Review Article

The Integration of Radiosurgery for the Treatment of Patients With Metastatic Spine Diseases

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Abstract

Significant evidence emerging in the spinal oncology literature recommends radiosurgery as a primary modality of treatment of spinal metastasis. Improvements in the methods of delivering radiation have increased the ability to provide a higher and more exacting dose of radiation to a tumor bed than previously. Using treatment-planning software, radiation is contoured around a specific lesion with the intent of administering a tumoricidal dose. Combined with a minimally invasive, tumor-load reducing surgery, this advanced form of radiation therapy can provide better local control of the tumor compared with conventional external beam radiation.

The treatment of patients with metastatic epidural spinal cord compression (MESCC) has undergone significant evolution in the past few decades. Initial studies that compared radiation therapy to noninstrumented spine surgery demonstrated no differences in treatment outcomes. Based on these data, the oncology community often recommended radiation treatment as the appropriate management. The introduction of spinal instrumentation, as well as improvement in techniques, has given the surgeon the opportunity to perform (near) complete tumor resections as well as stabilize the spine. This has led to improved surgical outcomes in caring for patients with MESCC. The most convincing evidence in support of surgical intervention has come through a randomized prospective trial conducted by Patchell et al.[1] This study demonstrated the benefit of surgery plus radiation therapy as a more effective strategy to maintain ambulation than radiation therapy alone in patients with spinal cord compression secondary to common solid-tumor metastases.

The development and adoption of stereotactic radiosurgery (SRS) in the treatment of patients with MESCC has provided additional treatment options for patients with spinal metastases. In the spine, SRS (or radiosurgery) allows for the delivery of a higher dose of radiation to the tumor site while sparing injury to the spinal cord. Tumors that have typically been considered radioresistant are now becoming target sites of treatment with SRS (ie, renal cell carcinoma). In addition, the integration of SRS into the treatment plan has allowed the spine surgeon to perform a limited intralesional resection for MESCC instead of gross total resections typically required to achieve local tumor control.

Physics of Radiation Treatment

Conventional external beam radiation therapy (cEBRT) to the spine is typically delivered as a total of 24 to

50 Gy in fractionated (multiple) doses of 1.8 to 3 Gy. With the newer techniques of radiosurgery, higher doses (10 to 24 Gy) can be safely given as a single fraction. A variety of dose and fractionation schedules has been used in the treatment of spinal tumors, ranging from high-dose single-fraction (16 to 18 Gy ×1) to multifractionated delivery using standard fraction sizes (8 Gy ×3). The fractionation schedule depends on the target volume, tolerance of surrounding normal tissues, prior radiation treatment, and the radiosensitivity of the tumor.[2] Drawing upon the experience of treating intracranial tumors, there has been a trend toward using high-dose single-fraction or multiple-fraction radiotherapy, even for tumors that are considered to be radioresistant.

One proposed theory for the effectiveness of high-dose radiation is that a more concentrated dose of radiation can incur irreparable double-stranded damage to the DNA of tumor cells. With cEBRT, it is hypothesized that only single-stranded DNA breaks occur in the tissue. These breaks can often undergo repair because the remaining intact single strand serves as a template upon which new DNA can be built.[2] This repair mechanism of single-stranded DNA breaks explains in part the radioresistance of tumors to conventional radiation therapy regimens. Double-stranded breaks can overwhelm the repair capacity of the cellular repair mechanisms. When a cell attempts replication with damaged double-stranded DNA, the end result can lead to an increase in the prevalence of abnormal cross linking of the DNA and, ultimately, to cell death. Furthermore, high-dose single-fraction radiation (ie, SRS) induces not only a large number of lethal double-stranded DNA breaks, but it also activates specific cell-death mechanisms that are not observed when conventional fractionated radiation is delivered. There is evidence that SRS at doses >8 to 10 Gy per fraction activate endothelial apoptosis in the vasculature[3] and are also able to overcome the radioresistance of certain stem cells.[4]

Understanding Radiation Dose Tolerance

A major limiting factor in the management of malignancies has been the need to "protect" the normal tissue from the diseased tissue. Radiation tolerance determined by conventional radiotherapy is not applicable to radiosurgery. The tolerance dose that was typically used for the majority of an organ required low doses. By contrast, radiosurgery is able to deliver a very high dose of radiation to the tumor; there is a subsequent drop-off rate that occurs with the remaining radiation.[5] When planning SRS in the spine, physicists have to ensure that the drop-off rate of radiation is safe for the spinal cord. A poor understanding of dose tolerance of the spinal cord has led to hesitance in considering higher doses of radiation to such a sensitive area. Different institutions have adopted a range of spinal cord dose constraints, with no ideal fractionation schedule set.[6]

Sohn and Chung[7] report that the prescribed radiation dose for SRS is based on tumor histology, spinal cord, or cauda equina tolerance and previous radiation dosage to normal tissue, especially to the spinal cord. The risk of developing radiation-induced myelopathy is considered the major limitation to SRS; this is believed to be dose dependent.

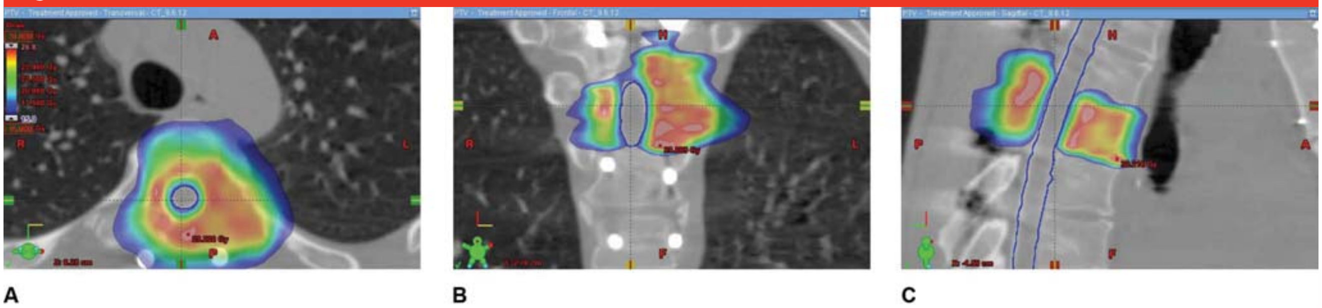
Currently there is a lack of consensus regarding varying dose tolerances of the different portions of the spinal cord. In a study by Gibbs et al,[8] three patients who had radiation-induced myelopathy all had thoracic lesions. This finding is consistent with an earlier observation of Wara et al[9] that the thoracic spinal cord exhibits a lower tolerance, potentially stemming from the physiologically less robust blood flow. This stands in contrast to Ryu et al[5] and others,[2,10,11] whose analyses claim that there is no difference in cord tolerance in the cervical, thoracic, or lumbar regions.

Ryu et al[5] also noted that most of the motor function is carried by the lateral corticospinal tracts, located in the posterolateral portion of the cord. Motor nuclei are located in the gray matter of the anterior horn, where there is a rapid dose falloff. Therefore, the radiation dose to the motor tract could be sufficiently lower than the actual tolerance. It is not known whether the sensory tracts may be more tolerant to radiation than the motor tracts or whether the cauda equina and spinal nerves have a greater tolerance to radiation simply because they are considered to be peripheral nerves.

Stereotactic Radiosurgery

Radiosurgery was developed by Leskell in the 1950s.[12] Fundamentally, radiosurgery allows for the delivery of a higher dose of radiation with a focused radiation beam. As a result, radiation can be delivered to a specific target (eg, vertebral body) while sparing the organ and the surrounding normal tissue (ie, spinal cord).[13] Because of the conformal nature of the beam, higher doses of radiation can be delivered to the target area. Radiosurgery has been shown to be an effective means of achieving durable local control in tumors that have traditionally been classified as radioresistant (eg, renal cell carcinoma). Initially used for treatment of intracranial tumors, radiosurgery of the spine has enabled the delivery of high-dose radiation while remaining within the constraints of spinal cord tolerance.[14]

Figure 1



The stereotactic radiosurgery treatment plan. **A,** Axial view. **B, C**oronal view. **C,** Sagittal view. Red represents the gross tumor volume, green represents the clinical target volume, and purple-blue represents the planning treatment volume.

Critical to the delivery of radiation is the need to precisely immobilize the patient to properly target the involved vertebrae. To precisely deliver radiation using SRS to the target tissue, two sets of images are necessary to ensure accuracy: a reference image of the treatment location for treatment planning and localization images during the treatment. Typically a patient who will undergo SRS will have a CT image taken during the process of simulation. The radiation oncologist, physicist, and surgeon plan the delivery of radiation using these images. A treatment plan is drawn on the reference images outlining the location of the tumor. Pairing a real-time CT scan with the treatment beam allows for the precise targeting of the radiation while sparing the normal adjacent tissues. Precise targeting is aided by having the patient lie on a treatment couch while the SRS software constantly confirms tumor location by continuously checking bony landmarks throughout the procedure.[2] Prior to the development of this technology, the treatment relied on less precise manual patient positioning.[13]

Various treatment volumes are planned with this reference image. During the treatment planning, factors such as the location of the critical structures (eg, spinal cord, kidney, colon), volume of tissue to be treated, and the dose to be delivered to the target are determined. The treatment plan represents a balance between delivering the maximal dose to the tumor while avoiding radiation to essential structures.

Three volumes typically are outlined in a treatment plan when conducting SRS (Figure 1). Gross tumor volume (GTV) refers to the radiographic visible tumor. If radiation is being delivered postoperatively, the GTV is contoured according to the preoperative tumor location.

Clinical target volume (CTV) encompasses the GTV and the suspected microscopic disease not detectable with imaging. Generally the entire marrow compartment of the GTV and adjacent marrow spaces are included in the CTV. Cox et al[15] recently published a set of consensus guidelines for defining CTV based on agreement between the independent contours of 10 experts. They recommend avoiding epidural CTV expansion without epidural disease and using only circumferential CTVs around the spinal cord when the vertebral body and bilateral posterior elements are involved.

Planning treatment volume (PTV) is a 2- to 3-mm expansion of the CTV. The PTV can account for potential errors occurring from inaccurate targeting of the CTV (and GTV), such as patient movement during treatment. PTV coverage is largely dictated by the maximal spinal cord dose. Sahgal et al[16] reported a 1.5- to 2-mm expansion of the CTV to be a reasonable PTV margin. The PTV can partially surround the spinal cord, with margins between the PTV and the cord as narrow as a few millimeters, necessitating a steep dose-gradient falloff between the PTV and the cord.

A large margin implies that a higher fraction of normal tissue is irradiated, with significant implications for spinal tumors. Relatively sensitive structures such as the spinal cord, esophagus, kidneys, and bowel are often in the immediate vicinity. Image-guided technology has allowed for extremely accurate treatment by eliminating or greatly reducing setup errors within 2 mm, allowing for smaller margins around the target volume without compromising tumor control.[2]

Integration of Radiosurgery With Spinal Surgery

The general indications for spine tumor surgery for metastatic disease are spinal instability; progressive symptomatic deformities; neurologic deficits, including cauda equina and nerve root compression from tumors resistant to cEBRT; and intractable pain that is unresponsive to other forms of therapy.[17] Patient-specific indications include life expectancy

>3 months, axial or translational instability resulting from pathologic fractures or tumor invasion, progressive symptomatic spinal metastasis after nonsurgical treatment, spinal cord compression with motor weakness, sensory abnormalities, and/or uncontrolled pain. Surgery is not an option for all patients. It is essential to consider factors such as tumor type, neurologic status, comorbid conditions, and life expectancy when evaluating a patient for surgical candidacy.

In 2005, Patchell et al[1] conducted a randomized controlled trial that compared radiotherapy alone with a combined program of surgery and radiotherapy for tumor treatment. This trial concretely demonstrated that both functional and survival outcomes for the combined therapy were superior to the treatment arm of the radiotherapy alone.[18,19] The trial was conducted using cEBRT; the benefits of this multimodality treatment program may be increased with advances in radiotherapy technique, namely radiosurgery.

Clinical Indications for Isolated Spinal Radiosurgery

The ideal candidate for radiosurgery is a patient with a life expectancy >1 month because most beneficial effects are expected to occur after 3 to 4 weeks, although some patients experience an immediate reduction in pain.[14,20] The efficacy of radiosurgery has been documented for pain palliation and tumor control. Patients with an isolated metastasis to the vertebral body without epidural compression are ideal candidates for SRS, regardless of tumor histology.

In a short-term study, Degen et al[20] reported that 97.3% of patients who presented with pain referable to a metastatic lesion had reported a decrease in the level of pain following treatment; 84.2% of patients reported an improvement after the first treatment; and 73.6% became pain free following the full course of radiosurgery. Ryu et al[21] reported that rapid pain relief is achieved within 14 days, with the earliest period of time being 24 hours. Yamada et al[6] reported a 90% rate of local control, regardless of histologic type, with high-dose (18 to 24 Gy), single-fraction, image-guided intensity-modulated radiation therapy, without transgressing spinal cord tolerance levels and without evidence of toxicity. Chang et al[22] reported an actuarial 1-year freedom from imaging tumor progression of 84%. In their analysis, they also found that lesions of the thoracic and lumbar spine, the pedicles, and posterior elements were not always properly radiated, leading to tumor recurrence. They also found failures related to recurrence within the adjacent epidural space and proposed more liberal spinal cord dose restraints. Gerszten et al[23] reported 88% to 90% radiographic tumor control of spinal metastasis.

One advantage of SRS treatment, when given as a single fraction, is that the total duration of therapy can be 1 day. This stands in contrast to conventional radiotherapy, in which typically 10 doses of 3 Gy each are given over the course of 2 weeks. The abbreviated time frame is especially favorable for patients with a limited life expectancy or for whom travelling for therapy may be difficult because of weakness or severe pain. Additionally, the clinical responses, such as pain palliation or neurologic deficit improvement, might be more rapid after SRS.[17]

There are typically three patient populations that would benefit from radiosurgery. The first group consists of patients who have never been treated with radiation. For lesions that are fully contained within the vertebral body with no epidural contact, radiosurgery could be used as the primary modality of treatment. The second group consists of patients who have received prior cEBRT, for whom a recurrent spinal metastasis in previously treated lesions can be targeted more specifically.[7] The final group consists of postoperative patients who have undergone a surgical excision of the tumor; in these patients, radiosurgery can be used to ensure local control, especially at the dural margin.[16] Some patients represent a combination of these three categories.[24]

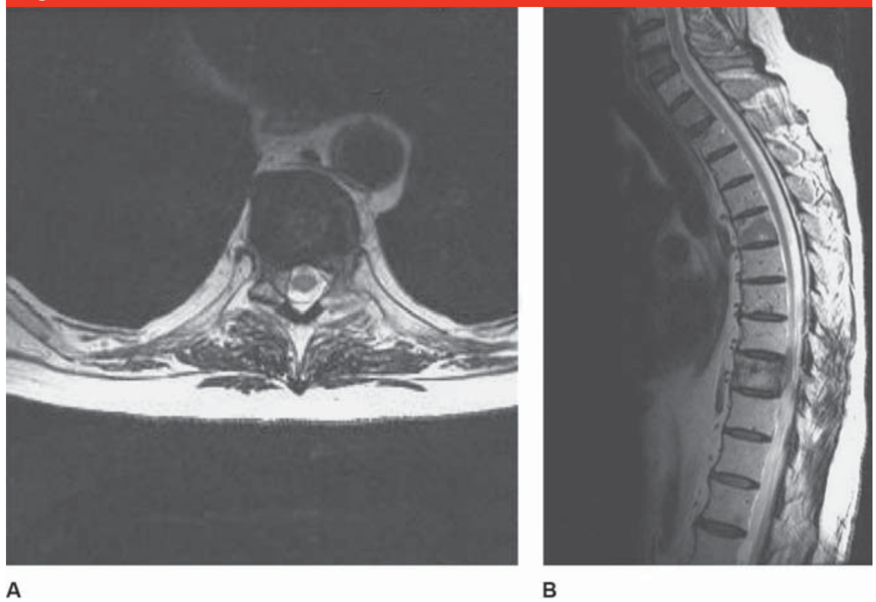
SRS After Spine Surgery

Achieving a wide margin excision in the spine remains difficult because of anatomic constraints. Intralesional resections are more commonly performed in the setting of epidural compression. Postoperative radiation is often administered as an adjuvant treatment. Unfortunately, the limiting factor of conventional radiotherapy is its lack of specificity. In an instance in which a higher dose may prove more meaningful, the potential for radiation damage to other organs, including the spinal cord, prevents its use. It is in a case such as this that a combination of surgery and radiosurgery may best target the lesion and prevent its recurrence.

Currently, only three reports detail the use of radiosurgery as a postoperative adjuvant therapy. Rock et al[25] investigated adjuvant radiosurgery toxicity and found that 92% of patients who presented with neurologic symptoms were stable or improved after radiosurgery. Moulding et al[26] addressed the notion of local control: postoperative SRS demonstrated better local control with a higher radiation dose per fraction (24 Gy). The

Moulding trial was based on tumors that are considered to be radioresistant, but the tumor control was histology independent. As a result, they suggest undertaking a limited surgery to resect the epidural tumor, followed by SRS to the affected site. This has been coined separation surgery. The adjuvant SRS would serve to ensure local control.[26] Laufer et al[27] published a larger analysis of 186 patients who underwent separation surgery followed by SRS. The 1-year recurrence risk was 16%, with high dose per fraction treatments providing superior tumor control. The 1-year tumor recurrence risk was 9% for single-fraction SRS (24 Gy) and 4% for high-dose hypofractionated SRS (ie, three fractions of 8 to 10 Gy).

Figure 2



Metastatic epidural compression at T9 from prostate cancer in a 68-year-old man. The patient had presented with signs of early myelopathy. He had received conventional radiation to the region 7 years previously. Because of the symptoms from his spinal cord compression, it was felt that a limited decompression followed by stereotactic radiosurgery would offer the best control of his disease. Preoperative T2-weighted magnetic resonance axial (**A**) and sagittal (**B**) images.

Minimally Invasive Separation Surgery

In our institution, patients with a favorable life expectancy who have MESCC with relatively radioresistant histologies are often candidates for surgery followed by postoperative radiosurgery. Our goal is to decompress the spinal cord circumferentially to allow an appropriate separation between the tumor and the spinal cord, such that a high dose of radiation can be delivered with minimal risk of spinal cord toxicity. This is often performed through a standard transpedicular approach. Stabilization is typically performed with the placement of pedicle screws two levels above and below the surgical level.

Newer instrumentation technologies have allowed for less invasive or minimally invasive surgical decompressions that remove only the compressive epidural component of a tumor and allow for rapid institution of SRS in the postoperative period to achieve durable local tumor control (as soon as 2 weeks postoperatively). This is achieved through the placement of percutaneous pedicle screws placed two levels above and below the target level using standard C-arm techniques. A tube or working portal is made over the diseased vertebrae. Once proper exposure is obtained, a standard laminectomy and transpedicular approach to the vertebral body is performed. This procedure is called minimally invasive separation surgery (Figures 2 through 4) because it separates the tumor from the spinal cord circumferentially in a minimally invasive method. Although experience with this technique is limited, it may allow for more rapid and better tolerated treatment protocols.

Complications

Short Term

In the short term, radiosurgery appears to be well tolerated. The complications described are self limiting and mild: wound breakdown at the surgical site, increased nocturia, esophagitis, dysphagia, paresthesias, transient diarrhea, hoarse voice, and limited toxicities in relation to the surrounding anatomy.[7,16,20]

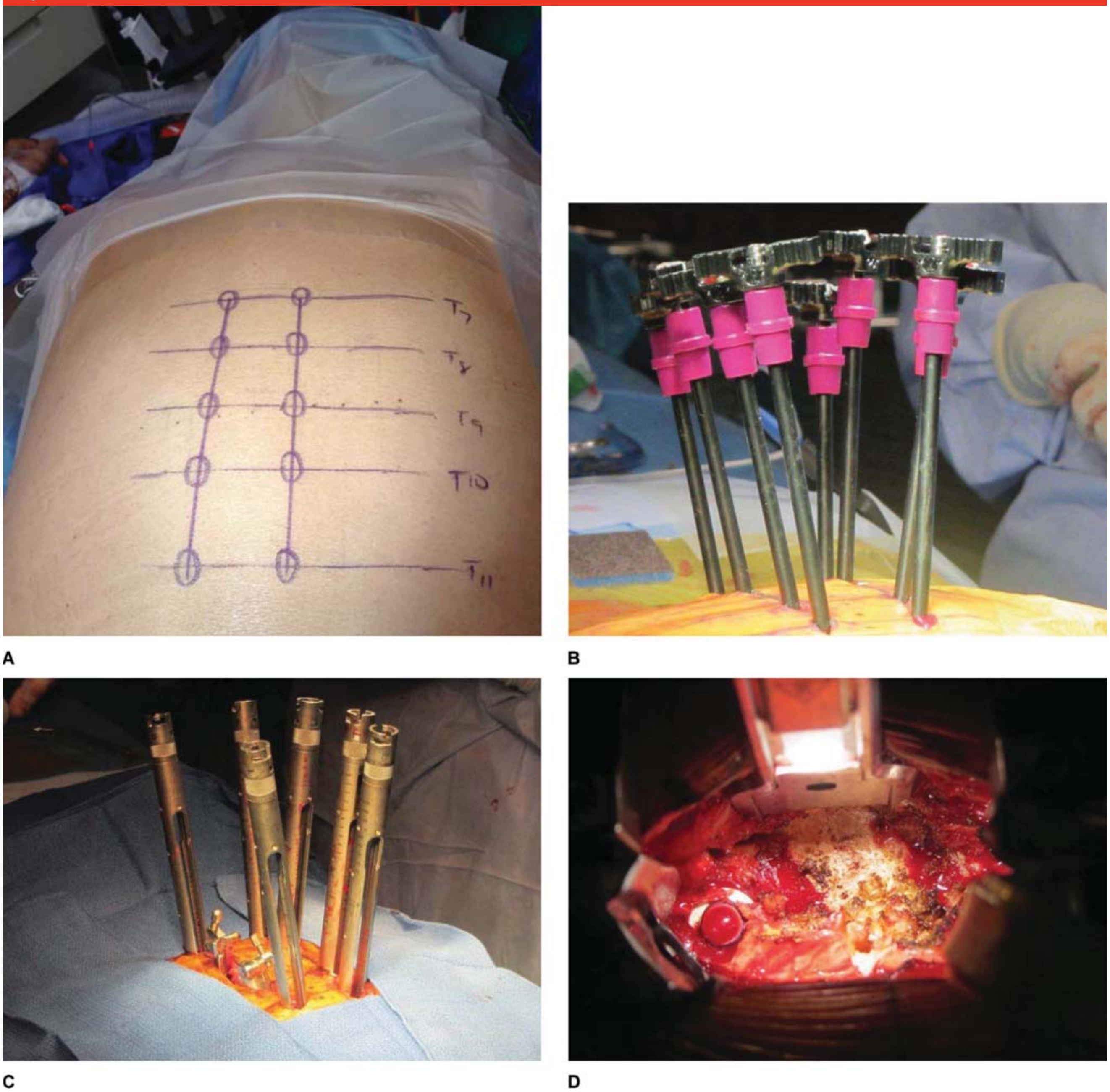
Long Term

Given the relatively short experience with spinal SRS, it is difficult to speculate on the long-term effects of the therapy.[5] The risk of permanent tissue damage when dealing with high doses per fraction radiation is much higher and may not manifest until several months to years following radiation.[16] Two rare consequences that have been noted are radiation myelopathy and vertebral compression fractures.

Myelopathy

The risk of radiation-induced myelopathy is believed to be a dose-dependent

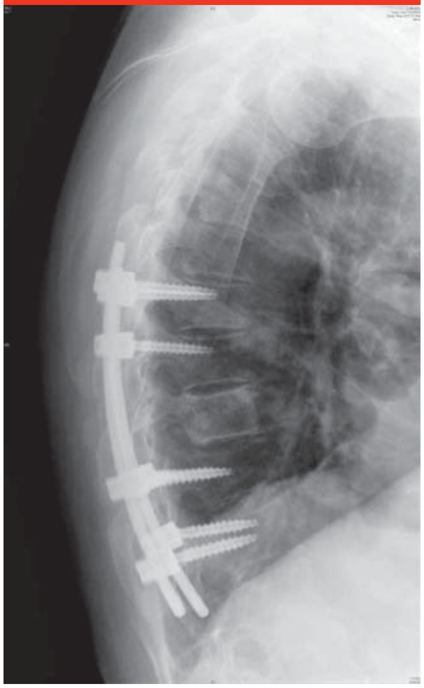
Figure 3



Same patient as in Figure 2. **A,** Intraoperative clinical photograph of the planning for percutaneous crews. **B,** Placement of trocars. **C,** Posts for screws. **D,** Intraoperative photograph of exposure of the right T9 lamina. The right side of the photograph is cephalad; the left side is caudal. The bottom part of the photograph represents the lateral position; the top represents the medial portion.

phenomenon, a problem compounded by the poor understanding of spinal cord tolerance. Standards have been set by practitioners as guidelines for safe radiosurgery: a dose <45 to 50 Gy in standard fractionation (18 to 20 Gy per fraction) is well within the radiation tolerance, given less than a 5% probability of myelopathy within 5 years. Yamada et al[2] reported on patients treated with high-dose radiation without reported myelopathy. However, this cohort had advanced metastatic disease, and they were not expected to achieve long-term survival. The problem of low survival rates following radiosurgery, coupled with

Figure 4



Same patient as in Figures 2 and 3. Postoperative sagittal radiograph.

the limited availability of radiosurgery as a therapeutic option, highlights the difficulties in studying these complications. Gibbs et al[8] reported that half of the complications they studied occurred beyond an 8-Gy equivalent dose. The predictive factors for myelopathy in this study were age, sex, primary site, dose per fraction, anatomic level, previous treatment, total dose, dose per fraction, maximum dose, maximum spinal cord dose, and tumor volume. Sahgal et al[10] reported that a maximum safe point of 10 Gy for single-fraction SRS posed a low risk for radiation-induced myelopathy.

Vertebral Fracture

Several studies have reported a compression fracture risk of between 11% and 39% after single-fraction image-guided intensity-modulated radiation therapy to spinal metastases. Lytic disease, increasing involvement of the vertebral body, location in the thoracolumbar or lumbar region, age >55 years, preexisting fracture or deformity, and pain are significant risk factors for fracture progression.[28,29] These risks have led some groups to perform prophylactic vertebroplasty before radiation or chemotherapy to avoid potential compression fractions.[30] However, many of the patients studied had excellent clinical outcomes.[31]

Other toxicities reported to date include late bone toxicity[16] and esophageal toxicity. One belief is that by planning treatment volumes to avoid the spinal cord, other organs were made vulnerable to exposure. This is a particular problem for a serial organ such as the esophagus, where local dysfunction can cause total organ failure.[32]

Summary

Rapid advances in the treatment of patients with metastatic spinal cord compression has allowed for significant gains in local tumor control for these patients. The integration of radiosurgery into these treatment plans has helped achieve greater tumor control in both favorable and unfavorable tumor histologies. Newer surgical techniques, such as the minimally invasive separation surgery procedure, can potentially expand the indications for treatment in these patients.

General orthopaedic surgeons as well as spine surgeons should be aware of the possibilities for less invasive palliation with spinal metastatic disease. Patients with pain and neurologic dysfunction can be improved with the appropriate intervention; the techniques discussed in this article can be used to effectively palliate the patient's symptoms without significant recovery time. Patients with symptomatic metastatic spinal disease should be referred to a spine surgeon for consideration of surgery and/or radiotherapy as potential treatments for their condition.

References

Evidence-based Medicine: Levels of evidence are described in the table of contents. In this article, reference 1 is a level I study. References 8, 10, 17, 19, and 28 are level III studies. References 5-7, 9, 11, 13, 16, 18, 20-27, 29, and 30-32 are reference IV studies. References 2, 12, and 14 are level V expert opinion.

References printed in **bold type** are those published within the past 5 years.

1. 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.
2. Yamada Y, Lovelock DM, Bilsky MH: A review of image-guided intensity-modulated radiotherapy for spinal tumors. *Neurosurgery* 2007;61(2):226-235.
3. Garcia-Barros M, Paris F, Cordon-Cardo C, et al: Tumor response to radiotherapy regulated by endothelial cell apoptosis. *Science* 2003;300(5622): 1155-1159.
4. Ch'ang H-J, Maj JG, Paris F, et al: ATM regulates target switching to escalating doses of radiation in the intestines. *Nat Med* 2005;11(5):484-490.
5. Ryu S, Jin JY, Jin R, et al: Partial volume tolerance of the spinal cord and complications of single-dose radiosurgery. *Cancer* 2007;109(3):628-636.
6. 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.
7. **Sohn S, Chung CK: The role of stereotactic radiosurgery in metastasis to the spine. *J Korean Neurosurg Soc* 2012;51(1):1-7.**
8. Gibbs IC, Patil C, Gerszten PC, Adler JR Jr, Burton SA: Delayed radiation-induced myelopathy after spinal radiosurgery. *Neurosurgery* 2009;64(2, suppl):A67-A72.
9. Wara WM, Phillips TL, Sheline GE, Schwade JG: Radiation tolerance of the spinal cord. *Cancer* 1975;35(6):1558-1562.
10. **Sahgal A, Ma L, Gibbs I, et al: Spinal cord tolerance for stereotactic body radiotherapy. *Int J Radiat Oncol Biol Phys* 2010;77(2): 548-553.**

11. Gibbs IC, Kamnerdsupaphon P, Ryu MR, et al: Image-guided robotic radiosurgery for spinal metastases. *Radiother Oncol* 2007; 82(2):185-190.

12. Young RF: Radiosurgery for the treatment of brain metastases. *Semin Surg Oncol* 1998;14(1):70-78.

13. Ryu SI, Chang SD, Kim DH, et al: Image-guided hypo-fractionated stereotactic radiosurgery to spinal lesions. *Neurosurgery* 2001;49(4):838-846.

14. Bartels RH, van der Linden YM, van der Graaf WT: Spinal extradural metastasis: Review of current treatment options. *CA Cancer J Clin* 2008;58(4):245-259.

15. **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.**

16. **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.**

17. **Yang SB, Cho W, Chang UK: Analysis of prognostic factors relating to postoperative survival in spinal metastases. *J Korean Neurosurg Soc* 2012;51(3):127-134.**

18. **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.**

19. Klimo P Jr, Thompson CJ, Kestle JR, Schmidt MH: A meta-analysis of surgery versus conventional radiotherapy for the treatment of metastatic spinal epidural disease. *Neuro Oncol* 2005;7(1):64-76.

20. Degen JW, Gagnon GJ, Voyadzis JM, et al: CyberKnife stereotactic radiosurgical treatment of spinal tumors for pain control and quality of life. *J Neurosurg Spine* 2005; 2(5):540-549.

21. Ryu S, Rock J, Rosenblum M, Kim JH: Patterns of failure after single-dose radiosurgery for spinal metastasis. *J Neurosurg* 2004;101(suppl 3):402-405.

22. Chang EL, Shiu AS, Mendel E, et al: Phase I/II study of stereotactic body radiotherapy for spinal metastasis and its pattern of failure. *J Neurosurg Spine* 2007;7(2):151-160.

23. Gerszten PC, Burton SA, Ozhasoglu C, Welch WC: Radiosurgery for spinal metastases: Clinical experience in 500 cases from a single institution. *Spine (Phila Pa 1976)* 2007;32(2):193-199.

24. 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.

25. Rock JP, Ryu S, Shukairy MS, et al: Postoperative radiosurgery for malignant spinal tumors. *Neurosurgery* 2006;58(5): 891-898.

26. **Moulding HD, Elder JB, Lis E, et al: Local disease control after decompressive surgery and adjuvant high-dose single-fraction radiosurgery for spine metastases. *J Neurosurg Spine* 2010;13(1):87-93.**

27. **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.**

28. 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 (30):5075-5079.

29. **Boehling NS, Grosshans DR, Allen PK, et al: Vertebral compression fracture risk after stereotactic body radiotherapy for spinal metastases. *J Neurosurg Spine* 2012; 16(4):379-386.**

30. **Rasulova N, Lyubshin V, Djalalov F, et al: Strategy for bone metastases treatment in patients with impending cord compression or vertebral fractures: A pilot study. *World J Nucl Med* 2011;10(1):14-19.**

31. **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.**

32. **Cox BW, Jackson A, Hunt M, Bilsky M, Yamada Y: Esophageal toxicity from high-dose, single-fraction paraspinal stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys* 2012;83(5):e661-e667.**