Metastatic epidural spinal cord compression

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Introduction

Metastatic epidural spinal cord compression (MESCC) is a devastating complication of cancer that occurs when cancer metastasises to the spine and then secondarily compresses the spinal cord. MESCC affects approximately 5–10% of all cancer patients [1–3], and those suffering from this condition have numerous quality of life problems such as incontinence, pressure sores, infections, and pain. If left untreated, virtually 100% of patients become paraplegic; therefore, MESCC is considered a medical emergency and immediate intervention is required.

Pathophysiology

MESCC occurs in one of three ways: (1) continued growth and expansion of a vertebral bone metastasis into the epidural space; (2) destruction of vertebral cortical bone by metastasis, causing vertebral body collapse with displacement of bony fragments into the epidural space, and (3) extension of a paraspinal mass through neural foramina into the epidural space. The cause of damage to the spinal cord from compression is complex and multifactorial, although two mechanisms predominate [1,2]. Direct compression results in edema, venous congestion, and demyelination. If the compression is of short duration, the effects are reversible; remyelination and recovery of function are possible. However, a prolonged compression will result in secondary vascular injury with infarction of the spinal cord. After this type of injury, no meaningful recovery is possible [4].

Clinical presentation

The vast majority of patients have a preexisting cancer diagnosis. However, MESCC should be suspected in any patient with symptoms of progressively worsening back pain, incontinence, or paraplegia. Also, high-risk populations such as long-time smokers or women with a strong family history of breast cancer may fall victim to MESCC without a prior cancer diagnosis. In a study of over 1000 patients with MESCC, the most common tumour type was breast cancer (29%), followed by lung cancer (17%) and prostate cancer (14%) [5]. The onset of new back pain in cancer patients needs to be taken seriously and worked up.

The osseous vertebral column is affected in 85% of cases, paravertebral sites in 10–15% and there are rare cases of isolated epidural or intramedullary metastasis [6]. Back pain is the most common presenting symptom (88–96%), followed by weakness (76–86%), sensory deficits (51–80%), and autonomic dysfunction (40–64%) [7–10]. The most common level of the MESCC involvement is in the thoracic spine (59–78%), followed by lumbar (16–33%) and cervical spine (4–15%), while multiple levels are involved in up to half of the patients [5,7,11].

Diagnosis

MRI, the standard modality for imaging of the central nervous system in cancer patients, is also the best test for suspected MESCC. It has a very high sensitivity (93%), specificity (97%), and accuracy (95%) in diagnosing MESCC [12]. Since patients can have multi-focal areas of cord compression, an MRI of the entire spine with and without contrast should be promptly performed in anyone suspected of having MESCC [13]. High-resolution CT scan or CT myelogram of the spine should be performed for those patients with contraindications to MRI.

Prognosis

In general, factors predicting survival after MESCC are similar to those in patients with brain metastases. In predicting ambulatory outcome, an important factor is the pretreatment ambulatory function. Other important prognostic factors include rapidity of symptom onset, and radiosensitive histology (e.g. multiple

myeloma, germ-cell tumours, lymphomas, and small-cell carcinoma). In a prospective study of 98 patients with MESCC reported by Rades and colleagues, the single strongest predictor for ambulatory status after therapy on multivariate ($P < 0.001$) analysis was time to development of motor deficits before radiation from the start of any symptoms [14]. This cohort was separated into three groups according to the time to motors deficits before radiation therapy: 1–7 days (Group I), 8–14 days (Group II), and >14 days (Group III). The ambulatory rates for Groups I, II, and III were 35%, 55%, and 86% ($P < 0.001$), respectively. The symptom improvement rates for Groups I, II, and III were 10%, 29%, and 86% ($P = 0.026$), respectively. The other factor significant on the multivariate analysis for post-therapy ambulatory status was favourable histology ($P = 0.005$). Only 10% of the patients in Group I had symptom improvement. Acute, rapid deterioration is predictive of irreversible spinal cord infarction; therefore, recognition, prompt diagnosis and treatment of MESCC are crucial.

Therapy

Corticosteroids

Although multiple retrospective studies have demonstrated the clinical efficacy of corticosteroids, there have been surprisingly few randomised trials assessing the use of steroids in MESCC. Sorensen and colleagues reported the only randomised controlled study on the utility of high-dose corticosteroids in MESCC from solid tumours [15]. The treatment arms consisted of 96 mg of intravenous (IV) bolus of dexamethasone followed by 96 mg oral (PO) per day for 3 days and a 10-day taper versus no corticosteroids at all before radiotherapy. This study found 3-month and 6-month ambulatory rates of 81% versus 63% and 59% versus 33% ($P < 0.05$), respectively, in favour of dexamethasone. Corticosteroids should be started as soon as possible in anyone suspected of having MESCC even before radiographic diagnosis, since steroids can be rapidly discontinued with a negative diagnosis. Steroids effectively decrease cord edema and serve as an effective bridge to definitive treatment.

Although a small randomised trial argued for a lower dexamethasone dose (4 mg per day) in patients with brain metastasis [16], the optimum maintenance dose of corticosteroids in patients with MESCC is unknown. With regards to IV loading dose for MESCC, Vecht and colleagues reported the only randomised study comparing IV dexamethasone loading dose of 10 mg versus 100 mg, followed in both arms by the same PO regimen of 16 mg per day [17]. Both arms demonstrated significant reductions in pain from baseline ($P < 0.001$); however, there was no difference between the two arms with respect to pain reduction, ambulation, or bladder function.

Very high doses of corticosteroids are associated with significant side-effects, mainly gastrointestinal (GI). The Sorensen phase III study reported an 11% frequency of serious side-effects for patients in the treatment arm, while Heimdal and colleagues reported a 14.3% frequency of serious GI side-effects (one fatal ulcer, one rectal bleeding, and two bowel perforations) in 28 consecutive patients treated with 96 mg of IV dexamethasone per day [15,18]. When the dexamethasone dose was decreased to 16 mg per day for the next 38 consecutive patients, there were no instances of serious side-effects in either group and no difference in ambulatory rates between the groups.

Based on these data, a loading of 10 mg of IV dexamethasone and followed by a maintenance dose of 4–6 mg (IV or PO) every 6–8 h should be sufficient for most patients. In addition, patients should be started on a proton-pump inhibitor for GI prophylaxis [19].

Radiotherapy

Palliative radiotherapy has long been the standard of care in the treatment of patients with MESCC. Although multiple fractionation schedules have been reported in the literature, a total of 30 Gy in ten fractions is the one most frequently employed in the USA [20]. In one of the largest studies to date, Rades and colleagues reported a retrospective series of 1304 patients with MESCC [21]. The patients were separated into five schedules: 8 Gy × 1 in 1 day ($n = 261$, Group I), 4 Gy × 5 in 1 week ($n = 279$, Group II), 3 Gy × 10 in 2 weeks ($n = 274$, Group III), 2.5 Gy × 15 in 3 weeks ($n = 233$, Group IV), and 2 Gy × 20 in 4 weeks ($n = 257$, Group V). All of the groups had similar post-treatment ambulatory rates (63–74%) and motor function improvements (26–31%). However, in-field recurrence rates were much lower for the protracted schedules. The 2-year in-field recurrence rates for Groups I, II, III, IV, and V were 24%, 26%, 14%, 9%, and 7% ($P < 0.001$). They recommend that a single fraction of 8 Gy should be used in MESCC patients with limited survival expectations, and that 30 Gy in ten fractions should be used for all other patients.

Maranzano and colleagues have reported the only randomised trial assessing radiation schedules for

patients with MESCC [22]. They compared two hypofractionation schemes, a short course (8 Gy × 1 followed by a 6-day break, then 8 Gy × 1; total of 16 Gy total in 1 week) versus a split course (5 Gy × 3 followed by a 4-day break, then 3 Gy × 5; total of 30 Gy total in 2 weeks). The study concludes that the treatment with short versus split courses of RT resulted in similar back pain relief (56% versus 59%), ambulatory maintenance (68% versus 71%), and good bladder function (90% versus 89%) rates. And so, they recommend that an 8 Gy × 2 schedule be used for patients with MESCC.

However, design problems in the study by Maranzano and colleagues [22] call into question the validity of the conclusions [23]. Although the response rates may seem impressive, when one limits the definition of response to regaining motor function and sphincter control, the rates of success decrease to 29% and 14%, respectively. Confounding variables included having patients with favourable histology, excellent performance status, and the use of non-standard, large fraction sizes in both arms. It is entirely conceivable that the 5% who progressed to paraplegia without in-field recurrence may have suffered from late radiation-induced toxicity, even if not scored as late toxicity by the authors. Therefore, it is difficult to interpret this study, and the question of optimum radiation dose and schedule remains open.

For patients with MESCC from solid tumors, 30 Gy in ten fractions is considered the standard of care in the USA. Short schedules (e.g. 8 Gy × 1 or 4 Gy × 5) should be avoided in newly-diagnosed, chemotherapy-naïve patients since the clinical course can be quite variable and unpredictable, and should be reserved only for those with clear evidence of progressive, chemotherapy-refractory disease. Upfront chemotherapy (with a planned consolidative radiation) may be considered in selected, newly-diagnosed patients with excellent neurological status and very chemosensitive tumours (e.g. multiple myeloma, germ-cell tumours, lymphoma or small-cell lung carcinoma). If the patient is found to have an unresectable/inoperable tumour, and otherwise has a good performance status and controlled primary disease, then consideration should be made to escalate the dose beyond 30 Gy since this dose will not be sufficient to achieve long-term control of gross tumour. Special techniques such as image-guided intensity modulated radiation therapy (IMRT) or stereotactic body radiation therapy (SBRT) should be considered. However, the routine use of IMRT or SBRT can not be recommended at this time since the technology is expensive, and it has yet to show definite benefit over conventional delivery of radiation in a patient population that has a median survival of 6 months or less.

Surgery

Radiation alone has been the standard treatment for MESCC, although results with radiation alone are disappointing. Less than 50% of patients so treated ever walk again and few patients who begin treatment paraplegic ever regain the ability to walk [1,24–26]. There are several reasons for the relatively poor results: (1) some tumours (e.g., renal cell, sarcoma, and melanoma) are simply not radiosensitive; (2) even in radiosensitive tumours, it may take several days to deliver a radiation dose large enough to cause a response, during which time the spinal cord damage may continue; and (3) the most commonly used radiation dose and schedule (30 Gy in ten fractions) is insufficient to provide long-term local control of gross tumour (except for very radiosensitive tumours), so tumour may regrow to cause a recurrence of MESCC even after an initial clinical response.

In the past, laminectomy and postoperative radiotherapy were frequently combined. However, retrospective studies suggested that radiotherapy alone was as effective as laminectomy plus postoperative radiotherapy in the treatment of MESCC [7,27]. Nevertheless, combined treatment remained a common treatment until 1980 when a small randomised trial suggested that radiotherapy alone was as effective as laminectomy plus radiotherapy in the treatment of MESCC. In that study, Young and colleagues randomised 29 patients with MESCC to decompressive laminectomy followed by radiation versus radiation alone [28]. Although this trial showed no benefit to surgery in terms of pain relief, ambulation, or sphincter function, it is impossible to draw any firm conclusion because of the small sample size.

Recently, many have advocated the use of direct decompressive and maximal-debulking surgery with intraoperative stabilisation of the spine (in appropriate cases) followed by postoperative radiation therapy. Since over 85% of spinal metastases arise anterior to the spinal cord, direct attempts at anterior surgical decompression seem logical. In the less common cases when the compressing tumour is located predominantly lateral or posterior to the spinal cord, direct surgical decompression involving removal of the tumour (using lateral or posterior approaches) is also possible and a logical approach to treatment. The advantages of direct decompressive surgery include: immediate relief of the cord compression; removal

Table 1
Key findings of the University of Kentucky phase III study of patients with metastatic spinal cord compression [30]

	Surgery + radiation (median n = 50)	Radiation alone (median n = 51)	*P*-value
Primary endpoint			
Ability to walk			
Rate	84% (42/50)	57% (29/51)	0.001
Time	122 days	13 days	0.003
In patients ambulatory at study entry ability to walk (maintaining)			
Rate	94% (32/34)	74% (26/34)	0.024
Time	153 days	54 days	0.024
In patients non-ambulatory at study entry ability to walk (regaining)			
Rate	62% (10/16)	19% (3/16)	0.012
Time	59 days	0 days	0.04
Secondary endpoints			
Maintenance of ASIA score[a,b]	566 days	72 days	0.001
Maintenance of Frankel score[b]	566 days	72 days	0.0006
Maintenance of continence	156 days	17 days	0.016
Overall survival	126 days	100 days	0.033
Other endpoints			
Mean daily morphine[c]	0.4 mg	4.8 mg	0.002
Mean daily dexamethasone[c]	1.6 mg	4.2 mg	0.0093

[a] ASIA = American Spinal Injury Association. [b] Measures of spinal function after injury. [c] Converted into equivalent doses.

of the tumour with a resultant decrease in tumour burden that allows for more effective post-operative radiotherapy; and immediate stabilisation of the spinal column which can be achieved by the same operation.

In uncontrolled studies using direct surgical decompression, the results appeared to be promising, with ambulatory rates >75% [29]. In several series, even about 50% of patients who could not walk at the time of treatment regained the ability to ambulate. These generally encouraging results were obtained in small series that contained only surgically treated patients. There were no control groups, and the patients were almost always selected from among those patients with the best overall prognoses. A controlled, randomised trial comparing direct decompressive surgery plus postoperative radiation therapy with radiation therapy alone was needed to determine the true value (if any) of the new treatment.

Patchell and colleagues reported the first phase III randomised trial testing the efficacy of direct decompressive surgery in patients with MESCC [30]. Table 1 summarises the key findings of this trial. The study population consisted of patients with known cancer who developed symptoms of MESCC. These patients had MRI scans to confirm the presence of a true spinal cord compression. Patients were started on dexamethasone 100 mg initially followed by 24 mg every 6 h until they began treatment. After that, steroids were decreased but continued until the completion of radiation therapy. After stratification for primary tumour type, ambulatory status and presence or absence of spinal stability, patients were randomly assigned to one of two treatment groups. Patients randomised to the radiation alone arm began radiation within 24 h after study entry and received 30 Gy in ten fractions. Patients randomised to the surgery plus radiation group were operated on within 24 h after study entry and received radiation within 2 weeks following surgery. The intent of surgery in all cases was to remove as much tumour as possible and provide immediate decompression and intraoperative spinal stabilisation (when needed). The major endpoint of the study was the ability to walk after treatment. This was measured in two ways. The immediate success of treatment was determined by comparing the proportion of patients in each group who were able to walk after treatment. The long term success of treatment was measured by comparing the length of time patients maintained the ability to walk over time. Secondary endpoints were post-treatment continence rates, and length of time patients maintained muscle strength

and functional status. Survival was also a secondary endpoint.

The original study design called for a sample size of 200 patients. However, after an interim analysis, the study was stopped because the criterion of a predetermined early stopping rule was met. One hundred-one patients were entered into the study. The percentage of patients able to walk after treatment was significantly ($P = 0.001$) higher in surgical patients (84%) than in the radiotherapy alone patients (57%). Patients treated with surgery also retained the ability to walk significantly longer than those with radiotherapy alone (median 122 days versus 13 days, $P = 0.003$). Thirty two patients (16 in each treatment group) entered the study unable to walk; patients in the surgery group regained the ability to walk in a significantly greater proportion than patients in the radiation alone group (62% versus 19%, $P = 0.01$). The need for corticosteroids and opioid analgesics was significantly lower in the surgical group, and muscle strength and functional status were also maintained for significantly longer in patients treated with surgery. Survival times were also significantly longer in the surgery group (median, 126 days versus 100 days, $P = 0.033$).

This phase III trial demonstrated that patients with MESCC treated with direct decompressive surgery plus postoperative radiotherapy *retain* the ability to walk longer and *regain* it more often than patients treated with radiotherapy alone. Surgery permits most patients to remain ambulatory for the remainder of their lives while patients treated with radiation alone spend a large portion of their remaining time paraplegic.

Conclusions

If operable, patients with MESCC should undergo maximal tumour resection and stabilisation, followed by post-operative radiotherapy. Even for radiosensitive tumours, surgery can often stabilise the spine. For patients with inoperable tumours, definitive radiotherapy still remains the standard of care. Although most patients with MESCC have short survival, prompt multi-disciplinary teamwork can minimise the risks of paraplegia.

Conflict of interest statement

There are no conflicts of interest.

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