Stereotactic body radiotherapy versus conventional external beam radiotherapy in patients with painful spinal metastases: an open-label, multicentre, randomised, controlled, phase 2/3 trial

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Summary

Background Conventional external beam radiotherapy is the standard palliative treatment for spinal metastases; however, complete response rates for pain are as low as 10–20%. Stereotactic body radiotherapy delivers high-dose, ablative radiotherapy. We aimed to compare complete response rates for pain after stereotactic body radiotherapy or conventional external beam radiotherapy in patients with painful spinal metastasis.

Methods This open-label, multicentre, randomised, controlled, phase 2/3 trial was done at 13 hospitals in Canada and five hospitals in Australia. Patients were eligible if they were aged 18 years and older, and had painful (defined as ≥2 points with the Brief Pain Inventory) MRI-confirmed spinal metastasis, no more than three consecutive vertebral segments to be included in the treatment volume, an Eastern Cooperative Oncology Group performance status of 0–2, a Spinal Instability Neoplasia Score of less than 12, and no neurologically symptomatic spinal cord or cauda equina compression. Patients were randomly assigned (1:1) with a web-based, computer-generated allocation sequence to receive either stereotactic body radiotherapy at a dose of 24 Gy in two daily fractions or conventional external beam radiotherapy at a dose of 20 Gy in five daily fractions using standard techniques. Treatment assignment was done centrally by use of a minimisation method to achieve balance for the stratification factors of radiosensitivity, the presence or absence of mass-type tumour (extraosseous or epidural disease extension, or both) on imaging, and centre. The primary endpoint was the proportion of patients with a complete response for pain at 3 months after radiotherapy. The primary endpoint was analysed in the intention-to-treat population and all safety and quality assurance analyses were done in the as-treated population (ie, all patients who received at least one fraction of radiotherapy). The trial is registered with ClinicalTrials.gov, NCT02512965.

Findings Between Jan 4, 2016, and Sept 27, 2019, 229 patients were enrolled and randomly assigned to receive conventional external beam radiotherapy (n=115) or stereotactic body radiotherapy (n=114). All 229 patients were included in the intention-to-treat analysis. The median follow-up was 6·7 months (IQR 6·3–6·9). At 3 months, 40 (35%) of 114 patients in the stereotactic body radiotherapy group, and 16 (14%) of 115 patients in the conventional external beam radiotherapy group had a complete response for pain (risk ratio 1·33, 95% CI 1·14–1·55; p=0·0002). This significant difference was maintained in multivariable-adjusted analyses (odds ratio 3·47, 95% CI 1·77–6·80; p=0·0003). The most common grade 3–4 adverse event was grade 3 pain (five [4%] of 115 patients in the conventional external beam radiotherapy group *vs* five (5%) of 110 patients in the stereotactic body radiotherapy group). No treatment-related deaths were observed.

Interpretation Stereotactic body radiotherapy at a dose of 24 Gy in two daily fractions was superior to conventional external beam radiotherapy at a dose of 20 Gy in five daily fractions in improving the complete response rate for pain. These results suggest that use of conformal, image-guided, stereotactically dose-escalated radiotherapy is appropriate in the palliative setting for symptom control for selected patients with painful spinal metastases, and an increased awareness of the need for specialised and multidisciplinary involvement in the delivery of end-of-life care is needed.

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Introduction

Spinal metastases are a frequent manifestation of systemic cancer that occurs in 5–30% of patients. The spinal column accounts for 70% of all bone metastases and is the third most common site of metastases. Conventional, palliative, short-course external beam radiotherapy is considered the first-line standard-of-care treatment for these patients;[1] however, complete response rates for pain are low, typically ranging from 10% to 20%.[2–4] Radiation dose-escalation within conventional

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*Trial investigators are listed in the appendix (pp 1–2)

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See Online for appendix

Research in context

Evidence before this study

No formal systematic review was done when planning this trial, as the available evidence was scarce; no data from randomised trials specific to spinal stereotactic body radiotherapy were available. Before this trial, the field of spine stereotactic body radiotherapy was considered as emerging, with mainly retrospective evidence and few prospective trials available to use as a basis for our assumptions of response. Optimal spinal stereotactic body radiotherapy dosing was also unknown, and preliminary technical and tolerability data supporting the delivery of 24 Gy in two daily fractions led to the selection of this dosing strategy for the experimental group in this trial. During the conduct of this trial, phase 2 randomised evidence was published and was used to inform the final sample size of this trial.

Added value of this study

To our knowledge, this is the first published randomised, controlled, phase 2/3 trial to provide evidence that stereotactic body radiotherapy at 24 Gy in two fractions was superior to conventional external beam radiotherapy at 20 Gy in five fractions in achieving complete pain relief at the treatment site. Stereotactic body radiotherapy significantly improved the complete response rate for pain compared with conventional external beam radiotherapy, and had a durable effect at the 6-month and final follow-up assessment.

Implications of all the available evidence

For patients with painful MRI-confirmed spinal metastases, in accordance with the eligibility criteria in this trial, spinal stereotactic body radiotherapy is to be considered a standard-of-care treatment option. In patients with a life expectancy of less than 3 months and in those with other sites of metastatic disease, including non-spine bone metastases, use of standard conventional external beam radiotherapy (as applicable) should still be considered effective for symptom response.

external beam radiotherapy practices has not improved these rates.[2–4]

Over the past decade, radiation oncology has undergone a technical transformation, allowing for stereotactic body radiotherapy to routinely deliver high-dose per fraction radiation precisely within the body in only a few treatment fractions.[5] Spinal stereotactic body radiotherapy was considered a high-risk, high-reward treatment option, given the potential for radiation-induced spinal cord injury and vertebral compression fractures.[6–8]

Before the current trial, the therapeutic benefit of stereotactic body radiotherapy in controlling symptoms associated with painful spinal bone metastases had yet to be shown in a randomised, controlled, phase 3 trial.[9] We aimed to assess whether spinal stereotactic body radiotherapy could improve the complete response rate for pain in a specific site of painful spinal metastasis when compared with conventional external beam radiotherapy.

Methods

Study design and participants

This open-label, multicentre, randomised, controlled, phase 2/3 trial was done at 13 hospitals in Canada and five hospitals in Australia (appendix p 3). Eligible patients were aged 18 years or older with painful (defined as a worst pain score of ≥2 of 10, according to the Brief Pain Inventory [BPI]) MRI-confirmed spinal metastases who had no intention of changing pain medications on the first day of protocol radiotherapy treatment, had no more than three consecutive spinal segments in the radiotherapy treatment volume site, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, had metastases arising from a solid primary tumour (excluding seminoma and small-cell lung cancer), had a Spinal Instability in Neoplasia Score (SINS) of 12 or less, had received no previous radiotherapy that would compromise the study interventions, had undergone no previous spinal surgical procedures at the study target volume site, and had no neurological deficits resulting from malignant epidural spinal cord or cauda equina compression. Systemic chemotherapy was not allowed at least 1 week before and after study radiotherapy delivery, and centre guidelines applied with respect to non-cytotoxic systemic therapy, with the proviso that no systemic anticancer therapy (excluding endocrine therapy) be administered within 24 h before or after radiotherapy.

Each participating centre obtained approval from their local research ethics board, and all patients provided written informed consent. The study protocol is available in the appendix.

Randomisation and masking

Patients were randomly assigned (1:1) by use of a web-based, computer-generated allocation sequence, based at the Canadian Cancer Trials Group (CCTG) central office (MANGO [an interactive web response system], Montreal, QC, Canada), to receive either conventional external beam radiotherapy or stereotactic body radiotherapy. Treatment assignment was done centrally by use of a minimisation method to achieve balance for the stratification factors of radioresistant (gastrointestinal cancer, sarcoma, melanoma, and renal cell cancer metastases) versus radiosensitive (all other histologies) histological type, the presence or absence of mass-type tumour (extraosseous or epidural disease extension, or both)[11] on imaging, and centre. Patients, caregivers, and investigators were not masked to treatment allocation.

Procedures

Conventional external beam radiotherapy consisted of a total dose of 20 Gy delivered in five consecutive daily

fractions by use of either a parallel-opposed pair (anteroposterior and posteroanterior fields), or a three-dimensional conformal technique allowing the delivery of up to four beams. Intensity-modulated radiotherapy and volumetric-modulated arc therapy were not permitted in the conventional external beam radiotherapy group. Stereotactic body radiotherapy consisted of a total dose of 24 Gy delivered in two consecutive daily fractions, according to standard spinal stereotactic body radiotherapy techniques specified in the study protocol and the radiotherapy quality assurance (RTQA) manual (appendix). The RTQA procedure involved the use of a facility questionnaire to ascertain the ability of each participating centre to comply with protocol specifications for stereotactic body radiotherapy treatment. Each centre required a minimum of two investigators to be credentialed by central review of a protocol-specific spinal stereotactic body radiotherapy treatment plan. Prospective centre-based review of all radiotherapy treatment plans before the start of radiotherapy by local credentialed investigators was mandated, and a central retrospective external review was done on treatment completion. Criteria for major and minor deviations are provided in the RTQA manual (appendix).

The painful spinal metastasis was identified as the radiation study target vetebral segment volume site by the radiation oncologist based on patient history, patient physical examination, and interpretation of the baseline spine MRI. This radiation study target vertebral segment volume site was subsequently tracked for clinical and radiographic response. When adjacent vertebral segments were deemed as clinically appropriate to be included in the radiation treatment volume site, no more than three consecutive segments were permitted to achieve the therapeutic intent. For example, if the radiation study target vertebral segment volume site was the sixth thoracic vertebral segment (T6), the treatment volume site could include T5, T6, and T7 vertebral segments.

Baseline tests consisted of a full spine MRI within 8 weeks of randomisation, assessment of ECOG performance status, a pain diary, which included the BPI instrument and a record of analgesic consumption, assessment of spinal instability by use of the SINS,[12] and quality-of-life (QOL) assessments with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and Bone Metastasis 22 (EORTC QLQ-BM22) modules, which were completed up to 7 days before randomisation. Follow-up assessments were identical in both groups, occurring at 1, 3, and 6 months after the last radiotherapy fraction was received (see appendix protocol for full details). Protocol treatment was stipulated to begin within 12 days of radiotherapy simulation. All patients were followed up from randomisation until the post-radiotherapy assessment at 6 months unless they withdrew consent for trial participation or died.

Assessment of grade 2–5 adverse events was done during radiotherapy and at each follow-up assessment by use of the Common Terminology Criteria for Adverse Events, version 4.0. However, the incidence of any grade of vertebral compression fracture (either a new fracture or fracture progression), the occurrence of symptomatic spinal cord or cauda equina compression, and any radiation myelopathy events were recorded at each assessment as prospectively defined adverse events of interest. In addition, the occurrence of pain flare, defined as a patient-reported subjective assessment of a worsening of pain at the radiation treatment spinal segment volume, and use of dexamethasone during radiotherapy and up to the 1-month follow-up assessment were prospectively recorded. Follow-up imaging, consisting of a full spine MRI, was mandated to be done at 3 months and 6 months after treatment to fully characterise the adverse event profile, regardless of previous clinical or radiographic progression on-study.

Pain severity at the radiation study target vertebral segment volume site was assessed by use of the BPI questionnaire.[13] Patients reported their worst pain within the previous 24 h on a scale of 0–10 (with 0 representing no pain and 10 representing severe pain) at each follow-up assessment visit. Analgesic consumption was converted to a daily oral morphine equivalent (OME) according to a standardised method. All centres uploaded pain diary and medication logs to the CCTG electronic data capture system, and these data were reconciled for any data entry errors.

Local progression was defined according to recommendations of the SPIne response assessment in Neuro-Oncology group,[14] which consisted of one or more of the following: a gross unequivocal increase in volume or linear dimension,[15] new or progressive tumour in the epidural space, or neurological deterioration attributable to pre-existing epidural disease with equivocal increased epidural disease dimensions specific to the target volume site. These data informed the secondary endpoint of radiation site-specific progression-free survival. A central blinded review of each baseline and follow-up spine MRI was done by a neuroradiologist to ensure fidelity of the images for interpretation; no deficiencies were observed.

Outcomes

The primary endpoint was the proportion of patients with a complete response for pain at the radiation study target vertebral segment volume site at 3 months after treatment, according to the criteria defined by the International Consensus on Palliative Radiotherapy Endpoints (ICPRE).[16,17] The ICPRE defines a complete response for pain as a worst pain score of 0 on the BPI with no associated increase in daily OME consumption. ICPRE criteria also included a partial response for pain and pain progression. In accordance with the ICPRE definitions, a partial response for pain is defined as a reduction in the worst pain score of 2 points or more compared with

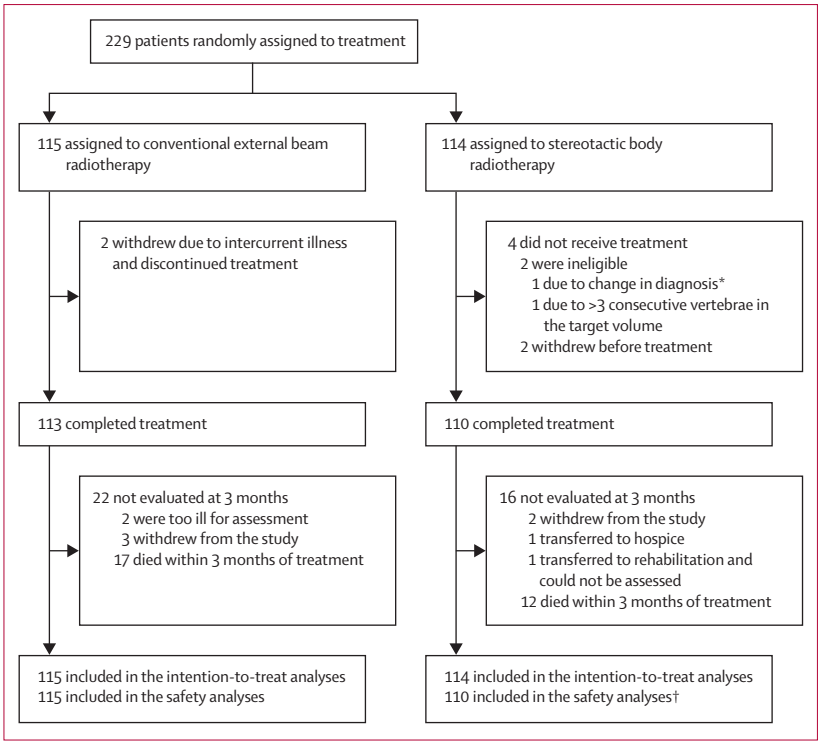

Figure: **Trial profile**
*Radiological assessment at the time of treatment planning showed no tumour. †Four patients who did not receive treatment were excluded from the safety analyses.

	Conventional external beam radiotherapy group (n=115)	Stereotactic body radiotherapy group (n=114)
Sex		
Female	54 (47%)	55 (48%)
Male	61 (53%)	59 (52%)
Age, years		
18–59	36 (31%)	47 (41%)
60–69	36 (31%)	25 (22%)
≥70	43 (37%)	42 (37%)
Median age, years	65 (55–73)	63 (56–72)
Primary malignancy		
Breast	27 (23%)	23 (20%)
Genitourinary (excluding renal cell carcinoma)	25 (22%)	21 (18%)
Lung	26 (23%)	35 (31%)
Gastrointestinal	15 (13%)	14 (12%)
Renal cell	7 (6%)	13 (11%)
Head and neck	3 (3%)	5 (4%)
Melanoma	5 (4%)	2 (2%)
Other	7 (6%)	1 (1%)
Primary tumour classification		
Radioresistant	30 (26%)	30 (26%)
Radiosensitive	85 (74%)	84 (74%)

(Table 1 continues on next page)

baseline and no increase in daily OME consumption, or no increase in the worst pain score and a reduction in daily OME consumption of at least 25%. Pain progression was defined as an increase from baseline in the worst pain score of 2 or more points without reduced daily OME consumption, or as no change in the worst pain score and an increase in daily OME consumption of at least 25%.

Secondary endpoints included complete response rates for pain at the final follow-up assessment at 6 months, radiation site-specific progression-free survival (defined as the time from randomisation to local progression or death) at 3 and 6 months, overall survival (defined as the time from randomisation to death due to any cause), change in the total SINS from baseline at 3 and 6 months, RTQA compliance, and QOL and adverse events, which were also assessed at 1 month after treatment (appendix). The economic analyses was also a prespecified secondary outcome; however, these results will be reported elsewhere.

Statistical analysis

This trial was initially designed as a randomised phase 2 trial in July 24, 2015, with a primary endpoint of feasibility. The target sample size was 54 patients to be accrued over an 18-month time period at participating centres in Canada. Given the high rate of accrual, absence of safety concerns, and high RTQA compliance, the trial was amended to a randomised phase 2/3 trial design on Feb 2, 2017, to test the hypothesis that stereotactic body radiotherapy is superior to conventional external beam radiotherapy in terms of achieving a complete response for pain, with the proportion of patients who have a complete response for pain at 3 months after radiotherapy as the primary endpoint. The 3-month timepoint for the assessment of the primary endpoint was based on our hypothesis that a durable complete response for pain was possible with stereotactic body radiotherapy, and clinically meaningful to the patient. The Trans Tasman Radiation Oncology Group participated in the phase 3 trial.

The sample size of 152 patients was calculated assuming a complete response rate for pain of 10% in the conventional external beam radiotherapy group and 30% in the stereotactic body radiotherapy group, with a two-sided 5% significance level, 80% power, and assuming that 5% of patients would dropout, not be evaluable, or both. The sample size was increased to 228 patients, to account for the possibility that 15% of patients would dropout, not be evaluable, or both, and that 17% of patients in the conventional external beam radiotherapy group and 34% in the stereotactic body radiotherapy group would have a complete response for pain. These assumptions were informed by data reported by Sprave and colleagues[3] for the intention-to-treat population as a final amendment to the study protocol in Oct 31, 2018. No interim analyses were done, and at no time was patient enrolment interrupted. The final analysis populations included the

intention-to-treat population (ie, all randomised patients in phase 2 and phase 3 parts of the trial), regardless of whether radiotherapy was given per protocol for the primary (and all efficacy) endpoints, and the as-treated population (ie, all enrolled patients who received at least one dose of study radiotherapy) for safety and quality assurance analyses.

For pain response analyses, patients who were not evaluable due to missing pain assessments were classified as non-responders. The primary test was the Cochran-Mantel-Haenszel, stratified by baseline stratification factors apart from centre, and the Breslow-Day test was used to test homogeneity of treatment effect across levels of stratification factors.[18] The treatment effect between the two groups was represented by the risk ratio (RR), which was defined by the complete response rate in the stereotactic body radiotherapy group divided by the complete response rate in the conventional external beam radiotherapy group. A sensitivity analysis was also done in all evaluable patients. The complete response rates for pain between the two groups, and the 95% CIs of the difference in rate between the two groups were generated. Logistic regression was used to estimate the treatment effect (odds ratio), while adjusting for prespecified prognostic factors (age, sex, primary malignancy, baseline pain score by the BPI, ECOG performance status, and the total SINS), and to ascertain whether these prespecified prognostic factors predicted a complete response for pain. Partial responses for pain and pain progression are presented descriptively only. We used a Wilcoxin rank-sum test to compare the change from baseline in the SINS score between the two groups. Additional post-hoc analyses of complete pain response were defined before the final analysis using prospectively collected pain response data collected at the 1-month assessment (table 3). Kaplan-Meier estimates for radiation site-specific progression-free survival and overall survival rates were calculated with 95% CIs, the groups were compared with the log-rank test, and Cox regression was used to estimate hazard ratios adjusted for prognostic factors (age, sex, primary malignancy, baseline pain score, ECOG performance status, and the total SINS). Visual inspection confirmed that the proportional hazards assumption was met (appendix p 6). QOL compliance was calculated by the number of questionnaires received divided by the number of questionnaires expected. The QOL data were analysed with standard CCTG QOL response analysis methods, categorising patients as either having an improved, stable, or worse QOL by EORTC domain.[19] A change in score of 10 points from baseline to 1, 3, and 6 months was defined a priori as clinically relevant. The χ^2 test was used to assess differences between the treatment groups, and the Mantel-Haenszel χ^2 trend test[20] was used to verify the direction of the difference. All comparisons between treatment groups were done with a two-sided test at a significance level of 5%, unless otherwise specified, and 95% CIs were computed on the basis of normal approximations.

	Conventional external beam radiotherapy group (n=115)	Stereotactic body radiotherapy group (n=114)
(Continued from previous page)		
Mass-type tumour*		
Absent	43 (37%)	41 (36%)
Present	72 (63%)	73 (64%)
ECOG performance status score		
0	14 (12%)	16 (14%)
1	90 (78%)	90 (79%)
2	11 (10%)	8 (7%)
Spinal location of target vertebrae		
Cervical	8 (7%)	11 (10%)
Thoracic	61 (53%)	50 (44%)
Lumbar	42 (37%)	41 (36%)
Sacral	4 (3%)	8 (7%)
Number of consecutive spinal segments in target volume		
1	46 (40%)	63 (55%)
2	37 (32%)	32 (28%)
3	32 (28%)	18 (16%)
>3	0	1 (1%)
Worst pain score		
2–4	43 (37%)	46 (40%)
5–7	45 (39%)	42 (37%)
8–10	27 (23%)	26 (23%)
Median pain score	5 (4–7)	5 (4–7)
SINS score		
0–6	46 (40%)	57 (50%)
7–12	69 (60%)	57 (50%)
Median SINS score†	7 (6–8)	7 (5–8)
Extent of epidural disease‡		
Unknown	0	4 (4%)
None	56 (49%)	61 (54%)
Low grade	53 (46%)	47 (41%)
High grade	6 (5%)	2 (2%)
Mean baseline oral morphine equivalent dose, mg	69·5 (105·4)	184·4 (816·7)
Geographical region		
Canada	103 (90%)	102 (89%)
Australia	12 (10%)	12 (11%)

Data are n (%) or median (IQR), or mean (SD), unless otherwise specified. ECOG=Eastern Cooperative Oncology Group. SINS=Spinal Instability in Neoplasia Score. *Refers to the presence or absence of extraosseous disease extension (paraspinal, epidural disease, or both). †The SINS ranges from 0 to 18, with higher values indicating greater instability; a SINS score of 0–6 is classified as stable, 7–12 as potentially unstable, and 13–18 as unstable.[12] Patients with a SINS of 13–18 were excluded from this trial. ‡The extent of epidural disease is at the target level and represents the worst extent of epidural disease; low grade refers to grade 1a, 1b, and 1c on the malignant epidural spinal cord compression scale, and high grade refers to grade 2 or 3.[11]

Table 1: **Baseline demographic and clinical characteristics of patients by treatment group**

The study chair (AS) and Trial Steering Committee designed the study in collaboration with the CCTG Statistics and Operations Office (Kingston, ON, Canada), which acted as the trial sponsor. In this role, CCTG was responsible for the overall conduct of the trial including protocol design and generation of informed consent documents, database compilation, maintenance, and analysis, and all aspects of trial oversight. The trial was

	Conventional external beam radiotherapy group (n=115)	Stereotactic body radiotherapy group (n=112)*
Location		
Junctional	47 (41%)	48 (43%)
Mobile spine	31 (27%)	33 (29%)
Semi-rigid	34 (30%)	27 (24%)
Rigid	3 (3%)	4 (4%)
Pain		
Mechanical pain	28 (24%)	19 (17%)
Occasional pain (not mechanical)	87 (76%)	93 (83%)
Pain-free lesion	0	0
Bone lesion		
Osteolytic	45 (39%)	50 (45%)
Mixed (osteolytic and osteoblastic)	40 (35%)	29 (26%)
Osteoblastic	30 (26%)	33 (29%)
Spinal alignment		
Subluxation or translation present	0	1 (1%)
Deformity (kyphosis or scoliosis)	3 (3%)	3 (3%)
Normal	112 (97%)	108 (96%)
Vertebral body collapse		
≥50% collapse	3 (3%)	1 (1%)
<50% collapse	37 (32%)	25 (22%)
No collapse with ≥50% body involvement	35 (30%)	21 (19%)
None of the above	40 (35%)	65 (58%)
Posterolateral element involvement		
Bilateral	38 (33%)	31 (28%)
Unilateral	48 (42%)	44 (39%)
None of the above	29 (25%)	37 (33%)

Data are n (%). SINS=Spinal Instability in Neoplasia Score. *Baseline SINS source forms were missing for two (2%) of 114 patients in this group.

Table 2: **Baseline SINS characteristics by treatment group**

independently monitored by the CCTG Data Safety Monitoring Board.

All analyses were done with SAS version 9.3. The trial is registered with ClinicalTrials.gov, NCT02512965.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Jan 4, 2016, and Sept 27, 2019, 229 patients were enrolled and randomly assigned to either the conventional external beam radiotherapy group (n=115) or the stereotactic body radiotherapy group (n=114; figure). The database was locked for analysis on July 8, 2020. All 229 patients were included in the intention-to-treat analysis. The median follow-up was 6·7 months (IQR 6·3–6·9).

Baseline characteristics (table 1) and baseline SINS criteria (table 2) were well balanced between the treatment groups. However, in terms of daily oral analgesic consumption, patients in the stereotactic body radiotherapy group had higher oral analgesic intake at baseline (mean daily OME 184·4 [SD 816·7]) than those in the conventional external beam radiotherapy group (69·5 [105·4]). Prostate cancer (41 [18%] of 229 patients), which was the most common genitourinary cancer (excluding renal cell carcinoma), breast cancer (50 [22%]), and lung cancer (61 [27%]) were the most common primary histological types (table 1).

The median time from randomisation to the start of assigned radiotherapy regimen was 6 days (IQR 3–7) in the stereotactic body radiotherapy group, and 9 days (5–11) in the conventional external beam radiotherapy group. According to the central review, minor protocol radiotherapy contour volume deviations were observed in two (2%) of 114 patients in the stereotactic body radiotherapy group and six (5%) of 115 patients in the conventional external beam radiotherapy group. No major radiotherapy contour volume deviations were observed in either treatment group. Minor dosimetric deviations were observed in two (2%) patients in the stereotactic body radiotherapy group, and five (5%) patients in the conventional external beam radiotherapy group. Major dosimetric deviations were observed in one (1%) patient in the stereotactic body radiotherapy group with respect to dose exposure in the spinal cord planning organ-at-risk volume, and two (2%) patients in the conventional external beam radiotherapy group with respect to target volume under-coverage and dose exposure in the spinal canal, respectively.

At 3 months, 22 (19%) of 115 patients in the conventional external beam radiotherapy group and 20 (18%) of 114 patients (when including the four patients who did not receive any assigned treatment) in the stereotactic body radiotherapy group were not evaluable for pain response, but they were included in the intention-to-treat analysis. Of all 229 patients in the intention-to-treat analysis, 56 (24%) patients had a complete response for pain; 40 (35%) of 114 patients in the stereotactic body radiotherapy group and 16 (14%) of 115 patients in the conventional external beam radiotherapy group (RR 1·33, 95% CI 1·14–1·55; p=0·0002; table 3).

At the 6-month assessment, 39 (34%) patients in the conventional external beam radiotherapy group and 36 (32%) patients in the stereotactic body radiotherapy group were not evaluable but were included in the intention-to-treat analysis. Significantly more patients achieved a complete response for pain in the stereotactic body radiotherapy group than in the conventional external beam radiotherapy group (RR 1·24 [95% CI 1·07–1·44], p=0·0036; table 3). According to the multivariable-adjusted analyses (table 4), a significant improvement in the complete response rate for pain from baseline to 3 months in the stereotactic body radiotherapy group compared with the conventional external beam radiotherapy group was observed, and this improvement

remained significant at 6 months. The results of the univariable analysis is provided in the appendix (p 12). No differential treatment effect was observed across baseline stratification factors at 3 or 6 months. Sensitivity analyses involving all evaluable patients showed similar results to the primary analysis; 40 (42·5%) of 94 patients in the stereotactic body radiotherapy group and 16 (17·2%) of 93 patients in the conventional external beam radiotherapy group had a complete response for pain (estimated RR 2·48 [95% CI 1·50–4·08], p=0·0002). At the 1-month assessment (post-hoc analysis) in the as-treated evaluated population, use of dexamethasone was observed in 30 (28%) of 106 patients in the conventional external beam radiotherapy group and 36 (34%) of 105 patients in the stereotactic body radiotherapy group, and pain flare was observed in 35 (34%) patients in the conventional external beam radiotherapy group and 45 (43%) patients in the stereotactic body radiotherapy group. Mean change in SINS from baseline is shown in table 3. No significant difference in daily OME consumption between the two groups was observed at 1, 3, or 6 months (table 3).

Of the 36 radiation site-specific progression events up to the 6-month follow-up assessment in the conventional external beam radiotherapy group, 12 (10%) of 115 patients had local progression and 24 (21%) died without local progression. Of the 28 events in the stereotactic body radiotherapy group, three (3%) of 114 patients had local progression and 25 (22%) died without local progression. In total, 56 (24%) of 229 patients had died by the 6-month follow-up assessment, including 30 (26%) of 115 patients in the conventional external beam radiotherapy group and 26 (23%) of 114 patients in the stereotactic body radiotherapy group. With the exception of two patients in the stereotactic body radiotherapy group who died due to *Legionella* infection and dermatomyositis, respectively, all other patients died from their underlying cancer (30 [26%] of 115 in the conventional external beam radiotherapy group and 24 [21%] of 114 in the stereotactic body radiotherapy group).

Radiation site-specific progression-free survival rates were 86% (95% CI 78–91) in the conventional external beam radiotherapy group and 92% (85–96) in the stereotactic body radiotherapy group at 3 months (p=0·18), and 69% (60–77) in the conventional external beam radiotherapy group and 75% (65–82) in the stereotactic body radiotherapy group at 6 months (p=0·34; appendix p 5). Overall survival at 3 months was 89% (95% CI 82–94) in the conventional external beam radiotherapy group and 93% (86–96) in the stereotactic body radiotherapy group (p=0·33), and overall survival at 6 months was 73% (64–81) in the conventional external beam radiotherapy group and 77% (68–84) in the stereotactic body radiotherapy group (p=0·42; appendix p 4).

The baseline QOL scores for symptom and functional domains are provided in the appendix (p 7); no differences between the two treatment groups were observed.

	Conventional external beam radiotherapy group (n=115)	Stereotactic body radiotherapy group (n=114)	p value
1-month assessment			
Complete response	20 (17%)	30 (26%)	0·10*
Partial response	33 (29%)	34 (30%)	..
Stable pain	38 (33%)	26 (23%)	..
Progressive pain	14 (12%)	9 (8%)	..
Indeterminant	10 (9%)	15 (13%)	..
Mean daily OME consumption, mg	44 (122)	27 (95)	0·26
3-month assessment			
Complete response	16 (14%)	40 (35%)	0·0002*
Partial response	29 (25%)	20 (18%)	..
Stable pain	34 (30%)	27 (24%)	..
Progressive pain	14 (12%)	7 (6%)	..
Indeterminant	22 (19%)	20 (18%)	..
Mean daily OME consumption, mg	43 (106)	37 (97)	0·70
Mean change in SINS from baseline	−0·49 (1·61)	−0·94 (1·69)	0·034
6-month assessment			
Complete response	18 (16%)	37 (32%)	0·0036*
Partial response	18 (16%)	10 (9%)	..
Stable pain	32 (28%)	26 (23%)	..
Progressive pain	8 (7%)	5 (4%)	..
Indeterminant	39 (34%)	36 (32%)	..
Mean daily OME consumption, mg	36 (126)	36 (84)	1·00
Mean change in SINS from baseline	−0·74 (1·99)	−0·73 (1·86)	0·88

Data are n (%) or mean (SD). Pain responses at 1, 3, and 6 months after treatment relative to baseline assessments were based on International Consensus on Palliative Radiotherapy Endpoints. OME=oral morphine equivalent. SINS=Spinal Instability in Neoplasia Score. *Adjusted for stratification factors of histology (radioresistant *vs* radiosensitive), and the the presence or absence of mass-type tumour (extraosseous or epidural disease extension, or both) on imaging.

Table 3: **Pain responses, mean daily OME consumption, and change in SINS score from baseline to 1, 3, and 6 months after treatment**

Compliance rates were 93% at baseline, and more than 80% at the 1-month, 3-month, and 6-month assessments (appendix p 11). Changes in health-related QOL from baseline in patients who completed the EORTC QLQ-C30 and QLQ-BM22 questionnaires are shown in the appendix (p 8), with similar changes between both treatment groups, except for financial burden. The mean change in QOL scores from baseline to each assessment are provided in the appendix (pp 9–10).

Grade 2–5 adverse events were as anticipated, with no grade 5 events recorded during the study period (table 5). The most common grade 3–4 adverse event was grade 3 pain (five [4%] of 115 patients in the conventional external beam radiotherapy group *vs* five [5%] of 110 patients in the stereotactic body radiotherapy group). Overall, 20 (17%) of 115 patients in the conventional external beam radiotherapy group and 12 (11%) of 110 patients in the stereotactic body radiotherapy group had a vertebral compression fracture of any grade. Most (30 [94%] of 32) vertebral compression fractures were grade 1 in severity; one (1%) of 115 patients in the conventional external beam radiotherapy group had a grade 4 vertebral compression

	3 months post treatment		6 months post treatment	
	OR (95% CI)	p value	OR (95% CI)	p value
Treatment group				
Conventional external beam radiotherapy	1 (ref)	..	1 (ref)	..
Stereotactic body radiotherapy	3·47 (1·77–6·80)	0·0003	2·45 (1·28–4·71)	0·0070
Age, years				
<65	1 (ref)	..	1 (ref)	..
≥65	1·58 (0·82–3·06)	0·17	0·65 (0·34–1·25	0·20
Sex				
Female	1 (ref)	..	1 (ref)	..
Male	1·33 (0·54–3·26)	0·54	1·39 (0·56–3·45)	0·48
ECOG performance status score				
0 or 1	1 (ref)	..	1 (ref)	..
2	0·74 (0·19–2·89)	0·67	0·39 (0·08–1·86)	0·24
Pain score at baseline				
2–4	1 (ref)	..	1 (ref)	..
8–10	0·92 (0·39–2·20)	0·85	1·39 (0·60–3·21)	0·44
5–7	0·74 (0·36–1·54)	0·43	0·94 (1·45–1·96)	0·86
Primary cancer histology				
Breast	1 (ref)	..	1 (ref)	..
Genitourinary (excluding renal cell carcinoma)	1·22 (0·32–4·65)	0·77	0·99 (0·26–3·79)	0·99
Lung	1·49 (0·54–4·08)	0·44	0·96 (0·36–2·63)	0·95
Other	0·58 (0·09–3·77)	0·57	0·74 (0·14–3·86)	0·72
SINS score at baseline				
≤6	1 (ref)	..	1 (ref)	..
7–12	1·12 (0·58–2·15)	0·57	0·91 (0·48–1·71)	0·78

OR=odds ratio. SINS=Spinal Instability in Neoplasia Score.

Table 4: **Multivariable-adjusted analyses for complete response rate for pain at 3 and 6 months after treatment**

	Conventional external beam radiotherapy group (n=115)			Stereotactic body radiotherapy group (n=110)		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Dysphagia	0	0	0	1 (1%)	1 (1%)	0
Oesophagitis*	2 (2%)	0	0	2 (2%)	0	0
Nausea	2 (2%)	1 (1%)	0	1 (1%)	0	0
Pain†	4 (3%)	5 (4%)	0	2 (2%)	5 (5%)	0
Fatigue	0	1 (1%)	0	0	0	0
Vertebral compression fracture	0	0	1 (1%)	0	1 (1%)	0

Data are n (%). Adverse events were graded according to the Common Terminology Criteria for Adverse Events version 4.0. No grade 5 adverse events were reported. *Oesophagitis events are presented as an aggregate of oesophageal pain, oesophagitis, and pharyngeal mucositis. †Pain events are presented as an aggregate of general disorders pain, neoplasm-related tumour pain, and musculoskeletal and connective tissue disorders.

Table 5: **Incidence of grade 2 or higher treatment-related adverse events in the safety analysis population**

fracture, and one (1%) of 110 patients in the stereotactic body radiotherapy group had a grade 3 vertebral compression fracture. Progression to symptomatic spinal cord compression was observed in only two (2%) patients in the conventional external beam radiotherapy group. No radiation myelopathy events were observed. There were no premature discontinuations of assigned treatments due to treatment-related toxicity. No treatment-related deaths were observed.

Discussion

In this randomised, controlled, phase 2/3 trial, stereotactic body radiotherapy was associated with significantly higher complete response rates for pain compared with conventional external beam radiotherapy at 3 months and 6 months after treatment, and the palliative benefit was conferred with a low risk of grade 2–4 adverse events and no grade 5 adverse events. Additionally, the low proportion of patients who had major protocol deviations on central quality assurance review also indicated good compliance with the radiotherapy specifications in a multicentre setting. The similar incidence of vertebral compression fractures between the two groups and the significant improvement in the total SINS from baseline at 3 months support the biomechanical safety of this regimen.

The current standard of care for patients with symptomatic spinal metastases is a low total dose of radiation delivered in one, five, or ten fractions of conventional external beam radiotherapy.[2] We chose conventional external beam radiotherapy at a dose of 20 Gy in five fractions for the standard-of-care treatment group in this trial rather than another commonly recommended dose of 8 Gy in a single fraction,[1] given the potential for higher short-term re-treatment rates with the second regimen.[2,4,21] With the advent of stereotactic body radiotherapy, and the potential to dose-escalate selected spinal metastases with an ablative dose,[15] stereotactic body radiotherapy at a dose of 24 Gy in two fractions was chosen as the experimental group on the basis of preliminary data showing feasibility and tolerability of this regimen.[10,22,23] We designed the trial to ascertain whether the complete response rate for pain with stereotactic body radiotherapy would be superior to conventional external beam radiotherapy. As a patient-reported outcome, complete response for pain was considered to be the most reliable assessment of treatment benefit. Moreover, a gain in complete response for pain was considered to be most clinically meaningful to justify a change in clinical practice, given that stereotactic body radiotherapy is a more resource-intensive and expensive treatment to deliver than conventional external beam radiotherapy.[24]

The results of the multivariable analyses showed that stereotactic body radiotherapy significantly improved the complete response rate for pain compared with conventional external beam radiotherapy. However, palliative, low-dose, conventional external beam radiotherapy has a short-term palliative benefit, consistent with previous studies,[2] hence it is a recommended treatment option for patients with low expected survival (ie, of <3 months) who otherwise do not meet this study's inclusion criteria.[25] Conversely, spinal stereotactic body radiotherapy should

now be considered a treatment option for patients presenting with sites of MRI-confirmed painful spinal metastases, in accordance with the eligibility criteria in this trial, irrespective of the overall burden of metastatic disease. Of note, we did not restrict the patient population to those with oligometastatic disease, as the intention was to ascertain the response to pain at the radiation study target vertebral segment volume site. Although the most common primary cancer types were represented, consisting of patients with breast, lung, and genitourinary (excluding renal cell) cancers, with either no or minimal epidural disease on their baseline MRI, most patients had mass-type tumours (extraosseous or epidural disease extension, or both).

A finding of this trial was the association of stereotactic body radiotherapy with an improved perception of financial strain compared with conventional external beam radiotherapy. This finding could reflect the financial burden faced by patients with a terminal illness, and the differential effect of 2 days of treatment as opposed to 5 days. Therefore, although the technical costs of delivering stereotactic body radiotherapy might be greater than conventional external beam radiotherapy,[24] the financial, in addition to the observed palliative benefits for the patient, might also support its use. Opportunities to reduce costs associated with delivery of stereotactic body radiotherapy, and to reduce disparities in access to spinal stereotactic body radiotherapy[26] need be pursued. We also found that all other QOL domains were not significantly different between the two treatment groups, which reflects the multidimensional nature of QOL domains, including the patient's perception of pain at other sites (ie, those not specific to the spine). For instance, in this palliative population, many patient, disease, and treatment factors influence global QOL, beyond pain control at the treated site. These findings also emphasise the importance of careful measurement of pain with the BPI, and clear directions to report pain at the radiation study target vertebral segment volume site.

The phase 2/3 NRG Oncology/RTOG 0631 trial, published in a conference abstract in 2019,[27] compared conventional external beam radiotherapy at a dose of 8 Gy in one fraction with stereotactic body radiotherapy at a dose of 16 Gy or 18 Gy in one fraction. In contrast to our study, no improvements in response rates for pain or QOL outcomes were observed. These discordant results could be due to differences in the stereotactic body radiotherapy dose and fractionation schemes evaluated in each trial. Our experimental group evaluated 24 Gy in two fractions, which represents a high biologically equivalent and fractionated stereotactic body radiotherapy dose, and this regimen could have beneficial radiobiological effects that might not otherwise be realised with lower single-fraction stereotactic body radiotherapy doses.[28]

One limitation of our trial includes the follow-up schedule, which was completed at the 6-month post-radiotherapy timepoint. However, longer term (ie, beyond 6 months) safety data associated with spinal stereotactic body radiotherapy has been provided by others. In the retrospective report by Tseng and colleagues,[10] no radiation myelopathy or plexopathy events were observed at a median follow-up of 15 months after stereotactic body radiotherapy at a dose of 24 Gy in two fractions, and the 2-year risk of vertebral compression fractures was 13·8%. Zeng and colleagues[29] retrospectively reported on a series of 79 patients surviving 3 years or more after receiving spinal stereotactic body radiotherapy; vertebral compression fracture rates were 10·4% at 3 years and 14·4% at 5 years, radiation plexopathy rates were 2·2% at 3 years and 5·1% at 5 years, and no radiation myelopathy events were observed. A second limitation is that we did not design the study to detect treatment differences with respect to radiation site-specific progression-free survival. Therefore, the apparent advantage of stereotactic body radiotherapy in terms of radiation site-specific progression-free survival should be considered exploratory and subject to further research. We also included patients with mixed histological types in this study, and there are inherent differences noted in retrospective analyses with respect to local control according to histological type,[30] such that appropriately designed and powered trials are needed to address this outcome. Finally, the nature of the trial did not allow for a masked design. The strengths of our study include the use of a standardised instrument for pain assessment (the BPI[13]) directed to the radiation study target vertebral segment volume site, application of the ICPRE,[16] exclusion of patients with frank instability based on SINS,[12] and the application of evidence-based spinal cord tolerance limits.[7,31] In addition, a strength of this study lies in the stereotactic body radiotherapy treatment regimen we selected to compare with the conventional external beam radiotherapy regimen. Stereotactic body radiotherapy at a dose of 24 Gy in two fractions[10,22,23] was developed as a pragmatic alternative to 24 Gy in one fraction, which was associated, at the time of study design, with high rates of vertebral compression fracture,[6,8,32] and to more protracted regimens, such as 24–40 Gy in 3–5 fractions. Future directions for spinal stereotactic body radiotherapy trials should focus on further refining histology-specific dose and fractionation schemes, identifying factors that are predictive and associated with symptomatic versus asymptomatic vertebral compression fracture,[33] evaluating the role of minimally invasive surgical procedures into the treatment framework,[34] and the application of spine metastases-specific QOL outcome measures.[35]

The results of this trial suggest that stereotactic body radiotherapy at a dose of 24 Gy in two fractions is superior to conventional external beam radiotherapy at a dose of 20 Gy in five fractions in achieving complete pain relief at the radiation study target vertebral segment volume site. This stereotactic body radiotherapy regimen

supports a shift toward the use of conformal, image-guided, stereotactically dose-escalated radiotherapy in the palliative setting for symptom control, and a heightened awareness of the need for specialised and multidisciplinary involvement in the delivery of end-of-life care for patients with spinal metastases.

Contributors

AS, SDM, GLM, PJM, MB, JB, EC, MGF, JG, MK, YL, ML, SKL, KD, RKW, and WRP contributed to study design. AS, SDM, SS, GLM, MF, ZG, JG, MK, ML, IT, and RKW accrued patients at participating centres. The data were analysed by KD, MH, AS, SDM, and WRP. AS, WRP, KD, MH, MB, and SDM interpreted the data. KD and WRP wrote the statistical analysis section of the protocol, and statistical analyses were done by KD. WRP, KD, AS, and MH verified the underlying data. AS, SDM, WRP, MB and KD were the main contributors to the writing of the manuscript, and the first draft was prepared by AS. All authors assisted in manuscript review and appraisal. All authors had full access to all the data in the study for interpretation and had final responsibility for manuscript generation and review, and the decision to submit for publication.

Declaration of interests

AS reports consulting services' fees, honorarium, or both for past educational seminars for Varian Medical Systems, Elekta, AstraZeneca, Medtronic Kyphon, and BrainLAB; and research grants from Elekta and Varian Medical Systems. SDM reports grants from Novartis Advanced Accelerator Applications and honorarium from Ipsen. SS reports research grants from Varian Medical Systems, Merck Sharp & Dohme, and Bayer Pharmaceuticals; and honorarium for past educational seminars and advisory board participation from AstraZeneca and Reflexion. MF reports grants from Elekta; and honorarium for past educational seminars from Elekta and Varian Medical Systems. JG, IT, MK, MGF, ML, PJM, YL, MB, JB, KD, GLM, RKW, SKL, WRP, EC, MH, and ZG declare no competing interests.

Data sharing

A CCTG data sharing policy is in place that is applicable to the current trial, and can be accessed at https://www.ctg.queensu.ca/public/policies.

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References

1 Lutz S, Balboni T, Jones J, et al. Palliative radiation therapy for bone metastases: update of an ASTRO evidence-based guideline. *Pract Radiat Oncol* 2017; **7:** 4–12.

2 Chow E, Harris K, Fan G, Tsao M, Sze WM. Palliative radiotherapy trials for bone metastases: a systematic review. *J Clin Oncol* 2007; **25:** 1423–36.

3 Sprave T, Verma V, Forster R, et al. Randomized phase II trial evaluating pain response in patients with spinal metastases following stereotactic body radiotherapy versus three-dimensional conformal radiotherapy. *Radiother Oncol* 2018; **128:** 274–82.

4 Foro Arnalot P, Fontanals AV, Galceran JC, et al. Randomized clinical trial with two palliative radiotherapy regimens in painful bone metastases: 30 Gy in 10 fractions compared with 8 Gy in single fraction. *Radiother Oncol* 2008; **89:** 150–55.

5 Sahgal A, Roberge D, Schellenberg D, et al. The Canadian Association of Radiation Oncology scope of practice guidelines for lung, liver and spine stereotactic body radiotherapy. *Clin Oncol (R Coll Radiol)* 2012; **24:** 629–39.

6 Sahgal A, Whyne CM, Ma L, Larson DA, Fehlings MG. Vertebral compression fracture after stereotactic body radiotherapy for spinal metastases. *Lancet Oncol* 2013; **14:** e310–20.

7 Sahgal A, Weinberg V, Ma L, et al. Probabilities of radiation myelopathy specific to stereotactic body radiation therapy to guide safe practice. *Int J Radiat Oncol Biol Phys* 2013; **85:** 341–47.

8 Rose PS, Laufer I, Boland PJ, et al. Risk of fracture after single fraction image-guided intensity-modulated radiation therapy to spinal metastases. *J Clin Oncol* 2009; **27:** 5075–79.

9 Husain ZA, Sahgal A, De Salles A, et al. Stereotactic body radiotherapy for de novo spinal metastases: systematic review. *J Neurosurg Spine* 2017; **27:** 295–302.

10 Tseng CL, Soliman H, Myrehaug S, et al. Imaging-based outcomes for 24 Gy in 2 daily fractions for patients with de novo spinal metastases treated with spine stereotactic body radiation therapy (SBRT). *Int J Radiat Oncol Biol Phys* 2018; **102:** 499–507.

11 Bilsky MH, Laufer I, Fourney DR, et al. Reliability analysis of the epidural spinal cord compression scale. *J Neurosurg Spine* 2010; **13:** 324–28.

12 Fisher CG, DiPaola CP, Ryken TC, et al. A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine Oncology Study Group. *Spine (Phila Pa 1976)* 2010; **35:** e1221–29.

13 Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore* 1994; **23:** 129–38.

14 Thibault I, Chang EL, Sheehan J, et al. Response assessment after stereotactic body radiotherapy for spinal metastasis: a report from the SPIne response assessment in Neuro-Oncology (SPINO) group. *Lancet Oncol* 2015; **16:** e595–603.

15 Sahgal A, Larson DA, Chang EL. Stereotactic body radiosurgery for spinal metastases: a critical review. *Int J Radiat Oncol Biol Phys* 2008; **71:** 652–65.

16 Chow E, Hoskin P, Mitera G, et al. Update of the international consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. *Int J Radiat Oncol Biol Phys* 2012; **82:** 1730–37.

17 Chow E, Wu JS, Hoskin P, Coia LR, Bentzen SM, Blitzer PH. International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. *Radiother Oncol* 2002; **64:** 275–80.

18 Agresti A. Categorical data analysis. Hoboken, NJ: John Wiley & Sons, 2002.

19 Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998; **16:** 139–44.

20 Wallenstein S, Wittes J. The power of the Mantel-Haenszel test for grouped failure time data. *Biometrics* 1993; **49:** 1077–87.

21 Hartsell WF, Scott CB, Bruner DW, et al. Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases. *J Natl Cancer Inst* 2005; **97:** 798–804.

22 Sangha A, Korol R, Sahgal A. Stereotactic body radiotherapy for the treatment of spinal metastases: an overview of the University of Toronto, Sunnybrook Health Sciences Odette Cancer Centre, Technique. *J Med Imaging Radiat Sci* 2013; **44:** 126–33.

23 Hyde D, Lochray F, Korol R, et al. Spine stereotactic body radiotherapy utilizing cone-beam CT image-guidance with a robotic couch: intrafraction motion analysis accounting for all six degrees of freedom. *Int J Radiat Oncol Biol Phys* 2012; **82:** e555–62.

24 Kim H, Rajagopalan MS, Beriwal S, Huq MS, Smith KJ. Cost-effectiveness analysis of single fraction of stereotactic body radiation therapy compared with single fraction of external beam radiation therapy for palliation of vertebral bone metastases. *Int J Radiat Oncol Biol Phys* 2015; **91:** 556–63.

25 Lutz S, Berk L, Chang E, et al. Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. *Int J Radiat Oncol Biol Phys* 2011; **79:** 965–76.

26 Kim E, McClelland S 3rd, Jaboin JJ, Attia A. Disparities in patterns of conventional versus stereotactic body radiotherapy in the treatment of spine metastasis in the United States. *J Palliat Care* 2020; **36:** 130–34.

27 Ryu S, Deshmukh S, Timmerman RD, et al. Radiosurgery compared to external beam radiotherapy for localized spine metastasis: phase III results of NRG oncology/RTOG 0631. *Int J Radiat Oncol Biol Phys* 2019; **105:** S2–S3.

28 Schaue D, Ratikan JA, Iwamoto KS, McBride WH. Maximizing tumor immunity with fractionated radiation. *Int J Radiat Oncol Biol Phys* 2012; **83:** 1306–10.

29 Zeng KL, Sahgal A, Tseng CL, et al. Prognostic factors associated with surviving less than 3 months vs greater than 3 years specific to spine stereotactic body radiotherapy and late adverse events. *Neurosurgery* 2021; **88:** 971–79.

30 Zeng KL, Sahgal A, Husain ZA, et al. Local control and patterns of failure for "radioresistant" spinal metastases following stereotactic body radiotherapy compared to a "radiosensitive" reference. *J Neurooncol* 2021; **152:** 173–82.

31 Sahgal A, Chang JH, Ma L, et al. Spinal cord dose tolerance to stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* 2019; **110:** 124–36.

32 Sahgal A, Atenafu EG, Chao S, et al. Vertebral compression fracture after spine stereotactic body radiotherapy: a multi-institutional analysis with a focus on radiation dose and the spinal instability neoplastic score. *J Clin Oncol* 2013; **31:** 3426–31.

33 Hardisty M, Wright T, Campbell M, et al. CT based quantitative measures of the stability of fractured metastatically involved vertebrae treated with spine stereotactic body radiotherapy. *Clin Exp Metastasis* 2020; **37:** 575–84.

34 Wardak Z, Bland R, Ahn C, et al. A phase 2 clinical trial of SABR followed by immediate vertebroplasty for spine metastases. *Int J Radiat Oncol Biol Phys* 2019; **104:** 83–89.

35 Laufer I, Lo SS, Chang EL, et al. Population description and clinical response assessment for spinal metastases: part 2 of the SPIne response assessment in Neuro-Oncology (SPINO) group report. *Neuro Oncol* 2018; **20:** 1215–24.