Stereotactic body radiation therapy for management of spinal metastases in patients without spinal cord compression: a phase 1–2 trial

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Summary

Background Spinal stereotactic body radiation therapy (SBRT) is increasingly used to manage spinal metastases, yet the technique's effectiveness in controlling the symptom burden of spinal metastases has not been well described. We investigated the clinical benefit of SBRT for managing spinal metastases and reducing cancer-related symptoms.

Methods 149 patients with mechanically stable, non-cord-compressing spinal metastases (166 lesions) were given SBRT in a phase 1–2 study. Patients received a total dose of 27–30 Gy, typically in three fractions. Symptoms were measured before SBRT and at several time points up to 6 months after treatment, by the Brief Pain Inventory (BPI) and the M D Anderson Symptom Inventory (MDASI). The primary endpoint was frequency and duration of complete pain relief. The study is completed and is registered with ClinicalTrials.gov, number NCT00508443.

Findings Median follow-up was 15·9 months (IQR 9·5–30·3). The number of patients reporting no pain from bone metastases, as measured by the BPI, increased from 39 of 149 (26%) before SBRT to 55 of 102 (54%) 6 months after SBRT (p<0·0001). BPI-reported pain reduction from baseline to 4 weeks after SBRT was clinically meaningful (mean 3·4 [SD 2·9] on the BPI pain-at-its-worst item at baseline, 2·1 [2·4] at 4 weeks; effect size 0·47, p=0·00076). These improvements were accompanied by significant reduction in opioid use during the first 6 months after SBRT (43 [28·9%] of 149 patients with strong opioid use at baseline *vs* 20 [20·0%] of 100 at 6 months; p=0·011). Ordinal regression modelling showed that patients reported significant pain reduction according to the MDASI during the first 6 months after SBRT (p=0·00003), and significant reductions in a composite score of the six MDASI symptom interference with daily life items (p=0·0066). Only a few instances of non-neurological grade 3 toxicities occurred: nausea (one event), vomiting (one), diarrhoea (one), fatigue (one), dysphagia (one), neck pain (one), and diaphoresis (one); pain associated with severe tongue oedema and trismus occurred twice; and non-cardiac chest pain was reported three times. No grade 4 toxicities occurred. Progression-free survival after SBRT was 80·5% (95% CI 72·9–86·1) at 1 year and 72·4% (63·1–79·7) at 2 years.

Interpretation SBRT is an effective primary or salvage treatment for mechanically stable spinal metastasis. Significant reductions in patient-reported pain and other symptoms were evident 6 months after SBRT, along with satisfactory progression-free survival and no late spinal cord toxicities.

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Introduction

Almost 40% of patients with cancer develop spinal metastases during the course of their disease.[1,2] Inadequately treated spinal metastases can lead to pain and neurological complications, including metastatic epidural spinal cord compression. As a result, patients might experience severe symptom burden and diminished health-related quality of life (HRQoL).[3–5]

Palliative radiotherapy effectively controls pain for patients with spinal metastases;[4] however, higher-dose radiotherapy might be needed for durable tumour control and prevention of bony destruction of the spinal column, which results in spinal instability. The spinal cord's sensitivity to radiation generally precludes high radiation doses to the spine or re-irradiation using conventional techniques.[6] Accordingly, new techniques have been developed to optimise radiation dose delivery to bone metastases while sparing the spinal cord. Stereotactic body radiotherapy (SBRT), an emerging technique, uses image guidance to deliver high-dose radiation precisely, creating a steep dose gradient at the interface between spinal cord and tumour. This approach increases the therapeutic window by lowering the risk for spinal cord myelopathy.[6–8] Delivered in high doses and one to five fractions, spinal SBRT is available on various platforms, some of which include CT image-guided stereotaxy. SBRT can be used in combination with or in lieu of surgery and allows patients to avoid possible perioperative risk factors, such as general anaesthesia, bleeding, infection, or hospitalisation.

Patients with late-stage cancer who are considering therapy options are often not informed about the symptom-reduction benefits associated with a particular treatment. In a preliminary report of a prospective phase 1–2 trial of SBRT, we detailed the safety, efficacy, and patterns of failure for SBRT using results from a

subset of patients (n=63) with spinal metastases who were followed for up to 50 months.[2] In the present analysis of the entire patient cohort, we investigated the symptom-reduction benefit of spinal SBRT during the first 6 months post-treatment, and clinical benefit for up to 2 years. We hypothesised that, for patients with mechanically stable spinal metastases, SBRT is a clinically effective therapy for tumour control (evidenced by radiographic depiction of tumour progression) and symptomatic improvement (evidenced by patient-reported outcomes).

Methods

Patients

This phase 1–2 trial was approved by the institutional review board of The University of Texas MD Anderson Cancer Center (Houston, TX, USA). Patients were accrued between Nov 6, 2002, and Jan 20, 2011, and all provided written informed consent before enrolling. Eligibility requirements included a diagnosis of cancer (excluding multiple myeloma), a Karnofsky performance status score of at least 40, and an MRI scan documenting spinal or paraspinal metastasis within 4 weeks of enrolment. Acceptable indications included oligometastatic disease arising from a known primary tumour, failure of previous conventional external beam radiotherapy or surgery, residual tumour after surgery, medical inoperability, and refusal to undergo surgery. A maximum of two distinct non-contiguous spinal metastases were allowed. Paraspinal tumours along the cervical, thoracic, or lumbar spine were included. The tumour could involve the vertebral column, but did not have to, nor did it need to enter the spinal canal. Patients receiving bisphosphonates or hormonal therapy were not excluded. Patients with mechanically unstable spine or epidural spinal cord compression were excluded; however, patients with previously documented spinal cord compression that had been decompressed and stabilised were eligible. Patients were excluded if they had a pacemaker, were unable to undergo MRI, or had received systemic radiotherapy (strontium 89) or cytotoxic chemotherapy within 30 days of enrolment, or spinal external beam radiotherapy within 3 months of enrolment.

Procedures

All patients underwent intensity-modulated, near-simultaneous, CT-guided SBRT (CT-LINAC system [ExaCT targeting system, Varian Medical Systems, Palo Alto, CA, USA] or Trilogy treatment delivery systems with On-Board Imager Cone Beam CT [Varian Medical Systems]) using a BlueBAG BodyFIX Total Body immobilisation system (Elekta, Stockholm, Sweden), consisting of a whole-body vacuum cushion, carbon fibre base plate, and plastic fixation sheet. Stereotactic localisation and target-positioning frames were used (Integra-Radionics, Burlington, MA, USA). Patients received a total dose of 27–30 Gy, typically delivered in three fractions given every other day, with 10-Gy radiation volume received by the spinal cord limited to 0·01 cm³. Gross target volume encompassed the lesion as visualised on the pretreatment CT scan. The clinical target volume encompassed the gross target volume and surrounding vertebral body (including superior and inferior endplates and any existing paraspinal component), along with all additional spinal structures deemed to be at risk for recurrence, such as the pedicle, lamina, and posterior elements. In patients with postsurgical metallic artifacts near the area of interest, intrathecal contrast injection with iohexol (GE Healthcare Canada Inc, Mississauga, ON, Canada) was done 30–60 min before CT image acquisition to assist with accurate spinal cord delineation. Spinal MRI was done within 4 weeks of study enrolment and every 3 months thereafter. Baseline MRI was fused in many instances to assist in target delineation.

The primary endpoint was frequency and duration of complete pain relief. We measured pain at metastatic sites treated with SBRT via the Brief Pain Inventory (BPI).[9] The BPI assesses pain at present and pain at its worst, least, and on average in the past 24 h, on a 0–10 scale. At the same time, we measured general symptom burden via the M D Anderson Symptom Inventory (MDASI).[10] The MDASI assesses 13 common cancer-related symptoms, including pain, and six symptom-interference items, each rated over a 24-h recall period on a 0–10 scale. A composite interference score was calculated as the mean of all six MDASI interference items for all patients. For the MDASI assessment, patients were instructed to rate their pain, but not their specific pain at the spine site. The BPI and MDASI are well validated in patients with various types of cancer.[9,10] The Medical Outcomes Study 12-Item Short-Form Health Survey (SF-12) was administered as an HRQoL measure.[11]

Patient-reported symptoms were assessed in the clinic via the BPI, MDASI, and SF-12 pre-SBRT (baseline) and at 3 months and 6 months post-SBRT; assessments at 2 weeks, 4 weeks, and 2 months were completed by the patient at home and returned by post, with a reminder call from a study nurse.

MRI scans of the region treated were done at 3, 6, 9, 12, 18, and 24 months post-SBRT and then every 6 months thereafter, as standard care. Lesions were classified as progressive (larger than at the previous assessment), stable (unchanged), or smaller by radiologists who were CNS specialists. These assessments were not time blinded. The radiologists' reports were subsequently discussed by a multidisciplinary spine tumour board.

History, neurological exam results, and McCormick functional classification[12] were obtained at baseline and at each follow-up visit (during the same timepoints as patient-reported outcomes assessments). Clinical data including age, sex, tumour volume, and diagnosis were obtained at enrolment. Use of pain medication, Karnofsky performance status, and metastatic tumour evaluation were also recorded at baseline and after SBRT. Opioid

use was documented as morphine equivalents. Toxicity was graded by the patient's treatment team according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 2.0.[13]

Statistical analysis

Descriptive statistics—mean, median, SD, and proportions—are used to describe patient and clinical characteristics. The patient, not the tumour, was the unit of analysis. For univariate testing, p values are two-tailed and considered significant if less than 0·05. To account for multiple comparisons in the symptom and HRQoL outcomes, which required eight modellings, we adjusted the individual type I error to be 0·05/8=0·00625 to maintain a conservative family-wise error rate of 0·05.

Using pain cutpoints established by Serlin and colleagues,[14] we categorised ratings of the BPI's pain-at-its-worst item as no pain (0), mild pain (1–4), moderate pain (5–6), and severe pain (7–10). We tracked proportions of patients in each of these categories over time during the study. Concordance between BPI and MDASI pain-at-its-worst ratings, both scored on a 0–10 scale in the past 24 h, was examined using paired *t* tests. Effect sizes were calculated to estimate the magnitude of change in BPI and MDASI ratings (composite score for all patients) between baseline and 4 weeks post-treatment.[15,16] For patient-reported outcomes measures, effect sizes are clinically meaningful at roughly one-half SD or higher, the level often used in distribution-based methods of determining meaningful differences.[17] Lowess curves,[18] which represent a smoothed estimate of average MDASI symptom severity and interference as a function of time, were constructed from baseline to 6 months post-SBRT.

Ordinal regression models[19] and generalised linear mixed models were fitted to examine symptom development for the five most-severe MDASI symptoms and the symptom-interference component score from baseline to 6 months post-SBRT. Individual symptom scores were treated as ordinal responses. Independent variables included weeks from start of therapy, age, sex, tumour volume of spinal metastasis at baseline, type of primary cancer, disease progression status 6 months after SBRT based on radiographic (spinal MRI) results, opioid use, and Karnofsky performance status at baseline.

Progression-free survival (PFS) and overall survival curves from date of enrolment were generated using the Kaplan-Meier method. Patient survival information was obtained from a retrospective review of medical records. Statistical analysis was done using SPSS version 17.0 and SAS version 9.2. This study is registered with ClinicalTrials.gov, number NCT00508443.

Role of the funding source

Neither the National Cancer Institute nor the National Institutes of Health had any role in the study design, data collection, analysis, interpretation, or preparation of the report. The authors were responsible for the design of the trial. XSW, IG, PL, PKA, and ELC had access to the raw data. The corresponding author had final responsibility for the decision to submit for publication.

Results

Table 1 shows patient demographic and clinical characteristics. Of the 184 patients approached and consented, 35 did not provide symptom data and thus were unevaluable. The remaining 149 patients, with 166 spinal metastases at cervical, thoracic, or lumbar vertebral levels, were included in the analysis. 17 of 149 patients had two distinct spinal metastasis sites treated in the same session, and 34 of 149 (23%) were receiving bisphosphonates at enrolment. Spinal MRIs were done for 142 of 149 patients (95%) at the 6-month follow-up.

	Baseline characteristics (N=149)
Number of lesions	166
Age in years	
Mean (SD)	56·4 (12·5)
Median (range)	58·0 (20·0–88·0)
Sex	
Male	77 (52%)
Female	72 (48%)
Karnofsky performance status	
100	8 (5%)
80–90	108 (72%)
70	30 (20%)
<70	3 (2%)
Previous therapy to spinal site	
Radiotherapy alone	40 (27%)
Surgery alone	22 (15%)
Radiotherapy and surgery	39 (26%)
None	48 (32%)
Primary histology	
Breast cancer	15 (10%)
Colon cancer	6 (4%)
Non-small-cell lung cancer	15 (10%)
Melanoma	4 (3%)
Thyroid cancer	14 (9%)
Renal cancer	47 (32%)
Sarcoma	17 (11%)
Other	28 (19%)
Unknown	3 (2%)
SBRT site	
Cervical	28 (19%)
Thoracic	66 (44%)
Lumbar	51 (34%)
Sacral	4 (3%)
Metastatic tumour volume in cm^3, median (range)	38·2 (1·6–357·9)

Data are number of patients (%) unless otherwise stated. SBRT=stereotactic body radiotherapy.

Table 1: **Patient demographic and clinical characteristics**

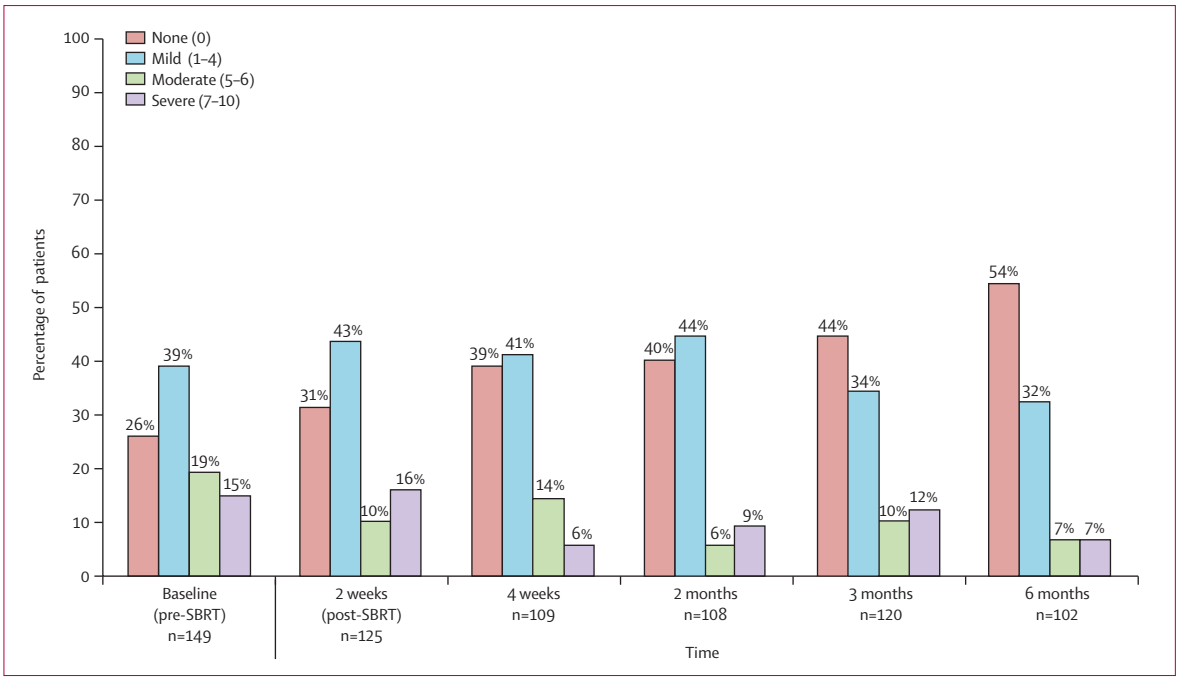

Figure 1: **Percentage of patients with no, mild, moderate, or severe pain on the BPI 0–10 scale, before and after SBRT**
BPI=Brief Pain Inventory. SBRT=stereotactic body radiotherapy.

At the time of analysis, 40 of 149 patients (27%) were still alive, with a median follow-up of 15·9 months (range 1·0–91·6; IQR 9·5–30·3) and mean 20·9 months (SD 17·1). Median overall survival was 23 months (95% CI 18·6–27·2) post-SBRT, with 1-year and 2-year actuarial survival of 68·5% (60·1–75·4) and 46·4% (37·8–54·7), respectively. Tumour progression was seen in 41 of 149 patients (28%) and occurred at a median of 13 months (range <1–101), based on MRI scans. Actuarial PFS based on MRI scans at 6 months, 1 year, and 2 years post-SBRT was 86·1% (95% CI 79·4–90·7), 80·5% (72·9–86·1), and 72·4% (63·1–79·7), respectively.

Figure 1 shows the proportion of patients with no pain to severe spinal pain, according to the BPI's pain-at-its-worst ratings, at baseline and post-SBRT assessments. We noted significant reductions in the severity of patient-reported pain between baseline and 4 weeks post-treatment (mean of 3·4 [SD 2·9] at baseline, 2·1 [2·4] at 4 weeks on the BPI's pain-at-its-worst item [0–10 scale]; effect size 0·47, p=0·00076), and between baseline and 6 months post-SBRT (mean 3·4 [SD 2·9] at baseline, 1·7 [2·4] at 6 months; effect size 0·64, p<0·0001). The proportion of patients reporting no spine pain on the BPI increased significantly between baseline and 4 weeks post-SBRT, from 39 of 149 (26%) to 43 of 109 (39%) (p=0·038). This improvement continued throughout the study, with 53 of 120 (44%) reporting no pain at 3 months (p=0·004) and 55 of 102 (54%) reporting no pain at 6 months (p<0·0001). Further, a significant decrease in the percentage of patients with moderate-to-severe BPI spine pain (rated ≥5 on the 0–10 scale) was noted from baseline to 4 weeks (p=0·003), 2 months (p<0·0001), and 6 months (p=0·002) post-SBRT.

We noted clinically meaningful reductions in mean MDASI pain ratings between baseline and 4 weeks post-treatment (from 3·4 [SD 3·1] at baseline to 2·1 [2·6] at 4 weeks on the MDASI's 0–10 scale; effect size 0·47). Differences in mean pain severity ratings between the BPI (metastatic bone pain) and MDASI (general pain) were noted only for the 6-month assessment (p=0·022; table 2). We noted significant reduction in opioid use from baseline to 3 months (p=0·021) and baseline to 6 months (p=0·011) post-SBRT (table 2).

During the 6 months of observation, the five most severe MDASI symptoms were fatigue, pain, disturbed sleep,

	BPI pain-at-its-worst score (0–10)*		MDASI pain score (0–10)*		Strong opioid use†
	n	Mean score (SD)	n	Mean score (SD)	n (%)
Baseline	148	3·4 (2·9)	148	3·4 (3·1)	43 of 149 (28·9%)
2 weeks	124	2·9 (2·8)	124	2·9 (3·0)	34 of 121 (28·1%)
4 weeks	109	2·1 (2·4)	109	2·1 (2·6)	26 of 110 (23·6%)
2 months	108	2·3 (2·6)	108	2·3 (2·7)	23 of 105 (21·9%)
3 months	120	2·1 (2·7)	120	2·1 (2·8)	31 of 121 (25·6%)
6 months	102	1·7 (2·4)	102	1·9 (2·5)	20 of 100 (20·0%)

SBRT=stereotactic body radiotherapy. BPI=Brief Pain Inventory. MDASI=M D Anderson Symptom Inventory.
*No significant differences between BPI pain-at-its-worst mean scores and MDASI pain item mean scores (paired *t* tests) were found at any timepoint other than the 6-month assessment (p=0·022). †The number of patients for whom analgesia data were available differed slightly from the number of patients who provided symptom data.

Table 2: **Pain severity scores and opioid use over time, before and after SBRT**

drowsiness, and distress. Figure 2 shows the smoothed estimate of average severity of each symptom over time using Lowess curves, with the week of SBRT completion shown as week 0. The Lowess curves in figure 2 show that symptom interference lessened over time.

Table 3 gives p values from ordinal regression modelling of MDASI symptom severity and interference, and SF-12 physical and mental health component scores, adjusted for independent variables. Patients reported significant pain reduction (p=0·00003) 6 months after SBRT, and significant reduction in disturbed sleep, drowsiness, sadness (all p<0·0001), fatigue, distress, lack of appetite, nausea, and difficulty remembering (all p<0·05). We observed no significant change over time for physical or mental health component scores. Ordinal regression modelling showed that a composite score of all six interference items decreased significantly at each successive assessment during the 6 months after SBRT (p=0·0066).

Patients whose lesions were categorised as progressive at the 6-month follow-up examination (19 of 149; 13%) reported significantly more-severe MDASI pain (p<0·0001), fatigue (p=0·01), and drowsiness (p=0·00008) than did patients with stable or smaller lesions. Patients who received opioids during the 6 months after SBRT reported more severe MDASI pain, fatigue (both p<0·0001), disturbed sleep, distress, and drowsiness (all p<0·001) than did patients not using opioids.

Mild toxic effects were documented during the study, including grade 1 and 2 transient numbness and tingling, nausea, and vomiting. Grade 3 toxicities were nausea (one event), vomiting (one event), diarrhoea (one event), fatigue (one event), non-cardiac chest pain (three events), dysphagia (one event), neck pain (one event), diaphoresis (one event), and pain associated with severe tongue oedema and trismus (two events). No grade 4 toxicities were reported, and we observed no radiation-related spinal cord myelopathy during the study.

Discussion

This study incorporated validated single-symptom (BPI) and multisymptom (MDASI) assessments to measure patient-reported outcomes for pain and other symptoms in patients with metastatic spine lesions who received SBRT. In accordance with our previous report documenting the safety, effectiveness, and patterns of failure of spinal SBRT,[2] here we showed significant reductions in the severity of pain and consistent reductions in other patient-reported symptoms and symptom interference 6 months after spinal SBRT, along with satisfactory PFS and no late spinal cord toxicities.

In a retrospective review, Sheehan and colleagues[20] found that pain was the most common presenting

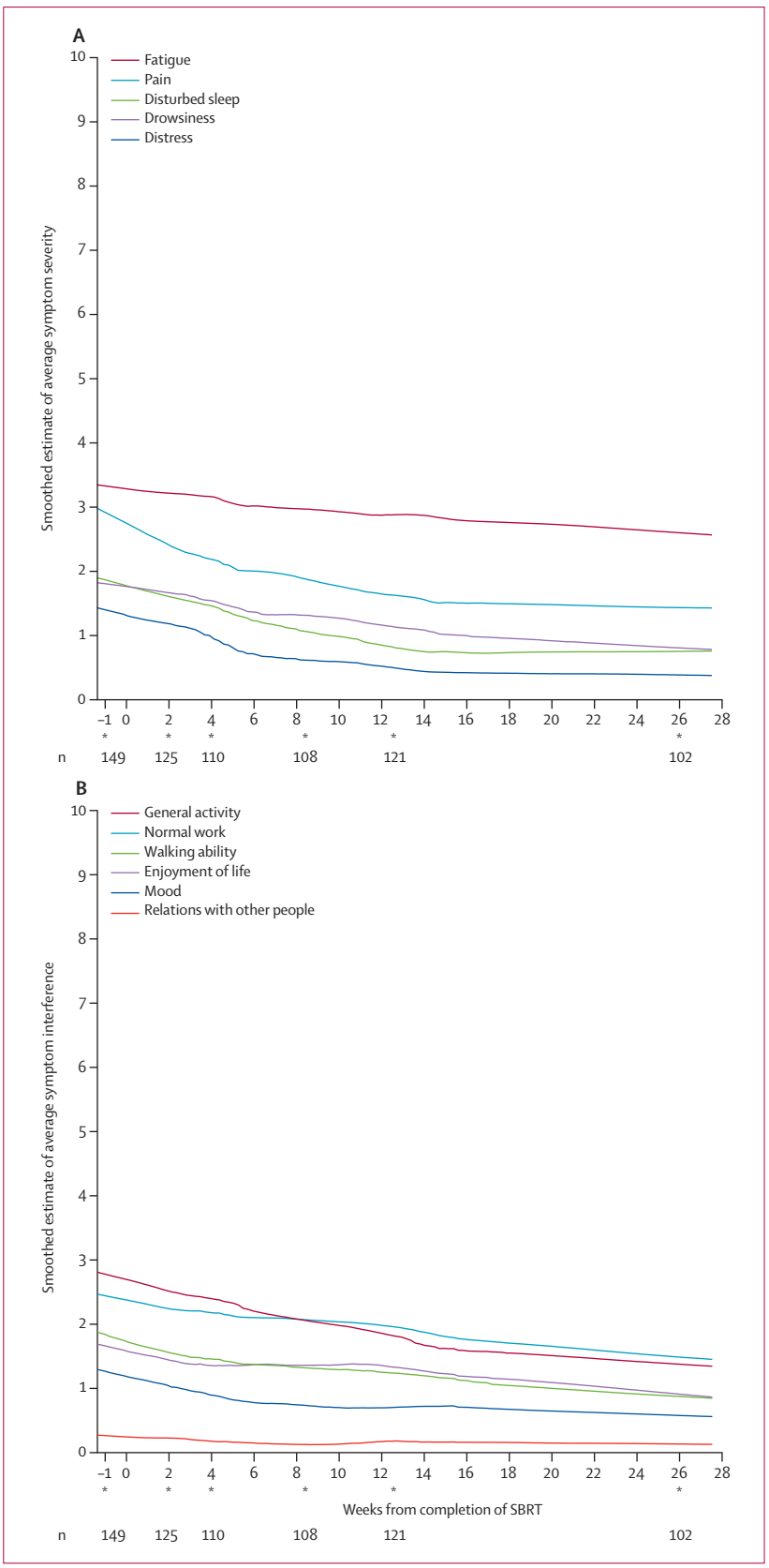

Figure 2: **Lowess curves of symptom severity (A) and symptom interference (B) on the MDASI 0–10 scale, before and after SBRT**
MDASI=M D Anderson Symptom Inventory. SBRT=stereotactic body radiotherapy. n=number of patients. *Assessment timepoint.

	MDASI symptom models*					MDASI symptom interference model (composite interference score)	HRQoL models (SF-12 component scores)	
	Pain	Fatigue	Distress	Disturbed sleep	Drowsiness		Physical	Mental health
Weeks of treatment	0·00003†	0·03651	0·00493†	0·00008†	0·00005†	0·0066	0·28	0·47
Age	0·59	0·85	0·36	0·06	0·28	0·47	0·16	0·98
Sex (female *vs* male)	0·00214	0·00298	0·00461	0·02484	0·03328	0·07	0·12	0·0347
Metastatic tumour volume	0·78	0·71	0·30	0·93	0·91	0·40	0·97	0·98
Diagnosis (lung *vs* renal)	0·97	0·20	0·15	0·56	0·25	0·16	0·25	0·58
Progression status at 6 months (failure *vs* no failure)	<0·0001†	0·0104	0·05	0·09	0·00008†	0·0022†	0·0001†	0·65
Opioid use over 6 months	<0·0001†	<0·0001†	0·0004†	0·00364†	0·0004†	0·0001†	<0·0001†	0·06
Baseline Karnofsky performance status	0·72	0·08	0·0073	0·67	0·29	0·0003†	0·0002†	0·033

Significance testing was done by mixed-effect regression analysis. Results shown are p values. SBRT=stereotactic body radiotherapy. MDASI=M D Anderson Symptom Inventory. HRQoL=health-related quality of life. *Ordinal regression modelling was done for each of the five most severe MDASI symptoms to assess development over time. †Significant at p<0·00625, after adjusting for multiple comparisons (eight models).

Table 3: **Significance of reduced score for patient-reported outcomes during the first 6 months after SBRT, adjusted for independent variables**

Panel: Research in context

Systematic review

In recent years, spinal stereotactic body radiation therapy (SBRT) has become an increasingly established technique for the management of spinal metastases; however, when this phase 1–2 trial was designed and activated in 2002, spinal SBRT literature was in its infancy, consisting of preliminary technical reports with sparse outcomes data. Accordingly, initial analyses of patients treated on this protocol focused on feasibility, safety, and tumour-control outcomes. Over the past decade, data from this patient cohort and from other studies[8] have contributed to the continued emergence of spinal SBRT for management of spinal metastases. However, there remains a relative paucity of literature describing the effectiveness of spinal SBRT in controlling the symptom burden of spinal metastases. Drawing on previous experience in symptom research,[25,26] we applied well-established symptom-assessment methods to analyse outcomes data acquired from our prospective cohort.

Interpretation

The results of this study show that SBRT is an effective primary or salvage treatment for mechanically stable spinal metastasis. Multiple symptoms were assessed simultaneously and longitudinally for each patient and compared with baseline, with each patient serving as his or her own control. Significant reduction in patient-reported pain and other symptoms was evident 6 months after SBRT, along with satisfactory progression-free survival and no late spinal cord toxicities. For patients with evidence of tumour progression 6 months after SBRT, such progression was significantly associated with more severe pain, as expected, suggesting a true (non-placebo) palliative effect for SBRT. This trial provides prospective data that support the careful use of spinal SBRT in selected patients, since SBRT safely and reliably halts the progression of disease while reducing patient symptoms and improving functioning in daily life, as measured by validated methods. This study also highlights the importance of integrating patient-reported symptom assessments with clinical outcome evaluations to fully demonstrate the benefit of SBRT in patients with metastatic spinal disease. The ongoing Radiation Therapy Oncology Group 0631 randomised trial is investigating this question.

symptom from spinal metastases. Our results show that SBRT is an effective treatment for metastatic spinal pain in patients with late-stage cancer. Between baseline and 4 weeks post-SBRT, we observed medium, but clinically meaningful, effect sizes for pain reduction as reported on both the BPI pain-at-its-worst and MDASI pain items, along with significant increase in the number of patients reporting complete pain relief as early as 4 weeks post-SBRT. Significant improvement in BPI pain ratings and effect size relative to pre-SBRT scores was even larger 6 months after treatment (effect size 0·64, p<0·0001), when only two patients had tumour progression and high pain severity and were receiving opioid therapy. The effectiveness of SBRT for tumour and pain control was further evidenced by a reduction over time in the use of strong opioids, a standard of care for managing severe pain.

Patient-reported data from the BPI and the MDASI, which use the same 0–10 pain-severity rating scale and 24-h recall period (table 2), did not differ significantly in this cohort of patients with advanced cancer. This result suggests that researchers can use either scale in clinical studies when pain at its worst is the outcome of interest, and the same rating is expected with either scale. However, the MDASI measures a broader array of critical symptoms and has modules tailored to specific treatments and types of cancer.

The present study shows that pain reduction and functional improvement can also be reflected in the reduction of associated symptoms, such as fatigue, distress, and disturbed sleep.[21] Using a sensitive multiple-symptom assessment method (the MDASI) with a highly selective but comprehensive set of symptom items,[22,23] we not only prospectively identified pain and other major symptoms in a cohort of patients who received spinal SBRT, but also showed how multiple symptoms improved over time after treatment. Frequent measurement allowed us to capture the quick response to SBRT and its durability over time. Significant reductions in the severity of several

symptoms in addition to metastatic pain suggest that spinal SBRT produces minimum symptom burden and toxic effects for patients with late-stage cancer. Renal-cell carcinomas that metastasise to the spine are among the most difficult to control and therefore are most often referred for spinal SBRT. We did not find a significant difference between renal-cell carcinoma and other primary histologies on patient-reported severity of any MDASI symptom (data not shown).

Fatigue was consistently the most severe symptom over time, possibly as a result of advanced disease and continuous use of opioids. Although fatigue improved over the 6 months post-SBRT ($p=0\cdot037$), the physical and mental health component scores of the SF-12 remained more or less constant in follow-up. These results are consistent with those of Degen and colleagues,[24] who reported significant pain reduction 4 weeks after spinal SBRT that was durable to 1 year, but no significant change in physical or mental well-being data from the SF-12. In the present study, lower baseline Karnofsky performance status was significantly associated with higher total symptom interference on the MDASI and worsening physical well-being as measured by the SF-12 (table 3).

The efficacy and safety of SBRT we report in this study are supported by the structured schedule with defined assessment intervals and follow-up serial spinal MRIs, which permitted close assessment of the procedure. MRI scans, obtained for 95% of study participants, showed a PFS of over 80% 1 year after SBRT. This result is similar to results reported by other investigators[8] and shows that spinal SBRT is an efficacious primary or salvage treatment of metastatic tumours of the spine. In this study, SBRT did not lead to any radiation-related spinal cord myelopathy; the numbness reported by some patients was probably caused by pre-SBRT chemotherapy. Only a few instances of non-neurological grade 3 toxicities (nausea, vomiting, diarrhoea, and fatigue) and no grade 4 toxicities occurred.

Patient compliance and missing data can be an issue in prospective studies. We observed a random missing pattern in the data. Ordinal regression modelling, which accounts for repeated measurements over time, allowed us to maximise use of the available data in a longitudinal fashion. No missing data imputation was performed in this modelling step. In the present study, 24 patients did not return their paper-and-pencil symptom assessment results by post at the 2-week assessment timepoint; nonetheless, most of these patients contributed symptom data at subsequent timepoints. One possibility for reducing the rate of random missing patient-reported outcomes is to have study staff conduct symptom surveys over the phone.

One limitation of this study is the absence of a control group against which to measure the effect of SBRT on symptom development. However, it is well accepted that SBRT has a quantifiable clinical effect on tumour growth with an accompanying reduction in pain at the radiation site, as shown in our previous report in a subset of this cohort of patients with stage IV cancer.[2] One strength of the present study is that multiple symptoms were assessed simultaneously and longitudinally for each patient and compared with baseline, with each patient serving as his or her own control. Tumour progression 6 months after SBRT was significantly associated with more-severe pain, as expected, suggesting a true (non-placebo) palliative effect. An even higher level of evidence could be provided by a randomised trial comparing stereotactic radiation with conventional radiation. Such a trial is currently ongoing with the Radiation Therapy Oncology Group 06-31 study.

In reviewing patient records, we found that 16 patients were positive for adrenal metastasis and 12 were positive for brain metastasis at enrolment. For this reason, although the protocol designated data collection up to 24 months, we did not use patient-reported outcomes data beyond 6 months, after which the symptom-reduction benefit from SBRT could be confounded by increased pain from rapid disease progression at or near the end of life in this cohort with very advanced cancer. Further study of this data is warranted to determine the entire profile of pain and other symptoms, from beyond 6 months post-SBRT to near the time of death.

The role of SBRT in treating mechanically stable spinal metastases without spinal cord compression is continuing to develop in an era in which new technologies and treatments are being highly scrutinised. Most patients with spinal metastases can still benefit from conventional palliative radiation therapy. Surgery or vertebral augmentation with cement should be considered for stabilising patients with mechanically unstable spines before proceeding to radiation therapy. Nonetheless, the current study provides additional data that support the clinical benefit of SBRT for carefully selected patients and suggests that SBRT reliably halts the progression of disease, reduces patient symptoms, and leads to improved functioning in daily life—thus demonstrating both symptomatic and clinical benefit (panel). This study also highlights the importance of integrating patient-reported symptom assessments with clinical outcome evaluations to fully demonstrate the benefit of SBRT in patients with metastatic spinal disease.

Contributors

XSW, LDR, ASS, JNY, SSA, CSC, and ELC conceived and designed the study. XSW and IG did the literature search. IG, PKA, HJS, and ELC collected the data. XSW, LDR, IG, PL, PKA, US, CSC, PDB, HJS, DCW, and ELC did the data analysis and interpretation. XSW, US, CSC, LDR, PDB, HJS, and ELC wrote the manuscript. CSC provided funding support.

Conflicts of interest

LDR has received teaching honoraria from Medtronic and Stryker. All other authors declare that they have no conflicts of interest.

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