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Treatment of metastatic spinal cord compression: CEPO review and clinical recommendations

S. L'Espérance PhD, F. Vincent MD,† M. Gaudreault MD,‡ J.A. Ouellet MD,§ M. Li MD CM,|| A. Tosikyan MD MPH,# S. Goulet PhD,** and the Comité de l'évolution des pratiques en oncologie*

ABSTRACT

Background

Metastatic spinal cord compression (MSCC) is an oncologic emergency that, unless diagnosed early and treated appropriately, can lead to permanent neurologic impairment. After an analysis of relevant studies evaluating the effectiveness of various treatment modalities, the Comité de l'évolution des pratiques en oncologie (CEPO) made recommendations on MSCC management.

Method

A review of the scientific literature published up to February 2011 considered only phase II and III trials that included assessment of neurologic function. A total of 26 studies were identified.

Recommendations

Considering the evidence available to date, CEPO recommends that

- cancer patients with MSCC be treated by a specialized multidisciplinary team.
- dexamethasone 16 mg daily be administered to symptomatic patients as soon as MSCC is diagnosed or suspected.
- high-loading-dose corticosteroids be avoided.
- histopathologic diagnosis and scores from scales evaluating prognosis and spinal instability be considered before treatment.
- corticosteroids and chemotherapy with radiotherapy be offered to patients with spinal cord compression caused by myeloma, lymphoma, or germ cell tumour without sign of spinal instability or compression by bone fragment.
- short-course radiotherapy be administered to patients with spinal cord compression and short life expectancy.
- long-course radiotherapy be administered to patients with inoperable spinal cord compression and good life expectancy.
- decompressive surgery followed by long-course radiotherapy be offered to appropriate symptomatic MSCC patients (including spinal instability, displacement of vertebral fragment); and
- patients considered for surgery have a life expectancy of at least 3–6 months.

KEY WORDS

Metastatic spinal cord compression, corticotherapy, dexamethasone, radiotherapy, surgery, clinical guidelines

1. INTRODUCTION

According to recent Canadian statistics, an estimated 186,400 new cases of cancer and 75,700 deaths from cancer are expected in Canada in 2012[1]. In general, between 40% and 70% of patients with advanced solid tumours such as those of breast, prostate, and lung will develop bone metastases[2]. The spine is the most common site for bone metastasis, affecting up to 30% of cancer patients[3]. Overall, between 5% and 10% of cancer patients will develop metastatic spinal cord compression (MSCC), an oncologic emergency requiring early diagnosis and immediate treatment[4,5]. Spinal cord damage including vascular injury, hemorrhage, white matter edema, and nerve damage such as demyelination and axonal damage, are frequently observed at the site of compression and cause symptoms such as back pain and motor or sensory deficits[6–9].

The main objectives of MSCC treatment are preservation or improvement of neurologic function (particularly walking capacity), pain relief, and preservation or improvement of quality of life[7]. The most-used treatment modalities are corticotherapy, radiotherapy, and surgery.

Corticosteroids (mainly dexamethasone) are widely used for the first-line treatment of MSCC. Steroids reduce edema and inflammation and promote stabilization of vascular membranes at the compression site, consequently reducing back pain and neurologic deficits[8]. The combination of corticotherapy and radiotherapy has for a long time been considered the preferred treatment in most MSCC patients. The efficacy of radiotherapy is generally accepted, but the optimum dose and regimen are not clearly established[4,9,10]. In actuality, a dose of 30 Gy administered in 10 fractions is among the most widely used regimens (particularly in North America); shorter courses (8 Gy or 20 Gy) are often used in Europe[6,11]. Surgery has been a more controversial approach, but its efficacy has been demonstrated in terms of maximal cytoreduction of the metastatic mass, immediate decompression, pain relief, stabilization of the spine, and removal of bone fragments[3]. Patients with MSCC usually benefit from postoperative radiotherapy, which results in better local control of metastatic lesions[12]. In some specific conditions, such as hematologic cancers, chemotherapy may also be used as primary management of MSCC[13].

The purpose of the present article is to review the efficacy and safety of MSCC treatment modalities and to make clinical recommendations based on the best available evidence.

2. METHODS

The scientific literature published up to February 2011 was reviewed through a PubMed search using the keywords "metastatic spinal cord compression" (MeSH), "neoplasm" (MeSH), "cancer," "treatment," "surgery," "radiotherapy," and "corticotherapy." Only prospective studies including an evaluation of neurologic function, in the English or French language, were considered. Economic studies, retrospective studies, studies reporting only the results of unplanned subgroup analyses, studies on intradural or intramedullary spinal cord lesions, and those investigating treatment of relapses were not considered. Abstracts from relevant international conferences held in 2009 and 2010 were reviewed, and only those presenting results from randomized controlled trials were considered. Recommendations for clinical practice and expert consensus issued by relevant international organizations and cancer agencies were also identified. The level of evidence of selected studies and the strength of the author's recommendations were evaluated using the American Society of Clinical Oncology and the European Society for Medical Oncology grading system (Table I). The original guideline was developed by a Comité de l'évolution des pratiques en oncologie (CEPO) subcommittee. The draft was reviewed by independent external experts and was finally adopted by the CEPO.

3. RESULTS

3.1 Corticotherapy

Three randomized controlled trials investigating the efficacy and toxicity of corticosteroids in the treatment of MSCC met the selection criteria (Table II, level II evidence). Results showed that corticotherapy was associated with back pain reduction, but that it had no significant impact on ambulatory capacity or median overall survival.

Vecht *et al.*[15] showed no difference between two intravenous loading doses of dexamethasone (10 mg and 100 mg) in terms of back pain relief, ambulatory capacity, and survival; however, the dose of corticosteroids seemed to correlate with the incidence of adverse events. Graham *et al.*[17] showed that severe treatment-related toxicities such as sepsis were reported with high-dose dexamethasone (96 mg daily) and that none were reported with low-dose treatment (16 mg daily). Sorensen *et al.*[16] also demonstrated that high-dose dexamethasone was associated with clinically significant adverse effects, including hypomania, psychosis with confusion, and gastric ulcer perforation.

3.2 Radiotherapy

Nine prospective trials assessing the efficacy and toxicity of radiotherapy in the treatment of MSCC were identified (Table III, level III evidence). In those studies, fractionated radiation doses ranging from 16 Gy to 30 Gy were delivered. The pretreatment ambulatory rate varied from 31% to 100%, depending on the population being evaluated. Overall, radiotherapy helped to maintain or improve ambulation in 59%–100% of MSCC patients. Aass and Fossa[26] showed a pretreatment ambulatory rate of 31% in hormone-resistant prostate cancer patients with MSCC; subsequently, at 2 and 6 months after a median radiation dose of 30 Gy, 69% and 59% of patients had respectively maintained or regained their ambulatory capacity. Similarly, a split-course regimen (15 Gy in 3 fractions, stopped for 4 days, and then resumed with 15 Gy in 5 fractions only in responders) allowed 84% of breast cancer patients with MSCC to maintain or regain their ability to walk[20].

Patient prognosis at MSCC diagnosis may affect clinical outcomes after radiotherapy. In this regard, Maranzano *et al.*[24] showed a pretreatment ambulation rate of 47% in MSCC patients with poor prognosis (low radioresponsive primary tumour, paraplegic or paraparetic, poor performance status, poor life expectancy) and a post-radiotherapy (16 Gy in 2 fractions) total motor function response rate of 63%. In MSCC patients with good prognosis (without neurologic deficit at diagnosis), a 30-Gy regimen resulted in an adequate motor function response for all patients[23].

TABLE I Levels of evidence and grades of recommendations[a]

Levels of evidence		*Grades of recommendation*	
Level	*Type of evidence*	*Grade*	*Recommendation*
I	Evidence demonstrated by means of meta-analyses of well-designed controlled trials or large randomized trials with clear-cut results (low false-positive and false-negative errors, high power)	A	Supported by level I evidence or multiple level II, III, or IV trials presenting concordant observations
II	Evidence demonstrated by means of small randomized trials with uncertain results (high false-positive and false-negative errors, low power)	B	Supported by level II, III, or IV trials presenting generally concordant observations
III	Evidence demonstrated by means of nonrandomized concurrent cohort comparisons with contemporaneous controls	C	Supported by level II, III, or IV trials presenting non-concordant observations
IV	Evidence demonstrated by means of nonrandomized historical cohort comparisons	D	Supported by little or no empiric evidence
V	Evidence demonstrated by means of case series without controls		

[a] Adapted from Cook *et al.*[14].

Overall, radiotherapy was associated with back pain relief in 67%–90% of MSCC patients. The median overall survival ranged from 3.5 months to 26 months. Adverse events included vomiting, esophagitis, dysphagia, and skin reactions[23,24].

Three prospective studies (level III evidence) and two randomized controlled trials (level II evidence) comparing radiotherapy regimens (long-course: 30 Gy in 10 fractions, 37.5 Gy in 15 fractions, or 40 Gy in 20 fractions; short-course: 8 Gy in 1 fraction, 16 Gy in 2 fractions, or 20 Gy in 5 fractions; and split-course: 15 Gy in 3 fractions, plus 15 Gy in 5 fractions) were identified (Table IV). All regimens showed similar efficacy in terms of post-treatment ambulatory capacity (60%–71%), back pain relief (52%–85%), and median overall survival (4–8 months). However, Rades *et al.* showed that, compared with short-course radiotherapy, long-course radiotherapy resulted in significantly better 1-year local control (81% vs. 61%, $p = 0.005$)[12]. The incidence of reported treatment-related adverse events was similar for all regimens, with dysphagia, esophagitis, diarrhea, and skin reaction being frequently reported[12,27,29,30].

3.3 Surgery

Six prospective studies assessing the efficacy of various surgical techniques (such as cytoreduction, vertebrectomy, and laminectomy) in the treatment of MSCC were reviewed (Table V, level III evidence). Four studies reported specifically on vertebrectomy (using a posterolateral, transpedicular, posterolateral, or anterior approach) and showed that between 80% and 100% of patients maintained or regained their ambulatory capacity after the intervention[31–33,35]. In a study investigating the efficacy of surgical decompression according to the location of the tumour in the spinal canal, the postoperative ambulatory rate after vertebrectomy was twice the rate after laminectomy (80% vs. 39%)[31]. Median overall survivals of 7.7 months and 16 months were observed after vertebrectomy in two studies[31,33]. Overall, back pain relief rate exceeded 90% in the selected studies.

Surgical complications including wound infections and dehiscence, spinal stabilization problems, pulmonary complications, and severe bleeding were reported[31–35]. The mean operative blood loss for patients undergoing decompressive and reconstructive surgery was lower with posterolateral vertebrectomy (1514 mL) than with posterior (2277 mL), anterior (4278 mL), or a combined approach (8300 mL). Two observational studies assessing the effectiveness of unspecified surgical interventions (*en bloc* excision, cytoreduction, palliative, and decompression surgery) showed maintenance of ambulatory capacity in 64%–80% of patients, back pain relief in 71% of patients, and a median overall survival ranging from 12 months to 13 months[34,36]. Medical and surgical complications such as cerebrospinal fluid leakage, thoracic duct injury, dysphagia, neurologic deterioration, wound infection, spinal instability, and gastrointestinal hemorrhage were reported in those studies[34,36]. After laminectomy, results showed that 39%–44% of patients maintained ambulation; reported complications included deterioration of neurologic function and delayed wound healing[31,37].

A meta-analysis and two randomized controlled trials compared the efficacy of surgery followed by radiotherapy with radiotherapy alone for the management of MSCC (Table VI)[3,37,38]. A meta-analysis by Klimo *et al.* included data from twenty-four surgical (n = 999) and four radiation oncology articles (n = 543), reporting mostly uncontrolled studies (Level I evidence)[3]. Results showed that, compared with patients treated with radiotherapy alone, those treated with

TABLE II Results of corticotherapy trials for treatment of metastatic spinal cord compression (level II evidence)

Reference	*Treatment*	*Pts (n)*	*Baseline ambulation rate (%)*	*Post-treatment*		*Median survival (months)*	*Treatment-related toxicity*
				Ambulation rate	*Pain*		
Vecht *et al.*, 1989[15]	(A) 10 mg DEX IV bolus, then 4 mg 4 times daily, plus RT 21–30 Gy	15	47	After 24 h: (A) 40%, (B) 64% After 1 week: (A) 54%, (B) 55%	After 3 h[a]: (A) 59%, (B) 47% After 24 h[a]: (A) 23%, (B) 41% After 1 week[a]: (A) 9%, (B) 23% (all p = NS)	NA	NA
	(B) 100 mg DEX IV bolus then 4 mg 4 times daily, plus RT 21–30 Gy	22	53				
Sørensen *et al.*, 1994[16]	(A) 96 mg DEX IV bolus, then 24 mg 4 times daily for 3 days, then tapered in 10 days, plus RT 28 Gy	27	63	(A) 81%, (B) 63%, p = NA	NA	(A,B): 6	(A) hypomania, psychosis with confusion or blurred consciousness, gastric ulcer perforation
	(B) RT 28 Gy	30	63				
Graham *et al.*, 2006[17]	(A) 16 mg DEX IV bolus, then 4 mg 4 times daily for 2 days, then tapered by day 15, plus RT 30 Gy	11	82	At day 28[b]: (A) 60%–90% (range: 6–9/10), (B) 33%–50% (range: 2–3/6), p = NS	Mean score after 7 days[c]: (A) 3.2, (B) 2.1, p = 0.23 Mean score after 14 days: (A) 2.9, (B) 2.1, p = 0.6	(A) 2.4, (B) 2.1; HR: 0.80; 95% CI: 0.31 to 2.05; p = 0.06	Serious adverse events: (A) 4, (B) 5 (only 1 being treatment-related: staphylococcal sepsis)
	(B) 96 mg DEX IV bolus, then 24 mg 4 times daily for 2 days, then tapered by day 15, plus RT 30 Gy	9	67				

[a] Percentage of patients that did not report pain relief after treatment.
[b] At day 28, 80% of patients were evaluable for functional outcomes [(A) 10 of 11, (B) 6 of 9]. Outcomes were measured depending on ambulation definition (Functional Independence measure, Barthel Index)
[c] Pain evaluated using the Visual Analogue Pain Scale.
Pts = patients; DEX = dexamethasone; IV = intravenously; RT = radiotherapy; NS = nonsignificant; NA = not available; HR = hazard ratio; CI = confidence interval.

TABLE III Results of radiotherapy trials for treatment of metastatic spinal cord compression (level III evidence)

Reference	*Radiotherapy regimen*	*Pts (n)*	*Baseline ambulation rate (%)*	*Post-treatment*		*Median survival (months)*
				Ambulation rate (%)	*Pain relief rate (%)*	
Latini *et al.,* 1989[18]	30 Gy in 10 fractions	51	45	74	90	NA
Maranzano *et al.,* 1991[19]	30 Gy in 10 fractions (radiosensitive cancer); split-course[a] (other cancer)	118	48	70	80	7
Maranzano *et al.,* 1992[20]	Split-course[a] (breast cancer)	56	54	84	89	13
Maranzano *et al.,* 1995[21]	30 Gy in 10 fractions (radiosensitive cancer); split-course[b] (other cancer)	209	52	76	71	6
Helweg-Larsen *et al.,* 1996[22]	28 Gy in 4 fractions	153	52	61	86	3.6
Maranzano *et al.,* 1996[23]	30 Gy in 10 fractions (pts with good prognosis)	20[b]	100	100	85	14
Maranzano *et al.,* 1997[24]	16 Gy in 2 fractions (pts with bad prognosis)	53	47	63	67	5
Zaidat *et al.,* 2002[25]	36 Gy	157	60	78	NA[c]	26[d]
Aass and Fossa, 2005[26]	30 Gy in 10 fractions (prostate cancer)	54	31	After 2 months: 69 After 6 months: 59	NA	3.5

[a] Patient without neurologic deficit.
[b] Split-course: 15 Gy in 3 fractions, then 4 days' rest, then 15 Gy in 5 fractions.
[c] Data not available in the publication, but authors stated that a significant reduction was observed after treatment ($p < 0.001$).
[d] Median survival for ambulant patients; post-treatment ambulant patients have better survival than non-ambulant patients ($p < 0.001$).
Pts = patients; NA = non available.

surgery followed by radiotherapy had an increased likelihood of remaining ambulant (relative risk: 1.28; 95% confidence interval: 1.20 to 1.37; $p < 0.001$) and of regaining ambulatory function (relative risk: 1.99; 95% confidence interval: 1.63 to 2.44; $p < 0.001$). Surgery plus radiotherapy was also associated with better pain relief (90% vs. 70%) and higher 1-year survival (41% vs. 24%). However, a higher recurrence rate (8% vs. 2.4%) was shown in the surgery group[3]. In a phase III trial, Young *et al.* showed no statistically significant difference in effectiveness between laminectomy followed by postoperative radiotherapy and radiotherapy alone in terms of ambulation rate (44% vs. 54%) and back pain relief (50% vs. 46%, level II evidence)[37]. No specific complication or premature death was reported in the surgery group. However, an early mortality rate of 24% was observed in the radiotherapy-alone group[37]. On the other hand, a phase III trial by Patchell *et al.* showed that, after treatment with decompressive surgery followed by radiotherapy (compared with radiotherapy alone), a significantly higher proportion of patients kept their ambulatory capacity (84% vs. 57%; odds ratio: 6.2; 95% confidence interval: 2.0 to 19.8; $p = 0.001$) and retained that ability for a significantly longer median period (122 days vs. 13 days, $p = 0.003$, level II evidence)[38]. No patient diagnosed with lymphoma, myeloma, or germ cell tumours were included in the study. A significantly increased median survival was reported in the surgery-plus-radiotherapy group (126 days vs. 100 days; relative risk: 0.60; 95% confidence interval: 0.38 to 0.96; $p = 0.033$). Substantial reductions in the median doses of dexamethasone (mean daily equivalent: 1.6 mg vs. 4.2 mg, $p = 0.0093$) and

TABLE IV Results of the comparison of radiotherapy regimens for treatment of metastatic spinal cord compression

Reference	*Radiotherapy regimen*	*Pts (n)*	*Baseline ambulation rate (%)*	*Post-treatment*		*Median survival (months)*	*Toxicity*
				Ambulation rate (%)	*Pain relief rate (%)*		
Maranzano *et al.,* 1998[27] (level III evidence)	(A) Split-course[a]	27	44	(A) 70, (B) 71, p = NS	(A) 85, (B) 76, p = NS	(A) 9, (B) 8, p = 0.86	Slight oesophagitis, dysphagia
	(B) 16 Gy in 2 fractions	17	47				
Rades *et al.,* 2004[28] (level III evidence)	(A) 30 Gy in 10 fractions	110	53	(A) 60, (B) 64, p = 0.708	NA	NA	No toxicity greater than grade 1
	B) 40 Gy in 20 fractions	104	56				
Maranzano *et al.,* 2005[29] (level I evidence)	A) 16 Gy in 2 fractions	142	65	(A) 68, (B) 71, p = NS	(A) 56, (B) 59, p = NS	(A) 4, (B) 4, p = NS	Esophageal dysphagia, oesophagitis, pharyngeal dysphagia, diarrhea
	(B) Split-course[a]	134 (300 total)[b]	68				
Maranzano *et al.,* 2009[30] (level I evidence)	(A) 8 Gy in 1 fraction	153	64	(A) 62, (B) 69, p = NS	(A) 52, (B) 53, p = NS	(A) 4, (B) 4, p = NS	(B) Oral or esophageal dysphagia, esophagitis, diarrhea
	(B) 16 Gy in 2 fractions	150 (327 total)	67				
Rades *et al.,* 2011[12] (level III evidence)	(A) Short-course[c]	131	61	NA[d]	NA	NA	Nausea, diarrhea, skin reaction
	(B) Long-course[e]	134	62				

[a] Split course: 15 Gy in 3 fractions, then 15 Gy in 5 fractions.
[b] Of the study cohort, 24 patients were lost to follow up or died prematurely. Those patients were not included in the analysis.
[c] Short course: 8 Gy in 1 fraction or 20 Gy in 5 fractions.
[d] No data on post-treatment ambulatory status are available. Published data demonstrated that, compared with short-course treatment, long-course treatment provided better 1-year local control of metastases recurrence (p = 0.005).
[e] Long course: 30 Gy in 10 fractions, 37.5 Gy in 15 fractions, or 40 Gy in 20 fractions.
Pts = patients; NA = not available; NS = nonsignificant.

TABLE V Results of the comparison of surgical approaches for treatment of metastatic spinal cord compression (level III evidence)

Reference	*Surgery*	*Pts (n)*	*Baseline ambulation rate (%)*	*Post-surgery*		*Median survival (months)*	*Perioperative mortality rate (%)*	*Complications*
				Ambulation rate (%)	*Pain relief rate (%)*			
Siegal and Siegal, 1985[31]	(A) Vertebral resection	54	28	80	91	16	7	(A) Wound infection, severe bleeding diathesis, and disseminated intravascular coagulopathy
	(B) Laminectomy	24	8	39	NA	NA	8	(B) Neurologic deterioration, wound healing delay
Siegal and Tiqva, 1985[32]	Vertebral body resection with anterior approach	40	26	80	93	NA	30	Wound infection, severe bleeding diathesis, and disseminated intravascular coagulopathy, spinal instrument failure
Wang *et al.,* 2004[33]	Single-stage posterolateral transpedicular and vertebral stabilization	140	99	99	96	7.7	4.3	Wound infection or dehiscence, pneumonia, pulmonary embolism, spinal instrument failure
Mannion *et al.,* 2007[34]	Decompressive surgery	62	68	80	NA	13	NA	Neurologic deterioration, wound infection, spinal instability, gastrointestinal hemorrhage
Street *et al.,* 2007[35]	Single-stage posterolateral vertebrectomy	96	85	100	NA[a]	NA	NA	Multiorgan failure, wound dehiscence or infection, spinal instrument failure
Ibrahim *et al.,* 2008[36]	En bloc excision, debulking, palliative	223	73	85	71	12	5.8	Cerebrospinal fluid leak, thoracic duct injury, dysphagia

[a] No data on pain relief after surgery are available. However, the authors reported a significant decrease in pain after surgery, based on a visual analog scale score (7.94 vs. 4.3).
Pts = patients; NA = not available.

TABLE VI Results of the comparison between surgery and radiotherapy for treatment of metastatic spinal cord compression

Reference	*Treatment*	*Pts (n)*	*Baseline ambulation rate (%)*	*Post-treatment*		*Survival*
				Ambulation rate (%)	*Pain relief rate (%)*	
Young *et al.,* 1980[37] (level II evidence)	(A) Laminectomy plus RT 30 Gy in 10 fractions	16	38	44	38	Mean: (A) 27.5 weeks,
	(B) RT 12 Gy in 3 fractions plus 17.5 Gy in 7 fractions	13	38	54	46	(B) 23.4 weeks
Klimo *et al.,* 2005[3] (meta-analysis, level I evidence)	(A) Decompressive surgery plus RT 28–32 Gy	999	NA	(A) vs. (B): RR: 1.28	90	1-Year mean: (A) 41%, (B) 24%
	(B) RT 28–32 Gy	543		(95% CI: 1.20 to 1.37), $p < 0.001$	70	
Patchell *et al.,* 2005[38] (level II evidence)	(A) Decompressive surgery plus RT 30 Gy in 10 fractions	50	68	84	NA[a]	Median: (A) 126 days,
	(B) RT 30 Gy in 10 fractions	51	68	57 ($p = 0.001$)		(B) 100 days; $p = 0.033$

[a] No data on post-treatment pain relief rate are available. However, the authors showed that use of corticosteroids ($p = 0.0093$) and opioid analgesics ($p = 0.002$) were significantly reduced in the surgery group.

Pts = patients; RT = radiotherapy; NA = not available; RR = relative risk; CI = confidence interval.

analgesics (0.4 mg vs. 4.8 mg, $p = 0.002$) were also reported in the surgery-plus-radiotherapy group than in the radiotherapy-alone group[38].

4. DISCUSSION

Metastatic spinal cord compression is an oncologic emergency which, unless diagnosed early and treated promptly, can lead to permanent neurologic impairment and can seriously affect a patient's quality of life[5]. Opinions regarding the aggressiveness of the interventions to be used in this palliative context are polarized. Some argue for a more aggressive approach; others favour supportive care. The most frequently used therapeutic modalities for MSCC are corticotherapy, radiotherapy, and surgery. The primary objective of corticotherapy is reduction of edema and inflammation in the area of spinal cord compression. More than 80% of metastatic cancer patients manifest pain that is caused directly by tumour infiltration into adjacent organs and structures or from the development of peritumoural edema. The efficacy of corticotherapy in the management of MSCC has been demonstrated in terms of pain relief and motor function[15–17]. The use of adjuvant high-dose steroid in addition to conventional radiotherapy has been shown to be beneficial, but was associated with an increased incidence of severe adverse events. Indeed, high-dose dexamethasone (>96 mg daily) has been associated with serious toxicities such as severe psychoses, gastric ulcer bleeding, rectal bleeding, gastrointestinal perforation, and sepsis[4,7,39]. To summarize, the available evidence demonstrates that high-dose corticosteroid does not appear to be more effective than low-dose treatment, and that dexamethasone at a total daily dose of 16 mg is effective and safe for the treatment of MSCC.

Twelve prospective studies evaluating effectiveness of radiotherapy for the management of MSCC were reviewed[12,18–28]. The use of radiotherapy has been shown to reduce back pain and to maintain or restore ambulatory capacity. Radiotherapy-related toxicities such as vomiting, esophagitis, dysphagia, and skin reactions have been reported[23,24]. Five studies of various radiation regimens showed no difference in terms of back pain relief, of post-treatment maintenance, improvement, or regain of ambulation, and of toxicities[12,27–30]. However, Rades *et al.*[12] demonstrated that long-course radiotherapy was associated with improved local control of spinal metastasis. Similar results have been observed in retrospective studies[40,41]. According to the evidence evaluated, radiotherapy appears to be effective for the maintenance and restoration of ambulatory function and for back pain relief in MSCC patients. Short-course radiotherapy (including split-course) has the advantage of being faster and less time-consuming for the patient; however, long-course radiotherapy allows for better local control at the site of the spinal cord compression.

Six prospective studies assessing the effectiveness of surgery followed by radiotherapy showed that surgery was associated with significant improvements in ambulatory capacity and back pain relief[31–36]. Results showed that vertebrectomy combined with spinal stabilization was an effective

surgical approach. However, that technique was associated with morbidities such as pulmonary, hemorrhagic, and wound complications[31–36]. Despite the reports of increased complications, surgery has been shown to significantly improve quality of life over a period of 6–9 months after treatment[42–44]. No randomized controlled trial comparing surgical approaches for the treatment of MSCC was identified. Such a comparison is difficult to make because surgical technique is linked directly to the location of the metastasis. In that regard, the use of laminectomy alone for lesions that are not posteriorly located is considered suboptimal because it could potentially lead to spinal instability.

A meta-analysis and two phase III studies evaluating the efficacy of surgery followed by radiotherapy compared with radiotherapy alone were selected[3,37,38]. The ground-breaking study by Patchell *et al.*[38] showed that, compared with patients treated with radiotherapy alone, those treated with direct decompressive surgery and radiotherapy combined had significantly better outcomes in terms of motor capacity, survival, and use of corticosteroids and analgesics. However, that study elicited criticisms from the scientific community (among others) for patient selection bias. The study included only patients who were more likely to benefit from surgery and excluded patients with very radiosensitive tumours. The two patient groups also differed in the delay between diagnosis of the primary tumour and development of MSCC, suggesting a difference in tumour biology in favour of the surgery group. It has also been suggested that the proportion of patients with vertebral body collapse might explain the poorer outcomes observed in the radiotherapy-alone group[45]. Indeed, it has been shown that, when treated with primary radiotherapy, patients with vertebral instability or vertebral bone fragment experienced less neurologic improvement than did those presenting compression from a soft-tissue mass[46]. Clinical guidelines and expert consensus recommend that patients presenting with unstable spine should be treated with surgery followed by radiotherapy to decompress and stabilize the spine[13,47–52]. Meanwhile, the study by Young *et al.*[37] showed no difference in post-treatment ambulatory function and pain relief in patients treated using laminectomy and radiotherapy compared with radiotherapy alone. The absence of significant differences and the lack of statistical power were attributed to the small number of patients recruited.

Altogether, studies have shown that each treatment modality is effective in reducing back pain and maintaining the ambulatory capacity of MSCC patients. Surgery followed by radiotherapy seems to be beneficial, especially for patients who are medically operable and have specific characteristics such as being symptomatic, having an expected survival of more than 3 months, and having only one level of spinal cord compression. The criterion for life expectancy set in the study by Patchell *et al.* is debatable. In fact, tools available to date for assessment of expected survival do not allow for such a level of precision, and an assessment of life expectancy of at least 6 months would probably be more appropriate.

A clinical challenge in the management of MSCC remains, and that challenge consists in identifying patients who will benefit most from each treatment. The patient's prognosis must be evaluated, and various classification systems can be used to predict survival[53–56]. In general, these tools consider the patient's performance status and primary tumour type, the presence of visceral metastases, and pretreatment ambulatory status. The scoring system by Tokuhashi *et al.*[54] is simple, practical and provides a reasonably good estimate of patient's prognosis based on the evaluation of various clinical parameters. The Tokuhashi tool has been validated in various cohorts of patients (breast, kidney, lung, and liver cancers), showing reliable and reproducible evaluation of survival[57–61]. Recently, Fisher *et al.*[62] published a novel comprehensive classification system for spinal instability in neoplastic disease that can guide clinicians in identifying when patients may benefit from surgical consultation.

Finally, the histopathology of the primary tumour can also influence the therapeutic decision. For instance, it has been shown that patients presenting with MSCC derived from myeloma, lymphoma, breast, or prostate cancer have an initial response rate to radiotherapy of up to 80%; patients with pulmonary or renal tumour or melanoma are generally considered to have radioresistant tumours[11,63,64].

5. CONCLUSIONS AND RECOMMENDATIONS

Management of MSCC aims at pain relief, ambulation maintenance or improvement, and preservation of quality of life. Considering the evidence available to date, the CEPO recommends that

- patients with an established diagnosis of cancer presenting with spinal cord compression be treated by a specialized multidisciplinary team (medical oncologists, radiation oncologists, and neurosurgeons or orthopaedic surgeons specializing in spinal cord decompression and reconstruction surgery) (grade D recommendation).
- corticotherapy consisting of dexamethasone 16 mg daily be immediately administered to symptomatic patients as soon as a spinal cord compression is diagnosed or suspected (grade B recommendation).
- high-loading-doses of corticosteroids (for example, 100 mg) be avoided (grade B recommendation).
- histopathologic diagnosis and scores on objective scales for prognosis (for example, Tokuhashi) and spinal instability (for example, Fisher) be considered before a therapeutic decision is made (grade D recommendation).

- corticotherapy and chemotherapy with radiotherapy be offered to patients with spinal cord compression caused by myeloma, lymphoma, or germ cell tumour without sign of spinal instability or spinal cord compression by bone fragment (grade B recommendation).
- short-course radiotherapy (8 Gy in 1 fraction or 20 Gy in 5 fractions) be administered to patients with spinal cord compression and poor life expectancy (Tokuhashi score 0–8) (grade B recommendation).
- long-course radiotherapy (30 Gy in 10 fractions, 37.5 Gy in 15 fractions, or 40 Gy in 20 fractions) be administered to patients with inoperable spinal cord compression and good life expectancy (Tokuhashi score 9–15) (grade B recommendation).
- decompressive surgery (including spinal stabilization) followed by long-course radiotherapy (30 Gy in 10 fractions, or more) be offered to patients diagnosed with symptomatic spinal cord compression. Patients presenting a spinal cord compression at a single level, with incomplete motor deficit within 48 hours of presentation, and a good performance status are appropriate candidates. Additional criteria in favour of surgery include spinal instability or displacement of a vertebral fragment (grade B recommendation).
- patients considered for surgery must have a life expectancy of at least 3–6 months (grade D recommendation).

Based on these recommendations, the CEPO proposes an algorithm for the treatment of MSCC (Figure 1).

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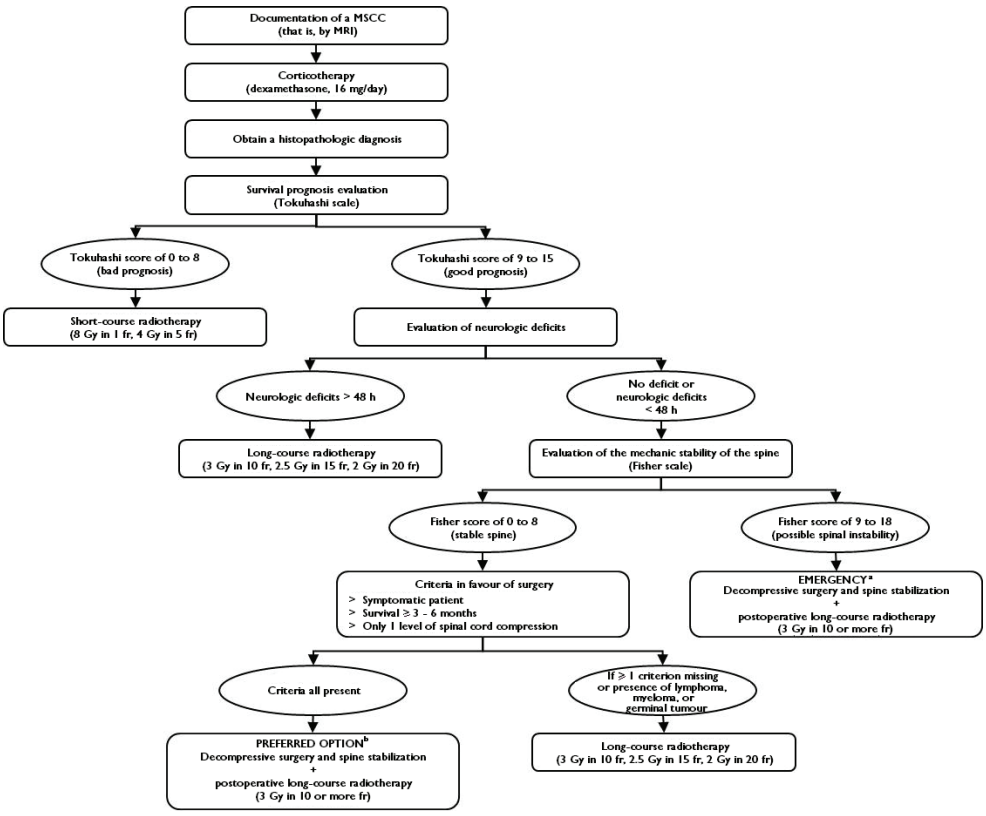

FIGURE 1 Treatment algorithm proposed by the Comité de l'évolution des pratiques en oncologie (CEPO) for metastatic spinal cord compression (MSCC). In the process of deciding on the appropriate treatment, some criteria may be more important than others. [a] If surgery is contraindicated, long-course radiotherapy may be offered (30 Gy in 10 fractions, 37.5 Gy in 15 fractions, or 40 Gy in 20 fractions). [b] For these patients, long-course radiotherapy (30 Gy in 10 fractions, 37.5 Gy in 15 fractions, or 40 Gy in 20 fractions) also constitutes a valuable option. MRI = magnetic resonance imaging; fr = fraction.

Sacré-Cœur de Montréal; Mélanie Gionet MD, Hôpital régional de Rimouski (CSSS de Rimouski–Neigette); Jean-Marc Lépine MD, Hôtel-Dieu de Québec (CHU de Québec); Nicolas Raymond MD, Hôpital Cité de la Santé (CSSS de Laval); and Éric Truffer MD, Pavillon Sainte-Marie (CSSS de Trois-Rivières) for their contribution as external reviewers of the original clinical practice guideline.

7. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare.

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Correspondence to: François Vincent, Pavillon Sainte-Marie (CSSS de Trois-Rivières), 1991 boulevard du Carmel, Trois-Rivières, Quebec G8Z 3R9.
E-mail: francois_vincent@ssss.gouv.qc.ca

* Comité de l'évolution des pratiques en oncologie, Quebec City, QC.
† Department of Radiation Oncology, Pavillon Sainte-Marie (CSSS de Trois-Rivières) Trois-Rivières, QC.
‡ Department of Radiation Oncology, Hôtel-Dieu de Québec (CHU de Québec), Quebec City, QC.
§ Department of Orthopedic Surgery, Montreal General Hospital (McGill University Health Centre), Montreal, QC.
‖ Department of Surgery, Hôpital Maisonneuve–Rosemont, Montreal, QC.
Department of Haematology and Oncology, Hôpital du Sacré-Cœur de Montréal, Montreal, QC.
** Direction québécoise de cancérologie, Ministère de la Santé et des Services sociaux, Quebec City, QC.
†† The Members of the Comité de l'évolution des pratiques en oncologie (CEPO) are Jim Boulanger PhD, CEPO; Gino Boily PhD, CEPO; Ghislain Cournoyer MD, Hôpital régional de Saint-Jérôme (CSSS de Saint-Jérôme); Félix Couture MD, Hôtel-Dieu de Québec (CHU de Québec); Suzanne Frenette BPharm DPH BCOP, Hôpital Maisonneuve-Rosemont; Normand Gervais MD, Centre hospitalier régional du Grand-Portage (CSSS de Rivière-du-Loup); Stéphanie Goulet PhD, Direction québécoise de cancérologie (MSSS); Marie-Pascale Guay BPharm MSc BCOP, Jewish General Hospital (MUHC); Mélanie Kavanagh PhD, Direction québécoise de cancérologie (MSSS); Sylvain L'Espérance PhD, CEPO; Julie Lemieux MD, Hôpital du Saint-Sacrement (CHU de Québec); Bernard Lespérance MD, Hôpital du Sacré-Cœur de Montréal; Nathalie Letarte BPharm MSc BCOP, Hôpital Notre-Dame (CHUM); Mélanie Morneau MSc MBA, Direction québécoise de cancérologie (MSSS); Jean-François Ouellet MD, Hôtel-Dieu de Québec (CHU de Québec); Gilles Pineau MD, INESSS; Raghu Rajan MD, Montreal General Hospital (MUHC); Isabelle Roy MD, Hôpital Notre-Dame (CHUM); Benoît Samson MD, Hôpital Charles LeMoyne; Lucas Sideris MD, Hôpital Maisonneuve-Rosemont; Lucie Surprenant BPharm MSc BCOP, Centre hospitalier St. Mary's; François Vincent MD, Pavillon Sainte-Marie (CSSS de Trois-Rivières).