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Original Article

Potential relationship among CT and MRI imaging, histological findings, and treatment outcomes in patients with medication-related osteonecrosis of the jaw undergoing segmental mandibulectomy—A retrospectives study

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KEYWORDS
CT;
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MRI;
Osteomyelitis

Abstract *Background/purpose:* Surgical treatment has recently been recommended as a standard therapy for medication-related osteonecrosis of the jaw (MRONJ). However, no established methods exist for determining the extent of bone resection. We aimed to compare preoperative computed tomography (CT) and magnetic resonance imaging (MRI) findings with the histopathological findings of resection materials in patients with MRONJ undergoing surgery.
Materials and methods: This was a retrospective, observational study. We analyzed the preoperative CT and MRI findings, histopathological characteristics of the resected materials, and treatment outcomes of 14 patients with MRONJ who underwent segmental mandibulectomy at Department of Oral and Maxillofacial Surgery, Nagasaki University Hospital.
Results: Areas showing osteolysis, gap-type or irregular-type periosteal reactions, and mixed-type osteosclerosis on CT were histologically confirmed to contain osteomyelitis or necrotic

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bone. On MRI, MRONJ lesions exhibited low signal intensity on T1-weighted images (T1WI) and variable signal intensities on T2-weighted images (T2WI). The extent of MRONJ lesions was difficult to delineate using T1WI and T2WI. In contrast, high signal intensity on short tau inversion recovery (STIR) images accurately reflected the extent of histologically confirmed osteomyelitis.
Conclusion: Osteomyelitis is present in areas with osteolysis, gap-type or irregular-type periosteal reactions, mixed-type osteosclerosis on CT, and high STIR signal intensity on MRI features. These findings may serve as reliable references for determining the extent of bone resection during surgery.

Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is a refractory form of osteonecrosis that occurs in patients receiving antiresorptive agents (ARA), such as bisphosphonates (BP) or denosumab (DMB), for fracture prevention in osteoporosis and managing skeletal-related events in cancer metastasis or multiple myeloma.[1] Previously, conservative treatments, such as the use of antibacterial mouthwashes and the administration of antibacterial drugs, were recommended as the first-line treatment for MRONJ.[2,3] However, recent studies have increasingly demonstrated the effectiveness of surgical treatment.[4,5] Despite this, there are almost no reports examining the methods for determining the extent of bone resection during surgery.

At our institution, we have adopted surgical treatment as the standard approach for MRONJ.[6] The extent of bone resection was initially determined to include areas showing sequestrum separation and osteolysis on radiography and computed tomography (CT). However, we observed a higher recurrence rate after surgery when periosteal reactions were present.[7] We classified periosteal reactions into three types: attached-type, gap-type, and irregular-type, and reported that gap—or irregular-type periosteal reactions were indicative of infectious lesions and should therefore be included in the resection area.[8,9] Although osteosclerosis is a common finding in patients receiving ARA and was initially excluded from the resection range, we later found that failure to include mixed-type osteosclerosis—characterized by numerous small radiolucent areas increased the risk of recurrence.[10] Furthermore, in recent years, some MRONJ cases where CT scans show only periosteal reactions with no evidence of osteolysis, and cases where CT scans show no abnormalities at all have been reported.[11–13] In these cases, it is difficult to determine the extent of bone resection based on CT scans alone. The purpose of this study was to compare preoperative CT and MR findings with histological findings of the resection materials and to investigate a method for determining the appropriate extent of bone resection in MRONJ surgery.

Materials and methods

Patients

This is a retrospective, observational study. The participants were patients with MRONJ who underwent segmental mandibulectomy at the Department of Oral and Maxillofacial Surgery, Nagasaki University Hospital, between April 2011 and March 2024. Patients who did not undergo CT or MRI before surgery, or whose follow-up status was unknown within 6 months after surgery, were excluded.

Factors examined

The following factors were investigated: age, sex, body mass index (BMI), MRONJ stage, primary disease (osteoporosis/malignancy), type of ARA (BP/DMB), and pre- and post-operative CT, MRI, and histopathological findings.[1] CT and MRI findings at the center of the lesion and resection margin were analyzed. CT was used to assess the presence and extent of osteolysis, sequestrum formation, periosteal reaction, and mixed-type bone sclerosis. Periosteal reaction was divided as three patterns: 1) Attached-type in which new bone is formed to the mandible without the presence of gap between the mandible and new bone, 2) Gap-type in which new bone is formed parallel to the mandible with the presence of gap between the mandible and new bone, and 3) Irregular-type showing an irregularly shaped periosteal reaction.[8,9] MRI was used to evaluate T1-weighted images (T1WI), T2-weighted images (T2WI), and short tau inversion recovery (STIR) sequences. When there was a mixture of different signal strengths, the classification was based on the higher signal strength. The interpretation of imaging findings was diagnosed by three oral surgeons who had previously agreed on the assessment methods. In cases of discrepancies, a discussion was held to reach a consensus. The CT scanner used was the Aquilion Precision (CANON MEDICAL SYSTEMS CORPORATION, Tochigi, Japan), and the MRI scanner used was the MAGNETOM Skyra, 3.0T (Siemens Healthcare K.K., Erlangen, Germany).

Histological examination of hematoxylin and eosin stained specimens was performed to identify the presence or absence of necrotic bone and osteomyelitis by observation of sequester, absence of osteocytes, absorption of cortical or cancerous bone, inflammatory cell infiltration, formation of new bone, and fatty marrow. Treatment outcomes were defined as 'healed' if all symptoms, including bone exposure, had disappeared 6 months postoperatively, and as 'non-healed' if these symptoms were observed.

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 was approved by the Institutional Review Board of Nagasaki University (#24080807). As this was a retrospective study, all identifiable patient information was removed, and the research plan was published on the websites of the participating hospitals, with an opt-out option provided in accordance with IRB guidelines.

Results

Patient characteristics

The summary of the 14 patients who underwent segmental mandibulectomy is shown in Table 1. There were six males and eight females, with an average age of 68.8 years. The primary disease was osteoporosis in one case and malignancy in 13 cases. BP and DMB were administrated to four and eight patients, respectively. Two patients were initially treated with BP, and later switched to DMB.

Relationship between CT imaging and histopathological findings

CT revealed osteolysis above the mandibular canal in one patient, while eight patients exhibited osteolysis involving the mandibular canal. Five patients presented with non-osteolytic MRONJ, in which no osteolysis was detected on the CT scan. Sequestrum separation was observed in three patients. Periosteal reaction was detected in 11 patients, categorized as follows: attached-type in two cases, gap-type in 8 cases, and irregular-type in one case. Mixed-type osteosclerosis was observed in three patients (Table 2).

Histologically, areas with sequestrum separation were characterized by inflammatory granulation tissue, predominantly neutrophil infiltration, surrounding necrotic bone devoid of osteocytes and necrotic soft tissue, and the presence of new trabecular bone with numerous osteoblasts and osteocytes (Fig. 1). Osteolytic lesions on CT scans consisted of necrotic tissue, fragments of necrotic bone, and inflammatory granulation tissue (Fig. 2). Histological findings in attached-type periosteal reactions showed continuous trabecular new bone from the cortical bone, without evidence of inflammatory tissue. In contrast, gap-type periosteal reactions exhibited infiltration of inflammatory cells, primarily neutrophils, in the gap between the cortical bone and trabecular new bone (Fig. 3). In osteosclerotic areas, mature cortical or new trabecular bone was present, with numerous osteocytes. In contrast, mixed-type osteosclerosis areas contained scattered granulation tissue with inflammatory cell infiltration, observed in regions showing pronounced sclerotic changes (Fig. 4).

Table 1 Patient characteristics.

Factor		Number of patients/ mean ± SD
Sex	Male	6
	Female	8
Age		68.8 ± 10.3
BMI		22.5 ± 4.63
Initial MRONJ stage	Stage 0	1
	Stage 1	2
	Stage 2	9
	Stage 3	2
Primary disease	Osteoporosis	1
	Malignant tumor	13
Sort of ARA	BP	4
	DMB	8
	BP → DMB	2

Abbreviation: BMI: body mass index; ARA: antiresorptive agent; BP: bisphosphonate; DMB: denosumab; SD: standard deviation.

Table 2 Summary of CT and MRI findings at the center of the lesion and at the surgical margins.

Imaging findings		Center of the lesion	Surgical margin
i) CT			
Osteolysis	(−)	5	26
	Above mandibular canal	1 (1)	2 (2)
	Including mandibular canal	8	0
Separation of sequestrum	(−)	11 (1)	28 (2)
	(+)	3	0
Periosteal reaction	(−)	3 (1)	19 (2)
	Attached-type	2	8
	Gap-type	8	1
	Irregular-type	1	0
Mixed-type Osteosclerosis	(−)	11 (1)	28 (2)
	(+)	3	0
ii) MRI			
T1WI	Low	14 (1)	10 (2)
	Intermediate	0	14
	High	0	4
T2WI	Low	6	12 (2)
	Intermediate	5 (1)	14
	High	3	2
STIR	Low	0	10
	Intermediate	0	16
	High	14 (1)	2 (2)

( ): recurrent cases.
Abbreviation: T1WI: T1 weighted image; T2WI: T2 weighted image; STIR: short TI inversion recovery.

Relationship between MR imaging and histopathological findings

All 14 patients exhibited low signal intensity on T1WI. On T2WI, there were 6 cases of low signal, 5 cases of medium signal, and 3 cases of high signal. STIR images showed high

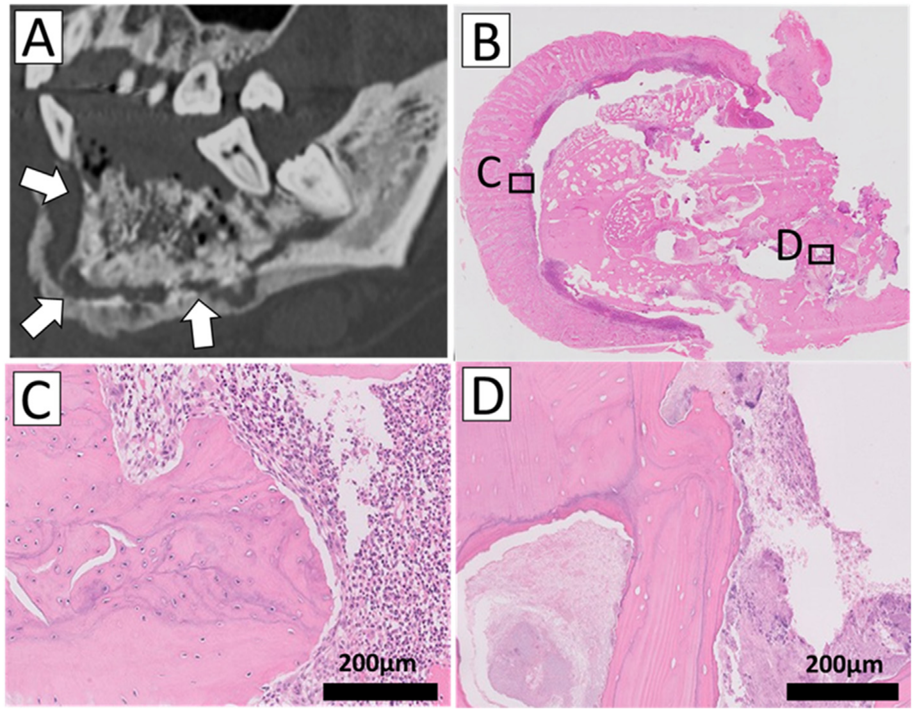

Figure 1 CT and histological findings of the osteonecrosis areas.
A: CT shows a radiolucent area around the osteonecrotic area (arrows). B: Histological image. C: Enlarged image of part B. Inflammatory cell infiltration, mainly by neutrophils, is observed in the gap. D: Enlarged image of part B. Osteocytes disappear from the cortical bone, and necrotic tissue is observed in the medullary cavity.
CT, computed tomography.

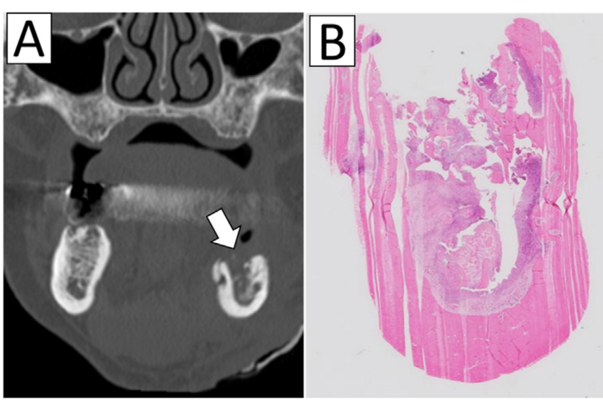

Figure 2 CT and histological findings of the osteolytic areas.
A: CT findings. Marked bone resorption is observed compared to the healthy side (arrow). B: Histological findings in the same area. The medullary cavity is filled with necrotic tissue.
CT, computed tomography.

signal intensity in all cases, not just low or medium signal intensity (Table 2).

The high-signal images on STIR showed either entirely high-signal lesions or a mixture of high, medium, and low signals. Lesions that were entirely high signal on STIR corresponded histologically to necrosis and inflammation

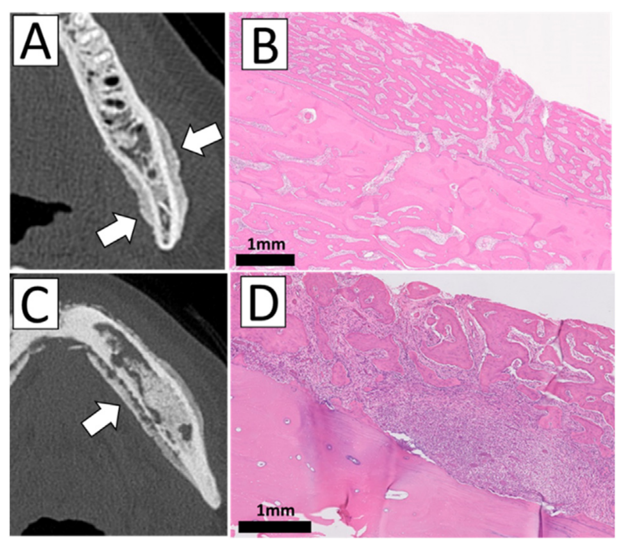

Figure 3 CT and histological findings of the periosteal reaction areas.
A, B: Attached-type periosteal reactions. New trabecular bone is formed that is continuous with the cortical bone (arrows). C, D: Gap-type periosteal reactions. A gap is noted between the cortical and new bones on CT (arrow), and inflammatory cell infiltration is observed.
CT, computed tomography.

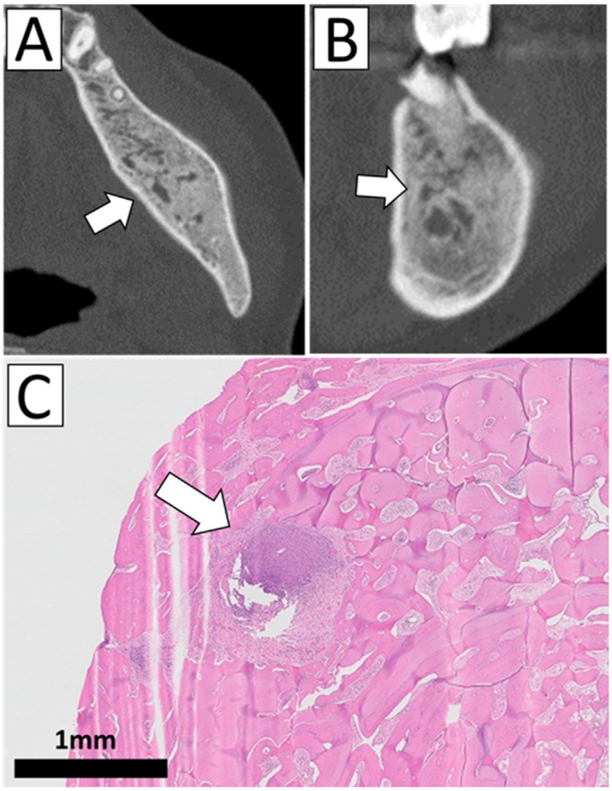

Figure 4 CT and histological findings of the mixed-type osteosclerosis areas.
A, B: Multiple small radiolucent areas are mixed in the sclerotic bone (arrow). C: Small inflammatory foci scattered within the marked sclerotic area of the medullary cavity (arrow).
CT, computed tomography.

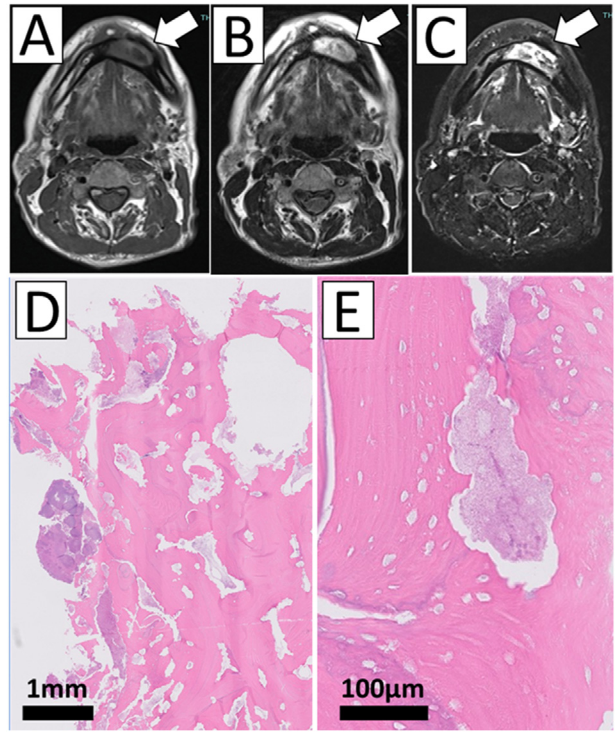

Figure 5 MRI and histopathological findings.
A-C: MRI findings. The entire lesion shows a low signal on T1WI (A) and a high signal on T2WI (B) and STIR (C) (arrows). D, E: Histopathological findings in the same area. The medullary cavity and cortical bone were necrotic, and the osteocytes had disappeared.
CT, computed tomography; MRI, magnetic resonance imaging.

occupying nearly the entire medullary cavity (Fig. 5). Lesions showing a mixture of low-medium and high signal images on STIR exhibited necrotic or inflamed areas as well as regions appearing normal on histopathology (Fig. 6).

Thus, the characteristic MRI findings of MRONJ include low signal on T1WI and high or mixed signals on STIR, which correspond to histopathological features.

Imaging and histological findings of the surgical margin

CT and MRI findings of the resection margins were evaluated. On CT, osteolysis was observed at the margins of two sides, and both of these sides experienced recurrence. Attached-type periosteal reaction was noted on eight margins, and gap-type periosteal reaction was found on one margin; however, no recurrences were observed in these cases. In terms of MRI, various signal intensities were noted on T1WI and T2WI, but in two margins, residual areas of high signal were present on STIR, and both cases experienced recurrence (Fig. 7) (Table 2).

The histological findings of the resection margins are summarized in Table 3. Overall, 12 margins had no evidence of necrotic bone or inflammatory cell infiltration, nine margins with no evidence of necrotic bone but with inflammatory cell infiltration, and seven margins with both necrotic bone and inflammatory cell infiltration (Fig. 8). Both relapsed margins showed signs of necrotic bone and inflammatory cell infiltration.

Discussion

This study is the first report that has demonstrated detailed comparison of both CT and MRI imaging with histopathological findings in patients with MRONJ.

While conservative treatment was previously recommended for MRONJ, recent reports have increasingly highlighted the effectiveness of surgical intervention. Hayashida et al. conducted a multicenter study of 361 MRONJ cases and demonstrated, through propensity score matching analysis, that surgical treatment achieved a significantly higher cure rate than conservative approaches.[6] The 2022 AAOMS position paper also acknowledges that both conservative and surgical treatments are viable options.[1] The 2023 Japanese Society of Oral and Maxillofacial Surgeons position paper states that surgical treatment is the first-line treatment and that conservative treatment should be used for patients who cannot undergo surgery.[14]

Although surgical treatment for MRONJ is becoming more common, there are limited reports that provide detailed examination of bone resection techniques. Rupel et al.,[4] Fliefel et al.,[5] and Hayashida et al.[6] reported that

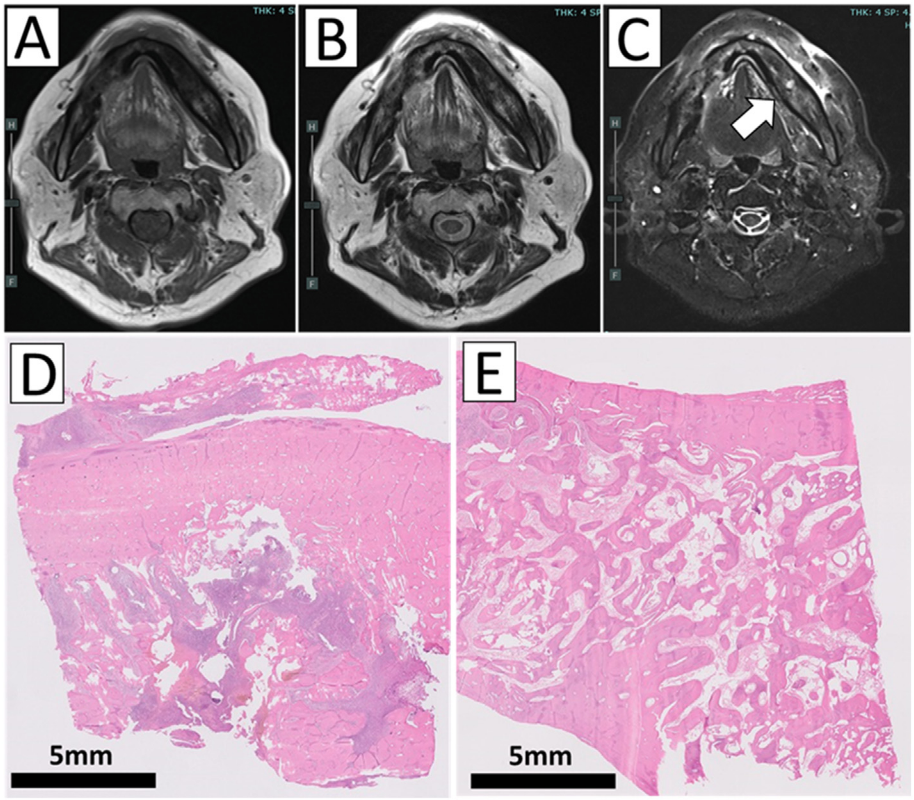

Figure 6 MRI findings and histological findings.
This case differs from the one shown in Fig. 5. A-C: MRI findings. The lesion shows low signal intensity on T1WI (A) and T2WI (B) images. On STIR (C), areas of high signal intensity are mixed with areas of medium signal intensity (arrow). Histologically, areas showing necrotic tissue and inflammation within the medullary cavity (D) and areas showing bone sclerosis without inflammation (E) are noted.
MRI, magnetic resonance imaging; T1WI, T1-weighted images; T2WI, T2-weighted images; STIR, short tau inversion recovery.

extensive surgery, which involves removing surrounding bone, has better outcomes than conservative surgery, which focuses only on removing necrotic bone. However, the extent of bone resection required around necrotic bone remains unclear. Recently, our research showed that cases with residual osteolysis, gap-type or irregular-type periosteal reactions, and mixed osteosclerosis had significantly higher recurrence rates. Thus, we consider that including these areas in the surgical resection range is recommended.[10] However, in cases where abnormalities are not detectable via CT, determining the lesion's extent using CT alone is challenging.

The incidence of non-osteolytic MRONJ, where CT do not reveal osteolysis, is increasing.[10–13] Interventional studies have shown that DMB is more effective than BP in preventing skeletal-related events associated with bone metastases and multiple myeloma.[15] As a result, high-dose DMB is being administered more frequently than high-dose BP in patients with malignancies. Our recent study showed that DMB strongly suppresses local expression of bone resorption-related genes in resected bone tissue and has a stronger inhibitory effect on osteoclasts compared to that of BP, leading to a higher incidence of non-osteolytic MRONJ in patients receiving DMB.[16] Sakamoto et al. identified non-osteolytic MRONJ in four out of 18 patients, all of whom had received high-dose DMB.[12] Similarly, Kojima et al. reported non-osteolytic MRONJ in eight out of 55 patients, with all cases involving high-dose DMB.[13] At our institution, non-osteolytic MRONJ was observed in 11 out of 206 patients, all of whom had been treated with DMB, and 10 of these cases involved patients with malignancies receiving high-dose DMB.[10] We believe that in patients receiving high-dose DMB, bone metabolism is significantly suppressed, resulting in osteomyelitis or osteonecrosis without osteoclast activation, which contributes to the development of non-osteolytic MRONJ. In such cases, the extent of the lesion cannot be determined via CT, making other modality an essential tool for preoperative planning.

Several studies have reported on MRI findings in MRONJ. Wongratwanich et al. reviewed various imaging findings in relation to the early diagnosis of MRONJ.[17] They reported that in stage 0 MRONJ, where there is no exposed bone, the lesion shows low signal on T1WI and high signal on T2WI and STIR, and that when exposed bone or bone necrosis occurs, the lesion shows low or intermediate signal on T1WI, T2WI and STIR. They also state that the area around necrotic bone shows high signal on T2WI, and that abnormal signals are seen in STIR in approximately 80 % of cases in the joint head. In a review by Khan et al., it is also stated that MRI is excellent for evaluating changes in the bone marrow in the early stages of MRONJ and changes in the soft tissue surrounding the bone necrosis site.[18] They reported that one

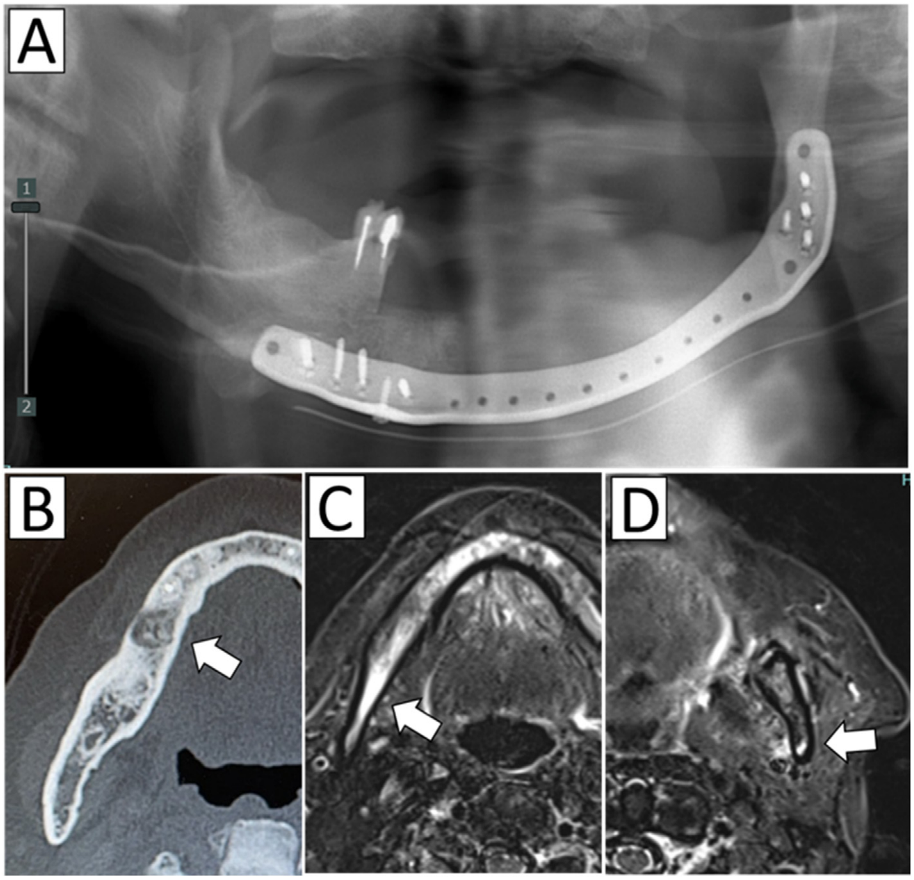

Figure 7 Imaging findings in a case where recurrence is observed from both the anterior and posterior margins.
Pain and swelling were localized in the left mandible; therefore, a segmental resection was performed from the right canine to the left mandibular notch (A). Osteolysis is noted in the right molar region (arrow) and a high STIR signal is noted from the right molar to the mandibular ramus region (arrow). However, these are not included in the area of resection (B, C). A high STIR signal is observed in the posterior margin of the left mandibular ramus; however, this is not included in the area of resection (D).
STIR, short tau inversion recovery.

Table 3 Histopathological findings at the surgical margins.

Necrotic bone	Imflammatory cell infiltration	Number of margins
(−)	(−)	12
(−)	(+)	9
(+)	(−)	0
(+)	(+)	7 (2)

( ): Recurrent cases.

of the most consistent and earliest MRI findings is a decrease of bone marrow signal intensity on T1WI, and in advanced disease, the signal intensity of exposed and necrotic bone decreases on T2-weighted and STIR images, while the signal intensity of unaffected diseased bone increases. These reports show that MRI can detect the presence of MRONJ at an early stage because it reflects changes in the bone marrow; however, whether it can accurately determine the extent of MRONJ remains unclear. Stockmann et al. also stated that despite MRI's high detectability, the relevance of MRI for the preoperative assessment of the extent of MRONJ lesions is limited.[19]

The purpose of this study was not to detect MRONJ but to clarify whether the determination of the extent of the lesion was possible using CT or MRI. As mentioned above, in non-osteolytic MRONJ, no abnormal findings are observed on panoramic radiography or CT scans; therefore, determining the extent of bone resection using other modalities such as preoperative MRI is necessary. As a preliminary study for this purpose, we compared the MRI and histopathological findings. The results of this study are as follows: On T1WI, MRONJ lesions showed a low signal. However, low signal on T1WI was not exclusive to MRONJ lesions, as areas of bone sclerosis also exhibited low signal. Since healing was achieved even when low-signal areas remained in the resection margin, T1WI low signal alone did not become a criterion for determining bone resection extent. T2WI images presented a range of signal intensities (low, medium, and high), which also proved unsuitable for determining resection boundaries. In contrast, all MRONJ lesions contained high signal on STIR images, with some showing homogeneous high signals and others displaying a mixture of high signals and low-medium signals.

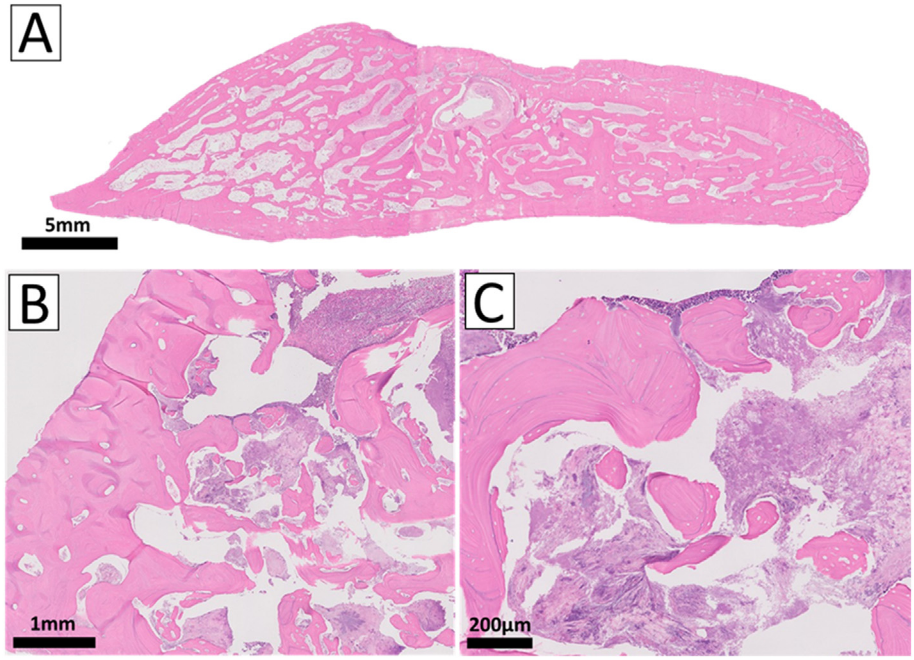

Figure 8 Histopathological findings of the resection margins.
A: A case with good treatment outcomes. Margins showed marked osteosclerosis of the medullary cavity; however, there is no evidence of osteomyelitis or necrotic bone formation. B, C: A case of recurrence. The margins showed necrotic tissue in the medullary cavity, and the osteocytes have disappeared.

Histopathologically, areas of osteomyelitis corresponded to high STIR signals, while areas of osteosclerosis without osteomyelitis displayed medium to low signals. Therefore, STIR images may accurately reflect the inflammatory extent in MRONJ. Furthermore, recurrence was observed in a case where the resection margins showed high signal on STIR, indicating that these high-signal areas should be included in the resection range. Regarding the image findings our study confirmed that osteonecrosis and osteomyelitis were present in areas of osteolysis, gap-type or irregular-type periosteal reactions, and mixed-type osteosclerosis on CT, as well as in high-signal regions on STIR images. Thus, we consider that these areas should be included in the extent of resection.

When the histopathological findings of the resection margins were observed, no recurrences were noted in the 12 margins where there was no necrotic bone or osteomyelitis in the resection margins. In contrast, there were 16 margins in which inflammatory cell infiltration was observed in the resected margin, that is, where the area of osteomyelitis remained. Of the nine margins in which osteomyelitis remained but no necrotic bone was observed, healing was achieved; however, in seven margins where both osteomyelitis and necrotic bone were observed, recurrence occurred in two margins. In actual surgery, after performing a segmental resection, the resection section is observed, and if there is a change in color tone or other abnormal findings, additional bone removal is performed. Accordingly, the actual resection margin does not necessarily match the margin of the tissue specimen; therefore, although it is not possible state with certainty, but it was suggested that some residual osteomyelitis does not immediately lead to recurrence; however, residual necrotic bone may lead to recurrence.

In summary, we compared the CT and MRI findings with the histopathological findings of patients with MRONJ who underwent segmental mandibulectomy. As a result, osteolysis, gap—or irregular-type periosteal reaction, mixed-type osteosclerosis on CT, and high signals of STIR images on MRI were thought to reflect the infection or bone necrosis areas, and were recommended to be included in the extent of resection.

This study has several limitations. First, it is a retrospective research of a small sample size, making it difficult to generalize the findings. Second, as mentioned above, it is possible that the histopathological specimen of the margin may not necessarily indicate the true resection margin. Histopathological examination of additionally resected bone materials should be performed to evaluate the true resection margins. Additionally, with only one case of recurrence, statistical analysis of the relationship between margin findings and recurrence was not feasible. Nevertheless, this study is the first research to examine the relationship between CT, MRI, and histopathological findings in MRONJ in detail and to propose a method for determining the extent of bone resection based on MRI findings. Future research should expand the number of cases to further investigate these findings.

Declaration of competing interest

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

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