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Evolution of treatment for metastatic spine disease

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Spinal metastases account for most spinal neoplasms and are a significant source of morbidity in patients with systemic cancer. Approximately 30% of patients with neoplastic conditions develop symptomatic spinal metastases during the course of their illness, and 20% of patients with spinal metastases have evidence of spinal cord compression at the time of presentation. By the time of death, metastatic deposits within the spinal column are found in up to 90% of cancer patients [1,2].

Recent advances in therapy may prolong the life expectancy of cancer patients and seem to result in more patients surviving long enough to present with spinal involvement. In addition, more patients with spinal metastasis are diagnosed at an early stage because of the widespread use of magnetic resonance imaging.

The management of metastatic spinal disease has remained controversial. There are few controlled studies comparing the currently available treatment modalities, and criteria to evaluate the response to treatment are not standardized. Early studies comparing the efficacy of radiation therapy and laminectomy found no difference in neurologic outcome or survival. In the last two decades, neurosurgeons have become familiar with a wide range of approaches to address spinal column pathologic findings. In addition, effective methods of anterior and posterior spinal stabilization have become widely available (Fig. 1).

New therapeutic modalities and techniques are also being evaluated in the setting of metastatic spinal disease, including endoscopically assisted spinal cord decompression [3]; minimally invasive procedures, such as percutaneous vertebroplasty and kyphoplasty [4]; advances in radiation delivery [5–7]; image-guided surgery; and novel surgical approaches for radical tumor resection and spinal reconstruction [8].

In summary, physicians and surgeons treating patients with metastatic spinal tumors have not only earlier and more frequent encounters with patients with spinal metastases but better means of treating these patients.

Goals of therapy

The management goals for patients with metastatic spinal disease are palliative and include the restoration or preservation of neurologic function via prompt decompression and the relief of pain. With timely treatment, approximately 80% of cancer patents with epidural spinal cord compression maintain their ability to walk [9].

The most frequent presenting complaint in patients with spinal metastases is pain [10,11]. Three types of pain are typically encountered: local pain, radicular pain, and axial pain. The type of pain has significant implications with regard to patient management.

Local pain is constant and, generally, there is neither worsening with movement nor any improvement with recumbency. Imaging studies usually reveal enlargement of the vertebral body without evidence of vertebral body collapse or spinal deformity. This type of pain has been attributed to stretching of the vertebral body periosteum by the expansile tumor. Radiation therapy reduces tumor mass and thus may relieve periosteal stretching.

Radicular pain is related to nerve root compression by the tumor mass. In the case of

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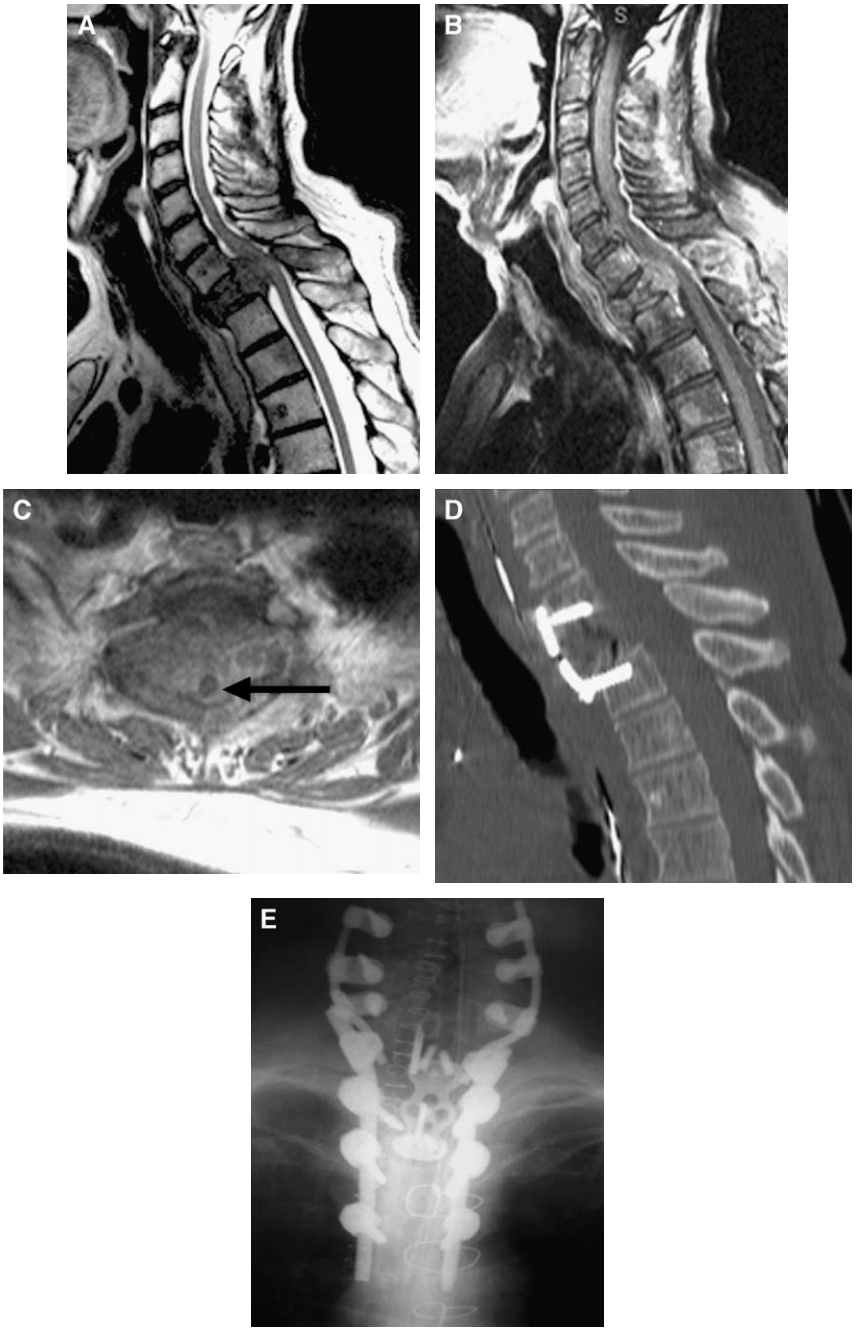

Fig. 1. A 73-year-old man with upper thoracic pain for several months presented with a 24-hour history of inability to ambulate. Preoperative sagittal T2-weighted (*A*) as well as postcontrast sagittal (*B*) and axial (*C*) T1-weighted MRI scans show spinal cord (*arrow*) compression by epidural disease at the T1 spinal level. The patient underwent an emergent T1 vertebrectomy and polymethylmethacrylate (PMMA) reconstruction via an anterior approach (combined anterior neck dissection and median sternotomy). (*D*) Postoperative CT sagittal reconstructed image shows the ventral plate and screws at C7 to T2. The patient recovered motor function. Prostate carcinoma of the spine was diagnosed. He later underwent T1 laminectomy and posterior instrumented fusion. (*E*) Postoperative anteroposterior radiograph demonstrates lateral mass screws (C5–C7) and pedicle screws (T2–T4), with a rod connector bridging the cervical and thoracic rods. Steinmann pins securing the PMMA ventrally are also seen.

pathologic fracture, nerve root compression may be secondary to bone or disk fragments. This pain occurs in a dermatomal distribution and is usually associated with dysesthesia. Depending on the cause of compression, the nerve root may need to be decompressed surgically (in the case of a radioresistant tumor or bone/disk fragments) or with the use of radiation therapy or chemotherapy (for radiosensitive epidural disease).

The third category of pain is axial pain, which is a significant cause of morbidity. It is caused by mechanical instability of the spinal column. Axial pain worsens with movement and is characteristically relieved at rest. Imaging studies usually reveal vertebral body collapse or spinal deformity. Spinal stabilization is usually effective in relieving this type of pain.

Evolution of treatment

The keystones of management for patients with metastatic spinal tumors consist of radiation therapy, surgery, and corticosteroids [9]. In the past, radiation therapy was the primary treatment option. Laminectomy was the earliest available surgical alternative. The usefulness of laminectomy was limited by the fact that metastatic disease typically arises from the vertebral body; thus, epidural compromise is most often ventral. In patients with anterior and middle column instability secondary to vertebral body destruction, laminectomy may further compromise spinal stability [10,11].

As effective methods to stabilize the spine have become widely available, the surgical treatment of metastatic spinal tumors has significantly improved. Surgeons have also become more experienced with anterior approaches to the spine, facilitating direct access to the diseased vertebral body for effective decompression and short-segment stabilization [10–12]. The recently reported results of the first well-designed, randomized, controlled trial of direct decompressive surgical resection and radiation therapy versus radiation therapy alone showed a significant improvement in the retention or recovery of ambulatory function in the group undergoing surgery [13]. Wider acceptance and judicious use of current surgical techniques may improve the quality of life of many patients too often denied such treatment [14].

Table 1 summarizes some of the large published series on the use of radiotherapy alone for treatment of metastatic spinal tumors. The effect of radiation therapy on pain was generally not reported in older studies. Satisfactory results, usually defined as retention or recovery of sufficient neurologic function to ambulate, ranged from 28% to 76%. Older series reported rates of neurologic improvement of 40% to 50%, whereas more recent studies [22,23] have produced better

Table 1
Results of treatment for symptomatic spinal metastases: radiotherapy alone

Authors	Year	Study	n	Results
Kahn et al [15]	1967	RS	82	39% complete or partial motor improvement
Gilbert et al [16]	1978	RS	170	49% ambulatory after treatment
Greenberg et al [17]	1980	PS	83	57% ambulatory after treatment
Stark et al [18]	1982	RS	31	35% improved
Constans et al [19]	1983	RS	108	39% improved, 26% worse
Obbens et al [20]	1984	RCT	83	RT versus RT + dexamethasone (combined results) 89% improved pain 29% improved motor 24% worse
Bach et al [21]	1990	RS	149	35% improved 18% worse
Maranzano and Latini [22]	1995	PS	209	82% improved pain 76% improved motor 44% improved sphincter function
Katagiri et al [23]	1998	PS	101	67% ambulatory post treatment 68% improved pain
Total			1016	

Abbreviations: PS, prospective case series; RCT, randomized controlled trial; RS, retrospective case series; RT, radiation therapy.

results, often greater than 70%. This development may be reflective of multiple factors, including earlier diagnosis with improved and more readily available imaging techniques, improvements in radiation therapy protocols, and more judicious selection of patients receiving radiotherapy rather than surgery as first-line treatment.

Some of the large published series on laminectomy, with or without adjuvant radiotherapy, are summarized in Table 2. Rates of neurologic improvement reported among these studies ranged from 28% to 58%. Where these results were compared with those obtained with radiotherapy alone, no significant differences were found. A small, randomized, prospective trial comparing the use of laminectomy and radiotherapy for spinal epidural metastases yielded inconclusive results [33]. Postoperative mortality, where reported, ranged from 10% to 15%, although among the older series, these numbers are biased by the relatively large number of patients dying from metastatic cancer. Wound complication rates as high as 35% were reported [34]. Pain was not assessed in most of the series using laminectomy alone, presumably because without spinal instrumentation, axial pain could not be effectively treated.

As effective methods of spinal stabilization became more widely used, the results of surgery improved (Table 3). As discussed previously, posterior decompression is not the most efficacious surgical procedure for spinal cord decompression in the cancer setting. The addition of posterior stabilization may have provided surgeons the opportunity to resect the tumor and manage spinal instability more completely. Rates of satisfactory neurologic improvement ranged from 48% to 88% in these series. Pain relief was addressed in most studies, with rates of improvement from 80% to 100%.

Table 4 summarizes many of the studies in which an anterior approach was selectively used as the primary mode of decompression, followed by spinal stabilization. Neurologic improvement was found in 62% to 100% of patients after surgery, and 81% to 95% reported an improvement in pain. Wound complication rates were low for anterior approaches.

In summary, the literature to date supports a pathology-directed approach for the treatment of metastatic spinal disease. The addition of spinal stabilization seems to be critical in improving the overall neurologic recovery rate and for managing axial spinal pain [48].

Indications for radiation therapy

An important prognostic factor in determining the clinical outcome in patients with metastatic spinal cord compression is the presence, severity, and duration of neurologic dysfunction [22]. The rate of ambulatory recovery in completely paraplegic patients is low, even for patients with highly radiosensitive tumors [16]. Thus, prompt surgical decompression should be considered the therapy of first choice for patients with symptomatic spinal cord compression, because improvement with radiotherapy alone only begins several days after the initiation of treatment, a delay that may result in an irreversible worsening of the neurologic condition. Radiation therapy is also not effective if spinal cord impingement is secondary to bone (vertebral body collapse) [49,50].

Radiation therapy alone is an option in patients with radiosensitive tumors who cannot tolerate surgery or in patients whose prognosis for survival makes surgery inappropriate. Highly radiosensitive tumors include lymphoma, neuroblastoma, seminoma, and myeloma. Breast and prostate carcinoma are considered moderately radiosensitive.

The recently reported study by Regine et al [13] concluded that in most cases in which patients meet clinical criteria for surgery, the role of radiation treatment is that of an adjuvant therapy. Radiotherapy as an adjuvant therapy is best performed after surgery. In several surgical series, patients who received preoperative radiotherapy had a greater likelihood of postoperative complications [10,17,34,51,52], particularly wound infection and dehiscence. These complications were especially prevalent among patients who underwent posterior surgical approaches [52]. Radiation-induced osteonecrosis also presents substantial obstacles to the fusion of corticocancellous bone grafts [53]. Graft incorporation is less problematic with the use of ventral rather than dorsal grafts, however, which is possibly related to the more substantial blood supply of the vertebral body and the compressive forces to which ventral grafts are subjected [54].

Indications for surgery

Selection criteria for surgical intervention are not rigid, and the treatment plan for patients with metastatic tumors remains highly individualized. General indications for surgical intervention (including tumor resection and spinal reconstruction) are (1) radioresistant tumor, (2) spinal

Table 2
Results of treatment for symptomatic spinal metastases: laminectomy with or without radiotherapy

Authors	Year	Study	n	Results
Hall and Mackay [24]	1973	RS	129	Sx ± adjuvant RT or chemotherapy 29% ambulatory with bladder control
Brady et al [25]	1975	RS	114	24 Sx alone, 30% motor improvement 90 Sx + RT, 61% motor improvement
Gilbert et al [16]	1978	RS	65	Sx + RT, 46% ambulatory after surgery
Livingston and Perrin [26]	1978	RS	100	Sx ± RT 58% ambulatory after surgery 19% improved motor, nonambulatory 40% ambulatory + urinary continence + survival >6 months 70% improved pain 10% postoperative morbidity
Baldini et al [27]	1979	RS	140	30% improved motor 19% worse motor 69% improved pain 15% postoperative mortality
Dunn et al [28]	1980	RS	104	Sx + RT 33% improved motor 23% worse motor 10% postoperative mortality
Stark et al [18]	1982	RS	84	37% improved motor
Constans et al [19]	1983	RS	465	Sx + RT 46% improved neurologic symptoms 12% worse neurologic symptoms
Klein et al [29]	1984	RS	197	44% ambulatory after surgery 47% improved motor 14% worse motor 47% improved pain
Kollman et al [30]	1984	RS	109	56% improved motor 75% improved pain
Garcia-Picazo et al [31]	1990	RS	53	48% ambulatory after surgery 55% sphincter function after surgery
Bach et al [21]	1990	RS	196	Sx alone: 46% improved, 10% worse Sx + RT: 59% improved, 11% worse
Landmann et al [32]	1992	RS	127	Sx + RT 58% improved motor, 39% no change, 2% worse 68% improved sphincter function 88% improved pain
Total			1883	

Abbreviations: RS, retrospective case series; RT, radiation therapy; Sx, surgery.

instability, (3) spinal cord compression by bone or disk fragments, (4) progressive neurologic deterioration, (5) previous radiation exposure of the spinal cord, and (6) uncertain diagnosis. With regard to the latter, the diagnosis of malignancy can often be established with computed tomography (CT)-guided needle biopsy.

In an attempt to clarify indications for surgical treatment, several authors have tried to delineate the factors that are most important in determining surgical success [55–57]. We favor aggressive resection of metastatic spinal tumors in most medically fit patients with solitary metastases with favorable histologic findings and minimal evidence of extraspinal disease so as to minimize local recurrence, neurologic compromise, and pain. Aggressive resection may also be considered in the presence of extraspinal disease for patients who are likely to respond to but have not yet received effective adjuvant therapy.

Table 3
Results of treatment for symptomatic spinal metastases: posterior decompression and stabilization

Authors	Year	Study	n	Results
Hansebout and Blomquist [35]	1980	RS	82	84% mobilized postoperative day 3 100% improved pain
Solini et al [36]	1985	RS	33	1 patient had corpectomy 76% neurologic symptoms improved 85% solid fixation + improved pain + improved motor function 12% failure of fixation device
Heller et al [37]	1986	RS	33	48% improved neurologic function 7% worse neurologic function 79% improved pain 45% alive, ambulatory, improved pain at 6 months after surgery
Perrin and McBroom [38]	1987	RS	200	65% ambulatory, 17% improved 4% worse motor 80% improved pain 8% postoperative mortality 42% ambulatory and continent at 6 months after surgery
Olerud and Jonsson [39]	1996	PS	102	Patients with cervical involvement 100% improved pain 83% (5/6) regained ambulation Patients with thoracolumbar involvement 100% improved pain 88% ambulatory after surgery 76% (19/25) regained ambulation
Bauer [40]	1997	PS	69	76% complete or partial recovery of neurologic deficit
Total			519	

Abbreviations: PS, prospective case series; RS, retrospective case series.

The life expectancy required to justify surgical intervention remains controversial. A period of 3 to 6 months of expected survival has been proposed [11], although it is often difficult to determine life expectancy for the individual patient accurately.

Among the surgical series, the longest survival periods are seen in patients with breast [10], thyroid [55], prostate [57], and renal cell carcinoma [58]. Given the short survival time in patients with melanoma [59] and lung cancer [10], spinal surgery is advocated only in exceptional circumstances. All patients should be assessed medically and for extent of disease by a medical internist and treating oncologist. Host factors associated with poor outcome include advanced age, obesity, malnutrition, diabetes, bone marrow suppression, and steroid therapy [60].

Other therapeutic advances

Innovative therapeutic advances are constantly being evaluated in the setting of metastatic spinal disease. These treatment modalities may be classified as novel chemotherapies, advances in radiation delivery, novel surgical approaches, and minimally invasive surgical techniques, such as vertebroplasty, kyphoplasty, and endoscopy.

Chemotherapy

Chemotherapy can be divided into antitumor drugs and drugs that prevent or ameliorate the effects of tumor. Antitumor chemotherapy continues to play a relatively limited role in the treatment of spinal metastases. It is important for the treatment of chemosensitive tumors, such as Ewing's sarcoma and neuroblastoma, which account for more than 50% of pediatric spinal epidural metastases, however [61].

The use of corticosteroids in the treatment of pain and spinal cord compression by metastatic tumors is widely accepted [9].

Bisphosphonates, which suppress bone resorption by inhibiting osteoclastic activity, are a relatively new class of drugs. Bisphosphonates are

Table 4
Results of treatment for symptomatic spinal metastases: vertebral body resection (anterior approach) and stabilization

Authors	Year	Study	n	Results
Harrington [41]	1984	RS	52	84% complete or significant neurologic recovery 81% improved pain 4% immediate postoperative mortality
Siegal and Siegal [14]	1985	RS	61	80% ambulatory after surgery (28% before surgery) 93% continent after surgery (51% before surgery) 91% improved pain 7% operative mortality
Sundaresan et al [42]	1985	RS	101	78% ambulatory after surgery 70% improved neurologic function 85% improved pain 8% postoperative mortality
Onimus et al [43]	1986	RS	36	72% motor improvement
Sundaresan et al [44]	1991	RS	45	100% ambulatory after surgery (56% before surgery) 6% postoperative mortality
Hosono et al [45]	1995	RS	82	64% recovery of ambulation 81% improved motor 94% improved pain
Gokaslan et al [11]	1998	RS	72	76% improved neurologic function 70% ambulatory after surgery 92% improved pain 29% major or minor surgical complications 3% postoperative mortality
Weigel et al [46]	1999	RS	52	62% improved neurologic function
Sundaresan et al [47]	2002	RS	80	86% improved neurologic 98% ambulatory after surgery 95% improved pain
Total			581	

Abbreviations: PS, prospective case series; RS, retrospective case series.

effective in the treatment of malignancy-associated hypercalcemia, can relieve pain secondary to osteolytic metastases [62], and may reduce the risk of pathologic fracture [63]. Side effects include febrile reactions, myalgia, neutropenia, thrombophlebitis, hypocalcemia, and, rarely, ocular complications (eg, uveitis) [64].

Radiation therapy

Advances in radiation delivery may improve outcomes either alone or in combination with surgery [5]. New methods include intraoperative radiation therapy and stereotactic radiosurgery. These technologies aim to provide a greater dose of radiation to the target tissue while maintaining the dose delivered to the spinal cord within an acceptable tolerance level.

Intraoperative radiation therapy involves the precise delivery of electron beams to the spine during surgery while protecting the spinal cord with a lead shield. In a retrospective review of 37 patients who underwent intraoperative radiation therapy [7], including 22 patients who also received fractionated external radiation therapy (either before or after surgery), local control was achieved in all patients at a median follow-up of 11 months. Radiation myelopathy developed in 1 patient whose spinal cord was not protected during radiation delivery.

Ryu et al [6] recently reported the use of a linear accelerator (LINAC)–based system—the CyberKnife (Accuray, Sunnyvale, CA)—to treat spinal lesions in 16 patients, including 5 patients with metastatic tumors. The application of radiosurgery to the spine has previously been limited

because of questions with regard to the accuracy of radiation delivery, especially with changes in the target location with patient respirations. An image-guided frameless system was used for localization, based on surgically implanted fiducials. A robotic arm adaptively changes the position of the LINAC during treatment to compensate for patient movements. Tests demonstrated alignment of the treatment dose with the target volume within ±1 mm. Patients with metastatic lesions received doses of 1100 to 17,000 cGy in two fractions. The authors reported no side effects directly attributable to the treatment sessions. Follow-up of at least 6 months demonstrated no progression of tumor.

Percutaneous vertebroplasty and kyphoplasty

Percutaneous vertebroplasty involves the injection, usually under local anesthesia, of polymethylmethacrylate (PMMA) bone cement into a cervical, thoracic, or lumbar vertebral body lesion [65]. The needle placement and injection of bone cement are performed under fluoroscopic or CT guidance. Kyphoplasty is a modification of vertebroplasty that includes the inflation of a balloon into a collapsed vertebral body to restore height and reduce kyphotic deformity before injection with PMMA [66]. Compared with vertebroplasty, kyphoplasty may have less risk of cement extravasation, although it is yet to be determined whether or not this is of clinical significance [4]. Most of the North American experience with these procedures is in the treatment of osteoporotic compression fractures. The relative merits of vertebroplasty and kyphoplasty in the setting of metastatic spine disease remain the subject of ongoing investigations.

Vertebroplasty and kyphoplasty are indicated in patients with well-localized disabling axial type pain secondary to vertebral body fracture or collapse, without evidence of epidural disease. Significant epidural compression is a major contraindication. Other contraindications include failure to localize symptomatic levels, spinal pain that is predominantly local or radicular rather than axial, uncorrected coagulopathy, infection at the planned injection site, and intolerance to prone positioning [4]. Vertebra plana deformity is a relative contraindication. Complications, although rare, include compression of the neural elements because of leakage of the polymer; therefore, significant destruction of the posterior vertebral body wall by tumor is also considered a relative contraindication.

Kyphoplasty is favored when there is kyphosis that is judged to contribute significantly to patient morbidity. It may also be the procedure of choice, relative to vertebroplasty, when there is disruption of the posterior vertebral cortex and more controlled delivery of bone cement is desired. Kyphoplasty is a more a complex procedure, however; it is also more costly and requires a general anesthetic.

Endoscopic vertebrectomy

In an attempt to reduce morbidity from the traditional thoracotomy, endoscopically assisted techniques have been used to achieve vertebrectomy and spinal cord decompression in patients with thoracic spinal metastases. Transthoracic anterior approaches [67] as well as posterolateral approaches [3] have been advocated. The posterolateral approach has its greatest advantage in the uppermost regions of the thoracic spine, because it is difficult to access this region from an anterior approach using current endoscopic technology. As experience with this promising surgical method grows, larger patient series may become available to assess morbidity, hospitalization time, treatment costs, and efficacy better compared with traditional combined approaches.

Surgical approaches

Traditional surgical approaches to the spine may be classified as those that provide access anteriorly, posteriorly, and posterolaterally. Recently, the senior author reported a series of 26 patients in whom a simultaneous anterior-posterior approach was used for the resection of thoracic and lumbar tumors, followed by reconstruction and stabilization [8]. Advantages of this simultaneous technique in comparison to staged anterior and posterior procedures include (1) wide exposure that allows for complete resection of tumor involving the anterior and posterior spinal elements simultaneously, including the chest wall; (2) direct access to feeding arteries and lateral positioning, optimizing hemostasis; (3) direct visualization of adjacent neurovascular and visceral structures; and (4) the ability to reconstruct and stabilize the spine anteriorly and posteriorly in a single operation.

This aggressive approach may prove most useful in cases of primary rather than metastatic spinal tumors, where en bloc resection is most

desirable. Complete spondylectomy for solitary spinal metastases has recently been advocated by some authors [8,47,57].

Summary

The management of patients with metastatic disease of the spine should be highly individualized and depends on several factors, including the clinical presentation, duration of symptoms, tumor type, anticipated radiosensitivity, tumor location, extent of extraspinal disease, integrity of the spinal column, and medical fitness and life expectancy of the patient. Early diagnosis and intervention are of paramount importance in improving the likelihood of functional neurologic recovery, with the maintenance of ambulation as the primary goal. Effective management of axial spinal pain involves reconstruction and stabilization of the spinal column. Although the ideal therapy has not been established, a wide range of management options is currently available.

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