Bone density and fracture risk following SBRT for non-spine bone metastases

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ABSTRACT

\textbf{Purpose/methods:} This retrospective study evaluated local recurrence (LR) and fracture risk in non-spine bone metastases treated with SBRT.

\textbf{Results:} 181 lesions in 116 patients are reported. The median dose was 27 Gy (range 15-40) in 3 fractions (range 1-6). The cumulative incidence of LR was 2.8\%, 7.2\% and 12.5\% at 6 mo, 1 yr and 2 yrs. Fractures occurred in 11 lesions (6\%). Radioresistant histology and increasing PTV predicted for LR on univariate analysis, while rib location was associated with control. Increasing PTV remained a significant predictor for LR on multivariate analysis. Univariate predictors of fracture risk included female gender, lytic lesions and poorer KPS. Average CT-approximated L1 trabecular attenuation in patients with fracture was significantly lower than in patients without fracture (112.2 vs. 142.6 Hounsfield units).

\textbf{Conclusion:} In the largest series to date, we report excellent local control for SBRT to non-spine bone metastases and a novel relationship between CT-based bone quality assessment and fracture risk.

\textbf{Keywords:} SBRT, non-spine bone, fracture

INTRODUCTION

Modern systemic treatments such as targeted therapy and immunotherapy have greatly changed the landscape of cancer care and altered the course of metastatic disease. As such, more cancer patients are surviving in a metastatic state [1], particularly those with histologies like breast and prostate cancer [2]. The prevalence of women living in the United States with metastatic breast cancer, for instance, is estimated to have increased by 4\% from 1990 to 2000, 17\% from 2000 to 2010, and by a projected 31\% from 2010 to 2020. Moreover, approximately one third of patients with metastatic breast cancer now live for five years or more with a stage IV diagnosis [3].
Bone metastases are a common source of morbidity in patients with advanced cancer, causing pain as well as increased fracture risk necessitating surgical stabilization. Conventional radiation therapy (RT) has long been a mainstay of treatment for symptomatic osseous metastases, and its ability to provide rapid and clinically significant palliation of pain has been consistently supported in the literature. Common treatment regimens such as 30 Gy in 10 fractions, 20 Gy in 5 fractions, and 8 Gy in 1 fraction have been shown to confer equivalent initial palliative efficacy, providing pain reduction in 60-70% of patients [4–6]. However, pain relapse occurs in as many as half of initial responders within one year after treatment and up to 40% of patients require re-irradiation [7]. Moreover, durable local control is often not achieved with these regimens.

Given these limitations, there has been increasing interest in using advanced radiation therapy techniques such as stereotactic body radiation therapy (SBRT) to deliver higher biologically effective dose (BED) to bone metastases than can be offered with conventional RT regimens. SBRT may therefore be able to provide more durable local control and pain relief in patients with symptomatic metastases. While SBRT has been increasingly explored in the treatment of spine metastases with promising local control rates, ranging from 70% to greater than 90% at 1-2 years [8–10], the literature for local control and toxicity rates in non-spine bone metastases treated with SBRT remains sparse. We present the largest series of SBRT to non-spine bone metastases published to date and perform a novel analysis of the relationship between CT-based bone quality assessment and the risk of radiation-induced fracture.

MATERIALS AND METHODS

A retrospective review was conducted of patients treated with SBRT to at least one non-spine bone lesion of any primary histology between the years of 2010 and 2018. Patients were excluded if they did not have at least one follow up visit subsequent to SBRT. Previous irradiation to the site of SBRT was allowed. Data collected included patient and disease characteristics (i.e. gender, age at treatment, performance status, tumor location and size, lytic or sclerotic nature of lesion), treatment characteristics (i.e. radiation therapy prescription and dates, planning tumor volume expansion margin, and planning target volume), and follow-up information (i.e. date of fracture adverse event, date of death and/ or last follow-up, and date of local recurrence). Patients were categorized as oligometastatic if they had five or fewer metastases. Radioresistant histologies were defined per Laufer et al. as renal cell carcinoma, non-small cell lung cancer, sarcoma, thyroid, hepatocellular carcinoma, and colorectal carcinoma [11]. Ewing sarcoma was categorized as a radioresistant histology within the sarcoma family [12]. Fracture events were recorded according to the date of first radiographic diagnosis. If accidental falls or other trauma caused fractures in areas clearly unrelated to the SBRT site (i.e. different part of the body), these were not recorded as a radiation-related event.

For bone quality assessment, a previously described CT-based method to approximate bone trabecular attenuation in the first lumbar vertebra was utilized [13]. For each CT, an ovoid region of interest was delineated on an axial slice of L1 between the superior end plate and the midline zone, and the average Hounsfield units (HU) within this region was recorded. The closest qualifying CT scan to the start of SBRT was used and was considered eligible if it was obtained within 12 months of SBRT, was performed at 120 kV, and showed no evidence of diffuse lumbar metastatic disease or other abnormality prohibiting representative density measurement (e.g. spinal hardware artifact or compression deformity). Diagnostic CT or PET/CT and simulation CT were all allowable if the above criteria were met.

Prescription doses for SBRT treatments ranged from 15-40 Gy in 1-6 fractions. BED calculations were performed using the equation $BED = D \times (1 + \left[\frac{d}{(\alpha/\beta)}\right])$, where $D$ is the total dose in Gy, $d$ is the dose per fraction, and the $\alpha/\beta$ is estimated to be 10 for all tumors. Gross tumor volume (GTV) was defined as the gross visible lesion on diagnostic PET/CT, CT or MRI imaging. An expansion margin at the treating radiation oncologist’s discretion was applied to the GTV to create a clinical target volume (CTV). The CTV was then expanded by a margin of 2-10mm to account for variability in daily treatment setup to create a planning target volume (PTV). Treatment was delivered using a linear accelerator-based machine with daily pre-treatment cone-beam CT image guidance. Local control was evaluated retrospectively for each treated bone lesion using follow-up notes, radiology reports, and imaging review to assess for local recurrence. Local recurrence was defined per the MD Anderson criteria as greater than 25% measurable or subjective increase in size of target lesion [14]. Each local recurrence was independently reviewed by two radiation oncologists for confirmation.

The cumulative incidence of local recurrence and fracture were estimated using competing risks analysis. Bivariate and multivariate relationships between clinical and treatment factors with both local recurrence and fracture toxicity were analyzed with Fine-Gray competing risks regression to report subdistribution hazard ratio estimates. Clinically meaningful variables or variables with $p<0.05$ on univariate analysis were included in multivariate analysis. Bone quality analysis (L1 trabecular attenuation) between patients who fractured at the site of
SBRT and patients who did not have evidence of fracture was conducted with a one-tailed student T-test.

RESULTS

Patient and Treatment Characteristics

One-hundred and eighty-one lesions in 116 patients were included in the analysis. Patient characteristics are summarized in Table 1, and Table 2 presents a summary of the treated lesions. The median patient age was 64 years (range 16-91), and 84.5% of patients were male. Most patients had favorable Karnofsky Performance Status (KPS) of 100 or 90 (44.8% and 41.5% respectively). The most common primary tumor histologies were prostate (62.1%), renal cell carcinoma (10.3%), and NSCLC (8.6%), with 26.7% overall categorized as radioresistant. Only three lesions had previously been irradiated. Lesions were located predominantly in the pelvis (37.6%), rib (34.3%), and hip/femur (12.7%). The majority (70.7%) of lesions were sclerotic type lesions. The median PTV was 23.9 cc (range 2.8-686.9). The most common dose regimens included 9 Gy x 3 (23.2%), 10 Gy x 3 (18.8%), and 6 Gy x 5 (14.9%). The median BED10 delivered was 51.3 Gy (range 28-81.6).

| Table 1. Summary of patient characteristics | n=116 |
|--------------------------|-------|
| **Gender**               |       |
| Male                     | 98 (84.5%) |
| Female                   | 18 (15.5%) |
| **Age, median (range)**  | 64 (16-91) |
| **KPS**                  |       |
| 100                      | 48 (44.8%) |
| 90                       | 44 (41.5%) |
| 80                       | 11 (10.4%) |
| 70                       | 3 (2.8%)  |
| **Oligometastatic**      | 100 (85.5%) |
| **Radioresistant histology** |      |
| Renal cell carcinoma     | 12 (10.3%) |
| NSCLC                    | 10 (8.6%)  |
| Sarcoma                  | 3 (1.7%)   |
| Thyroid                  | 3 (2.6%)   |
| Hepatocellular carcinoma| 2 (2.6%)   |
| Colorectal               | 1 (0.9%)   |
| **Non-radioresistant histology** | |     |
| Prostate                 | 72 (62.1%) |
| Breast                   | 4 (3.4%)   |
| Pancreas                 | 2 (1.7%)   |
| Ewing sarcoma            | 1 (0.9%)   |
| Small cell lung          | 1 (0.9%)   |
| Esophageal               | 1 (0.9%)   |
| Other                    | 4 (3.4%)   |

| Table 2. Summary of lesion and treatment characteristics | n=181 |
|----------------------------------------------------------|-------|
| **Location of lesion**                                   |       |
| Pelvis                                                   | 68 (37.6%) |
| Rib                                                      | 62 (34.3%) |
| Hip/femur                                                | 23 (12.7%) |
| Shoulder/humerus                                         | 13 (7.2%)  |
| Sternum                                                  | 6 (3.3%)   |
| Skull                                                    | 9 (5.0%)   |
| **Type of lesion**                                       |       |
| Lytic                                                    | 37 (22.2%) |
| Sclerotic                                                | 118 (70.7%) |
| Mixed                                                    | 12 (7.2%)  |
| **GTV, median (range, cc)**                             | 5.7 (0.19–552) |
| **PTV, median (range, cc)**                             | 23.9 (2.8–686.9) |
| **Prescription regimen (Fractional dose in Gy x fractions)** | |     |
| 9 × 3                                                    | 42 (23.2%) |
| 10 × 3                                                   | 34 (18.8%) |
| 6 × 5                                                    | 27 (14.9%) |
| 15 × 1                                                   | 12 (6.6%)  |
| 5 × 5                                                    | 11 (6.1%)  |
| 8 × 3                                                    | 9 (5.0%)   |
| 7 × 3                                                    | 8 (4.4%)   |
| 8 × 5                                                    | 8 (4.4%)   |
| 11 × 3                                                   | 4 (2.8%)   |
| Other                                                    | 21 (11.6%) |
| **BED10, median (range, Gy)**                            | 51.3 (28–81.6) |

Local Control Outcomes

Median follow up was 18.6 months (range 1.6-60.8), during which 22 patients died. Local recurrence was recorded in 21 of the 181 treated lesions at a median
time to failure of 9.9 months (range 1.4-41.1). The cumulative incidence of local recurrence at 6 months, 1 year, and 2 years was 2.8%, 7.2%, and 12.5%, respectively (Figure 1).

The univariate and multivariate analyses are summarized in Table 3 a) and b), respectively. On univariate analysis, radioresistant histology was predictive of local failure (HR 2.77, p=0.0278), while rib metastases were associated with a decreased risk of local recurrence (HR 0.18, p=0.0211). Increasing size of GTV and PTV were both predictive of local recurrence as continuous variables, with each 1 cc increase in GTV conferring a 4% increased risk of local failure (p=0.0287) and each 5 cc increase in PTV conferring a 3% increased risk of local failure (p=0.0003). No significant association of BED10 with local control was observed. On multivariate analysis while accounting for BED10, increasing PTV volume remained a significant predictor of local recurrence (HR 1.02, p=0.0292), suggesting that each 5 cc increase in PTV conferred a 2% increased risk of local recurrence.

**Fracture Toxicity Outcomes**

Radiographic fractures were recorded in 11 out of the 181 treated sites, with a median time to fracture of 7.5 months (range 1.1-22.4). The cumulative incidence of fracture at 6 months, 1 year, and 2 years was 2.3%, 4.7% and 7.7% respectively (Figure 2). One fracture occurred following accidental trauma. Fractures occurred in 6 rib lesions, 2 scapular lesions, 2 pubic bone lesions, and 1 ilium lesion. No post-treatment fractures were recorded for lesions in the hip/ lower extremity or sacroiliac joint (i.e. traditionally weight-bearing bones). None of the three previously irradiated sites had evidence of fracture. Seven of these fractures were symptomatic, while the rest were diagnosed incidentally on surveillance/re-staging imaging alone. All of the fractures were managed conservatively and did not require surgical management. The univariate and multivariate analyses are summarized in Table 4 a) and b), respectively. On univariate analysis, female gender (HR 8.33, p=0.0006) and lytic and mixed lytic/blastic type lesions (i.e. lesions with a lytic component, HR 4.35, p=0.0211) correlated with fracture toxicity. Additionally, better performance status significantly correlated with decreased fracture risk, with each 10-point increase in KPS conferring a 62% relative decrease in risk of fracture. On multivariate analysis incorporating BED10, gender, KPS, and lesion type, none of the variables remained statistically significant.

**Bone Integrity Analysis**

The mean L1 trabecular attenuation value was available for 97 of 116 patients, including nine of the 11 patients who had recorded fracture. The median absolute time between start of SBRT and imaging used to obtain the L1 attenuation value was 0.95 months (range 0-8.04). The mean attenuation value for patients who fractured at the SBRT site was 112.2 HU, while this value was 142.6 HU for patients without recorded fracture (p=0.036).

**DISCUSSION**

SBRT for non-spine bone metastases is being increasingly utilized. A recent phase II trial of predominantly non-spine bone metastases demonstrated improved pain relief and local control with SBRT compared to conventional RT, and importantly, with comparable risk of post-treatment fracture[15]. Nonetheless, factors impacting local control and toxicity following non-spine bone SBRT remain uncertain. We present the largest report of SBRT outcomes for non-spine bone metastases as well as the longest patient follow-up in the current literature. Our local control rates of 92.8% at 1 year and 87.5% at 2 years are comparable to the outcomes reported in the two prior series that focus on SBRT in non-spine bone metastases. Specifically, Owen et al. reported a 1-year local control rate of 91.8% in 74 patients treated to 85 lesions [16], and Erler et al.
Our results are consistent with previously published data in showing an association between local recurrence and PTV volume [17]. In addition, we identified radioresistant histology as a predictor for higher risk of local recurrence, suggesting that these patients may benefit from further dose escalation beyond the common fractionation schemes such as 9-10 Gy x 3 fractions or 6 Gy x 5 fractions prescribed in our series.

Our cumulative fracture rate of 6% is consistent with the two prior studies that reported the risk as 2% and 8%, respectively [16, 17]. However, our study is a unique contribution to the literature in that our larger cohort allowed for a detailed analysis of risk factors for SBRT-induced fracture. Consistent with the spine SBRT literature, univariate analysis found that lesions with a lytic component were at higher risk of fracture compared to sclerotic lesions [18–20]. In addition, female gender and poor performance status were associated with higher fracture risk. Because dual-energy x-ray absorptiometry (DXA) scans are rarely performed in our patient population, to further investigate the relationship between bone density and fracture risk following SBRT, we utilized CT trabecular attenuation values in the L1 vertebra to examine the relationship between baseline bone density and fracture risk.

### Table 3. Local recurrence

| Variable                              | Hazard Ratio | 95% Confidence Interval | p-Value |
|---------------------------------------|--------------|-------------------------|---------|
| a) Univariate analysis                |              |                         |         |
| Radioresistant histology              | 2.77         | 1.12–6.88               | 0.0278  |
| Lesion location                       |              |                         |         |
| Pelvis vs. non-pelvis                 | 2.08         | 0.88–4.90               | 0.0939  |
| Rib vs. non-rib                       | 0.18         | 0.04–0.77               | 0.0211  |
| Hip/femur vs. non-hip/femur           | 1.09         | 0.20–1.14               | 0.8912  |
| Shoulder/humerus vs. non-shoulder/humerus | 2.43         | 0.71–8.31               | 0.1561  |
| Sternum vs. non-sternum              | 1.66         | 0.22–12.35              | 0.6229  |
| Skull vs. non-skull                   | 0.80         | 0.11–5.99               | 0.8301  |
| GTV volume (per 1cc interval)         | 1.04         | 1.00–1.07               | 0.0287  |
| PTV volume (per 5cc interval)         | 1.03         | 1.01–1.04               | 0.0003  |
| BED10†                                | 1.03         | 0.99–1.06               | 0.1458  |
| PTV expansion†                        | 0.86         | 0.52–1.40               | 0.5330  |
| b) Multivariate analysis              |              |                         |         |
| Radioresistant histology              | 1.95         | 0.70–5.46               | 0.2022  |
| BED10†                                | 1.02         | 0.98–1.06               | 0.3567  |
| PTV volume (per 5cc interval)†        | 1.02         | 1.00–1.04               | 0.0292  |
| Rib location                          | 0.24         | 0.05–1.04               | 0.0558  |

†Continuous variable

**Figure 2.** Cumulative incidence plot of fracture reported on 106 lesions treated in 81 patients, describing 1- and 2-year local control rates of 95% and 87%.
This measure correlates well with T-scores from DXA [21,22] and is widely available for cancer patients. It is generally thought that values of less than 100 HU using this method of assessment are concerning for osteoporosis and higher fracture risk. We found that bone density estimated in this manner was significantly lower in patients who developed fractures than in those who did not. Although larger multi-institutional studies are necessary to confirm these results, this important finding may be used to distinguish patients who are appropriate candidates for SBRT alone from those that warrant prophylactic stabilization.

As a retrospective study, we acknowledge several inherent biases, including patient and treatment selection. Furthermore, our analysis was limited by the low number of fracture events in our cohort. Notably, L1 attenuation values could not be obtained for two of the 11 patients who fractured, one due to diffuse metastatic disease in the lumbar spine and the other due to pre-existing L1 compression fracture. In addition, while the series from Owens et al. and Erler et al. also both included a majority of patients with prostate cancer (31-32%), our series includes a greater predominance of prostate primary histology, accounting for over 60% of the patients. We recognize this as a limitation of our study that may decrease the generalizability of our findings. Moreover, our univariate analysis identified radioresistant histology as a statistically significant predictor of local recurrence, and therefore our local control rates may be somewhat inflated by a disproportionate representation of a radiosensitive histology. Nonetheless, this series represents an important contribution to the literature given the large cohort and mature follow-up with 78% of treated lesions followed for at least 1 year post-treatment.

In conclusion, our study demonstrates that SBRT to non-spine bone metastases results in excellent rates of local control with low risk of radiation-associated fracture. Importantly, we report a relationship between bone density – as measured by a well-validated and highly accessible CT-based tool – and risk of SBRT-associated fracture. This novel finding may serve as a foundation for future studies to identify patients who are appropriate candidates for SBRT alone from those that warrant prophylactic stabilization.

**SYMBOLS AND ABBREVIATIONS**

- Biologically effective dose (BED)
- Clinical target volume (CTV)
- Dual-energy x-ray absorptiometry (DXA)
- Gross tumor volume (GTV)
- Hounsfield units (HU)
- Karnofsky performance status (KPS)
- Local recurrence (LR)
- Non-small cell lung cancer (NSCLC)
- Planning target volume (PTV)
- Stereotactic body radiation therapy (SBRT)
Bone density and fracture risk following SBRT for non-spine bone metastases

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Authors’ disclosure of potential conflicts of interest

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REFERENCES

1. Milano MT, Katz AW, Zhang H, Okunieff P. Oligometastases treated with stereotactic body radiotherapy: Long-term follow-up of prospective study. Int J Radiat Oncol Biol Phys. 2012;83: 878–886. doi:10.1016/j.ijrobp.2011.08.036
2. De Felice F, Piccioli A, Musio D, Tombolini V. The role of radiation therapy in bone metastases management. OncoTarget. 2017. pp. 25691–25699. doi:10.18632/oncotarget.14823
3. Mariotto AB, Etzioni R, Hurlbert M, Penberthy L, Mayer M. Estimation of the number of women living with metastatic breast cancer in the United States. Cancer Epidemiol Biomarkers Prev. 2017. doi:10.1158/1055-9965.EPI-16-0889
4. Chow E, Harris K, Fan G, Tsao M, Sze WM. Palliative radiotherapy trials for bone metastases: A systematic review. Journal of Clinical Oncology. 2007. pp. 1423–1436. doi:10.1200/JCO.2006.09.5281
5. Rich SE, Chow R, Raman S, Liang Zeng K, Lutz S, Lam H, Silva MF, Chow E. Update of the systematic review of palliative radiation therapy fractionation for bone metastases. Radiat Oncol. 2018. doi:10.1016/j.radonc.2018.01.003
6. 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. 2012;24: 112–124. doi:10.1016/j.clon.2011.11.004
7. Huisman M, Van Den Bosch MAAJ, Wiljemaans JW, Van Vulpen M, Van Der Linden YM, Verkooijen HM. Effectiveness of reirradiation for painful bone metastases: A systematic review and meta-analysis. Int J Radiat Oncol Biol Phys. 2012. doi:10.1016/j.ijrobp.2011.10.080
8. Ahmed KA, Stauder MC, Miller RC, Bauer HJ, Rose PS, Olivier KR, Brown PD, Brinkmann DH, Naack NN. Stereotactic body radiation therapy in spinal metastases. Int J Radiat Oncol Biol Phys. 2012;82. doi:10.1016/j.ijrobp.2011.11.036
9. Chang EL, Shiu AS, Mendel E, Mathews LA, Mahajan A, Allen PK, Weinberg JS, Brown BW, Wang XS, Woo SY, Cleeland C, Maor MH, Rhines LD. Phase III study of stereotactic body radiotherapy for spinal metastasis and its pattern of failure. J Neurosurg Spine. 2007;7: 151–160. doi:10.3171/SPIN-07/08/151
10. Gerszten PC, Burton SA, Ozhassoglu C, Welch WC. Radiosurgery for spinal metastases: Clinical experience in 500 cases from a single institution. Spine (Phila Pa 1976). 2007;32: 193–199. doi:10.1097/BRS.0b013e318032c156
11. Laufer I, Rubin DG, Lis E, Cox BW, Stubblefield MD, Yamada Y, Blisky MH. The NOMS Framework: Approach to the Treatment of Spinal Metastatic Tumors. Oncologist. 2013. doi:10.1634/theoncologist.2012-0293
12. Bernstein M, Kovar H, Paulussen M, Randall RL, Schuck A, Teot LA, Juergens E. Ewing's Sarcoma Family of Tumors: Current Management. Oncologist. 2006;11: 503–519. doi:10.1634/theoncologist.11-5-503
13. Jang S, Graffy PM, Ziemlewicz TJ, Lee SJ, Summers RM, Pickhardt PJ. Opportunistic osteoporosis screening at routine abdominal and Thoracic CT: Normative L1 trabecular attenuation values in more than 20 000 adults. Radiology. 2019. doi:10.1148/radiol.2019181648
14. Costelloe CM, Chuang HH, Madewell JE, Ueno NT. Cancer response criteria and bone metastases: RECIST 1.1, MDA and PERCIST. Journal of Cancer. 2010. pp. 80–92. doi:10.7150/jca.1.80
15. Nguyen QN, Chun SG, Chow E, Komaki R, Liao Z, Zacharia R, Szeto BK, Welsh JW, Hahn SM, Fuller CD, Moon BS, Bird JE, Satcher R, Lin PP, Jeter M, O’Reilly MS, O’Lewis V. Single-Fraction Stereotactic vs Conventional Multifraction Radiotherapy for Pain Relief in Patients with Predominantly Nonspine Bone Metastases: A Randomized Phase 2 Trial. JAMA Oncol. 2019. doi:10.1001/jamaoncol.2019.0192
16. Owen D, Laack NN, Mayo CS, Garces YI, Park SS, Bauer HJ, Nelson K, Miller RW, Brown PD, Olivier KR. Outcomes and toxicities of stereotactic body radiation therapy for non-spine bone oligometastases. Pract Radiat Oncol. 2014. doi:10.1016/j.prro.2013.05.006
17. Erler D, Brotherston D, Sahgal A, Cheung P, Loblaw A, Chu W, Soliman H, Chung H, Kiss A, Chow E, Poon I. Local control and fracture risk following stereotactic
body radiation therapy for non-spine bone metastases. Radiother Oncol. 2018;127: 304–309. doi:10.1016/j.radonc.2018.03.030

18. Cunha MVR, Al-Omair A, Atenafu EG, Masucci GL, Letourneau D, Korol R, Yu E, Howard P, Lochray F, da Costa LB, Fehlings MG, Sahgal A. Vertebral compression fracture (VCF) after spine stereotactic body radiation therapy (SBRT): Analysis of predictive factors. Int J Radiat Oncol Biol Phys. 2012;84. doi:10.1016/j.ijrobp.2012.04.034

19. Boyce-Fappiano D, Elibe E, Schultz L, Ryu S, Siddiqui MS, Chetty I, Lee I, Rock J, Movsas B, Siddiqui F. Analysis of the Factors Contributing to Vertebral Compression Fractures After Spine Stereotactic Radiosurgery. Int J Radiat Oncol Biol Phys. 2017;97: 236–245. doi:10.1016/j.ijrobp.2016.09.007

20. Thibault I, Whyne CM, Zhou S, Campbell M, Atenafu EG, Myrehaug S, Soliman H, Lee YK, Ebrahimi H, Yee AJM, Sahgal A 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. doi:10.1016/j.ijrobp.2016.09.029

21. Pickhardt PJ, Pooler BD, Lauder T, del Rio AM, Bruce RJ, Binkley N. Opportunistic screening for osteoporosis using abdominal computed tomography scans obtained for other indications. Ann Intern Med. 2013. doi:10.7326/0003-4819-158-8-201304160-00003

22. Gerety EL, Hopper MA, Bearcroft PWP. The reliability of measuring the density of the L1 vertebral body on CT imaging as a predictor of bone mineral density. Clin Radiol. 2017;72: 177.e9-177.e15. doi:10.1016/j.crad.2016.09.022