Review Article | Palliative Medicine and Palliative Care for Incurable Cancer

Emergent radiotherapy for spinal cord compression/impingement—a narrative review※

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Contributions: (I) Conception and design: P Zaki, SS Lo; (II) Administrative support: None; (III) Provision of study materials or patients: P Zaki; (IV) Collection and assembly of data: P Zaki, SS Lo, AG Amin, A Sahgal; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background and Objective: Malignant epidural spinal cord compression (MESCC), often presenting with back pain and motor/sensory deficits, is associated with poor survival, particularly when there is loss of ambulation. The purpose of this review is to evaluate the literature and discuss appropriate workup and management of MESCC, specifically in the emergent setting.

Methods: A PubMed search was conducted on "spinal cord compression" and "radiation therapy." Articles were analyzed for the purpose of this narrative review.

Key Content and Findings: If MESCC is suspected, neurologic examination and complete spine imaging are recommended. Emergent treatment is indicated if there is radiographic evidence of high-grade compression and/or clinically significant motor deficits. Treatment involves a combination of medical management, surgical decompression, radiation therapy (RT), and rehabilitation. For motor deficits, emergent initiation of high dose steroids is recommended. Circumferential surgical decompression ± stabilization followed by RT provides superior clinical outcomes than RT alone. For patients whom surgery is not reasonable, RT alone may provide significant treatment response which depends on radioresponsiveness of the pathology. Systemic therapy, if indicated, is typically reserved till after primary treatment of MESCC, but patients with chemoresponsive tumors may receive primary chemotherapy. The selected RT schedule should be personalized to each patient and commonly is 30 Gy in 10 fractions (fx), 20 Gy in 5 fx, or 8 Gy in 1 fx. MESCC recurrence may be treated with additional RT, if within the spinal cord tolerance, or surgery. Stereotactic body radiation therapy (SBRT) has been used for high grade MESCC in patients with relatively intact neurologic function at a few centers with a very robust infrastructure to support rapid initiation of treatment within a short period of time, but is generally not feasible for most clinical practices. SBRT may be advantageous for low grade MESCC, recurrence, or in the post-operative setting. Detection of MESCC

※ Special series on Radiotherapy for Oncologic Emergencies.

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prior to development of high-grade compression or deterioration of neurologic function may allow patients to benefit more from advanced therapies and improve prognosis.

Conclusions: MESCC is a devastating condition; optimal treatment should be personalized to each patient and approached collaboratively by a multidisciplinary team.

Keywords: Epidural compression; malignant epidural spinal cord compression (MESCC); decompression; stereotactic body radiation therapy (SBRT); palliative radiation

Submitted Mar 25, 2023. Accepted for publication Aug 28, 2023. Published online Sep 22, 2023.
doi: 10.21037/apm-23-342
View this article at: https://dx.doi.org/10.21037/apm-23-342

Introduction

Background

Malignant epidural spinal cord compression (MESCC) is a devastating consequence of disease progression. An estimate of 3–5% of all cancer patients develop MESCC, which translates to about 20,000–30,000 yearly cases in the US (1-3). The incidence peaks at age 40–60 and commonly affects patients with breast, prostate, lung, myeloma, kidney, melanoma, and lymphoma (1,4-7). Patients most often present with back pain and commonly have motor/sensory deficits (4). Due to volume of bone and blood flow, about 70% of MESCC cases involve the thoracic spine and about 15% each involve the cervical or lumbosacral spine (4). In about 17–32% of cases, there is multilevel involvement (4,8,9). Treatment for MESCC typically involves a combination of medical management (e.g., pain medication and steroids), surgical decompression, and radiation therapy (RT).

Historically, patients with MESCC underwent laminectomy alone. Following the advent of RT, patients were treated with surgery alone or surgery followed by RT. By the 1970s, studies showed patients treated with RT alone had similar clinical outcomes to those treated with laminectomy followed by RT (4,10). Thus, RT became the definitive therapy for MESCC, until the surgical approach was modified. In 2005, Patchell *et al.* showed that circumferential surgical decompression ± stabilization followed by RT was superior to RT alone (11). Since then, additional studies have analyzed various conventional RT fractionation schemes for emergent treatment of MESCC, and spinal stereotactic body radiation therapy (SBRT) has been increasingly utilized in the non-emergent setting (12-19). With the evolution and availability of different treatment approaches, determining the optimal therapy for a patient may be challenging. Personalizing treatment of MESCC to each patient is paramount as outcomes (e.g., ambulation) and prognosis can be variable.

Objectives

(I) Review the initial work-up and medical management of MESCC;
(II) Discuss the emergent use of RT for MESCC and when primary surgery, primary systemic therapy, or definitive RT may be favored;
(III) Discuss various doses and fractionations of RT and when each may be favored;
(IV) Discuss the non-emergent use of SBRT for MESCC;
(V) Comment on future areas of research for MESCC.

We present this article in accordance with the Narrative Review reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-23-342/rc).

Methods

A PubMed database search was conducted on March 24, 2023 using the terms "spinal cord compression" and "radiation therapy" for all published articles in the English language with full text available (*Table 1*). The search yielded 1,672 results, of which 103 were clinical trials. After manually filtering for prospective trials involving RT for MESCC, 44 remained, and a total of 29 incorporated conventional radiation. These articles were analyzed and supplemented with an additional trial listed in the references, review papers, and well-designed retrospective studies for the purpose of this narrative review. In areas where there was limited data, discussion consisted of expert opinion based on the authors' clinical experiences.

Primary work up and medical management

If MESCC is clinically suspected, full neurologic

Table 1 The search strategy summary

Items	Specification
Date of search	March 2023
Databases and other sources searched	PubMed
Search terms used	Combinations of keywords such as, but not limited to spinal cord compression and radiation therapy
Timeframe	All publication years considered
Inclusion criteria	All English language full manuscripts and abstracts were eligible for consideration; preference was given to prospective trials (when applicable)
Selection process	Initial selection was conducted by P Zaki and SS Lo, supplemented by AG Amin and A Sahgal, and approved by all authors

examination and complete spine imaging are recommended. While computed tomography (CT) depicts bony anatomy well and may be completed first due to logistics, magnetic resonance imaging (MRI) is recommended in addition to CT of the spine due to better soft tissue delineation which helps detect MESCC and characterize the degree of compression. A CT myelogram can be used for patients who cannot undergo an MRI spine and/or if there is significant hardware artifact on MRI. An MRI brain is not routinely obtained but may be recommended depending on the case, symptoms, or neurologic exam. The extent of spinal compression is commonly described using a 6-point scale developed by Bilsky *et al.* in 2010 (20). As depicted in *Figure 1*, bone-only disease is described as grade 0, epidural impingement as grade 1a, deformation of thecal sac as grade 1b, spinal cord abutment as grade 1c, spinal cord compression as grade 2, and spinal cord compression without visible cerebrospinal fluid as grade 3 (20). In general, grade ≥2 is considered high grade. The radiographic grade of compression as well as clinical symptoms suggest the level of urgency for treatment. Although a focused MRI on just the spine level of interest would be faster to obtain, an MRI of the full spine is generally recommended since MESCC can affect multiple levels (4,8,9) and symptoms could be localized to different sites of spinal compression.

If the patient has significant MESCC symptoms (e.g., pain, urinary/bowel continence/retention, and/or weakness) then steroids should be promptly initiated to help improve symptoms (21) as long as infectious etiology is unlikely or ruled out. If the patient does not have symptoms related to MESCC, then steroids may be reasonably omitted (22). The optimal dexamethasone steroid dose is unclear as there is limited data, but the available research shows that 16 mg total daily dose has similar effectiveness to 96–100 mg and less side effects (23-26). The typical dexamethasone steroid regimen consists of 10 mg IV initial dose followed by 4 mg IV or PO every 6 hours and tapered according to the patient's response. Although less studied in MESCC, 8 mg twice per day may be a reasonable alternative to 4 mg every 6 hours, based on the half-life of dexamethasone, in an effort to minimize disruption in the patient's sleep/wake cycle. If present, acute pain should be adequately managed medically (with the assistance of pain specialists if needed) while still allowing the patient to provide informed consent for procedures if recommended. Staging scans (e.g., CT of the chest, abdomen, and pelvis) should be performed, if not done recently, to confirm a primary malignancy and/or the extent of metastasis as this information would help guide a biopsy if needed or the next steps in management. Additional preoperative workup may include deep venous thrombosis (DVT) screening in high-risk patients, as 24% of non-ambulatory patients with spine metastasis have been shown to have a DVT (27). Spine surgery (e.g., neurosurgery or orthopedic surgery), radiation oncology, and medical oncology should be consulted. Management of these complex cases involves a multidisciplinary approach considering the neurological status, radiosensitivity of the pathology, mechanical spinal instability, overall systemic disease burden (28), prognosis, and performance status. Depending on various factors, primary treatment usually consists of either surgery followed by RT or RT alone. Thereafter, systemic therapy may be given if indicated to help provide overall disease control. Less commonly, systemic therapy may be the primary treatment modality. Physical medicine and rehabilitation should be consulted to help optimize patient functionality and independence (29,30). As many MESCC patients harbor life-limiting illness, a palliative care consult should also be considered to help ensure treatment recommendations align with patient goals and values.

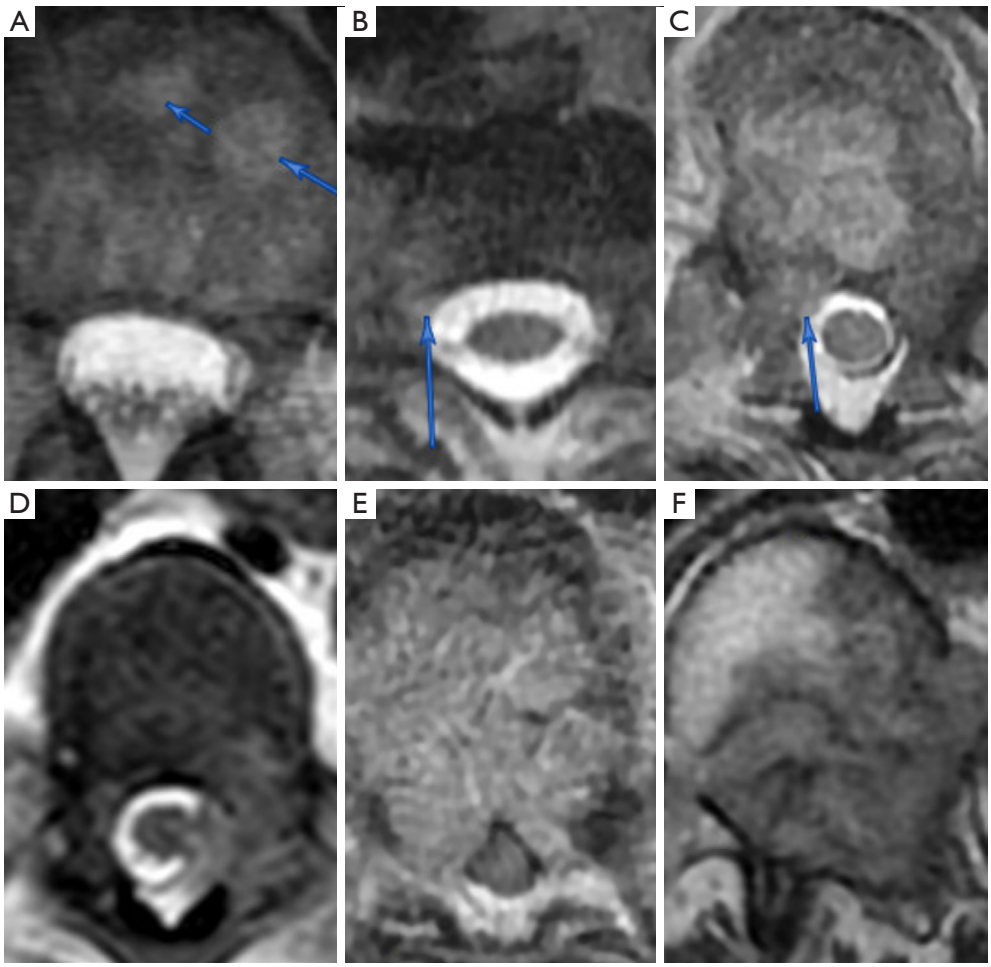

Figure 1 ESCC classification depicted by T2-weighted MRI. ESCC grade 0 (A) includes a vertebral metastatic lesion (blue arrows) without epidural involvement. ESCC grade 1a (B) includes minimal epidural extension (blue arrow) without thecal sac impingement. ESCC grade 1b (C) involves epidural extension and thecal sac compression (blue arrow) without abutment of the spinal cord. ESCC grade 1c (D) is abutment of the spinal cord without compression. ESCC grade 2 (E) is spinal cord compression but with visible cerebrospinal fluid. ESCC grade 3 (F) is spinal cord compression with complete effacement of the subarachnoid space. The ESCC classification system was originally described by Bilsky *et al.* (20). ESCC, Epidural Spinal Cord Compression; MRI, magnetic resonance imaging.

Primary surgery followed by RT or primary RT

Since the pivotal randomized control trial by Patchell *et al.*, surgical decompression followed by RT is recommended when patients have an expected survival of at least 3 months (11,31). Patchell *et al.* showed circumferential surgical decompression ± stabilization followed by RT had significantly better rates of maintained/improved strength (P=0.0064), maintained/regained function (P=0.0008), maintained urinary continence (P=0.016), steroid use (P=0.0093), morphine use (P=0.002), maintained ambulation (P=0.024), regained ambulation (P=0.012), and survival (P=0.033) compared to RT alone (11). On intention-to-treat analysis, 84% of patients in the surgery + RT group could ambulate following treatment compared to 57% of patients in the RT alone group [odds ratio (OR) =6.2; 95% confidence interval (CI): 2.0–19.8; P=0.001] which resulted in meeting the predetermined early stopping rule criterion and early closure of the trial (11). Notably, 20% of patients in the RT alone group had worsening motor strength during RT and underwent surgery (11). Furthermore, a prospective quality of life (QoL) analysis by Morgen *et al.* in 2016 showed patients who underwent surgery + RT had a higher Euroqol-5 dimensions questionnaire (EQ-5D) QoL

Table 2 Prospective studies of MESCC involving conventional postoperative RT

Patient cohort	N	Baseline ambulatory	Radiosensitive histology	Response	Survival
30 Gy in 10 fractions					
Young (10), laminectomy only	16	38%	25%	Pain: 38% improved; urinary continence: 75% maintained, 12.5% regained; ambulation: 50% maintained, 44% regained	Mean 6.4 months
Patchell (11), circumferential decompression ± stabilization	50	68%	0%	Medications: MDDED 1.6 mg, MDMED 0.4 mg; urinary continence: median 5.2 months maintained; strength: 86% maintained/improved; ambulation: 94% maintained, 62% regained, median 4.1 months	Median 4.2 months
Morgen (31)	47	NR	NR	QoL: EQ-5D score increased from 0.28 to 0.44 after 6 weeks and 0.71 after 1 year	Median 10.8 months

MESCC, malignant epidural spinal cord compression; RT, radiation therapy; N, number of patients; MDDED, mean daily dexamethasone equivalent dose; MDMED, mean daily morphine equivalent dose; NR, not reported; QoL, quality of life; EQ-5D, Euroqol-5 dimensions questionnaire.

score (0.71; 95% CI: 0.64–0.71) than patients treated with RT alone (0.63; 95% CI: 0.56–0.70) even though patients who underwent surgery had lower baseline EQ-5D scores (0.28; 95% CI: 0.19–0.36 compared to 0.42; 95% CI: 0.38–0.46) (31). *Table 2* summarizes the results of prospective trials of MESCC in patients treated with primary surgery followed by RT, and *Table 3* summarizes those with primary RT using the most common conventional palliative radiation schedules. Additionally, a propensity matched analysis by Rades *et al.* in 2022 compared patients who received surgery + RT to patients who received RT alone and showed improved motor function occurred more often (39.2% *vs.* 21.5%, P=0.015) in patients who received surgery + RT (32). However, not everyone may benefit from surgery. Patients with tandem stenosis, or distinct levels of MESCC, were excluded from the Patchell study. Hence, the primary treatment for these patients is less clear but may include a variety of approaches such as surgery to multiple sites of MESCC, particularly if accessible from a single incision, surgery to only the most advanced site of MESCC with RT to the remaining sites, or RT to all sites. The previously mentioned study by Morgen *et al.* showed that patients who underwent surgery and survived less than 6 months had a decline in EQ-5D QoL score (baseline of 0.21; 95% CI: 0.08–0.35) at each follow-up and measured 0.12 (95% CI: –0.09 to 0.34) after 12 weeks (31). In addition, Rades *et al.* showed 15.2% of patients died within 30 days following surgery (compared to 12.7% following RT alone, P=0.65), and 36.7% of surgically treated patients did not complete RT as planned due to death or decreased performance following surgery (36). Also, the need for adequate wound healing may potentially delay RT. Therefore, when considering surgery, one should consider the total disease burden of the patient—including stage, presence of multilevel disease, and non-skeletal involvement—as well as available therapies. Prognostic tools such as the revised Tokuhashi scoring system and the more recently validated SORG Orthopaedic Research Group machine learning algorithm and nomogram can aid in survival estimation of patients with spinal metastases (37-42). Medical comorbidities and age should be taken into consideration for perioperative risk and survival. A secondary analysis of the landmark Patchell study showed that patients 65 years of age and older benefited less, in terms of ambulation and survival, from surgery than patients less than 65 years of age (43). Thus, surgery followed by RT should be considered first-line as primary therapy for MESCC, but a patient's expected survival, risk of perioperative mortality, and rehabilitative capability should be considered alongside the benefits of surgery.

In addition to survival and surgical tolerability, there are several factors to consider when deciding between primary surgery or radiation. If there is spinal instability associated with the lesion of interest, then surgical stabilization would be favored to primary RT. Spinal stability should be characterized by the Spine Instability Neoplastic Score (SINS) described by Fisher *et al.*; a score of 0 to 6 is considered stable, 7 to 12 indeterminate or possible impending instability, and 13 to 18 unstable (44). A score of greater than 7 warrants surgical evaluation for consideration of spinal stabilization. Orthotic bracing, with confirmatory upright X-rays of the spine, may also assist

Table 3 Prospective studies of MESCC involving emergent primary RT stratified by the most common radiation schedules

Patient cohort	N	Baseline ambulatory	Radiosensitive histology	Response	Survival
30 Gy (3 Gy × 10 fractions)					
Maranzano (22)	20	80%	0%	Pain: 85% improved; ambulation: 100% maintained, 100% regained	Median 14 months
Rades (32)	110	53%	16%	Strength: 73% maintained/improved; ambulation: 88% maintained, 29% regained, 75% ambulatory after 6 months	6-month OS 69%
Patchell (11)	51	69%	0%	Medications: MDDED 4.2 mg, MDMED 4.8 mg; urinary continence: median 17 days maintained; strength: 60% maintained/improved; ambulation: 74% maintained, 19% regained, median 13 days	Median 3.3 months
Graham (25)	20	75%	0%	Pain: mean score of 4.8 decreased to 2.7 after 1 day; ambulation: 81% after 1 month	Median 2.3 months
Abu-Hegazy (33)	100	61%	12%	Pain: 56% improved; sensation: 32% regained; urinary continence: 70% regained; ambulation: 100% maintained, 67% regained; 2-year IFR: 16% occurred at med 5 months	2-year OS 56%
Rades (15) and Rades (16)	102	58%	8%	Pain: 57% improved, 20% resolved; strength: 90% maintained/improved; ambulation: 74% after 1 months; 6-month LPFS: 82%	6-month OS 38%
20 Gy (4 Gy × 5 fractions)					
Rades (15) and Rades (16)	101	59%	8%	Pain: 53% improved, 24% resolved; strength: 87% maintained/improved; ambulation: 72% after 1 month; 6-month LPFS: 75%	6-month OS 42%
Thirion (12) and Lee (13)	59	76%	0%	EORTC QLQ-C30 QoL: summary score 10.8 improved, function 8.1 improved, and pain 25.7 improved; urinary continence: 75% maintained/improved; ambulation: 57% maintained, 44% regained; re-irradiation: 5% after med 6.6 months	Median 6 months
Hoskin (34)	176	66%	0%	Ambulation: 83% maintained, 41% regained	3-month OS 55%
8 Gy (8 Gy × 1 fraction)					
Maranzano (18)	153	64%	4%	Pain: 57% improved, 27% resolved; urinary continence: 95% maintained, 35% regained; ambulation: 88% maintained, 16% regained	Median 4 months
Abu-Hegazy (33)	95	60%	7%	Pain: 55% improved; sensation: 28% regained; urinary continence: 70% regained; ambulation: 100% maintained, 66% regained; 2-year IFR: 22% occurred at median 5 months	2-year OS 57%
Giraldo (35)	35	43%	0%	Pain: mean score of 8 decreased to 5; urinary continence and ambulation: 100% maintained, 0% regained	Median 1.5 months
Hoskin (34)	166	66%	0%	Ambulation: 78% maintained, 50% regained	3-month OS 50%

MESCC, malignant epidural spinal cord compression; RT, radiation therapy; N, number of patients; OS, overall survival; MDDED, mean daily dexamethasone equivalent dose; mg, milligram; MDMED, mean daily morphine equivalent dose; IFR, in-field recurrence; LPFS, local progression free survival; EORTC, European Organization for Research and Treatment of Cancer; QLQ-C30, Quality of Life Questionnaire Core 30; QoL, quality of life.

with spinal stabilization. However, if there is displacement of normal bone causing spinal cord compression, then surgery is recommended (45). Primary surgery is typically favored when tumors cause high grade Bilsky compression or significant symptoms since surgery is more likely to improve symptoms (11) and offer more rapid decompression than a progressive response from radiation. Still, significant responses are still possible with RT alone

(11,12,15,18,22,25,32-34). Time to developing motor symptoms can be a prognostic indicator of response to RT. Rades *et al.* categorized the time from onset of any symptoms to time of developing motor deficits into three groups: 1–7, 8–14, and >14 days (46). Patients in the >14 day group were significantly more likely to have functional improvement (86% *vs.* 29% and 10%, P<0.001) and ambulate post-RT (86% *vs.* 55% and 35%, P=0.026) than those in the 8–14 day group and 1–7 day group, respectively (46). Furthermore, patients who developed motor deficits in <48 hours mostly had irreversible symptoms with RT alone (46,47). The reasoning is that acute onset of motor symptoms is due to arterial blockage leading to spinal cord infarction, while slow onset is due to venous congestion. Based on this data, for patients with rapid onset of motor symptoms, emergent surgery should be preferred over RT. Besides time to developing motor deficits, duration of symptoms is also prognostic. Symptoms lasting <48 hours are favorably prognostic for regaining ambulatory function with primary surgery followed by RT (48). Regardless of whether RT is delivered adjuvantly or as primary treatment, history of RT should be taken into account, and re-irradiation should only occur if there is acceptable risk from the cumulative dose of radiation. Radiation dosing will be discussed below. Another instance when primary surgery may be preferred is when a diagnosis needs to be established, and emergent treatment cannot await a biopsy result. However, when patients are known to have a radioresponsive tumor (e.g., lymphoma, multiple myeloma, leukemia, Ewing sarcoma, germ cell, and small cell lung cancer), patients may achieve excellent response with primary RT (7,49-51). The decision regarding primary surgery followed by RT versus primary RT is multifactorial and should involve input from both spine surgeons and radiation oncologists.

When to consider primary systemic therapy

Systemic therapy, or chemotherapy, is rarely given emergently for MESCC, and primary therapy usually consists of tumor directed treatment either with surgery or RT (1,4,11,52). Systemic therapy can be given after primary treatment, and the decision is based on several factors including but not limited to tumor histology, stage, metastatic extent of disease, performance status, tolerability, and patient goals. If given, systemic therapy may help provide control to both MESCC and other sites of disease. A comprehensive discussion on systemic therapy options following primary treatment of MESCC is beyond the scope of this paper. However, depending on tumor histology, systemic therapy may be given as primary treatment for MESCC. Tumors that may benefit from primary chemotherapy include chemoresponsive histologies such as germ cell, neuroblastoma, Ewing sarcoma, leukemia, lymphoma, and myeloma, which have an 86–100% response rate with nonsurgical management of MESCC (53-56).

In some cases, chemotherapy may be safer given alone, while in other cases, more effective when combined with RT. For patients with germ cell tumors, a retrospective study by Grommes *et al.* with unbalanced patient characteristics showed worse survival in patients who received chemotherapy combined with RT compared to those who received chemotherapy alone (53). For patients with MESCC as the initial manifestation of lymphoma, a randomized controlled trial by Avilés *et al.* showed a combination of systemic therapy and RT provided greater event-free survival and overall survival but similar neurologic recovery compared to either modality alone (57). In a group of patients with MESCC secondary to lymphoma or myeloma, Wallington *et al.* reported 6 of 24 patients (25%) who received chemotherapy died due to toxicity from chemotherapy (52). If considering combined modality, one should weigh the potential benefits with the increased risk of toxicity on a case-by-case basis. Furthermore, if treatment intent is curative, one should convert to a definitive dose of radiotherapy after emergent initiation for durable local control. Medical oncology should be involved in the care of patients with MESCC to help provide additional information on prognosis and potential systemic therapy options whether given emergently or following primary treatment.

Is there an optimal RT dose and schedule?

Clinical outcomes of primary RT for MESCC vary widely so it is important to compare RT regimens using randomized control trials and well designed, balanced retrospective studies. Recovery of ambulation ranges from 0–100%, 6-month overall survival 38–90%, and 2-year survival 4–81% depending on factors such as tumor histology, number of involved vertebra, ambulatory function pre and post treatment, time from diagnosis to development of MESCC, time to development of motor symptoms, response to treatment, presence of non-skeletal metastasis, receipt of systemic therapy, and performance status (4,6,7,11,12,15,18,22,25,32-35,48,50,58-65). *Table 3* summarizes the results of prospective MESCC

trials involving the most common palliative radiation schedules (30 Gy in 10 fx, 20 Gy in 5 fx, and 8 Gy in 1 fx), although several other regimens have been reported (6,7,11,12,14,15,18,21,22,25,32-35,46,49,50,54,66-68).

Multiple studies have analyzed different conventional palliative RT regimens for MESCC. A multicenter randomized control trial by Hoskin *et al.* showed patients treated with 8 Gy in 1 fx had non-inferior ambulation at 12 weeks compared to patients who received 20 Gy in 5 fx (34). Also, a randomized control trial by Maranzano *et al.* compared 8 Gy in 1 fx to 16 Gy in 2 fx (separated by 1 week) in patients with a life expectancy ≤6 months and found similar duration of response (4.5 *vs.* 5 months, respectively, P=0.4) (18). A randomized control trial by Abu-Hegazy *et al.* showed similar improvement in ambulation (P=0.32) and sphincter control (P=0.41) for patients treated with 8 Gy in 1 fx, 30 Gy in 10 fx, and 40 Gy in 20 fx, respectively (33). Potential disadvantages of single fx RT, however, include a greater risk of recurrence and need for re-treatment. Abu-Hegazy *et al.* found that the risk of recurrence at 2 years was 22% with 8 Gy in 1 fx, 16% with 30 Gy in 10 fx, and 14% with 40 Gy in 20 fx (P=0.01); yet, recurrences occurred at a median of 5 months following RT (33) which may not be relevant in patients with shorter survival. In another randomized control trial, Thirion *et al.* showed non-inferior treatment responses, but re-treatment at a median follow-up of 6.6 months was more common (25% *vs.* 5.4%, P=0.024) in patients who received 10 Gy in 1 fx than 20 Gy in 5 fx (12). A balanced multicenter retrospective analysis of 5 fractionation schedules (8 Gy in 1 fx, 20 Gy in 5 fx, 30 Gy in 10 fx, 37.5 Gy in 15 fx, and 40 Gy in 20 fx) by Rades *et al.* showed similar post-treatment ambulatory response (69%, 68%, 63%, 66%, and 74%, P=0.578, respectively) and improved motor function; although, in-field recurrence at 2 years (24%, 26%, 14%, 9%, and 7%, P<0.001) was more common with short course than with long course RT (60). Neither the difference between 8 Gy in 1 fx and 20 Gy in 5 fx (P=0.44) nor among 30 Gy in 10 fx, 37.5 Gy in 15 fx, and 40 Gy in 20 fx (P=0.71) was significant (60). Similarly, the SCORE-1 prospective trial by Rades *et al.* showed that short course (8 Gy in 1 fx or 20 Gy in 5 fx) RT compared to long course (30 Gy in 10 fx, 37.5 Gy in 15 fx, or 40 Gy in 20 fx) RT achieved similar improvement in motor function (P=0.95) but was associated with lower 1-year local control (61% *vs.* 81%, P=0.005, multivariate P=0.018) (14,64). The SCORE-2 randomized control trial by Rades *et al.* compared 20 Gy in 5 fx to 30 Gy in 10 fx and found non-inferior 1-month motor function overall response (87% and 90%, P=0.73) (15). Motor function improvement (P=0.44) and 6-month local progression-free survival (LPFS) (75% *vs.* 82%, P=0.51) were also similar between 20 Gy in 5 fx and 30 Gy in 10 fx (15). Still, since longer-term outcomes at 1- and 2-years were superior with 30 Gy in 10 fx than 20 Gy in 5 fx (14,60), but the first regimen is twice as long, Rades *et al.* designed the multicenter prospective pre-mode trial (17). Volumetric modulated arc therapy (VMAT) was used to deliver 25 Gy in 5 fx, which has similar biologic effectiveness to 30 Gy in 10 fx (17). When propensity matched to patients who received 20 Gy in 5 fx, patients who received 25 Gy in 5 fx had similar improvement in motor function (P=0.51) but superior 6-month LPFS (95% *vs.* 79%, P=0.026) (17). Patients who received 25 Gy in 5 fx in the Pre-mode trial were also propensity matched to patients who received 30 Gy in 10 fx, and both patient groups had similar response in motor function (P=0.71) as well as 6-month LPFS (94% *vs.* 87%, P=0.36) (69). A multicenter prospective randomized control trial by Rades *et al.* compared 30 Gy in 10 fx to 40 Gy in 20 fx and showed similar improvement in motor function (P=0.928) as well as post-RT ambulatory rates (P=0.777) (32). The RT schedules mentioned in the above studies all had similar overall survival when baseline patient characteristics were controlled and were associated with minimal toxicity, which would be expected within the spinal cord tolerance dose (11-18,22,25,32-35,70).

Based on the available studies, the following interpretations can be made regarding conventional RT for MESCC. Split course regimens have not been shown to be advantageous compared to daily schedules (7,18,66) and prolong treatment time in a population of patients that have limited survival, so split course RT is not recommended. For patients with poor expected survival (i.e., ≤4–5 months), 8 Gy in 1 fx is generally preferred as it involves the least patient time and would likely have an initial response similar to that of multi-fraction regimens, (12,14,18,33,34,60,64) although 20–25 Gy in 5 fx may be used in select patients (e.g., those with radioresistant tumors). For patients with longer expected survival (i.e., ≥6 months), 30 Gy in 10 fx is generally favored to help reduce the risk of recurrence (14,33,60,64), and 20–25 Gy in 5 fx may be considered (15,17). While alternate RT schedules (e.g., 28 Gy in 7 daily fx or 16–20 Gy in 4 fx given twice daily) exist (6,67), these have not been directly

compared to more common fractionations for MESCC and may have less re-irradiation options due to the maximum cumulative spinal cord tolerance. Treatment courses longer than 30 Gy in 10 fx are not recommended as these have not been shown to be more effective (32,60), would prolong the treatment course, as well as limit the ability to provide re-irradiation if needed. Additional factors to consider when determining the optimal RT schedule include but are not limited to the patient's goals of care, systemic therapy plan, ability to return for re-treatment, and disposition.

The discussion on different radiation schedules thus far has been regarding primary RT for MESCC. In contrast, post-operative RT fractionation is less heterogenous. Post-operative conventional RT studies typically utilizes 30 Gy in 10 fx (10,11,31,32) given 2–4 weeks following surgery. Compared to some primary RT regimens, smaller fraction sizes (e.g., 3 Gy instead of 8 Gy fx) are used postoperatively as this likely reduces late normal tissue toxicity and there is less need for accelerated RT since the spinal cord is already surgically decompressed. In addition, Koswig *et al.* showed bone remineralization is less compromised with 30 Gy in 10 fx than 8 Gy in 1 fx (71). Patients who undergo surgery are typically those expected to have appreciable expected survival. Therefore, in the post-operative setting, 30 Gy in 10 fx is favored to minimize risk of recurrence and toxicity.

If recurrence occurs (expected in 23–39% of patients depending on chosen RT schedule), treatment with surgery, re-irradiation, and/or systemic therapy may be considered (33,60,64,72). If re-irradiation is considered, the cumulative biological effective dose is recommended to be below 120–140 Gy_2 and ideally at least 6 months would have passed from the initial treatment to minimize risk of RT myelopathy (62,72-75). In a multicenter retrospective study by Rades *et al.*, patients who were initially treated with primary RT and recurred had 85%, 35%, and 0% improvement in motor function with surgery, re-irradiation, and chemotherapy, respectively (60). Patients who initially received a longer course of RT were less likely to receive retreatment (60). Additional studies showed 0–36% of patients who received re-irradiation had improvement in motor function and 50–86% had stable motor function (62,72) with a median duration of 4.5 months (72). While these studies used conventional RT, SBRT may be safely used for re-irradiation with local control rates ranging from 83–95% at 1 year (76-79). Although data is limited, surgery and SBRT may be preferred to conventional RT for MESCC recurrence.

Stereotactic body RT

Primary spinal SBRT, which involves a relatively high dose of radiation delivered to a focused area with steep dose-falloff, may potentially offer better local control and symptom improvement than conventional RT (11,15,80-84). *Figure 2* shows an example case of SBRT for decompression of MESCC. As can be appreciated in the figure, SBRT minimizes dose to surrounding organs, particularly bowel in this case, compared to conventional RT with anterior/posterior beams. However, SBRT is generally less feasible for emergent treatment of MESCC as the planning is more complex and time-consuming (85). There are institutions with the ability to deliver spinal SBRT within 24–48 hours of consult resulting in favorable rate of epidural tumor shrinkage (81,86-88). Nonetheless, conventional RT can be delivered more quickly, and surgery would offer the most immediate decompression which is invaluable for patients with significant motor deficits (e.g., motor strength ≤3/5) who are expected to respond to therapy. In addition, SBRT is not well suited for patients with rapid development of motor symptoms, spinal instability, compression from a retropulsed bone fracture, or high grade (Bilsky ≥2) epidural compression (81,82,89). If SBRT is used for high grade MESCC, it should be used with extreme caution, and the epidural space may need to be underdosed in order to respect the tolerance of the spinal cord, which may inadvertently reduce local control (90,91). In cases with high grade compression, patients with poor expected survival may receive primary conventional RT as previously described, while those with more favorable prognosis may benefit from primary separation surgery, which may be done with minimally invasive techniques, followed by post-operative SBRT (92-94). Of note, if significant metal artifact is present or expected on a post-operative MRI, a CT myelogram (which may be uncomfortable for some patients) may be needed to better delineate the target volume and spinal cord (30,93,95). In the non-emergent setting (i.e., patients with spine metastases or low-grade MESCC without neurologic deficits), a randomized control trial by Sahgal *et al.* showed SBRT of 24 Gy in 2 fx had improved complete response in pain (35% *vs.* 14% at 3 months, P=0.0002; 32% *vs.* 16% at 6 months, P=0.0036) (83). Although not statistically significant, SBRT also had improved local control rate (97% *vs.* 90% at 6 months) and radiation site-specific PFS (92% *vs.* 86% at 3 months, P=0.18; 75% *vs.* 69% at 6 months, P=0.34) compared to conventional RT of 20 Gy in 5 fx (83). However, SBRT is

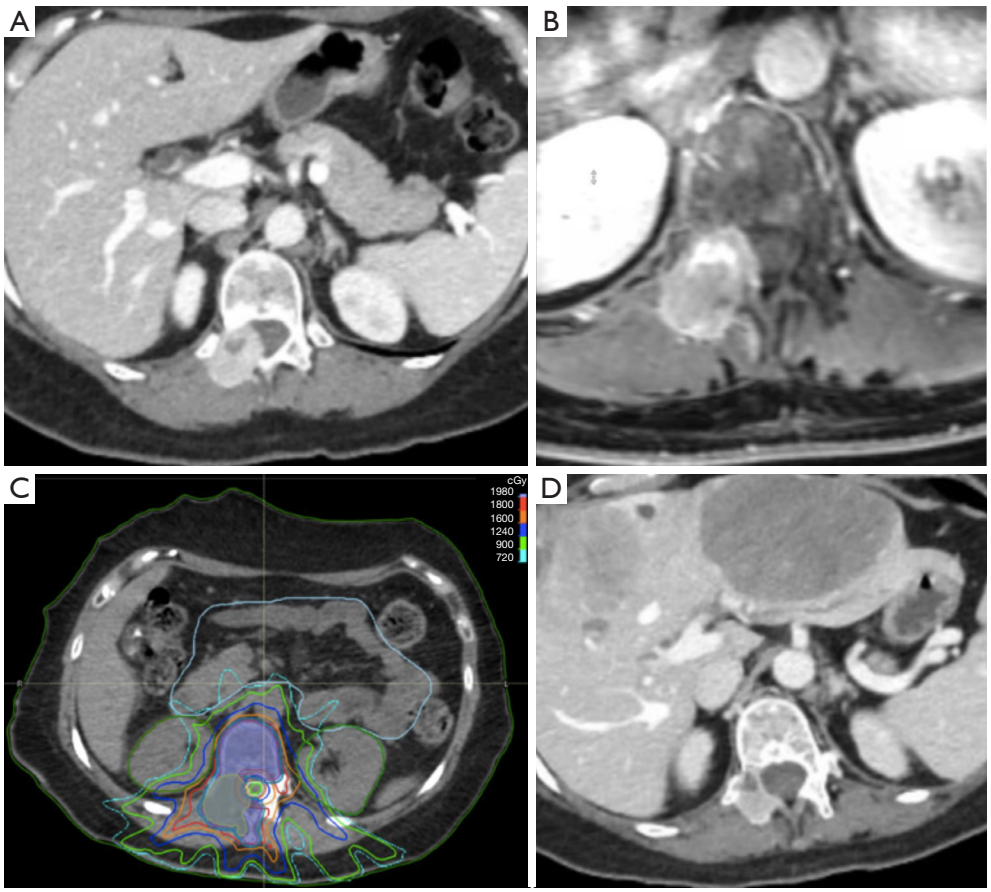

Figure 2 SBRT for MESCC. A 51-year-old female with metastatic non-small cell lung cancer to T12 spine with Bilsky grade 2 MESCC (A: CT; B: MRI). Her brief pain inventory was 8/10. She was neurologically intact. SBRT of 18 Gy in 1 fx was delivered to T11 and T12 (C), 5 working days from CT sim to treatment. Pain decreased to 0/10 two days after SBRT. A radiographic response was noted 5 weeks after SBRT (D). SBRT, stereotactic body radiation therapy; MESCC, malignant epidural spinal cord compression; CT, computed tomography; MRI, magnetic resonance imaging.

not as widely available and conventional RT may still be favored in patients with radioresponsive tumors, diffuse multilevel disease, or poor performance status (89). An in-depth analysis of spinal SBRT is beyond the scope of this paper. For additional details, please see the practice guidelines by Jabbari *et al.* for criteria and contraindications for SBRT (89). A review paper on spinal metastases by Spratt *et al.* also illustrates an algorithm which may be helpful with therapeutic decision-making (30). If SBRT is planned, contouring should be performed according to guidelines by Cox *et al.* and Redmond *et al.* for the primary and post-operative settings, respectively (95-98). Studies on dose constraints are also available for reference (74,89,99-101). Although SBRT may be advantageous for early MESCC and in the post-operative setting, either primary surgery or conventional RT would be generally preferred for emergent cases.

Future research

While advancements in both surgery and RT have improved clinical outcomes for the treatment of MESCC, prognosis is still poor for many patients, particularly those with loss of ambulation (65). Therefore, future research should investigate the possibility of early detection. If MESCC is detected prior to high-grade compression or deterioration of neurologic function, patients may potentially benefit more from SBRT over conventional RT. Additionally, if MESCC is controlled prior to development of significant motor deficits, emergent treatment with surgery or RT may

Table 4 Clinical decision-making tool with various scenarios for when each modality (surgery, conventional radiation therapy, stereotactic body radiation therapy, or chemotherapy) may be preferred for primary treatment of MESCC

Primary surgery followed by radiation therapy
Significant motor deficit
Rapid development of deficits (<48 h)
Significant epidural compression (grade ≥2)
No contraindication to surgery (e.g., life expectancy ≤3 months)
Primary conventional radiation therapy
Not surgical candidate
Stable spine
Radiosensitive/radioresponsive
Diffuse disease
Cumulative radiation normal tissue tolerance would not be exceeded
Primary stereotactic body radiation therapy
Nonemergent treatment (due to planning time)
Stable spine
Radioresistant
Prior radiation
Mild epidural compression (ideally ≥2 mm from cord)
Longer life expectancy
Primary chemotherapy ± radiation therapy
Chemosensitive/chemoresponsive*
Chemotherapy can be started urgently
No contraindication to chemotherapy (e.g., low blood cell counts)
Best supportive care
Poor life expectancy
Rapid development of deficits with loss of ambulation
Not a candidate for surgery or chemotherapy

*, chemosensitive/chemoresponsive tumors are often also radiosensitive/radioresponsive. MESCC, malignant epidural spinal cord compression.

potentially be avoided. While a randomized control trial comparing primary SBRT to conventional RT exists (83), further research should also include randomized control trials comparing primary SBRT to surgery in appropriately selected patients, post-operative SBRT to conventional RT, and SBRT to conventional RT in the re-irradiation setting. Importantly, future studies should ideally report standard response assessments when comparing treatments as recommended by the SPINO group (102,103).

Conclusions

MESCC is a devastating condition that is associated with limited survival although outcomes are variable based on prognostic factors. Patients with high grade MESCC or significant symptoms necessitate emergent treatment. Primary treatment includes steroids followed by either surgery with RT or RT alone. In select uncommon situations for chemosensitive histologies, chemotherapy ± RT may be used as primary treatment. Various fractionations of conventional RT exist, although 8 Gy in 1 fx is favored in patients with poor expected survival (i.e., ≤4–5 months) and 30 Gy in 10 fx is preferred in patients with longer (≥6 months) survival. However, the decision regarding optimal fractionation is multifactorial and should be personalized to each patient. SBRT may improve symptom and local control although level I data is limited, and SBRT in general is not well suited for emergent treatment or high grade MESCC. See *Table 4* for a clinical decision-making tool summarizing scenarios when each modality (surgery, conventional RT, SBRT, or chemotherapy) may be preferred as primary treatment for MESCC. Future research should investigate the possibility of improving early detection so patients may benefit more from advancements in therapy. Emergent MESCC should be approached collaboratively by a multidisciplinary team including spine surgeons, radiation oncologists, and medical oncologists.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Palliative Medicine*, for the series "Radiotherapy for Oncologic Emergencies". The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-23-342/rc

Peer Review File: Available at https://apm.amegroups.com/article/view/10.21037/apm-23-342/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-23-342/coif). The series "Radiotherapy for Oncologic Emergencies" was commissioned by the editorial office without any funding or sponsorship. S.S.L. and S.K.S. served as unpaid Guest Editors of the series. S.S.L. serves as an unpaid Associate Editor-in-Chief of *Annals of Palliative Medicine* from February 2022 to January 2024. Unrelated to this work, A.B. reports stock holdings in Pfizer and GSK plc; Y.D.T. reports leadership role as Chair of the ASTRO scientific committee Palliative Care track and honoraria for ASTRO refresher course (2020–2021). A.G.A. reports travel support from ICOTEC; B.V. reports honoraria from Elekta AB and travel expenses from Elekta AB and Brainlab AG; J.D.P. reports honoraria from Varian, ICOTEC, and Novocure, travel support from Varian and ICOTEC, and advisory board role for Novocure. S.T.C. reports honoraria from Varian, and honoraria and travel support from Blue Earth Diagnostics. M.F. reports consultancy fees and honoraria from Elekta and Varian, travel support from Elekta, and Ex Officio Board Member role for ISRS. K.R. reports research funding to her institution from Accuray, Canon, and Elekta, consulting fees from ICOTEC; honoraria from Accuray, travel support from Brainlab, Accuray, and Elekta, payments from BioMimetix, a patent under development for radiogenomics in collaboration with Canon, and leadership role as CNS track chair for ASTRO education committee; A.S. reports research grants from Elekta AB, Varian, Seagen, and BrainLab, consulting fees from Elekta AB, Varian, Merck, Abbvie, Roche, and BrainLab, honoraria from AstraZeneca, Elekta AB, Varian, Seagen, Accuray, and BrainLab, and leadership roles as Vice President of ISRS, Co-Chair of the AO Spine Knowledge Forum, and Member of the Elekta MR Linac Research Consortium. S.S.L. reports research funding from the NCI and Kuni foundation, travel support from JASTRO, and leadership roles as Assistant Councilor and Chair of CARROS Nominating Committee for the ACR and Member of the Board of Directors and Medical Director of Distinction in Practice in Stereotactic Radiotherapy Program for the Radiosurgery Society. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Zaki P, Barbour A, Zaki MM, Tseng YD, Amin AG, Venur V, McGranahan T, Vellayappan B, Palmer JD, Chao ST, Yang JT, Foote M, Redmond KJ, Chang EL, Sahgal A, Lo SS, Schaub SK. Emergent radiotherapy for spinal cord compression/impingement—a narrative review. Ann Palliat Med 2023;12(6):1447-1462. doi: 10.21037/apm-23-342

