Malignant Extradural Spinal Cord Compression: Diagnosis and Management

D.A. Loblaw, N. Laperriere, J. Perry, A. Chambers, and members of the Neuro-oncology Disease Site Group

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Neuro-oncology Disease Site Group

Report Date: January 2004

An assessment conducted in December 2012 put Evidence-based Series (EBS) 9-9 in the Education and Information section. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).

ES 9-9 consists of a Summary and a Full Report and is available on the CCO website (http://www.cancercare.on.ca) PEBE Neuro-Oncology DSG page at: https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/neuro-ebs/

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Malignant Extradural Spinal Cord Compression: Diagnosis and Management
Evidence Summary Report #9-9

D.A. Loblaw, N. Laperriere, J. Perry, A. Chambers, and members of the Neuro-oncology Disease Site Group

ORIGINAL SUMMARY: May 12, 2003
MOST RECENT LITERATURE SEARCH: January 2004
NEW EVIDENCE ADDED TO GUIDELINE REPORT: January 2004

New evidence found by update searches since completion of the original guideline is consistent with the original recommendations.

An evidence summary report is a systematic overview of the best evidence available on a specific clinical question when there is insufficient high-quality evidence on which to base a practice guideline.

SUMMARY

Questions
1. What are the clinical symptoms of malignant spinal cord compression (MSCC)?
2. What is the optimal approach for investigating suspected MSCC?
3. Is there a role for systemic steroids in the management of MSCC, and if there is, what is the optimal dose?
4. What are the indications for surgery in the management of MSCC?
5. What are the indications for radiotherapy in the management of MSCC?
6. Is there an optimal dose prescription for radiotherapy?
7. What are the treatment options for recurrent MSCC in an area previously irradiated?

Target Population
This evidence summary applies to adult patients with a suspected or confirmed diagnosis of extradural malignant spinal cord compression. Patients with intramedullary or leptomeningeal cord compression are not considered in this report.
Methods

Entries to MEDLINE (1966 to January 2004), CANCERLIT (1986 to October 2002), and Cochrane Library (2003, Issue 3) databases and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology (1997 to 2003) and the American Society of Therapeutic Radiology and Oncology (1997 to 2003) were systematically searched for evidence relevant to this evidence summary.

Evidence was selected and reviewed by three members of the Practice Guidelines Initiative Neuro-oncology Disease Site Group and methodologists. This evidence summary has been reviewed and approved by the Neuro-oncology Disease Site Group, which comprises medical and radiation oncologists, neuro-oncologists, neurosurgeons, a neuroradiologist; a neuropathologist, an oncology nurse, and a patient representative.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the evidence summary report was obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each evidence summary report. This process consists of the periodic review and evaluation of the scientific literature and where appropriate, integration of this literature with the original evidence summary.

Key Evidence

- This evidence summary is an update of Loblaw and Laperriere’s systematic review (1998) that included 14 studies. In addition to the 14 studies, one randomized controlled trial, one prospective cohort study, one case-control study, two cross-sectional studies, five case series, and eight retrospective reviews have been included in this update.

Update

- Seven additional studies have been identified that meet the inclusion criteria for this evidence summary: three studies (one retrospective review, two prospective cohorts) regarding the symptoms of MSCC; one randomized trial comparing surgery with radiotherapy to radiotherapy alone; and three studies (one prospective phase II, two retrospective reviews) examining the role of radiotherapy in patients with MSCC.

Symptoms of MSCC

- Seven studies (one prospective cohort, one cross-sectional, five retrospective reviews) attempted to identify factors which were associated with higher risks of symptomatic or subclinical MSCC. Symptoms for MSCC can include sensory changes, autonomic dysfunction, and back pain; however, due to the frequency of back pain across all patients (those with and without MSCC) it was not predictive of MSCC.

Diagnosis of MSCC

- Six studies (four case series, two retrospective reviews) described interventions for diagnosing MSCC. The sensitivity for magnetic resonance imaging ranges from 0.44 to 0.93, and the specificity ranges from 0.90 to 0.98 in the diagnosis of MSCC. The sensitivity for myelography ranges from 0.71 to 0.97, and specificity ranges from 0.88 to 1.00 in the diagnosis of MSCC. Magnetic resonance imaging yields additional information over myelography, which may be more helpful in determining the etiology of the MSCC.

Management of MSCC

- A randomized study detected higher ambulation rates in patients with MSCC who received high-dose dexamethasone (100 mg IV bolus + 24 mg po q6h) before radiotherapy compared with patients with MSCC who did not receive steroids prior to radiotherapy (81% versus 63% at 3 months, Wilcoxon test, p = 0.046). A case-control study demonstrated that high-dose dexamethasone had a higher incidence of serious adverse effects (14% versus 0%) compared with moderate-dose dexamethasone (10 mg IV bolus + 4 mg po q6h).
However, due to the small sample size, there is insufficient evidence to conclude that neither high-dose (100 mg) nor moderate-dose bolus (10 mg) results in superior ambulatory outcomes.

- There is no direct evidence which supports or refutes:
  a. The type of surgery patients should have for the treatment of MSCC.
  b. Whether surgical salvage should be attempted if progressing on or shortly after radiotherapy.
  c. Whether patients with spinal instability should be treated with surgery.

**Update**

- One randomized trial (abstract) has been identified that compared decompression surgery with radiotherapy to radiotherapy alone. The trial was terminated early because a predetermined stopping rule was met (rule not specified in abstract). The analysis of the 101 patients included in the trial detected a significant improvement in the duration of ambulation for patients who had undergone surgery compared to those who did not (p=0.006), however there was not an overall survival difference between the two groups.

- There is no evidence that patients with a remote or no previous history of cancer have improved ambulatory outcomes when treated with surgery in lieu of core biopsy followed by radiotherapy.

- There are seven studies (two prospective cohort, two case-control, two case series, one retrospective review) which use different radiotherapy prescriptions for patients with MSCC. After adjusting for pre-treatment ambulatory status, no regimen is associated with better ambulatory rates than any other.

- Evidence from a retrospective study of patients with MSCC who received at least two courses of radiotherapy overlapping the spinal cord reported 90% and 43% ambulatory rates for patients who were ambulatory and non-ambulatory before treatment, respectively. These outcomes are equivalent to historical controls who are radiation naïve. There was one episode of radiation myelitis (1.9%) in the 54 patients reviewed in this study.

**Opinions of the Neuro-oncology Disease Site Group**

The lack of sufficient high quality evidence precludes definitive recommendations from being made. Instead, the Neuro-oncology Disease Site Group offers the following opinions based on the evidence reviewed:

**Symptoms and Diagnosis of MSCC**

Patients with symptoms of MSCC, such as motor weakness, sensory changes, and autonomic dysfunction, should be managed to minimize treatment delay. This may include prompt and appropriate investigations, direct referral to a cancer centre, and/or timely initiation of treatment. Patients at high risk for MSCC (i.e. patients with known myeloma, breast, prostate, or kidney cancer) should be followed more diligently, educated about the symptoms of MSCC, and/or screened radiographically with magnetic resonance imaging and given prophylactic radiotherapy if there is evidence of an impending cord compression.

Patients with symptoms of MSCC should be investigated with magnetic resonance imaging, if available and not contraindicated. Magnetic resonance imaging sequences should include T1- and T2-weighted sagittal images and selected T1-weighted axial images. Where the patient has contraindications to magnetic resonance imaging or where no magnetic resonance imaging is available, myelography with or without computed tomography should be used. In centres where no myelography or magnetic resonance imaging is available, referral to a cancer centre with access to magnetic resonance imaging should be done.
Management of MSCC

Treatment for patients with MSCC should be individualized and should consider: pre-treatment ambulatory status, co-morbidities, technical surgical factors, the presence of bony compression and spinal instability, potential surgical complications, potential radiotherapy reactions, and patient preferences.

Systemic dexamethasone should be instituted on the diagnosis of MSCC, although the optimal dose is currently unknown. Patients who are ambulatory do not need to be prescribed dexamethasone but should be educated about the symptoms of MSCC and started on dexamethasone if any of these symptoms arise before the end of radiotherapy.

While there are no definitive studies documenting the need for surgery in the presence of spinal instability or bony compression, current opinion in both the radiation and surgical communities support the strong consideration of surgery in this situation.

The radiation oncologist should determine the dose of radiotherapy. No dose-fractionation prescription has demonstrated higher rates of ambulation in comparison to any other. The use of supportive treatments (analgesia, antiemetics, laxatives, bladder care, etc.) should be considered where appropriate.

Patients who deteriorate neurologically or who recompress after radiotherapy could be considered for re-irradiation, as well as for surgery, especially if it has been more than six weeks since the completion of their last course.

For further information about this evidence summary, please contact Dr. James Perry, Chair, Neuro-oncology Disease Site Group, Sunnybrook and Women’s College Health Science Centre, Rm A-402, 2075 Bayview Avenue, Toronto, Ontario, Canada, tel: (416) 480 4766; fax: (416) 480 5054.

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The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care (PEBC). The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.¹

An evidence summary report is a systematic overview of the best evidence available on a specific clinical question when there is insufficient high-quality evidence on which to base a practice guideline. The report is intended as information for individuals and groups to use in making decisions and policies where the evidence is uncertain. For example, the evidence comes from uncontrolled studies, from studies with control groups that are not relevant to current practice in Ontario, or from subgroup analyses, or the evidence consists solely of preliminary results from ongoing trials. The PEBC will monitor the scientific literature and will develop a practice guideline on this topic when more evidence becomes available.

This evidence summary report has been formally approved by the Practice Guidelines Coordinating Committee (PGCC), whose membership includes oncologists, other health providers, patient representatives, and Cancer Care Ontario executives. Formal approval of an evidence summary by the Coordinating Committee does not necessarily mean that the evidence summary has been adopted as a practice policy of CCO. The decision to adopt an evidence summary as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:

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I. QUESTIONS
1. What are the clinical symptoms of malignant spinal cord compression (MSCC)?
2. What is the optimal approach for investigating suspected MSCC?
3. Is there a role for systemic steroids in the management of MSCC, and if there is, what is the optimal dose?
4. What are the indications for surgery in the management of MSCC?
5. What are the indications for radiotherapy in the management of MSCC?
6. Is there an optimal dose prescription for radiotherapy?
7. What are the treatment options for recurrent MSCC in an area previously irradiated?

II. CHOICE OF TOPIC AND RATIONALE
Malignant spinal cord compression (MSCC) is one of the most dreaded complications of metastatic cancer. Its natural history, if untreated, is usually one of relentless and progressive pain, paralysis, sensory loss, and sphincter dysfunction (1). At presentation, 90% of patients have pain (local and/or radicular, and up to 50% of patients may be unable to walk with 10-15% of patients having paraplegia) (2). Sensory dysfunction and bowel and/or bladder dysfunction is present in 50% of patients (2). The pain intensifies over weeks to months and is eventually associated with weakness and numbness (3). The neurologic progression is subacute in the majority but if left untreated evolves relentlessly to complete paraplegia over days to weeks (3). Those with paralysis either at presentation or post-treatment have a much shorter life expectancy (4-8). In addition, the deterioration is devastating for the patient and the patient’s family and is more difficult to manage medically (9-11).

A population-based study recently completed in Ontario (12) showed that MSCC is relatively common: over 3950 patients were admitted to an Ontario hospital at least once for MSCC between January 1, 1990 and December 31, 1995. This number translated into 2.9% of all cancer patients who died from their disease having at least one admission for MSCC. This number may actually underestimate the true lifetime incidence as documentation is dependent upon the patient being admitted and diagnosed with spinal cord compression. The incidence varied widely by primary cancer site—from 8.4% in patients with myeloma to 0.2% in patients with pancreatic cancer (13;14).

Despite the frequency of spinal cord compression, there is variation in its management and a paucity of high-quality evidence on which to base management decisions (15). For these reasons, the Neuro-oncology Disease Site Group (DSG) decided to develop an evidence summary regarding the management of MSCC.

III. DEFINITIONS
The definition of MSCC contains both clinical and radiographic criteria and encompasses the anatomy of the cord as well as the cauda equina. This evidence summary will use the following definition of MSCC:

“Compression of the dural sac and its contents (spinal cord and/or cauda equina) by an extradural tumour mass. The minimum radiological evidence for cord compression is indentation of the theca at the level of clinical features. Clinical features include any or all of the following: pain (local or radicular), weakness, sensory disturbance, and/or evidence of sphincter dysfunction” (1).

Subclinical cord compression uses the above definition and is defined as the presence of the radiographic features in the absence of the clinical features. For the purposes of this evidence summary, three terms regarding motor function need to be defined. “Ambulatory” refers to
patients who are able to walk with or without assistance and who may be mildly paraparetic; “paretic” refers to patients who are non-ambulatory and paraparetic; and “paraplegic” refers to those patients who have only a flicker of or no muscle movement (15).

IV. METHODS
Evidence Summary Development

This evidence summary report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario’s Program in Evidence-based Care (PEBC), using methods of the Practice Guidelines Development Cycle (16). Evidence was selected and reviewed by three members of the PGI Neuro-oncology DSG and methodologists. Members of the Neuro-oncology DSG disclosed potential conflict of interest information.

The evidence summary report is a convenient and up-to-date source of the best available evidence on the surgical management of MSCC, developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. In contrast to the practice guidelines, the body of evidence in an evidence summary is less mature and is comprised of data primarily from non-randomized controlled trial data or data available only in abstract form. This precludes the development of definitive recommendations, and instead, opinions of the DSG are offered. The report is intended as information for individuals and groups to use in making decisions and policies where the evidence is uncertain. The Practice Guidelines Initiative is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the evidence summary report, the interpretation of the available evidence, and whether there is a need to develop an evidence-based practice guideline when sufficient evidence is available. Final approval of the evidence summary was obtained from the Practice Guidelines Coordinating Committee (PGCC).

The PGI has a formal standardized process to ensure the currency of each evidence summary report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original evidence summary.

Literature Search Strategy

An a priori decision was to use the Loblaw and Laperriere systematic review (1998) (15) as the foundation of this evidence summary and to search for evidence since the review’s completion. The Loblaw and Laperriere systematic review clearly documented its literature search strategy by listing the electronic databases and search terms used to identify eligible studies. Although the evidence base is generally weak, the systematic review by Loblaw and Laperriere was thorough and attempted to develop strategies for managing MSCC.

For the first two questions regarding symptoms and diagnosis of MSCC, MEDLINE (1966 to April 2002), CANCERLIT (1975 to March 2002), and Cochrane Library (2002, Issue 1) databases were searched using the search strategy [“spinal cord compression/” or “cauda equina/ and nerve compression syndromes/”] and “spinal cord neoplasms/ or spinal neoplasms/” and (17) or (“CT scan” and “magnetic resonance imaging”) or (“CT scan” and “myelograph:”) or (“magnetic resonance imaging” and “myelograph:”). These terms were then combined with the search terms for the following publication types and study designs: practice guidelines, systematic reviews, meta-analyses, reviews, randomized controlled trials, and controlled clinical trials. Also, conference proceedings of the American Society of Clinical Oncology (1997 to 2002) were searched for abstracts.

For questions that were the same as those in the Loblaw and Laperriere review (i.e. use of steroids, surgery, radiotherapy, dosage of radiotherapy, and recurrent MSCC), the literature search strategy used in the original publication was adopted. Loblaw and Laperriere’s literature search included articles up to January 1997. This evidence summary searched for data published after January 1997 to March 2002. MEDLINE (1997 to April 2002), CANCERLIT (1997 to March
2002), and Cochrane Library (2002, Issue 1) databases were searched using the search strategy [(“spinal cord compression/” or “cauda equina/ and nerve compression syndromes/”) and “spinal cord neoplasms/ or spinal neoplasms/”] and [laminectomy/ or exp steroids/ or vertebral body resect:.tw or therapy.xs or compression.tw]. These terms were then combined with the search terms for the following publication types and study designs: practice guidelines, systematic reviews or meta-analyses, reviews, randomized controlled trials, and controlled clinical trials. Also, conference proceedings of the American Society of Clinical Oncology (1997 to 2002) were searched for abstracts.

In addition, the Physician Data Query (PDQ) clinical trials database (www.cancer.gov/search/clinical_trials/) was searched for new or ongoing trials. The Canadian Medical Association Infobase (mdm.ca/cpgsnew/cpgs/index.asp) and the National Guidelines Clearinghouse (www.guideline.gov/index.asp) were searched for evidence-based practice guidelines.

**Update**

The original search has been updated using MEDLINE (through January 2004), and the Cochrane Library (2003, Issue 3) databases. Abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology (through 2003) and the American Society of Therapeutic Radiology and Oncology (1997 to 2003) were systematically searched for evidence relevant to this evidence summary.

**Inclusion Criteria**

Table 1 describes the details of the inclusion criteria and outcome variables for each question addressed in this evidence summary. For each question, only studies of adult patients with extradural cord compression, but not intramedullary and leptomeningeal cord compression, were included. Both full publications and abstracts were eligible for review.
Table 1. Details of inclusion criteria and outcome variables.

<table>
<thead>
<tr>
<th>Question</th>
<th>Inclusion Criteria</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What are the clinical symptoms of MSCC?</td>
<td>• Observational and analytical studies investigating patients at risk for MSCC</td>
<td>• Occurrence</td>
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<tr>
<td></td>
<td></td>
<td>• Risk factors</td>
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<tr>
<td></td>
<td></td>
<td>• Symptoms</td>
</tr>
<tr>
<td>2. What is the optimal approach for investigating suspected MSCC?</td>
<td>• RCTs comparing imaging modalities</td>
<td>• Sensitivity of tests</td>
</tr>
<tr>
<td></td>
<td>• Phase II studies or retrospective reviews describing imaging modalities</td>
<td>• Specificity of tests</td>
</tr>
<tr>
<td></td>
<td>• All raters must be blinded from clinical information and the test</td>
<td>• Complications of tests</td>
</tr>
<tr>
<td>3. Is there a role for systemic steroids in the management of MSCC, and if so, what is the optimal dose?</td>
<td>• RCTs comparing the use of steroids to other steroid regimens or no steroids</td>
<td>• Rate of retaining or regaining ambulation</td>
</tr>
<tr>
<td></td>
<td>• Phase II studies or retrospective reviews reporting use of steroids</td>
<td>• Adverse effects</td>
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<tr>
<td>4. What are the indications for surgery in the management of MSCC?</td>
<td>• RCTs comparing surgical procedures to other procedures or no surgery at all</td>
<td>• Rate of retaining or regaining ambulation</td>
</tr>
<tr>
<td></td>
<td>• Phase II studies or retrospective reviews reporting surgical procedures</td>
<td></td>
</tr>
<tr>
<td>5. What are the indications for radiotherapy in the management of MSCC?</td>
<td>• RCTs comparing radiotherapy to other treatments (i.e. surgery)</td>
<td>• Rate of retaining or regaining ambulation</td>
</tr>
<tr>
<td></td>
<td>• Phase II studies or retrospective reviews reporting indications for radiotherapy</td>
<td>• Mortality rates</td>
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<tr>
<td></td>
<td></td>
<td>• Complication rates</td>
</tr>
<tr>
<td>6. Is there an optimal dose prescription for radiotherapy?</td>
<td>• RCTs comparing dosages of radiotherapy</td>
<td>• Rate of retaining or regaining ambulation</td>
</tr>
<tr>
<td></td>
<td>• Phase II studies or retrospective reviews reporting dosages of radiotherapy</td>
<td>• Mortality rates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Complication rates</td>
</tr>
<tr>
<td>7. What are the treatment options for recurrent MSCC in an area previously irradiated?</td>
<td>• RCTs comparing treatments for patients with recurrent MSCC in an area previously irradiated</td>
<td>• Rate of retaining or regaining ambulation</td>
</tr>
<tr>
<td></td>
<td>• Phase II studies or retrospective reviews reporting treatments for patients with recurrent MSCC in an area previously irradiated</td>
<td>• Mortality rates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Complication rates</td>
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<tr>
<td></td>
<td></td>
<td>• Adverse effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Response rate</td>
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</table>

Note: MSCC, malignant spinal cord compression; RCT, randomized controlled trials.

Exclusion Criteria (for all questions)
1. Letters and editorials were not considered.
2. Papers published in a language other than English were not considered.
3. Papers describing a pediatric population were not considered, because the types of tumours that affect children differ from adults (18).
4. Papers describing the majority of patients with intramedullary or leptomeningeal cord compression were not considered.

Study Quality Assessment

Articles on Diagnostic Tests
Articles addressing the accuracy of diagnostic tests were assessed using the Jaeschke et al Evidence-Based Medicine Working Group criteria (19). The primary criteria are: 1. The use of an independent, blind comparison with a reference standard; 2. The use of a spectrum of patients similar to those for whom the diagnostic test will be applied in clinical practice. The secondary criteria are: 1. Whether the results of the test being evaluated influenced the decision to perform the reference standard; 2. Whether the test methodology is described in sufficient detail to permit replication. The article was rated “good” if it met Jaeschke’s primary and secondary criteria, “fair” if it met only the primary criteria, and “poor” if it failed both criteria. These criteria were used solely for description purposes.
Articles on Therapy

The articles were assessed using the criteria of the Canadian Task Force on the Periodic Health Examination (20). The level of evidence supporting or refuting a statement is based on the type of study and its quality (Appendix A). The criteria used to assess study quality varied depending on the type of study. For randomized controlled trials (RCTs), the criteria of Guyatt et al of the Evidence-Based Medicine Working Group were used (21;22) (Appendix B). A RCT was rated “good” if it met all Guyatt’s criteria, “fair” if it met only the primary criteria, “poor” if it failed both criteria, and “inconclusive” if the study did not have sufficient power to detect a clinically important difference. These criteria were used for description purposes.

Synthesizing the Evidence

The ambulation rates (i.e., positive response to treatment) for the studies that addressed radiotherapy regimens were pooled. Unfortunately, the remaining studies presented in the evidence summary were too heterogeneous to pool. Generally, the evidence identified was of poor quality.

V. RESULTS

Literature Search Results

Loblaw and Laperriere published the only systematic review of the management of MSCC (15). Prior to the Loblaw and Laperriere review, four reviews (1;23-25) that suggested strategies for the management of MSCC were published; however, none were systematic.

Although the evidence base is generally weak, the review by Loblaw and Laperriere attempted to develop strategies for managing MSCC. They included 14 studies in the review (some studies addressed more than one question): four studies investigating the role of systemic steroids, one study examining the role of surgery, six studies investigating the indications for radiotherapy, five studies investigating the dose of radiotherapy, and two studies investigating treatment options for reoccurrence of MSCC. No studies on the role of surgery were found in the Loblaw and Laperriere review. Since the publication in 1998, there have been six additional studies identified (14;26-30), including one randomized controlled trial (26). To provide a more thorough description of the available evidence on MSCC, this evidence summary also addresses two diagnostic questions not covered in the original review: 1. What are the clinical symptoms of MSCC? 2. How should a physician investigate the possibility of MSCC? The studies that met the eligibility criteria for each of the two new questions and the five original questions are listed in Table 2.

Update

Since the last literature search, seven additional studies have been identified that meet the inclusion criteria (1u-8u). Four studies examined the clinical symptoms and prognostic factors: two retrospective reviews (one abstract) (1u-2u) and two prospective cohort studies (3u, 4u). One randomized trial (abstract) compared surgery with radiotherapy to radiotherapy alone (5u). The remaining three studies examined radiotherapy (6u-8u). Of the three studies, one was a prospective phase II study that examined the role of brachytherapy after surgery in patients with MSCC (6u). The other two studies retrospectively compared radiotherapy regimens. One of the studies compared two regimens (7u), and the other compared three regimens (8u). The two latter studies were by the same authors and used overlapping patient populations.
### Table 2. The studies that met the inclusion criteria for each question.

<table>
<thead>
<tr>
<th>Question</th>
<th>Intervention</th>
<th>No. of studies [reference]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 1. Clinical symptoms of MSCC* | Not applicable | 1 prospective cohort (17)**  
1 cross-sectional (28)**  
5 retrospective (12;31-34)** |
| **Diagnosis** | | |
| 2. Investigating suspected MSCC* | Diagnosis:  
• Accuracy of Myelo. vs MRI | 4 case series (35-38)**  
2 retrospective (39;40)** |
| **Management** | | |
| 3. Role of systemic steroids | Steroids: Dose | 2 RCTs (26)** (41)  
1 prospective cohort (4)  
1 case-control (42)  
1 case series (43) |
| 4. Indications for surgery in management of MSCC | Surgery:  
• Bone compression  
• Spinal instability  
• Neurologic progression on RT  
• Questionable primary site  
• Radioresistant tumours* | 1 retrospective (27)** 0  
0  
1 prospective cohort (14)**  
1 case series (44) |
| 5. Indications of radiotherapy in management of MSCC | RT:  
• No compression / instability  
• Subclinical cord compression | 1 prospective cohort (4)  
2 retrospective (8;45)  
3 prospective cohort (4;46;47)  
1 cross-sectional (28)**  
1 case series (43) |
| 6. Optimal dose for RT? | RT dose | 2 prospective cohort (4;48)  
2 case-control (29)** (49)  
2 case series (30)** (43)  
1 retrospective (50) |
| 7. Treatment options for recurrence of MSCC | Recurrent MSCC in previously radiated field | 2 retrospective (51;52) |

Note: MRI, magnetic resonance imaging; MSCC, malignant spinal cord compression; Myelo, myelography; RT, radiotherapy.  
*Question/intervention was not addressed in the Loblaw & Laperriere review.  
**Studies not included in the Loblaw & Laperriere review

### Symptoms of MSCC

**What are the clinical symptoms of malignant spinal cord compression?**  
Seven studies attempted to identify the clinical symptoms of MSCC. There was one prospective cohort study (17), one cross-sectional study (28), and five retrospective reviews (12;31-34).

A population-based study of MSCC revealed that the cumulative incidence of MSCC varied widely by primary cancer site (12). According to the study, patients with myeloma, breast, prostate, or kidney cancer have the highest risk of developing cord compression in Ontario (12).

A prospective cohort study by Helweg-Larsen and Sorensen (17) attempted to identify the common symptoms of MSCC in 153 patients. Back pain was the most common complaint among all patients (88%). Patients with tumours localized in the lumbo-sacral area were more likely to report radicular pain (91%) than patients with tumours localized in the thoracic region (69%, p=0.005). Helweg-Larsen and Sorensen also reported motor weakness, sensory changes, and bladder dysfunction as frequent symptoms of patients with MSCC. Bach et al (33) and Gilbert et al (32) noted a similar pattern of symptoms (back pain, weakness, bladder dysfunction, and sensory changes) at patient presentation.

Talcott et al (34) performed a multivariate analysis of patient, radiographic, and neurologic factors of 342 computed tomography (CT) scans in 258 patients to predict which patients were at highest risk for MSCC. They identified five predictive risk factors for MSCC including the inability
to walk, increased deep tendon reflexes, compression fractures on radiographs of spine, bone metastases diagnosed more than one year earlier, and age less than 60 years. Talcott et al concluded that patients with more risk factors were at a greater risk of MSCC: patients with none of the five risk factors had a 4% risk of MSCC, compared to an 87% risk of MSCC in patients with all five risk factors. Back pain was nearly universal across the entire study population, and it failed to differentiate between those with and those without MSCC.

Using likelihood ratios calculated from Talcott’s data (34), the histology-specific incidence data from their population-based study (12) and Bayesian methodology, Loblaw et al estimated the lifetime incidence of MSCC for different groups of asymptomatic patients (i.e. no neurological symptoms) in Ontario according to their primary tumour site (31). The estimated lifetime risk of MSCC was 0.048% for asymptomatic patients with the following primary tumours: ovary, stomach, leukemia, and pancreas, and the estimated lifetime risk of MSCC was 19.3% for asymptomatic patients with the following primary tumours: prostate, female breast, myeloma, and kidney.

Bayley et al (28) published a cross-sectional study examining factors that predict subclinical spinal cord compression, (i.e., cord compression or thecal sac indentation without neurologic abnormalities) in patients with metastatic prostate carcinoma. Bayley et al examined several potential predictors of MSCC including: presence of back pain, alkaline phosphatase levels, hemoglobin concentration, use of narcotic analgesics, bone scan extent of disease (EOD) score, and the duration of hormonal therapy prior to entering the study. Three predictors were significant using univariate logistic regression: EOD score, duration of hormonal therapy, and hemoglobin concentration. Using multivariate logistic regression analysis, the EOD score and duration of hormonal therapy were predictive of subclinical cord compression (p=0.02 and p=0.04, respectively). Patients with extensive bone scan disease (>20 metastases) had a 32% risk of MSCC prior to starting hormone therapy, and they were at a 44% risk of MSCC after 24 months of hormone therapy. Bayley et al’s findings were consistent with those of Talcott et al (34), in that back pain was not predictive of MSCC, and suggest that patients with high-risk bone scans should be examined further in order to detect potential MSCC early.

Any situation where spinal cord compression is suspected should be considered an emergency, and immediate arrangements for appropriate investigations should be undertaken.

Update
There were four studies (two retrospective reviews (1u, 2u), two prospective cohort studies (3u, 4u)) identified that examined the symptoms and prognostic factors indicating MSCC. Loblaw et al (1u) published an abstract of a retrospective review of 775 patients with 914 episodes of MSCC. Their results indicated that pre-treatment motor functional status predicted post-treatment motor, sensory, and autonomic function and time to functional recovery. They reported that breast (25%), lung (21%), and prostate (18%) cancers were the most common cancers among patients with MSCC. In another publication, Loblaw et al (2u) reviewed Ontario’s population-based cancer registry from 1990 to 1995 to identify the incidence and treatment of MSCC in Ontario. They reported that the cumulative incidence of MSCC was disease-specific, ranging from 0.22% in patients with pancreatic cancer to 7.91% in patients with myeloma. Myeloma, prostate, nasopharynx, breast, and kidney cancers had the highest cumulative incidence of MSCC. Levack et al (3u) also reported that these were the most common cancer sites among patients with MSCC in their prospective study. Of the 319 patients in the study, 248 patients agreed to be interviewed about their symptoms. Ninety-four percent of the patients interviewed reported either spinal nerve root or localized back pain. However, it is important to recall Talcott et al’s study (34), which reported that back pain failed to differentiate between those with and those without MSCC because back pain was nearly universal across the entire study population (patients with and without MSCC).

The fourth new study identified examined the time to develop motor deficits before irradiation (4u). There were 98 patients included in the study (31 patients in the 1-7 days prior to irradiation; 31 patients in the 8-14 days prior to irradiation, and 36 patients in the >14 days prior to
Rades et al (4u) reported that the patients with the slowest development of motor deficits before irradiation (>14 days) had the best functional outcome compared to patients with faster development of motor deficits (<14 days) (p<0.01). Loblaw et al’s review (1u) also reported that a greater interval from cancer diagnosis to the cord compression independently predicted for improved survival. Each of these factors may reflect tumors of a less aggressive nature.

**Diagnosis of MSCC**

*What is the optimal approach for investigating suspected malignant spinal cord compression?*

The Neuro-oncology DSG included this section because the more neurologically preserved the patient is before treatment, the better their chances of being ambulatory post-treatment and surviving longer (13;14;53). Four case series (35-38) and two retrospective reviews (39;40) met the inclusion criteria for this question.

The accuracy of magnetic resonance imaging (MRI) or myelography has been examined in four studies (35;37;38;40). Table 3 summarizes the sensitivity and specificity for MRI and myelography with or without CT.

**Table 3. Test characteristics for magnetic resonance imaging and myelography in the detection of MSCC.**

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Prevalence of MSCC</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>MRI</td>
<td>Myelo</td>
</tr>
<tr>
<td>Husband, 2001 (38)</td>
<td>280</td>
<td>72%</td>
<td>0.44</td>
<td>NR</td>
</tr>
<tr>
<td>Carmody, 1989 (37)</td>
<td>70</td>
<td>36%</td>
<td>0.92</td>
<td>0.95</td>
</tr>
<tr>
<td>Li &amp; Poon, 1988 (40)</td>
<td>75</td>
<td>59%</td>
<td>0.93</td>
<td>0.97</td>
</tr>
<tr>
<td>Hagenau, 1987 (35)</td>
<td>31</td>
<td>23%</td>
<td>0.83</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Note: MSCC, malignant spinal cord compression; MRI, magnetic resonance imaging; Myelo, myelography; NR, not reported.

Two additional studies evaluated the ability for MRI to identify MSCC (36;39). The results of both of the studies (one case series, one retrospective) supported the use of whole-spine MRIs for patients with known malignancy and suspected MSCC. Benefits of MRI include: it is non-invasive; there is the opportunity to image the full length of the cord and multiplanar views; there is high signal contrast between cord, cerebral spinal fluid (CSF), and tumour; the nature of compression can be determined; no uncomfortable positioning is required; and paraspinal masses can be more readily identified (35-40). Disadvantages of MRI include: possible contraindications due to intracorporeal metallic objects; poor image quality due to patient movement; and patient claustrophobia (36;39). Although myelogram has been linked with possible complications, Hagenau et al (35) detected no episodes of neurologic decline after myelography, and in their institution’s experience, this complication rarely occurred.

**Management of MSCC**

*Is there a role for systemic steroids in the management of malignant spinal cord compression, and if there is, what is the optimal dose?*

Two RCTs (26;41), one case-control study (42), and one case series (43) were identified that addressed the role of steroids in the management of MSCC. The evidence for the use and optimal dose of steroids is summarized in Table 4.

Vecht et al (26) reported the results of a small RCT that compared high-dose bolus dexamethasone to moderate-dose bolus dexamethasone in patients with complete myelographic obstruction. All patients (n=37) were treated with radiotherapy and maintenance dexamethasone of 16 mg/day orally. Maintenance steroids are those given after the initial bolus, usually for the
duration of the radiotherapy treatment, and then tapered, often over a several week period. Randomization was stratified by tumour type (carcinoma versus lymphoma). At one week, one of 13 (8%) patients given the moderate dose and five of 20 (25%) patients given the high dose showed improved neurologic status (defined as more than one grade difference in a 5-point neurologic score). This difference was not statistically significant (p=0.22, Fisher’s exact test, calculated by Neuro-oncology DSG) but is clinically significant if a difference of this magnitude truly exists. Pain improvement and contrast passage were no different between the two arms. The results of this study by Vecht et al (26) need to be interpreted cautiously because this was a small study that may not have been powered to detect a true difference between high-dose and moderate-dose dexamethasone, and the difference observed may have been influenced by other factors than steroid dose in such a small study.

Sorensen et al (41) randomized 57 patients with MSCC treated with radiotherapy to either high-dose maintenance dexamethasone or no steroids (control group). Sorensen et al (41) concluded that high-dose maintenance dexamethasone significantly improves ambulation (p=0.046), but the adverse effects of high-dose maintenance dexamethasone are also greater than no steroid treatment. Three patients (11%) in the high-dose maintenance dexamethasone group had serious adverse effects, including severe psychoses and gastric ulcers requiring surgery.

Heimdal et al (42) reported their experience with high- and moderate-dose maintenance steroids in patients with MSCC treated with radiotherapy in a single-institution, case-control study. They reported a statistically and clinically significant increase in the number of serious adverse effects in the high-dose group (4/28 = 14%) compared with the moderate-dose group (0/38 = 0%). Serious adverse effects included ulcers with hemorrhage, rectal bleeding, and gastrointestinal perforations. Adverse effects of any severity were seen in the high- and moderate-dose groups, 29% and 8% respectively. Although Heimdal et al (42) reported that there was no difference in the number of ambulatory subjects in each cohort, or any difference in the ambulatory rate post-treatment, none of this data were formally reported. As a result, the reader is not able to conclude with any certainty that moderate-dose maintenance dexamethasone is as effective as high-dose dexamethasone.

Recognizing the toxicity of maintenance steroids (particularly at a high-dose), a case series by Maranzano et al (43) reported that steroids may not be necessary for patients with good motor function. All the patients in their study (n=20) regained (or maintained) ambulation after radiotherapy without steroids.
Table 4. Summary of systemic steroid treatments.

<table>
<thead>
<tr>
<th>Manoeuvre</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone vs methylprednisolone</td>
<td>No studies report ambulatory outcomes of patients that compare the use of the two drugs.</td>
</tr>
<tr>
<td>High-dose dexamethasone maintenance ( ^{a} ) used with RT ( ^{41} )</td>
<td>Small RCT ( (n=57) ) comparing high-dose ( ^{a} ) dexamethasone to nothing: 81% vs 63% patients ambulatory 3 months post-RT. Eleven percent serious toxicity rate was observed in patients who received high-dose steroids.</td>
</tr>
<tr>
<td>High-dose dexamethasone bolus ( ^{b} ) vs moderate-dose ( ^{c} ) dexamethasone ( ^{26} )</td>
<td>Small RCT ( (n=37) ) with short follow-up comparing high-dose bolus to moderate-dose bolus dexamethasone: 25% vs 8% improvement in motor status favouring high-dose bolus ( (p=0.22) ) at 1 week.</td>
</tr>
<tr>
<td>Moderate-dose dexamethasone maintenance ( ^{d} ) ( ^{42} )</td>
<td>Case-control study. Patients taking high-dose ( ^{a} ) steroids had 3/28 (14.2%) serious adverse effects and 8/28 (28.6%) total adverse effects ( ^{d} ) compared with patients taking moderate-dose steroids who had no serious adverse effects and 3/38 (7.9%) total adverse effects. Insufficient data to compare ambulatory outcomes.</td>
</tr>
<tr>
<td>Steroids for patients with subclinical cord compression taking RT ( ^{e} ) ( ^{43} )</td>
<td>Case series. All 20 patients receiving RT without steroids remained ambulatory as did all the 73 patients who received radiotherapy and steroids using same RT protocol.</td>
</tr>
</tbody>
</table>

Note: RCT, randomized controlled trial; RT, radiotherapy; vs, versus.  
\( ^{a} \) dexamethasone 96 mg IV bolus then 24 mg po QID x 3 days then taper x 10 days.  
\( ^{b} \) dexamethasone 100 mg IV bolus.  
\( ^{c} \) dexamethasone 10 mg IV bolus.  
\( ^{d} \) dexamethasone 10 mg IV bolus then 4 mg IV QID with taper over 2 weeks.  
\( ^{e} \) no neurological deficits, only radiculopathy with \( \leq \) 50% of the diameter of the spinal cord compressed on magnetic resonance imaging or CT.


**What are the indications for surgery in the management of malignant spinal cord compression?**

One prospective cohort study \( (14) \), one case series \( (44) \), and one retrospective study \( (27) \) have been identified that describe the indications for surgery in the management of MSCC. The aim of this evidence summary was to present the role of surgery in terms of bony compression, spinal instability, neurologic progression, primary site of the tumour, and radioresistant tumours.

**Bony compression**

One retrospective chart review has been published that compared radiotherapy prior to surgical decompression to surgical decompression with postoperative radiotherapy \( (27) \). Ghogawala et al \( (27) \) reported that patients who underwent radiotherapy and then surgery were more likely to suffer from an infection requiring intravenous antibiotics or a prolonged hospital stay than patients receiving postoperative radiotherapy. The major wound complication rate for patients receiving radiation followed by surgery was 32% compared to a 12% complication rate for patients undergoing surgery and then radiation \( (p<0.05) \). The patients undergoing surgery and then radiotherapy also experienced significantly less neurological deterioration \( (p < 0.01) \); however, this was a retrospective review, and one is unable to arrive at conclusions on this basis.

**Update**

Patchell et al \( (5u) \) reported in abstract form the results of a randomized trial comparing decompressive surgical resection with radiotherapy to radiotherapy alone. There were 101 patients included in the trial before it was stopped because a “criterion of a predetermined early stopping rule was met.” Patchell et al did not specify in the abstract what the criterion was. When the results of the 101 patients were analyzed, Patchell et al detected that patients undergoing
surgery in addition to radiotherapy were more likely to retain or maintain their ambulatory status longer compared to patients receiving only radiotherapy (p=0.006). However, non-ambulatory patients in this trial who received radiotherapy alone had significantly worse ambulatory rates (3/16 = 19%) than those seen with paretic (60%) or paraplegic patients (15%) (4). In comparison, the ambulatory rates for the non-ambulatory patients who were randomized to surgery + RT had ambulatory rates (9/16 = 58%) which are similar to those seen in other surgery trials reported previously (55%) (15). In part, these findings may be explained by the inclusion of 35% of patients in the RT arm having an unstable spine, described below as a relative contraindication for RT. It may be that for a highly selected group of patients reflected in the selection criteria of this trial that surgery and RT represents a better management strategy in order to maximize ambulation for the remainder of the patient's lifetime, however more details of the study are required.

**Spinal instability**

There were no studies that addressed spinal instability. Despite the lack of evidence, spinal instability is a surgical indication that is generally accepted by both radiation oncology and surgical professional communities (1;4;25;54).

**Neurologic progression during or after radiotherapy**

There were no studies addressing the role of surgery in patients with neurologic progression during or after radiotherapy. Radiation oncologists and surgeons tend to consider surgical salvage if the symptoms of cord compression progress during or shortly after radiotherapy (1;24;54). The effectiveness of salvage surgery, however, was not elucidated from the studies reviewed in this document.

**Questionable primary site**

There were no studies describing situations where there was a questionable primary site. If the patient has no diagnosis of cancer or has a remote history of cancer, surgical decompression is sometimes recommended in order to obtain a tissue diagnosis and to decompress the cord (1;4;25). However, there is no direct evidence found that supports or refutes this manoeuvre over obtaining tissue from a biopsy and treating with radiotherapy.

**Radioresistant tumours**

There are two studies of functional outcomes (i.e. ambulation post-treatment) that examined the radiosensitivity of the tumour as one of the prognostic variables, one prospective cohort study (14), and a case series (44). In the past, patients with tumours less sensitive to radiation (tumours arising from liver, kidney, prostate, melanoma, and sarcoma) underwent surgery rather than radiotherapy, presumably because of poorer outcomes of these patients. In the case series by Kim et al (44), 59 patients with MSCC were treated with radiation (although six patients also received laminectomy as part of their treatment). After radiation, an improvement (i.e. ability to walk) was seen in 11 of the 27 patients with radiosensitive tumours (tumours arising in breast, lung, myeloma, or lymphoma) compared to an improvement in three of the 21 patients with tumours less sensitive to radiation (p=0.048) (time of assessment not specified). In multivariate analysis, this difference in response between radiosensitive and radioresistant tumours was only of borderline significance (p = 0.071).

In their prospective cohort study, Helweg-Larsen et al (14) also assessed the primary tumour type as a variable in post-treatment ambulation. On multivariate analysis, tumour type did not significantly predict post-treatment ambulation (p=0.29).

Neither study indisputably identified radioresistant tumours as having worse post-treatment ambulation rates. These studies do not make a strong case about the need for surgery for radioresistant tumours. In most instances factors other than the presence of a radioresistant
tumour influence the decision about surgery or radiation (extent of vertebral involvement, extent of other metastatic disease, bony instability, etc.).

**What are the indications for radiotherapy in the management of malignant spinal cord compression?**

Two retrospective reviews (8;45), three prospective cohort studies (4;46;47), one cross-sectional study (28), and one case series (43) were identified that address the role of radiotherapy in the management of MSCC.

**Radiotherapy for patients without bony compression or spinal instability**

In a retrospective study by Pigott et al (45), information regarding 46 patients, who had previously been treated with radiotherapy for MSCC, was reviewed. Eleven of these patients had evidence of bony compression on MRI. Of these patients, 27% (3/11) were ambulatory post-treatment compared to 66% (23/35) who had no bony compression (p=0.025, Chi-square test, calculated by the Neuro-oncology DSG) (45). A retrospective study by Zelefsky et al (8) reported that 66% (4/6) of those with a compression fracture more than 50% at the level of the compression had no improvement after radiotherapy compared with 11% (3/28) of those who had a compression fracture less than or equal to 50% (p=0.007, Fisher’s exact test, calculated by the Neuro-oncology DSG). However, neither study reported the pre-treatment motor status in each group and, therefore, no firm conclusions can be made.

Of the radiotherapy studies, Maranzano et al (4) was the only one to specifically exclude patients with bony compression in their prospective cohort study. However, this study has one important shortcoming. The study excluded 25 patients from the analysis who died before their ambulation could be assessed, and the pre-treatment motor function was not reported for all patients. The exclusion of the patients who died early may bias the results as these patients may have had a higher chance of not being ambulatory after treatment. To attempt to correct the data, this evidence summary will calculate rates of ambulation assuming that all 25 censored patients would have failed to recover ambulatory ability after treatment.

In Maranzano et al’s (4) study, 60% of the paraparetic patients regained ambulation (53%, if correcting for inappropriately censored patients). In contrast, 40.1% (weighted mean by number of patients in each trial) of paraparetic patients in studies where bony compression was included regained ambulation (95% confidence interval 31.4 to 48.8%) (8;29;30;43;47-49).

The chance of retaining or regaining ambulation was compared for radiotherapy by pooling the ambulatory outcomes of eight studies (4;8;29;30;43;47-49). Table 5 lists the results, by pre-treatment motor strength and according to the results from Maranzano et al (4). Patients who are paraplegic at presentation have a guarded prognosis and are unlikely to regain ambulation regardless of the intervention: between 10.8% and 15.1% of the paraplegic patients undergoing radiotherapy regained ambulation after treatment.
Table 5. Comparison of pooled ambulatory outcomes of patients undergoing radiotherapy using corrected and uncorrected data from Maranzano et al (4).

<table>
<thead>
<tr>
<th>Studies</th>
<th>% of AMB patients ambulatory post RT (95% CI)</th>
<th>% of AA patients ambulatory post RT (95% CI)</th>
<th>% of PP patients ambulatory post RT (95% CI)</th>
<th>% of PPL patients ambulatory post RT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies (8;29;30;43;47-49) with Maranzano, uncorrected (4)</td>
<td>95.3% (92.7-97.9%)</td>
<td>62.8 (54.9-70.7%)</td>
<td>35.6% (29.0-42.2%)</td>
<td>13.3% (6.8-19.8%)</td>
</tr>
<tr>
<td>All studies (8;29;30;43;47-49) with Maranzano, corrected (4)</td>
<td>87.0% (83.1-90.9%)</td>
<td>55.9% (48.4-63.4%)</td>
<td>31.8% (25.8-37.8%)</td>
<td>10.8% (5.5-16.1%)</td>
</tr>
<tr>
<td>All studies (8;29;30;43;47-49) except Maranzano (4)</td>
<td>93.5% (90.0-97.0%)</td>
<td>65.2% (56.3-74.1%)</td>
<td>40.1% (31.4-48.8%)</td>
<td>15.1% (7.6-22.6%)</td>
</tr>
</tbody>
</table>

Note: AA, assisted ambulation; AMB, ambulatory; NR, not reported; PP, paraparetic; PPL, paraplegic; RT, radiotherapy.

Radiotherapy for patients with subclinical cord compression

Prophylactic radiotherapy for subclinical cord compression is addressed in five studies: three prospective cohort studies (4;46;47), one cross-sectional study (28), and one case series (43). Helweg-Larsen et al (46) prospectively reported ambulatory outcomes for 37 patients with synchronous compressions due to malignancy. They irradiated symptomatic synchronous compressions with a one to two vertebral body margin in the superior and inferior directions (and did not extend radiation portals to include asymptomatic lesions). Twenty-three patients had lesions outside the irradiated volume, and 14 patients had lesions within the irradiated volume. Follow-up was for 3.5 years. Three of the 23 (13%) patients who had lesions outside the irradiated volume and none of the 14 patients who had lesions within the irradiated volume relapsed in the same area as the previous lesion.

In three independent studies by Maranzano et al (4;43;47), radiotherapy was given to asymptomatic patients with evidence of MSCC on CT, myelogram, or MRI. Patients with back pain and evidence of vertebral metastatic disease were offered screening for MSCC. All 93 asymptomatic patients remained ambulatory after radiotherapy with or without steroids, in contrast to a rate of 76% (158/209) when all patients were combined across the three studies. This overall ambulation rate would be expected to be better than other studies since Maranzano et al screened for asymptomatic cord compression and thus included in their cohort patients with subclinical cord compression who ultimately do better.

Bayley et al (28) reported on a series of 68 neurologically intact patients with metastatic prostate cancer who were screened for cord compression using MRI. Twenty-two patients (32%) had evidence of thecal sac indentation and were treated with radiotherapy. Only one patient (4.5%) had an in-field failure 18 months after his prophylactic radiotherapy and was treated successfully with surgery. While the natural history of thecal sac indentation is unknown, it is conceivable that the majority of patients would become symptomatic over time. While ambulatory outcomes were not the primary objective of this study, the results imply that radiotherapy may be effective for patients with subclinical cord compression.
Update

There was one small prospective phase II study identified that examined brachytherapy in 24 patients who had undergone decompression surgery (6u). Permanent radioactive iodine (\(^{125}\)I) seeds were placed with open exposure after the resection. Twenty-two of the patients also received external beam radiotherapy in addition to the \(^{125}\)I. Rogers et al (6u) reported that 84% of the patients had improved their ambulatory status after treatment. The two- and three-year actuarial survival rates were 24% and 16%, respectively. There were four cases of morbidity reported: one cerebrospinal fluid leak, two wound infections, and one pulmonary embolus.

*Is there an optimal prescription for radiotherapy?*

Seven studies were identified that attempted to specify an optimal dosage of radiotherapy: two prospective cohort (4;48), two case-control (29;49), two case series (30;43), and one retrospective review (50).

Dose schedule

The prescription of radiotherapy given to treat MSCC varies within and between studies. One study stratified the results by dosing (29) and the six other studies gave the same prescription to the entire cohort—two of these prescribed 30 Gy in 10 fractions over two weeks (43;50), another gave 28 Gy in seven fractions (continuous over one week) (48), and four gave a split dose of 15 Gy in three fractions, four days break and then 15 Gy in five fractions (over two weeks) (4;30;49). The one study that compared two treatment doses was a case-control study which compared split dose to 16 Gy in two fractions split dose one week apart (29). No one regimen demonstrates superiority over the others for any cohort of patients. Table 6 compares the outcomes of the regimens. It is important to recognize that there are no RCTs attempting to determine the optimal radiotherapy regimen: all results need to be interpreted with caution.

Update

Two retrospective studies compared radiotherapy regimens in patients with MSCC (7u, 8u). The two studies included overlapping patients. One study compared two radiotherapy regimens (30Gy in 10 fractions and 37.5Gy in 15 fractions) (7u), the other study compared three regimens (30Gy in 10 fractions, 37.5Gy in 15 fractions and 40Gy in 20 fractions) (8u). Neither of the studies reported significant differences in functional outcome among the radiotherapy regimens. The authors of the studies recommended that patients with a markedly reduced life expectancy should be treated with the least time consuming regimen (i.e. 30Gy in 10 fractions).
Table 6. Radiotherapy regimens according to ambulatory status of patients.

<table>
<thead>
<tr>
<th>Studies</th>
<th># of ambulatory patients (AMB)</th>
<th># of assisted ambulation patients (AA)</th>
<th># of paraparetic patients (PP)</th>
<th># of paraplegic patients (PPL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AMB Pre RT</td>
<td>AMB Post RT</td>
<td>AA Pre RT</td>
<td>AMB Post RT</td>
</tr>
<tr>
<td>RT: 30 Gy in 10 fractions (43;50)</td>
<td>38</td>
<td>35 (92%)</td>
<td>30</td>
<td>24 (80%)</td>
</tr>
<tr>
<td>RT: 28 Gy in 7 fractions (48)</td>
<td>60</td>
<td>58 (97%)</td>
<td>19</td>
<td>14 (74%)</td>
</tr>
<tr>
<td>RT: 15 Gy in 3 fractions, 15 Gy in 5 fractions (4;29;30;49)</td>
<td>131</td>
<td>126 (96%)</td>
<td>75</td>
<td>49 (65%)</td>
</tr>
<tr>
<td>RT: 8 Gy twice (29)</td>
<td>8</td>
<td>8 (100%)</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Note: AA, assisted ambulation; AMB, ambulatory; Gy, Gray; NR, not reported; PP, paraparetic; PPL, paraplegic; RT, radiotherapy.

*Not all studies divided results into paraparetic and paraplegic patients. If they did not specify, it was assumed patients were paraparetic.

What are the treatment options for recurrent malignant spinal cord compression in an area previously irradiated?

The literature search identified two retrospective studies (51;52) that addressed recurrent MSCC.

The options for treating MSCC in an area previously irradiated include surgery, systemic therapies, radiotherapy, or comfort measures alone. While surgery is often recommended, the risk-benefit ratio given the medical and technical factors present may be too high (51). Systemic or hormonal therapies are generally ineffective but can be considered if the patient has chemotherapeutically sensitive tumours (e.g., hematologic, neuroendocrine, germ cell tumours, or hormonally naïve breast and prostate cancer).

Some authors suggest that irradiating a patient who has had previous radiotherapy in the same region of the cord is contraindicated (1;4;24;44). Radiotherapy may not be desirable for two potential reasons. The first is that a tumour which compresses the cord in an area that has been previously irradiated may be radioresistant and, therefore, may not respond as well the second time. The second is the risk that re-treating the spinal cord may lead to radiation myelitis in a relatively short interval. However, there is some weak evidence refuting these propositions. Schiff et al retrospectively reviewed 54 patients with MSCC who had at least two radiation treatments (cumulative dose: range 36.5-81 Gy, median 54 Gy) overlapping the spinal cord (range 5-25 cm, median 10 cm) (51). There were equivalent neurological outcomes to radiation-naive patients with MSCC (ambulatory rate of 90% in ambulatory patients, 43% in non-ambulatory patients) and only one episode of radiation myelopathy over an 18-year retrospective chart review. In addition, the Wong et al retrospective review found no myelopathy when spinal cord received less than 100 Gy2 (corrected for biologically equivalent dose, $\alpha/\beta = 2$) of radiotherapy (52).
VI. INTERPRETIVE SUMMARY

The purpose of this evidence summary is to summarize the literature pertaining to several issues in the diagnosis and management of MSCC. Unfortunately, for many situations, the current evidence precludes conclusion but should serve as a springboard for future research initiatives.

Symptoms and Diagnosis of MSCC

A major thrust in improving the outcomes of patients with MSCC is to detect problems early before deep neurologic deficits are present. The strongest prognostic factor for overall survival and ability to ambulate post-treatment is pre-treatment neurological status, most importantly, motor function (34). Delay in diagnosis and referral can lead to neurological decline (53). Practitioners may consider having the whole spine evaluated on an emergent basis with MRI or myelogram with CT for any patient with neurological symptoms and a recent history of cancer. Steroids may be started prophylactically.

Management of MSCC

High-dose dexamethasone may be an effective adjunct to radiotherapy in improving post-treatment ambulation but carries the risk of serious toxicity. However, more high quality studies (i.e. RCTs) need to establish the benefits and risks of high-dose versus moderate-dose bolus and maintenance schedules of dexamethasone. There is little consensus among surgeons and radiation oncologists for the indications for surgery in patients with MSCC. Many worry about recommending a procedure with high complication rates and long convalescent periods for palliation. However, many surgery departments and a few radiation oncology departments included bony compression causing MSCC as an indication to consider surgery (1;25;43). A review of the evidence backing this recommendation reveals only weak support.

Several studies support the irradiation of subclinical cord compression as a method of preserving neurologic function. Predictive risk models are emerging which may help to define a population of patients at higher risk of developing cord compression (12;28;34) but the optimal screening strategy, population, and intervention have yet to be elucidated.

VII. ONGOING TRIALS

No ongoing trials could be found for patients with MSCC.

VIII. OPINIONS OF THE NEURO-ONCOLOGY CANCER DISEASE SITE GROUP

The lack of sufficient high quality evidence precludes definitive recommendations from being made. Instead, the Neuro-oncology DSG offers the following opinions based on the evidence reviewed:

**Symptoms and Diagnosis of MSCC**

Patients with symptoms of malignant spinal cord compression (MSCC), such as motor weakness, sensory changes, and autonomic dysfunction, should be managed to minimize treatment delay. This may include prompt and appropriate investigations, direct referral to a cancer centre, and/or timely initiation of treatment. Patients at high risk for MSCC (i.e. patients with known myeloma, breast, prostate, or kidney cancer) should be followed more diligently, educated about the symptoms of MSCC, and/or screened radiographically with MRI and given prophylactic radiotherapy if there is evidence of an impending cord compression.

Patients with symptoms of MSCC should be investigated with MRI, if available and not contraindicated. Magnetic resonance imaging sequences should include T1- and T2-weighted sagittal images and selected T1-weighted axial images. Where the patient has contraindications to magnetic resonance imaging or where no MRI is available, myelography with or without CT should be used. In centres where no myelography or MRI is available, referral to a cancer centre with access to MRI should be made.
Management of MSCC

Treatment for patients with MSCC should be individualized and should consider: pre-treatment ambulatory status, co-morbidities, technical surgical factors, the presence of bony compression and spinal instability, potential surgical complications, potential radiotherapy reactions, and patient preferences.

Systemic dexamethasone should be instituted on the diagnosis of MSCC, although the optimal dose is currently unknown. Patients who are ambulatory do not need to be prescribed dexamethasone but should be educated about the symptoms of MSCC and started on dexamethasone if any of these symptoms arise before the end of radiotherapy.

While there are no definitive studies documenting the need for surgery in the presence of spinal instability or bony compression, current opinion in both the radiation and surgical communities support the strong consideration of surgery in this situation.

The radiation oncologist should determine the dose of radiotherapy. No dose-fractionation prescription has demonstrated higher rates of ambulation in comparison to any other. The use of supportive treatments (analgesia, antiemetics, laxatives, bladder care, etc.) should be considered where appropriate.

Patients who deteriorate neurologically or who recompress after radiotherapy could be considered for re-irradiation, as well as for surgery, especially if it has been more than six weeks since the completion of their last course.

IX. EXTERNAL REVIEW OF THE EVIDENCE SUMMARY REPORT

Practitioner Feedback

A draft version of this report was reviewed by Ontario practitioners. Any changes made to the report as a result of practitioner feedback are described in the ‘Modifications’ section below.

Methods

Practitioner feedback was obtained through a mailed survey of 124 practitioners in Ontario (10 medical oncologists, 30 surgeons, 71 neurologists, and 13 radiation oncologists). The survey consisted of items evaluating the methods, results, and interpretive summary. Written comments were invited. The practitioner feedback survey was mailed out on December 2, 2002. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Neuro-oncology DSG reviewed the results of the survey.

Results

Forty-four responses were received out of the 124 surveys sent (35% response rate). Responses include returned completed surveys as well as phone, fax and email responses. Of the practitioners who responded, 34 indicated that the report was relevant to their clinical practice and completed the survey. Results of the practitioner feedback survey are summarized in Table 7.
Table 7. Results of the practitioner feedback survey.

<table>
<thead>
<tr>
<th>Item</th>
<th>Strongly agree or agree</th>
<th>Neither agree nor disagree</th>
<th>Strongly disagree or disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>The rationale for developing an evidence summary, as stated in the “Choice of Topic” section of the report, is clear.</td>
<td>31 (91%)</td>
<td>3 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>There is a need for an evidence summary on this topic.</td>
<td>31 (91%)</td>
<td>2 (6%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>The literature search is relevant and complete in this evidence summary.</td>
<td>28 (82%)</td>
<td>4 (12%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>I agree with the methodology used to summarize the evidence.</td>
<td>30 (88%)</td>
<td>2 (6%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>I agree with the overall interpretation of the evidence in the evidence summary.</td>
<td>30 (91%)</td>
<td>2 (6%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>The <strong>Opinions of the Disease Site Group</strong> section of this evidence summary is useful.</td>
<td>24 (71%)</td>
<td>7 (20%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>An evidence summary of this type will be useful for clinical decision making.</td>
<td>25 (73%)</td>
<td>6 (18%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>At present, there is insufficient evidence to develop a practice guideline on this topic.</td>
<td>24 (71%)</td>
<td>4 (11%)</td>
<td>6 (18%)</td>
</tr>
<tr>
<td>There is a need to develop an evidence-based practice guideline on this topic when sufficient evidence becomes available.</td>
<td>30 (88%)</td>
<td>3 (9%)</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

**Response Rate**

There was a poor response rate from practitioners for this evidence summary. An explanation for the poor rate of return could be that the evidence summary was sent at the beginning of December and thus went through the practitioner feedback process during the December holidays. Another possible reason for the poor response rate is that 71 neurologists new to the practitioner feedback process were sent the evidence summary to review. Only twenty-two of them responded, and thirteen completed the survey because it was relevant to their practice.

**Summary of Written Comments**

Seventeen respondents (50%) provided written comments. Six of the respondents noted the paucity of high quality data but did not suggest modifications to the evidence summary. The main points in the written comments that required a response from the Neuro-oncology DSG were:

1. The evidence summary needs to provide more recommendations.
2. The evidence summary suggested that patients at high risk should have radiographic screening.
3. When no RCTs exist about a topic, lesser degrees of evidence need to be reviewed and considered until better evidence is developed—it is not good enough to say that there is no evidence for a topic.
4. One respondent suggested two recently published studies to include.
5. One respondent suggested changing the opinion stating “The dose of dexamethasone should be tailored to the individual but high-dose dexamethasone (100 mg IV bolus + 24 mg IV/po q6h) should be considered” to “The optimal dose of steroids in not known”.

6. The evidence summary makes no distinction between those cases of metastatic spinal cord compression presenting with and without pathological fracture and spinal instability.

**Modifications/Actions**

1. As an evidence summary, this document is not designed to make recommendations. The Neuro-oncology DSG has formed opinions regarding MSCC, but they will not make recommendations until there is more evidence available to support recommendations.

2. It was not indicated that patients at high risk had to be screened radiographically; other options were also suggested. The reality borne out by several studies is that patients typically have long delays between the onset of symptoms and the start of treatment during which time the majority of patients lose motor and bladder function. The chances of recovery are worse for those with worse neurologic function before treatment. While radiographic screening is expensive, the previous Ontario population-based study calculated that people who had an admission for cord compression, and who later died from cancer, spent 30 days more in hospital in their last year of life than those who died from cancer but did not experience cord compression. At $750 per bed-day, preventing cord compression could save on average $22,500, not to mention the unmeasured cost to patients, their family, and society.

3. The Neuro-oncology DSG completed a thorough search of the literature and was unable to make a comment regarding some aspects of malignant spinal cord compression. This evidence summary includes many types of studies, as indicated in the inclusion criteria. It is unfortunate that there is not more evidence related to this topic.

4. After reviewing the suggested studies, the Neuro-oncology DSG decided that these studies were relevant. The results of both studies are consistent with the evidence presented in the evidence summary; these studies will be included in the update of the evidence summary (Summer 2003).

5. The Neuro-oncology DSG decided to leave the wording of the opinion the same because they wanted to offer some guidance to practitioners about the optimal steroid dosage.

6. The evidence summary discusses malignant spinal cord compression in the context of bony compression and spinal instability (p. 8,9). The guideline does not specifically address patient diagnosis nor management in patients with those conditions without spinal cord compression. After review of the target patient population, the Neuro-oncology DSG did not feel that it needed further clarification.

**Practice Guidelines Coordinating Committee Approval Process**

The evidence summary report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Twelve of 14 members of the PGCC returned ballots. Ten PGCC members approved the evidence summary report as written, with four members providing suggestions for consideration by the DSG. Two members approved the report conditional on the Neuro-oncology DSG addressing specific concerns.

The PGCC noted that the types of studies were not clearly defined throughout the evidence summary and that a further description beyond prospective and retrospective was required. Also, suggestions were offered to clarify some sections by providing more detailed descriptions of studies and results and to include critical appraisal components throughout the report. The PGCC felt that the Choice of Topic and Rationale section did not offer enough information of MSCC in the clinical context. Two comments concerning the literature search were made: the search was one year out of date and a search of the proceedings of the American Society of Therapeutic Radiology and Oncology (ASTRO) was missing. The PGCC also recommended that the Neuro-oncology DSG search the proceedings of the ASTRO meeting in the future.
oncology DSG reconsider their statement regarding the optimal steroid dosage in their opinions section.

Modifications/Actions

The Neuro-oncology DSG provided more detailed descriptions of the types of studies reviewed and also clarified sections throughout the report as suggested. The Neuro-oncology DSG re-worked the Choice of Topic and Rationale section to provide more clinical information about MSCC. The Neuro-oncology DSG acknowledges that the evidence summary is one year out of date and commits to updating the review in the summer of 2003. The Neuro-oncology DSG decided not to update the evidence summary at this time because this report has been in development for a long time, and the DSG did not want to delay it any further. The DSG will also review the proceedings of the annual meetings of the American Society of Therapeutic Radiology and Oncology (ASTRO) from 1997 to 2002 at that update search. Reconsidering a similar comment made by a practitioner through practitioner feedback, the DSG decided to modify the statement regarding steroids so that it supported the use of steroids, without a suggested dosage. Editorial changes were also made in accordance with the suggestions of the PGCC.

X. CONCLUDING REMARKS

The opinions section was modified after the DSG members received comments from practitioner feedback and the PGCC regarding a statement which described the optimal steroid dosage. One practitioner feedback respondent and one PGCC member thought that the statement “the dose of dexamethasone should be tailored to the individual but high-dose dexamethasone (100 mg IV bolus + 24 mg IV/po q6h) should be considered” was too strongly worded, considering the evidence available. The Neuro-oncology DSG decided to reword the sentence to read “systemic dexamethasone should be instituted on the diagnosis of MSCC, although the optimal dose is currently unknown.” Also, an additional statement regarding surgery was also added, based on a suggestion from a PGCC member.

XI. JOURNAL REFERENCE

XII. ACKNOWLEDGEMENTS

The Neuro-oncology Disease Site Group would like to thank Dr D. Andrew Loblaw, Dr Normand Laperriere, Dr James Perry, and Ms. Alexandra Chambers for taking the lead in drafting and revising this Evidence Summary.

For a complete list of the Neuro-oncology Disease Site Group members and the Practice Guidelines Coordinating Committee members, please visit our Web site at: http://www.cancercare.on.ca/.
REFERENCES

21. Guyatt GH, Sackett DL, Cook DJ. Users’ guides to the medical literature. II. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group. *JAMA* 1994; 271:59-63.

22. Guyatt GH, Sackett DL, Cook DJ. Users’ guides to the medical literature. II. How to use an article about therapy or prevention. A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA* 1993; 270:2598-601.


**Update**


Appendix A. Level of evidence criteria. Based on the Canadian Task Force on the Periodic Health Examination 1979 criteria (20).

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Evidence obtained from at least one properly designed randomized control trial</td>
</tr>
<tr>
<td>II-1</td>
<td>Evidence obtained from well-designed controlled trials without randomization</td>
</tr>
<tr>
<td>II-2</td>
<td>Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group</td>
</tr>
<tr>
<td>II-3</td>
<td>Evidence obtained from comparisons between times or places with or without the intervention</td>
</tr>
<tr>
<td>III</td>
<td>Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees</td>
</tr>
</tbody>
</table>

Appendix B. Guyatt’s criteria from the Evidence-Based Medicine Working Group for evaluating randomized controlled trials (22).

Primary criteria
(a) Was the assignment of patients to treatment randomized?
(b) Were all patients who entered the trial properly accounted for and attributed at its conclusion?
   (i) Was follow-up complete?
   (ii) Were patients analyzed in the groups to which they were randomized?

Secondary criteria
(a) Were patients, their clinicians, and study personnel “blind” to treatment?
(b) Were the groups similar at the start of the trial?
(c) Aside from the experimental intervention, were the groups treated equally?