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Clinical trials and evidence-based medicine for metastatic spine disease

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Fifty percent to 70% of all cancer patients have metastases at the time of their death, with the spine being the most common osseous site [1–3]. As shown in Fig. 1, approximately 5% to 10% of cancer patients and up to 40% of patients with preexisting nonspinal bone metastases develop metastatic epidural spinal cord compression from metastases [2,4–8]. Of those with spinal disease, 10% to 20% develop symptomatic spinal cord compression, resulting in more than 25,000 cases per year, with the number expected to grow [7,9,10].

Approximately 50% of spinal metastases arise from one of three primary sites—breast, lung, or prostate [6,11]—with additional cases from renal, gastrointestinal, and thyroid metastases; sarcoma; and the lymphoreticular malignancies of lymphoma and multiple myeloma. Metastases from the prostate, breast, melanoma, and lung commonly cause spinal metastases in 90.5%, 74.3%, 54.5%, and 44.9% of patients, respectively [2]. The risk of neurologic deficits as a result of epidural spinal cord compression varies with the site of primary disease as follows: 22% with breast cancer, 15% with lung cancer, and 10% with prostate cancer [7]. Overall, 10% of patients present with no known history of cancer, although in some of the older surgical literature, this figure was as high as 70% of the study population [10,12–15]. In more than 50% of these cases, the lung is the primary source of malignancy [7,14].

The thoracic spine is the most common site of disease (70%), followed by the lumbar (20%) and cervical (10%) spine [6,7,16]. As shown in Fig. 2, metastatic spinal disease can arise in one of three locations: the vertebral column (85%), the paravertebral region (10%–15%), and, rarely, the epidural or subarachnoid/intramedullary space itself (<5%) [6,7,16]. The posterior half of the vertebral body is usually involved first, with the anterior body, lamina, and pedicles invaded later [17]. Intradural metastases, including intramedullary metastases, from nonneural primary tumors are extremely rare but have been reported [18,19]. Multiple lesions at noncontiguous levels occur in 10% to 40% of cases [6,7,16,20].

Treatment should generally be considered palliative. En bloc oncologic resections are rarely performed [21]. With aggressive surgical management, the 6-month and 1-year survival rates range from 36% to 50% and 12% to 62%, respectively [15,22–26]. This compares with 40% to 50% and 20% to 56% in the radiation literature [27–29]. It is imperative that treatment be rendered as soon as possible, because neurologic outcome after treatment is primarily dependent on the neurologic status before treatment [30,31]. The primary histology and posttreatment ambulatory status are the most important factors in determining survival.

A recent well-conducted, population-based, cohort study by Loblaw et al [32] highlights many of the issues outlined in this introduction. The authors identified patients with malignant spinal cord compression by linking electronic hospital discharge records and cancer center records to the

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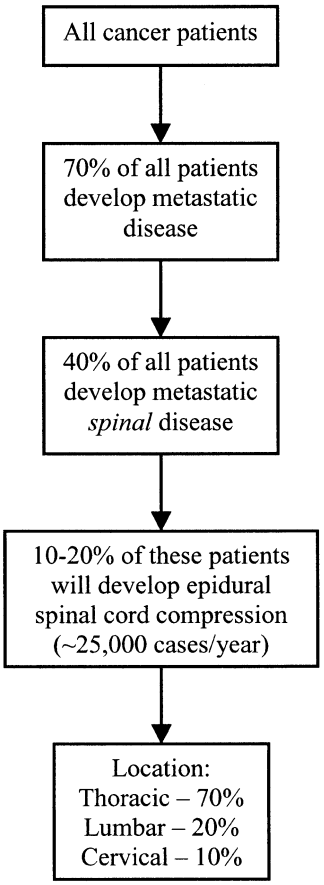

Fig. 1. Diagram depicting the proportion of cancer patients affected by spinal metastases and epidural spinal cord compression and the distribution of involvement within regions of the spine.

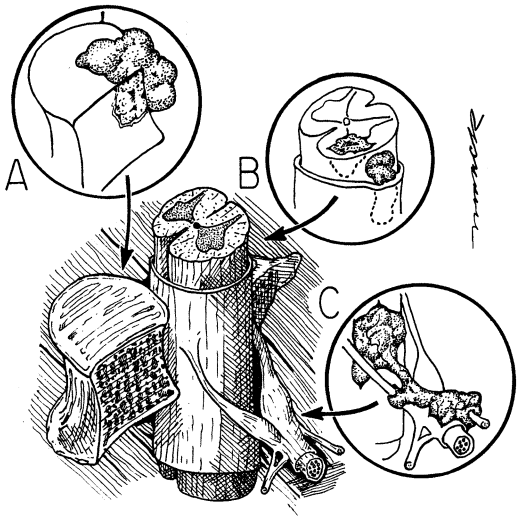

Fig. 2. Locations of metastases to the spine. Most malignancies embolize to the vertebral column surrounding the spinal cord, with the posterior half of the vertebral body being the most common initial focus (*A*). Tumor can also originate in a paravertebral location and track along the spinal nerves to enter the spinal column by way of the neural foramina (*C*). Both of these mechanisms can lead to epidural spinal cord compression. Intramedullary and subdural/leptomeningeal metastatic deposits are rarely encountered (*B*).

province of Ontario's population-based cancer registry. Between January 1990 and December 1995, they identified 3458 patients with spinal cord compression out of 258,069 cases of cancer (1.89%). The average patient age was 62 years; 57% were men; and lung, prostate, and breast cancer accounted for 61.2% of the cases. During the same period, 121,435 patients died of their cancer, and of these, 2.54% had metastatic spinal disease. The cumulative incidence ranged from 0.22% for pancreatic cancer to 7.91% for multiple myeloma, with rates for prostate, breast, and renal cell cancers of 7.24%, 5.52%, and 4.98%, respectively. Surgery was performed initially in 16.1% of the patients, whereas radiation was the primary treatment in 60.2%. Surgery was most frequently used for melanoma and renal cell carcinoma and consisted of a laminectomy in 81.6% of patients. Survival was primarily dependent on the site of the primary cancer—lung cancer had the worst prognosis, whereas lymphoma and myeloma had the best. The median survival after the first admission for metastatic spinal disease was 2.9 months, and only 8.4% of patients were alive at 3 years. The authors believe that their rates (prevalence and cumulative incidence) were underestimates of the true values by at least 15%.

We have previously reviewed the literature on the effectiveness of various treatments for metastatic spinal disease, specifically surgery, radiation, and chemotherapy [33]. The quality of the literature was categorized as class I to III using the definitions originally set forth by Woolf et al (Table 1) [34]. The primary outcome for this literature review was ambulatory status, which was further defined as "success" and "rescue." The success rate is defined as the proportion of all patients within the study who retained or regained ambulatory function after treatment. The rescue rate is the percentage of patients who were

Table 1
Classification of evidence on therapeutic effectiveness

Evidence class	Definition
I	Evidence obtained from at least one properly designed, randomized, controlled trial
II	Evidence obtained from well-designed controlled trials without randomization, such as nonrandomized cohort studies, case-control studies, and other comparable studies, including less well-designed, randomized, controlled trials
III	Evidence from case series, comparative studies with historical controls, case reports, and expert opinion as well as significantly flawed, randomized, controlled trials

nonambulators before treatment and regained the ability to ambulate, either with assistance or independently. Secondary outcomes included pain, treatment-related morbidity, survival, and autonomic function. These outcomes were not universally reported in the literature reviewed here and are mentioned only with reference to specific articles.

Chemotherapy

Steroids

There is strong evidence to support the use of steroids in patients with newly diagnosed metastatic spinal disease that causes spinal cord dysfunction. Steroids have numerous theoretic benefits, including reducing vasogenic edema, protecting against lipid peroxidation and hydrolysis, enhancing blood flow, preventing ischemia and intracellular calcium accumulation, stabilizing lysosomal membranes, attenuating the inflammatory response, and supporting cellular energy metabolism [35]. Dexamethasone is the most widely used steroid in patients with cancer, but methylprednisolone is more commonly used in trauma.

The optimal dose of dexamethasone in metastatic spinal cord compression is controversial. Loading doses range from 10 to 100 mg, followed by 4 to 24 mg four times a day and tapered down over several weeks [5,6,16,36–39]. Larger doses are often used for those patients who present with a severe baseline or worsening neurologic examination. Some physicians advocate using the trauma dose protocol in patients with rapid neurologic deterioration [40]. In a well-designed, randomized controlled trial (RCT, class I) that compared high-dose dexamethasone followed by radiotherapy with radiotherapy alone, 81% of patients in the treatment group were ambulatory after treatment compared with 63% in the control group [39]. In another RCT, patients with a complete myelographic block who received a bolus of 100 mg followed by a standard maintenance dose had no better pain relief, ambulation, or bladder function than those who received a 10-mg bolus and the same maintenance therapy [41]. It is clear, however, that higher doses are associated with more complications [42]. Therefore, an appropriate regimen of dexamethasone would be an initial bolus of 10 mg followed by 16 mg/d and tapered over several weeks.

Steroids are not necessary for patients who present without any clinical evidence of spinal cord compression. In a cohort study of 20 patients published by Maranzano et al [43], all presented without neurologic deficits or with only a radiculopathy. After radiation without steroids, all patients remained ambulatory. Finally, steroids do have an oncolytic effect on some tumors, namely, lymphoma and thymoma. For patients in whom these tumors are suspected, steroids should be withheld until enough tissue is obtained to make a diagnosis [5].

Other chemotherapeutic agents

Bisphosphonates are a family of drugs that have been shown to be effective in treating or preventing some of the complications related to osseous metastases in various cancers [44,45]. There are two types of bisphosphonates: pyrophosphates (eg, clodronate, etidronate) and aminobisphosphonates (eg, pamidronate, zoledronic acid). These drugs work by inhibiting osteoclast activity, decreasing bone resorption. They also have a direct tumoricidal effect. There has been an explosion of class I data evaluating the use of bisphosphonates in the prevention of skeletal-related events (SREs), defined as pathologic fracture, spinal cord compression, radiation or surgery for bone metastases, or hypercalcemia. When these SREs are taken collectively, bisphosphonates have been shown to decrease the number of and time to SREs in prostate cancer [46,47], breast cancer [48,49], multiple myeloma [48,50], lung cancer [51], and renal cell carcinoma

[52]. It should be mentioned that not all bisphosphonates are equally effective. For example, in a recent article by Small et al [53], pamidronate was not found to prevent SREs, decrease analgesic use, or increase mobility in patients with metastatic prostate cancer compared with placebo. Conversely, zoledronic acid has been shown to be of benefit in prostate cancer [54].

Ross et al [55] recently performed a meta-analysis of the evidence for the use of bisphosphonates in skeletal metastases from various cancers. Only randomized trials were analyzed, and the primary outcome measures were time to first SRE and reduction in skeletal morbidity assessed by pathologic fractures (vertebral, nonvertebral, and combined), treatment (orthopedic surgery or radiotherapy), hypercalcemia, and spinal cord compression. Data from 18 studies were eligible for the meta-analyses, allowing the authors to analyze the effect of bisphosphonates on individual SREs rather than as a whole. They found that bisphosphonates significantly reduced the odds of suffering vertebral, nonvertebral, or combined fractures and hypercalcemia but not spinal cord compression. Fewer patients underwent radiotherapy, but orthopedic surgery rates were not decreased. Benefits seemed to be apparent only after 6 months. Therefore, based on currently available data, bisphosphonates can reduce the incidence of morbidity related to skeletal metastases but should not be used in the hope of preventing spinal cord compression or as a treatment once it develops.

Few tumors causing spinal cord compression are treated solely with chemotherapy. There are numerous reports in the literature documenting successful decompression in lymphoma [56–62], breast cancer [63], prostate cancer [64], germ cell tumors [65–68], hepatoblastoma [69], neuroblastoma [70,71] and Ewing's sarcoma [71,72]. Most of the literature is in the form of small case series and case reports and is disproportionately represented by pediatrics [71,73,74].

Surgery

Posterior decompressive laminectomy

For many years, laminectomy was the only surgical option offered to patients with metastatic spine disease. In fact, "surgery" is to some extent still equated with laminectomy, contributing to the radiotherapy bias. One of the reasons why laminectomy was the dominant surgical procedure is its relative ease. It can be performed quickly by any neurosurgeon with minimal intraoperative risk and does not require spinal column reconstruction or placement of internal stabilization devices. Despite its widespread use, there was no consensus among surgeons at the time regarding its effectiveness. Some thought that it was the only reasonable hope for recovering neurologic deficits, whereas others found it to be of little value, except for obtaining tissue to make a diagnosis and relieving pain [75,76].

Much of the existing literature on decompressive laminectomy is in the form of uncontrolled cohort studies (class III). Outcomes usually include ambulatory status before and after treatment, pain relief, and treatment-related complications. As shown in Table 2, 14% to 58% of patients who underwent a posterior decompressive laminectomy were ambulatory after their surgery. Not shown in Table 2 are the significant nonneurologic complications that follow laminectomy, specifically wound infection/dehiscence and spinal instability. Findlay's review of the literature [77] found the incidence of these complications to be approximately 11%.

A number of articles, including controlled cohort studies (class II), compared the efficacy of laminectomy alone versus radiation alone versus laminectomy followed by radiation [14,16,75,77–82]. For instance, in 1978, Gilbert et al [16] published a single-institution retrospective analysis of 235 patients treated with either decompressive laminectomy followed by radiation (n = 65) or radiation alone (n = 170). After treatment, 46% of those who underwent the combination treatment were ambulatory compared with 49% of those who had radiation alone. The pretreatment neurologic function was the most reliable indicator of posttreatment function. There was no significant difference in the rate of neurologic recovery between the two groups. Of the 22 patients who developed rapidly progressive weakness (<48 hours), 9 underwent surgery and 13 received radiation. None of the surgical patients improved, but 7 of the radiation patients did. The authors concluded that radiation should be the treatment of choice and that a decompressive laminectomy is indicated in only three situations: to establish a diagnosis, to treat a relapse if the patient is unable to undergo further radiation, and if symptoms progress during radiation.

Despite the obvious need and repeated requests by investigators to conduct an RCT, only one was attempted. Young et al [78] randomized

Table 2
Ambulatory outcome after various treatments

Treatment	N	Success[a] (%)	Mean (%)
Posterior decompressive laminectomy alone			30
Barron et al [8] (1959)	38	29	
Wild and Porter [109] (1963)	22	26	
Wright [110] (1963)	21	14	
Brice and McKissock [13] (1965)	139	32	
Smith [111] (1965)	52	25	
Auld and Buerman [112] (1966)	41	42	
Hall and MacKay [113] (1973)	129	30	
Livingston and Perrin [114] (1978)	100	58	
Baldini et al [115] (1979)	140	30	
Dunn et al [116] (1980)	104	33	
Stark et al [14] (1982)	32	16	
Findlay [117] (1987)	80	24	
Sorensen et al [81] (1989)	105	34	
Radiation alone			47
Mones et al [118] (1966)	41	34	
Khan et al [119] (1967)	82	41	
Posner [120] (1971)	75	47	
Cobb et al [121] (1977)	18	50	
Gilbert et al [16] (1978)	170	49	
Greenberg et al [38] (1980)	83	57	
Stark et al [14] (1982)	32	35	
Constans et al [79] (1983)	108	39	
Martenson et al [80] (1985)	42	64	
Sorensen et al [81] (1989)	149	38	
Ruff and Lanska [28] (1989)	41	73	
Posterior decompressive laminectomy + radiation			47
Mullan and Evans [122] (1957)	21	43	
Wild and Porter [109] (1963)	23	44	
Wright [110] (1963)	17	47	
Gilbert et al [16] (1978)	65	45	
Stark et al [14] (1982)	52	37	
Constans et al [79] (1983)	465	46	
Martenson et al [80] (1985)	21	57	
Sherman and Waddell [84] (1986)	111	57	
Sorensen et al [81] (1989)	91	53	

[a] Success is defined as the ability to walk after the operation (ie, gait was maintained, improved, or regained as a result of the laminectomy).

patients with a symptomatic epidural spinal lesion to receive either laminectomy followed by radiotherapy or radiotherapy alone. Sixteen patients were randomized to the surgical arm, and 13 were treated with radiotherapy alone. No significant difference was found between the groups with respect to pain relief, ambulatory status, or sphincter function. There were no treatment-related complications for surgery or radiotherapy. The major limitation with the study, as the authors clearly state, was that it was too small to detect a difference in the treatments. Rather, the major goal of the study was to demonstrate that a properly conducted RCT was feasible.

Because of these articles and others shown in Table 3, laminectomy was viewed as a procedure of minimal neurologic benefit with significant morbidity, and it was believed that radiation should assume the primary treatment role. Indiscriminate use of decompressive laminectomy was prone to failure, because the tumor lies ventral to the thecal sac in most cases, making it impossible to accomplish a meaningful decompression or tumor resection without significant retraction on the thecal sac. Furthermore, a laminectomy

Table 3
Results of circumferential spinal cord decompression

		Postoperative results			
Authors (year)	N	Pain (% improved)	Success	Rescue	Complications
Harrington [123] (1984)	52	N/A	85% of those with preoperative neurologic deficit had improvement; gait function N/A	N/A	Mortality = 11.5% Morbidity = 17.3% Surgical-2 Hardware-5 Neurologic-1 Medical-2
Siegal et al [124] (1985)	40	92%	80%	74%	Mortality = 7.5% Morbidity = 20% Surgical-20 Hardware-3 Neurologic-1 Medical-2
Fidler [125] (1986)	18	N/A	78%	75%	Mortality = 5.6% Morbidity = N/A
Kostiuk et al [126] (1988)	100	81%	72%-anterior 38%-posterior	N/A	Mortality = 0% Morbidity = 21% Surgical-3 Hardware-10 Neurologic-4 Medical-4
Harrington [127] (1988)	77	N/A	73%	50%	Mortality = 6.5% Morbidity = 18% Surgical-5 Hardware-5 Neurologic-1 Medical-3
Manabe et al [91] (1989)	28	100%	86%	79%	Mortality = 7.1% Morbidity = 0%
Moore and Uttley [128] (1989)	26	71%	77%	63%	Mortality = 31% Morbidity = 7.7% Surgical-2
Sundaresan et al [129] (1991)	54	90%	94%	86%	Mortality = 5.5% Morbidity = 15% Surgical-2 Hardware-1 Neurologic-1 Medical-4
Hammerberg [130] (1992)	56	91%	88%	71%	Mortality = 3.6% Morbidity = 16.7% Surgical-6 Hardware-3
Cooper et al [131] (1993)	33	97%	88%	25%	Mortality = 3% Morbidity = 42% Surgical-1 Neurologic-2 Medical-11

Table 3 (*continued*)

Authors (year)	N	Postoperative Results			Complications
		Pain (% improved)	Success	Rescue	
Sundaresan et al [15] (1996)	110	90%	82%	59%	Mortality = 5% Morbidity = 48% Surgical-45 Hardware-11 Neurologic-2 Medical-10
Akeyson et al [23] (1996)	25	80%	72%	42%	Mortality = 0% Morbidity = 44% Surgical-7 Hardware-4
Gokaslan et al [24] (1998)	72	92%	93%	61%	Mortality = 3% Morbidity = 43% Surgical-10 Neurologic-6 Medical-15
Weigel et al [25] (1999)	76	89%	93%	90%	Mortality = 7% Morbidity = 24% Surgical-6 Hardware-4 Neurologic-4 Medical-4
Wise et al [132] (1999)	80	N/A	89%	41%	Mortality = 2.5% Morbidity = 36% Surgical-9 Hardware-2 Neurologic-2 Medical-16
Hatrick et al [89] (2000)	42	90%	86%	57%	Mortality = 0 Morbidity = 19% Surgical-3 Hardware-2 Neurologic-3
Bilsky et al [133] (2000)	25	100%	88%	0%	Mortality = 12% Morbidity = 32% Surgical = 1 Neurologic = 2 Medical = 5
Fourney et al [22] (2001)	100	87%	86%	46%	Mortality = 0 Morbidity = 65% Surgical-21 Hardware-3 Neurologic-3 Medical-19
Jackson et al [134] (2001)	79	89%	N/A	50%	Mortality = 2.5% Morbidity = 37% Surgical-11 Hardware-2 Neurologic-2 Medical-14

(*continued on next page*)

Table 3 (*continued*)

Authors (year)	N	Postoperative Results			Complications
		Pain (% improved)	Success	Rescue	
Sundaresan et al [92] (2002)	80	95%	98%	94%	Mortality = 1.3% Morbidity = 29% Surgical-16 Hardware-4 Neurologic-1 Medical-2

Success is defined as the proportion of patients ambulatory after treatment, whereas Rescue is the proportion of non-ambulators who regained ambulatory function, either with assistance or independently. N/A indicates that data were not available in the selected paper. Mortality and Morbidity are defined as death or complication within 30 days of the operation. Morbidity is the number of complications divided by the number of patients in the study; thus, overestimates may arise if one patient suffered more than one complication. These complications are subdivided into surgical, medical, hardware, and neurologic, categories. The number of patients in each complication category is recorded for the studies listed. Surgical complications include wound infection, hematomas, and cerebrospinal fluid leaks. Examples of hardware complications include broken screws and graft migration/dislodgement. Medical complications are those that are not directly related to the surgery such as pneumonia, myocardial infarction, and deep venous thrombosis/pulmonary embolism. Patients who suffered new neurologic deficits were considered to have neurologic complications. Local recurrence and pseudoarthrosis were not counted as complications.

can cause or worsen preexisting spinal instability. This can lead to progressive deformity, which, in turn, can result in pain, deformity, and neurologic compromise. Based on these data, we believe that decompressive laminectomy alone without supplemental internal fixation, except in cases where the pathologic findings are strictly confined to the lamina and spinous process, should not be used in patients with metastatic spinal disease. Despite the evidence, it continues to be performed by some surgeons [83].

The results of decompressive laminectomy do seem to be improved if internal fixation (eg, pedicle screws) and fusion are performed as well. In a review of 134 patients treated with either a laminectomy (n = 111) or laminectomy with stabilization (n = 23), Sherman and Waddell [84] found that the latter group had better posttreatment ambulatory status (92% versus 57%), sphincter function, and pain control and less recurrent neurologic dysfunction. These results have been supported by other studies [40,84–89].

Circumferential decompression

With the failure of laminectomy, the treatment of metastatic disease has largely been confined to radiation. Over the last 20 years, however, a new philosophy on the surgical management of metastatic spinal disease has emerged. In his 1984 article, Findlay [77] reviewed the small amount of data that existed at the time on anterior spinal surgery and found "dramatic results" with regard to neurologic function but warned that "...it is unclear as to how often such success could be achieved." As surgeons realized the limitations of the laminectomy, they began to decompress the ventral spinal cord, the most common site of metastatic spread. Thus, a new philosophy began to emerge—circumferential spinal cord decompression.

To achieve a circumferential decompression, surgical approaches must be tailored to the location of the tumor with respect to the spinal cord (Fig. 3). The result is to have the spinal cord free of any malignant compression. Approaches can broadly be classified as anterior (eg, transthoracic, retroperitoneal) or posterior, including posterolateral trajectories (eg, laminectomy, transpedicular, costotransversectomy, lateral extracavitary). In addition to decompressing the cord, reconstruction and immediate stabilization of the spinal column form the pillars of surgical management today.

A large amount of literature on spinal cord decompression has emerged over the last 20 years (see Table 3). Although the articles are in general more detailed than their laminectomy counterparts, they still are uncontrolled cohort studies and thus represent class III data. The change in surgical philosophy from laminectomy to aggressive resection is apparent in some articles that span many years [90]. One of the earlier reports

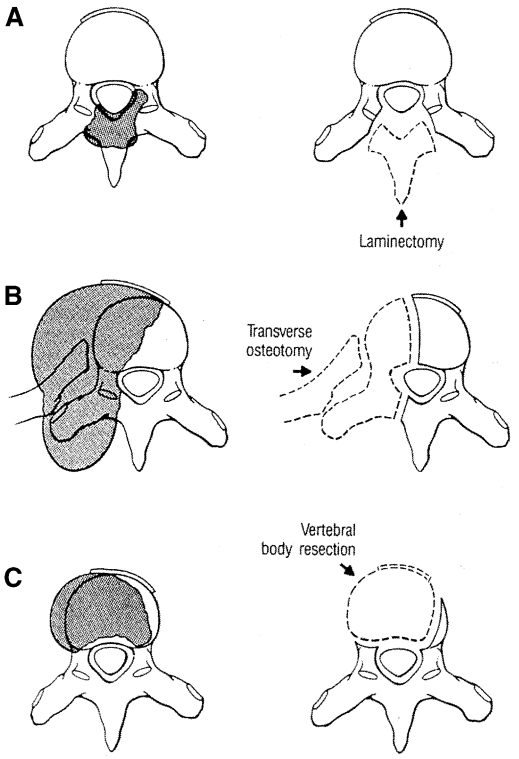

Fig. 3. Circumferential spinal cord decompression. Depending on the location of tumor within the vertebrae, different surgical approaches are required such that the end result in each scenario is to have the spinal cord free of any malignant compression. (*A*) If the tumor is isolated to the posterior elements, a laminectomy is appropriate. (*B*) A posterolateral approach, such as a costotransversectomy, can remove disease within the posterior and anterior elements. (*C*) Disease isolated to the vertebral body can be removed with a corpectomy using, for example, a transthoracic trajectory. (*From* Sundaresan N, Digiacinto GV, Hughes JE, Cafferty M, Vallejo A. Treatment of neoplastic spinal cord compression: results of a prospective study. Neurosurgery 1991;29:645–50; with permission.)

was by Manabe et al [91]. Twenty-eight patients underwent an anterior, posterior, or combined approach if tumor was located in the vertebral body/pedicle, posterior column, or anterior/posterior columns, respectively. Before surgery, 14 patients were nonambulatory. After surgery, 25 were ambulatory and all patients had relief of pain. In one of the largest reports, Sundaresan et al [92] described their results in 80 patients with a solitary metastatic spinal lesion. Depending on the anatomic and radiologic extent of the tumor, they used a variety of approaches: an anterior approach was used in 32 patients, a strictly posterior or posterolateral approach was used in 8 patients, and a combined anteroposterior approach was used in 40 patients. Before surgery, 48 patients (60%) were ambulatory and 55 (69%) had a significant amount of pain. After surgery, 78 (98%) were ambulatory, including 94% of those who were initially nonambulatory. Pain was improved in 95%, with 76% having complete relief. Although the overall length of survival was 30 months, there was a considerable range with the various tumor types. Patients with breast and renal cell carcinoma had a median survival of 36 months compared with 15 and 12 months for patients with gastrointestinal and unknown primary carcinoma, respectively. Gokaslan et al [24] reported their results with transthoracic vertebrectomy in 72 patients. Pain was improved in 92% of patients, and 93% of patients were able to walk after surgery. Of the 13 preoperatively nonambulatory patients, 10 regained ambulatory ability after surgery, with 3 of those regaining normal function. The 1-year survival rate for the entire cohort was 62%.

Overall, the data shown in Table 3 suggest that neurologic outcomes achieved with circumferential

decompression are far superior to those achieved with decompressive laminectomy or radiation. On average, nearly 90% of patients experienced an improvement in their pain. Ambulatory function was present, on average, in 85% of the patients after surgery and was regained in 60%. Not surprisingly, the morbidity and mortality associated with this more aggressive surgical management are significant.

Analogous to the controversy of laminectomy versus radiation in the "old era," it is clear that an RCT was needed to answer the question more adequately of how circumferential surgery compares with radiation in this "new era." At the most recent annual meeting of the American Society of Clinical Oncology (Chicago, 2003), Patchell et al [93] presented results from an RCT comparing direct decompressive surgical resection followed by adjuvant radiation (n = 50) with conventional radiation alone (n = 51). Both groups were treated with the same steroid protocol, and both received the same total radiation dose (30 Gy). Patients treated with surgery retained ambulatory and sphincter function significantly longer than patients in the radiation group (median: 126 versus 35 days; $P = 0.006$). In addition, 56% of nonambulators in the surgical group regained the ability to walk compared with 19% in the radiation group ($P = 0.03$). Surgical patients also maintained continence and functional ambulatory scores significantly longer compared with radiation patients. Surgery allowed most patients to remain ambulatory for the remainder of their lives, whereas patients treated with radiation spent approximately 66% of their time nonambulatory and incontinent. Survival, as expected, was not significantly different between the two groups.

This landmark study represents the first good class I data in the metastatic spinal disease literature. Although the full report has yet to be published, the results support a change in the current management of metastatic epidural spinal disease. Traditional indications for surgery include radioresistant tumors (eg, sarcoma, lung, colon, renal cell), obvious spinal instability, clinically significant neural compression secondary to retropulsed bone or from spinal deformity, intractable pain unresponsive to nonoperative measures, and radiation failure (progression of deficit during treatment or spinal cord tolerance reached). According to this study, surgery should be considered the primary treatment modality in all patients with newly diagnosed metastatic disease who do not harbor any of the indications for radiotherapy (see next section). It will take some time to reverse the radiotherapy bias, however. Even with this new RCT and with the plethora of previous cohort studies, some authors continue to publish incorrect statements that patients do only "slightly better with surgery compared with radiotherapy" and that surgery should still only be performed if traditional indications (as listed previously), including paraplegia at diagnosis, are present [11].

Radiation

Conventional radiotherapy

Indications for radiotherapy are radiosensitive tumors (eg, lymphoma, multiple myeloma, small cell lung carcinoma, seminoma of testes, neuroblastoma, Ewing's sarcoma), expected survival of less than 3 to 4 months, inability of the patient to tolerate an operation, total neurologic deficit below the level of compression for more than 24 to 48 hours, and multilevel or diffuse spinal involvement. The standard radiation portal involves the diseased level with a 5-cm margin, which effectively includes two vertebral bodies above and below [94]. The total radiation dose is usually 3000 cGy (range: 2000–4000 cGy) and is administered over a 10- to 14-day course, with higher doses delivered in the first few days and then tapered down [94]. Patients with radiosensitive tumors (eg, breast, myeloma, lymphoma) overall have a better functional outcome than those who have more radioresistant tumors (eg, sarcoma, lung, colon, renal cell), especially when the diagnosis of spinal cord compression is made late [95]. Many patients have disease isolated to the spine, usually the vertebral body, without epidural compression. For these patients, a single dose, usually 8 Gy, provides good pain relief and is as efficacious as various fractionated regimens [96,97].

Table 2 depicts the results of radiotherapy during the era in which decompressive laminectomy was the predominant surgical procedure. There have been a number of reports since then, all uncontrolled cohort studies, which are shown in Table 4. One of the largest reports is by Maranzano and his colleagues [27,37,98], who treated 209 patients with radiation (30 Gy) and steroids. Pain was present in 98% of patients before treatment, and 65% had some degree of neurologic dysfunction. The average follow-up

Table 4
Results of recent radiotherapy trials

Authors (year)	Patients	Post-radiation results		
		Pain (% improved)	Success	Rescue
Leviov et al [135] (1993)	70	N/A	39%	24%
Maranzano et al [27,37,98] (1995) (1991) (1989)	209	71%	76%	51%
Helweg-Larsen [99] (1996)	153	83%	61%	28%
Katagiri et al [136] (1998)	101	57%	64%	19%
Chamberlain and Kormanik [137] (1999)	108	75%	N/A	5%
Zaidat and Ruff [138] (2002)	139	100%	78%	47%
Rades et al [139] (2002)	98	N/A	60%	N/A

Success is defined as the proportion of patients ambulatory after treatment, whereas Rescue is the proportion of non-ambulators who regained ambulatory function, either with assistance or independently. N/A indicates that data were not available in the selected paper.

was 49 months. Pain was improved in 71% of patients, ambulatory function was improved in 36%, and bladder function was improved in 44%. Overall, 76% recovered or preserved the ability to walk. The median survival for the whole group was 6 months, with a 1-year survival rate of 28%. Favorable factors for survival included ambulatory status before and after treatment and histology. Helweg-Larsen [99] followed 153 patients for a median of 2.6 months. Normal gait was present in 60 (39%) patients, assisted ambulation in 19 (12%), paresis without gait function in 31 (20%), and paraplegia in 43 (29%). Neurogenic bladder was present in 57 (37%). The total radiation dose was 28 Gy, given in fractions of 4 Gy on 7 consecutive days. In total, 21 of the 74 initially nonambulatory patients (12 paretic and 9 plegic) recovered some gait function. Seven patients (2 with normal gait and 5 with assisted gait) progressed to a nonambulatory state because of treatment failure. Of those patients who presented with sphincter dysfunction, 10 (18%) regained bladder function. The median survival was 5.4 months. More recently, Hoskin et al [29] presented their results in 102 patients who underwent one to five radiation fractions. They found no difference in ambulation, sphincter function, and pain control in patients who underwent single compared with multiple fractions. The study suffers a major flaw, however, in that posttreatment outcomes could not be assessed in half of the patient population because they were lost to follow-up.

The average pain improvement, ambulatory success, and rescue for the articles listed in Table 4 are 77%, 63%, and 29%, respectively. These figures are similar to those found by Falkmer et al [95] in their recent review article but seem to be inferior to those found in the newer surgical literature (see Table 4). As stated previously, the recently released results of the first well-designed RCT comparing stand-alone radiotherapy and surgery with adjuvant radiotherapy show a marked benefit for surgery [100]. Thus, for patients who meet surgical criteria, the role of standard radiotherapy is as adjuvant therapy only. Conversely, there are many patients who cannot tolerate surgery or in whom surgery would be inappropriate (eg, highly radiosensitive tumors, short life expectancy). In these patients, radiation should still serve as the primary mode of treatment.

Nonconventional radiotherapy

With conventional external beam radiation, a significant amount of normal tissue, including the spinal cord, is exposed to radiation, which can lead to radiation-induced myelopathy [101–103]. If radiation could be delivered to the target while decreasing the amount delivered to normal tissue, injury to the spinal cord would theoretically be reduced. Nonconventional radiotherapy, which includes stereotactic radiosurgery (SRS) and intensity-modulated radiotherapy (IMRT), is able to do just that. The data thus far consist of several case series (class III) [104–108]. Follow-up in these studies is short, and outcome measures, such as pain and neurologic function, are rarely available. The research has shown nonconventional radiotherapy to be a safe intervention, although its effectiveness has not been rigorously tested against other current therapies (surgery or conventional radiotherapy). Such data are

needed before a treatment recommendation can be rendered.

Summary

Treatment of metastatic epidural spinal disease has undergone significant changes over the last 20 years. No longer is indiscriminate decompressive laminectomy offered as the only surgical treatment. It carries all the risks associated with an invasive procedure and offers the patient little benefit unless it is used to remove disease isolated to the posterior elements. The existing literature suggests that surgery that frees the spinal cord at the site of compression in addition to reconstructing and stabilizing the spinal column is more effective at preserving and regaining neural function, notably ambulatory function and sphincter function, than conventional radiotherapy. It is also highly effective in relieving pain. The preliminary results of a recent RCT provide the first class I evidence to support a reversal in the current philosophy of primary treatment for many patients with metastatic disease. Conventional radiotherapy has a clearly defined role as adjuvant therapy and as primary therapy in those who are unable to tolerate or benefit significantly from surgery. The role of nonconventional radiation therapy, such as IMRT and SRS, remains to be elucidated.

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