Radiol Oncol 2008; 42(1): 23-31. *doi:10.2478/v10019-007-0035-4*

review

Malignant spinal cord compression

Mirjana Rajer and Vilijem Kovač

Department of Radiotherapy, Institute of Oncology Ljubljana, Ljubljana, Slovenia

Background. *Malignant spinal cord compression (MSCC) is a common and debilitating neurological complication of cancer. Because of the rapid progression of the neurological dysfunction, it is considered a medical emergency that demands a prompt diagnosis and treatment. Almost all of the MSCC are caused by an epidural compression from a tumour or a bony fragment from the collapsed vertebra affected by the metastasis. The most common of the tumours that metastasize to the spinal cord are breast and lung cancer, followed by lymphoma, myeloma, prostate cancer and sarcoma.*

Conclusions. *The most common symptom of MSCC is pain, followed by muscular weakness and autonomic dysfunction. MRI provides the best information regarding MSCC, so all patients should have a MRI as soon as possible. If the MRI is contraindicated, patients should have the CT scan done. All patients with newly diagnosed MSCC should receive corticosteroids immediately, even before the definitive diagnosis is made. Other treatment options are surgery with postoperative radiotherapy, radiotherapy only, specific medical therapies according to the tumour type and symptomatic therapy, (mainly opiates). The decision of treatment modalities should be made according to the NOMS (neurological, oncological, mechanical and systemic) principles. In spite of the advances, the treatment is still palliative and many patients with MSCC have a poor prognosis and a short survival.*

Key words: spinal cord; compression; surgery; radiotherapy

Introduction

Malignant spinal cord compression (MSCC) is a serious event that has a major impact on patient's life quality. It occurs in 5-14% of all cancer patients and is the second most common neurological complication of cancer after brain metastasis.[1] The consequences of MSCC can be devastating, leaving the patient with pain, paralysis and incontinence. Most of the affected patients have an advanced cancer with limited survival. Even though it is estimated that up to one third will survive at least a year after MSCC, it is considered a medical emergency that requires immediate diagnostics and treatment.[2]

Received 28 December 2007
Accepted 7 January 2008

Correspondence to: Mirjana Rajer, MD, Department of Radiotherapy, Institute of Oncology Ljubljana, Zaloška 2, 1000 Ljubljana, Slovenia; Phone: + 386 41 26 99 46; Fax: +386 1 5879 400; E-mail: mrajer@onko-i.si

Epidemiology

Spine is the most common site of osseous metastases. It is involved in up to 40% of all cancer patients.[3] More or less every type of cancer can cause MSCC, the most common are breast cancer causing 29% of

MSCC and lung cancer with 17%, followed by lymphoma, myeloma, prostate cancer and sarcoma.[1,2,4] This statistics reflects the high incidence of these tumours.[2] Thoracic spine is affected in more than 70% of cases, followed by lumbosacral in 20% and cervical in 10% of cases. The statistics refers to the number (and consequent share) of the vertebrae in the different segments.[1] Around 20% of cancer patients with metastatic disease to the spine will experience MSCC.[4]

Patophysiology

Almost all MSCC (98%) are caused by an epidural compression.[1] It can develop in one of the following ways:[2]

1. Vertebral bone metastasis grows into the epidural space and compresses the spinal cord.
2. Para spinal mass grows through the neural foramina.
3. Metastasis in the vertebral body causes its collapse and bone fragments are displaced in the epidural space.

All mechanisms cause venous plexus compression, which leads to oedema of the spinal cord. Oedema and high vascular permeability cause increased pressure to the small arterioles which results in diminished blood flow causing ischemia of the white matter and, if this continues long enough, cord damage.[2] If the time of the compression is short, the effects are reversible. This is supposed to be the explanation for better treatment results of direct decompressive surgery compared to radiotherapy, which produces results only after several days.[5]

Most commonly the vertebral body is affected, which results in the anterior compression of the spinal cord (85-90%). Para vertebral masses growing trough foramina are less frequent (10-15%) and often caused by lymphoma, neuroblastoma and sarcoma. In these cases, bone is intact and plain radiography is not useful for the diagnostics.[1]

Other mechanisms that include intradural, intramedullary or leptomeningeal metastases are much less frequent, accounting only for about 2% of MSCC.[1]

Symptoms and signs

Most of the patients with MSCC experience one or more of the following symptoms: pain (88-96% of patients), motor weakness (76-78%), autonomic dysfunction (40-64%) and sensory loss 51-80%.[2,4] Some patients (8-37%) with MSCC also have asymptomatic involvement of other vertebral bodies.[1]

Pain

Every cancer patient with new back pain should be investigated for MSCC.[6] The reason for this sweeping approach is that progressive pain is the initial symptom in 96% of patients and it can be present weeks or even months before the development of the true MSCC.[4]

Pain is located at the level of compression and can be present with or without the radicular component. Backache can be elicited or worsened by a movement, vertebral compression, *valsalva* manoeuvre or the percussion of vertebral bodies.[1,6] It can be similar to pain of the degenerative disease of the spine. The difference between these two pains is that pain from MSCC can not be relieved by rest; actually with lying down it worsens. Occasionally Lhermitte's sign is positive (electric shock like sensation elicited in the spinal column and the limbs by neck flexion).[1]

Some authors differentiate between biologic "tumour related" pain and mechanical pain. Biologic pain is worse at night and early

in the morning and resolves during the day. It reflects the diurnal variation of endogen steroid secretion which is smaller at night. Patients experience flairs of pain because of the inflammatory mediators expressed by the tumour. It's an early symptom of the bone involvement without the involvement of the epidural space and is responsive to steroids and radiation. Mechanical instability pain differs from biological pain. It is rare and it worsens with movement. It is not so well respondent to steroids and irradiation. The radicular pain, that is mechanical instability pain in its nature, reflects the involvement of the epidural space and demands immediate diagnostic procedures. Most of the patients complain of biological pain but it may progress to mechanical one.[7]

Neurologic impairment

The second most common symptom is motor weakness. It develops in 80% of patients with MSCC. It usually involves the lower limbs (thoracic spine involvement) and causes difficulties with walking. Weakness can progress to paresis or to paraplegia. Gait disorders can also be seen with sensory ataxia as a symptom of posterior column compression. This sign can be misinterpreted as a polineuropathy due to the drug toxicity or as a part of the paraneoplastic syndrome.[1]

Sensory disturbances are present in half of the patients. They can have an ascending natural history beginning in the toes and progressing to the upper part as stocking-like sensations.[1,6]

Sympathetic involvement with loss of bowel and bladder function (incontinence, impotence and or retence) frequently appears very late in the course of the disease with the exception of *conus medullaris* involvement. It is present in 60% of MSCC patients and it is associated with a very poor prognosis. Bowel and bladder loss is related with perineal numbness. In the absence of numbness one should think of other causes such as narcotics.[1,6,7]

Intramedullary spinal cord metastases (ISCM)

ICSM is a very rare condition and accounts for only 1% of all spinal cord compressions. The most common cause is lung cancer followed by breast cancer. Back pain is less common as in epidural (ESCS) spinal cord compression (only in 38% *vs.* 90%). Other symptoms of ISCM are sensory deficits in 79% of cases, sphincter dysfunction in 60% and weakness in 91% of cases. The difference between ESCS and ISCM is also the incidence of brain metastases, which is very high in ISCM. It is estimated that 41% of ISCM patients have synchronous brain metastases. MRI of the whole spine and brain is the standard diagnostic procedure and therapy consists of corticosteroids in combination with irradiation without the surgical procedure.[2,4]

Diagnostic

Even if plain radiographs, bone scans and CT have some importance in diagnosis of MSCC, the best diagnostic modality is magnetic resonance (MRI). It provides to the clinician the best information on the three dimensional extension of the tumour and is an essential tool for planning the treatment (Figures 1a, 1b). MRI with and without the contrast should be performed in every patient where MSCC is suspected, because patients can have the synchronous MSCC in different spinal segments. Spinal cord compression is graded using T2-weighted MRI images (Table 1).[1-8]

Grades 2 and 3 are considered a high grade epidural spinal cord compression.

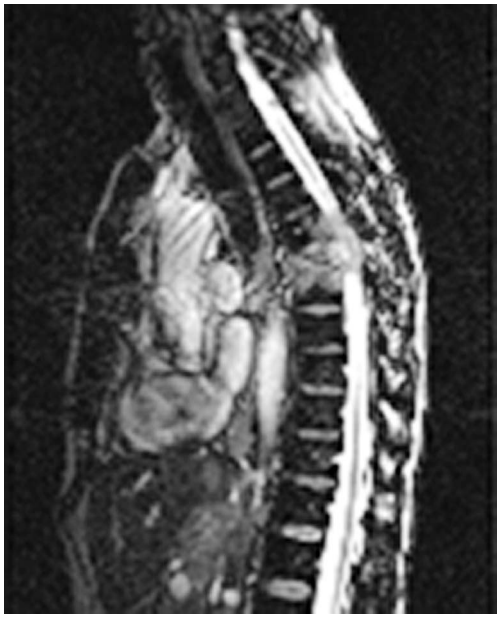

Figure 1a. MRI of patients with multiple vertebral metastases, which caused spinal cord compression.

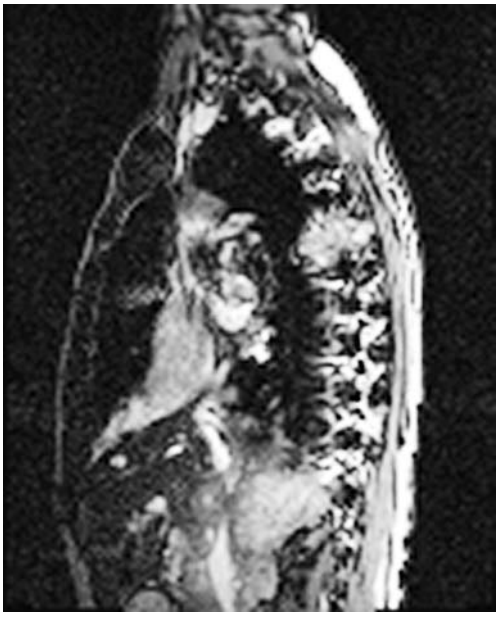

Figure 1b. MRI of patient with multiple vertebral metastases, which caused spinal cord compression.

Patients, who have contraindications for the MR, should be investigated with CT.[1-8]

Treatment

Despite advances in the treatment of cancer patients, the current treatment of MSCC is still palliative.[9] The principal treatment options are corticosteroids, surgery and radiotherapy in different combinations. The goals of such procedures are: improvement or preservation of neurological function and spinal cord stability, local tumour control and pain relief.[7,9] The treatment (irrespective of the type) should be administered immediately after the diagnosis, since it has been proven that the delay in treatment of only a few hours can cause permanent neurological impairment.[6]

Pharmacological approach

Patients with MSCC having neurological symptoms should receive a bolus of dexamethasone 10-20 mg intravenously, followed by 4-8 mg every six to eight hours.[6,8] Dexamethasone should be administered immediately, before any diagnostic or therapeutic procedures are started.[4,6,8]

High dose corticosteroids reduce the oedema by their anti-inflammatory func-

Table 1. Grading score of MSCC

Score number	Description
0	Involvement of the vertebral body without epidural space
1	Subarachnoid space impingement with no spinal cord deformation
2	Obliterated subarachnoid space and spinal cord deformation
3	Spinal cord deformation with no cerebrospinal seen

tion and they serve as an effective bridge to definitive treatment. Although there is a well known effectiveness of steroids, there is only one prospective randomized study that demonstrated it (and several retrospective). Sorensen *et al.* confirmed the superiority of steroids by comparing the results of treatment in patients who received 96 mg of bolus plus 96 mg in the first three days of treatment versus patients who did not receive steroids during the treatment. Three months and six months ambulatory status were better in the steroid group (81% *vs* 63% and 59% *vs* 33%).[10]

The question of the appropriate dosage of corticosteroids has arisen in the last years. Vecht *et al.* reported a study which compared the results of 10 mg versus 100 mg of loading dose plus 16 mg of maintenance dose. There were no differences in ambulatory status, pain reduction or bladder function in the two groups. The conclusion was that the use of a high dose of dexammethasone does not have significant benefits over lower doses, but leads to more serious side effects. That is why at the moment high doses are not recommended.[11]

Patients can be switched to oral steroids after 24-48 hours because corticosteroids have good oral bioavailability.[2] Patients on steroids should be monitored carefully for hyperglycemia, hypertension and electrolyte disorders. All patients should receive H2 blockers for gastric protection. Steroids must be tapered gradually.[4,8]

Surgical approach

First reports of treatment are from a hundred years ago, when Elsberg reported the first therapeutic recommendations regarding MSCC. The only therapeutic goal at that time was pain relief. This was due to the fact that therapeutic procedures for the underlying cancer were modest and because of the lack of appropriate diagnostic and therapeutic procedures. He recommended three interventions: surgical section of the affected nerve root, surgical section of the spinothalamic tracts or immobilization with a plaster.[12]

With the development of myelography and with better understanding of MSCC patophysiology in the 1970s, surgeons developed laminectomy for the decompression of the spinal cord. At that time the standard procedure was urgent laminectomy followed by postoperative RT. In the late 70s some studies were carried, which demonstrated that laminectomy combined with postoperative radiotherapy was not superior to the radiotherapy without surgical procedures. Consequently, surgery was abandoned for a long period.[5]

Today some authors think that laminectomy is not a good surgical option because most spinal metastases are located in the vertebral body anterior to the spinal cord. Laminectomy removes posterior elements of the spine while not removing the tumour. Furthermore, it can cause additional spine instability, because posterior elements, which are not affected by the tumour, are removed.[5]

New imaging modalities (MR, CT) that were developed, provided three-dimensional information about spinal cord compression. It became clear that most of the MSCC are caused by anterior compression of the spine because epidural tumour most often begins in the vertebral body. This information led the surgeons to develop new techniques. They developed the so called "anterior approach" in the 1980. The intention of this procedure is to remove the tumour and accomplish direct decompression of the spine and if needed at the same time to stabilize the spine with immediate spine reconstruction.[5]

In spite of the development of new techniques there were no, until recently, published randomized trials demonstrating

the superiority of surgery alone to another treatment.[5,12]

In the 2005 Patchell *et al* published a randomized trial. They compared radiotherapy and direct decompressive surgery plus postoperative radiotherapy. The study included patients with high grade epidural compression from a radioresistant tumour (confirmed with MRI as a true displacement of the spinal cord) and at least one of the neurological symptoms including pain. Another condition was that the patients should not have had total paraplegia for more than 48 hours before study entry. Compression could only be in one area and tumours of the cauda or spinal roots were excluded. Patients with other neurological impairments (including brain metastases) were also excluded. Other restrictions were: no previous irradiation to the spine and life expectancy of at least three months. Patients were randomized to two treatment groups. One group received surgery (the type of surgery was planned for each patient individually according to the type, extension of the tumour and spinal stability) and postoperative radiotherapy, and the other radiotherapy only. Radiation regimens were the same (10 x 3 Gy) in both groups. The primary study end point was the ability to walk after the treatment. Significantly more patients in the surgery group were able to work than in the radiotherapy group (84% *vs* 57%, p=0.01). Operated patients were able to walk for a longer time (median 122 days, vs. 13 days, p=0.003), and significantly more hospital patients (before treatment) regained the ability to walk (62% vs 19%, p=0.01). The conclusion was that direct decompressive surgery plus postoperative radiotherapy is superior to radiotherapy in the treatment of MSCC.[5]

Bilski reported that the surgical treatment also resulted in the prolonged survival. This is supposed to happen because operated patients remain ambulatory for a longer time and have less infections, thrombosis and other problems causing death in paraplegic patients. Patients treated with surgery also need less corticosteroids and analgesics.[7]

Some authors point out that the study of Patchell did not include patients with radiosensitive tumours, with total paraplegia of more than 48 hour of duration, with multiple areas of spinal cord compression and a large group of patients with only back pain and no neurological impairment who do benefit with radiotherapy. The role of surgery in these patients has not been established yet. A number of patients have radiosensitive tumours with or without spinal cord compression or radioresistant tumours without spinal cord compression. Radiosensitive tumours such as lymphoma, myeloma or breast cancer respond quickly to radiotherapy. They can be safely treated with irradiation because tumour will experience apoptosis soon enough resulting in an early decompression of the cord. The indication for operation in these patients is either progression during radiotherapy (which occurs rarely), prior irradiation of affected segment or spine instability.[7,12]

The goal in the future is to minimize the need for major operations. This can be achieved with the development of medical and radiotherapeutic treatments and with the evolving use of minimally invasive surgical procedures.[12]

Radiotherapeutical approach

Radiotherapy (RT) either with or without surgery is the most common treatment modality. The goals of administrating RT to the patients with MSCC are to reverse neurological impairment or at least to prevent further loss of motor function.[13]

Treatment planning begins with the information gained by MRI. Treatment fields are dependent on the site of the involved cord. Cervical spine is usually treated with

opposite lateral fields to avoid the oral cavity, thoracic spine with posterior field alone, and lumbar spine with the two opposite fields – one anterior and other posterior, and if needed, some alternative field positioning can be used.[4]

The standard radiotherapy regimen is 30 Gy in 10 fractions in two weeks. In spite of the effectiveness of this dose and fractionation, 10-27% of patients have a worse motor function after RT and the question of whether there is a benefit in administering a higher dose of radiation has consequently arisen.[13,14]

Rades *et al* compared the treatment results in patients receiving 30 Gy (10 x 3 Gy) compared to those receiving 37.5-40 Gy (15 x 2.5 Gy or 20 x 2 Gy). The escalation of the dose has not shown any benefit in motor function improvement, local control and survival, but did prolong the overall treatment time and the number of the visits to the RT department, which is a heavy burden for the frail and debilitated patients with MSCC. At the present time the escalation of the dose beyond 10 x 3 Gy is thus not recommended.[13,14]

Another dilemma regarding RT is if the same treatment results can be achieved with a lesser dose or less fractions. The questions arose because patients with MSCC are incapacitated and transport to the radiotherapy department and positioning for treatment causes them a major discomfort.

Different studies compared a standard radiotherapy regimen (10 x 3 Gy) with shorter courses (5 x 4 Gy, 1 x 8 Gy). The functional outcome was similar between different courses, but local control was worse in the "shorter" group. Patients who had a long-term survival needed more re-irradiations. Presently, 1 x 8 Gy is recommended for patients with a very bad prognosis and short survival where there would not be enough time to develop the relapse and other "late" consequences of such treatment.[14] However, some authors disagree with the use of this fractionation and propose 10 x 3 Gy as the best regimen. This is because they are being very cautious about late effects which are not presently known and progression after such treatment. Another argument is that the prediction of duration of life for patients can be quite misleading. Patients usually live longer that the doctors predict they would.[14,15]

Recurrence

Patients that live long enough have a high chance of having a local relapse. Progression leads to a greater need of pain medications, and more devastating events such as paraplegia and loss of the motor function.[2] In some reports as much as 69% of patients relapsed in the first and 94% 4 years after the first diagnosis of MSCC. Pain is the first symptom of recurrence and every new back pain should raise the suspicion. Recurrences are treated with re-operation or radiotherapy whenever possible.[7]

Decision on type of treatment

How to decide which patient should receive which treatment? The decision should be based on the fact that patients with MSCC have a metastatic disease with a poor prognosis, so treatment should be directed toward optimal palliation and minimal side effects.[16,17]

One of the decision making methods is NOMS and it has been developed at the Memorial Sloan-Kettering Cancer Center:[7,17]

1. N - Neurological (the degree of myelophaty, the degree of radiculopathy, the degree of radiologic spinal cord compression)
2. O - Oncological (the known radiosensibility of the tumour)

3. M - Mechanical instability (movement related pain)
4. S - Systemic disease (the extent of the disease, comorbidities and patient status)

Ad 1, 2. Neurological and oncological

The current treatment recommendations, using the NOMS system are:[7,17]

a. Patients with grade 0 or 1 (Table 1) of compression from a radioresistant tumour can be treated with radiotherapy only.
b. Patients with grade 2 or 3 of compression from a radioresistant tumour should be treated with surgery and radiotherapy.
c. Patients with radiosensitive tumours regardless of the degree of compression should be treated with radiotherapy only.

Ad 3. Mechanical instability

Mechanical instability is independently assessed. Instability pain is a movement related pain and differs depending on the level of the spinal cord affected. All patients with mechanical instability should be examined by a surgeon and, if medically suitable, should be operated independently of the N and O.[7,17]

Ad 4. Sistemic disease

If a patient has a high probability of dying from the procedure based on medical issues or would not derive benefit from the operation because related comorbidities would not allow for good rehabilitation, surgery is not offered. The decision to operate should be made on a multidisciplinary basis (surgeon, internist, medical and radiation oncologist).[7,17]

Some authors do not use the NOMS systems, but propose simpler rules instead:

– Surgery is indicated for patients that have a good performance status, expected survival of more than three months and involvement of only one spinal segment.[13-15]
– In the study of Jansson and coworkers the most important surgical indication was neurological impairment due to MSCC and not pain like in other studies.[17]
– The recommendations are that all the patients with MSCC should be evaluated by a surgeon and if the process is operable, patients should undergo surgical decompression, with or without stabilization and postoperative irradiation. Even for radiosensitive tumours surgery can often stabilize the spine. For patients with inoperable tumours definitive radiotherapy still remains the standard of care.[2]
– Because the indication for surgery of MSCC is usually limited to patients with involvement of one spinal segment who have a good performance status and expected survival of more than three months, RT alone is still an important modality in the treatment.[18]

Factors predicting survival

Most patients with MSCC have a bad prognosis, living only a few months after the diagnosis. Different survival rates have been reported in studies. One year survival rates range from 26 to 75%. This reflects the different criteria in selecting patients entering the study.[17]

Patients, who have visceral metastases, have shorter survival compared to those without (one year survival 8% *vs.* 65%; $p=0.01$).[1,18] Ambulatory patients survive longer than non-ambulatory (one year survival of 56% *vs.* 21%; $p<0.01$). A negative prognostic factor is also a short time between tumour diagnosis and development of MSCC. Patients with an interval of less than 15 months have a one year survival rate of 29%, compared to 59% of those with longer intervals ($p<0.01$). This reflects the faster growth of more aggressive tumours

and also explains the rapidity of development of motor dysfunction before the start of the treatment. Faster progression is associated with a worse prognosis (27% *vs.* 64%; p<0.01). Another important prognostic factor is the type of primary tumour. Lung cancer patients have the worst survival with the median survival time of 1 month, compared to breast with 2.5 months and prostate with 4 months.[19,20]

The post-treatment ambulatory status also has an impact on the survival. More mobile patients develop less potentially fatal complications like thrombosis or pneumonia and this is the reason why they survive longer.[17]

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