Author/s:
Abbouchie, H;Chao, M;Tacey, M;Lim Joon, D;Ho, H;Guerrieri, M;Ng, M;Foroudi, F

Title:
Vertebral fractures following stereotactic body radiotherapy for spine metastases

Date:
2020-04-01

Citation:
Abbouchie, H., Chao, M., Tacey, M., Lim Joon, D., Ho, H., Guerrieri, M., Ng, M. & Foroudi, F. (2020). Vertebral fractures following stereotactic body radiotherapy for spine metastases. Journal of Medical Imaging and Radiation Oncology, 64 (2), pp.293-302. https://doi.org/10.1111/1754-9485.13010.

DR. HUSSEIN ABBOUCHIE (Orcid ID : 0000-0002-7913-8584)
DR. MICHAEL CHAO (Orcid ID : 0000-0002-3497-3746)
A/PROF. FARSHAD FOROUDI (Orcid ID : 0000-0001-8387-0965)

Article type : Radiation Oncology Review Article

Abstract

Stereotactic body radiotherapy has emerged as one of the preferred treatments for patients with spine metastases, with the potential for long-term control from lesion irradiation. Post-treatment vertebral compression fractures are a known complication of this therapy, contributing to worsening pain and reduced quality of life, sometimes requiring surgical intervention. This review explores the current knowledge of post-radiotherapy fractures, in terms of the rates and associated predictive factors.

Search of databases including Medline, Embase and the Cochrane Library were conducted using keywords such as “vertebral compression fracture”, “stereotactic body radiotherapy” and “spine metastases”. The search was limited to published studies up to March 2019, reporting clinical outcomes including both the post-treatment fracture rate and statistical identification of associated risk factors.

Rates of post-treatment fractures ranged from 4-39%. A variety of factors were found to increase the risk, including the appearance of lytic vertebral disease, degree of pre-existing compression, spinal malalignment, increased dose per fraction and a Spinal Instability Neoplastic Score >6. This knowledge can enable clinicians to counsel patients when considering management options for spine metastases, maintaining the balance between local tumour control and the risk of subsequent fracture.

Key words: Compression Fractures, Metastases, Spine, Stereotactic Body Radiotherapy, Stereotactic Radiosurgery

Introduction

The vertebral column is one of the most common sites of metastatic spread from solid tumours. Approximately one-third of cancer patients will suffer bone metastases at some stage during their illness, with most involving the spine, frequently the thoracic and lumbar regions.[1] A common presentation is oligometastatic disease of the spine, which is a state of limited metastatic burden, for which locally ablative therapy may be curative.[2] The oligometastatic state is commonly defined as 5 or fewer metastatic sites systemically.[3] In the spine, bony metastases can cause complications such as severe pain, neurological compromise and mechanical instability leading to vertebral compression fracture (VCF).[4] Hence, one of the primary goals of care for spine metastases is long-term tumour control with ablative therapy.[5]

The historical treatment of choice for spine metastases was palliative conventional external beam radiotherapy (EBRT), where short-term pain relief and local control (LC) were achievable with doses designed to minimise normal tissue toxicity.[6] Stereotactic body radiotherapy (SBRT) has emerged over the last decade as an option for patients with spine oligometastases.[7] SBRT uses highly focused beams to deliver 1-5 hypofractionated doses to the vertebral target with greater precision than EBRT, in the order of 1-2mm accuracy.[8,9] This allows the biologically effective dose of SBRT to be approximately 2-8 times that of conventional palliative dose EBRT, with the potential for dose escalation being one reason for the growth of SBRT.[4] Multiple studies have shown 1-year LC rates with spine SBRT in the order of 80-90% for de novo lesions, including tumour types classically considered radio-resistant such as sarcoma and renal cell carcinoma.[10-12] More recently, Palma and colleagues demonstrated that SBRT to oligometastatic tumours elsewhere in the body resulted in improvements in overall survival and progression-free survival, with no change to quality of life compared to the palliative standard of care.[13] Randomised controlled trials are also currently in progress to assess whether spine SBRT is superior to EBRT in terms of pain control and improved quality of life.[14,15]

The adverse effects of spine SBRT have been reported widely. In the acute phase post-treatment, pain flares occur with a frequency ranging from 23-68%, with higher rates and severity following high dose single-fraction SBRT.[16,17] In terms of late toxicities, radiation myelopathy was a concern in the early period of spine SBRT use. Newer treatment guidelines based on analysis of cases have been implemented to mitigate this risk.[18] VCF then became arguably the most clinically important adverse effect following spine SBRT, both in the acute and late phase post-treatment, causing significant pain and increasing surgical burden.[19,20] Balancing radiation doses for optimal LC of lesions with the risk of VCF is one of the challenges clinicians continue to face.[21] This requires an understanding of the factors predisposing patients to post-treatment VCF, enabling a more personalised approach to management.

This review outlines the current knowledge of post-SBRT VCF, with particular focus on fracture rates and the associated predictive factors identified on statistical analysis.

Methods

Literature review was conducted using the Medline and Embase databases and the Cochrane Library up to March 27th 2019, with the search algorithm shown in Table 1. Reference lists and data tables from previously published works were also consulted. Inclusion criteria for this review are studies published in the English language (prospective and retrospective) that reported both the post-SBRT VCF rate and identification of predictive factors based on univariate/multivariable models. This includes both de novo and reirradiation spine SBRT, as well as single-fraction and multi-fraction treatment. Studies with patient populations of 10 or fewer, conference abstracts and those reporting VCF rate without risk factor analysis were excluded.

A flowchart outlining the process of study selection is shown in Figure 1. The initial search yielded 223 citations, with removal of 48 duplicates, leaving 175 results. These were reviewed based on title and abstract, leaving 91 citations suitable for full-text review. Following application of the inclusion and exclusion criteria, data from 15 studies was extracted for the final quantitative analysis.

Results

The 15 studies identified are listed in table 2 with the relevant findings.[10,19,20,22-33] The majority involved patients with diverse primary tumour locations or histologies. Thibault et al focused specifically on patients with renal cell carcinoma (RCC) metastases and Yoo et al only reported lesions from hepatocellular carcinoma (HCC) origin.[10,22] Most studies were retrospective analyses of data compiled during the follow-up period.

Patient and lesion characteristics

Approximately 3394 spinal segments in 2147 patients were treated with SBRT overall. The estimation is due to Jawad et al not specifying the final number of patients involved in their analysis.[23] Median follow-up duration ranged from 7 months to 81.6 months, with the latter due to the 10-year follow-up period by Ling et al.[24] Otherwise, the majority of patients were followed up to a median of approximately 7 to 21.2 months.

Eleven studies included differentially reported de novo fractures from progression of pre-existing VCF. When combined, 192 de novo fractures occurred within 2183 previously intact vertebral bodies, a rate of 8.8%. In contrast, 201 of 907 vertebral bodies with pre-existing VCF progressed post-treatment, a rate of 22.2%. The proportion of vertebral bodies with baseline lytic tumour ranged from 27% to 95%,

with a median of 58%. The percentage of vertebral bodies with pre-existing VCF prior to irradiation ranged from 5% to 42%, with a median of 24%.

SBRT regimens

There were a variety of dose and fractionation schemes utilised. Ling at al and Tseng at al employed a consistent approach, being 16Gy in 1 fraction and 24Gy in 2 fractions respectively.[24,25] SBRT delivered in a single fraction was the most common method in 7 studies. Four primarily involved SBRT in three fractions and 3 reports mainly used a two fraction approach. Overall, when comparing the median SBRT dose and fractionation across each individual study, there was a range from 16 to 27Gy in 1 to 3 fractions.

Treatment outcomes

Of the 3394 spinal segments treated, 462 fractures were reported in the follow-up period, resulting in a crude overall VCF rate of 13.6%. Rates of VCF ranged from 4.2% to 39%, whilst the median time to VCF varied from 1.5 months to 25 months, with most studies reporting times within the 1 to 5 month interval. The exceptions being the 10.2 months and 25 months reported by Ling et al and Rose et al.[19,24] The median rate of therapeutic surgical interventions for VCF was 41.5%, ranging from 11% to 60%.

A variety of predictive factors for post-SBRT VCF were identified on univariate and multivariable models, shown in Table 2. These have been summarised in Table 3. On multivariable analysis, lytic disease and pre-existing VCF were the most frequently occurring risk factors, followed by higher treatment dose parameters, spinal malalignment, advanced age and burden of vertebral body disease. Other factors appeared only once and their significance as predictive factors is less certain, such as a Spinal Instability Neoplastic Score (SINS) >6, single-fraction SBRT, treatment of solitary metastasis, lung or HCC primary tumour and 3 or more treated vertebral levels. Elevated SINS was associated with fracture on univariate analysis in 3 other studies, however, did not retain significance in multivariable analyses as an independent predictive factor.

Discussion

Relationship between SBRT and VCF

Clarifying the association between spine SBRT and increased rates of VCF was a priority in the early stages of SBRT use. In a multi-institutional analysis, Saghal at al demonstrated a positive correlation between the dose administered and the VCF rate; risk after high-dose single-fraction SBRT ≥24Gy was 39% ($p<0.001$), risk after 20-23Gy per fraction was 23% ($p<0.001$) and risk after ≤19Gy per fraction was 11%.[15] Cunha et al and Thibault et al also found that doses per fraction of ≥20Gy were associated with higher VCF rates in their analyses.[10,28] This data is consistent with the 39% rate of VCF with high-dose single-fraction SBRT by Rose et al and the modest 8.5% rate of VCF with 24Gy in 2 fractions by Tseng et al.[19,25] The benefit of high-dose single-fraction radiotherapy is higher rates of local control, especially with tumours considered radio-resistant such as renal cell carcinoma.[34,35] However, there has not been a published randomised trial assessing the efficacy and adverse effect profile of varying SBRT fractionations for spine metastases. SBRT with 24Gy in 2 fractions is currently being evaluated in the ongoing Canadian-led phase 3 randomised controlled trial.[15]

The mechanism of SBRT-induced VCF has yet to be formally established, although multiple studies have used histopathology to generate hypotheses. Al-Omair et al analysed biopsies from two patients treated with 20Gy in 1 fraction and 24Gy in 2 fractions respectively.[36] They found that friable necrotic tissue replaced both the intact vertebral bone and tumour. This led to osteoradionecrosis being proposed as the mechanism for SBRT-induced VCF, causing mechanical instability and increased risk of fracture. More recently, Foerster et al showed that the incidence of osteonecrosis, soft tissue necrosis and viable tumour in VCF specimens was not significantly increased compared to non-VCF specimens.[37] In contrast, VCF specimens showed greater bone marrow fibrosis, leading to the hypothesis that fractures occur from disruption in

bone remodelling due to marrow fibrosis and collagen damage from high-dose radiation.[37,38] Bone is a metabolically active tissue with ongoing deposition of collagen and matrix, and this disruption may compromise its structural integrity.[39]

The effect of SBRT on bone density and VCF risk has also been investigated. Sprave et al conducted a randomised trial assessing rates of VCF and bone density following single-fraction (24Gy) SBRT versus conventionally-fractionated (30Gy in 10 fractions) three-dimensional conformal radiotherapy for spine metastases.[40] Although overall bone density increased significantly at 3 and 6 months following both treatments, there was no difference between the two groups. This effect of remineralisation and structural remodelling of bone after radiotherapy is well established, with the sequence of rim sclerosis followed by recalcification of the bone centrally.[41] Bone density of osteolytic lesions at 3 and 6 months post-SBRT showed a trend towards increasing from the baseline, which was not evident post-conventionally-fractioned radiotherapy. A closer comparison between the two arms did not reveal a statistically significant difference. At 3 months the rate of new pathological fractures in the SBRT arm was 8.7% compared to 4.3% in the conventional arm, suggesting that changes in bone density alone following treatment were not able to explain the discrepancy in VCF rate.[40]

Predictive and protective factors for post-SBRT VCF

The multivariable analysis data shown in Table 3 provide insight into the patient, disease and treatment factors associated with post-SBRT VCF. These include: lytic spinal lesions, pre-existing VCF, spinal malalignment/deformity, advancing age, increased dose per fraction, greater proportion of the vertebral body affected and baseline SINS >6. Many are intuitive; lytic lesions compromise the integrity of the vertebral body by disrupting the trabecular bone architecture, causing bone loss and decreased mineralisation.[39,42] Having a pre-existing fracture in situ further destabilised by high doses of radiation also increases the risk of post-SBRT VCF.[43] Reduction in bone strength with

advancing age and the mechanical stress associated with spinal malalignment and deformity contribute to VCF risk.[26] Increased VCF risk with greater doses per fraction as well an overall higher dose to 90% of the planning target volume are also consistent with the dose-complication relationship observed with post-treatment VCF.[15]

The effect of lytic disease and degree of tumour burden on fracture risk have been studied extensively. The study by Boehling et al involved utilising digital volume measurements and evaluating the CT appearance of lesions to classify them as either lytic, sclerotic or mixed.[26] Greater than 80% lytic tumour within the vertebral body increased the risk of post-treatment VCF. Rose et al also assessed the effect of tumour burden on subsequent rates of VCF.[19] They used a similar approach to Boehling et al, quantifying the degree of vertebral body involvement with digital volume measurements. The extent of tumour burden, particularly in the range of 40-60% vertebral involvement, was identified as a predictive factor for VCF.

Certain factors have also been shown to delay the onset of VCF. Ozdemir et al retrospectively reviewed 125 spinal metastases in 78 patients undergoing single-fraction SBRT with 16-18Gy, resulting in a VCF rate of 4%.[45] Multivariable analysis showed that the lowest vertebral body collapse score, female sex and >6 months bisphosphonate use were associated with longer vertebral compression fracture-free survival (FFS). The female sex being associated with longer FFS seems counter-intuitive given the effects of aging on bone mineral density with estrogen deficiency and the onset of osteoporosis.[46] Although, all the females in this study had breast cancer with more than 90% having concurrent treatment with bisphosphonates, potentially contributing to the association observed. Bisphosphonates have been shown to independently protect against the development of VCF. Particularly with longer-term use over 6 months, they are associated with a 3-4% rise in lumbar spine bone density and decreased VCF risk.[47,48]

The SINS classification system

Many risk factors associated with post-SBRT VCF are integrated into the SINS system, as shown in table 4.[49] SINS grades tumour-related instability of the vertebral column and is scored on a scale from 0-18, where 0-6 is stable, 7-12 considered potentially unstable and 13-18 in the unstable range. This information can be utilised to determine which patients would benefit from consultation with a spine surgeon and potential operative management, recommended for scores of 7 and above.[30] SINS is generated by calculating scores from one clinical and five radiographic parameters, relating to the spinal level of the lesion, the presence of mechanical or non-mechanical pain, whether the lesion is lytic, sclerotic or a combination of both, the presence of spinal malalignment or deformities, the extent of vertebral body collapse and the involvement of posterolateral spinal elements.[50] SINS >6 was shown to be associated with elevated VCF rates, placing patients in the potentially unstable/mechanically unstable categories.[30] Within SINS, lytic vertebral lesions, pre-existing VCF and spinal malalignment were identified on multivariable analyses across multiple studies as independent risk factors for VCF.[4,20,25,28]

The reliability of SINS in relation to therapeutic decision making has been assessed in various independent reports. Fourney et al showed that total SINS scores demonstrated strong intra- and inter-observer reliability in defining the three states of stability, potential instability and mechanical instability. The combined sensitivity and specificity for the categories of potentially unstable and mechanically unstable was 96.7% and 79.5%.[51] Importantly, no unstable spine was classified as stable nor the converse, which is essential given the differing levels of expertise in image interpretation across clinicians.

Experience in treating spinal metastases also increases the reliability of SINS scoring.[52] In their studies, Campos et al and Teixeira et al showed excellent

inter-observer reliability for total SINS scores, with observers in these studies being mostly spinal surgeons.[52,53] When Arana et al conducted a similar study using various medical specialists, such as neurosurgeons, radiation oncologists, medical oncologists, diagnostic radiologists and orthopaedic surgeons, there was only moderate inter-observer reliability for the total SINS score.[54] Therefore, although SINS is a useful tool to stratify spinal instability, its reliability should be interpreted in the context of the medical professional grading the segment.[55]

There are some limitations to the utility of SINS in therapeutic decision making. Mechanical pain is a clinical feature which has yet to be identified as an independent predictor for VCF in the literature.[4,56] Its presence confers 3 points to the total score, and from a surgical perspective is key in determining whether patients are suitable candidates for stabilisation.[30] Often patients with mechanical pain and frank spinal instability progress to surgical stabilisation rather than immediate spine SBRT. This can lead to their exclusion from studies, making it difficult to assess the impact of mechanical pain on subsequent VCF risk.[4] Another issue is the clinical subjectivity in classifying mechanical pain, as being exacerbated by movement or position.[20] Finally, there are factors which contribute to spinal instability SINS does not account for. Issues such as a history of surgical procedures, previous radiotherapy, poor bone quality or osteoporosis, patient body weight and activity level all impact spinal loading and mechanical instability.[55]

Recent studies have evaluated the predictability of SINS score on VCF risk. Yoo et al analysed data from 42 spinal metastases of hepatocellular carcinoma (HCC) origin treated with a median dose of 18Gy in 1 fraction.[22] They observed 12 VCFs, 6 each in the de novo and pre-existing categories, resulting in a post-SBRT fracture rate of 28.6%. When assessed according to SINS categories, 3 of the 19 segments which were stable fractured (15.8%). In the potentially unstable category, 8 of the 22 treated segments fractured (36.4%). The single vertebral body assessed as unstable proceeded to fracture. On univariate

analysis; baseline SINS >6, pre-existing VCF and lytic vertebral disease were risk factors for VCF. On multivariable analysis, only pre-existing VCF retained significance. In another report, Tseng et al demonstrated an increased risk of VCF with lytic lesions and mixed lytic/blastic lesions, spinal malalignment and dose to 90% of planning target volume (PTVD90).[25] Of the 161 treated segments that were SINS stable, 15 (9.3%) sustained a VCF. In the potentially unstable category, 16 of the 113 segments fractured (14.2%). There were only 5 vertebrae classified as unstable, with 2 of those fracturing post-treatment (40%). Although there was a trend towards greater risk of fracture with severity of SINS categories, there was not a statistically significant difference observed.

Conclusion

VCF is a known complication following spine SBRT, having major effects for patients by reducing quality of life due to pain and neurological symptoms. Numerous factors increase the risk of post-SBRT VCF, such as the presence of pre-existing vertebral body collapse, lytic disease, increased radiation dose per fraction, spinal malalignment and greater baseline instability, defined in terms of the SINS score. Given that at least 4 of these factors relate to SINS classification, it is a useful tool to differentiate lesions which are mechanically stable from those which are mechanically unstable and more prone to post-treatment fracture. This may enable prophylactic surgical interventions to be targeted to patients at greatest risk of this complication. However, there are gaps in the literature, including the preferred spine SBRT dose-fractionation scheme for optimal LC of tumours weighed against the risk of VCF and validation of remaining components of the SINS score as predictive factors for VCF (e.g. mechanical pain).

References

1. Wong DA, Forsnasier VL, MacNab I. Spinal metastases: the obvious, the occult, and the impostors. *Spine*. 1990;15(1):1-4.

2. Niazi T, Elakshar S, Stroian G. Local ablative stereotactic body radiotherapy for oligometastatic prostate cancer. *Curr Opin Support Palliat Care*. 2018 Sep;12(3):351-358.

3. Barzilai O, Versteeg AL, Sahgal A, et al. Survival, local control, and health-related quality of life in patients with oligometastatic and polymetastatic spinal tumors: A multicentre, international study. *Cancer*. 2019 Mar 1;125(5):770-778.

4. Faruqi S, Tseng CL, Whyne C, et al. Vertebral compression fracture after spine stereotactic body radiation therapy: a review of the pathophysiology and risk factors. *Neurosurgery*. 2018 Sep 1;83(3):314-322.

5. Saghal A, Roberge D, Schellenberg D, et al. The Canadian Association of Radiation Oncology scope of practice guidelines for lung, liver and spine stereotactic body radiotherapy. *Clin Oncol (R Coll Radiol)*. 2012;24:629-639.

6. Sze WM, Shelley M, Held I, Mason M. Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy – a systematic review of the randomised trials. *Cochrane Database Syst Rev*. 2004;2:CD004721.

7. Husain ZA, Sahgal A, De Salles A, et al. Stereotactic body radiotherapy for de novo spinal metastases: Systematic review. *J Neurosurg Spine*. 2017;27:295-302.

8. Foote M, Letourneau D, Hyde D, et al. Technique for stereotactic body radiotherapy for spinal metastases. *J Clin Neurosci.* 2011 Feb;18(2):276-279.

9. Hyde D, Lochray F, Korol R, et al. Spine stereotactic body radiotherapy utilizing cone-beam CT image-guidance with a robotic couch: Intrafraction motion analysis accounting for all six degrees of freedom. *Int J Radiat Oncol Biol Phys.* 2012 Mar 1;82(3):e555-562.

10. Thibault I, Al-Omair A, Masucci GL, et al. Spine stereotactic body radiotherapy for renal cell cancer spinal metastases: analysis of outcomes and risk of vertebral compression fracture. *J Neurosurg Spine*. 2014 Nov;21(5):711-718.

11. Jabbari S, Gerszten PC, Ruschin M, Larson DA, Los SS, Saghal A. Stereotactic body radiotherapy for spinal metastases. *Cancer J.* 2016 July-Aug;22(4):280-289.

12. Chang JH, Shin JH, Yamada YJ, et al. Stereotactic body radiotherapy for spinal metastases: what are the risks and how do we minimize them? *Spine*. 2016 Oct 15;41(20):S238-245.

13. Palma DA, Olson RA, Harrow S, et al. Stereotactic ablative radiation therapy for the comprehensive treatment of oligometastatic tumors

(SABR-COMET): results of a randomized trial. *Int J Radiat Oncol Biol Phys.* 2018 Nov 1;102(2):S3-S4.

14. Ryu S, Pugh SL, Gerszten PC, et al. RTOG 0631 phase 2/3 study of image-guided stereotactic radiosurgery for localized (1-3) spine metastases: phase 2 results. *Pract Radiat Oncol.* 2014 Mar-Apr;4(2):76-81.

15. Saghal A, Myrehaug S, Dennis K, et al. A randomized phase II/III study comparing stereotactic body radiotherapy (SBRT) versus conventional palliative radiotherapy (CRT) for patients with spinal metastases (NCT02512965). *J Clin Oncol.* 2017 May;35(15_suppl):TPS10129-TPS10129.

16. Pan HY, Allen PK, Wang XS, et al. Incidence and predictive factors of pain flare after spine stereotactic body radiation therapy: secondary analysis of phase 1/2 trials. *Int J Radiat Oncol Biol Phys.* 2014 Nov 15;90(4):870-876.

17. Chiang A, Zeng L, Zhang L, et al. Pain flare is a common adverse event in steroid-naïve patients after spine stereotactic body radiation therapy: a prospective clinical trial. *Int J Radiat Oncol Biol Phys.* 2013 Jul 15;86(4):638-642.

18. Sahgal A, Weinberg V, Ma L, et al. Probabilities of radiation myelopathy specific to stereotactic body radiation therapy to guide safe practice. *Int J Radiat Oncol Biol Phys.* 2013 Feb 1;85(2):341-347.

19. Rose PS, Laufer I, Boland PJ, et al. Risk of fracture after single fraction image-guided intensity-modulated radiation therapy to spinal metastases. *J Clin Oncol.* 2009 Oct 20;27(30):5075-5079.

20. Sahgal A, Atenafu EG, Chao S, et al. 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 Sep 20;31(27):3426-3431.

21. Al-Omair A, Masucci L, Masson-Cote L, et al. Surgical resection of epidural disease improves local control following postoperative spine stereotactic body radiotherapy. *Neuro Oncol.* 2013 Oct;15(10):1413-1419.

22. Yoo GS, Park HC, Yu JI, et al. Stereotactic ablative body radiotherapy for spinal metastasis from hepatocellular carcinoma: its oncologic outcomes and risk of vertebral compression fracture. *Oncotarget*. 2017 Sep 22;8(42):72860-72871.

23. Jawad MS, Fahim DK, Gerszten PC, et al. Vertebral compression fractures after stereotactic body radiation therapy: a large, multi-institutional, multinational evaluation. *J Neurosurg Spine.* 2016 June;24(6):928-936.

24. Ling DC, Flickinger JC, Burton SA, et al. Long-term outcomes after stereotactic radiosurgery for spine metastases: radiation dose-response for late toxicity. *Int J Radiat Oncol Biol Phys.* 2018 Jul 1;101(3):602-609.

25. Tseng CL, Soliman H, Myrehaug S, et al. Imaging-based outcomes for 24 Gy in 2 daily fractions for patients with de novo spinal metastases treated with spien stereotactic body radiation therapy (SBRT). *Int J Radiat Oncol Biol Phys.* 2018 Nov 1;102(3):499-507.

26. Boehling NS, Grosshans DR, Allen PK, et al. Vertebral compression fracture risk after stereotactic body radiotherapy for spinal metastases. *J Neurosurg Spine.* 2012 Apr;16(4):379-386.

27. Boyce-Fappiano D, Elibe E, Schultz L, et al. Analysis of the factors contributing to vertebral compression fractures after spine stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys.* 2017 Feb 1;97(2):236-245.

28. Cunha MV, Al-Omair A, Atenafu EG, et al. Vertebral compression fracture (VCF) after spine stereotactic body radiation therapy (SBRT): analysis of predictive factors. *Int J Radiat Oncol Biol Phys.* 2012 Nov 1;84(3):e343-349.

29. Germano IM, Carai A, Pawha P, Blacksburg S, Lo YC, Green S. Clinical outcome of vertebral compression fracture after single fraction spine radiosurgery for spinal metastases. *Clin Exp Metastasis.* 2016 Feb;33(2):143-149.

30. Lee SH, Tatsui CE, Ghia AJ, Amini B, Li J, Zavarella SM. Can the spinal instability neoplastic score prior to spinal radiosurgery predict compression fractures following stereotactic spinal radiosurgery for metastatic spinal tumour?: a post hoc analysis of prospective phase II single-institution trials. *J Neurooncol.* 2016 Feb;126(3):509-517.

31. Mehta N, Zavitsanos PJ, Moldovan K, et al. Local failure and vertebral body fracture risk using multifraction stereotactic body radiation therapy for spine metastases. *Adv Radiat Oncol*. 2018 Jul-Sep;3(3):245-251.

32. Sung SH, Chang UK. Evaluation of risk factors for vertebral compression fracture after stereotactic radiosurgery in spinal tumor patients. *Korean J Spine.* 2014 Sep;11(3):103-108.

33. Thibault I, Whyne CM, Zhou S, et al. Volume of lytic vertebral body metastatic disease quantified using computed tomography-based image

segmentation predicts fracture risk after spine stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys.* 2017 Jan 1;97(1):75-81.

34. Yamada Y, Katsoulakis E, Laufer I, et al. The impact of histology and delivered dose on local control of spinal metastases treated with stereotactic radiosurgery. *Neurosurg Focus.* 2017 Jan;42(1):E6.

35. Zelefsky MJ, Greco C, Motzer R, et al. Tumour control outcomes after hypofractionated and single-dose stereotactic image-guided intensity-modulated radiotherapy for extracranial metastases from renal cell carcinoma. *Int J Radiat Oncol Biol Phys*. 2012 Apr 1;82(5):1744-1748.

36. Al-Omair A, Smith R, Kiehl TR, Lao L, Yu E, Massicotte EM. Radiation-induced vertebral compression fracture following spine stereotactic radiosurgery: clinicopathological correlation. *J Neurosurg Spine.* 2013 May;18(5):430-435.

37. Foerster R, Cho BCJ, Fahim DK, Gerszten PC, Flickinger JC, Grills IS. Histopathological findings after reirradiation compared to first irradiation of spinal bone metastases with stereotactic body radiotherapy: a cohort study. *Neurosurgery*. 2019 Feb 1;84(2):435-441.

38. Currey JD, Foreman J, Laketic I, Mitchell J, Pegg DE, Reilly GC. Effects of ionizing radiation on the mechanical properties of human bone. *J Orthop Res.* 1997 Jan;15(10):111-117.

39. Guo XE, Kim CH. Mechanical consequence of trabecular bone loss and its treatment: a three-dimension model simulation. *Bone*. 2002 Feb;30(2):404-411.

40. Sprave T, Verma V, Forster R, et al. Randomized phase II trial evaluating pain response in patients with spinal metastases following stereotactic

body radiotherapy versus three-dimensional conformal radiotherapy. *Radiother Oncol.* 2018 Aug;128(2):274-282.

41. Wachenfeld I, Sanner G, Bottcher HD, Kollath J. The remineralization of the vertebral metastases of breast carcinoma after radiotherapy. *Strahlenther Onkol.* 1996 Jun;172(6):332-341.

42. Guise TA. Molecular mechanisms of osteolytic bone metastases. *Cancer.* 2000 Jun 15;88(12 Suppl):2892-2898.

43. Barth HD, Zimmermann EA, Schaible E, Tang SY, Alliston T, Ritchie RO. Characterization of the effects of x-ray irradiation on the hierarchical structure and mechanical properties of human cortical bone. *Biomaterials*. 2011 Dec;32(34):8892-8904.

44. Lee J, Rhee WJ, Chang JS, Chang SK, Koom WS. Evaluation of predictive factors of vertebral compression fracture after conventional palliative radiotherapy for spinal metastasis from colorectal cancer. *J Neurosurg Spine.* 2018 Mar;28(3):333-340.

45. Ozdemir Y, Torun N, Guler OC, et al. Local control and vertebral compression fractures following stereotactic body radiotherapy for spine metastases. *J Bone Oncol*. 2019 Jan 24;15:100218.

46. Cheng Z, Yao W, Zimmermann EA, Busse C, Ritchie RO, Lane NE. Prolonged treatments with antiresorptive agents and PTH have different effects on bone strength and the degree of mineralization in old estrogen-deficient osteoporotic rats. *J Bone Miner Res.* 2009 Feb;24(2):209-220.

47. Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal

624 osteoporosis. The alendronate phase III osteoporosis treatment study
625 group. *N Engl J Med*. 1995 Nov 30;333(22):1437-1443.
626
627 48. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment
628 on vertebral and nonvertebral fractures in women with postmenopausal
629 osteoporosis: a randomized controlled trial. Vertebral efficacy with
630 risedronate therapy (VERT) study group. *JAMA*. 1999 Oct
631 13;282(14):1344-1352.
632
633 49. Fisher CG, DiPaola CP, Ryken TC, et al. A novel classification system
634 for spinal instability in neoplastic disease: an evidence-based approach
635 and expert consensus from the Spine Oncology Study Group. *Spine*
636 *(Phila Pa 1976).* 2010 Oct 15;35(22):E1221-1229.
637
638 50. Leone A, Cianfoni A, Zecchi V, Cortese MC, Rumi N, Colosimo C.
639 Instability and impending instability in patients with vertebral metastatic
640 disease. *Skeletal Radiol.* 2019 Feb;48(2):195-207.
641
642 51. Fourney DR, Frangou EM, Ryken TC, et al. Spinal instability neoplastic
643 score: an analysis of reliability and validity from the spine oncology study
644 group. *J Clin Oncol.* 2011 Aug 1;29(22):3072-3077.
645
646 52. Teixeira WG, Coutinho PR, Marchese LD, et al. Interobserver agreement
647 for the spine instability neoplastic score varies according to the
648 experience of the evaluator. *Clinics (Sao Paulo).* 2013 Feb;68(2):213-
649 218.
650
651 53. Campos M, Urrutia J, Zamora T, et al. The Spine Instability Neoplastic
652 Score: an independent reliability and reproducibility analysis. *Spine J.*
653 2014 Aug 1;14(8):1466-1469.
654

54. Arana E, Kovacs FM, Royuela A, Asenjo B, Perez-Ramirez U, Zamora J. Spine Instability Neoplastic Score: agreement across different medical and surgical specialties. *Spine J.* 2016 May;16(5):591-599.

55. Versteeg AL, Verlaan JJ, Sahgal A, et al. The Spinal Instability Neoplastic Score: impact on oncologic decision-making. *Spine (Phila Pa 1976).* 2016 Oct 15;41 Suppl 20:S231-S237.

56. Sahgal A, Whyne CM, Ma L, Larson DA, Fehlings MG. Vertebral compression fracture after stereotactic body radiotherapy for spinal metastases. *Lancet Oncol.* 2013 Jul;14(8):e310-e320.

687

688 **Table 1.** Database search strategy

689

Number	Search term
1	exp Spinal Fractures
2	exp Compression Fractures
3	vertebral compression fracture.mp.
4	VCF.mp.
5	(vertebr* adj2 fracture*).mp.
6	exp Spinal Neoplasms
7	spin* metastas*.mp.
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	exp Radiosurgery
10	stereotactic body radiotherapy.mp.
11	stereotactic ablative body radiotherapy.mp.
12	(stereotactic adj3 radio*).mp.
13	SBRT.mp.
14	SABR.mp.
15	9 or 10 or 11 or 12 or 13 or 14
16	8 and 15
17	limit 16 to English language

690

691 Abbreviations: VCF, vertebral compression fracture; SBRT, stereotactic body
692 radiotherapy; SABR, stereotactic ablative body radiotherapy.

693

694

695

696

697

698

699

700

701
702
703
704
705 **Table 2.** Data extracted from 15 studies reporting rates of post-SBRT VCF and
706 associated predictive factors

	Boehling et al, 2012[26]	Boyce-Fappiano et al, 2017[27]	Cunha et al, 2012[28]	Germano et al, 2016[29]	Jawad et al, 2016[23]
Patient (segments)	93 (123)	448 (1070)	90 (167)	79 (143)	(594)
Median dose/fraction (range)	27Gy/3fx (18-30Gy/1-5fx)	18Gy/1fx (10-60Gy/2-5fx)	20-27Gy/3fx (8-35Gy/1-5fx)	18Gy/1fx (10-18Gy/1fx)	20Gy/1fx (8-40Gy/1-5fx)
Proportion of lytic lesions	58%	27%	48%	39%	71%
Proportion of pre-existing VCF	28%	42%	17%	42%	24%
VCF rate (de novo/progression)	20% (11%/9%)	11.9% (5.0%/6.8%)	11.4% (7.2%/4.2%)	21% (6.3%/14.7%)	5.7% (3%/2.7%)
Proportion of VCF surgically salvaged	60%	29%	47%	30%	NR
Median time to VCF (months)	3	2.7	2	5 (mean)	3
Median follow-up (months)	16	17.7	7.4	16	10.1
Risk factors on MVA (HR or p-value)	Age >55 (5.67) Pre-existing VCF (4.12) Lytic lesion (2.76)	<3 vs 3+ treated levels (4-4.3) Lytic lesion (2.49-3.04) Pre-existing VCF (1.69)	HCC histology (34) Lytic lesion (12.2) Kyphosis/scoliosis (11.1) Dose/fx ≥ 20Gy (6.82)	None significant	Solitary metastasis (OR 3.46) Pre-existing VCF (OR 2.82) Prescription dose to target volume dose ≥38.4 Gy EQD2 (OR

			Lung histology (4.3)		2.28)
Risk factors on UVA (HR or p-value)	Age >55 (6.05) Pre-existing VCF (5.05) Baseline pain (1.31) and narcotic use (2.98) Post-SBRT pain (1.34) and narcotic use(3.63)	Lytic lesion (2.85-3.07) Haematologic malignancies (2.68) Pre-existing VCF (1.99) <3 vs 3+ treated levels (4.17-5.26) Female sex (1.54) Thoracic spine (1.54)	Kyphosis/scoliosis Lytic lesion Pre-existing VCF Histology Dose/fx ≥ 20Gy	Histology SINS VB collapse Pre-existing VCF Baseline pain	Short interval from diagnosis to SBRT (<37d) Solitary metastasis No additional bony metastases No prior chemotherapy Pre-existing VCF No MRI for target delineation EQD_2 tumour ≥41.8 Gy Max dose to spinal cord >46.1 Gy EQD_2 Tumour volume >37.3cm

Table 2. Continued

	Lee et al, 2016[30]	Ling et al, 2018[24]	Mehta et al, 2018[31]	Rose et al, 2009[19]	Saghal et al, 2013[20]
Patient (segments)	79 (100)	43 (54)	83 (98)	62 (71)	252 (410)
Median dose/fraction (range)	24-27Gy/3fx (16-27Gy/1-3fx)	16Gy/1fx	24Gy/3fx (14-44Gy/2-5fx)	24Gy/1fx (18-24Gy/1fx)	18-26Gy/1fx (8-35Gy/1-5fx)
Proportion of lytic lesions	NR	42.6%	44%	65%	62%
Proportion of pre-existing VCF	22%	26.7%	30%	28%	20%
VCF rate (de novo/progression)	32% (20%/12%)	17% (13%/4%)	4.2% (NR)	39% (NR)	13.9% (6.6%/7.3%)
Proportion of VCF surgically salvaged	47%	55.6%	NR	11%	43%
Median time to VCF (months)	3.3	10.2	5.8	25	2.5
Median follow-up (months)	21.2	81.6	7.6	13	11.5
Risk factors on MVA (HR or p-value)	SINS 0-6 vs 7-12 (5.63) Age <65 vs ≥65 (2.15)	None significant	NR	Lesions occupying 41% to 60% of VB (3.9) Lytic lesion (3.8)	Dose/fx compared to ≤19Gy: ≥24Gy (5.25) and 20-23Gy (4.91) Pre-existing VCF: <50% (8.98) and >50% (6.92) >50% VB involved by Tumour (4.46) Lytic lesion (3.53) Spinal malalignment (2.99)
Risk factors on UVA (HR or p-value)	SINS Score (6.01) ESCC classification (3.91) Dose/fraction	None significant	Pre-existing VCF (p<0.01)	NR	Dose/fraction Vertebral body collapse >50% VB involved by tumour Bone lesion type Spinal malalignment

	<20Gy vs 24Gy (2.91) Age <65 vs ≥65 (2.47) RT failure (2.19)				Paraspinal/epidural extension

713
714
715
716
717 **Table 2.** Continued

	Sung et al, 2014[32]	Thibault et al, 2014[10]	Thibault et al, 2017[33]	Tseng et al, 2018[25]	Yoo et al, 2017[22]
Patient (segments)	72 (72)	37 (71)	55 (100)	145 (279)	29 (42)
Median dose/fraction (range)	(18-45Gy/1-5fx)	24Gy/2fx (18-30Gy/1-5fx)	24Gy/2fx (12-35Gy/1-5fx)	24Gy/2fx	18Gy/1fx (16-45Gy/1-3fx)
Proportion of lytic lesions	NR	95%	56%	59%	76%
Proportion of pre-existing VCF	NR	21%	24%	5%	NR
VCF rate (de novo/progression)	36% (NR)	16% (5%/11.5%)	17% (5%/12%)	11.8% (8.6%/3.2%)	28.6% (14.3%/14.3%)
Proportion of VCF surgically salvaged	58%	40%	NR	39.4%	33%
Median time to VCF (months)	1.5 (mean)	1.6	1.68	NR	NR
Median follow-up (months)	11 (mean)	12.3	7.3	15	7
Risk factors on MVA (HR or p-	VB osteolysis	Pre-existing VCF (9.25)	≥11.6% lytic (OR 51.7)	Lytic (12.0) or mixed lytic/blastic	Pre-existing VCF (p=0.03)

value)	rate ≤60% vs >60% (8.5)	Single-fraction	Pre-existing VCF (OR 37)	lesion (11.3) Spinal	

Risk factor	Total studies reporting this risk factor	Range of hazard ratios
Lytic disease	8	2.76-12.2
Pre-existing VCF	7	1.69-9.25
Dose per fraction/PTVD90 (dosimetry related)	5	1.21-6.82
Spinal	3	2.38-11.1
Advanced age (>55 or ≥65)	2	2.15-5.67
Proportion of VB involved	2	3.9-4.46

Risk factors on malalignment/deformity	Pre-SBRT deformity	NR	Pre-existing VCF (OR	NR	Baseline SINS >6 (p=0.037)
UVA (HR or p-	osteolysis rate (11.5) SINS (10.9) Whole VB involvement (4)		Lytic lesion (OR 7.68) Dose ≥20Gy (2.6)		(p=0.017) Pre-existing VCF (p<0.001)

VCF, vertebral compression fracture; VB, vertebral body; UVA, univariate analysis; MVA , multivariate analysis; fx, fraction; HR, hazard ratio; NR, not reported; OR, odds ratio; p, p-value; SBRT, stereotactic body radiotherapy; PTVD90, dose to 90% of the planning target volume; EQD_2, equivalent dose in 2Gy/fx; SINS, Spinal Instability Neoplastic score; RT, radiation.

by tumour		
SINS>6	1	5.63
Single-fraction SBRT	1	5.03
Solitary metastasis	1	(OR) 2.46
Histology (e.g. lung & HCC)	1	4.33 & 34
3+ treated vertebral levels	1	4-4.3

Table 3. Statistically significant risk factors for VCF identified on multivariable analysis with accompanying range of hazard ratios

VCF, vertebral compression fracture; PTVD90, dose to 90% of the planning target volume; VB, vertebral body; SINS, Spinal Instability Neoplastic Score; SBRT, stereotactic body radiotherapy; OR, odds ratio; HCC, hepatocellular carcinoma.

751 **Table 4.** Spinal Instability Neoplastic Score

752

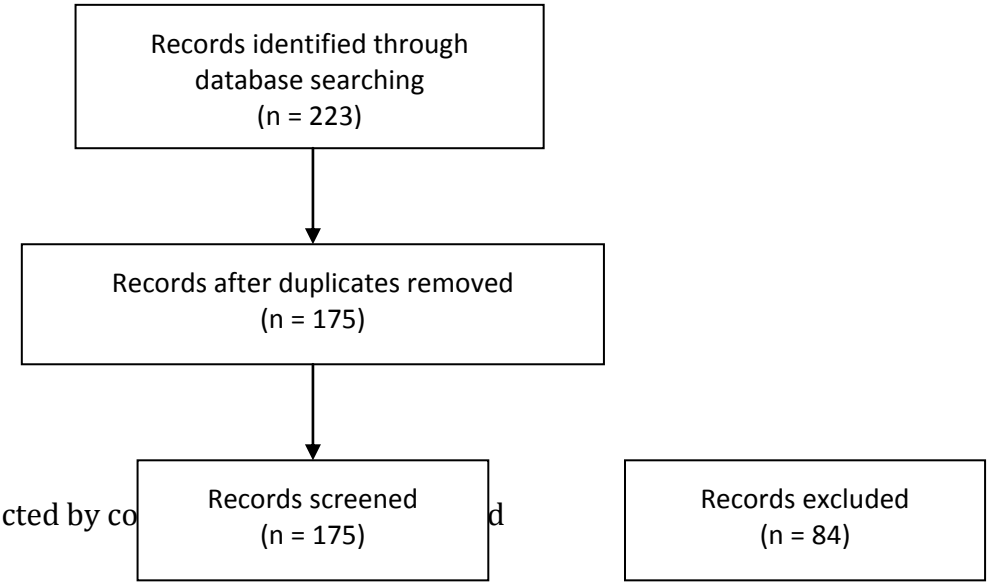
Component	Score
Location	
Junctional (occiput-C2, C7-T2, T11-L1, L5-S1)	3
Mobile spine (C3-C6, L2-L4)	2
Semirigid (T3-T10)	1
Rigid (S2-S5)	0
Pain	
Mechanical	3
Occasional/non-mechanical	1
Pain free	0
Bone lesion type	
Lytic	2
Mixed	1
Blastic	0
Spinal alignment	
Subluxation/translation	4
Kyphosis/scoliosis	2
Normal	0
Vertebral body collapse	
>50%	3
≤50%	2
No collapse but >50% body involved by tumour	1
None of the above	0
Involvement of posterolateral elements	

Bilateral	3
Unilateral	1
None of the above	0
SINS classification	
Stable	0-6
Potentially unstable	7-12
Unstable	13-18

Figure legends:

Figure 1. Flowchart of studies selected for quantitative and qualitative data analysis

Figures:



776
777
778
779