Prophylactic Effect of Liaison Treatment on the Occurrence of Skeletal-Related Events in Patients with Metastatic Spinal Tumours: An Exploratory Interrupted Time Series Study

Kazuo Nakanishi[1], Yasukazu Hijikata[2], Kazuya Uchino[1], Seiya Watanabe[1], Kosuke Misaki[1] and Hideaki Iba[1]

1) Department of Orthopaedic Surgery, Kawasaki Medical School, Okayama, Japan
2) Spine and Low Back Pain Center, Kitasuma Hospital, Hyogo, Japan

Abstract:

Introduction: There is a growing momentum for the collaboration between multiple disciplines for the prevention and treatment of skeletal-related events (SREs) in patients with metastatic spinal tumors. However, the effectiveness of multidisciplinary approaches remains unclear. Hence, we conducted an exploratory study to examine the impact of liaison treatment for metastatic spinal tumor (LMST) on the prevention of SREs among patients with a metastatic spinal tumor.

Methods: This study was an exploratory interrupted time series conducted in a single medical center. Overall, 1,043 patients with a metastatic spinal tumor diagnosed between January 2011 and December 2020 were included. The LMST was implemented in January 2014. The LMST team consisted of the orthopedic surgery, thoracic surgery, breast and thyroid surgery, clinical oncology, urology, and radiology departments. Monthly joint conferences were held for patients with spinal instability, and the incidence of SRE was measured at 6-month intervals.

Results: Throughout the study period, we identified 66 SRE incidences. After the implementation of the LMST, a level change of −5.2% (95% confidence interval [CI]: −11.7 to 1.3, p = 0.11) was observed. Subsequently, a post-implementation trend change of −0.3% (95% CI: −2.0 to 1.5, p = 0.75) beyond the baseline was noted.

Conclusions: We suggest both immediate and gradual effects of the introduction of the LMST on deterring the development of SREs. Our results support the global trend of introducing a multidisciplinary approach for the treatment of metastatic spinal tumors.

Keywords:
skeletal-related event, metastatic spinal tumor, multidisciplinary approach, liaison, interrupted time series

Spine Surg Relat Res 2022; 6(1): 26-30
dx.doi.org/10.22603/ssrr.2021-0041

Introduction

Metastatic spinal tumors are common, with spinal metastases reported in 36% of deaths due to malignant neoplasms[1]. The number of patients with metastatic spinal tumors is expected to increase with the advent of an ultra-aged society and the development of diagnostic imaging techniques. Skeletal-related events (SREs) are skeletal complications that are associated with bone metastases and include cancer-induced bone pain, hypercalcemia, pathological bone fractures, and spinal cord compression[2]. SREs develop in approximately 20% of the metastatic spinal tumor cases;[3] they cause an excruciating pain and a significant reduction in the quality of life due to the neurological deficits in the affected patients. The recent developments in chemotherapy, advent of bone-modifying drugs, and internal irradiation for bone metastases are changing the landscape in which metastatic spine tumors are treated. Accordingly, the goal of the treatment is shifting from traditional palliation to maintaining neurological function (e.g., gait function) and the quality of life, with an increased focus on SREs[4].

There is a growing momentum for the collaboration among departments across multiple disciplines, such as radiology, orthopedics, oncology, palliative care, and rehabilitation, for the prevention and treatment of SREs in patients with metastatic spinal tumors[5]. Specifically, a neurologic, oncologic, mechanical, and systemic decision framework, in which the departments of radiology, orthopedics, and medi-

cal oncology work together, has been proposed[6]. However, the effectiveness of these multidisciplinary approaches remains unclear. Hence, we conducted an exploratory study to examine the association between the introduction of a multidisciplinary collaboration and the reduction in the incidence of SREs.

Materials and Methods

Data source

From January 2011 to December 2020, we extracted data on metastatic spinal tumors from the hospital database, including the demographics, longitudinal records of care, and outcomes for each consecutive patient. We introduced liaison treatment for metastatic spinal tumor (LMST) on January 1, 2014, and the database provided us with 3 years (6 timepoints) of pre-LMST data and 7 years (14 timepoints) of post-LMST data. This study was approved by the certified institutional review boards. All data were retrospectively aggregated in an anonymized form, and individual informed consent was not required.

Details of intervention

The LMST team included the departments of orthopedic surgery, thoracic surgery, breast and thyroid surgery, clinical oncology, urology, and radiology. All patients initially diagnosed with a metastatic spinal tumor by radiologists were referred to an orthopedic surgeon in the LMST team. Each spinal metastasis was evaluated using the spinal instability neoplastic score (SINS), where scores of 7 or more implied spinal instability[7]. All patients with an SINS of ≥7 and those with an SINS of ≤6, who were suspected by the attending physician to have impending SREs, were reviewed during the monthly LMST conference for the discussion of possible treatments. In addition to the LMST team, anesthetists, otolaryngologists, hematologists, dermatologists, and nurses were present at that conference as required. Details of the LMST have been previously described elsewhere[8].

Outcome measures

The primary outcome in this study was the incidence rate of SRE. The denominator was all individuals registered at the hospital with a metastatic spinal tumor, except for those who had already developed an SRE or had dropped out at previous timepoints. The incidence of SRE was identified using individual medical records. The definition of SRE includes the following[9]:
- symptomatic, radiographically confirmed pathological fractures,
- spinal cord or nerve root compression,
- radiotherapy on the bone or orthopedic surgery on the bone.

In the present study, prophylactic surgery or radiation therapy administered prior to the occurrence of significant symptoms based on the SINS were not included under the definition of SRE.

Statistical analysis

We first conducted a descriptive analysis of the incidence rate of SRE in the periods before and after the implementation of the LMST. Values were expressed as medians and interquartile ranges (IQRs) for continuous variables and as numbers and proportions for dichotomous variables.

Subsequently, we estimated the effect of the LMST on the prevention of SRE using an interrupted time series regression (ITS)[10]. In this design, population-level outcomes (rates of SRE incidence) were calculated over time, and statistical regression was adopted to investigate the two primary outcomes of interest: the level change in SRE incidence immediately after the LMST implementation and the trend, which is independent of the baseline trend, that is affected by a population-level exposure (introduction of the LMST on January 1, 2014). To conduct ITS, we adhered to the appropriate guidelines recognized for ITS[11]. ITS assumes counterfactually that the preintervention trend would have persisted if the intervention had not occurred. We fitted a simple linear regression model that included only a continuous term for times (6-month intervals), representing the baseline trend in the SRE incidence. We then employed another linear regression with a continuous term for times, an indicator variable for whether the time was before or after the LMST (representing the level change), and a continuous term for times after implementation (representing the post-implementation change in the trend) to estimate these effects. All statistical analyses were conducted using the software R (version 3.6.2, R Foundation for Statistical Computing, Vienna, Austria) and Stata (version 15.1, StataCorp LLC, College Station, TX, USA), and two-sided 95% confidence intervals (CIs) were calculated for statistical tests.

Results

Our analysis included 1,043 patients with metastatic spinal tumors, and each individual was observed for a median of 249.5 days (IQR: 46-743 days). Table 1 presents an overview of the study populations for each year. The number of eligible patients increased over time, with a parallel decline in the Katagiri score[12], performance status, and SINS.

Throughout the study period, we identified 66 SRE incidences. There were only two cases of SRE occurring in 2018, five in 2019, and none beyond 2020.

Fig. 1 presents the estimated level and trend change in the incidence of SRE. After the implementation of the LMST, a level change of −5.2% (95% CI: −11.7 to 1.3; p = 0.11) was observed. This was followed by a post-implementation trend change of −0.3% (95% CI: −2.0 to 1.5; p = 0.75) beyond the baseline trend. This decreasing post-implementation trend might mean that by the end of the study, the estimated reduction in the SRE incidence would be 8.7% lower than the counterfactual incidence.

Table 1. Characteristics of the Patients in Each Year of the Study Period.

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
	N=20	N=48	N=97	N=197	N=244	N=296	N=331	N=364	N=380	N=381
Age (years)	67 (56–77)	67 (58–73)	68 (60–75)	68 (61–76)	68 (62.5–77.5)	69 (60–77)	68 (60–76)	68 (60–76)	69 (60–77)	69 (60–76)
Sex (female)	10 (50)	26 (54)	50 (52)	85 (43)	115 (47)	133 (45)	152 (46)	181 (50)	180 (47)	185 (49)
Katagiri score	4 (2.5–6)	5 (3–7)	6 (4–7)	6 (4–7)	5 (3–6)	5 (3–6)	4 (3–6)	4 (3–6)	4 (3–6)	4 (3–6)
Performance status	1 (1–2)	2 (1–3)	2 (1–3)	2 (1–3)	1 (1–2)	1 (0–2)	1 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)
SINS	6 (5.5–9)	6 (5–8)	6 (5–8)	6 (4–8)	5 (4–7)	5 (3–7)	4 (3–6)	4 (3–6)	4 (3–6)	4 (3–6)
≥7	7 (35)	18 (38)	43 (44)	78 (39)	72 (30)	78 (26)	82 (25)	75 (21)	82 (22)	81 (21)
Primary lesion location										
Breast	9 (45)	22 (46)	34 (35)	56 (28)	68 (28)	83 (28)	96 (29)	111 (30)	122 (32)	115 (30)
Prostate	8 (40)	10 (21)	21 (22)	34 (17)	47 (19)	61 (21)	72 (22)	75 (21)	75 (20)	70 (18)
Lung	0	4 (8.3)	12 (12)	41 (21)	52 (21)	63 (21)	54 (16)	57 (16)	59 (16)	61 (16)
No. of SREs	2 (10)	11 (23)	8 (8.2)	8 (4.1)	11 (4.5)	10 (3.4)	9 (3)	2 (0.5)	5 (1.3)	0
SRE: surgery	1 (0.5)	3 (6.3)	8 (8.2)	5 (2.5)	6 (2.5)	1 (0.3)	2 (0.6)	1 (0.3)	2 (0.5)	0
SRE: radiation	1 (0.5)	5 (10)	0	1 (0.5)	3 (1.2)	5 (1.7)	2 (0.6)	1 (0.3)	3 (0.8)	0
Prophylactic treatment										
Surgery	3 (15)	4 (8.3)	4 (4.1)	10 (5.1)	20 (8.2)	20 (6.8)	24 (7.3)	24 (6.6)	18 (4.7)	16 (4.2)
Radiation	8 (40)	14 (29)	89 (30)	69 (35)	73 (30)	89 (30)	88 (27)	91 (25)	92 (24)	89 (23)
Zoledronic acid	7 (35)	16 (33)	32 (33)	52 (26)	52 (21)	60 (20)	60 (18)	56 (15)	62 (16)	57 (15)
Denosumab	8 (40)	24 (50)	47 (48)	86 (43)	104 (43)	141 (48)	157 (47)	174 (49)	169 (44)	156 (41)

SRE, Skeletal-related events; SINS, Spinal instability neoplastic score.

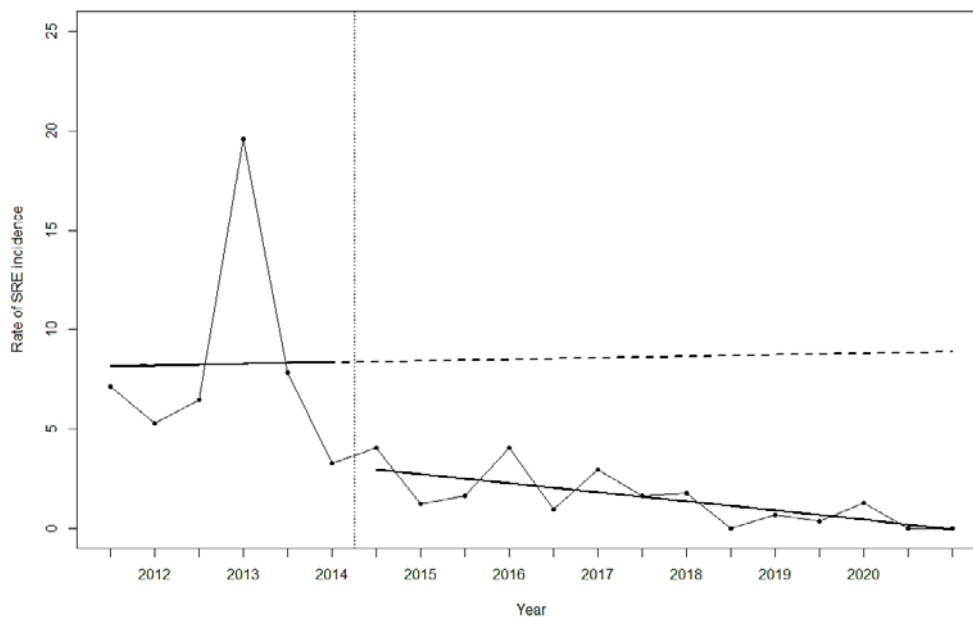Data are expressed as numbers (%) and medians (interquartile range).

Figure 1. Prophylactic effect of liaison treatment for metastatic spinal tumor (LMST) on the occurrence of skeletal-related events (SREs).
The X-axis indicates the timepoint (6-month intervals), and the Y-axis indicates the percentage of the SRE incidence at each timepoint. The dots on each timepoint represent the percentage of the SRE incidence during the 6 months before that timepoint. The LMST was introduced in January 2014.

Discussion

The survey of the registry of patients with metastatic spinal tumors at our hospital revealed that while the number of patients in the registry increased every year, the SRE incidence peaked in 2015 (11/243 cases), 1 year after the introduction of the LMST, and decreased until 2020, during which no cases were reported. Although the results were not

statistically significant, these findings suggest immediate and gradual positive effects of the introduction of the LMST on deterring the development of SREs.

We believe that pre-emptive treatment through a multi-departmental collaboration is the major factor that explains the effectiveness of the LMST. Metastatic spinal tumors are progressive, and conventional isolated treatments in each department would lead to significant delays in their diagnosis and indication. The main interventions that constitute pre-emptive treatment are prophylactic surgery and radiotherapy as well as the administration of bone modifiers[13]. In the period after 2017 when the incidence of SREs notably decreased, the actual number of cases administered with denosumab seems to have increased. Although it is beyond the scope of this study to discuss the effects of each of the multifaceted interventions that constituted the LMST, we have interpreted the results as particularly suggestive of the effectiveness of bone modifiers.

Implications for clinical practice

Our results suggest that the introduction of the LMST as a standard in clinical practice would reduce the incidence of subsequent SREs, thereby improving patient outcomes. Various studies[5,6,14-18] and clinical guidelines[4,13,19] have reported the need for the introduction of a multidisciplinary approach, and the results of the present study support this global trend.

The difficulty of standardization is a hindrance to the widespread use of LMST, as its effectiveness encompasses not only the aforementioned early treatment but also timely and well-informed clinical decisions on when and how to treat spinal metastases. The SINS was used as an objective measure of the urgency of SREs within the LMST framework. However, the SINS is a scale developed to visualize spinal instability and is not a direct predictor of the development of SRE. The introduction of SINS has led to the improvement of uniform reporting within the literature, but the prognostic value of SINS is controversial[20]. In the LMST, the clinical decision on the timing of the intervention was mainly based on the clinical experience of various specialists, which is difficult to standardize. There are various treatment options to prevent SRE. Surgery is a viable option for "impending SRE," but the indications, choice of technique (e.g., decompression, fixation, or both), and extent of treatment (i.e., how many vertebrae to treat) are difficult to determine for each patient. While the effectiveness of decompressive surgical resection has been reported[21], some reports suggest that new randomized controlled trials (RCTs) are required owing to its limited effectiveness[22]. The lack of evidence leaves clinical decisions mainly to the experiences of the orthopedic surgeon, also making standardization difficult. However, it takes an enormous amount of time for sufficient evidence to accumulate and a standardized system of treatment to be established. We believe that the introduction of the LMST, in which each specialist brings his/her clinical experiences and available evidence to collaborate, will be beneficial for patients who are suffering right now.

Strengths and limitations

The strength of the present study is its novelty in examining the effects of a multidisciplinary collaboration for the treatment of metastatic spinal tumors. The ideal study design is a cluster RCT, but it is impractical due to the difficulty of standardizing interventions between each site and the huge research cost. Furthermore, the treatment of metastatic spinal tumors is an ever-evolving process, and it is important to consider the changes in the treatment over time to investigate the effect of a multidisciplinary collaboration. We believe that the adoption of ITS addresses some of these difficult issues.

However, the present study has several limitations. First, the small sample size resulted in a low statistical power. While the overall sample size was relatively large (approximately 1,000 cases), the incidence of SRE was low (66 cases in total). Therefore, we could not adequately consider the origin of the metastasis and the competing risk of mortality. Second, there was no control group. Third, there were few timepoints for pre-LMST. Hence, the estimated regression line for pre-LMST might be less precise, as indicated by the positive trend. While the results of this study alone could not provide a strong recommendation for the introduction of the LMST, the negative impact of a multi-departmental collaboration on the patients is minimal, and thus, the impact of misleading readers by insisting on the introduction of LMST is likely to be small. Finally, the number of participants and the severity of their condition differed between the pre-LMST and post-LMST periods. As the SRE incidence is strongly influenced by an increase in the denominator, the slope of the estimated regression line might be far from the true value. However, despite the fact that the number of patients with an SINS of ≥7 has not changed since 2014, the actual incidence of SRE has distinctly declined. We believe that this reflects the true effects of the LMST.

In conclusion, using our database of metastatic spinal tumors, we suggest both immediate and gradual effects of the LSMT introduction on deterring the development of SRE. Our results support previous literature and trend in the field, supporting the introduction of a multidisciplinary approach for the treatment of metastatic spinal tumors.

Project administration KN
Software YH
Supervision KN
Writing original draft KN, YH
Writing review & editing KU, AW, KM, HI

Ethical Approval: This study was approved by the Ethics Committee of Kawasaki Medical School and Hospital (No. 3579).

Informed Consent: As this study was a retrospective survey without any personal information, the need for written informed consent was waived.

References

1. Wong DA, Fornasier VL, MacNab I. Spinal metastases: the obvious, the occult, and the impostors. Spine. 1990;15(1):1-4. doi: 10.1097/00007632-199001000-00001
2. Tsuzuki S, Park SH, Eber MR, et al. Skeletal complications in cancer patients with bone metastases. Int J Urol. 2016;23(10):825-32. doi:10.1111/iju.13170
3. Klimo P Jr, Schmidt MH. Surgical management of spinal metastases. Oncologist. 2004;9(2):188-96. doi:10.1634/theoncologist.9-2-188
4. Shibata H, Kato S, Sekine I, et al. Diagnosis and treatment of bone metastasis: comprehensive guideline of the Japanese Society of Medical Oncology, Japanese Orthopedic Association, Japanese Urological Association, and Japanese Society for Radiation Oncology. ESMO Open. 2016;1(2):e000037. doi:10.1136/esmoopen-2016-000037
5. Kimura T. Multidisciplinary approach for bone metastasis: a review. Cancers (Basel). 2018;10(6):156. doi:10.3390/cancers10060156
6. Laufer I, Rubin DG, Lis E, et al. The NOMS framework: approach to the treatment of spinal metastatic tumors. Oncologist. 2013;18(6):744-51. doi:10.1634/theoncologist.2012-0293
7. Fisher CG, DiPaola CP, Ryken TC, et al. A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the spine oncology study group. Spine (Phila Pa 1976). 2010;35(22):E1221-9. doi: 10.1097/BRS.0b013e3181e16ae2
8. Nakanishi K, Uchino K, Watanabe S, et al. Liaison treatment for metastatic spinal tumors. Spine Surg Relat Res. 2020;4(3):223-8. doi:10.22603/ssrr.2019-0105
9. Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst. 2002; 94(19):1458-68. doi:10.1093/jnci/94.19.1458
10. Kontopantelis E, Doran T, Springate DA, et al. Regression based quasi-experimental approach when randomisation is not an option: interrupted time series analysis. BMJ. 2015;350:h2750. doi: 10.1136/bmj.h2750
11. Jandoc R, Burden AM, Mamdani M, et al. Interrupted time series analysis in drug utilization research is increasing: systematic review and recommendations. J Clin Epidemiol. 2015;68(8):950-6. doi:10.1016/j.jclinepi.2014.12.018
12. Katagiri H, Okada R, Takagi T, et al. New prognostic factors and scoring system for patients with skeletal metastasis. Cancer Med. 2014;3(5):1359-67. doi:10.1002/cam4.292
13. Grávalos C, Rodríguez C, Sabino A, et al. SEOM clinical guideline for bone metastases from solid tumours (2016). Clin Transl Oncol. 2016;18(12):1243-53. doi:10.1007/s12094-016-1590-1
14. Ibrahim T, Flamini E, Fabbri L, et al. Multidisciplinary approach to the treatment of bone metastases: osteo-oncology center, a new organizational model. Tumori. 2009;95(3):291-7. doi:10.1177/030089160909500304
15. Soeharno H, Povegliano L, Choong PF. Multimodal treatment of bone metastasis-a surgical perspective. Front Endocrinol (Lausanne). 2018;9:518. doi:10.3389/fendo.2018.00518
16. D'Oronzo S, Coleman R, Brown J, et al. Metastatic bone disease: pathogenesis and therapeutic options: up-date on bone metastasis management. J Bone Oncol. 2019;15:004-4. doi:10.1016/j.jbo.2018.10.004
17. Macedo F, Ladeira K, Pinho F, et al. Bone metastases: an overview. Oncol Rev. 2017;11(1):321. doi:10.4081/oncol.2017.321
18. Barzilai O, Laufer I, Yamada Y, et al. Integrating evidence-based medicine for treatment of spinal metastases into a decision framework: neurologic, oncologic, mechanicals stability, and systemic disease. J Clin Oncol. 2017;35(21):2419-27. doi:10.1200/JCO.2017.72.7362
19. Szendrői M, Antal I, Szendrői A, et al. Diagnostic algorithm, prognostic factors and surgical treatment of metastatic cancer diseases of the long bones and spine. EFORT Open Rev. 2017;2(9): 372-81. doi:10.1302/2058-5241.2.170006
20. Versteeg AL, Verlaan JJ, Sahgal A, et al. The spinal instability neoplastic score: impact on oncologic decision-making. Spine (Phila Pa 1976). 2016;41(Suppl 20):S231-7. doi:10.1097/BRS.0000000000001822
21. Patchell RA, Tibbs PA, Regine WF, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. Lancet. 2005;366 (9486):643-8. doi:10.1016/S0140-6736(05)66954-1
22. Rades D, Huttenlocher S, Dunst J, et al. Matched pair analysis comparing surgery followed by radiotherapy and radiotherapy alone for metastatic spinal cord compression. J Clin Oncol. 2010; 28(22):3597-604. doi:10.1200/JCO.2010.28.5635