Essential Concepts for the Management of Metastatic Spine Disease: What the Surgeon Should Know and Practice

Ori Barzilai, MD1, Stefano Boriani, MD2, Charles G. Fisher, MD, MHSC, FRCSC3,4, Arjun Sahgal, MD7, Jorrit Jan Verlaan, MD7, Ziya L. Gokaslan, MD8,9,10, Aron Lazary, MD, PhD11, Chetan Bettegowda, MD, PhD12, Laurence D. Rhines, MD13, and Ilya Laufer, MD, MS1; on behalf of the AOSpine Knowledge Forum Tumor

Abstract

Study Design: Literature review.

Objective: To provide an overview of the recent advances in spinal oncology, emphasizing the key role of the surgeon in the treatment of patients with spinal metastatic tumors.

Methods: Literature review.

Results: Therapeutic advances led to longer survival times among cancer patients, placing significant emphasis on durable local control, optimization of quality of life, and daily function for patients with spinal metastatic tumors. Recent integration of modern diagnostic tools, precision oncologic treatment, and widespread use of new technologies has transformed the treatment of spinal metastases. Currently, multidisciplinary spinal oncology teams include spinal surgeons, radiation and medical oncologists, pain and rehabilitation specialists, and interventional radiologists. Consistent use of common language facilitates communication, definition of treatment indications and outcomes, alongside comparative clinical research. The main parameters used to characterize patients with spinal metastases include functional status and health-related quality of life, the spinal instability neoplastic score, the epidural spinal cord compression scale, tumor histology, and genomic profile.

Conclusions: Stereotactic body radiotherapy revolutionized spinal oncology through delivery of durable local tumor control regardless of tumor histology. Currently, the major surgical indications include mechanical instability and high-grade spinal cord compression, when applicable, with surgery providing notable improvement in the quality of life and functional status for appropriately selected patients. Surgical trends include less invasive surgery with emphasis on durable local control and spinal stabilization.

Keywords
tumors, metastases, oncology, stereotactic body therapy (SBRT), surgery

1 Memorial Sloan-Kettering Cancer Center, New York, NY
2 IRCCS Galeazzi Orthopedic Institute, Milan, Italy
3 University of British Columbia, Vancouver, British Columbia, Canada
4 Vancouver General Hospital, Vancouver, British Columbia, Canada
5 Sunnybrook Odette Cancer Center, Toronto, Ontario, Canada
6 University of Toronto, Toronto, Ontario, Canada
7 University Medical Center Utrecht, Utrecht, the Netherlands
8 The Warren Alpert Medical School of Brown University, Providence, RI, USA
9 Rhode Island Hospital, Providence, RI, USA
10 The Miriam Hospital, Providence, RI, USA
11 National Center for Spinal Disorders and Buda Health Center, Budapest, Hungary
12 Johns Hopkins University School of Medicine, Baltimore, MD, USA
13 The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Corresponding Author:
Ilya Laufer, Department of Neurosurgery, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA.
Email: lauferi@mskcc.org
Introduction

Recent advances in cancer therapy have dramatically improved overall survival times in multiple cancer subtypes. Subsequently, the incidence of patients with metastatic spine disease is on the rise and will likely continue to grow. The subjective and objective outcomes of patients with spinal metastases have been shown to improve with proper treatment. Goals of treatment for metastatic spine disease remain palliative and aside from traditional goals such as local tumor control, strive toward symptom palliation and improved health-related quality of life (HRQoL). The recent integration of modern diagnostic tools, targeted and personalized treatments, and widespread use of new technologies have revolutionized treatment of spinal metastases. Alongside the improvement in care for spinal metastases, this wealth of knowledge and breadth of modern treatment tools has complicated treatment paradigms tremendously. Spine cancer treatment requires a multidisciplinary team effort, including surgeons, radiation and medical oncologists, pain and rehabilitation specialists, and interventional radiologists. This review aims to highlight current concepts to inform and help guide spine surgeons to undertake a leadership role in the modern management of spinal cancer.

Patient Evaluation and Treatment Indications

The field of spinal oncology has made great progress in defining the key parameters necessary for clear patient description. Consistent utilization of the requisite patient descriptors facilitates communication, delineation of treatment indications and outcomes, and comparative clinical research. The key parameters used to define the salient characteristics of patients with spinal metastases include HRQoL, spinal mechanical stability, neurologic examination and functional assessment, the extent of epidural tumor extension, tumor histology, and genomic tumor profile.

Health Related Quality of Life

A main treatment goal for patients with spinal metastases is symptom palliation and maintenance or improvement of HRQoL. Historically, clinical outcomes of metastatic spine patients relied primarily on clinician-based measures such as gross measures of function. In recent years, we have witnessed an increase in utilization of patient-reported outcomes (PRO) since patient self-assessment tools express a direct measure of the value of care as perceived by the recipient. Several generic outcome measures have been widely used for PRO reporting in the spinal oncology population, including EuroQol 5-D (EQ-5D), Oswestry Disability Index (ODI), visual analogue scale (VAS), and Short Form 36 (SF-36); however, none of these instruments focus on cancer-specific symptoms that are important to patients with spinal tumors. While the MD Anderson Symptom Inventory (MDASI) has a spinal oncology–specific module, the majority of the questionnaire examines broad cancer-associated symptoms and also lacks the specific focus on symptoms associated with spinal tumors.

A systematic literature review conducted in 2009 revealed the absence of PRO instrument specifically designed for assessment of HRQoL among patients with spinal oncologic disease. The Spine Oncology Study Group Outcome Questionnaire (SOSOQ) was designed to address this need and represents the only PRO instrument fully focused on assessment of patients with spinal tumors. Psychometric evaluation and clinical validation of the SOSOQ among an international cohort of patients with spinal metastases who were treated with surgery and/or radiotherapy confirmed the SOSOQ as a reliable and valid PRO instrument with strong correlation with SF-36 and ability to discriminate between clinically distinct patient groups. Additional testing confirmed that the SOSOQ provides excellent quality of life assessment among patients with spinal metastases and superior internal consistency and coverage compared with EuroQol-5 Dimensions (EQ-5D). Further component analysis indicated that Patient-Reported Outcomes Measurement Information System (PROMIS) might perform better than the SOSOQ in assessing pain intensity and physical function and requires further investigation in large cohort analysis. Currently, the extensive validity and reliability testing of the SOSOQ positions this survey as the best instrument for PRO assessment among patients with spinal tumors.

With growing interest in PRO data, the impact of surgical treatment of metastatic spine disease on HRQoL has recently been the focus of investigation. Fehlings et al analyzed prospectively collected data from the AOSpine North American Clinical Research Network and demonstrated that surgery combined with radiation and systemic therapies provides immediate and sustained improvement in pain, neurologic, and HRQoL outcomes showing improvement in ODI, EQ-5D, pain interference, and SF-36 scores. Additional prospective cohort studies demonstrated improvement in HRQOL following open surgery, as well as following minimally invasive surgery for treatment of spinal metastases. In a recent analysis of the Epidemiology, Process and Outcomes of Spine Oncology (EPOSO) data, significant improvement in HRQoL was demonstrated using both SF-36 and the SOSOQ in patients with oligometastatic and widespread metastatic disease demonstrating improvement in HRQoL for all surgically treated patients, regardless of the extent of systemic disease. Furthermore, among patients with mechanically stable metastatic tumors without compression of the spinal cord, treatment with SBRT resulted in significant reduction in pain and symptom interference with daily life. Hence, consistent attention and reporting of HRQoL provide high-quality data that demonstrate the benefit of surgery and radiotherapy among appropriately selected patients with spinal metastatic tumors.

Neoplastic Spinal (In)Stability

Loss of structural integrity of the spinal column represents one of the most debilitating sequelae of spinal metastases. In 2010, the Spine Oncology Study Group (SOSG) defined cancer-
related spinal instability as “loss of spinal integrity as a result of a neoplastic process that is associated with movement-related pain, symptomatic or progressive deformity, and/or neural compromise under physiologic loads.” The Spinal Instability Neoplastic Score (SINS) was developed to facilitate diagnosis and classification of spinal instability and provide a common language across clinical disciplines and among spine surgeons. This score assesses the degree of spinal instability in a standardized and reproducible manner and can be used by nonspine specialists. The introduction of SINS has improved the uniform reporting of spinal instability in the published literature and lead to improved communication among treating and referring physicians.

Patients with spinal mechanical instability typically require surgical stabilization. Since radiation or systemic treatment do not treat spinal instability, an unstable spine should be surgically stabilized to allow pain palliation and to prevent neurologic compromise and spinal deformity progression. Increasing SINS correlates with increasing severity of pain and functional disability. Patients with low SINS typically experience resolution of pain after radiotherapy treatment, while patients with higher SINS have a higher risk of radiotherapy failure. On the other hand, patients with indeterminate (7-12) and high (13-18) SINS experience significant benefit from surgical stabilization leading to pain relief and functional improvement. These data support the treatment of mechanically stable patients with radiotherapy and illustrate the need for surgical stabilization among mechanically unstable patients.

Epidural Spinal Cord Compression

Epidural spinal cord compression (ESCC) places patients at risk for the development of neurologic deficits and, if not detected early and treated expeditiously, results in significant functional disability. Therefore, assessment of patients with spinal tumors must involve a thorough discussion of ambulation changes, timing of symptom onset, careful neurologic examination, and magnetic resonance imaging (MRI) of the spine.

Loss of ambulation and bowel and bladder dysfunction represent the most severe and debilitating sequelae of MESCC. The severity of neurologic deficits due to MESCC is associated with the severity of HRQoL impairment among cancer patients and subtle neurologic deficits may lead to significant quality of life impairment (unpublished data). Furthermore, the functional status of cancer patients correlates with survival, with ambulatory patients surviving longer than patients who have lost the ability to ambulate. Multiple clinical studies demonstrate neurological improvement after surgery for patients experiencing neurologic deficits due to MESCC, as measured by American Spinal Injury Association (ASIA) Impairment Scale (AIS) and ambulation. However, the true functional benefit of surgery represented by clearly defined useful ambulation, restoration of activities of daily living and return to work requires further study.

A prospective randomized trial demonstrated that surgery followed by radiotherapy provides superior outcomes when compared with radiotherapy alone for the treatment of symptomatic MESCC. Surgery resulted in superior functional outcomes such as preservation and restoration of ambulation and bowel and bladder function, pain control, and survival. Several additional studies focused on the functional and neurologic outcomes after surgery for MESCC. The duration of ambulation loss, bladder dysfunction and Medical Research Council (MRC) muscle strength <III served as the strongest prognostic indicators of ambulation recovery after surgery. Therefore, patients experiencing loss of ambulation due to MESCC caused by solid tumors require timely diagnosis and, in the absence of strong contraindications, benefit from prompt surgical treatment. Surgeons should aim to shorten the duration of neurologic deficit and prevent further neurologic deterioration.

Physicians commonly administer steroids at the time of MESCC diagnosis. The data to support steroid utilization as part of the treatment of MESCC largely rest on animal studies and limited clinical evidence in the setting of radiotherapy. The role of dexamethasone administration in patients undergoing surgery for the treatment of MESCC has not been examined to date and is the focus of a prospective cohort study incorporated into the Metastatic Tumor Research and Outcomes Network (MTRON). Currently, utilization of low-dose dexamethasone protocol (16 mg daily) is recommended for patients with MESCC, since the potential neuroprotective benefit may outweigh the dexamethasone toxicity risk.

The radiographic degree of epidural spinal cord compression is an important component of the MESCC assessment. Fortunately, the ready availability of MRI leads to early diagnosis of MESCC among cancer patients, with most spinal metastases diagnosed at the time of early symptoms, usually starting with pain. Clear description and communication of epidural tumor extension has been facilitated through the development of the ESCC scale (also known as the Bilsky scale). Grades 0 and 1 represent tumor confined to bone or impinging on the thecal sac without compression or displacement of the spinal cord. Grades 2 and 3 are considered high-grade spinal cord compression with displacement and/or compression of the spinal cord and obliteration of the surrounding cerebral spinal fluid (CSF) space. Utilization of T2-weighted and T1-weighted gadolinium-enhanced axial MR images in order to assess the ESCC grades showed good inter- and intrarater reliability in validation studies of the scale. Clear description of ESCC severity is required in order to determine whether the patient can safely undergo SBRT and whether they require surgical decompression. Spinal metastases confined to bone or with minor epidural extension (ESCC 0 and 1) can be definitively treated with SBRT without requiring decompressive or excisional surgery. However, patients with spinal cord compression (ESCC 2 and 3) generally require surgical decompression prior to SBRT to optimize the radiation dose delivered to the entire tumor volume without delivering excessive radiation dose to the spinal cord. Hybrid therapy with
surgical decompression and postoperative SBRT results in durable local control and improvement in HRQoL.12,35

**Precision Medicine**

Oncology has made great strides in the understanding of genetic basis of disease, deciphering the molecular drivers of tumor proliferation and development of drugs that specifically target the aberrant molecular pathways. Giant technological advances in sequencing lead to the development of next-generation sequencing, which can be readily performed at the point of care and already serves as one of the standard techniques for clinical classification of tumors. Genomic profiling currently guides clinical management of tumors such as melanoma, sarcomas, and carcinomas of the lung, breast, thyroid, ovary, and colon.36 Clinical trials support treating several mutations with targeted therapy, with a continuously growing list of potential targets undergoing clinical testing. Epidermal growth factor receptor (EGFR) mutation in lung cancer serves as one of the most notable examples of targeted therapy success, with tyrosine kinase inhibition of the EGFR pathway resulting in the extension of survival from 8-11 months to 24-36 months among patients with metastatic non–small lung carcinoma (NSCLC) with targetable EGFR mutations.37 Evaluation of literature specifically reporting survival among patients with NSCLC metastatic to the spine showed that while the overall survival of patients with lung cancer metastases to the spine was 3.6 to 9 months, the median reported survival of NSCLC patients with targetable EGFR mutations was 18 months.38 Thus, while previously, patients with NSCLC metastases were considered poor surgical candidates due to very short expected survival, current therapy provides extended survival among subgroups of NSCLC patients making them realistic surgical candidates. Similar extended survival groups were identified among patients with metastatic melanoma harboring BRAF mutation and tumors responsive to immunotherapy.36,39 While the effect of systemic therapy on osseous metastases has been limited, a recent clinical trial showed favorable response of osseous renal cell carcinoma metastases treated with cabozantinib, which is a small molecule tyrosine kinase inhibitor, indicating that new systemic therapy agents may offer local tumor control for osseous metastases.40 With the popularization of precision medicine through patient education, research, and clinical implementation, surgeons treating cancer patients will need to increasingly gain familiarity with the clinical genomic and molecular oncology landscape in order to make informed decisions in patient care.

The NOMS framework facilitates treatment decisions for patients with spinal metastatic tumors through incorporation of the key parameters discussed above into 4 patient evaluation categories: Neurologic, Oncologic, Mechanical, and Systemic.41 The combination of the neurologic evaluation, ESCC grade and tumor histology guide the selection of radiotherapy modality and the need for surgical decompression. The mechanical evaluation of the spine determines the need for spinal stabilization. The systemic component considers the medical comorbidities, the extent of systemic tumor burden and the genomic profile of the tumors to determine the patient’s ability to tolerate treatment and the desired durability of therapy.

**Treatment Techniques**

**Radiotherapy**

**Conventional Radiotherapy.** Conventional external beam radiotherapy (cEBRT) has been used as the primary and adjuvant treatment of spinal metastatic tumors for decades. cEBRT generally delivers wide-field radiation in small additive doses, such as 30 Gy in 10 fractions, with the dose delivered to the tumor limited by the dose that can be tolerated by the surrounding organs at risk, such as the spinal cord.42 Tumors exhibit a wide range of response duration and recurrence after cEBRT treatment. Examination of cEBRT treatment outcomes among patients with spinal metastases resulted in classification of tumors as radiosensitive and radioresistant based on the primary tumor histology.43,44 Tumors that respond well to cEBRT include most hematologic malignancies (ie, lymphoma, multiple myeloma, and plasmacytoma), as well as selected solid tumors (ie, breast, prostate, ovarian, and seminoma).45,46 However, most solid tumors respond poorly to cEBRT (ie, radioresistant), including renal cell carcinoma (RCC), colon, NSCLC, thyroid carcinoma, hepatocellular carcinoma, melanoma, and sarcoma.44-47

**Stereotactic Body Radiation Therapy.** The incorporation of stereotactic body radiation therapy (SBRT) into the metastatic spine tumor realm has revolutionized treatment paradigms and changed surgical indications along with the type and extent of surgery currently performed. Radiosurgery overcomes tumor radioresistance through safe delivery of high doses of radiation to the tumor while minimizing radiation dose to the surrounding organs at risk, such as the spinal cord.48,49 The basis of overcoming radioresistance lies in the recruitment of additional tumoricidal pathways when delivering a high dose per fraction radiation treatment compared to the known mechanisms of cell death secondary to cEBRT.50-53 Since the introduction of spinal SBRT, an abundance of data has established the safety and efficacy of SBRT. In a single institution experience, Yamada et al54 analyzed 811 spine radiosurgery targets and showed local control rates of up to 98% over 4 years, noting that response rates were irrespective of tumor histology or volume but rather dose-dependent. Other series with single-fraction or hypofractionated SBRT report comparable rates of local control.54-56 Recent interest focuses on evaluation of dosing and fractionation regimens as optimal dosing and fractionation remain controversial and various treatment regimens are currently utilized. For example, Tseng et al57 recently described a single-institution experience using 24 Gy in 2 fractions, showing this regimen to be safe and effective, leading to 1-year and 2-year local failure rates of 9.7% and 17.6%, respectively. SBRT has been shown to not only affect local control
but also shown to result in significant reduction in patient-reported pain and symptom interference among mechanically stable patients. Currently, SBRT is used not only in the de novo setting but also for patients who were previously irradiated. For example, a prospective study of 59 patients, using doses of 30 Gy in 5 fractions or 27 Gy in 3 fractions, showed 1-year local control rate of 76%, and significant improvements in pain control.

The currently accepted dose constraints limit utilization of SBRT in the setting of high-grade epidural disease. However, with technological improvement and better understanding of spinal cord radiation tolerance, SBRT may become a viable approach in select cases of high-grade MESCC. Ryu et al performed single-session radiosurgery on 85 lesions (from 62 patients), showing mean epidural tumor volume reduction was 65% 2 months postradiosurgery. However, several patients experienced neurologic deterioration and currently utilization of SBRT for the treatment of high-grade MESCC is limited to experimental protocols.

Dose constraints and the toxicity risks have been established for all major organs at risk, including para- and intraspinal structures. Fortunately, high-grade toxicity after SBRT seldom occurs and most complications are mild. Long-term data is becoming more readily available and a series of patients who were followed for at least 5 years after SBRT exhibited a 17% rate of grade ≥2 toxicity; yet, many of these patients underwent SBRT as salvage treatment after failed cEBRT. Vertebroplasty compression fractures (VCFs) are one complication that require assessment of spine surgeons. VCFs following SSRS have been described in up to 40% of treatments compared with a less than 5% risk following cEBRT. The majority of post-SBRT VCF are asymptomatic radiographic findings, with interventions such as kyphoplasty required for a small proportion of these fractures.

The International Spine Radiosurgery Consortium developed contouring and planning guidelines for spinal radiosurgery planning and recent consensus guidelines have also been created for postoperative target contouring. It is recommended that spine surgeons familiarize with these guidelines and actively participate in the treatment planning.

In summary, SBRT provides safe and durable local control for patients with spinal metastases and serves as one of the integral treatment modalities in modern spinal oncology. While the availability and utilization of SBRT for the treatment of spinal tumors has been steadily growing and has become the standard treatment modality in many spinal oncology centers, many regions and medical centers throughout the world do not have SBRT readily available. In places with limited SBRT availability, cEBRT remains the major radiation modality for spinal tumors, requiring greater utilization of excisional tumor surgery to optimize local tumor control. Surgeons should work closely with their radiation oncology colleagues to select the optimal treatment modality for their patients and to tailor their surgical indications according to the expected response to the available radiotherapy.

Surgery

Surgical stabilization and decompression is strongly recommended for patients with radioresistant tumors in the setting of high-grade spinal cord compression. The primary evidence for this recommendation was provided by Patchell et al, who conducted a prospective randomized trial that illustrated improved ambulation outcomes after direct surgical decompression compared with radiotherapy for patients with solid tumor metastases causing symptomatic ESCC. Furthermore, stabilization surgery is recommended for patients with mechanical instability of the spinal column, even in the absence of high-grade spinal cord compression. A wide range of surgical decompression and stabilization techniques has been described. Corpectomy, laminectomy, and transpedicular decompression represent the most commonly used decompression techniques.

Prior to popularization of SBRT, gross total surgical excision of radioresistant tumors was required for local control. The excision can be carried out using intralesionel and en bloc techniques. The excellent local tumor control that can be achieved with excisional surgery in appropriately selected patients and the surgical approaches and techniques required for such surgeries have been thoroughly described. Integration of SBRT into the treatment of spinal tumors, lead to the development of less invasive surgical options, since significant tumor excision is no longer required to achieve durable local control, except in select cases of recurrent tumors. Methods for spinal stabilization vary and may entail open surgery, percutaneous stabilization or, in select cases of isolated anterior column compromise, kyphoplasty/vertebroplasty. Separation surgery and minimal access surgery represent some of the most recent advances in decompression and stabilization techniques for spinal tumor surgery and may well be changing the conventional surgical indications for this patient population. In places with limited access to SBRT, surgeons and oncologists must continue to rely on the more aggressive excisional surgical techniques to improve HRQoL and local control for patients with spinal tumors.

Separation Surgery. While SBRT provides effective and durable local control for spinal metastases regardless of tumor histology, volume, and prior radiation history, SBRT is less effective when delivered to tumors causing spinal cord compression. Avoiding radiation-induced spinal cord injury while maximizing treatment dose requires sufficient distance between the radiation target and the spinal cord. Hence, patients with high-grade epidural spinal cord compression are not considered candidates for “up-front” radiation treatment. Separation surgery was first described in 2000 as decompression surgery that provides the foundation for concomitant SBRT. The goal of separation surgery is to create distance (typically 1-2 mm) between the tumor and spinal cord providing an optimal target for SBRT while also circumferentially decompressing the spinal cord and stabilizing the spinal column. Generally, this is performed though a single-stage posterolateral...
transpedicular approach. Through this approach, circumferential epidural decompression is achieved, without the need for significant cytoreduction or gross tumor removal. Resection of the posterior longitudinal ligament allows ventral tumor separation, and cement augmentation can aid in ventral column reconstruction without need for cage placement or more extensive reconstruction. It is important to realize that although this is a posterior-only approach, a simple laminectomy may not provide adequate ventral separation. Among patients with adequate separation between the tumor and the spinal cord, more than 90% local control at 1-year follow-up has been reported. However, patients with persistent high-grade epidural tumor extension after separation surgery remain at significant risk of postoperative tumor recurrence. A variety of intraoperative navigational tools can facilitate the intraoperative assessment of tumor extent and allow integration of ablative therapies. Robot-assisted spine surgery is currently under investigation and aims to reduce human error and further improve the accuracy of spinal instrumentation along with reducing potential complications. Initial experience with such techniques in spine tumor surgery demonstrate its feasibility, yet larger experience is required to determine its efficacy and necessity.

**Stabilization Techniques.** Cancer patients frequently have poor bone quality secondary to osteolytic disease, chemotherapy, radiation therapy, steroid use, and osteoporosis. Low probability of arthrodesis in the setting of radiation and chemotherapy along with the poor bone quality provide a challenging substrate for spinal stabilization. Furthermore, the increasing duration of postoperative survival due to advances in systemic therapy, requires durable stabilization constructs. A systematic literature review and expert survey support the use of prefabricated prosthetic and/or polymethylmethacrylate bone cement among patients requiring anterior column reconstruction. The posterior column should be stabilized using bilateral pedicle screw fixation above and below the level of the tumor. Fenestrated screws facilitate screw cement augmentation and may be used in order to improve osseous purchase in osteoporotic patients with cancer.

Implant material selection must take into consideration postoperative radiation plans. Cobalt chrome causes significant beam scatter thus altering the dose delivered to the tumor and organs at risk whereas titanium has been shown to cause minimal radiation beam scatter. Carbon fiber implants may provide a superior stabilization option for patients with planned postoperative proton beam therapy treatment, since the presence of metallic implants has been shown to have a detrimental effect on local tumor control after proton therapy. Implants based on from carbon fiber also offer superior MR image quality, which may be beneficial for long-term surveillance/monitoring of local tumor control. Stabilization with polymethylmethacrylate does not appear to alter radiation dosimetry.

**Conclusions**

Great strides in systemic therapy, radiotherapy, and surgical techniques have vastly improved the outcomes for patients with spinal metastases. Standardization of patient population description and outcome reporting results in clear delineation of treatment indications, care team communication and comparative research. SBRT provides durable local control for the majority of patients with spinal metastases. Surgical indications include mechanical instability and high-grade spinal cord compression. Surgical trends include less invasive surgery with emphasis on durable local control and spinal stabilization. Extensive evidence supports current radiotherapy and surgical indications with clear evidence of patient benefit.

**Declaration of Conflicting Interests**

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Boriani reports educational commitments with K2M and Nuvasive, which are outside the submitted work. Dr Fisher reports consulting and royalties from Medtronic; research grants from OREF; and fellowship support paid to institution from AOSpine and Medtronic, which are all outside the submitted work. Dr Sahgal reports past
educational seminars with Elekta AB, Accuray Inc, and Varian medical systems; research grant with Elekta AB; travel accommodations and expenses from Elekta and Varian; and belongs to the Elekta MR Linac Research Consortium. Dr. Gokaslan reports research support from AOSpine North America and stock ownership of Spinal Kinetics, which are all outside the submitted work. Dr. Rhines reports educational commitments with Stryker, which are outside the submitted work. Dr. Laufer reports receiving consulting fees from Globus, Depuy/Synthes, and SpineWave.

**Funding**

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was organized and funded by AOSpine International through the AOSpine Knowledge Forum Tumor, a focused group of international spine oncology experts acting on behalf of AOSpine. Study support was provided directly through the AOSpine Research Department.

**ORCID iD**

Ori Barzilai https://orcid.org/0000-0002-4037-8716

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