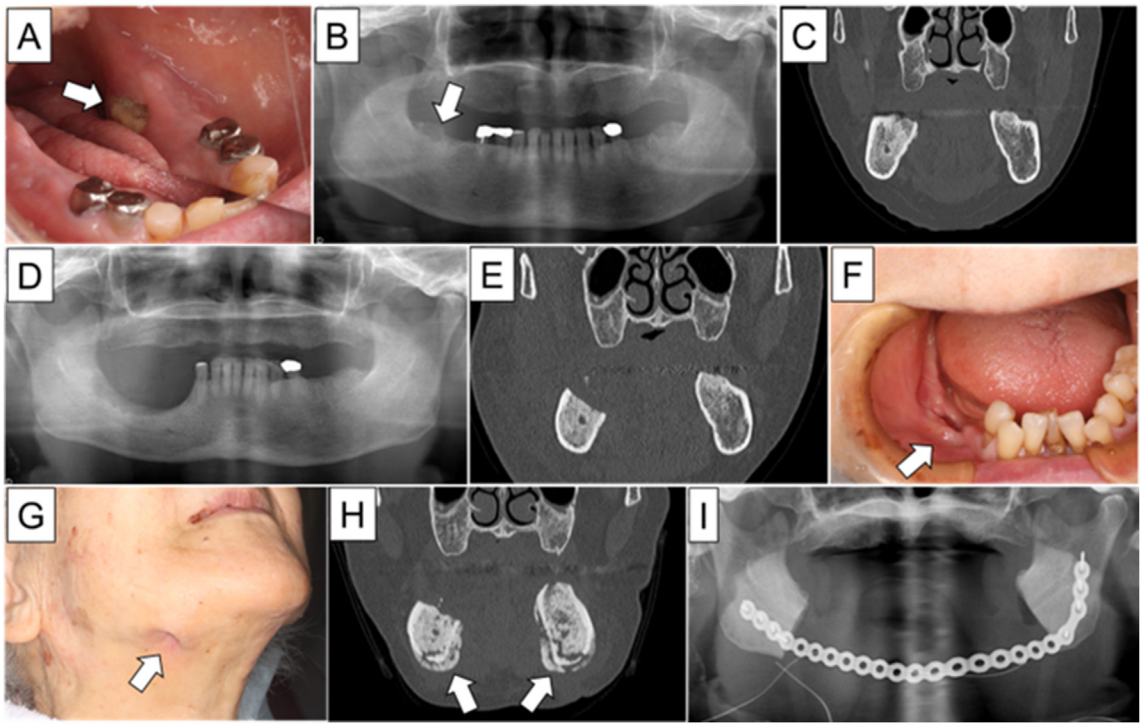

Figure 6 Example of non-osteolytic medication-related osteonecrosis of the jaw. A: Intraoral findings at first visit. B, C: No abnormal findings were seen on panoramic radiography and computed tomography. D, E: Images after marginal mandibulectomy, F, G: Bone exposure and fistula formation one year after marginal mandibulectomy, H: Periosteal reaction extended to the contralateral region three years after the initial surgery, I: The patient finally underwent segmental mandibulectomy with metal plate reconstruction.

Table 6 Detection rate of bacteria at various sites.

Site	Total bacteria	Streptcocci	MRSA	*Candida albicans*	*Porphyromonas gingivalis*
i) Abnormal CT findings					
Osteolysis	6/6 (100%)	6/6 (100%)	0/4 (0%)	4/4 (100%)	4/4 (100%)
Gap type periosteal reaction	5/5 (100%)	5/5 (100%)	1/5 (20%)	4/5 (80%)	5/5 (100%)
Mixed type Osteosclerosis	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
Total	12/12 (100%)	12/12 (100%)	2/10 (20%)	9/10 (90%)	10/10 (100%)
ii) Normal CT findings					
Surgical margin	0/2 (0%)	0/2 (0%)	0/2 (0%)	0/2 (0%)	0/2 (0%)

CT: Compted Tomography, MRSA: Methicillin-resistant *Staphylococcus aureus*.

2017, and all patients were treated with DMB. ARA is administered to prevent or treat skeletal-related events associated with bone metastases of solid cancer or multiple myeloma, and DMB was reported to be more effective than zoledronic acid.[27] More patients with malignancies may expectedly receive DMB in the future, and the number of patients with this non-osteolytic MRONJ may increase.

Non-osteolytic MRONJ does not show abnormal findings on panoramic radiography or CT; thus, the extent of the lesion cannot be diagnosed using these modalities. Bone marrow changes in patients with MRONJ can be diagnosed using magnetic resonance imaging (MRI). According to a review by Wongratwanich et al.,[28] the MRI of early stage MRONJ displays low intensity on T1 weighted images (T1WI) and high intensity on both T2 weighted images (T2WI) and short tau inversion recovery (STIR) images, indicating existing inflammation. In advanced-stage MRONJ, the intensity becomes hypointense on T1WI, T2WI, and STIR, or intermediate intensity is seen in some cases. The effectiveness of bone single-photon emission CT (SPECT/CT) for the diagnosis of MRONJ has recently been reported.[29,30] Miyashita et al.[31] reported a three-dimensional radiologic-pathologic correlation of MRONJ using 3D bone SPECT/CT imaging. MRI and bone SPECT/CT may be effective in delineating the extent of non-osteolytic MRONJ lesions and may be used in the future to determine the extent of bone resection in non-osteolytic MRONJ. Future studies should examine MRI and SPECT/CT in patients with non-osteolytic MRONJ.

This study has some limitations. As this was a single-center retrospective study, the results may not be generalized. Further, for non-osteolytic MRONJ, we were unable to suggest how the extent of bone resection could be

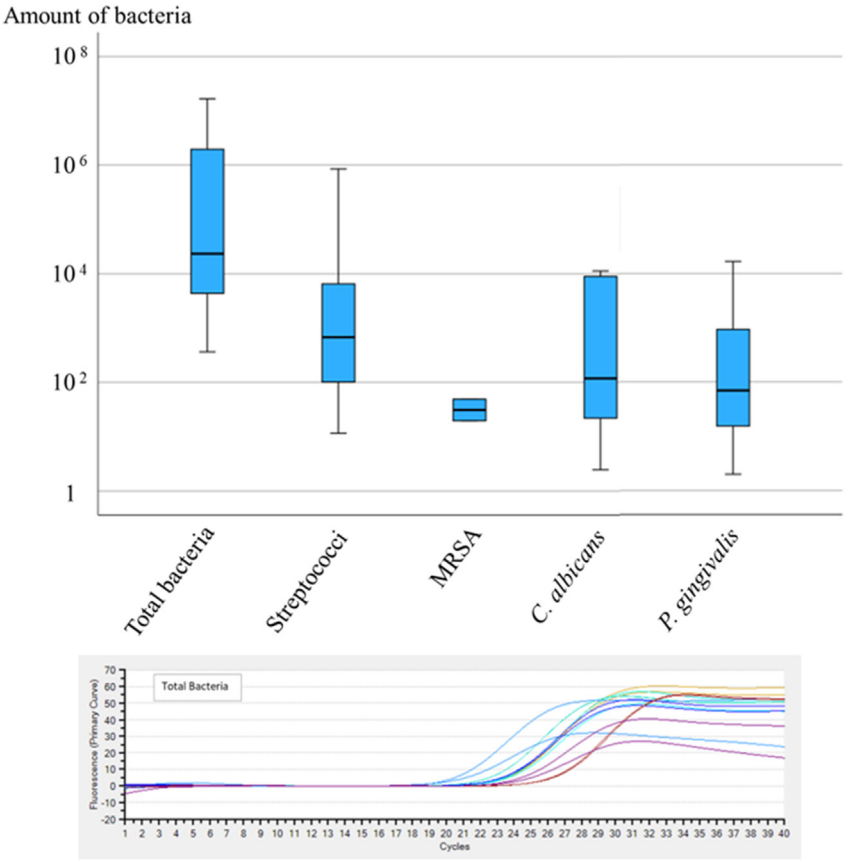

Figure 7 Results of real-time polymerase chain reaction showing the presence of bacteria in the bone tissue.

determined because only panoramic radiography and CT were performed; MRI was performed only in some patients, and SPECT/CT was not performed in all patients. However, this is the first report of an attempt to determine the extent of bone resection based on CT findings during mandibular MRONJ surgery. The usefulness of MRI and SPECT/CT in determining the best bone resection method for non-osteolytic MRONJ warrant further research.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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