Clinical, oncological, and prognostic differences of patients with subsequent skeletal-related events in bone metastases

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Aims

Advances in treatment have extended the life expectancy of patients with metastatic bone disease (MBD). Patients could experience more skeletal-related events (SREs) as a result of this progress. Those who have already experienced a SRE could encounter another local management for a subsequent SRE, which is not part of the treatment for the initial SRE. However, there is a noted gap in research on the rate and characteristics of subsequent SREs requiring further localized treatment, obligating clinicians to extrapolate from experiences with initial SREs when confronting subsequent ones. This study aimed to investigate the proportion of MBD patients developing subsequent SREs requiring local treatment, examine if there are prognostic differences at the initial treatment between those with single versus subsequent SREs, and determine if clinical, oncological, and prognostic features differ between initial and subsequent SRE treatments.

Methods

This retrospective study included 3,814 adult patients who received local treatment – surgery and/or radiotherapy – for bone metastasis between 1 January 2010 and 31 December 2019. All included patients had at least one SRE requiring local treatment. A subsequent SRE was defined as a second SRE requiring local treatment. Clinical, oncological, and prognostic features were compared between single SREs and subsequent SREs using Mann-Whitney U test, Fisher's exact test, and Kaplan–Meier curve.

Results

Of the 3,814 patients with SREs, 3,159 (83%) patients had a single SRE and 655 (17%) patients developed a subsequent SRE. Patients who developed subsequent SREs generally had characteristics that favoured longer survival, such as higher BMI, higher albumin levels, fewer comorbidities, or lower neutrophil count. Once the patient got to the point of subsequent SRE, their clinical and oncological characteristics and one-year survival (28%) were not as good as those

with only a single SRE (35%; $p < 0.001$), indicating that clinicians' experiences when treating the initial SRE are not similar when treating a subsequent SRE.

Conclusion

This study found that 17% of patients required treatments for a second, subsequent SRE, and the current clinical guideline did not provide a specific approach to this clinical condition. We observed that referencing the initial treatment, patients in the subsequent SRE group had longer six-week, 90-day, and one-year median survival than patients in the single SRE group. Once patients develop a subsequent SRE, they have a worse one-year survival rate than those who receive treatment for a single SRE. Future research should identify prognostic factors and assess the applicability of existing survival prediction models for better management of subsequent SREs.

Article focus

- What proportion of patients develop a subsequent skeletal-related event (SRE) requiring local treatment?
- Do patients who develop a subsequent SRE have a more favourable prognosis when they initially present with the first SRE?
- Is the presentation for the subsequent SRE unique from the initial SRE presentation in terms of patient characteristics and prognosis?

Key messages

- This study underscores the need for personalized follow-up plans for metastatic bone disease patients with good prognoses, due to a notable rate of subsequent SREs.
- The survival rates for single SRE and subsequent SRE were similar within the first 200 days, which indicates that clinicians' experiences in managing the single SRE could be a reliable guide when treating a subsequent SRE.
- The poorer one-year survival rate at subsequent SRE presentation compared to single SRE highlights the importance of cautious intervention, where less invasive treatments may be favoured.

Strengths and limitations

- This study provides insights into the high incidence of subsequent SREs, enhancing clinical decision-making for these patients.
- The retrospective analysis may hinder confirmation of the unplanned nature of subsequent SRE treatments, and sample size constraints may impact result generalizability.

Introduction

The management of metastatic bone disease (MBD) remains a challenge for medical, radiation, and orthopaedic oncologists,[1] as it is often accompanied by a diverse range of debilitating symptoms including severe pain, functional impairment, mental health issues, and poor prognosis.[2] Despite these challenges, advances in various molecular treatments have contributed to increased life expectancies.[3,4] As a result of this increased survival, patients experience more skeletal-related events (SREs).[5,6] Patients who have already experienced a SRE can develop a second, subsequent SRE necessitating additional localized management outside of the initial treatment regimen.[6] However, to our knowledge, there are no studies investigating the rate of a second, subsequent SRE development in MBD. Additionally, there is a lack of research into the differences in clinical, oncological, and prognostic features between single SRE and subsequent SRE requiring local treatment such as surgery or radiotherapy. This knowledge gap obliges clinicians to extrapolate from experiences with initial SREs when confronting subsequent ones. This practice may not always translate well to the management of later events, potentially leading to less-than-optimal treatment outcomes for patients facing subsequent SREs.

We aimed to answer the following three questions to allow clinicians and patients to make informed treatment decisions in line with their goals and expectations: 1) what proportion of patients, who already underwent local treatment for SREs due to MBD, develop a subsequent SRE also requiring local treatment?; 2) are there differences in prognostic features between patients who underwent treatment for single SRE versus subsequent SRE at the time of the initial SRE treatment, i.e. do patients who develop a subsequent SRE have a more favourable prognosis when they initially present with the first SRE?; 3) lastly, and most importantly, are there differences in clinical, oncological, and prognostic features between the single SRE treatment and the subsequent SRE treatment? Namely, is the presentation for the subsequent SRE unique from the initial SRE presentation in terms of patient characteristics and prognosis?

Methods

This study was approved by the institutional research ethics committee of National Taiwan University Hospital, and informed consent was waived due to the retrospective nature. We followed the STROBE guidelines during the study.[7]

Study design and participants

We retrospectively enrolled all adult patients (≥ 20 years old) with MBD, who received local treatment for SREs between 1 January 2010 and 31 December 2019 at National Taiwan University Hospital (n = 4,159; Figure 1). The reason for not including patients aged under 20 years is due to the institutional policy. In this study, a SRE was defined as any event such as bone pain, spinal cord compression, or (impending) pathological fracture requiring surgery or radiotherapy based on a multidisciplinary assessment by a medical oncologist, anaesthesiologist, and orthopaedic oncologist. In general, the indications for radiotherapy were local tumour control, clinical symptom relief such as pain, sphincter incontinence, partial/complete paralysis, sensation abnormality, and any combination of the above. The indications for surgery were patients with an American Society of Anesthesiologists (ASA) grade ≤ IV,[8] and for limb metastases, the presence of a complete pathological fracture, or an impending pathological

fracture deemed unlikely to heal with nonoperative treatment alone. For spinal metastasis patients who suffered from spinal instability with intolerable mechanical pain, acute neurological dysfunction, such as immobility, sensation abnormality, or the primary tumour (such as renal cell carcinoma), is believed to be insensitive to radiotherapy or molecular treatment. Spine instability was measured by the Spinal Instability Neoplastic Score,[9] and an impending fracture was diagnosed if the lesion in question had a Mirels score ≥ 9.[10] We excluded patients with malignant primary bone tumours (n = 74), patients whose initial treatment for MBD was carried out at another institution (n = 109), and patients with multiple documented primary cancers where the metastatic tumour histology could not be ascertained pathologically (n = 162), leaving 3,814 patients for final analysis. The median follow-up time was 5.3 years (IQR 4.6 to 7.3)

Explanatory variables

The following values were extracted: age; sex; BMI; any Charlson comorbidity in addition to metastatic cancer;[11] primary tumour type by Katagiri et al;[4] Eastern Cooperative Oncology Group (ECOG) score; tumour location; visceral (lung and/or liver) or brain metastases; previous systemic therapy; the use of bone targeted agents (denosumab or zoledronate); and 11 laboratory values. If multiple laboratory values were present, the most recent one was considered.[12] The primary tumour type was categorized as slow-growth (i.e. hormone-dependent breast cancer, hormone-dependent prostate cancer, malignant lymphoma, malignant myeloma, thyroid cancer), intermediate (i.e. non-small cell lung cancer with molecularly targeted therapy, hormone-independent breast cancer, hormone-independent prostate cancer, renal cell carcinoma, sarcoma, other gynecological cancer, and others), and rapid-growth (i.e. other lung cancer, colon and rectal cancer, gastric cancer, hepatocellular carcinoma, pancreatic cancer, head and neck cancer, other urological cancer, oesophageal cancer, malignant melanoma, gallbladder cancer, cervical cancer, unknown origin). For the third question around which our study was focused, time-dependent variables, such as age and laboratory data, were updated at the time of the subsequent treatment for SRE. Thus, patients who had a subsequent SRE had two timepoints for gathering variables: at their initial SRE and their subsequent SRE.

Outcomes

The primary outcome was a subsequent SRE requiring local treatment. A subsequent SRE was defined by two criteria. First, the metastatic site of subsequent SRE had to differ from the metastatic site of the initial SRE. Local treatments administered at previously treated locations were viewed as revision or rescue treatments, which is different from the study design. Second, the second treatment had to be carried out at least 12 weeks after the initiation of the initial treatment. This 12-week timespan should make sure that the second SRE was not present at the first SRE, because 'planned' subsequent treatments were usually performed within 12 weeks after the initiation of the initial treatment. Any additional non-skeletal metastases such as visceral metastases and brain metastases were registered at the initial and subsequent SRE presentation, but they were not considered in defining the outcome.

The secondary outcome was survival after local treatment for SRE, defined as death from any cause. Survival was measured starting from three different timepoints using local SRE treatment as anchor point: one for the 'single SRE group', and two for the 'subsequent SRE group'. For patients in the subsequent SRE group, survival duration was analyzed twice. In study question 2, survival duration started at the initial SRE treatment (orange in Figure 2). In study question 3, survival duration started at the subsequent SRE treatment (red in Figure 2). Survival cutoffs included six weeks, 90 days, and one year. These timepoints are traditionally viewed as key milestones into the effectiveness of various therapeutic interventions.[13,14]

Statistical analysis

Continuous variables were presented using medians with IQRs, and comparisons were made using Mann-Whitney U test since many of them did not follow a normal distribution. Categorical variables were presented as frequencies and percentages, and were analyzed using Fisher's exact test. Survival curves were demonstrated using Kaplan–Meier plots, and log-rank tests were used to compare survival. Missing data were imputed using the MissForest algorithm,[15] and the missing proportion of each variable was also provided (Supplementary Table i). Python packages "lifelines" and "scipy" (version 3.8) were employed.[16,17] The statistical significance level was set at $p < 0.05$.

Subgroup analysis

Clinicians often tailor their therapeutic approach based on different metastatic locations. For instance, it usually takes months to recover from surgery for spine metastasis.[18] The recovery time after a hemiarthroplasty for proximal femoral metastasis is usually shorter.[19–21] Thus, survival rates at different timepoints would be referenced in different clinical situations, and separate survival analyses would be provided for patients with spinal or limb metastases. As well as stratifying the patients by the metastatic locations, we also stratified the patients by the primary tumour type since different tumour types were associated with different prognoses.[4]

Immortal time bias and sensitivity analysis

The operationalization of a SRE within this study introduces an immortal time bias spanning 12 weeks,[22] wherein patients categorized under the subsequent SRE cohort have to survive the initial 12-week period post-initial treatment; otherwise, their risk of experiencing a subsequent SRE within this timeframe was precluded. This methodological approach may inflate survival estimates for the subsequent SRE cohort when addressing study question 2. To mitigate the influence of immortal time bias, we implemented a sensitivity analysis by excluding the immortal period from the analysis. Specifically, we initiated the survival analysis for the subsequent SRE group 12 weeks post-initial treatment (green in Figure 2), and this was contrasted with the survival duration observed in the single SRE group (blue in Figure 2). In the context of study question 2, should the adjusted survival duration of the subsequent SRE group surpass that of the single SRE group, it suggests that the observed prognostic advantage in the

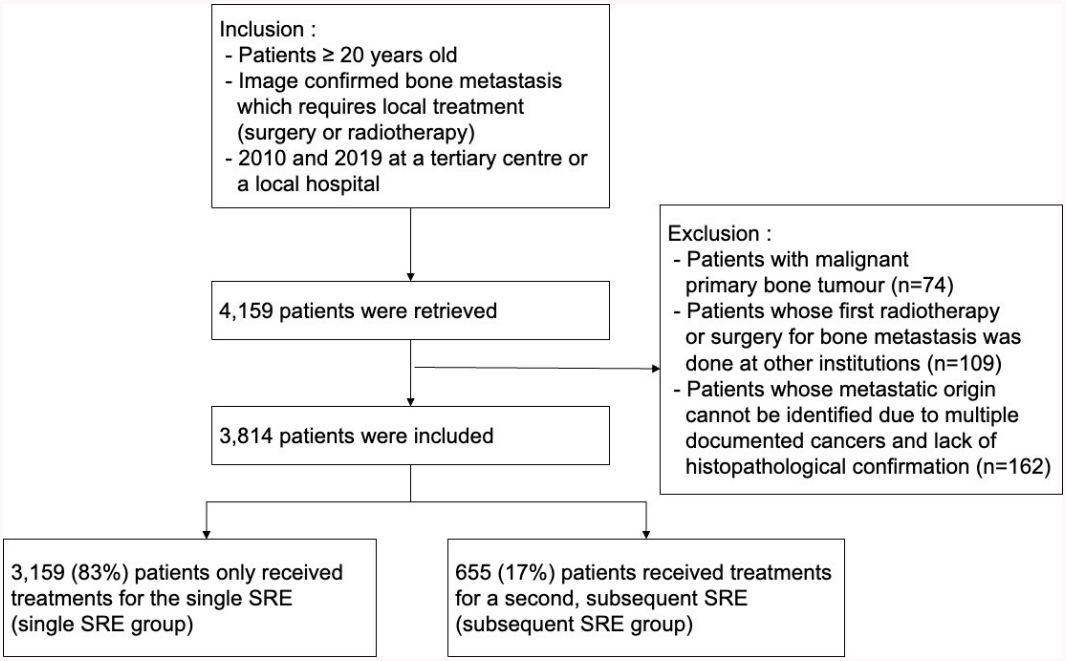

Fig. 1
Flowchart of patient enrolment. SRE, skeletal-related event.

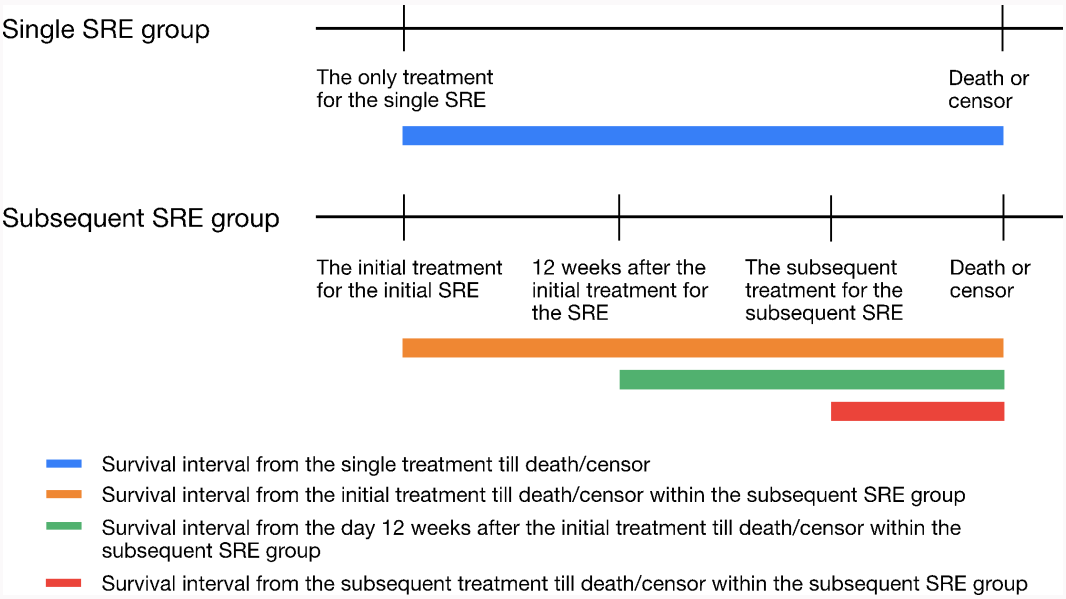

Fig. 2
Illustration of three different survival durations, anchoring different starting points. In study question 2, we compared the blue and orange survival durations. In the corresponding sensitivity analysis eliminating the immortal bias time, we compared the blue and green survival durations. In study question 3, we compared the blue and red survival durations. SRE, skeletal-related event.

subsequent SRE cohort may not be significantly attributed to immortal time bias.

Results

What proportion of patients develop a subsequent SRE requiring a second local treatment?

Overall, 17% (655/3,814) of the patients had a subsequent SRE and the remaining 83% (3,159/3,814) had a single SRE without development of a subsequent SRE. The median time to receive subsequent SRE treatment after the initial SRE treatment was 289 days (IQR 150 to 565). Overall, 24% of patients (758/3,159) underwent surgery, and 92% of patients (2,906/3,159) underwent radiotherapy for the single SRE. Of the 655 subsequent treatments, 96% (627/655) were radiotherapy and 20% (132/655) were surgery.

Prognostic differences between groups when receiving initial SRE treatment

Patients in the subsequent SRE group at the time of their initial SRE treatment had a better survival than patients with

Table I. Comparison of patients in single skeletal-related event (SRE) group and patients in subsequent SRE group at the time of their initial SRE treatment.

Variable	Single SRE group (n = 3,159)	Subsequent SRE group at initial treatment (n = 655)	p-value
Demographic			
Median age, yrs (IQR)	62.0 (53.4 to 71.0)	59.3 (50.3 to 67.3)	< 0.001*
Sex (female), n (%)	1,424 (45.1)	321 (49.0)	0.070†
Median BMI, kg/m^2 (IQR)	22 (20 to 25)	25 (23 to 27)	0.010*
Oncological			
Metastatic site, n (%)			0.001†
Spine	2,290 (72.5)	431 (65.8)	
Limb	869 (27.5)	224 (34.2)	
Primary tumour, n (%)			0.001†
Slow growth	377 (11.9)	71 (10.8)	
Intermediate	1,004 (31.8)	256 (39.1)	
Rapid growth, n (%)	1,778 (56.3)	328 (50.1)	
Brain metastasis, n (%)	504 (16.0)	182 (27.8)	< 0.001†
Visceral metastasis, n (%)	864 (27.4)	258 (39.4)	< 0.001†
Previous medical treatment, n (%)			
Chemotherapy	2,064 (65.3)	337 (51.5)	< 0.001†
Hormone therapy	1,571 (49.7)	269 (41.1)	< 0.001†
Targeted therapy	1,192 (37.7)	250 (38.2)	0.870†
Local management, n (%)			
Surgery	758 (24.0)	194 (29.6)	0.002†
Radiotherapy	2,906 (92.0)	562 (85.8)	< 0.001†
Clinical			
ECOG performance status, n (%)			0.004†
0 to 1	1,295 (41.0)	344 (53.0)	
2 to 4	998 (32.0)	200 (30.5)	
Additional Charlson's comorbidity, n (%)	1,080 (34.2)	188 (28.7)	0.008†
Median laboratory values (IQR)			
Alanine transaminase	20 (13 to 33)	19 (13 to 30)	0.220*
Albumin	3.7 (3.2 to 4.2)	4.0 (3.4 to 4.3)	< 0.001*
Alkaline phosphatase	103.0 (69.0 to 201.0)	107.0 (71.0 to 188.5)	0.200*
Calcium	2.23 (2.06 to 2.34)	2.26 (2.11 to 2.36)	0.730*
Creatinine	0.8 (0.6 to 1.0)	0.8 (0.6 to 0.9)	0.110*
Haemoglobin	11.3 (9.9 to 12.8)	12.2 (10.6 to 13.4)	< 0.001*
Lymphocyte	1.14 (0.71 to 1.67)	1.31 (0.88 to 1.80)	< 0.001*
Neutrophil	5.08 (3.37 to 7.60)	4.61 (3.32 to 6.43)	< 0.001*
Platelet	239.0 (175.0 to 314.0)	234.0 (180.8 to 301.0)	0.260*
Sodium	136.0 (132.0 to 138.2)	137.0 (134.0 to 139.0)	0.990*
White blood cell	7.2 (5.3 to 9.8)	6.7 (5.3 to 8.8)	0.001*

Rapid-growth tumours were defined as hormone-dependent breast cancer, hormone-dependent prostate cancer, malignant lymphoma, malignant myeloma, and thyroid cancer. Intermediate-growth tumours were defined as non-small cell lung cancer with molecularly targeted therapy, hormone-independent breast cancer, hormone-independent prostate cancer, renal cell carcinoma, sarcoma, other gynaecological cancer, and other cancers. Slow-growth tumours were defined as other lung cancer, colon and rectal cancer, gastric cancer, hepatocellular carcinoma, pancreatic cancer, head and neck cancer, other urological cancer, oesophageal cancer, malignant melanoma, gallbladder cancer, cervical cancer, and cancers of unknown origin. Bone target agents included high-dosage denosumab (brand name Xgeva) and zoledronate (brand name Zometa).
*Mann-Whitney U test.
†Fisher's exact test.
ECOG, Eastern Cooperative Oncology Group; SRE, skeletal-related event.

a single SRE treatment (six weeks: 100% vs 83%, p < 0.001; 90 days: 100% vs 69%, p < 0.001; one year: 68% vs 35%, p < 0.001, all Fisher's exact test; Figure 2). The survival difference remained significant after eliminating the immortal time (i.e. the first 12 weeks in the subsequent SRE group). The better prognosis was reflected in the fact that favourable clinical and oncological features were generally more common in the subsequent SRE group: younger age, higher BMI, less exposure to chemotherapy or hormone therapy, fewer rapid-growth tumours as origin, fewer comorbidities, better ECOG score, higher albumin level, higher haemoglobin concentration, higher lymphocyte count, lower neutrophil count, and lower white blood cell count (Table I).

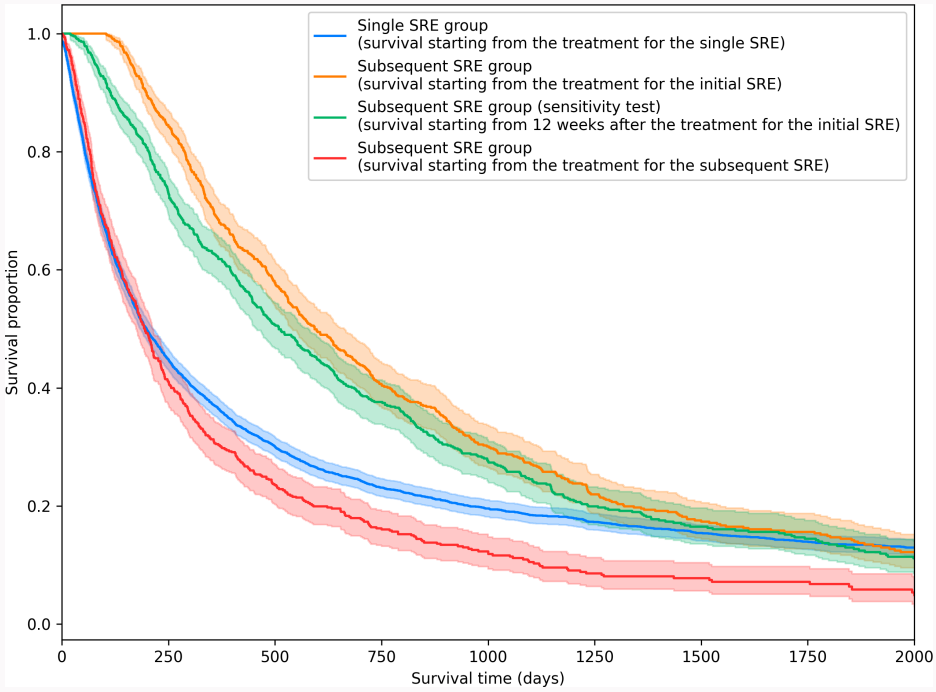

Fig. 3
Kaplan–Meier curves with 95% CIs of overall survival stratified by patients in the single skeletal-related event (SRE) group and subsequent SRE group.

Clinical, oncological, and prognostic differences between groups when receiving subsequent SRE treatment

The survival rates for both groups were similar within the first 200 days after the index treatment for SREs. However, after 200 days, the survival curve for patients in the single SRE group consistently remained better than that of the subsequent SRE group (blue vs red lines, respectively; Figure 3). Specifically, the subsequent SRE group, compared with the single SRE group, had a slightly higher six-week survival (87% vs 83%; $p = 0.048$), no 90-day survival difference (68% vs 69%; $p = 0.961$), and a lower one-year survival (28% vs 35%; $p < 0.001$, all Fisher's exact test). Subgroup analyses yielded similar results, suggesting that the observed survival trend can be generalized to patients treated for either spinal or limb metastasis (Supplementary Figures a and b) and patients with different primary tumour types (Supplementary Figures c to e).

Furthermore, analyses within the subsequent SRE group showed that patients at the time of their subsequent treatment, compared to the time of their first treatment, exhibited differences in several regards. They had a higher incidence of metastasis to limbs and brain or visceral organs, poorer ECOG score, lower albumin levels, lower haemoglobin concentrations, lower lymphocyte counts, lower sodium levels, lower white blood cell counts, and were exposed to a more extensive range of therapeutic interventions including chemotherapy, hormone therapy, and targeted therapy (Table II).

Discussion

The management of MBD is complicated and aims to provide symptom relief and function preservation, balanced with complications, prosthesis durability, and stability. The therapeutic approach has evolved substantially over time with the progress of systemic treatments and advanced radiological techniques.[3,4] These advances have resulted in improved life expectancy, but also increased the lifetime risk of subsequent SREs. However, this study found that nearly 20% of patients required treatments for a second, subsequent SRE, and the current clinical guideline did not provide a specific approach to this clinical condition.[23] Therefore, it is crucial to provide a detailed characterization of their clinical, oncological, and prognostic data to improve clinical decision-making. In this study, we observed that referencing the initial treatment, patients in the subsequent SRE group had longer median survival than patients in the single SRE group. Once patients develop a subsequent SRE, they have a worse one-year survival rate than those who receive treatment for the single SRE, which clinicians should be aware of when considering treatment options. Future research should focus on identifying prognostic factors and assessing the applicability of existing survival prediction models to provide a better management of subsequent SREs. Additionally, exploring the potential of prophylactic local interventions for the prevention of further SREs in patients at elevated risk warrants further investigation.[24,25]

This study has several limitations. First, as a retrospective analysis, we were unable to confirm whether the included subsequent SRE treatments were part of the initial treatment. However, we believe this limitation to be minor, as a previous study has shown that patients who underwent surgery for MBD were mostly discharged within two months.[26] Therefore, a predetermined interval of 12 weeks should be enough to exclude 'planned' subsequent treatment. Second, we only included patients treated at two branches of our institution, which may limit the generalizability of our results. However, no international differences in patients' survival rates were previously observed.[27–30] Third, while we did present data regarding brain and visceral metastases at both the

Table II. Comparison of patients within the subsequent skeletal-related event (SRE) group at the time of the initial treatment for SRE and subsequent treatment for SRE.

Variable	Subsequent SRE group at the initial treatment (n = 655)	Subsequent SRE group at the subsequent treatment (n = 655)	p-value
Demographic			
Median BMI, kg/m^2 (IQR)	25 (23 to 27)	22 (20 to 25)	0.077*
Oncological			
Metastatic site, n (%)			< 0.001†
Spine	431 (65.8)	327 (49.9)	
Limb	224 (34.2)	328 (50.1)	
Brain metastasis, n (%)	182 (27.8)	216 (33.0)	0.040†
Visceral metastasis, n (%)	258 (39.4)	279 (42.6)	0.240†
Previous medical treatment, n (%)			
Chemotherapy	337 (51.5)	506 (77.3)	< 0.001†
Hormone therapy	269 (41.1)	395 (60.3)	< 0.001†
Targeted therapy	250 (38.2)	377 (57.6)	< 0.001†
Local management, n (%)			
Surgery	194 (29.6)	132 (20.2)	< 0.001†
Radiotherapy	562 (85.8)	627 (95.7)	< 0.001†
Clinical			
ECOG performance status, n (%)			0.210†
0 to 1	344 (53.0)	298 (45.4)	
2 to 4	200 (30.5)	203 (30.8)	
Additional Charlson's comorbidity, n (%)	188 (28.7)	227 (34.7)	< 0.001†
Median laboratory values (IQR)			
Alanine transaminase	19 (13 to 30)	18 (12 to 29)	0.080*
Albumin	4.0 (3.4 to 4.3)	3.8 (3.3 to 4.2)	0.001*
Alkaline phosphatase	107 (71 to 189)	107 (70 to 191)	0.860*
Calcium	2.26 (2.11 to 2.36)	2.25 (2.11 to 2.36)	0.600*
Creatinine	0.8 (0.6 to 0.9)	0.8 (0.6 to 1.0)	0.310*
Haemoglobin	12.2 (10.6 to 13.4)	11.2 (9.9 to 12.6)	< 0.001*
Lymphocyte	1.31 (0.88 to 1.80)	0.99 (0.63 to 1.42)	< 0.001*
Neutrophil	4.61 (3.32 to 6.43)	4.43 (3.12 to 6.40)	0.240*
Platelet	234.0 (180.8 to 301.0)	223.0 (169.0 to 290.8)	0.080*
Sodium	137.0 (134.0 to 139.0)	136.0 (133.0 to 139.0)	0.040*
White blood cell	6.7 (5.3 to 8.8)	6.3 (4.7 to 8.6)	0.005*

*Mann-Whitney U test.
†Fisher's exact test.
ECOG, Eastern Cooperative Oncology Group; SRE, skeletal-related event.

initial and subsequent SRE, our primary focus was not on how these non-skeletal metastases influenced the ultimate treatment decisions for metastatic patients, including whether further treatment at a skeletal site was necessary. Exploring additional treatment approaches and their distinct outcomes could have been interesting, but was beyond the scope of this study as we focused on the effect of SRE. Fourth, it is important to consider factors beyond survival when deciding treatment, such as postoperative ambulatory status, reoperations, systemic complications, pain intensity, and quality of life. Future studies, and ideally prospectively, should examine these outcomes in detail, as they are crucial aspects of medical care for patients with MBD. Despite these limitations, to our knowledge, this is the first study investigating subsequent SREs in MBD. These study results provide a comprehensive overview of patients with a subsequent SRE, which can help both patients and clinicians in shared decision-making as discussed below.

Patients in the subsequent SRE group at the time of the initial treatment, compared with those in the single SRE group, generally had more factors associated with better prognosis.[30–32] These observations could be related to longer median survival duration, which might explain the increased risk of subsequent SREs in patients with a good prognosis. In contrast, higher levels of alkaline phosphatase (ALP) and more brain/visceral metastases were also observed in the subsequent SRE group. Higher ALP levels might be related to more active osteolysis,[33] and brain/visceral metastases might indicate a more advanced malignancy state. These characteristics may make patients more vulnerable to subsequent SREs, although the poorer prognosis might prevent the development of a subsequent SRE.[34] For better clinical application, future analysis should be applied to consider death as a competing risk.[35] In the meantime, personalized follow-up

plans could be considered for patients at higher risk of developing subsequent SREs. For instance, more frequent radiological scanning for these patients might aid in the early detection and treatment of subsequent SREs such as timely fixing of impending pathological fractures, which has been shown to provide better clinical outcomes than treating actual pathological fractures.[36] Prophylactic radiotherapy, as another example, could also be considered to further improve patients' life expectancy and quality of life.[24,25]

Survival estimation plays a crucial role in determining the appropriate treatment for patients with MBD. For those with spinal metastasis without acute neurological deterioration, short-term survival probabilities, such as six-week[13,14] and 90-day survival probabilities,[37–40] are often considered critical in deciding whether to surgically intervene. For those with limb metastasis, tumours rarely progress, and implants rarely fail within the first three months,[41,42] making nail fixation, with its minimal invasiveness, a suitable implant choice for patients with a lower 90-day survival probability. We demonstrated that the short-term survival rates (e.g. 90-day survival probability) of the two patient groups, after the treatments for the single and the subsequent SRE, were similar. The similarity indicates that clinicians' experiences in managing a single SRE could be a reliable guide when treating a subsequent SRE. However, we also found a difference in the one-year survival rate between the two patient groups.[43] Treatment options, such as durable prosthesis arthroplasty, higher radiation dosage, or more radical tumour curettage, are believed to be more suitable for patients with a higher one-year survival probability due to a higher lifetime treatment failure rate.[1,44] Therefore, when considering these interventions for patients with subsequent SREs, radiological and orthopaedic oncologists should keep the survival gap in mind and weigh the necessity with caution as the clinical benefit of these interventions might be less prominent.

In conclusion, the risk of developing a subsequent SRE is high and those patients with subsequent SREs have different clinical, oncological, and prognostic features compared to those with single SRE presentations. These results warrant several considerations. First, personalized follow-up plans in patients with a good prognosis may be necessary as they are at higher risk of developing a subsequent SRE. Second, the poorer one-year survival rate at subsequent SRE presentation highlights the importance of carefully weighing the risk and benefits of intervention. Third, current prognostic tools may not be entirely accurate. Therefore, along with increasing awareness among clinicians, there is a need to create specialized tools tailored to this specific population. Future research is warranted to validate or refute our findings as this study is, to our knowledge, the first to report on the high rate of subsequent SREs and their differences with initial SREs.

Supplementary material

Table showing missing proportion of included variables, and figures showing Kaplan–Meier curves with 95% CIs of overall survival stratified by patients in the single skeletal-related event (SRE) group and subsequent SRE group, with subgroup analyses in patients who: were treated for spinal metastasis; were treated for limb metastasis; had a rapid-growth primary tumour; had an intermediate-growth primary tumour; and had a slow-growth primary tumour.

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