Forty percent of all cancer patients will develop spinal metastases. These patients often present with pain and, if the cancer is sufficiently advanced, neurological complications as well. Conventional irradiation of spinal metastatic tumors is useful for palliation, but its effectiveness is limited by spinal cord tolerance. In addition, reirradiation of spinal metastases by conventional means is generally not possible.

In patients who harbor spinal metastases not causing cord compression, SBRT can be used to overcome some of the dose limitation associated with conventional radiotherapy. Characterized by a single or a few fractions of high-dose radiation delivered precisely to an extracranial target, various SBRT spine techniques have been described including our own that involves the use of near-simultaneous CT-guided stereotaxy. The results from the Phase I portion of a Phase I/II study demonstrating the safety, feasibility, and precision of our technique have previously been published. In the present study we provide additional data detailing the safety, effectiveness, and patterns of failure in the Phase I/II trial.
Clinical Material and Methods

A Phase I/II study designed to evaluate near-simultaneous CT scan–guided SBRT in patients with spinal or paraspinal metastasis was initiated at the University of Texas M. D. Anderson Cancer Center in November 2002. The primary objectives of the study were to establish the safety, feasibility, and effectiveness of the procedure. The study was approved for use in humans by the hospital’s clinical research committee for scientific integrity and by the institutional review board. In general, the protocol was intended for patients with spinal metastatic disease characterized by, but not limited to, any of the following scenarios: 1) presentation as a solitary spinal metastatic lesion without evidence of other metastases; 2) failure of prior conventional irradiation or surgery; 3) primary melanoma, RCC, or sarcoma; 4) gross residual tumor after surgery; 5) concern that there is high risk for recurrence following resection; 6) patient refusal of spinal surgery; and 7) medically inoperable cases. Cases were discussed at a multidisciplinary spinal tumor board composed of members from the neurosurgery, radiation oncology, and radiation physics departments. Most patients were jointly seen in consultation by a radiation oncologist and spine neurosurgeon whenever possible.

Eligibility Criteria

All study participants were required to sign informed consent forms prior to study registration. To be eligible, a diagnosis of cancer (excluding multiple myeloma), Karnofsky Performance Scale score of at least 40, and an MR imaging study documenting a spinal or paraspinal metastasis within 4 weeks of registration were required. In general, acceptable tumor configurations were those that did not abut the spinal cord and were at least 5 mm away. If the tumor was closer than 5 mm, the neurosurgical investigators on occasion would resect it prior to SBRT. If this was not possible, the total prescription dose was lowered to limit that which the spinal cord received to 9 to 10 Gy. A maximum of two distinct noncontiguous spinal metastases were treated in a single course. One prior course of spinal irradiation up to 45 Gy to the region of interest was permitted. Patients with an unstable spine or compromised motor function due to radiographically confirmed cord compression were excluded from the study. The determination of an “unstable spine” was based on the clinical judgment of the spine neurosurgeon and took the following factors into account: 1) extent of collapse, 2) presence of spinal deformity (kyphosis), 3) involvement of all three columns of the spine, and 4) severe mechanical pain. It should be noted that we considered eligible for enrollment patients with previously documented cord compression managed with decompression and stabilization and in whom there was now no evidence of spinal cord compression as a result of their surgery.

Patients in whom a delay in initiating treatment might have adversely affected neurological outcome were excluded. We also excluded any patient with a pacemaker, unable to undergo MR imaging, unable to lie flat for at least 30 minutes, receiving systemic radiotherapy (90Sr) or chemotherapy within 30 days of starting protocol treatment, or with a history of spinal external-beam radiotherapy within 3 months of registration.

Pretreatment and Treatment Evaluation

History taking, neurological examination, and administration of the BPI were performed at baseline and follow-up visits. Neurological function was graded according to the scheme devised by McCormick and associates. Follow-up visits including MR imaging studies of the spine were scheduled 3, 6, 9, and 12 months after treatment and then every 6 months thereafter. The neurological examination comprised motor testing of all extremities, bilateral sensory testing, Romberg test, and tandem gait. Details of prior radiotherapy and surgery were collected. The records and simulation x-ray films and treatment plan (if available) from previous irradiation were reviewed prior to enrollment to determine patient eligibility. The MR images were typically obtained before any surgery as part of routine preoperative evaluation. If surgery had recently been performed and a patient was being considered for the protocol, postoperative MR images were always obtained to evaluate the status of the spine postoperatively and extent of tumor resection to determine eligibility for the protocol. If postoperative MR imaging could not be performed for any reason, the patient was excluded from the protocol.

Treatment Procedure and Target Delineation

Patients underwent intensity-modulated, near-simultaneous, CT image–guided SBRT, as previously described in detail. Briefly, each patient was immobilized in an Elekta BodyFix stereotactic body frame system, consisting of a carbon fiber base plate, whole-body vacuum cushion, vacuum system, and plastic fixation sheet. A commercially available stereotactic localizer and target-positioning frame were used (Integra-Radionics). Treatment planning for SBRT was performed with inverse-planning IMRT software (version 6.2, PIMRT; Pinnacle, Philips Medical Systems). Pretreatment CT scanning and IMRT treatment delivery were performed using an EXaCT targeting system (Varian Medical Systems), which integrates a high-speed CT scanning on rails (GE Medical Systems) and a 21EX linear accelerator equipped with a Millennium 120 multileaf collimator into the same treatment suite (Fig. 1).

Fig. 1. Photograph showing the CT scanner–on-rails linear accelerator treatment suite.
Stereotactic radiotherapy for spinal metastases

For the treatment of patients with cervical tumors, a head and neck frame with a custom moldable bite block (Integra Radionics) was used for immobilization. A specialized head and neck stereotactic localization frame (Integra Radionics) was used to pinpoint tattoos placed on the patient's skin. A head and neck stereotactic target-positioning frame (Integra Radionics) was used to set up the treatment isocenter.

The first 32 patients were treated with five 6-Gy fractions to a total dose of 30 Gy. The biologically effective dose = nd × (1 + d/(α/β)). The α/β portion of the formula indicates the dose at which the proportion of cells that are killed by a single event and resulting in double chromosome breaks is equal to the proportion of cells killed by two separate electrons causing two distinct chromosome breaks. The BED_{06} equivalent for early-responding tissues (for example, skin, jejunum, colon, and testis) is 40 Gy and for late-responding tissues (such as spinal cord, kidney, lung, and bladder) is 54 Gy. The total dose was reduced if necessary to meet the spinal cord constraint of less than or equal to 10 Gy. Because of the lengthy treatment duration, the protocol was amended for subsequent patients to get three 9-Gy fractions to a total dose of 27 Gy (BED_{06} 42 Gy) for early-responding tissues and 64 Gy for late-responding tissues assuming α/β of 10 and 3 Gy, respectively. The total dose was reduced if necessary to meet the spinal cord constraint of 9 Gy or less.

Treatment plans originally specified dose as a percentage of the isocenter dose, and later on as a percent of the mean gross tumor volume dose. The dose was prescribed to the isodose line that matched the monitor units for each field generated by the inverse treatment–planning software. In general this resulted in 80 to 90% coverage of the target volume receiving at least the prescription dose. Radiation treatments were given on alternating days.

Target delineation was performed with input from the spine surgeon who discussed each case with the tumor board to include any additional spinal structures deemed to be at risk for recurrence, such as the pedicle, lamina, and posterior elements, and any areas suspicious for residual microscopic disease in the postoperative cases. In general, the target was defined as the entire involved VB, up to and including the superior and inferior endplates, but excluding the disc and posterior elements. Any paravertebral component present was also delineated in the target volume. In cases of paravertebral tumor alone, the tumor was contoured excluding the VB. In complicated cases, the judgment of the tumor board was exercised based on imaging and intraoperative findings, if available, to create an optimal treatment plan.

To help overcome imaging difficulties created by metallic artifact from surgical instrumentation, intrathecal injection of iohexol (Omnipaque, Amersham Health) was performed 30 to 60 minutes before acquisition of planning CT images to accurately delineate the spinal cord for radiation treatment planning.

Medical Management

Patients were routinely premedicated with antiemetic agents for thoracic and lumbar lesions near the stomach. Patients with pain were advised to continue on their pain medications and were given transmucosal fentanyl lozenges during each treatment. Steroids were not routinely given to patients.

Toxicity Monitoring

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0 and the Late Effects of Normal Tissue scoring system. Toxicity assessments were performed at each follow-up visit.

Patterns of Failure

To analyze the patterns of failure, an effort was made to determine the anatomical location of each tumor failure and its relationship to the portion of the irradiated spine. This was accomplished by comparing the first MR image demonstrating tumor progression with the corresponding radiotherapy treatment plan for each patient. For the purposes of this study, the operational definition of failure is limited to the MR imaging–documented progression of the treated spinal tumor.

Statistical Analysis

The statistical portion of the trial incorporated early stopping rules for terminating the study (and a lower dose studied) if there was evidence that the probability of paralysis (Grade 4 motor neuropathy) caused by the treatment was greater than 1%. The Clopper–Pearson method was used to estimate the probability of paralysis. Actuarial freedom from tumor progression and survival curves were generated using the Kaplan–Meier method and Stata 9.0 statistical software (Stata Corp.) from the date of registration on the protocol.

Results

Patient Characteristics and Follow-Up

Sixty-three patients (38 men and 25 women) with 74 tumors (61 spinal and 13 paraspinal) were enrolled in the study between November 2002 and March 2005. The median age of the patients was 59 years (range 21–82 years). The 74 spinal metastatic tumors were located in the cervical (five lesions [6.7%]), thoracic (43 lesions [58.1%]), lumbar (25 lesions [33.8%]), and sacral (one lesion [1.3%]) spine. The median tumor volume was 37.4 cm³ (range 1.6–358 cm³). Primary cancer diagnoses were RCC in 25 (39.7%) of 63 patients, breast cancer in nine (14.3%), sarcoma in eight (12.7%), lung cancer in seven (11.1%), melanoma in two (3.2%), colon cancer in one (1.6%), unknown primary cancer in two (3.2%), and other in nine (14.3%). In 51 patients (81%) SBRT was used to treat a single spinal metastasis and in 12 (19%) it was used to treat two spinal metastases. Baseline Karnofsky Performance Scale scores were 90 in 25 patients (39.7%), 80 in 17 (27%), 70 in 17 (27%), and 60 in four (6.3%).

The median follow-up period was 21.3 months (range 0.9–49.6 months). The follow-up range was 10.3 to 30.7 months in the 25th to 75th percentile of cases. The lower range of follow-up (0.9 months) is due to the fact that one patient died of systemic cancer progression shortly after undergoing stereotactic spinal radiotherapy. For patients still alive in the study, the minimum follow-up duration was 13.1 months.
Prior Treatments

Prior spine irradiation to the site of interest occurred in 35 (55.6%) of 63 patients prior to study enrollment. The previous median prescribed dose was 33 Gy (range 30–54 Gy). However, the previous spinal cord dose did not exceed 45 Gy, a requirement for eligibility for the study. A surgical spine procedure had been performed in 29 patients (46%) before study enrollment. Previous operations included stabilization involving the placement of cortical screws and plates, rods, carbon fiber cages, cement, and bone allograft when necessary (Table 1). Postoperative treatment is defined as SBRT administered with postoperative intent as part of the overall treatment plan in patients within 6 months of surgery. Using this definition, the number of patients undergoing surgery in conjunction with postoperative SBRT was 15 (23.8%). Salvage SBRT is defined as targeting the spine in the setting of disease progression or recurrence after previous surgery or radiation therapy. In the current study, SBRT was undertaken as salvage treatment in 10 patients (15.9%) and definitive treatment in 38 (60.3%). The median interval between prior surgery and SBRT for postoperative and salvage cases is summarized in Table 2.

Statistical Assessment of Probability of Safety

There were no cases of Grade 4 neurological toxicity including paralysis in the 63 patients. If we postulated before the study that any paralysis rate was as likely as any other (a very pessimistic view), then the evidence of no cases of paralysis in 63 patients would provide strong evidence that the paralysis rate was less than 0.05. In this trial there is a 95% probability that the paralysis rate is less than 0.046.

Treatment Effectiveness

At the time of analysis, 17 cases of tumor progression were documented on imaging studies, and 37 patients (59%) had died. The actuarial 1-year rate of freedom from imaging-documented tumor progression was 84% and the 1-year survival rate was 69.8% (Fig. 2). The median survival time was 24.3 months. Tumor categorization by volume (≤ 40 cm³ or > 40 cm³), history of irradiation, history of surgery, and history of fraction number (five or three) did not reveal statistical differences in freedom from tumor progression for any of these variables. Based on results of the BPI, the extent of mean worst pain declined over time (Fig. 3) compared with the mean pretreatment baseline BPI measurement. Documented narcotic usage fell from 60% at baseline to 36% at 6 months.

The McCormick neurological function scores are provided in Table 3. At the last follow-up examination Grade 3 neurological function was noted in two patients and was attributed to disease progression in one patient and a recent hip replacement in the other.

Patterns of Failure

Seventeen (23%) of 74 treated tumors exhibited imaging progression. A summary of the patient and tumor characteristics of those in whom SBRT treatment failed is given in Table 4. The corresponding locations for representative tumor failures are also provided—in the thoracic (Fig. 4 left) and lumbar (Fig. 4 right) spine. Two patterns of failure were identified in this series as occurring in the following regions: 1) the osseous margin posterior to the site of VB treatment, and 2) the epidural space.

Recurrences in the epidural space were documented in eight (47%) of 17 tumors that progressed. These recurrences were probably due in part to radiation underdosing in the region as a result of spinal cord constraints (Tumors
Stereotactic radiotherapy for spinal metastases

2, 3, 6, 8, 12, 14, 15, and 17 in Table 4). In addition to disease encroachment into the epidural space, Tumor 8 also failed in the superior endplate of the VB immediately below by spreading across the anterior longitudinal liga-

Recurrent disease in the pedicles and posterior elements was identified in three (17.6%) of 17 tumors that pro-
gressed (Tumors 1, 9, and 13 [Table 4]). These recurrences were due to the fact that these structures were not routine-
ly included in the target volume unless visibly involved with tumor.

Other types of failure also occurred. Tumor 5 progressed in the pre- and paravertebral regions after irradiation of the VB only. For Tumors 4 and 7 (both in the same patient), tumor progression developed in the posterior edge of the VBs due to radiation underdosing regulated by spinal cord con-
straints. This patient had also previously undergone vertebroplasty. Tumor 9 was a large paraspinal lesion aris-
ing from an RCC that progressed in situ. The case of Tu-
mor 12 involved progression of a superior sulcus lung can-
cer 1.9 months after treatment of disease encroaching into the C7–T2 neural foramen. Tumor 15 involved a massive L3–5 paraspinal leiomyosarcoma that progressed in the irradiated regions of the vertebral, parapinsal, and epidural disease. Tumor 16 involved irradiated lung adenocarcin-
oma metastatic to the L1–3 vertebrae, which subsequently collapsed, causing spinal cord compression, and intractable pain. The patient underwent salvage surgery in which we performed an L-1 vertebrectomy, reconstruction with ex-
pandable titanium cage, and T11–L3 fusion. Tumor 17 in-
volved breast cancer in the posterior elements of T10–11. The patient developed new epidural disease 4.3 months after undergoing radiotherapy and also developed lepto-
meningeal seeding throughout the spine.

Clinical Toxicity

There have been no cases of Grade 3 or 4 neurological toxicity to date. There was one case of Grade 3 nausea, vomiting, and diarrhea; one case of Grade 3 dysphagia and trismus; and one case of Grade 3 noncardiac chest pain. The chest pain was an isolated case, which may have been due to radiation-related costochondritis, but a cardiac origin

![Fig. 3. Graph depicting mean BPI scores reflecting patients’ worst pain. Tx = treatment.](image)

![Fig. 4. Illustrations of the location and pattern of representative selected treatment failures in the thoracic (left) and lumbar (right) spine. Each number indicates the location where a particular irradiated tumor failed and corresponds to the numbered tumor listed in Table 4.](image)

<table>
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<tr>
<th>Neurological Function Grade*</th>
<th>Baseline</th>
<th>Last Follow-Up</th>
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</thead>
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<tr>
<td>1</td>
<td>54 (94.7)</td>
<td>47 (82.5)</td>
</tr>
<tr>
<td>2</td>
<td>3 (5.3)</td>
<td>8 (14)</td>
</tr>
<tr>
<td>3</td>
<td>0 (0)</td>
<td>2 (3.5)</td>
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<tr>
<td>4</td>
<td>0 (0)</td>
<td>0 (0)</td>
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* Neurological function definitions: Grade 1, normal to mild focal def-
cit; Grade 2, moderate deficit, significant motor or sensory loss, but able
to function independently; Grade 3, moderate to severe deficit, requires as-
sistance to ambulate; and Grade 4, severe deficit, unable to function inde-
pendently to ambulate.
† Of 63 study patients, 57 had baseline and follow-up neurological func-
tion data available.
was ruled out. One patient, mentioned previously, developed Grade 3 dysphagia and trismus after treatment of a large RCC metastasis centered on C-2. This patient underwent occipitocervical fusion prior to coming to our institution and already had some dysphagia due to the position in which his head was stabilized. The beam arrangement, radiation treatment plan, and dose–volume histogram are shown in Fig. 5.

The patient underwent an elective tracheostomy to protect his airway passage prior to the simulation. Grade 3 dysphagia and trismus developed, after the patient’s first treatment and he required hospitalization for supportive care.

There were no cases of Grade 4 toxicities observed in any category. Eight patients reported numbness or tingling categorized as Grade 1 toxicity that was difficult to distinguish from chemotherapy-related neuropathy. One patient who underwent repeated radiotherapy with SBRT for recurrent posterior element metastasis developed radiation-induced hyperpigmentation of the skin on the back 9 months after treatment.

Early Study Withdrawal

Three patients who did not receive treatment had to be withdrawn early from the study. The first patient had a large abdominal girth that distorted the stereotactic body frame, making accurate stereotactic localization impossible. The second patient had coexisting spinal metastases and spinal hemangiomatous originally misinterpreted as metastases. When the diagnosis of the targeted lesion was clarified, we aborted the procedure, and the patient was removed from the study. The third patient was prepared for the procedure but suffered rapid clinical deterioration and went into hospice, never receiving the treatment.

Discussion

Safety and Feasibility

This current report extends our previous findings on the safety and feasibility of SBRT for spinal metastases in the cervical, thoracic, lumbar and sacral segments. It appears that frame-based SBRT is feasible except for morbidly obese patients. With a median follow-up duration of 21.3 months and an end range of 49.6 months, we have not observed any evidence of myelitis, myelopathy, or paralysis. Meticulous attention was paid to the accuracy of patient setup to maximize safety. No case of Grade 3 or 4 neurological toxicity was observed despite the fact that 55 and 46% of the patients had undergone previous radiotherapy and surgery, respectively. Acute gastrointestinal tract toxicity was minimal with routine prophylactic antiemetic med-

<table>
<thead>
<tr>
<th>Tumor No.</th>
<th>Patient Age (yrs)</th>
<th>Histology</th>
<th>Original Site</th>
<th>Level</th>
<th>Tumor Vol (cm³)</th>
<th>TTP (mos)</th>
<th>Prior Treatments</th>
<th>POF</th>
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<td>T-11</td>
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<td>ped, lam</td>
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<td>PE†</td>
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<td>ES</td>
<td>PE†, dose‡</td>
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<td>dose‡</td>
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* Tumors 4 and 7 were treated in the same patient. Abbreviations: ALL = anterior longitudinal ligament; ASC = anal squamous carcinoma; ES = epidural space; HC = hepatocellular; IFF = in field failure; kypho = kyphoplasty; LA = lung adenocarcinoma; lam = lamina; LMD = leptomeningeal disease; LMS = leiomyosarcoma; MF = marginal failure; OCCA = ovarian clear cell carcinoma; PE = posterior element; ped = pedicle; PM = paraspinal muscle; POF = pattern of failure; PRS = partial resection and stabilization; TTP = time to tumor progression; VS = vertebrectomy and stabilization; Vst = vertebroplasty.
† Posterior elements not treated.
‡ Underdosing due to spinal cord constraints.
Stereotactic radiotherapy for spinal metastases

In our experience the cervical portion of the spine remains the most challenging to immobilize and localize because of shoulder interference with the stereotactic frame, and the deformability of the neck in which spatial relationships between the target and critical anatomical structures change on a day-to-day basis. Neck flexion, extension, and twisting of the upper and lower portions of the cervical spine in opposite directions can occur. Targets in the cervicothoracic junction are difficult to treat because the shoulders can impede the placement of the stereotactic body frame. Furthermore, head and neck immobilization is difficult in situations in which targets located at the C7–T1 level are at the greatest distance from the immobilization device.

We do not believe that more rigid fixation devices (except for the cervical spine) would be advantageous dosimetrically, as we have already demonstrated the ability to deliver stereotactic radiation therapy with an accuracy of within 1 mm. In addition, more rigid fixation devices may sacrifice patient comfort and may unwittingly contribute to involuntary patient movement. We currently plan and deliver stereotactic radiotherapy in our spine cases based on a setup uncertainty of 1 mm. The current 5-mm distance required for critical structures is related most to the physical

Patient Immobilization

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penumbra of multiple beams and to a much lesser extent, setup uncertainty.

**Treatment Effectiveness**

The actuarial 1-year rate of freedom from imaging tumor progression was 84%. Although spinal SBRT is relatively new, there are now published reports reflecting institutional experiences related to the adoption of this modality. We have summarized selected studies in which the investigators used fractionated and single-session treatments (Table 5). Yamada et al., using image-guided and stereotactic IMRT for paraspinal primary and metastatic tumors, reported a local control rate of 75 to 81% with 90% of patients experiencing palliation of pain, weakness, or paresthesias. Ryu et al. reported that complete or partial pain relief was achieved in 85% of the 49 patients who underwent stereotactic radiosurgery for spinal metastases. Using the Cyber-
Stereotactic radiotherapy for spinal metastases

Knife, Gerszten et al. reported 88–90% radiographic tumor control of spinal metastases and no spinal cord damage attributable to the radiation dose. The common use of large fraction sizes with SBRT may help overcome the shoulder in radioresistant tumors as well as those tumors that have progressed after conventional radiation therapy. This may be an advantage in particular for late-responding tissues with low α/β.

Palliation of Spinal Metastases

The aggressive treatment of spinal metastases with SBRT appears worthwhile given the patients’ median survival time of 24.3 months from the time of enrollment. One of the goals of spinal SBRT is to achieve pain control so that reliance on narcotic medication can be reduced or eliminated. In our study, we were able to demonstrate that narcotic medication usage declined by 6 months compared with baseline usage. In addition, there was a reduction in mean worst pain as assessed by BPI at 4 weeks posttreatment.

Patterns of Failure and Target Delineation

A total of 17 spinal metastases were shown on imaging studies to have progressed after SBRT. Three tumors were very large (113, 149, and 358 cm²). Analyzing each failure in conjunction with the radiotherapy treatment plan, it is apparent that there were two major reasons for tumor progression as follows: 1) the failure to adequately extend the radiation field posteriorly beyond the area of visible tumor to include the pedicles and posterior elements, and 2) the underdosing of the epidural space in an attempt to limit the spinal cord dose. This latter reason must be viewed in the context of their being recurrent cases—seven of 17 in which SBRT was a repeat treatment. To rectify the first cause, it is conceivable that one could routinely include the pedicles and posterior elements in the high-dose region of radiation field, thereby widening the osseous margin. This may complicate dose delivery to the tumor and protection of the spinal cord. The problem of irradiating the epidural space is also difficult, because this may increase the risk of radiation-related myelopathy. The spinal cord constraint of 9 to 10 Gy may be overly conservative for previously unirradiated cases, but it is probably appropriate for previously irradiated cases. Future trials that involve dose escalation of SBRT will be of interest and the authors will need to evaluate the safety of using higher doses of radiation than those used in our trial because the true limit on spinal cord tolerance is still not well defined. In the meantime, spinal SBRT appears to be safe, feasible, and effective for patients with a wide variety of tumor types.

Conclusions

These data support the safety and effectiveness of SBRT for spinal metastases. It appears prudent to routinely treat the pedicles and posterior elements using a wide bone margin posterior to the diseased vertebrae because of possible direct extension into these structures. For previously unirradiated cases, more liberal spinal cord dose constraints than those used in the present study could be applied to help reduce failures in the epidural space.

References


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