The current status and future of radiotherapy for spinal bone metastases

Yasuo Ejima1 · Yoshiro Matsuo1 · Ryohei Sasaki1

Abstract The management of spinal bone metastases is complex. In this review, the efficacy, methodology, and utilization of radiotherapy (RT) for spinal bone metastases are discussed. A number of randomized trials have evaluated the efficacy of 8 Gy, single-fraction RT for the palliation of painful bone metastases. However, RT for metastatic spinal cord compression has not been evaluated with respect to its optimal dose, palliative potential, or its ability to improve motor function. Two highly sophisticated RT techniques — stereotactic body RT (SBRT) and intensity-modulated RT (IMRT) — have recently been adapted for the treatment of spinal bone metastases, and both have the potential to achieve excellent control while minimizing acute and late toxicity. SBRT and IMRT are particularly well suited for the treatment of spinal bone metastases when they are localized or require re-irradiation, and may provide superior tumor control. Predicting the prognosis of patients with bone metastases and assessing spinal instability are both important when selecting the optimal RT method and deciding whether to perform surgery. The proper care of spinal bone metastases patients requires an interdisciplinary treatment approach.

Introduction

Bone metastases are a common manifestation of malignancy that can cause severe and debilitating effects, including pain, spinal cord compression, hypercalcemia, and pathologic fractures. The proper care of patients with bone metastasis requires interdisciplinary treatment delivered by orthopedic surgeons, radiation oncologists, medical oncologists, pain medicine specialists, radiologists, and palliative care professionals. Radiotherapy (RT) can provide successful palliation of painful bone metastasis in 50–80% of patients in a time efficient manner, and is associated with very few adverse effects, allowing complete pain relief at the treated site in up to one-third of patients [1]. Recently, in the field of radiation oncology, emerging novel techniques have been developed and adapted for the treatment of bone metastases. In light of these advances, the focus of this review includes the efficacy of RT, new RT methods, and relevant prognostic factors. The significance of each of these in the management of spinal bone metastases is discussed.

Radiation dose and schedule

RT is commonly used to provide pain relief in cases of painful bone metastases. Chow et al. [2] conducted a meta-analysis of 25 randomized palliative RT trials for uncomplicated painful bone metastases comparing 8 Gy in single and 20–30 Gy in multiple fractions. They concluded that both the overall pain relief rate (60% in the single-fraction arm and 61% in the multiple-fraction arm) and the complete pain relief rate (23 and 24%, respectively) were similar with no significant difference between these schedules. Although retreatment rates were higher in those who received single-fraction therapy, 8 Gy in single-fraction RT was suggested as the standard of care for the palliation of uncomplicated painful bone metastases in the recent American Society for Therapeutic Radiology and Oncology guidelines [3].
It is possible that patients with metastatic spinal cord compression (MSCC) will benefit more from higher-dose multiple-fraction RT than they would from lower-dose single-fraction RT, although currently, there is little data to support this (Table 1). In their review, Chow et al. [1] found that spinal cord compression occurred in 5.7 and 4.1 % of patients who received single-fraction and multiple-fraction RT, respectively. Although there was a trend favoring multiple-fraction RT, this did not reach statistical significance ($P = 0.31$). Rades et al. [4] evaluated the local control achieved using different RT schedules for MSCC. In their prospective, non-randomized study, local control was found to be significantly better after a long course of treatment (30 Gy in 10 fractions, 37.5 Gy in 15 fractions, and 40 Gy in 20 fractions) compared to a shorter course (8 Gy in a single-fraction, and 20 Gy in 4 fractions). In contrast, Maranzano et al. [5] demonstrated that a single-fraction RT was sufficient, and resulted in only minimal toxicity for patients with a poor prognosis.

Rades et al. [6] suggested in their retrospective study that dose escalation beyond 30 Gy in 10 fractions did not improve motor function and local control of MSCC in radioresistant tumors, such as renal cell carcinoma, colorectal cancer, and malignant melanoma. However, in another report [7], dose escalation beyond 30 Gy was found to give better local control and extend overall survival in patients with breast cancer, prostate cancer, myeloma/lymphoma, and others who had a favorable prognosis. Thus, 30 Gy in 10 fractions could be regarded as the standard therapeutic dose for MSCC. Although the available evidence is limited, dose escalation beyond 30 Gy may improve local control and overall survival in patients with a favorable survival prognosis, but it may not improve functional outcome, and dose escalation to 40 Gy in 20 fractions may still be insufficient for radioresistant tumors.

**IMRT and stereotactic body RT**

Recently, two sophisticated RT techniques, stereotactic body RT (SBRT; including stereotactic radiosurgery and stereotactic RT) and intensity-modulated RT (IMRT) have been adapted for the treatment of spinal bone metastases. SBRT uses more beams from many more directions than conventional opposed-field RT and consequently delivers much higher doses in a hypofractionated manner (either as a single fraction or as a smaller number of fractions). IMRT makes it possible to deliver optimal radiation doses safely to an irregularly shaped target while minimizing the dose to the surrounding normal structures. In order to achieve a high standard of targeting precision, these approaches require that the exact location and shape of the tumor be determined using imaging techniques (Fig. 1). In general, the term “spinal SBRT” refers to the use of both IMRT techniques and SBRT. The most important additional benefit of spinal SBRT is the possibility of achieving excellent dose coverage of the target, while avoiding the spinal cord, which is often the major limiting factor when delivering high-dose RT (Figs. 1, 2). Multiple retrospective studies have demonstrated that SBRT could feasibly be used to treat spinal metastases, and could control target lesions with only low toxicity [8, 9]. The local control rate based on imaging and/or pain management criteria was reported to be greater than 80 %, with only rare cases of toxicity.

**Table 1 Outcomes of conventional RT for MSCC**

| References | Study design | State of disease | Dose | Ambulatory rate before treatment (%) | Motor function improvement (%) | LC | Overall survival |
|------------|-------------|-----------------|------|--------------------------------------|------------------------------|----|-----------------|
| Maranzano [5] | RCT | Unfavorable prognosis | 8 Gy/1 Fr 16 Gy/2 Fr | 64 67 | 12 21 | NA NA | 4 months (median) 4 months (median) |
| Rades [4] | Prospective non-RCT | Various | 8 Gy/1 Fr, 20 Gy/4 Fr | 61 | 37 | 61 % at 1 years 81 % at 1 years | 23 % at 1 year 30 % at 1 year |
| Rades [7] | Matched cohort | Favorable prognosis | 30–40 Gy/10–20 Fr 30 Gy/10 Fr | 62 85 | 39 40 | 81 % at 1 years 71 % at 2 years | 68 % at 2 years |
| Rades [6] | Retrospective | Radio-resistant tumor | 37.5 Gy/15 Fr 40 Gy/20 Fr 30 Gy/10 Fr | 85 | 41 | 92 % at 2 years | NA |

*RT radiotherapy, MSCC metastatic spinal cord compression, LC local control, RCT randomized controlled trial, Fr fraction, NA not available*
Fig. 1 Upper panels the CyberKnife apparatus (left); a 3-dimensional rendered image (right) blue lines indicate beam directions. Lower panels Xsight, the image-guidance system used in the CyberKnife system, enables the automatic tracking of skeletal structures (left). Representative dose distribution (right).

Fig. 2 Comparison of radiation dose distributions between conventional radiotherapy (left) and intensity-modulated radiotherapy (right). Each colored line indicates an isodose curve. A higher radiation dose is concentrated on the vertebral bone metastasis while avoiding the heart and lungs (right).
The indication and appropriateness of SBRT in the treatment of spinal bone metastases should be carefully considered. The published efficacy and safety data for SBRT have mostly been from retrospective, single institution studies. Neither the exact dosing and target delineation requirements, nor the most appropriate inclusion and exclusion criteria for SBRT have been fully defined. In most previous studies of spinal SBRT, the primary endpoint for efficacy was the local control rate based on imaging and/or pain control, while motor function and ambulatory status were rarely considered. In their guidelines for RT of bone metastasis, Lutz et al. [3] suggested that SBRT might be useful for treating spinal bone metastases, although they also advised that this should preferably be within the confines of a clinical trial.

**Postoperative irradiation**

Surgery plays an important role in the management of patients with symptomatic MSCC. For patients with severe MSCC, Patchell et al. [10] demonstrated that surgical decompression was beneficial in the only randomized, multi-institutional trial to date. Significantly more patients who underwent surgery plus postoperative RT regained the ability to walk compared to those who only received RT. Patients treated with surgery also retained the ability to walk significantly longer than those treated with RT alone. Moreover, surgery only restored the ability to walk in 30% of patients who failed to respond to earlier RT, which compares unfavorably with the 62% post-treatment ambulatory rate of the patients who were originally not able to walk and received surgery as their first treatment. Based on these findings, the authors claimed that surgery plus RT was the best first-line treatment for MSCC. However, this result conflicts with the findings of Rades et al. [11], who showed that surgery plus RT for MSCC patients with various primary tumors did not significantly improve their functional outcome compared to RT alone. They also showed that surgery was beneficial for patients with relatively radioresistant primary tumors [12] (Table 2).

Although the exact criteria for surgery in MSCC patients continue to be debated, the following are generally agreed to be necessary: a favorable survival prognosis, a good performance status, a relatively radioresistant tumor type, and MSCC accompanied with mechanical instability [13, 14]. RT alone is recommended for MSCC from highly radiosensitive tumors, such as hematological malignancies and germ cell tumors. A dose of 30 Gy in 10 fractions for MSCC in a postoperative setting is the most frequently used and is now considered to be the standard treatment [10–12]. Higher doses may also be administered to patients with a favorable prognosis. However, these doses are based

| Table 2  | Outcome of conventional RT with or without surgery for MSCC |
|-----------|------------------------------------------------------------|
| References | Study design | Type of primary tumor | Surgery Dose | Overall survival |
| Patchell [10] | RCT | Excluded highly radio-sensitive tumors | Surgery + RT | 30 Gy/10 Fr | 126 days (median) |
| Rades [11] | Matched cohort | Various | Surgery + RT | 30–40 Gy/10–20 Fr | NA |
| Rades [12] | Matched cohort | Unfavorable | Surgery + RT | 30–40 Gy/10–20 Fr | 100 days (median) |

| | | | | | |
| | Ambulatory rate before treatment (%) | Ambulatory rate after treatment (%) | LC | Regained ability to walk (%) | |
| Patchell [10] | 68 | 84 | 62 | 69 | 57 |
| Rades [11] | 63 | 69 | 63 | 64 | 68 |
| Rades [12] | 64 | 61 | 64 | 67 | 61 |

RT radiotherapy, MSCC metastatic spinal cord compression, LC local control, RCT randomized controlled trial, Fr. fraction. NA not available.
on the use of RT alone for MSCC, and there are no reports comparing optimal postoperative RT doses.

A number of retrospective reports have focused on the postoperative efficacy of SBRT in MSCC patients (Table 3). The study with the largest cohort, by Laufer et al. [16], reported that high-dose hypofractionated SBRT provided better local tumor control compared with low-dose hypofractionated SBRT. Epidural disease is one of the major factors limiting the efficacy of spinal SBRT. Al-Omair et al. [17] showed that epidural disease progression was the most common treatment failure after spinal SBRT, and postoperative epidural disease grade was a significant predictor of local control. Ideally, in order to administer a tumoricidal radiation dose by SBRT more safely, it may be possible to create a small margin of 2–3 mm between the tumor and the spinal cord by performing separation surgery. This allows a full dose to be administered to the entire tumor volume while minimizing the radiation exposure to the spinal cord. A treatment approach reported by Bate et al. [18] that included SBRT alone for patients with minimal MSCC, and separation surgery followed by SBRT for patients with high-grade MSCC, seems a reasonable strategy.

### Re-irradiation of spinal bone metastases

Notably, re-irradiation is effective in improving or maintaining motor function. Rades et al. [19] conducted a retrospective study of re-irradiation for MSCC, and found that motor function improved in 36 % of patients, was stable in another 50 % of patients, and deteriorated in 14 % of patients, and that there were no cases of late toxicity, such as radiation myelopathy. The degree of motor function after re-irradiation was associated with the effectiveness of the initial RT, performance status, time to development of motor deficits, and visceral metastases, whereas the re-irradiation schedule had no significant impact. A recent multicenter, randomized trial [20] of re-irradiation for painful bone metastases, of which 28 % were in the spine, showed that treatment with 8 Gy in a single fraction was as effective as, and less toxic than 20 Gy in multiple fractions; however, these findings were not robust in per-protocol analysis.

SBRT is well suited for re-irradiation of the spine and may provide superior tumor control compared to conventional techniques, with reported local control rates of 66–93 % [21–23] (Table 4). Several studies identified potential risk factors for local recurrence after re-irradiation by spinal SBRT. Garg et al. [21] reported in their prospective study of spinal re-irradiation by SBRT that 13 of 16 patients with local progression after SBRT had tumors within 5 mm of the spinal cord, and 6 of them eventually developed MSCC. Damast et al. [22] studied the dose–response with SBRT used for re-irradiation, and found that there were significantly fewer local failures after SBRT with 30 Gy in 5 fractions compared to 20 Gy in 5 fractions.

Relatively little is known regarding the long-term toxicities of re-irradiation. Because re-irradiation has the potential to exceed normal tissue tolerance, care must be taken when the re-irradiated volume contains the spinal cord, and it might be appropriate to sum the biologically effective

### Table 3 Outcomes of postoperative SBRT or SBRT alone for MSCC

| References | Patients/lesions | Pre-RT Treatment | Dose | Neurological response | Postop MSCC | LC at 1 year |
|------------|-----------------|------------------|------|-----------------------|-------------|-------------|
| Ryu [15]   | 62/85           | 0                | 12–20 Gy/1 Fr | Remained intact in 94 %, improved in 52 %, stable in 11 %, progression in 16 % | NA          | NA          |
| Laufer [16]| 186             | 0                | Surgery + SBRT | NA                  | 11 %        | 83.6 %      |
|            | 109             | 75               | 18–36 Gy/5–6 Fr | 77.4 %              |
|            | 37              | 14               | 24–30 Gy/3 Fr  | 95.9 %              |
|            | 40              | 2                | 24 Gy/1 Fr     | 91 %                |
| Al-Omair [17]| 80              | 0                | Surgery + SBRT | NA                  | 10 %        | 84 %        |
|            | 35              | 0                | 18–26 Gy/1–2 Fr| 100 %               |
|            | 45              | 0                | 18–40 Gy/3–5 Fr| 70 %                |
| Bate [18]  | 57/69           | 0                | Surgery + SBRT | NA                  | 94.2 %      |
|            | 21 lesions      | 6                | 16–23 Gy/1 Fr,| Frankel score improved in 14 %, stable in 81 %, and declined in 5 % | 90.5 %      |
|            | 20–30 Gy/3–5 Fr |                  |                  |                      |
|            | 48 lesions      | 24               | SBRT alone     | Frankel score improved in 10 %, and stable in 90 % | 95.8 %      |
|            | 16–23 Gy/1 Fr,  |                  |                  |                      |
|            | 20–30 Gy/3–5 Fr |                  |                  |                      |

**SBRT** stereotactic body radiotherapy, **MSCC** metastatic spinal cord compression, **LC** local control, **Fr** fraction, NA not available
doses (BEDs) from the initial and repeat treatment regimens in order to estimate the risk of radiation myelopathy [3]. Radiation-induced myelopathy can occur 3–25 months after RT [24, 25], although complications associated with spinal re-irradiation are only rarely reported. Higher cumulative RT doses (BED > 135.5 Gy2), higher doses of each RT course (BED > 98 Gy2), and a short interval between the courses (<6 months) could be associated with a higher probability of developing radiation-induced myelopathy [24].

Assessment for spinal instability in the treatment of spinal bone metastases

Spinal instability is associated with the development of neurologic deficits, mechanical pain, and progressive deformity [26]. Therefore, early recognition of impending instability may prevent painful collapse and loss of function by prompting timely referral and treatment. In order to create a simple, standardized referral tool for non-spine specialists, the Spine Oncology Study Group developed the spinal instability neoplastic score (SINS) [26], which is based on clinical and radiologic findings. Huisman et al. [27] showed that a higher SINS increased the risk of RT failure in patients with spinal metastases, independent of the performance status, primary tumor type, and symptoms. They hypothesized that metastatic spinal bone pain, predominantly caused by mechanical instability, responds less well to RT than pain that results mainly from local tumor activity.

Vertebral fracture is common after RT for metastatic spine lesions (Fig. 3). Rose et al. [28] demonstrated that lytic disease involving more than 40% of the vertebral body and located at or below T10 confers a high risk of fracture, with correspondingly poorer clinical outcomes. Sahgal et al. [29] reported the results of the first multi-institutional study of SBRT-induced vertebral compression fractures (VCFs), including whether the SINS can predict this adverse event. The crude risk of fracture was 14%, the median time to VCF was 2.5 months, and the majority (65%) of VCFs occurred in the first 4 months following SBRT. Moreover, multivariable analysis identified dose per fraction (greatest risk for ≥20 Gy), in addition to 3 of the 6 original SINS criteria: baseline VCF, a lytic tumor, and spinal deformity, as significant predictors of VCF. In a review of SBRT-induced VCF, 11–47% of patients who developed VCFs needed a salvage spinal reconstructive procedure, such as percutaneous cement augmentation procedures or open spinal reconstructive surgery [30]. These results may help clinicians identify high-risk patients who would benefit from prophylactic vertebro- or kyphoplasty.
Conclusion

RT is typically the mainstay of treatment for spinal bone metastases. A number of studies have shown that palliative RT can be effective for painful bone metastases, while relatively little is known about the management of spinal bone metastases, especially MSCC. The management of MSCC requires a consideration of motor function and spinal instability as well as pain and local control. SBRT can safely administer a higher dose to the target, and can potentially provide lasting local control. SBRT is a promising method; however, epidural recurrence after SBRT and SBRT-induced VCF continue to be problematic, and require the appropriate application of combination SBRT and surgery. An evaluation of functional outcomes following spinal SBRT and the identification of indicators for surgery are needed to establish an optimal treatment strategy for spinal metastases.

Acknowledgments  The authors thank Professor Masahiro Kurosaka for his encouragement. They also thank all the members of the Bone Meta Board conference, and Dr. H. Nishimura, Dr. H. Mayahara, and Dr. M. Fuji of the Kobe Minimally Invasive Cancer Center for their kind support regarding IMRT and CyberKnife treatment.

Conflict of interest  None of the authors have any conflict of interest to declare.

References

1. Chow E, Harris K, Fan G, Tsao M, Sze WM. Palliative radiotherapy trials for bone metastases: a systematic review. J Clin Oncol. 2007;25(11):1423–36.
2. Chow E, Zeng L, Salvo N, Dennis K, Tsao M, Lutz S. Update on the systematic review of palliative radiotherapy trials for bone metastases. Clin Oncol R Coll Radiol. 2012;24(2):112–24.
3. Lutz S, Berk L, Chang E, Chow E, Hahn C, Hoskin P, Howell D, Konski A, Kachnic L, Lo S, Sahgal A, Silverman L, von Gunten C, Mendel E, Vassil A, Bruner DW, Hartsell W, American Society for Radiation Oncology (ASTRO). Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. Int J Radiat Oncol Biol Phys. 2011;79(4):965–76.
4. Rades D, Lange M, Veninga T, Stalpers LJ, Bajrovic A, Adamietz IA, Rudat V, Schild SE. Final results of a prospective study comparing the local control of short-course and long-course radiotherapy for metastatic spinal cord compression. Int J Radiat Oncol Biol Phys. 2011;79(2):524–30.
5. Maranzano E, Trippa F, Casale M, Costantini S, Lupatelli M, Bellavita R, Marafioti L, Pergolizzi S, Santacaterina A, Mignogna M, Silvano G, Fusco V. 8 Gy single-dose radiotherapy is effective in metastatic spinal cord compression: results of a phase III randomized multicentre Italian trial. Radiother Oncol. 2009;93(2):174–9.
6. Rades D, Freundt K, Meyners T, Bajrovic A, Basic H, Karstens JH, Adamietz IA, Wildfang I, Rudat V, Schild SE, Dunst J. Dose escalation for metastatic spinal cord compression in patients with relatively radioresistant tumors. Int J Radiat Oncol Biol Phys. 2011;80(5):1492–7.
7. Rades D, Panzer A, Rudat V, Karstens JH, Schild SE. Dose escalation of radiotherapy for metastatic spinal cord compression (MSCC) in patients with relatively favorable survival prognosis. Strahlenther Onkol. 2011;187(11):729–35.
8. Sahgal A, Bilsky M, Chang EL, Ma L, Yamada Y, Rhines LD, Létourneau D, Foote M, Yu E, Larson DA, Fehlings MG. Stereotactic body radiotherapy for spinal metastases: current status, with a focus on its application in the postoperative patient. J Neurosurg Spine. 2011;14(2):151–66.
9. Guckenberger M, Mantel F, Gersztien PC, Flickinger JC, Sahgal A, Létourneau D, Grills IS, Jawad M, Fahim DK, Shin JH, Winay B, Sheehan J, Kersh R. Safety and efficacy of stereotactic body radiotherapy as primary treatment for vertebral metastases: a multi-institutional analysis. Radiat Oncol. 2014;9(1):226.
10. Patchell RA, Tibbs PA, Regine WF, Payne R, Sana S, Kryscio RJ, Mohiuddin M, Young B. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. Lancet. 2005;366(9486):643–8.
11. Rades D, Huttenlocher S, Dunst J, Bajrovic A, Karstens JH, Rudat V, Schild SE. Matched pair analysis comparing surgery followed by radiotherapy and radiotherapy alone for metastatic spinal cord compression. J Clin Oncol. 2010;28(22):3597–604.
12. Rades D, Huttenlocher S, Bajrovic A, Karstens JH, Adamietz IA, Kazic N, Rudat V, Schild SE. Surgery followed by radiotherapy versus radiotherapy alone for metastatic spinal cord compression from unfavorable tumors. Int J Radiat Oncol Biol Phys. 2011;81(5):e861–8.

13. Lee CH, Kwon JW, Lee J, Hyun SJ, Kim KJ, Jahng TA, Kim HJ. Direct decompressive surgery followed by radiotherapy versus radiotherapy alone for metastatic epidural spinal cord compression: a meta-analysis. Spine. 2014;39(9):E587–92.

14. Lobb MA, Perry J, Chambers A, Laperriere NJ. Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the Cancer Care Ontario Practice guidelines initiative’s Neuro-oncology Disease Site Group. J Clin Oncol. 2005;23(9):2028–37.

15. Ryu S, Rock J, Jain R, Lu M, Anderson J, Jin JY, Rosenblum M, Movsas B, Kim JH. Radiosurgical decompression of metastatic epidural spinal compression. Cancer. 2010;116(9):2250–7.

16. Laufer I, Iorgulescu JB, Chapman T, Lis E, Shi W, Zhang Z, Cox BW, Yamada Y, Bilsky MH. Local disease control for spinal metastases following “separation surgery” and adjuvant hypofractionated or high-dose single-fraction stereotactic radiosurgery: outcome analysis in 186 patients. J Neurosurg Spine. 2013;18(3):207–14.

17. Al-Omair A, Masucci L, Masson-Cote L, Campbell M, Atenafu EG, Parent A, Letourneau D, Yu E, Rampersaud R, Massicotte E, Lewis S, Yee A, Thibault I, Fehlings MG, Sahgal A. Surgical resection of epidural disease improves local control following postoperative spine stereotactic radiotherapy. Neuro Oncol. 2013;15(10):1413–9.

18. Bate BG, Khan NR, Kimball BY, Gabrick K, Weaver J. Stereotactic radiosurgery for spinal metastases with or without separation surgery. J Neurosurg Spine. 2015;30(5):1–7.

19. Rades D, Rudat V, Veninga T, Stalpers LJ, Hoskin PJ, Schild SE. Prognostic factors for functional outcome and survival after reirradiation for in-field recurrences of metastatic spinal cord compression. Cancer. 2008;113(5):1090–6.

20. Chow E, van der Linden YM, Roos D, Hartsell WF, Hoskin P, Wu JS, Brundage MD, Nabil A, Tissing-Tan CJ, Oei B, Babington S, Demas WF, Wilson CF, Meyer RM, Chen BE, Wong RK. Single versus multiple fractions of repeat radiation for painful bone metastases: a randomised, controlled, non-inferiority trial. Lancet Oncol. 2014;15(2):164–71.

21. Garg AK, Wang XS, Shiu AS, Allen P, Yang J, McAleer MF, Azeem S, Rhines LD, Chang EL. Prospective evaluation of spinal reirradiation by using stereotactic body radiation therapy: the University of Texas MD Anderson Cancer Center experience. Cancer. 2011;117(15):3509–16.

22. Damast S, Wright J, Bilsky M, Hsu M, Zhang Z, Lovelock M, Cox B, Zatzky J, Yamada Y. Impact of dose on local failure rates after image-guided reirradiation of recurrent paraspinal metastases. Int J Radiat Oncol Biol Phys. 2011;81(3):819–26.

23. Mahadevan A, Floyd S, Wong E, Jeyapalan S, Groff M, Kasper E. Stereotactic body radiotherapy reirradiation for recurrent epidural spinal metastases. Int J Radiat Oncol Biol Phys. 2011;81(3):1500–5.

24. Nieder C, Grosu AL, Andratschke NH, Molls M. Proposal of human spinal cord reirradiation dose based on collection of data from 40 patients. Int J Radiat Oncol Biol Phys. 2005;61(3):851–5.

25. Sahgal A, Ma L, Weinberg V, Gibbs IC, Chao S, Chang UK, Werner-Wasik M, Angelov L, Chang EL, Sohn MJ, Soltys SG, Letourneau D, Ryu S, Gerszen PC, Fowler J, Wong CS, Larson DA. Reirradiation human spinal cord tolerance for stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys. 2012;82(1):107–16.

26. Fisher CG, DiPaola CP, Ryken TC, Bilsky MH, Shaffrey CI, Berven SH, Harrop JS, Fehlings MG, Boriani S, Chou D, Schmidt MH, Polly DW, Biagini R, Burch S, Dekutoski MB, Gunja A, Gerszen PC, Gokaslan ZL, Groff MW, Liebsch NJ, Mendel E, Okuno SH, Patel S, Rhines LD, Rose PS, Scibba DM, Sundaresan N, Tomita K, Varga PP, Vialle LR, Vrionis FD, Yamada Y, Fournier DR. A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine Oncology Study Group. Spine. 2010;35(22):E1221–9.

27. Huisman M, van der Velden JM, van Vulpen M, van Vulpen M, van den Bosch MA, Chow E, Oner FC, Yee A, Verkouwen HM, Verlaan JJ. Spinal instability as defined by the spinal instability neoplastic score is associated with radiotherapy failure in metastatic spinal disease. Spine J. 2014;14(12):2835–40.

28. Rose PS, Laufer I, Boland PJ, Hanover A, Bilsky MH, Yamada J, Lis E. Risk of fracture after single fraction image-guided intensity-modulated radiation therapy to spinal metastases. J Clin Oncol. 2009;27(30):5075–9.

29. Sahgal A, Atenafu EG, Chao S, Al-Omair A, Boehling N, Balagamwala EH, Cunha M, Thibault I, Angelov L, Brown P, Suh J, Rhines LD, Fehlings MG, Chang E. Vertebral compression fracture after spine stereotactic body radiotherapy: a multi-institutional analysis with a focus on radiation dose and the spinal instability neoplastic score. J Clin Oncol. 2013;31(27):3426–31.

30. Sahgal A, Whyne CM, Ma L, Larson DA, Fehlings MG. Vertebral compression fracture after stereotactic body radiotherapy for spinal metastases. Lancet Oncol. 2013;14(8):e310–20.