

Prognosis By Cancer Type and Incidence of Zoledronic Acid-Related Osteonecrosis of the Jaw: A Single-Center Retrospective Study

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Abstract

Purpose

Survival time after bisphosphonate use has been increasingly recognized to be associated with the incidence of medication-related osteonecrosis of the jaw (MRONJ); however, this has not been elucidated sufficiently in the literature. This study aimed to clarify the incidence of MRONJ and the corresponding survival rate of patients treated with zoledronic acid (ZA) for each type of cancer and obtain useful information for the oral management of cancer.

Methods

We evaluated 988 patients who were administered ZA at our hospital; among them, 862 patients with metastatic bone tumors or myeloma were included.

Results

The median survival time (MST) after ZA initiation was 35, 34, 8, 41, 12, and 6 months for patients with breast, prostate, lung, myeloma, renal, and other cancers, respectively. Patients with cancers that had a short survival time (lung and other cancers [MST = 8 and 6 months, respectively] and cancers with MST < 10 months) did not develop MRONJ; this could be attributed to the shorter duration of ZA administration. The cumulative incidence of MRONJ in breast cancer, prostate cancer, and multiple myeloma was related to the frequency of anti-resorptive drug use and the increased risk over time. In renal cancer, the cumulative incidence of MRONJ increased early, although the MST was 12 months.

Conclusion

For the dentists in charge of dental management, it is essential to be aware of prognosis-related factors, predict MRONJ risk for each cancer treatment, and use risk prediction in dental management planning, particularly for cancers with non-poor prognosis.

Background

Bisphosphonate (BP) or denosumab (Dmab) has been used to prevent and treat skeletal-related adverse events caused by cancer bone metastases and multiple myeloma. Many patients benefit from such bone-modifying agents (BMAs). However, medication-related osteonecrosis of the jaw (MRONJ), a serious adverse event, sometimes severely reduces the patient's quality of life [1]. MRONJ is a disease common to both the medical and dental fields, with no established treatment strategy; therefore, more emphasis should be placed on its prevention. The risk of developing MRONJ can be reduced significantly through dental evaluation and patient management by a team of healthcare providers before and during drug

therapy and in the long term [2, 3]. Non-restorable teeth and those with a poor prognosis should be extracted before initiating BMA administration [4]. Various recommendations, including the need for BP withdrawal, have been proposed for tooth extraction after BP use in non-cancer patients [4, 5]. However, there has been little discussion of the criteria for extracting teeth with poor prognosis before BP treatment in patients with and without cancer. The frequency of adverse events is between 0.2% and 6.7% in cancer patients exposed to BMA, whereas the risk of developing MRONJ in patients affected by osteometabolic diseases, including osteoporosis, is very low, with a prevalence between 0% and 0.4% [4]. Although patients with cancer are at a higher risk of developing MRONJ than those with bone metabolic diseases, the criteria for extraction of teeth with poor prognosis prior to BMA use should be considered more carefully from the perspective of the relationship between life expectancy and cancer type. Recent advances in cancer drug therapy have contributed to improving the prognosis of cancer patients with bone metastases, but prolonging survival leads to an increase in the cumulative dose of BP preparations and long-term BP treatment. These are the most important risk factors for the development of BP-related osteonecrosis of the jaw [6]. The survival time after initiating BP administration has been recently recognized to be associated with MRONJ incidence. However, to our knowledge, no studies have comprehensively demonstrated the relationship between the survival time of patients with each cancer type after bone metastasis or the survival time of patients with myeloma and MRONJ incidence, with the time of BP initiation as the baseline. Patients with a survival time of < 1 year after bone metastasis unsurprisingly have a low chance of MRONJ; in contrast, some cancer types appear to have a high MRONJ incidence, although the survival time is relatively short. Hence, we hypothesized that survival after bone metastasis was not simply related to MRONJ incidence; there are other factors at play. This study aimed to clarify the survival rate and MRONJ incidence in patients treated with zoledronic acid (ZA) at our hospital for each type of cancer and obtain useful information for oral management of cancer.

Methods

Patient selection and study design

This retrospective, observational, single-center study included consecutive cancer patients with bone metastasis or multiple myeloma who were diagnosed in our hospital and administered ZA from July 2008 to December 2014.

The inclusion criteria were as follows: ZA initiated at our institution for bone metastases or multiple myeloma and an assessment for MRONJ at the time of evaluation. The exclusion criteria were as follows: starting ZA for reasons other than bone metastases and multiple myeloma and having a history of taking other BP preparations before initiating ZA therapy. The evaluation point was February 2018, and the observation period was from ZA initiation to the evaluation point. The occurrence of MRONJ and survival after ZA treatment initiation were confirmed at the evaluation point.

Bone metastasis was detected by whole-body scintigraphy or positron emission tomography/computed tomography (CT) and other imaging modalities (e.g., standard X-rays, CT, or magnetic resonance imaging

of the skeleton). The data related to each patient covered the whole course of the disease and all cancer treatments. Assessed variables included sex, age, sites of bone metastases, survival after bone metastasis diagnosis, survival after MRONJ diagnosis, times of BP therapy, and occurrence of MRONJ. For patients whose survival was difficult to confirm in the medical records of our hospital, confirmation was made through inquiries to the transferring facility or resident registration inquiries with the cooperation of our hospital cancer registry. Finally, the patients' cancer types were classified into breast, prostate, lung, multiple myeloma, renal, and other cancers, and the 3- and 5-year survival rates for each type and the 8-year cumulative incidence rate of MRONJ were investigated. Breast and prostate cancers were divided into two groups: exclusively bone metastasis (BM) and visceral metastasis (VM; including metastasis to the lung, liver, brain, skin, muscle, pleura, and peritoneum). Thereafter, subgroup analysis was performed. In cases where patients were switched to Dmab after initiating ZA, data on the frequency of ZA and Dmab use were compiled. The total frequency of BMA use was compared among cancer types.

Statistical analysis

Statistical analysis was performed using JMP 14 (SAS Institute, Cary, NC). The 3- and 5-year survival rates and the 8-year cumulative incidence of MRONJ were calculated using the Kaplan–Meier method. Any significant inter-group differences were evaluated using the log-rank test. The Wilcoxon rank-sum test was used to compare the duration to MRONJ occurrence in each group and box plots were used to display the frequency of BMA use. Statistical significance was established at $p < 0.05$.

Results

Patient details

As shown in the flow chart (Fig. 1), 126 of the 988 enrolled patients were ineligible. These included patients with hypercalcemia ($n = 112$), osteosarcoma ($n = 12$), bone invasion of solid tumors ($n = 1$), and non-metastatic pelvic fracture ($n = 1$). Among 862 included patients, the median age (interquartile range [IQR]) was 65 (57–73) years. The proportions of males (46%) and females (54%) were similar. The cancers were classified into six groups: breast cancer ($n = 287$, 33%), prostate cancer ($n = 163$, 19%), lung cancer ($n = 134$, 16%), multiple myeloma ($n = 86$, 10%), renal cancer ($n = 40$, 5%), and other cancers ($n = 152$, 18%).

Among 862 patients, 757 (88%) received ZA alone, while the remaining 106 (12%) switched to Dmab after ZA administration. Almost all patients received a base dose of 4 mg of ZA intravenously every 4 weeks, but some patients received a reduced dose in the range of 3.0–3.5 mg considering renal function. Dmab was administered at 120 mg/4 weeks. Among patients with breast and renal cancers, 73 (25%) and 7 (17%), respectively, switched to Dmab, mainly because of decreased renal function; in other cancer types, >90% of patients received ZA alone (Table 1).

Table 1
Baseline demographic and clinical characteristics

Characteristic	Patients <i>n</i> (%)		Median (IQR) age, years		Females, <i>n</i> (%)		ZA only, <i>n</i> (%)		ZA+ Dmab, <i>n</i> (%)	
All patients	862	(100)	65	(57–73)	466	(54)	757	(88)	106	(12)
Type of cancer										
Breast	287	(33)	58	(50–66)	286	(100)	214	(75)	73	(25)
Prostate	163	(19)	71	(66–77)	0	(0)	156	(96)	7	(4)
Lung	134	(16)	66	(60–72)	54	(40)	129	(96)	5	(4)
Myeloma	86	(10)	69	(61–76)	45	(52)	82	(95)	4	(5)
Renal	40	(5)	65	(58–75)	12	(30)	33	(83)	7	(17)
Other*	152	(18)	66	(59–73)	69	(45)	138	(91)	14	(9)
<i>IQR</i> , interquartile range; <i>ZA</i> , zoledronic acid; <i>Dmab</i> , denosumab										
*Includes bladder or urinary duct (<i>n</i> = 21), bile duct (<i>n</i> = 3), colorectal (<i>n</i> = 14), esophagus (<i>n</i> = 6), gastric (<i>n</i> = 16), head and neck (<i>n</i> = 4), liver (<i>n</i> = 12), lymphoma (<i>n</i> = 9), ovarian or cervix uteri (<i>n</i> = 19), pancreatic (<i>n</i> = 6), primary unknown (<i>n</i> = 12), thyroid (<i>n</i> = 11), and other (<i>n</i> = 19)										

Cumulative survival rate after ZA initiation, cumulative MRONJ incidence rate, and time to MRONJ onset

Overall and sex differences

The overall median survival time (MST) after ZA administration was 21 months. Sixty-five patients (7.5%) developed MRONJ, and the 8-year cumulative incidence of MRONJ was 32.1%. The MST was 14 and 26 months for males and females, respectively, with a significant inter-group difference observed with log-rank test ($p = 0.002$). Although 30 males and 35 females developed MRONJ, the 8-year cumulative MRONJ incidence was 34.2% and 30.4% for males and females, respectively, with the log-rank test showing no statistically significant difference ($p = 0.18$; Table 2).

Table 2
Survival rate and incidence rate of patients with osteonecrosis of the jaw

	Patients, <i>n</i>	3-year survival rate, %	5-year survival rate, %	MST, month after ZA admin.	Log- rank test	MRONJ occurrence, <i>n</i>	Cumulative incidence of MRONJ, % (8 years)	Log- rank test
All	862	34.6	23.1	21		65	32.1	
Males	396	29.3	21.3	14	<i>p</i> = 0.002	30	34.2	<i>p</i> = 0.18
Females	466	39.0	24.7	26		35	30.4	
Type of cancer								
Breast	287	47.9	29.6	35		29	34.8	
BM	53	69.6	63.1	NR	<i>p</i> < 0.0001	11	47.2	<i>p</i> = 0.25
VM	234	43.0	22.2	31		18	26.5	
Prostate	163	47.1	36.8	34		23	39.4	
BM	145	49.6	38.1	35	<i>p</i> = 0.067	22	42.5	<i>p</i> = 0.66
VM	18	27.8	27.8	23		1	7.7	
Lung	134	6.1	2.7	8		0	NA	
Myeloma	86	53.5	35.9	41		7	19.4	
Renal	40	26.0	14.5	12		6	37.9	
Other	152	11.6	9.0	6		0	NA	
Abbreviations: <i>admin</i> , administration; <i>ONJ</i> , medication-related osteonecrosis of the jaw; <i>MST</i> , median survival time; <i>NA</i> , not available; <i>NR</i> , not reached; <i>BM</i> , bone metastasis only; <i>VM</i> , visceral metastasis (including lung, liver, brain, skin, muscle); <i>ZA</i> , zoledronic acid								

Overall, the cumulative incidence of MRONJ increased steadily after initiating ZA therapy: 4.7%, 18.1%, and 32.1% at 2, 5, and 8 years, respectively (Fig. 2a).

Comparison between types of cancer

The MST of each cancer type after initiating ZA administration is shown in Table 2. Breast cancer, prostate cancer, and myeloma had a long MST (> 30 months). However, lung cancer and other cancers had an MST < 10 months. Renal cancer showed an intermediate survival curve between these with an MST of 12 months (Fig. 2b).

The incidence of MRONJ and cumulative incidence for 8 years for each cancer type are shown in Table 2. The 8-year cumulative incidence rate for MRONJ was the highest for prostate cancer, the group with the

best prognosis, followed by renal and breast cancer. Unlike other cancers, renal cancer was characterized by the early occurrence of MRONJ. The log-rank test showed a significant difference in the cumulative incidence between renal and breast cancer ($p = 0.0035$) and between renal cancer and myeloma ($p = 0.0148$; Fig. 2c). Subgroup analysis was performed on breast and prostate cancer, which are solid cancers with a good prognosis. The 5-year survival rates for the BM and VM groups were 63.1% and 22.2%, respectively, for breast cancer ($p < 0.0001$) and 38.1% and 27.8%, respectively, for prostate cancer ($p = 0.067$). In breast cancer, the prognosis was significantly better in the BM group than in the VM group. The 8-year cumulative incidences of MRONJ in the BM and VM groups were 47.2% and 26.5%, respectively, for breast cancer ($p = 0.25$) and 42.5% and 7.7%, respectively, for prostate cancer ($p = 0.66$). There was a tendency for the BM group to show a high cumulative incidence, but no significant difference was observed (Table 2).

Frequency of BMA use and time to MRONJ occurrence

The median number of times BMA was used for each cancer type was 26, 18, 10, 7, 3.5, and 3 for breast cancer, prostate cancer, myeloma, renal cancer, lung cancer, and other cancers, respectively. The frequency of BMA use was significantly different between most cancer types (Fig. 3a). When comparing the time to MRONJ onset exclusively in patients with MRONJ ($n = 65$), the median time to onset of MRONJ was 44, 27, 32, and 17 months for breast cancer, prostate cancer, multiple myeloma, and renal cancer, respectively. Breast cancer had a significantly longer time to MRONJ development than prostate ($p = 0.0187$) or kidney cancer ($p = 0.0062$; Fig. 3b).

The four cancer types in which MRONJ occurred ($n = 576$) were divided into two groups, an MRONJ group ($n = 65$) and a non-MRONJ group ($n = 511$), and the median number of times of BMA use was compared. Median BMA usage in the MRONJ and non-MRONJ groups was 45 and 24 times, respectively, for breast cancer ($p < 0.0001$); 27 and 17 times, respectively, for prostate cancer ($p < 0.0087$); 28 and 10 times, respectively, for myeloma ($p < 0.0065$); and 19 and 5 times, respectively, for renal cancer ($p < 0.0302$). That is, the frequency of BMA use was significantly higher in the MRONJ group than in the non-MRONJ group in each cancer type. In the MRONJ development group ($n = 65$), the median frequency of BMA use until the onset of MRONJ was 45 times for breast cancer, which was significantly higher than 27 times for prostate cancer ($p = 0.0023$) and 19 times for renal cancer ($p = 0.0031$; Fig. 3c).

Myeloma showed different MRONJ risks for two solid cancers, breast and prostate cancer. The 5-year cumulative incidence of MRONJ was 19.2%, 22.1%, and 13.2% for breast cancer, prostate cancer, and myeloma, respectively. The cumulative incidence over the subsequent 8 years was 34.8%, 39.4%, and 19.4% for breast cancer, prostate cancer, and myeloma, respectively. That is, a high increase of 15% or more was observed in bone metastases of solid tumors over 3 years, whereas a low increase of about 6% was observed in myeloma (Fig. 3b). The median frequency of BMA use was significantly lower for myeloma ($n = 10$) than for breast cancer ($n = 26$) and prostate cancer (18.5; $p < 0.0001$ and $p = 0.0071$, respectively; Fig. 3a).

Discussion

We conducted a retrospective survey of the survival time after ZA administration and cumulative incidence of MRONJ in patients taking ZA, based on the hypothesis that MRONJ risk differs depending on the cancer type and that it may be related to prognosis—or the number of times BMA is administered. Overall, the 8-year cumulative incidence of MRONJ after ZA use was 32.1% and the 3-year cumulative incidence was 9.1% in this study. Soutome et al. reported a 3-year cumulative incidence of 29.2% [7]; therefore, our hospital had a lower cumulative incidence of MRONJ. The significant difference in survival time between males and females was considered to reflect the effects of renal and lung cancers, as MSTs for prostate and breast cancer were almost consistent. However, there was no significant difference between the sexes in the cumulative incidence of MRONJ. Although prostate cancer had a higher cumulative incidence than breast cancer, the absence of osteonecrosis in lung cancer, which occurred more often in males than females, led to a lower cumulative incidence among males. Therefore, we presumed that there was no sex difference in the cumulative incidence of MRONJ. The cumulative incidence of MRONJ increased over time (4.7%, 18.1%, and 32.1% at 2, 5, and 8 years, respectively) (Fig. 2a); however, further analysis of each cancer type revealed that this was not a simple increase over time.

Breast cancer, prostate cancer, and multiple myeloma

In multiple myeloma, the Mayo Clinic consensus statement on the use of BMAs recommends discontinuing BP after 2 years of treatment for patients who achieve a complete response and/or plateau phase and suggests that patients with active disease, no response, or impending bone disease for > 2 years can have treatment frequency reduced to every 3 months [8]. Corso et al. also reported that the group receiving ZA monthly for 1 year and every 3 months thereafter had a similar incidence of skeletal-related events but had a one-eighth reduction in risk of osteonecrosis than the group that continued to receive ZA monthly [9]. We believe that the low number of BP doses for myeloma in the three carcinomas with good prognosis at our institution is the reason why the cumulative incidence of MRONJ remained low. However, for bone metastases of solid tumors, there is no indication for BP discontinuation or reduction, and after initiation, MRONJ risk tends to increase as the frequency of BMA administration continues to increase according to survival. Among breast cancer patients with distant metastasis, patients with BM and VM showed poor prognosis in the internal VM group [10–12]. Similarly, in the prostate cancer group, those with VM generally had a worse prognosis than those with BM [13, 14]. In our study, breast and prostate cancers showed a better prognosis in the BM group, and in breast cancer, the difference was significant. The cumulative incidence of MRONJ also tended to be higher in the BM group. Katagiri et al. found that six items, including primary tumor and presence of visceral metastases, were important prognostic factors in patients with bone metastases and scored these items to show their correlation with prognosis [15]. PathFX has been developed to depict survival trajectories based on machine learning, which is useful for predicting survival in cancer patients with bone metastases [16–19]. This tool can help orthopedic surgeons avoid invasive reconstructive procedures for patients with bone metastases and a short survival prognosis. In addition, it may also improve dental management.

Renal cancer

Although renal cancer has an MST of 12 months after ZA administration, approximately 24 months shorter from average than the abovementioned three carcinomas with good prognosis, it has a high MRONJ incidence, with an 8-year cumulative incidence rate of 37.9%, second only to that of prostate cancer. It is characteristic that the MRONJ incidence rate reaches 25.5% as early as 20 months. Only renal cancer developed MRONJ in the early stage, causing us to investigate further. van Cann et al. reported that the MRONJ incidence rate was 11% in patients treated with both BMA and vascular endothelial growth factor receptor-tyrosine kinase inhibitor, and the risk of developing MRONJ was 5–10 times higher than that in patients treated with BMA alone [20]. In Vallina et al.'s review of MRONJ patients treated with sunitinib alone or with BP, 49 of 58 patients (84%) were treated with BP [21]. Sunitinib may also cause MRONJ when used alone, although this is very rare [22–26]. Sunitinib-induced suppression of angiogenesis impairs host defense against infection and may increase the risk of osteonecrosis [25]. Bone exposure was sometimes preceded by oral mucositis [27], leading to oral mucosal damage, gingival inflammation and mucositis, delayed wound healing, and infection [23, 25]. In this study, 10 of 40 patients (25.0%) with renal cancer received only palliative irradiation or best supportive care and no intense therapy, whereas 26 of 30 patients (86.7%) who received cancer drug therapy received molecular targeted drugs, three patients (10.0%) received interferon, and one patient (3.3%) received cytotoxic agents. Nineteen patients (63.3%) were treated with sunitinib; 5 of 6 (83%) patients with MRONJ were treated with sunitinib. The time to MRONJ development was 17 months, which was clearly shorter than that of other cancers. Dentists need to make concentrated efforts to prevent MRONJ while considering these factors.

Lung cancer and other cancers

In lung cancer and other cancers with poor prognosis after BM, MRONJ did not occur. The MSTs were as short as 7 and 5 months, respectively, and the median BMA usage was only 4 and 3 times, respectively. We concluded that the low frequency of BMA use was the reason MRONJ did not develop.

There are a few reports on the prognosis of patients with bone metastases from lung cancer. Sugiura et al. reported an MST of 7.2 months [28], which is in close agreement with our findings. Few papers mention MRONJ incidence in patients with bone metastases from lung cancer. Scagliotti et al. found no difference in the cumulative incidence of MRONJ between patients administered ZA or Dmab (0.8% vs. 0.7%, respectively). Moreover, MST was higher in the Dmab group than in the ZA group (8.6 vs. 6.4 months; hazard ratio, 0.68; $p = 0.035$) [29] In this study, lung cancer was classified as a group with poor prognosis after BM. However, targeted therapy and immunotherapy have rapidly improved the prognosis of lung cancer in recent years; therefore, dentists should consider the associated increased risk of MRONJ.

Dental management after bone metastasis

In this study, the average MST of breast cancer, prostate cancer, and myeloma was 34 months. Currently, it is predicted that the prognosis for each cancer type after BMA initiation will improve with advance in cancer treatment. In order to avoid the occurrence of MRONJ, it is necessary to prevent odontogenic infections through dental management after the initiation of BMA from a more long-term perspective. On

the other hand, before BMA initiation, applying the same tooth extraction criteria used for patients with a good prognosis to patients with a poor prognosis who have an extremely low or no risk of MRONJ may lead to unnecessarily invasive overtreatment. From that point of view, our results showing that MRONJ did not occur in cancers such as lung, bladder, urinary duct, or gastrointestinal cancer is useful information. Many studies have established that preventive oral care methods combined with effective oral health practices are associated with a lower rate of MRONJ [30–43]. Ongoing collaboration among dentists, dental specialists, and oncologists is essential to optimal patient care [44]. In addition to the concept of preventing odontogenic infections, the dentists in charge of dental management before the initiation of BMA need to obtain information on prognosis based on the histological type of cancer, the presence or absence of gene mutation or VM, and the content of cancer treatment from the oncologist or cancer therapist.

Limitations of this study

This was a retrospective cohort study conducted at a single facility. Additionally, the dental management status and MRONJ staging difference after initiating BMA need to be further investigated as secondary endpoints. Since Dmab was launched in Japan in 2012, there have been fewer cases treated with it than ZA and the observation period may have been shorter than the target period of this study. Therefore, patients who started BMA with Dmab were excluded from our study. In a study by Hallmer et al., the incidence of MRONJ was higher among breast cancer patients treated with Dmab than among those treated with ZA (13.6% vs. 4.1%) and the MRONJ risk was higher among the former ($p = .0011$) [45]. Future studies are necessary to investigate patients who mainly used Dmab, including the content of their cancer drug therapy.

Conclusion

We found that MRONJ did not occur in lung cancer or other cancers with poor prognosis after BM administration. This was partially consistent with our hypothesis. For cancers without a poor prognosis, survival time was not the sole determinant of MRONJ risk. The comparisons between patients' prognoses after initiating BMA therapy and occurrence of MRONJ on the same time axis for each cancer type could be pivotal for oncologists and dentists.

Declarations

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Competing Interests: The authors have no conflicts of interest to declare that are relevant to the content of this article.

Availability of data and materials: The datasets used and/or analyzed during the current study are not openly and universally available due to human data and are available from the corresponding author on reasonable request.

Code Availability: Not applicable

Authors' Contributions: Hironobu Hata, Kenji Imamachi, and Michihiro Ueda conceptualized and designed the study. Hironobu Hata and Kenji Imamachi collected and assembled the data. Masashi Matsuzaka and Hiroaki Hiraga performed the statistical analysis of the data. Hiroaki Hiraga, Toshihisa Osanai, Toru Harabayashi, Katusya Fujimoto, Satoshi Oizumi, and Masato Takahashi analyzed and interpreted the data. Hironobu Hata drafted the manuscript. Kazuhito Yoshikawa, Jun Sato, Yutaka Yamazaki, and Yoshimasa Kitagawa proofread the manuscript and provided insights to improve it. All authors read and approved the final *manuscript*.

Ethics approval and consent to participate: All procedures performed on human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This single-center, retrospective, observational study protocol and patient information were approved by the Hokkaido Cancer Center Hospital Ethics Review Board (clinical study number 02-10), and informed consent was waived by this board because of the retrospective design of the study. Permission to access raw data from hospital cancer registries for life prognosis survey was also granted by the ethics review board.

Consent for publication: Not applicable

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Figures

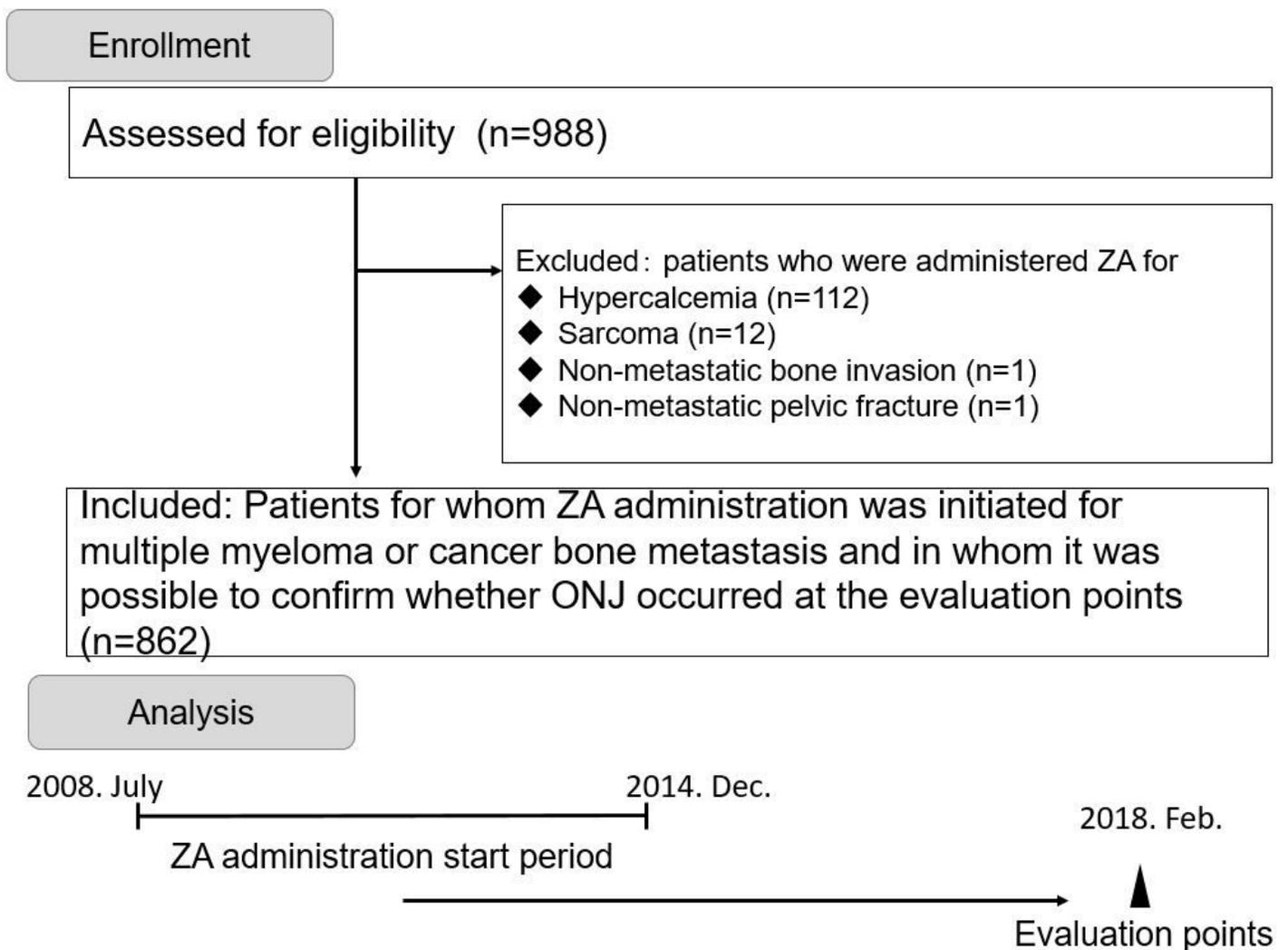


Figure 1

Flow chart of study selection We enrolled 988 patients who started receiving zoledronic acid (ZA) at our hospital between July 2008 and December 2014. Of the 988 patients, the following 126 who were administered ZA for reasons other than bone metastases and multiple myeloma were ineligible: hypercalcemia (n=112), osteosarcoma (n=12), bone infiltration of solid tumors (n=1), and non-metastatic pelvic fractures (n=1). Thus, 862 people were surveyed, the evaluation points were set in February 2018, and the observation period extended between the initiation of ZA therapy to the evaluation points.

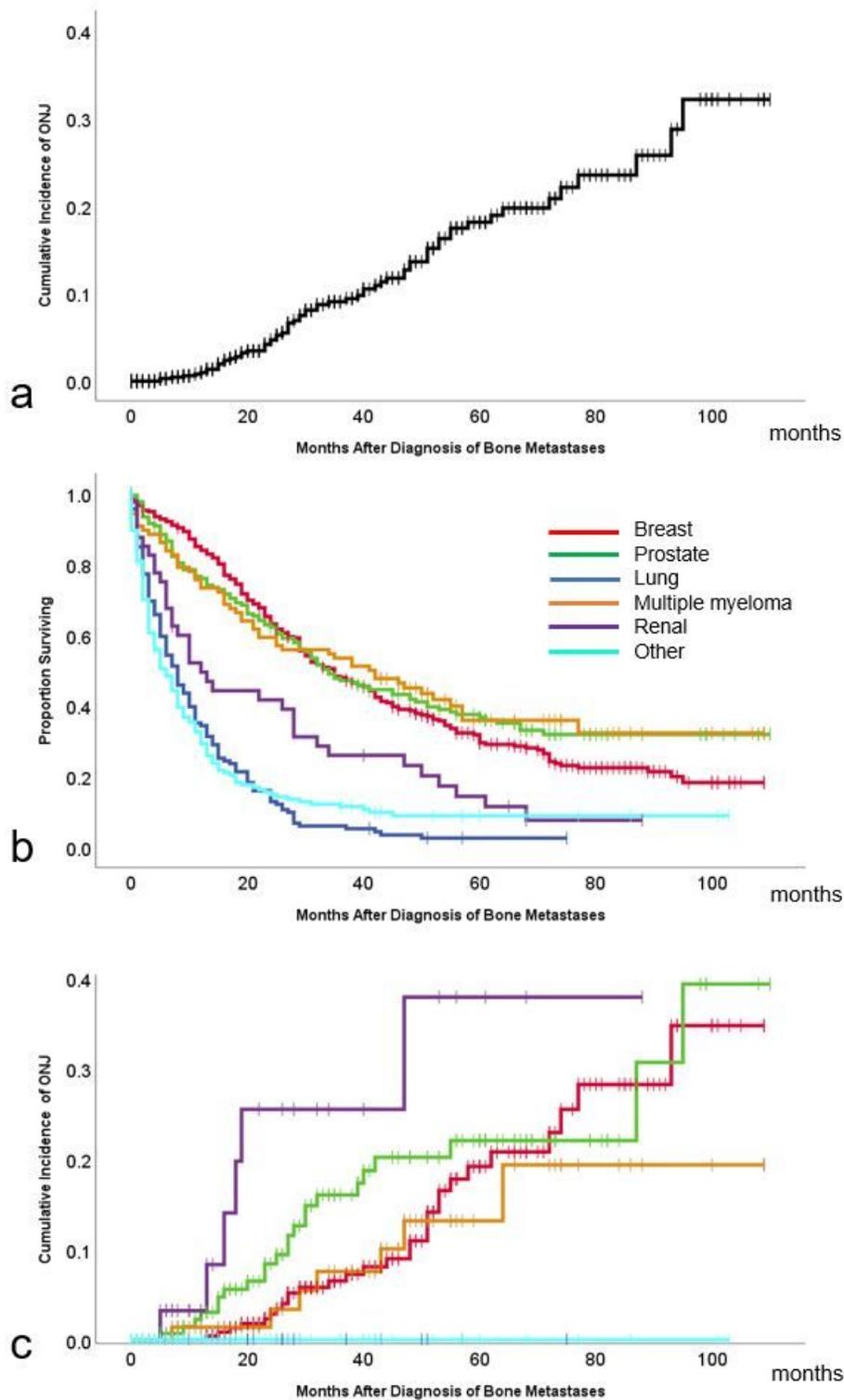


Figure 2

Survival curve after zoledronic acid use and cumulative incidence of osteonecrosis of the jaw (a) Overall, the cumulative incidence of medication-related osteonecrosis of the jaw (MRONJ) increased yearly since initiating zoledronic acid (ZA) administration. The 2-, 5-, and 8-year cumulative incidences were 4.7%, 18.1%, and 32.1%, respectively. (b) The median survival time (MST) of patients with each cancer type after initiating ZA administration was as follows: breast cancer, 35 months; prostate cancer, 34 months;

lung cancer, 8 months; myeloma, 41 months; renal cancer, 12 months, and other cancers, 6 months. The three cancer types with the longest MST (breast cancer, prostate cancer, myeloma) had a long and good prognosis. Contrastingly, lung cancer and other cancers had a poor prognosis. Renal cancer showed a survival curve between that of the above two groups. (c) The cumulative incidence of MRONJ was highest in prostate cancer, which had a good prognosis, followed by renal and breast cancer. Unlike other cancers, renal cancer was characterized by MRONJ development at an early stage. No bone necrosis occurred in patients with bone metastases from lung cancer or other cancers with poor prognosis. The log-rank test showed a significant difference in cumulative incidence between renal and breast cancer ($p=0.0035$) and between renal cancer and myeloma ($p=0.0148$).

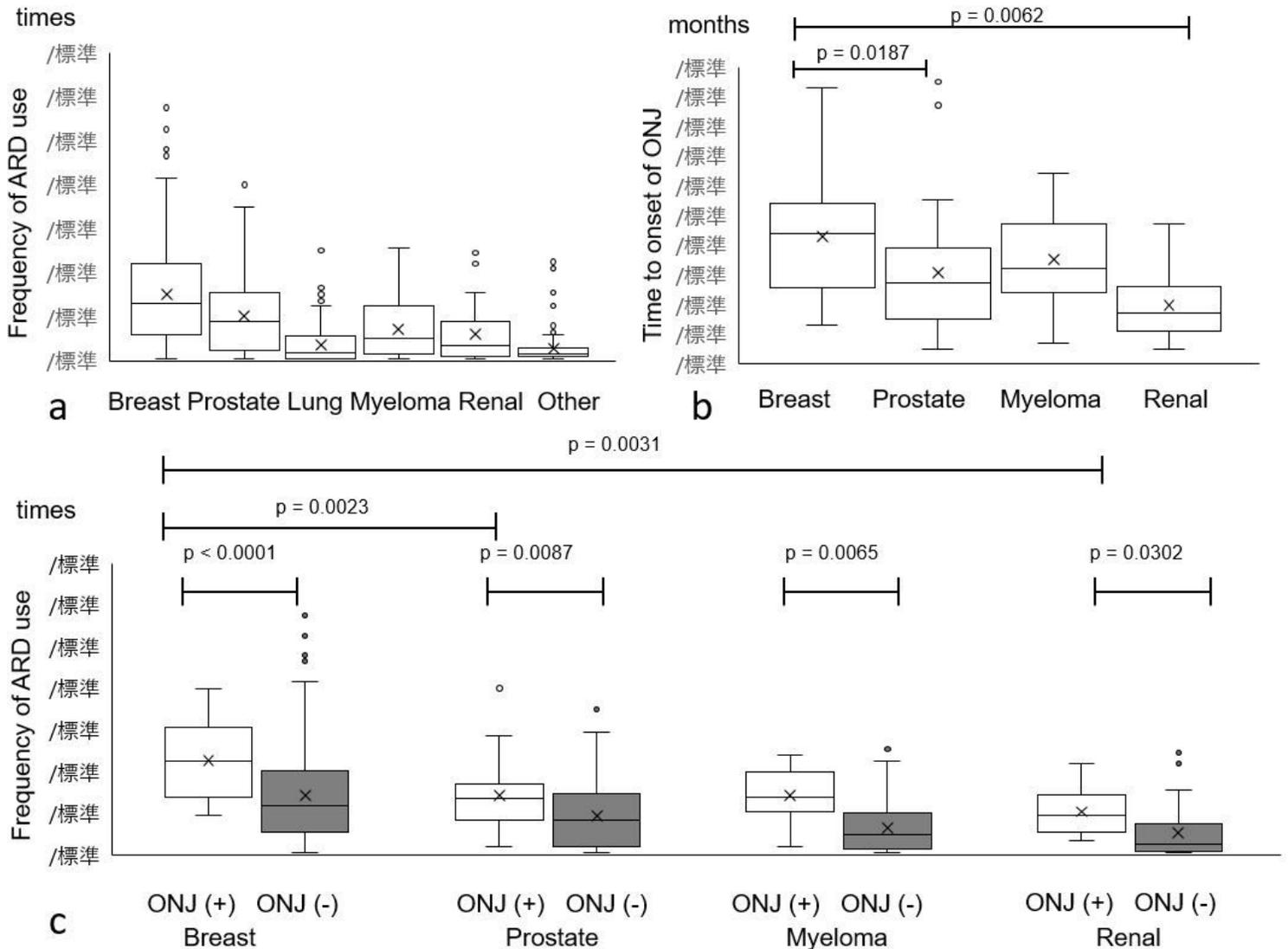


Figure 3

Comparison of bone-modifying agent (BMA) usage frequency for each cancer type, period until medication-related osteonecrosis of the jaw (MRONJ) occurrence, and BMA usage frequency in MRONJ group and non-MRONJ group (a) The median frequency of BMA was use for cancer types with MRONJ was as follows: breast cancer, 26 times; prostate cancer, 18.5 times; myeloma, 10 times; and renal cancer, 7 times. In lung cancer and other cancers, wherein MRONJ did not occur, the median BMA usage was 4

and 3 times, respectively. (b) The box plot displays the duration from BMA therapy initiation to onset of MRONJ for four cancer types. Breast cancer had a significantly longer duration to MRONJ development than prostate or renal cancer ($p=0.019$, $p=0.006$, respectively). (c) BMA therapy was used significantly more frequently in the MRONJ group than in the non-MRONJ group in each cancer type. In the MRONJ group, the median BMA usage was 45 times for breast cancer, which was significantly higher than that for prostate (27 times, $p=0.002$) or renal cancer (19 times; $p=0.003$).