Is there any role for stereotactic body radiotherapy in the management of metastatic epidural spinal cord compression?

Simon S Lo^{*1}, Charlotte D Kubicky², Eric L Chang³ & Arjun Sahgal⁴

The standard treatment of metastatic epidural spinal cord compression (MESCC) in a symptomatic patient with good performance status, histology that is not exquisitely radiosensitive (lymphoma, small cell, myeloma and germinoma), and a single level of compression, is surgical decompression followed by external beam radiotherapy (EBRT). This treatment approach is supported over EBRT alone in these well-selected patients by level I evidence [1]. The landmark Patchell study showed that the addition of surgery improved the likelihood of patients being able to walk, and was associated with a survival benefit (although this study was not powered for survival). Unfortunately, some patients are unable to undergo decompressive surgery and, as a result, EBRT alone is the treatment of choice despite inferior functional

outcomes [2]. In patients who have been exposed to prior EBRT to the same spinal segments with MESCC, and who are not surgical candidates, repeat EBRT is feasible, but the radiation dose that can be delivered is limited. Ultimately, to respect spinal cord tolerance, we have to underdose the tumor and, therefore, the expectation is short-term gains and not necessarily long-term tumor control.

Stereotactic body radiotherapy (SBRT) is a relatively new technique that takes advantage of modern radiation technology that sculpts the radiation conformally to the tumor boundaries and is able to bend it away from the spinal cord, such that we can dose-escalate and ablate the spinal tumor while still respecting spinal cord tolerance. It is now increasingly a treatment of choice for patients with uncomplicated spinal

KEYWORDS

- epidural • spinal cord compression
- stereotactic body radiotherapy

“[Stereotactic body radiotherapy] is now increasingly a treatment of choice for patients with uncomplicated spinal metastasis with a relatively large body of data demonstrating efficacy and safety.”

¹Department of Radiation Oncology, University Hospitals Seidman Cancer Center, Case Comprehensive Cancer Center, 11100 Euclid Avenue, Lerner Tower B181, Cleveland, OH 44106, USA

²Department of Radiation Medicine, Oregon Health Science Center, OR, USA

³Department of Radiation Oncology, Keck School of Medicine & Norris Cancer Center, University of Southern California, CA, USA

⁴Department of Radiation Oncology, Odette Sunnybrook Health Sciences Centre, University of Toronto, ON, Canada

*Author for correspondence: Tel.: +1 216 286 6740; Fax: +1 216 844 2005; Simon.Lo@UHhospitals.org

“Upon review of the literature, stereotactic body radiotherapy has in fact been used to treat spinal metastases causing metastatic epidural spinal cord compression as primary treatment and, more commonly, as adjuvant post-operative treatment.”

metastasis with a relatively large body of data demonstrating efficacy and safety. However, most of the current data are either retrospective studies or single-arm prospective trials [3,4]. The question that is being put forward now is: what is the role of SBRT in the setting of complex spinal metastases such as those causing MESCC? Furthermore, what is the role of SBRT as an alternative to EBRT as the adjuvant therapy once surgery performed.?

Upon review of the literature, SBRT has in fact been used to treat spinal metastases causing MESCC as primary treatment and, more commonly, as adjuvant post-operative treatment. As an alternative to EBRT in the adjuvant setting an early study from Henry Ford Hospital (HFH) reported the first outcomes. Rock *et al.* treated 18 patients with post-operative single-fraction SBRT to 11.4 Gy (range: 6–16 Gy) with ten of them having extremity weakness presumably from spinal cord compression before surgical decompression [5]. Ten patients had metastatic carcinoma, four had multiple myeloma, three had sarcoma, and one had a giant cell tumor. Among the patients initially presenting with neurological deficits, 92% either remained neurologically stable or improved after surgery and post-operative SBRT [5]. The Memorial Sloan–Kettering Cancer Center (MSKCC) recently reported a major series with 186 patients initially presenting with MESCC who were treated with surgical decompression and instrumentation followed by postoperative SBRT. Their total dose was either 24 Gy in one fraction (40 patients), 24–30 Gy in three fractions (37 patients), or 18–36 Gy in five or six fractions (109 patients). Local progression rate at 1 year was 16.4% [6]. A significant better local control was observed in patients receiving 24–30 Gy in three fractions compared to those receiving 18–36 Gy in five or six fractions (95.9 vs 77.4% in 1 year) [6]. Patients treated with 24 Gy in fraction had a local progression rate of <10%. Al-Omair *et al.* reported a series from the University of Toronto where 80 patients had been treated with post-operative SBRT, and observed a 1 year actuarial rate of local control of 84% [7]. They classified the degree of epidural disease according to the Bilsky system. Ultimately, they reported that maximal debulking of high-grade epidural disease has a therapeutic impact with respect to local control. This had not been previously reported and proves the utility of surgery. Furthermore, they also observed that patients treated with more hypofractionated schedules of

24 Gy in one or two fractions (predominantly 24 Gy in two fractions) had better outcomes than more fractionated courses of SBRT (three to five fractions) [7].

SBRT has also been used as the primary treatment for MESCC. This is controversial practice as the epidural space is relatively under-dosed to meet spinal cord tolerance criteria and criteria suggest a minimum distance of at least 2 to 5 mm from tumor to spinal cord to maximize the dose distribution. The first study from HFH reported outcomes of 24 patients with 31 myeloma lesions presenting with MESCC treated with single-fraction SBRT to a dose of 16 Gy (range: 10–18 Gy). Complete and partial pain relief were achieved in 54 and 32% of patients, respectively. This result was based on a median follow-up of 11.2 months [8]. Five (71%) of the seven patients with neurologic deficits had improved or normalized neurologic function after treatment. The complete and partial radiologic response rates were 81.2 and 18.8%, respectively, among 16 out of 24 evaluable patients. There were no neurologic toxicities observed [8]. Their second study reported outcomes of 62 patients with 85 sites of MESCC, from non-radiosensitive spinal tumors, treated with SBRT and a total dose of 16 Gy (range: 12–20 Gy) in one fraction [9]. 27 patients presented with various neurologic deficits including decreased motor strength (n = 21), sensory deficits (n = 2) and radiculopathy (n = 4). Among those with motor deficits, all had muscle power of at least 4 out of 5 (based on Medical Research Council Grading of Strength) prior to SBRT [9]. Steroid therapy and SBRT were initiated within 24–48 h from the time of consultation. The median follow-up was 11.5 months. In the 35 patients who had intact neurologic function before SBRT, the neurological status remained intact in 33 of them (94%). For the 27 patients presenting with neurologic deficit, 14 (52%) achieved complete recovery to normal, three (11%) had improved function, and three (11%) had stable function [9]. The mean epidural tumor volume reduction was 65% at 2 months after SBRT. There was a reduction of epidural tumor area at the level of the most severe spinal cord compression from 0.82 to 0.41 cm², and an increase in the thecal sac patency from 55 to 76% after SBRT. No neurologic toxicities were observed. Investigators from Cleveland Clinic Foundation also reported their experience with single fraction SBRT for the treatment of 21

patients with 33 epidural spinal cord compression sites who were poor surgical candidates in abstract form [10]. Indications for SBRT included pain (69.7%), neurologic deficits (12.1%), both pain and neurological deficits (15.2%) and radiologic diagnosis (3%). The median dose given was 14 Gy (range: 8–16 Gy) in one fraction. At a median follow-up was 6.9 months, the median survival was 10.4 months. Renal cell carcinoma was the most common histology (39.4%). 16 (48.5%) and 13 (39.4%) lesions had prior external beam radiotherapy and previous surgery, respectively. Pain relief was achieved in 60.6% of patients. Radiographic and pain control was achieved in 22 (66.7%) and 25 (75.8%) of treatment sites, respectively [10]. Neurological improvement was observed in four out of nine (44.4%) patients who presented with neurologic deficits after SBRT. Neurologic toxicities were limited to grade 1 or 2 (6.1%). Other observed toxicities included pain flare (9.1%) and vertebral compression fracture (3%) [10].

Investigators from the MD Anderson Cancer Center (MDACC) have reported their preliminary results for two concurrent Phase I trials of SBRT for medically inoperable radiation naive and previously irradiated patients with MESCC, respectively [11]. All patients were required to have a motor strength of at least four out of five. The prescribed doses to the gross tumor volume and clinical target volume were 18 Gy and 16 Gy in one fraction, respectively. The spinal cord constraints were 10 and 8 Gy to 0.01 cc of spinal cord for radiation-naïve and previously irradiated patients, respectively. The cord constraints could be relaxed in 2 Gy increments when there would be recurrence or progression. Utilizing a generalizable class solution for treatment planning, the mean time from consultation to simulation was 5.25 days (range: 0–19 days) [11]. At a mean follow-up of 5.07 months (range: 0.59–10.59 months), four of 12 patients developed disease progression and died. The mean time from SBRT to local recurrence was 6.42 months (range: 1.41–8.98 months) [11]. No radiation myelopathy cases have been observed thus far.

Based on the limited data available so far, SBRT seems to be a promising treatment modality for patients with MESCC, in the post-operative setting. High-quality prospective studies and, ultimately, a randomized trial comparing adjuvant EBRT to adjuvant SBRT are much needed. With respect to SBRT as the primary

therapy for MESCC, which ultimately competes with the role of surgery for these patients, its role is not well defined. The limited data discussed in this editorial reveal that the patients were highly selected such that they were required to have a motor strength of at least four out of five [8–11]. It is imperative to realize that spinal SBRT is extremely resource intensive, and a significant amount of time is needed for each step for the procedure, from preparation to treatment, to ensure safe delivery. This time period is typically over days, and during that time there is a significant risk for neurologic deterioration due to progressive spinal cord compression. To be able to initiate treatment within a short time, a dedicated physics team and a very streamlined clinical pathway are crucial. Investigators from MDACC used a generalizable class solution for treatment planning for their spinal SBRT cases and were able to generate a plan for first review from submission of contours in an average of 8.18 h with the shortest time interval of 2.25 h [11]. However, such resources may not be available in the majority of radiotherapy centers. Another concern is the underdosing of the tumor volume abutting or compressing on the spinal cord in an attempt to avoid overdosing the spinal cord. It has been recognized that epidural progression is the most common pattern of failure and likely due to this relative under-dosing within the epidural space required to meet spinal cord tolerance constraints [12]. That may result in an increased risk of progressive or recurrent spinal cord compression with more mature follow-up. Therefore, SBRT remains a relative contraindication for patients with high-grade MESCC.

So, where do we stand in 2014? For patients presenting with single level symptomatic MESCC, surgery with circumferential decompression followed by post-operative SBRT is deemed appropriate. At this time SBRT alone is not appropriate in these patients as there are few data, as discussed above, and longer follow-up and analysis of patterns of failure will define who in this clinical scenario may be treated with SBRT as opposed to the standard of care which would be urgent EBRT. If the patient is not symptomatic and presents with high-grade epidural disease, then surgery should still be performed followed by post-operative adjuvant SBRT to maximize SBRT outcomes, and that treatment decision requires multidisciplinary collaboration. If surgery is not performed, EBRT alone is at this time the standard of care and the

“For low-grade epidural disease, stereotactic body radiotherapy alone is a reasonable option as opposed to external beam radiotherapy...”

use of SBRT is controversial. For low-grade epidural disease, SBRT alone is a reasonable option as opposed to EBRT, and in selected clinical situations (e.g., in patients previously irradiated), surgery to maximize the space between tumor and the spinal cord followed by SBRT may be appropriate to improve local control outcomes.

Financial & competing interests disclosure

SS Lo is a member of the Elekta Oligometastasis CORE Group (Elekta AB) and has received travel funds and honorarium from Varian Medical System for educational presentation. EL Chang has received speaking honorarium for

Elekta Users Group Meeting at American Society for Radiation Oncology (ASTRO). A Sahgal is a member of the Elekta Oligometastasis Core Group, Elekta Spinal Metastasis Group, has received research funds from Elekta AB and has received prior honorarium for educational presentations from Elekta and Medtronic Kyphoplasty Division. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

- 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* 366(9486), 643–648 (2005).
- Shiue K, Sahgal A, Chow E *et al.* Management of metastatic spinal cord compression. *Expert Rev. Anticancer Ther.* 10(5), 697–708 (2010).
- Sahgal A, Larson DA, Chang EL. Stereotactic body radiosurgery for spinal metastases: a critical review. *Int. J. Radiat. Oncol. Biol. Phys.* 71(3), 652–665 (2008).
- Lo SS, Sahgal A, Wang JZ *et al.* Stereotactic body radiation therapy for spinal metastases. *Discov. Med.* 9(47), 289–296 (2010).
- Rock JP, Ryu S, Shukairy MS *et al.* Postoperative radiosurgery for malignant spinal tumors. *Neurosurgery* 58(5), 891–898; discussion 891–898 (2006).
- 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* 18(3), 207–214 (2013).
- 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.* 15(10), 1413–1419 (2013).
- Jin R, Rock J, Jin JY *et al.* Single fraction spine radiosurgery for myeloma epidural spinal cord compression. *J. Exp. Ther. Oncol.* 8(1), 35–41 (2009).
- Ryu S, Rock J, Jain R *et al.* Radiosurgical decompression of metastatic epidural compression. *Cancer* 116(9), 2250–2257 (2010).
- Suh JH, Balagamwala EH, Reddy CA *et al.* The use of spine stereotactic body radiation therapy for the treatment of spinal cord compression. *Int. J. Radiat. Oncol. Biol. Phys.* 84(3), S631 (2012).
- Sharp HJ, Brown P, Settle SH *et al.* Feasibility of Radiosurgical Decompression of Metastatic Epidural Spinal Cord Compression (MESCC) in Nonoperable Patients. *Int. J. Radiat. Oncol. Biol. Phys.* 84(3), S282 (2012).
- 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* 14(2), 151–66 (2011).