

Recurrence - Related Factors of Medication Related Osteonecrosis of the Jaw (MRONJ) ; a Retrospective study

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ABSTRACT

Recurrence - Related Factors of Medication Related Osteonecrosis of the Jaw (MRONJ) ; a Retrospective study

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Duration of administration of related medications, presence of bacterial infections in necrotic areas, and methods of treatment have been suggested as factors related to the recurrence of MRONJ. The purpose of this study was to investigate recurrence risk factors in patients who had undergone surgical treatment. The recurrence rate was statistically significant when the teeth affected by alveolar bone necrosis were removed together. When comparing patients who received post-operative antibiotic treatment, recurrence was significantly reduced. Comprehensive surgical approaches, including the extraction of adjacent teeth during surgery, and appropriate post-operative antibiotic therapy can be effective strategies for reducing the recurrence rate of MRONJ.

Key words : MRONJ, Bisphosphonate, Recurrence, Drug-holiday

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I . Introduction

The clinical concept of Medication-related osteonecrosis of the jaw (MRONJ) was introduced in 2007 by The American Association of Oral and Maxillofacial Surgeons (AAOMS) as Bisphosphonate-related osteonecrosis of the jaw (BRONJ), marking the initiation of a systematic approach. Subsequently, with the addition of antiresorptive agents and antiangiogenic medications, the term was updated to MRONJ¹⁾. In 2022, further updates were presented, focusing on the use of antiresorptive agents in cancer patients and new osteoporosis drugs such as Romosozumab.

MRONJ should be distinguished from other forms of osteonecrosis of the jaw (ONJ) and confirmed through patient history and clinical examinations. Establishing the diagnosis of MRONJ requires the following three clinical criteria²⁾.

- 1) History of receiving or currently receiving anti-resorptive agents alone or in conjunction with immune modulators or antiangiogenic medications, or a history of prior use.
- 2) Exposed or non-exposed bone that can be probed through intraoral or extraoral fistulas persisting for more than 8 weeks in the maxillofacial region.
- 3) Absence of a history of radiation therapy to the jaw or presence of metastatic disease in the jaw.

MRONJ is not a commonly occurring condition but rather a serious disorder characterized by necrosis of the maxilla and mandible bones. It is known to significantly impact patients' quality of life³⁾.

The risk factors for this condition can be categorized into systemic factors and local factors. Systemic factors include the duration of medication use, steroid use, age, diabetes, and genetic factors. Local factors encompass a history of invasive intraoral surgery, mucosal thickness, and periodontal conditions^{4,5)}.

For early-stage MRONJ patients, conservative treatments such as pain management, antibiotics, and oral hygiene measures are recommended. The surgical goal is to remove necrotic bone tissue and prevent further progression^{6,7)}.

Research on patients experiencing recurrence after surgical intervention has been relatively limited. Some previous studies have explored factors such as the duration of medication use, bacterial infections, and surgical techniques as potential contributors to recurrence^{8,9)}. Therefore, it is necessary to assess the risk factors for MRONJ and consider alternative approaches for patients at high risk of recurrence. The purpose of this study is to investigate the factors influencing recurrence in MRONJ patients who have undergone surgical intervention.

II. Patients and Methods

1. Patients

The study included patients who visited the Department of Oral and Maxillofacial Surgery at Chonnam National University Hospital and underwent surgical intervention from January 2011 to Decem-

ber 2020. Among a total of 362 patients, those who had been followed up for a minimum of 4 weeks were considered eligible for this study, resulting in a final cohort of 331 patients.

2. Methods

(1) Medical records

The study involved an investigation based on the medical records of the Department of Oral and Maxillofacial Surgery at Chonnam National University Hospital. Patient demographics, including age and gender, MRONJ stage, the type and extent of surgical procedures (Primary closure vs. Secondary healing), the history of bisphosphonates (BPs) and denosumab use, the duration of preoperative medication hold, and the triggering event leading to the initial onset of MRONJ, were examined.

(2) Statistical analysis

All statistical analyses conducted in this study were performed using Rstudio (version 4.2.1; Rstudio, Inc., Boston, MA, USA). The recurrence rate was analyzed using Kaplan-Meier estimation and the Cox proportional hazards model. Use the Kaplan-Meier survival curve to estimate the cumulative probability of event occurrence (recurrence). This is used to estimate the recurrence rate over time. Plot the Kaplan-Meier curve and visualize and interpret the recurrence rate over time. This allows you to understand the likelihood of recurrence at specific time intervals. Compare Kaplan-Meier survival curves to statistically evaluate differences in recurrence rates

between different subgroups. This helps assess the impact of specific factors on the likelihood of recurrence.

(3) Pre-op antibiotic medication vs Post-op antibiotic medication

In the study, the duration of preoperative antibiotic use and postoperative antibiotic use was classified into three groups. Group 1 consisted of patients with a duration of 1 week, Group 2 with 2 weeks, and Group 3 with 3 weeks or more.

(4) Analysis of Bone grinding depth

To accurately determine the depth of bone grinding in a systematic manner, the ruler tool in M6 was primarily employed. The baseline reference point for accurate identification was established by comparing preoperative and postoperative panoramic images of the patient. In most cases, the distance ratio between the length of a single tooth and the Mandible angle on both sides was adjusted and recalculated. However, in cases where the reference point was ambiguous in the imagery, a clear landmark from the same patient was measured and calculated in another location(Fig. 1). The Bone grinding group was divided into three categories: Group 1 had a grinding depth of less than 6mm, Group 2 had a depth exceeding 6mm but less than 10mm, and Group 3 had a depth exceeding 10mm. Tooth root lengths vary different anatomically between the anterior, posterior, and upper and lower jaws, and previous studies have reported a range of 11 to 15 mm as the for Koreans. Considering that the ma-

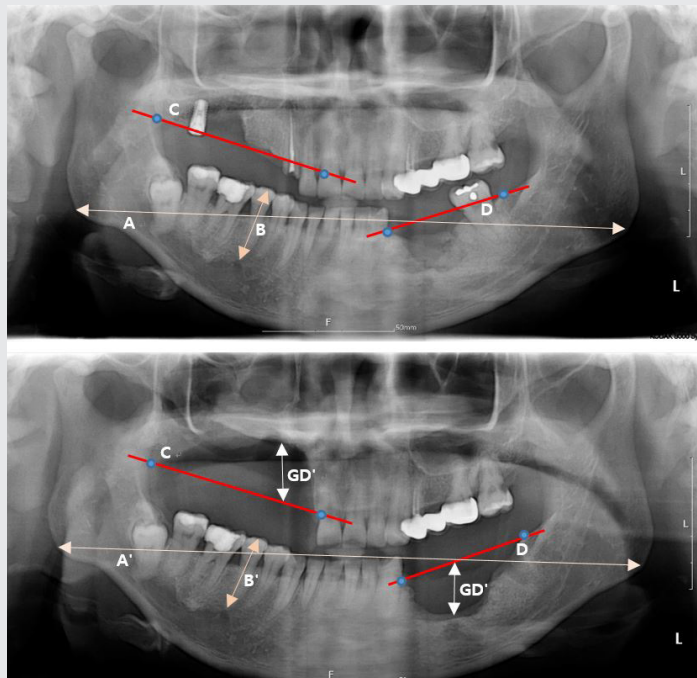


Fig 1. Analysis of Bone grinding depth

Prediction value of vertical grinding depth(GD) = $\frac{B'}{B} \times GD'$ (M6 measure value)

A. The distance between the bilateral mandible angles on preoperative images

B. The length of the reference tooth on preoperative images

C. D. Line connecting two anatomically distinct points that can serve as a clear anatomical reference A'. The distance between the bilateral mandible angles on postoperative images B'. The length of the reference tooth on postoperative images GD'. The height of the removed elevated maxillary bone during surgery.

majority of our patients were elderly and had general alveolar bone resorption, and in cases where the distance from the upper teeth to the maxillary sinus was shorter than the length of the tooth roots lengths, we established a reference point of 10mm. To mitigate the potential statistical errors due to a limited sample size for the half of this value, which is 5mm, we expanded it to 6mm.

(5) Surgery Method

The study classified patients based on the presence or absence of soft tissue coverage following alveolar bone resection and cortical bone decortication procedures (Sequestrectomy & Decortication). The Primary closure group involved direct suturing of soft tissues after surgery, while the Secondary closure group involved packing with Vaseline gauze

Table 1. The number of patients taking BPs and denosumab according to their disease.

Drug Disease	Zoledronate	Alendronate	Ibandronate	Pamidronate	Risedronate	Denosumab
Osteoporosis	29	62	88	14	46	59
Cancer	31	0	0	0	0	2

Table 2. Patient's characteristics

Factors	Data
Mean age (year)	74.0 (45~98)
Mean drug holiday period (month)	6.2 (0~42)
Mean medication period (month)	52.2 (3~240)
Mean pre-operative period of antibiotics (week)	7.1 (0~28)
Mean post-operative period of antibiotics (week)	3.2 (1~14)
Surgical method, n(%)	
Primary closure	241 (73.0)
Secondary healing	90 (27.0)
Medication hold after surgery, n(%)	
Yes	282 (85.0)
No	49 (15.0)
Complication, n(%)	
Bone exposure	26 (7.8)
Hypoesthesia	21 (6.4)
Pathologic fracture	7 (2.1)
No	277 (83.7)
Recurrence, n(%)	
Yes	40 (12.1)
No	291 (87.9)

while leaving the soft tissues open. Vaseline gauze was first replaced on the 5th postoperative day and subsequently changed every 2 days.

III. Results

Among a total of 331 patients who underwent surgical treatment at Chonnam National University Hospital's Department of Oral and Maxillofacial Surgery from January 2011 to December 2020, there were 29 male and 302 female patients. The most common trigger point for MRONJ development was tooth extraction, accounting for 63%, followed by dental implant placement and bone grafting procedures. Among the stages of MRONJ, Stage 2 was the most prevalent, with 66% of patients, followed by Stage 1 at 22% and Stage 3 at 12%. The mandibular posterior region was the most frequently affected site.

Patients were categorized based on their medical history into Osteoporosis and cancer groups, and their ongoing medication use was classified. In the Osteoporosis group, the most commonly used medications were Ibandronate (88 patients), Alendronate (62 patients), Denosumab (59 patients), Risedronate (46 patients), Zoledronate (29 patients), and Pamidronate (14 patients). Among cancer patients, 31 were using Zoledronate, and 2 were using Denosumab, both of which led to MRONJ complications during medication use (Table 1).

The average age of the patients was 74 years (ranging from 45 to 98 years), and the discontinu-

ation of antiresorptive agents or antiangiogenic inhibitors before surgery was performed on average 6.2 months prior (ranging from 0 to 42 months). Furthermore, it was found that patients had been taking medications on average for approximately 52.2 months (ranging from 3 to 240 months) before surgery. The preoperative antibiotic use duration averaged around 7.1 weeks (ranging from 0 to 28 weeks), while postoperative antibiotic use lasted for approximately 3.2 weeks (ranging from 1 to 14 weeks). During surgery, primary closure was achieved in 73% of cases, whereas 27% underwent secondary healing.

Among the patients, 85% (282 individuals) discontinued antiresorptive agents or antiangiogenic inhibitors after surgery, while 15% (49 individuals) were unable to discontinue. Notably, 83.5% (277 patients) did not experience any significant complications, while 6.5% (21 patients) exhibited exposed alveolar bone, and 5.5% (18 patients) reported hypoesthesia. Among the total of 331 patients, 12% (40 individuals) experienced recurrence and required further treatment (Table 2).

(1) Depth of bone grinding

The Kaplan-Meier Estimation analysis revealed that in Bone Grinding Group 2 and Group 3, recurrence began to occur more prominently around 12 months (1 year). However, upon long-term follow-up observation, there was no statistically significant correlation between the Bone Grinding Groups ($p=0.68$) (Fig. 2).

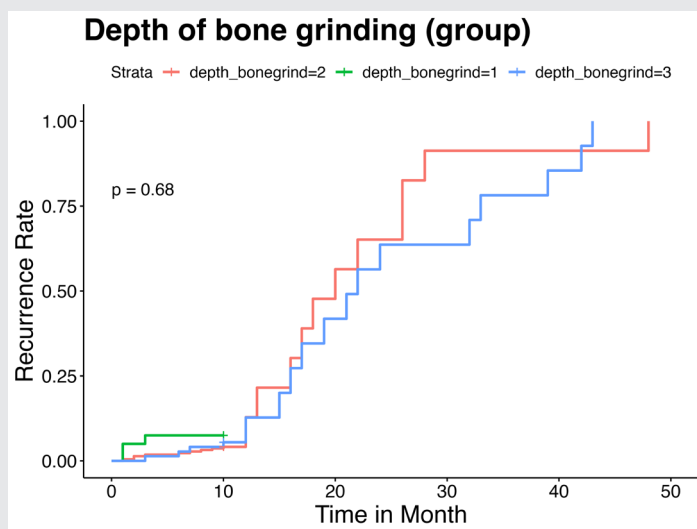


Fig 2. Kaplan-Meier Estimation (Depth of bone grinding)

(2) Surgery method

The Kaplan-Meier Estimation analysis revealed that there was no statistically significant correlation between the group that underwent primary closure after surgery and the group in which vaseline gauze was packed in the bone grinding site, allowing for secondary healing ($p=0.57$)(Fig. 3).

(3) The group based on disease

The Kaplan-Meier Estimation analysis revealed that there was no statistically significant correlation between the patient group with osteoporosis and the patient group with cancer ($p=0.94$)(Fig. 4)

(4) Drug holiday after surgery

The Kaplan-Meier Estimation analysis results

compared the recurrence rates between patients who held Antiresorptive agents or antiangiogenic medications after alveolar bone resection and cortical bone decortication procedures and those who did not, but it was not statistically significant ($p=0.53$)(Fig. 5).

(5) Adjacent tooth extraction

The Kaplan-Meier Estimation analysis results compared the recurrence rates between cases where teeth affected by alveolar bone necrosis at the time of surgery were extracted together and cases where they were not extracted. It was statistically significant that the recurrence rate was lower when teeth were extracted ($p=0.013$)(Fig. 6).

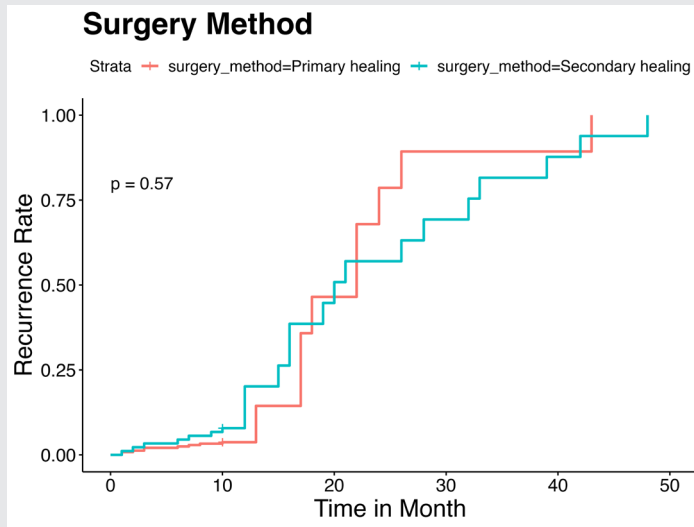


Fig 3. Kaplan-Meier Estimation (Surgery method)

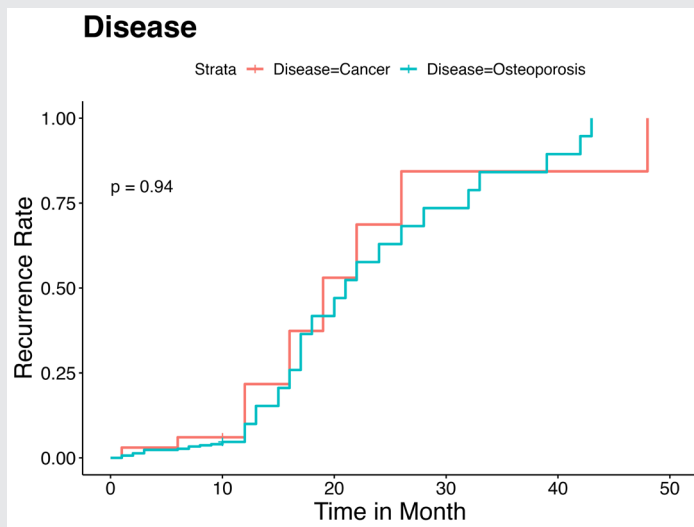


Fig 4. Kaplan-Meier Estimation (Group by disease)

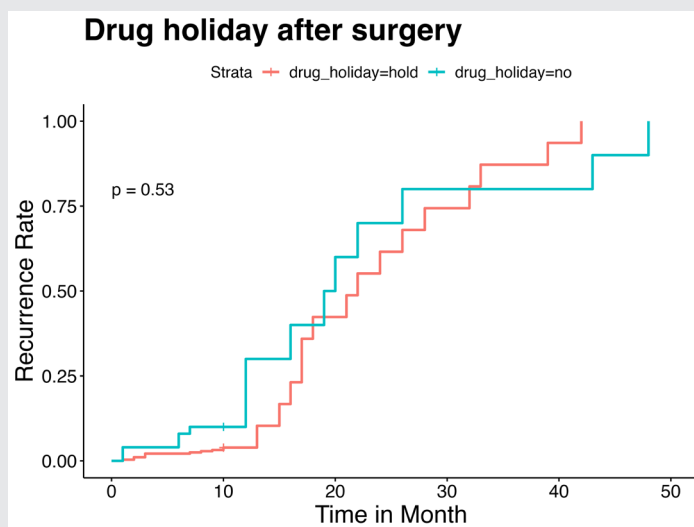


Fig 5. Kaplan-Meier Estimation (Group by Drug holiday)

(6) Duration of medication (BPs, denosumab)

The duration of Bisphosphonate and denosumab use due to Osteoporosis and Cancer before surgery was divided into three groups for analysis. Group 1 included durations of 24 months or less, Group 2 comprised durations between 24 and 48 months, and Group 3 consisted of durations exceeding 48 months. However, there was no statistically significant difference among these groups ($p=0.52$)(Fig. 7).

(7) Reconstruction plate plating

Following alveolar bone resection and cortical bone decortication procedures, an additional surgical procedure involving the use of a reconstruction plate was performed for patients at high risk of mandibular fracture due to the limited remaining

mandibular bone. However, a comparison between the group that underwent plating and the group that did not showed no statistically significant difference ($p=0.56$)(Fig. 8).

(8) Cox proportional hazards model(Fig.9)

To identify potential risk factors influencing the recurrence of MRONJ, a Cox proportional hazards model analysis was performed. Patients in Group 1, who underwent less bone resection compared to Group 2 as a reference, exhibited a higher recurrence rate, while patients in Group 3, who had more extensive bone grinding, showed a relatively lower recurrence rate, although it was not statistically significant. When comparing the group with primary closure and the group with secondary healing after

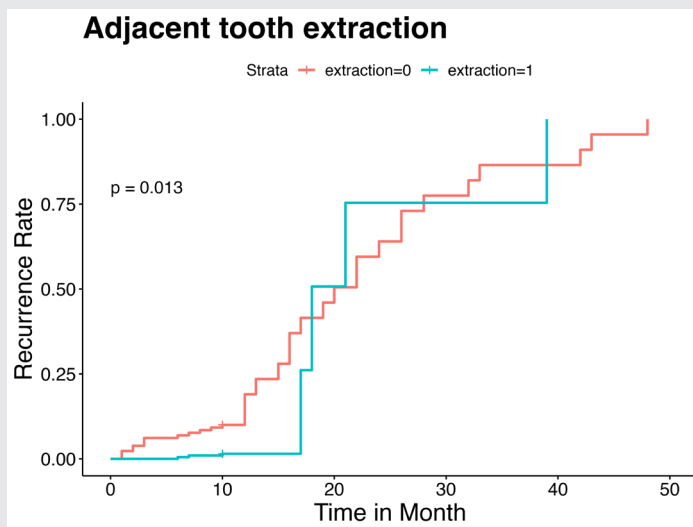


Fig 6. Kaplan-Meier Estimation (Group by adjacent tooth extraction)

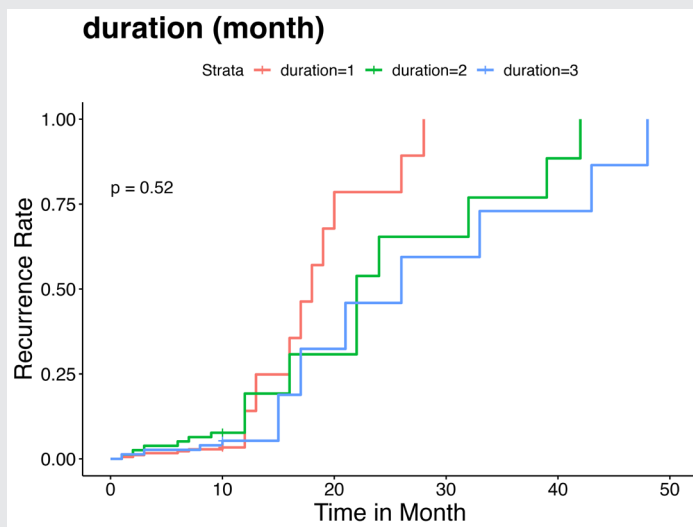


Fig 7. Kaplan-Meier Estimation (Group by medication duration)

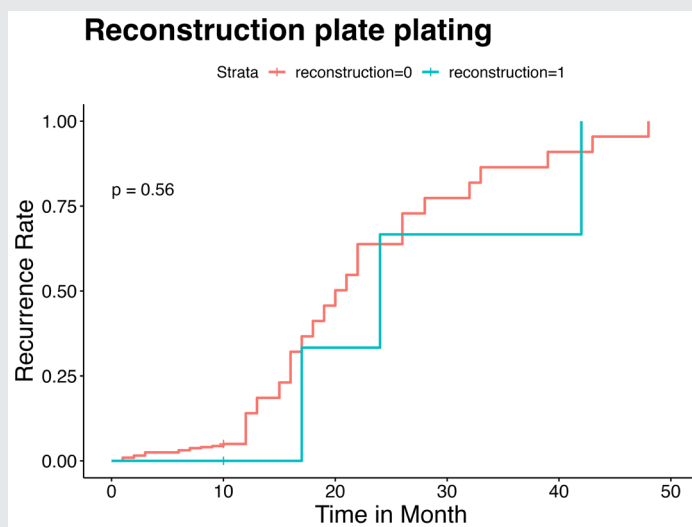


Fig 8. Kaplan-Meier Estimation (presence or absence of plating)

surgery, the secondary healing group had a higher recurrence rate, but it was not statistically significant. Comparing patients who held Antiresorptive agents or antiangiogenic medications after alveolar bone resection and cortical bone decortication procedures with those who did not, the non-hold group had a higher recurrence rate, though not statistically significant. When comparing patients in whom teeth affected by alveolar bone necrosis at the time of surgery were extracted together versus those where they were not extracted, it was statistically significant that the recurrence rate was lower when teeth were extracted ($p=0.002$). Additionally, when comparing patients who received antibiotics medication after surgery, the recurrence rate significantly decreased in Groups 2 and 3 compared to Group 1.

IV. Discussion

This study retrospectively evaluated the factors associated with recurrence in patients who underwent surgical treatment for MRONJ at the Department of Oral and Maxillofacial Surgery, Chonnam National University Hospital. Initially, we hypothesized that patients with a longer duration of antiresorptive agent or antiangiogenic medication use before MRONJ surgery or a shorter discontinuation period, as well as those in the late-stage of MRONJ, would experience more recurrences. Additionally, we hypothesized that there would be a higher recurrence rate in the Secondary healing group compared to the Primary closure group.

However, when comparing the recurrence rates

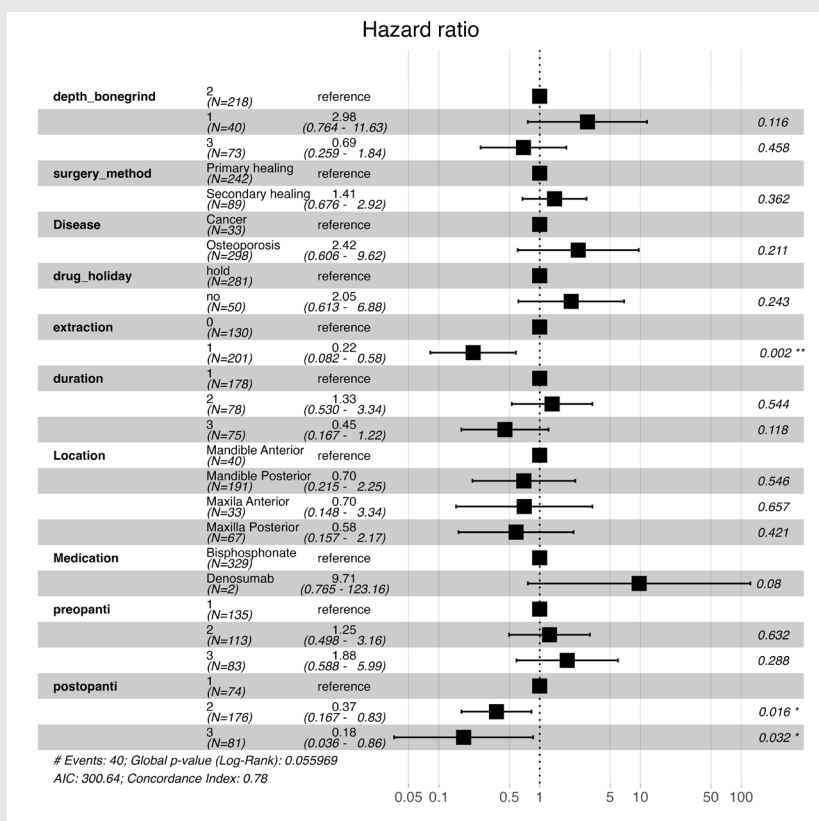


Fig 9. Cox proportional hazards model

- Depth of bone grinding Group1(~6mm), Group2(6mm~10mm), Group3(10mm~)
- Duration Group1(~24months), Group2(24~48months), Group3(48months~)
- Preopanti ; Pre-operation antibiotics medication duration , Group1(~1wks), Group2(1wks~2wks), Group3(more than 3wks)
- Postopanti ; Post-operation antibiotics medication duration, Group1(~1wks), Group2(1wks~2wks), Group3(more than 3wks)

based on preoperative medication discontinuation periods or the presence of Stage 3 MRONJ patients and between the Secondary healing group, it was found that there was no statistically significant impact on MRONJ recurrence. Additionally, previous studies have suggested that surgery, including

extensive procedures, can reduce the probability of recurrence and result in better outcomes¹⁰. However, this study demonstrated that these factors were not statistically significant. The interpretation of this could be attributed to the fact that surgical procedures were extended until spontaneous bleeding

from the bone was confirmed during the grinding of the affected maxillary and mandibular bones. Consequently, all necrotic bone tissue was removed in all patients with Stage 1, 2, and 3 MRONJ before concluding the surgery. Therefore, it can be inferred that there were no significant factors within the scope of the surgical procedures that would increase the risk of recurrence.

Moreover, it is presumed that differences between the primary closure group and secondary healing group may have arisen due to various variables such as the extent of alveolar bone involvement at the lesion site, the scope and depth of the surgery, and the presence of extractions. In conclusion, it is considered difficult to generalize the recurrence rates based solely on how the postoperative treatment was conducted. To obtain meaningful evaluations of recurrence rates, it is believed that Randomized Controlled Trials (RCTs) should be conducted.

In the overall MRONJ patient cohort, there were 29 males (8.8%) and 302 females (91.2%). As observed in previous studies, this study also confirmed a higher incidence of MRONJ in females. However, it's worth noting that females are more commonly affected by conditions like rheumatoid arthritis and osteoporosis compared to males, so this difference may be coincidental¹¹⁾. Additionally, it has been consistently reported that MRONJ occurs more frequently in the mandible than in the maxilla, and this study reached the same conclusion. There is little doubt about the site of MRONJ occurrence^{7,14)}.

The discussion of MRONJ incidence and recurrence rates in relation to age has been a topic in

many previous studies. While some research found no statistically significant correlation between aging and MRONJ^{15,16)}, others have included old age as a contributing factor to higher MRONJ incidence and recurrence rates^{17,18)}. These associations have been analyzed in the context of differences in immune function, decreased blood flow, and altered abilities of mandibular remodeling^{19,20,21)}. In other studies, differences in oxidative stress have been examined²²⁾. In fact, in this study, it was observed that patients experiencing MRONJ recurrence were older on average than the entire patient cohort of 331 individuals.

To accurately determine the association between the extent of bone grinding at the lesion site and recurrence, a three-dimensional volumetric approach is required, rather than relying on a two-dimensional criterion like depth. However, from a clinical perspective, quantifying volume during surgery is more challenging for clinicians. Instead, utilizing depth as the criterion may provide more practical guidance to clinicians during the surgical procedure. Therefore, our investigation was conducted based on the depth criterion.

This study also has its limitations. While efforts were made to measure the depth of bone grinding as accurately as possible using radiographic methods, it was not possible to precisely measure the actual depth of removal during surgery. Additionally, there was an inherent limitation in that all experimental data values were dependent on the stage of MRONJ, as it is expected that the depth of bone grinding would naturally be greater in stage 3

patients compared to stage 1 patients. Furthermore, when defining the extent of surgery, we aimed to compare cases with extensive extraction and those without, but there was insufficient quantitative evidence to determine whether teeth at the margin of the lesion were affected or not. In this study, such determinations were made based on the subjective judgment criteria of the researchers.

Furthermore, it would have been desirable to observe the recurrence rates based on the respective mechanisms of action of Bisphosphonate drugs and Denosumab. However, it is a limitation that we were unable to differentiate the groups, as there was only one patient (n=1) in the recurrence group who was taking Denosumab, which posed a potential statistical error.

V. Conclusion

While prior research on MRONJ recurrence has identified numerous potential factors, this study

revealed some parallels but did not find statistical significance with regard to the duration of preoperative medication use, the type of medication, or the affected site. Instead, it suggests that Decortication boundary during operation(including extraction tooth) and after the procedure (medication) may play a crucial role in preventing recurrence. Extensive decortication during surgery, along with the extraction of adjacent teeth, could contribute to recurrence prevention. Additionally, postoperative antibiotics treatment should be administered for an adequate duration.

VI. Conflicts of Interest

The authors declare that they have no competing interests.

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