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Original Article

A preliminary clinical study of segmental mandibulectomy on medication-related osteonecrosis of the jaw

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Abstract *Background/purpose:* Recently, many reports have recommended surgical treatment for medication-related osteonecrosis of the jaw (MRONJ). However, MRONJ is more likely to occur in older patients with poor general condition and often necessitates extensive surgery, such as segmental mandibulectomy. The purpose of this study was to investigate treatment outcome of patients with MRONJ undergoing segmental mandibulectomy.
Materials and methods: This retrospective study included 137 patients with medication-related osteonecrosis of the lower jaw who underwent surgical treatment at our hospital between 2011 and 2019. A total of 168 surgeries (155 marginal mandibulectomies and 13 segmental mandibulectomies) were performed. The relationship between clinical and imaging factors and the treatment outcome was investigated in the segmental mandibulectomy cases.
Results: Preoperative computed tomography (CT) showed osteolytic lesions in 13/13, periosteal reaction (PR) in 12/13, and osteosclerosis in 12/13 cases of segmental mandibulectomy. On postoperative CT, no residual osteolytic lesion and PR were noted, and 9 cases showed osteosclerosis. Twelve patients (92.3%) undergoing segmental mandibulectomy had complete healing, whereas the cure rate of those undergoing marginal mandibulectomy was 104/155 (67.1%). One patient with relapse after segmental mandibulectomy showed healing after an additional resection. In the patients who underwent segmental mandibulectomy, clinical symptoms, such as pain and purulent discharge, disappeared, and oral intake was possible.
Conclusion: Segmental mandibulectomy is a treatment option for end-of-life care of refractory MRONJ, because it can eliminate clinical symptoms early. When performing segmental

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mandibulectomy, the area of the osteolytic lesion and periosteal reaction needs to be included.

Introduction

Bone modifying agents (BMA), such as bisphosphonate and denosumab, are used as first-line agents to prevent osteoporosis-related fractures and to treat skeletal-related events in malignancies.[1] These drugs have a strong inhibitory effect on bone resorption, but can cause medication-related osteonecrosis of the jaw (MRONJ) as a serious late adverse event. MRONJ may cause excruciating suffering, such as pathologic fracture, fistula formation, chronic pain, and infection. The causes and treatment of MRONJ remain unclear.

Conservative treatment has been recommended as the first-line treatment, but surgical treatment is also an option when conservative treatment fails to produce favorable results.[1,2] In recent years, there have been many reports recommending surgical treatment of MRONJ. However, MRONJ is more likely to occur in older patients or patients with poor general condition and often necessitates extensive surgery, such as segmental mandibulectomy. There are few reports on segmental mandibulectomy of mandibular MRONJ.[3] Is segmental mandibulectomy for MRONJ an overtreatment? The purpose of this study was to investigate the treatment outcomes of patients with MRONJ undergoing segmental mandibulectomy.

Materials and methods

We have followed the tenets of the Helsinki Declaration in this investigation. This study was approved by the Institutional Review Board of our hospital (#21021509). The research protocol and guaranteed opportunity to opt-out were posted on the hospital's official website. The study was not registered as this was a retrospective observational study.

Patients

A total of 137 patients with medication-related osteonecrosis of the lower jaw who underwent surgical treatment at our hospital between 2011 and 2019 were enrolled in the study. We identified a total of 168 surgeries: 155 marginal mandibulectomies and 13 segmental mandibulectomies. Sixteen patients underwent two to three mandibulectomies, and eight patients underwent one to two mandibulectomies followed by mandibular segmental resection. The comparison between segmental and marginal mandibulectomies should be made at the first operation, but because segmental mandibulectomies are often performed in patients with a poor prognosis of marginal mandibulectomies, the total number of each operation was compared.

Methods

We examined age, sex, primary disease, type of BMA, administration period of a BMA, corticosteroid administration, presence of diabetes, stage of MRONJ, surgical method, and treatment outcome.

For patients who underwent segmental mandibulectomy, we evaluated the duration from the first visit to surgery (days), inferior alveolar nerve palsy, cutaneous fistula, pathological fracture, and dietary form before surgery and after discharge. Osteolytic lesions, periosteal reaction (PR), osteosclerosis, thickening of the cortical bone of the mandible (TCB), and thickening of the mandibular canal wall (TCW) were also examined using pre- and postoperative computed tomography (CT). TCB and TCW were considered positive if they were enlarged compared to the opposite side. Interpretation of CT images was performed by an oral surgeon blinded to the clinical course.

Statistical analysis

All statistical analyses were performed using SPSS software (version 24.0; Japan IBM Co., Ltd., Tokyo, Japan). The correlation between each variable and surgical method was analyzed using the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables. A two-tailed probability of less than 0.05 was considered significant.

Data availability

The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

Results

The demographic characteristics of the 137 patients are summarized in Table 1. There were 104 women and 33 men, with a median age of 79 years. The primary disease was osteoporosis in 87 patients and malignant tumors in 50 patients. The initial surgical method was marginal mandibulectomy in 132 patients and segmental mandibulectomy in five patients. The final cure rate was 111/137 (81.0%), including cases with multiple surgeries.

A total of 168 surgeries were performed, of which 155 were marginal mandibulectomies, and 13 were segmental

Table 1 Demographic factors of 137 patients with mandibular MRONJ undergoing surgery.

Factor	Category	Number of patients/Median (minimum—maximum)
Age (years)		79 (47—95)
Sex	Male	33
	Female	104
Primary disease	Osteoporosis	87
	Malignant tumor	50
Type of BMA	BP	91
	Dmab	46

AbbreviationsBP, bisphosphonate; Dmab, denosumab; BMA, bone modifying agents; MRONJ, medication-related osteonecrosis of the jaw

mandibulectomies. Segmental mandibulectomy was indicated in patients with a more advanced stage than in those with marginal mandibulectomy. Twelve of 13 patients (92.3%) who underwent segmental mandibulectomy achieved complete healing, whereas the cure rate of those undergoing marginal mandibulectomy was 104/155 (67.1%) (Table 2).

Non-healing case of segmental mandibulectomy: One patient, a 67-year-old man with a history of prostate cancer bone metastasis, relapsed after his segmental mandibulectomy. He was initially referred to our hospital because of cellulitis of the neck caused by mandibular medication-related osteonecrosis. The CT scan revealed extended osteolysis and osteosclerosis. After eliminating the inflammation by drainage surgery, the patient underwent segmental mandibulectomy. Postoperative CT showed that the cortical bone around the extraction socket remained. Eight months later, MRONJ recurred in the remaining bone around the socket and led to additional resection. Eighteen months after the last surgery, there was no recurrence of MRONJ (Fig. 1).

Of the 13 patients who underwent segmental mandibular osteotomy, only two did so as initial treatment. Conservative therapy was selected as the initial treatment, but segmental mandibulectomy was performed due to poor outcomes in three cases. Marginal mandibulectomy was performed as an initial treatment; however, segmental mandibulectomies were performed later due to the recurrence of symptoms in eight cases. The time from the first visit to surgery in the 13 patients who underwent segmental mandibulectomy ranged from 17 to 938 days (median, 246 days). Inferior alveolar nerve palsy (8/13), cutaneous fistula (8/13), and pathological fracture (3/13) were observed (Table 3). Preoperative CT revealed osteolytic lesions in 13 patients, PR in ten patients, osteosclerosis in 12 patients, TCB in eight patients, and TCW in 11 patients. In the postoperative CT, we did not observe any residual osteolytic lesions or PR (Fig. 2). However, two TCBs, four TCWs, and nine osteosclerosis patients remained (Table 4, Fig. 3). The dietary patterns before and after surgery worsened in some cases from solid to paste (4/13) and from paste to liquid (1/13) but improved in others from paste to solid (2/13) and from liquid to paste (1/13). Malocclusion worsened dietary patterns in some cases but improved in others due to pain relief from surgery (Table 3).

In six cases, reconstruction was performed to prevent deterioration of respiratory status and facial appearance.

Table 2 Univariate analysis comparing marginal mandibulectomy and segmental mandibulectomy (N = 168).

		Marginal mandibulectomy (N = 155)	Segmental mandibulectomy (N = 13)	P
Age (Years)		47-95 (78)	48-91 (79)	0.912
Sex	Male	40	5	0.322
	Female	115	8	
Primary disease	Malignant tumor	62	7	0.330
	Osteoporosis	93	6	
Type of BMA	BP	102	8	0.756
	Dmab	53	5	
Administration period of BMA	≧4 years	62	3	0.478
	<4 years	85	9	
	Unknown	8	1	
Corticosteroid	-	119	10	0.990
	+	36	3	
Diabetes	-	128	10	0.609
	+	27	3	
MRONJ Stage	Stage 1	1	0	0.019
	Stage 2	115	5	
	Stage 3	39	8	
Treatment outcome	Healing	104	12	0.059
	Non-Healing	51	1	

AbbreviationsBMA, bone modifying agents; BP, bisphosphonates; Dmab, denosumab; MRONJ, medication-related osteonecrosis of the jaw

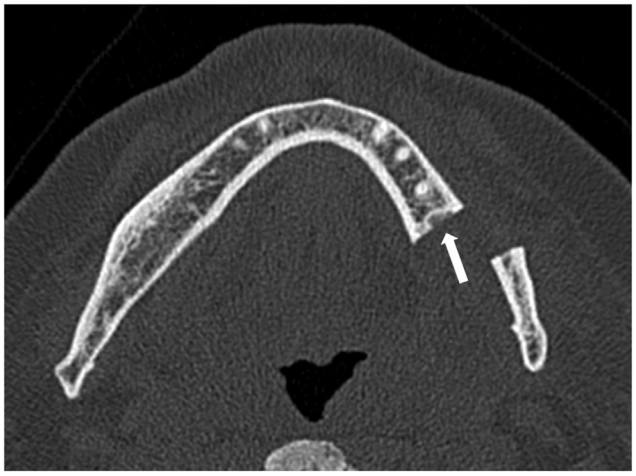

Figure 1 Preoperative CT findings. Case 2: Cortical bone around the extraction socket remained (white arrow).

Free fibula flap transplantation was performed in two cases, and reconstruction with a metal plate was performed in four cases. The other patients did not undergo reconstructive surgery because of old age, poor general condition, or the patient's will (Fig. 4). In addition, only one of the reconstructed cases showed improvement in dietary patterns, and reconstruction itself did not necessarily improve dietary habits (Table 3).

Discussion

A position paper of the American Association of Oral and Maxillofacial Surgeons (AAOMS) and the Guidelines of Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) state that conservative therapies, such as administration of antibiotics and gargling with antiseptic mouthwash, are the first choice of treatments for MRONJ.[1,2] Surgical therapy can be performed for refractory cases. On the contrary, many investigators have reported the superiority of surgical therapy over conservative therapy.[4—6] In a multi-center observational study, we previously reported that the treatment outcomes of patients undergoing surgery were significantly better than those of patients undergoing conservative therapy using propensity score matching analysis.[7]

The quality of life (QOL) of patients with MRONJ decreases as the MRONJ stage progresses.[8] The prognosis for life may not be favorable because many patients with MRONJ are older or have cancer with distant metastases. Therefore, when choosing a treatment for MRONJ, it is necessary to consider the cure of the disease and the QOL of patients. Persistent pain and pus discharge during the remaining survival period can be very distressing for the patient. We believe that "terminal care" for patients with MRONJ, which aims to maintain and improve QOL by relieving patients' physical and mental pain, is necessary to choose the treatment method. For this reason, segmental mandibulectomy should be included as an option in the treatment of older patients and cancer-bearing patients, as it is more likely to be a cure. In 13 of our included patients, segmental mandibulectomy was performed in consideration of the QOL, including the unbearable pain and the unimproved pus drainage, and the patient's request to have surgery.

Hanasono et al. reported no recurrence in 13 patients with MRONJ who underwent segmental mandibulectomy and free flap reconstruction.[3] In the present study, we focused on segmental mandibulectomy for MRONJ. The results showed that segmental mandibulectomy had a higher healing rate than marginal mandibulectomy. There was only one recurrence in which the cortical bone of the extraction socket of a tooth was left behind. That patient was cured by additional resection. Of course, since segmental mandibulectomy is highly invasive, marginal mandibulectomy should be performed if the lesion can be controlled. However, conservative therapy and marginal mandibulectomy were performed for more than one year, but no cure was obtained; segmental mandibulectomy was eventually performed in some cases. Therefore, it is necessary to consider the indications for conservative therapy and marginal mandibulectomy.

Bone reconstruction is generally performed because segmental mandibulectomy breaks the continuity of the mandible, resulting in facial deformity and malocclusion. In this study, free fibula flaps were transplanted in two cases, and reconstruction plates were transplanted in four cases, but reconstruction surgery was not performed in the remaining seven cases. Reconstruction was performed in cases of segmental mandibulectomy, including the anterior part of the mandible. All cases without reconstruction were cases of segmental mandibulectomy of the posterior part of the mandible. Reconstructive surgery increases the surgical invasion and poses a risk of postoperative infection and reoperation. Therefore, reconstruction was not performed in seven cases of resection only in the posterior part of the mandible after consultation with the patient. If bone reconstruction is not carried out, malocclusion may lead to masticatory disturbance. In this study, some patients had a worse diet after surgery than before surgery. However, others had a better diet postoperatively than before surgery, and all patients could eat after surgery. The improvement in feeding status despite segmental resection may be due to the relief from symptoms such as pain. As mentioned above, we believe that segmental mandibulectomy is one of the treatment options for patients with intolerable physical and mental pain or persistent discomfort due to pus discharge despite conservative therapy or marginal mandibulectomy.

The resection range for segmental mandibulectomy was also examined. Marx et al. recommend performing resection until some bone marrow remains, bone color is normal, and bleeding is noted.[9] Nocini et al. reviewed the pathological characteristics of patients who underwent segmental mandibulectomy and found that only one patient had a residual lesion in the resection specimen. The patient had a recurrence of MRONJ within six months.[10] Similarly, Bedogni et al. analyzed 32 jaws resected for MRONJ and reported that the presence of osteomyelitis at the pathological resection edge was a strong predictor of BRONJ recurrence.[11] However, this is only a diagnosis of pathological specimens and intraoperative findings and not a preoperative diagnosis. We examined factors for

Table 3 Summary of patients who underwent segmental mandibulectomy (clinical findings).

No.	Age	Sex	Stage	Primary disease	Treatment outcome	Resection area	Duration from the first visit to surgery (days)	Dietary form before surgery	Dietary form after surgery	Inferior alveolar nerve palsy	Cutaneous fistula	Pathological fracture	Reconstruction
1	84	Female	2	O	Healing	Molar	17	Solid	Paste	+	+	−	−
2	67	Male	3	MT	Non-healing	Molar	28	Solid	Paste	−	+	−	−
3	78	Female	3	O	Healing	Molar	62	Paste	Paste	+	−	−	Reconstruction plate
4	50	Female	2	MT	Healing	Molar	938	Solid	Paste	+	−	−	Fibula
5	81	Male	3	MT	Healing	Molar	495	Paste	Solid	−	−	−	−
6	84	Female	2	O	Healing	Molar, front tooth	110	Paste	Liquid	+	−	−	Reconstruction plate
7	51	Female	2	MT	Healing	Molar, front tooth	853	Solid	Solid	+	+	+	Reconstruction plate
8	83	Male	3	MT	Healing	Molar	374	Paste	Paste	+	+	−	−
9	48	Female	3	MT	Healing	Molar, front tooth	208	Paste	Paste	−	+	−	Fibula
10	77	Female	3	O	Healing	Molar	246	Paste	Solid	+	+	+	−
11	89	Male	3	O	Healing	Molar	283	Solid	Paste	−	+	−	−
12	91	Female	2	O	Healing	Molar	143	Paste	Paste	+	+	+	−
13	79	Male	3	MT	Healing	Molar, front tooth	319	Liquid	Paste	−	−	−	Reconstruction plate

AbbreviationsO, osteoporosis; MT, malignant tumor

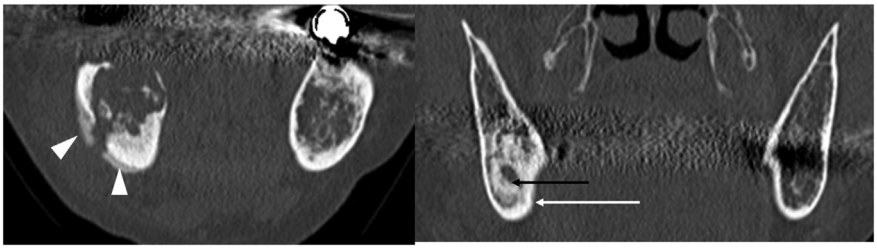

Figure 2 Preoperative CT findings. Left: Case 1: Extensive osteolytic lesion and PR (white arrow), and osteosclerosis in the right mandible. Right: Case 3: Thickening of cortical bone of mandibular (white arrow) and thickening of mandibular canal wall (black arrow).

Table 4 Summary of patients who underwent segmental mandibulectomy (CT findings).

No.	CT findings before surgery					CT findings after surgery				
	Osteolytic lesion	PR	Osteosclerosis	TCB	TCW	Osteolytic lesion	PR	Osteosclerosis	TCB	TCW
1	+	+	+	+	+	−	−	+	+	−
2	+	−	+	−	+	−	−	+	−	+
3	+	+	+	+	+	−	−	+	−	−
4	+	+	+	+	+	−	−	+	−	−
5	+	+	+	−	+	−	−	−	−	−
6	+	+	+	+	+	−	−	+	−	−
7	+	+	+	−	−	−	−	+	−	−
8	+	+	+	+	+	−	−	+	+	+
9	+	+	+	+	+	−	−	−	−	−
10	+	−	+	+	+	−	−	−	−	−
11	+	+	+	+	+	−	−	+	−	+
12	+	−	+	−	+	−	−	+	−	+
13	+	+	−	−	−	−	−	−	−	−

Abbreviations: CT, computed tomography; PR, periosteal reaction; TCB, thickening of cortical bone of mandibular; TCW, thickening of mandibular canal wall

Figure 3 Postoperative CT findings. Case 4: Residual osteosclerotic area at the margins of the segmental mandibulectomy (white arrow).

preoperatively assuming the resection range of the segmental mandibulectomy. In this study, we examined osteolytic lesions, PR, osteosclerosis, TCB, and TCW. Osteolytic lesions and PR can be adequately removed by segmental mandibulectomy. Soutome et al. reported that PR should also be considered when determining the extent of osteotomy.[12] Segmental mandibulectomy seemed more likely to eliminate osteolytic lesions and PR than marginal mandibulectomy.

In nine cases, the osteosclerotic lesion remained, but it was not always necessary to include osteosclerosis in the resection field since healing was obtained. We also hypothesized that enlargement of the cortical bone is involved in blood flow disorder when considering blood flow from the periosteal and inferior alveolar arteries. However, there is no apparent relationship between the residual TCB of TCW and the cure rate. Finally, we believe that it is necessary to resect osteolytic lesions and PR when performing segmental mandibulectomy for medication-related osteonecrosis of the mandible.

This study has some limitations. First, this is a retrospective case series of a small number of patients; therefore, it is difficult to generalize the results. Second, because we did not conduct a detailed study of QOL, it was not possible to clarify whether segmental mandibulectomy contributed to improving the patient's QOL. In the future, we would like to examine the decision on the indication for segmental mandibulectomy and verify its effectiveness in a larger number of cases.

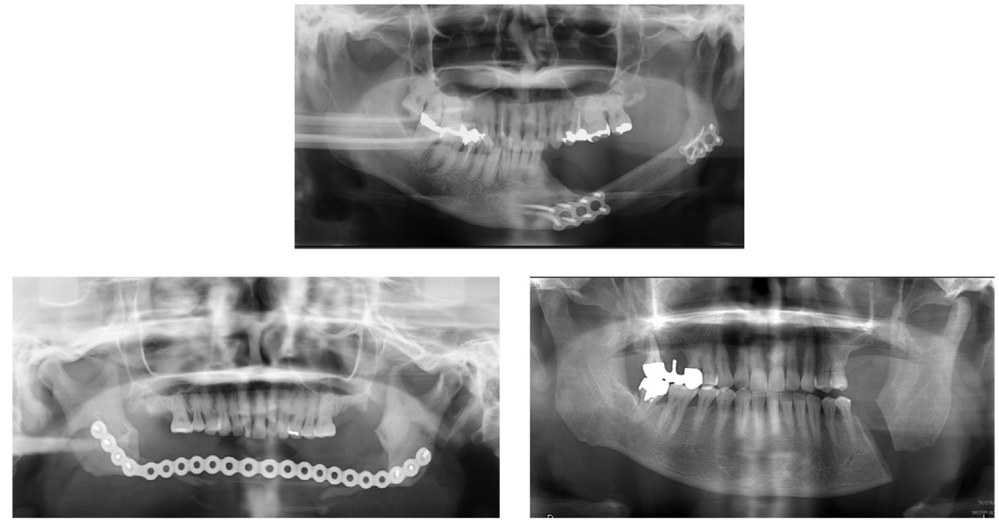

Figure 4 Reconstruction after segmental mandibulectomy. Upper central: free fibula flap transplantation, Lower left: reconstruction with a metal plate, Lower right: no reconstruction

Declaration of competing interest

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

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References

1. Yarom N, Shapiro CL, Peterson DE, et al. Medication-related osteonecrosis of the jaw: MASCC/ISOO/ASCO clinical practice guideline. *J Clin Oncol* 2019;37:2270—90.
2. Ruggiero SL, Dodson TB, Fantasia J, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw–2014 update. *J Oral Maxillofac Surg* 2014;72:1938—56.
3. Hanasono MM, Militsakh ON, Richmon JD, Rosenthal EL, Wax MK. Mandibulectomy and free flap reconstruction for bisphosphonate-related osteonecrosis of the jaws. *JAMA Otolaryngol Head Neck Surg* 2013;139:1135—42.
4. Rupel K, Ottaviani G, Gobbo M, et al. A systematic review of therapeutical approaches in bisphosphonates-related osteonecrosis of the jaw (BRONJ). *Oral Oncol* 2014;50:1049—57.
5. Fliefel R, Tröltzsch M, Kühnisch J, Ehrenfeld M, Otto S. Treatment strategies and outcomes of bisphosphonate-related osteonecrosis of the jaw (BRONJ) with characterization of patients: a systematic review. *Int J Oral Maxillofac Surg* 2015;44:568—85.
6. Khan AA, Morrison A, Hanley DA, et al. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. *J Bone Miner Res* 2015;30:3—23.
7. Hayashida S, Soutome S, Yanamoto S, et al. Evaluation of the treatment strategies for medication-related osteonecrosis of the jaws (MRONJ) and the factors affecting treatment outcome: a multicenter retrospective study with propensity score matching analysis. *J Bone Miner Res* 2017;32:2022—9.
8. Miksad RA, Lai KC, Dodson TB, et al. Quality of life implications of bisphosphonate-associated osteonecrosis of the jaw. *Oncol* 2011;16:121—32.
9. Marx RE. Reconstruction of defects caused by bisphosphonate-induced osteonecrosis of the jaws. *J Oral Maxillofac Surg* 2009;67:107—19.
10. Nocini PF, Saia G, Bettini G, et al. Vascularized fibula flap reconstruction of the mandible in bisphosphonate-related osteonecrosis. *Eur J Surg Oncol* 2009;35:373—9.
11. Bedogni A, Saia G, Bettini G, et al. Long-term outcomes of surgical resection of the jaws in cancer patients with bisphosphonate-related osteonecrosis. *Oral Oncol* 2011;47:420—4.
12. Soutome S, Yanamoto S, Sumi M, et al. Effect of periosteal reaction in medication-related osteonecrosis of the jaw on treatment outcome after surgery. *J Bone Miner Metabol* 2021;39:302—10.