Title

The era of stereotactic body radiotherapy for spinal metastases and the multidisciplinary management of complex cases

Journal

Neuro-Oncology Practice, 3(1)

ISSN

2054-2577

Authors

Kumar, Rachit
Nater, Anick
Hashmi, Ahmed
et al.

Publication Date

2016-03-01

DOI

10.1093/nop/npv022

Peer reviewed

Neuro-Oncology Practice

Neuro-Oncology Practice 3(1), 48–58, 2016
doi:10.1093/nop/npv022
Advance Access date 27 July 2015

The era of stereotactic body radiotherapy for spinal metastases and the multidisciplinary management of complex cases

Rachit Kumar, Anick Nater, Ahmed Hashmi, Sten Myrehaug, Young Lee, Lijun Ma, Kristin Redmond, Simon S. Lo, Eric L. Chang, Albert Yee, Charles G. Fisher, Michael G. Fehlings, and Arjun Sahgal

Division of Radiation Oncology, Banner MD Anderson Cancer Center, Gilbert, AZ (R.K.); Division of Neurosurgery, Department of Surgery, Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada (A.N., M.G.F.); Department of Radiation Oncology, Sunnybrook Odette Health Sciences Centre, University of Toronto, Toronto, ON, Canada (A.H., S.M., Y.L., A.S.); Department of Radiation Oncology, University of California San Francisco, San Francisco, CA (L.M.); Department of Radiation Oncology, Johns Hopkins University School of Medicine, Baltimore, MD (K.R.); Department of Radiation Oncology, University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, OH (S.S.L.); Department of Radiation Oncology, University of Southern California, Los Angeles, CA (E.L.C.); Division of Orthopedic Surgery, Sunnybrook Odette Health Sciences Centre, University of Toronto, Toronto, ON, Canada (A.Y.); Division of Orthopedic Surgery, Vancouver General Hospital, University of British Columbia, Vancouver, BC, Canada (C.G.F.)

Corresponding Author: Rachit Kumar, MD, Adjunct Assistant Professor, Division of Radiation Oncology, Banner MD Anderson Cancer Center, 2946 E. Banner Gateway Dr., Gilbert, AZ 85204 (rachit.kumar.md@gmail.com).

Spinal metastases are increasingly becoming a focus of attention with respect to treating with locally "ablative" intent, as opposed to locally "palliative" intent. This is due to increasing survival rates among patients with metastatic disease, early detection as a result of increasing availability of spinal MRI, the recognition of the oligometastatic state as a distinct sub-group of favorable metastatic patients and the advent of stereotactic body radiotherapy (SBRT). Although conventionally fractionated radiation therapy has been utilized for decades, the rates of complete pain relief and local control for complex tumors are sub-optimal. SBRT has the advantage of delivering high total doses in few fractions (typically, 24 Gy in 1 or 2 fractions to 30–45 Gy in 5 fractions) that can be considered "ablative". With mature clinical experience emerging among early adopters, we are realizing beyond efficacy the limitations of spine SBRT. In particular, toxicities such as vertebral compression fracture, and epidural disease progression as the most common pattern of local tumor progression. As a result, the multidisciplinary evaluation of cases prior to SBRT is emphasized with the intent to identify patients who could benefit from surgical stabilization or down-staging of epidural disease. The purpose of this review is to provide an overview of the current literature with respect to outcomes, technical details for safe delivery, patient selection criteria, common and uncommon side effects of therapy, and the increasing use of minimally invasive surgical techniques that can improve both safety and local control.

Keywords: metastasis, SABR, SBRT, spine, stereotactic.

Spinal metastases are a common complication arising from several solid malignancies, most commonly from prostate, lung and breast cancer. Over 20,000 patients are affected annually.[1] While some patients present with asymptomatic tumors diagnosed on staging or screening imaging, many will present with pain, fracture, or the potentially devastating and irreversible state of symptomatic malignant epidural spinal cord compression (MESCC).

Conventional external beam radiotherapy (cEBRT) is a mainstream therapeutic modality with the intent to reduce the pain associated with spinal metastases, and typical doses include 8 Gy in 1 fraction, 20 Gy in 5 fractions, and 30 Gy in 10 fractions.[2] A representation of a cEBRT dose distribution is depicted in Figure 1A. cEBRT has been proven to yield high rates of partial pain relief; however, complete pain relief rates remain poor ranging from 0% to 20%.[3,4] With respect to imaging-based local tumor control, it has been suggested that isolated, marrow-confined disease may be effectively controlled with fractionated cEBRT and control rates are ~85% at 1 year; however, complex, bulky "mass" type tumors may be associated with poor imaging-based local control rates of ~45% at 1 year.[5] These results suggest room for improvement.

With the intent to maximize complete pain relief response and local control rates, the technique of stereotactic body radiotherapy (SBRT) was adapted to treat spinal metastases. The intent of SBRT is to deliver "locally ablative" doses of radiation in a convenient and effective schedule, typically no more than 5 fractions.[6] Spine SBRT doses, ranging from 24 Gy delivered in 1 to 2 fractions to 30 to 45 Gy in 5 fractions, represent up to 5 to 8 times the

Received 7 April 2015, Advance Access publication 27 July 2015

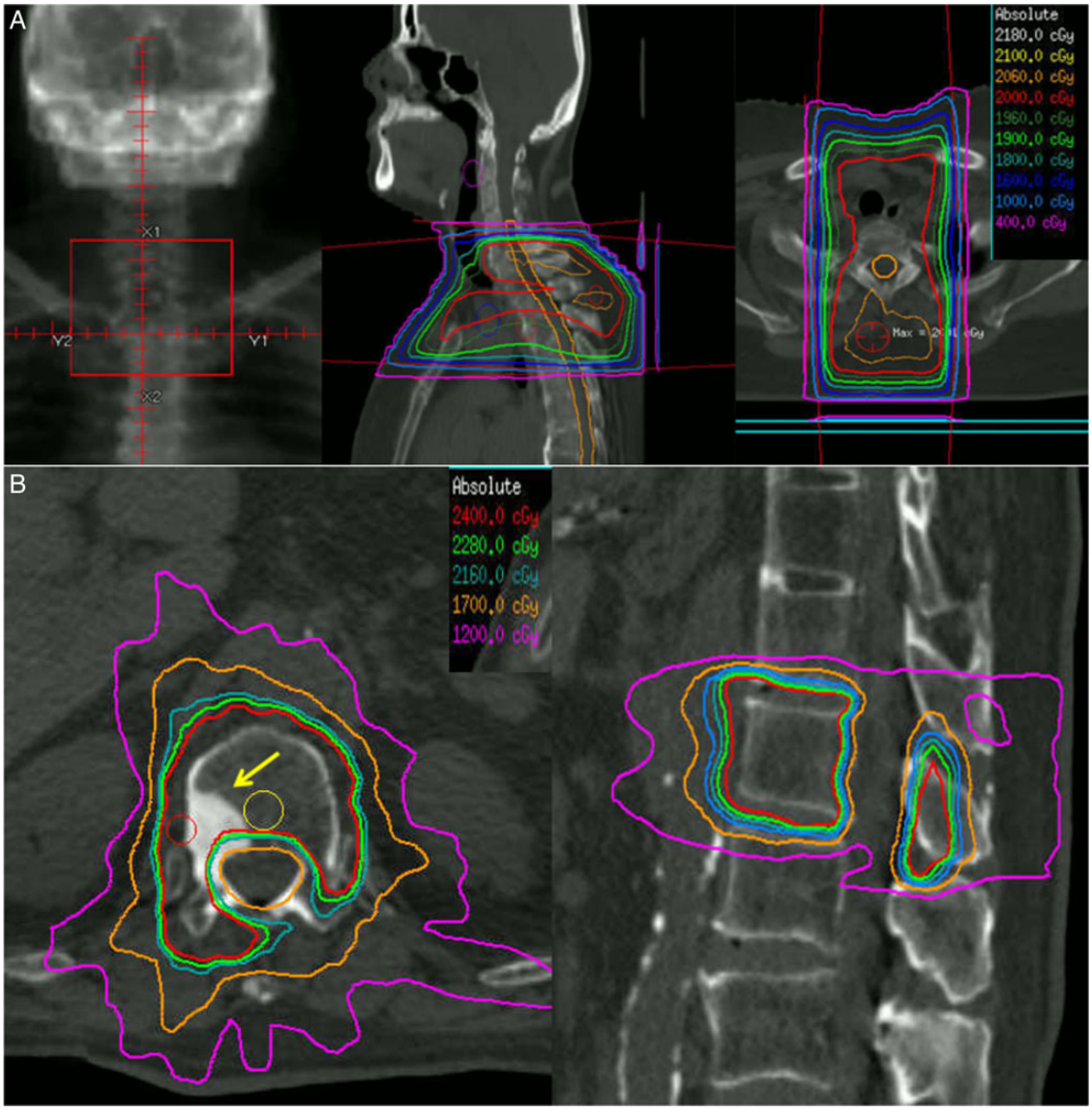

Fig. 1. (A) Patient with C7, T1 and T2 metastatic breast cancer treated with conventional external beam radiation therapy (cEBRT) with anterior-posterior beams. The radiation portal is shown on the left-most panel and represents a field encompassing the vertebral bodies from C5 to T4, the middle panel illustrates on sagittal view the dose distribution, and the entire anatomy (vertebrae and normal tissues in the beams' path) within the field is radiated to 95% of the prescribed dose of 20 Gy in 5 fractions. The right most panel is the axial view of the dose distribution illustrating again the entire anatomy within the radiation field (vertebrae and normal tissues in the beams' path) exposed to the prescribed dose. In both the middle and right panels the anterior and posterior beams are illustrated. The aim with cEBRT is not to spare the normal tissue but bathe the entire anatomy with a dose of radiation that is safe to the normal tissues and provides some efficacy with respect to the symptoms associated with the vertebral metastases. (B) Patient with a T12 sclerotic metastasis (yellow arrow) from prostate cancer involving the vertebral body and ipsilateral pedicle treated with 24 Gy in 2 fractions. The clinical target volume included the entire vertebral body and ipsilateral pedicle, lamina, and transverse process. The high-dose isodose lines (2400, 2280 cGy) are conforming around the anatomy with sparing of the contralateral posterior elements and spinous process. The thecal sac maximum dose was 17 Gy and the isodose line again wraps tightly around the spinal canal. There is limited dose exposure into the normal tissues.

equivalent of those doses typically delivered with cEBRT. One of the major initial barriers to the adoption of SBRT for spinal indications was the risk of radiation myelopathy, given the high doses and steep dose gradients directly adjacent to the spinal cord (Fig. 1B); however, with the advent of standardized contouring guidelines, strict technical requirements for delivery, and normal tissue tolerance guidelines for safe spinal cord practice, spine SBRT is currently regarded as a safe technique and being evaluated in a randomized trial.

The aim of this review is to provide a current update on the technological requirements, patient selection criteria and rationale, tumor and toxicity outcomes, and the integration with novel minimally invasive spine surgery to improve outcomes and safety.

Technical Aspects of SBRT Delivery in Spinal Metastases

Spine SBRT represents one of the most technically demanding treatments in radiation oncology. The process begins with a rigorous approach to radiation simulation. Near-rigid body immobilization has become a standard of care, and it has been shown that such devices increase patient position stability more than standard evacuated vacuum cushion immobilization devices during delivery.[7] Furthermore, it is patient bulk motion as opposed to physiologic cord motion that is significant, as recently reported by Tseng et al.[8] With respect to contouring, both thin slice CT and T1/T2 weighted axial MRI sequences are required, typically without contrast to ensure accurate target and spinal cord delineation. In cases with significant spinal hardware a CT myelogram may be required for spinal cord delineation. The accuracy of delineation and delivery is of paramount importance as even millimetric motions can have significant consequences on spinal cord dosimetry as shown by Ma and colleagues.[9]

There was initial controversy with respect to the appropriate target volume for spine SBRT. Some advocated for treatment of only the gross tumor volume (GTV), as visualized on CT and MRI (analogous to the principles of brain radiosurgery), while others treated a clinical target volume (CTV), which represents the GTV plus an anatomic region at risk of microscopic disease extension. At present, one series reported higher recurrence rates when treating GTV alone versus CTV.[10] As a result of a consortium of experts contouring several spine SBRT cases, it was observed that the most common approach was indeed to practice CTV-based spine SBRT.[11] The standard of care at this time is to delineate and treat the CTV.

The ideal total dose and fractionation remains controversial. There are conflicting reports regarding outcomes following single-fraction versus multiple-fraction SBRT, and no dose-finding randomized trials have been completed. There is no randomized evidence to support the superiority of spine SBRT over cEBRT, although RTOG 0631 is a randomized trial currently ongoing comparing 8 Gy in 1 cBERT to 16–18 Gy SBRT in 1 fraction (http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0631). Therefore, at this time the dose fractionations typical of spine SBRT can be considered equivalent with respect to efficacy. However, there may be differences in efficacy and toxicity, which future prospective data will better delineate.

Most modern image-guided radiation delivery technologies have the ability to deliver high precision SBRT. Examples include CyberKnife [a miniature LINAC mounted onto a robotic arm able to move the LINAC in all six degrees of freedom (Accuray, Inc., Sunnyvale, CA, USA)], and LINAC-based systems equipped with image-guidance, a sub-centimeter multileaf collimator, and a robotic couch top to adjust the patient's position in six degrees of freedom with millimetric accuracy.[12–15] Ultimately, strict adherence is required with respect to commissioning and quality assurance programs to ensure the apparatus to deliver SBRT is in accordance with American Association of Physicists in Medicine (AAPM) guidelines. There are no definitive data to support the superiority of one system over another.

Indications and Patient Assessment

The American Society of Therapeutic Radiation Oncology (ASTRO) formed a working group of experts in the treatment of bone and spinal metastatic disease to generate patient guidelines.[16] Key inclusion and exclusion criteria specific to spine SBRT were developed, but the field continues to evolve. A more modern and relevant approach to patient selection is shown in Table 1. This incorporates spinal instability based on the more recent and

Table 1. Guidelines for Spine SBRT

Criteria	Inclusion	Cautionary/Relative Contraindication	Exclusion
Radiographic	Spinal/paraspinal metastatic tumor	>3 contiguous segments	
	Bilsky epidural disease grade 0-1	Bilsky epidural disease grade 2	Bilsky epidural disease grade 3
	Maximum of 2-3 contiguous or 3 noncontiguous segments	Spinal malalignment	
Patient	Age >18 years		Inability to lie flat and tolerate treatment
	KPS ≥40–50		Contraindication to MRI and/or CT myelogram
	Oligometastatic disease	Widespread metastatic disease	Symptomatic spinal cord compression or cauda equina syndrome
	Life expectancy of at least 3 months		
Tumor	Histologic proof of malignancy	Radiosensitive histology such as myeloma/lymphoma	
	Oligometastatic spinal metastasis	>50% baseline vertebral fracture	
Previous Treatment	Previous external beam irradiation	Previous SBRT to the same level	EBRT within 90 days prior to SBRT
	Postoperative		Systemic radionuclide within 30 days prior to SBRT
Spinal Instability	No spinal instability (SINS score 0-6 points)	Potential spinal instability (SINS score 7–12 points)	Frank spinal instability (SINS score > 12 points)

KPS, Karnofsky performance status; EBRT, External beam radiation therapy; SBRT, Stereotactic body radiation therapy; SINS, Spinal Instability in Neoplastic Syndrome.

validated approach known as the Spinal Instability in Neoplastic Disease Score (SINS) classification.[17]

SINS identifies spinal metastases as stable, potentially stable, or unstable based on anatomic factors (location, spinal alignment, type of tumor [lytic, blastic, mixed], presence of fracture, posterior element involvement) and clinical factors (type of pain).[17] It has been validated among surgeons, radiation oncologists, and radiologists.[17–20] Patients with frank SINS instability warrant a surgical consult, which should be also considered prior to SBRT for patients with potential instability.[20]

One controversial topic remains the degree of epidural disease prior to SBRT. The ASTRO guideline stipulated a distance <5 mm between the cord and disease as a relative contraindication.[16] The Bilsky grading system characterizes the degree of epidural extension.[21] A Bilsky grade 0 implies no extension of the lesion beyond the vertebral body into the epidural space, Bilsky grade 1–2 demonstrates epidural disease with cerebrospinal fluid still visible, and a Bilsky grade 3 implies frank circumferential compression of the spinal cord without visible cerebrospinal fluid. A schematic representation of the Bilsky grading system is represented in Figure 2. Spinal metastases graded as a Bilsky 3 should have surgical consultation for consideration of decompression, and if surgery is contraindicated, then cEBRT at this time may be most appropriate. There is emerging evidence for spine SBRT in patients with cord compression but at present it should not be considered the standard of care and caution should be utilized unless in the context of a prospective clinical trial.[22] For Bilsky 2 tumors, if decompression is feasible, then there may be therapeutic benefit to downgrading the epidural disease to a Bilsky 0 or 1 following SBRT, as reported by Al-Omair et al.[23] Otherwise, SBRT for Bilsky 2 disease remains appropriate as a relative contraindication. Ideally, there should be at least 2 to 3 millimeters between the disease and the spinal cord to maximize tumor coverage considering that the typical dose fall-off at this interface ranges between 15% and 20% per millimeter.

Spine SBRT should be strongly considered in patients with oligometastatic disease, which is distinct from widely metastatic disease.[24] In these patients, aggressive ablative therapy to all known sites of metastatic disease may have an impact on long-term disease free status and these patients may remain curable despite the metastatic phenotype.[24] Specific to spine oligometasatic disease, from the analysis presented by Thibault et al, it is clear that the subset of renal cell patients with oligometastatic disease (5 or fewer sites of metastases) survived longer than patients with more extensive disease.[25] Therefore, in this population it may be imperative to treat with a modality that is aimed at long-term local tumor control.

Outcomes of Spinal SBRT in the Treatment of Metastases

Spine SBRT as Primary Treatment

There have been several reports of outcomes for spine SBRT in patients without a history of radiation (de novo metastases) and

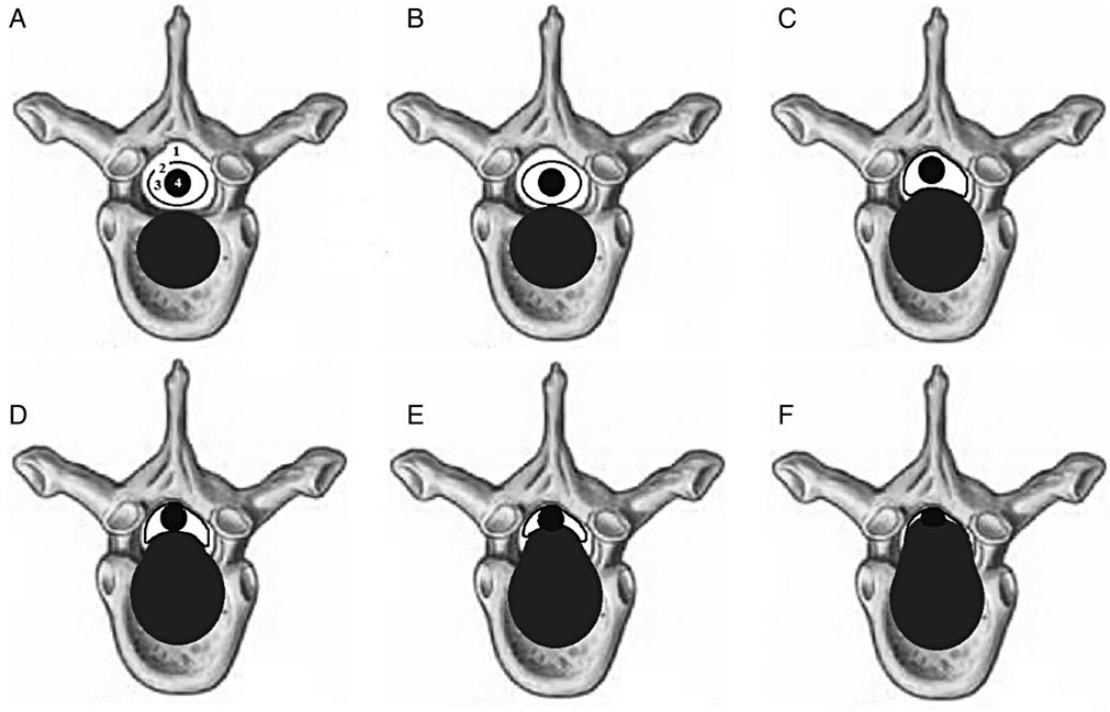

Fig. 2. Schematic of Bilsky 6-point grading system applied to the thoracic spine depicting epidural spinal cord compression.[21] (**A**) (1) Epidural space; (2) dural sac; (3) cerebrospinal fluid (CSF); (4) spinal cord. **Grade 0**, bone involvement only; (**B**) **Grade 1a**, epidural impingement without deformation of the thecal sac; (**C**) **Grade 1b**, deformation of the thecal sac without spinal cord abutment; (**D**) **Grade 1c**, deformation of thecal sac with spinal cord abutment, but without spinal cord compression; (**E**) **Grade 2**, spinal cord compression with CSF visible around the cord; (**F**) **Grade 3**, spinal cord compression without CSF visible around the cord.

selected series are summarized in Table 2.[25–35] Rates of local control range from 80% to 95% with various dose-fractionation approaches. Importantly, local control is high even in histologies traditionally considered radioresistant, for example, renal cell carcinoma and sarcoma. As a result, spine SBRT is redefining the concept of radioresistance, and suggesting that with enough dose these tumors can be controlled.

With respect to clinical pain response following SBRT, high rates of complete pain relief are also reported. For example, the Phase 1-2 study from MD Anderson measured quantitative pain response using the 11-point brief pain inventory in patients treated with spine SBRT.[36] Fifty-four percent of patients had no pain at 6 months following spine SBRT. Furthermore, important endpoints, including opioid use, quality of life, fatigue, malaise, appetite, nausea, and memory, all improved following treatment with spine SBRT. The current data support superior efficacy in this regard to cEBRT where complete pain response rates are low ranging from 0% to 25%.[2,28,37]

Spine SBRT Following Previous Radiation

cEBRT has been extremely limited in the re-treatment indication for spinal metastases. In order to respect the cumulative dose tolerance of the spinal cord, re-treatment cEBRT practice is to deliver a second course of radiation that is of a lower biologically effective dose than the first. This is somewhat counterintuitive with respect to tumor efficacy, as disease that fails initial radiation could be considered relatively radioresistant and, hence, to retreat with a lower dose implies strictly palliative intent with potential for only short-term gains in partial pain relief. This was shown in the randomized trial reported by Chow et al, in which reirradiation partial response rates and complete response rates for pain of up to 50% and 14%, respectively, were observed at the 2-month time point post-treatment.[38] These results are disappointing and there is significant room for improvement in these complex cases.

Given that spine SBRT allows for tumor dose escalation while simultaneously minimizing spinal cord dose exposure, one of the most common indications for this technique is reirradiation. Higher doses than previously treated with cEBRT may be delivered with the intent to maximize pain relief and local tumor control. The outcomes from selected re-treatment SBRT series are summarized in Table 2.[25,35,39–42] These data indicate high rates of local control ranging from 66% to 93%. In fact, two retrospective series have compared their re-treatment outcomes to those of de novo spinal metastases treated with spine SBRT, and observed equivalent rates of local control.[34,35] The comparison is limited by the retrospective nature of the studies, however valuable in that it shows the potential for spine SBRT to maximize tumor control and pain control as a more aggressive strategy. Furthermore, these comparisons imply that SBRT can overcome the radioresistance that led to tumor progression following cEBRT. A prospective study specific to re-irradiation was reported by Garg et al, which confirms local control of 76% at 1 year and an improvement in pain levels.[41] A randomized control trial would be ideal in this cohort, however, many practitioners question equipoise and ability to justify randomizing patients to a clearly inferior dose. Re-irradiation spine SBRT will unlikely be tested in a randomized control trial, and based on good prospective series and pooled analysis will be considered a standard of care.

Postoperative SBRT

Postoperative cEBRT has been the standard adjuvant treatment following spinal surgery for metastatic disease, but the long-term benefit of this treatment has not been well studied with imaging-based follow-up. In the few series reported, local recurrence rates are as high as 69.3% at 1 year following cEBRT.[43] After a major surgical procedure, it seems counterintuitive to apply a suboptimal adjuvant radiation therapy; however, management options were limited in this regard until the development of spine SBRT. Several postoperative spine SBRT series have been reported with imaging-based follow-up and summarized in Table 2.[23,44–48] Essentially, local control rates range between 70% and 100% taking into account the different dose fractionations and surgical techniques.

Two major postoperative spine SBRT series have been reported following predominantly open invasive surgery. Laufer et al reported on 186 patients with MESCC who initially underwent surgical decompression and instrumentation.[47] The 1-year local control rate was 83.6%. Al Omair et al reported on 80 patients treated at the University of Toronto with postoperative spine SBRT with a median SBRT dose of 24 Gy in 2 fractions, and reported a 1-year local control rate of 84%.[23] On further analysis, postoperative Bilsky grade was observed to be an important predictor of local control, and confirmed that the extent of epidural disease is indeed an important predictor of local failure. In both studies the median duration between surgery and starting adjuvant SBRT was 1.6 months and 1.2 months, respectively.[23,47] One concern that had been initially considered specific to postoperative spine SBRT was hardware failure; however, both series reported a very low incidence of this adverse event (under 5%). As postoperative spine SBRT becomes increasingly practiced, further series will emerge and prospective studies initiated to generate the high-level evidence to support more widespread adoption. As radiation technology has impacted delivery, surgical technology is also advancing and changing the traditional concepts of spine surgery. The focus is now directed on less invasive procedures to compliment SBRT and reduce complications. Furthermore, implants such as Peek Rods and Cages are being used to minimize imaging artifact and facilitate radiation planning.

The Evolution to Minimally Invasive Spine Surgery

Traditional indications for spine surgery specific to metastatic disease have included neurological deficits (sensorimotor, bowel/bladder, or sexual dysfunction) due to neural compression, imminent or frank instability including intractable mechanical or neurological pain, radioresistant tumors (eg, sarcoma, colon, renal cell), and radiation therapy failure, ie, tumor progression during or after radiotherapy.[49–51]

Given that metastatic spinal disease typically arises at the junction of the vertebral body and the pedicle and extends posteriorly to invade the spinal canal, surgery has typically required extensive approaches to access the vertebral body via an anterior, posterior, or combined (ie, both anterior and posterior) approach.[49,50] Although thoractomomy-based anterior approaches, which include transthoracic and retropleural procedures, provide the best direct access to the vertebral bodies, they are technically challenging and offer specific problems. Alternatively, anterior

Table 2. Results from select series using spine SBRT

Author (Year)	Tumor/ Patients Treated	Histology	Follow-Up (median months)	Local Control	Complete Pain Response	Overall Survival	Tumor Dose/Number of Fractions (range)
De Novo Treatment							
Yamada (2008)[30]	60/39	Mixed	15	90% (1 yr)	nr	Median 15 mos	24 Gy/1 fx
Sahgal (2009)[35]	23/14	Mixed	21	85% (1 yr)/69% (2 yr)	nr	nr	Median 24 Gy/3 fx
Wang (2012)[31]	166/149	Mixed	16	81% (1 yr)/72% (2 yr)	54%	Median 23 mos	27–30 Gy/3 fx
Ahmed (2012)[32]	63/46	Mixed	8.2	91%	nr	59% (1 yr)	Median 24 Gy/3 fx
Park (2014)[34]	45/28	Mixed	7.4	95% (1 yr)	nr	47% (1 yr)/28% (2 yr)	Median 27 Gy/3 fx (18–35 Gy/1–5 fx)
Folkert (2014)[29]	120/88	Sarcoma	12.3	87.9% (1 yr)	nr	Median 16.9 mos	Median 28.5 Gy/3–6 fx or 24 Gy/1 fx
Sohn (2014)[28]	13/13	Renal cell	nr	85.7% (1 yr)	23.1%	Median 15 mos	Mean 38 Gy/4 fx
Guckenberger (2014)[27]	387/301	Mixed	11.8	90% (1 yr)/84% (2 yr)	76.8%	65% (1 yr)/44% (2 yr)	Median 24 Gy/3 fx (10–60 Gy/1–20 fx)
Thibault (2014)[25]	60/37	Renal cell	12.3	83.4%*	nr	64.1% (1 yr)*	Median 24 Gy/2 fx
Sellin (2015)[33]	40/37	Renal cell	49.0	57%	32.4%	Median 16.3 mos	Median 24 Gy/1 fx
Anand (2015)[26]	76/52	Mixed	8.5	94% (1 yr)/83% (2 yr)	92.3%	68% (1 yr)/45.4% (2 yr)	24–27 Gy/3 fx or 14–18 Gy/1 fx
Postoperative Treatment							
Gerszten (2005)[44]	36/36	Mixed	16	nr	92% (1 yr)	nr	Mean 18 Gy/1 fx
Gerszten (2009)[45]	11/11	Mixed	11	100%	90%	nr	Mean 19 Gy/1 fx
Massicotte (2012)[46]	10/10	Mixed	13	70%	80%	nr	Median 24 Gy/3 fx
Laufer (2013)[47]	186/186	Mixed	7.6	83.6% (1 yr)	nr	Median 5.6 mos	24 Gy/1 fx or 27 Gy/3 fx or 30 Gy/5 fx
Al Omair (2013)[23]	80/80	Mixed	8.3	84%	nr	64% (1 yr)	Median 24 Gy/2 fx
Bate (2015)[48]	21/21	Mixed	9.8	90.5% (1 yr)	nr	nr	16–23 Gy/1 fx
Reirradiation Treatment							
Sahgal (2009)[35]	37/25	Mixed	7	92% (1 yr)	nr	45% (2 yr)	24 Gy/3 fx (previous mean dose 36 Gy/14 fx)
Choi (2010)[39]	51/42	Mixed	7	87% (6 mos)/73% (1 yr)	65%	68% (1 yr)	Median 20 Gy/2 fx (previous mean dose 40 Gy/20 fx)
Mahadevan (2010)[40]	81/60	Mixed	12	93%	nr	11 mos	25–30 Gy/5 fx or 24 Gy/3 fx (previous mean dose 30 Gy/10 fx)
Garg (2011)[41]	63/59	Mixed	17.6	76%	nr	76% (1 yr)	27 Gy/3 fx or 30 Gy/5 fx (previous mean dose 30 Gy/nr fx)
Damast (2011)[42]	97/94	Mixed	12.1	66% (1 yr)	46%	52–59%	20 Gy/5 fx or 30 Gy/5 fx (previous mean dose 30 Gy/nr fx)
Thibault (2014)[25]	11/37	Renal cell	12.3	83.4%*	nr	64.1% (1 yr)*	Median 24 Gy/2 fx (previous mean dose 30 Gy/10 fx)

SBRT: stereotactic body radiation therapy; RT: radiation therapy; Gy: Gray; yr: year; nr: not reported; mos: months; fx: fractions.
*Denotes combined analysis of de novo treatment and reirradiation patients.

decompression can be achieved via posterior-based approaches, such as transpedicular or costotransversectomy, and via posterolateral extracavitary approaches, in which the access is more lateral with regards to the paravertebral muscles.[50,52] However, regardless of the approach used, circumferential decompression is generally associated with significant spinal destabilization, which commands stabilization/reconstruction of the spinal column.[50,53] With the recent advancements in posterolateral exposures, they have now become the preferred method to safely decompress anterior pathology and stabilize the spine through one incision.

Numerous studies support the positive impact of traditional open spinal decompression combined with stabilization/reconstruction on functional, neurological, and health-related quality of life outcomes in selected symptomatic spinal metastases patients.[54–66] However, conventional surgical interventions are associated with non-negligible mortality rates within 30 days after surgery, and significant complication rates. A recent systematic review summarized the risks and reported a 30-day postoperative mortality rate of 5% (range 0%–22%), and an overall complication rate of 29% (range 5%–65%).[66] This adverse event profile, coupled with the considerable physical frailty exhibited by most

patients with spinal metastatic disease, necessitates careful patient selection when considering surgical intervention.[53,67]

With the Patchell[56] randomized study supporting the role of surgery to improve neurologic and functional outcomes for patients with single level MESCC, demands for spinal surgery have increased and there is pressure to modernize the approach to minimize the morbidity. As a result, minimally invasive spine surgery (MISS) emerged, and stemmed from the development of recent surgical technical advances, including visualization aids and spinal instrumentation methods.[53,68] According to McAfee et al, a MISS procedure is "one that by virtue of the extent and means of surgical technique results in less collateral tissue damage, resulting in measurable decrease in morbidity and more rapid functional recovery than traditional exposures, without differentiation in the intended surgical goal."[69] A MISS procedure, therefore, involves (i) reduced iatrogenic tissue damage, which is associated with greater postoperative pain, chronic pain and muscle atrophy; (ii) measurable clinical benefits, such as decreased blood loss, infection rates, hospitalization times, postoperative analgesic usage, and earlier return to normal life activities; (iii) clinical effectiveness; and (iv) favorable socioeconomic effect.[53,69]

Molina et al further distinguished two main modalities of spinal MISS: endoscopic video-assisted thoracospoic surgery (VAST) and minimal access spine surgery (MASS).[67] "Mini-open," "tubular," and "percutaneous" are examples of terms seen in the MASS literature, which reflect the various degrees at which these techniques attempt to minimize exposure-related morbidity.[69] Spinal decompression and reconstruction can be performed via mini-open and percutaneous (ie, stab incision, notably used for pedicle screw placement) techniques.[70,71] In addition, decompression and interbody fusion can be achieved under endoscopic or direct visualization through narrow surgical corridors (ie, tubes), typically placed following sequential tissue dilation, thus preserving the integrity of the multifidus muscles.[46,53,69]

Polymethylmethacrylate (PMMA) or methylmethacrylate bone cement have immediate stability and superb load-bearing properties when placed for anterior column support.[72] They are used for vertebral body stabilization/reconstruction in spinal surgeries as well as percutaneous vertebral augmentation procedures, namely vertebroplasty and kyphoplasty. The latter techniques are not only becoming increasingly used for the treatment of painful pathological fractures due to metastatic spine disease, but also in stabilization after decompression of metastatic spinal lesion.[45,46,70,73–76]

MISS techniques offer promising advancements in the treatment of metastatic spinal lesions and, most importantly, may broaden the spectrum of surgical candidacy. Although the superiority of MISS compared with traditional open surgery in these patients appears obvious and intuitive, there is no Class I evidence; such a trial is unlikely to be conducted given the questionable surgical equipoise. Therefore, as these techniques develop further and gain acceptance in mainstream practice, MISS will likely become a prominent approach in metastatic patients; however, many patients will still require traditional open spinal surgery to achieve surgical objectives necessary for a successful outcome.

Postoperative SBRT combined with MISS

Evidence is emerging from studies of combined MISS and SBRT, and Gerszten et al were among the first to explore a change in the paradigm of treating patients with painful pathologic vertebral compression fracture (VCF) with kyphoplasty followed by SBRT. Of the 26 patients studied, 92% achieved complete pain control at 1 year. With respect to MISS-based decompression, both Gerszten et al and Massicotte et al have reported initial experiences, but with two distinct techniques. Gerzten et al reported on 11 patients treated initially with a completely percutaneous transpedicular cavitation and cement augmentation approach. This novel technique uses Coblation technology to remove tissue with a radiofrequency plasma dissolution process. A Cavity SpineWand (ArthroCare Corp., Sunnyvale, CA, USA) is introduced percutaneously and this is followed by kyphoplasty with PMMA inserted into the created cavity. SBRT then followed within a median time of 14 days and a mean dose of 19 Gy in a single fraction. All patients were free from local recurrence given the median follow-up of 11 months, 90% had improvement in pain, and no wound complications were reported. Massicotte et al uniquely performed MASS using a tubular retractor, and cement augmentation as needed, as an outpatient day surgery.[46] SBRT with a median dose of 24 Gy in 3 fractions was delivered and the median time from surgery to SBRT was 7 days. The study reported local control in 70% of the 10 patients given a median follow-up of 13 months, and no patient had wound complications. These series provide preliminary evidence to support MISS-based approaches combined with SBRT, with benefits of significantly shortening recuperation times and potential for lower rates of wound and other complications, which would ultimately minimize delays in further oncologic management.

Patterns of Failure

With multiple series now reported in the literature, and the increasing practice of reporting patterns of failure, epidural disease progression is the most common site of failure despite the indication (de novo, re-treatment, postoperative).[77] This observation may be secondary to aggressive tumor biology, relative underdosing of disease within the epidural space to maintain spinal cord tolerance, or outright avoidance of the area due to the conformal design inherent to spine SBRT versus cEBRT.

In addition, there appears to be a relationship between the epidural disease grade (based on the Bilsky system, Fig. 2) and the risk of local failure. Patients with high-grade disease (epidural disease compressing the cord) had inferior rates of local control compared with low-grade epidural disease.[23] Furthermore, if surgery effectively downstaged high-grade disease, those with maximal debulking to a Bilsky 0/1 vs a Bilsky 2 had superior rates of local tumor control. These data were first to show a therapeutic advantage to epidural disease resection for local control. Therefore, with high-grade epidural disease, such as a Bilsky 3, surgery is optimal, followed by postoperative spine SBRT. Bilsky 2 disease remains a relative contraindication with the recommendation to surgically downgrade when feasible.

Toxicities of Spine SBRT

One of the major initial barriers to the widespread adoption of spine SBRT was the fear of radiation-induced myelopathy. This stemmed from the lack of knowledge of spinal cord tolerance

for high-dose hypofractionated radiation. However with protocols such as RTOG 0613 and evidence-based guidelines as published by Sahgal et al, for both patients with and without prior radiation exposure, radiation myelopathy is a rare and unexpected toxicity; indeed, we encourage adopters of spine SBRT to reference both of these sources to maximize safety during radiation planning and plan evaluation.[78]

A more common, serious, and SBRT-specific toxicity is the development of VCF.[2,79] It has been observed, in a large multi-institutional study, that the risk of VCF is 12.4% at 1 year and 13.5% at 2 years post-spine SBRT. However, factors such as delivery of high-dose-per-fraction SBRT ($\geq$24 Gy v 20 to 23 Gy v $\leq$19 Gy), baseline VCF, lytic tumor, and spinal deformity increase the risk. These data suggest that patient selection is a major issue and predictive tools or algorithms to identify who would benefit most from prophylactic stabilization are in need. SINS is one such tool for mechanical instability, and the presence of 3 of 6 criteria may be predictive of SBRT-induced VCF.[80]

The choice of dose fractionation is one factor that is controllable and can be used as a strategy to mitigate the VCF risk. At 24 Gy in 1 fraction, the risk of VCF was 40% in the multi-institutional analysis, and this confirmed an earlier report. However, the time of onset varied between the two series.[2,79] With a lower dose per fraction, the rate of VCF significantly drops to 20% with 20 to 23 Gy/fraction and 10% with $<$20 Gy/fraction. At the University of Toronto, the preferred prescription is 24 Gy in 2 fractions (12 Gy/fraction) associated with a VCF rate of 10%, which is clinically acceptable given multiple factors influencing this outcome.[80,81] Presently, without clear evidence of superior efficacy with dose per fraction SBRT regimens exceeding 20 Gy, based on VCF rates, these practices are hard to justify.

One important area of consideration when treating and consenting spine SBRT patients is the risk of acute side effects, in particular pain flare. This phenomenon is well known following cEBRT and recently the incidence was reported by Chiang et al after a prospective study.[82] Within the first 10 days of treatment, the risk of pain flare was found to be clinically significant and 68% of patients suffered this adverse event. With the use of rescue dexamethasone, the pain was shown to be effectively palliated. Prophylactic dexamethasone (4 or 8 mg orally prior to SBRT and for 4 days upon completion) has recently been shown to reduce the incidence of pain flare to 20%.[82] However, at this time it is unknown if all patients should routinely be treated; a randomized control trial would provide evidence to optimize patient management. A dose-response relationship has been observed based on the pain flare analysis reported by Pan and colleagues.[83] Although this study was not intended a priori to look at pain flare and did not specifically collect outcomes during and for the first 10 days post-SBRT, nor exclude patients already on dexamethasone; they did observe, based on their much larger study (with respect to sample size), that high-dose single-fraction SBRT yielded greater rates of pain flare than fractionated spine SBRT regimens. This observation makes sense with the overall trends we are observing with single-fraction SBRT.

Conclusion

Spine SBRT has emerged as a treatment option for selected patients with spinal metastases and is increasing in practice. As mature outcomes from early adopters are increasingly reported, we continue to observe high rates of local tumor and pain control. Standardization with respect to radiation planning, treatment delivery, and dose limits to the organs-at-risk are serving to expand availability beyond large academic centers. Surgery has a major role in optimizing spine SBRT outcomes, and multidisciplinary case discussion is therefore imperative. In particular, MISS has major potential to expand upon traditional indications such that more patients can derive benefit. The management of spinal metastases is undergoing considerable change and we are at the leading edge of a paradigm shift.

Conflict of interest, financial disclosures. Dr. Arjun Sahgal has received honorarium for previous educational seminars and research funding from Elekta AB. Dr. Simon Lo has received research support from Elekta AB and travel expenses and honorarium from Varian Medical Systems. Dr. Kristin Redmond has received research support from Elekta AB. Otherwise there are no conflicts of interest to disclose.

References

1. Schmidt MH, Klimo P Jr., Vrionis FD. Metastatic spinal cord compression. *J Natl Compr Canc Netw*. 2005;3(5):711–719.
2. Chow E, Harris K, Fan G, et al. Palliative radiotherapy trials for bone metastases: a systematic review. *J Clin Oncol*. 2007;25(11):1423–1436.
3. Howell DD, James JL, Hartsell WF, et al. Single-fraction radiotherapy versus multifraction radiotherapy for palliation of painful vertebral bone metastases-equivalent efficacy, less toxicity, more convenient: a subset analysis of Radiation Therapy Oncology Group trial 97–14. *Cancer*. 2013;119(4):888–896.
4. Nguyen J, Chow E, Zeng L, et al. Palliative response and functional interference outcomes using the Brief Pain Inventory for spinal bony metastases treated with conventional radiotherapy. *Clin Oncol (R Coll Radiol)*. 2011;23(7):485–491.
5. Mizumoto M, Harada H, Asakura H, et al. Radiotherapy for patients with metastases to the spinal column: a review of 603 patients at Shizuoka Cancer Center Hospital. *Int J Radiat Oncol Biol Phys*. 2011;79(1):208–213.
6. Hall EJ, Giaccia AJ. *Radiobiology for the radiologist*. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.
7. Foote M, Letourneau D, Hyde D, et al. Technique for stereotactic body radiotherapy for spinal metastases. *J Clin Neurosci*. 2011;18(2):276–279.
8. Tseng C-L, Sussman MS, Atenafu EG, et al. Magnetic resonance imaging assessment of spinal cord and cauda equina motion in supine patients with spinal metastases planned for spine stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys*. 2015;91(5):995–1002.
9. Ma L, Sahgal A, Cozzi L, et al. Apparatus-dependent dosimetric differences in spine stereotactic body radiotherapy. *Technol Cancer Res Treat*. 2010;9(6):563–574.
10. Patel VB, Wegner RE, Heron DE, et al. Comparison of whole versus partial vertebral body stereotactic body radiation therapy for spinal metastases. *Technol Cancer Res Treat*. 2012;11(2):105–115.
11. Cox BW, Spratt DE, Lovelock M, et al. International Spine Radiosurgery Consortium consensus guidelines for target volume

definition in spinal stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys*. 2012;83(5):e597–e605.

12. 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(3):e555–e562.
13. Li W, Sahgal A, Foote M, et al. Impact of immobilization on intrafraction motion for spine stereotactic body radiotherapy using cone beam computed tomography. *Int J Radiat Oncol Biol Phys*. 2012;84(2):520–526.
14. Stoiber EM, Lechsel G, Giske K, et al. Quantitative assessment of image-guided radiotherapy for paraspinal tumors. *Int J Radiat Oncol Biol Phys*. 2009;75(3):933–940.
15. Wang C, Shiu A, Lii M, et al. Automatic target localization and verification for on-line image-guided stereotactic body radiotherapy of the spine. *Technol Cancer Res Treat*. 2007;6(3):187–196.
16. 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(4):965–976.
17. 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*. 2010;35(22):E1221–E1229.
18. Fourney DR, Frangou EM, Ryken TC, et al. Spinal instability neoplastic score: an analysis of reliability and validity from the spine oncology study group. *J Clin Oncol*. 2011;29(22):3072–3077.
19. Fisher CG, Versteeg AL, Schouten R, et al. Reliability of the spinal instability neoplastic scale among radiologists: an assessment of instability secondary to spinal metastases. *AJR Am J Roentgenol*. 2014;203(4):869–874.
20. Fisher CG, Schouten R, Versteeg AL, et al. Reliability of the Spinal Instability Neoplastic Score (SINS) among radiation oncologists: an assessment of instability secondary to spinal metastases. *Radiat Oncol*. 2014;9:69.
21. Bilsky MH, Laufer I, Fourney DR, et al. Reliability analysis of the epidural spinal cord compression scale. *J Neurosurg Spine*. 2010;13(3):324–328.
22. Lo SS, Kubicky CD, Chang EL, et al. Is there any role for stereotactic body radiotherapy in the management of metastatic epidural spinal cord compression? *CNS Oncol*. 2015;4(1):1–4.
23. Al-Omair A, Masucci L, Masson-Cote L, et al. Surgical resection of epidural disease improves local control following postoperative spine stereotactic body radiotherapy. *Neuro Oncol*. 2013;15(10):1413–1419.
24. Tree AC, Khoo VS, Eeles RA, et al. Stereotactic body radiotherapy for oligometastases. *Lancet Oncol*. 2013;14(1):e28–e37.
25. Thibault I, Al-Omair A, Masucci GL, et al. Spine stereotactic body radiotherapy for renal cell cancer spinal metastases: analysis of outcomes and risk of vertebral compression fracture. *J Neurosurg Spine*. 2014;21(5):711–718.
26. Anand AK, Venkadamanickam G, Punnakal AU, et al. Hypofractionated stereotactic body radiotherapy in spinal metastasis - with or without epidural extension. *Clin Oncol (R Coll Radiol)*. 2015;27(6):345–352.
27. Guckenberger M, Mantel F, Gerszten PC, et al. Safety and efficacy of stereotactic body radiotherapy as primary treatment for vertebral metastases: a multi-institutional analysis. *Radiat Oncol*. 2014;9(1):226.
28. Sohn S, Chung CK, Sohn MJ, et al. Stereotactic radiosurgery compared with external radiation therapy as a primary treatment in spine metastasis from renal cell carcinoma: a multicenter, matched-pair study. *J Neurooncol*. 2014;119(1):121–128.
29. Folkert MR, Bilsky MH, Tom AK, et al. Outcomes and toxicity for hypofractionated and single-fraction image-guided stereotactic radiosurgery for sarcomas metastasizing to the spine. *Int J Radiat Oncol Biol Phys*. 2014;88(5):1085–1091.
30. Yamada Y, Bilsky MH, Lovelock DM, et al. High-dose, single-fraction image-guided intensity-modulated radiotherapy for metastatic spinal lesions. *Int J Radiat Oncol Biol Phys*. 2008;71(2):484–490.
31. Wang XS, Rhines LD, Shiu AS, et al. Stereotactic body radiation therapy for management of spinal metastases in patients without spinal cord compression: a phase 1–2 trial. *Lancet Oncol*. 2012;13(4):395–402.
32. Ahmed KA, Stauder MC, Miller RC, et al. Stereotactic body radiation therapy in spinal metastases. *Int J Radiat Oncol Biol Phys*. 2012;82(5):e803–e809.
33. Sellin JN, Reichardt W, Bishop AJ, et al. Factors affecting survival in 37 consecutive patients undergoing de novo stereotactic radiosurgery for contiguous sites of vertebral body metastasis from renal cell carcinoma. *J Neurosurg Spine*. 2015;22(1):52–59.
34. Park HJ, Kim HJ, Won JH, et al. Stereotactic body radiotherapy (SBRT) for spinal metastases: who will benefit the most from SBRT? *Technol Cancer Res Treat*. 2015;14(2):159–167.
35. Sahgal A, Ames C, Chou D, et al. Stereotactic body radiotherapy is effective salvage therapy for patients with prior radiation of spinal metastases. *Int J Radiat Oncol Biol Phys*. 2009;74(3):723–731.
36. Nguyen QN, Shiu AS, Rhines LD, et al. Management of spinal metastases from renal cell carcinoma using stereotactic body radiotherapy. *Int J Radiat Oncol Biol Phys*. 2010;76(4):1185–1192.
37. van der Linden YM, Lok JJ, Steenland E, et al. Single fraction radiotherapy is efficacious: a further analysis of the Dutch Bone Metastasis Study controlling for the influence of retreatment. *Int J Radiat Oncol Biol Phys*. 2004;59(2):528–537.
38. Chow E, Meyer RM, Chen BE, et al. Impact of reirradiation of painful osseous metastases on quality of life and function: a secondary analysis of the NCIC CTG SC.20 randomized trial. *J Clin Oncol*. 2014;32(34):3867–3873.
39. Choi CY, Adler JR, Gibbs IC, et al. Stereotactic radiosurgery for treatment of spinal metastases recurring in close proximity to previously irradiated spinal cord. *Int J Radiat Oncol Biol Phys*. 2010;78(2):499–506.
40. Mahadevan A, Floyd S, Wong E, et al. Stereotactic body radiotherapy reirradiation for recurrent epidural spinal metastases. *Int J Radiat Oncol Biol Phys*. 2011;81(5):1500–1505.
41. Garg AK, Wang XS, Shiu AS, et al. Prospective evaluation of spinal reirradiation by using stereotactic body radiation therapy: The University of Texas MD Anderson Cancer Center experience. *Cancer*. 2011;117(15):3509–3516.
42. Damast S, Wright J, Bilsky M, et al. Impact of dose on local failure rates after image-guided reirradiation of recurrent paraspinal metastases. *Int J Radiat Oncol Biol Phys*. 2011;81(3):819–826.
43. Klekamp J, Samii H. Surgical results for spinal metastases. *Acta Neurochir. (Wien)*. 1998;140(9):957–967.
44. Gerszten PC, Germanwala A, Burton SA, et al. Combination kyphoplasty and spinal radiosurgery: a new treatment paradigm for pathological fractures. *J Neurosurg Spine*. 2005;3(4):296–301.
45. Gerszten PC, Monaco EA 3rd. Complete percutaneous treatment of vertebral body tumors causing spinal canal compromise using a transpedicular cavitation, cement augmentation, and radiosurgical technique. *Neurosurg Focus*. 2009;27(6):E9.

46. Massicotte E, Foote M, Reddy R, et al. Minimal access spine surgery (MASS) for decompression and stabilization performed as an out-patient procedure for metastatic spinal tumours followed by spine stereotactic body radiotherapy (SBRT): first report of technique and preliminary outcomes. *Technol Cancer Res Treat*. 2012;11(1):15–25.
47. Laufer I, Iorgulescu JB, Chapman T, et al. Local disease control for spinal metastases following "separation surgery" and adjuvant hypofractionated or high-dose single-fraction stereotactic radiosurgery: outcome analysis in 186 patients. *J Neurosurg Spine*. 2013;18(3):207–214.
48. Bate BG, Khan NR, Kimball BY, et al. Stereotactic radiosurgery for spinal metastases with or without separation surgery. *J Neurosurg Spine*. 2015;22(4):409–415.
49. Akram H, Allibone J. Spinal surgery for palliation in malignant spinal cord compression. *Clin Oncol (R Coll Radiol)*. 2010;22(9): 792–800.
50. Witham TF, Khavkin YA, Gallia GL, et al. Surgery insight: current management of epidural spinal cord compression from metastatic spine disease. *Nat Clin Pract Neurol*. 2006;2(2):87–94. quiz 116.
51. Klimo P Jr., Schmidt MH. Surgical management of spinal metastases. *Oncologist*. 2004;9(2):188–196.
52. Uribe JS, Dakwar E, Le TV, et al. Minimally invasive surgery treatment for thoracic spine tumor removal: a mini-open, lateral approach. *Spine (Phila Pa 1976)*. 2010;35(26 Suppl):S347–S354.
53. Smith ZA, Fessler RG. Paradigm changes in spine surgery: evolution of minimally invasive techniques. *Nat Rev Neurol*. 2012;8(8):443–450.
54. Lee CH, Kwon JW, Lee J, et al. Direct decompressive surgery followed by radiotherapy versus radiotherapy alone for metastatic epidural spinal cord compression: a meta-analysis. *Spine (Phila Pa 1976)*. 2014;39(9):E587–E592.
55. Klimo P Jr., Thompson CJ, Kestle JR, et al. A meta-analysis of surgery versus conventional radiotherapy for the treatment of metastatic spinal epidural disease. *Neuro Oncol*. 2005;7(1):64–76.
56. Patchell RA, Tibbs PA, Regine WF, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. *Lancet*. 2005;366(9486): 643–648.
57. Wai EK, Finkelstein JA, Tangente RP, et al. Quality of life in surgical treatment of metastatic spine disease. *Spine (Phila Pa 1976)*. 2003; 28(5):508–512.
58. Falicov A, Fisher CG, Sparkes J, et al. Impact of surgical intervention on quality of life in patients with spinal metastases. *Spine (Phila Pa 1976)*. 2006;31(24):2849–2856.
59. Jansson KA, Bauer HC. Survival, complications and outcome in 282 patients operated for neurological deficit due to thoracic or lumbar spinal metastases. *Eur Spine J*. 2006;15(2):196–202.
60. Ibrahim A, Crockard A, Antonietti P, et al. Does spinal surgery improve the quality of life for those with extradural (spinal) osseous metastases? An international multicenter prospective observational study of 223 patients. Invited submission from the Joint Section Meeting on Disorders of the Spine and Peripheral Nerves, March 2007. *J Neurosurg Spine*. 2008;8(3):271–278.
61. Quan GM, Vital JM, Aurouer N, et al. Surgery improves pain, function and quality of life in patients with spinal metastases: a prospective study on 118 patients. *Eur Spine J*. 2011;20(11):1970–1978.
62. Pointillart V, Vital J-M, Salmi R, et al. Survival prognostic factors and clinical outcomes in patients with spinal metastases. *J Cancer Res Clin Oncol*. 2011;137(5):849–856.
63. Tokuhashi Y, Ajiro Y, Umezawa N. Outcome of treatment for spinal metastases using scoring system for preoperative evaluation of prognosis. *Spine*. 2009;34(1):69–73.
64. Fujibayashi S, Neo M, Miyaki K, et al. The value of palliative surgery for metastatic spinal disease: satisfaction of patients and their families. *Spine J*. 2010;10(1):42–49.
65. Cho DC, Sung JK. Palliative surgery for metastatic thoracic and lumbar tumors using posterolateral transpedicular approach with posterior instrumentation. *Surg Neurol*. 2009;71(4):424–433.
66. Kim JM, Losina E, Bono CM, et al. Clinical outcome of metastatic spinal cord compression treated with surgical excision +/- radiation versus radiation therapy alone: a systematic review of literature. *Spine (Phila Pa 1976)*. 2012;37(1):78–84.
67. Molina CA, Gokaslan ZL, Sciubba DM. A systematic review of the current role of minimally invasive spine surgery in the management of metastatic spine disease. *Int J Surg Oncol*. 2011; 2011:598148.
68. Harel R, Angelov L. Spine metastases: current treatments and future directions. *Eur J Cancer*. 2010;46(15):2696–2707.
69. McAfee PC, Phillips FM, Andersson G, et al. Minimally invasive spine surgery. *Spine (Phila Pa 1976)*. 2010;35(26 Suppl):S271–S273.
70. Tancioni F, Navarria P, Pessina F, et al. Early surgical experience with minimally invasive percutaneous approach for patients with metastatic epidural spinal cord compression (MESCC) to poor prognoses. *Ann Surg Oncol*. 2012;19(1):294–300.
71. Rao PJ, Thayaparan GK, Fairhall JM, et al. Minimally invasive percutaneous fixation techniques for metastatic spinal disease. *Orthop Surg*. 2014;6(3):187–195.
72. Riaz S, Fox R, Lavoie MV, et al. Vertebral body reconstruction for thoracolumbar spinal metastasis--a review of techniques. *J Ayub Med Coll Abbottabad*. 2006;18(1):70–77.
73. Berenson J, Pflugmacher R, Jarzem P, et al. Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial. *Lancet Oncol*. 2011;12(3): 225–235.
74. Tancioni F, Lorenzetti MA, Navarria P, et al. Percutaneous vertebral augmentation in metastatic disease: state of the art. *J Support Oncol*. 2011;9(1):4–10.
75. Kassamali RH, Ganeshan A, Hoey ET, et al. Pain management in spinal metastases: the role of percutaneous vertebral augmentation. *Ann Oncol*. 2011;22(4):782–786.
76. Chi JH, Gokaslan ZL. Vertebroplasty and kyphoplasty for spinal metastases. *Curr Opin Support Palliat Care*. 2008;2(1):9–13.
77. Sahgal A, Bilsky M, Chang EL, et al. Stereotactic body radiotherapy for spinal metastases: current status, with a focus on its application in the postoperative patient. *J Neurosurg Spine*. 2011;14(2): 151–166.
78. 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(2): 341–347.
79. Al-Omair A, Smith R, Kiehl TR, et al. Radiation-induced vertebral compression fracture following spine stereotactic radiosurgery: clinicopathological correlation. *J Neurosurg Spine*. 2013;18(5): 430–435.
80. 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(27):3426–3431.

81. Cunha MV, Al-Omair A, Atenafu EG, et al. Vertebral compression fracture (VCF) after spine stereotactic body radiation therapy (SBRT): analysis of predictive factors. *Int J Radiat Oncol Biol Phys*. 2012;84(3):e343–e349.

82. Chiang A, Zeng L, Zhang L, et al. Pain flare is a common adverse event in steroid-naive patients after spine stereotactic body radiation therapy: a prospective clinical trial. *Int J Radiat Oncol Biol Phys*. 2013;86(4):638–642.

83. Pan HY, Allen PK, Wang XS, et al. Incidence and predictive factors of pain flare after spine stereotactic body radiation therapy: secondary analysis of phase 1/2 trials. *Int J Radiat Oncol Biol Phys*. 2014;90(4):870–876.