Clinical outcomes following stereotactic body radiation therapy (SBRT) for Non-Spinal Bone Metastases: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: There is limited data available on clinical outcomes following stereotactic body radiation therapy (SBRT) for non-spinal bone metastases. We performed a systematic review and meta-analysis to characterize local control (LC), overall survival (OS), pain response rates, and toxicity following SBRT.

Methods: Primary outcomes were 1-year LC, incidences of acute and late Grade 3-5 toxicities, and overall pain response rate at 3 months. The secondary outcome was 1-year OS. The Newcastle-Ottawa scale was employed for assessment of study bias, with a median score of 5⋆ for included studies (range: 4-8). Weighted random effects meta-analyses were conducted to estimate effect sizes.

Results: We identified 528 patients with 597 non-spinal bone lesions across 9 studies, 1 prospective and 8 retrospective observational, treated with SBRT. The estimated 1-year LC rate was 94.6% (95% CI: 87.0-99.0%). The estimated 3-month combined partial and complete pain response rate following SBRT was 87.7% (95% CI: 55.1-100.0%). The estimated combined acute and late Grade 3-5 toxicity rate was 0.5% (95% CI: 0-5.0%) with an estimated pathologic fracture rate of 3.1% (95% CI: 0.2-9.1%). The estimated 1-year OS rate was 71.0% (95% CI: 51.7-87.0%). **Conclusions**: SBRT resulted in excellent LC and palliation of symptoms with minimal related toxicity. Prospective investigations are warranted to further characterizes long-term outcomes with SBRT for patients with non-spinal bone metastases.

Keywords: stereotactic body radiation therapy; bone metastases; non-spine; pain control; local control; fracture risk

INTRODUCTION

Bone metastases constitute one of the most common sites of metastatic disease.[1-3] In adults, the most common primary sites are those of the lung, prostate, and breast with median overall survival (OS) ranging from 4-33 months dependent on primary site (with prostate and breast primaries associated with favorable OS compared to lung primaries).[3] Notably, the incidence of bone metastases among patients with prostate primaries have been gradually increasing over time.[3] Non-spinal bone metastases are a source of significant morbidity and potentially mortality due to local destruction causing focal pain and the risk of pathologic fracture.[1-2] While studies have noted an initial benefit with the use of palliative conventional radiotherapy (RT) for non-spinal bone metastases with roughly 60% of patients having improvement in pain and 20-25% having an initial complete response (CR), pain responses are noted to gradually decline over time.[4] Given improving OS of patients with osseous metastatic disease, the need for more durable pain responses and local control (LC) is imperative.[3]

Recent early investigations have suggested a potential OS benefit to prophylactic RT for asymptomatic, high-risk bone metastases based on size or location (particularly of the hip, sacroiliac joint, or long bone of the body).[5] Dose escalation through stereotactic body radiation therapy (SBRT) has been shown in the context of both spinal and non-spinal bone metastases to result in superior LC and CR rates compared to RT.[6-10, 38] Also, in the context of asymptomatic oligometastatic disease, there is a growing body of evidence that SBRT in combination with standard of care systemic therapy may improve survival vs. systemic therapy alone.[11] However, there is a limited amount of data on LC, OS, overall pain response rate, and toxicities associated with SBRT specifically for

non-spinal bone metastases. As such, we performed a systematic review and meta-analysis to characterize these clinical outcomes and to examine for potential dose-response relationships for both LC and pain response.

MATERIALS AND METHODS

Literature Selection

PubMed, EMBASE, and the Cochrane Library were queried for publications regarding SBRT for non-spinal bone metastases up to July 1st, 2021. The Population, Intervention, Control, Outcomes, Study Design (PICOS) method (**Supplementary Table 1**) was employed to define the population of interest for the analysis.[12-14] The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) selection algorithm (**Supplementary Figure 1)**, PRISMA guidelines (**Supplementary Figure 2**), and the Meta-analysis of Observational Studies in Epidemiology (MOOSE checklist guidelines (**Supplementary Figure 3**) were employed for both search methods and implementation of the analysis.[15-16]

Multiple permutations of the following terms were employed for identification of relevant studies: stereotactic body radiation therapy, stereotactic ablative radiation therapy, SBRT, SABR, non-spinal bone, bone, metastasis, local control, local failure, local recurrence, pain response, partial response, complete response, overall survival, progression-free survival, and toxicity. References from papers initially identified from the query above were also reviewed to aide in identification of additional manuscripts.

Inclusion criteria for this analysis included: (1) patients with non-spinal bone metastases; (2) available information on one or more of the primary outcomes (1-year LC, acute and/or late Grade 3-5 toxicity rates, and pain response at 3 months); (3) patients treated with SBRT (defined as at least 5 Gy/fraction delivered in 1-5 fractions); (4) studies with either $\geq$ 10 patients or $\geq$ 10 lesions with information on one of the primary outcomes. Both prospective and observational studies were eligible for inclusion. Exclusion criteria were: (1) patients not treated with SBRT or without information specific to patients that received SBRT; (2) studies involving

patients included in more than one study; (3) studies involving non-human subjects; (4) studies not published in English; (5) unfinished manuscripts.

Data Extraction

Review and extraction of data from all studies were performed by two independent authors (RS, AV) that included the primary and secondary outcomes in addition to descriptive characteristics of patient and treatment data. A plot digitizer application (https://automeris.io/WebPlotDigitizer/) was utilized to extract data from Kaplan Meier curves for relevant outcomes when available and if not explicitly reported in included manuscripts.[10,17-18, 34] For studies that met inclusion criteria and had missing data relating to primary or secondary outcomes, authors of included manuscripts were contacted. For the study by Cao et al. data specific to non-spinal bone metastases were obtained as the manuscript also reported on outcomes for spinal metastases treated with SBRT; otherwise, study-level data was employed.[17] Of note, McDonald et al. was utilized only for toxicity estimates as an updated series from the same institution by Erler et al. did not report on grading of toxicities.[18, 19] The Newcastle-Ottawa Scale (NOS) was utilized to assess the risk of bias by three independent authors (RS, AV, EJL) for studies meeting inclusion criteria.[20]

Outcome Measures

One-year LC rates, acute and/or late Grade 3-5 toxicities, and 3-month pain response rates (including both partial and complete responders) following SBRT were the primary endpoints for this analysis. Partial response was defined across studies as a decline in pain (but with persistence of some pain) following SBRT and complete response as complete resolution of pain following SBRT. In Nguyen et al., a score of 0-10 was used, with patients with an improvement in pain score noted to be included as having a pain

response. The other 3 papers for pain response (Gerzten et al., Owen et al., and Yu et al.) defined pain response as patients voicing a subjective improvement in pain following SBRT. One-year OS from date of SBRT was defined as the secondary endpoint. Acute toxicities were defined as those occurring within 3 months of SBRT and late toxicities as those occurring at least 3 months after completion of SBRT. The majority of papers utilized Common Terminology Criteria for Adverse Events (CTCAE) for grading of toxicities. LC was generally defined across included manuscripts as having radiographic stable disease or a partial or complete response after SBRT of the primary irradiated lesion, with some studies specifically employing the Response Evaluation Criteria in Solid Tumors (RECIST). Data utilized for the analysis was available upon reasonable request.

Statistical Analysis

The Meta-Analysis for R (metafor) package version 2.0-0 of R Studio Version 1.1.383 (Boston, MA) was employed for statistical analyses.[21-22] The DerSimonian and Laird method were followed to determine variances with proportions for primary and secondary outcomes calculated for each study.[23] Relevant effect sizes for both primary and secondary outcomes were calculated with a weighted random effects model dependent on respective sample sizes and forest plots were generated for both primary and secondary outcomes.[24-26] Heterogeneity for all outcomes were assessed with the I^2 statistic and Cochran Q-Test (τ), with significant heterogeneity being defined as $I^2>50\%$.[27-28] Potential publication bias was assessed with the use of funnel plots, and the t test was based on weighted linear regression, with the null hypothesis being rejected if $p < 0.05$ with a two-sided test.[29] Code utilized for the analysis is available upon reasonable request.

RESULTS

Characteristics of Studies Included for Quantitative Analysis

Our analysis included 528 unique patients with 597 non-spinal bone metastases treated with SBRT across 9 published studies.[10;17-19;30-34] Studies were published from 2003-2021 with patients from the United States, Canada, Italy, Australia, Japan, and the Republic of Korea. One study (Nguyen et al.) was a prospective randomized controlled trial (roughly 13.5% of included lesions and 15% of included patients) while all other studies were retrospective observational studies. A summary of the bias assessment per the NOS for included studies can be found in **Table 1**, with a median score of 5⋆ for included studies (range: 4-8) representing a moderate risk of bias that is inherent to studies examining patients with metastatic disease with limited prognoses and follow-up following treatment with a significant competing risk (ie. death vs. local failure or toxicity) and also only one study (Nguyen et al.) having a control/non-exposed cohort for comparison. **Table 2** shows respective data on both primary and secondary outcomes for each study and other relevant information including patient age, extent of follow-up, primary cancer histologies, primary lesion locations, and dose and fractionation schemes. The median patient age was 64 years (range: 36-91). The most common primaries were prostate (132 patients; 25%), lung (106 patients; 20.1%), renal cell carcinoma (76 patients; 14.4%), and breast (66 patients; 12.5%). For those with information on weight-bearing status, 424/571 lesions (74.3%) were weight-bearing. The most common locations of treated lesions when specified were those involving the pelvis (205/597 lesions; 34.3%), ribs (101/597 lesions; 16.9%), and sacrum (75/597 lesions; 12.6%). The median SBRT dose and fractionation were 35 Gy and 5 fractions, respectively, with a median BED_{10} of 59.5 Gy (range: 26.4-81.6 Gy). Clinical target volume (CTV) and planning target volume (PTV) expansions ranged from 0-10 millimeters and

0-5 mm, respectively. The median planning target volume (PTV) was 80.9cc (range: 2.2-1030.8cc). The median follow-up was 11.7 months (range: 0.25-47.4 months).

Local Control

Across 6 studies, 580 lesions had available information on 1-year LC among 460 patients.[10;17-18;32-34] The estimated pooled 1-year LC rate following SBRT was 94.6% (95% CI: 87.0-99.0%); **Figure 1**). Significant heterogeneity was noted with respect to 1-year LC (I^2 = 80%, τ = 0.11) . **Supplementary Figure 4** shows the corresponding funnel plot with an associated p-value of the weighted linear regression test of 0.78, indicating a lack of publication bias.

Pain Response

Across 4 studies, 107 patients had information on 3-month partial and complete pain response.[10;28;32-34] The estimated 3-month combined partial and complete pain response rate following SBRT was 87.7% (95% CI: 55.1-100.0%; **Figure 2**). Significant heterogeneity was noted with respect to partial and complete pain response rates (I^2 = 77%, τ = 0.20). **Supplementary Figure 5** shows the corresponding funnel plot with an associated p-value of the weighted linear regression test of 0.33, indicating a lack of publication bias.

Toxicity and Pathologic Fracture Risk

Across 6 studies, 256 patients had available information on acute and/or late Grade 3-5 toxicities following SBRT.[10, 19, 30-33] The estimated pooled acute and late Grade 3-5 toxicity rate was 0.5% (95% CI: 0-5.0%; **Figure 3a**). Significant heterogeneity was noted with respect to acute and/or late Grade 3-5 toxicities (I^2 = 80%, τ = 0.14), with notably one study (Nguyen et al.) having an approximately 10% acute and late Grade 3 toxicity rate reported (acute Fatigue), though with other low rates of Grade 3 toxicities. **Supplementary Figure 6** shows the corresponding funnel plot with an associated p-value of the weighted linear regression test of 0.78, indicating a lack of publication bias.

Across 5 studies, 326 lesions had available information on the incidence of pathologic fractures following SBRT.[10, 18, 31-32, 34] The estimated pooled rate of pathologic fractures following SBRT was 3.1% (95% CI: 0.2-9.1%; **Figure 3b**). Significant heterogeneity was noted with respect to incidence of pathologic fracture risk (I^2 = 60%, τ = 0.08). **Supplementary Figure 7** shows the corresponding funnel plot with an associated p-value of the weighted linear regression test of 0.41, indicating a lack of publication bias.

Overall Survival

Across 6 studies, 460 patients had available information on 1-year OS.[10,17-18;32-34] The estimated pooled 1-year OS rate was 71.0% (95% CI: 51.7-87.0%); **Figure 4**). Significant heterogeneity was noted with respect to 1-year OS (I^2 = 93%, τ = 0.18). **Supplementary Figure 8** shows the corresponding funnel plot with an associated p-value of the weighted linear regression test of 0.42, indicating a lack of publication bias.

DISCUSSION

Historically, RT has been offered for symptomatic non-spinal bone metastases as a means of palliation for pain with limited life expectancy with initial response and CR rates of approximately 60 and 25%, respectively, that decline over time.[4] Median OS in patient with osseous metastases has been improving (exceeding two years for a number of primary sites), potentially owing to earlier detection with superior imaging modalities or improved systemic therapies and highlighting the need for durable LC and symptom palliation.[3] Also, interest continues to rise in the use of SBRT for asymptomatic oligometastatic disease given encouraging improvements in OS compared to systemic therapy alone.[11] Our analysis noted favorable outcomes following SBRT for non-spinal bone metastases with an excellent 1-year LC rate of roughly 95% and roughly 88% of patients having improvement in pain with minimal morbidity.

Recent prospective randomized trials have assessed the potential benefit of SBRT over RT for symptomatic bone metastases. The SC.24 trial compared SBRT (24 Gy/2 fractions) to RT (20 Gy/5 fractions) for patients with limited spinal metastatic disease. At time of initial publication, it was found that 3-month CR rates were higher with SBRT (35%) vs. RT (14%).[6] More recently, based on the SC.24 patients enrolled at Sunnybrook Health Science Centre, 1-year local failure rates were significantly lower with SBRT vs. RT (6.1% vs. 28.4%).[7] Further potential improvements in LC with higher prescription doses have been suggested by two recent analyses, one demonstrating 1-year local failure rates of 5.4% vs. 12.5% with SBRT to 28 Gy/2 fractions over 24 Gy/2 fractions and another analysis estimating a roughly 5% increase in 1-year LC for every 10 Gy increase in BED_{10}.[8-9] However, higher rates of vertebral compression fractures have been observed with use of single fraction vs. fractionated SBRT (19.5% vs. 9.6%; p=0.039).[8] It

has been theorized that higher VCF rates may be the reason for no significant difference in pain control following single fraction SBRT (12-16 Gy/1 fraction) vs. RT (8 Gy/1 fraction) noted in RTOG 0631 for treatment of limited spinal metastatic disease.[35]

With respect to symptomatic non-spinal bone metastases, the only prospective evidence currently available on the topic by Nguyen et al. compared SBRT (12-16 Gy/1 fraction, with 12 Gy if ≥4-cm and 16 Gy if < 4 cm) to RT (30 Gy/10 fractions) and observed higher pain response rates at 3-months with SBRT (72%) vs. RT (49%). Of note, durable pain responses were also noted at the 9-month time point (77% with SBRT vs. 46% with RT), suggesting SBRT as a preferred treatment modality over RT for both initial and long-term pain control for symptomatic non-spinal bone metastases.[10] However, larger prospective trials with longer follow-up are indicated to further assess the potential benefit of SBRT over RT with respect to superior pain control as well as LC. Of note, there was a roughly a 10% rate of acute and late Grade 3 toxicities noted in this study (that led to a higher estimate of toxicities noted in our meta-analysis), though these were mainly attributed to acute fatigue (10%) with low incidences of both acute nausea (1.2%) and fracture (1.2%) following SBRT.

In addition to potentially offering improved palliative outcomes, SBRT is an attractive therapeutic option for asymptomatic non-spinal osseous metastatic disease. The SABR-COMET trial examined the benefit of SBRT in combination with standard systemic therapy and noted superior 8-year OS for patients with oligometastatic disease (with roughly 1/3 of patients having osseous metastatic disease) compared to standard-of-care therapy alone (27.2% vs. 13.6%).[11] The largest multi-institutional experience reported on SBRT for non-spinal bone metastases by Cao et al. examined prognostic factors associated with LC and progression/OS. Significantly poorer LC was noted in patients with radioresistant histologies (which were defined as renal cell carcinoma (RCC), non-small cell lung

cancer (NSCLC), sarcoma, thyroid, hepatocellular carcinoma, and colorectal carcinoma primaries). Improved LC was seen among patients with prostate primaries (with poorer outcomes among patients with RCC and NSCLC) primaries and those with larger PTVs). Patients also with prostate primaries and solitary metastasis at the time of SBRT for bone metastases had a significantly lower risk of widespread progression and improved OS following SBRT.[17] These results suggest that primary histology, particularly prostate vs. non-prostate primary, should play a role in patient selection for SBRT as well as choice of SBRT dose/fractionation given significantly higher rates of local failure with RCC (hazard ratio (HR) = 10.8) and NSCLC (HR =6.48) non-spinal bone metastases vs. other histologies (HR = 2.60) with prostate primaries as a reference. [17]

In the context of metastatic prostate cancer with osseous oligometastatic disease, the ORIOLE and STOMP trials demonstrated that SBRT results in longer periods of androgen deprivation therapy (ADT)-free survival and in doing so can afford significant improvements in quality-of-life by deferring associated side effects with ADT.[36-38] SBRT may also be employed to treat oligoprogessive sites of disease to allow patients to remain on first-line (and often times less cytotoxic) systemic therapy. The CURB trial examined the potential benefit of SBRT for oligoprogessive NSCLC or breast cancer and noted a significant PFS benefit following SBRT for patients with NSCLC but not breast primaries.[39] Recent concordant findings for patients with oligometastatic breast cancer were observed in the NRG BR-002 trial that did not note either a PFS or OS benefit with the addition of SBRT to standard systemic therapy.[40] These results highlight that in the absence of symptoms that the primary site is an important factor to consider in patient selection for SBRT, potentially owing to lines of systemic therapy options (being higher in hormone positive breast cancers vs. NSCLC).

Of note, our analysis does have limitations. Due to inclusion of patients with metastatic disease with heterogenous expected OS due to primary tumor type, extent of disease, and performance status, the median follow-up was limited at roughly one year that may lead to underestimates of long-term fracture risk or other late toxicities or overestimates of LC (ie. under-estimates of local failures due to the competing risk of death and lack of radiographic follow-up for assessment of LC). Included experiences were conducted at a variety of institutions with differing treatment guidelines resulting in significant heterogeneity (which was noted with respect to all primary and secondary outcomes) that could not be accounted for (ie. age, primary site, performance status, prescription dose and fractionation, number of metastases, gross tumor volume, and weight-bearing or non-weight-bearing site). We also incorporated both prospective as well as retrospective experiences of SBRT, which also raises the possibility of bias in our effect estimates due to the potential for selection bias in included studies, lack of assessment of a control arm (ie. conventional RT), and potential confounding due to lack of patient-level data that could impact effect estimates that were unable to be controlled for. Also as we did not have patient-level data, we were unable to address heterogeneity that was noted across all outcomes including that introduced based on primary tumor type/histology, site of lesion treated, tumor volume, whether SBRT was utilized in a prior irradiated field, and dose-response. We also were unable to perform meta-regressions to address potential heterogeneity with respect to the impact of dose/fractionation due to lack of patient-level data. Similarly, due to lack of patient-level data, we were unable to address confounding or effect modification. We would have ideally reported on CR and overall pain response separately, but only one study (Nguyen et al.) reported 3-month CR rates after SBRT and thus an effects estimate was unable to be provided. We also had a limited portion of the cohort with information on pain response (107 patients). Additionally, estimates of both long-term overall and

CR rates would ideally have been able to be presented, but once again only Nguyen et al. reported on outcomes past 3-months. A comparison of RT and SBRT also would have been preferred to be presented but there are no studies to our knowledge that have examined the benefit of RT for non-spinal bone metastases without a significant proportion of patients with spinal bone metastases outside of Nguyen et al. As such, we also were unable to comment on potential confounding between SBRT and RT or examine for potential differences between these potential treatment arms as all but one study (Nguyen et al., a prospective RCT) were single arm retrospective experiences examining outcomes following SBRT. Although we did examine the potential impact of dose escalation on LC and toxicity, this was limited by the use of median BEDs for each fractionation schedule.

Conclusion

In the largest meta-analysis to date of patients with non-spinal bone metastases treated with SBRT, excellent LC and pain response exceeding historical outcomes with RT with minimal severe treatment-related toxicity were observed. Additional prospective comparisons of RT and SBRT are warranted. Further studies are indicated to further characterize long-term pain response with SBRT and to characterize both LC and palliative outcomes based on primary histology to better inform the ideal dose/fractionation scheme and maximize the therapeutic ratio for patients with non-spinal bone metastases.

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Figures and Tables

Table 1: Newcastle-Ottawa Scale for assessment of potential bias of included studies

	Selection of cohorts (A)			**Comparability of cohorts (B)**			**Outcome (C)**		
Study	**Representativeness of the exposed cohort (A)[1]**	**Selection of the non exposed cohort (A)[2]**	**Ascertainment of exposure (A)[3]**	**Demonstration that outcome of interest was not present at start of study (A)[4]**	**Comparability of cohorts on the basis of the design or analysis (B)[5]**	**Assessment of outcome (C)[6]**	**Was follow up long enough for outcomes to occur (C)[7]**	**Adequacy of follow up of cohorts (C)[8]**	**Total (9⋆)**
Eiler et al.	*	-	*	*	-	*	*	-	**5⋆**
Gertzen et al.	*	-	*	*	-	*	-	-	**4⋆**
Ito et al.	*	-	*	*	-	*	*	-	**5⋆**
McDonald et al.	*	-	*	*	-	*	*	-	**5⋆**
Nguyen et al.	*	*	*	*	**	*	*	-	**8⋆**
Owen et al.	*	-	*	*	-	*	*	-	**5⋆**
Yu et al.	*	-	*	*	-	*	*	-	**5⋆**
Cao et al.	*	-	*	*	-	*	*	-	**5⋆**
Zeng et al.	*	-	*	*	-	*	*	-	**5⋆**

Criteria for stars awarded:

1. Patients with non-spinal bone metastases treated with SBRT with patient-level data and outcomes of interest
2. Non-exposed cohort defined as standard conventional radiation therapy for comparison to stereotactic body radiation therapy (SBRT), with only Nguyen et al. comparing SBRT to conventional radiation therapy
3. Secure patient-level medical records utilized for data collection
4. Patients not previously treated with SBRT for non-spinal bone metastases or had been treated with conventional radiation therapy previously with SBRT utilized for local failure
5. Nguyen et al. controlled for extent of disease treated with radiation therapy and exclusion of patients with prior radiation, untreated spinal cord compression, and pre-existing pathologic fracture. No other studies compared SBRT to conventional radiation therapy.
6. Assessment of outcomes of interest available in each study (acute and/or late Grade 3+ toxicities, LC, or pathologic fractures) if included in quantitative meta-analysis estimates

7. “Long enough follow-up” was defined as studies with a median follow-up of 6 months with review of ranges or 95% confidence intervals for follow-up as available for assessment of LC and acute and late toxicities in the context of metastatic disease and poor prognosis being a limiting factor in studies examining patients with metastatic disease
8. In the context of metastatic disease and poor prognosis/survival being a limiting factor/competing risk, all studies were deemed at risk of bias of patients being lost to follow-up due to death or other competing risks leading to underestimates of toxicity or local failures following SBRT

Table 2: Studies examining clinical outcomes following SBRT for non-spinal bone metastases

Study	*n* (Patients/ Lesions)	Mean/ Median Age (years) (range)	Mean/ Median Follow-Up (range)	Primary Site	Sites and Characteristics of Treated Lesions	CTV and PTV margin (mm)	Mean/ Median PTV (cc) (range)	Mean/Median Prescription Dose (range)	LC Rate	PFS and OS Rate	Acute and Late Toxicities, Pain Response, and Additional Comments
Erler et al. (2018)	81 (106)	66.4 (36-86)	13 months (0.25-45.6 months)	Prostate: 26 Kidney/ Renal Cell: 17 Lung: 16 Breast: 12 Colon: 3 Melanoma: 2 Endometrium: 1 Gallbladder: 1 Ovary: 1 Thymus: 1	Pelvis:44 Rib: 38 Hip/Femur: 13 Shoulder/ Humerus: 7 Sternum: 4 Sclerotic: 52	CTV: 5mm of contiguous tissue ITV: if 4D-CT PTV: 2-5mm	110.3 (2.2-644.9)	35 Gy/ 5 fractions (42.5%) 30 Gy/5 fractions (30.2%) 20-50 Gy/ 1-5 fractions Median BED_{10}: 52.8 Gy (37.5-100 Gy)	6-month LC: 1-year LC: 95% 18-month LC: 8.3% 2-year LC: 13.3%	1-year OS: 71.9% 2-year OS: 62.5%	9/106 patients (8.5%) with radiologic fracture 5/8 local failures were marginal 51/81 patients had oligometastatic disease as indication for therapy
Gerszten et al. (2003)	15 (15) One patient with schwannoma and two patients with multiple myeloma of total 18 patients	57 (47-72)	6 months	Kidney/ Renal Cell: 3 Multiple Prostate: 2 Unknown Primary: 2 Colon: 2 Cervical: 2 Sarcoma: 2 Breast: 1 Melanoma: 1 Bladder: 1	Sacrum: 15	No CTV or PTV margin	Mean tumor volume: 90 cc (23.6-187.4)	15 Gy/ 1 fraction (12-20 Gy)	**N/A**	**N/A**	All 13 symptomatic patients with improvement in pain following SBRT No acute and or late SBRT-related toxicities

Ito et al. (2017)	17 (17)	64 (48-79)	13 months (2-44 months)	Kidney/ Renal Cell: 29.4% Lung: 23.5% Liver/ hepatocellular: 11.8% Colorectal: 11.8%	Ilium: 14 Pubis: 3 Ischium: 4 (3 lesions crossed over multiple regions)	CTV: 5-10mm PTV: 3mm	N/A	30-35 Gy/ 5 fractions	8 cases with intra-osseous recurrences (1 in-field recurrence and 7 margin/out-of-field recurrences)	N/A	No acute or late Grade 3 or greater toxicities reported No fractures reported
McDonald et al. (2015) (Estimates only utilized for toxicity as Erler, et al, did not report on graded toxicities)	33 (42)	64 (49-85)	7 months (Maximum duration: 1 year)	Kidney/ Renal Cell: 33.3% Lung: 24.2% Prostate: 18.2%	Lytic: 57.1% Sclerotic: 28.6% Mixed: 14.3%	N/A	Median PTV: 39cc (3-806cc)	35 Gy/ 5 fractions	LC of 86% at last follow-up for sclerotic or lytic lesions	**N/A**	No acute or late Grade 3 or greater toxicities reported
Nguyen et al. (2019)	81 (81) Phase 2 non-inferiority trial comparing SBRT to conventional radiotherapy (30 Gy in 10 fractions) All painful bone metastases Primary endpoint:	62.0 (SD: 10.1)	N/A	Lung: 32 Prostate: 14 Breast: 11 Kidney/ Renal Cell: 9 Esophagus: 4 Bladder: 3 Liver: 3 Head and Neck: 2 Pancreas: 1	Abdomen: 3 Thorax: 10 Extremities: 14 Head/Neck: 3 Pelvis: 46 Spine: 3	No CTV margin PTV: 5mm	N/A	12-16 Gy/ 1 fraction 12 Gy if ≥ 4 cm, if < 4 cm 16 Gy	6-month LC: 100% 1-year LC: 100% 2-year LC: 100%	Median OS: 6.7 months (4.6-10.9) 1-year OS: 39.4%	1.2% fracture rate after SBRT 11.1% rate of acute and/or late Grade 3 or greater toxicities (1.2% nausea, 9.9% fatigue) 3-month pain response rate of 72% vs. 49% with SBRT vs. conventional palliative radiotherapy

	Pain response (complete and partial response)			Unknown: 1							Durable 9-month pain response of 77% vs. 46% with SBRT vs. conventional palliative radiotherapy Improved LC with SBRT vs. conventional RT
Owen et al. (2013)	74 (85) 36 patients with pain	60 (18-87)	7.6 months (0.1-41)	Prostate: 23 Sarcoma: 12 Melanoma: 6 Breast: 6 Head and Neck: 5 Kidney/ Renal Cell: 5 Colon: 3 Lung: 3 Thyroid: 2 Cervix: 1 Endometrial: 1 Liver/ Hepatocellular: 1 Endocrine: 1 Testis: 1 Bladder: 1 Unknown primary: 1 Carcinoid: 1 Paraganglioma: 1	Sacrum: 23 Ilium: 18 Rib: 10 Pelvis: 8 Ischium: 7 Acetabulum: 3 Scapula: 3 Sternum: 2 Coccyx: 2 Femur: 2 Chest wall: 1 Clavicle: 1 Mandible: 1 Shoulder: 1 Sphenoid sinus: 1 Trochanter: 1	"Low-dose PTV" (14-18 Gy) CTV: 1 cm of contiguous tissue and soft tissue extension if present PTV: 2mm margin for "High-dose PTV" No CTV or PTV margin	Median: 25 (2.7-1030.8)	Median: 24 Gy/1 fraction 15-50 Gy/ 1-5 fractions Mean BED_{10}: 62.4 Gy	1-year LC: 91.8%	1-year PFS: 31.5% 1-year OS: 81.4%	No acute or late Grade 3 or greater toxicities attributable to SBRT 2 patients with asymptomatic pathologic fractures after SBRT 88% of patients initially with symptoms with improvement in symptoms Radioresistant histologies with poorer median PFS (12.1 vs. 5.5 months) and poorer LC Number of metastases at simulation (< 5 or >5) associated with poorer median

										OS (10.8 months vs. 6.4 months)
Yu et al. (2018)	33 (38) 15 symptomatic lesions	59 (36-75)	10.4 months (2.5-47.4)	Lung: 12 Breast: 8 Liver/ hepatocellular: 3 Kidney/ Renal Cell: 3	Pelvis: 25 Femur: 5 Ribs: 5 Lytic: 25	GTV + 1-2mm ITV if 4D-CT PTV: 1-3mm	N/A	18-50 Gy/ 1-5 fractions Median BED_{10}: 64.8 Gy (43.2-180)	1-year and 2-year LC: 94.2%	Median OS: 20.2 months 1-year OS: 66.0% 2-ytear OS: 44.7% Median PFS: 6.9 months 1-year PFS: 34.1% 2-year PFS: 17.1%	No acute or late Grade 3 or greater toxicities attributable to SBRT 80% of patients with symptomatic lesions with partial or complete response
Cao et al. (2021)	169 (233) Non-spinal bone specific data provided by authors for LC and OS treated with SBRT	66.4 (13.4)	24.2 months	Prostate: 56 Lung: 22 Breast: 13 Kidney/ Renal Cell: 13 Melanoma: 4 Sarcoma: 3 Pancreas: 3 Colorectal: 2 Bladder: 1 Nasopharynx: 1 Cutaneous non-melanoma: 1 Other: 6	Pelvis: 82 Rib: 68 Hip/Lower Limb: 38 Shoulder/Upper Limb: 27 Sternum: 10 Skull: 3 Other: 5 Soft tissue/ paraspinal extension: 37	N/A	Mean PTV: 71.7 (SD: 123.3)	15-50 Gy/10 fractions Most common: 30-35 Gy/ 3-5 fractions (37.3%) 50 Gy/5 fractions (20.2%) Mean BED_{10}: 66.5	1-year LC: 91.5% Each 1 Gy increase increase in BED_{10} associated with 1% decreased risk of local recurrence Prostate primaries	1-year OS: 88.4%	Solitary oligometastatic at time of SBRT: 66.4% Bone-only metastatic disease at time of SBRT: 85.6% Lesions with radioresistant histology with 3x risk of local failure

									associated with improved LC; renal cell and lung associated with poorer LC		Soft tissue extension associated with poorer LC as was extra-osseous extension
Zeng et al. (2019)	22 (37) Sacral specific lesions included for analysis, cervical spine lesions excluded	67.0 (44-88)	19.5 months (1.5-54.7) (entire cohort)	Breast: 9 Kidney/ Renal Cell: 5 Lung: 3 Prostate: 2 Other: 2 Colorectal: 1	All sacral metastases	CTV: extended laterally to include the ala to the sacroiliac joint PTV: 2mm	Median PTV: 168.83 (14.73-499.51)	24 Gy/ 2 fractions 24-30 Gy/ 2-5 fractions	1-year LC: 86.5% 2-year LC: 78.7%	Median OS: 28.5 months 6-month OS: 91% 1-year OS: 72% 2-year OS: 52%	Two cases of vertebral compression fractures following SBRT; one case of lumbosacral plexopathy

Abbreviations: SBRT = stereotactic body radiation therapy; LC = local control; PFS = progression-free survival; OS = overall survival; MPD = median prescription dose; PTV = planning target volume; BED = biologically effective dose; SD = standard deviation; CTV = clinical target volume; GTV = gross tumor volume; ITV = internal target volume

Figure 1: Forest plot examining one-year local control (LC) following SBRT

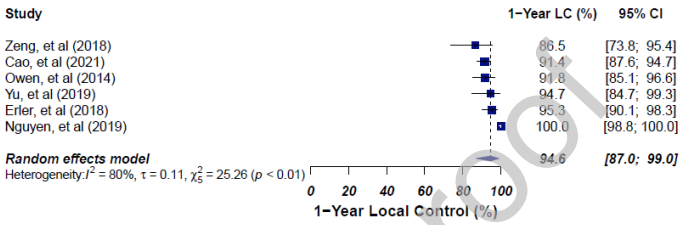

Figure 2: Forest plot examining 3-month overall pain response following SBRT

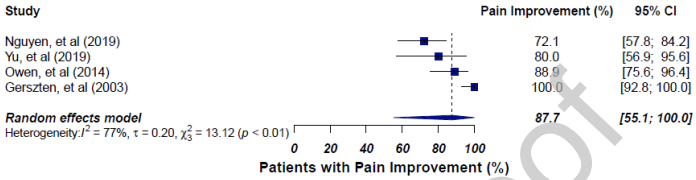

Figure 3: Forest plot examining acute and/or late Grade 3-5 toxicities following SBRT (a) and Forest plot examining incidence of pathologic fractures following SBRT (b)

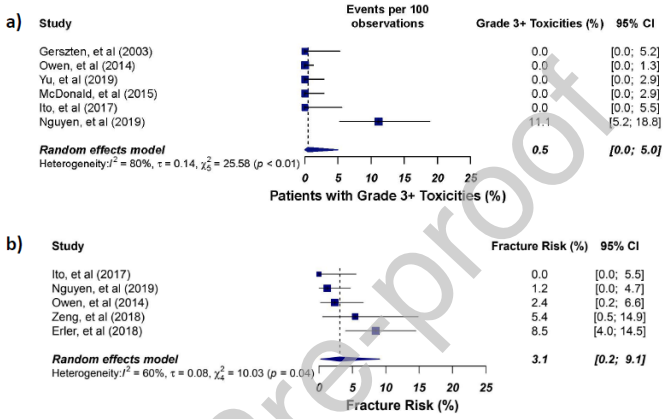

Figure 4: Forest plot examining one-year overall survival (OS) following SBRT