Editor's note:
"Palliative Radiotherapy Column" features articles emphasizing the critical role of radiotherapy in palliative care. Chairs to the columns are Dr. Edward L. W. Chow from Odette Cancer Centre, Sunnybrook Health Sciences Centre in Toronto and Dr. Stephen Lutz from Blanchard Valley Regional Cancer Center in Findlay, gathering a group of promising researchers in the field to make it an excellent column. The column includes original research manuscripts and timely review articles and perspectives relating to palliative radiotherapy, editorials and commentaries on recently published trials and studies.

Palliative Radiotherapy Column (Original Article)

Radiological changes on CT after stereotactic body radiation therapy to non-spine bone metastases: a descriptive series

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Background: In recent years, stereotactic body radiation therapy (SBRT) has become increasingly used for the management of non-spine bone metastases. Few studies have examined the radiological changes in bone metastases after treatment with SBRT and there is no consensus about what constitutes radiologic response to therapy. This article describes various changes on CT after SBRT to non-spine bone metastases in eight selected cases.

Methods: A retrospective review was conducted for patients treated with SBRT to non-spine bone metastases between November 2011 and April 2014 at Sunnybrook Health Sciences Centre. A musculoskeletal radiologist identified eight illustrative cases of interest and provided a description of the findings.

Results: Different radiological changes following SBRT were described, including: remineralization of lytic bone metastases, demineralization of sclerotic bone metastases, pathologic fracture, size progression and response in different lesions, as well as lung fibrosis after SBRT to a rib metastasis.

Conclusions: We reviewed the radiological images of eight selected cases after SBRT to nonspine bone metastases and a number of characteristic findings were highlighted. We recommend future studies to correlate radiologic changes with clinical outcomes including pain relief, toxicity and long-term local control.

Keywords: Stereotactic body radiation therapy (SBRT); non-spine bone metastases; CT

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Introduction

Bone metastases are commonly observed in patients with advanced cancer, with an approximate incidence of 70–85% (1). Single-fraction or conventionally-fractionated external beam radiation therapy (EBRT) has traditionally been used to treat non-spine bone metastases, and has been shown to decrease pain and improve quality of life (2). Stereotactic body radiation therapy (SBRT) is a more recently developed form of image-guided radiation therapy (3). SBRT allows for more precise delivery of higher biologically effective doses (BED) of radiation to smaller target volumes (4), thus minimizing the dose to surrounding organs at risk (5). In addition, with its increased precision and higher dose of radiation, SBRT may shift the aim of therapy from pain and symptom relief alone towards greater local tumor control and durable pain reduction, making it a promising treatment for patients with oligometastatic disease.

SBRT is also a treatment option for patients who have been irradiated previously with low dose radiation treatment (5), and can be effective in patients with radio-resistant tumors (6). For the above reasons, SBRT has become a more frequently-used option for the management of non-spine bone metastases. Few studies have examined the outcomes after SBRT to non-spine bone metastases patients (7). The use of CT imaging to analyze changes in tumors before and after SBRT may be one modality by which to predict clinical outcomes and determine response to therapy. The current report reviews the various radiological changes after SBRT in eight selected cases.

Methods

A retrospective review was conducted for patients treated with SBRT to non-spine bone metastases between November 2011 and April 2014 at Sunnybrook Health Sciences Centre. All patients underwent at least one CT scan prior to SBRT and at least one CT scan after treatment. A musculoskeletal radiologist identified eight illustrative cases of interest with CT images before and after SBRT for these patients.

Results and discussion

Case 1: lung cancer lytic metastasis becomes more sclerotic after SBRT

Figures 1-3 are axial CT images through the chest of a patient with a lytic lesion in the right lateral rib. The patient had a primary lung cancer and started SBRT (35 Gy in 5 fractions) on January 23, 2012. Ten months after radiation, the lesion decreased in size and become more sclerotic. However, follow up imaging five months later showed an increase in the size of the lesion.

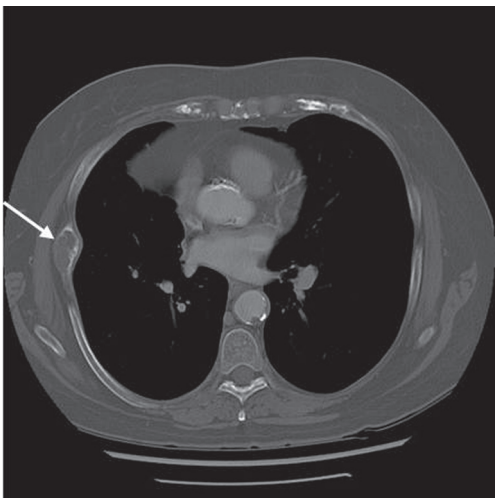

Figure 1 Baseline image (Dec 7, 2011).

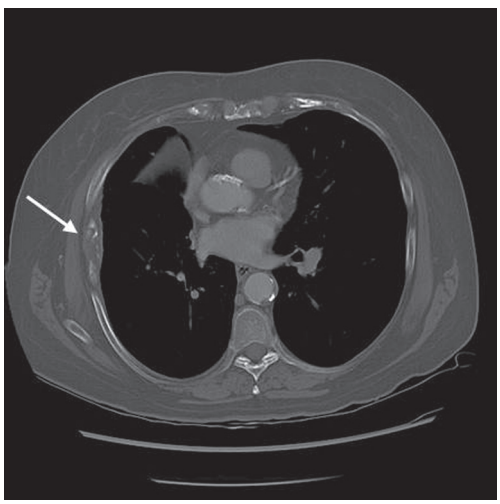

Figure 2 Follow-up image (Nov 1, 2012).

In the context of conventional EBRT, studies investigating CT density after radiotherapy have been published and the remineralization of osteolytic bone metastases has been well-documented (8,9). In a randomized controlled trial investigating bone remineralization published in 1999, Koswig *et al.* found percent bone density change following

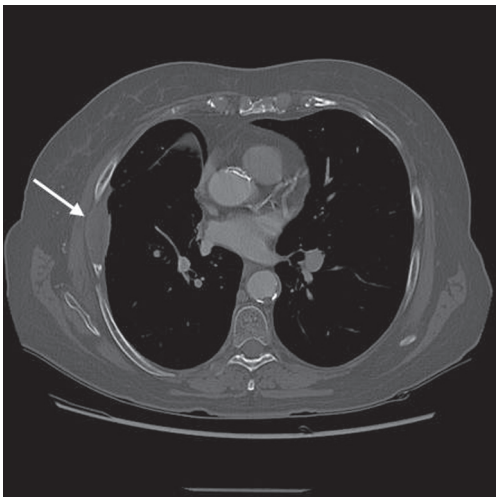

Figure 3 Follow-up image (Apr 25, 2013).

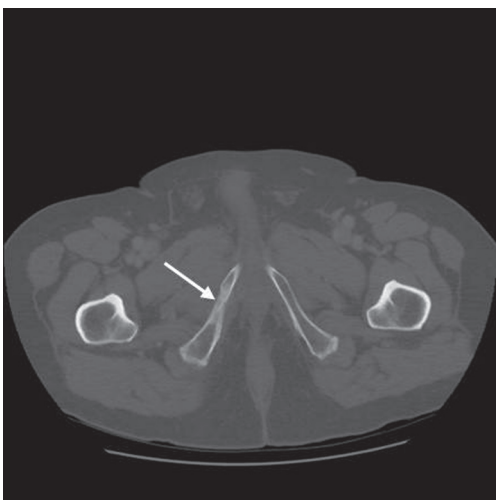

Figure 4 Baseline image (Apr 18, 2013).

radiation to be 173% and 120% in the multiple and single fraction groups, respectively (9). The observation of the lesion in this case becoming more sclerotic is consistent with the response that should be expected of a typical lytic tumor following radiation. As this patient's lesion became more sclerotic 10 months after radiation, this case suggests that SBRT also causes remineralization of lytic non-spine bone metastases. However, though it seems the patient had an initial response with sclerosis of the lesion, local control was not durable, as evidenced by an increase in the size of the lesion five months later. The patient ultimately required a salvage rib rection 18 months after treatment due to tumor progression.

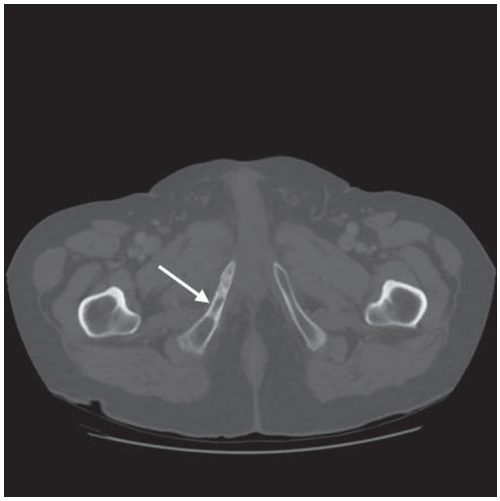

Figure 5 Follow-up image (Dec 14, 2013).

Case 2: prostate cancer sclerotic bone metastasis becomes less dense after SBRT

Figures 4,5 are axial CT images through the pelvis of a patient with a sclerotic lesion in the right inferior pubic ramus. The patient had a primary prostate cancer and started SBRT (35 Gy in 5 fractions) on June 11, 2013. Follow-up CT imaging 6 months later demonstrated increased lucency in the lateral aspect of the lesion suggesting interval improvement.

In the context of conventional EBRT, the demineralization of sclerotic metastases following radiation is less well-documented than the remineralization of lytic metastases; however, it has been explored previously (10). In a study of 14 patients with vertebral metastases arising from breast carcinoma, Wachenfeld *et al.* observed a decrease in bone density following radiation for sclerotic lesions (10). The observation of the sclerotic lesion in our present prostate cancer metastasis case becoming more lucent is consistent with the response Wachenfield *et al.* described of a typical sclerotic tumor following radiation.

Review of this patient's clinical history showed that the lesion was asymptomatic before treatment and as of September 2014, he continued to have durable local control of the lesion. This case suggests that demineralization of sclerotic non-spine bone metastases after SBRT could also be suggestive of reponse.

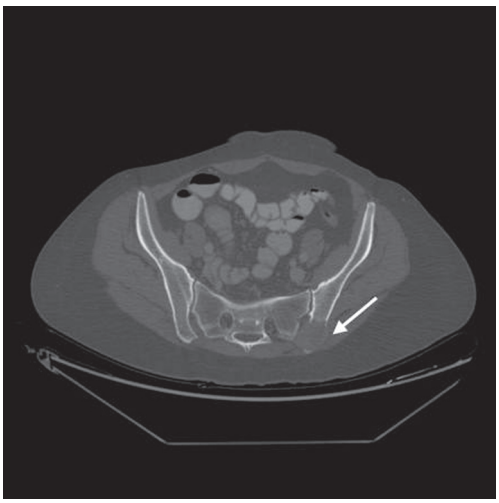

Figure 6 Baseline image (Oct 3, 2013).

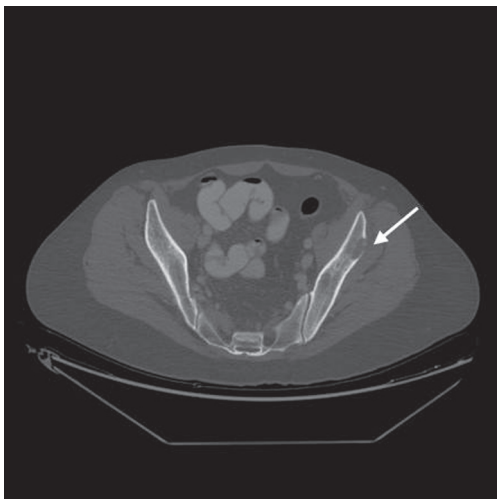

Figure 8 Baseline image (Oct 3, 2013).

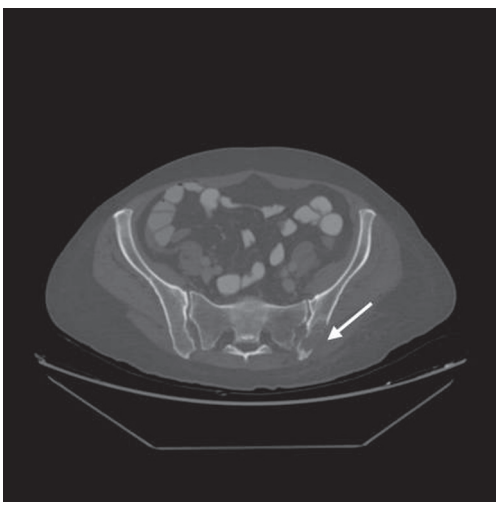

Figure 7 Follow-up image (Jun 19, 2014).

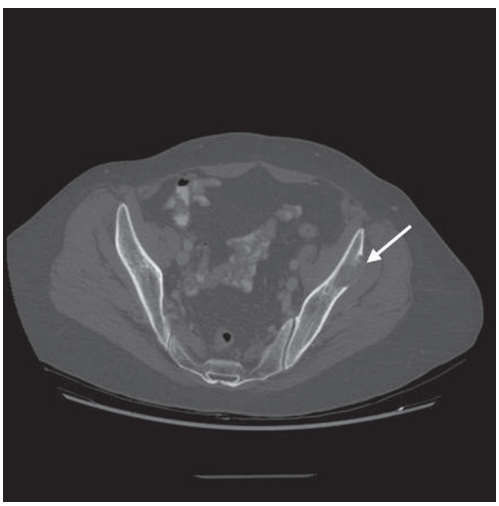

Figure 9 Follow-up image (Dec 5, 2013).

Case 3: lytic pelvic metastasis decreases in size after SBRT

Figures 6,7 are axial CT images through the pelvis of a patient with a lytic lesion in the left ilium. The patient had a primary renal cell carcinoma and started SBRT (30 Gy in 5 fractions) on November 25, 2013. Images demonstrate that the lesion decreased in size after 7 months. This case is one example of a lesion's clear decrease in size following SBRT.

Case 4: renal cell carcinoma lytic metastasis shows more lysis immediately after SBRT then becomes more sclerotic

Figures 8-10 are axial CT images through the pelvis (on bone windows) of a patient with a lytic lesion in the left ilium. The patient had a primary renal cell carcinoma and started SBRT (30 Gy in 5 fractions) on November 25, 2013 Initially, 1 month after radiation, the lesion increased in size and became more lytic; it then decreased in size 4 months later with increased sclerosis. The patient's lesion has been stable as of April 24, 2015.

Metastases arising from renal cancer have had a reputation of being radio-resistant (6,9,11). However, more recent studies suggest that SBRT can overcome radio-resistance with higher BED (6,11-14). The radiosensitivity of renal cancer to SBRT is believed to be due to the generation

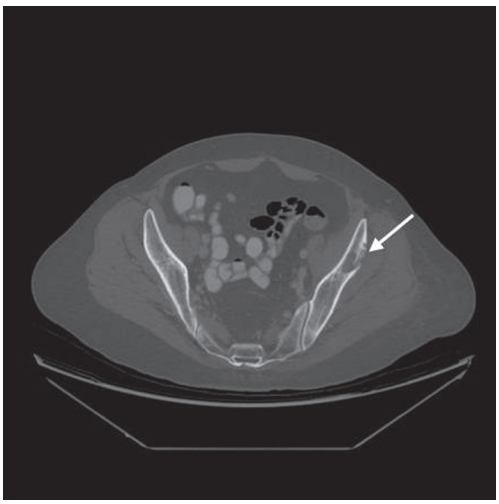

Figure 10 Follow-up image (Apr 24, 2014).

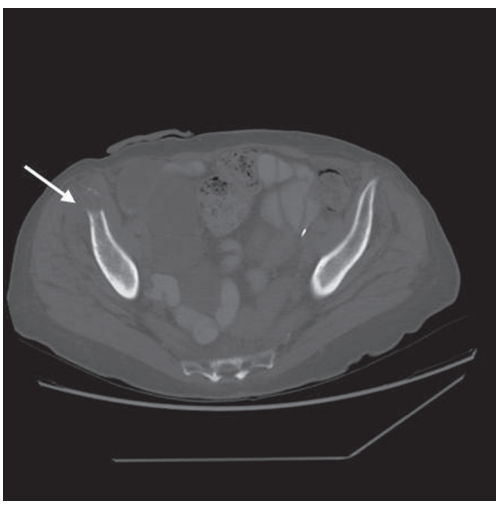

Figure 11 Baseline image (Sep 1, 2011).

of ceramide, which induces endothelial apoptosis—the main cause of radiation-induced cell death in renal cell carcinoma (15). However, the ceramide pathway is activated only in response to a high-dose of radiation per fraction (15). Therefore, SBRT is believed to be more effective than conventional EBRT in the renal cancer population due to its use of higher-dose radiation. With radiological evidence of increased sclerosis after SBRT, the current case suggests that SBRT can cause remineralization of lytic lesions arising from renal cell carcinoma. In addition, as illustrated by the initial increase in size and lytic activity of the lesion in *Figure 11*, initial changes observed in the radiological

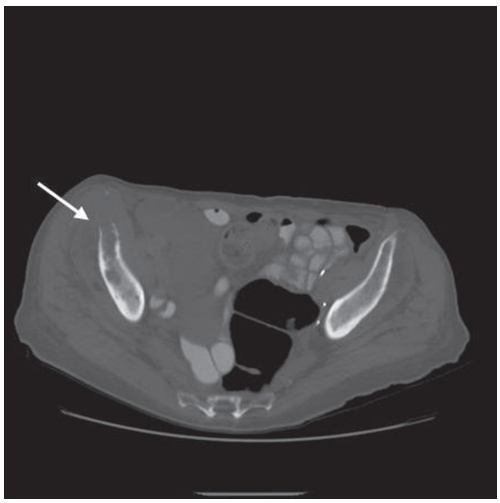

Figure 12 Follow-up image (Mar 9, 2012).

imaging may not accurately represent a patient's long-term response to SBRT. As such, a longer follow-up period may be required to determine a patient's true response to SBRT.

Case 5: bone metastasis progression after SBRT

Figures 11,*12* are axial CT images through the pelvis of a patient with a lytic lesion in the anterior right ilium. The patient had a primary lung cancer and started SBRT (35 Gy in 5 fractions) on November 21, 2011. Images demonstrate that the lytic lesion increased in size after 4 months.

Prospective phase II studies from several centers have consistently showed very high levels of local tumor control with SBRT (16). Despite high reported levels of local tumor control with SBRT, tumor progression can still occur—as in the present case. For example, in the series by Owen *et al.*, 7 out of 74 patients treated with SBRT for non-spine bone metastases all developed local progression with a median time to failure of 2.8 months (7). The current case is an example where no initial response or control was seen, and the bone metastasis progressed shortly after SBRT.

Case 6: breast cancer lytic metastasis improves after SBRT

Figures 13,*14* are axial CT images through the chest (on bone windows) of a patient with a lytic lesion in the left aspect of the sternal body. The patient had a primary breast cancer and started SBRT (35 Gy in 5 fractions) on April 11, 2013. Eleven months after radiation treatment, the lesion has become more lucent/lytic with decreased soft tissue

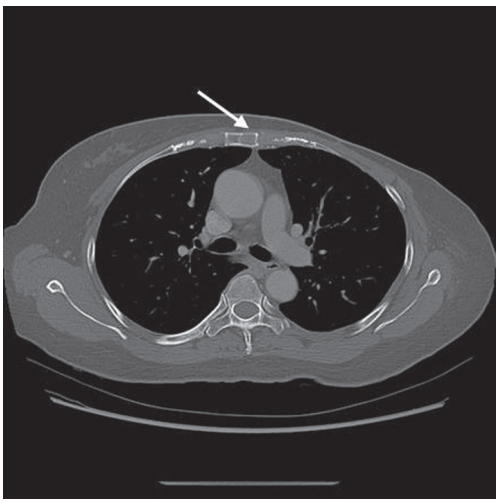

Figure 13 Baseline image (Mar 6, 2013).

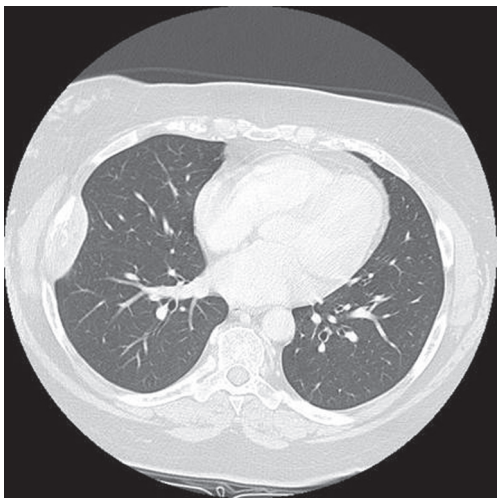

Figure 15 Baseline image (Dec 12, 2013).

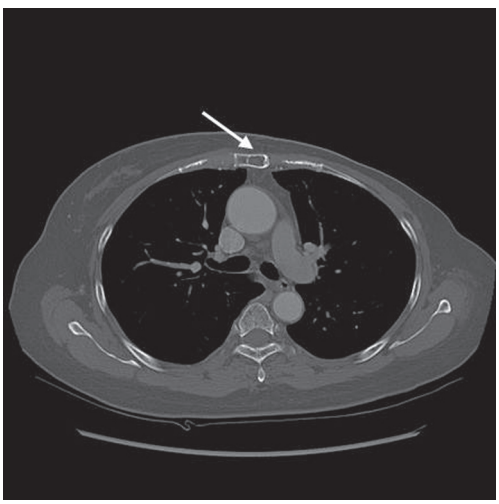

Figure 14 Follow-up image (Mar 21, 2014).

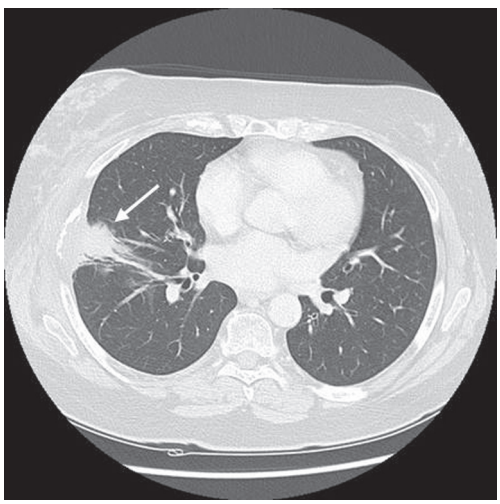

Figure 16 Follow-up image (May 3, 2015).

attenuation representing increased marrow fat at the site of the lesion.

Review of the patient's clinical history shows that despite the lesion becoming more lytic initially following SBRT, the patient experienced significant pain relief and had durable local control as of January 2015. This clinical observation is consistent with the radiologic observation of decreased soft tissue in the tumor and represents an improvement in the metastasis after SBRT.

Case 7: lung fibrosis after SBRT

Figures 15,16 are axial CT images through the chest of a patient with a lytic lesion in the right lateral rib. The patient had a primary renal cell carcinoma and started SBRT (50 Gy in 5 fractions) on January 13, 2014. Fifteen months after SBRT, the lesion decreased in size and there were associated post-radiation fibrotic changes in the right lung with bronchiectasis, subpleural airspace opacity, and volume loss.

Pulmonary fibrosis has been well documented as a possible SBRT-induced lung injury (17,18). For example, Guckenberger *et al.* noted that after single fraction treatment in lung SBRT, dense consolidation and retraction of pulmonary tissue indicating fibrosis were observed in 43% and 50% after 6 and 12 months, respectively (18). For

Table 1 Classifying late radiological changes in lung after SBRT (20)

Name	Description
Modified conventional pattern	Consolidation, volume loss, and bronchiectasis similar to, but usually less extensive than, conventional radiation fibrosis. Larger than the original tumor size. Occasionally with associated ground glass opacity
Mass-like fibrosis	Well-circumscribed focal consolidation limited to area surrounding the tumor. The abnormality must be larger than the original tumor
Scar-like fibrosis	Linear opacity in the region of the tumor associated with volume loss
No evidence of increased density	No new abnormalities. Includes patients with tumors that are stable, regressing or resolved, or fibrosis in the position of the original tumor that is not larger than the original tumor

SBRT, stereotactic body radiation therapy.

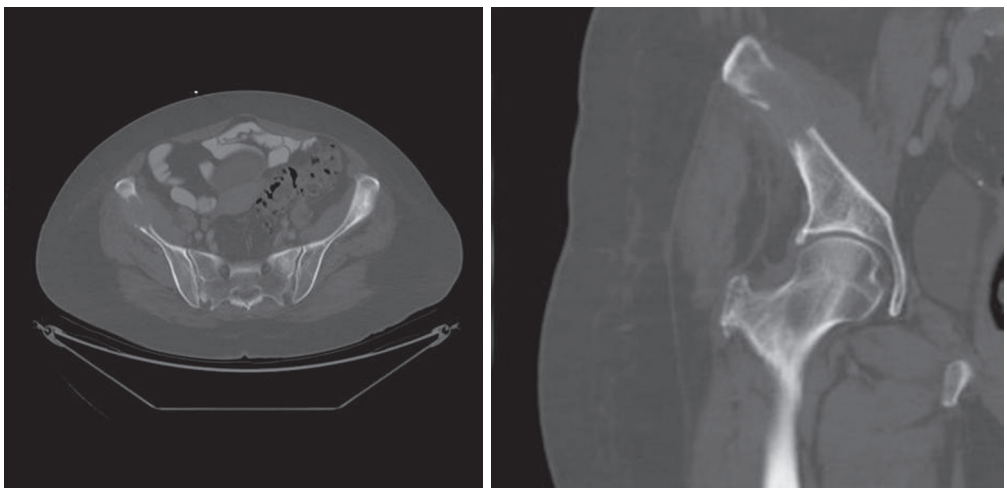

Figure 17 Baseline image (Mar 18, 2015).

fractionated treatment, pulmonary fibrosis was observed in 33% and 74% after 6 and 12 months, respectively (18). Various methods have been proposed to classify radiologic changes on CT after SBRT to the lung (17,19). Broadly, radiological changes can be categorized into acute findings (within 6 months of treatment) and late findings (after 6 months) (19). Pulmonary fibrosis after SBRT is often a late finding; one proposed scoring system categorizes late SBRT changes into four groups, as described in *Table 1*.

Although the aforementioned classification system was developed for use after SBRT to early stage lung cancers, this case illustrates that similar radiographic changes can occur after SBRT to bone metastases that are in close proximity to the lung; and consideration must be given to the possibility of lung injury following SBRT to these lesions. In this particular case, the patient did not develop any pulmonary symptoms after their SBRT treatment.

Case 8: right iliac metastasis and pathologic fracture

Figures 17,18 are axial and coronal CT images through the pelvis of a patient with an osseous metastasis in the lateral right ilium with a large soft tissue component. The patient had a primary NSCLC and started SBRT (30 Gy in 5 fractions) on May 28, 2015 to the right iliac lesion. She previously received two courses of radiation treatment to overlapping areas of the right pelvis in March 2015 (20 Gy in 5 fractions) and June 2014 (8 Gy in 1 fraction). Two weeks after SBRT was completed, the CT scan was repeated and showed increased sclerosis in the irradiated bone, decrease of the soft tissue mass and a new pathologic fracture.

Given the short time interval between SBRT and repeat imaging, it is difficult to determine the extent of treatment response. On the radiation planning CT scan from May 19, 2015, there was no evidence of a pre-existing fracture;

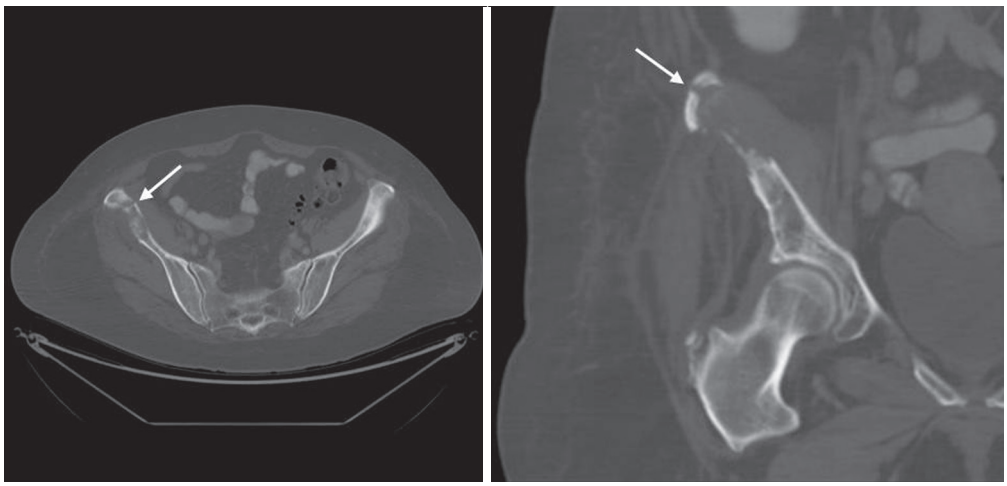

Figure 18 Follow-up image (Jun 16, 2015).

therefore the new pathologic fracture might be related to treatment effect. The development of fractures is a known complication after SBRT to spinal metastases (20). From one series, the median time to vertebral compression fractures after treatment was 3.3 months and the major predictive factors for fracture development were spine alignment, presence of lytic lesions, primary lung/liver histologies and large SBRT dose per fraction (21). Pathologic fractures have also been infrequently observed after SBRT to non-spine bone metastases (7). However, further studies need to be performed to understand the pathophysiology and risk factors for the development of pathologic fractures after treatment to non-spine bone metastases. All patients receiving SBRT to non-spine bone metastases must routinely be informed about fracture risk as a potential complication of treatment.

Conclusions

Few studies have examined the clinical outcomes and radiologic changes in patients receiving SBRT for non-spine bone metastases patients. We reviewed the radiological images of eight selected cases after SBRT. Various radiological changes following SBRT are described, including: remineralization of lytic bone metastases, demineralization of sclerotic bone metastases, progression and response in different lesions, as well as lung fibrosis after SBRT to a rib metastases. We recommend future studies to correlate radiologic changes with clinical outcomes including pain relief, toxicity and long-term local control. In addition, it would be useful to perform prospective studies with larger numbers of patients with bone metastases from various primary malignancies to determine short and long term outcomes post-SBRT.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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