Technology in Cancer Research & Treatment
Volume 18: 1-8

DOI: 10.1177/1533033819853532
journals.sagepub.com/home/tct
SAGE

Changes in Volume and Density Parameters Measured on Computed Tomography Images Following Stereotactic Body Radiation Therapy of Nonspine Bone Metastases

Samuel Finkelstein, BSc(c)[1], Srinivas Raman, MD[1], Joanne Van Der Velden, MD[1,2], Liying Zhang, PhD[3], Carolyn Tan, MD[1], Amanpreet Dhillon, BSc[4], Frances Tonolete, BSc[4], Nicholas Chiu, MD(c)[1], Linda Probyn, MD[4], Rachel McDonald, MD(c)[1], Arjun Sahgal, MD[1], Edward Chow, MD[1], and Lee Chin, PhD[3]

Abstract

Introduction: Volumetric and density parameters measured from computed tomography scans were investigated for evaluating treatment response of nonspine bone lesions following stereotactic body radiation therapy. **Methods:** Twenty-three patients treated with stereotactic body radiation therapy to nonspine bone metastases with pre- and post-treatment radiological follow-up with computed tomography imaging were identified in a retrospective review. An expert radiologist classified 26 lesions by type (lytic, sclerotic) and by response. Two independent radiation oncologists created separate contours of the bone and soft tissue lesion volumes. Density and volume were assessed relative to baseline values. **Results:** For bone-only lesions, all lesions designated as local control decreased in volume or remained within 20% of baseline volumes. Lytic lesions classified as progressive disease exhibited much larger volume increases. Lytic bone lesions showed indications of remineralization with some exhibiting immediate increases in density (1-6 months) and others decreasing initially then increasing back toward baseline between 7 and 12 months. The majority of sclerotic lesions, all classified as local control, decreased slightly in both volume and density. Lesions with both soft tissue and boney involvement resulted in contradictory results when employing both radiological and size parameters for assessing treatment response. Classification was dominated by changes in soft tissue volume, despite associated volume or density changes in the corresponding boney lesion. In contrast, when soft tissue volume changes were minimal (<20% increase), classification appeared to be related primarily to density changes and not bone volume. **Conclusions:** Volume and density changes show promise as quantitative parameters for classifying treatment responses of nonspine osseous lesions. Further work is required for clarifying how these metrics can be applied to lesions with both boney and soft tissue components.

Keywords

nonspine bone metastases, stereotactic body radiation therapy, computed tomography, mean bone density changes, tumour volume changes, response criteria

[1] Department of Radiation Oncology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada
[2] Department of Radiation Oncology, University Medical Center Utrecht, Utrecht, The Netherlands
[3] Department of Medical Physics, Odette Cancer Centre, University of Toronto, Toronto, Ontario, Canada
[4] Department of Medical Imaging, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada

Corresponding Author:
Samuel Finkelstein, BSc(c), Department of Radiation Oncology, Sunnybrook Health Sciences Centre, University of Toronto, 2075 Bayview Avenue, Toronto, Ontario, Canada M4N 3M5.
Email: sam.finkelstein@sunnybrook.ca

Abbreviations

BLV, boney lesion volume; CR, complete response; CT, computed tomography; LC, local control; MDA, MD Anderson; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; RCC, renal cell carcinoma; SBRT, stereotactic body radiation therapy; SD, stable disease; STV, soft tissue volume; μ, mean bone density; *V*, volume

Received: November 02, 2018; Revised: February 20, 2019; Accepted: May 02, 2019.

Introduction

The evidence-based use of stereotactic body radiation therapy (SBRT) has become increasingly common for the treatment of nonspine bone metastases.[1,2] Stereotactic body radiation therapy delivery is more conformal than conventional radiotherapy allowing the administration of higher biologically equivalent doses of radiation to tumour target volume(s) while minimizing exposure to surrounding organs at risk.[3] Potential advantages of SBRT include improved local control (LC), prolonged disease-free survival, and faster, more durable pain relief. Additionally, there has been accruing evidence to support the use of ablative local therapies in various oligometastatic cancers.[4-6] Traditional end points for radiotherapy to bone metastases have focused on pain response.[7] Given that a primary goal for SBRT is LC and that patients may be asymptomatic, additional radiographic end points are required to assess the efficacy of SBRT to bone metastases. However, current guidelines for assessing radiographic response for bone metastases are not well-defined.

The most commonly used criteria, Response Evaluation Criteria in Solid Tumors (RECIST), is primarily based on tumour size assessments of the lesions' greatest longitudinal dimension and was originally limited to soft tissues.[8] The criteria was recently updated to include bone metastases (RECIST 1.1) but only for lytic metastases with soft tissue involvement measuring at least 10 mm on computed tomography (CT) imaging. These criteria do not address osteoblastic lesions or bone metastases that lack a soft tissue component. However, the widespread use of RECIST has allowed for standardized comparison of results with other studies.

Conversely, the University of Texas MD Anderson (MDA) Cancer Center developed bone-specific response-criteria based on radiographic assessment that also incorporates lesion size.[9] A partial response (PR) for lytic lesions under MDA criteria constitutes the appearance of a sclerotic rim on CT and complete response (CR) if the bone density normalizes.[9] The MDA criteria does not define when lesions should be classified by size or density potentially leading to inconsistent results.[8] Further, these criteria have not been validated in the setting of SBRT and the radiological criteria are based on qualitative assessment, which may have interobserver variability.

Consensus definitions of nonspine SBRT response would ideally utilize quantitative parameters that incorporate the best elements of both RECIST 1.1 (size evaluation of soft tissue) and MDA (size and radiological evaluation of bone). This work investigates both anatomical and radiological changes in the soft tissue and osseous components of nonspine bone metastases after SBRT on serial CT imaging using volumetric contours of the metastatic lesion. To our knowledge, no studies have quantitatively evaluated the combination of these features relative to an established response criterion. Radiological changes in bone are measured quantitatively using the mean density of the contoured lesion volumes which have previously been shown to be a surrogate for bone mineralization and demineralization as a response to SBRT.[10] The quantitative data acquired in this study was used to evaluate how the changes observed in volume and density compare to response classifications using RECIST 1.1 determined by an independent radiologist. The results of this work provide insight into the relationship between boney/soft tissue tumour volume and density changes following SBRT that could potentially lead to more accurate response labels for nonspine bone metastases.

Methods

A retrospective review, approved by the research ethics board of Sunnybrook Health Sciences Centre, was performed between November 2011 and April 2014 for 23 patients who underwent SBRT at Sunnybrook Health Sciences Centre. To be eligible, all patients underwent one CT scan prior to treatment and at least one CT scan after treatment. An independent musculoskeletal radiologist classified 26 lesions as lytic or sclerotic at baseline. At each follow-up, all lesions were designated as stable disease (SD), progressive disease (PD), PR, or CR per RECIST 1.1 criteria. We note that although the RECIST 1.1 criteria pertain to lytic bone metastases with soft tissue components, for consistency of classification, they were also applied to lytic and sclerotic lesions without soft tissue components, as well. Local control was defined as lesions classified as SD, PR, or CR. Overall lesion response, either LC or PD, was classified based on the last acquired follow-up. Two independent radiation oncologists determined the lesion volume of the bone and soft tissue separately; one delineated the lesion volumes, and the other reviewed and approved the contours (Figure 1).

Mean bone density (μ) in Hounsfield units was calculated with the use of in-house software written in MATLAB (R2017b, Mathworks Inc, Natrick, Massachusetts) that calculated the mean bone density in Hounsfield units within the contour volume. Volumes of the contours in cubic centimeters were acquired from the Pinnacle[3] treatment planning system (V9.8, Andover, Massachusetts). Boney lesion volume (BLV)

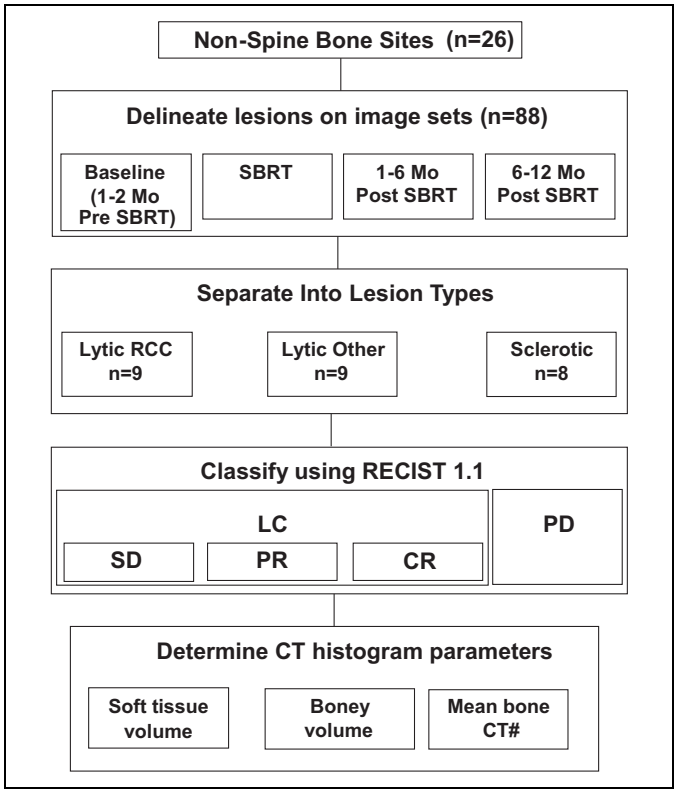

Figure 1. Analysis workflow.

and soft tissue volume (STV) were determined separately. Mean bone density and volume for each lesion were categorized into 3 time points; baseline, months 1 to 6, and months 7 to 12. Due to more frequent follow-up imaging in some cases, data closest to month 6 and month 12 were used. Follow-up mean bone density data and volumes were normalized relative to baseline values as: $Y_{\text{ratio}} = Y_{\text{follow-up}}/Y_{\text{baseline}}$ where Y represents μ or volumes.

Twenty-six nonspine metastatic bone lesions were divided into 4 categories; lytic lesions from renal cell carcinoma (RCC), lytic lesions other than from RCC (non-RCC), and sclerotic lesions from multiple primary cancers. Descriptive analysis of normalized CT parameters was conducted for 26 lesions divided into bone-only and soft tissue containing lesions.

A Wilcoxon signed rank nonparametric test was used to detect significant difference in relative density or relative bone volume comparing the follow-up time periods of 1 to 6 months and 7 to 12 months to baseline, respectively. Lesions with LC and PD were separate in this analysis. This was repeated for lesions containing a soft tissue component. A Wilcoxon rank-sum nonparametric test was also performed among bone-only lesions and lesions with soft tissue separately to detect significant differences between LC and PD within each follow-up period. Spearman correlation coefficients were acquired between relative density and relative bone volume at both follow-up periods for all lesions. In addition, correlations between STV and bone density were also investigated for all applicable lesions.

Table 1. Patient and Treatment Characteristics.

Age, years					
N					23
Median (range)					64 (49-86)
Gender, n (%)					
Female					10 (43.5%)
Male					13 (56.5%)
Primary site, n (%)					
Renal cell					8 (34.8%)
Lung					6 (26.1%)
Prostate					3 (13.0%)
Breast					2 (8.7%)
Colon					2 (8.7%)
Pancreatic					1 (4.3%)
Melanoma					1 (4.3%)
Site treated, n (%)					
N	Rib	Iliac	Acetabulum	Ischium	Manubrium
26	16 (61.5%)	6 (23.1%)	2 (7.7%)	1 (3.8%)	1 (3.8%)
Dose schedules, n (%)					
20 Gy/1					1 (3.8%)
24 Gy/1					1 (3.8%)
24 Gy/2					2 (7.7%)
30 Gy/5					7 (26.9%)
35 Gy/5					12 (46.2%)
40 Gy/5					2 (7.7%)
50 Gy/5					1 (3.8%)

Given the small sample size, a power calculation was performed to determine the number of samples needed to achieve statistical power based on the current cohort. It should be noted that an analysis of power for all 26 lesions was not feasible as sclerotic and lytic lesions were expected to respond differently to SBRT. Instead, the analysis was performed for only lytic lesions to differentiate between LC and PD.

All statistical analysis was conducted using Statistical Analysis Software (SAS version 9.4 for Windows, Cary, North Carolina). A P value $<.05$ was considered statistically significant.

Results

The majority of cases were RCC (35%), lung cancer (26%), and prostate cancer (13%; Table 1). Of 26 sites treated, 18 bone metastases were lytic lesions and 8 were sclerotic lesions. The most common dose-fractionations were 35 Gy/5 (46%) and 30 Gy/5 (27%). A total of 88 contours were produced.

Bone-Only Lesions

Seventeen of 26 lesions in this study lacked soft tissue tumour involvement. Thirteen of those 17 were categorized as LC. Twelve of 13 lesions with LC remained within ∼20% of baseline volumes at final follow-up (Figures 2 and 3) with a single LC lesion exhibiting a final relative increase of ∼80% (Figure 3). Eight lesions with LC decreased in volume (up to 20%) at final follow-up (Figures 2 and 3). The 4 lesions with larger volumes exhibiting LC increased by no greater than

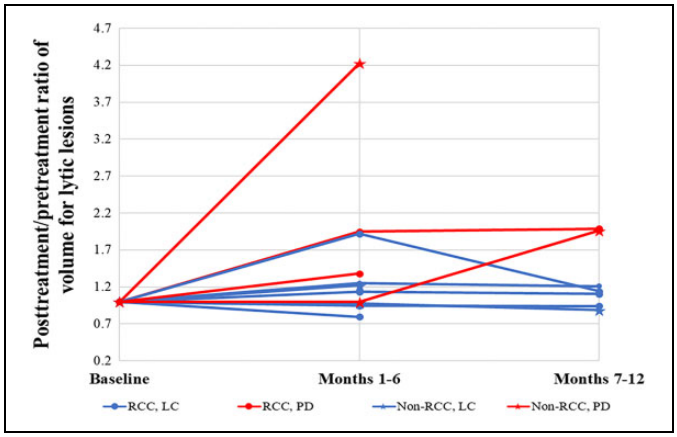

Figure 2. Postreatment/pretreatment ratios of volume for 11 lytic lesions without soft tissue tumour involvement from renal cell carcinoma and primary cancers other than renal cell carcinoma.

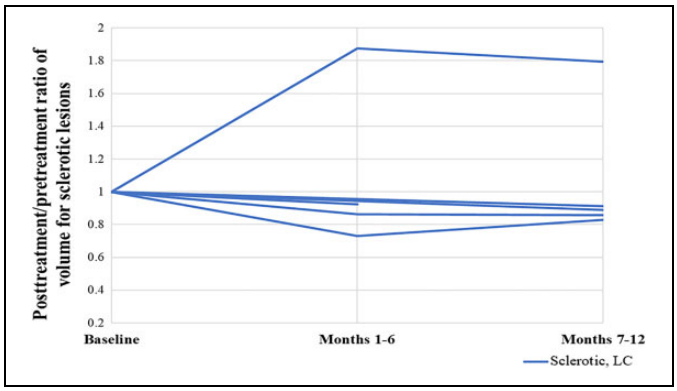

Figure 3. Posttreatment/pretreatment ratios of volume for 6 sclerotic lesions without soft tissue tumour involvement from multiple primary cancers.

$\sim$20% from baseline (Figures 2 and 3). The average relative change in volume at 1 to 6 months for lesions with LC was 1.21 $\pm$ 0.39, 1.1 $\pm$ 0.12, and 1.1 $\pm$ 0.45 for lytic RCC, lytic non-RCC, and sclerotic lesions (Table 2). The average relative change in volume at 7 to 12 months for lesions with LC was 1.10 $\pm$ 0.10, 0.89, and 1.06 $\pm$ 0.37 for lytic RCC, lytic non-RCC, and sclerotic lesions (Table 2).

The 4 bone-only lesions with PD were all classified as lytic and exhibited larger increases in relative volume (up to 4.2 X) at final follow up (Figure 2). The average relative change in volume at 1 to 6 months for lesions with PD was 1.66 $\pm$ 0.28 and 2.61 $\pm$ 1.62 for lytic RCC and lytic non-RCC lesions (Table 2). The average relative change in volume at 7 to 12 months for lesions with PD was 1.99 and 1.96 for lytic RCC and lytic non-RCC lesions (Table 2).

Lytic lesions from RCC tended to remineralize in the latter stages of follow-up imaging (Figure 4). For bone-only cases of lytic lesions from RCC, the 5 cases who had a follow-up in the months 7 to 12 (4 LC and 1 PD) exhibited an increase in μ relative to months 1 to 6 (Figure 4). All lytic RCC lesions that demonstrated LC with follow-ups in the month 7 to 12 range were within 20% of baseline volumes (Figure 2). Of 4 bone-only lytic lesions not from RCC, μ in the 2 lesions with LC increased at months 1 to 6 while μ decreased slightly from baseline values at months 1 to 6 for lesions with PD (Figure 4). The 2 non-RCC lesions exhibiting LC remained within $\sim$20% of baseline volumes (Figure 2). Both non-RCC lesions with PD increased in volume 2-fold or more compared to baseline.

Overall, the average relative change in μ for lytic lesions with LC was 0.67 $\pm$ 0.32 and 1.47 $\pm$ 0.4 at 1 to 6 months and 0.88 $\pm$ 0.39 and 1.84 at 7 to 12 months for RCC and non-RCC, respectively (Table 2). The average relative change in μ for lytic lesions with PD was 1.02 $\pm$ 0.26 and 0.69 $\pm$ 0.17 at 1 to 6 months and 1.46 and 1.41 at 7 to 12 months for RCC and non-RCC, respectively (Table 2).

All 8 sclerotic lesions were designated as LC. For the 6 sclerotic without soft tissue involvement, μ was either stable compared to baseline or decrease slightly with an average relative change in μ of 0.96 $\pm$ 0.09 at 1 to 6 months and 0.88 $\pm$ 0.14 at 7 to 12 months (Figure 5).

Lesions With Soft Tissue Component

For 7 of 8 cases with LC who had soft tissue tumour involvement, the STV remained within 50% of baseline values (Table 3). The exception was case 9, which was a sclerotic lesion classified as LC but demonstrated more than a 2-fold relative increase in STV and large relative increases in bone density (2.63$\times$). In cases 2 through 4, the boney component of the lesion demonstrated increased density and stable or decreased tumour volume, which was also consistent with the soft tissue response for these osteolytic lesions exhibiting LC (Table 3). Boney lesion volumes of cases 1 and 5 (osteolytic lesions) and case 8 (osteoblastic lesion) increased as opposed to their STVs, which decreased. In all 3 cases μ decreased. Case 6 (LC) and 7 (PD) experienced minimal STV changes but substantial boney tumour volume changes in response to SBRT. Case 6 demonstrated an overall increase in μ (1.64) while in case 7, μ decreased (0.87).

Statistical Analysis

No statistical significance was observed for all Wilcoxon and correlation tests performed. An ad hoc power analysis using a 2-sided Wilcoxon test showed 6% power when comparing 11 bone-only lytic and sclerotic lesions. The same power-analysis including all lytic lesions, yielded 23% power. If considering lytic lesions with and without a soft tissue component, 87 lesions would be needed to achieve 80% power for determining statistical significance in comparing lesions with LC and PD.

Discussion

Currently, no quantitative radiographic response criterion for SBRT of nonspine bone metastases exists. In this work, we attempted to understand the relationship between tumour size and density for different types of lesions (lytic renal cell, lytic

Table 2. Summary of Mean Density and Volume Changes for 17 Lesions With Boney Tumour Only.

	Lytic Lesions RCC, n = 7			Lytic Lesions Non-RCC, n = 4			Sclerotic Lesions, n = 6		
		Months 1 to 6	Months 7 to 12		Months 1 to 6	Months 7 to 12		Months 1 to 6	Months 7 to 12
Responder (LC), n = 13	μ ± SD (relative)	0.67 ± 0.32	0.88 ± 0.39	μ ± SD (relative)	1.47 ± 0.40	1.84	μ ± SD (relative)	0.96 ± 0.09	0.88 ± 0.14
	V ± SD (relative)	1.21 ± 0.39	1.10 ± 0.10	V ± SD (relative)	1.10 ± 0.12	0.89	V ± SD (relative)	1.10 ± 0.45	1.06 ± 0.37
Nonresponder (PD), n = 4	μ ± SD (relative)	1.02 ± 0.26	1.46	μ ± SD (relative)	0.69 ± 0.17	1.41			
	V ± SD (relative)	1.66 ± 0.28	1.99	V ± SD (relative)	2.61 ± 1.62	1.96			

Abbreviations: μ, mean bone density; LC, local control; PD, progressive disease; RCC, renal cell carcinoma; SD, standard deviation; V, volume.

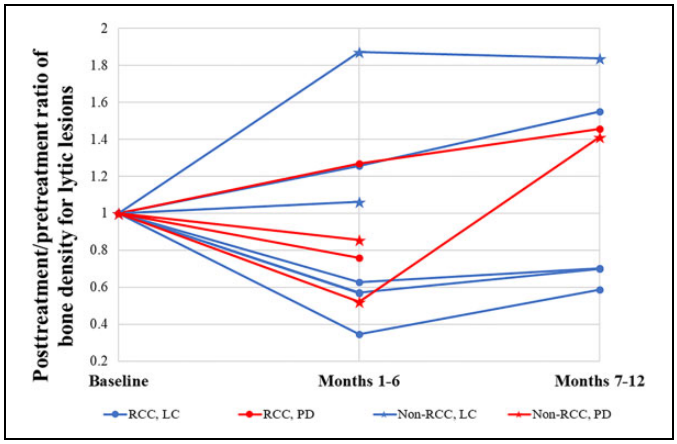

Figure 4. Postreatment/pretreatment ratios of mean bone density for 11 lytic lesions without soft tissue tumour involvement from renal cell carcinoma and primary cancers other than renal cell carcinoma.

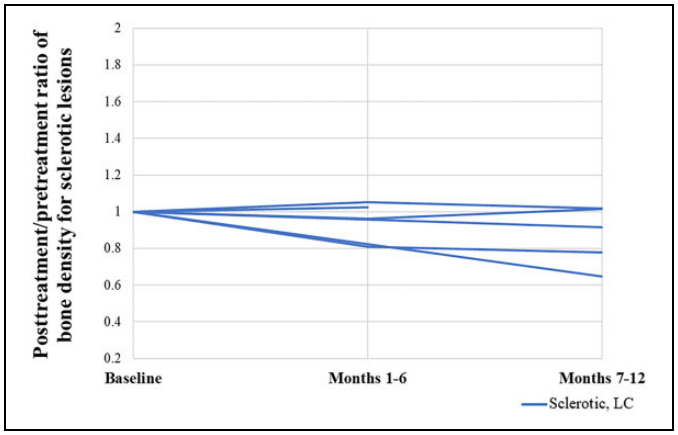

Figure 5. Posttreatment/pretreatment ratios of mean bone density for 6 sclerotic lesions without soft tissue tumour involvement from multiple primary cancers.

nonrenal cell, sclerotic) exhibiting LC or PD. Tumour size was measured considering the volume of the boney component and soft tissue component separately. This was done with the goal to eventually establish a set of parameters to adequately characterize response of nonspine bone metastases post SBRT. Bone density and tumour size changes were evaluated by changes relative to baseline at various follow-up points after treatment.

Changes in CT density has been shown to be a feasible method for evaluating the remineralization of lytic lesions.[10,11] In previous studies by Chow *et al,* and Mcdonald *et al,* the median bone density of the most representative CT slice was used to assess bone remineralization instead of the entire 3D contour. This approach is subjective and prone to bias with potentially different density values reported depending on the chosen representative slice by the radiologist. In our study, μ of the whole BLV was calculated providing a more systematic and quantitative methodology that may be more reliable in clinical practice. Similarly, while traditional size criteria employ relative changes in the largest tumour dimension for assessing response, employing volumetric changes provides an unbiased quantitative parameter that is representative of the entire tumour.

Our study achieved similar results to the study by Koswig and Budach which noted an increase by 173% for bone density of osteolytic metastases 6 months after multifractioned radiotherapy.[12] Furthermore, Sprave e*t al* observed significant increases in bone density with median percentage increases of 33.8% and 72.1% for 3 months and 6 months, respectively, following spinal SBRT, along with higher significant increases in density in the subgroup of osteolytic lesions.[13] Our results have also reaffirmed previous findings by Mcdonald *et al.*[10] The majority of sclerotic lesions in this study exhibiting LC decreased in μ or remained within 5% above baseline value. With regard to remineralization, a distinct difference in time-to-treatment response was also observed between lytic lesions from RCC and other primary tumours (Table 2). For non-RCC lytic lesions, μ increased immediately in the first 6 months following SBRT. However, the majority of lytic lesions from RCC decreased in μ during the first 6 months following SBRT following by an increase in μ between 6 to 12 months that did not surpass baseline values. These results are in agreement with previous reports suggesting that RCC lesions may exhibit a unique temporal response after SBRT compared to other primary tumours.[5]

A challenge that can occur when trying to define LC of bone metastases post-SBRT is pseudoprogression.[2,14] Pseudoprogression can be described as a transient increase in tumour growth that mimics tumour progression. First described in brain tumours, pseudoprogression has since been observed in multiple sites after stereotactic radiotherapy including brain metastases, liver metastases, and lung tumours. In the setting of bone metastases, there are increasing reports of pseudoprogression after high-dose radiotherapy to the spine.[15-17] In particular, lytic lesions and RCC metastases appear to have an increased incidence of pseudoprogression after SBRT. This was also seen in our study where some of the lesions increased in volume or decreased in density initially but were ultimately classified as having LC on follow-up imaging. In particular, lytic lesions classified using RECIST as PD exhibited this trend.

Currently, a challenge exists for using RECIST 1.1 when measuring boney lesions and lesions with soft tissue involvement. Strictly following these criteria yields only 11 of 26 measurable lesions in this study. While measuring quantitative changes of the volume and density of bone lesions provides additional information for response assessment, the presence of an associated soft tissue component can further increase the reliability of response classification and avoid misclassification due to pseudoprogression or early follow-up. Although there may be temporal differences, it should be assumed that both the boney component and soft tissue component have the same biological response to radiotherapy.

In this work, 3 cases with bone metastases with soft tissue involvement would have been labeled PD over LC if boney

Table 3. Boney Lesion Versus Soft Tissue Tumor Component Volume Changes in Response to SBRT With Associated Mean Bone Density Changes.

		Boney Response					Soft Tissue Response		
Case #	Lesion Category, Response Category	Baseline Value (CC)	Mo 1 to 6 Volume Change (Relative)	Mo 1 to 6 Mean Density Ratio to Baseline	Mo 7 to 12 Volume (Relative)	Mo 7 to 12 Mean Density Ratio to Baseline	Baseline Value (CC)	Mo 1 to 6 Volume (Relative)	Mo 7 to 12 Volume (Relative)
1	Lytic RCC, LC	6.53	1.88	0.44			30.51	0.52	
2	Lytic RCC, LC	2.77	1.22	1.24			2.83	1.16	
3	Lytic non-RCC, LC	52.73	0.31	1.27			7.24	0.55	
4	Lytic non-RCC, LC	11.38	0.86	4.1			65.50	0.65	
5	Lytic non-RCC, LC	3.93	2.03	0.99	1.45	1.15	10.30	0.87	0.90
6	Lytic non-RCC, LC	23.21	1.48	1.64			111.22	1.01	
7	Lytic non-RCC, PD	17.93	0.67	1.37	0.73	0.87	2.04	1.97	2.06
8	Sclerotic, LC	27.50	1.36	0.94			169.55	0.86	
9	Sclerotic, LC	0.53	0.32	2.63			8.27	2.07	

Abbreviations: CC, cubic centimeters; LC, local control; PD, progressive disease; RCC, renal cell carcinoma; SBRT, stereotactic body radiation therapy.

response was solely considered (Table 3). Case 1 described a lytic RCC lesion designated as LC by the radiologist where BLV increased and μ decreased 4 months post SBRT. This suggested demineralization and disease progression for this lesion. However, STV decreased to 52% and given the later-time response of RCC lesions, it is possible that remineralization would have occurred at a later follow-up. Case 8 described a sclerotic lesion labelled as LC that increased in BLV, potentially due to pseudoprogression, but decreased in STV. Finally, case 6 described a non-RCC lytic lesion for which BLV increased but STV remained constant at 5 months post SBRT. In this case, the stable soft tissue disease combined with an increased μ in the boney component of the lesion likely resulted in a label of SD. These findings suggest changes in STV were the dominant factor for assessing response to SBRT by our internal radiologist. A possible exception was case 9 in Table 3, which was classified as LC despite substantial increases in STV. Regardless, further work is needed to develop unified criteria to classify response for the entire lesion based on bone and soft tissue changes.

The principal limitation to this study was the small sample size. The uneven distribution of lesions with a small sample size may introduce bias. Future studies should increase sample size by several-fold and consider dividing lesion categories by primary cancer, as our study showed different response patterns based on tumour histology and baseline density. We believe this finding of a differential response is important for future studies to consider for calculating an appropriately powered sample size. According to our power analysis, an additional 69 lesions would be required to achieve statistical power.

The prospect of there being a dose–response relationship and observing time-related trends of parameter changes should also be investigated with a greater sample size. Moreover, confounding factors such as the effect of systemic therapies should be taken into consideration. Systemic therapies were sequential to SBRT according to institutional policy. Another limitation of the study is the ability to accurately and consistently delineate the tumour volumes of CT imaging alone.[18] Possible bias arising from manual segmentation was mitigated by having an independent reviewer approve all contours. Future studies could investigate other first order and second order CT features such as standard deviation, skewness, kurtosis, as well as textural features as radiomic analyses in other tumor settings demonstrate the potential for additional information from these parameters.[19] A clear biological rationale for these additional CT histogram features remains undetermined but if they show distinctive trends in response or nonresponse to SBRT, they may serve as additional, complementary response criteria. Other promising modalities such as magnetic resonance imaging and nuclear imaging-based biomarkers may also serve as useful adjuncts.[20] However, a significant advantage of using CT-based markers only is that these tests are routinely performed as restaging investigations in metastatic cancer, limiting other follow-up tests is a cost effective strategy that places minimal burden on patients with advanced cancer.

It is hoped with future studies, specific guidelines can be developed like the criteria outlined in the spine response assessment in Neuro-Oncology group.[14] The current knowledge gap in assessing response to SBRT in nonspine bone metastases may increase the subjectivity and variability of assessing tumour response in clinical trials and routine practice. Radiologic criteria that incorporate quantitative, objective parameters such as those outlined in this study should be developed for assessing response to nonspine bone metastases to complement existing clinical criteria such as pain response.

Authors' Note

Our study was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre (approval no. 284-2014). It was determined that an informed consent form was not required for this study.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Samuel Finkelstein, BSc(c) https://orcid.org/0000-0002-4488-3293

References

1. Pan H, Simpson DR, Mell LK, Mundt AJ, Lawson JD. A survey of stereotactic body radiotherapy use in the United States. *Cancer*. 2011;117(19):4566-4572. doi:10.1002/cncr.26067.
2. Erler D, Brotherston D, Sahgal A, et al. Local control and fracture risk following stereotactic body radiation therapy for non-spine bone metastases. *Radiother Oncol*. 2018;127(2):304-309. doi:10.1016/J.RADONC.2018.03.030.
3. Sahgal 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*. 2012;24(9):629-639. doi:10.1016/j.clon.2012.04.006.
4. Ahmed KA, Barney BM, Davis BJ, Park SS, Kwon ED, Olivier KR. Stereotactic body radiation therapy in the treatment of oligometastatic prostate cancer. *Front Oncol*. 2013;2:215. doi:10.3389/fonc.2012.00215.
5. Balagamwala EH, Angelov L, Koyfman SA, et al. Single-fraction stereotactic body radiotherapy for spinal metastases from renal cell carcinoma. *J Neurosurg Spine*. 2012;17(6):556-564. doi:10.3171/2012.8.SPINE12303.
6. Blanco AI, Teh BS, Amato RJ. Role of radiation therapy in the management of renal cell cancer. *Cancers (Basel)*. 2011;3(4):4010-4023. doi:10.3390/cancers3044010.
7. Chow E, Hoskin P, Mitera G, et al. Update of the international consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. 2012;82(5):1730-1737. doi:10.1016/j.ijrobp.2011.02.008.
8. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247. doi:10.1016/j.ejca.2008.10.026.
9. Hamaoka T, Madewell JE, Podoloff DA, Hortobagyi GN, Ueno NT. Bone imaging in metastatic breast cancer. *J Clin Oncol*. 2004;22(14):2942-2953. doi:10.1200/JCO.2004.08.181.
10. McDonald R, Probyn L, Poon I, et al. Computed tomography evaluation of density following stereotactic body radiation therapy of nonspine bone metastases. *Technol Cancer Res Treat*. 2016;15(5):683-688. doi:10.1177/1533034615604068.
11. Chow E, Holden L, Rubenstein J, et al. Computed tomography (CT) evaluation of breast cancer patients with osteolytic bone metastases undergoing palliative radiotherapy—a feasibility study. *Radiother Oncol*. 2004;70(3):291-294. doi:10.1016/j.radonc.2004.01.009.
12. Koswig S, Budach V. Remineralization and pain relief in bone metastases after after different radiotherapy fractions (10 times 3 Gy vs. 1 time 8 Gy). A prospective study [in German]. *Strahlenther Onkol*. 1999;175(10):500-508. doi:10.1007/S000660050061.
13. Sprave T, Verma V, Förster R, et al. Local response and pathologic fractures following stereotactic body radiotherapy versus three-dimensional conformal radiotherapy for spinal metastases—a randomized controlled trial. *BMC Cancer*. 2018;18(1):859. doi:10.1186/s12885-018-4777-8.
14. Chang EL, Guckenberger M, Thibault I, et al. Response assessment after stereotactic body radiotherapy for spinal metastasis: a report from the SPIne response assessment in Neuro-Oncology (SPINO) group. *Lancet Oncol*. 2015;16(16):e595-e603. doi:10.1016/S1470-2045(15)00166-7.
15. Jabehdar Maralani P, Winger K, Symons S, et al. Incidence and time of onset of osseous pseudoprogression in patients with metastatic spine disease from renal cell or prostate carcinoma after treatment with stereotactic body radiation therapy. *Neurosurgery*. 2019;84(3):647-654. doi:10.1093/neuros/nyy075.
16. Bahig H, Simard D, Létourneau L, et al. A study of pseudoprogression after spine stereotactic body radiation therapy. *Int J Radiat Oncol*. 2016;96(4):848-856. doi:10.1016/J.IJROBP.2016.07.034.
17. Amini B, Beaman CB, Madewell JE, et al. Osseous pseudoprogression in vertebral bodies treated with stereotactic radiosurgery: a secondary analysis of prospective phase I/II clinical trials. *AJNR Am J Neuroradiol*. 2016;37(2):387-392. doi:10.3174/ajnr.A4528.
18. Raman S, Chin L, Erler D, et al. Impact of magnetic resonance imaging on gross tumor volume delineation in non-spine bony metastasis treated with stereotactic body radiation therapy. *Int J Radiat Oncol*. 2018;102(4):735-743.e1. doi:10.1016/J.IJROBP.2018.03.010.
19. Aerts HJ, Velazquez ER, Leijenaar RT, et al. Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. *Nat Commun*. 2014;5(1):4006. doi:10.1038/ncomms5006.
20. Soliman M, Taunk NK, Simons RE, et al. Anatomic and functional imaging in the diagnosis of spine metastases and response assessment after spine radiosurgery. *Neurosurg Focus*. 2017;42(1):E5. doi:10.3171/2016.9.FOCUS16350.