Modern approaches to the management of metastatic epidural spinal cord compression

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Metastatic epidural spinal cord compression (MESCC) is an oncologic emergency requiring prompt treatment to maximize neurologic function, ambulatory function and local control. Traditionally, options for MESCC included external beam radiation therapy with or without surgery. Surgery has usually been reserved for the patient with optimal performance status, single level MESCC or mechanical instability. Advances in external beam radiation therapy such as the development of stereotactic body radiation therapy have allowed for the delivery of high-dose radiation, allowing for both long-term pain and local control. Surgical advances, such as separation surgery, minimal access spine surgery and percutaneous instrumentation, have decreased surgical morbidity. This review summarizes the latest advances and evidence in MESCC to enable modern management.

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Metastatic epidural spinal cord compression (MESCC) is a common complication of metastatic cancer, with approximately 80,000 new cases each year in the USA [1]. In a study of over 15,000 patients hospitalized with MESCC, the most common associated diagnoses were lung cancer (25%), prostate cancer (16%) and multiple myeloma (11%) [2]. Approximately 60% of cases involve the thoracic spine, 25% the lumbosacral spine and 15% present in the cervical spine [3].

Clinical presentation

Pain is the most common presenting symptom of MESCC, with an incidence of 80–90% [4]. Other symptoms include motor weakness, autonomic dysfunction and sensory loss [5]. Motor symptoms usually precede sensory symptoms, with incontinence often representing a late sign [1].

• Pathophysiology

The pathology of MESCC is described as occurring in three stages [6]. Initially epidural tumor leads to compression and obliteration of the vertebral venous plexus leading to vasogenic edema within

KEYWORDS

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the spinal cord. Further tumor growth leads to mechanical compression of the spinal cord with disturbances in spinal cord blood flow. In the final stages spinal cord blood becomes critically low leading to infarction and irreversible cord damage.

• Assessment & diagnosis

Delays in diagnosis of MESCC are unfortunately common. A study of 301 patients with MESCC noted a delay of 14 days from the development of symptoms to the start of treatment [7]. Given that prompt intervention increases the probability that a patient will regain function, there should be a high index of suspicion for MESCC in any patient with new back pain or weakness and a history of cancer. Following physical examination, MRI is the imaging study of choice [8] and is associated with a sensitivity of 93%, a specificity of 97% and an overall accuracy of 95% for diagnosing MESCC [9]. It is recommended the entire spine should be scanned, as up to 20% of patients will have multiple sites of MESCC [10,11].

Evaluation & grading of MESCC

An MRI based grading system by the Spine Oncology Study Group (SOSG) helps classify the degree of MESCC using a six-point system (Table 1), and was found to have favorable inter- and intra-rater reliability [12]. Of note, and as will be discussed further below, Grades 2 and 3 MESCC are considered high-grade, warranting surgical consultation.

Prognosis

The median survival for patients with MESCC is approximately 7 months with primary tumor histology serving as one of the primary determinants of survival [13–15]. Outcomes are better for those patients ambulatory compared with those nonambulatory prior to starting therapy [13,16].

Treatment

• General approach

The treatment of spinal metastases is palliative. Goals include maximizing pain relief, neurologic function, local tumor control, mechanical stability and quality of life. Patients should be evaluated from a neurologic and oncologic viewpoint, and from a surgical perspective, in terms of the level and degree of epidural disease and for instability.

The physical exam should focus on neurologic symptoms such as weakness, radicular pain, sensory level deficits and bowel or bladder incontinence. The duration of symptoms is important, as patients with long standing neurologic deficits may be less likely to respond to surgery. MRI should be reviewed for vertebral compression fractures as well as the presence and grade of epidural disease. CT-myelography can be substituted in patients where an MRI is unattainable.

Melanoma, renal cell carcinoma and sarcoma are traditionally thought to be radiosensitive, increasing the consideration for surgical or radiosurgical approaches. In contrast, radiosensitive histologies such as germ cell tumors, hematologic tumors, myeloma and small-cell carcinoma can be approached with conventional radiation therapy (RT), or occasionally systemic therapy, without a role for resection [17].

Mechanical instability, which often presents as pain with movement, is an independent consideration for surgery. The Spine Instability in Neoplasia scoring system (Table 2) can help identify patients with instability [18], which is crucial, as RT does not help restore stability nor palliate this type of pain.

The primary operative indications include high-grade MESCC from a nonradiosensitive tumor and instability. Additionally, the presence of retropulsed bone fragments into the spinal canal should warrant surgical consideration as RT will not provide meaningful decompression

Table 1. Spine oncology study group cord compression grading.	
Grade	Description
0	Bone involvement only
1a	Epidural impingement but no thecal sac deformation
1b	Deformation of the thecal sac without spinal cord abutment
1c	Deformation of the thecal sac with spinal cord abutment, but without compression
2	Spinal cord compression but CSF visible
3	Spinal cord compression but no CSF seen
CSF: Cerebrospinal fluid.	

Table 2. Summary table including all elements of the spine Instability in neoplasia.

Element of SINS	Score
Location	
Junctional (occiput-C2, C7-T2, T11-L1, L5-S1)	3
Mobile spine (C3-C6, L2-L4)	2
Semi-rigid (T3-T10)	1
Rigid (S2-S5)	0
Pain relief with recumbency and/or pain with movement/loading of the spine	
Yes	3
No (occasional pain but not mechanical)	1
Pain free lesion	0
Bone lesion	
Lytic	2
Mixed (lytic/blastic)	1
Blastic	0
Radiographic spinal alignment	
Subluxation/translation present	4
De novo deformity (kyphosis/scoliosis)	2
Normal alignment	0
Vertebral body collapse	
>50% collapse	3
<50% collapse	2
No collapse with >50% body involved	1
None of the above	0
Posterolateral involvement of the spinal elements (facet, pedicle or CV joint fracture or replacement with tumor)	
Bilateral	3
Unilateral	1
None of the above	0

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SINS: Spine Instability in neoplasia.

nor palliation [17]. Of note, MESCC is an oncologic emergency requiring prompt surgical evaluation, ideally within 24 h [7,19].

Steroids

Steroids should be considered in any patient with suspected MESCC, even when the ensuing work up is incomplete. A randomized study of 57 MESCC patients confirmed the benefit of steroids [20]. In this study, patients were given either 96 mg of dexamethasone for 4 days followed by a 10 days taper, or no dexamethasone. Significantly more patients in the dexamethasone group remained ambulatory both at the end of radiation (81 vs 63%) as well as at 6 months (59 vs 33%) [20].

A Cochrane meta-analysis analyzing steroid dosing in MESCC found that serious adverse effects, including gastric ulcers and infections, were significantly higher in the high-dose steroid

arms [21]. The authors concluded the data were insufficient to make a dosing recommendation based on efficacy. We typically start with 10 mg of intravenous dexamethasone, followed by 8 mg by mouth twice daily and taper depending on the clinical situation.

Initial treatment

• Surgical resection

Laminectomy, previously the standard operation for MESCC, was abandoned due to a 29-patient randomized study comparing laminectomy plus RT versus RT alone for patients with MESCC. The study found no difference in pain relief, motor function or sphincter function preservation ($p > 0.05$ for all) [22].

In contrast to laminectomy, which does not involve tumor removal, direct decompressive surgery results in tumor resection, stabilization and immediate decompression of the spinal cord. A

Phase III study investigated this approach, and has shaped the modern management of MESCC. Patchell *et al.* randomized 101 MESCC patients to decompressive surgery followed by radiation to radiation alone [23]. Exclusion criteria included radiosensitive tumors, multiple sites of MESCC, or the inability to walk for more than 48 h. The primary end point was ability to walk post treatment. More patients in the surgery group were able to walk following surgery than in the radiation alone group (84 vs 57%; $p = 0.001$) respectively. More patients in the surgical arm also regained the ability to walk (62 vs 19%, respectively; $p = 0.01$). Improvements in urinary continence, the duration of continence, use of corticosteroid and opioid analgesics were also observed in the surgical group. Criticisms of this study include that it took over 10 years to accrue the necessary patients, the surgery was not standardized and instability was not formally assessed. These limitations suggest that the patients were highly selected, and the results applicable to a selected subset of MESCC patients.

More recently, a multi-institutional Phase II study detailing surgical outcomes in 142 patients undergoing surgery (usually with adjuvant radiation) for MESCC was reported by Fehlings *et al.* Results were evaluated in terms of both clinically assessed criteria, and patient reported quality of life using validated instruments [15]. The study demonstrated a statistically significant improvement in the ability to walk four steps independently at time points ranging from 6 weeks to 12 months ($p < 0.05$ for all). Most importantly, the study demonstrated that surgery decreased pain and improved motor function and quality of life. This study is of major significance as it reflects current surgical practice with high-quality prospective data and study monitoring.

Modern surgical approaches range from conventional open surgery to minimally invasive techniques with goals that include tumor resection, spinal cord decompression and/or spinal stabilization [24]. Regardless of the procedure, it is recommended that patients should have a life expectancy of at least 3 months to be considered for surgery [10]. Despite the development of prognostic scoring systems, estimating survival in metastatic patients remains challenging [25–28].

Conventional external beam radiation therapy

The optimal dose of conventional external beam RT (cEBRT) to use in the setting of MESCC

was assessed in a systematic review and meta-analysis of 2239 patients. Radiation doses were divided into short course, meaning 1 week of treatment or less, typically including doses such as 8 Gy in one fraction or 20 Gy in five fractions, and long-course irradiation defined as 2 weeks or more typically including 30 Gy in ten fractions or 37.5 Gy in 15 fractions. The study demonstrated no differences between short and long-course RT in terms of survival or motor function (p for all > 0.05). However, a benefit in terms of local control was observed with long course RT (relative risk [RR] = 0.83; 95% CI: 0.71–0.97; $p = 0.02$) [29].

A randomized study compared 203 patients with MESCC and poor expected survival to either 20 Gy in five fractions or 30 Gy in ten fractions [30]. Patients were required to have motor deficits of the lower extremities. The primary end point was the 1 month overall response in motor function. Both the overall response rate, and the percentage of patients ambulatory after treatment were similar, regardless of radiation dose. The authors concluded that short-course RT was not significantly inferior to long-course RT in patients with poorly predicted survival. Given that these patients are usually not candidates for surgery, short-course RT is a reasonable approach in this scenario.

Technically, cEBRT consists of opposed anterior and posterior beams that extend one vertebral body above and below the affected levels. This leads to a dose bath that extends from the vertebral body anteriorly to the chest or abdominal wall, with tissues such as the heart or small bowel receiving dose. However, given the modest doses, this is generally well tolerated. While in today's era, cEBRT is often accomplished with CT planning, it can also be performed using 2D approaches and can be started within 24 h in emergent cases.

Stereotactic body radiation therapy

The advent of high-dose stereotactic body radiation therapy (SBRT) has changed the way spinal metastases are approached at many large cancer centers. SBRT has been defined as 'the precise delivery of highly conformal and image-guided hypofractionated external beam radiotherapy, delivered in a single or few fraction(s), to an extracranial body target with doses considered curative or ablative' [31]. Spine SBRT requires extreme precision within 1–2 mm, image guidance allowing for pretreatment confirmation

Figure 1. These images are from a 45-year-old female with EGFR mutant non-small-cell lung cancer and a previously radiated (20 Gy in five fractions conventionally) spinal metastases at T10. (A) The patient presented with progressive epidural disease graded as a SOSG Grade 2. (B) Minimal access spine surgery with tubular based decompression and direct cement augmentation was performed with resultant MRI seen here. (C) SBRT with 20 Gy in one fraction was delivered 7 days postoperatively, with the radiation plan depicted here, (D) and the patient remained well until 14 months later, when she presented with frank epidural progression (SOSG Grade 3) with diffuse bony and paraspinal disease progression as seen on this MRI from the time of recurrence. SBRT: Stereotactic body radiation therapy; SOSG: Spine Oncology Study Group.

of tumor specific alignment, as well as advanced radiation treatment planning and delivery equipment [32]. The fundamental objective of SBRT is to provide high-dose ablative intent radiation with the goal of improving local control. In contrast to cEBRT, SBRT only treats the target lesion and there is a steep dose gradient with relative sparing of adjacent tissues. SBRT for spinal metastases achieves high rates of local control ranging from 70 to 90% at 1 year, regardless of histology [33–40]. Furthermore, rates of complete pain response at the treated site are approximately 50% [33,37].

The excellent outcomes generally achieved with SBRT for spinal metastases, have led to its investigation for MESCC. This is despite theoretical concerns that previously led to MESCC being considered a contraindication for SBRT [41]. The major concern regarding SBRT for MESCC is that SBRT-based decompression is a slow process (if it occurs), while direct decompressive surgery immediately restores blood flow to the affected spinal cord. In addition, SBRT is complex procedure, even in a high-volume center with a robust infrastructure, the time from consultation to spine SBRT initiation can average 12 days during which permanent neurologic deterioration can occur [42]. Additionally, the closer the tumor to the spinal cord and the more the circumferential area of the cord affected, the more underdosing of the tumor there will be. An analysis of the distance of tumor to the thecal sac demonstrated worse local control when disease touches the thecal sac [43,44]. Furthermore, lower minimum doses of irradiation to the gross disease have been associated with recurrence. [45,46] Together, these results explain why the most common site of failure after spine SBRT is the epidural space and, therefore, a potential limitation of the utility of spine SBRT for MESCC [44,47–51].

Evidence for SBRT alone in patients with MESCC

A study of SBRT for MESCC examined 24 patients with 31 lesions from multiple myeloma [52]. The median dose was 16 Gy in one fraction. With a median follow-up of 11 months, the pain control rate was 86%. Seven patients presented with neurologic symptoms prior to treatment, and five had improvement or a complete reversal of symptoms. Epidural disease was found to have a complete response on follow-up MRI in 81% of cases at 3 months. However, as multiple myeloma is a radio-sensitive histology, it is controversial as to whether ablative radiotherapy is necessary. For example, in a study of outcomes for patients with MESCC and

Figure 2. Example of separation surgery for an L1 metastases. The pre-operative MRI (A), T2-weighted MRI (B), postoperative CT myelogram (C) and final treatment plan (D) are shown. Note resection of epidural disease, and placement of right sided hardware, which is covered in the target volume only in regions believe to be at risk of tumor involvement.

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oligometastatic disease, the radiosensitive tumors myeloma and lymphoma were analyzed together. The results demonstrated a 98% actuarial rate of 1 year local control with conventional irradiation, suggesting that the radiosensitive nature of these tumors may not require SBRT to achieve high control rates [16].

The largest series examining SBRT for patients with MESCC caused by nonradiosensitive solid tumors included 62 patients with 85 lesions [50]. MESCC was defined radiographically, and ranged from minimal canal compromise, thecal indentation, to actual spinal cord displacement. Of note, patients were carefully selected and were required to have a minimum muscle strength of 4/5. Surgery was recommended for muscle strength scores of 3/5 or less, rapid neurologic deterioration and retropulsed compression fractures. Treatments were delivered to a median dose of 16 Gy in one fraction. For patients with documented post treatment imaging, the mean epidural tumor volume reduction was 65% at 2 months. Overall neurologic function was improved in 81%. Radiographic tumor progression was seen in 6% of patients, and neurologic progression was seen in 16%. Notably, 52% of

patients with initial neurologic symptoms had a complete response to treatment, and an additional 11% demonstrated improvement. The authors conclude here, and in later publications, that SBRT is a reasonable approach for patients with epidural disease but without cord displacement by tumor who also have good motor function (i.e., at least 4/5 muscle strength) [53]. Taken together, the high rates of epidural regression and neurologic improvement are promising. Further study will be necessary, however, to alleviate concerns about the adverse effects of potential delays, as well as to better characterize the 16% rate of neurologic progression seen in the latter study. Prospective studies analyzing SBRT for patients with MESCC are ongoing (NCT01256554, NCT01826058) and will be informative. Images from a patient undergoing SBRT for MESCC appear in Figure 1. The dose distribution in this case is circumferential due to near circumferential epidural involvement on MRI. The case highlights that while many of these patients are felt to have a very poor prognosis and median survivals of only a few months some can live for a year or more after MESCC; so it is important to consider each patient individually regarding their suitability for more aggressive approaches to treatment. The patient's recurrence also highlights that further research needs to be done in regard to optimal strategies to improve local control in these patients.

Separation surgery followed by SBRT

Separation surgery is a technique aimed at circumferential resection of epidural tumor, occasionally with partial vertebral body resection and/or spinal fixation, without vertebrectomy. It is achievable from a posterolateral approach, potentially preserving spinal stability, and limiting the additional blood loss and operative time associated with anterior approaches [54]. This is a significant departure from previous techniques whereby surgical resection was performed with the goal of maximal tumor resection. The concept here is that the extent of resection can be limited given the expectation that residual disease can be controlled with high-dose SBRT [44,54–57]. Images from a patient treated with this technique are seen in Figure 2.

The benefits of separation surgery are highlighted in a 186 patient series from MSKCC [59], in which patients underwent circumferential resection of epidural disease. Preoperatively, 73.1% had high-grade MESCC while

Figure 3. Suggested approach to patients with suspected spinal cord compression.

postoperatively only 11% had high-grade compression. The local control rate was favorable at 81.7%. The authors concluded that the ability to reduce the aggressiveness of the resection while still achieving tumor control with high-dose radiation made this an attractive approach.

Similar results were seen in an experience from Al-Omair *et al.* [44]. This study analyzed 80 patients treated with postoperative SBRT. High-grade epidural disease was seen in 55%. Patients were treated to a median dose of 24 Gy in two fractions. With a median follow up of 8.3 months, the 1 year local control rate was 84%. A significant benefit in local control was seen ($p = 0.009$) when patients with high-grade preoperative epidural disease were surgically downgraded to an SOSG score of 0–1 versus an SOSG score of 2. This is a critical point as it reflects the rationale for separation surgery, in that patients who have improved epidural clearance of disease have improved local control rates after SBRT.

Toxicities of surgery

In a meta-analysis of 999 patients with metastatic tumors and epidural disease undergoing surgery, a 6.3% 30 day mortality rate and 23% complication rate was reported [60,61]. For comparison, in the prospective multicenter AOSpine study, the 30 days mortality rate was 9% and the 30 days complication rate was 29.6% [15]. Of note, the

median number of levels involved surgically was 5, suggesting that these were extensive surgeries. It remains to be seen whether minimally invasive separation surgery approaches will lead to lower perioperative morbidity and mortality.

Toxicities of high-dose SBRT

SBRT is a generally well-tolerated outpatient procedure. Pain flare has been reported as occurring in up to 70% of patients, and steroid prophylaxis has been recommended as a strategy to mitigate the risk [62–64]. Fatigue can occur, as can esophagitis depending on the proximity of the esophagus to the target [65]. In terms of late toxicity, vertebral compression fractures are a known potential risk with a frequency that appears to be related to the dose and fractionation of radiation [66]. In general for commonly used fractionation schemes this risk appears to be approximately 10–20%, but can be as high as 40% with 24 Gy in a single fraction [67–70]. The most concerning toxicity, radiation myelopathy, is fortunately quite rare. Guidelines exist to maintain the risk below 5% in both the *de novo* and reirradiation setting [71,72].

Post-SBRT imaging follow-up

The SPIne response in Neuro-Oncology group, an international panel of experts in SBRT [73],

Table 3. Major therapies available.

Effect of treatment	Outcome	Level of evidence	Comments	Ref.
Improved ambulatory rate (6 months)	81% (steroids) vs 63% (no steroids)	I		Steroids [20]
Improved ambulatory rate	84% (surgery + RT) vs 57% (RT alone) (odds ratio: 6.2 [95% CI: 2.0–19.8]; p = 0.001)	I		Decompressive surgery [23]
Improved ambulatory rate	68% after radiation alone (nonrandomized)	IV		cEBRT [30]
Improvement in neurologic function	81% after SBRT (non randomized)	IV	Single institution experience, highly selected patients	SBRT [50]

cEBRT: Conventional external beam radiotherapy; RT: Radiation therapy; SBRT: Stereotactic body radiation therapy.

recommend an initial MRI at 2–3 months following SBRT and then every 8–12 weeks to assess tumor response. Given that MRI has a superior ability to detect soft tissue tumor extent, it remains the preferred imaging study for follow up.

Conclusion

MESCC is a common problem faced by cancer patients. An algorithm to aid in decision making appears as **Figure 3**. **Table 3** summarizes the evidence and clinical outcomes associated with major therapies available for patients with MESCC. Steroids are an important part of the initial management of this syndrome and should be started promptly even before radiographic confirmation. Patients with high-grade MESCC and neurologic symptoms should be promptly evaluated for surgical resection. Novel surgical strategies, designed to minimize morbidity while achieving the goals of decompression and stabilization, followed by postoperative SBRT will play an increasingly larger role in the future management of such patients.

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EXECUTIVE SUMMARY

- Consider starting steroids in any patient with suspected metastatic epidural spinal cord compression.
- MRI is the diagnostic study of choice for patients with metastatic epidural spinal cord compression.
- Utilize the Spine Instability in Neoplasia and Spine Oncology Study Group scores to help stratify which patients would have the most potential benefit from surgical resection.
- Newer surgical techniques may limit some of the toxicities traditionally associated with larger operations.
- Radiation therapy should be considered in patients following surgery, and for patients who are not surgical candidates.

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