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# Denosumab-related osteonecrosis of the jaw after tooth extraction and the effects of a short drug holiday in cancer patients: A multicenter retrospective study

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**Short title:** Factors associated with DRONJ after extraction

**MINI ABSTRACT**

Pre-existing inflammation, corticosteroid therapy, periapical periodontitis, longer duration of denosumab therapy, and female sex were significantly associated with an increased risk of denosumab-related osteonecrosis of the jaw after tooth extraction in patients with cancer on oncologic doses of denosumab. A short drug holiday did not protect against this complication.

**ABSTRACT**

**Purpose**

This study retrospectively investigated the relationship between various risk factors, including brief discontinuation of denosumab, and development of denosumab-related osteonecrosis of the jaw (DRONJ) after tooth extraction in patients with cancer who were receiving oncologic doses of this agent.

**Methods**

Data were collected on demographic characteristics, duration of denosumab therapy, whether or not denosumab was discontinued before tooth extraction (drug holiday), duration of discontinuation, presence of pre-existing inflammation, and whether or not additional surgical procedures were performed. Risk factors for DRONJ after tooth extraction were evaluated by univariate and multivariate analyses.

**Results**

A total of 136 dental extractions were performed in 72 patients (31 men, 41 women) with cancer who were receiving oncologic doses of denosumab. Post-extraction DRONJ was diagnosed in 39 teeth (28.7%) in 25 patients. Tooth extraction was significantly associated with development of DRONJ only in patients with pre-existing inflammation (odds ratio [OR] 243.77), those on corticosteroid therapy (OR 73.50), those with periapical periodontitis (OR 14.13), those who had been taking oncologic doses of denosumab for a

longer period (OR 4.69), and in women (OR 1.04). There was no significant difference in the occurrence of DRONJ between patients who had a drug holiday before tooth extraction and those who did not.

**Conclusions**

These findings suggest that inflamed teeth should be extracted immediately in patients with cancer who are receiving oncologic doses of denosumab. Drug holidays have no significant impact on the risk of DRONJ.

**Key words:** medication-related osteonecrosis of the jaw, denosumab-related osteonecrosis of the jaw, denosumab, discontinuation, drug holiday

## INTRODUCTION

Many patients worldwide are treated with bone-modifying agents (BMAs), including bisphosphonates and denosumab, which act as antiresorptive agents. BMAs suppress bone remodeling and are used to treat osteoporosis, metastatic bone cancer, and multiple myeloma [1, 2]. BMAs have also been used to treat malignancy-induced hypercalcemia and to reduce the risk of skeletal-related events [3, 4]. Since the first reports of bisphosphonate-related osteonecrosis of the jaw by Marx et al and Migliorati et al, medication-related osteonecrosis of the jaw (MRONJ) induced by bisphosphonates and denosumab has become widely recognized [5, 6, 7].

The MRONJ position paper published by the American Association of Oral and Maxillofacial Surgeons (AAOMS) acknowledged that tooth extraction was a major trigger for MRONJ, with 52%–61% of patients reporting tooth extraction as the precipitating event [1]. The incidence rate of MRONJ after tooth extraction in patients with osteoporosis is 0.09%–2.8% [8-10], and the risk is higher in patients with cancer who receive cumulative doses of BMAs approximately 10–12 times those administered for osteoporosis [1, 2]. Although tooth extraction itself is the main risk factor for MRONJ, excessive delay in extracting an inflamed tooth also increases the risk of MRONJ [11]. We have previously demonstrated that pre-existing inflammation is a more important risk factor for MRONJ in patients on oncologic doses of BMAs than tooth extraction per se [12]. Moreover, there is doubt about the effectiveness of a short-term drug holiday, given that the available evidence suggests that drug holidays have no significant impact on the incidence of MRONJ [10, 12].

Denosumab has been found to be more effective than bisphosphonates in terms of increasing bone mineral density in patients with osteoporosis [13] and suppressing bone remodeling in those with cancer [14]. Denosumab can be used more safely than bisphosphonates in patients with impaired renal function [15]. Furthermore, denosumab does not accumulate in bone tissue and has a considerably shorter half-life than the

bisphosphonates (28 days vs 10–12 years) [16]. Clinically, there have been cases where the monthly dose of denosumab was skipped before tooth extraction. However, there is no evidence to suggest that a drug holiday reduces the risk of denosumab-related osteonecrosis of the jaw (DRONJ) or prevents it after tooth extraction. Moreover, no study has comprehensively analyzed the influence of a drug holiday and other potential risk factors, such as pre-existing inflammation and surgery-related factors, on the incidence of DRONJ after dental extraction in patients on denosumab. We hypothesized that pre-existing inflammation and surgery-related factors, including primary wound closure, would influence the risk of DRONJ. In this study, we investigated the relationships between the various putative risk factors for DRONJ after tooth extraction in patients with cancer on oncologic doses of denosumab.

## METHODS

This multicenter nonrandomized retrospective cohort validation study included pooled data for patients from ten institutions that are members of the Japanese Study Group of Co-operative Dentistry with Medicine. A total of 168 patients who were receiving denosumab therapy underwent tooth extraction at these institutions between January 2008 and December 2019. Two hundred and eleven extractions were performed in 96 patients receiving denosumab for osteoporosis. Post-extraction DRONJ was diagnosed in three teeth (1.4%) in three patients (3.1%). Patients with osteoporosis were excluded from the study because the number of events was too small for analysis of the study variables. Finally, 136 dental extractions performed in 72 patients (31 men, 41 women) with cancer and receiving an oncologic (120 mg) dose of denosumab once a month were included in the study. The mean patient age was 65.2 ± 11.8 (range, 41–85) years.

The study was approved by the institutional review board of Kobe University Graduate School of Medicine and by the institutional review boards of the other participating hospitals (authorization number: 190273). All patients consented to treatment after being informed about MRONJ and other extraction-associated risks. The definition of MRONJ was taken from the position paper published by the AAOMS [1]. For a diagnosis of MRONJ, the following three criteria should be met: 1) current or previous treatment with antiresorptive or antiangiogenic agents; 2) exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region and has persisted for longer than 8 weeks; and 3) no history of radiation therapy to the jaw or obvious metastatic disease of the jaw. The demographics and clinical characteristics of all patients were investigated, including duration of oncologic doses of denosumab, whether or not denosumab was discontinued for 30 days before tooth extraction (i.e., a drug holiday), additional surgical procedures such as incision, bone removal, tension-relieving incision, root amputation, and suturing, whether antibiotics were administered before extraction, pre-existing inflammation, bone loss around the tooth, duration of follow-up, and time until

primary wound healing without evidence of infection. The definition of discontinuation was a drug holiday of more than one month (30 days) before extraction. Pre-existing inflammation was defined as clinical symptoms (pain, swelling, redness, or purulent discharge) requiring administration of antibiotics within the 2 weeks before extraction. As a practical matter, the majority of inflamed teeth designated for extraction are infected. The reason for extraction, number of teeth extracted, and site of extraction were also investigated. Alveolar bone loss was measured at the mesial and distal surfaces of the tooth between the apex of the root and the cervical margin using orthopantomography. Bone loss around a tooth was defined as (average [medial and distal) length)/(distance between root apex and cervical margin) × 100 ≥50% and a tooth with alveolar bone loss of more than two-thirds of the root and a probing depth of more than 6 mm was defined as P4 periodontitis. A tooth with caries reaching the tooth roots or a residual root stump was defined as C4 caries. The data were entered into a multiple logistic regression model in which patients were divided according to number of teeth extracted (single vs multiple), wound status (open vs closed), type of cancer (breast vs non-breast and prostate vs non-prostate), and Eastern Cooperative Oncology Group performance status (0 or 1 vs 2 or 3) [17]. The primary outcome was the occurrence of DRONJ. Possible development of DRONJ was noted and, if present, classified according to stage, in line with the AAOMS position paper (stage 0, no clinical evidence of necrotic bone, with nonspecific clinical findings, radiographic changes, and symptoms; stage 1, exposed and necrotic bone or fistulas that probe to bone in patients who are asymptomatic, no evidence of infection; stage 2, exposed and necrotic bone or fistulas that probe to bone, associated with infection as evidenced by pain and erythema in the region of exposed bone, with or without purulent drainage; and stage 3, exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and more than one of the following: exposed and necrotic bone extending beyond the region of alveolar bone [i.e., inferior border and ramus of the mandible, maxillary sinus, and zygoma in the maxilla] resulting in pathologic fracture,

extraoral fistula, oral antral or oral nasal communication, or osteolysis extending to the inferior border of the mandible or the sinus floor) [1].

**Statistical analysis**

The statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA) and Ekuseru-Toukei 2012 software (Social Survey Research Information Co., Ltd., Tokyo, Japan). The association of each variable with DRONJ was analyzed using the Mann-Whitney *U* nonparametric test for ordinal variables and with Fisher's exact test or the chi-squared test for categorical variables. A p-value $<0.05$ was accepted as statistically significant. Smoking history was excluded from multivariate analysis because it was not a significant risk factor in univariate analysis and the data needed were incomplete. The remainder of the variables were introduced into a multiple logistic regression model. Forward stepwise algorithms were used; variables that did not fit the model significantly were rejected. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. The cumulative incidence rate of DRONJ was calculated using the Kaplan-Meier product limit method.

The discriminatory ability of the duration of administration of oncologic doses of denosumab as an indicator of possible DRONJ was evaluated by receiver-operating characteristic (ROC) curve analysis. The ROC curve was used to determine the cutoff values for clinical tests. The area under the ROC curve measures the accuracy of discrimination (range, 0.5 to 1). The cutoff value was chosen to minimize the number of false-positive and false-negative results.

## RESULTS

The patient demographics and clinical characteristics are shown in Tables 1 and 2. The cumulative incidence rates of DRONJ at 6, 12, 18, and 24 months were 4.6%, 7.7%, 17.6%, and 34.3%, respectively (Figure 1). There was no significant difference in the incidence of DRONJ according to age, sex, smoking history, or performance status. The duration of oncologic doses of denosumab was significantly longer in patients who developed DRONJ than in those who did not ($p < 0.001$; Table 1 and 2). There was a significant difference in the incidence of DRONJ between patients treated with oncologic doses of denosumab for ≥18 months and those treated for <18 months. The time interval between the most recent dose of denosumab and tooth extraction was longer in patients who developed DRONJ than in those who did not (Tables 1 and 2); however, differences in the incidence of DRONJ were not significantly different between patients on corticosteroid therapy, those with diabetes mellitus, those with other drug-induced risk factors, and those who had a drug holiday before tooth extraction and patients without these factors in univariate analysis (Tables 1 and 2). Periapical periodontitis was a significant predictor of DRONJ ($p = 0.014$; Table 2). However, there was no significant difference in the likelihood of development of DRONJ according to site of extraction (anterior vs posterior region or maxillary vs mandibular), bone volume around the tooth, or number of teeth extracted. Extraction of a tooth with pre-existing inflammation was a significant predictor of DRONJ ($p < 0.001$; Tables 1 and 2). Procedure-related factors, such as bone removal, root amputation, and wound status, were not significant risk factors. DRONJ was less likely to develop in patients who had complete wound closure with tension-relieving incisions and/or removal of bone edges; however, the difference was not statistically significant.

Applying a logistic regression model and forward stepwise algorithms, we found significant associations of DRONJ with tooth extraction in patients with pre-existing inflammation (OR 243.77), those on corticosteroid therapy (OR 73.50), those with periapical periodontitis (OR 14.13), those on oncologic doses of denosumab for a longer

period (OR 4.69), and women (OR 1.04; Table 3).

The area under the ROC curve was 0.71. Maximization of the harmonic mean of specificity and sensitivity put the cutoff value for duration of oncologic doses of denosumab for predicting post-extraction DRONJ at 18 months (Figure 2). The sensitivity was 0.72 and the specificity was 0.69.

## DISCUSSION

The incidence rate of DRONJ was 0%–11.4% in several studies performed in patients with solid tumors and bone metastasis [18-22]. In a systematic review and meta-analysis of MRONJ in patients with cancer, the incidence rate of DRONJ ranged from 0.5% to 2.1% after 1 year, 1.1% to 3.0% after 2 years, and 1.3% to 3.2% after 3 years of exposure [23]. However, the incidence rate of DRONJ in patients undergoing tooth extraction has been very high (14.3%–31.6%) [24, 25]. In the present study, the incidence rate of DRONJ after tooth extraction was 28.7%, which is similar to that in the previous studies. However, it may be difficult to distinguish stage 0 MRONJ from tooth infection, and it is possible that our cases of DRONJ included patients who had already developed MRONJ before tooth extraction. Pre-existing inflammatory dental disease causes MRONJ in 50% of patients with cancer [26, 27]. In our study, 97.4% of all patients who developed DRONJ had pre-existing inflammation. Soutome et al investigated factors related to development of MRONJ in patients with cancer who had received oncologic doses of bisphosphonates or denosumab and concluded that the factors putting patients at increased risk of MRONJ were the underlying infection and not the extraction itself [28]. Other investigators have reported that extraction of noninflamed ankylosed primary teeth in bisphosphonate-treated children with osteogenesis imperfecta rarely, if ever, leads to MRONJ [29, 30]. In our study, multivariate analysis identified pre-existing inflammation (OR 243.77) and periapical periodontitis (OR 14.13) to be significant risk factors for MRONJ, as in other studies [22, 24, 28]. Therefore, patients with fractured or extensively caries-damaged and unrestorable teeth without active periodontal or periapical inflammation may be at low risk of DRONJ after extraction.

Corticosteroids and immunosuppressant therapy delay postoperative wound healing [31-34]. Corticosteroids reduce angiogenesis and the activity of various cells, including osteoclasts and osteoblasts [33-35]; these cells are induced into early apoptosis, which decreases bone turnover [34]. Avascular osteonecrosis of the femur and vertebra has

been reported [33, 34]. In a study by Aljohani et al, 11.1% of 63 patients with MRONJ were receiving long-term corticosteroid therapy [36]. There has also been a case report of a non-healing socket after tooth extraction in a patient who had been receiving long-term corticosteroid therapy without any other MRONJ-causing agent [37]. In the present study, multivariate analysis identified corticosteroid therapy (OR 73.50) to be a significant risk factor for DRONJ.

The majority of oncology patients who develop DRONJ have either prostate cancer or breast cancer [19, 20, 22-24]. Breast cancer was the most common type of cancer in patients with DRONJ in our study, which is consistent with other reports [22, 36, 38]. Although women have not been confirmed to be at higher risk for DRONJ, we identified female sex to be a significant risk factor in multivariate analysis, although the OR was low (1.04). This finding may reflect the female-specific nature of particular cancers, such as those affecting the breast or reproductive system.

Theoretically, long-term treatment with bisphosphonates carries a high risk of MRONJ. However, given that denosumab does not accumulate in bone tissue and has a short half-life, it is controversial as to whether or not the cumulative dose of denosumab affects the risk of development of MRONJ in the same way as that of a bisphosphonate. Saad et al reported that the incidence of MRONJ was 0.5%–0.8% at 1 year and 1.0%–1.8% at 2–3 years in patients with cancer receiving zoledronate or denosumab [26]. In their study, the median duration of drug exposure before diagnosis of MRONJ was 14 months in both treatment groups. Juras et al reported an increase in the incidence rate of DRONJ with increasing duration of follow-up in patients with cancer on denosumab therapy (3% at 1 year, 7% at 2 years, and 8% beyond 30 months). In our present study, the cumulative incidence rates of DRONJ at 6, 12, 18, and 24 months were 4.6%, 7.7%, 17.6%, and 34.3%, respectively. Moreover, in multivariate analysis, we found a longer duration of oncologic doses of denosumab to be a significant risk factor for DRONJ (OR 4.69).

Physicians should refer all patients who are on oncologic doses of denosumab for

an immediate oral examination and treatment planning by a dental professional familiar with DRONJ. Tooth extraction in patients taking oncologic doses of denosumab is less likely to lead to DRONJ when the duration of denosumab therapy has been less than 18 months. Therefore, teeth that are not salvageable or have a poor prognosis should be extracted as soon as possible, preferably before the start of denosumab therapy. Our data indicate that inflamed teeth should be extracted immediately in oncology patients who are taking denosumab, especially those with breast or prostate cancer and a favorable prognosis.

Theoretically, tooth extraction should be performed in patients with cancer without discontinuation of oncologic doses of a BMA, given that they are needed for management of skeletal-related events. We recently reported that a short (2-month) drug holiday from oral bisphosphonates before tooth extraction did not reduce the incidence of MRONJ in patients with osteoporosis [10]. Similarly, a short drug holiday from oncologic doses of a BMA before tooth extraction did not reduce the incidence of MRONJ in patients with cancer [12]. Denosumab does not accumulate in bone tissue and its elimination half-life (28 days) is much shorter than that of the bisphosphonates [16]. However, its pharmacodynamic half-life, that is, the duration of its antiresorptive effect, is longer than its elimination half-life [39, 40]. In a study by Bone et al, the time to full reversal of the antiresorptive effects of a 60 mg dose of denosumab for osteoporosis was 9 months [39]. As with the 60 mg dose, the antiresorptive effects of a 120 mg dose of denosumab may be at least 9 months after the last dose in oncology patients, although there is as yet no supporting evidence for this. Several investigators have demonstrated the effectiveness of a 1-2 year drug holiday from denosumab in the treatment of MRONJ [41, 42]. However, in most oncology patients, denosumab is a life-prolonging medication that cannot be discontinued for such a long period. Others have concluded that a drug holiday has no effect on the healing outcome in patients with MRONJ [36, 38, 43]. In this study, we could not confirm the effectiveness of a short drug holiday before tooth extraction, which

indicates that drug holidays are likely to have no significant impact on the incidence of MRONJ. Demographic features and local factors, such as pre-existing inflammation, appear to be more important risk factors for DRONJ than continuation of oncologic doses of denosumab before or after tooth extraction. Moreover, in patients with osteoporosis, discontinuation of 6-monthly injections of denosumab resulted in a rebound increase in bone resorption, rapid bone loss, and clusters of fractures after 9–12 months [44]. Therefore, denosumab should not be delayed or stopped before tooth extraction.

This study was limited by its retrospective non-matched design, which meant that other risk factors, such as indices of oral hygiene, could not be examined. Although multivariate analysis was performed to decrease the effect of confounding factors as far as possible, the possibility of selection bias could not be completely excluded. A large-scale, prospective cohort study is needed to evaluate predictors of DRONJ in patients with cancer who are on denosumab.

In conclusion, we have successfully demonstrated relationships between various risk factors and DRONJ after tooth extraction in patients with cancer who are receiving oncologic doses of denosumab. Pre-existing inflammation, corticosteroid therapy, extraction of teeth with periapical periodontitis, longer duration of oncologic doses of denosumab, and female sex were significantly associated with development of DRONJ. These findings suggest that inflamed teeth should be extracted immediately in patients with cancer who are receiving oncologic doses of denosumab. DRONJ is more likely to occur in patients with cancer who have taken denosumab for longer than 18 months than in those who have taken it for a shorter period. Drug holidays for less than 9 months have no significant impact on the risk of DRONJ.

**Conflicts of interest:** Takumi Hasegawa, Nobuhiro Ueda, Shin-ichi Yamada, Shinichiro Kato, Eiji Iwata, Saki Hayashida, Yuka Kojima, Mitsuyo Shinohara, Itaru Tojo, Hirokazu Nakahara, Taihei Yamaguchi, Tadaaki Kirita, Hiroshi Kurita, Yasuyuki Shibuya, Sakiko

Soutome, and Masaya Akashi declare that they have no conflicts of interest.

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## TABLE AND FIGURE CAPTIONS

Tab.1 Characteristics of patients according to whether or not denosumab-related osteonecrosis of the jaw was present

Tab. 2 Characteristics of extracted teeth according to whether or not denosumab-related osteonecrosis of the jaw was present

Tab. 3 Results of multivariate logistic regression analysis of risk factors for denosumab-related osteonecrosis of the jaw

Fig. 1 Cumulative incidence rate of denosumab-related osteonecrosis of the jaw in patients with cancer on denosumab therapy.

Fig. 2 Receiver-operating characteristic curve for duration of administration of denosumab as an indicator of possible denosumab-related osteonecrosis of the jaw.

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**Table 1.** Characteristics of patients according to whether or not denosumab-related osteonecrosis of the jaw was present

| Variable | DRONJ | | P-value |
|---|---|---|---|
| | Present | Absent | |
| | n (%) | n (%) | |
| Patients, n | 25 (34.7) | 47 (65.3) | |
| Stage 0 | 1 (4.0) | - | |
| Stage 1 | 10 (40.0) | - | |
| Stage 2 | 11 (44.0) | - | |
| Stage 3 | 3 (12.0) | - | |
| Sex | | | |
| Male | 10 (40.0) | 21 (43.1) | 0.805 * |
| Female | 15 (60.0) | 26 (56.9) | |
| Age | | | |
| Range (years) | 44–82 | 41–85 | |
| Mean ± SD | 66.3 ± 11.3 | 64.60 ± 12.2 | 0.534 ** |
| Performance status | | | |
| 0 or 1 | 23 (92.0) | 44 (93.6) | 1.000 * |
| 2 or 3 | 2 (8.0) | 3 (6.4) | |
| Smoking history | | | |
| Yes | 3 (12.0) | 9 (19.1) | 0.735* |
| No | 18 (72.0) | 33 (70.2) | |
| Unknown | 4 (16.0) | 5 (10.6) | |
| Duration of oncologic doses of denosumab | | | |
| Range (months) | 5–51 | 1–85 | |
| Mean ± SD | 22.4 ± 13.5 | 13.7 ± 15.3 | < 0.001** |
| ≥ 18 months | 16 (66.7) | 10 (27.8) | < 0.001* |
| < 18 months | 9 (33.3) | 37 (72.2) | |
| Comorbidity or drug-induced risk factors | | | |
| Diabetes mellitus | | | |
| Yes | 2 (8.0) | 3 (6.4) | 1.000* |
| No | 23 (92.0) | 44 (93.6) | |
| Corticosteroid therapy | | | |
| Yes | 4 (16.0) | 8 (17.0) | 1.000* |
| No | 21 (84.0) | 39 (83.0) | |
| Additional chemotherapy | | | |

| | | | |
|---|---|---|---|
| Yes | 17 (72.3) | 34 (70.8) | 0.787* |
| No | 8 (27.7) | 13 (28.2) | |
| Type of cancer | | | |
| Breast cancer | 8 (32.0) | 12 (25.5) | 0.171*** |
| Prostate cancer | 2 (8.0) | 12 (25.5) | |
| Multiple myeloma | 1 (4.0) | 4 (8.5) | |
| Lung cancer | 2 (8.0) | 6 (12.8) | |
| Other | 1 (4.0) | 4 (8.5) | |
| Unknown | 11 (44.0) | 9 (19.1) | |
| Interval between tooth extraction and last denosumab injection | | | |
| Range (days) | 1–283 | 2–272 | |
| Mean ± SD | 66.0 ± 61.7 | 58.9 ± 63.5 | 0.367** |
| Drug holiday before tooth extraction | | | |
| Yes | 18 (46.2) | 54 (55.7) | 0.347* |
| No | 21 (53.8) | 43 (44.3) | |
| Reason for tooth extraction | | | |
| Periapical periodontitis | | | |
| Yes | 16 (64.0) | 25 (56.9) | 0.457* |
| No | 9 (36.0) | 22 (43.1) | |
| P4 periodontitis | | | |
| Yes | 3 (12.0) | 10 (21.3) | 0.521* |
| No | 22 (88.0) | 37 (78.7) | |
| Pericoronitis | | | |
| Yes | 4 (16.0) | 2 (4.6) | 0.173* |
| No | 21 (84.0) | 45 (95.7) | |
| | | | |
| Jawbone | | | |
| Maxillary | 10 (40.0) | 23 (48.9) | 0.881*** |
| Mandibular | 14 (56.0) | 21 (44.7) | |
| Maxillary and mandibular | 1 (4.0) | 3 (6.4) | |
| Site of tooth extraction | | | |
| Anterior region | 2 (8.0) | 5 (10.6) | 0.562*** |
| Molar region | 22 (88.0) | 37 (78.7) | |
| Anterior and molar region | 1 (4.0) | 5 (10.6) | |
| Bone volume around tooth | | | |
| Adequate alveolar bone volume | 19 (76.0) | 31 (66.0) | 0.432* |
| Bone loss | 6 (24.0) | 16 (44.0) | |
| Pre-existing inflammation | | | |
| Yes | 24 (96.0) | 29 (61.7) | 0.002* |

| | | | |
|---|---|---|---|
| No | 1 (4.0) | 18 (38.3) | |
| Preoperative antibiotics administration | | | |
| Yes | 24 (61.5) | 51 (52.6) | 0.446* |
| No | 15 (38.5) | 46 (47.4) | |
| Number of teeth extracted | | | |
| Single | 11 (44.0) | 20 (42.6) | 1.000* |
| Multiple | 14 (56.0) | 27 (57.4) | |
| Additional surgical procedure | | | |
| Bone removal | | | |
| Yes | 11 (44.0) | 11 (23.4) | 0.106* |
| No | 14 (56.0) | 36 (76.6) | |
| Root amputation | | | |
| Yes | 5 (20.0) | 6 (12.8) | 0.497* |
| No | 20 (80.0) | 41 (87.2) | |
| Wound status after extraction | | | |
| Open | 12 (48.0) | 15 (31.9) | 0.736*** |
| Closed with suture | 12 (48.0) | 28 (59.6) | |
| Completely closed with relaxation incision or removal of bone edge | 1 (4.0) | 4 (8.5) | |

*Fisher's exact test, **Mann-Whitney *U* test, ***chi-squared test. DRONJ, denosumab-related osteonecrosis of the jaw; SD, standard deviation

**Table 2.** Characteristics of extracted teeth according to whether or not denosumab-related osteonecrosis of the jaw was present

| Variable | DRONJ | | P-value |
|---|---|---|---|
| | Present n (%) | Absent n (%) | |
| Teeth, n | 39 (28.7) | 97 (71.3) | |
| Sex | | | |
| Male | 16 (41.0) | 47 (48.5) | 0.454* |
| Female | 23 (59.0) | 50 (51.5) | |
| Age | | | |
| Range (years) | 44–82 | 41–85 | |
| Mean ± SD | 66.6 ± 10.0 | 66.0 ± 13.0 | 0.860** |
| Performance status | | | |
| 0 or 1 | 36 (92/3) | 87 (89.7) | 0.355* |
| 2 or 3 | 3 (7.7) | 10 (10.3) | |
| Duration of oncologic doses of denosumab | | | |
| Range (months) | 5–51 | 1–85 | |
| Mean ± SD | 23.4 ± 13.1 | 15.7 ± 14.0 | < 0.001** |
| ≥18 months | 26 (66.7) | 27 (27.8) | < 0.001* |
| <18 months | 13 (33.3) | 70 (72.2) | |
| Comorbidity or drug-induced risk factors | | | |
| Diabetes mellitus | | | |
| Yes | 2 (5.1) | 16 (6.2) | 1.000* |
| No | 37 (94.9) | 91 (93.8) | |
| Corticosteroid therapy | | | |
| Yes | 9 (23.1) | 13 (13.4) | 0.200* |
| No | 30 (76.9) | 84 (86.6) | |
| Additional chemotherapy | | | |
| Yes | 27 (69.2) | 63 (64.9) | 0.692* |
| No | 12 (30.8) | 34 (35.1) | |
| Type of cancer | | | |
| Breast cancer | 13 (33.3) | 32 (33.0) | 0.386*** |
| Prostate cancer | 6 (15.4) | 34 (35.1) | |
| Multiple myeloma | 1 (2.6) | 6 (6.2) | |
| Lung cancer | 3 (7.7) | 9 (9.3) | |

| | | | |
|---|---|---|---|
| Other | 3 (7.7) | 4 (4.1) | |
| Unknown | 13 (33.3) | 12 (12.4) | |
| Duration between tooth extraction and last denosumab injection | | | |
| Range (days) | 1–283 | 2–272 | |
| Mean ± SD | 61.5 ± 53.1 | 84.6 ± 77.3 | 0.376** |
| Drug holiday before tooth extraction | | | |
| Yes | 18 (46.2) | 54 (55.7) | 0.347* |
| No | 21 (53.8) | 43 (44.3) | |
| Reason of tooth extraction | | | |
| Periapical periodontitis | 24 (61.5) | 37 (38.1) | 0.009*** |
| Periapical periodontitis + radicular cyst | 1 (2.6) | 1 (1.0) | |
| P4 periodontitis | 7 (18.0) | 33 (34.0) | |
| C4 caries | 1 (2.6) | 17 (17.5) | |
| Pericoronitis | 4 (10.3) | 3 (3.1) | |
| Root fracture | 1 (2.6) | 6 (6.2) | |
| Other | 1 (2.6) | 0 (0) | |
| | | | |
| Periapical periodontitis | | | |
| Yes | 25 (64.1) | 38 (39.2) | 0.014* |
| No | 14 (35.9) | 59 (60.8) | |
| P4 periodontitis | | | |
| Yes | 7 (18.0) | 33 (34.0) | 0.095* |
| No | 32 (82.0) | 64 (66.0) | |
| Pericoronitis | | | |
| Yes | 4 (10.3) | 3 (3.1) | 0.104* |
| No | 35 (89.7) | 94 (96.9) | |
| | | | |
| Jawbone | | | |
| Maxillary | 16 (41.0) | 54 (55.7) | 0.134* |
| Mandibular | 23 (59.0) | 43 (44.3) | |
| Site of tooth extraction | | | |
| Anterior region | 8 (20.5) | 25 (25.8) | 0.659* |
| Molar region | 31 (79.5) | 72 (74.2) | |
| Bone volume around tooth | | | |
| Adequate alveolar bone volume | 26 (66.7) | 49 (50.5) | 0.127* |
| Bone loss | 13 (33.3) | 48 (49.5) | |
| Pre-existing inflammation | | | |
| Yes | 38 (97.4) | 65 (67.0) | < 0.001* |
| No | 1 (2.6) | 32 (33.0) | |

| | | | |
|---|---|---|---|
| Preoperative administration of antibiotics | | | |
| Yes | 24 (61.5) | 51 (52.6) | 0.446* |
| No | 15 (38.5) | 46 (47.4) | |
| Number of teeth extracted | | | |
| Single | 15 (38.5) | 33 (34.0) | 0.693* |
| Multiple | 24 (61.5) | 64 (66.0) | |
| Additional surgical procedure | | | |
| Bone removal | | | |
| Yes | 17 (43.6) | 30 (30.9) | 0.169* |
| No | 22 (56.4) | 67 (69.1) | |
| Root amputation | | | |
| Yes | 8 (20.5) | 8 (8.2) | 0.073* |
| No | 31 (79.5) | 89 (91.8) | |
| Wound status after extraction | | | |
| Open | 17 (43.6) | 33 (34.0) | 0.297*** |
| Closed with suture | 20 (51.3) | 51 (52.6) | |
| Completely closed with relaxation incision or removal of bone edge | 2 (5.1) | 13 (13.4) | |

*Fisher's exact test, **Mann-Whitney *U* test, ***chi-squared test. DRONJ, denosumab-related osteonecrosis of the jaw; SD, standard deviation

**Table 3.** Results of multivariate logistic regression analysis of risk factors for denosumab-related osteonecrosis of the jaw

| Variable | P-value | Odds ratio | 95% CI | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Pre-existing inflammation | 0.001 | 243.77 | 11.03 | 5390.17 |
| Steroid therapy | < 0.001 | 73.50 | 7.45 | 724.71 |
| Periapical periodontitis | 0.001 | 14.13 | 3.06 | 65.29 |
| Longer duration of high-dose denosumab therapy | 0.016 | 4.69 | 1.34 | 16.49 |
| Female sex | 0.037 | 1.04 | 1.00 | 1.09 |

CI, confidence interval

Fig. 1

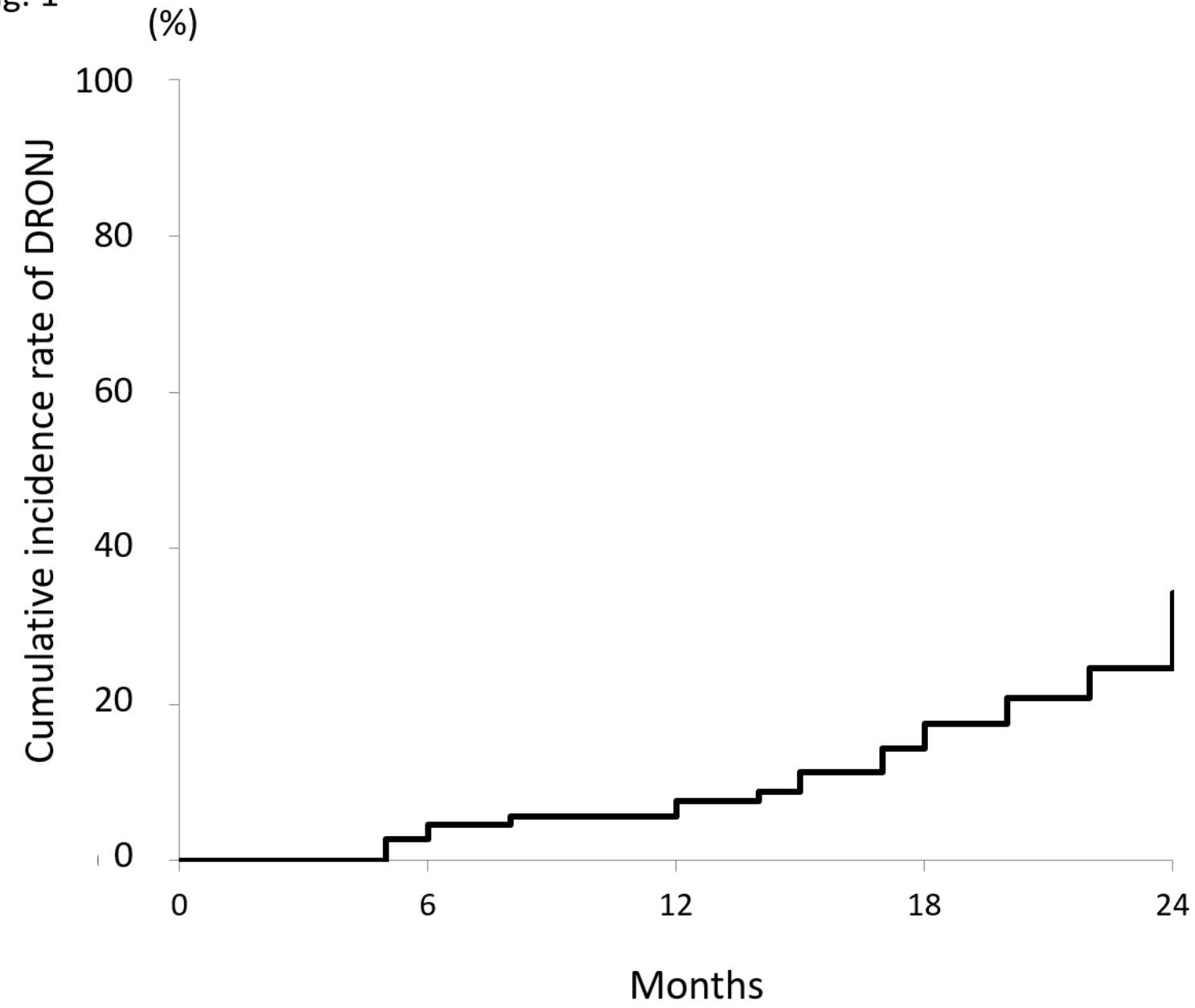
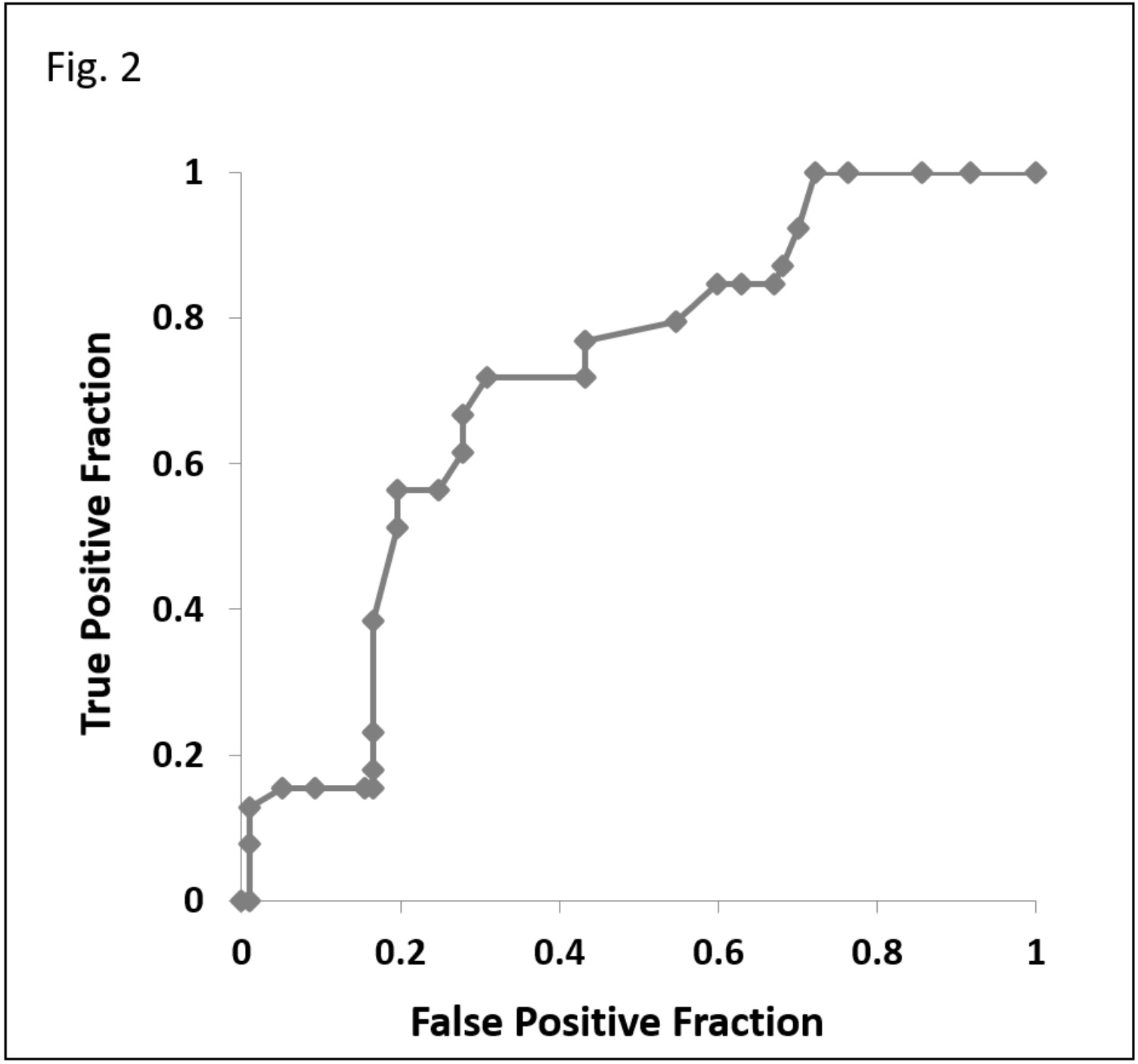

(%)
100
80
60
40
20
0
Cumulative incidence rate of DRONJ
0
6
12
18
24
Months

Fig. 2


True Positive Fraction
False Positive Fraction
0
0.2
0.4
0.6
0.8
1
0
0.2
0.4
0.6
0.8
1