Spinal Extradural Metastasis: Review of Current Treatment Options

Ronald H. M. A. Bartels, MD, PhD; Yvette M. van der Linden, MD, PhD; Winette T. A. van der Graaf, MD, PhD

ABSTRACT Bone metastases, especially to the spine, are frequently encountered during the course of a malignancy. Due to a worldwide increase of cancer incidence and to a longer life expectancy of patients with cancer, a rise in incidence of bone metastases is observed. A brief historical overview is the base of a review of current treatment options. Despite new developments in the surgical and radiotherapeutic fields, as well as in medical oncology, external beam radiotherapy is the cornerstone of the treatment of spinal metastases. In selected cases, surgical treatment is a proven option. Vertebroplasty or kyphoplasty can also be considered. Supportive medical care does not differ from that given for symptomatic lesions to the skeletal system elsewhere in the body. After discussing the treatment options, an algorithm is given.

INTRODUCTION The occurrence of spinal metastases in patients with advanced cancer can cause significant morbidity, with pain and/or neurological deficit adversely affecting the patients’ quality of life. Spinal metastases can be classified according to their anatomic location: intradural (intramedullary or extramedullary) or extradural. The extradural lesions account for up to 95% of spinal lesions and can also be divided into pure epidural lesions and those originating from the vertebra and subsequently impinging on the thecal sac. Pure epidural metastases are rare. Because of their more frequent prevalence, we will focus on extradural spinal metastases originating from the vertebra. In this review, an overview of current treatment options for spinal extradural metastases is given. Finally, an algorithm for the treatment of spinal extradural metastases is proposed for use in daily practice.

Epidemiology After the lungs and the liver, the skeletal system, of which the spine is a part, is the third most often involved system by metastases. Due to a worldwide increase of cancer incidence and to a longer life expectancy of patients with cancer, a rise in incidence of bone metastases is observed. Depending on their localization, bone metastases can have debilitating consequences. In this respect, spinal metastases are well known for potential serious consequences for daily life.

Spinal metastases occur in all age groups, with the highest incidence between age 40 and 65 years. The location of predilection is the thoracic spine (60% to 80%), followed by the lumbar spine (15% to 30%), and finally the cervical spine (less than 10%). Bone metastases, especially those of the spine, are most frequently observed in patients with cancer of the lung, prostate, breast, and hemopoetic organs. Other malignant tumors, such as those of the gastrointestinal tract, rarely produce bone metastases. Although 30% to 70% of the patients who die of cancer have spinal metastases at postmortem examination, about 14% will have symptomatic lesions during their illness. The majority of patients with symptomatic spinal metastases receive palliative radiotherapy, and it is estimated that less than 10% of the patients will undergo surgical treatment.

Clinical Presentation, Radiological Imaging, and Clinical Monitoring of Treatment The clinical and radiological presentation of spinal extradural metastases has been clearly reported elsewhere. In short, the major presenting symptoms are local or radicular pain with or without motor weakness, sensory loss, and
loss of sphincter control. Although some authors advocate that pain is the starting symptom and is consequently followed by neurological symptoms, only 3% of 342 patients with spinal metastases who were irradiated within a randomized prospective trial for pain progressed to a spinal cord compression. If a cancer patient presents with pain or neurological symptoms, a magnetic resonance imaging (MRI) scan should be made to detect the presence, number, and extent of the lesions in order to start the most appropriate treatment. An additional bone scintigram for detection of other metastases is necessary in tumors that are sensitive for this radiological modality. The predictive value of plain radiographs is regarded to be insufficient to warrant their routine use.

In order to monitor response to treatment objectively, we recommended use of practical numerical or visual rating scales. For pain, an 11-point pain scale ranging from 0 (no pain) to 10 (worst imaginable pain) like the Brief Pain Inventory is suggested. For neurological symptoms, the Frankel scale is most practical in routine use.

**Historical Aspects of the Treatment of Spinal Metastases**

Surgical treatment of spinal metastases was already advocated in the early 1900s. Its effect on pain was especially emphasized, but the positive effect of surgery on a neurologic deficit was also known. The treatment consisted of decompressive laminectomy, removal of accessible tumor, and, in some cases, division of the posterior roots. However, already in those days, it was clearly stated that surgery did not have any effect on survival. In this respect, it should be remembered, however, that metastasis of the spine is most often located within the vertebral body, and the anterior column at the affected level is weakened. A dorsal approach will compromise the stability of the spinal column by destruction of the middle and posterior column. This may contribute to more pain and neurologic deficit.

Soon after the discovery of x-rays, their analgesic effect on painful bone metastases was recognized. From that time on, surgery and external beam radiation therapy were the keystones of the treatment of spinal metastases. In 1953, the first patient was treated with a linear accelerator. This introduced a widespread use of radiotherapy with more precise radiation dose delivery and fewer treatment-related side effects.

Several retrospective studies comparing decompressive laminectomy with radiotherapy with radiotherapy alone have been reported. Although a difference in results could not be established, the patients treated with surgery harbored significantly more complications. Therefore, most authors concluded that radiotherapy was the treatment of choice for the majority of patients with spinal metastases. The only candidates for surgery were patients in whom a histological diagnosis was needed or the neurological deficit progressed during radiotherapy. It was clearly stated that in cases of spinal instability or direct compression of neural tissue because of a pathological fracture, radiotherapy cannot be expected to have any effect. In these cases, radiotherapy had to follow surgical decompression and fusion, if feasible. In 1980, a small, randomized controlled study of only 29 patients comparing radiotherapy alone with laminectomy followed by radiotherapy showed the equivalence of both treatments with regard to pain relief, improved ambulation, and sphincter function.

Since the 1980s, with the advent of spinal implants such as pedicle screws and hooks, rods and plates, and cages, constructs preventing instability of the spinal column have been possible. For radiotherapy, recent developments such as intensity-modulated radiation therapy (IMRT), stereotactic radiosurgery, and stereotactic radiotherapy yield promising results toward more precise dose delivery, fewer side effects for adjacent normal tissues, and the possibility of reirradiation in already pretreated patients. These improvements introduced a new era in the treatment of spinal metastases.

**CURRENT TREATMENT OPTIONS**

**Biopsy**

The histology of a tumor should be known in order to predict the likely response to nonsurgical treatments. If the patient is recently diagnosed with primary cancer, the histology of the
spinal metastasis is assumed to be the same. However, when the spinal metastasis is the first presentation of a malignancy and a survey for a primary lesion fails, a biopsy is warranted.\textsuperscript{30,31} In approximately 20% of patients, the first presentation of a malignancy is a spinal problem.\textsuperscript{13} The only indication for a biopsy from the extradural tumor mass in patients with a known primary tumor is to confirm prior histology from cancer, especially in patients with a long interval between primary tumor and this new suspected metastatic lesion, in patients with double or triple tumors, or in patients for whom no other representative tumor tissue is available to do a biological marker status with therapeutic relevance. This might be the determination of the estrogen, progesterone, or HER2/neu receptor.

A thorough prebiopsy workup is essential since it narrows the differential diagnosis, helps to define the extent of the tumor, and provides confidence in the frozen-section analysis. It may help to distinguish between a metabolic, infectious, or a neoplastic process.\textsuperscript{1,32,33} A poorly planned biopsy can result in misdiagnosis and complications and adversely limit potential treatment options. The choice of open or closed biopsy techniques depends on the results of the prebiopsy workup. Percutaneous biopsy is an important diagnostic tool with a high success rate.\textsuperscript{1,32,33}

**Estimated Life Expectancy**

In general, survival in patients with bone metastases is highly dependent on their primary tumor. In a large randomized trial with 1,157 patients treated with radiotherapy for pain, patients with breast cancer had a median overall survival of 16 months (95% confidence interval [CI], 14.2 to 18.5 months), followed by patients with prostate cancer, who had a median overall survival of 9.5 months (95% CI, 7.8 to 11 months). Patients with lung cancer suffered the worst median overall survival, with only 3.2 months (95% CI, 2.8 to 3.5 months).\textsuperscript{34}

One criterion to consider a patient eligible for surgery is an expected survival of at least 3 months.\textsuperscript{35–39} For radiotherapy, a minimum life expectancy of at least a month is considered appropriate since most beneficial effects are expected to occur after 3 to 4 weeks.\textsuperscript{40,41} The estimation of life expectancy is difficult, warranting a multidisciplinary approach. However, even the judgment of experienced specialists seems to be inaccurate.\textsuperscript{42–44} Therefore, schemes have been developed to categorize whether a patient is a surgical candidate.\textsuperscript{45–47} A model has also been developed to predict the survival of the patient with spinal extradural metastasis.\textsuperscript{48}

The scoring scheme by van der Linden et al was based on a large randomized study of radiotherapy for painful bone metastases from cancers other than renal cell carcinoma, melanoma, or multiple myeloma. Furthermore, patients with neurological impairment, a pathological fracture, or a cervical spine location of the metastasis were also excluded.\textsuperscript{47} Although the system was successfully externally validated,\textsuperscript{49} surgical candidates often suffer from cancer with one of the excluded features. Therefore, this score is not applicable in their situation. The schemes by Tomita and Tokuhashi were originally developed to select the most suitable candidates for surgical treatment. However, they were retrospectively developed on small samples of patients with diverse tumor histology. As a result, the standard deviation is large and accuracy is limited. After revision of the system by Tokuhashi,\textsuperscript{50} the prediction of survival improved, but patients had to live for at least 6 months to be included. Finally, neither system has been externally validated, and both were mainly tested in the Japanese population. Based on the retrospective data of 219 patients with spinal metastases that were treated radiotherapeutically between 1998 and 2003, Bartels et al developed a model to predict the survival of patients with spinal metastases. Whereas the other systems need a more or less extensive search to find other visceral and/or bone metastases, this model is simple. Only 5 parameters are assessed: gender, location of the primary tumor, curative intention of treatment of the primary tumor, cervical location of the spinal metastasis, and Karnofsky’s Performance Score. Within the office, an estimated survival curve of the patient can be presented. The wide CIs, particularly with poorer prognoses, require great caution in interpreting these results. An international external validity study has been designed, and the results will be presented separately in the near future.\textsuperscript{48}
Radiotherapy

Despite new developments in surgery and medical oncology, radiotherapy remains the cornerstone in the treatment of spinal metastatic disease. Radiotherapeutic options are conventional external beam radiotherapy (using a single posterior or a 2 parallel opposed-field technique) and more advanced techniques, such as IMRT (using multiple beams with varying beam intensity aimed at a tumor from many angles), stereotactic radiosurgery (single-fraction treatment), and stereotactic radiotherapy (fractionated treatment). Another treatment option is the systemic application of radioisotopes.

The effectiveness of radiotherapy for pain and/or neurological symptoms depends on the sensitivity of tumor cells to ionizing radiation. In general, primary tumors that are very sensitive are lymphomas, myeloma, and seminomatosus germ-cell tumors. Most solid tumors, such as breast cancer, prostate cancer, and lung cancer, are considered to have intermediate radiosensitivity. Melanomas, osteosarcomas, and renal cell carcinomas are usually considered to be radioresistant.51

In the following section and in analogy to the radiotherapeutic literature, the effectiveness of radiotherapy will be discussed for pain and for neurological deficit separately, although overlap in complaints is possible. Finally, the more advanced radiation techniques and treatment with radioisotopes are mentioned.

External Beam Radiotherapy: Pain

For patients presenting with painful metastases without neurologic deficit to the bone, single-fraction radiotherapy is considered a valuable treatment. A single dose of 8 Gy has gained widespread acceptance, with response rates for pain of 60%.52–54 For painful spinal metastases specifically, response percentages of 73% were reported in 342 patients who were treated within a randomized trial comparing single fraction of 8 Gy versus 24 Gy in 6 fractions.47 If the diagnostic radiological investigations show extensive bone destruction, more irradiation (>25 Gy) is usually applied to induce remineralization and, hence, strengthening of the involved bone.55,56

Treatment is generally given in an outpatient setting. Therefore, from a palliative point of view, for patients with painful spinal metastases, single-fraction radiotherapy reduces the number of painful and tiring visits to the hospital. Even patients with a disseminated breast cancer or prostate cancer who have favorable prognoses (expected survival >1 year) benefit from single-fraction radiotherapy for pain.34 Several studies reported more reirradiation after single-fraction radiotherapy when compared with multiple fractions (ie, 24 Gy in 6 fractions or 30 Gy in 10 fractions). In 2002, a Cochrane study was published reviewing short- versus long-course radiotherapy for bone metastases. In 3 studies, 2,206 patients were randomized, of which 739 patients had spinal metastases. In this subgroup, the overall conclusions did not alter: single-fraction was as effective as multifraction radiation therapy in relieving pain. These findings were confirmed by other meta-analyses in 2003 and 2007.52,54 However, all studies reported that more retreatments were given after single-fraction radiotherapy than multifraction radiotherapy. This higher retreatment regimen seems to reflect more the uncertainty of both radiation oncologist and patient on the effect of such a “simple” treatment than its true ineffectiveness since patients who were treated by a single fraction were retreated with lower pain scores.50,57 An ongoing prospectively randomized trial is currently studying the effectiveness of retreatment after single- and multiple-fraction radiotherapy using different treatment schedules.58,59

If a patient suffers from neuropathic pain (ie, presence of a radiating cutaneous component in the distribution of one or more spinal nerves or peripheral nerves), a single fraction of 8 Gy improves a 4-grade pain scale by at least one grade in 53% of the patients.60 The study on which this result was based concluded that single-fraction radiotherapy was “not as good, but neither worse” than multifraction radiotherapy. Overall response rate and time to failure following a single dose were somewhat poorer, although the differences were not statistically significant. The authors recommend a single fraction for significant subsets of patients, such as those with a short expected survival.60
External Beam Radiotherapy: Neurologic Deficit

In a recent overview, the effect on functional status after short- and long-course radiotherapy for spinal metastases was presented. A short-course regimen is defined as a single fraction of 8 Gy or any other scheme that needs about 1 week to complete the treatment. In the case of a long-course treatment, the patient is exposed to a minimum dose of 30 Gy in fractionated doses. Reviewing recent prospective, randomized, retrospective studies showed that short- and long-course treatments resulted in the same functional outcome. An exception was the treatment of myeloma patients. Functionally, they fared better with long-course radiotherapy. At 12 months, 76% of the patients with myeloma who underwent a long-course schedule noticed an improvement in motor function, whereas 40% of those that underwent short-term radiotherapy improved in motor function (P = .003). Ambulatory function was not studied separately. The only randomized study that was discussed in the overview reported no differences in the ability to walk (68.3% versus 70.8%). Neither differed regarding the outcome of good bladder function (90.1% versus 88.7%).

Local control of neurological deficit is another major goal of the treatment. Recurrences within the radiotherapeutically treated field occurred significantly more with short-course radiotherapy than with long-course radiotherapy (at 1 year, 18% versus 5%, P < .001). Especially in patients with tumors with a relatively good survival prognosis, such as carcinoma of the breast or prostate, a long-course schedule gave a significantly better local control at 1 year. If necessary, spinal reirradiation can be safely performed if the patient suffers from recurring pain or neurological symptoms. Based on the last study, short-course radiotherapy was recommended for all patients with spinal metastases, except for those with myeloma, breast carcinoma, or prostate cancer with an expected longer survival (ie, more than 1 year).

Overall, several prognostic factors were identified that predict functional outcome after radiotherapy, such as favorable histology, longer interval between tumor diagnosis and spinal cord compression (>24 months), involvement of 1 to 2 vertebrae, slow development of motor deficits (>14 days), being ambulatory before radiotherapy, and good performance status.

IMRT, Stereotactic Radiosurgery, and Stereotactic Radiotherapy

Recent retrospective publications have reported on the effectiveness of newer, sophisticated radiation techniques in spinal metastases, with about 85% relief of pain using IMRT, stereotactic radiosurgery, or stereotactic radiotherapy. These techniques make it possible to deliver higher radiation doses safely; however, they require a high standard of precision in targeting the beam to the tumor shape and exact location. Therefore, these techniques are highly time-consuming and costly when compared with conventional radiotherapy. The most important additive value of implementing these techniques at a wider scale is that they make it possible to irradiate the spine without treating the spinal cord, which is often the major limiting factor for high-dose radiation because of its intrinsic radiosensitivity. After maximum spinal radiation tolerance has been reached, complications such as radiation-induced spinal cord injury may occur. These advanced techniques provide the possibility to reirradiate in already heavily pretreated patients. In addition, smaller radiation-field sizes can be applied without the necessity of including elective adjacent vertebrae.

In the study by Jin and colleagues, 270 lesions in 196 patients were treated. The preliminary results of 49 patients were reported. The single doses increased with yearly experience from 10 Gy to 16 Gy. The average duration, including setup, position localization and verification, and radiation delivery, was 50 minutes. Although pain relief was achieved in 85% of the patients, functional outcome was not reported. Dose-related spinal cord complications were presented in another publication by the same group. One hundred seventy-seven patients suffered from 230 radiosurgically treated lesions. Up to 3 circumscript lesions (up to 2 adjacent vertebrae) were treated. The median survival was 4.2 months. In this series, patients received a single fraction ranging from 8 to 18 Gy per lesion. Only one instance (0.4%) of a dose-related myelopathy occurred in a patient who received 16 Gy.
In a cohort of 500 histologically proven metastases to the spine in 344 patients, 86% of the patients had a long-term improvement of the pain.\textsuperscript{69} Median follow up was 21 months (range 3 to 53 months). Radiation-induced spinal cord injury did not occur. About 70% of the patients had conventional radiotherapy at the involved level before radiosurgery. Although patients with neurologic deficit were excluded from treatment, as were those with overt spinal instability, in 35 cases, progressive neurologic deficit was reported before the start of the treatment. Of these, 85% experienced some improvement. The average duration of the treatment (including setup, position localization and verification, and radiation delivery) was 90 minutes. In another prospective cohort of 74 patients harboring 102 metastatic lesions, 83.9% of the patients reported relief or improvement of the symptoms (pain and neurologic deficit).\textsuperscript{68} Only patients who did not present with paralysis, spinal instability, or lesions extending more than 2 adjacent vertebral segments were treated radiosurgically. Although not explicitly stated, it can be assumed that these criteria will generally exclude radiosurgical therapy. A detailed analysis was not provided, but 3 patients (4%) were mentioned who developed symptoms due to a radiation-induced myelopathy.

Although not proven in a randomized trial, these studies suggest that IMRT, stereotactic radiosurgery, and stereotactic radiotherapy seem to be effective treatment options for a selection of patients with spinal metastases. The theoretical advances are obvious, and the clinical results are promising, but it should be emphasized that worldwide, external beam radiotherapy is still the gold standard for spinal metastases. Its availability and costs prohibit widespread use of advanced techniques for these palliative indications. Further long-term studies and cost-effectiveness studies are needed before widespread use of advanced-technique treatments can be justified.

\textit{Systemic Radioisotope Therapy}

Intravenously admitted radioisotopes such as Strontium-89 or Rhenium-186 have the potential to treat multiple lesions simultaneously using short-term emitting radionuclides. A characteristic of these radioisotopes is that they have affinity to osteoblastic bone (ie, bone that is under construction). They can have a local antitumor effect, as well as an analgesic effect. A meta-analysis of the literature on treatment with systemic radioisotopes revealed that compared with placebo, after 1 and 6 months, reduction of pain was seen. Generally, it was applied in patients with cancer of the breast or the prostate. Adverse effects such as leucopenia and thrombocytopenia were described, although these were mostly temporary.\textsuperscript{74} Two recent publications confirmed the usefulness of systemic radioisotopes in the treatment of multiple painful bone metastases, as well as the adverse effects, although no specific remarks were made on patients with spinal metastases only.\textsuperscript{75,76}

Based on the potential severe side effects of irreversible bone marrow depression, the use of systematic radioactive isotopes is recommended only in patients with multiple synchronous painful sites and good bone marrow function.\textsuperscript{75} It can also be considered in those patients for whom no other treatment options are available anymore.

\textbf{Surgical Treatment}

In the 1980s, studies reported on surgical decompression of the spinal cord with concomitant stabilization of the spine. Surgery consisted of circumferential decompression. Stabilization of the anterior spinal column was performed by methyl methacrylate interposition with or without support by a system applied by a dorsal surgical approach.\textsuperscript{77,78} Siegal reported patients’ ability to walk postoperatively in 80% of the 47 procedures and postoperative retention of urinary control in 93%. Only 7% had persistent pain. Complication rates were similar to those described for the laminectomy.\textsuperscript{77} Similar results are described by Sundaresan: 78% of 45 patients were postoperatively able to walk and 84% had relief of their pain.\textsuperscript{78} These operative results were superior to the results achieved by radiation alone or in combination with laminectomy.\textsuperscript{78,79}

With the advent of spinal implants such as cages, pedicle screws, and laminar hooks, all composed of better materials than stainless steel (such as titanium), addressing the front of the spinal column became more feasible. This was further encouraged by improved constructions and better material compositions of the implants.
Nowadays, laminectomy is restricted to very rare cases (eg, only involvement of the spinous process or the lamina, or a pure epidural lesion). If surgery is performed, the anterior column is addressed through several surgical approaches. Even a posterior approach does not exclude access to the vertebral bodies and reconstruction of the anterior column (Figures 1 and 2). It should be emphasized that it is not the histology of the tumor that determines the amount of pain or the neurologic deficit, but rather the local spinal pathology.

Major goals of surgery are obtaining tissue in case of an unknown diagnosis; relief of neurologic symptoms by decompression of the neural tissue; and, finally, relief of pain by stabilization and reconstruction of the spinal column. A spinal extradural metastasis presents in about 20% as the initial cancer presentation. Stabilization prevents deformation, which could produce pain and neurologic deficit of the spinal column at the affected level in the future.

The results of more recent surgical series (Table 1) were promising. Reviewing this selection of recent surgical series, recovery of the ambulatory function is impressive, as is the relief of pain. The number of complications is also notable.

The study by Patchell et al presented at the American Society of Clinical Oncology annual meeting in 2003 and published in 2005 caused a major breakthrough in favor of the surgical treatment followed by radiotherapy. The study reported the results of a randomized, multicenter, nonblinded trial in which 101 patients were included. The major goal was to compare the efficacy of surgery followed by radiotherapy with radiotherapy alone. Because of the clear results of an interim analysis, the study was stopped prematurely. Fifty patients were assigned to surgery followed by radiotherapy and 51 to radiotherapy alone. Significantly more patients were able to walk after surgery followed by radiotherapy (84%) than after radiotherapy alone (57%). In addition, maintenance of walking was longer: median 122 days versus 13 days ($P = .03$). The duration of maintenance of walking ability was strongly associated with the pretreatment walking status. None of the nonambulatory patients regained walking ability after radiotherapy alone. In the surgery plus radiotherapy group, patients maintained longer continence for urine, used less daily dexamethasone, and used fewer daily morphine equivalents. All of these results were statistically significant. The 30-day mortality rate

---

**FIGURE 1** Radiological Example of Symptomatic Spinal Metastasis. This 63-year-old woman suffered from an acute-onset paraparesis due to a spinal process at the 12th thoracic vertebral body. She was recently diagnosed with a clear cell carcinoma of the left kidney. At the T2 sagittal preoperative MRI (A), a collapse of the 12th vertebral body was seen, with compression on the spinal cord (arrow). She underwent an emergency decompression and resection of the vertebral body through a posterior lateral approach. The spine was afterward stabilized anteriorly as well as posteriorly. Radiotherapy was instituted postoperatively. The postoperative lateral radiograph (B) of the involved segments depicts the spinal construct consisting of a cage, screws, and rods. The postoperative course was uneventful, and 2 years postoperatively, she was still able to walk.

**FIGURE 2** Illustration Shows that a Spinal Surgeon Dealing with Metastatic Spinal Disease Should Be Able to Approach Every Region Within the Spine from All Sides.
was the same for both groups, as was their length of hospital stay.38

At the same time, a carefully performed meta-analysis of uncontrolled cohort studies by Klimo et al also concluded that surgery should usually be considered as a primary treatment option for patients, followed by radiotherapy.85 They concluded also that the neurological status, overall health, extent of disease (spinal and extraspinal), and primary tumor histology were important risk factors that influence proper treatment selection. For the surgical group, a greater rate of ambulatory function was preserved (1.3 times higher than radiotherapy solely) and regained (2 times higher), as was pain relief (90% versus 70%) and urinary control (66% versus 26%).85

Although the Patchell study clearly demonstrated that the patients presenting with spinal cord compression randomized to the surgical group fared significantly better and for longer than those in the radiotherapy-only group, some points deserve attention. The median survival time is 26 days longer in the surgery group, and this is statistically significant.38,39 Analyses did not include adjustment for confounding variables such as the ability to walk and urinary control or regaining them. People who walk have fewer thromboembolic events and decubital ulcers. Those who retain urinary control have fewer urinary infections. However, assuming a similar impact on quality of life in both groups, one could question whether the statistically significant difference in survival of this magnitude is also clinically significant. This must be discussed by clinical epidemiologists, clinical ethicists, and patients.

Patients with radiosensitive tumors, with neurologic deficit longer than 48 hours, with lumbar lesions or lesions only compressing spinal roots, with multiple spinal lesions, and with previous spinal radiotherapy were excluded. Therefore, any general statements about the optimal treatment of these patients are not justified. Since radiosensitive tumors are excluded, the less favorable outcome of radiotherapy solely is explained.86

The surgical complications were not explicitly discussed. Morbidity was expressed in decline of functional scores of the spinal cord: the Frankel score and the American Spinal Injury Association score. More common surgical complications,

| Author, Year | Huang, 200688 | Hirabayashi, 200281 | Holman, 200582 | Villavicencio, 200583 | North, 200584 |
|--------------|--------------|-------------------|----------------|---------------------|-------------|
| Number of patients (m/f) | 46 (28/18) | 81 (58/23) | 139 (85/54) | 58 (?) | 61 (34/27) |
| Neurological improvement | ?† | 49.4% | 41% | 60% | ? |
| Neurological impairment | 0% | 1.2% | 5% | 3.4% | 8.1% |
| Ambulatory preoperatively | 29.6%‡ | 38.3% | 71.9% | 58.6% | 85% |
| Ambulatory postoperatively | 76.1% | 71.3% | 90.6% | 77.5% | 96.7% |
| Preoperative pain; number (%) | ? | 63 (79%) | 133 (96%) | 53 (92%) | 59 (97%) |
| Postoperative complete or partial relief of pain | ? | 77% | 96% | 92.9% | 56% |
| Complications (major)* | 19.5% (8.7%) | 23.5% (12.3%) | 32.4% (12.9%) | 20.6% (10.3%) | 11.4% (4.9%) |
| Survival | Mean | Median | Mean | Median | Mean | Median |
| 26.4 months | 10.6 months | 14.8 months | 13 months§ | 10 months |

*Major complications are pneumothorax, sepsis, wound infection, wound dehiscence, pulmonary embolism, and hardware failure. Minor complications are urinary infection, pulmonary infection, and cerebrospinal fluid leaks treatable with cerebrospinal fluid diversion. Disease progression or recurrence are not considered as complications.
†No discrimination had been made between patients that improved neurologically and those whose neurological situation did not alter.
‡These are patients with only Frankel grade E. Frankel grade D (ambulatory) was included in the group paraparetic or paraplegic patients.
§14 patients were still alive at the moment the article was written.
such as hardware failure, misplacement of the spinal implants, urinary infection, pulmonary infection, wound infection, wound dehiscence, and cerebrospinal fluid leakage, were not addressed separately.

Recently, a very nice overview has been published by Patil et al. In this study, the National Implant Sample was utilized to identify surgically managed spinal metastases in the United States from 1993 through 2003. The complication rate of the identified 26,233 discharges was 21.9% (17.5% of the patients). Pulmonary complications (6.7%) and postoperative hemorrhage (5.9%) followed by thromboembolic complications (3%) were the most frequent complications. The authors state that the complication rate is an underestimation since only select complications were examined.

In addition, the sequence of treatment options must be emphasized as an important determinant of complications. In a retrospective series of 123 patients treated for spinal metastases, the rate for major wound complications (dehiscence or wound infection) was 32% in the group that underwent radiotherapy before surgery, whereas it was 12% in the group of patients first treated by surgery. Based on these results, it was concluded that surgery should precede radiotherapy.

Furthermore, the Patchell study lasted 10 years. Only 101 patients entered the study. Considering the multicenter design, there must have been more patients with this disease entity that were eligible for this study. This is confirmed by the large number of actual surgically treated patients in the study by Patil. Significant but unrecognized selection bias may be a possibility.

Despite these limitations, the Patchell study is the only recent, valuable, comparative study that clearly favors surgery followed by radiotherapy in selected patients. Based on the data from the study by Patchell et al, a study was performed that determined the incremental cost-effectiveness ratio from a societal perspective. Although methodological questions are raised by the authors themselves, strong evidence was found that surgery followed by radiotherapy was cost-effective. However, it would be appropriate to initiate a second multicenter study to confirm the superiority of surgery followed by radiotherapy in selected cases.

Irrespective of the chosen surgical approach, current indications for surgery are radioresistant tumor; progressive neurologic deficit before, under, or after radiotherapy; bone fragment in the spinal canal; instability of the spine due to pathologic fracture causing intractable pain or neurologic deficit; neurologic deficit not longer than 24 hours; circumscript spinal lesion; and life expectancy of at least 3 months.

Vertebroplasty/Kyphoplasty

Vertebroplasty involves the injection of polymethyl methacrylate (PMMA) into the involved vertebral body under fluoroscopic guidance. Reinforcement of the bone and stabilization of the anterior column relieves pain and prevents pathological fractures. Furthermore, PMMA could have an antitumor activity as a result of cytotoxicity, thermal effects, and ischemia. The indication for this procedure is painful vertebral metastasis without neurologic compromise. Contraindications are compression of neurologic structures, significant coagulopathy, infection, known allergic reactions against PMMA, pregnancy, poor general condition, or short expected life expectancy. The major advantage of these procedures compared with radiotherapy alone is the immediate positive contribution to spinal stability. The rate of symptomatic complication following vertebroplasty is approximately 10%. Asymptomatic cement leakage occurs in up to 73% of patients. Using PMMA with quick polymerization and relatively small injection volumes (range 2 to 8 mL) may prevent cement leakage. The pressurized filling of the vertebral body certainly contributes to this phenomenon. Partial emptying of the vertebral body and creating a cavity within the body can prevent the leakage of cement. This can be done by laser or by a balloon. The last method is called kyphoplasty. Both methods can be performed percutaneously or as an open procedure during a regular posterior approach. In a recent overview of vertebroplasty procedures, up to 85% of the patients noticed a partial or complete relief of the pain. It should be emphasized that these procedures are also performed in radiosensitive tumors such as multiple myeloma, followed by radiotherapy.
Systemic Therapeutic Options

The medical treatment of spinal metastases can be divided into antitumoral treatment and adjuvant supportive care. Antitumoral medical therapy alone has a very limited indication in the treatment of acutely symptomatic spinal metastases. However, there are a few indications in which chemotherapy is administered combined with either radiotherapy and/or surgery or in which chemotherapy is applied as adjuvant treatment modality after surgery and/or radiotherapy. In this respect, it is of utmost importance that the effect of chemotherapy on acute symptomatology of extradural metastases can only be expected in very chemosensitive tumors, such as lymphoma, some pediatric tumors (especially neuroblastoma), and seminoma. However, in the acute situation, only very rarely can concomitant local treatment, especially radiotherapy, be omitted. Notably, in cases of neurological deterioration, acute neurosurgical decompression is still necessary. Spinal extradural metastases of pediatric tumors are rare. Patients with spinal cord compression from metastatic sarcoma showed a significantly greater improvement with decompressive laminectomy alone or before chemotherapy compared with those who received radiation therapy and/or chemotherapy without posterior decompression. Two-thirds of patients with pediatric tumors treated at St. Jude’s Children’s Research Hospital who had no evidence of motor or sensory function below the level of the compression became ambulatory after surgical decompression and chemotherapy.101,102

In breast cancer, chemotherapy can be started directly after local treatment. In patients with HER2/neu-positive tumors, this should be combined with the monoclonal antibody trastuzumab. Also, in patients with Hodgkin and non-Hodgkin lymphoma treated with chemotherapy and/or local radiotherapy, a functional recovery (70% to 80%) and even long-term survival can be achieved.103,104

Hormonal treatment can be applied in estrogen and/or progesterone receptor-positive breast cancer and prostate cancer patients. However, it should be emphasized that, in general, the clinical benefit effect of hormonal treatment takes weeks to months. Therefore, it can only be prescribed in cases of extradural metastases after adequate and prompt local treatment. In addition, in the majority of cases, only the status of the hormonal receptors of the primary tumor is available, which might not be the same as those of the extradural metastatic lesions.105,106

In lymphomas, corticosteroids might be used symptomatically to reduce tissue edema and minimize neurological deficits, but also as active antitumoral therapy.

At present, it is too early to accurately predict the effect of new targeted agents in the treatment of extradural metastases. It is to be expected that for most tumors these new treatment options (eg, monoclonal antibodies, receptor tyrosine kinase inhibitors, or angiogenesis inhibitors) are useful as adjuncts to local treatment but will not offer a possibility to refrain from prompt local treatment in the acute clinical neurological setting.

Supportive Care

Corticosteroids

It is generally accepted that corticosteroids should be prescribed for patients presenting with spinal cord compression due to spinal metastases. Many theoretical beneficial effects are assigned to corticosteroids: reduction in vasogenic edema, protection against lipid peroxidation and hydrolysis, enhanced blood flow, prevention of ischemia and intracellular calcium accumulation, stabilization of lysosomal membranes, attenuation of inflammatory response, and support of cellular energy metabolism.107 The optimal dose is still a matter of debate. However, several studies did not show a clear beneficial effect of high-dose dexamethasone (96 mg daily followed by a gradual tapering scheme) over low-dose dexamethasone (10 to 16 mg daily). Both schemes are followed by gradual tapering during the radiotherapy.

Three studies addressing this point will be reviewed. First, in a multicenter study, 37 patients were randomized to receive either 10 mg or 100 mg dexamethasone initially, followed by 16 mg daily. A difference in ambulatory function, urinary control, or decrease in pain was not demonstrated for either group. Eventual adverse effects were not reported.108 The second study compared 2 historical cohorts of patients. The first 28 patients received a high-dose schedule of dexamethasone
(96 mg on day 1 followed by tapering the dose during 14 successive days). Because of the high incidence of adverse effects, the next 38 consecutive patients received a low-dose regimen (16 mg initially reduced to 0 in 14 days). In the first Group, 8 adverse effects occurred, of which 4 were considered serious. In the second group, only 3 adverse events occurred, and none of them were serious. The ambulatory rate was the same for both groups. In the third study, patients were, after stratification for primary tumor and gait function, randomly allocated to either high-dose dexamethasone (27 patients) or no dexamethasone (30 patients). In the treatment group (administering dexamethasone), the ambulatory function was significantly better (81% versus 63% after treatment). However, the incidence of adverse effects was also higher (11%) in the treatment group. The authors concluded that corticosteroids should be given as an adjunct to radiotherapy without any advice regarding the dose. We are not aware of any other study comparing high- and low-dose dexamethasone treatment. Amongst the adverse effects are gastrointestinal bleeding, gastrointestinal perforation, pneumonia, hyperglycemia, and wound infection. Based on the available literature, there is no sound base to prescribe a high-dose regimen of dexamethasone. However, in patients with neurologic deficits, radiotherapy should be supplemented by dexamethasone. Perioperatively, a short course of corticosteroids is often prescribed.

**Bisphosphonates**

Bisphosphonates are widely used in medical oncology to treat hypercalcemia and to prevent metastatic bone complications. They are potent inhibitors of normal and pathological bone resorption. The also have antiangiogenic effects and antitumoral activity. Their exact mechanism of action is complex and beyond the scope of this article. Clodronate, pamidronate, and zoledronate are representatives of the successive generations, with zoledronate belonging to the third generation bisphosphonates. Probably due to their high prevalence, most reports describe the effects of bisphosphonates in advanced breast or prostate cancer. All studies conclude that bisphosphonates in selected patients with metastases to the bone provide relief of pain and improved quality of life. Also, fewer pathologic bone fractures, fewer events with spinal cord compression, and less hypercalcemia of malignancy were noted in breast cancer patients with newly diagnosed bone metastases who received zoledronic acid. Although the efficacy of bisphosphonates has been established for the treatment of skeletal metastases in general, their role for spinal metastases has never been established separately. Nevertheless, spinal extradural metastases are generally bone metastases and could, therefore, likely benefit from bisphosphonate treatment. Bisphosphonates can reasonably be expected to prevent further resorption of bone, provide relief of pain, and prevent spinal instability and the accompanying problems. Finally, their role in metastases to the spine by other tumors should be investigated.

**Treatment Algorithm**

After careful study of the literature, we propose the following treatment algorithm for symptomatic (pain, neurologic deficit, or a combination of these) metastatic spinal disease (Figure 3). If the radiological studies are suggestive of a metastatic process within the spine, in some cases histological examination is needed. In all cases, a multidisciplinary approach is warranted: medical oncologist/hematologist, radiation oncologist, spinal surgeon, and radiologist.

If pain is the presenting symptom, analgesic treatment is initiated. Instability of the spine as a cause should be eliminated; if present, surgical stabilization can be considered. Estimated life expectancy of more than 3 months and general condition of the patient will ultimately determine the feasibility of this option. Radiotherapy is a very efficient option for pain relief in cases of extradural spinal metastases. In hospitals with available experience, vertebroplasty or kyphoplasty may be considered. In selected cases (eg, cancer of the breast or of the prostate), bisphosphonates are prescribed to provide pain relief and to prevent progression with a possible pathological fracture.

In patients presenting with neurologic deficit, an emergency whole-spine MRI should be made to monitor the extensiveness of the metastatic process. Subsequently, dexamethasone should
be started. If the estimated life expectancy is shorter than 3 months or when the patient's general condition is very poor, short-course radiotherapy is indicated.

Otherwise, the radiosensitivity of the lesion will determine the recommended treatment. If the tumor is radiosensitive and the spine is stable, radiotherapy is the treatment of choice. If the tumor is radioresistant, a neurologic deficit is present for fewer than 24 hours, and the patient is not in a very poor condition, surgical decompression and stabilization followed by radiotherapy should be considered. If the duration of the neurologic deficit is greater than 24 hours, surgery should nonetheless be considered if the deficit improved following administration of dexamethasone. It should be emphasized that in patients with spinal metastases from an unknown primary tumor and a rapidly progressing neurologic deficit, prompt decompression of the spinal cord and stabilization should be considered. This allows for a concomitant biopsy to provide material for histological examination.

**REFERENCES**

1. Perrin RG, Laxton AW. Metastatic spine disease: epidemiology, pathophysiology, and evaluation of patients. Neurosurg Clin N Am 2004;15:365–373.
2. Jacobs WB, Perrin RG. Evaluation and treatment of spinal metastases: an overview. Neurosurg Focus 2001;11:e10.
3. Witham TE, Khavkin YA, Gallia GL, et al. Surgery insight: current management of epidural spinal cord compression from metastatic spine disease. Nat Clin Pract Neurol 2006;2:87–94.
4. Manabe J, Kawaguchi N, Matsumoto S, Tanizawa T. Surgical treatment of bone metastasis: indications and outcomes. Int J Clin Oncol 2005;10:103–111.
5. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2007. CA Cancer J Clin 2007;57:43–66.
6. Loblaw DA, Perry J, Chambers A, Lapierre NJ. Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the Cancer Care Ontario Practice Guidelines Initiative’s Neuro-Oncology Disease Site Group. J Clin Oncol 2005;23:2028–2037.
7. Agarwal JP, Swangsilpa T, van der Linden Y, et al. The role of external beam radiotherapy in the management of bone metastases. Clin Oncol (R Coll Radiol) 2006;18:747–760.
8. Lewandowski KU, Bell GR, McLain RF. Cancer of the spine: how big is the problem? in McLain RF. Cancer in the Spine: Comprehensive Care. Totowa, NJ: Humana Press; 2006:1–5.
10. Perrin RG. Metastatic tumors of the axial spine. Curr Opin Oncol 1992;4:525–532.
11. Simmons ED, Zheng Y. Vertebral tumors: surgical versus nonsurgical treatment. Clin Orthop Relat Res 2006;443:233–247.
12. Moore KR. Radiology of metastatic spine cancer. Neurosurg Clin N Am 2004;15:381–390.
13. Schif D, O’Neill BP, Sunan VJ. Spinal epidural metastasis as the initial manifestation of malignancy: clinical features and diagnostic approach. Neurology 1997;49:452–456.
14. Bilsky MH. New therapies in spine metastases. Expert Rev Neurother 2005;5:831–840.
15. van der Linden YM, Dijkstra SP, Vonk EJ, et al. Prediction of survival in patients with metastases in the spinal column: results based on a randomized trial of radiotherapy. Cancer 2005;103:320–328.
16. Hamaoka T, Madewell JE, Podoloff DA, et al. Bone imaging in metastatic breast cancer. J Clin Oncol 2004;22:2942–2953.
17. Kienstra GE, Terwee CB, Dekker FW, et al. Prediction of spinal epidural metastases. Arch Neurol 2000;57:690–695.
18. Cleland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore 1994;23:129–138.
19. Frankel HL, Hancock DO, Hlysol G, et al. The value of postural reduction in the initial management of closed injuries of the spine with para-plagia and tetraplegia. I. Paraplegia 1967;3:179–192.
20. Frazier CH. Surgery of the Spine and Spinal Cord. New York, NY: Appleton and Co.; 1918.
21. Béard L. Les tumeurs du rachis. Second Internat Congress of Surgery 1908;2:735–784.
22. Tietze A. Chirurgische Eingriffe bei metatatischem Carcinom der Wirbelsäule. Beitr z klin Chir 1911;73:785–814.
23. Leddy ET. The roentgen treatment of metastasis as the initial manifestation of malignancy: clinical features and diagnostic approach. Neurology 1997;49:452–456.
24. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res 2006;12:6243–6249.
25. Gilmore RD, Kim JH, Posner JB. Epidural spinal cord compression from metastatic tumor: diagnosis and treatment. Ann Neurol 1978;3:40–51.
26. Klemm WB, Kienman HA, Michelsen WJ. Metastatic cancer of the spinal column. Clin Orthop Relat Res 1978;136:166–172.
27. Black P. Spinal metastasis: current status and recommended guidelines for management. Neurosurgery 1979;5:726–746.
28. Young RE, Post EM, King GA. Treatment of spinal epidural metastases. Randomized prospective comparison of laminectomy and radiotherapy. J Neurosurg 1980;53:741–748.
60. Roos DE, Turner SL, O’Brien PC, et al. Randomized trial of 8 Gy in 1 versus 20 Gy in 5 fractions of radiotherapy for neuropathic pain due to bone metastases (Trans- Tasman Radiation Oncology Group, TROG 96.05). Radiother Oncol 2005;75:54–63.

61. Maranzano E, Bellavia R, Rossì R, et al. Short-course versus split-course radiotherapy in metastatic spinal cord compression: results of a phase III, randomized, multicenter trial. J Clin Oncol 2005;23:3358–3365.

62. Rades D, Fehlauer F, Stalpers LJ, et al. A prospective evaluation of two radiotherapy schedules with 10 versus 20 fractions for the treatment of metastatic spinal cord compression: final results of a multicenter study. Cancer 2004;101:2687–2692.

63. Rades D, Stalpers LJ, Veninga T, et al. Evaluation of five radiation schedules and prognostic factors for metastatic spinal cord compression. J Clin Oncol 2005;23:3366–3375.

64. Rades D, Stalpers LJ, Veninga T, Hoskin PJ. Spinal reirradiation after short-course RT for metastatic spinal cord compression. Int J Radiat Oncol Biol Phys 2005;63:872–875.

65. Hoskin PJ, Grover A, Bhana R. Metastatic spinal cord compression: radiotherapy outcome and dose fractionation. Radiother Oncol 2003;68:175–180.

66. Helweg-Larsen S, Sørensen PS, Kreiner S. Prognostic factors in metastatic spinal cord compression: a prospective study using multivariate analysis of variables influencing survival and gait function in 153 patients. Int J Radiat Oncol Biol Phys 2000;46:1163–1169.

67. Chang EL, Shiu AS, Mendel E, et al. Phase I/II study of stereotactic body radiotherapy for spinal metastases and its pattern of failure. J Neurosurg Spine 2007;7:151–160.

68. Gibbs IC, Kamerdzhiev P, Ryyu MR, et al. Image-guided robotic radiosurgery for spinal metastases. Radiother Oncol 2007;82:185–190.

69. Gerszten PC, Burton SA, Ozhassouglu C, Welch WC. Radiosurgery for spinal metastases: clinical experience in 500 cases from a single institution. Spine 2007;32:193–199.

70. Jin HY, Chen Q, Jin R, et al. Technical and clinical experience with spine radiosurgery: a new technology for management of localized spine metastases. Technol Cancer Res Treat 2007;6:127–133.

71. Ryyu S, Fang Y, Rock J, et al. Image-guided and intensity-modulated radiosurgery for patients with spinal metastasis. Cancer 2003;97:2013–2018.

72. Nieder C, Grosu AL, Andratschke NH, Molls M. Update of human spinal cord reirradiation tolerance based on additional data from 38 patients. Int J Radiat Oncol Biol Phys 2006;66:1446–1449.

73. Ryyu S, Jin HY, Jin R, et al. Partial volume tolerance of the spinal cord and complications of single-dose radiosurgery. Cancer 2007;109:628–636.

74. Roquie M, Martinez-Zapata MJ, Alonso-Coello P, et al. Radioisotopes for metastatic bone pain. Cochrane Database of Systematic Reviews [database online] 2003;4:CD003347. Available at: http://www.cochrane.org/reviews/en/ab003347.html. Accessed December 10, 2007.
spine disease. Neurosurg Clin N Am 2004;15:549–564.

108. Vecht CJ, Haaxma-Reiche H, van Putten WL, et al. Initial bolus of conventional versus high-dose dexamethasone in metastatic spinal cord compression. Neurology 1989;39:1253–1257.

109. Heimdal K, Hirschberg H, Slettebo H, et al. High incidence of serious side effects of high-dose dexamethasone treatment in patients with epidural spinal cord compression. J Neurooncol 1992;12:141–144.

110. Sørensen S, Helweg-Larsen S, Mourniøen H, Hansen HH. Effect of high-dose dexamethasone in carcinomatous metastatic spinal cord compression treated with radiotherapy: a randomised trial. Eur J Cancer 1994;30A:22–27.

111. Veri A, D’Andrea MR, Bonginelli P, Gasparini G. Clinical usefulness of bisphosphonates in oncology: treatment of bone metastases, antitumoral activity and effect on bone resorption markers. Int J Biol Markers 2007;22:24–33.

112. Heidenreich A, Hofmann R, Engelmann UH. The use of bisphosphonate for the palliative treatment of painful bone metastasis due to hormone refractory prostate cancer. J Urol 2001;165:136–140.

113. Lipton A, Theriault RL, Hortobagyi GN, et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. Cancer 2000;88:1082–1090.

114. Yuen KK, Shelley M, Sze WM, et al. Bisphosphonates for advanced prostate cancer. Cochrane Database of Systematic Reviews [database online] 2006;4:CD006250. Available at: http://www.cochrane.org/reviews/en/ab006250.htm. Accessed December 10, 2007.

115. Carteni G, Bordonaro R, Giotta F, et al. Efficacy and safety of zoledronic acid in patients with breast cancer metastatic to bone: a multicenter clinical trial. Oncologist 2006;11:841–848.