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Original Article

Risk factors for the development of medication-related osteonecrosis of the jaw and effects of tooth extraction with local infection

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Abstract *Background/purpose:* Tooth extraction has been avoided in patients receiving antiresorptive agent (ARA) therapy. This study aimed to investigate dental findings associated with medication-related osteonecrosis of the jaw (MRONJ) development in patients.
Materials and methods: First, in patients treated with high-dose ARAs, the relationship between dental findings and MRONJ development was examined. Next, in patients with MRONJ undergoing surgery, the relationship between dental findings and MRONJ occurring at a site distant from the initial site was examined.
Results: MRONJ occurred in 13 of 172 patients (80 of 3725 teeth) during observation. Multiple tooth loss, periodontal ligament space enlargement, alveolar bone loss, periapical osteosclerosis, and local infection symptoms were associated with MRONJ development. Tooth extraction significantly reduced MRONJ development. Regarding other-site recurrence, new MRONJ developed at other sites in 54 of 357 patients with MRONJ (171 of 5038 teeth). Multiple tooth loss, apical lesions, periodontal ligament space enlargement, and periapical osteosclerosis were significantly associated with MRONJ development. In patients with malignant tumors, tooth extraction significantly reduced the subsequent incidence of MRONJ, while in patients

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with osteoporosis, there was no difference in the incidence of MRONJ between patients with and without tooth extraction.
Conclusion: MRONJ was more likely to develop from teeth with local infections. Extraction of teeth with local infection in patients with malignancy may be more effective than tooth preservation in preventing MRONJ.

Introduction

Antiresorptive agents (ARAs) are widely used to prevent fractures in osteoporosis and treat skeletal-related events associated with bone metastases of malignant tumors and multiple myeloma.[1,2] However, a serious side effect of ARAs is medication-related osteonecrosis of the jaw (MRONJ). Conservative treatment was previously recommended for MRONJ[3,4]; however, the effectiveness of surgical treatment is now widely recognized.[5–9] Although surgical treatment cures many MRONJ cases, MRONJ can occur in older patients with osteoporosis and cancer patients with bone metastases and has a short prognosis; in such cases, surgery is unfeasible owing to poor general condition. Although surgery cures most MRONJ cases, MRONJ can often recur with continued ARA administration; thus, establishing methods to prevent MRONJ and its recurrence is important.

Systemic risk factors for MRONJ development include patients whose primary disease is malignancy and are receiving high-dose ARAs and concomitant medications such as tyrosine kinase inhibitors, vascular endothelial growth factor, mammalian target of rapamycin inhibitors, radiopharmaceuticals, selective estrogen receptor modulators, and immunosuppressants (methotrexate and corticosteroids). Regarding local risk factors for MRONJ development, dentoalveolar surgery (e.g., tooth extraction) is the most common identifiable predisposing factor.[10] The Japanese Society of Oral and Maxillofacial Surgeons position paper 2016,[11] Multinational Association of Supportive Care in Cancer Guidelines 2019,[12] and Korean Association of Oral & Maxillofacial Surgeons (KAOMS) position paper[13] also state that surgical procedures invasive to the bone (e.g., tooth extraction) are a major risk factor for MRONJ development.

Most reports on tooth extraction as a risk factor for MRONJ development are based on the observation that a large number of MRONJ patients develop the disease due to tooth extraction.[14–17] Conversely, the American Association of Oral and Maxillofacial Surgeons (AAOMS) 2022 cites concomitant oral disease (e.g., periodontal disease) or periapical pathology as a risk factor.[10] The KAOMS position paper states that dental procedures accompanying alveolar bone exposure and damage (e.g., tooth extraction, dental implant installation and removal) and periodontal and periapical operations may increase MRONJ occurrence, advising caution in ARA-treated patients. Furthermore, it indicates that infections are the main reasons necessitating dental extraction or dentoalveolar surgery; thus, infections, rather than dentoalveolar surgery, may be responsible for MRONJ occurrence.[13] Otto et al.[18] stated that MRONJ is not caused by the extraction itself but by local infection present in the tooth requiring extraction, and Soutome et al.[19,20] reported that infected teeth should be extracted.

It remains unclear whether the local risk factor for MRONJ is tooth extraction or local infection present in the tooth to be extracted, and whether it is better to preserve or extract the infected tooth. Thus, this study aimed to answer these clinical questions: what are the local risk factors for MRONJ development; do patients with infected teeth have a higher risk of MRONJ development if the teeth are extracted or preserved; and which teeth need to be extracted.

Materials and methods

Risk factors for MRONJ development and effects of tooth extraction in cancer patients receiving high-dose ARAs

This study included cancer patients receiving high-dose ARAs who visited the Nagasaki University Hospital, between 2011 and 2021 for perioperative oral management. Patients with MRONJ at their initial visit, those without a panoramic radiographic examination, and those who stopped visiting the hospital within 1 month were excluded. The following data were retrieved from medical records and radiographs: age, sex, smoking habit, drinking habit, diabetes, corticosteroid administration, ARA type, duration of ARA administration, number of remaining teeth, white blood cell count, serum albumin, serum creatinine, panoramic radiographic findings (apical lesions >3 mm, degree of alveolar bone resorption, periodontal ligament space enlargement, and periapical osteosclerosis) (Fig. 1), intraoral infection symptoms (gingival redness, swelling, pus discharge, etc.), tooth extraction, MRONJ development, and timing and location of MRONJ development.

Risk factors for MRONJ recurrence at other sites and effects of tooth extraction in MRONJ patients undergoing surgery

This study included MRONJ patients who underwent surgery at the Nagasaki University Hospital from 2011 to 2021. After complete healing of MRONJ at the operated site, we examined whether new MRONJ developed at a different site. Patients with recurrence from a site adjacent to the

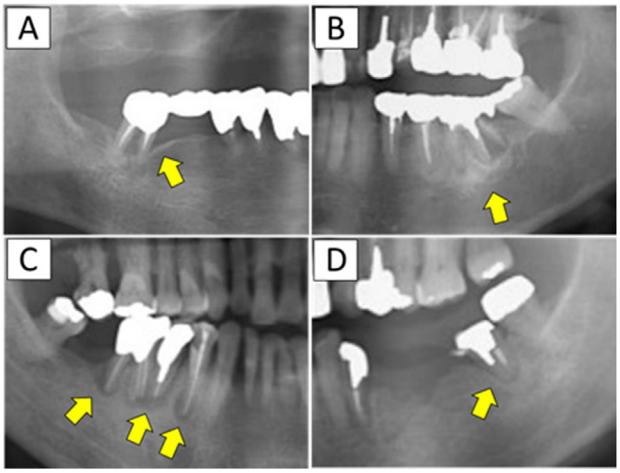

Figure 1 Panoramic radiographic findings. A: alveolar bone resorption, B: periapical osteosclerosis, C: apical lesion, D: enlargement of periodontal ligament space.

first MRONJ site, those who stopped visiting the hospital within 1 month post-surgery, and those without panoramic radiographic examinations were excluded. The following data were retrieved from medical records and radiographs: age, sex, primary disease, smoking habit, drinking habit, diabetes, corticosteroid administration, ARA type, duration of ARA administration, drug holiday, number of remaining teeth, white blood cell count at initial visit, serum albumin, serum creatinine, panoramic radiographic findings (root apex lesions >3 mm, degree of alveolar bone resorption, periodontal ligament space enlargement, and osteosclerosis around root apex), local infection symptoms (gingival redness, swelling, pus drainage, etc.), presence or absence of tooth extraction, presence or absence of MRONJ in other parts of the mouth, MRONJ development, and timing and location of MRONJ development.

Statistical analysis

All statistical analyses were performed using SPSS software of version 26.0 (International Business Machines Corporation: IBM, Armonk, New York, USA). First, univariate and multivariate Cox regression analyses were performed for the association between each factor and MRONJ incidence. Next, the effect of tooth extraction was examined. Because extractions were performed on teeth with severe local infection, a large bias between extraction and non-extraction cases was expected. Therefore, we performed propensity score matching after adjusting for dental background findings in the extraction and non-extraction groups, and the subsequent MRONJ incidence in both groups was determined using the Kaplan–Meier method and tested using the log-rank test.

Ethics

This study conformed to the ethical guidelines of the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research involving Human Subjects by the Ministry of Health, Labour and Welfare of Japan. Ethical approval was obtained from the Institutional Review Board (IRB) of Nagasaki University Hospital (#20081722). As this was a retrospective study, patient-identifiable information was removed. The research plan was published on the homepages of the participating hospitals' websites, with an opt-out option according to IRB instructions.

Results

Risk factors for MRONJ development and effects of tooth extraction in cancer patients receiving high-dose ARAs

In total, 172 patients were enrolled in the study (men: 70, women: 102), with a mean age of 62.3 years. Of these, 77 received bisphosphonates and 87 received denosumab; eight patients were initially administered bisphosphonates, which was changed to denosumab (Table 1). During follow-up, 13 patients (7.6 %) developed MRONJ. One of them developed MRONJ from a site where no tooth was present. In a per-person analysis of 172 patients, no factors were significantly associated with MRONJ development (Table 2).

From a total of 3725 teeth, 80 were associated with MRONJ development. Factors significantly associated with MRONJ development in the tooth-by-tooth analysis using univariate analysis included older age, diabetes mellitus, steroid medication, high serum creatinine levels, few remaining teeth, enlarged periodontal ligament space,

Table 1 Characteristics of 172 patients receiving high dose ARAs. ARA: antiresorptive agent, BP: bisphosphonate, DMB: denosumab, HR.

Variable		Number of patients/value
Age	Mean ± SD	62.3 ± 11.7 years
Sex	Male	70
	Female	102
Smoking	(−)	143
	(+)	29
Diabetes	(−)	153
	(+)	19
Corticosteroid	(−)	153
	(+)	19
Leukocytes	Mean ± SD	5260 ± 4170/μL
Serum albumin	Mean ± SD	3.33 ± 0.725
Serum creatinine	Mean ± SD	0.768 ± 0.273
Sort of ARA	BP	77
	DMB	87
	BP → DMB	8
Duration of ARA administration	≤ 180 dsays	136
	>180 days	36
Number of teeth	Median [25, 75 % tile]	24 [17, 27]
Development of MRONJ	(−)	159
	(+)	13
Total		172

Table 2 Factors related to development of MRONJ (172 patients, person-by-person analysis). ARA: antiresorptive agent, BP: bisphosphonate, DMB: denosumab, HR: hazard ratio, CI: confidence interval.

Variable		*P*-value	HR	95 % CI
Age	Years	0.189	1.036	0.983–1.091
Sex	Male vs. female	0.513	0.646	0.175–2.391
Smoking habit	(−) vs. (+)	0.384	1.791	0.482–6.651
Diabetes	(−) vs. (+)	0.678	0.647	0.083–5.043
Corticosteroid	(−) vs. (+)	0.523	0.512	0.066–3.982
Leukocytes	/μL	0.817	1.000	1.000–1.000
Serum albumin	g/L	0.828	1.102	0.459–2.649
Serum creatinine	mg/dL	0.572	0.484	0.039–5.982
Sort of ARA	BP vs. DMB vs. both	0.066	2.276	0.948–5.465
Duration of administration	<4 years vs. ≥ 4 years	0.355	1.762	0.530–5.857
Drug holiday during treatment	(−) vs. (+)	0.159	2.386	0.711–8.005

Cox regression analysis.

alveolar bone resorption, periapical osteosclerosis, local infection symptoms, and long-term ARA use. Multivariate analysis using the stepwise method revealed that male sex ($P = 0.011$), few remaining teeth ($P < 0.001$), enlarged periodontal ligament space ($P < 0.001$), local infection symptoms ($P < 0.001$), and long-term ARA use ($P < 0.001$) were significantly associated with MRONJ development (Table 3; Fig. 2).

Tooth extraction was performed on 73 teeth; 3725 teeth were examined before propensity score matching to determine the relationship between extraction and MRONJ incidence. Although MRONJ incidence was slightly higher in extraction cases than in non-extraction cases, this finding was not significant ($P = 0.101$). Tooth extractions are performed in dental infection cases that are difficult to manage with conservative treatment; therefore, a large bias exists in dental findings between extraction and non-extraction cases. Accordingly, we adjusted the dental finding factors using propensity score matching. Propensity scores were calculated for all patients by logistic regression analysis of the abovementioned five dental variables associated with tooth extraction. The concordance index (c-index) was 0.699, indicating an ability to differentiate between the tooth extraction and non-extraction groups, and

Table 3 Factors related to the development of MRONJ (3725 teeth, tooth-by-tooth analysis). ARA: antiresorptive agent, BP: bisphosphonate, DMB: denosumab, HR: hazard ratio, CI: confidence interval.

Variable		*P*-value	HR	95 % CI
i) Univariate analysis				
Age		*0.003	1.030	1.010–1.050
Sex	Female vs. male	0.118	1.434	0.912–2.254
Diabetes	(−) vs. (+)	*<0.001	3.249	1.932–5.464
Steroid	(−) vs. (+)	*0.044	0.356	0.130–0.974
Leukocytes		0.527	1.000	1.000–1.000
Albumin		0.516	1.119	0.798–1.570
Creatinine		*0.012	2.942	1.272–6.804
Sort of ARA	BP vs. DMB vs. both	0.657	1.086	0.755–1.562
Number of teeth		*<0.001	0.881	0.856–0.908
Apical lesion > 3 mm	(−) vs. (+)	0.149	2.809	0.690–11.441
Enlargement of periodontal ligament	(−) vs. (+)	*<0.001	5.006	3.167–7.913
Alveolar bone loss	<1/3 vs. 1/3–1/2 vs. >1/2	*<0.001	2.055	1.543–2.736
Osteosclerosis around dental root	(−) vs. (+)	*<0.001	6.961	4.252–11.396
Symptoms of local infection	(−) vs. (+)	*<0.001	11.957	7.457–19.175
Tooth extraction during ARA therapy	(−) vs. (+)	0.157	2.069	0.755–5.671
ARA administration	(−) vs. (+)	*0.011	1.012	1.003–1.021
ii) Multivariate analysis (stepwise selection)				
Sex	Female vs. male	*0.011	1.963	1.167–3.301
Number of teeth		*<0.001	0.899	0.870–0.929
Enlargement of periodontal ligament	(−) vs. (+)	*<0.001	3.506	2.146–5.730
Symptoms of local infection	(−) vs. (+)	*<0.001	9.419	5.462–16.243
Duration of administration	Months	*<0.001	1.025	1.014–1.036
Cox regression analysis (*significant)				

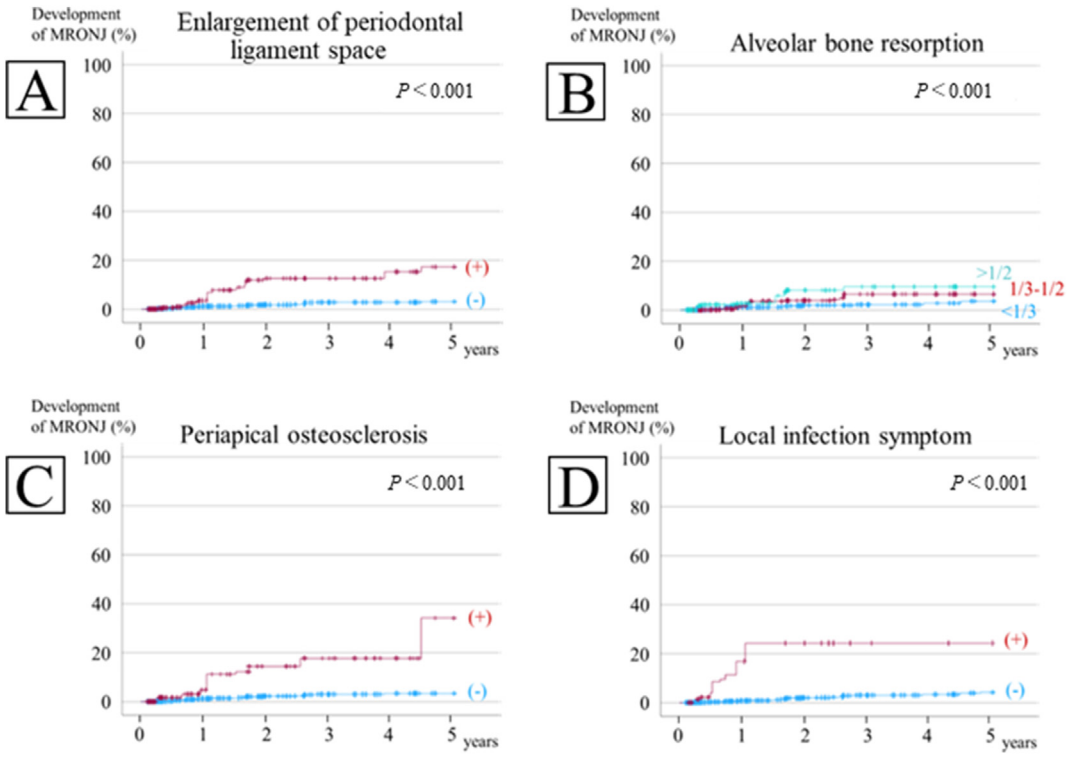

Figure 2 Relationship between radiographic findings and MRONJ development in patients with cancer receiving high-dose ARAs. A: enlargement of periodontal ligament space, B: alveolar bone resorption, C: periapical osteosclerosis, D: local infection symptoms ARAs, antiresorptive agents; MRONJ, medication-related osteonecrosis of the jaw.

the Hosmer–Lemeshow statistic was 0.047, indicating good calibration. The propensity score, which reflected the probability that a patient would receive tooth extraction, was 0.01292–0.38423 in the non-extraction group and 0.01009–0.38423 in the extraction group.

When the MRONJ incidence rate was calculated for the 146 matched teeth, the 5-year cumulative incidence rate was higher in the non-extraction cases (24.6 %) than in the extraction cases (7.4 %). Although the small number of extractions performed was not significant ($P = 0.055$), this suggests that extraction of an infected tooth may reduce MRONJ incidence (Fig. 3).

Risk factors for MRONJ recurrence at other sites and effects of tooth extraction in MRONJ patients undergoing surgery

In total, 357 patients were enrolled in the study (men: 150, women: 207), with a mean age of 76.0 years. Of these, 221 received bisphosphonates and 100 received denosumab; 36 patients initially received bisphosphonates but switched to denosumab (Table 4). Fifty-four patients (15.1 %) developed MRONJ at other sites during follow-up after MRONJ surgery; three of them developed MRONJ in areas where no teeth were present. By primary disease, MRONJ occurred in 22 of 218 osteoporosis patients (10.1 %) and 32 of 218 patients with malignancy (23.0 %). In a per-person analysis of 357 patients, no factors were significantly associated with MRONJ recurrence at other sites (Table 5).

From a total of 5038 teeth, 171 were associated with MRONJ recurrence. In a tooth-by-tooth analysis using univariate analysis, factors significantly associated with MRONJ recurrence at other sites were older age, diabetes, steroid medication, high serum creatinine levels, few remaining teeth, enlarged periodontal ligament space, alveolar bone resorption, periapical osteosclerosis, local infection symptoms, and long-term ARA administration. Multivariate analysis using the stepwise method revealed that diabetes mellitus, few remaining teeth, apical lesions >3 mm, enlarged periodontal ligament space, and periapical osteosclerosis were significantly associated with MRONJ development; furthermore, extraction of teeth with local infection significantly reduced the MRONJ relapse rate (Table 6; Fig. 4).

The effect of tooth extraction was examined using propensity score matching as described above. The c-index was 0.913, and the Hosmer–Lemeshow statistic was <0.001. In the 5038 pre-matched teeth, 299 extracted teeth were significantly more associated with MRONJ development than 4739 non-extracted teeth. When adjusted for dental background factors using propensity score matching, the 5-year cumulative incidence rate for the 532 matched teeth was significantly higher in the non-extraction cases (71.2 %) than in the extraction cases (15.0 %; $P = 0.005$). This indicates that extraction of an infected tooth was associated with a lower incidence of MRONJ recurrence (Fig. 5).

The effect of tooth extraction was further examined separately for osteoporosis and malignancy as the primary

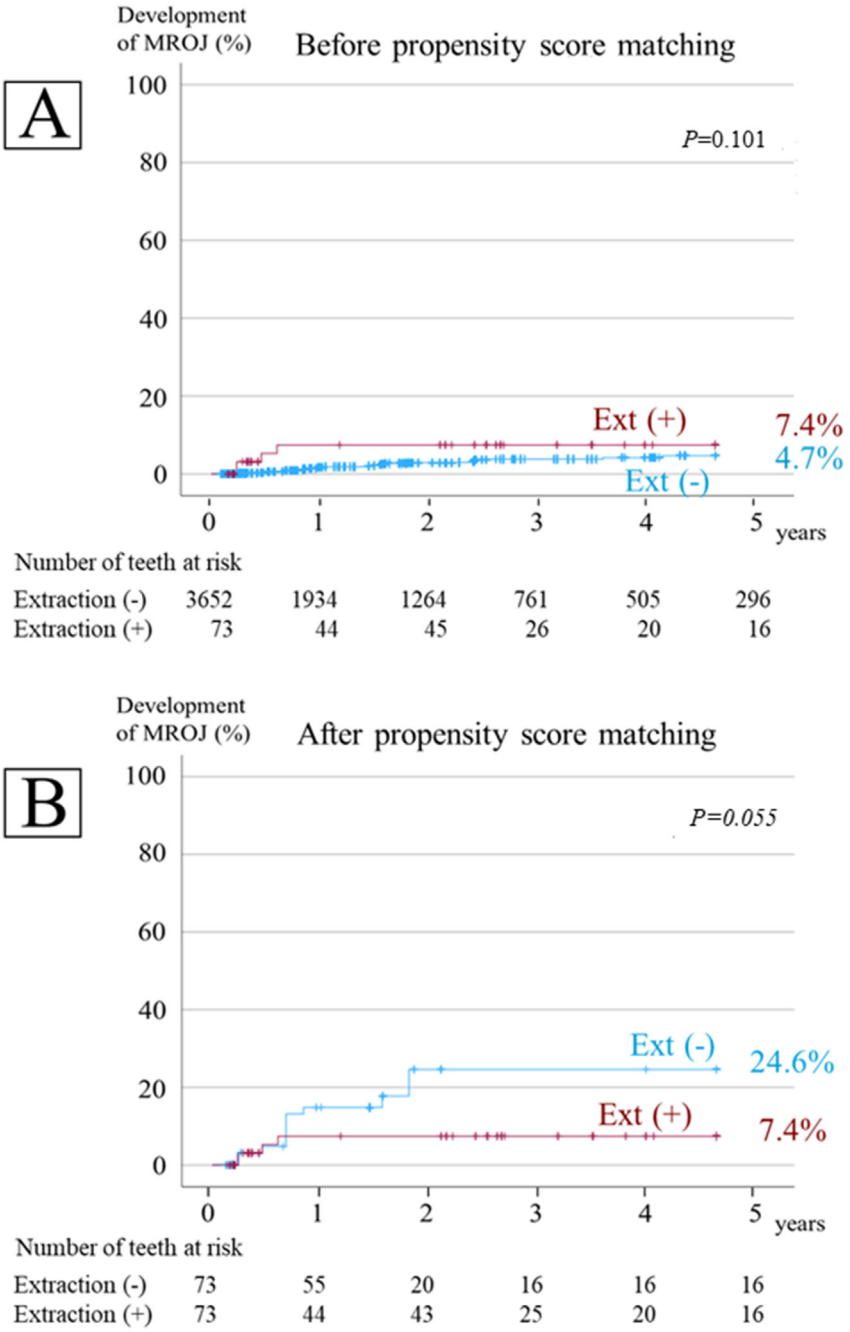

Figure 3 Relationship between tooth extraction and MRONJ development in patients with cancer receiving high-dose ARAs. A: before propensity score matching, B: after propensity score matching. ARAs, antiresorptive agents; MRONJ, medication-related osteonecrosis of the jaw.

disease. In 2936 teeth of osteoporosis patients, the MRONJ recurrence rate was significantly higher in the extraction cases ($P < 0.001$) when all cases were examined. Next, propensity score matching was performed; the c-index was 0.917, and the Hosmer–Lemeshow statistic was 0.003. With 344 matched teeth, there was no significant difference in MRONJ recurrence at other sites between the extraction and non-extraction cases ($P = 0.781$) (Fig. 6).

For 2198 teeth with malignancy, the MRONJ recurrence rate was significantly higher in the extraction cases when all cases were examined. For 154 teeth after propensity score matching (c-index, 0.928; Hosmer–Lemeshow statistic, 0.014), the 5-year cumulative incidence rate was 46.5 % for extracted teeth and 58.8 % for non-extracted teeth, indicating that extraction significantly reduced MRONJ recurrence ($P = 0.042$) (Fig. 7).

As described above, the extraction of infected teeth in patients with malignant tumors was associated with a low incidence of MRONJ recurrence at other sites; however, there was no significant difference in MRONJ recurrence rates between extraction and non-extraction cases in osteoporosis patients.

Table 4 Characteristics of 357 patients undergoing surgery for MRONJ. ARA: antiresorptive agent, BP: bisphosphonate, DMB: denosumab.

Variable		Number of patient/Mean ± SD
Age	Years	76.0 ± 11.6
Sex	Male	150
	Female	207
Primary disease	Osteoporosis	218
	Malignant tumor	139
Diabetes	(−)	301
	(+)	56
Corticosteroid	(−)	277
	(+)	80
Leukocytes ($10^2/\mu L$)	Mean ± SD	66.7 ± 24.7
Serum albumin (g/L)	Mean ± S	3.69 ± 0.627
Serum creatinine (mg/dL)	Mean ± SD	0.950 ± 0.719
Sort of ARA	BP	221
	DMB	100
	BP→DMB	36
Duration of ARA administration	<4 years	160
	≥ 4 years	156
	Unknown	41
Drug holiday during treatment	(−)	219
	(+)	117
	Unknown	21
Number of teeth	Median [25, 75 % tile]	18.0 [11.0, 24.0]
Total		357

Table 5 Factors related to recurrence at other site in patients with MRONJ (357 patients, person-by-person analysis). ARA: antiresorptive agent, BP: bisphosphonate, DMB: denosumab, HR: hazard ratio, CI: confidence interval.

Variable		*P*-value	HR	95 % CI
Age	Years	0.726	0.996	0.974−1.019
Sex	Male vs. female	0.551	0.846	0.487−1.468
Primary disease	Osteoporosis vs. malignant tumor	0.194	1.460	0.825−2.585
Diabetes	(−) vs. (+)	0.110	1.729	0.884−3.383
Corticosteroid	(−) vs. (+)	0.419	1.288	0.697−2.377
Leukocytes	/μL	0.951	1.000	0.987−1.012
Serum albumin	g/L	0.990	1.003	0.632−1.591
Serum creatinine	mg/dL	0.524	0.781	0.365−1.672
Sort of ARA	BP vs. DMB vs. both	0.125	1.345	0.921−1.965
Duration of administration	<4 years vs. ≥ 4 years	0.551	1.186	0.677−2.077
Drug holiday during treatment	(−) vs. (+)	0.132	1.537	0.879−2.688

Cox regression analysis.

Discussion

Observations of a large number of teeth in patients receiving ARAs showed that the risk of MRONJ development from teeth with local infection was significantly increased. The study findings also revealed that extraction of infected teeth, rather than avoiding extraction, significantly reduces subsequent MRONJ development, especially in patients receiving high-dose ARAs.

Twenty years have passed since the first MRONJ report,[21] and various studies have been conducted on its treatment and prevention. Regarding MRONJ frequency, the AAOMS position paper 2022[10] described that, based on the results of clinical trials and systematic reviews, MRONJ incidence in cancer patients treated with zoledronic acid was <5 %, with a risk of MRONJ development 2−10 times higher than that in cancer patients treated with placebo. Conversely, the low dose in osteoporosis patients has been associated with an MRONJ incidence of 0.02−0.05 %, which is comparable to that in the placebo group (0−0.02 %). Furthermore, MRONJ incidence in Japanese patients is reported as 1.6−12.4 % in high-dose patients and 0.104 % or 22.9/100,000 person-years in low-dose patients, suggesting that MRONJ incidence in Japan is approximately one digit higher than that in Western countries, although the details remain unknown.[21−23]

Table 6 Risk factors associated with recurrence at another site (5038 teeth, tooth-by-tooth analysis). ARA: antiresorptive agent, BP: bisphosphonate, DMB: denosumab, HR: hazard ratio, CI: confidence interval.

Variable		*P*-value	HR	95 % CI
i) Univariate analysis				
Age		0.533	1.004	0.992–1.016
Sex	Female vs. male	0.304	0.850	0.623–1.159
Primary disease	Osteoporosis vs. malignant tumor	*0.013	1.507	1.092–2.080
Diabetes	(−) vs. (+)	*0.002	1.781	1.244–2.550
Steroid	(−) vs. (+)	0.229	1.224	0.880–1.702
Leukocytes		0.149	1.000	1.000–1.000
Albumin		0.560	0.912	0.669–1.243
Creatinine		0.933	0.988	0.750–1.301
Sort of ARA	BP vs. DMB vs. both	0.070	1.222	0.984–1.518
Number of teeth		*<0.001	0.904	0.884–0.924
Site of tooth	Upper vs. lower jaw	*<0.001	2.158	1.558–2.989
Apical lesion >3 mm	(−) vs. (+)	*<0.001	15.618	9.312–26.194
Enlargement of periodontal space	(−) vs. (+)	*<0.001	9.539	7.031–12.942
Alveolar bone loss	<1/3 vs. 1/3–1/2 vs. >1/2	*<0.001	3.156	2.600–3.832
Periapical osteosclerosis	(−) vs. (+)	*<0.001	76.093	45.416–127.493
Local infection symptom	(−) vs. (+)	*<0.001	4.120	2.373–7.154
Tooth extraction	(−) vs. (+)	*<0.001	3.529	2.223–5.600
ARA administration (days)		0.183	1.000	1.000–1.000
ii) Multivariate analysis (stepwise selection)				
Diabetes	(−) vs. (+)	*<0.001	2.198	1.501–3.219
Steroid	(−) vs. (+)	0.050	1.421	1.001–2.019
Number of teeth		*<0.001	0.949	0.925–0.974
Apical lesion >3 mm	(−) vs. (+)	*0.005	2.164	1.262–3.711
Enlargement of periodontal space	(−) vs. (+)	*0.013	1.530	1.094–2.140
Periapical osteosclerosis	(−) vs. (+)	*<0.001	56.741	32.866–97.958
Tooth extraction	(−) vs. (+)	*<0.001	0.389	0.239–0.632

Cox regression analysis (*significant).

Risk factors for MRONJ development include systemic factors, such as diabetes mellitus, rheumatoid arthritis, steroid and anticancer medications, advanced age, female sex, smoking, and obesity, as well as local factors, such as poor oral hygiene and bone-damaging procedures including tooth extraction, dental implant installation and removal, and periodontal or periapical operations.[10–13] The 2009 AAOMS position paper[24] suggested avoiding elective dentoalveolar surgical procedures in patients with established MRONJ, because these surgical sites could cause additional areas of exposed necrotic bone. It also recommended that the sequestra, which may affect soft tissues, should be curetted only to a minimal extent without exposing the normal bone, and the separated sequestra should be removed without exposing the normal bone. At the time, it was believed that surgical procedures that reached the bone in ARA-treated patients could cause new MRONJ. A Japanese Association of Oral Surgeons position paper also states that tooth extraction, dental implants, apical surgery, and periodontal surgery with bone invasion may be risk factors for MRONJ; therefore, invasive dental procedures that reach the bone have been avoided during ARA treatment.[4] Furthermore, it indicated that in cancer patients receiving high-dose ARAs, conservative procedures are desirable, unnecessary aggressive curettage is contraindicated, and dental treatments should be avoided as much as possible; if dental treatments are urgently required, nonsurgical treatments are suggested rather than surgical treatments (e.g., tooth extraction or dental implants). Nevertheless, the number of MRONJ patients is increasing in Japan.[22,23] This may be largely due to increased number of ARA prescriptions, but it is also possible that the prophylactic approach of avoiding tooth extraction has been ineffective.

MRONJ often develops in ARA-treated patients following tooth extraction. However, most teeth requiring extraction have severe local infection that is difficult to manage with conservative treatment. It is controversial whether MRONJ development is due to the invasiveness of the extraction procedure, local infection, or both. Few studies have examined the effect of extracting infected teeth on MRONJ prevention. Soutome et al.[20] found a higher MRONJ incidence in a group of high-dose ARA patients who underwent tooth extraction compared to a non-extraction group; however, dental findings significantly differed between both groups. Propensity score matching after adjusting for background factors revealed that MRONJ incidence was higher in the tooth-sparing group.[19,20] However, their study only included

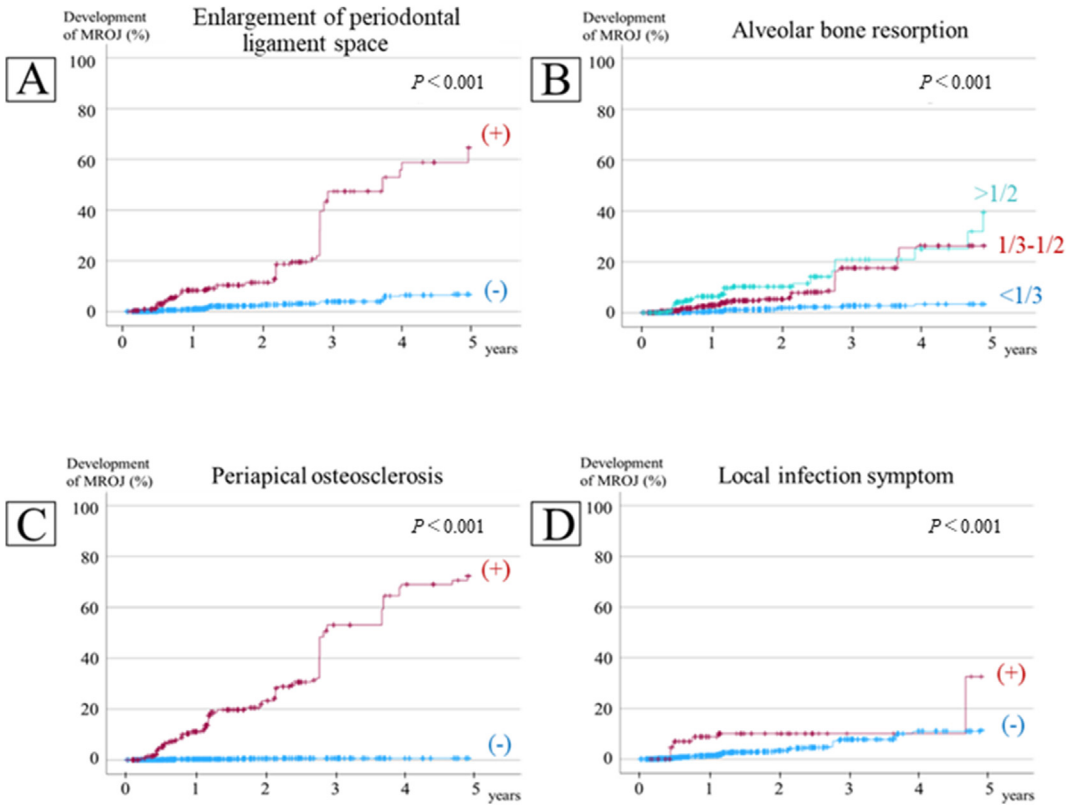

Figure 4 Relationship between radiographic findings and MRONJ recurrence at other sites. A: enlargement of periodontal ligament space, B: alveolar bone resorption, C: periapical osteosclerosis, D: local infection symptoms. MRONJ, medication-related osteonecrosis of the jaw.

patients with teeth having abnormal radiographic findings. To the best of our knowledge, no studies have compared MRONJ incidence in patients with extracted and non-extracted teeth, including those without abnormal findings.

In this study, we first examined patients who were receiving high-dose ARAs but did not develop MRONJ. Our results suggest that, in addition to known factors such as diabetes, steroids, and long-term ARA administration, a decreased number of remaining teeth and dental findings, such as enlarged periodontal ligament space, alveolar bone resorption, periapical osteosclerosis, and local infection symptoms, were associated with MRONJ development. Although many studies have reported that poor oral hygiene is a risk factor for MRONJ development, ours was a retrospective study, and oral hygiene indicators (e.g., plaque score and oral hygiene index) were unknown; therefore, the influence of oral hygiene status could not be directly examined. However, poor oral hygiene can lead to severe dental caries and periodontal disease, which ultimately causes tooth extraction and a decrease in the number of remaining teeth. In our study, the decrease in the number of remaining teeth being significantly associated with MRONJ development indicates, albeit indirectly, that poor oral hygiene is a risk factor for MRONJ development. In the univariate analysis, MRONJ developed significantly more efficiently from teeth with dental findings, such as enlarged periodontal ligament space, alveolar bone resorption, periapical osteosclerosis, and local infection symptoms. In the multivariate analysis, male sex, few remaining teeth, enlarged periodontal ligament space, local infection symptoms, and long-term ARA administration were independent risk factors. The effect of tooth extractions in preventing MRONJ was examined by adjusting dental findings between the extraction and non-extraction groups using propensity score matching, which showed that MRONJ incidence was significantly lower in the extraction group. These findings suggest that in cancer patients receiving high-dose ARAs, extraction of teeth within a short period of ARA administration is recommended if the patient's general condition permits, because a large number of MRONJ cases develop subsequently from infected teeth.

Next, based on MRONJ surgery cases, we examined the risk factors for new MRONJ development from a site different than the surgical site. Once a patient develops MRONJ, the risk of developing subsequent MRONJ from a different site is considered high, as the patient may have systemic factors that predispose them to MRONJ development. In our study, a high frequency of MRONJ development at a new site was observed in 10.1 % of osteoporosis patients and 23.0 % of patients with malignant tumors. In the tooth-by-tooth analysis, the incidence of new MRONJ was higher in patients with fewer remaining teeth, older

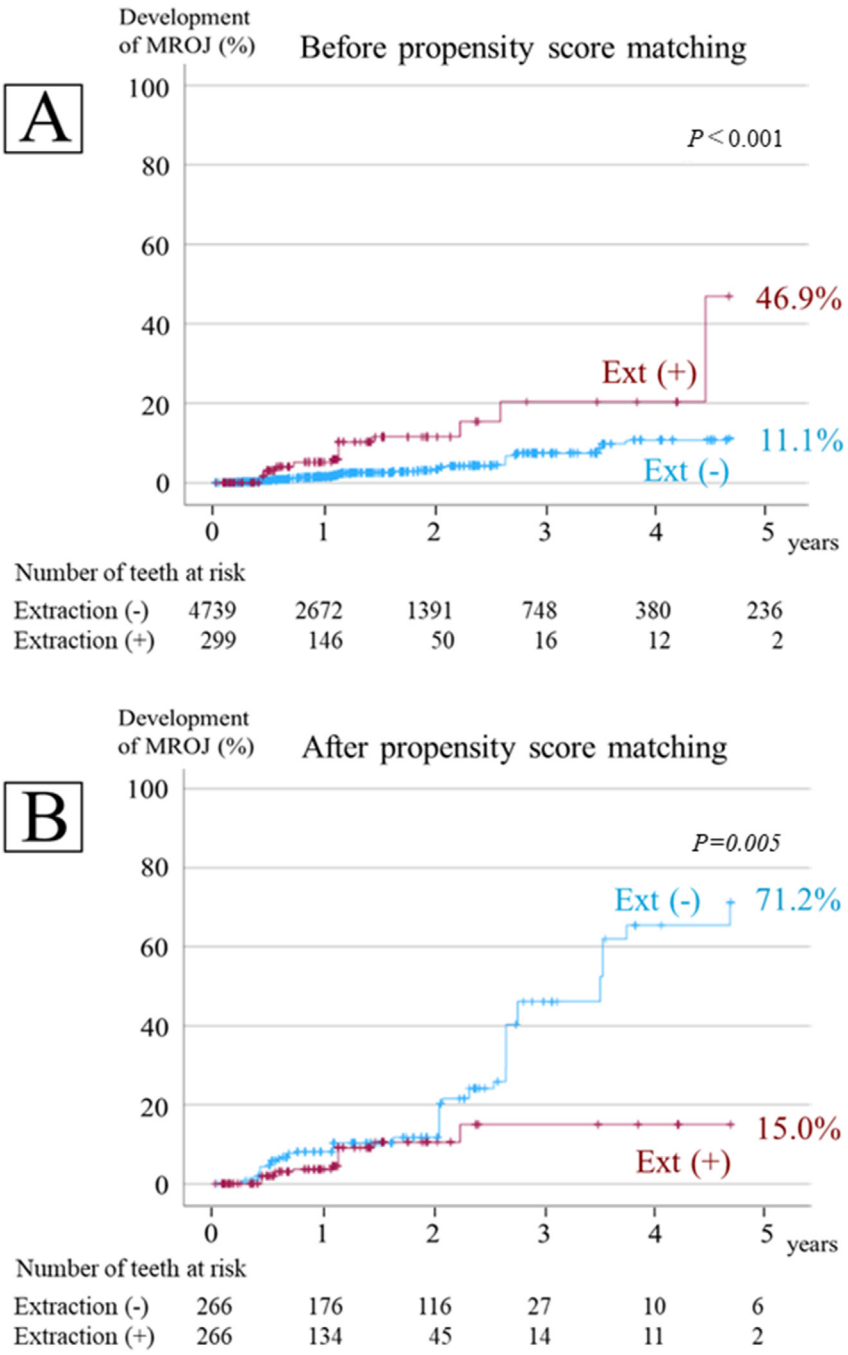

Figure 5 Relationship between tooth extraction and MRONJ recurrence at other sites in patients receiving ARAs. A: before propensity score matching, B: after propensity score matching. ARAs, antiresorptive agents; MRONJ, medication-related osteonecrosis of the jaw.

age, diabetes, and steroid administration, which may be owing to poor oral hygiene in patients with fewer remaining teeth, as mentioned earlier. Dental factors such as apical lesions, enlarged periodontal ligament space, alveolar bone resorption, periapical osteosclerosis, and local infection symptoms were also associated with MRONJ development. A propensity score matching analysis of the effects of tooth extraction on MRONJ recurrence prevention showed that in patients with malignant tumors, similar to the above results, extracting an infected tooth significantly reduced MRONJ recurrence at other sites, even when the patient was receiving ARAs. Conversely, for osteoporosis patients, MRONJ incidence did not significantly differ between the extracted and non-extracted groups, suggesting that tooth

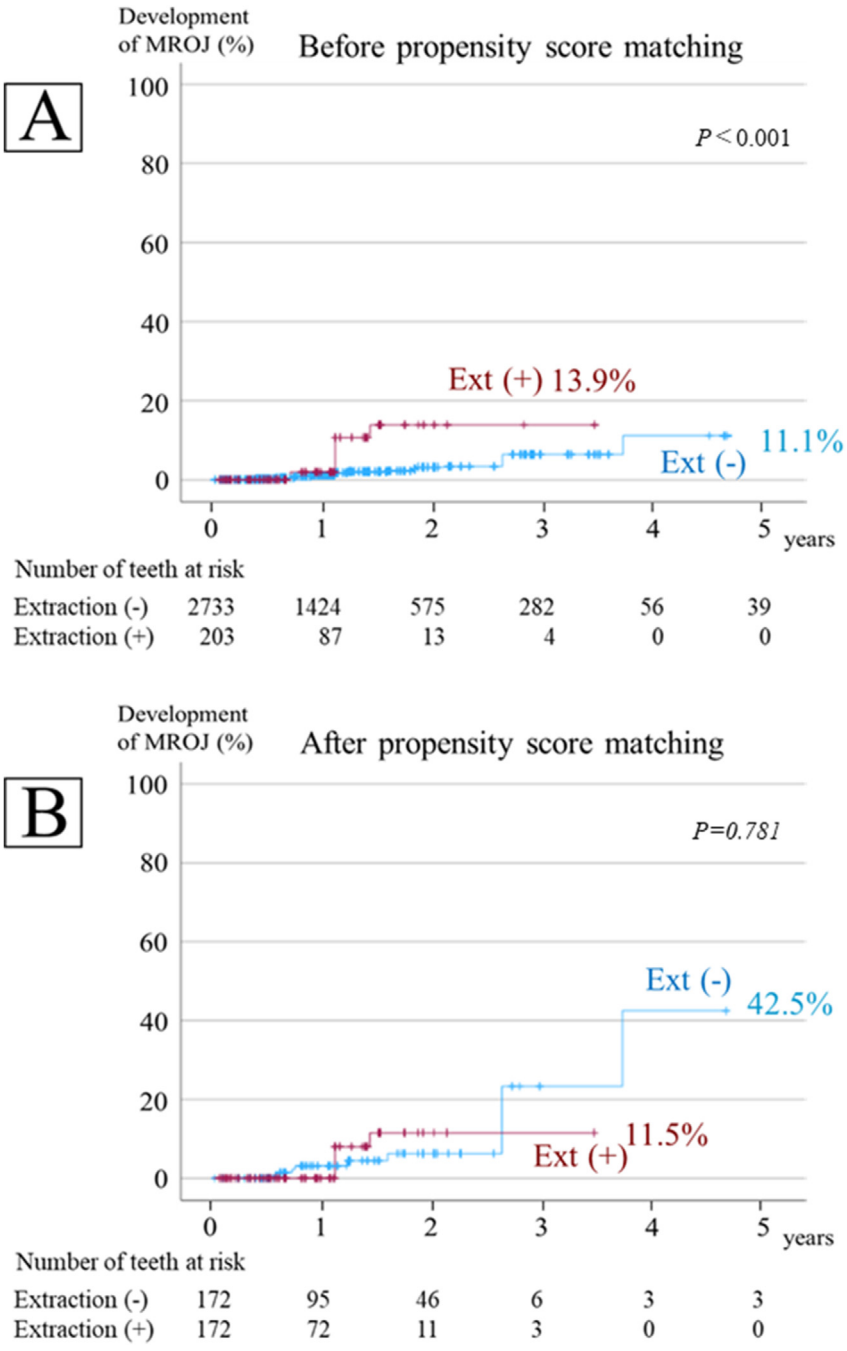

Figure 6 Relationship between tooth extraction and MRONJ recurrence at other sites in patients with osteoporosis receiving low-dose ARAs. A: before propensity score matching, B: after propensity score matching. ARAs, antiresorptive agents; MRONJ, medication-related osteonecrosis of the jaw.

extraction decisions may be determined by clinical symptoms and patient preference.

Our study has some limitations. It is unclear whether our results can be generalized because the study patients' oral hygiene status could not be determined owing to the study's retrospective nature. Moreover, there are no established standards for educating patients about oral hygiene. Nonetheless, to our knowledge, this is the first study to examine the relationship between dental findings and MRONJ development using a large number of teeth and to demonstrate the preventive effect of tooth extraction on MRONJ development. Future investigation of methods for preventing MRONJ development via multicenter prospective studies is warranted.

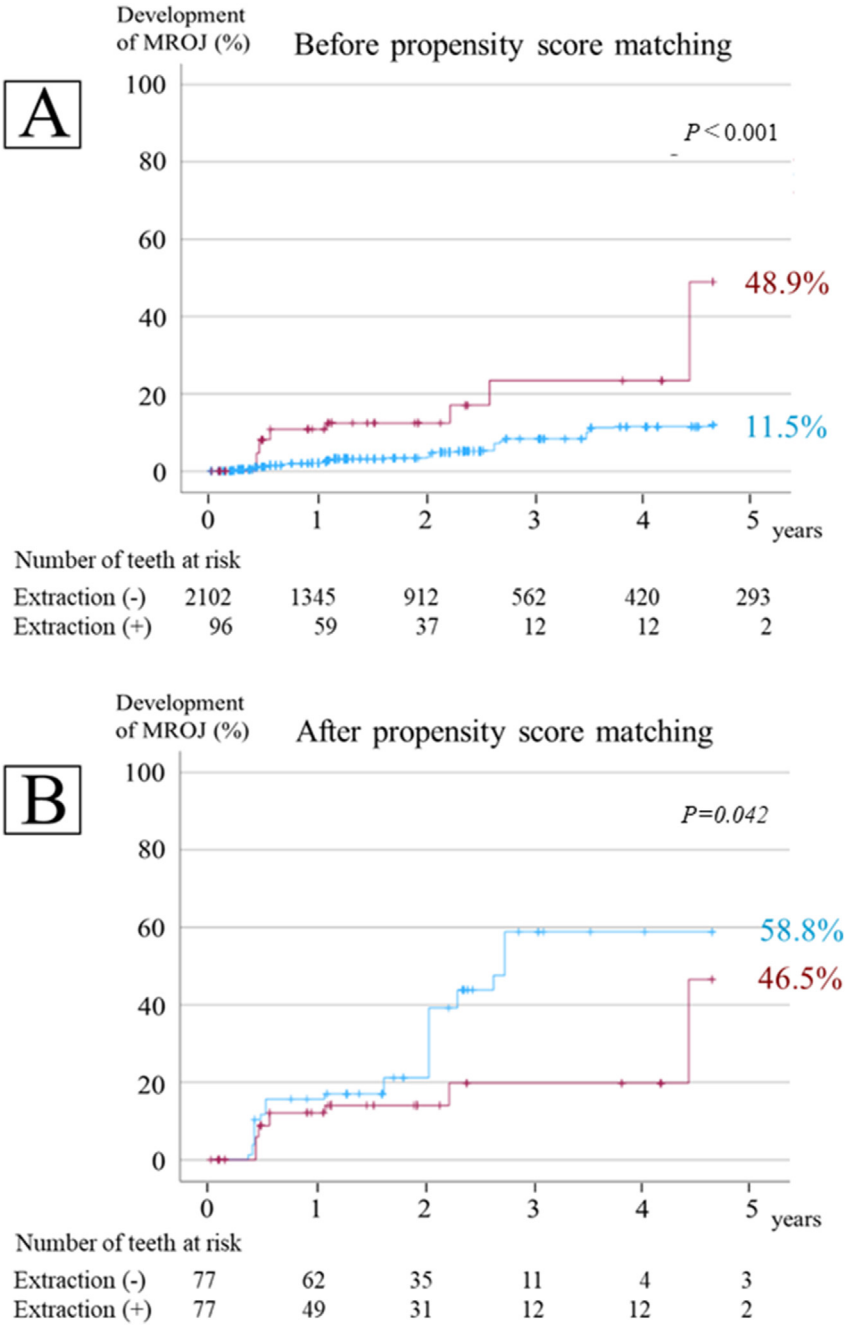

Figure 7 Relationship between tooth extraction and MRONJ recurrence at other sites in patients with cancer receiving high-dose ARAs. A: before propensity score matching, B: after propensity score matching. ARAs, antiresorptive agents; MRONJ, medication-related osteonecrosis of the jaw.

Declaration of competing interest

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

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