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 (Review Article)

Stereotactic body radiation therapy for non-spine bone metastases—a review of the literature

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Background: Stereotactic body radiation therapy (SBRT) has the ability to deliver significantly higher biologically equivalent doses (BED) compared to conventional radiation treatment. The main goal of SBRT is to improve local tumor control while reducing pain. The side effects however may be greater than those of conventional treatment.

Methods: A review of the literature was conducted and articles pertaining to studies of SBRT in non-spine bone metastases were included. Data on outcomes and toxicities were collected in addition to inclusion and exclusion criteria for each study.

Results: A total of 14 studies were included in this review. Very rarely were grade 3 and 4 toxicities reported. Endpoints for the studies varied significantly, which made conclusions of overall local control and progression free survival near impossible. In studies that reported local control rates, these rates were all greater than 85%. Progression free survival varied significantly between studies.

Conclusions: Due to the lack of consistency in endpoint definitions, it is difficult to compare outcomes across trials. There is a need for consensus in endpoint definitions.

Keywords: Stereotactic radiation therapy; bone metastases; oligometastases; review

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Introduction

Bone metastases are common in advanced cancer, with 70–85% of patients diagnosed with bone metastases at the time of autopsy (1). Conventional palliative radiation therapy has been proven to decrease pain and improve quality of life; however, no increase in overall survival has been reported (2-4). New advances in radiation treatment, however, may be able to improve overall survival and local control rates.

Stereotactic body radiation therapy (SBRT) for bone metastases is a recent technological advance for the treatment of oligometastatic disease. SBRT is able to deliver significantly higher biologically equivalent doses (BED) as compared to conventional radiation. As defined by the Canadian Association of Radiation Oncologists (CARO), SBRT is "*the precise delivery of highly conformal and image-guided hypofractionated external beam radiotherapy, delivered in a single or few fraction(s), to an extra-cranial body target with doses at least biologically equivalent to a radical course when given over a protracted conventionally fractionated (1.8–3.0 Gy/fraction) schedule*" (5). Thus, SBRT is able to shift the goal of therapy to maximizing both local tumour control and pain reduction, as opposed to pain and symptom relief alone. As SBRT is still a relatively new field, information on the toxicities, and outcomes associated with such treatment are still to be learned.

In bone metastases, there are three main potential indications for utilizing SBRT as a treatment. The first indication is retreatment to a site that has previously been irradiated with conventional external beam radiation (5,6). The next indication is in oligometastases with five or less metastatic sites (7). The third indication is oligometastatic progression in patients with widespread metastases; however, one or two areas may be significantly worse. SBRT is able to target these few areas that are either causing pain or have progressed on radiography. The purpose of this literature review was to determine the outcomes as well as toxicities associated with SBRT treatment of non-spine bone metastases.

Methods

A literature search was conducted to find studies that pertained to SBRT in patients with non-spine bone metastases. Articles were examined independently by Bedard G and Chow E to determine eligibility for the review. Articles that involved bones of the skull base were excluded. Due to the relatively small number of studies investigating SBRT treatment of non-spine bone metastases, studies that included other sites of metastases as well as bone metastases were included.

Studies were then examined for their inclusion and exclusion criteria. Data was extracted under the headings of: sample size, age, primary cancer site, SBRT dose, areas of treatment, concurrent treatment, endpoints, local control, survival, and toxicity. As the dosing regimens varied between studies, we calculated the BED for each study (8). A α/β of 7 was used for renal cell carcinoma as it is relatively radioresistant, while a α/β of 10 was used for all other tumors (8).

Results

Fourteen studies were found that fit the search criteria. Only two studies by Jhaveri *et al.* (8) and Owen *et al.* (9) specifically reported outcomes and toxicities of SBRT for non-spine bone metastases. All other studies included other sites of metastases in their analysis of outcomes and toxicities. Sample size of the studies ranged from 8 to 206 patients. There was also a large variance in primary cancer site, SBRT dose and areas of treatment (*Table 1*). Inclusion and exclusion criteria for each individual study were extracted (*Table 2*). The majority of studies required patients to be over the age of 18 with a pathologically confirmed metastatic cancer. Most studies included patients with oligometastatic disease (five or less metastases), a relatively good performance status, and a life expectancy greater than 3 months.

Typical outcomes included local control, overall survival and progression free survival. Local control was defined as: stable disease, partial response or complete response based on imaging (9), lack of tumor progression at the treated site (12), or using the RECIST criteria (7,21). As per the RECIST criteria: complete response is the disappearance of all lesions, partial response is a ≥30% decrease in size from baseline, progressive disease is defined as a ≥20% increase in size and stable disease is neither a partial response nor progressive disease (21). Some studies did not give a definition for local control (18).

In studies that reported local control rates, these rates were greater than 85% in all studies (7,9,10,16,18,19). Median overall survival varied and was cited as 9.3 months (9), 13.5 months (11), 31.7 months (14), and 32 months (15). Progression free survival also varied significantly between the studies. Due to the large variance in endpoints among

Table 1 Study outcomes and toxicity for SBRT non-spine bone metastases studies

Author	Studied patients	Age (years), [rang]	Primary cancer site [%]	SBRT dose [%], BED in Gy	Areas of treatment	Concurrent treatment	Endpoints	Local control	Survival	Toxicity [%]	Notes
Owen *et al.* (9)	74 patients (85 bone mets)	Median 60 [18–87]	Breast [8]; prostate [31]; sarcoma [16]; melanoma [8]; other [36]	24 Gy/1 [19], 81.6; 18 Gy/1 [18], 50.4; 30 Gy/3 [12], 60; other [52]	Sacrum (27%); ilium (21%); rib (12%); other (40%); range: 15 Gy/1 to 50 Gy/5	N/A	Local control; OS; PFS; toxicity	91.8% at 1 year	Median overall: 9.3 months; PFS: 9.7 months	• Acute: Gr 1 pain flare [4]; Gr 2 pain flare [5]; Gr 3 pain flare [1]; Gr 1 fatigue [9]; Gr 1 nausea [4]; dermatitis [1] • Late: Gr 1 fracture [3]; Gr 1 lymphedema [1]; Gr 2 lymphedema [1]; Gr 1 pulmonary fibrosis [1]; Gr 2 neuralgia [3]; Gr 2 chest pain [1]; Gr 2 pneumonitis/ dyspnea [1]	N/A
Berkovic *et al.* (10)	24 patients; 29 lesions (16 bone mets)	N/A	Prostate	Median 50 Gy/10, 75	N/A	N/A	• Primary: ADT-FS, defined as the time interval between the first day of SBRT and the initiation of palliative ADT • Secondary: clinical; failure; toxicity	100%	Median time androgen deprivation therapy was deferred was 38 months	• Acute: Gr 2 GU [8]; Gr 2 GI [6] • Late: Gr 2 GU [6]; Gr 2 GI [3]	Patients had bone and/or lymph node mets
De Ruysscher *et al.* (11)	40 patients (7 with bone mets)	Mean: 62 [44–81]	Lung	54 Gy/30 twice daily for bone mets, 63.7	Bone; adrenal brain; lung; lymph nodes; axilla; pleura	38.5% sequential chemo; 53.8% concurrent chemoradiation	• Primary: OS • Secondary: PFS; toxicity	N/A	Median survival: 13.5 months for bone	• Acute: Gr 3 oesophagitis [15]; Gr 2 dyspnea [7.7]; Gr 3 cough [2.6]; Gr 2 paresis [2.6]; Gr 2 seizures [2.6]; Gr 2 sensory neuropathy [5]; Gr 1 dizziness [5]; Gr 2 headache [5] • No late toxicity	Toxicity data did not differentiate different sites of mets

Table 1 *(continued)*

Table 1 *(continued)*

Author	Studied patients	Age (years), [rang]	Primary cancer site [%]	SBRT dose [%], BED in Gy	Areas of treatment	Concurrent treatment	Endpoints	Local control	Survival	Toxicity [%]	Notes
Jhaveri *et al.* (8)	18 patients (24 bone mets)	N/A	RCC	18–40 Gy (3–5 fractions); 24 Gy/3 [33], 51; 40 Gy/5 [37.5], 85.7; other [29.5]	Spine; ribs; clavicle pelvis	N/A	Pain relief; toxicity	78% symptomatic relief; 32% symptomatic recurrence at mean of 10 weeks	N/A	Gr 1 skin toxicity [5.5]	Spine and other bone mets combined
Ahmed *et al.* (12)	8 patients (9 lesions)	N/A	Prostate	18 Gy/1 [33], 50.4; 24 Gy/1 [44], 81.6; 24 Gy/3 [11], 43.2; 30 Gy/3 [11], 60	Ribs; scapula; sacrum; ischium; pelvis; acetabulum	N/A	Local control; freedom from distant mets; toxicity	N/A for bone non-spine only	N/A for bone non-spine only	Gr 2 dyspnea [11]	N/A
Zelefsky *et al.* (13)	105 lesions	N/A	RCC	18–37.5 Gy in 1–5 fractions, 50.4–65.6	Femur; spine; pelvis; lymph nodes	N/A	Local response PFS	Median time to relapse: 2 months (0–25 months)	PFS 44%	Gr 2 dermatitis [2]; fractures [4]; Gr 4 erythema [1]	Include spine lesions
Solanki *et al.* (14)	31 patients (58 lesions—11 osseous lesions)	N/A	NSCLC [29]; arcoma [16]; breast [13]; head and neck [13]; colon [13]	24 Gy/3 [33], 43.2; 30 Gy [35]; 36 Gy [14]; 42 Gy [16]; 50 Gy/10 [3], 75	Osseous and other	None	Response to therapy on PET	55% CR on PET; 45% PR on PET	Time to progression—4.5 months; PFS at 6 months—45%, 1 year—39%; median survival—31.7 months	N/A	N/A
Milano *et al.* (15)	32 patients (155 lesions)	Median 60 [35–88]	Breast [37]; colorectal [30]; lung [16]; other [17]	N/A	Lung; lymph nodes; liver; brain; bone	N/A	OS; PFS	18 lesions failed locally	2- and 4-year OS rate was 65% and 33%, respectively; 2- and 4-year PFS rate was 54% and 28%, respectively; median OS—32 months; median PFS—28 months	N/A	Only 2 bone sites—cannot separate from all others

Table 1 *(continued)*

Table 1 *(continued)*

Author	Studied patients	Age (years), [rang]	Primary cancer site [%]	SBRT dose [%], BED in Gy	Areas of treatment	Concurrent treatment	Endpoints	Local control	Survival	Toxicity [%]	Notes
Rajagopalan *et al.* (16)	22 patients (42 mets, 14.3% bone)	Mean: 60	N/A	18–24 Gy/1 to bone mets [50.4–81.6]	N/A	Varied by patient	Local control PFS	Local control 1 year—87.3%	PFS 1 year—81.2%	Gr 3+ toxicity [4.5]	Cannot differentiate bone from other mets
Parikh *et al.* (17)	206 patients (41% had bone mets)	Median: 61.2	NSCLC	N/A	N/A	N/A	N/A	N/A	Median survival—18 months	N/A	Unable to separate bone
Merrell *et al.* (18)	18 patients	N/A	Breast	24 Gy/1 for bone most common [81.6]	N/A	N/A	Local control; OS	6 months local control—100%; 12 months local control—90%; 40 months local control—90%	CR—9; PR—4	No Gr 3 or 4 early toxicity; late 3 osteonecrosis of the jaw [5.5]	Unable to separate bone from all else
Milano *et al.* (7)	121 patients (154 lesions)	Median 60 [34–88]	Breast [32]; colorectal [26]; lung, head/neck [19]; other [23]	50 Gy/5—most common [100]	Lung (32%); lymph nodes (16%); liver (35%); pelvis/abdomen (4%); brain (3%); bone (10%)	N/A	Freedom from widespread mets; OS	Local control at 2 years—87%; at 6 years—65%	OS—47% at 2 years; at 6 years—9%	Gr 3 toxicity of nonmalignant pleural and pericardial effusion [1]	Unable to tease out bone mets only
Bhattacharya *et al.* (19)	76 patients (22 bone/spine lesions)	Median 60 [31–89]	Colorectal [38.2]; breast [18.4]; prostate [11.8]; head and neck [7.9]; other [11.8]	Bone mets: 21–33 Gy/3–4 fractions [41.6]; 19.5–40 Gy/3–4 fractions for retreatment [39.4]	Lymph node (42.1%); bone + spine (29.0%); liver (6.6%); head and neck (7.9%); abdominal (14.5%)	N/A	Local control; OS; PFS	Local control at 3 weeks—89%	OS: 84.4% at 1 year, 63.2% at 2 years; PFS: 49.1% at 1 year, 26.2% at 2 years	None in patients treated to bone	Unable to tease out bone mets only for local control and OS
Azzam *et al.* (20)	24 patients (39 sites)	Median 69 [53–88]	Prostate [100]	Median: 24 Gy/3–5 fractions [18–50]	Bone (62.5%); lymph node (29.2%); CNS (4.2%); lung (4.2%)	N/A	OS	N/A	Median time to death—13 months	Gr 1 diarrhea [4.2]; Gr 2 pelvic pain [4.2]	Unable to tease out bone mets alone

SBRT, stereotactic body radiation therapy; BED, biologically equivalent doses; mets, metastases; N/A, not available; OS, overall survival; PFS, progression free survival; Gr, grade; ADT-FS, androgen deprivation therapy-free survival; GU, genitourinary; GI, gastrointestinal; RCC, renal cell cancer; NSCLC, non-small cell lung cancer; PET, positron emission tomography; CR, complete response; PR, partial response; CNS, central nervous system.

Table 2 Study inclusion and exclusion criteria for SBRT non-spine bone metastases studies

Study	Inclusion criteria	Exclusion criteria
Owen *et al.* (9)	Non-spine bony metastases	N/A
Berkovic *et al.* (10)	• Biochemical recurrence after treatment with curative intent • ≤3 synchronous asymptomatic lesions • Normal testosterone levels (180–740 ng/mL)	N/A
De Ruysscher *et al.* (11)	• Histologically or cytologically proven NSCLC • Less than 5 metastases at time of diagnosis • All tumor sites amendable for radical treatment • WHO performance status 0 to 2 • Other malignancy controlled (in clinical complete remission at time of diagnosis)	• Not NSCLC, or mixed NSCLC and other histologies • T4 tumor
Jhaveri *et al.* (8)	Pathology proven RCC with MRI or CT documentation of bony metastatic disease	• Spinal cord compression • Previous radiation to the tumor site • Fracture risk
Ahmed *et al.* (12)	• Biopsy-proven prostate cancer • KPS >40 • Life expectancy >3 months • Confirmation of metastases using [11]C-choline PET-CT, MRI, biopsy, CT	N/A
Zelefsky *et al.* (13)	Extracranial metastatic lesions from renal cell primaries	N/A
Solanki *et al.* (14)	• Pathologically confirmed stage IV metastastic cancer • ≥18 years of age • Life expectancy >3 months • Metastases amenable to radiation therapy as seen on standard imaging	• Coexisting malignancies • Uncontrolled medical comorbidity • Active infectious processes • Exudative, bloody or cytologically malignant effusions • Concurrent systematic chemotherapy during radiation
Milano *et al.* (15)	• One to five radiographically apparent metastatic lesions • ≥18 years • KPS ≥70	N/A
Rajagopalan *et al.* (16)	Five or fewer metastases involving three organs or less	N/A
Parikh *et al.* (17)	• Stage IV disease at diagnosis of NSCLC • Five or fewer discrete metastatic lesions on PET and/or MRI present synchronously at time of initial staging	N/A
Merrell *et al.* (18)	Less than three metastatic lesions without brain involvement	N/A
Milano *et al.* (7)	Five or less detectable metastases	N/A
Bhattacharya *et al.* (19)	Maximum three sites	N/A
Azzam *et al.* (20)	• Biopsy-proven prostate cancer • Previous treatment of disease • Prostate metastases confirmed • Rising PSA	N/A

SBRT, stereotactic body radiation therapy; N/A, not available; NSCLC, non-small cell lung cancer; WHO, World Health Organization; RCC, renal cell cancer; MRI, magnetic resonance imaging; CT, computed tomography; KPS, Karnofsky performance status; PET-CT; positron emission tomography-computed tomography.

the studies, conclusions of overall local control and progression free survival were near impossible to make.

Jhaveri *et al.* found that in patients who were treated with a BED greater than 85, mean time to decrease in pain score was 1 week and 83% of patients had a response to treatment, which was an improvement over those who were treated with a BED less than 85 (8). Through a review of the BED of all other studies, and evaluation of the local control and overall survival of each of the studies, it appears that patients who received a higher BED had a better outcome to treatment, echoing the findings of Jhaveri *et al.* There was no difference in patients who received multiple fractions as opposed to single fraction treatment.

Toxicity data are listed in *Table 1*. Very rarely were grade 3 and 4 toxicities observed (7,11,13,16). Toxicities that occurred most frequently included dermatitis (8,9,13), dyspnea (9,11), and fracture (9,13). There was no trend between BED and severity of toxicity. However, single fraction treatments appear to have a greater percentage of patients experiencing toxicity than multiple fraction treatments (9,12,16). For studies where greater than 50% of patients were treated with single fraction treatment, toxicity data was pooled and overall percentages of patients who experienced toxicity was calculated. Approximately 24% of patients undergoing single fraction treatment (9,12,16,18) *vs.* 12% of patients undergoing multiple fraction treatments (7,8,10,11,20) experienced some sort of acute or late treatment toxicity. The numbers above are estimates based on the reported toxicities of each of the studies; bearing in mind that sites treated other than bone metastases may have been included in the analysis in each of the studies as well. Due to the variance in dose between and within studies, we are unable to determine which toxicities were more likely for single and multiple fraction treatments.

Discussion

SBRT appears to be a feasible and safe treatment option for patients with non-spine bone metastases. However, due to the lack of endpoint consistency between clinical trials, it proves to be difficult to pool and analyze data. A consensus on SBRT endpoints is necessary in order to standardize the reporting of outcome assessment and allow comparison across trials.

In the conventional radiation setting, the international consensus of bone metastases has been developed for clinical endpoints (3). Response categories were based on patient reported pain scores and analgesic consumption. A complete response to treatment was defined as a pain score of 0 out of 10 at the treated site with no concomitant increase in analgesic intake, while a partial response was defined as a pain reduction of 2 or more at the treated site without analgesic increase, or an analgesic reduction of 25% with no increase in pain score or 1 point above baseline. Pain progression was defined as an increase in pain score of 2 or more above baseline with stable analgesic intake or an analgesic increase of 25% with stable pain score. Lastly an indeterminate response was any response not captured in the above definitions (3). These definitions, however, are not directly transferable to the SBRT patient population, due to the differing indications for treatment with SBRT.

The three major potential indications for SBRT differ from those of conventional treatment (5). These include: need for retreatment, oligometastatic disease and oligometastatic progression. If the treatment goal is to decrease pain; this can be evaluated by using the endpoints outlined by the international consensus. For patients with oligometastatic disease, utilizing the Response Evaluation Criteria in Solid Tumors (RECIST) criteria for asymptomatic lesions (21) is appropriate. In asymptomatic lesions, radiological imaging becomes increasingly important. When there is soft tissue involvement in the bone metastases, as per the RECIST criteria, the response rates should be defined as follows: complete response is the disappearance of all lesions, partial response is a ≥30% decrease in size from baseline, progressive disease is defined as a ≥20% increase in size and stable disease is neither a partial response or progressive disease (21). The RECIST criteria however are not feasible to use to determine response of bone metastases without soft tissue involvement.

In bone metastases after radiation treatment, remineralization may occur. There have been two publications in conventional radiation treatment assessing the remineralization and computed tomography (CT) density changes following treatment (22,23). Koswig and Budach observed that a more fractionated schedule was more effective for the recalcification of bone most likely due to the greater biological efficacy (22). Another study also reported that remineralization of osteolytic lesions occurs after palliative radiotherapy with gradual increases in median percent density change as the dose and fractionation increases (23). There may be increased recalcification in patients undergoing SBRT due to the higher BED of this treatment. Future studies should investigate the use of CT density in order to determine response rates.

In these oligometastatic patients, the endpoints of

local control and prevention of distant metastases would be useful in determining the outcomes of SBRT. Tumor markers such as prostate specific antigen (PSA) in prostate cancer, progression free and overall survival are important secondary endpoints. In patients who have widespread metastases with oligometastatic progression, differing endpoints again need to be defined. These patients may perhaps have one to two new areas that are causing increased symptoms or are increasing in size. If these lesions are symptomatic, the international consensus endpoint definitions should be followed. If they are asymptomatic, the RECIST criteria for response assessment can be used if a soft tissue component is involved. In this population the occurrence of distant metastases becomes a less significant issue as these patients already have metastases elsewhere. As there are differing indications for SBRT, there should also be different ways to assess the treatment outcomes.

The majority of the studies included in this review involved numerous sites of metastases, and some did not differentiate between bone and non-bone metastatic sites. Therefore, pooled toxicity and outcome data may not be completely accurate for the non-spine bone metastatic sites alone. This review suggests that single and multiple fraction SBRT treatment have similar outcomes in terms of local control and severity of side effects, albeit single fraction treatment may have an increased frequency of toxicity. A randomized trial of single *vs.* multiple fraction SBRT treatment is warranted to determine if there is a dose-response phenomenon.

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Footnote

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