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# Timing of Bone-Modifying Agent Initiation and Skeletal-Related Event Risk in Patients With Bone Metastases From Solid Tumors: A Retrospective Landmark and Propensity Score–Matched Analysis

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## Abstract

# Purpose

Bone-modifying agents (BMAs) prevent skeletal-related events (SREs) in patients with bone metastases; however, optimal BMA initiation timing remains unclear. This study evaluated the association between BMA initiation timing and SRE risk in patients with solid tumors.

# Methods

This retrospective observational study included patients with solid tumors and newly diagnosed bone metastases who received zoledronic acid or denosumab at a single institution between 2010 and 2024. A 6-month landmark analysis minimized immortal time and lead-time biases. Patients alive and SRE-free at the landmark were classified into early (≤ 6 months) or delayed (> 6 months) BMA initiation groups. Propensity score matching (PSM) balanced baseline characteristics. Time to first SRE after the landmark was compared using Kaplan–Meier analysis and log-rank test.

# Results

Among 1,363 eligible patients, 912 met the 6-month landmark criteria. After PSM, each group included 194 patients. During follow-up, 44 patients (11.3%) experienced at least one SRE. Kaplan–Meier analysis demonstrated that delayed BMA initiation was associated with significantly shorter time to first SRE compared with early initiation (log-rank test, $P < 0.05$).

# Conclusions

Delayed BMA therapy initiation beyond 6 months after bone metastases diagnosis was associated with earlier SRE occurrence. Once BMA therapy is clinically appropriate, avoiding unnecessary treatment delays may improve SRE prevention.

## Introduction

Bone metastases develop in approximately 10%–30% of patients with advanced solid tumors [1] and cause clinically significant complications including pain, pathologic fractures, spinal cord compression, and hypercalcemia. These bone metastasis-related complications and their therapeutic interventions are collectively termed skeletal-related events (SRE). SREs impair physical function and quality of life (QOL), adversely affect anticancer therapy continuation, and worsen overall prognosis. The overall SRE incidence is approximately 45% [1], with 65%–75% of patients with breast cancer experiencing at least one SRE during disease progression [2–4]. Appropriate bone metastases management is therefore essential for maintaining QOL and optimizing clinical outcomes in patients with advanced cancer.

Bone-modifying agents (BMAs), including zoledronic acid and denosumab, prevent SREs by inhibiting osteoclast-mediated bone resorption. Their efficacy in reducing SRE risk has been demonstrated across multiple tumor types [5–12]. Although clinical practice guidelines recommend BMA use in patients with bone metastases [13, 14], they provide limited guidance on optimal treatment initiation timing. Evidence addressing how BMA initiation timing after bone metastases diagnosis influences subsequent SRE risk remains limited, and real-world data are scarce.

Therefore, this study retrospectively evaluated the association between the interval from bone metastases diagnosis to BMA initiation and SRE risk in patients with solid tumors.

## Methods

# Ethical Considerations

This study was approved by the Ethics Committee of Iwate Medical University (approval No. MH2024-155). All procedures were conducted in accordance with the Declaration of Helsinki and its subsequent amendments. Given the retrospective observational design, the ethics committee waived written informed consent requirements; however, all patients were provided with the opportunity to opt out of participation.

## Study Design and Participants

This retrospective observational study included patients with solid tumors who were newly diagnosed with bone metastases and received BMA therapy with zoledronic acid or denosumab at Iwate Medical University Hospital (Iwate, Japan) between April 1, 2010, and December 31, 2024. Clinical data were obtained from electronic medical records. For patients who developed an SRE, the first SRE date was defined as the event date. For patients without SRE, follow-up was censored at the earliest occurrence of death, transfer to another institution, or May 7, 2025 (data cutoff).

Eligible patients met all criteria: (1) aged ≥ 18 years, (2) radiologic confirmation of bone metastases, and (3) first administration of an eligible BMA at our institution. Patients were excluded if they received BMA for indications other than bone metastases or if clinical data were insufficient for reliable analysis.

## Definitions and Study Outcomes

The primary outcome was time to first SRE after the 6-month landmark following bone metastases diagnosis. In this study, SREs were defined as pathologic fracture, hypercalcemia, or spinal cord compression. Radiation therapy and orthopedic surgery—although commonly included in broader SRE definitions—were excluded because these interventions are frequently planned for symptom management and do not necessarily reflect natural bone metastases progression.

As a secondary exploratory objective, we evaluated the consistency of the association between delayed BMA initiation and SRE risk across predefined clinical subgroups. Cutoff values for age and laboratory parameters defining these subgroups were determined from previously published studies [13–15].

## Landmark Analysis

To minimize lead-time bias and immortal time bias related to BMA initiation timing, a landmark analysis was performed using a single landmark at 6 months after bone metastases diagnosis. The 6-month landmark was selected because previous studies suggested that initiating BMA within 6 months after bone metastases diagnosis may reduce SRE risk [5, 16], and this interval was considered clinically reasonable.

Patients were classified into early- or delayed-initiation groups according to their BMA treatment status at the 6-month landmark. Only patients alive and SRE-free at this time point were included, allowing unbiased comparison of subsequent SRE occurrence between groups.

## Propensity Score Matching (PSM)

To adjust for baseline imbalances between early- and delayed-initiation groups, PSM was performed within the 6-month landmark cohort. Propensity scores were estimated using a logistic regression model incorporating age, sex, primary tumor site, presence of spinal metastases, renal function, serum albumin level, corrected calcium level, and BMA type. One-to-one nearest-neighbor matching without replacement was conducted using a caliper width of 0.2 of the standard deviation of the logit of the propensity score. Covariate balance after matching was assessed using standardized mean differences (SMDs), with values < 0.1 indicating adequate balance.

# Statistical Analysis

Categorical and continuous variables were summarized as numbers (percentages) and medians with interquartile ranges (IQRs; 25th–75th percentiles), respectively. Group comparisons were performed using the $\chi^2$ test, Fisher's exact test, or Mann–Whitney U test, as appropriate.

After PSM, time-to-event outcomes were evaluated using the Kaplan–Meier method, and differences between early- and delayed-initiation groups were assessed using the log-rank test. The primary comparison focused on time to first SRE after the 6-month landmark in the PSM cohort. Additionally, exploratory subgroup analyses were performed in the matched cohort. Within each predefined subgroup, hazard ratios for delayed versus early BMA initiation were estimated using univariate Cox proportional hazards models, and results were summarized using a forest plot. To evaluate the primary analysis robustness and the 6-month landmark appropriateness, sensitivity analyses were conducted by varying the landmark time from 1 to 12 months at 1-month intervals. For each landmark setting, the association

between delayed versus early BMA initiation and SRE risk was re-evaluated using univariate Cox proportional hazards models in the PSM cohorts.

All statistical analyses were performed using R software, version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided P value < 0.05 was considered statistically significant.

## Results

# Patient Selection and Baseline Characteristics

During the study period, 1,644 patients received BMA therapy at our institution. After applying exclusion criteria, 1,363 patients were included in the overall cohort. For the 6-month landmark analysis, patients who developed an SRE, died, or were transferred to another institution within 6 months after bone metastases diagnosis were excluded. Remaining patients were classified into an early-initiation group (BMA initiated within 6 months, n = 689) and a delayed-initiation group (BMA initiated after 6 months, n = 223). After PSM, 194 patients were included in each group in the final analysis cohort (Fig. 1).

Baseline characteristics of the early- and delayed-initiation groups before and after PSM are summarized in Table 1. Before matching, spinal metastases were more frequent in the early-initiation group, whereas other baseline characteristics were generally comparable between groups. After matching, baseline characteristics—including sex, primary cancer type, bone metastases sites, laboratory values, and BMA type—were well balanced between groups. Although age remained statistically different after matching, the absolute difference was small and distributions largely overlapped.

Table 1
Baseline Characteristics of Patients in the 6-Month Landmark Cohort Before and After Propensity Score Matching

| Clinical parameters | Before PSM | | | After PSM | | |
|---|---|---|---|---|---|---|
| | Early group n = 689 | Delayed group n = 223 | p value | Early group n = 194 | Delayed group n = 194 | p value |
| Age, years | 66.0 [56.0, 73.0] | 68.0 [59.0, 74.5] | < 0.05 | 63.5 [55.0, 72.0] | 67.0 [59.0, 74.0] | < 0.05 |
| Sex | | | 0.210 | | | 0.477 |
| Male | 354 (51.4%) | 126 (56.5%) | | 97 (50.0%) | 105 (54.1%) | |
| Female | 335 (48.6%) | 97 (43.5%) | | 97 (50.0%) | 89 (45.9%) | |
| Primary cancer type | | | | | | |
| Lung | 172 (25.0%) | 48 (21.5%) | 0.340 | 40 (20.6%) | 43 (22.2%) | 0.804 |
| Breast | 202 (29.3%) | 58 (26.0%) | 0.386 | 57 (29.4%) | 55 (28.4%) | 0.911 |
| Prostate | 150 (21.8%) | 45 (20.2%) | 0.682 | 33 (17.0%) | 39 (20.1%) | 0.514 |
| Kidney | 48 (7.0%) | 18 (8.1%) | 0.686 | 14 (7.2%) | 17 (8.8%) | 0.708 |
| Gynecological | 22 (3.2%) | 4 (1.8%) | 0.390 | 7 (3.6%) | 4 (2.1%) | 0.541 |
| Liver | 23 (3.3%) | 7 (3.1%) | 1.000 | 5 (2.6%) | 7 (3.6%) | 0.769 |
| Head and neck | 7 (1.0%) | 4 (1.8%) | 0.567 | 3 (1.5%) | 3 (1.5%) | 1.000 |
| Stomach | 9 (1.3%) | 1 (0.4%) | 0.484 | 4 (2.1%) | 1 (0.5%) | 0.368 |
| Colorectal | 14 (2.0%) | 10 (4.5%) | 0.080 | 8 (4.1%) | 6 (3.1%) | 0.785 |
| Pancreas | 6 (0.9%) | 1 (0.4%) | 0.852 | 2 (1.0%) | 1 (0.5%) | 1.000 |
| Others | 36 (5.2%) | 29 (13.0%) | < 0.01 | 21 (10.8%) | 18 (9.3%) | 0.736 |
| Cancer treatment | | | | | | |

Values are presented as n (%) or median (interquartile range [25th–75th percentile]).

Multiple selections were allowed for treatment modality, site of bone metastases, and type of BMA.

p values after matching are provided for descriptive purposes only.

eGFR: estimated glomerular filtration rate; BMA: bone-modifying agents

| Clinical parameters | Before PSM | | | After PSM | | |
|---|---|---|---|---|---|---|
| | Early group<br>n = 689 | Delayed group<br>n = 223 | p value | Early group<br>n = 194 | Delayed group<br>n = 194 | p value |
| Chemotherapy | 596 (86.5%) | 198 (88.8%) | 0.441 | 176 (90.7%) | 173 (89.2%) | 0.736 |
| Hormone therapy | 298 (43.3%) | 94 (42.2%) | 0.833 | 75 (38.7%) | 85 (43.8%) | 0.353 |
| Others | 11 (1.6%) | 5 (2.2%) | 0.730 | 5 (2.6%) | 4 (2.1%) | 1.000 |
| Sites of bone metastasis | | | | | | |
| Spine | 512 (74.3%) | 144 (64.6%) | < 0.01 | 134 (69.1%) | 128 (66.0%) | 0.588 |
| Long bones | 125 (18.1%) | 30 (13.5%) | 0.129 | 30 (15.5%) | 29 (14.9%) | 1.000 |
| Others | 442 (64.2%) | 127 (57.0%) | 0.064 | 117 (60.3%) | 115 (59.3%) | 0.918 |
| Laboratory values at BMA initiation | | | | | | |
| Body weight, kg | 58.0 [50.5, 67.0] | 56.6 [50.0, 67.0] | 0.206 | 58.3 [50.0, 67.0] | 57.2 [50.0, 67.0] | 0.612 |
| Serum creatinine, mg/dL | 0.70 [0.59, 0.87] | 0.74 [0.62, 0.92] | < 0.05 | 0.71 [0.60, 0.88] | 0.74 [0.62, 0.92] | 0.291 |
| eGFR, mL/min/1.73 m² | 73.7 [61.7, 88.7] | 70.9 [55.2, 86.0] | < 0.05 | 72.3 [61.5, 87.2] | 70.1 [56.0, 84.7] | 0.264 |
| Albumin, g/dL | 3.9 [3.5, 4.3] | 3.8 [3.3, 4.2] | < 0.01 | 3.9 [3.4, 4.2] | 3.8 [3.3,4.2] | 0.504 |
| Corrected calcium, mg/dL | 9.3 [9.0, 9.6] | 9.4 [9.0, 9.7] | 0.123 | 9.3 [9.0,9.6] | 9.3 [9.0,9.7] | 0.626 |
| Type of BMA | | | | | | |
| Denosumab | 588 (85.3%) | 180 (80.7%) | 0.124 | 163 (84.0%) | 159 (82.0%) | 0.685 |

Values are presented as n (%) or median (interquartile range [25th–75th percentile]).

Multiple selections were allowed for treatment modality, site of bone metastases, and type of BMA.

p values after matching are provided for descriptive purposes only.

eGFR: estimated glomerular filtration rate; BMA: bone-modifying agents

| Clinical parameters | Before PSM | | | After PSM | | |
|---|---|---|---|---|---|---|
| | Early group | Delayed group | p value | Early group | Delayed group | p value |
| | n = 689 | n = 223 | | n = 194 | n = 194 | |
| Zoledronic Acid | 159 (23.1%) | 56 (25.1%) | 0.595 | 46 (23.7%) | 46 (23.7%) | 1.000 |
| Values are presented as n (%) or median (interquartile range [25th–75th percentile]). | | | | | | |
| Multiple selections were allowed for treatment modality, site of bone metastases, and type of BMA. | | | | | | |
| p values after matching are provided for descriptive purposes only. | | | | | | |
| eGFR: estimated glomerular filtration rate; BMA: bone-modifying agents | | | | | | |

# SRE After Initiation of BMA

In the 6-month landmark cohort after PSM, 44 patients (11.3%) developed at least one SRE during follow-up. The median time from landmark to first SRE was 22.3 months ([IQR], 6.2–42.7 months). A total of 44 SREs were observed, including spinal cord compression (n = 16), pathologic fracture (n = 16), and hypercalcemia (n = 12).

# Kaplan–Meier Analysis of Time to First SRE in the Propensity Score–Matched Cohort

In the PSM cohort, Kaplan–Meier analysis demonstrated that delayed BMA initiation (> 6 months) was associated with significantly increased SRE risk compared with early initiation (≤ 6 months) (hazard ratio [HR], 2.14; 95% confidence interval [CI], 1.05–4.35; log-rank test, P < 0.05) (Fig. 2). For descriptive purposes, cumulative SRE incidence at 3 years after the 6-month landmark was calculated. At 3 years, cumulative SRE incidence was 14.9% (95% CI, 8.3–21.0) in the delayed-initiation group and 10.3% (95% CI, 3.5–16.6) in the early-initiation group.

Consistent with these findings, Kaplan–Meier analyses conducted in the overall cohort before PSM showed a similar trend toward higher SRE risk in the delayed-initiation group (Supplementary Fig. S1).

# Exploratory Subgroup Analyses

Exploratory subgroup analyses were conducted in the PSM cohort to examine the consistency of the association between delayed BMA initiation (> 6 months) and SRE risk across predefined clinical subgroups. Results are summarized in a forest plot (Fig. 3).

Across most subgroups, estimated hazard ratios exceeded 1.0, indicating a generally consistent association between delayed initiation and higher SRE risk. Although statistically significant associations were observed in certain subgroups, including patients aged < 65 years, female patients,

and those receiving denosumab, confidence intervals were wide in several subgroups, reflecting limited event numbers. Similar trends were observed in the pre-matched cohort (Supplementary Figure S2).

# Sensitivity Analyses

Results of sensitivity analyses using alternative landmark times are summarized in Table 2. When landmark times of 4, 5, and 6 months were applied, delayed BMA initiation was significantly associated with increased SRE risk, with hazard ratios of 1.73 (95% CI, 1.00–2.97), 2.06 (95% CI, 1.12–3.81), and 2.14 (95% CI, 1.05–4.35), respectively. In contrast, no statistically significant associations were observed at earlier (1–3 months) or later (7–12 months) landmark times, although estimated hazard ratios generally exceeded 1.0 across most landmark settings.

Table 2
Sensitivity Analyses Using Alternative Landmark Times: Univariate Cox Proportional Hazards Models After Propensity Score Matching

| Landmark time (months) | Matched (n) | Early (n) | Delayed (n) | Hazard ratio (Delayed vs Early) | 95% CI | P value |
|---|---|---|---|---|---|---|
| 1 | 982 | 491 | 491 | 1.18 | 0.78–1.79 | 0.441 |
| 2 | 894 | 447 | 447 | 1.03 | 0.69–1.54 | 0.893 |
| 3 | 690 | 345 | 345 | 1.27 | 0.82–1.97 | 0.288 |
| 4 | 552 | 276 | 276 | 1.73 | 1.00–2.97 | < 0.05 |
| 5 | 460 | 230 | 230 | 2.06 | 1.12–3.81 | < 0.05 |
| 6 | 388 | 194 | 194 | 2.14 | 1.05–4.35 | < 0.05 |
| 7 | 346 | 173 | 173 | 1.87 | 0.91–3.85 | 0.090 |
| 8 | 322 | 161 | 161 | 1.10 | 0.56–2.14 | 0.782 |
| 9 | 286 | 143 | 143 | 1.10 | 0.55–2.20 | 0.785 |
| 10 | 262 | 131 | 131 | 1.25 | 0.59–2.62 | 0.561 |
| 11 | 244 | 122 | 122 | 2.05 | 0.88–4.81 | 0.098 |
| 12 | 216 | 108 | 108 | 1.92 | 0.77–4.82 | 0.164 |

Hazard ratios were estimated using univariate Cox proportional hazards models in propensity score–matched cohorts, comparing delayed initiation with early initiation of bone-modifying agent therapy.

Abbreviations: CI, confidence interval; BMA, bone-modifying agents; SRE, skeletal-related event; PSM, propensity score matching

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Abbreviations: CI, confidence interval; BMA, bone-modifying agents; eGFR, estimated glomerular filtration rate.

Consistent with the primary analysis, sensitivity analyses conducted in the overall cohort before PSM also demonstrated increased SRE risk associated with delayed BMA initiation across multiple landmark settings (Supplementary Table S1).

## Discussion

This retrospective study examined the association between BMA initiation timing after bone metastases diagnosis and SRE risk in patients with solid tumors. Using 6-month landmark analysis with PSM, BMA therapy initiation beyond 6 months was associated with increased SRE risk versus initiation within 6 months, suggesting that treatment postponement in clinical practice may compromise SRE prevention.

Although prospective studies have not established optimal BMA initiation timing for bone metastases, previous observational studies and trials suggested BMA therapy is commonly initiated within several months of diagnosis [5–12] and that initiation within 6 months may reduce SRE risk [5, 16]. However, these studies primarily evaluated post-initiation treatment effects without explicitly addressing delayed initiation impact while accounting for time-dependent biases.

This study extends previous evidence by directly examining BMA initiation timing after bone metastases diagnosis using landmark analysis with PSM. By minimizing immortal time bias and balancing baseline characteristics, our approach enabled conservative, clinically interpretable assessment of the association between delayed BMA initiation and subsequent SRE risk in a real-world, cancer type-agnostic population. The observed increased SRE risk with initiation beyond 6 months highlights treatment timing relevance rather than treatment exposure alone.

Sensitivity analyses using alternative landmark times provide important insight into the clinical interpretation of these findings. When shorter landmark times of 1–3 months after bone metastases diagnosis were applied, no statistically significant association between delayed BMA initiation and SRE risk emerged. This likely reflects that, although patients were formally classified into early and delayed groups, initiation beyond 1–3 months in clinical practice does not necessarily represent clinically meaningful delay. Short postponements during early post-diagnostic periods often relate to necessary clinical preparation and may not translate into increased SRE risk. Conversely, when longer landmark times of ≥ 7 months were used, the association between delayed initiation and SRE risk was attenuated, possibly reflecting selection of lower-risk populations who remained alive and SRE-free beyond this period, plus reduced statistical power from fewer patients and events. Collectively, these results suggest landmark times around 4–6 months after bone metastases diagnosis may capture a clinically meaningful window wherein delayed initiation reflects relevant postponement of osteoclast inhibition associated with subsequent SRE risk.

In clinical practice, BMA initiation delays often arise unintentionally from practical and clinical considerations rather than inappropriate decision-making. Dental evaluation and preventive dental care before BMA initiation are widely recommended to reduce medication-related osteonecrosis of the jaw (MRONJ) risk, potentially necessitating treatment postponement [17, 18]. Additionally, renal function

optimization, metabolic abnormality correction (e.g., hypercalcemia), recovery from systemic anticancer therapy adverse events, anticancer treatment prioritization in patients with rapidly progressive disease, and logistical challenges involving multidisciplinary coordination and outpatient scheduling can contribute to delays. These real-world constraints indicate that while short-term delays from appropriate clinical management may be unavoidable, prolonged postponement beyond several months warrants reconsideration once BMA therapy is deemed appropriate.

In exploratory subgroup analyses, the association between delayed BMA initiation and increased SRE risk was generally consistent across predefined clinical subgroups. Significant associations emerged in patients aged < 65 years, female patients, and patients receiving denosumab, suggesting delayed initiation adverse effects may be more pronounced in these populations.

Previous studies showed inconsistent or absent associations between SRE risk and age or sex but primarily examined specific tumor types rather than heterogeneous cancer populations [19–22]. This study found no apparent heterogeneity across primary cancer types, suggesting the association between delayed BMA initiation and SRE risk applies broadly across solid cancers. Furthermore, findings in patients treated with denosumab may indicate that delayed initiation during potent anti-resorptive therapy results in greater loss of opportunity for early, effective bone resorption suppression. However, all subgroup estimates derive from limited event numbers with wide confidence intervals; thus, these findings are hypothesis-generating rather than hypothesis-supporting.

This study has several limitations. First, as a single-center retrospective observational study, residual confounding cannot be fully excluded despite PSM. Second, detailed reasons for delayed BMA initiation—including dental procedure duration or type, comorbidity severity, patient preferences, and adherence to subsequent BMA dosing schedules—could not be fully characterized. Additionally, although landmark analysis mitigated immortal time bias, time-dependent biases from clinical status or treatment pattern changes over disease course cannot be completely eliminated. Nevertheless, this study provides clinically meaningful real-world evidence that unnecessary delays in BMA initiation after bone metastases diagnosis may increase SRE risk. By focusing on BMA initiation timing rather than post-initiation outcomes alone, this study adds novel insight into an underexplored bone metastasis management aspect.

# Conclusion

In this retrospective study using landmark analysis and PSM, delayed BMA therapy initiation beyond 6 months after bone metastases diagnosis was associated with increased subsequent SRE risk in patients with solid tumors. These findings suggest treatment postponement in clinical practice may disadvantage SRE prevention. Although residual confounding cannot be excluded, results underscore the clinical importance of avoiding unnecessary delays once BMA therapy is deemed appropriate. Prospective studies are warranted to clarify optimal BMA initiation timing and confirm these observations.

## Declarations

# Ethics Approval and Consent to Participate:

This study was conducted in compliance with the Ethical Guidelines for Medical and Biological Research Involving Human Subjects issued by the Ministry of Health, Labour, and Welfare of Japan and the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of Iwate Medical University (MH2024-155). Due to the retrospective nature of the study, which involved the analysis of existing clinical data, the requirement for individual informed consent was waived by the ethics committee. All patient data were anonymized and de-identified before analysis to ensure confidentiality.

**Consent to Publish:**

Not applicable.

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# Author Contribution

This study was designed by TI, SN, and JS. TI performed the statistical analysis and drafted the manuscript, which was critically reviewed by SN and JS. KS supported statistical analysis, and KK supervised the study. All authors read and approved the final version of the manuscript.

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# Figures

**Fig. 1** Flow Diagram of Patient Selection and Study Cohort Construction

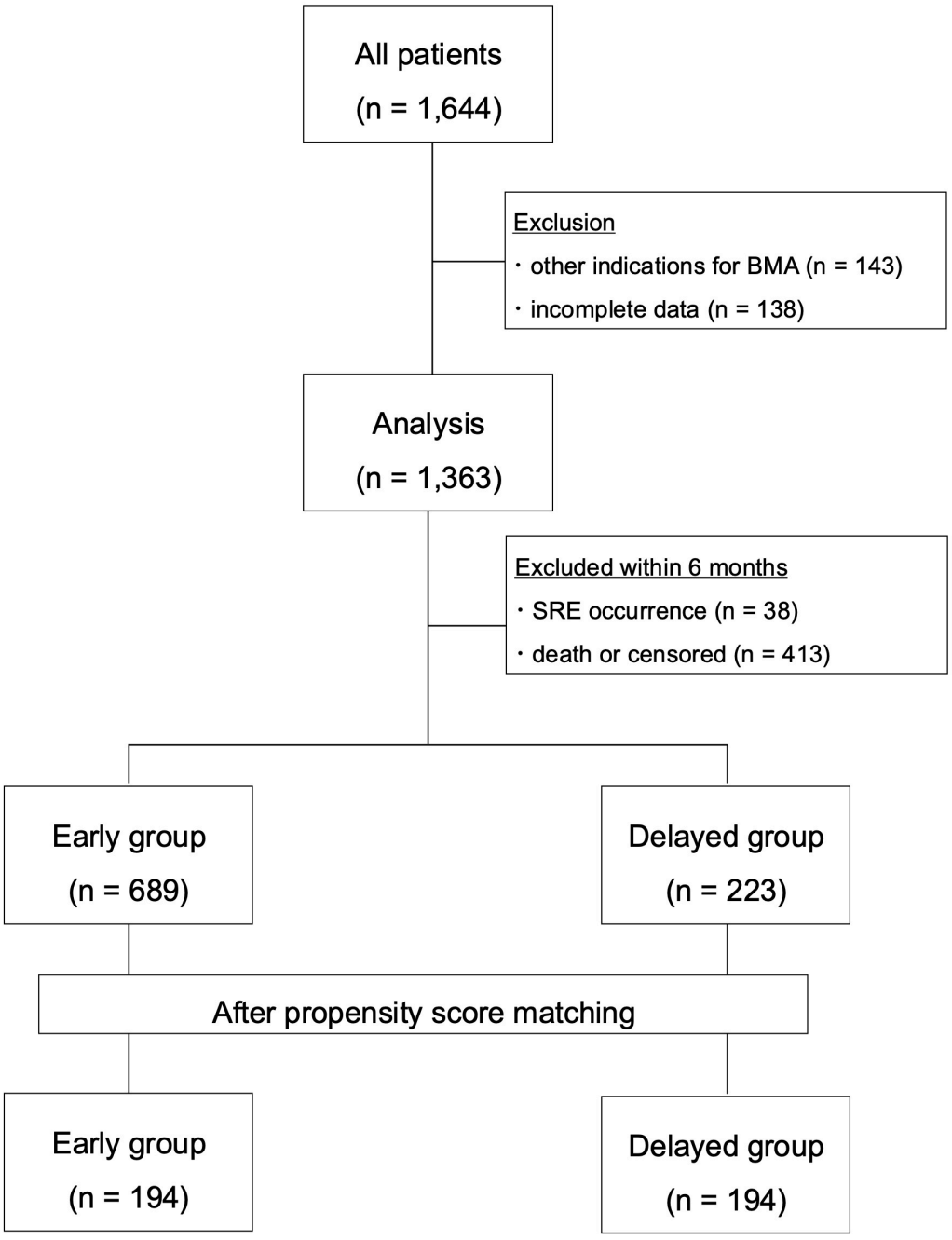


**Figure 1**

Flow Diagram of Patient Selection and Study Cohort Construction

A total of 1,644 patients who received BMA therapy were screened. Patients treated with BMA for indications other than bone metastases (n = 143) and those with incomplete clinical data (n = 138) were excluded, yielding 1,363 eligible patients. For the 6-month landmark analysis, patients who experienced an SRE (n = 38) or were censored due to death or transfer to another institution (n = 413) within 6 months after bone metastases diagnosis were excluded. Remaining patients were classified into early-initiation (≤6 months, n = 689) and delayed-initiation (>6 months, n = 223) groups. After propensity score matching, 194 patients were included in each group for final analysis.

Abbreviations: BMA, bone-modifying agent; SRE, skeletal-related event.

**Fig. 2** Kaplan–Meier Curves for Time to First SRE After Propensity Score Matching

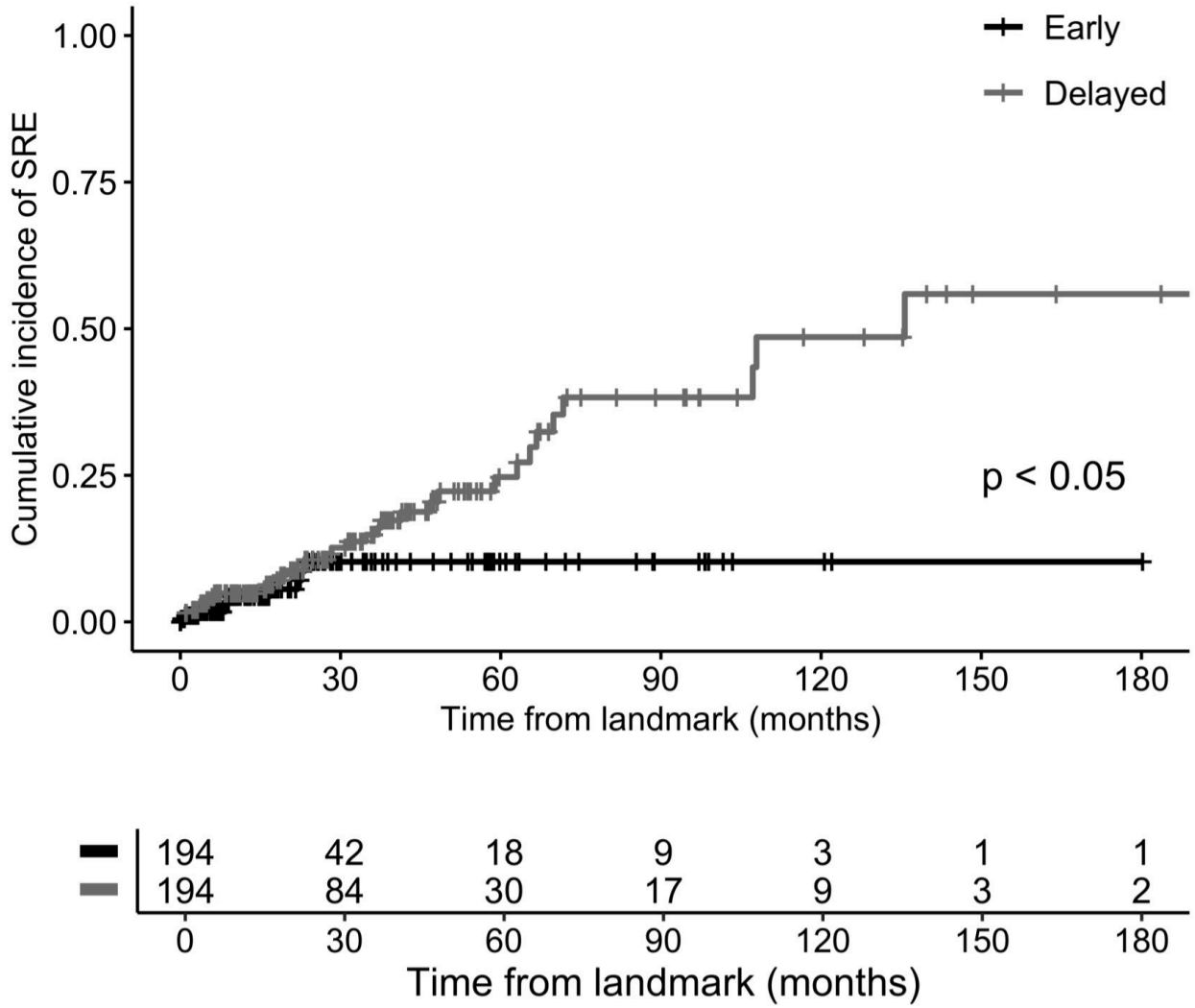



**Figure 2**

Kaplan–Meier Curves for Time to First SRE After Propensity Score Matching

Kaplan–Meier curves comparing time to first SRE between early-initiation (≤6 months) and delayed-initiation (>6 months) groups in the 6-month landmark cohort after propensity score matching. Patients in the delayed-initiation group experienced significantly shorter time to first SRE compared with those in the early-initiation group (log-rank test, P < 0.05).

X-axis: Time from landmark (months)

Y-axis: Cumulative incidence of SRE

Legend (within the figures):

Black line = Early initiation group (≤6 months)

Gray line = Delayed initiation group (>6 months)

Abbreviations: SRE, skeletal-related event.

## **Fig. 3** Forest Plot of the Association Between Delayed BMA Initiation and Risk of Across Clinical Subgroups

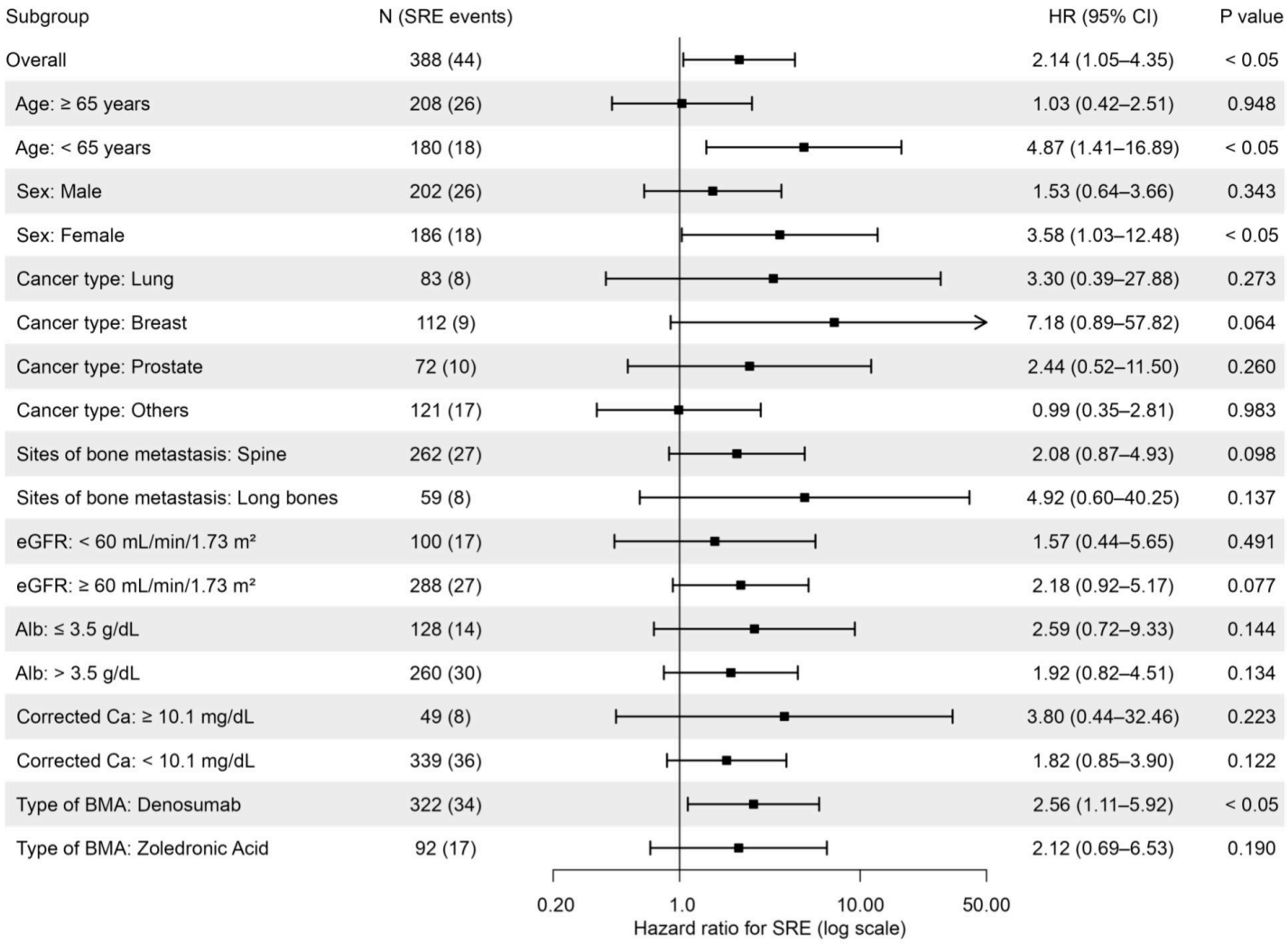



**Figure 3**

Forest Plot of the Association Between Delayed BMA Initiation and Risk of Across Clinical Subgroups

Forest plot showing hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between delayed versus early BMA therapy initiation and SRE risk across predefined clinical subgroups. HRs were estimated using univariate Cox proportional hazards models in the 6-month landmark cohort after propensity score matching.

Early BMA therapy initiation was the reference category; therefore, HRs represent the relative SRE risk associated with delayed versus early initiation. An HR >1.0 indicates increased SRE risk with delayed initiation. The vertical dashed line indicates an HR of 1.0.

Multiple selections were allowed for bone metastases sites and BMA type.

Abbreviations: CI, confidence interval; BMA, bone-modifying agents; eGFR, estimated glomerular filtration rate.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterial.docx